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Abstract

Introduction: Influenza vaccination is recommended to pregnant women in Spain to reduce the risk of influenza-related complications. Influenza related hospitalizations pose a significant disease burden in children every year. Although children below 6 months are too young to be vaccinated, they can receive protection against influenza through vaccination of their mothers during pregnancy. We estimated the effectiveness of maternal influenza vaccination to prevent influenza hospitalizations in infants under 6 months of age.

Methods: This is a retrospective pilot study, using data from the Severe Hospitalized Confirmed Influenza Cases (SHCIC) surveillance system in seasons 2017/18 and 2018/19 in Spain. Maternal vaccination status during pregnancy was collected for cases in children 6 months and younger hospitalized with confirmed influenza infection. Influenza vaccine effectiveness was estimated using the screening method, by comparing the proportion of children with vaccinated mothers during pregnancy (proportion of cases vaccinated, PCV), with the vaccination coverage among pregnant women in Spain (proportion of population vaccinated, PPV).

Results: For all the study period, the PCV was 17% and the PPV was 35%. Influenza vaccination in mothers during pregnancy prevented influenza confirmed hospitalizations in infants aged 6 months and younger with a 61% (95%CI: 27 - 79%) effectiveness.

Conclusions: In line with evidence from other countries, influenza vaccination during pregnancy protects infants up to 6 months of age from influenza hospitalizations in Spain. These results support current recommendations of influenza vaccination in pregnant women, and more studies are needed in Spain to confirm the double protection of maternal vaccination in mothers and infants.

1. Introduction

Influenza is responsible for a significant number of hospital admissions in young children every year (1). In Spain, infants under 6 months represent an important proportion of pediatric hospitalizations with confirmed influenza (20%) and have the highest average annual incidence of hospitalization compared to older children (2), similar to other countries like England (3) and the United States of America (US) (4), where infants under 6 months have the highest consultation and hospital admission rates for illness attributable to influenza. Preventing influenza in this population would contribute to reduce the heavy burden that pediatric hospitalizations pose for health services in primary care and hospitals during the influenza season and should therefore be considered a public health priority.

During the first six months of life, infants are too young to be vaccinated but they can receive protection against influenza through maternal vaccination and transplacental transfer of maternal antibodies (5). There is consistent evidence indicating that influenza vaccination is safe during all trimesters of pregnancy and reduces the risk of influenza infection and influenza-related hospitalizations and complications, protecting both the mother and the newborn. (6–15).

The World Health Organization (WHO) recommends seasonal influenza vaccination for all pregnant women to protect them and their newborn babies from infection, and to reduce the risk of influenza-related complications (16), and has been promoting global efforts in recent years to increase acceptance and uptake of maternal influenza vaccination (17). In Spain, influenza vaccination is recommended and free of charge for pregnant women in any stage of pregnancy. However, and despite its effectiveness and safety, influenza vaccine coverage in this population remains low in Spain and other European countries (18,19). There is an increasing interest to understand the benefits of maternal influenza vaccination in Spain, due to the high risk of severe influenza women during pregnancy (20), the great burden of influenza pediatric hospitalizations (2), and the dual protection that the seasonal influenza vaccine provides for the mother and the baby. More studies are needed to confirm the protective effect of maternal vaccination on infants, which would help increase its acceptance in mothers and also among health professionals, such as obstetricians, nurses and midwifes, who are the main sources of vaccine information and recommendations for expectant mothers (21,22).

Several countries have estimated vaccine effectiveness in pregnant women (12,13,23), but to our knowledge, this is the first study in Spain to address the protective effect of influenza vaccination during pregnancy to prevent influenza outcomes in children. Moreover, we evaluate the effectiveness of the influenza vaccine against severe influenza infection in infants, which few studies have addressed before. Using information from influenza surveillance in Spain, the objective of this pilot study was to estimate the effectiveness of the seasonal influenza vaccine administered to women during pregnancy in Spain in seasons 2017/18 and 2018/19 to prevent influenza confirmed hospitalizations in young children up to 6 months of age.

2. Methodology

Study design

We conducted a retrospective study, based on surveillance data on hospitalized children with confirmed severe influenza, reported within the Severe Hospitalized Confirmed Influenza Cases

(SHCIC) surveillance system in Spain. The severe influenza surveillance was implemented in Spain after the 2009 influenza pandemic and, during the 2018-19 season, included 100 hospitals from all Spanish regions, covering 52% of the total Spanish population. Briefly, the system is based on the notification of any hospitalized patient with confirmed influenza infection who meet at least one of the following severity criteria: pneumonia, septic shock, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), admission to ICU, or death. Clinical, epidemiological and virological data are collected, as well as the patient outcome. A further description of the SHCIC surveillance system in Spain is available (24).

We identified SHCIC of 6 months or less notified through SHCIC surveillance in 2017-18 and 2018-19 influenza seasons, contacted those responsible for the influenza surveillance in each of the Spanish regions who reported these cases and requested additional information, not routinely collected by surveillance: the infant's age in months, if the infant's mother had been vaccinated for influenza during pregnancy and if so, the vaccination date.

In addition to cases coming from SHCIC surveillance, during data collection we received information of children aged six months or younger with confirmed influenza who were admitted to hospitals outside of the SHCIC surveillance network, and did not necessarily meet the SHCIC severity criteria. Data on maternal vaccination was also provided. To increase our sample size, we decided to include them in the analysis. Therefore, cases in this study were defined as children younger than 6 months hospitalized with confirmed influenza infection, notified in seasons 2017/18 and 2018/19, and with known maternal vaccination status during pregnancy.

Data analysis

The demographic, clinical and virological characteristics of children hospitalized with influenza, were compared between those with unvaccinated mothers and those whose mothers had received influenza vaccination during pregnancy. We used the median test, the $\chi 2$ test or Fisher's exact test, as appropriate.

As children are excluded from vaccination recommendations if younger than 6 months, we restricted the main analysis to cases younger than 6 months, and included cases aged 6 months in a sensitivity analysis.

Estimation of vaccine effectiveness (VE)

We estimated the VE in this study using the screening method (25), a type of case cohort design which compares the proportion of vaccinated individuals among the cases (PCV) and in a reference population (PPV).

In our analysis, the PCV was the proportion of hospitalized children with vaccinated mothers during pregnancy. Our reference group was the population of pregnant women in Spain, and the PPV was the vaccinated proportion of this population, thus, the influenza vaccination coverage among pregnant women. This information, based on administrative records of number of doses of vaccine administered in the country, was available from the Spanish Ministry of Health for seasons 2017/18 and 2018/19, stratified by autonomous region (18).

Using PCV and PPV, the VE is calculated as 1-OR:

$$VE = 1 - \left(\frac{PCV}{(1 - PCV)} \times \frac{(1 - PPV)}{PPV}\right)$$

3. Results

Participation in the study

Sixteen out of the 19 (84%) Spanish autonomous regions agreed to participate in the study, including a total of 67 hospitals from the SHCIC surveillance network (Figure 1). Fourteen of the regions reported cases during the study period. There were 81 infants hospitalized with laboratory-confirmed influenza infection, of which 77 were finally selected after exclusion of 1 case from a previous season and 3 cases with unknown maternal vaccination status (Figure 2). 69 children were younger than 6 months and included in the main analysis. The sensitivity analysis included all 77 children up to 6 months. 8 out of 77 children (10%) were admitted to hospitals not belonging to the SHCIC surveillance network.

Description of cases

The weekly presentation of hospitalized cases in children and their maternal vaccination status is shown in Figure 3. There were 45 cases in children notified in the 2017/18 season, when there was a co-circulation of influenza B and A(H3N2), and 24 in the 2018/19 season, with co-circulation of both influenza A subtypes (Figure 3).

The median age of the cases was 2 months (range 1-4 months) and 41 cases (59.4%) were male. A total of 20 cases (29%) tested positive for influenza B, and 48 (70%) for influenza A, with subtypes A(H1N1)pdm09 and A(H3N2) represented in similar proportions (Table 1).

Of all hospitalized influenza cases included in this study, 13 (20%) had at least one chronic condition, 43 (69%) developed one or more complications, 36 (55%) received antiviral treatment, 40 (58%) were admitted to ICU and 2 (3%) died (Table 1).

Regarding vaccination status of the cases, 12 out of 69 mothers had been vaccinated during pregnancy (PCV: 17.4%). We found no significant differences in PCV when stratifying by sex, age group or influenza virus type/subtype (Table 1). The PCV was higher among cases with at least one chronic condition compared with those with no chronic conditions but this difference was not statistically significant (31% vs. 13%; p=0.2). The PCV of children who had complications was lower and the PCV of children who were admitted to ICU or died was higher, compared to those who did not, although none of these differences were statistically significant. Cases who received antiviral treatment had a significantly lower PCV than those who were not treated with antivirals (8% vs. 32%; p=0.03) (Table 1).

Five out of 45 mothers were vaccinated in 2017/18 (PCV: 11.1%) and 7 out of 24 mothers in season 2018/19 (PCV: 29.2%). When we included cases of 6 months of age for the sensitivity analysis the PCV slightly changed, increasing to 13.7% in season 2017/18 and decreasing to 26.9% in season 2018/19 (Table 2).

Vaccination coverage in the reference group

Nationally, 72,550 out of 246,375 pregnant women (PPV: 29.4%), and 95,703 out of 234,747 pregnant women (PPV: 40.8%) had received one dose of the seasonal influenza vaccine in 2017/18 and 2018/19 seasons, respectively. There was considerable variability in the influenza vaccination coverage of pregnant women by region, PPV ranging between 7% and 54% (18).

Influenza vaccine effectiveness

The crude influenza VE was 70% (95% CI: 24-88%) in season 2017/18, 40% (95% CI: -44-75%) in season 2018/19, and 61% (95% CI: 27-79%) for the whole study period. The sensitivity analysis including cases of 6 months showed similar results (Table 2).

4. Discussion

For the first time in Spain, we estimated the protective effect of maternal influenza vaccination to prevent severe influenza outcomes in infants. Our results indicate that vaccinating women during pregnancy prevents influenza confirmed hospitalizations in children in the first six months of life, with a 61% (95%CI: 27 - 79%) effectiveness. This result is comparable with a 64% effectiveness found in the UK using the same screening approach (12), and is supported by previous evidence of the benefits of maternal vaccination showing protection among pregnant women and their infants in systematic reviews (6,26), observational studies (8,13) and also randomized control trials in Nepal (9), South Africa (10), Bangladesh (14) and Mali (15). Part of the variability observed in the VE between seasons could be explained by the matching between the circulating influenza strains and the influenza viruses included in the vaccine, which varies in different seasons.

Our study generated interest and the participation was high throughout the country, with 84% of the Spanish regions agreeing to participate and providing information. The number of infants aged up to 6 months hospitalized with confirmed influenza in 14 Spanish regions during the last two seasons was considerably high, demonstrating the clinical seriousness of this disease in this age group. At first, the study was designed to include severe cases notified by hospitals within the SHCIC surveillance system, which must meet at least one of the SHCIC severity criteria. However, we decided to include 8 additional cases hospitalized outside of the SHCIC hospital network, as hospitalization itself can be considered an indicator of severe influenza disease in young infants. Even though we found that less than 20% of the mothers of children hospitalized with influenza in our study were vaccinated during pregnancy, influenza vaccination coverage among pregnant women experienced a considerable increase at the national level in season 2018/19 (40.8%) compared to the previous season (29.4%) (18), suggesting a raise in the awareness of health professionals and mothers regarding the benefits of influenza vaccination during pregnancy.

The screening method has been frequently used in different settings to estimate the effectiveness of influenza vaccination administered to pregnant women (12), and children 2 to 6 years to prevent laboratory-confirmed influenza hospitalization in children in the UK (27). Also, to evaluate the effectiveness of influenza vaccines during the 2009 pandemic in the US (28), as well as to conduct real-time monitoring of annual influenza vaccine effectiveness in European countries (29,30). In situations when vaccination data on the control group is limited but vaccine coverage in the population is robust and routinely collected, the screening method is a simple approach that quickly

provides an early approximation to the VE by comparing the vaccine coverage among the cases (in our study, vaccine uptake in mothers of hospitalized children) with the proportion of vaccinated individuals in the community (31–33). In Spain, influenza vaccination data is routinely collected by the Ministry of Health, and vaccine coverage is estimated every year for target groups, including pregnant women since season 2017/18. Using this robust source of vaccine information, which is the only one available for pregnant women at national level, the screening approach is the appropriate methodology to make a first estimation of influenza vaccine effectiveness in pregnant women in Spain. With this methodology, the control is external to the study, which is one of the limitations compared to case control and cohort studies, as bias can be introduced when the cases and the reference group come from different source populations. If the vaccine coverage in the community is lower than in the study population where the cases come from, the VE could be underestimated (33,34).

Also, the screening approach limits the possibility to control for confounding because information of factors like age or specific chronic conditions would need to be available for both the cases and the reference population. In Spain, information of vaccine uptake among pregnant women is very limited. Influenza vaccination coverage for this group is only available by region, but not stratified by age of the women, risk group or any other factor that could potentially modify the effect of maternal vaccination on the baby, such as trimester of pregnancy or breastfeeding. Thus, we were unable to adjust our analysis by any of these potential confounders. Even with study designs including a more robust method of ascertaining case vaccination status and the ability to adjust for specific comorbidities, certain level of residual confounding cannot be avoided (35). However, if these biases are constant over time, VE can be repeatedly estimated and compared between seasons, and the screening method can be used to easily monitor changes in the effectiveness of vaccines over time (30,32,33).

As a strength of our study we present the first estimation at national level of the protective effect of maternal influenza vaccination in young infants in Spain, providing evidence of the potential benefits of vaccinating women during pregnancy to prevent severe influenza outcomes in young children. Despite the methodological limitations, our results are encouraging, and in line with existing evidence from other countries. Given the public health burden of pediatric influenza hospitalizations and the current interest on the potential benefits of maternal influenza vaccination in Spain, future studies including more seasons are strongly recommended to confirm the dual protective effect of maternal vaccination in both mothers and infants during the first six months of life and to support influenza vaccine recommendations during pregnancy.

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Table 1. Characteristics of cases in children under 6 months of age hospitalized with confirmed influenza. Seasons 2017/18 (n=45) and 2018/19 (n=24).

	Children under 6 months n = 69	Maternal vaccination			*p*
	n/n (%)	No n=57	Yes n=12	% vaccinated	
Sex					
Female	28/69 (40.6)	23	5	17.9	
Male	41/69 (59.4)	34	7	17.1	0.9
Age					
Median; months (IQR)	2 (1-4)	2 (1-4)	3 (1-3)		0.9
Age group					0.5
< 1 month	15/69 (21.7)	13	2	13.3	
1 - 3 months	36/69 (52.2)	28	8	22.2	
4 - 6 months	18/69 (26.1)	16	2	11.1	
Influenza vaccination in the mother					
No	57/69 (82.6)				
Yes	12/69 (17.4)				
Influenza type/subtype					0.1
B	20/69 (29.0)	18	2	10.0	
A(H1N1)pdm09	10/69 (14.5)	10		0	
A(H3N2)	9/69 (13.0)	8	1	11.1	
A not subtyped	29/69 (42.0)	20	9	31.0	
C	1/69 (1.5)	1		0	
Chronic conditions					
No	52/65 (80.0)	45	7	13.5	
Yes	13/65 (20.0)	9	4	30.8	0.2
Chronic respiratory disease	7/66 (10.6)	5	2	28.6	0.3
Chronic cardiovascular disease	6/66 (9.1)	5	1	16.7	1
Immunodeficiency	3/64 (4.7)	1	2	66.7	0.07
Chronic liver disease	1/65 (1.5)		1	100	0.2
Complications					
No	19/62 (30.7)	14	5	26.3	
Yes	43/62 (69.3)	37	6	14.0	0.2
Pneumonia	28/65 (43.1)	24	4	14.3	0.7
Bacterial coinfection	7/47 (14.9)	7		0	0.3
Acute respiratory distress syndrome	16/59 (27.1)	15	1	6.3	0.3
Multiple organ dysfunction syndrome	1/57 (1.8)		1	100	0.2
Admission to ICU					
No	29/69 (42.0)	26	3	10.3	
Yes	40/69 (58.0)	31	9	22.5	0.2
Death					
No	63/65 (96.9)	53	10	15.9	
Yes	2/65 (3.1)	1	1	50.0	0.3
Antiviral treatment					
No	29/65 (44.6)	20	9	31.0	
Yes	36/65 (55.4)	33	3	8.3	0.03

Table 2. Influenza vaccine effectiveness in pregnant women to prevent hospitalization with confirmed influenza infection in children under six months of age. Spain, seasons 2017/18 and 2018/19

	Hospitalized confirmed influenza cases				VE % (95% CI)
	Cases vaccinated	Total cases	PCV (%)	PPV (%)	
Children <6 m					
2017/18	5	45	11.1	29.4	70 (24; 88)
2018/19	7	24	29.2	40.8	40 (-44; 75)
Total	12	69	17.4	35.1	61 (27; 79)
Sensitivity analysis					
Children ≤6 m					
2017/18	7	51	13.7	29.4	62 (15; 83)
2018/19	7	26	26.9	40.8	47 (-27; 78)
Total	14	77	18.2	35.1	59 (27; 77)

PCV: Proportion of cases whose mother was had received the influenza vaccine during pregnancy
PPV: Proportion of pregnant women vaccinated in the population. (Source: Influenza vaccine coverage in pregnant women, available from the Ministry of Health, Consumer Affairs and Social Welfare, Government of Spain.

Figure 1. Participating hospitals from the Spanish Severe Hospitalized Influenza Confirmed Cases (SHCIC) surveillance network, season 2018-2019.

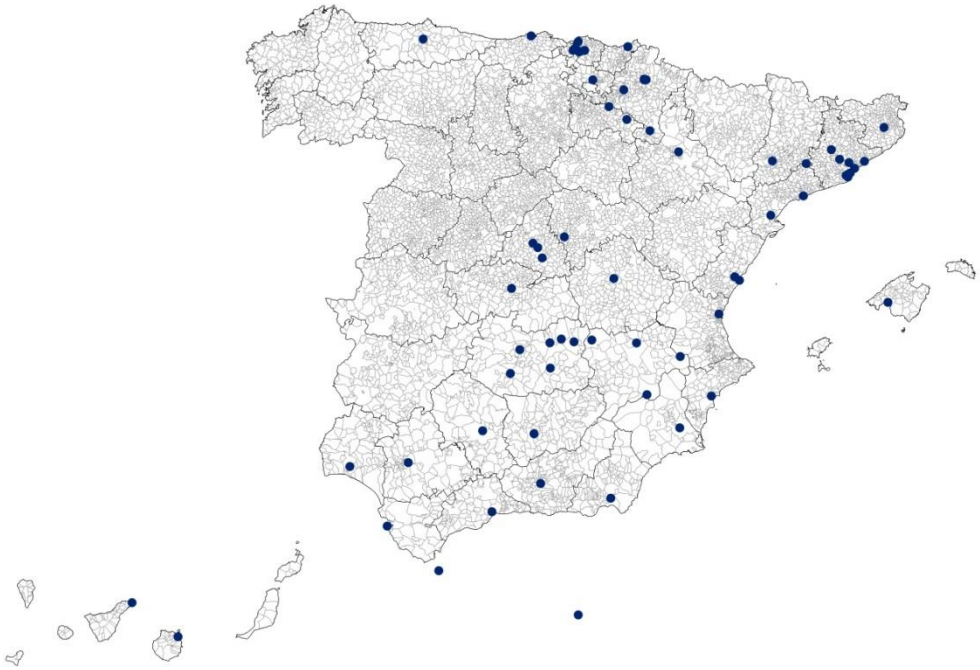


Figure 2. Flowchart for the inclusion of hospitalized cases in children with confirmed influenza

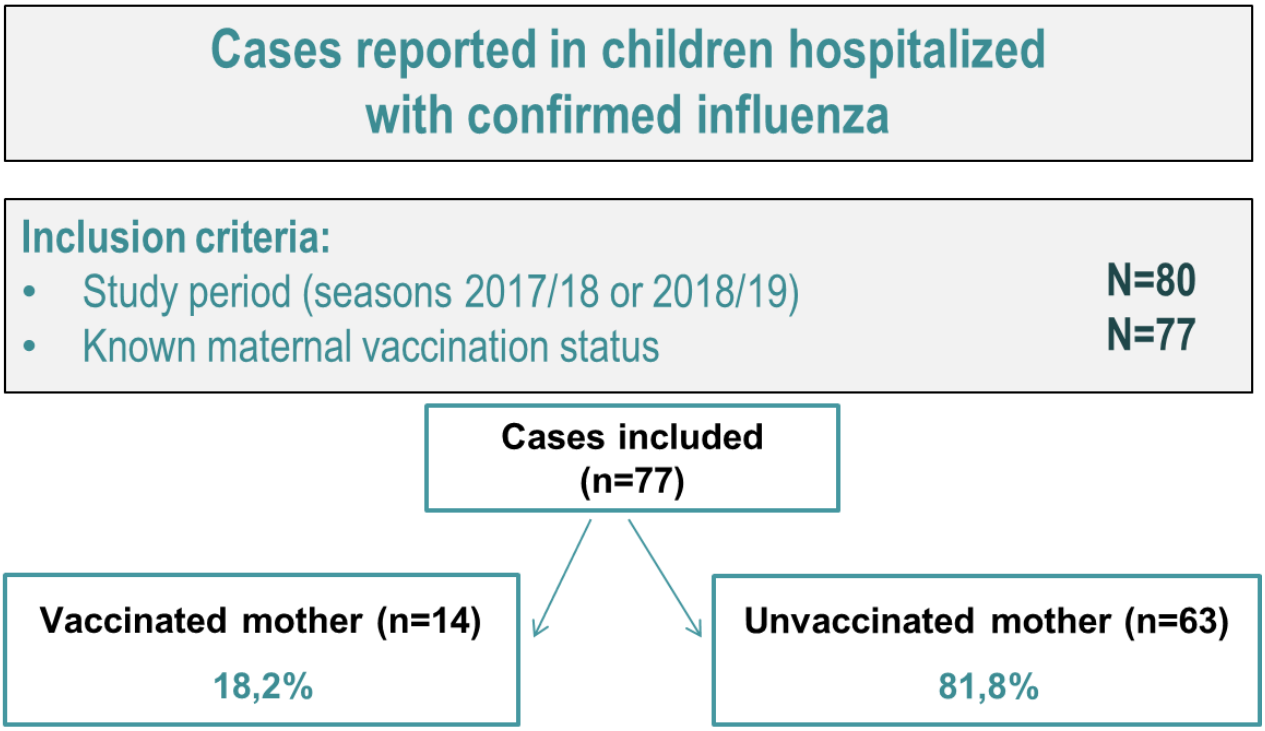
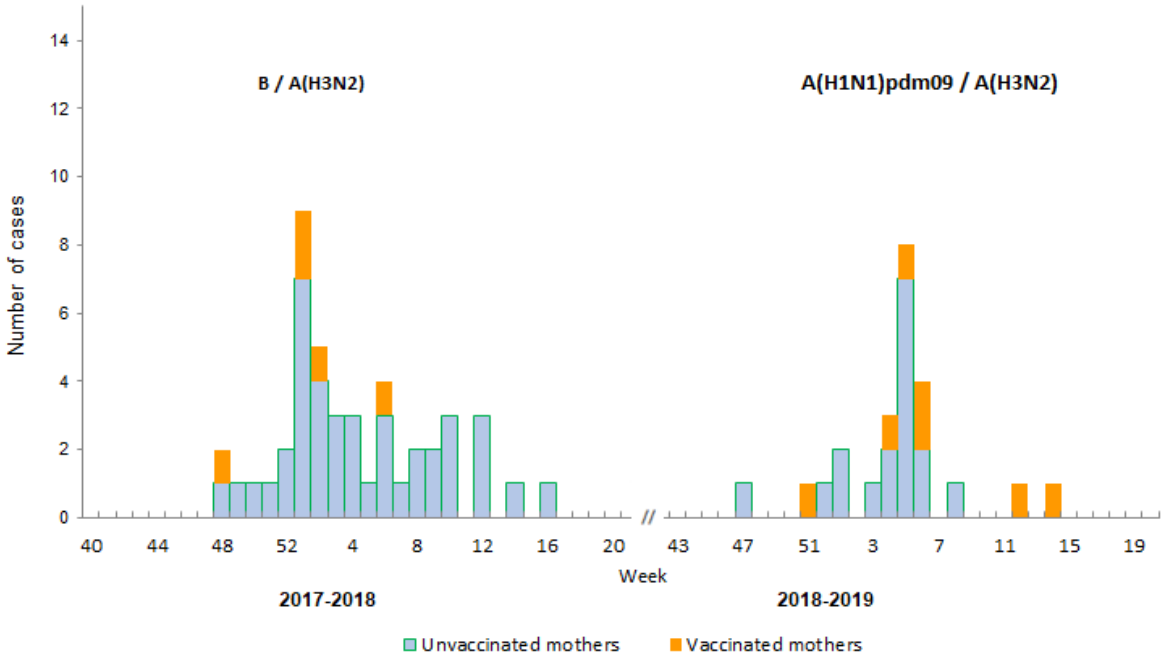


Figure 3. Weekly number of hospitalized cases with confirmed influenza in children under six months of age, by vaccination status of their mother and seasonal epidemic week. Spain, seasons 2017-2018 and 2018-2019.



Type/subtype on the top of cases indicates the predominant influenza virus circulating each season.