Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data

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We aimed to estimate influenza vaccine effectiveness (VE) against laboratory-confirmed influenza during three influenza seasons (2010/11 to 2012/2013) in Spain using surveillance data and to compare the results with data obtained by the cycEVA study, the Spanish component of the Influenza Monitoring Vaccine Effectiveness (I-MOVE) network. We used the test-negative case–control design, with data from the Spanish Influenza Sentinel Surveillance System (SISS) or from the cycEVA study. Cases were laboratory-confirmed influenza patients with the predominant influenza virus of each season, and controls were those testing negative for any influenza virus. We calculated the overall and age-specific adjusted VE. Although the number of patients recorded in the SISS was three times higher than that in the cycEVA study, the quality of information for important variables, i.e. vaccination status and laboratory results, was high in both studies. Overall, the SISS and cycEVA influenza VE estimates were largely similar during the study period. For elderly patients (> 59 years), the SISS estimates were slightly lower than those of cycEVA, and estimates for children (0–14 years) were higher using SISS in two of the three seasons studied. Enhancing the SISS by collecting the date of influenza vaccination and reducing the perce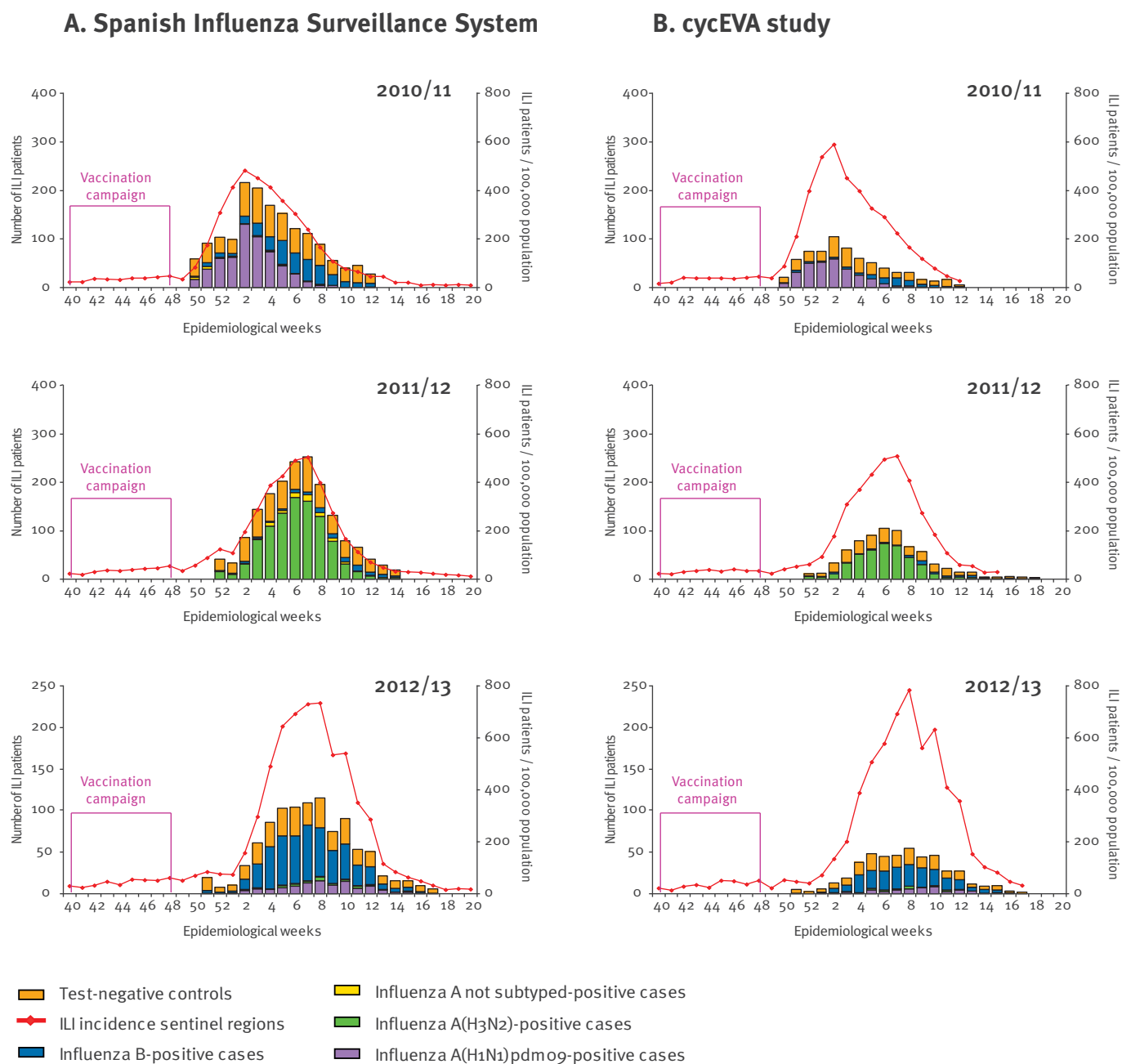ntage of patients with incomplete information would optimise the system to provide reliable annual influenza VE estimates to guide influenza vaccination policies.

Introduction

Influenza causes considerable morbidity worldwide, even among those who are not in vulnerable high-risk groups, and therefore represents a public health problem with socio-economic implications [1]. Influenza vaccination has the potential to prevent annual morbidity and premature mortality. The influenza vaccine is reformulated every year and consequently its effectiveness must be estimated annually [1]. In Europe, seasonal and pandemic influenza vaccine effectiveness (VE) has been monitored since the 2008/09 influenza season through the Influenza Monitoring Vaccine Effectiveness (I-MOVE) project [2], a publicly funded network supported by the European Centre for Disease Prevention and Control (ECDC) and European Union (EU) Member States in the framework of the European sentinel influenza systems. Since the inception of I-MOVE, Spain has participated through an observational case–control study to monitor influenza VE in Spain (cycEVA). This study is conducted within the framework of well-established sentinel influenza networks comprising the Spanish Influenza Sentinel Surveillance System (SISS).

FIGURE 1

Test-negative controls and laboratory-confirmed influenza cases by type/subtype of influenza virus and epidemiological week, Spanish Influenza Sentinel Surveillance System (A) and cycEVA study (B), 2010/11, 2011/12 and 2012/13 seasons, Spain

A. Spanish Influenza Surveillance System

B. cycEVA study

Legend:
- Test-negative controls
- ILI incidence sentinel regions
- Influenza B-positive cases
- Influenza A not subtyped-positive cases
- Influenza A(H3N2)-positive cases
- Influenza A(H1N1)pdm09-positive cases

cycEVA study: the Spanish component of the Influenza Monitoring Vaccine Effectiveness (I-MOVE) network; ILI: influenza-like illness.

Participating sentinel physicians follow a European protocol specifically designed for this study [3]. The protocol includes systematic swabbing of recruited patients and recording the date of influenza vaccination and information on potential confounding factors that have not been historically collected during influenza surveillance. Through five influenza seasons, the cycEVA study has provided timely and reliable [4-8] influenza VE estimates and has been useful in guiding public vaccination policy at the national and European level [9]. However, after the initial ECDC funding was exhausted (December 2012), the Spanish cycEVA study encountered serious difficulties in continuing to measure influenza VE. Therefore, a major challenge in Spain and the rest of Europe is sustaining these VE studies.

Influenza surveillance data have been used in Australia, the United Kingdom (UK) and Canada [10-12] to monitor influenza VE using the test-negative control approach, an efficient method of estimating VE [13]. Because

surveillance data are already available, this method is less costly than observational studies.

The SISS was established in 1996 to provide timely epidemiological and virological information on influenza activity in Spain [14]. The SISS also participates in the European Influenza Surveillance Network (EISN). After more than 15 years, the SISS has been demonstrated to be a robust system for monitoring seasonal influenza [15]. Since the 2009/10 pandemic season, the SISS has been enhanced by increasing the number of swabs taken for virological confirmation, adopting a systematic sampling procedure and collecting information on the presence of chronic conditions and risk factors [16]. These approaches have positively affected the SISS by improving the quality and accuracy of its surveillance information and, consequently, enabling it to provide estimates of influenza VE [17]. In the present study, we aimed to estimate influenza VE against laboratory-confirmed influenza using surveillance data from the SISS during the three influenza seasons (2010/11 to 2012/13) following the A(H1N1)pdm09 pandemic and to compare these results with data obtained by the cycEVA study, to explore the feasibility and validity of monitoring the effectiveness of the influenza vaccine in Spain using surveillance data.

Methods

The Spanish Influenza Sentinel Surveillance System and cycEVA study

SISS was implemented more than a decade ago, in accordance with established national and international guidelines [18]. The system meets the surveillance requirements (European Influenza Surveillance Scheme, ECDC) regarding the minimum population covered (>1%) and representativeness in terms of age, sex and degree of urbanisation [19].

The SISS comprises 17 networks of sentinel physicians (general practitioners and paediatricians) in 17 of the 19 Spanish regions as well as network-affiliated laboratories, including the National Influenza Reference Laboratory (National Centre for Microbiology, World Health Organization National Influenza Centre in Madrid). Sentinel physicians report cases of influenza-like illness (ILI) detected in their reference populations on a weekly basis according to a definition that is based on the EU ILI case definition [20].

For influenza surveillance, sentinel physicians systematically swab (nasal or nasopharyngeal) the first two patients presenting with ILI each week and send the swabs to the network-affiliated laboratories for influenza virus detection.

The information collected in the SISS includes the patient's sex, age, symptom onset date, swabbing date, clinical symptoms, virological information (type and subtype detected and strain characterisation), chronic conditions (i.e. chronic cardiovascular diseases, chronic pulmonary diseases, congenital or acquired immunodeficiency, diabetes mellitus, chronic hepatic disease and chronic renal disease) and risk factors (i.e. pregnancy (in women aged 15–44 years) and morbid obesity (defined as body mass index (BMI) ≥ 40 kg/m2)).

Vaccination status is collected as a dichotomous variable (yes/no); this information is collected either by asking the patient (or parent/guardian if the patient is too young) whether they have received the current influenza seasonal vaccine ≥ 14 days before the onset of symptoms or from sentinel physician records.

The data are entered weekly by each regional sentinel network in a web-based application and analysed centrally by the National Centre of Epidemiology in Madrid to provide timely information on the evolving influenza activity in Spanish regions and at the national level [15] Physicians from sentinel networks participating in the cycEVA study collect additional information from patients, including date of vaccination, type of vaccine, previous seasonal influenza vaccination and information on confounding factors [8,21].

Study design and population
To measure influenza VE, we conducted two test-negative case–control studies on laboratory-confirmed influenza cases during the 2010/11, 2011/12 and 2012/13 influenza seasons using surveillance data (SISS) and data from the cycEVA study. Most of the patients included in the cycEVA analysis were also included in the SISS analysis, but the information collected in cycEVA was more exhaustive and accurate. The study period used was the same as that previously evaluated in the cycEVA study, i.e. the epidemic weeks of each season: week 50 2010 to week 11 2011 for the 2010/11 season, week 50 2011 to week 14 2012 for the 2011/12 season, and week 51 2012 to week 17 2013 for the 2012/13 season.

The study population using data from the SISS comprised all patients with ILI who consulted sentinel physicians belonging to the SISS. The first two ILI patients each week were swabbed and tested for influenza virus. The targeted vaccination groups were as follows: individuals older than 59 or 64 years (depending on the Spanish region), individuals with at least one chronic condition (i.e. cardiovascular disease, chronic pulmonary disease, congenital or acquired immunodeficiency, diabetes mellitus, hepatic disease or renal disease), pregnant women and/or morbidly obese individuals (BMI ≥ 40 kg/m2).

Cases were defined as patients with ILI with laboratory-confirmed influenza infection, as determined by reverse transcription (RT)-PCR analysis of samples obtained from respiratory specimens and/or cell culture using the Madin–Darby canine kidney (MDCK) cell line. Controls were defined as patients with ILI with who tested negative for any influenza virus strain.

Influenza VE was estimated by comparing the vaccination statuses of influenza virus-positive patients with those of influenza virus-negative patients.

The population, sampling protocol and definitions of cases and controls of the cycEVA study have been previously described [8,21].

Data analysis

Analyses were performed for the study population and for the population targeted for vaccination. Influenza VE estimates were compared using SISS and cycEVA data [8,21,22]. We estimated seasonal influenza VE against laboratory-confirmed influenza with the predominant influenza viruses A(H1N1)pdm09, A(H3N2) and B for the 2010/11, 2011/12 and 2012/13 seasons [15], respectively. We also studied the protective effect of the seasonal influenza vaccine by age group using the same categories used by the I-MOVE network (0–14 years, 15–59 years and ≥60 years) in the study population during the three seasons studied. We included in the analyses ILI patients with information available on vaccination status, laboratory confirmation of infection and swabbing date.

To reduce the risk of misclassification over time because of false-negative results, we restricted our analyses to ILI patients with a delay between symptom onset and swabbing: we included those swabbed less than eight days after symptom onset [23] in the 2010/11 and 2011/12 seasons and those swabbed less than four days after symptom onset in the 2012/13 season. For the analysis using SISS data, a sensitivity analysis was also undertaken: if dates of onset and/or swabbing were missing (in 15–17% of patients) then the delay between symptom onset and swabbing was assumed to have been less than eight days (98% of the patients with complete information on dates of symptom onset and swabbing had a delay of less than eight days).

Baseline characteristics of cases and controls were compared using chi-squared or Fisher's exact tests, as appropriate. Chi-squared test was used to compare proportions and p<0.05 was considered to be statistically significant. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were obtained. Influenza VE was calculated using (1 − OR) × 100. Logistic regression models were used to estimate the unadjusted and adjusted ORs. For both the cycEVA study and SISS data, we adjusted for age group, week of swabbing and sentinel region. A comparison between influenza VE estimates for the three influenza seasons studied was performed for each data source (SISS and cycEVA), using a linear regression fit and testing whether the slopes and intercepts were significantly different [24].

Statistical analyses were conducted using STATA/IC 12.1 (StataCorp., College Station, Texas).

This study was performed within the framework of Spanish influenza surveillance activities, with no personal data collected. The patients or patient/guardian provided verbal informed consent to participate in the study. Consequently, the study did not require the approval of the Human Research Ethics Committee.

Results

Influenza season and characteristics of patients with influenza-like illness

The three influenza seasons included in the study in Spain differed in the presentation time of the epidemic, the type and subtype of the dominant virus (Figure 1) and the concordance between the vaccine and circulating influenza strains. On the basis of data from the SISS (Figure 1A) and the cycEVA study (Figure 1B), the weekly number of laboratory-confirmed influenza cases of influenza and test-negative controls recruited into the studies followed the same progression as the weekly ILI incidence in the participating regions during the three seasons studied.

In the 2010/11 influenza season, influenza A(H1N1)pdm09 predominantly circulated until the epidemic peak in week 2/2011 (240 ILI cases per 100,000 population), whereas influenza B virus became predominant after the epidemic period. Both circulating viruses were antigenically similar to the vaccine strains. Influenza activity in Spain during the 2011/12 season was associated with a predominance of circulating subtype A(H3N2) influenza virus and a lower contribution of influenza B virus, which emerged primarily after the influenza epidemic had peaked. The 2011/12 season was a late season, with the maximum peak of influenza activity occurring in mid-February 2012 (Figure 1) and with a limited match between the vaccine and the circulating strains. Influenza activity during the 2012/13 season also occurred late and peaked in February 2013. That season was clearly dominated by circulation of the influenza B/Yamagata lineage virus, co-circulating with both the A(H3N2) and the A(H1N1)pdm09 influenza A subtypes (Figure 1), which were all antigenically similar to the vaccine strains [25].

The annual influenza vaccination campaign in Spain lasted from September to November during the three influenza seasons studied (Figure 1).

During those seasons, the number of physicians participating in the SISS ranged from 867 to 885 (including 225–236 paediatricians) covering a population of 2.2–2.6% of the total Spanish population, which was representative in terms of age, sex and degree of urbanisation (Table 1). Of ILI patients visiting physicians who reported to the SISS during the study period (n = 48,000), between 4,454 and 4,583 per season were swabbed and received laboratory confirmation of influenza virus infection, which ranged from 27% in the 2012/13 season to 29% in the 2010/11 season.

The percentage of patients with incomplete information on laboratory results, vaccination status or date of

Adjusted influenza vaccine effectiveness of the seasonal trivalent vaccine against A(H1N1)pdm09 (2010/11 season), A(H3N2) (2011/12 season) and B influenza virus (2012/13 season) in the study population and target groups for vaccination[a], Spanish Influenza Sentinel Surveillance System and cycEVA study, Spain
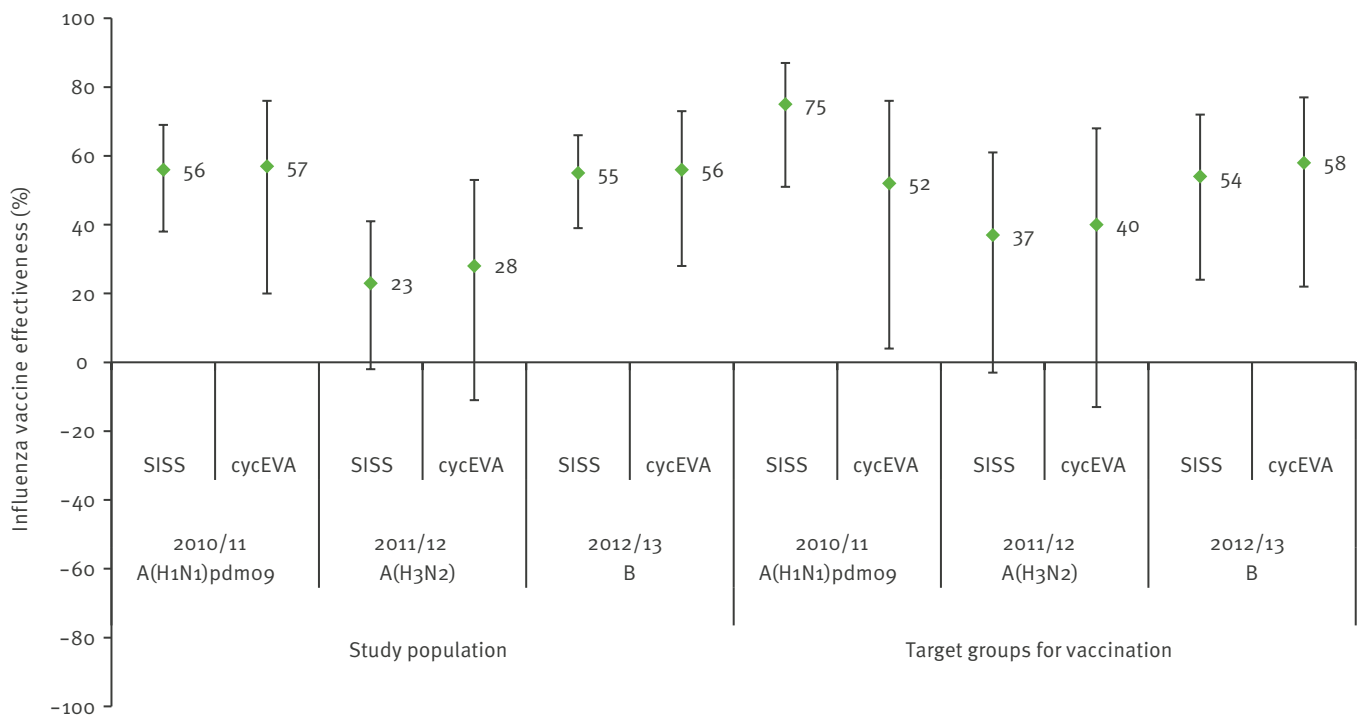
cycEVA study: the Spanish component of the Influenza Monitoring Vaccine Effectiveness (I-MOVE) network; SISS: Spanish Influenza Sentinel Surveillance System.

The bars represent 95% confidence intervals.

[a] Individuals older than 59 or 64 years (depending on the Spanish region), individuals with at least one chronic condition (i.e. cardiovascular disease, chronic pulmonary disease, congenital or acquired immunodeficiency, diabetes mellitus, hepatic disease or renal disease), pregnant women and/or morbidly obese individuals (body mass index≥40 kg/m2).

symptom onset ranged from 3% to 5% of the patients who were swabbed (Table 1): these patients were excluded from the analysis. We also excluded 15–17% of the patients who were swabbed because the swabbing date was unknown. In addition, patients with laboratory-confirmed influenza A virus infection without any subtype information were not included in the specific analysis of influenza VE against the predominant influenza strain (range of 3.6–6% of the recruited patients in the study period).

After applying the exclusion criteria, we included 93% of the recruited patients from the 2012/13 season in the analysis (restricted to those patients swabbed less than four days after symptom onset) and 98% of the recruited patients for the 2010/11 and 2011/12 seasons (restricted to patients swabbed less than eight days after symptom onset) (Table 1).

From the patients who were included, we collected information on the presence of any chronic conditions or risk factors. This information was missing in 16–18% of the patients in the SISS in the first two seasons studied and only 3% in 2012/13 season (Table 1).

The number of GPs participating in the cycEVA study was 246, 231 and 239 for the 2010/11, 2011/12 and 2012/13 seasons, respectively, covering 2.1% of the total population of the Spanish regions participating in the cycEVA study (Table 1). Compared with the number of cycEVA GPs, the number of participating sentinel physicians within the SISS was more than 3.5 times greater (Table 1). The SISS also included a higher proportion of paediatricians, averaging 26% in the three seasons compared with 19% in the cycEVA study (p<0.01) (data not shown). Additionally, the number of patients with ILI determined using the SISS was three times higher than the number in the cycEVA study during the study period (Table 1). However, the information collected in the cycEVA study showed a lower percentage of incomplete information than that in the SISS; therefore, a lower percentage of recruited patients was excluded from the analysis (ranging from 0.1% to 5%, compared with 24–29% for the SISS). Information regarding possible confounding factors, such as the presence of any chronic conditions or risk factors, was also more comprehensive in the cycEVA study, with none of the recruited patients having incomplete data during the last two seasons of the study period (2011/12 and 2012/13).

Spanish Influenza Sentinel Surveillance System and cycEVA study data, 2010/11, 2011/12 and 2012/13 seasons, Spain

Characteristic	2010/11 influenza season[a]		2011/12 influenza season[b]		2012/13 influenza season[c]	
	SISS	cycEVA	SISS	cycEVA	SISS	cycEVA
Number of participating Spanish regions	17	7	17	7	17	7
Number of participating GPs (percentage population covered)[d]	885 (2.6)	246 (2.1)	877 (2.4)	231 (2.1)	867 (2.2)	239 (2.1)
Number of ILI patients reported	15,302	1,376	16,286	1,471	16,486	1,471
Number of ILI patients swabbed (%)[e]	4,468 (29)	1,376 (100)	4,583 (28)	1,471 (100)	4,454 (27)	1,471 (100)
Exclusions (n (%))[f,z]						
Laboratory result missing	228 (5.1)	0 (0.0)	151 (3.3)	14 (0.9)	184 (4.1)	7 (0.5)
Vaccination status missing	130 (2.9)	1 (0.07)	131 (2.9)	0 (0.0)	151 (3.4)	0 (0.0)
Date of symptom onset missing	234 (5.2)	0 (0.0)	198 (4.3)	0 (0.0)	14 (0.3)	0 (0.0)
Date of swabbing missing	778 (17)	0 (0.0)	686 (15)	0 (0.0)	753 (17)	0 (0.0)
Information on patients included in the analysis (n (%))[f]						
Swabbing restriction: patients with swabbing delay < 8 days[g]	3,180 (98)	1,369 (99)	3,484 (98)	1,446 (98)	3,357 (91)	1,432 (97)
Missing information on chronic conditions[h,i]	571 (18)	280 (20)	541 (16)	0 (0.0)	88 (2.0)	2 (0.13)
Missing information on risk factors[h,j]	574 (18)	83 (6.0)	1,020 (29)	0 (0.0)	615 (18)	1 (0.07)
Genetic characterisation of influenza viruses[k]	274 (11)	119 (15)	422 (14)	145 (16)	447 (17)	142 (16)
Patients with swabbing delay < 8 days[g] included in the subtype-/type-specific analysis[l]	2,480 (78)	1,165 (85)	3,189 (92)	1,325 (92)	2,875 (86)	1,225 (86)

cycEVA study: the Spanish component of the Influenza Monitoring Vaccine Effectiveness (I-MOVE) network; GP: general practitioner; ILI: influenza-like illness; SISS: Spanish Influenza Sentinel Surveillance System.

[a] Week 50 2010 to week 12 2011.

[b] Week 50 2011 to week 14 2012.

[c] Week 51 2012 to week 17 2013.

[d] Of the total Spanish population for the SISS and of the population of the Spanish regions participating in the cycEVA study.

[e] Of the reported patients.

[f] Of the swabbed patients.

[g] Patients with missing date of swabbing not included.

[h] Of patients with swabbing delay < 8 days.

[i] Defined as diabetes mellitus, cardiovascular disease, chronic pulmonary disease, renal disease, hepatic disease, congenital or acquired immunodeficiency.

[j] Pregnancy (women 15–44 years-old) and morbid obesity (defined as body mass index >40 kg/m²).

[k] Of the total laboratory-confirmed influenza cases.

[l] A(H1N1)pdm09 in 2010/11 season, A(H3N2) in 2011/12 season and B in 2012/13 season.

Genetic sequencing of the haemagglutinin gene of the circulating influenza viruses isolated from patients in the SISS increased over the seasons studied, from 274 to 447 influenza strains, accounting for 11% and 17% of the total number of laboratory-confirmed influenza cases reported during the first and last seasons, respectively. The proportion of characterised viruses in the cycEVA study (among those included in the analysis) was similar to that in the SISS, with 16% of the viruses characterised in the last two seasons (2011/12 and 2012/13) studied (Table 1).

Taking into account that we estimated seasonal influenza VE against laboratory-confirmed influenza due to the predominant influenza viruses A(H1N1)pdm09, A(H3N2), and B, we finally included SISS data of 2,480, 3,189, and 2,707 patients from the 2010/11, 2011/12 and 2012/13 seasons, respectively, in the analysis. The sample obtained from the cycEVA study was

Table 2

Characteristics of laboratory-confirmed influenza cases and test-negative controls in the study population, Spanish Influenza Sentinel Surveillance System, 2010/11, 2011/12 and 2012/13 seasons, Spain

Characteristic	2010/11 Influenza season (n = 2,480)			2011/12 Influenza season (n = 3,189)			2012/13 influenza season (n = 2,707)		
	Controls	A(H1N1)pdm09 cases	P value[d, e]	Controls	A(H3N2) cases	P value[d,f]	Controls	B cases	P value[d,g]
	n/N (%)[a]	n/N (%)[a]		n/N (%)[b]	n/N (%)[b]		n/N (%)[c]	n/N (%)[c]	
Median age (range years)	22 (0–95)	26 (0–87)	**0.036**	26 (0–88)	31 (0–93)	**0.013**	27 (0–97)	17 (0–84)	**0.009**
Age group in years									
0–4	184/1,319 (14)	132/1,161 (11)	**0.000**	198/1,221 (16)	330/1,968 (17)	**0.021**	210/1,151 (18)	185/1,556 (12)	**0.000**
5–14	359/1,319 (27)	269/1,161 (23)		276/1,221 (23)	451/1,968 (23)		266/1,151 (23)	564/1,156 (36)	
15–64	694/1,319 (53)	733/1,161 (63)		678/1,221 (55)	1017/1,968 (52)		593/1,151 (52)	752/1,556 (48)	
≥65	78/1,319 (5.9)	25/1,161 (2.2)		69/1,221 (5.7)	169/1,968 (8.6)		81/1,151 (7.0)	53/1,556 (3.4)	
Missing information	4/1,319 (0.3)	2/1,161 (0.2)	0.800	0/1,221 (0.0)	1/1,968 (0.05)	**0.000**	1/1,151 (0.09)	2/1,556 (0.1)	0.793
Sex									
Male	665/1,319 (50)	593/1,161 (51)	0.820	638/1,221 (52)	949/1,968 (48)	0.081	600/1,151 (52)	772/1,556 (50)	0.382
Missing information	5/1,319 (0.4)	6/1,161 (0.5)	0.986	3/1,221 (0.2)	4/1,968 (0.2)	**0.000**	4/1,151 (0.3)	4/1,556 (0.3)	1.000
Chronic conditions									
Any chronic condition[h] reported	130/1,319 (10)	88/1,161 (7.6)	**0.000**	139/1,221 (11)	195/1,968 (10)	0.135	165/1,151 (14)	169/1,556 (11)	**0.025**
Missing information	229/1,319 (17)	294/1,161 (25)	**0.000**	182/1,221 (15)	338/1,968 (17)	0.130	27/1,151 (2.3)	38/1,556 (2.4)	0.839
Risk factors									
Any risk factor reported[i]	31/1,319 (2.3)	21/1,161 (1.8)	**0.000**	22/1,221 (1.8)	39/1,968 (2.0)	0.936	14/1,151 (1.2)	17/1,556 (1.1)	0.753
Missing information	432/1,319 (33)	478/1,161 (41)	**0.000**	364/1,221 (30)	587/1,968 (30)	0.998	209/1,151 (18)	267/1,556 (17)	0.518
Vaccine status[j]									
All ages	155/1,319 (12)	64/1,161 (5.5)	**0.000**	149/1,221 (12)	222/1,968 (11)	0.430	142/1,151 (12)	83/1,556 (5.3)	**0.000**
Vaccine eligibility									
Eligible for vaccination	66/183 (36)	27/128 (21)	**0.005**	77/173 (44)	117/284 (41)	0.487	72/176 (41)	39/182 (21)	**0.000**

P values in bold are statistically significant.

[a] Cases and controls recruited between week 50 2010 and week 12 2011 and with an interval between symptom onset and swabbing of less than eight days.

[b] Cases and controls recruited between week 52 2011 and week 14 2012 and with an interval between symptom onset and swabbing of less than eight days.

[c] Cases and controls recruited between week 51 2012 and week 17 2013 and with an interval between symptom onset and swabbing of less than four days.

[d] Non-parametric test of the median or chi-squared test or Fisher's exact test, when appropriate.

[e] A(H1N1)pdm09 cases vs controls p value.

[f] A(H3N2) cases vs controls p value.

[g] B cases vs controls p value.

[h] Defined as diabetes mellitus, cardiovascular disease, chronic pulmonary disease, renal disease, hepatic disease, congenital or acquired immunodeficiency.

[i] Defined as pregnancy (women 15–44 years-old) and/or morbid obesity (body mass index ≥ 40 kg/m²).

[j] Only patients with known vaccination status were included in the analysis.

1.8–2.4 times smaller in size (1,165, 1,325 and 1,192 patients, respectively). Among the SISS patients analysed, we identified 1,319 controls and 1,161 A(H1N1) pdm09 cases for the 2010/11 season; 1,221 controls and 1,968 A(H3N2) cases for the 2011/12 season; and 1,151 controls and 1,556 B cases for the 2012/13 season (Table 2).

The main characteristics of cases and controls during the study period are shown for the SISS (Table 2) and

Table 3

Characteristics of laboratory-confirmed influenza cases and test-negative controls in the study population, cycEVA study, 2010/11, 2011/012 and 2012/13 seasons, Spain

Characteristic	2010/11 Influenza season (n=1,165)			2011/12 Influenza season (n=1,348)			2012/13 influenza season (n=1,192)		
	Controls	A(H1N1) pdm09 cases	P value[d, e]	Controls	A(H3N2) cases	P value[d,f]	Controls	B cases	P value[d,g]
	n/N (%)[a]	n/N (%)[a]		n/N (%)[b]	n/N (%)[b]		n/N (%)[c]	n/N (%)[c]	
Median age in years (range)	32 (0–95)	31 (0–85)	0.493	33 (0–87)	36 (0–93)	0.067	32 (0–85)	31 (0–84)	0.711
Age group (years)									
0–4	46/591 (8)	43/574 (7)	**0.000**	41/528 (8)	96/820 (12)	**0.001**	75/535 (14)	68/657 (10)	**0.000**
5–14	111/591 (19)	73/574 (13)		90/528 (17)	133/820 (16)		102/535 (19)	197/657 (30)	
15–64	387/591 (65)	441/574 (77)		358/528 (68)	491/820 (60)		323/535 (60)	362/657 (55)	
≥65	47/591 (8)	17/574 (3)		39/528 (7)	100/820 (12)		35/535 (7)	30/657 (5)	
Missing information	0/591 (0)	0/574 (0)	NA	0/528 (0)	0/820 (0)	NA	0/535 (0)	0/657 (0)	NA
Sex									
Male	293/591 (50)	271/574 (47)	0.419	265/528 (50)	402/820 (49)	0.676	277/535 (52)	333/657 (51)	0.708
Missing information	0/591 (0)	0/574 (0)	NA	0/528 (0)	0/820 (0)	NA	0/535 (0)	0/657 (0)	NA
Chronic conditions									
Any chronic condition reported	79/591 (13)	60/591 (10)	0.174	78/528 (15)	117/820 (14)	0.797	103/535 (19)	96/657 (15)	**0.033**
Missing information	126/591 (21)	112/574 (20)	0.673	0/528 (0)	0/820 (0)	NA	0/535 (0)	0/657 (0)	NA
Risk factors									
Any risk factor reported[h]	13/591 (2.2)	7/574 (1.2)	0.091	9/528 (1.7)	18/820 (2.2)	0.530	9/535 (1.7)	9/657 (1.4)	0.490
Missing information	30/591 (5)	44/574 (8)	**0.037**	0/528 (0)	0/820 (0)	NA	1/535 (0.2)	0/657 (0)	**0.000**
Vaccine status[i]									
All ages	63/591 (11)	23/574 (4)	**0.000**	69/528 (13)	111/820 (14)	0.805	56/535 (10)	31/657 (5)	**0.000**
Vaccine eligibility									
Eligible for vaccination	57/184 (31)	20/135 (15)	**0.001**	50/123 (41)	88/226 (39)	0.755	45/133 (34)	26/139 (19)	**0.005**

cycEVA study: the Spanish component of the Influenza Monitoring Vaccine Effectiveness (I-MOVE) network; NA: not applicable.

P values in bold are statistically significant.

[a] Cases and controls recruited between week 50 2010 and week 12 2011 and with an interval between symptom onset and swabbing of less than eight days.

[b] Cases and controls recruited between week 52 2011 and week 14 2012 and with an interval between symptom onset and swabbing of less than eight days.

[c] Cases and controls recruited between week 51 2012 and 17 2013 and with an interval between symptom onset and swabbing of less than four days.

[d] Non parametric test of the median or chi-squared test or Fisher's exact test, when appropriate.

[e] A(H1N1)pdm09 cases vs controls p value.

[f] A(H3N2) cases vs controls p value.

[g] B cases vs controls p value.

[h] Defined as pregnancy (women 15–44 years-old) and/or morbid obesity (body mass index≥40 kg/m²).

[i] Only patients with known vaccination status were included in the analysis.

cycEVA study (Table 3). Regarding the main characteristics of the patients included in the analysis, overall, the most represented age group was 15–64 year-olds, who accounted for 50–58% of all recruited patients from each season according to the SISS data (Table 2) and 57–71% according to the cycEVA data (Table 3).

Vaccine effectiveness*

Adjusted influenza VE estimates for the study population were similar using data from the SISS and cycEVA study: 56% (95% CI: 38 to 69) and 57% (95% CI: 20 to 76), 23% (95% CI: −2 to 41) and 28% (95% CI: −11 to 53), and 55% (95% CI: 39 to 66) and 56% (95% CI:

28 to 73) in the 2010/11, 2011/12 and 2012/13 influenza seasons, respectively (Figure 2). Adjusted influenza VE estimates in the population targeted for vaccination were also consistent using both data sources, although the SISS point estimates were slightly higher for the 2010/11 season (75% (95% CI: 51 to 87)) than the 52% (95% CI: 4 to 76) in the cycEVA study (Figure 2). The comparison analyses showed no statistically significant differences in the slopes of influenza VE estimates along the three studied seasons for the two data sources, either for the study population ($F^1_5 = 0.03$; p = 0.88) or for the population targeted for vaccination ($F^1_5 = 0.51$; p = 0.55).

On the assumption that patients with missing dates of onset and/or swabbing were swabbed within eight days from symptom onset, we estimated VE for the study population to be 64% (95% CI: 51 to 73), 9% (95% CI: −16 to 27) and 60% (95% CI: 47 to 70) for the 2010/11, 2011/12 and 2012/13 seasons, respectively. For the target groups for vaccination, VE estimates were 70% (95% CI: 48 to 83), 33% (95% CI: −1 to 55) and 62% (95% CI: 38; to 77) for the 2010/11, 2011/12 and 2012/13 seasons, respectively.

The analysis by age group in the study population showed that influenza VE for patients aged 15–59 years and those older than 59 years were similar using data from either the SISS or cycEVA study (Table 4).

For patients aged 15–59 years, the VE estimates using both data sources ranged from 30% to 74%, with a higher and optimal protective effect of the vaccine during the 2012/13 season using the cycEVA study data (74% (95% CI: 38 to 89)) and lower but not statistically significant difference in the 2011/12 season with SISS data (30% (95% CI: −8 to 54)). For elderly patients (>59 years), adjusted VE estimates ranged from 42% to 72%, with a higher and optimal protective effect of the vaccine during the 2012/13 season using the cycEVA study data (72% (95% CI: 15 to 91)). In general, the sample size was 1.7 to 2.4 times higher using SISS compared with cycEVA study data and, consequently, SISS-estimates by age group generally showed narrower confidence intervals (Table 4).

However, estimates from the two data sources for patients aged 0–14 years were not comparable. We did not find any protective effect of the vaccine using cycEVA study data; however, using SISS data, the VE estimates were 31% (95% CI: −17 to 60) and 57% (95% CI: 22 to 76) in 2011/12 and 2012/13, respectively. For the 2010/11 season, the adjusted VE estimates were identical for the two data sources (Table 4). Regarding sample size, using SISS data we included in the specific 0–14 years analysis 2.6–5 times more patients than with the cycEVA study data.

Lower VE estimates in each age group were generally observed during the late 2011/12 influenza season using both data sources (Table 4).

Discussion

Our estimates of influenza VE against laboratory-confirmed influenza using surveillance data were largely similar to those obtained from the observational cycEVA study [8,21,22] and showed a moderate protective effect for the trivalent influenza seasonal vaccine during the study period.

For the 2010/11 season, adjusted VE estimates against the predominant A(H1N1)pdm09 influenza virus, was 56% and 57% using SISS and cycEVA, respectively, in line with those described by the I-MOVE network [26], the UK [27] and the Navarre region of Spain [28], which ranged from 55% to 62%. Lower estimates against A(H3N2) virus (23% (SISS) and 25% (cycEVA)) were also observed in the Navarre region (29%) [29] and in the I-MOVE network (25%) [30] during the late 2011/12 influenza season, as well as in previous A(H3N2) dominant seasons (31%) in Spain [31]. For the 2012/13 season, adjusted VE estimates against B virus were 56% and 62% using SISS and cycEVA, respectively, similar to those observed in the I-MOVE network [32].

Limitations arising from surveillance versus research-oriented systems

When studying the protective effect of the seasonal influenza vaccine among the groups targeted for vaccination, we observed some difference in the influenza VE point estimates using the SISS and cycEVA data, although they were not statistically significant. Some of these could have been caused by limitations arising from use of surveillance data, which will be described below.

The quality of the information collected by the SISS and the cycEVA study on exposure (influenza vaccination) and outcome (laboratory confirmation) was satisfactory, with low percentages of incomplete information in both systems (around 0–3.5%) [11,33].

A more substantial limitation of our surveillance data was missing information on swabbing date (in 15–17% of recruited patients): this information is crucial when restricting the analysis according to time between symptom onset and swabbing, and helps to minimise the possibility of misclassification as false-negative RT-PCR results [23]. However, the sensitivity analyses, which included patients with missing dates of onset and/or swabbing, on the assumption that they were swabbed within eight days from symptom onset (as did 98% of the patients with complete information), showed VE estimates that differed by 4–8% and with narrower CIs. In spite of that, the differences were higher (14%) for the study population for the 2011/12 season, a season characterised by a late epidemic peak and a limited match between the circulating A(H3N2) influenza virus and the vaccine strain, and in which the trivalent seasonal vaccine showed a lower protective effect compared with other influenza seasons [25].

SISS data also contained a high proportion of patients with missing co-morbidity data, which could bias VE

estimates from the surveillance data. Although the SISS point estimates were only 7–8% lower than those observed with cycEVA data during the last two seasons studied (Figure 2), the VE estimates using SISS could be overestimated for the 2010/11 season (75% compared with 52% with cycEVA for the target groups). This discrepancy could be related to a higher vaccine coverage for patients with information on chronic conditions/risk factors (included in analysis for the target groups) than for patients with missing information on chronic conditions/risk factors (not included in the analysis for the target groups), with coverage of 9% and 7%, respectively (p<0.05).

Results of a sensitivity analysis excluding patients with missing information on chronic conditions (data not shown) showed similar adjusted VE estimates (point differences ranged from 4% to 7% in 2010/11 and 2011/12 and an exact point estimate of 55% in 2012/13). In addition, inclusion of the variable chronic conditions into the regression models did not significantly change VE estimates. Therefore, missing information on chronic conditions was unlikely to have biased our VE estimates using SISS data. Imputation techniques will be used in further analyses in order to adjust for missing values in key variables [34,35].

Another reason for the observed discrepancies between the results from the two data sources could be possible differences in the main characteristics of the study populations. The median age of patients in the SISS were 6–10 years younger than that of the patients in the cycEVA study.

Information on vaccine status was collected by the sentinel physicians based on patient self-report at the time of specimen submission, before the test result was known, thus minimising differential recall bias. Although this could generate a potential source of misclassification, studies in other settings have reported consistency between self-reported and registry-based influenza vaccination status [36,37].

A more general limitation of the surveillance strategy is that the system does not currently collect the vaccination dates of patients. However, the likelihood of vaccination status misclassification within the SISS it is low since the seasonal influenza vaccination campaign usually finishes in Spain well before the beginning of the influenza season. Only unusual scenarios, such as influenza pandemics [7,12] or when the influenza season starts early, would require a specific observational study to estimate influenza VE.

A further limitation of our study could arise from the fact that comparison of VE estimates was made among two data sources that are not mutually exclusive. Patients in the cycEVA study were a subset of SISS patients for whom GPs collected additional information on confounders and date of influenza vaccination.

We also have to be aware that the distribution of influenza virus strains might differ by time of the epidemic and region: this could explain certain differences in the VE estimates obtained in this study, which was focused on influenza VE against the predominant circulating influenza subtype.

Age-specific vaccination effectiveness estimates
By age group, the SISS influenza VE estimates were quite similar to those from the cycEVA study for 15–59 age group (±10–13%), who comprised the most represented age group in both study populations, and for the elderly (±5–12%), except for the 2012/13 season, with 19% points of difference between the SISS and cycEVA estimates.

In general, point estimates using the surveillance data were lower for both age groups compared with cycEVA study estimates. Differences in the estimates for elderly patients could be related to different swabbing practices (all patients in cycEVA study but the first two patients of any age each week in the SISS). However, both criteria for selecting patients for swabbing were recently shown to give similar influenza VE estimates [37]. Considering the difference in the extent of data collection for important confounders in elderly patients, the influenza VE estimates for this group could have been under estimated using the surveillance data. By improving the quality of information and the swabbing protocol in the future [30], we should be able to overcome the limited accuracy of our current influenza VE estimates for elderly patients using SISS data.

Comparison with published data
In general, our age-specific VE estimates were comparable to those in other European countries and regions. Point estimates for patients aged 15–59 years were in the range of those described by the Navarre region, the I-MOVE network and the UK [28,32,34]. Point estimates lower than 50% in preventing A(H3N2) infections in the late 2011/12 season (30% with SISS and 41% with cycEVA) were also described in patients younger than 65 years in the UK (19%) [35] and the Navarre region (44%) [29], although a higher protective effect was observed by the I-MOVE network (63%) [30]. In addition, protective estimates against influenza B virus observed during the 2012/13 season, 64% (SISS) and 74% (cycEVA), were comparable to the 64% observed by I-MOVE [32]. Our point estimates for elderly patients were in line with those published by the UK: 48% protection against A(H3N2) virus in the 2011/12 season [35] (47% (SISS), 42% (cycEVA)) and higher protective effect against B virus in 2012/13 season (65% in UK [34] vs 53% (SISS) and 72% (cycEVA)). In the 2010/11 season, our VE estimates for elderly patients were lower than those from the I-MOVE network [26], 47–59% vs 72%. The differences observed could be related to differences in vaccine coverage, vaccine brands used, proportion of people with chronic conditions, and/or characteristics of influenza circulating strains.

Adjusted influenza vaccine effectiveness of the seasonal trivalent vaccine against the predominant circulating influenza virus in the study population by age group, Spanish Influenza Sentinel Surveillance System and cycEVA study, 2010/11, 2011/12 and 2012/13 influenza seasons, Spain

Influenza season	Age group in years	Data source	Total number of cases/ controls	Number of vaccinated cases/ vaccinated controls	Adjusted influenza VE % (95% CI)
2010/11	0–14	SISS	476/725	20/58	60 (28 to 78)[a]
		cycEVA	116/157	2/6	60 (−180 to 94)[a]
	15–59	SISS	910/917	35/76	56 (32 to 72)[b]
		cycEVA	419/358	9/18	43 (−41 to 77)[b]
	≥60	SISS	65/146	24/65	47 (−23 to 78)[c]
		cycEVA	39/76	12/39	59 (−19 to 76)[c]
2011/12	0–14	SISS	781/474	37/34	31 (−17 to 60)[a]
		cycEVA	229/128	13/8	2 (−186 to 66)[a]
	15–59	SISS	944/638	59/51	30 (−8 to 54)[b]
		cycEVA	452/334	21/22	41 (−16 to 70)[b]
	≥60	SISS	242/109	126/64	47 (3 to 72)[c]
		cycEVA	141/63	77/39	42 (−29 to 74)[c]
2012/13	0–14	SISS	749/476	24/31	57 (22 to 76)[a]
		cycEVA	265/177	8/5	−22 (−305 to 63)[a]
	15–59	SISS	701/560	28/50	64 (40 to 79)[b]
		cycEVA	334/305	8/22	74 (38 to 89)[b]
	≥60	SISS	104/114	31/60	53 (5 to 77)[c]
		cycEVA	58/53	15/29	72 (15 to 91)[c]

CI: confidence interval; cycEVA study: the Spanish component of the Influenza Monitoring Vaccine Effectiveness (I-MOVE) network; SISS: Spanish Influenza Sentinel Surveillance System; VE: vaccine effectiveness.

[a] Model adjusted for age group (0–4, 5–9 and 10–14 years), week of swabbing and Spanish region.
[b] Model adjusted for age group (15–40 and 41–59 years), week of swabbing and Spanish region.
[c] Model adjusted for age group (60–69, 70–79, 80–89 and 90–105 years), week of swabbing and Spanish region.

Regarding the younger age groups, the SISS estimates were generally higher and more precise than the cycEVA estimates (the sample size of the cycEVA study being 2.5–5 times lower than for the SISS (Table 3)). Children monitored by the cycEVA study were under-represented compared with children in the SISS because of a low proportion of paediatricians among the participating sentinel physicians. We would therefore like to highlight the importance of performing influenza VE analysis by age group, especially in elderly patients, the main group recommended for vaccination. Age group-specific VE estimates shown in this study, although limited by a lack of precision with wide CIs that do not indicate statistical significance, will allow comparisons to be drawn among countries and regions and across seasons.

After five influenza seasons, the cycEVA study has become a system that is capable of rapidly providing and disseminating reliable information on influenza VE on an annual basis at the national and European level [4-8,21,22,26,30,38]. This research-oriented system was able to address ancillary questions, such as the effect of repeated annual vaccination, waning immunity, potential sources of bias and confounding (beyond what is collected by sentinel networks) and other issues. Currently, however, cost is a critical factor limiting the sustainability of this study.

Surveillance networks have been shown to be excellent frameworks for conducting influenza VE studies [10-12,39]. By using data from existing systems, surveillance networks are simpler and less expensive than observational studies. In addition, these networks have the advantage of larger sample sizes and being representative of the entire country. Larger sample sizes would allow increasingly important early in-season estimates to be carried out, when the virus is still circulating. This ability is crucial to contribute to the World Health Organization's seasonal vaccine composition consultation for deliberation on influenza viruses for vaccines for the next season [40] and supports the possibility of obtaining more accurate subgroup

estimates (e.g. for target groups, virus types/subtypes and patient age groups).

Most of the limitations described in the current sentinel surveillance system could be overcome without costly modifications, including collection of the date of influenza vaccination and a reduction in the percentage of patients for whom there is incomplete information. To enhance the exhaustiveness of the data, we recommend emphasising to sentinel physicians the importance of improving the completeness of collected data at the regional level, with subsequent checking and validation of the data at the national level. Although strengthening the national influenza surveillance system does not require extra costs, it will require a long-term commitment of both human and material resources.

In conclusion, while acknowledging a role for a spectrum of VE research approaches, real-time monitoring of influenza VE using routine surveillance data is currently feasible in Spain and meets the minimum requirements described for influenza VE studies [41]. Enhancing the SISS by overcoming the drawbacks mentioned would optimise the system to provide reliable annual influenza VE estimates that guide national health authorities who implement influenza vaccination policies.

The sustainability of the well-established Spanish cycEVA study, as part of the I-MOVE network, is a crucial factor for more efficient validation and optimisation of the Spanish Influenza Sentinel Surveillance System.

Conflict of interest

None declared.

Authors' contributions

Silvia Jiménez-Jorge and Amparo Larrauri designed the study. Silvia Jiménez-Jorge wrote the first draft of the manuscript and undertook the statistical analysis. Silvia Jiménez-Jorge, Salvador de Mateo and Amparo Larrauri participated in data analysis, writing and interpretation of the results. Francisco Pozo and Inmaculada Casas established the microbiology database and contributed with the interpretation of the virological data. All authors participated in the interpretation of the data, contributed to the revision of the draft manuscript and approved the final version.

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* Authors' correction

The adjusted influenza vaccine effectiveness estimates in the text for 2012/13 for the study population obtained from SISS data and cycEVA study data were corrected. These changes were made on 21 July 2015, at the request of the authors.

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