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Influenza vaccine effectiveness assessment through sentinel virological data in three post-pandemic seasons

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Abbreviations: ARI, Acute Respiratory Infection; CI, Confidence Interval; ICS, Catalan Institute of Health; PIDIRAC, Surveillance of Catalonia; EISN, European Influenza Surveillance Network; EU, European Union; GP, General Practitioner; ILI, Influenza-Like Illness; IV, Influenza Virus; SISAP, Information System for Primary Health Care Centers; IR, Incidence Rate; RT-PCR, Reverse-transcription Polymerase Chain Reaction; RF, Risk factor; UK, United Kingdom; USA, United States of America; VE, Vaccine Effectiveness

Influenza vaccination aims at reducing the incidence of serious disease, complications and death among those with the most risk of severe influenza disease. Influenza vaccine effectiveness (VE) through sentinel surveillance data from the PIDIRAC program (Daily Acute Respiratory Infection Surveillance of Catalonia) during 2010–2011, 2011–2012, and 2012–2013 influenza seasons, with three different predominant circulating influenza virus (IV) types [A(H1N1)pdm09, A(H3N2) and B, respectively] was assessed. The total number of sentinel samples with known vaccination background collected during the study period was 3173, 14.7% of which had received the corresponding seasonal influenza vaccine. 1117 samples (35.2%) were positive for IV. A retrospective negative case control design was used to assess vaccine effectiveness (VE) for the entire period and for each epidemic influenza season. An overall VE of 58.1% (95% CI:46.8–67) was obtained. Differences in VE according to epidemic season were observed, being highest for the 2012–2013 season with predominance of IV type B (69.7% ;95% CI:51.5–81) and for the 2010–2011 season, with predominance of the A(H1N1) pdm09 influenza virus strain (67.2% ;95%CI:49.5–78.8) and lowest for the 2011–2012 season with A(H3N2) subtype predominance (34.2% ;95%CI:4.5–54.6).

Influenza vaccination prevents a substantial number of influenza-associated illnesses. Although vaccines with increased effectiveness are needed and the search for a universal vaccine that is not subject to genetic modifications might increase VE, nowadays only the efforts to increase vaccination rates of high-risk population and healthcare personnel let reduce the burden of influenza and its complications.

Introduction

Influenza vaccination aims at reducing the incidence of serious disease, complications and death among those with high risk of severe influenza disease. Every winter there are sharp rises in medical visits, hospitalizations and deaths from acute respiratory illness worldwide. Influenza is an important cause of these and is the only common viral respiratory pathogen with licensed vaccines available that are safe and effective in preventing disease. In Catalonia, as in over 50 countries which have national vaccination programs focusing on the elderly population and those at high risk,[1] every season a vaccination campaign is set forth to immunize targeted population.[2] But there remains a need for further improvement in vaccine effectiveness, vaccine administration and compliance.

Influenza vaccine composition is reviewed each year, and often changed, in an effort to maintain their effectiveness against drifted influenza viruses. Estimates of vaccine effectiveness can help decide the changes to be made in future seasons regarding target groups to be addressed and risk management.[3,4] Four major factors affect most epidemiological studies of vaccine efficacy: case definition, case ascertainment detecting cases among both

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vaccinated and unvaccinated populations, vaccination status ascertainment accurately based on a recorded date of vaccination and comparability of exposure to infectious agent for both vaccinees and non-vaccinees.

The ideal vaccine efficacy study is a clinical trial starting with persons susceptible to disease and the vaccine effectiveness (VE) can be determined by a variety of means including screening, outbreak investigations, secondary attack rates in clusters, vaccine coverage assessments, and case-control studies.[5] Mathematical models of disease transmission and vaccination typically assume that protective vaccine efficacy (i.e., the relative reduction in the transmission rate among vaccinated individuals) is equivalent to direct effectiveness of vaccine.[4] Vaccine efficacy measures the protective effects of vaccination by the reduction in the infection risk of a vaccinated individual relative to that of a susceptible, unvaccinated individual in ideal conditions. In contrast, vaccine effectiveness is defined as the reduction in the transmission rate for an average individual in a population with a vaccination program at a given level of coverage compared with an average individual in a comparable population with no vaccination program.[6] It is possible to use a negative case control method to estimate vaccine effectiveness from sentinel surveillance data when all patients in a surveillance system are tested for influenza and their vaccination status is known.[7] Influenza sentinel surveillance data collection relies on morbidity and virological indicators from primary care reporting of ILI (Influenza-like Illness) cases by the sentinel surveillance physicians' network. In Catalonia influenza surveillance is based on well-established network of sentinel practitioners (PIDIRAC: Daily Acute Respiratory Infection Surveillance of Catalonia)[8] that includes general practitioners (GPs) and pediatricians who report cases of acute respiratory infections (ARI) or influenza like illness to the Public Health Agency of Catalonia coordinating centre. Physicians take nose and/or throat swabs from a sample of cases and send the specimens to the reference centre where they are tested for influenza and other respiratory viruses.[9,10]

The PIDIRAC network was established to provide timely epidemiological and virological information on influenza activity in Catalonia. In addition, it also participates in the Spanish and the European Influenza Surveillance Network (EISN). Since the 2009–2010 pandemic season, the PIDIRAC has been enhanced by including severe influenza cases which require hospitalization and collecting information on the presence of chronic conditions and risk factors. This approach has positively impacted by improving the quality and accuracy of surveillance information.

Influenza surveillance data have been used in Australia, USA, UK, Canada, and Spain[7,11-14] to monitor influenza VE using the test-negative control approach for a rapid estimation of VE.[3] Yet there is no regular review of influenza vaccine effectiveness at the end of influenza seasons in Catalonia. The aim of this study was to assess influenza vaccine effectiveness through sentinel surveillance data from the PIDIRAC program during 2010–2013 seasons which had three different predominant circulating influenza virus (IV) types: A(H1N1)pdm09, A(H3N2), and B, respectively.

Results

The total number of sentinel samples collected during the three seasons was 3609, of which, those with known vaccination background collected during the study period were 3173. Registers with unknown immunization status (436) were not included in the analysis. Statistically significant difference was observed as to the number of samples with available information on immunization status, with a lower compliance in the 2011–2012 season (10.3% of samples with unknown vaccination information). The overall percentage of vaccinated ILI cases was 14.7% (464/3173). No differences between seasons were observed as to percentage of vaccinated ILI cases (**Table 1**). Positivity rate to IV was 35.2% (1117/3173). Evolution of ILI activity for the three influenza seasons included in the study is shown in **Figure 1**.

Distribution by age group of vaccinated samples was highest for the >60 y (65.5%) followed by the 15–59 y group (8.2%) and the 0–14 y (7.1%). No differences in percentage of vaccinated confirmed IV patients by age group was observed, being highest for the 10–14 y group (22.7%) followed by the 15–59 y (20%) and for the >60 y (19.3%) (**Table 2**). A subsample of 463 patients corresponding to cases who presented at least one risk factor for complications due to influenza was analyzed. Of these cases, information as to vaccination status was available for 445 (96%), and 223 (50.1%) were vaccinated for seasonal influenza. Distribution of vaccinated cases fulfilling recommendation criteria for vaccination for underlying chronic diseases is shown on **Table 3** according to age group. Statistically significant differences were found in the <14 y age group (48.8% vs. 32.5%) and older than 60 y (72.8% vs. 52.8%) in the influenza vaccine coverage observed in sentinel practitioners and in the SISAP register.

VE estimates were calculated for the 3173 patients for whom age, laboratory results, and vaccination status data were available. The estimate of VE for each of the three seasons ranged from

Table 1. Distribution according to influenza season of number of samples with available information and percentage of vaccinated cases. Catalonia, 2010–2013

Season	Number of samples with immunization record	Number of samples with no immunization record	OR (95%CI) *P* value
2010–2011	1117	154 (12.1%)	0.83(0.64–1.07) 0.16
2011–2012	1092	125 (10.3%)	ref
2012–2013	964	157 (14%)	0.70(0.54–0.91) 0.006

OR, odds ratio; CI, confidence interval.

34.2% to 69.7%. Combined VE for the three seasons was estimated at 58.1% (95% CI:46.8–67). Differences in VE according to epidemic season were observed, being highest for the 2012–2013 season with predominance of IV type B [69.7% (95% CI:51.5–81)], for the 2010–2011 season with predominance of IV type A(H1N1)pdm09 being 67.2% (95%CI:49.5–78.8) and lowest for the 2011–2012 season with IV A(H3N2) predominance [34.2% (95%CI:4.5–54.6)] (**Table 4**).

Discussion

The total number of sentinel samples collected during the three seasons was high and, although quality of data upon collection could be improved, the overall availability of data was suitable to allow for seasonal characterization. In our study, the overall percentage of vaccinated ILI cases was 14.7%, being highest in the >60 y old with a 65.5%. The vaccination coverage required to establish herd immunity for influenza ranges from 13–30% depending on the circulating seasonal epidemic virus[15] which would set our findings within the lower range. Although the set objectives of vaccination coverage proposed in Europe are 75% in elderly and high-risk persons[16] we observed a 65.5% of sampled population 60 y and over showing that vaccine coverage even in the elderly must be improved. The higher vaccine coverage for targeted at risk groups in our results from sentinel physicians with respect to the overall targeted at risk population reflects the positive advocacy effect for vaccination by those healthcare professionals who are closely engaged in preventive and public health collaborative tasks.

Lower VE in the 2011/12 influenza season could be explained by its late presentation (**Fig. 1**) and because of mismatching of strain contained in the vaccine with the circulating strain as a result of viral drift.[17] As herd immunity increases during the epidemic season, we should expect to see more antigenic drift; however, if immunity is high enough to prevent the population-wide

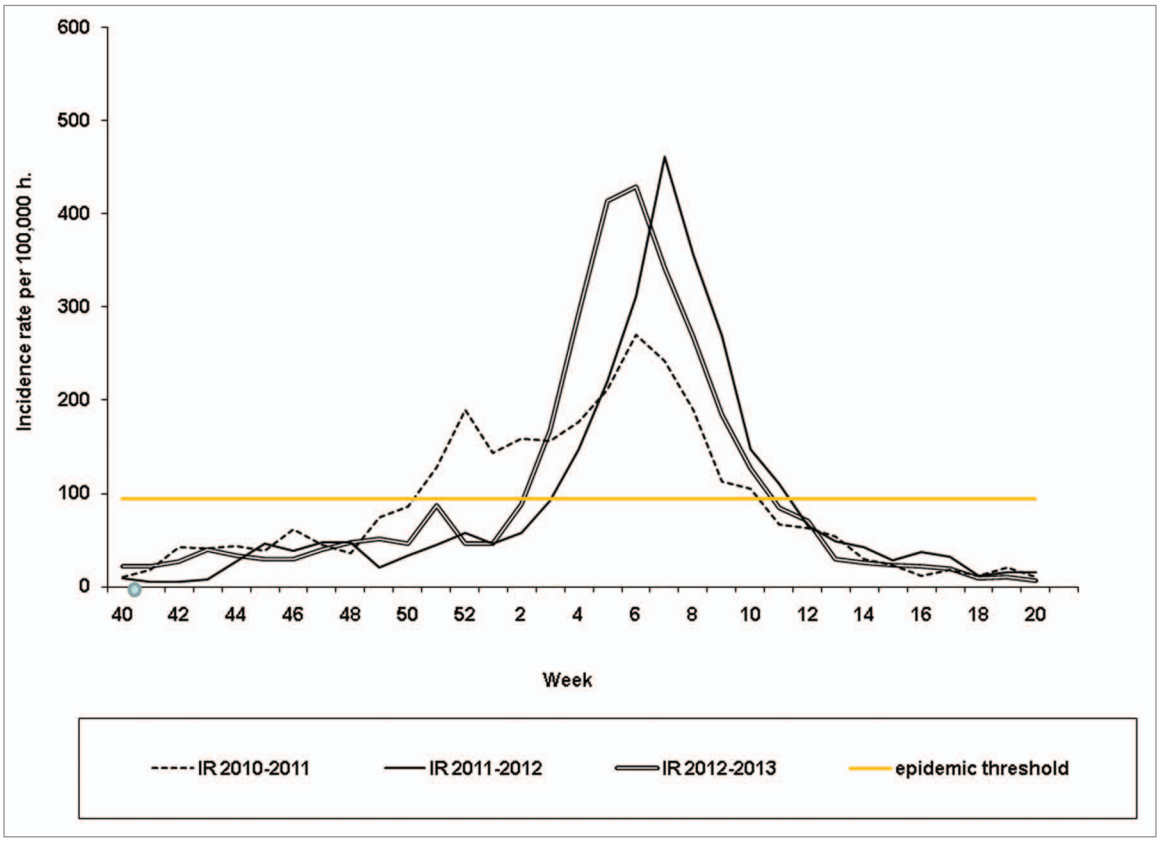

Figure 1. Evolution of ILI activity for the three influenza seasons 2010-2011, 2011-2012 and 2012-2013. Catalonia, Spain.

Table 2. Distribution according to influenza season of samples with available information and percentage of vaccinated and unvaccinated patients. Catalonia, 2010–2013

Season	Vaccinated patients	Not vaccinated patients	OR (95%CI) *P* value
2010–2011	165/ (13%)	952 (87.9%)	0.98 (0.76–1.26) 0.92
2011–2012	159/ (13.1%)	933 (89.7%)	0.99 (0.77- 1.28) 0.97
2012–2013	140/ (12.5%)	824 (86%)	ref

OR, odds ratio; CI, confidence interval.

spread of the pathogen, the epidemic cannot take off and the virus does not evolve. Thus, an intermediate amount of population-wide immunity results in the most antigenic drift.[18] In our study, the only season with a slight mismatch was the 2012–2013 season with IV type B predominance; no mismatch was observed in the other two seasons. The 2011–12 influenza season was a late season, thus patients presenting with influenza had a long delay between onset of symptoms and the vaccination because campaigns were performed in the autumn of 2011. The observed fall in VE may also be due in part to waning of the immunity induced by the vaccine.[19,20] Besides waning, other circumstances could eventually affect VE, such as manufacturing and processing alterations or cold chain disruption; therefore understanding suboptimal VE requires broad consideration of complex factors within the full epidemiologic triad of agent, host, and environment interactions. Differentiating their separate effects and varying contributions from year to year will require in-depth and adequately powered immunoepidemiologic investigation across multiple seasons.[21,22]

Our results are in accordance with the moderate protective effect of the trivalent seasonal vaccine against influenza A(H1N1) pdm09 virus and a low effect against A(H3N2) virus found in other studies such as in the UK (51% for the 2012–2013 season), the USA (60%),[23] but slightly higher than the VE obtained in Navarre (Spain) which was 31%.[24]

Designing better influenza vaccines[25] to improve the selection of strains contained in the vaccine should be a priority for future vaccines, yet even in seasons in which the effectiveness of influenza vaccine is low, vaccination may appreciably reduce the number of cases and hospitalizations in high-risk persons.[26-29] Furthermore, the fact that our results from sentinel surveillance practitioners showed higher vaccine coverage also reflect the effect of attitude towards vaccination, showing higher advocacy for those professionals who are motivated for disease prevention and public health.

There are some limitations to the study that must be pointed out. Because of the observational nature of this study, we cannot exclude biases. We used a test-negative design which is subject to the usual selection biases particularly for the control group.[30] The test-negative design is a commonly used, but not validated study design.[31] Using test-negative controls is considered to adjust for healthcare-seeking behavior more so than if community controls were selected, as vaccination coverage varies by healthcare seeking behavior.[32] In our study, participants were selected according to a systematic sampling procedure by practitioners, who are blinded to the case and control status of the patients, so this should minimize selection bias. Another limitation is that our study focus on VE assessment conducted within sentinel practitioner networks and therefore it only addresses issues arising when measuring VE against outcomes that are observed in primary care settings. Hospital based studies can also estimate VE against severe outcomes like all hospitalizations, hospitalizations for respiratory or cardiovascular diseases or for severe acute respiratory infections confirmed as influenza.[33] In addition, early detection and investigation of influenza clusters (e.g., schools, work place) could also provide prompt VE estimates.[3]

In conclusion, influenza vaccination prevents a substantial number of influenza-associated illnesses. Efforts to increase vaccination rates of population at risk of complications and healthcare personnel will further reduce the burden of influenza. Sentinel data reflect the greater awareness of influenza complications in at risk population by physicians engaged in public health surveillance.

Although vaccines with increased effectiveness are needed towards the search for a universal vaccine that is not subject to genetic modifications, in the meantime improving vaccine recommendation practices in all primary care facilities should be advocated. Further virological studies are needed on an annual basis quantifying drift over time and production of an improved seasonal influenza vaccine with greater effectiveness should be given a high priority.

Table 3. Distribution of vaccination coverage in two different sources of information according to age group in ILI cases sampled with at least one risk factor for complications. Catalonia, 2010–2013

	Age group		
Population Studied	**0–14 y**	**15–59 y**	**60 y or more**
Recorded at SISAP (for at risk population in Catalonia)	32.47%*	21.01%	52.82%**
Sentinel practitioners (for at risk population sampled)	48.8%*	26.5%	65.5%, 72.8%**(with RF)

*$P = 0.02$, **$P = 0.005$; SISAP, Information System for Primary Health Care Centers; RF, Risk factor.

Table 4. Vaccine effectiveness for influenza vaccines in three epidemic seasons. Catalonia, 2010–2013

Season (predominant influenza virus)	Number of ILI samples	Number of positive IV samples/Negative IV samples	Number of vaccinated positive IV /total positive IV (% vaccinated), vaccinated negative IV/total negative samples (% vaccinated)	Vaccine effectiveness (95%CI)
2010–2011 [A(H1N1) pdm09]	1117	383/734	27/383 (7.2%), 138/734 (13.6%)	67.2% (49.5–78.8%)
2011–2012 [A(H3N2)]	1092	387/705	44/387 (11.4%), 115/705 (16.3%)	34.2% (4.5–54.6%)
2012–2013 (B)	964	347/617	23/347 (6.6%), 117/617 (19%)	69.7% (51.5–81%)
Total	**3173**	**1117/2056**	**94/1117 (8.4%), 370/2056 (18%)**	**58.1% (46.8–67%)**

Methods

Practitioners used standardized questionnaires to collect information on ILI signs and symptoms, gender, age, seasonal influenza vaccination in the corresponding season, pregnancy and chronic conditions (including obesity). Using systematic sampling, practitioners swabbed ILI/ARI patients within seven days of symptom onset. Among ILI patients fulfilling the inclusion criteria, we defined an influenza case as a study participant whose swab tested positive for influenza virus by reverse-transcriptase polymerase chain reaction (RT-PCR). Swabs' testing for influenza and genetic characterization was performed at the Influenza Sentinel Surveillance System Reference Laboratory of Catalonia.

A retrospective case negative control design was used to assess[7,34] seasonal influenza VE estimates against laboratory-confirmed infections for the each of the predominant influenza viruses A(H1N1)pdm09, A(H3N2), and B for the 2010–2011, 2011–2012, and 2012–2013 seasons, respectively. We included in the analyses only those ILI patients with available information on vaccination status. Influenza VE was computed counting all patients whose swabs were positive for influenza virus RNA as cases and all other patients whose swabs were negative or positive for another respiratory virus as controls.

Database was compiled with information from three post-pandemic seasons' feedback from the PIDIRAC network reference laboratory. We compared influenza-positive to influenza laboratory-negative patients among those meeting the EU ILI case definition.[35]

We defined cases and controls as vaccinated if they had received at least one dose of corresponding seasonal influenza vaccine more than 14 d prior to ILI/ARI symptom onset. All others were classified as unvaccinated. We performed an analysis restricted to the influenza seasonal surveillance period. Analyses for vaccine information availability of each of the three influenza seasons and vaccine coverage for the sentinel population included in the study were performed. Coverage of target groups for vaccination[2] among the sentinel population stratified by age groups (0–14, 15–59, and >60 y) were compared with the mean coverage data given by the SISAP (Sistemes d'Informació dels Serveis d'Atenció Primària del'ICS) of the Catalan Health Institute according to three age groups.

We estimated vaccine effectiveness as a percentage: VE = (1-OR)x100, where OR was the odds of being a vaccinated case divided by the odds of being a vaccinated control. The baseline characteristics of cases and controls were compared using Chi-square or Fisher's exact tests, as appropriate. The Chi-square test was used to compare proportions and $P < 0.05$ was considered to be statistically significant. Odds ratios (OR) and their corresponding 95% confidence intervals (95%CI) were obtained. Data was analyzed on SPSS® 18 (IBM Statistical Package Inc. Chicago, USA).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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