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Original

Seasonal influenza surveillance: Observational study on the 2017–2018 season with predominant B influenza virus circulation

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ABSTRACT

Introduction: Influenza is a common respiratory infectious disease affecting population worldwide yearly. The aim of this work is to describe the 2017–2018 influenza season and how it affected elderly population in Catalonia despite moderate vaccine coverage among this age group.

Methods: Influenza surveillance based on a primary care sentinel surveillance, virological indicators systematic sampling of ILI attended and severe influenza confirmed cases (SHLCI) admitted to hospital.

Analysis of data by Chi-squared, ANOVA, multiple regression and negative control test or case to case for vaccine effectiveness assessment in primary care and SHLCI respectively.

Results: Moderate-high intensity and early onset season with predominance of influenza B virus (IVB) (63%) followed by an increase of circulation of influenza A virus (IVA). A total of 419 IV from primary care samples. Vaccine effectiveness (VE) in primary care setting was 14% (95%CI: 0–47%). 1306 severe cases (adjusted cumulative incidence 18.54/100,000 inhabitants (95%CI: 17.54–19.55)). The highest proportion of severe cases were in the >64 (65.1%) (aOR 15.70; 95%CI: 12.06–20.46; $p < 0.001$) followed by 45–64 yo (25.4%) (aOR 6.03; 95%CI: 4.57–7.97). VE in preventing intensive care unit (ICU) admission was 35% (95%CI: 10–54%). Final outcome death while hospitalized occurred in 175 SHLCI cases with a case fatality rate of 13.4%.

Conclusions: 2017–2018 influenza season was an unusual epidemic season with an early onset, great predominance of influenza B (Yamagata strain) virus with a high hospitalization rate of severe cases among elderly stressing the need to upgrade vaccine uptake in this age group.

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Vigilancia de la gripe estacional: estudio observacional sobre la temporada 2017-2018 con circulación predominante del virus de la gripe B

Palabras clave:
Vigilancia gripe
Gripe grave
Efectividad vacunal
Síndrome gripal

RESUMEN

Introducción: La gripe es una enfermedad infecciosa respiratoria común que afecta cada año a una proporción importante de la población mundial. El objetivo de este trabajo es describir la temporada de influenza 2017-2018 y cómo afectó a la población anciana en Cataluña a pesar de la cobertura moderada de vacunas en este grupo de edad.

Métodos: Vigilancia de la gripe basada en la vigilancia centinela de atención primaria (AP), indicadores virológicos por muestreo sistemático semanal de pacientes con síndrome gripal (SG) atendidos en AP y casos graves de gripe confirmada grave ingresados ??en el hospital. Las estadísticas utilizadas para el análisis fueron el test ANOVA, la prueba de Chi-cuadrado, el análisis de regresión múltiple y la prueba de control negativo y caso a caso para la evaluación de la efectividad de la vacuna (EV, por sus siglas en inglés) en AP y casos graves hospitalizados, respectivamente.

Resultados: La temporada 2017-2018 se caracterizó por presentar una intensidad moderadamente alta, con inicio temprano y de larga duración. El predominio del virus de la gripe B (VGB) (63%) seguido por un aumento de la circulación del virus de la gripe A (VGA). Un total de 419 IV de muestras de AP. La VE para prevención de la infección en casos con SG en AP fue del 14% (IC 95%: 0-47%). Se registraron 1.306 casos graves (incidencia acumulada ajustada 18,54/100.000 habitantes (IC 95%: 17,54-19,55)). La proporción más alta de casos graves fue en > 64 años (65,1%) (OR: 15,70: IC 95%: 12,06-20,46; p < 0,001) seguido del grupo de 45-64 años (25,4%) (OR: 6,03; IC 95%: 4,57-7,97). La VE en la prevención de ingreso en la UCI fue del 35% (IC 95%: 10-54%). Se registraron 175 defunciones con una tasa de letalidad del 13,4%.

Conclusiones: La temporada de gripe 2017-2018 fue una temporada epidémica inusual con un inicio temprano, gran predominio del VGB (cepa Yamagata) con una elevada tasa de hospitalización de casos graves en ancianos, lo que subraya la necesidad de mejorar la aceptación de la vacuna en este grupo de edad.

Introduction

Influenza is a common respiratory infectious disease that affects an important proportion of population worldwide every year. Clinical manifestations can vary from a relatively mild disease characterized by sudden onset of fever, headache, myalgia and cough to a severe disease due to complications such as pneumonia and death especially in people at high risk, mostly aged 65 or older.[1,2]

Of the four types of seasonal influenza viruses (IV) (A, B, C and D), A and B viruses cause seasonal epidemics of disease. Most cases of human influenza are clinically diagnosed as Influenza-like Illness (ILI) making differentiation from other winter circulating respiratory viruses such as rhinovirus, respiratory syncytial virus, parainfluenza and adenovirus difficult.[3] Yet those cases requiring hospitalizations because of a more severe outcome are laboratory tested and confirmed as severe cases of influenza infection that need to be hospital admitted.

Surveillance of influenza is essential for the early detection of epidemics, annual updates of vaccine components and evaluation of new variants or subtypes of IV. Although seasonal influenza vaccine does not display high effectiveness, especially when there is a high rate of mismatching between circulating and vaccine strain composition, it is the best preventive measure for preventing deaths and hospitalizations in at risk population.[4] The 2017–2018 influenza season presented a predominant circulation of influenza virus type B during the first epidemic weeks with a high rate of severe influenza hospitalizations, especially among the elderly.

The aim of this work is to describe the 2017–2018 influenza season according to the PIDIRAC Sentinel Influenza Surveillance System and how it affected elderly population in Catalonia despite moderate vaccine coverage among this age group.

Methods

The surveillance of influenza in Catalonia started during the season 1988–1989 and was modified from season 1999–2000, in order to achieve major geographical and major representativeness coverage, in the obtaining of samples for the viral study.

Primary care Surveillance: The number of sentinel doctors participating in the season was of 60 physicians (35 general practitioners and 25 pediatricians), located in 43 primary care centers, distributed across several regions and covering 1.03% of the population of Catalonia.

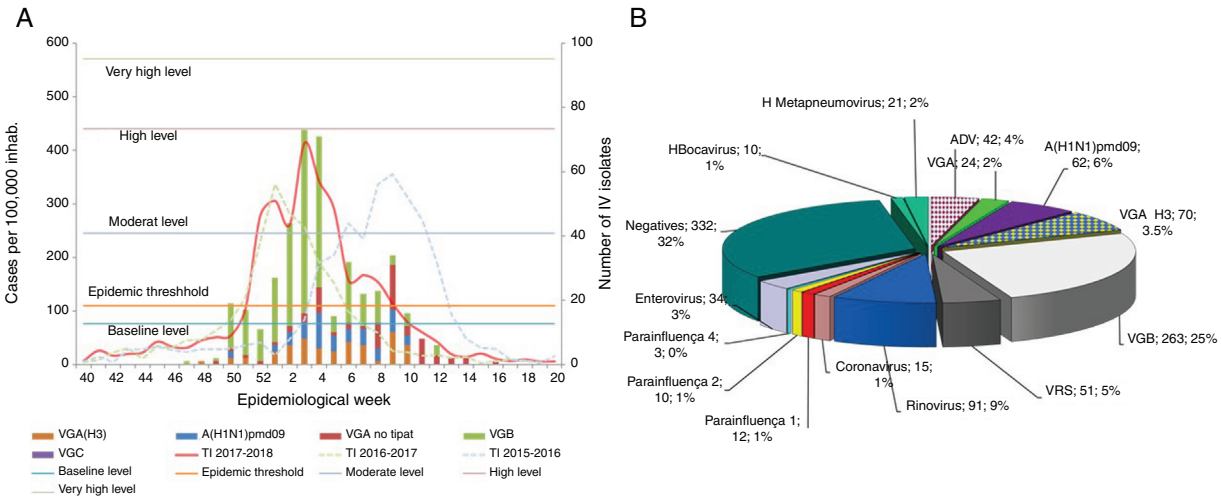

Fig. 1 – (A) Sentinel primary care influenza like illness (ILI) incidence rates and (B) distribution of virological results. PIDIRAC 2017–2018.

To achieve morbidity and virological indicators, these practitioners collect pharyngeal and nasal samples during the entire epidemic season, and forward data on attended morbidity. Systematic sampling of the first 2 weekly ILI attended by each sentinel physician was carried out. A panel of respiratory viruses is investigated: Influenza virus A (IVA), influenza B (IVB) and C virus (IVC), and other respiratory viruses: Respiratory syncytial (RSV), parainfluenza 1, 2, 3 and 4 (PIV) viruses, adenovirus (ADV), coronavirus (CoV), enterovirus (EV), human rhinovirus (HRV), human metapneumovirus (HMPV) and human bocavirus (HBoV).

Morbidity indicators were collected automatically on a daily basis from sentinel practitioners: home calls performed, number of ILI cases diagnosed including data on gender, age and vaccination status.

The thresholds for weekly incidence rates of ILI to assess intensity of epidemic activity (baseline, low, moderate, high and very high) were obtained by the Mobile Epidemics Method (MEM)[5] from data from 12 previous influenza epidemic seasons. For the 2017–2018 season these values were: 75.84–109.40 – 244.92–440.56 and 571.09 respectively. Epidemic threshold was settled at 109.4 cases per 100,000 inhabitants.[6]

Hospital surveillance

Since 2010, severe hospitalized laboratory confirmed influenza cases (SHLCI) were included in sentinel seasonal influenza surveillance to assess severity of influenza epidemics.

SHLCI case definition is as follows:

- Anyone presenting with ILI that requires hospital admission because of pneumonia, acute respiratory distress, multiorganic impairment, septic shock, ICU admission or
- Anyone who develops the latter symptoms during their hospital stay having being admitted to the hospital for any reason other than influenza or

Table 1 – Comparison of adjusted cumulative incidence rates of Influenza Like Illness (ILI) according to age group. PIDIRAC 2017–2018 vs. 2016–2017.

Season	0–4 age	5–14 age	15–64 age	>64 age
2016–2017	4596.92	2681.99	1277.38	965.61
2017–2018	6921.96	4065.04	1935.72	1347.78

- Anyone with confirmed influenza infection who dies during their hospital stay.[7,8]

Statistics

Studied variables were age, gender, vaccine status, hospital and intensive care unit admission (ICU), underlying diseases, pregnancy, antiviral treatment and death. Statistics used for the analysis were Chi-squared test for continuous variables, and ANOVA test for categorical variables, and their 95% Confidence intervals (CI). Test negative control,[9] case to case and multiple regression analysis was carried out to calculate adjusted vaccine effectiveness. SPSS® 18 (PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.) package was used for the calculations.

Results

Primary care surveillance network

The influenza epidemic activity in Catalonia during the 2017–2018 season was moderately high, with an early onset by the end of 2017 and a long duration. The ILI weekly incidence curve shows that the duration of the epidemic wave was longer that the former season, lasting 13 weeks, with a maximum incidence of 413.3/100,000 inhabitants (Fig. 1).

The cumulative incidence rate adjusted by age was 2295.26/100,000 h. (IC 95% 2187.94–2402.58) being children

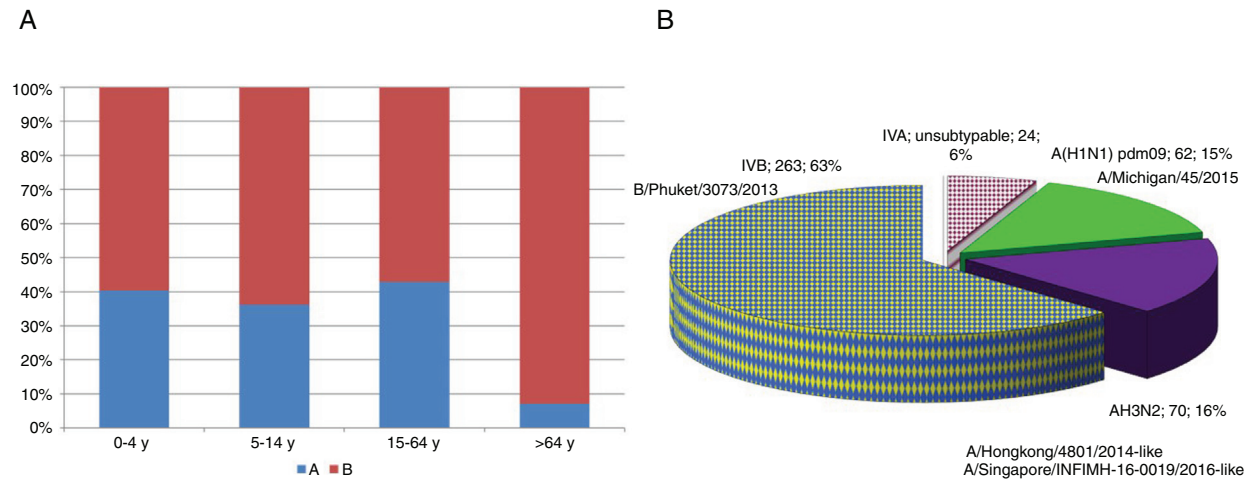

Fig. 2 – (A) Sentinel primary care Influenza virus isolate according to type-subtype and age group and (B) distribution of influenza virus subtypes and strains in sentinel primary care samples. PIDIRAC 2017–2018.

younger than 5 years old the age group with the highest disease burden (6921.96/100,000 h.). Comparing with the previous season, the cumulative incidence rates were higher in all age groups as shown in Table 1.

The predominant virus was IVB virus followed by an increase of circulation influenza AH3N2 and A(H1N1)pdm09, after peak of epidemic activity was attained on week 3 (Fig. 1).

A total of 419 IV were isolated from the 977 samples collected from the primary care sentinel network, 50.2% of them were pediatric samples, with a positivity rate of 67.5% (332/492) to respiratory viruses included in the panel for the virological assessment and of these 57.8% (192/332) were positive to IV. The positivity rate for all respiratory viruses in adult samples (>14 yo) was 64.3% (313/485); of these 72.5% (227/313) corresponded to influenza IVA. Statistically significant difference was observed in the IV positivity in the >14 yo (OR 0.52: 95%CI: 0.37–0.72; $p < 0.001$).

The distribution of IV according to type showed predominance of the IVB with 63% vs. IVA (37%). The distribution of the type/subtype of IV is shown in Fig. 2.

According to the phylogenetic analysis of the IV circulating during the season, 80% of the AH3N2 virus characterized belonged to the genetic group of the A/HongKong/4801/2014like (also designated like A/Bolzano/7/2016) which was included in the seasonal anti-influenza vaccine. The remaining 20% belonged to the A/Singapore/INFIMH-16-0019/2016 strain not included in the seasonal influenza vaccine. All A(H1N1)pdm09 strains belonged to A/Michigan/45/2015 (H1N1)pdm09-like, included in the seasonal anti-influenza vaccine. An influenza A(H1N1)pdm09 (A/Michigan/45/2015) strain presented the H275Y resistance mutation to oseltamivir.

The IVB strains identified correspond to the B/Phuket/3073/2013 (lineage Yamagata), strain not included in the trivalent anti-influenza vaccine.

Thirty four (8%) of the laboratory confirmed IV had been vaccinated. Vaccine effectiveness (VE) to prevent infection against laboratory confirmed IV in primary care setting was 14% (95%CI: 0, 47); stratifying by type of IV the VE was 69% (95%CI: 31, 88) for IVA and 2% (95%CI: 0.69, 5.62) for IVB.

Table 2 – Distribution of SHLCI cases according to age groups. PIDIRAC 2017–2018.

Age group	*n* (%)	ORa (95%CI)
<15	54 (4.2)	1
15–44	78 (6.1)	1.44 (1.03–2.03)
45–64	326 (24.5)	6.03 (4.57–7.97)
>64	848 (65.1)	15.70 (12.06–20.46)*
65–84	573 (43.7)	10.61 (8.11–13.87)*
>84	275 (21.4)	5.09 (3.84–6.75)*

* $p < 0.001$.

Hospital severe influenza surveillance network

During the 2017–2018 season, 1306 SHLCI cases were reported by the 14 sentinel hospitals of the PIDIRAC surveillance network. The cumulative incidence adjusted by age was 18.54/100,000 inhabitants (95%CI: 17.54–19.55).

The highest proportion of SHLCI cases are in the >64 age group accounting for 65.1% (848) of cases (aOR 15.70; 95%CI: 12.06–20.46; $p < 0.001$) followed by the 45–64 age group with 25.4% (326) (aOR 6.03; 95%CI: 4.57–7.97) (Table 2).

Highest incidence rate of SHLCI also corresponds to >64 yo age group (60.95/100,000 h.) followed by the 0–4 age group (12.22/100,000 h.).

A total of 17.9% of the cases required ICU admission; 79.8% of them had at least one risk factor (excluding >64 age group); 63.5% presented or developed *pneumonia* as a complication during hospitalization. 91.3% SHLCI cases received oseltamivir treatment, 78.3% before 48 h after admission and 29.5% 48 h after onset of *symptoms*. No statistically significant difference was observed in the mean duration of hospital stay (DOS) when antiviral treatment was administered

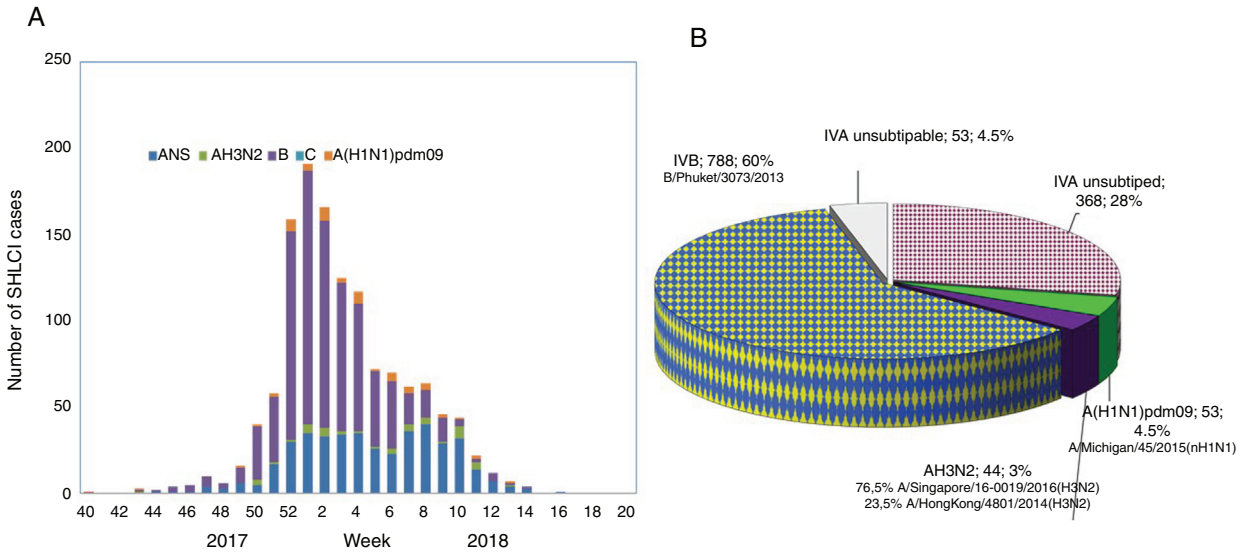

Fig. 3 – (A) Cumulative incidence rates for SHLCI and (B) Distribution of isolates from SHLCIC samples according to influenza virus type and subtype. PIDIRAC 2017–2018.

Table 3 – Risk factors for severe influenza hospitalization (SHLCI) and complications.

Risk factor	*n* (%)
Cardiovascular disease	494 (38)
Asma	97 (7.4)
Chronic obstructive pulmonary disease (COPD)	339 (26.1)
Diabetes	328 (25.3)
Immunodeficiency	207 (15.8)
Other (Hematologic disorders, cognitive impairment, neuromuscular disease)	173 (13.4)
Chronic kidney impairment	221 (17)
Obesity (BMI ≥ 40)	92 (7.1)
Chronic liver impairment	68 (6)

Cases may present more than one risk factor.

Table 4 – Summary of 2017–2018 influenza epidemic season's main epidemiological data. PIDIRAC 2017–2018.

ILI Cumulative incidence rate*	2295.27 × 100,000 h (95%CI: 2187.95–2402.58)
Peak ILI incidence rate	413.3 × 100.000 h (week 3)
Total SHLCI cases	1306
Cumulative incidence rate*	18.54 × 100.000 h (95%CI: 1754–1955)
Influenza virus (IV) type/subtype	39.7%(A) (45.4%H3N2); 54.6%A(H1N1)pdm09; 60.3% (B)
Vaccinated (%) by IV type	A = 23.5%; B = 28.4%
Outcome death (%)	175 (13.4%)
SHLCI cases with ICU admission (%)	234 (17.9%)
Vaccinated SHLCI admitted to ICU (%)	58 (29.3%)
Vaccine effectiveness for ICU admission prevention	35% (95%CI: 10–54%)

* ILI Cumulative incidence rate adjusted to age according to Catalonia's population for 2017. *Source*: IDESCAT.

before 48 h of onset of *symptoms* vs. before 48 h of admission. Statistical difference was observed in ICU admission for those patients who received antiviral treatment up to 48 h after hospital admission (32.4%) in contrast to those who did so more than 48 h after admission (67.6%) (OR: 0.64; 95%CI: 0.47–0.88; $p < 0.01$)

As to risk factors the most frequent was cardiovascular disease (38%) followed by chronic obstructive pulmonary disease (26.1%) and diabetes (25.3%). Seven SHILC cases were pregnant women, 5 (72%) of whom were not vaccinated (Table 3).

A clear predominance of IVB was observed (60.3%: 788 cases) during the season, followed by a late increase in circulation of IVA virus which accounted for 39.7% (518 cases) of SHLCI. By subtypes, SHLCI IVA viruses were mainly A H3N2 (63.5%) (Fig. 3).

All IVB strains studied were identified as B/Phuket/3073/2013 – Yamagata lineage.

Of the influenza A H3N2 isolates subtyped, 76.6% were identified as A/Singapore/16-0019/2016(H3N2) strain not included in the seasonal vaccine. All A (H1N1)pdm09 strain analyzed belonged to the A/Michigan/45/2015(H1N1) strain included in the seasonal vaccine. VE in preventing ICU admission rendered 35% (95%CI: 10, 54) (Table 4).

Pneumonia was the main complication occurring in 63.9% (829) SHLCI cases, 48.1% (382) of which presented bacterial coinfection. Acute respiratory distress syndrome accounted for 46% (596) and multiorganic failure for 7.3% (95) cases. Five influenza associated encephalitis occurred unvaccinated

SHLCI patients aged 42-to 67 years old. Three were caused by IVB and 2 by IVA (1 A(H1N1)pdm09 and 1 not subtyped).

Final outcome death while hospitalized occurred in 175 SHLCI cases with a case fatality rate of 13.4%. The average age of the deceased was 78.76 years (SD 12.9) and the median age was 82 years (rank inter-quartile 71–88 years), 93.7% had at least one risk factor for developing severe complications and death from their influenza infection (not taking into account old age as a risk factor), 57.3% of them were not vaccinated. IVB was identified in 70% (122) of the deceased. Case fatality rate for IVB was 15.48% vs. 10.23% for IVA (OR 1.6:95%CI: 1.1–2.2; $p = 0.006$) while there was no statistical difference for vaccinated patients (13.7%) vs. unvaccinated (13%) (OR 1.02:95%CI: 0.72–1.46; $p = 0.48$). Summary of the main features of the 2017–2018 influenza epidemic season are shown in Table 4.

Discussion

Influenza virus infection is still a topic of great relevance to global health.[1] The high percentage of hospitalizations (65.1%) and mortality in the age group of over 64 (17.5%), especially those over the age of 80, where mortality is higher (33.3%), reflects the increase in the life expectancy of the population. This fact makes it necessary to deepen in the knowledge of how they affect aging, their interaction with the most prevalent chronic diseases in the elderly and their immune response in order to apply preventive measures that offer a better protection to this population group.[10] The 2017–2018 influenza season showed a moderate, early-onset activity (approximately 2 weeks) with longer epidemic duration than usual (13 weeks). The pattern of atypical circulation with circulation of initial influenza B viruses and a rebound of influenza A virus could be responsible for this longer duration of the activity.

The prevalence of virus B/Phuket/3073/2013 – Yamagata lineage not included in the trivalent vaccine of the 2017–2018 season and the contribution of virus circulation A/Singapore/16-0019/2016 (H3N2), also not included in the vaccine as well as the high proportion of elderly cases (65% >64 years old) may have been the cause of the great number of SHLCI cases. This fact has also been reported in the Spanish influenza surveillance network 2017–2018 report.[11]

At the primary care level, the most affected were those under 15 years of age with a cumulative incidence of 6921.96 in the 0–4 age group or 4065.04 in the 5–14 age group.

The VE has shown low values in >64 age group. However, it should be taken into account that vaccination has an impact on the reduction of hospitalization and admission to ICU. In severe case hospitalizations due to severe influenza, >64 age group presented the highest hospitalization rates (60.95/100,000) compared to other age groups, which highlights the need to increase vaccine coverage in this age group to prevent mortality.[12]

The delay in the administration of antiviral drugs, from the onset of symptoms in those patients with a risk condition of complication identified such as elderly people or people with underlying chronic illnesses, is likely to be a bad prognosis of the flu vaccine. This fact evidences the need to administer early treatment (within 48 h of admission) to be effective.[13]

Most frequent influenza infection complication is pneumonia, yet in this season five influenza encephalitis were registered among adult SHLCI patients. Acute encephalopathy syndromes as a complication of influenza infection has been previously described by other authors in children and adults, but our observation in unvaccinated adult population with risk factors to develop influenza complications underscores the need for higher vaccination coverage in at risk population despite age.[14–16]

There are some limitations to be taken into account, such as the fact that the total hospitalization burden including non-severe hospital admitted cases with laboratory confirmed influenza is not included. This data would be desirable to be included in influenza surveillance in order to have a broader assessment of influenza burden of disease in the population and in turn have a more exhaustive treatment and vaccine effectiveness estimation.

In conclusion the 2017–2018 influenza season in Catalonia was, as in the rest of Spain,[10] an unusual epidemic season with an early onset, great predominance of influenza B (Yamagata strain) virus circulation followed by a second wave of influenza A (subtypes H3N2 and (H1N1)pdm09) that resulted in a high hospitalization rate of severe cases especially among the elderly. The low vaccine coverage among >64 age group stresses the need to upgrade vaccine uptake in this age group as well as in those of any age with a risk factor for presenting influenza related complications.

Ethical issues

Analysis of data and samples are performed under the epidemiologic surveillance of influenza and acute respiratory infections established for Public Health Surveillance purposes, there is no need for individual signed consent. Nevertheless verbal consent is requested by each physician upon sampling.

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Conflict of interests

The authors declare there is no conflict of interest.

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