Burden of Severe 2009 Pandemic Influenza A (H1N1) Infection in Children in Southeast Spain

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\textbf{Abstract}

\textbf{Introduction:} Most of the published studies on patients admitted with 2009 pandemic influenza are not population based. We have compiled the clinical information regarding all children admitted with 2009 pandemic influenza A (H1N1) infection during the season 2009-2010 in our defined population, in order to have an unbiased view of the most severe side of the clinical spectrum of the infection and to quantify its burden.

\textbf{Methods:} Children <15 years-old admitted to any of 3 hospitals in South-East Spain with 2009 pandemic influenza A (H1N1) detected by means of reverse transcriptase polymerase chain reaction. High quality data were extracted from clinical records specially designed for the pandemic.

\textbf{Results:} Eighty two children fulfilled the inclusion criteria. The hospitalization rate was 68 per 100,000 children <15 years-old; in those <5 years-old the rate was of 131 and in <1 year-old, 234 per 100,000. An estimated 0.7% of the children who suffered from pandemic influenza were admitted (1.7% in <5 years-old). Intensive care was required for 5% of the hospitalized patients living in the study area. Mortality was roughly estimated about 1 per 100,000 children <15 years-old and was associated with the presence of very severe comorbidities or co-infections. Only 20% of the admitted children were ≥5 years-old and without risk factors. The disease followed a generally benign course despite the modest use of oseltamivir (49% of the patients).

\textbf{Conclusions:} Clinical and epidemiological data are very similar to those observed in other places and in interpandemic seasons with a high influenza activity.

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Palabras clave:
Gripe
Pandemia
Hospitalización
Burden
España

\textbf{Hospitalización por gripe pandémica A (H1N1) 2009 en niños en el sureste de España}

\textbf{Resumen}

\textbf{Introducción:} Pocos artículos sobre pacientes ingresados por la gripe pandémica de 2009 tienen una perspectiva poblacional. Hemos revisado la información clínica de todos los niños que han requerido hospitalización por gripe pandémica A (H1N1) 2009 durante la temporada 2009-2010 en nuestra población, para obtener una visión no sesgada de la faceta más grave de esta grípe y cuantificar su impacto.

\textbf{Métodos:} Se incluyeron los niños menores de 15 años ingresados en 3 hospitales del sureste de España con infección por influenza A (H1N1) 2009 confirmada por reacción en cadena de la polimerasa. Los datos se obtuvieron de registros específicos diseñados durante la pandemia.

\textbf{Resultados:} Ochenta y dos niños cumplieron los criterios de inclusión. La tasa de hospitalización fue de 68/100.000 niños <15 años; 131/100.000 en los menores de 5 años y 234/100.000 en menores de 1 año. Se estimó que el 0,7% de los niños que padecieron la gripe pandémica requirió ingreso (1,7% en menores de 5 años). El 5% de los niños hospitalizados precisaron cuidados intensivos. La mortalidad se calculó en torno al 1/100.000 menores de 15 años y se asoció con la presencia de otras enfermedades o infecciones graves. Solo 20% de los hospitalizados eran mayores de 5 años y sin factores de riesgo. La enfermedad siguió un curso generalmente benigno pese al uso modesto de oseltamivir (49% de los pacientes).

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Introduction

Every year influenza causes high morbidity and mortality among the pediatric and general population. High risk groups for severe influenza include, young children, elderly people, and patients who suffer from chronic diseases. The declaration of the last pandemic influenza included young children, elderly people, and patients who are high risk groups for severe influenza. Some series of pediatric patients admitted with 2009 pandemic influenza A (H1N1) infection have been published, but very few include the whole pandemic with a population perspective, and none in Spain. The alert caused by the declaration of the pandemic in our country provoked an extreme vigilance, stimulating the detection of the virus by means of high reliability techniques in many of the patients with symptoms compatible with influenza, so it is likely that the number of hospitalized patients who have been through an undetected infection caused by 2009 pandemic influenza A (H1N1) is minimal. This exceptional circumstance has led us to retrospectively compile the clinical information regarding pediatric patients admitted with confirmed 2009 pandemic influenza A (H1N1) infection, once the pandemic had ended, in order to determine the most severe side of the clinical spectrum of the infection, as well as to quantify its burden in our population.

Patients and methods

The study was conducted in three hospitals in the province of Alicante: Hospital General Universitario of Alicante (HA), Hospital General of Elda (HE) and Hospital Vega Baja of Orihuela (HO). These hospitals gave public health care to 42,797, 35,051 and 30,178 people <15 years of age in their respective health departments (108,026 in total, 7,269 <1 year of age), according to official data from the Population Information System of the Valencian Community in November 2009. The HA is the only one that has an intensive care unit (ICU) for children older than one month of age, being the reference pediatric ICU for the other two, and the rest of the hospitals of the province, where 298,335 children <15 years of age were registered. Pediatric hospitalization in private facilities is almost non-existent in the province of Alicante.

We went through all the records of children hospitalized from June 2009 to July 2010 and in whom the presence of 2009 pandemic influenza A (H1N1) was analyzed on respiratory tract secretions by means of reverse transcriptase polymerase chain reaction. Patients with a positive result were included in the present study. Data from the medical history of these patients, specially registered during the pandemic, were reviewed and extracted using a form designed to record the relevant information. This included demographic data, the presence of risk factors for severe influenza, the symptoms and signs at admission, the care and treatment needed during their hospitalization, the outcomes and the dates in which they occurred. Infections were considered nosocomial when symptoms started during hospitalization for another reason. Otherwise, they were considered infections acquired in the community. The study was approved by the Clinical Research Ethics Committee of the Hospital General Universitario of Alicante.

Data were entered, reviewed and analyzed using SPSS (v17.0, SPSS, Chicago, IL, USA). Descriptive statistics included frequency analysis for categorical variables and medians for continuous variables. We used two sample t tests or Mann-Whitney U test (depending on whether the criteria for normality were fulfilled or not) for continuous variables and χ² test or Fisher exact test for categorical variables in bivariate analysis. Probabilities were two tailed and a P value of <.05 was considered significant.

Results

Data from 82 children who fulfilled the inclusion criteria were collected. Fifty two patients (63%) were male, with a median of 4 years of age (Fig. 1). All the patients were hospitalized between August and December (Fig. 2). However, most of them were admitted in November: between the epidemiological weeks 44 and 48 (November 1 to December 5) when 68 cases were admitted (83% of the total). No differences were observed in the temporal distribution between the three centers. The infection was considered of nosocomial origin in 5 cases, all of them between weeks 45 and 48, with symptoms of infection appearing 4 to 35 days after admission. No new cases were detected in 2010.

Thirty nine patients were hospitalized in HA, 21 patients in HE and 22 in HO. Nine of the patients admitted to HA came from other areas not included in the study, 7 of them transferred from their hospitals because of the severity of the disease or for the risk of worsening. When excluding these 9 patients, the hospitalization rate was 70, 60 and 73 per 100,000 children <15 years of age for the

![Figure 1.](image1.png) Distribution of the patients by age split by the presence or absence of risk factors.

![Figure 2.](image2.png) Date of admission of pandemic (H1N1) 2009 influenza infected patients. Cases have been grouped in epidemiological weeks. For nosocomial infections, the date of test sampling for the detection of the virus has been chosen.
Table 1
Risk factors in 30 patients admitted with 2009 pandemic influenza A (H1N1) infection

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic cardiovascular diseases</td>
<td>2</td>
</tr>
<tr>
<td>Chronic respiratory diseases</td>
<td>10***</td>
</tr>
<tr>
<td>Asthma</td>
<td>1***</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobinopathy and anemia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1***</td>
</tr>
<tr>
<td>Neuro muscular diseases</td>
<td>5</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>4***</td>
</tr>
<tr>
<td>Morbid obesity</td>
<td>2***</td>
</tr>
<tr>
<td>Prolonged treatment with acetylsalicylic acid</td>
<td>1</td>
</tr>
</tbody>
</table>

The extraordinary surveillance of 2009 pandemic influenza A (H1N1) allows us to be confident that the 82 patients included in our study are all those who had required hospitalization in our hospitals and were infected by 2009 pandemic influenza A (H1N1) throughout the pandemic season. This is the major strength of the study, as it gives us an unbiased population perspective of the burden and the clinical characteristics of the severe 2009 pandemic influenza A (H1N1) infection in our area. As in other locations in the northern hemisphere, pandemic activity peaked in autumn, where a massive contagion took place, most of the severe cases emerging at that time. Other epidemiological aspects were similar to those known for seasonal influenza in children in our contry.17

Slightly more than one third of the patients had any risk factor for influenza, mainly asthma and other chronic respiratory...
Children admitted to ICU (in chronological order); epidemiologic characteristics, time course, treatment received, final diagnosis and outcome

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age in years</th>
<th>Risk factor</th>
<th>Department of residence</th>
<th>Time between symptoms and admission to hospital - ICU (days)</th>
<th>Length of stay in hospital – ICU (days)</th>
<th>Oseltamivir before 48 hours since onset of disease</th>
<th>Type of respiratory support (time, in days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>7</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HA</td>
<td>1 – 1</td>
<td>8 – 5</td>
<td>No</td>
<td>Noninvasive (2)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>2</td>
<td>No</td>
<td>OSA</td>
<td>3 – 3</td>
<td>11 – 9</td>
<td>No</td>
<td>Noninvasive (4)</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>0 (4 d)</td>
<td>No</td>
<td>HA</td>
<td>1 – 1</td>
<td>9 – 9</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>0 (10 d)</td>
<td>No</td>
<td>HA</td>
<td>1 – 1</td>
<td>8 – 7</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>13</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HA</td>
<td>0 – 0</td>
<td>8 – 4</td>
<td>Yes</td>
<td>Noninvasive (2)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>0 (35 d)</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>OSA</td>
<td>Nosocomial – 0</td>
<td>47 – 47&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No</td>
<td>Invasive (12)</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>1</td>
<td>No</td>
<td>OSA</td>
<td>1 – 3</td>
<td>34 – 32</td>
<td>Yes</td>
<td>Invasive (32)</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>4</td>
<td>No</td>
<td>OSA</td>
<td>4 – 5</td>
<td>2 – 1</td>
<td>No</td>
<td>Invasive (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case</th>
<th>Final diagnosis (in addition to 2009 pandemic influenza A (H1N1) infection)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pneumonitis</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Middle lobe pneumonia</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Neonatal seizures (with normal CSF, EEG and cranial MRI)</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Late onset neonatal Klebsiella pneumoniae sepsis, neonatal seizures</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Severe asthmatic exacerbation</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Prematurity (28 weeks, 830 g), bronchopulmonary dysplasia, patent ductus arteriosus, bronchopneumonia</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Bilateral necrotizing pneumonia, Streptococcus pneumoniae sepsis, pneumothorax, mechanical ventilation associated Pseudomonas pneumonia</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Streptococcus pneumoniae septic shock, acute lymphoblastic leukemia onset</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mild heart damage as a result of Kawasaki disease.
<sup>b</sup> Asthma (and CHARGE syndrome).
<sup>c</sup> Bronchopulmonary dysplasia as a consequence of prematurity, respiratory distress syndrome and patent ductus arteriosus.
<sup>d</sup> Only the last 12 days related to 2009 pandemic influenza A (H1N1) infection, corresponding to time under invasive ventilation. Previously assisted with CPAP since birth.

d, days; HA, Hospital of Alicante; OSA, out of study area.

The rate of hospitalization associated to 2009 pandemic influenza A (H1N1) in 6 public hospitals of the metropolitan area of Buenos Aires (during the one-wave pandemic of southern hemisphere) was lower than in our study, 21 per 100,000 <18-year-olds, not reaching 200 per 100,000 in <1-year-olds. Patients of that series were, younger than ours (75% <2-years-old), 17% were co-infected with respiratory syncytial virus, and were admitted later than ours (at an average of 4 days from disease onset). Oxygen was required for 82% of patients, intensive care for 19% of patients, and mechanical ventilation for 17%, figures greater than ours. Mortality was 7.6 per 100,000 in <1-year-olds and 1.1 per 100,000 in <18-year-olds. In other southern hemisphere locations, for example, Australia, the hospitalization rate in <5-year-olds was about 60 per 100,000, slightly higher than that observed in previous influenza seasons but lower than that observed in our study. The clinical profile was similar to that observed in our patients. The cumulative hospitalization rate associated with 2009 pandemic influenza A (H1N1) registered by the Emerging Infections Program (EIP) in the United States was 83 per 100,000 <5 years of age and 34 per
100,000 children 5–17 years of age. In a population based study, the hospitalization rate for 2009 pandemic influenza A (H1N1) in <17-year-olds was 25 per 100,000, 1.5% of those infected, while in the two previous years it had been 15 and 50 per 100,000. These figures are high but not so different from those reported for seasonal influenza, although there were marked variations between seasons and locations, and possibly they underestimated the true data. Three series of pediatric patients hospitalized in the United States showed similar characteristics to ours, although in those reports more children with risk factors were admitted (67–81%), more frequently were obese, the majority were given antiviral drugs (64–99%), and required more interventions, including ICU in 19–30%. A population based, whole-pandemic study in Israel showed very similar results to ours, with a hospitalization rate of 72 per 100,000 <19-year-olds. They concluded that the severity and mortality of 2009 pandemic influenza A (H1N1) were similar to the figures reported in the literature on seasonal influenza. The number of estimated deaths associated to 2009 pandemic influenza A (H1N1) in England was 70 in <18-year-olds, which gave a mortality of 0.6 per 100,000, particularly high in <1-year-olds. Children hospitalized in Canada and the United Kingdom showed similar characteristics to those of our series and those of previous inter-pandemic influenza seasons.

In conclusion, our review is comparable to, and reinforces, those studies showing that pediatric hospitalization related to 2009 pandemic influenza A (H1N1) infection has been high, although it does not appear to be very different from that seen in years with intense activity of seasonal influenza. The majority of our patients followed a satisfactory clinical course, in spite of the limited use of oseltamivir. The 3 deceased patients had very severe associated comorbidities and bacterial co-infections. Given the resemblance of the disease provoked by the 2009 pandemic influenza A (H1N1) with other seasonal influenza viruses, this study gives us an outlook of the burden of influenza on our pediatric population in a high activity year. This last influenza pandemic has increased some previous uncertainties on aspects related to the epidemiology and the measures for the control of the disease, as well as raising new concerns on the way experts and authorities must deal with these uncertainties in usual and exceptional influenza seasons.

Conflict of interests

The authors declare that they have no conflicts of interest related to this study.

References