Vaccine xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Intradermal and virosomal influenza vaccines for preventing influenza hospitalization in the elderly during the 2011–2012 influenza season: A comparative effectiveness study using the Valencia health care information system

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ARTICLE INFO

Article history:
Received 22 February 2014
Received in revised form 25 June 2014
Accepted 30 July 2014
Available online xxx

Keywords:
Comparative effectiveness research
Cohort studies
Aged
Hospitalization
Influenza vaccines

ABSTRACT

Background: The use of intradermal vaccination or virosomal vaccines could increase protection against influenza among the vulnerable population of older adults. Studies assessing the comparative effectiveness of these two influenza vaccine types in this age group are lacking.
Methods: We conducted a retrospective cohort study to estimate the comparative effectiveness of intradermal seasonal trivalent-influenza vaccine (TIV) delivered by a microneedle injection system and a virosomal-TIV intramuscularly delivered for prevention of influenza hospitalization in non-institutionalized adults aged ≥65 years. We obtained administrative data on immunization status and influenza hospitalization for the 2011–2012 influenza season, and used Cox regression models to assess comparative effectiveness. We estimated crude and adjusted (age, sex, comorbidity, pharmaceutical claims, recent pneumococcal vaccination and number of hospitalizations for all causes other than influenza between the previous and current influenza seasons) hazard ratios (HR).
Results: Overall, 164,021 vaccinated subjects were evaluated. There were 127 hospitalizations for influenza among 62,058 subjects, contributing 914,740 person-weeks at risk in the virosomal-TIV group, and 133 hospitalizations for influenza among 101,963 subjects, contributing 1,504,570 person-weeks at risk in the intradermal-TIV group. The crude HR of intradermal-TIV relative to virosomal-TIV was 0.64 (95% confidence interval (CI): 0.50–0.81), and the adjusted Cox estimated HR was 0.67 (95% CI: 0.52–0.85).
Conclusions: During the 2011–2012 influenza season the risk of hospitalization for influenza was reduced by 33% in non-institutionalized elderly adults who were vaccinated with intradermal-TIV compared with virosomal-TIV.

1. Introduction

Most of the serious morbidity and mortality associated with seasonal influenza occur in people 65 and older [1–6]. This increasingly large part of the population is a priority for influenza vaccination, but the current vaccine is less effective in older than younger adults [7,8]. In response to the demand for new vaccines that elicit a stronger immune response in older adults, various types of influenza trivalent inactivated vaccines (TIVs) are available [9–13]. Influenza vaccine effectiveness (VE) is a major consideration in the choice of vaccine, but the relative effectiveness of TIVs in older adults is not well established. Data from direct comparisons of TIVs are needed to inform decisions about which vaccine to use.

Abbreviations: TIV, trivalent influenza vaccine; HR, hazards ratio; CI, confidence interval; VE, vaccine effectiveness; VHA, Valencia Health Agency; HSA, hospital service area; VAHNSI, Valencia Hospital Network for the Study of Influenza and Respiratory Virus Diseases; RedMIVA, Microbiological Surveillance Network; CMBD, minimum set of basic data.

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http://dx.doi.org/10.1016/j.vaccine.2014.07.095

To be used during the 2011–2012 season, three vaccines were acquired by public tender by the Valencia Autonomous Community (Valencia region) government, and centrally distributed to be offered free of charge to groups targeted for influenza vaccination [14]: a split trivalent classical intramuscular vaccine (Gripavac®; Sanofi-Pasteur MSD, Lyon, France); a virosomal trivalent subunit vaccine (Inflexal-V®, Crucell, Leiden, The Netherlands); and a split trivalent intradermal vaccine (Intanza® 15 μg, Sanofi-Pasteur MSD, Lyon, France). The intradermal TIV seasonal influenza vaccine delivered by a microneedle injection system (Intanza® 15 μg) and the virosomal TIV, intramuscularly delivered influenza vaccine (Inflexal® V) were targeted free of charge to adults ≥65. Enhanced immune response in the elderly is thought to be achieved differently by each vaccine type. Intradermal vaccination provides direct access to the immune system through the dermis, which is rich in immune cells and highly vascularized with an extensive lymphatic network [11] while virosomal vaccination induces high virus-neutralizing antibody titers and primes the cellular arm of the immune system [15]. Health authorities expressed no preference for either vaccine, and both vaccines were widely distributed [14].

Several sources of data can be used to estimate relative TIV effectiveness in Valencia region. The Valencia Health Agency (VHA) operates an extensive network of acute care hospitals and primary healthcare centers, which provide free medical care to 97% of the population (approximately 5 million inhabitants) [16]. The use of health care resources within this network is highly localized, with 24 geographically distinct hospital service areas (HSA). Each HSA offers all hospital care for residents within the given service area. Nine of these 24 HSAs (48% of the population) participate in a hospital-based seasonal influenza active surveillance program (Valencia Hospital Network for the Study of Influenza and Respiratory Virus Disease/VAHNSI) that has provided clinical and laboratory data from hospitalizations during each influenza season since 2009 [17]. In addition, a passive sentinel Microbiological Surveillance Network of VHA laboratories (RedMIVA) [18] records laboratory-confirmed influenza hospitalizations. Clinical, pharmaceutical, microbiological, and demographic data for each person under VHA coverage are routinely stored in the VHA Health Information System. These data allowed us to construct a retrospective cohort of people aged 65 and older who were vaccinated against influenza during the 2011–2012 season. Our aim was to evaluate the relative effectiveness of intradermal versus virosomal influenza vaccines against laboratory-confirmed influenza-related hospitalizations during the 2011–2012 influenza season.

2. Methods

2.1. Study population and setting

All community-dwelling adults aged ≥65 years as of 1 October 2011, residing in Valencia Autonomous Community, Spain, and who were vaccinated against influenza during the 2011–2012 influenza season were included in the study.

We identified through the minimum set of basic data (CMBD), the VHA electronic health system with clinical and administrative information on all hospital discharges [19], all admissions between 1 October 2011 and 31 March 2012 in the nine VHA hospitals that participate in a yearly influenza active surveillance program (Hospital General de Castellon, Hospital de la Plana, Hospital Arnau de Vilanova, Hospital La Fe, Hospital Dr Pesset, Hospital de Xativa-Ontinyent, Hospital San Juan de Alicante, Hospital General de Elda, and Hospital General de Alicante). We excluded admissions in the 30 days following hospital discharge, duplicate cases (if the patient had more than one case admission, only the first was included), and institutionalized adults. Because of sample size limitations, we also excluded recipients of the split trivalent non-adjuvanted vaccine (Gripavac®, Sanofi-Pasteur MSD, Lyon, France).

2.2. Vaccines

The trivalent split intradermal vaccine (Intanza® 15 μg, Sanofi-Pasteur MSD, Lyon, France: batches H81904, H81931, H81902, and H81922) and the virosomal trivalent subunit vaccine (Inflexal-V®, Crucell, Leiden, The Netherlands; batches 300220701, 300210802, 300214905, 300215802, 300214701, 300213101, 300212501, and 300214601) were licensed and approved for the 2011–2012 influenza season. Following World Health Organization recommendations, each vaccine contained the following strains: A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like [20]. The virosomal trivalent subunit vaccine was exclusively distributed in four VAHNSI HSAs (Hospital de Xativa-Ontinyent, Hospital San Juan de Alicante, Hospital General de Elda, and Hospital General de Alicante), whereas the trivalent split intradermal vaccine was exclusively distributed in five other VAHNSI HSAs (Hospital General de Castellon, Hospital de la Plana, Hospital Arnau de Vilanova, Hospital La Fe, and Hospital Dr Pesset) [14]. Vaccination targeted people 65 and older during the vaccination program (which ran from 1 October 2011 and 30 November 2011) [14]. Individuals were considered immunized if their vaccination record in the Vaccine Information System, an electronic database that stores vaccination records from both public and private vaccination facilities, indicated administration of vaccine at least 15 days prior to the date of hospitalization.

2.3. Outcome

An influenza-related hospitalization case was defined by at least one of the following: (1) a main discharge diagnosis for hospital admission of influenza (ICD-9-CM: 487–488.89), at least 15 days following the date of vaccination, between 1 October 2011 and 31 March 2012, or (2) admissions identified through the VAHNSI scheme between 3 November 2011 and 31 March 2012, at least 15 days following the date of vaccination, and positive for influenza by a real-time PCR assay as previously described [21], or (3) influenza positive specimens from patients hospitalized between 1 October 2011 and 31 March 2012 reported to the RedMIVA [18] and hospitalized at least 15 days following the date of vaccination.

2.4. Covariates

We used several VHA information systems to search sociodemographic and clinical data: (1) the hospital CMBD electronic records, (2) the Population Information System, which provides an identification number for each person under VHA coverage and registers demographic characteristics, as well as dates and causes of VHA discharge, including death, and (3) the pharmaceutical module GAIA which includes information on pharmacy claims. We identified the following variables: age at study entry (1 October 2011), sex, country of birth (coded as Spain or other), the HSA of patient residence, seasonal influenza and pneumococcal vaccination in the previous 3 years, type of VHA coverage, and total number of hospitalizations from 1 October 2010 to 30 June 2012.

The presence and severity of chronic medical conditions was ascertained based on pharmacy claims from 1 January 2011 to 31 December 2011 for each study subject. In brief, dispensed drugs from any therapeutic class (anatomical therapeutic chemical (ATC) classification) were identified using the GAIA pharmaceutical module. Drugs from three therapeutic classes were selected according to their association with risk for influenza-related hospitalization in our study population [22]: (1) antithrombotic drugs (ATC: B01),

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respiratory drugs (ATC: R03) or cardiovascular drugs (ATC: C01, C02, C03, C07, C08, C09, C10) alone; (2) antithrombotic drugs (ATC: B01) in combination with cardiovascular drugs (ATC: C01, C02, C03, C07, C08, C09, C10); (3) respiratory drugs (ATC: R03) in combination with cardiovascular drugs (ATC: C01, C02, C03, C07, C08, C09, C10); (4) antithrombotic drugs (ATC: B01), respiratory drugs (ATC: R03) and cardiovascular drugs (ATC: C01, C02, C03, C07, C08, C09, C10) in combination. Sporadic dispensations from pharmacy claims, as defined by <6 packs/year dispensed for each drug class, were not included in these groups. Data on co-morbidities, as reported by the general practitioner, was available from the Vaccine Information System database.

2.5. Statistical analysis

Cohort characteristics were described using proportions. Differences in the proportions between each vaccine group with regard to socio-demographic and clinical characteristics were examined with the chi square test. Parameters that were not normally distributed were transformed prior to analysis. A *P*-value of less than 0.05 was considered to indicate statistical significance.

Confounding was assessed by analysis of the hazard ratio (HR) for individuals vaccinated with intradermal-TIV relative to virosomal-TIV, adjusted for each baseline characteristic separately, and compared with the unadjusted HR. Biological plausibility and previous knowledge were taken into account in the assessment of confounding. The presence of possible effect modifiers was explored using interaction terms (likelihood-ratio (LR) test; $P < 0.05$). Departure from linearity was assessed using the LR test ($P < 0.05$).

Crude and adjusted comparative influenza vaccine effectiveness (VE) were estimated by calculating the hazard ratio (HR) of laboratory-confirmed influenza hospitalization in one vaccine group compared with the other vaccine group (intradermal-TIV versus virosomal-TIV), with confidence intervals by Cox regression models. Point estimates of vaccine effectiveness were calculated as $(1 - \mathrm{HR}) \times 100$. Departure from proportional hazards assumption was carried out by observing the curves of the adjusted rates by exposure on a cumulative hazards graph, and evaluating whether the HR changed with time by a LR test for interaction. Number of hospitalizations for all causes other than influenza between the previous and current influenza seasons was modeled as a fixed or random effects parameter to account for both, propensities of each

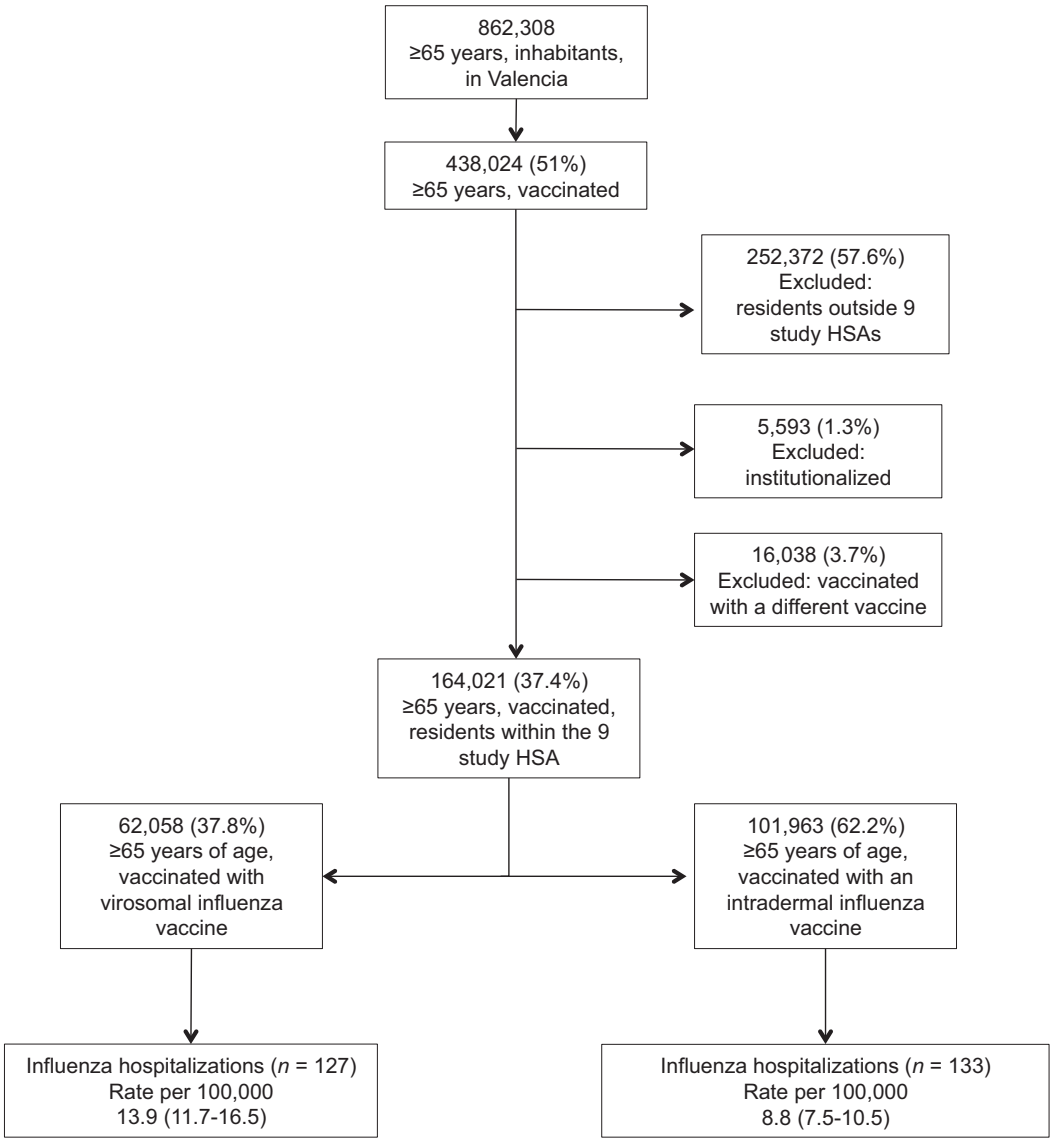

Fig. 1. Flow-chart of study subjects. Vaccinated patients included in the comparative effectiveness study. 2011–2012 H3N2 predominant influenza season. Valencia, Spain.

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individual to be hospitalized and of his/her assigned hospital to hospitalize a patient. Sensitivity analyses were carried out by excluding outliers (i.e. patients with the largest number of hospitalizations or hospitals with the most extreme hospitalization rates). Analyses were restricted to the time period starting the week in which two or more positive influenza hospitalizations were identified on two consecutive weeks (18 December 2011) and ended the week in which no identifications were observed for at least two consecutive previous weeks (31 March 2012). All statistical analyses were performed using Stata 12.0 (StataCorp, College Station, TX, USA) statistical software.

2.6. Ethics

The study was conducted according to Ethical Principles for Medical Research Involving Human Participants of the World Medical Association, the Declaration of Helsinki, and the International Ethical Guidelines for Epidemiological Studies. The Ethic Research Committee of the Directorate of Public Health and Public Health Research Center of Valencia approved the study protocol and provided the exemption from obtaining individual informed consent to obtain and merge individual data from the different registries.

3. Results

3.1. Description of the cohort

Overall, 438,024 adults aged 65 years and older on 1 October 2011 were vaccinated against influenza during the 2011–2012 season (51% of the total population ≥65 years old in Valencia region). We excluded 252,372 who resided outside the nine HSAs under study, 5593 that were institutionalized, and 16,038 who had received a different vaccine to those being compared. This left 164,021 (19% of the total population ≥65 years old in Valencia region) subjects for the analysis (Fig. 1). The cohort mean age was 76.7 (standard deviation: 7.2) years, and 55.3% were female. A total of 49.7% of cohort members were recorded as suffering from "chronic cardio-respiratory conditions" in the Vaccine Information System database, but only 8% were on chronic cardiovascular and respiratory medication.

3.2. Vaccines

A total of 62,058 (37.8%) people were vaccinated with virosomal-TIV and 101,963 (62.2%) were vaccinated with intradermal-TIV (Fig. 1, Table 1). The age and sex distribution

Table 1
Study subjects characteristics by vaccine type received during the 2011–2012 influenza season.

	Virosomal (*N* = 62,058, 37.8%)		Intradermal (*N* = 101,963, 62.2%)	
	n	%	*n*	%
Age groups (in years)				
65–69	13,553	22.8	21,776	21.4
70–74	13,790	22.2	22,734	22.3
75–79	14,399	23.2	23,996	23.5
80–84	11,488	18.5	18,479	18.1
85+	8828	14.2	14,978	14.7
Gender				
Male	28,017	45.2	45,310	44.4
Female	34,041	54.9	56,653	55.6
Comorbidities				
No	15,660	25.2	42,731	41.6
Yes	46,398	74.8	59,592	58.4
Therapeutic drug classes dispensed[a]				
No drugs dispensed	8835	14.2	13,881	13.9
Cardiovascular alone	37,532	60.5	61,903	60.6
Cardiovascular and antithrombotic in combination	11,883	19.2	20,191	19.8
Cardiovascular and respiratory in combination	1631	2.6	2733	2.7
Antithrombotic, cardiovascular and respiratory in combination	2177	3.5	3255	3.2
Seasonal vaccination 2010–11				
No	7557	12.2	13,304	13.1
Yes	54,501	87.8	88,659	87.0
Recent pneumococcal vaccination				
No	61,162	98.6	100,416	98.5
Yes	896	1.4	1547	1.5
Health insurance/coverage				
Public	60,370	97.3	100,381	98.5
International	887	1.4	641	0.6
Miscellaneous[b]	756	1.2	888	0.9
Missing	45	0.1	53	0.1
All hospitalizations[c]				
None	49,128	79.2	82,598	81.0
One	8618	13.9	13,084	12.8
Two	2619	4.2	3896	3.8
Three	965	1.6	1360	1.3
Four	396	0.6	563	0.6
Five or more	332	0.5	462	0.5

[a] Patients grouped according to drugs dispensed to each individual, from 1 January 2011 to 31 December 2011. Drugs from 3 therapeutic classes (antithrombotic drugs and drugs for obstructive airway diseases drugs and the cardiovascular system) were selected through codes of the anatomical therapeutic chemical classification.
[b] Private, without insurance or other.
[c] Number of hospitalizations of all-causes except for influenza from October 2010 to June 2012.

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of patients vaccinated with each vaccine were similar (Table 1). Subjects vaccinated with virosomal-TIV were more likely to be reported as belonging to the "cardio-respiratory risk group" (59.3% for virosomal versus 43.8% for intradermal TIV; $P < .001$). However, pharmaceutical claim distributions were similar between both groups of vaccinees (Table 1).

3.3. Laboratory confirmed influenza hospitalizations

During the time influenza was circulating in the community, we identified 127 hospitalizations related to influenza among subjects vaccinated with virosomal-TIV, out of 914,740 total person-weeks at risk. We also identified 133 hospitalizations related to influenza among subjects vaccinated with intradermal-TIV, out of 1,504,570 total person-weeks at risk (Fig. 1, Table 2). From the total of 260 cases, 241 were identified through the VAHNSI scheme, 12 were reported to the Microbiological Surveillance Network (RedMIVA) and 15 (0.6%) patients were ascertained from the CMBD because of a discharge diagnosis for influenza (ICD9-CM 487–488.89), seven of these (five virosomal-TIV and two intradermal-TIV vaccinees) lacked a laboratory result for the confirmation of influenza virus infection. The most frequent primary diagnosis among those with a positive laboratory result for influenza was chronic obstructive pulmonary disease (COPD) (24.5%), followed by pneumonia (21.3%). A total of 24.9% of patients with a positive PCR result for influenza had a discharge primary diagnosis corresponding to other diseases of the respiratory system. COPD and pneumonia were more commonly reported among patients vaccinated with intradermal-TIV compared with virosomal TIV (Supplementary Table 1). There was no significant difference between vaccine groups in the mean duration of hospitalization ($P = 0.254$).

Supplementary Table 1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.07.095.

Regardless of the vaccine type, rates of influenza-related hospitalization increased with age and were higher among males, subjects who were dispensed a combination of cardiovascular, antithrombotic and obstructive pulmonary drugs during 2011 and subjects who had received at least one dose of the pneumococcal vaccine in the previous 3 years (Table 2).

There were differences in hospitalization with influenza rates among HSAs. In particular, one HAS (Hospital General de Elda) showed higher hospitalization rates than the other eight areas (Fig. 2).

Table 2
Influenza-hospitalization rates and relative risk (RR) of influenza-related hospitalization by type of vaccine.

	Virosomal-TIV			Intradermal-TIV			Crude RR (95% CI)[b]	*P*-value
	Person-weeks	Influenza-related admissions (*n*)	Rates[a]	Person-weeks	Influenza-related admissions (*n*)	Rates[a]		
All cohort subjects	914,740	127	13.9	1,504,570	133	8.8	**0.64 (0.50–0.81)**	**0.0002**
Age groups (in years)							**0.63 (0.50–0.81)**	**0.0002**
65–69	200,780	12	6.0	322,480	6	1.9	0.31 (0.12–0.83)	
70–74	204,140	18	8.8	336,570	20	5.9	0.67 (0.36–1.27)	
75–79	212,540	33	15.5	354,720	37	10.4	0.67 (0.42–1.07)	
80–84	168,990	34	20.1	272,340	35	12.9	0.64 (0.40–1.02)	
≥85	128,280	30	23.4	218,460	35	16.0	0.68 (0.42–1.14)	
Gender							**0.64 (0.50–0.82)**	**0.0003**
Male	412,560	74	17.9	667,740	85	12.7	0.71 (0.52–0.97)	
Female	502,180	53	10.6	836,840	48	5.7	0.54 (0.37–0.80)	
Comorbidities							**0.67 (0.52–0.86)**	**0.0015**
No	231,470	20	8.6	625,700	48	7.7	0.89 (0.53–1.50)	
Yes	683,270	107	15.7	878,870	85	9.7	0.62 (0.46–0.82)	
Therapeutic drug classes dispensed							**0.64 (0.50–0.81)**	**0.0002**
No drugs dispensed	130,510	5	3.8	204,900	7	3.4	0.89 (0.28–2.81)	
Cardiovascular drugs alone	553,970	64	11.6	914,100	72	7.9	0.68 (0.49–0.96)	
Cardiovascular and antithrombotic in combination	174,570	31	17.8	297,740	27	9.1	0.51(0.30–0.85)	
Cardiovascular and respiratory in combination	23,990	10	41.7	40,240	14	34.8	0.84 (0.37–1.88)	
Antithrombotic, cardiovascular and respiratory in combination	31,700	17	53.6	47,590	13	27.3	0.51 (0.25–1.05)	
Seasonal vaccination 2010–11							**0.64 (0.50–0.81)**	**0.0003**
No	110,970	12	10.8	195,350	16	8.2	0.76 (0.36–1.60)	
Yes	1,430,750	115	14.3	1,309,220	117	8.9	0.62 (0.48–0.81)	
Recent pneumococcal vaccination							**0.64 (0.50–0.81)**	**0.0002**
No	901,700	124	13.8	1,481,830	126	8.5	0.62 (0.48–0.79)	
Yes	13,040	3	23.0	22,740	7	30.8	1.34 (0.35–5.17)	
Health insurance/coverage							**0.64 (0.50–0.81)**	**0.0002**
Public	889,810	127	14.3	1,481,270	130	8.8	0.62 (0.48–0.79)	
International	13,070	0	-	9410	2	21.2	-	
Miscellaneous[c]	11,230	0	-	13,110	1	7.6	0.71 (0.05–11.43)	
Hospitalizations[d]							**0.67 (0.52–0.85)**	**0.0011**
None	727,650	31	4.3	1,222,990	66	5.4	1.27 (0.83–1.84)	
One	125,480	55	43.8	191,380	41	21.4	0.49 (0.33–0.73)	
Two	37,700	22	58.3	56,280	12	21.3	0.36 (0.18–0.74)	
Three	13,670	11	80.5	19,360	9	46.5	0.58 (0.24–1.40)	
Four	5560	4	72.0	8010	4	50.0	0.69 (0.17–2.76)	
Five or more	4680	4	85.5	6540	1	15.3	0.18 (0.02–1.59)	

[a] Rates per 100,000 person-weeks.
[b] Maximum likelihood estimate of the rate ratio (RR; virosomal versus intradermal vaccine), controlling for time from entry and for each co-variable individually and by co-variable categories. CI: confidence interval.
[c] Private, without insurance or other.
[d] Number of hospitalizations of all-causes except for influenza from October 2010 to June 2012.

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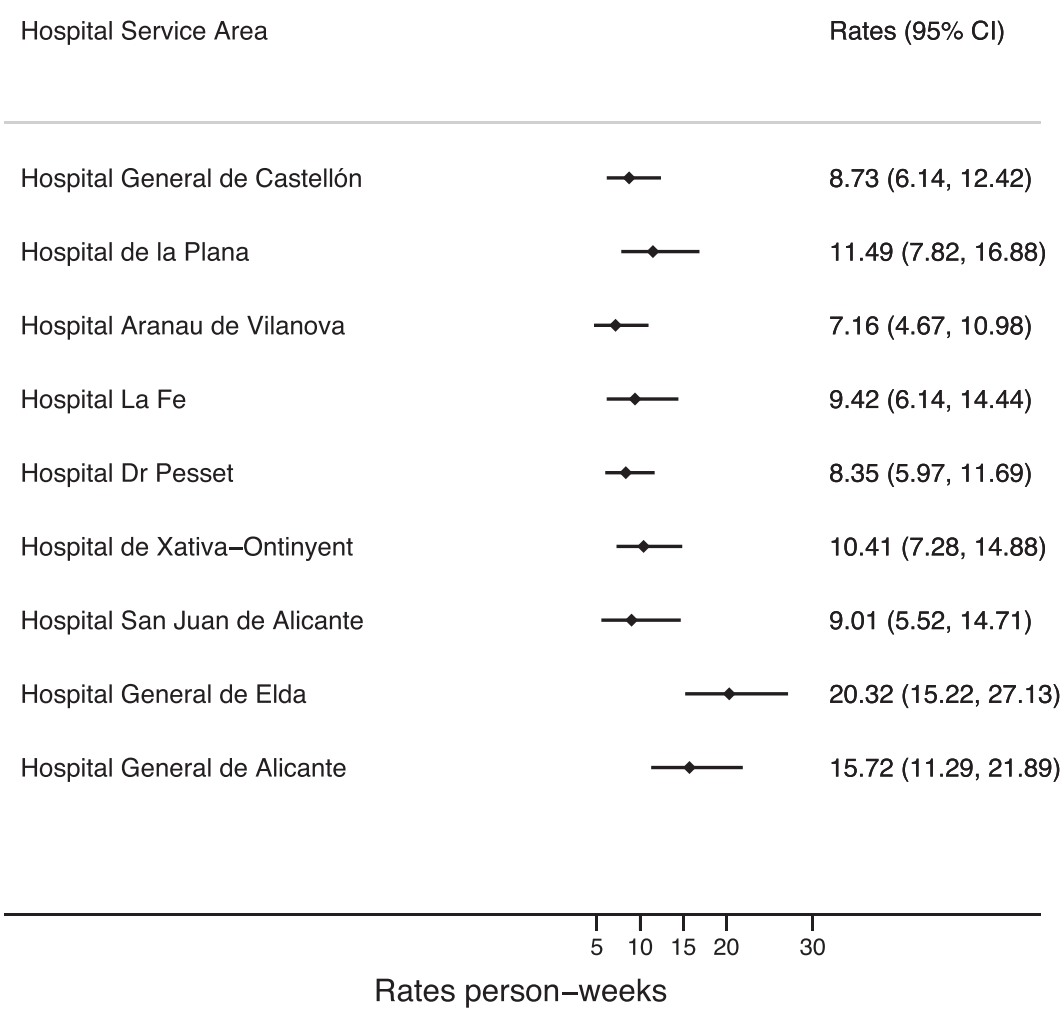

Fig. 2. Admission rates per 100,000 person-weeks in each of the nine Health Service Areas included in the study.

3.4. Comparative influenza vaccine effectiveness estimates

We observed a comparative crude influenza VE of 36% (95% CI, 19–50%) against laboratory-confirmed influenza hospitalization; i.e., recipients of the intradermal-TIV vaccine showed a 36% reduction in the risk of influenza-related hospitalization compared with recipients of the virosomal-TIV vaccine (Table 3). This difference in vaccine effectiveness was similar after adjustment for age group, sex, prescription claims, recent pneumococcal vaccinations (previous 3 years) and number of hospitalizations for all causes other than influenza between the previous and current influenza seasons (influenza VE: 33% (95% CI: 15–48%) (Table 3, Fig. 3).

The sensitivity analyses (Table 3) also suggested higher vaccine effectiveness of the intradermal-TIV versus virosomal-TIV vaccine. After excluding all residents within Hospital General de Elda HSA (the HSA that showed higher hospitalization rates than the rest

Table 3
Comparative effectiveness of intradermal and virosomal influenza vaccines according to outcome definition.

Confirmation of influenza hospitalization	Virosomal-TIV	Intradermal-TIV	Intradermal-TIV vs virosomal-TIV					
	N = 62,058	*N* = 101,963	Crude			Adjusted[a]		
	n (cases)	*n* (cases)	HR	95%CI	*P*	HR	95%CI	*P*
Laboratory and clinical diagnosis (all)	127	133	0.64	0.50–0.81	<0.001	0.67	0.52–0.85	0.001
Laboratory confirmed cases(discharge code only excluded)	122	131	0.65	0.51–0.84	0.001	0.69	0.54–0.88	0.003
Sensitivity analysis								
Residents in HAS Hospital General de Elda excluded	81	133	0.75	0.57–0.99	0.042	0.77	0.58–1.01	0.058
Subjects with more than 4 hospitalizations[b] excluded	123	132	0.65	0.51–0.83	0.001	0.68	0.53–0.87	0.002

TIV: trivalent influenza vaccine. HR: hazard ratio. CI: confidence interval. ICD9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification. HSA: Hospital Service Area.

[a] Adjusted by age, sex, dispensed drugs, recent pneumococcal vaccination and number of hospitalizations for all causes other than influenza between the previous and current influenza seasons.

[b] Subjects with more than 4 hospitalizations for all causes other than influenza between the previous and current influenza seasons.

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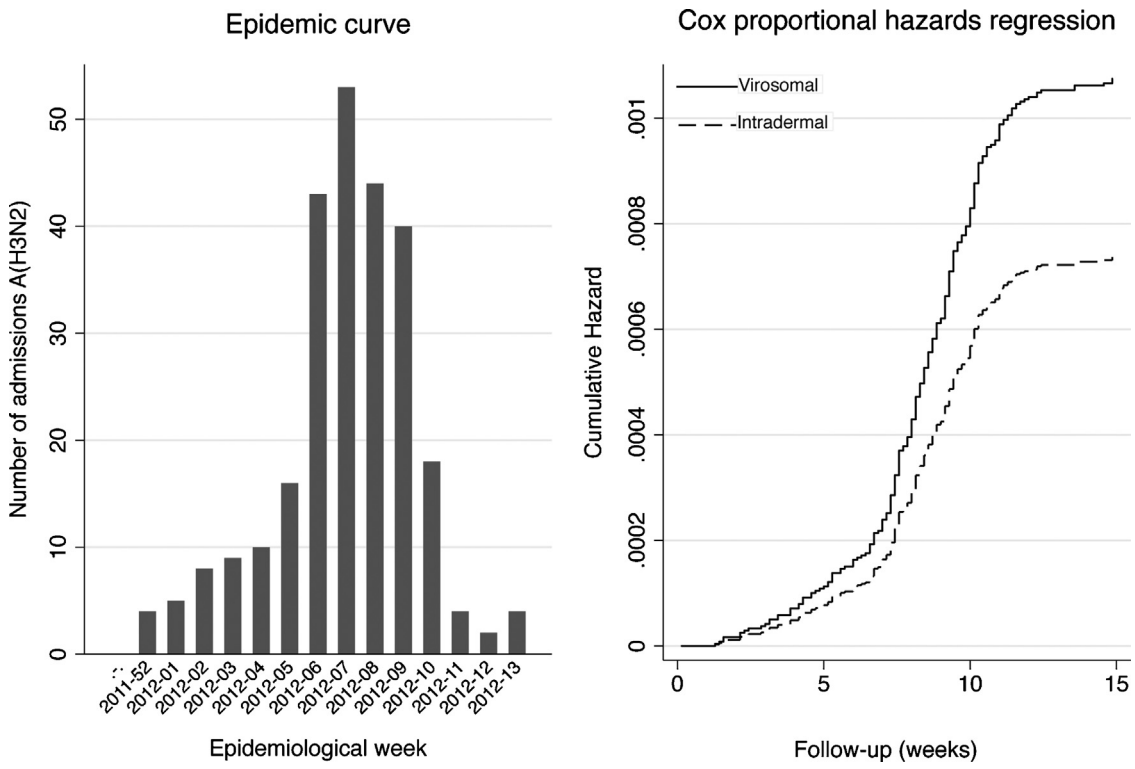

Fig. 3. Epidemic curve (number of A(H3N2)-admissions vs epidemiological week) and Cox proportional hazards regression of admissions with A(H3N2) by vaccine*. *Adjusted by age, sex, dispensed drugs, recent pneumococcal vaccination and number of hospitalizations for all causes other than influenza between the previous and current influenza seasons.

of the hospital areas) the adjusted comparative influenza VE of 23% (95% CI, −1% to 42%); whereas, when patients with the highest number of outside the influenza season hospitalizations (more than four) were excluded the adjusted comparative effectiveness was 32% (95% CI: 13–47%).

4. Discussion

In this large retrospective study, we compared the effectiveness of intradermal-TIV Intanza® 15 μg with virosomal-TIV, intramuscularly delivered influenza vaccine (Inflexal® V). Both vaccines were administered routinely during the 2011–2012 influenza season to adults aged ≥65 years. The risk of hospitalization for laboratory-confirmed influenza was reduced by 33% in non-institutionalized elderly adults who were vaccinated with intradermal-TIV compared with virosomal-TIV.

To our knowledge this is the first study to compare the effectiveness of intradermal-TIV (Intanza® 15 μg) and virosomal-TIV (Inflexal® V) vaccines in preventing clinical outcomes in older adults. We also report that the intradermal vaccination showed significantly superior effectiveness compared with the virosomal vaccination. This observation is in agreement with the findings of a recent head-to-head randomized phase IV clinical trial of healthy elderly volunteers in which an intradermal-TIV 15 μg vaccine was associated with consistently higher seroprotection rates against homologous and heterologous strains when compared with a virosomal-TIV vaccine [23]. Other clinical studies have shown that in elderly volunteers the immunogenicity of intradermal-TIV 15 μg is comparable with that of an intramuscular subunit vaccine adjuvanted with MF59 [24].

Data from clinical trials indicate that intradermal delivery of influenza vaccines results in significantly enhanced immune responses compared with the conventional intramuscular vaccination route [25,26]. This superiority is consistent with the idea of a large number of dendritic cells present in the skin, which act as potent antigen-presenting cells important in immune surveillance, resulting in a strong humoral and cellular immune responses [27,28].

Our comparison of two groups that had both received the seasonal influenza vaccine overcame confounding by indication. We derived an accurate indicator of chronic illness based on dispensed cardiovascular and respiratory medication during 2011, assuming prescription composition and duration as a proxy for chronic comorbidity [29]. We were able to find a positive laboratory result for influenza virus in over 97% of all hospitalizations, 93% were confirmed by PCR, suggesting a high specificity of the case definition in our study.

Most of our study cases (241 out of 260; 93%) were ascertained through active surveillance; therefore, the variability in the quality of CMBD registers, or the likelihood of specimen sampling variability for laboratory confirmation of influenza virus across hospitals should not have significantly affected our results. However, a potential limitation of our study is that, although the same study protocol was used to detect influenza-like illness (ILI) admissions within 7 days of symptom onset across hospitals, ILI hospital admission criteria may vary among hospitals. This could result in a differential sensitivity to detect the actual number of influenza-related hospitalizations across study hospitals. Under this scenario, it is possible that bias was introduced by the fact that only one type of vaccine was distributed for the catchment area of each hospital, because the probability of cases going undetected could be associated with vaccine type. However, sensitivity analysis excluding the hospital showing higher admission rates for influenza-related hospitalizations did not vary the conclusions of this study.

Our data suggest that intradermal-TIV vaccination performed using a microinjection system provides higher protection against influenza-related hospitalization in elderly adults compared with the virosomal-TIV, intramuscularly delivered influenza vaccine in 2011–2012, a season where A(H3N2) dominated [30].

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Concerns about both, A/Perth/16/2009 vaccine strain match/mismatch to circulating A(H3N2) strains related to antigenic drift in circulating viruses and mutations in the egg-adapted AH3N2 vaccine strain, have been raised to explain the relatively low IVE estimates observed in the Northern hemisphere during the 2011–2012 season [31–36]. Our study does not include antigenic and genetic data of circulating strains so we cannot comment on suboptimal antigenic match between the 2011–2012 vaccine and circulating strains in Valencia. Further studies should be conducted over several influenza seasons to assess the variability of comparative vaccine effectiveness with the degree of antigenic match between vaccine and circulating viruses.

Acknowledgements

We are grateful to Julián Librero for his comments on the various drafts of the manuscript, Isabel Muñoz and Manuel Escolano for their continuous support to the research team during the conduct of this study, the Microbiological Surveillance Network in the Valencia Autonomous Community (redMIVA) for their assistance and for sharing their data and to all the members of the Valencia Hospital Network for the Study of Influenza and Respiratory Virus Diseases.

Conflict of interest: JPB, ANS, SMU and JDD work in FISABIO's Vaccines Research Area, FISABIO has received funding for GSK, Novartis, Pfizer, SanofiPasteur, SanofiPasteur MSD for conducting epidemiological studies on infectious disease epidemiology, vaccine effectiveness, pharmacoeconomics, and safety studies. The Vaccines Research Area is and has been involved in various randomized clinical trials with GSK, Novartis, Pfizer and MSD vaccines. No conflicts related to the submitted paper are declared by the rest of the authors.

Funding: This work was supported by a grant from the Spanish Ministry of Health to support independent clinical research, Order SPI/2885/2011, October 20, 2011 [grant number EC11-480].

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