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Influenza hospitalizations in children under 1 year old in Spain: the importance of maternal immunization

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ABSTRACT

This study estimates the burden of influenza in infants up to 12 months of age in Spain over 8 seasons (2009/10-2016/17). The survey was conducted by reviewing the Spanish Surveillance System for Hospital Data. Over the eight seasons, 5,618 hospital admissions were recorded for patients younger than 12 months that included codes related to influenza in any diagnostic position (487–488 ICD-9-CM and J9, J10 and J11 CIE 10). In total, 2,363 admissions (42.1%) were female patients whose median age was 3.05 months. Patients younger than 6 months accounted for 3,856 admissions (68.6%). Among them, 59.2% were male, and 40.8% were female ($p < .05$). Overall, 37.1% (2,084 patients) were younger than 2 months. The hospitalization rate for the entire period studied was 156.09 admissions per 100,000 children under 12 months of age (95% CI: 152.4–160.6). The average duration of hospitalization was 6.6 days (95% CI: 6.4–6.8). Eighteen deaths were recorded for hospitalized patients over the entire period. Of these, 12 patients (66.7%) were younger than 6 months. There is a significant burden of influenza disease in children under 1 year of age in Spain, mainly in children under 6 months of age. Improvements to prevention strategies through increased vaccination coverage in family environments and vaccination strategies involving pregnant woman can contribute decisively and effectively to reducing these hospitalizations.

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Introduction

Influenza is an infectious disease with primarily respiratory symptoms and, in humans, is caused by influenza A (genus *Influenzavirus A*) and influenza B (genus *Influenzavirus B*). It has a fairly extensive clinical spectrum ranging from mild forms, with approximately 500,000 cases in the general population per season in Spain (most of those affected recover in 1 or 2 weeks without medical treatment), to more serious forms that require hospital admission and can cause death, involving between 30,000 and 40,000 hospitalizations per year. Approximately 6,000 to 7,000 deaths are attributed to influenza per season, with this outcome being more likely in children, pregnant women, the elderly and people with comorbidities.[1]

Seasonal influenza epidemics result in a large number of cases and impact the health system in January and February of each year in the Northern Hemisphere, causing an increase in and demand for resources over the duration of these seasonal epidemics.[2] In addition, pandemics occur with uncertain frequency and have a much greater impact.[3] The last influenza pandemic occurred in 2009 and was caused by influenza virus type A subtype H1N1 (AH1N1 pdm09).[4] [2]. Since then, the new subtype has been present in all seasonal influenza epidemics, causing high levels of morbidity and mortality. Healthy children younger than one year of age are hospitalized for illnesses attributable to influenza at rates similar to those for adults at high risk for influenza, with higher risk in children <6 months old because they have not generated antibodies through a previous infection and are immunologically immature.[5] It is estimated that during the winter season in the United States, up to 10% of all children under 1 year of age require medical attention for influenza-associated diseases,[6] and worldwide, influenza causes approximately 374,000 hospitalizations per year in this age group, of which 228,000 occur in children <6 months old.[7] In addition, influenza in children tends to cause otitis media and abdominal discomfort[8] and, with less frequency, severe disease, leading in some cases to death, although such figures are not systematically reported for Spain or most other European countries.

The main strategy for the prevention of influenza in the last 60 years has been vaccination.[9] However, as current influenza vaccines cannot be administered to children under 6 months of age,[8] to protect them, pregnant women are instead vaccinated. Efforts to immunize children between 6 and 12 months of age through direct vaccination have not been successful because, in most western countries, including Spain, national recommendations only apply to children with associated chronic diseases.[10] There are no data available on the influenza vaccination coverage in children in Spain. Despite the high incidence of influenza in children, in Spain, as in other European countries, the vaccination of children between 6 months and 2 years of age is only recommended in high-risk children, such as those with metabolic diseases, morbid obesity, renal insufficiency, hemoglobinopathies and

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anemias, asplenia, chronic liver disease, severe neuromuscular diseases, immunosuppression, cochlear implant (or pending), disorders that lead to cognitive dysfunction, such as Down syndrome, and those with chronic cardiovascular or pulmonary diseases.[8] During pregnancy, influenza vaccination is recognized as an important measure for the prevention of infection, both in pregnant women and their babies; vaccination is recommended and prioritized in this group.[11] However, in Spain, during the 2018–2019 vaccination campaign against influenza, only 38.5% of pregnant women were vaccinated; in the last vaccination campaign (2019–2020), almost 50% coverage was achieved.[12] With this article, we wish to highlight the hospital burden of influenza in children through a study of the Spanish hospital data system for influenza disease in children to help guide future influenza vaccine recommendations for children.

Materials and methods

This article presents an analytical study based on Spain's national hospital data system (Minimum Basic Data Set; MBDS), which is updated annually by the Spanish Ministry of Health. The MBDS includes hospital discharge data based on a list of clinical codes to establish diagnoses justifying admission based on the 9th International Classification of Diseases (ICD-9 CM), Spanish version to 2015 and using the ICD-10 thereafter. It includes hospital discharge information from approximately 98% of public hospitals in Spain, which provide health coverage to approximately 99.5% of the Spanish population. All hospital discharge data, including, in any diagnostic position, a diagnosis of influenza caused by unspecified viruses (ICD-9-CM 487) or other specified viruses (ICD-9-CM 488) in children under 1 year of age recorded over 6 seasons (from October 1, 2009 to September 20, 2015) and including codes J9, J10 and J11 for seasons 2015–2016 and 2016–2017, were collected. Age, sex, hospitalization duration and outcome data were collected. The annual incidence of hospital admissions (per 100,000 inhabitants), the death rate per 100,000 inhabitants and the in-hospital lethality rate were calculated as percentages (%). As a denominator, figures for the Spanish population obtained from the projection of the Spanish census for the studied period and for children under 12 months of age provided by the National Statistics Center were used. In all tests, a $p < .05$ level of statistical significance was used. Tests for equality of proportions were performed using the SPSS statistical package for Windows version 22.0 (Chicago, Illinois, USA).

Patient information was anonymized and deidentified prior to analysis. The local ethics committee (Comité de Ética de la Investigación de la Universidad Rey Juan Carlos) ruled that no formal ethics approval was required for this study.

Results

During the eight seasons analyzed (2009–2010 to 2016–2017), 5,618 hospital admissions were recorded for patients younger than 12 months that included codes related to influenza in any diagnostic position (487–488 ICD-9-CM and J9, J10, J11 CIE 10).

The diagnosis of influenza was used as the main diagnosis in 3,901 cases (69.4%). Of these, 2,732 admissions were coded using the ICD-9-CM (until the 2014–2015 season), and 1,169 admissions were coded using the ICD-10 (2015–2016 and 2016–2017 seasons). Among these infants, 54.5% were hospitalized for influenza as the sole diagnosis (no comorbidities), 20.6% reported an additional comorbidity, 12.6% reported two additional comorbidities, and 12.3% reported more than two comorbidities. Among the infants with one, two or more than two additional comorbidities, the 10 most frequent additional diagnostic codes related to other respiratory infections, otitis and other illnesses commonly associated with the onset or progression of influenza in each comorbidity group.

Overall, 2,363 admissions (42.1%) were female patients, with similar proportions maintained for the individual seasons. The median age was 3.05 months. Males were slightly younger than females, with median ages of 3.0 months and 3.2 months, respectively ($p < .04$). Patients younger than 6 months accounted for 3,856 admissions (68.6%). Among them, 59.2% were male, and 40.8% were female ($p < .05$). In total, 37.1% (2,084 patients) were younger than 2 months.

The hospitalization rate for the entire period studied was 156.09 admissions per 100,000 children under 12 months of age (95% CI: 152.4–160.6) and 160.17 per 100.000 (95%-CI: 155.72–164.63) after excluding the 2009–2010 pandemic year. Different rates of hospitalization were observed throughout the different seasons. The lowest hospitalization rate was observed in the 2012–2013 season, with 101.48 admissions per 100,000 children under 12 months of age (95% CI: 92.21–110.75), while the highest rate, 253.7 admissions per 100,000 children under 12 months of age (95% CI: 238.5–268.9), was observed in the 2015–2016 season. Figure 1 shows the differences in hospitalization rates over the eight seasons of the study. The average duration of hospitalization was 6.6 days (95% CI: 6.4–6.8).

In total, 18 deaths were recorded among hospitalized patients during the entire period. Of these, 12 patients (66.7%) were younger than 6 months. The overall mortality rate for the entire period was 0.5 deaths per 100,000 children under 12 months of age (95% CI 0.27–0.73). The maximum occurred in the 2009–2010 season, with 1.01 deaths per 100,000 children under 12 months of age (95% CI 0.12–1.90). Excluding the 2009–2010 season from the average, the overall mortality rate was 0.42 (95%-CI: 0.19–0.65) and was associated with 13 deaths observed between 2010/2011 and 2016/2017.

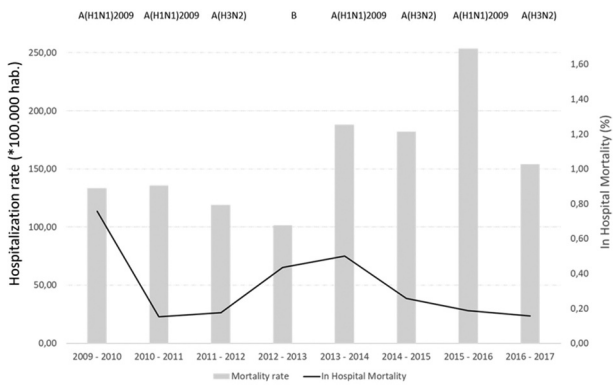

Figure 1. Hospitalization rate (x 100,000 inhabitants) and in-hospital mortality (%) among hospitalizations with influenza in children less than 1 year of age by year from 2009–2017.

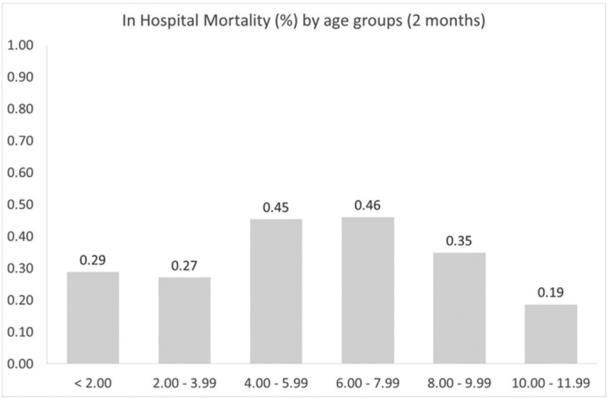

Figure 2. Average in-hospital mortality (%) by month of age (2-month intervals).

Likewise, the overall hospital lethality was 0.32% (95% CI: 0.17–0.47) for patients admitted during the study period and 0.31% (95% CI: 0.14–0.49) and 0.34% (95% CI: 0.07–0.61) for children under 6 and 6 to 12 months of age, respectively. For the pandemic year 2009/2010, the in-hospital mortality was 0.76% (95%-CI: 0.10% – 1.42%); excluding this season from the average resulted in a slightly lower average in-hospital mortality rate of 0.26% (95%-CI: 0.12% – 0.40%). No statistically significant differences were observed between the groups. Figure 2 shows the in-hospital lethality by age group (2-month age increments).

Discussion

The results of our study show the impact of influenza in children under 1 year of age as well as the need to establish a prevention strategy that protects this group. In the study period, 5,618 hospital admissions of patients younger than 12 months were recorded. The diagnosis of influenza was used as the first diagnostic position in 69.4% of admissions, which shows that the diagnosis of influenza is an admission criterion for pediatricians in this population group. The median age was 3.05 months, which suggests that the most critical period in children is the first months of age. In fact, those younger than 2 months accounted for almost one-third of admissions, and those younger than 6 months accounted for 68%. The hospitalization rate for the entire period studied was recorded as 156.09 admissions per 100,000 children under 12 months of age. The lethality rate was 0.3%, with two-thirds of deaths in children under 6 months of age. The overall mortality rate for the entire period was 0.5 deaths per 100,000 children under 12 months of age. These values are slightly lower than but close to those published by Neuzil et al.[5] and the data highlight the burden of severe disease in children and the importance of reducing such figures by adopting universal vaccination. More recently, it has been shown that children under 6 months of age usually only develop a fever but are very likely to be hospitalized with a favorable outcome in most cases, as described by Bender et al.[13] Most published articles insist and conclude that influenza rates in infants can be reduced by adopting a cocoon strategy that involves vaccinating close contacts and mothers during pregnancy and even during lactation for those not previously vaccinated.[14-21] It is necessary to promote and stimulate vaccination in all pregnant women,[22] which, in Spain, barely reaches 50% coverage in the best scenario. López-Medina et al.[23] showed that during the 2009 pandemic, most Spanish newborns developed a community-acquired influenza infection, which was found to be associated with hospital admissions and favorable short-term results. However, there were also significant complications, including some deaths. The WHO recommends giving the highest vaccination priority to pregnant women and has established and supported projects to see to what extent the vaccination of this population group has had on children younger than 6 or 12 months.[24]

Recent studies with quadrivalent vaccines have shown vaccine effectiveness in pregnant women as well as the benefits for children.[25] This has allowed some vaccines to have, among their indications, the protection of pregnant women as well as children under 6 months of age by the transfer of antibodies from the mother to the child both during pregnancy and during lactation; i.e., passive protection of the infant from birth to 6 months of age after vaccination of the pregnant woman.[26] Other novel approaches, such as assessing both the safety of the seasonal influenza vaccine administered earlier in life, 3–4 months earlier than the current recommendation, especially in preterm infants that are at increased risk for influenza associated complications, and the impact of maternal antibodies on influenza vaccine responses are also being explored.[27,28] Some studies have shown that early preterm and late preterm infants had a lower rate of 7-vaccine series completion compared with term/post-term infants, including full influenza vaccination coverage by 19 months.[28]

In a recent study conducted in Spain, children under 15 years of age had greater transmissibility of the influenza virus than did older groups.[29] They also found a delay of approximately 2 weeks in individuals older than 64 years compared to those younger than 15 years when the circulating virus was type B, indicating that children are drivers of epidemics when the influenza B virus is predominant. In our study, the highest hospitalization levels among <12-month-old children were found in one H1N1 predominant influenza season and in another mainly caused by the B-type virus. Therefore, it is reasonable to assume that in seasons involving considerable circulation of the influenza B virus, the disease would probably begin within this population group,[29] suggesting that prevention in children and adolescents should be carried out with tetravalent vaccines as in most European countries recommending influenza vaccination for children.

While influenza has a high incidence in children, complications and mortality are more common in adults over 65 years of age; therefore, vaccination recommendations focus on the latter group. In this study, we analyzed the first year of life, from which we found the incidence to be very close to that of the older population. In fact, the Spanish Ministry of Health recommends the vaccination of pregnant women because of a triple effect: protection of the mother, the newborn and the infant during the first months of life.[8] Our study shows that hospitalization figures by influenza for an 8-year period and the number of deaths among Spanish children with influenza are

concerning. Following WHO indications, while most countries recommend the systematic vaccination of pregnant women, fewer recommend the vaccination of children. In fact, in Europe, only 50% of countries recommend it. Interestingly, most European countries with particular recommendations for children are among those with the lowest vaccination rates for the main target groups (i.e., the elderly). Some scientific societies, such as the Spanish Association of Pediatrics, only recommend the vaccination of children included in risk groups and those in regular contact with people at risk of any age as established by the Ministry of Health.[30] For several years, the US has adopted a universal vaccination strategy that covers children from 6 months of age. In Latin America, in 27 countries linked to the Pan American Health Organization (PAHO), without epidemiological records similar to those presented in this paper, the vaccination of pregnant women is recommended; in 25, the vaccination of healthy children is also recommended. All of these strategies have been gradually incorporated since 2008 [28].[31] Countries, such as Canada and Australia, have implemented national pediatric hospital surveillance networks relevant to vaccine programs and emerging infectious diseases with great potential to supplement routine public health surveillance and provide scalability for emergency responses that could be applied to other countries.[32]

This study presents some limitations related to its use of a nationwide hospital database. Potential biases associated with coding or the assumption of causality between the disease and potential complications could have resulted in misclassification. Among the limitations of this study is the fact that Spain's national hospital data system (Minimum Basic Data Set; MBDS) refers to discharge reports after hospitalization and therefore does not cover patients treated through emergency services. The MBDS does not include information on vaccination status, meaning that some of the children hospitalized for influenza might actually have been vaccinated prior to hospitalization. Moreover, there is no national data base of pediatric influenza vaccine uptake, given that the indication of the vaccine is limited to children included in high risk groups and those in close contact with people at risk of any age. A significant proportion of influenza cases in the child population is mainly treated through overload emergency services.[33] It has been shown that the estimated burden of outpatient visits associated with influenza in children is 10 times higher for children younger than 5 months and up to 250 times greater for those 24–59 months of age than the average annual hospitalization rate.[6] The same study found that children younger than 5 months of age account for 49% of influenza admissions and for the highest hospitalization rates among those younger than 59 months of age, ranging from 2.4 (1.0–3.9) to 4.5 (3.4–5.5) per 1,000 children in the seasons studied (2000–2004).[6] For Spain, a previous study of 88 admitted children found that the vaccination of domestic contacts could be a protective factor for the admission of children under 6 months of age with influenza.[34]

In conclusion, in Spain, there is a significant burden of influenza disease in children under 1 year of age, mainly among children under 6 months of age. The improvement of prevention strategies, such as increased vaccination coverage in the family environment and the vaccination strategies involving pregnant woman, can contribute decisively and effectively to reducing these hospitalizations.

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Disclosure of potential conflicts of interest

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