Research article

Effects of previous episodes of influenza and vaccination in preventing laboratory-confirmed influenza in Navarre, Spain, 2013/14 season

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We estimated whether previous episodes of influenza and trivalent influenza vaccination prevented laboratory-confirmed influenza in Navarre, Spain, in season 2013/14. Patients with medically-attended influenza-like illness (MA-ILI) in hospitals (n = 645) and primary healthcare (n = 525) were included. We compared 589 influenza cases and 581 negative controls. MA-ILI related to a specific virus subtype in the previous five seasons was defined as a laboratory-confirmed influenza infection with the same virus subtype or MA-ILI during weeks when more than 25% of swabs were positive for this subtype. Persons with previous MA-ILI had 30% (95% confidence interval (CI): −7 to 54) lower risk of MA-ILI, and those with previous MA-ILI related to A(H1N1)pdm09 or A(H3N2) virus, had a, respectively, 63% (95% CI: 16–84) and 65% (95% CI: 13–86) lower risk of new laboratory-confirmed influenza by the same subtype. Overall adjusted vaccine effectiveness in preventing laboratory-confirmed influenza was 31% (95% CI: 5–50): 45% (95% CI: 12–65) for A(H1N1) pdm09 and 20% (95% CI: −16 to 44) for A(H3N2). While a previous influenza episode induced high protection only against the same virus subtype, influenza vaccination provided low to moderate protection against all circulating subtypes. Influenza vaccine remains the main preventive option for high-risk populations.

Introduction

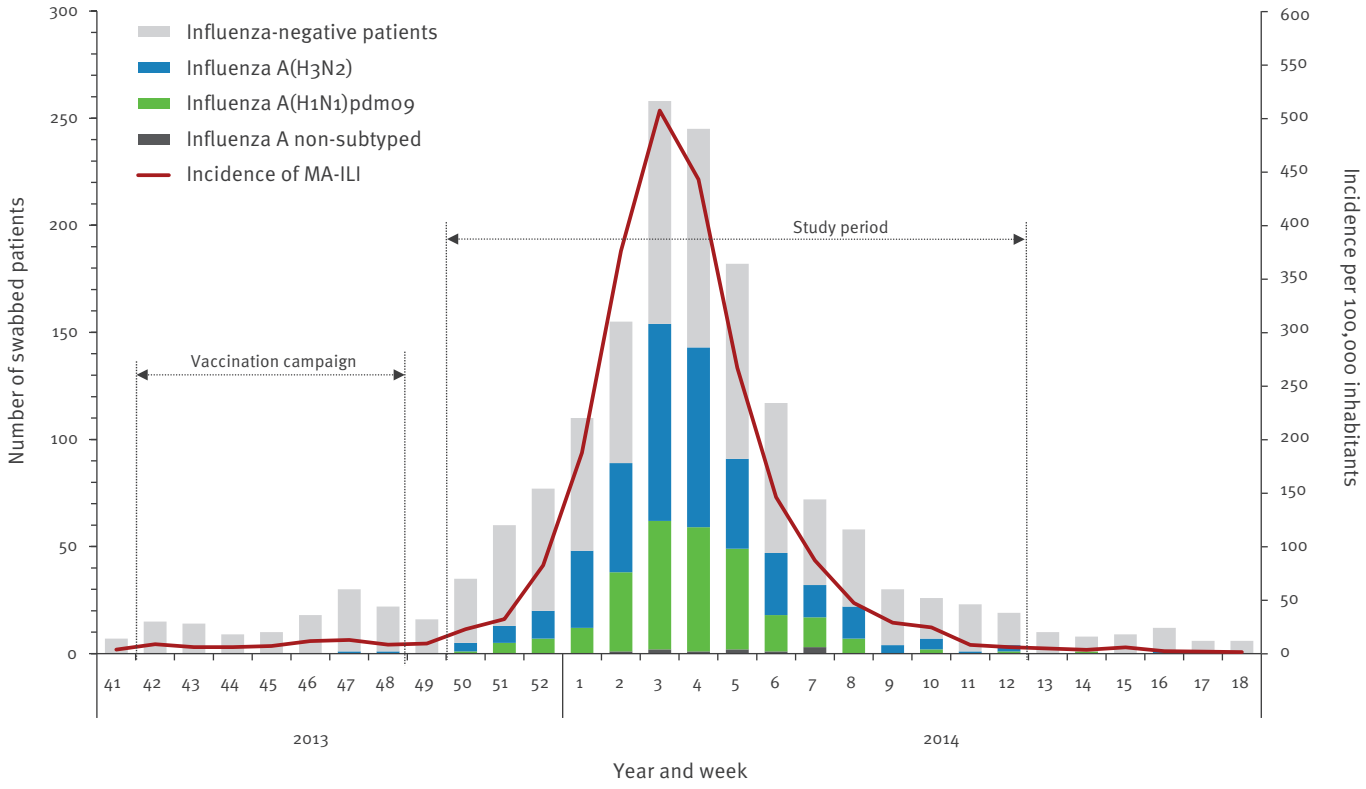
Influenza produces annual epidemics that spread widely in the susceptible population. About 20% of children and 5% of adults worldwide develop symptomatic influenza each year [1]. This exposure could confer immunity that would protect against the same virus type and subtype in subsequent seasons. Since the 2009 pandemic, influenza virus A(H1N1)pdm09, A(H3N2) and B have been alternating, thus part of the population may have acquired natural immunity after exposure to these viruses [2].

In serological surveys, nearly all children aged nine years or older had antibodies against influenza A [3]. However, this does not mean that they are totally protected against this virus type, since antigenic drift of the influenza virus allows it to escape immune control. Differences in protection could not be accounted for by differences in serum haemagglutination inhibition titres, demonstrating that multiple immune mechanisms induced by natural infection confer resistance to influenza [4,5].

Annual influenza vaccination is the primary measure to prevent influenza and its consequences [1]. Trivalent seasonal influenza vaccines include strains of influenza A(H1N1), A(H3N2) and B. In the 2013/14 season, the influenza vaccine composition recommended in the northern hemisphere included an A/California/7/2009(H1N1)pdm09-like virus, an A(H3N2) virus antigenically similar to the cell-propagated prototype virus A/Victoria/361/2011, and a B/Massachusetts/2/2011-like virus [6].

Figure

Weekly incidence of patients with medically attended influenza-like illness and number of swabbed patients by test result, Navarre, Spain, influenza season 2013/14 (n = 1,170 in the study period)



MA-ILI: medically attended influenza-like illness.

During the 2013/14 season, influenza A(H1N1)pdm09 and A(H3N2) viruses co-circulated in Spain and the rest of Europe, and most characterised isolates were A/StPetersburg/27/2011(H1N1)pdm09-like and A/Texas/50/2012(H3N2)-like [7-9].

Although both natural infection and vaccination with inactivated vaccine stimulate serum haemagglutination inhibition antibodies and provide protection against homologous wild-type influenza strains, the protection associated with natural infection lasts longer and is broader than that induced by inactivated vaccine [10,11]. However, the effect of natural immunity and its practical relevance are not generally evaluated. The aim of this study was to estimate the effects of previous influenza episodes and of the trivalent vaccine in preventing inpatient and outpatient cases with laboratory-confirmed influenza in Navarre, Spain, in the 2013/14 season.

Methods

Study population

This study was performed in the region of Navarre, Spain. The Regional Health Service provides healthcare, free at point of service, to 97% of the population. The Navarre Ethical Committee for Medical Research approved the study protocol.

The seasonal vaccination campaign took place from 14 October to 30 November 2013. The trivalent inactivated split 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 [12]. Other people were also vaccinated if they paid for the vaccine.

In the 2013/14 season and the preceding seasons, influenza surveillance was based on automatic reporting of cases of medically-attended influenza-like illness (MA-ILI) from all primary healthcare centres and hospitals. ILI was considered to be the sudden onset of any general symptom (fever or feverishness, malaise, headache or myalgia) and any respiratory symptom (cough, sore throat or shortness of breath). In addition, a sentinel network composed of a representative sample of primary healthcare physicians, covering 16% of the Navarre population, was asked to take double

Table 1

Predominant circulating influenza virus strains in Navarre, Spain, in the season analysed (2013/14) and the five previous seasons (2008/09–2012/13)

Influenza season	Predominant influenza type/subtype	Predominant genotype	Periods when more than 25% of patients tested positive to the predominant virus type/subtype	Proportion of positive swabs
2008/09	A(H3N2)	A/Brisbane/10/2007(H3N2)	16 Nov 2008 – 1 Feb 2009	70%
2009/10	A(H1N1)pdm09	A/California/7/2009(H1N1)	28 Jun 2009 – 9 Sep 2009 4 Oct 2009 – 20 Dec 2009	51%
2010/11	A(H1N1)pdm09	A/California/07/2009(H1N1)	21 Nov 2010 – 13 Feb 2011	59%
2011/12	A(H3N2)	A/Victoria/361/2011(H3N2) A/England/259/2011(H3N2) A/Iowa/19/2010(H3N2)	23 Dec 2011 – 11 Mar 2012	67%
2012/13	B	B/Estonia/55669/2011 B/Wisconsin/1/2010	31 Dec 2012 – 7 Apr 2013	64%
2013/14	A(H3N2) A(H1N1)pdm09	A/Texas/50/2012(H3N2) A/StPetersburg/27/2011(H1N1)	9 Dec 2013 – 23 Mar 2014	50%

swabs, nasopharyngeal and pharyngeal, after obtaining verbal informed consent, from all their patients diagnosed with ILI whose symptoms had begun less than five days before the consultation. The protocol for influenza cases in hospitals foresees nasopharyngeal and pharyngeal swabbing of all hospitalised patients with ILI.

Swabs were analysed by real-time RT-PCR, using either of two commercial real-time RT-PCR assays: RealCycler FLURSV (Progenie Molecular, Spain) and Real Time Ready Influenza A(H1N1) Detection Set (Roche Diagnostics, Switzerland). Detection of influenza A and B was based on the matrix protein gene and subtyping was based on the haemagglutinin (HA) gene. The internal amplification control was positive in all influenza-negative samples, indicating that failure to detect influenza virus was not due to inhibition.

Strains systematically selected among culture-positive samples by week and virus type/subtype were sent to the National Influenza Centre laboratory in Madrid for genetic characterisation based on partial sequencing of the HA gene (subunit HA1).

Study design and statistical analysis

We carried out a test-negative case–control study in 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 included the consecutive weeks in which influenza virus was detected, i.e. the period from 9 December 2013 (week 50) to 23 March 2014 (week 12). All information related to patients was linked using a unique identification number.

The cases were MA-ILI patients in primary healthcare or in hospitals for whom influenza virus infection was confirmed by RT-PCR, and the controls were MA-ILI patients who tested negative for influenza virus. Their vaccination status for the trivalent seasonal influenza vaccine was obtained from the regional vaccination register [13]. Subjects were considered to be protected starting 14 days after vaccine administration.

From the electronic records of epidemiological and virological surveillance we obtained information on MA-ILI diagnosis and RT-PCR-positive patients in previous seasons for the study subjects. We defined previous MA-ILI related to a specific virus subtype as a laboratory-confirmed influenza infection with this virus subtype (virological criterion) that had occurred in the seasons from 2008/09 through 2012/13 or as MA-ILI that occurred in these seasons in weeks where more than 25% of swabs were confirmed for this influenza virus subtype (epidemiological criterion). Five previous seasons were considered given the long-lived protection associated with natural infection [10,11] and because no major shift had affected the circulating viruses involved in the analysis. Table 1 shows the periods when more than 25% of patients tested positive to the predominant virus type/subtype and the average percentage of swabbed patients who tested positive for the predominant circulating influenza virus by season. Finally, previous MA-ILI related to any influenza virus included all laboratory-confirmed influenza cases or MA-ILI patients that had occurred in the seasons 2008/09 through 2012/13 in weeks with more than 25% of swabs confirmed for any influenza virus, although on average 64% of swabbed patients tested positive for any influenza virus during these periods.

Percentages were compared by chi-square test. The odds of influenza vaccination and the odds of MA-ILI in the previous five seasons were compared between cases and controls. Logistic regression was used to calculate the odds ratios (OR) with their 95% confidence intervals (CI), adjusting for sex, age group (<5, 5–14, 15–44, 45–64 and ≥65 years), major chronic conditions (heart disease, respiratory disease, renal disease,

Table 2

Characteristics of patients with medically-attended influenza-like illness included in the test negative case–control analysis, by test result, Navarre, Spain, 2013/14 season (n = 1,170)

	Test-negative controls		Influenza cases[a]		p value	A(H1N1)pdm09		A(H3N2)		p value
	n	%	n	%		n	%	n	%	
Age groups (years)					<0.001					<0.001
<5	108	19	29	5		13	6	16	5	
5–14	36	6	34	6		16	7	18	5	
15–44	125	22	196	33		84	36	111	32	
45–64	108	19	163	28		80	34	81	23	
≥65	204	35	167	28		42	18	123	35	
Sex					0.295					0.754
Male	290	50	312	53		127	54	184	53	
Female	291	50	277	47		108	46	165	47	
Month of sample collection					<0.001					0.508
December	99	17	49	8		15	6	34	10	
January	306	53	435	74		179	76	253	72	
February	140	24	96	16		38	16	56	16	
March	36	6	9	2		3	1	6	2	
Residence					0.933					0.970
Rural	167	29	168	29		67	29	99	28	
Urban	414	71	421	71		168	71	250	72	
Major chronic conditions					0.116					0.021
No	285	49	316	54		140	60	174	50	
Yes	296	51	273	46		95	40	175	50	
Healthcare setting [b]					<0.001					0.969
Primary healthcare	182	31	345	59		139	59	205	59	
Hospital	400	69	245	42		97	41	144	41	
Seasonal influenza vaccine 2013/14					<0.001					0.001
No	383	66	445	76		195	83	246	70	
Yes	198	34	144	24		40	17	103	30	
Seasonal influenza vaccine 2012/13					0.006					0.003
No	395	68	443	75		192	82	247	71	
Yes	186	32	146	25		43	18	102	29	
Previous MA-ILI [c]					0.251					0.631
No	523	90	527	89		208	89	314	90	
Virological criteria	13	2	7	1		4	2	3	1	
Epidemiological criteria	45	8	55	9		23	10	32	9	
Previous MA-ILI related to A(H1N1)pdm09 [c]					0.487					0.240
No	546	94	559	95		226	96	328	94	
Yes	35	6	30	5		9	4	21	6	
Previous MA-ILI related to A(H3N2) [c]					0.719					0.022
No	559	96	569	97		222	94	342	98	
Yes	22	4	20	3		13	6	7	2	
Total	**581**	**100**	**589**	**100**		**235**	**100**	**349**	**100**	

MA-ILI: medically attended influenza-like illness.

[a] Includes seven cases of not subtyped influenza A. Two patients had simultaneous positive test results for influenza A(H1N1)pdm09 and influenza A(H3N2).

[b] Two patients were attended in primary healthcare and referred to hospital.

[c] Medically-attended influenza-like illness virologically or epidemiologically related to influenza in the previous five seasons.

Table 3

Characteristics of patients with medically-attended influenza-like illness, by previous influenza diagnosis and influenza vaccination status, Navarre, Spain, 2013/14 season (n = 1,170)

	Total tested	Previous MA-ILI[a]		p value	Influenza vaccination		p value
	n	n	%		n	%	
Age groups (years)				<0.001			<0.001
<5	137	5	4		15	11	
5–14	70	25	36		9	13	
15–44	321	53	17		28	9	
45–64	271	24	9		53	20	
≥65	371	13	4		237	64	
Sex				0.597			0.249
Male	602	59	10		167	28	
Female	568	61	11		175	31	
Residence				0.939			0.896
Rural	835	86	10		245	29	
Urban	335	34	10		97	29	
Major chronic conditions				0.046			<0.001
No	601	72	12		72	12	
Yes	569	48	8		270	47	
Healthcare setting [a]				<0.001			<0.001
Primary healthcare	527	88	17		74	14	
Hospital	645	32	5		269	42	
Previous MA-ILI [b]				NA			0.001
No	1,050	0	0		322	31	
Yes	120	120	100		20	17	
Total	**1,170**	**120**	**10**		**342**	**29**	

MA-ILI: medically attended influenza-like illness; NA: not applicable.

[a] Two patients were attended in primary healthcare and referred to hospital.

[b] Medically-attended influenza-like illness virologically or epidemiologically related to any influenza virus in the previous five seasons.

cancer, diabetes mellitus, liver cirrhosis, dementia, stroke, immunodeficiency, rheumatic disease and body mass index ≥ 40 kg/m^2), month of sample collection and healthcare setting (primary healthcare and hospital). Separate analyses were done by type/subtype of influenza, age group and healthcare setting. The fraction of prevented disease in exposed individuals or vaccine effectiveness (VE) was estimated as (1 – OR) x 100.

Results

During the 2013/14 season in Navarre, the incidence of MA-ILI, the number of swabbed patients and the number of influenza-positive cases followed similar trends, peaking in week 3 of 2014 (Figure).

In the study period, a total of 1,170 MA-ILI patients were swabbed, of whom 525 were attended in primary healthcare and 645 were hospitalised. A total of 589 (50%) were confirmed for influenza virus, all of them for influenza A. Influenza A(H3N2) virus was detected in 349 cases, influenza A(H1N1)pdm09 in 235, and seven remained non-subtyped. Two patients had a simultaneous positive test result for influenza A(H1N1)pdm09 and A(H3N2). Sequence analysis of the amplification product (the HA1 fragment of the haemagglutinin gene) was available for 114 influenza viruses. All 42 A(H1N1) pdm09 viruses were A/StPetersburg/27/2011-like and all 72 A(H3N2) viruses were A/Texas/50/2012-like.

Compared with the test-negative controls (n = 581), confirmed cases of influenza were more frequent among 15 to 64 years-olds (61% vs 40%; p < 0.001) and those attended in primary healthcare (58% vs 31%; p < 0.001). Compared with influenza A(H1N1)pdm09, influenza A(H3N2) was more frequently detected in persons 65 years or older (35% vs 18%; p < 0.001) and in persons with major chronic conditions (50% vs 40%; p = 0.021). The proportion of hospitalised patients was the same for both influenza A(H1N1)pdm09 and A(H3N2) cases (41% vs 41%; p = 0.970) (Table 2).

A similar proportion of laboratory-confirmed cases and influenza-negative controls had had MA-ILI in the previous five seasons (11% vs 10%; p = 0.759), but only 17% of them (20/120) had been laboratory-confirmed for influenza virus in the previous episode. Of the 120 patients who had had any MA-ILI episode in the previous five years, 18 had had more than one episode and only one had had two episodes related to the same virus subtype. Among the 589 cases, 144 (24%) had

Table 4a

Preventive effect of previous episodes of medically-attended influenza-like illness and of the trivalent inactivated influenza vaccine against new cases of laboratory-confirmed influenza in Navarre, Spain, 2013/14 season (n = 1,170)

	Cases; controls	Crude prevented fraction % (95% CI)	p value	Adjusted prevented fraction % (95% CI)[a]	p value
All influenza cases vs controls					
All swabbed patients	589; 581				
Previous MA-ILI related to any influenza[b]	62; 58	−6 (−55 to 27)	0.759	30 (−7 to 54)	0.098
Vaccinated	144; 198	37 (19 to 51)	<0.001	31 (5 to 50)	0.023
Age<65 years	422; 377				
Previous MA-ILI related to any influenza[b]	56; 51	2 (−47 to 35)	0.915	32 (−9 to 57)	0.107
Vaccinated	44; 61	40 (9 to 60)	0.017	35 (−5 to 60)	0.081
Age≥65 years	167; 204				
Previous MA-ILI related to any influenza[b]	6; 7	−5 (−218 to 65)	0.933	21 (−153 to 75)	0.694
Vaccinated	100; 137	27 (−12 to 52)	0.147	28 (−11 to 54)	0.139
Primary healthcare patients[c]	345; 182				
Previous MA-ILI related to any influenza[b]	52; 36	28 (−15 to 55)	0.169	34 (−9 to 60)	0.103
Vaccinated	47; 27	9 (−51 to 46)	0.703	21 (−45 to 57)	0.452
Hospitalised patients[c]	245; 400				
Previous MA-ILI related to any influenza[b]	10; 22	27 (−57 to 66)	0.422	21 (−82 to 65)	0.585
Vaccinated	97; 172	13 (−20 to 37)	0.394	35 (4 to 56)	0.030
Influenza A(H1N1)pdm09 cases vs controls					
All swabbed patients	235; 581				
Previous MA-ILI related to A(H1N1)pdm09[b]	9; 35	38 (−31 to 71)	0.213	63 (16 to 84)	0.017
Vaccinated	40; 198	60 (42 to 73)	<0.001	45 (12 to 65)	0.013
Age<65 years	193; 377				
Previous MA-ILI related to A(H1N1)pdm09[b]	6; 33	67 (19 to 86)	0.016	78 (43 to 91)	0.002
Vaccinated	16; 61	53 (16 to 74)	0.010	52 (8 to 75)	0.028
Age≥65 years	42; 204				
Previous MA-ILI related to A(H1N1)pdm09[b]	3; 2	−677 (−4,700 to −26)	0.027	−613 (−4,470 to −11)	0.038
Vaccinated	24; 137	35 (−28 to 67)	0.216	37 (−27 to 69)	0.193
Primary healthcare patients[c]	139; 181				
Previous MA-ILI related to A(H1N1)pdm09[b]	7; 24	65 (16 to 85)	0.018	70 (26 to 88)	0.010
Vaccinated	13; 27	41 (−20 to 71)	0.144	43 (−28 to 75)	0.171
Hospitalised patients[c]	97; 400				
Previous MA-ILI related to A(H1N1)pdm09[b]	2; 11	25 (−242 to 84)	0.704	−6 (−427 to 79)	0.944
Vaccinated	27; 172	49 (17 to 69)	0.007	45 (1 to 69)	0.047

CI: confidence interval; MA-ILI: medically attended influenza-like illness.

a Results obtained from a logistic regression model adjusted for sex, age group (<5, 5–14, 15–44, 45–64 and≥65 years), month of sample collection, major chronic conditions, healthcare setting (primary healthcare and hospital), medically-attended influenza-like illness virologically or epidemiologically related to the analysed influenza virus in the previous five seasons, and 2013/14 influenza vaccine.

b Medically-attended influenza-like illness virologically or epidemiologically related to influenza in the previous five seasons.

c Patients attended in primary healthcare and referred to hospital were included in both subanalyses.

Table 4b

Preventive effect of previous episodes of medically-attended influenza-like illness and of the trivalent inactivated influenza vaccine against new cases of laboratory-confirmed influenza in Navarre, Spain, 2013/14 season (n = 1,170)

	Cases; controls	Crude prevented fraction % (95% CI)	p value	Adjusted prevented fraction % (95% CI)[a]	p value
All influenza cases vs controls					
Influenza A(H3N2) cases vs controls					
All swabbed patients	349; 581				
Previous MA-ILI related to A(H3N2)[b]	7; 22	48 (−23 to 78)	0.137	65 (13 to 86)	0.024
Vaccinated	103; 198	19 (−8 to 39)	0.150	20 (−15 to 45)	0.228
Age < 65 years	226; 377				
Previous MA-ILI related to A(H3N2)[b]	5; 19	57 (−16 to 84)	0.095	70 (15 to 90)	0.024
Vaccinated	28; 61	27 (−19 to 55)	0.205	9 (−59 to 48)	0.727
Age ≥ 65 years	123; 204				
Previous MA-ILI related to A(H3N2)[b]	2; 3	−11 (−573 to 82)	0.911	29 (−400 to 90)	0.731
Vaccinated	75; 137	24 (−22 to 52)	0.257	24 (−24 to 53)	0.269
Primary healthcare patients[c]	205; 182				
Previous MA-ILI related to A(H3N2)[b]	6; 14	64 (7 to 86)	0.042	64 (−1 to 87)	0.051
Vaccinated	34; 27	−14 (−99 to 34)	0.637	0 (−94 to 48)	0.995
Hospitalised patients[c]	144; 400				
Previous MA-ILI related to A(H3N2)[b]	1; 8	66 (−176 to 96)	0.315	65 (−198 to 96)	0.334
Vaccinated	69; 172	−22 (−79 to 17)	0.309	28 (−14 to 54)	0.159

CI: confidence interval; MA-ILI: medically attended influenza-like illness.

a Results obtained from a logistic regression model adjusted for sex, age group (<5, 5–14, 15–44, 45–64 and ≥65 years), month of sample collection, major chronic conditions, healthcare setting (primary healthcare and hospital), medically-attended influenza-like illness virologically or epidemiologically related to the analysed influenza virus in the previous five seasons, and 2013/14 influenza vaccine.

b Medically-attended influenza-like illness virologically or epidemiologically related to influenza in the previous five seasons.

c Patients attended in primary healthcare and referred to hospital were included in both subanalyses.

received the 2013/14 seasonal vaccine, vs 198 (34%) of the 581 controls (p < 0.001) (Table 2).

The proportion of patients vaccinated in the current season was lower among those with previous MA-ILI than in those without a history of MA-ILI (17% vs 31%; p = 0.001). While previous MA-ILI was more frequent in patients between five and 44 years-old, in those without major chronic conditions and in those attended in primary healthcare, vaccination in the current season was more frequent in patients 65 years and older, in those with major chronic conditions and in patients attended in hospitals (Table 3).

In the analysis adjusted by influenza vaccination and other potential confounders, previous MA-ILI related to any influenza virus showed a 30% (95% CI: −7 to 54) protection against a new episode of laboratory-confirmed influenza, although this did not reach statistical significance. The overall adjusted estimate of the influenza VE was 31% (95% CI: 5–50). The estimate of the VE was 21% (95% CI: −45 to 57) in the analysis restricted to primary healthcare patients, and 35% (95% CI: 4–56) in hospitalised patients (Table 4).

In the comparison between influenza A(H1N1)pdm09 cases and controls, previous episodes of MA-ILI related to A(H1N1)pdm09 virus were 63% (95% CI: 16–84) protective against laboratory-confirmed A(H1N1)pdm09 influenza, even though the natural exposure had in most cases occurred more than two years before. The protective effect was similar in the analysis restricted to patients attended in primary healthcare and to those younger than 65 years. One case without comorbidity that had been confirmed with influenza A(H1N1)pdm09 in the 2009/10 season was again confirmed with influenza from the same virus subtype in the 2013/14 season. In the same models, the overall adjusted VE was

45% (95% CI: 12–65), and similar estimates of the VE were found in the analysis stratified by age group or healthcare setting (Table 4).

The comparison of influenza A(H3N2) cases and controls showed that previous episodes of MA-ILI related to A(H3N2) virus were 65% (95% CI: 13–86) protective against laboratory-confirmed influenza A(H3N2) and 70% (95% CI: 15–90) protective in the analysis restricted to patients younger than 65 years. On the other hand, the overall adjusted VE was 20% (95% CI: −15 to 45), and other estimates of the VE for subgroups of patients were also low and not statistically significant (Table 4). In most cases, the natural exposure had occurred more than a year before.

Minor differences in the VE estimates were seen in the sensitivity analysis performed after excluding the variable of previous MA-ILI from the model. The overall estimate of the influenza VE was 31% (95% CI: 5–50) against any laboratory-confirmed influenza, 45% (95% CI: 12–65) against influenza A(H1N1)pdm09, and 20% (95% CI: −16 to 44) in preventing influenza A(H3N2) cases. The same estimates after excluding from the analysis the patients with previous MA-ILI that was probably related to influenza were 33% (95% CI: 6–52), 48% (95% CI: 27–68) and 19% (95% CI: −18 to 44), respectively.

The sensitivity analysis excluding vaccinated patients also showed similar protective effects of previous episodes of MA-ILI probably related to influenza: 32% (95% CI: −8 to 58) for any influenza, 77% (95% CI: 40–91) for influenza A(H1N1)pdm09 and 63% (95% CI: −3 to 86) for influenza A(H3N2).

Discussion

In this study we estimated at the same time the protection conferred by previous episodes of MA-ILI and by influenza vaccination in a season with intense co-circulation of influenza A(H1N1)pdm09 and A(H3N2). People with a history of MA-ILI attributable to a specific virus subtype in the previous five seasons had a markedly lower risk of disease due to the same subtype. The trivalent inactivated vaccine showed moderate VE in preventing laboratory-confirmed influenza A(H1N1)pdm09 and low effectiveness against influenza A(H3N2). Even though the natural exposure had in most cases occurred more than a year before, it conferred the same or greater protection against the same virus subtype than the vaccine administered a few months previously. In accordance with McLean et al., five previous seasons were considered for natural protection [14] because the protection following natural exposure is stronger and longer-lasting and covers a greater variety of viral strains, which has been related to activation of a more complete immune response that includes mechanisms of cellular immunity [4,15,16]. No major shift had affected the circulating viruses involved in the analysis.

It was possible to define the virus that most probably caused the cases of MA-ILI in the previous five seasons thanks to the fact that one virus clearly predominated in Navarre in each of those five seasons. In seasons with simultaneous co-circulation of various viruses, it would be more difficult to attribute the cases of MA-ILI with certainty to a specific virus subtype.

Since the appearance of the A(H1N1)pdm09 virus in 2009, the circulating strains of this virus have been well matched with the vaccine strain A/California/7/2009(H1N1) [2], which could explain the protection of the vaccine and of influenza episodes in previous seasons.

Although the influenza A(H3N2) virus strains which circulated in the 2013/14 season had a good genetic match with the vaccine strain [2], the observed VE was low. However, this virus showed a high cross protection with the strains circulating in the previous seasons 2008/09 and 2011/12. This difference between natural and vaccine protection with matched strains should encourage the exploration of alternative ways of obtaining better vaccines against influenza.

In the study population, natural and vaccine immunity were distributed in a complementary manner. A history of MA-ILI was more frequent in persons aged five to 44 years, which explains why this protective mechanism was more important in population groups that do not normally get vaccinated against influenza.

Although previous diagnosis of disease from the same virus subtype was associated with high protection, previous MA-ILI related to any influenza virus but not restricted to the same virus subtype conferred only low protection against a new episode of laboratory-confirmed influenza. This is mainly explained by the likelihood of infection by a different type or subtype of influenza virus. Therefore, in persons with risk factors for influenza complications, having had the disease in previous seasons should not be a reason not to get vaccinated. While natural exposure protects specifically against the virus subtype to which one has been exposed, the protection conferred by the trivalent vaccine, although less strong, covers all three virus types/subtypes simultaneously.

Previous episodes of influenza are not usually taken into account as potential confounding factors in studies evaluating influenza VE. To our knowledge, only McLean et al. had adjusted for influenza diagnoses in the prior five seasons in the analysis of influenza vaccine effectiveness [14]. In this and in our study, the estimated VE did not change regardless of whether the models included this history, suggesting that this variable does not act as a confounding factor that needs to be controlled.

Although our end-of-season estimate of VE was additionally adjusted for previous episodes of influenza,

it was consistent with mid-season estimates obtained in Navarre and Spain for this same season [17,18], and with estimates obtained at the end of the season in a European multicentre study and in Greece [19,20]; it was less consistent, however, with estimates from other countries with different distribution of virus types, subtypes and strains detected in the same season [21-23].

Some limitations should be considered in interpreting the results of this study. Previous episodes of MA-ILI reflect the history of exposures to the influenza virus from the healthcare perspective and may be considered a proxy for natural immunity. Some 10% of subjects included in the study had a history of MA-ILI in the previous five seasons. However, the proportion of the population with natural immunity against influenza could be considerably higher, since it is estimated that 30–50% of influenza infections are asymptomatic [24]. In one study conducted in Navarre, 36% of symptomatic cases had not sought medical care [25]. It should also be added that there is possible immunity from exposures occurring more than five years previously. This misclassification in the previous influenza infection is probably non-differential and would bias the estimates towards the null effect. In the absence of this bias, the protection due to previous episodes would have been higher.

Of the patients with a previous episode of MA-ILI, only 17% had a laboratory-confirmed diagnosis, while the rest met only one epidemiological criterion for the disease. Based on the percentage of swabs confirmed for influenza in each season (Table 1), we estimate that this criterion ensures the correct classification of 70% of cases with a history of influenza A(H3N2), of over 50% of cases with a history of influenza A(H1N1) pdm09, and of 64% of cases with a history of any influenza in the previous five years. Accordingly, we cannot totally rule out the possibility of incorrect classification that arose from considering cases that could have been due to another cause such as previous episodes related to a specific virus. If we had had laboratory confirmation of all the cases of influenza in previous years, the protective effect of this history would probably have been greater.

The results presented had limited statistical power for some analyses, mainly because of the low numbers of cases and controls with previous MA-ILI included in the study. Laboratory-confirmed cases were compared with controls recruited in the same healthcare settings before either patient or physician knew the laboratory result, a fact that reduced selection bias [26].

This study included MA-ILI patients recruited from the same population in both primary healthcare centres and hospitals. The healthcare setting could have acted as a confounding factor, therefore the analyses were adjusted for this variable. The possibility that the healthcare setting might have modified the effect or biased the results can be ruled out given the consistency of the estimates obtained in these two patient groups and in the joint analysis. The joint analysis achieved representation of the whole spectrum of patients with influenza in the population.

Conclusion

Our results suggest low to moderate influenza VE in the 2013/14 season, which prevented almost a third of the influenza cases and hospitalisations in the vaccinated population; while not entirely satisfactory, this result is important in terms of individual and public health. Previous influenza episodes were highly effective against new influenza illness by the same virus subtype, and this effect seemed to persist over various seasons, which may point to possible avenues of obtaining better vaccines against influenza. In any case, annual influenza vaccination remains the principal preventive option in persons at high risk of developing complications if they contract influenza.

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Conflict of interest

None declared.

Authors' contributions

J Castilla, I Martínez-Baz and M Guevara designed the study, coordinated the activities, and undertook the statistical analysis. A Navascués, M Fernández-Alonso, G Reina and C Ezpeleta were responsible of the virological analysis and the interpretation of laboratory results. M García Cenoz, N Álvarez, F Irisarri and I Casado participated in the data collection. E Albéniz coordinated the activities in primary health care. F Pozo was responsible for the virus characterizations. J Castilla, M Guevara and I Martínez-Baz wrote the draft manuscript, and all authors revised and approved the final version.

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