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# Does vaccination date affect influenza vaccine effectiveness? Valencia Hospital Network, a hospital-based test-negative study in three consecutive influenza seasons

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## INTRODUCTION

Concerns have been raised regarding a progressive lesser effectiveness as the time since vaccination with the seasonal influenza vaccine increases. This has been attributed to a too early waning protective effect.

We propose to analyse the behaviour of the influenza vaccine effectiveness (IVE) during three consecutive seasons with respect to vaccine administration date as the best unbiased approximation to time elapsed since vaccination to being an admission with confirmed influenza.

## METHODS

### Population

Subjects included in the study were all immunized admissions with a written record of vaccination date in three consecutive seasons, belonging to target groups for vaccination, 18 or more years old, non-institutionalized and residents for at least 6 months in each hospitals' catchment area. We considered as an immunized patient an individual whose vaccine administration was 14 or more days before the onset of symptoms.

### Statistical analysis

For each season, immunized individuals whose vaccination status has been confirmed with the official vaccine registry were split in tertiles according to their date of vaccination.

a) A multinomial logistic regression was used to explore if variables such as age, number of chronic conditions, smoking habits or socioeconomic occupational class were related with vaccination date.

b) We estimated IVE adjusted by age, sex, smoking habits, number of chronic conditions, socioeconomic class (according to occupation), time from symptoms onset to swab, hospitalized last 12 months (yes/no), recruitment hospital and epidemiological week.

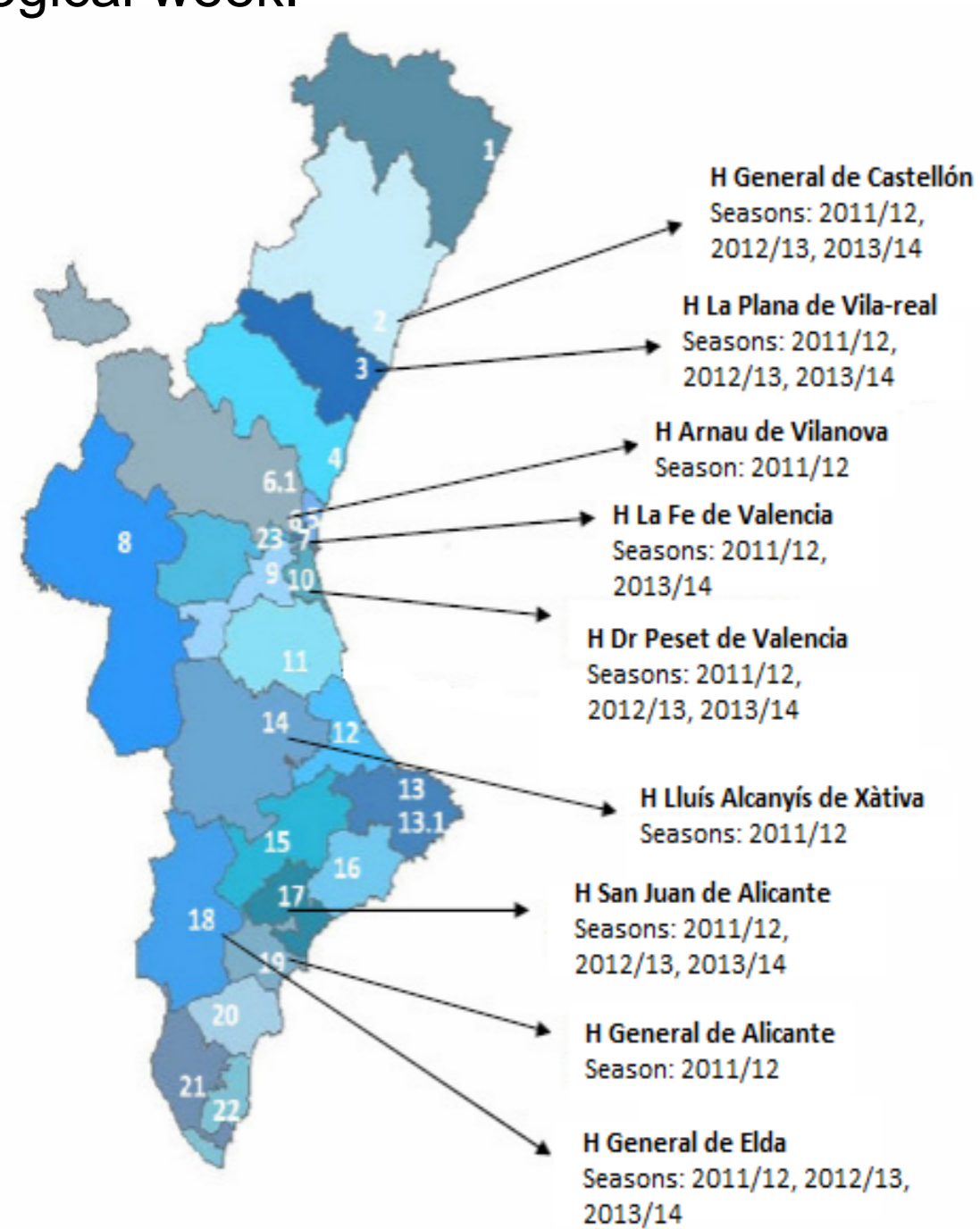


Fig 1. Population

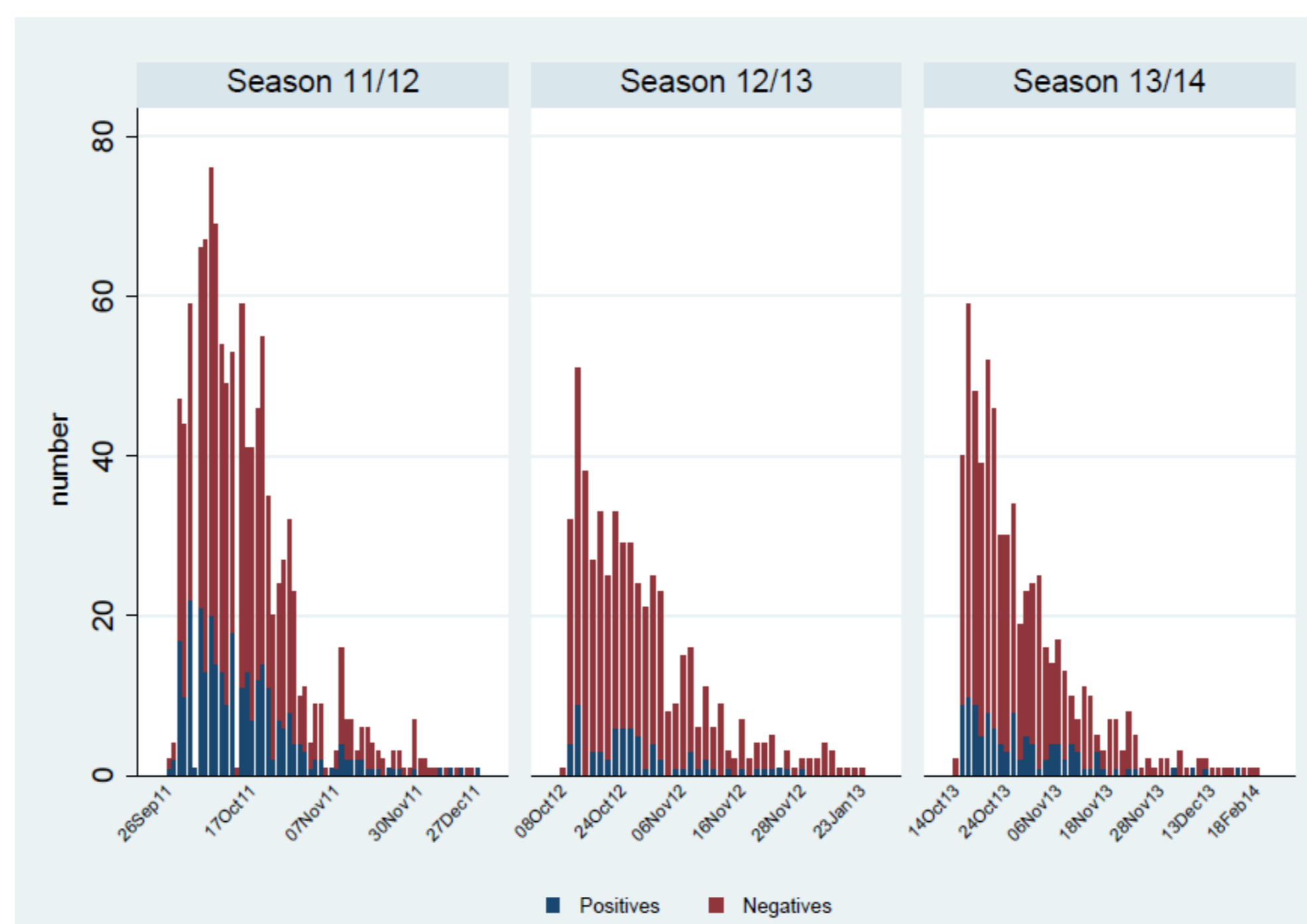


Fig 3. Vaccination date according to RT/PCR result (influenza positive or negative). Vaccinated subjects, 18 years or older, belonging to target groups in three consecutive seasons.

	Season 11/12				Season 12/13				Season 13/14			
	N	Negatives %	Positives %	OR <sup>a</sup> IC 95%	N	Negatives %	Positives %	OR <sup>a</sup> IC 95%	N	Negatives %	Positives %	OR <sup>a</sup> IC 95%
DOV (tertiles) <sup>b</sup>												
1	38	41	1		36	28	1		38	39	1	
2	31	28	0.8 [0.6, 1.1]		35	44	1.6 [0.9, 3]		29	26	0.9 [0.5, 1.5]	
3	31	31	0.9 [0.6, 1.2]		29	28	1.2 [0.6, 2.4]		33	35	1 [0.6, 1.7]	
Age group (years)												
>=18 - <50	2	0	1		1	3	1		3	2	1	
>50 - <65	11	7	2.8 [0.3, 22.5]		10	10	0.5 [0.1, 2.7]		10	24	3.8 [0.8, 17.7]	
>65 - <75	20	18	3.7 [0.5, 28.9]		22	23	0.5 [0.9, 2.6]		24	27	1.9 [0.4, 8.5]	
>75 - <85	39	50	5.4 [0.7, 42.1]		39	46	0.5 [0.1, 2.7]		35	34	1.5 [0.3, 7]	
>85	28	25	3.7 [0.5, 28.6]		28	18	0.3 [0.0, 1.6]		28	13	0.8 [0.2, 3.7]	
Sex												
Male	59	62	1		61	60	1		59	60	1	
Female	41	38	0.9 [0.7, 1.1]		39	40	1 [0.6, 1.8]		41	40	0.9 [0.6, 1.4]	
Smoking habits												
Never smoker	45	46	1		44	49	1		44	38	1	
Current smoker	6	11	1.6 [1.2, 6]		11	13	1 [0.5, 2.3]		10	18	2.1 [1.1, 4]	
Past smoker	49	43	0.8 [0.6, 1.1]		45	38	0.8 [0.4, 1.3]		46	44	1.1 [0.7, 1.8]	
Number of chronic conditions												
None	9	14	1		5	12	1		6	8	1	
One	29	33	0.7 [0.4, 1.1]		27	25	0.4 [0.2, 1.1]		28	33	0.9 [0.4, 2.2]	
More than one	62	53	0.5 [0.3, 0.8]		68	63	0.4 [0.2, 1]		66	59	0.7 [0.3, 1.6]	
Social class (occupation) <sup>c</sup>												
Professional	16	12	1		12	12	1		18	21	1	
Skilled	26	26	1.3 [0.8, 2]		44	35	0.8 [0.3, 1.9]		38	37	0.8 [0.5, 1.4]	
Unskilled	58	62	1.4 [0.9, 2.1]		44	53	1.2 [0.5, 2.8]		44	42	0.8 [0.5, 1.4]	
Hospitalized in the last 12 months												
No	61	71	1		60	69	1		59	73	1	
Yes	39	29	0.6 [0.5, 0.8]		40	31	0.7 [0.4, 1.2]		41	27	0.5 [0.3, 0.8]	
Days from onset to swab												
1 to 2	19	13	1		24	25	1		21	25	1	
3 to 4	33	44	1.9 [1.2, 2.8]		46	50	1.1 [0.4, 2]		46	53	0.9 [0.6, 1.6]	
5 to 7	35	36	1.5 [1.2, 2]		30	25	0.8 [0.4, 1.7]		30	21	0.9 [0.3, 1.1]	
More than 7	13	7	0.7 [0.4, 1.3]		0	0	(**)		3	1	0.3 [0.0, 2]	
Hospital												
General Castellón	15	11	1		19	24	1		15	16	1	
La Plana	8	9	1.4 [0.8, 2.6]		23	13	0.5 [0.2, 1.1]		15	14	0.8 [0.4, 1.8]	
Dr Peset	18	13	1.1 [0.6, 1.8]		33	25	0.6 [0.3, 1.3]		21	23	1 [0.5, 2]	
San Juan	9	8	1.3 [0.7, 2.4]		11	19	1.3 [0.6, 3.0]		17	22	1.2 [0.6, 2.4]	
Elda	13	7	2 [1.2, 3.3]		14	19	1.1 [0.5, 2.4]		17	15	0.8 [0.4, 1.7]	
La Fe	7	7	1.3 [0.7, 2.5]						15	10	0.6 [0.3, 1.5]	
Arnaú de Vilanova	10	8	1.1 [0.6, 2.1]									
Lluís Alcanyis	12	11	1.4 [0.8, 2.4]									
General Alicante	8	15	2.6 [1.5, 4.5]									

DOV (days of vaccination)  
<sup>a</sup> 2011/12 season: 1/26/2011-1/30/2011, 2/27/2011-3/1/2011, 3/19/2011-3/23/2011  
 2012/13 season: 1/8/2012-1/12/2012, 2/22/2012-3/1/2012, 3/1/2012-3/13/2012  
 2013/14 season: 1/14/2013-1/18/2013, 2/22/2013-3/1/2013, 3/1/2013-1/8/2014  
<sup>b</sup> Unadjusted  
<sup>c</sup> 1/37 missing in 11/12 and 1 missing in 13/14  
 (\*\*) It can not be calculated

Table 1. Characteristics of positives and negatives for influenza in immunized patients.

## RESULTS

The 2011/12 season was dominated by influenza A (H3N2) and reached its peak in the week 7 of 2012 (Figure 2).

The 2012/13 influenza season was characterised by a first influenza B (Yamagata) wave, followed by influenza A (H1N1) and, to a lesser extent by influenza A (H3N2). In this season, the peak of influenza was located in weeks 7 and 8 of 2013 (Figure 2).

In the season 2013/14, the influenza peak was reached at week 4 2014 (Figure 2), with a first predominant wave due to influenza A (H1N1), followed by influenza A (H3N2) (Figure 2).

### Vaccination periods

In the season 2011/12 we collected the dates of vaccination in 1,127 patients, vaccinated between the 26th of September and the 27th of December of 2011. In the season 2012/13 we enrolled 520 individuals with a known date of vaccination who were vaccinated the 8th of October of 2012 to the 23rd of January of 2013. In the last season we enrolled 633 individuals with a known date of vaccination who were vaccinated the 14th of October of 2013 to the 18th of February of 2014 (Figure 3).

### Waning effect

The probability of being a case of flu did not change significantly with date of vaccination in the seasons 2012/13 and 2013/14. Conversely, in the season 2011/12 we observed a significant waning effect. Individuals who were vaccinated closer to the beginning of the influenza season had a higher protective effect.

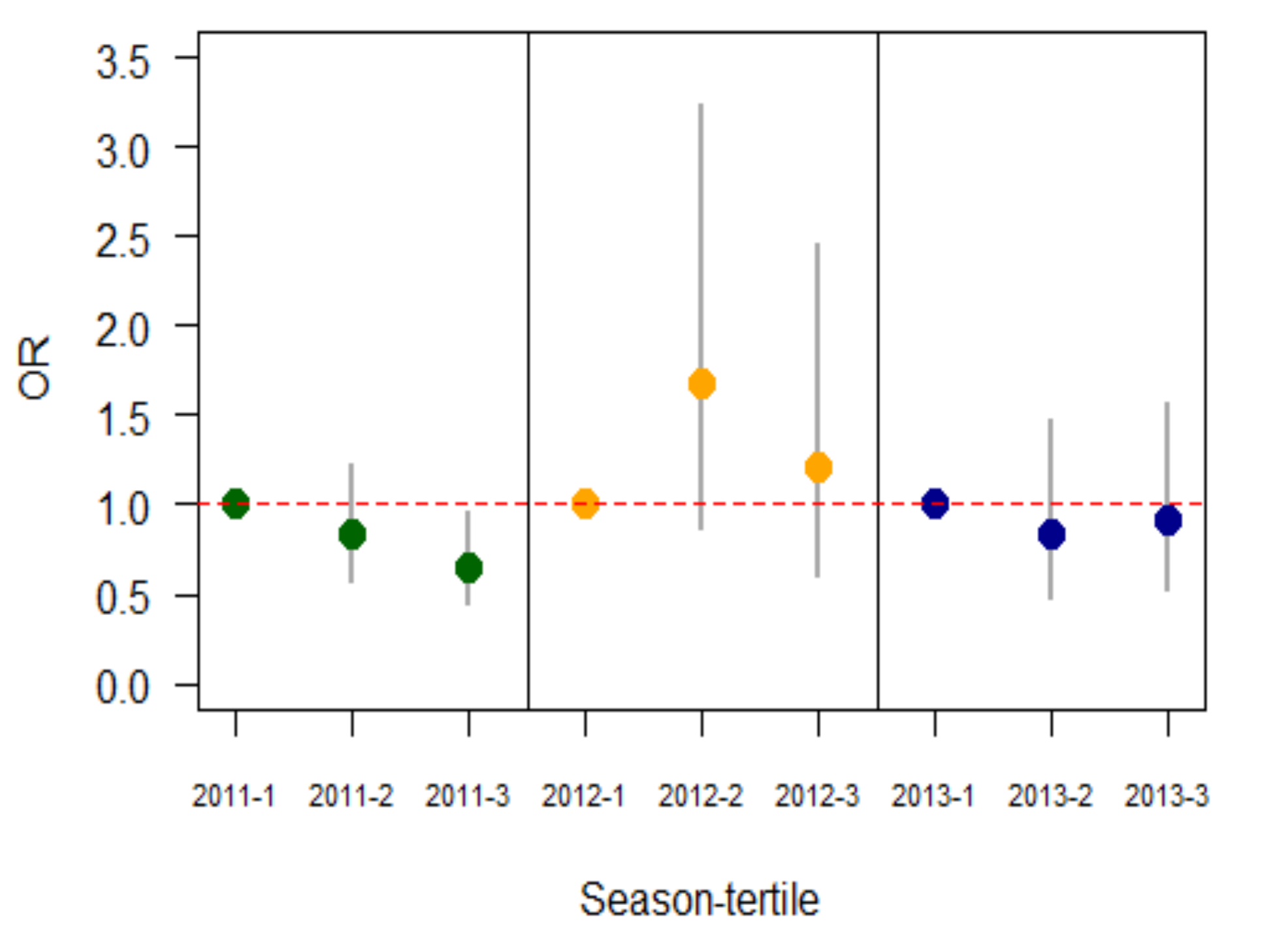


Figure 5. Vaccine effectiveness according to vaccination date (adjusted by age, sex, smoking habits, socioeconomic occupational class, number of chronic conditions, being hospitalized in the last 12 months, epidemiological week at admission, days from onset of symptoms to swab and hospital where recruited).

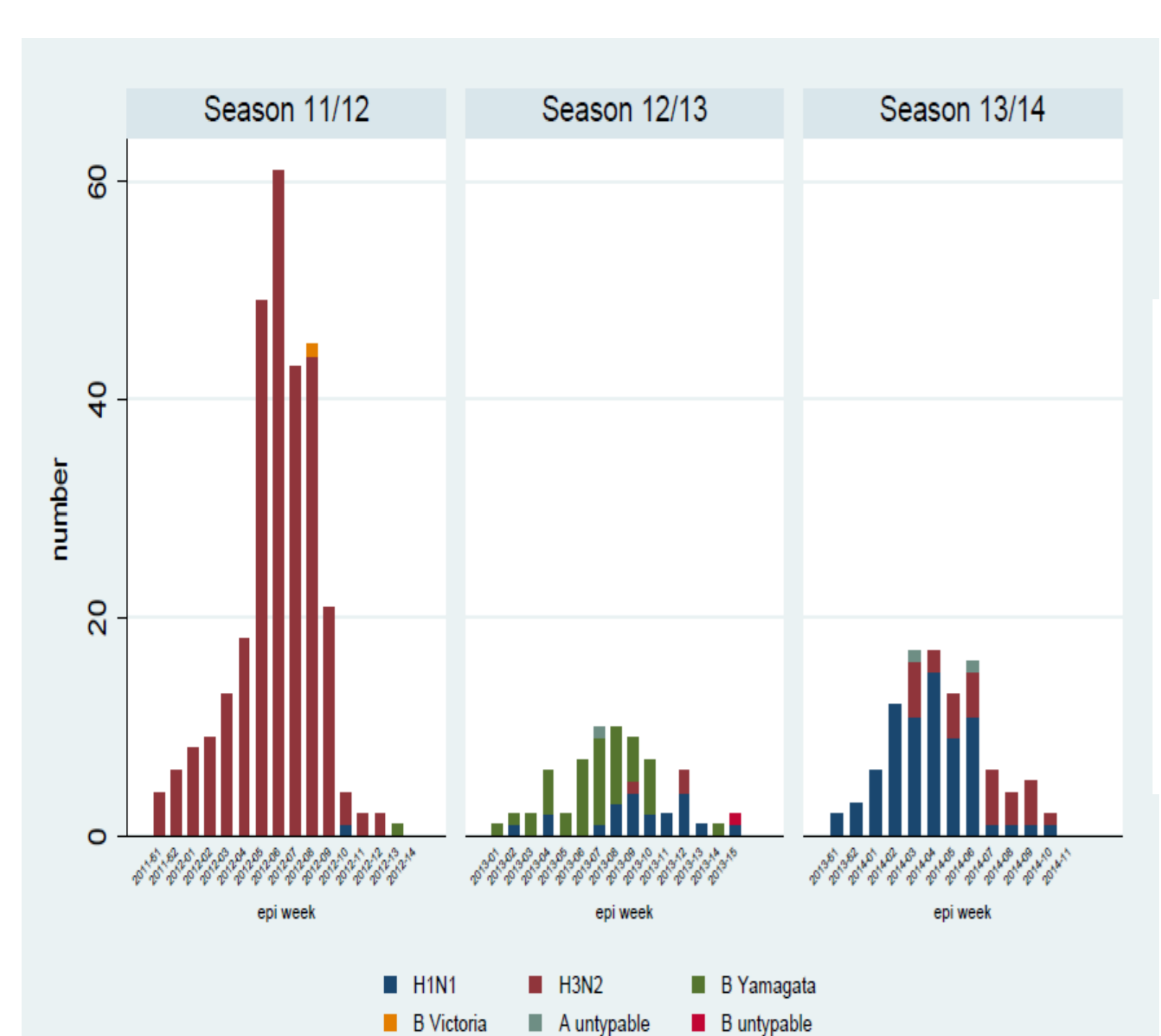


Fig 2. Admissions with influenza by subtype and epi week in three consecutive seasons

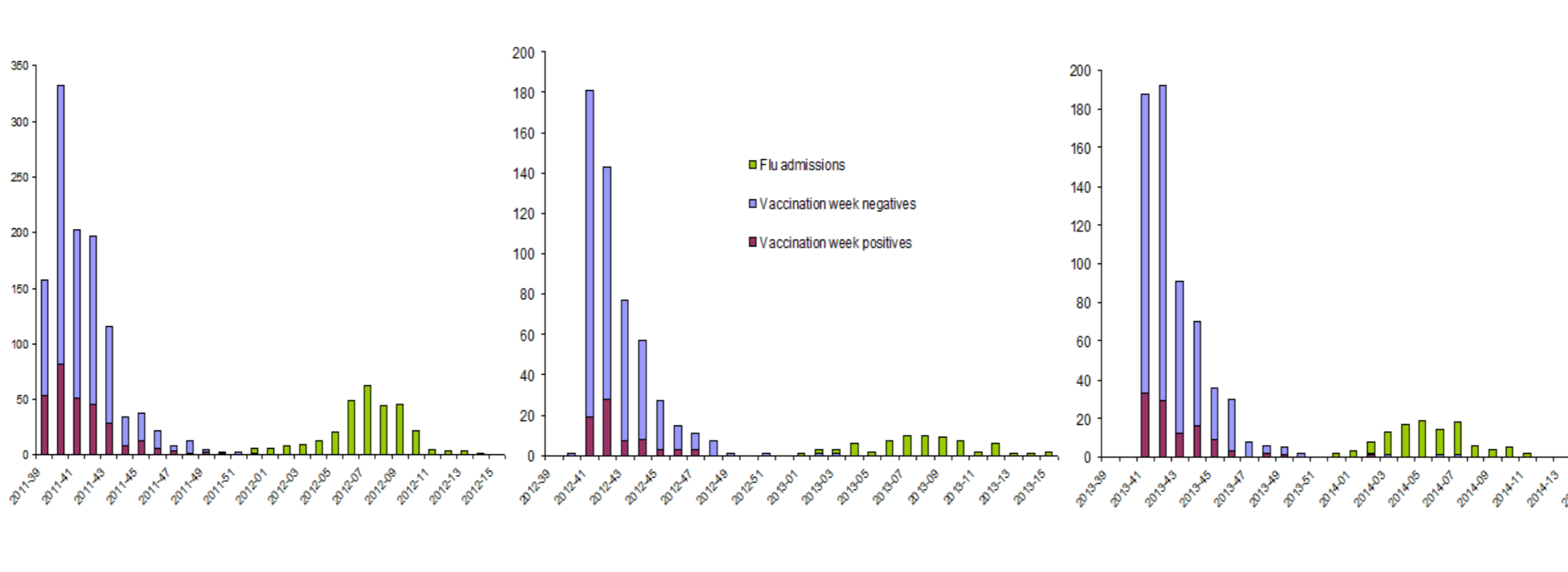


Fig 4. Vaccination of Influenza positives and negatives by week, and number of influenza admissions by week.

## CONCLUSION

The protection conferred by the vaccine did not change according to earlier or later dates of vaccination in 2012/13 and 2013/14 seasons. We observed, however, an intra-seasonal waning effect of the influenza vaccine in the 2011/12 season.

In an age stratified analysis this waning effect was only observed in those aged 70 or over, who, in fact, were the most affected by the predominant virus (H3N2) in that season.

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