Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12

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This study evaluates the influenza vaccine effectiveness (VE) in preventing laboratory-confirmed cases in Navarre, Spain, in the 2011/12 season in which the peak was delayed until week 7 of 2012. We conducted a test-negative case–control study. Patients with influenza-like illness in hospitals and primary healthcare were swabbed for testing by reverse transcription-polymerase chain reaction. Influenza vaccination status and other covariates were obtained from healthcare databases. The vaccination status of confirmed cases and negative controls was compared after adjusting for potential confounders. VE was calculated as (1-odds ratio)x100. The 411 confirmed cases (93% influenza A(H3)) were compared with 346 controls. Most characterised viruses did not match the vaccine strains. The adjusted estimate of VE was 31% (95% confidence interval (CI): -21 to 60) for all patients, 44% (95% CI: -11 to 72) for those younger than 65 years and 19% (95% CI: -146 to 73) for those 65 or older. The VE was 61% (95% CI: 5 to 84) in the first 100 days after vaccination, 42% (95% CI: -39 to 75) between 100 and 119 days, and zero thereafter. This decline mainly affected people aged 65 or over. These results suggest a low preventive effect of the 2011/12 seasonal influenza vaccine, and a decline in VE with time since vaccination.

Introduction

Influenza is an important health problem that can lead to serious complications in persons with risk factors [1,2]. Annual vaccination is the primary measure for preventing influenza and its complications [3]. Because the influenza vaccine composition is adapted each season to the viruses in circulation, its effectiveness varies [4].

Observational studies are the main way to evaluate vaccine effectiveness (VE) in each season, however, possible biases affecting comparability between vaccinated and unvaccinated persons must be overcome [5-8]. Studies with non-specific outcomes tend to underestimate the VE [6], a problem that is resolved by analysing virologically confirmed cases [4,9]. A design that compares confirmed influenza cases with test-negative controls ensures good comparability and is easy to carry out, thus this type of study has come to be widely used [4,9].

Song et al., in an immunogenicity study of the influenza vaccine, found that the antibody levels decline progressively, beginning in the first months after vaccine administration [10]. In addition, people with higher risk of complications due to influenza may have a weaker immune response due to the immunodepression associated with some chronic diseases or to the immunosenescence associated with aging [11,12].

In Spain, influenza circulation in the 2011/12 season reached a peak in week 7 of 2012, the second latest peak in the past 15 seasons, after the 2005/06 influenza wave [13]. Influenza A(H3N2) was the predominant virus in circulation, and a certain degree of vaccine–virus mismatch was observed [13]. The objective of this study was to describe the effectiveness of the influenza vaccine in the 2011/12 season in preventing laboratory-confirmed influenza, including both outpatients and hospitalised patients.

Methods

Study population

The present study was based on electronic clinical records in the region of Navarre, Spain in the 2011/12 season. The Navarre Ethical Committee for Medical Research approved the study protocol. The Navarre Health Service provides healthcare, free at point of

service, to 97% of the 642,051 inhabitants of the region (private companies provide healthcare to the remaining 3% of the population). The clinical records have been computerised since the year 2000 and include reports from primary care, hospital admissions, vaccination register, and laboratory test results.

The seasonal vaccination campaign took place from 10 October to 25 November 2011. In Navarre the trivalent inactivated non-adjuvanted vaccine was recommended and offered free of charge to people aged 60 years or older and to those with risk factors or major chronic conditions [14]. Other people can also be vaccinated if they pay for the vaccine. In the 2011/12 season, the vaccine included the strains A/California/07/2009(H1N1)-like, A/Perth/16/2009(H3N2)-like and B/Brisbane/60/2008-like virus [15]. Precise instructions for registering each dose were given to all vaccination points [14].

Influenza surveillance was based on automatic reporting of cases of influenza-like illness (ILI) from all primary healthcare centres and hospitals. Following the European Union case definition, ILI was considered to be the sudden onset of any general symptom (fever or feverishness, malaise, headache or myalgia) in addition to any respiratory symptom (cough, sore throat or shortness of breath) [16]. A sentinel network composed of a representative sample of 76 primary healthcare physicians and paediatricians, covering 15% of the population, was asked to take nasopharyngeal and pharyngeal swabs, after obtaining verbal informed consent, from all their patients diagnosed with ILI whose

symptoms had begun preferably less than five days previously. An agreed protocol of care for influenza cases was applied in hospitals, which specified early detection and nasopharyngeal swabbing of all hospitalised patients with ILI. Swabs were analysed by reverse transcription polymerase chain reaction (RT-PCR), and influenza-positive samples were subsequently typed/subtyped as influenza A(H1 and H3), A(H1N1)pdm09 and B. About one in four positive swabs was randomly selected each week and sent to the National Influenza Centre–Madrid laboratory for genetic characterisation.

Study design and statistical analysis

We carried out a case–control study nested in the cohort of the population covered by the Navarre Health Service. Healthcare workers, persons living in nursing homes and children under six months of age were excluded. The study began in the first week in which influenza virus was detected, 12 December 2011 (week 50), and ended in the last week in which ILI patients tested positive for influenza, 20 May 2012 (week 20).

The cases were patients diagnosed with ILI in primary care or in hospitals who were confirmed for influenza virus by RT-PCR. The controls were patients with ILI in primary healthcare or in hospitals who were negative for influenza virus. Their vaccination status for the trivalent 2011/12 seasonal influenza vaccine was obtained from the online regional vaccination register [17]. Subjects were considered to be protected starting 14 days after vaccine administration.

Figure

Number of influenza cases and test-negative controls, and incidence of influenza-like illness by week, Navarre, 3 Oct 2011–20 May 2012
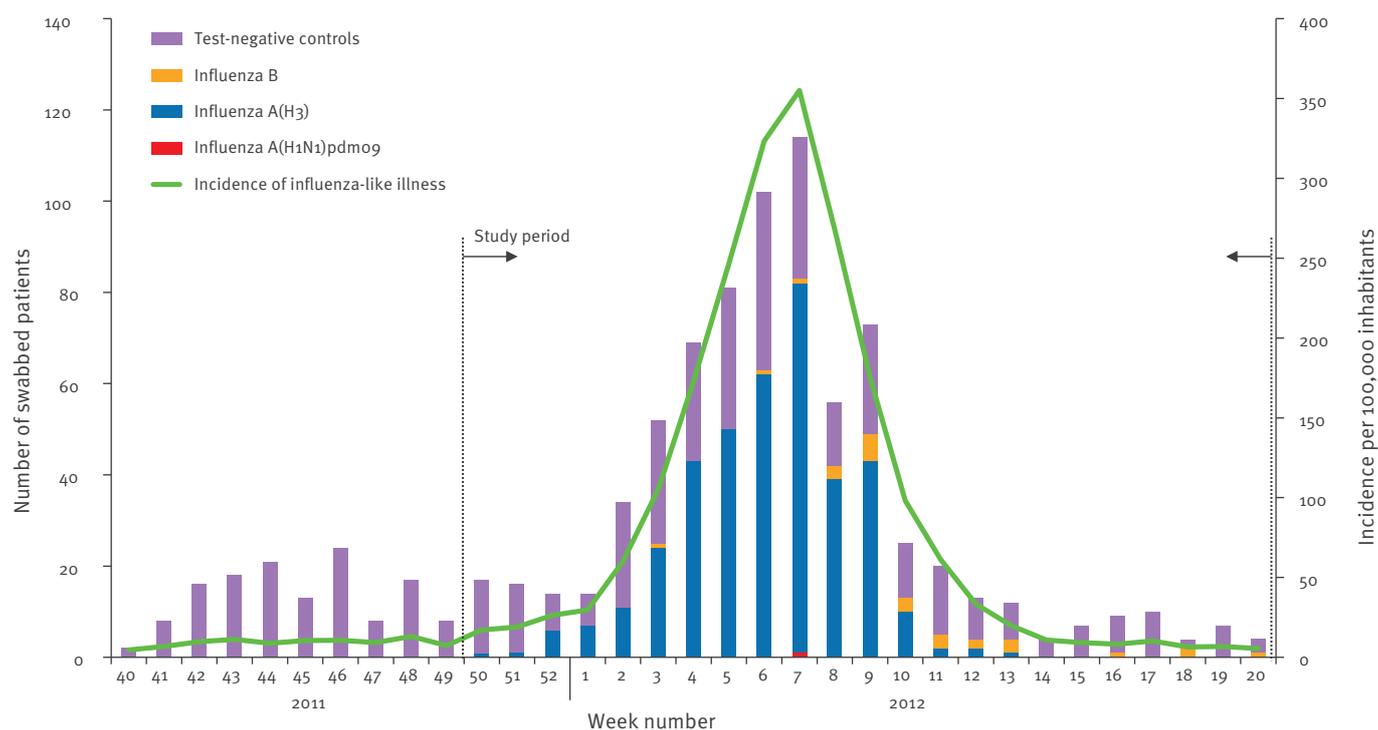
From the electronic healthcare records we obtained the following baseline characteristics: sex, age, district of residence, migrant status (country of birth other than Spain has been related to a different pattern of use of healthcare services [18]), major chronic conditions (heart disease, lung disease, renal disease, cancer, diabetes mellitus, cirrhosis, dementia, stroke, immunodeficiency, rheumatic disease and body mass index of 40 kg/m2 or greater), hospitalisation in the previous 12 months and outpatient visits in the previous 12 months.

Vaccination status was compared between cases and controls. Different analyses were done: (i) comparing cases of each type of influenza with negative controls, (ii) including only patients in whom influenza vaccination was indicated because they were 60 years or older or had a major chronic condition, (iii) considering only patients in primary care, and (iv) including only swabs taken in the first four days after symptom onset. VE was also evaluated separately in two age strata (<65 and ≥65 years; a cut-off age different from that of the vaccination target population was chosen to match the one commonly used in similar studies), in two periods (weeks 50/2011 to week 8/2012 and weeks 9/2012 to 20/2012) and in three strata according to time since vaccination (<100, 100–119 and ≥120 days).

Percentages were compared by chi-square test. Logistic regression techniques were used to calculate the odds ratios (OR) with their 95% confidence intervals (CI). ORs were adjusted for potential confounders including healthcare setting, and for date of diagnosis grouped into four-week periods. VE was estimated as (1-OR)x100.

Results

Description of cases and controls
The weekly number of swabbed patients followed the pattern of ILI incidence in the population (Figure). During the study period, 757 ILI patients were swabbed, 588 in primary healthcare and 169 in hospitals. Some 411 (54.3%) were confirmed for influenza virus: 382 for influenza A(H3), 28 for influenza B and one for influenza A(H1N1)pdm09.

Compared with confirmed cases of influenza, the group of test-negative controls had a higher proportion of males, of persons under the age of five years, people who had consulted a physician five or more times in the past year, who had major chronic conditions, and who were treated in hospital. There were no significant differences regarding migrant status or urban/rural residence, and these variables were therefore not included in the multivariate analysis (Table 1). Vaccine coverage in controls (18.8%) was slightly higher than in the overall population cohort in which the study was nested (14.2%, p=0.015).

Effectiveness of the 2011/12 seasonal influenza vaccine
Compared with test-negative controls, a smaller proportion of confirmed influenza cases had received the 2011/12 seasonal influenza vaccine (OR: 0.60; 95% CI: 0.40 to 0.89; p=0.012). In the adjusted analysis, the VE was 31% (95% CI: -21 to 60; p=0.200). The VE was somewhat higher between weeks 50/2011 and 8/2012

TABLE 1

Characteristics of laboratory-confirmed influenza cases (n=411) and test-negative controls (n=346), Navarre, 12 Dec 2011–20 May 2012

	Laboratory-confirmed influenza cases n (%)	Test-negative controls n (%)	p value
Age groups (years)			<0.001
<5	28 (6.8)	56 (16.2)	-
5–14	50 (12.2)	40 (11.6)	-
15–44	164 (39.9)	123 (35.5)	-
45–64	115 (28.0)	74 (21.4)	-
≥65	54 (13.1)	53 (15.3)	-
Sex			0.006
Male	188 (45.7)	194 (56.1)	-
Female	223 (54.3)	152 (43.9)	-
Residence			0.164
Rural	103 (25.1)	103 (29.8)	
Urban	308 (74.9)	243 (70.2)	
Migrant status			0.097
No	381 (92.7)	308 (89.0)	-
Yes	30 (7.3)	38 (11.0)	-
Major chronic conditions			0.002
No	301 (73.2)	217 (62.7)	-
Yes	110 (26.8)	129 (37.3)	-
Hospitalisation in the previous year			<0.001
No	384 (93.4)	292 (84.4)	-
Yes	27 (6.6)	54 (15.6)	-
Outpatient visits in the previous year			0.016
0	44 (11.4)	32 (9.3)	-
1 to 5	195 (47.5)	133 (38.4)	-
>5	172 (41.9)	181 (52.3)	-
Health care setting			<0.001
Primary healthcare	378 (92.0)	210 (60.7)	-
Hospital	30 (7.3)	119 (34.9)	-
Emergency rooms	3 (0.7)	17 (4.9)	-
Period			<0.001
Weeks 50/2011 to 8/2012 (12 Dec 2011–26 Feb 2012)	332 (80.8)	237 (68.5)	-
Weeks 9/2012 to 20/2012 (27 Feb–20 May 2012)	79 (19.2)	109 (31.5)	-
Seasonal influenza vaccine 2011/12			<0.015
No	361 (87.8)	281 (81.2)	-
Yes	50 (12.2)	65 (18.8)	-
Total	**411 (100)**	**346 (100)**	**-**

(37%; 95% CI: -18 to 67), and lower between weeks 9/2012 and 20/2012 (19%; 95% CI: -176 to 76). The estimates of VE were very similar in the analyses that were restricted to cases of influenza A(H3) (29%; 95% CI: -26 to 60), to subjects with an indication for vaccination (30%; 95% CI: -34 to 63), to patients in primary care (31%; 95% CI: -32 to 64), and to patients swabbed within the first four days after symptom onset (29%; 95% CI: -38 to 63). The point estimate of the VE was higher in subjects under the age of 65 years (44%; 95% CI: -11 to 72) than in those aged 65 years or older (19%; 95% CI: -146 to 73), although these differences did not

reach statistical significance. In none of all the analyses was the VE statistically significant (Table 2).

The VE was 61% (95% CI: 5 to 84) in the first 100 days after vaccination, dropping to 42% (95% CI: -39 to 75) between days 100 and 119, and ceasing to confer any protection after 120 days (-35%, 95% CI: -211 to 41) (Table 3). Persons vaccinated more than 120 days before diagnosis versus those vaccinated less than 100 days before diagnosis were at an increased risk for contracting influenza, with an OR of 3.45 (95% CI: 1.10 to 10.85; p=0.034).

TABLE 2

Influenza vaccine effectiveness in preventing laboratory-confirmed influenza by patient characteristic, comparisons of influenza-positive cases (n=411) and test-negative controls (n=346), Navarre, 12 Dec 2011–20 May 2012

	Cases/controls	Crude vaccine effectiveness % (95% CI)	p value	Adjusted vaccine effectiveness % (95% CI)[a]	p value
All swabbed patients					
Unvaccinated	361/281	Reference	-	Reference	-
Vaccinated	50/65	40 (11 to 60)	0.012	31 (-21 to 60)	0.200
Weeks 50/2011 to 8/2012 (12 Dec 2011–26 Feb 2012)					
Unvaccinated	298/195	Reference	-	Reference	-
Vaccinated	34/42	47 (14 to 67)	0.011	37 (-18 to 67)	0.151
Weeks 9/2012 to 20/2012 (27 Feb 2012–20 May 2012)					
Unvaccinated	63/86	Reference	-	Reference	-
Vaccinated	16/23	15 (-94 to 54)	0.888	19 (-176 to 76)	0.741
Influenza A(H3)[b]					
Unvaccinated	335/281	Reference	-	Reference	-
Vaccinated	47/65	39 (9 to 60)	0.011	29 (-26 to 60)	0.247
Influenza B[b]					
Unvaccinated	25/281	Reference	-	Reference	-
Vaccinated	3/65	48 (-77 to 85)	0.295	54 (-102 to 90)	0.301
Target population for vaccination[c]					
Unvaccinated	112/98	Reference	-	Reference	-
Vaccinated	43/54	30 (-13 to 57)	0.143	30 (-34 to 63)	0.286
Primary healthcare patients					
Unvaccinated	337/185	Reference	-	Reference	-
Vaccinated	41/25	10 (-53 to 47)	0.697	31 (-32 to 64)	0.262
Hospitalised patients					
Unvaccinated	21/85	Reference	-	Reference	-
Vaccinated	9/34	-7 (-157 to 65)	0.877	9 (-212 to 73)	0.879
Primary care patients swabbed <5 days after symptom onset					
Unvaccinated	334/182	Reference	-	Reference	-
Vaccinated	41/24	7 (-59 to 45)	0.793	29 (-38 to 63)	0.319
Patients aged <65 years					
Unvaccinated	337/258	Reference	-	Reference	-
Vaccinated	20/35	56 (22 to 75)	0.005	44 (-11 to 72)	0.095
Patients aged ≥65 years					
Unvaccinated	24/23	Reference	-	Reference	-
Vaccinated	30/30	4 (-106 to 55)	0.913	19 (-146 to 73)	0.710

CI: confidence interval.

[a] Vaccine effectiveness adjusted for sex, age (<5; 5–14; 15–44; 45–64; ≥65 years), major chronic conditions, outpatient visits in the previous year, hospitalisation in the previous year, healthcare setting, and period of diagnosis.

[b] There was one case of influenza A(H1N1)pdm09, not shown in this table.

[c] Target population for vaccination includes people ≥60 years-old and people with major chronic conditions.

Influenza vaccine effectiveness in preventing laboratory-confirmed influenza by vaccination status and time after vaccination, comparison of influenza-positive cases (n=411) and test-negative controls (n=346), Navarre, 12 Dec 2011–20 May 2012

	Cases/controls	Crude vaccine effectiveness % (95% CI)	p value	Adjusted vaccine effectiveness % (95% CI)[a]	p value
All swabbed patients					
Unvaccinated	361/281	Reference	-	Reference	-
<100 days after vaccination	11/24	64 (26 to 83)	0.006	61 (5 to 84)	0.039
100–119 days after vaccination	15/16	27 (-50 to 64)	0.392	42 (-39 to 75)	0.222
≥120 days after vaccination	24/25	25 (-34 to 58)	0.326	-35 (-211 to 41)	0.476
Influenza A(H3) cases					
Unvaccinated	335/281	Reference	-	Reference	-
<100 days after vaccination	11/24	62 (20 to 81)	0.010	61 (4 to 84)	0.040
100–119 days after vaccination	15/16	21 (-62 to 62)	0.514	39 (-48 to 74)	0.275
≥120 days after vaccination	21/25	29 (-29 to 61)	0.255	-55 (-283 to 37)	0.342
Target population for vaccination [b]					
Unvaccinated	112/98	Reference	-	Reference	-
<100 days after vaccination	7/21	71 (28 to 88)	0.007	69 (6 to 90)	0.038
100–119 days after vaccination	15/14	6 (-104 to 57)	0.871	39 (-49 to 75)	0.277
≥120 days after vaccination	21/19	3 (-90 to 51)	0.923	-51 (-298 to 42)	0.397
Primary healthcare patients					
Unvaccinated	337/185	Reference	-	Reference	-
<100 days after vaccination	10/13	58 (2 to 82)	0.045	63 (2 to 96)	0.045
100–119 days after vaccination	14/5	-54 (-333 to 45)	0.417	-2 (-215 to 67)	0.971
≥120 days after vaccination	17/7	-33 (-227 to 46)	0.530	-2 (-194 to 65)	0.971
Hospitalised patients					
Unvaccinated	21/85	Reference	-	Reference	-
<100 days after vaccination	1/10	59 (-234 to 95)	0.401	65 (-277 to 97)	0.383
100–119 days after vaccination	1/9	55 (-275 to 95)	0.460	78 (-126 to 98)	0.202
≥120 days after vaccination	7/15	-89 (-522 to 32)	0.220	-182 (-1,219 to 40)	0.187
Primary care patients swabbed <5 days after symptom onset					
Unvaccinated	334/182	Reference	-	Reference	-
<100 days after vaccination	10/12	55 (-7 to 81)	0.072	58 (-12 to 84)	0.084
100–119 days after vaccination	14/5	-53 (-330 to 46)	0.425	0 (-211 to 68)	0.999
≥120 days after vaccination	17/7	-32 (-225 to 46)	0.541	0 (-189 to 66)	0.991
Week 50/2011 to 8/2012 (12 Dec 2011–26 Feb 2012)					
Unvaccinated	298/195	Reference	-	Reference	-
<100 days after vaccination	10/24	73 (42 to 87)	0.001	65 (11 to 86)	0.027
100–119 days after vaccination	13/16	47 (-13 to 75)	0.101	48 (-32 to 79)	0.168
≥120 days after vaccination	11/2	-260 (-1,541 to 21)	0.098	-375 (-2,513 to 14)	0.073
Patients aged <65 years					
Unvaccinated	337/258	Reference		Reference	
<100 days after vaccination	6/13	65 (6 to 87)	0.038	47 (-63 to 83)	0.269
100–119 days after vaccination	6/7	34 (-98 to 78)	0.454	54 (-55 to 86)	0.210
≥120 days after vaccination	8/15	59 (2 to 83)	0.044	32 (-111 to 78)	0.503
Patients aged ≥65 years					
Unvaccinated	24/23	Reference		Reference	
<100 days after vaccination	5/11	56 (-145 to 87)	0.176	85 (-8 to 98)	0.059
100–119 days after vaccination	9/9	4 (-184 to 68)	0.939	24 (-224 to 82)	0.715
≥120 days after vaccination	16/10	-53 (-307 to 42)	0.390	-208 (-1,563 to 43)	0.192

CI: confidence interval.

[a] Vaccine effectiveness adjusted for sex, age (<5; 5–14; 15–44; 45–64; ≥65 years), major chronic conditions, outpatient visits in the previous year, hospitalisation in the previous year, healthcare setting, and period of diagnosis.

[b] Target population for vaccination includes people ≥60 years-old and people with major chronic conditions.

The point estimates of the influenza VE ranged between 61% and 69% during the first 100 days after vaccination in the analyses restricted to cases of influenza A(H3), to persons with an indication for influenza vaccination, to primary care patients, and to hospitalised patients, although this last result was not statistically significant. However, in all these analyses the vaccine had practically zero effectiveness at 120 or more days after vaccination (Table 3). In persons under 65 years of age the VE declined little with time since vaccination, whereas in those aged 65 years or older the OR for the risk of influenza was 20.81 (95% CI: 2.14 to 202.71; p=0.009) for those vaccinated more than 120 days previously versus those vaccinated less than 100 days previously.

Genetic characterisation

In total 102 isolates obtained from the confirmed cases, were further characterised by phylogenetic analysis of the HA1 sequence of the haemagglutinin gene in the National Influenza Centre - Madrid laboratory: 90 were influenza A(H3N2), 11 influenza B and one was influenza A(H1N1)pdm09. The strains most frequently identified were similar to A/Victoria/361/2011(H3N2) (41.2%), A/England/259/2011(H3N2) (24.5%), A/Iowa/19/2010(H3N2) (20.6%) and B/Bangladesh/3333/2007(Yamagata) (9.8%). The proportions of strains were similar in the two periods from week 50/2011 to 8/2012 (12 December 2011 to 26 February 2012) and from week 9/2012 to 20/2012 (27 February to 20 May 2012), except for a reduced proportion of characterisations of strain A/England/259/2011(H3N2) and an increase of B/Bangladesh/3333/2007(Yamagata) (Table 4).

Discussion

The results of this study suggest that on average, the seasonal influenza vaccine had a low protective effect in preventing laboratory-confirmed influenza during the 2011/12 season in Navarre. Most of the strains we characterised showed reduced reactivity with post-infection ferret antiserum raised against the vaccine viruses, suggesting a certain degree of vaccine-virus mismatch [19]. Although the confidence intervals were wide, similar estimates were obtained in analyses restricted to the target population for vaccination, to primary healthcare patients, or to patients swabbed within the first four days after symptom onset, which strengthens the conclusion and rules out possible biases. Evaluation of VE in preventing cases of influenza A(H3) only, also yielded similar estimates.

The early estimates of influenza VE for the first part of the season were higher than what we found for the complete season [20,21], which suggests a decline in VE over time. Two possible mechanisms, or a combination of both, could explain this reduced VE. The first is a change in the viruses circulating during the season, either due to appearance of another virus type or due to antigenic drift of circulating viruses, resulting in a loss of the match with the vaccine viruses. Our results do not support this mechanism, since the only relevant change in the circulating viruses was an increase in influenza B viruses, and low VE was also observed when we evaluated the effectiveness of the vaccine against influenza A(H3) only.

The second possible mechanism is waning immunity in those who received the vaccine. It has been reported that antibody levels begin to fall one month after

TABLE 4

Distribution of influenza cases by type of virus and distribution of cases with characterisation by strains in two calendar periods. Navarre, Spain, 2011-2012

	Week 50/2011 to 8/2012 (12 Dec 2011–26 Feb 2012) n (%)	Week 9/2012 to 20/2012 (27 Feb –20 May 2012) n (%)	p value
All cases			
Influenza A(H3)	325 (97.9)	57 (72.2)	<0.001
Influenza A(H1N1)pdm09	1 (0.3)	0 (0)	1.000
Influenza B	6 (1.8)	22 (17.8)	<0.001
Total	332 (100)	79 (100)	-
Cases with characterisation			
Influenza A/Victoria/361/2011(H3N2)	34 (42.5)	8 (36.4)	0.635
Influenza A/England/259/2011(H3N2)	24 (30.0)	1 (4.5)	0.012
Influenza A/Stockholm/18/2011(H3N2)	2 (2.5)	0 (0)	1.000
Influenza A/Iowa/19/2010(H3N2)	17 (21.3)	4 (18.2)	1.000
Influenza B/Bangladesh/3333/2007(Yamagata)	2 (2.5)	8 (36.4)	<0.001
Influenza B/Brisbane/60/2008(Victoria)	0 (0)	1 (4.5)	0.216
Influenza A/St Petersburg/100/2011(H1N1) pdm09	1 (1.3)	0 (0)	1.000
Total	80 (100)	22 (100)	-

administration of the influenza vaccine [10]. This loss of immune response is more pronounced in older persons [10-12]. The results of our study show a decline in the VE beginning 100 days after vaccination, primarily in persons aged 65 years or older. This finding could be explained by an immunosenescence phenomenon, aggravated by the long time between vaccination and virus circulation, which was longer than in most other seasons [13], and the limited match between vaccine and circulating strains [20,21].

Longer time between symptom onset and swabbing has been associated with reduced sensitivity in virus detection, which could underestimate VE [6]. We controlled for this effect mainly in the design of our study, since 99% of the swabs from primary healthcare patients were taken within the first four days after symptom onset. Moreover, we repeated the analysis after eliminating the cases swabbed after the first four days, and no relevant changes in the estimate of VE were found.

The present study included both outpatient and hospital cases systematically recruited in a previously defined population. Primary care patients made up the bulk of subjects in our study and, when the analysis was limited to these patients, the VE was maintained. The number of cases treated in hospitals was small, which did not allow us to obtain a specific estimate of the VE in preventing hospitalised cases.

Although institutionalised patients were not included in this study, several influenza outbreaks in nursing homes with high vaccination coverage were detected in Navarre in the 2011/12 season [22]. This may be considered another consequence of the low VE.

This case−control analysis included only laboratory-confirmed cases and compared them with test-negative controls recruited in the same healthcare settings before either patient or physician knew the laboratory result, a fact that provides better comparability and reduces selection bias [6]. This type of design has been used in other studies that have evaluated influenza VE [20,21,23,24]. The case¬−control study was nested in a population cohort for which extensive and reliable databases were available, and which was treated in hospitals and primary healthcare by physicians trained to detect and swab ILI patients, all of which can prevent unmeasured confounding [25].

In interpreting the results, some limitations must be kept in mind. The study size was insufficient to demonstrate a VE under 40%, which was reflected in wide confidence intervals that included zero. It may not be possible to generalise the results and apply them to other geographical areas, although other published studies in the same influenza season are consistent with our data [20,21]. Although RT-PCR has high sensitivity for the detection of influenza virus, we cannot completely rule out some false negative results,

which would cause a small underestimation of the VE. Although all the analyses were adjusted for the commonly recognised confounding factors, some residual confusion is possible [6].

These results suggest that VE may vary throughout the influenza season. The early estimates of influenza VE obtained in mid-season may drop during the season. This situation should be kept in mind given its implications for clinical practice and public health; it should not be interpreted as an error in the estimates, but as a description of reality. These early estimates remain enormously useful in redirecting preventive strategies during the influenza season and because they can aid the selection of strains to be included in the following season's vaccine [20,21].

The description of situations in which influenza VE is low should serve as a stimulus to design better influenza vaccines [26], to improve the selection of strains contained in the vaccine, to choose the most appropriate time for vaccination in each area, to encourage vaccination of caregivers of high-risk individuals, and to highlight the importance of other preventive measures that complement vaccination in high-risk populations, such as promotion of basic hygiene measures and avoidance of contact with influenza cases [27]. Early treatment with antiviral drugs should be considered in persons diagnosed with influenza who have a high risk of complications, regardless of vaccination status [28]. In seasons when influenza starts late, it may be useful to revaccinate persons with a high risk of complications, especially those who may have a reduced immune response due to immunosenescence or immunodepression.

Even in seasons in which the effectiveness of influenza vaccine is low, it may appreciably reduce the number of cases and hospitalisations in high-risk persons. In the 2011/12 season in Navarre, the vaccine managed to avoid almost one third of the influenza cases in the vaccinated at-risk population; while not entirely satisfactory, this result is important in terms of individual and public health.

Conclusions
Our results support a low protective effect of the 2011/12 seasonal vaccine in Navarre and suggest a decline in VE in the elderly with time since vaccination. Even under these conditions, annual immunisation of high-risk populations against influenza remains of interest, although it should be complemented with other preventive initiatives such as basic hygiene measures, vaccination of caregivers and avoidance of contact with influenza cases.

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