Effectiveness of influenza vaccination programme in preventing hospital admissions, Valencia, 2014/15 early results

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Preliminary results for the 2014/15 season indicate low to null effect of vaccination against influenza A(H3N2)-related disease. As of week 5 2015, there have been 1,136 hospital admissions, 210 were due to influenza and 98% of subtype A strains were H3. Adjusted influenza vaccine effectiveness was 33% (range: 6–53%) overall and 40% (range: 13% to 59%) in those 65 years and older. Vaccination reduced by 44% (28–68%) the probability of admission with influenza.

Introduction

The 2014/15 influenza season in the northern hemisphere is characterised by the circulation of A(H3N2) viruses belonging to clade 3C.2a and 3C.3a, distinct from the A/Texas/50/2012(H3N2)-like (clade 3C.1) reference strain used in the 2014/15 northern hemisphere vaccine [1]. Preliminary influenza vaccine effectiveness (IVE) estimates from Canada [2,3] and Europe [4], report a null effect of the current vaccine in preventing laboratory-confirmed influenza A(H3N2) with 3.4% (95% confidence interval: (–44.8 to 35.5) against medically attended acute respiratory infection (ARI) and –16.8% (–48.9 to 8.3) against hospital admissions. Early estimates from the United States (US) [5], reported a low effect of 23% (8–36%) against medically attended ARI associated with laboratory-confirmed influenza.

An active annual surveillance scheme in the Valencia Region in Spain monitors IVE in preventing laboratory-confirmed influenza requiring hospitalisation [6]. In the current season, a split trivalent vaccine (Vaxigrip; SANOFI PASTEUR MSD, S.A. Madrid, Spain) was acquired by public tender and offered free of charge to non-institutionalised people targeted for influenza vaccination because of age or the presence of comorbidity [7].

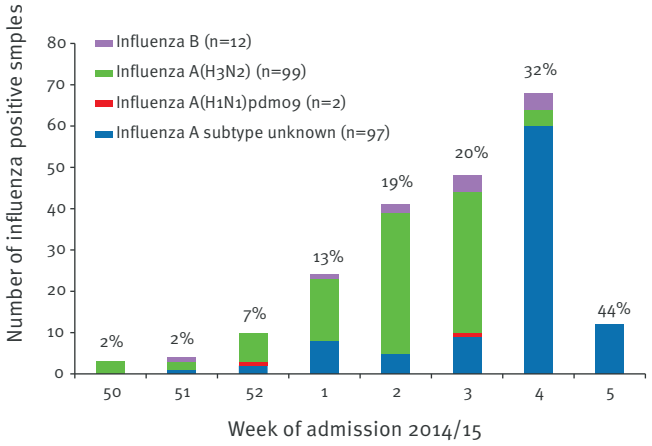
We report 2014/15 influenza IVE in preventing laboratory-confirmed influenza admissions in patients admitted during the first eight weeks of the 2014/15 influenza season, from 7 December 2014 to 25 January 2015.

Methods

We performed a test-negative study in 10 hospitals that provide healthcare to 48% of the 4,937,044 inhabitants of Valencia. The influenza season began in week 50 2014 (Figure 1), as defined by two or more positive

Figure 1

Hospital admissions with laboratory-confirmed influenza per week, Valencia, 7 December 2014–28 January 2015 (n = 210)



Numbers on top of bars: percentage of samples positive for influenza.

Source: Valencia Hospital Network for the Study of Influenza and Other Respiratory Viruses (VAHNSI).

influenza hospitalisations identified in two consecutive weeks.

Study procedures have been published [6]. Study staff screened emergency admissions for eligible subjects. Patients were included after written consent if they reported symptoms of influenza-like illness (ILI) [8] within seven days of admission. We collected a combined nasopharyngeal and pharyngeal flocked swab and sociodemographic and clinical information. A patient was considered immunised if they had received influenza vaccine more than 14 days before the onset of ILI (as recorded by the Vaccine Information System or by recall).

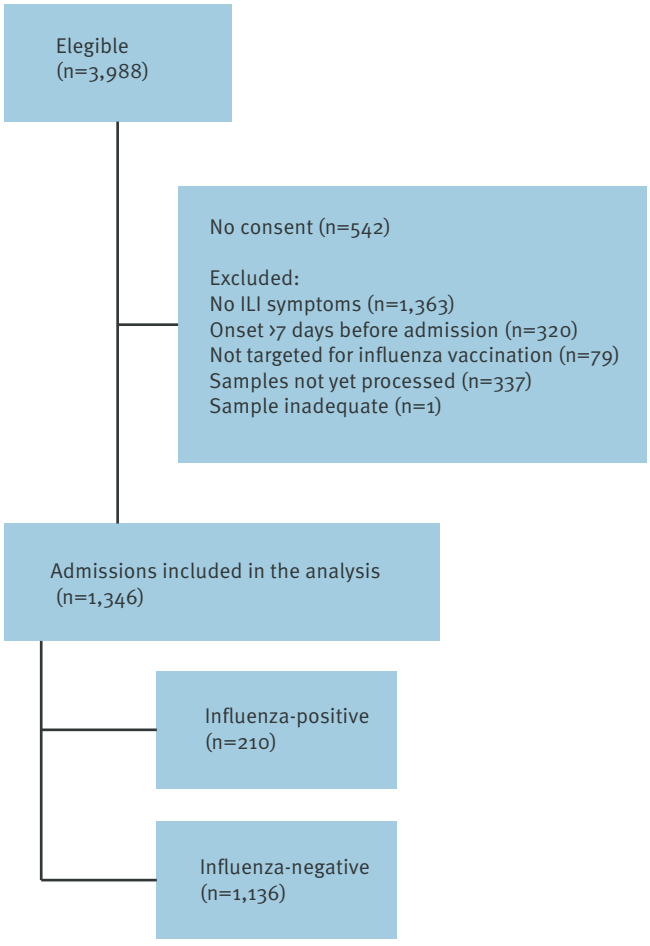
Laboratory confirmation was by semiquantitative reverse-transcription polymerase chain reaction. The specimens were tested in a centralised virology laboratory at Fundación para el Fomento de la Investigación Sanitaria y Biomédica (the Foundation for the Promotion of Health and Biomedical Research; FISABIO) following the World Health Organization (WHO) protocol [9].

Influenza-positive admissions were compared (vaccination odds ratio (OR)) with influenza-negative admissions [10,11]. Adjusted IVE was defined as 100 x (1 - adjusted OR). We defined two groups for IVE estimation: (i) all subjects 18 years and older targeted for vaccination, and (ii) subjects aged 65 and older. Other subgroups were not considered to avoid a sparse-numbers bias [2,12]. The sample size sufficient to provide 80% statistical power to detect an IVE of at least 50%, for a vaccine coverage of 50 to 60%, with a delta of 10%, was 130 to 150 influenza cases.

The adjusted OR were obtained by logistic regression. Previous knowledge and directed acyclic graphs (DAG) [13,14] were used to define the variables finally used to improve comparability and exchangeability between vaccinated and non-vaccinated subjects and to clarify the minimum set of variables to be included in the regression logistics models and in the inverse probability-weighted regression adjustment models. The roles of 'previous vaccination' as an instrumental variable highly correlated with current vaccination and 'time to swab', which cannot be considered a confounder but is clearly related to outcome, were made explicit with the use of DAG. We assessed departure from linearity in categorical ordered variables, interaction between potential confounders and vaccination, and clustering by enrolment site or epidemiological week.

Figure 2

Flowchart showing exclusion criteria, study of mid-season influenza vaccine effectiveness in preventing hospital admissions related to influenza, Valencia, 7 December 2014–28 January 2015 (n = 3,988)



ILI: influenza-like illness.

Source: Valencia Hospital Network for the Study of Influenza.

Table 1

Characteristics of included hospital admissions, Valencia, 7 December 2014–28 January 2015 (n = 1,346)

	Test result status					Vaccination status			
	Influenza-positive		Influenza-negative		p value	Vaccinated			p value
	n	%	n	%		n	Total	%	
Overall	210	100	1,136	100		832	1,346	61.8	
Sex					0.275				0.002
Male	112	53.3	652	57.4		499	764	65.3	
Female	98	46.7	484	42.6		333	582	57.2	
Age group (years)					0.824				0
18–64	36	17.1	202	17.8		85	238	35.7	
≥ 65	174	82.9	934	82.2		747	1,108	67.4	
Risk factors (number)					0.034				0.001
0	28	13.3	99	8.7		63	127	49.6	
1	77	36.7	376	33.1		269	453	59.4	
≥ 2	105	50.0	661	58.2		500	766	65.3	
Admission in the past 12 months					0.029				0.015
No	142	67.6	677	59.6		485	819	59.2	
Yes	68	32.4	459	40.4		347	527	65.8	
Outpatient contacts					0.742				0
0	39	18.6	227	20		132	266	49.6	
1	37	17.6	216	19		148	253	58.5	
2	54	25.7	254	22.4		198	308	64.3	
≥ 3	80	38.1	439	38.6		354	519	68.2	
Smoking habits					0.106				0
Never	109	51.9	501	44.1		379	610	62.1	
Ex-smoker	71	33.8	458	40.3		360	529	68.1	
Current	30	14.3	177	15.6		93	207	44.9	
Days from onset to swab					0.805				0.632
≤ 2	53	25.2	275	24.2		203	328	61.9	
3–4	86	41.0	493	43.4		367	579	63.4	
5–7	65	31.0	326	28.7		235	391	60.1	
>7	6	2.9	42	3.7		27	48	56.3	
Influenza test result									0.552
Negative			1,136	100.0		722	1,136	63.6	
A(H1N1)pdm09	2	1.0				1	2	50.0	
A(H3N2)	99	47.1				47	99	47.5	
A subtype pending	97	46.2				56	97	57.7	
B	12	5.7				6	12	50	
Vaccinated 2013/14					0.15				0
No	93	44.3	443	39		98	536	18.3	
Yes	117	55.7	693	61		734	810	90.6	
Vaccinated 2012/13					0.369				0
No	95	45.2	476	41.9		148	571	25.9	
Yes	115	54.8	660	58.1		684	775	88.3	

Source: Valencia Hospital Network for the Study of Influenza.

Table 2

Influenza vaccine effectiveness, preliminary results, Valencia, 7 December 2014–28 January 2015 (n = 1,346)

	Influenza-positive			Influenza-negative			OR (95% CI)	Adjusted[a] OR (95% CI)	AVE[b] (95% CI)
	Vaccinated	Total sample	Vaccinated	Vaccinated	Total sample	Vaccinated			
	n	n	%	n	n	%			
Overall	110	210	52.4	722	1,136	63.6	0.63 (0.47–0.85)	0.67 (0.47–0.94)	44 (28–60)
≥ 65	96	174	55.2	651	934	69.7	0.53 (0.38–0.74)	0.60 (0.41–0.87)	48 (32–64)
Swab (≤ 4 days)									
Overall	78	139	56.1	492	768	64.1	0.72 (0.50–1.04)	0.79 (0.51–1.21)	32 (11–53)
≥ 65	68	115	59.1	448	642	69.8	0.62 (0.41–0.94)	0.73 (0.46–1.18)	32 (9–55)
VIS									
Overall	108	185	58.4	720	987	73.0	0.52 (0.38–0.72)	0.54 (0.37–0.78)	49 (34–63)
≥ 65	95	157	60.5	649	838	77.5	0.44 (0.31–0.64)	0.49 (0.33–0.74)	50 (35–66)
VIS and Swab[c]									
Overall	76	120	63.3	490	677	72.4	0.66 (0.44–0.99)	0.67 (0.41–1.09)	37 (17–57)
≥ 65	67	103	65.1	446	581	76.8	0.56 (0.36–0.88)	0.62 (0.36–1.05)	37 (15–59)

AVE: average vaccination effect; CI: confidence interval; OR: odds ratio; VIS: vaccine Information system.

[a] Adjusted by indicator variables: sex, age in deciles, smoking (never, ex-smoker, current smoker), number of outpatient contacts in the past three months (0, 1, 2, > 2), number of comorbidities (0, 1, 2, ≥ 2), hospital admissions in the past 12 months (yes, no), recruitment hospital, epidemiological week of admission, days from onset of symptoms to swab (≤ 2, 3–4, 5–7, > 7).

[b] Average vaccination effect (percentage of reduction) on the probability of admission with confirmed influenza. Admission with influenza was conditioned on age in deciles, smoking (never, ex-smoker, current smoker), number of outpatient contacts in the past three months (0, 1, 2, > 2), number of comorbidities (0, 1, 2, ≥ 2), hospital admissions in the past 12 months (yes, no), recruitment hospital, epidemiological week of admission, days from onset of symptoms to swab (≤ 2, 3–4, 5–7, > 7). Vaccination was conditioned on the same indicator variables, but days to swab was omitted and record of influenza vaccination in 2012 and 2013 were added to the model.

[c] Patients included are those with records of any vaccination in the VIS and swabbed ≤ 4 days after symptoms onset.

Source: Valencia Hospital Network for the Study of Influenza.

We used inverse probability-weighted regression adjustment to estimate the vaccination average effect from observed data [15,16] after conditioning influenza admissions on indicator variables: age in deciles, epidemiological week, number of comorbidities, smoking habits, hospital admission in the last 12 months, number of outpatient contacts in the last three months, time to swab, and recruitment hospital. We conditioned vaccination on the same covariates, excluding time to swab and adding influenza vaccination in the past two seasons.

Sensitivity analyses were performed according to time to swab and vaccination ascertainment in the vaccine information system. All probabilities were two-tailed; $p < 0.05$ was considered significant. Analyses were performed with Stata 13.1 (StataCorp, College Station, TX).

The Ethics Research Committee of the Dirección General de Salud Pública-Centro Superior de Investigación en Salud Pública (DGSP-CSISP) approved the protocol of the study.

Results

We enrolled 1,136 hospital admissions, 210 with influenza (Figure 2), 196 of them influenza A. Of the 101 influenza A subtyped strains, 99 (98%) were H3. Of all admissions, 1,108 (82%) were patients older than 65 years (Table 1). Of the 210 influenza-positive patients, 110 (52%) were vaccinated compared with 722 (64%) of 1,136 influenza-negative patients (Table 2).

Adjusted IVE was 33% (6–53%) overall and 40% (13–59%) in those 65 years and older (Table 2). The probability of influenza-related admission in vaccinated individuals was 13% (10–15%) compared with 22% (18–27%) in those unvaccinated (data not shown). Vaccination reduced by 44% (28–68%) the overall probability of hospital admission with influenza (Table 2). These results were not altered in the sensitivity analysis (Table 2).

Discussion

Our estimate suggests that the 2014/15 influenza vaccine was moderately effective in preventing hospital admissions related to influenza in a season in which

most influenza A(H3N2) viruses were different from the component in the 2014/15 influenza vaccine [17]. We can only provide information regarding the genetic characteristics of strains analysed at the Centro Nacional de Microbiología, Instituto de Salud Carlos III in Madrid [17]. According to their data, 67% of A(H3N2) clades could be considered antigenically and genetically different from the vaccine strain. We cannot make inferences regarding the impact on IVE of the type of vaccine used in Valencia as only one brand of vaccine was used throughout the region (99% of doses according to the vaccination registry).

Previous reviews and reports have shown that the trivalent inactivated vaccine can confer substantial protection against mismatched influenza A [18-20]. Unfortunately, data from mismatched seasons on IVE in people 65 years and older are scarce [21].

There can be considerable variation in reported IVE estimates due to differences in strain circulation among countries, strain proportion within one region, the vaccines used, age-specific vaccine coverage, the population studied, season definition, case definition, ascertainment of vaccination status, differences in the period of surveillance, the variables included or omitted in the statistical model, how they are modelled, and measured outcome (admission, outpatient contact or infection) [11]. A major caveat are sparse numbers. The absence of statistical significance should be expected in studies with low vaccine coverage, IVE or a limited sample size [2,12], as reflected in our sensitivity analysis (Table 2).

Influenza VE estimates generated from surveillance data using the test-negative design have already been presented at the WHO's annual strain selection meeting [11] as a way to improve the vaccine composition. However, variation in the estimates may undermine their credibility and usefulness, particularly early in the season. It is important to focus on sufficient sample size, robustness of the design, representativeness of the population, and validity of adjustment to inform vaccine reformulation and vaccination policies based on epidemiological data.

Our results support the substantial benefit of vaccination in preventing hospital admissions with laboratory-confirmed influenza in the first weeks of the 2014/15 season in Valencia.

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Conflict of interest

The study was funded by a contract between FISABIO and Sanofi-Pasteur. SanofiPasteur did not participate in the design, conduct of the study, analysis or decision to publish the study.

Authors' contributions

JPB: study coordinator, data analysis and draft of the manuscript; AMI: data management and data analysis; XLL: molecular analysis; MTG, ABV, MCF, ECF, CCM, RLR, JMM, MOR, GSC, JTH and VGG: investigators. Critical review and approval of the manuscript: all

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