Vaccine 31 (2013) 3995–4002

Contents lists available at SciVerse ScienceDirect

Vaccine

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

MF59-adjuvanted and virosomal influenza vaccines for preventing influenza hospitalization in older people: Comparative effectiveness using the Valencia health care information system

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ARTICLE INFO

Article history:
Received 8 March 2013
Received in revised form 1 May 2013
Accepted 18 May 2013
Available online 1 June 2013

Keywords:
Comparative effectiveness research
Cohort studies
Aged
Hospitalization
Influenza vaccines
Vaccines
Subunit

ABSTRACT

Background: Adjuvanted influenza vaccines offer greater and broader immunogenicity to older adults than conventional vaccines. Studies assessing the comparative effectiveness of adjuvanted influenza vaccines in this age group are lacking.
Methods: We conducted a retrospective cohort study to estimate the comparative effectiveness of MF59-adjuvanted trivalent influenza vaccine (TIV) and virosomal-TIV for prevention of influenza hospitalization in adults aged ≥65 years. We obtained administrative data on immunization status and influenza hospitalization for the 2010–2011 influenza season. We used Cox regression models to assess comparative effectiveness; crude and adjusted by age, sex, comorbidity, deprivation, type of insurance, and travel time to hospital. We accounted for data clustering at the hospital level by using a multilevel random effects model.
Results: Overall, 373,798 vaccinated subjects were evaluated. There were 40 hospitalizations for influenza among 176,618 subjects, contributing 4,288,109 person–weeks at risk in the virosomal-TIV group, and 37 hospitalizations for influenza among 197,180 subjects, contributing 4,786,360 person–weeks at risk in the MF59-TIV group. The crude hazard ratio (HR) was 0.83 (0.53–1.30), and the adjusted Cox estimated HR of MF59-TIV relative to virosomal-TIV was 0.86 (0.55–1.35). After accounting for data clustering, the HR of influenza hospitalization associated with MF59-TIV relative to virosomal-TIV was 0.94 (0.37–2.38).
Conclusion: During the 2010–2011 influenza season, we found no differences in the risk of influenza hospitalization in subjects aged ≥65 years vaccinated with MF59-TIV compared with those vaccinated with virosomal-TIV.

1. Introduction

Influenza is a major public-health problem, with seasonal epidemics leading to substantial increases in morbidity and mortality. Annual vaccination is the cornerstone of influenza prevention [1] and is recommended to people aged ≥65 years because most influenza-associated comorbidity and deaths in industrialized countries occur in this age group [1–3]. Conventional influenza vaccines do not offer optimal protection in older adults [4] because the activity of multiple components of the immune system decreases with aging, which jeopardizes the ability to resist influenza infection and to respond to vaccination [5]. In addition, mismatch between vaccine formulation and the circulating virus can occur and have a negative impact on influenza vaccine effectiveness [6]. Adjuvanted vaccines have been developed to enhance immune response and improve cross-protection [7].

The MF59-adjuvanted influenza vaccine is a 0.5 ml oil in water solution that contains 15 μg of each one of the purified subunits of H3N2, H1N1 and B hemagglutinin antigens of the influenza strains plus the MF59 adjuvant (9.75 mg of squalene, 1.175 mg of polysorbate-80, 1.175 mg of sorbitan trioleate), the MF59 adjuvant aims to increase the immune response to influenza antigen in older adults by recruiting and activating antigen-presenting cells at the injection site [8]. Virosomal influenza vaccines are based on virosomes, a virosome is a liposome consisting of a biodegradable, non-toxic and non-immunogenic phospholipids membrane

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http://dx.doi.org/10.1016/j.vaccine.2013.05.070

that is used to reconstitute a virus-like particle with hemagglutinin (HA) and neuraminidase proteins in 0.5 ml solution that contains 15 μg of each one of the purified subunits of H3N2, H1N1 and B hemagglutinin antigens of the recommended influenza strains, virosomal influenza vaccines aim to increase the immune response to influenza by inducing antibody and cell-mediated immunity responses and by activating cytotoxic T cells [9]. Several studies have shown that both confer greater and broader immunogenicity in older adults than non-adjuvanted influenza vaccines [10–14]. However, antibody response is not the sole predictor of vaccine efficacy in older people [15], and differences in the immunogenicity of each vaccine type may not translate into differences in clinical protection from influenza-related illness. A few head-to-head studies have compared the clinical effectiveness of adjuvanted and non-adjuvanted vaccines [16], but head-to head studies of adjuvanted influenza vaccines in preventing laboratory confirmed outcomes are lacking.

During the 2010–2011 influenza season, adults aged ≥65 years who were living in Valencia Autonomous Community (Spain) were offered, free of charge, a single dose of either MF59-adjuvanted trivalent influenza vaccine (TIV) or virosomal-TIV. As only one vaccine type was distributed to each of the health care districts in the study region, adults aged ≥65 years received one or the other vaccine type according to their place of residence. Both vaccines reduced the risk of laboratory-confirmed influenza hospitalization in the same population of older adults [17]. This situation gave us the opportunity to perform a comparative effectiveness study of virosomal-TIV and MF59-TIV for prevention of influenza-related hospitalization during the 2010–2011 influenza season.

2. Methods

2.1. Study population and setting

This was a comparative effectiveness study [18] based on a cohort of community-dwelling adults aged ≥65 years as of October 1, 2010, resident in Valencia Autonomous Community, Spain, who were vaccinated against influenza during the 2010–2011 influenza season.

The cohort was assembled by identifying, from the regional Vaccine Information System (VIS), those aged ≥65 years on October 1, 2010, who were registered as vaccinated with any of the available seasonal influenza vaccines. VIS is a population-based register that systematically records vaccine doses given at public and private vaccination points (primary care centers, hospitals, residential facilities in the public sector, and any private sector facility that applies for access). The sensitivity and specificity of VIS are estimated to be 90% and 99%, respectively [19]. The VIS was estimated to be 93% complete for the 2010–2011 influenza season [17].

Vaccination against influenza in the 2010–2011 season began on September 27, 2010. Influenza vaccine was offered free of charge to persons aged ≥65 years. Three vaccine formulations were used: subunit trivalent non-adjuvanted TIV (Influvac, batch numbers V4, V20 and V23; Abbott–Solvay, Abbott Park, IL, USA) offered to subjects aged < 60 years; virosomal-TIV (Inflexal-V, batch numbers 300187601, 300189301 and 300194401; Crucell, Leiden, Netherlands) offered to subjects aged ≥60 years; and MF59-TIV (Chiromas, batch numbers 104603, 104702, 104802 and 105001; Novartis Vaccines and Diagnostics, Cambridge, MA, USA) offered by licensure requirements to those aged ≥65 years. In line with the World Health Organization recommendations, the 2010–2011 TIV composition included A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like and B/Brisbane/60/2008/like, which matched well the circulating strains [17]. MF59-TIV was distributed in 11 health care districts and virosomal-TIV was distributed in the remaining 13 within the Valencia Autonomous Community. MF59-TIV or virosomal-TIV was administered according to this distribution scheme to subjects 65 years old or older [20]. For this study, individuals were considered immunized if their VIS vaccination record indicated administration of vaccine over 14 days prior to the date of hospitalization.

2.2. Outcomes

Our study outcome was influenza-related hospitalization in any of the 24 hospitals of the public network in Valencia. We identified hospital discharges with a diagnosis of influenza, listed as any of the first 3 diagnosis codes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9] codes 487–488.89), at least 15 days following the date of vaccination. We further identified influenza-related hospitalization by linking to individual hospital discharge records the positive laboratory results for influenza from (1) the Valencia Microbiological Surveillance Network (redMIVA) [21]; and (2) the ongoing influenza active surveillance study on respiratory virus admissions in 2010–2011 in 5 of the 24 hospitals [17,22].

Hospitalization and discharge electronic records were obtained from the Minimum Basic Data Set (*Conjunto Mínimo Básico Datos*; CMBD) for hospital discharges. CMBD is a homogeneous and standardized register for administrative and clinical data collected from all Spanish public health sector hospitals since 1990 [23]. For patients with more than 1 hospital admission, only the 1st was included in the analysis. Admission occurring within 30 days of hospital discharge was not included to avoid readmission or nosocomial infections.

2.3. Covariates

Variables assessed as potential confounders were: age (5-year groups with the oldest consisting of those ≥85 years); sex; seasonal influenza and pneumococcal vaccination in the previous 3 years; comorbidity; deprivation; and access to health care.

2.4. Comorbidity

The presence and severity of chronic medical conditions was assessed by the number of dispensed drugs [24] from January 1, 2010 to December 31, 2010, defined for each subject to the 4th level of the Anatomical Therapeutic Chemical (ATC) classification system, and obtained from the electronic database for the management of drugs dispensed in Valencia (GAIA). Groups of individuals at risk of hospitalization for influenza were defined according to whether non-sporadic annual dispensation (>6 prescriptions/year) was associated with risk of influenza hospitalization (Supplementary Table 1). We then generated a variable in which each subject was given a value indicating whether prescription had been continuous or sporadic for cardiovascular or obstructive airway disease, or for antithrombotic drugs, and if these drugs had been prescribed in combination. A variable named “Drugs dispensed during 2010” was created with the following categories: (1) subjects who had not been prescribed any drug for any of the 3 groups, or lacked GAIA records; (2) subjects who had been prescribed antithrombotic, respiratory or cardiovascular drugs, but sporadically or not combined; (3) subjects who had been continuously prescribed both antithrombotic and cardiovascular drugs; (4) subjects who had been continuously prescribed both respiratory and cardiovascular drugs; and (5) subjects who had been continuously prescribed concurrent antithrombotic, respiratory and cardiovascular drugs.

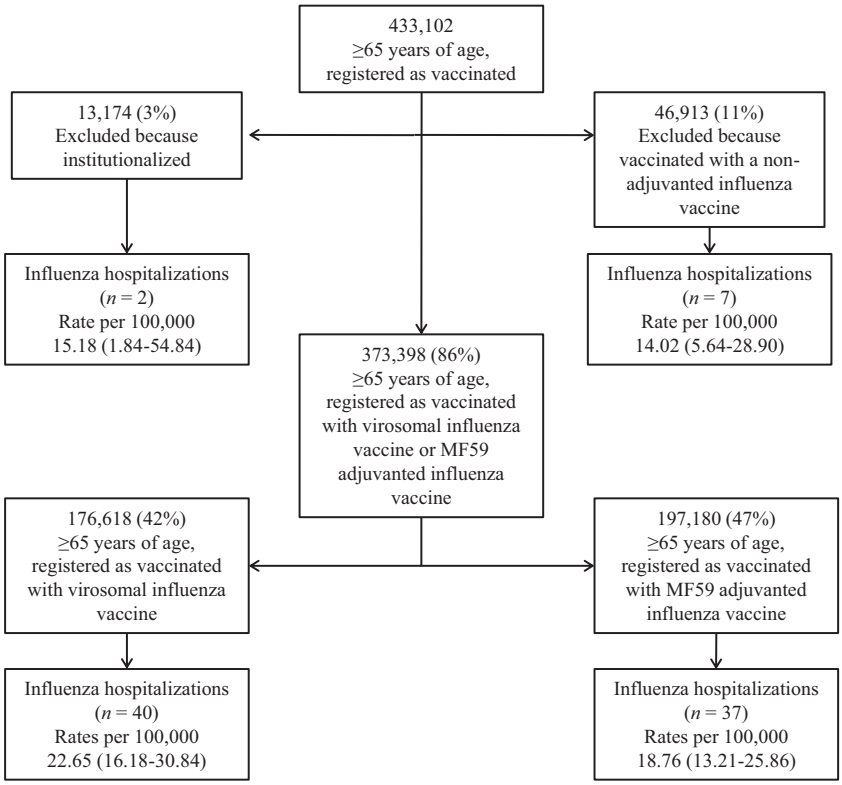

Fig. 1. Flow chart of study subjects (rates per 100,000 as Poisson-distributed counts; exact Poisson confidence intervals).

2.5. Socioeconomic status and access to health care

Two sociodemographic variables were used as proxies of socioeconomic status: medical insurance/coverage (public, private, international travel medical and health insurance, without insurance, or other) obtained from the Valencia vital and health statistics registry and a deprivation index based on illiteracy rate, unemployment rate and percentage of manual laborers by municipality [25]. Deprivation index quartiles were used to develop four categories, from low deprivation (for those municipalities with lowest levels of unemployment, illiteracy and percentage of manual laborers), followed by medium, high to highest deprivation (for those municipalities with the highest levels of the three mentioned deprivation index component). Finally, we obtained information on driving distance to the nearest hospital calculated for each subject, based on municipality of residence, as a proxy of access to health services.

2.6. Statistical analysis

Baseline characteristics of subjects in the two vaccine groups (MF59-TIV and virosomal-TIV) were compared using Fisher's exact test, Pearson χ^2, Student's t test or Kruskal–Wallis equality of population rank test, depending on the nature of the variable. Parameters that were not normally distributed were transformed prior to analysis. Confounding was assessed by analysis of the hazard ratio (HR) for individuals vaccinated with either vaccine, 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; $P < .05$). Departure from linearity was assessed using the LR test.

Crude and adjusted comparative influenza vaccine effectiveness (VE) estimates were calculated by Cox regression models as $(1 - \mathrm{HR}) \times 100\%$ against the study outcome. Departure from proportional hazards assumption was carried out observing the curves of the adjusted rates by exposure on a cumulative hazards graph, and evaluating whether the HR changed with time by an LR test for interaction. A multilevel shared-frailty Cox model with health care district (equivalent to hospital assignment) as shared-effect parameter was used to account for hospital effects [26], estimating the adjusted HR of influenza admission in subjects vaccinated with MF59-TIV relative to those vaccinated with virosomal-TIV. We conducted all statistical analysis using Stata version 12 (StataCorp, College Station, TX, USA).

We defined a priori by consensus on the basis of the clinical notion of a minimally important difference [27] that the upper limit of the 95% confidence interval (CI) of the adjusted comparative effectiveness estimate of MF59-TIV compared with virosomal-TIV, measured as adjusted HR, should be <0.9, or the lower limit >1.10, for the comparative effectiveness estimate between both vaccines to be considered clinically meaningful in favor of one of the vaccines.

We followed the International Ethical Guidelines for Epidemiological Studies [28]. The Ethic Research Committee of the Directorate of Public Health and Public Health Research Centre of Valencia approved the study protocol and provided the exemption from obtaining individual informed consent to obtain and merge individual data coming from the different registries.

3. Results

3.1. Population characteristics

Our cohort included 433,102 adults aged ≥65 years who were registered as vaccinated against seasonal influenza during the 2010 vaccination campaign (Fig. 1). We excluded institutionalized adults ($n = 13.174$; 3% of the cohort) who were on average older, more likely to be female and to lack dispensation records. We also excluded 46.913 (11%) individuals who were given non-adjuvanted

TIV. The age and sex distribution of this group was similar to that of the overall cohort, but the percentage of subjects that were regularly dispensed a combination of cardiovascular, obstructive airway disease and antithrombotic drugs was higher ($P < .001$) among this group compared with subjects vaccinated with either MF59-TIV or virosomal-TIV vaccines; 6% for the non-adjuvanted TIV group compared with 3% in both the MF59-TIV and virosomal-TIV vaccinated subjects.

After exclusions, our study population was 373,798 adults aged ≥65 years who were vaccinated with either virosomal-TIV (176,618; 42%) or MF59-TIV (197,180; 47%) (Fig. 1). The two vaccine groups showed similar age and sex distributions (Table 1). The proportions of dispensed drugs during 2010 for the ATC groups associated with influenza-related hospitalization were similar in both vaccine groups (Table 1). The cohort subjects in the virosomal-TIV group were more likely to have international travel medical and health insurance (7% versus 1%), and live further away from the nearest hospital and in towns with less deprivation (Table 1).

3.2. Influenza hospitalization

During the 2010–2011 influenza season, we confirmed 40 hospitalizations related to influenza among 176,618 subjects vaccinated with virosomal-TIV, which contributed 4,288,110 person–weeks at risk, and 37 among 197,180 subjects vaccinated with MF59-TIV, which contributed 4,786,360 person–weeks at risk (Fig. 1 and Table 2). From these 77 cases, 65 (84%) were laboratory-confirmed; 36 of 40 (90%) in virosomal-TIV- and 29 of 37 (78%) in MF59-TIV-vaccinated subjects.

After accounting for type of vaccine administered and time at risk, rates of influenza-related hospitalization were highest among subjects who had been dispensed combinations of cardiovascular, antithrombotic or obstructive pulmonary drugs; lived at a short distance to the nearest hospital; or had public or no information on insurance coverage (Table 2). Rate ratios of influenza-related hospitalization by vaccine type did not vary significantly across the strata of the covariates considered (Table 2).

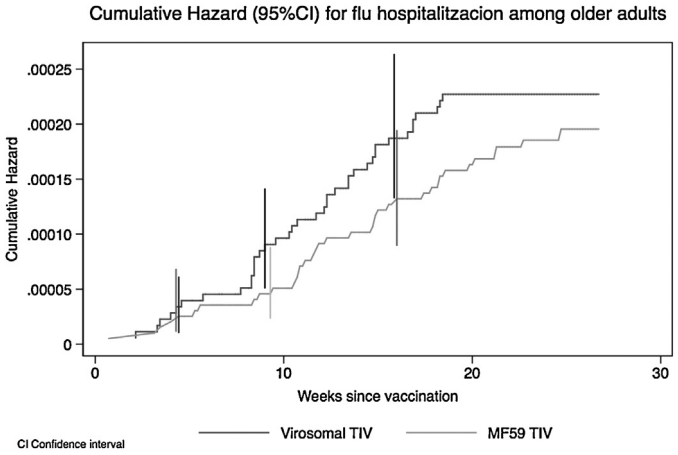

Fig. 2. Cumulative hazard (95% CI at spaced intervals) for flu hospitalization in adults ≥65 years.

3.3. Comparative vaccine effectiveness estimates

Crude influenza hospitalization rates were lower among subjects vaccinated with MF59-TIV compared with virosomal-TIV (HR 0.83; 95% CI, 0.53–1.30), with a comparative effectiveness of 17% (95% CI, −30 to 47%). After adjustment for age, sex, drugs prescribed, traveling time to hospital, deprivation and insurance, the HR estimate was 0.85 (95% CI, 0.54–1.34), with a comparative effectiveness of 15% (95% CI, −34 to 46%). There was no significant difference in comparative effectiveness of MF59-TIV relative to virosomal-TIV (Table 3 and Figs. 2 and 3). After accounting for hospital clustering by multilevel modeling, the HR was 0.94 (94% CI, 0.37–2.38), with a comparative effectiveness of 6% (95% CI, −138 to 63%).

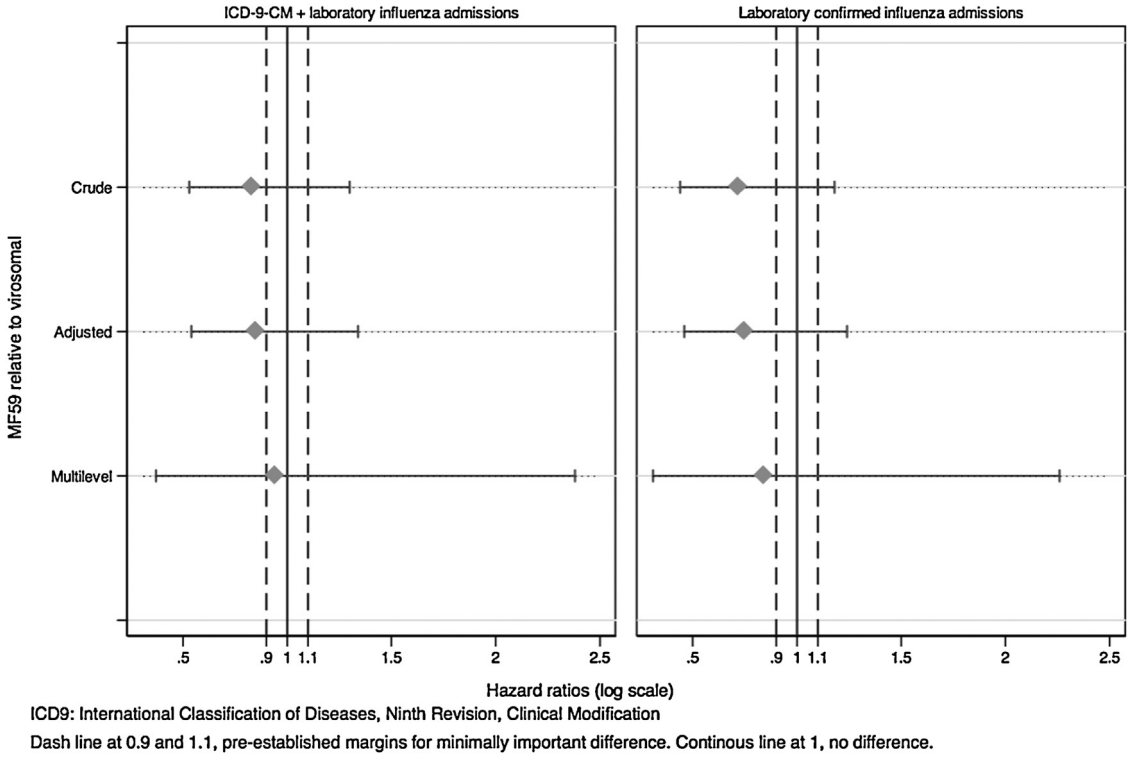

Fig. 3. Effectiveness of MF59 relative to virosomal influenza adjuvanted vaccine.

Table 1
Study subject characteristics by vaccine type.

	Virosomal-TIV (n = 176,618)		MF59-TIV (n = 197,180)	
	n	%	n	%
Age groups (years)				
65–69	39,053	22	43,140	22
70–74	43,055	24	46,413	24
75–79	42,369	24	46,515	24
80–84	30,262	17	34,819	18
≥85	21,879	12	26,293	13
Sex				
Male	79,887	45	86,741	44
Female	96,731	55	110,439	56
Drugs prescribed, 2010[a]				
No cardiorespiratory drugs prescribed or no drug dispensing recorded	29,222	17	39,959	16
Cardiorespiratory drugs not dispensed in combination	106,380	60	121,830	62
Combination of cardiovascular and antithrombotic drugs	31,812	18	33,971	17
Combination of cardiovascular and respiratory drugs	4010	2	5247	3
Combination of antithrombotic, cardiovascular and respiratory drugs	5194	3	5173	3
Seasonal vaccination 2007–2008				
No	37,613	21	40,670	21
Yes	139,005	79	156,510	79
Seasonal vaccination 2008–2009				
No	27,918	16	30,720	16
Yes	148,700	84	166,460	84
Seasonal vaccination 2009–2010				
No	77,655	44	80,227	41
Yes	98,963	56	116,953	59
Pneumococcal vaccine (all times)				
No	173,376	98	193,399	98
Yes	3242	2	3781	2
Driving time to hospital				
<60 min	98,613	56	134,197	68
≥60 min	78,005	44	62,983	32
Health insurance/coverage				
Miscellaneous[b]	1609	1	2215	1
International	11,620	7	1301	1
Public	155,405	88	187,016	95
No information	7984	5	6648	3
Deprivation				
Low	26,783	15	85,245	43
Medium	57,736	33	13,634	7
High	73,665	42	85,654	43
Highest	18,418	10	12,643	6

P values omitted, given the number of subjects included, all differences in the distribution of variables between both groups had P values < 0001, with the exception of seasonal 2008–2009 influenza vaccine (P = .0560) and pneumococcal vaccine (all times; P = .0650)

[a] Patients grouped according to drugs dispensed to each cohort member, from January 1, 2010 to December 31, 2010. Drugs classified by Anatomical Therapeutic Chemical (ATC) classification system codes. Non-sporadic prescription, means >6 packs/year prescribed for each drug class.

[b] Private, without insurance, or other.

When we restricted the analysis to admissions associated with laboratory-confirmed influenza (n = 65), the crude and adjusted HR was 0.72 (95% CI, 0.44–1.18) and 0.75 (95% CI, 0.46–1.24), respectively (Table 3 and Fig. 3). When we adjusted for between-hospital variability, HR estimate was 0.84 (95% CI, 0.31–2.26).

In both multilevel analyses, there was strong evidence (P < .001) of variability between hospitals. The upper and lower limits of the 95% CI of the adjusted HR of MF59 relative to virosomal vaccine were >0.9 or <1.10, respectively, in all analyses performed (Fig. 3).

4. Discussion

In this large retrospective study, we compared two adjuvanted TIVs administered routinely during the 2010–2011 influenza season to adults aged ≥65 years. We found no significant differences in the rates of influenza-related hospitalization between the MF59 and virosomal vaccines in a season in which the predominant circulating influenza strains, A(H1N1)pdm09 and B, shared most of the antigenic characteristics of the strains included in the vaccine, and in which vaccination provided protection against laboratory-confirmed hospitalization for influenza [17].

Our observational study provides important insights about the applicability of previous trial results reporting differences between MF59 and virosomal vaccines in terms of immunogenicity [13,29–31], and the comparative vaccine effect in a real setting. Our results are valuable because, to the best of our knowledge, there are no randomized controlled trials or observational studies comparing adjuvanted influenza vaccines in older adults in terms of clinical outcomes. However, the quality of evidence from observational studies can be questioned because of confounding by indication or biases related to unmeasured covariates. We compared two groups that had both been registered as vaccinated with influenza vaccine in the studied season, this circumstance should minimize confounding by indication. We derived an accurate indicator of severe illness based on dispensed cardiovascular and respiratory medication during 2010 to account for higher rates of influenza

Table 2
Influenza hospitalization rates and relative risk of influenza-related hospitalization by recorded influenza vaccine and subject characteristics.

	Virosomal-TIV			MF59-TIV			Crude RR (95% CI)[b]	*P* value[c]
	Person–weeks	Influenza-related admissions (*n*)	Rates[a]	Person–weeks	Influenza-related admissions (*n*)	Rates[a]		
All cohort subjects	4,288,110	40	0.93	4,786,360	37	0.77	0.83 (0.53–1.30)	.4100
Age groups (years)[d]								.1658
65–69	943,600	7	0.74	1,044,310	7	0.67	0.90 (0.32–2.58)	
70–74	1,044,480	8	0.76	1,128,060	8	0.71	0.93 (0.35–2.47)	
75–79	1,031,770	10	0.97	1,131,580	9	0.80	0.82 (0.33–2.02)	
80–84	736,850	9	1.22	846,290	6	0.71	0.58 (0.21–1.63)	
≥85	531,400	6	1.13	636,130	7	1.10	0.97 (0.33–2.90)	
Sex								.2909
Male	1,941,270	17	0.88	2,110,360	22	1.04	1.19 (0.63–2.24)	
Female	2,346,840	23	0.98	2,676,010	15	0.56	0.57 (0.30–1.10)	
Drugs dispensed, 2010[d]								<.0001
No cardiorespiratory drugs dispensed or no dispensing record	292,690	0	0.00	303,600	3	0.99	–	
Cardiorespiratory drugs not dispensed in combination	2,585,760	21	0.81	2,959,550	14	0.47	0.58 (0.30–1.15)	
Combination of cardiovascular and antithrombotic drugs	773,520	7	0.91	826,420	7	0.85	0.94 (0.33–2.67)	
Combination of cardiovascular and respiratory drugs	97,650	3	3.07	128,090	5	3.90	1.28 (0.31–5.34)	
Combination of cardiovascular, respiratory and antithrombotic drugs	126,650	9	7.11	126,360	8	6.33	0.89 (0.34–2.31)	
Seasonal vaccination 2007–2008								.0734
No	896,970	4	0.45	972,780	6	0.62	1.39 (0.39–4.92)	
Yes	3,391,140	36	1.06	3,813,580	31	0.81	0.77 (0.47–1.24)	
Seasonal vaccination 2008–2009								.7546
No	663,700	3	0.45	734,510	8	1.09	2.42 (0.64–9.12)	
Yes	3,624,410	37	1.02	4,051,850	29	0.72	0.70 (0.43–1.14)	
Seasonal vaccination 2009–2010								.5282
No	1,903,710	17	0.89	1,969,300	13	0.66	0.74 (0.36–1.52)	
Yes	2,384,400	23	0.96	2,817,070	24	0.85	0.88 (0.50–1.56)	
Pneumococcal vaccine (all times)								.2505
No	4,209,900	39	0.93	4.695.320	35	0.75	0.81 (0.51–1.27)	
Yes	78,210	1	1.28	91.040	2	2.20	1.72 (0.16–18.92)	
Drive time to hospital group								.0210
<60 min	2,393,620	30	1.25	3.254.550	27	0.83	0.66 (0.39–1.11)	
≥60 min	1,894,490	10	0.53	1.531.810	10	0.65	1.24 (0.52–2.97)	
Health insurance								<.0001
Miscellaneous[e]	38,010	0	0	53,120	0	0	–	
International	269,410	0	0	31.020	0	0	–	
Public	3,787,420	28	0.74	4,511,710	31	0.68	0.92 (0.55–1.54)	
No information	193,270	12	6.21	160,510	6	3.74	0.60 (0.23–1.60)	
Deprivation[d]								.1248
Low	648,370	3	0.46	2,059,760	13	0.63	1.36 (0.39–4.79)	
Medium	1,399,890	10	0.71	331,760	5	1.51	2.12 (0.73–6.21)	
High	1,792,710	18	1.00	2,085,690	16	0.77	0.76 (0.39–1.50)	
Highest	446,760	9	2.01	309,060	3	0.97	0.48 (0.13–1.78)	

[a] Rates per 100,000 person–weeks.
[b] Maximum likelihood estimate of the rate ratio. All tests for effect modification between covariate's strata, $P > 0.05$.
[c] Likelihood ratio, χ^2 test for association of the covariate with influenza hospitalization, after controlling for vaccine administered and for time (Cox model).
[d] Likelihood ratio, χ^2 test for departure from linearity, $P > 0.05$
[e] Private, without insurance, or other.

Table 3
Comparative effectiveness of MF59 and virosomal influenza vaccines according to outcome definition.

MF59 relative to virosomal influenza vaccines	Outcome definition			
	All influenza related admissions[a] $n = 77$		Laboratory-confirmed influenza admissions $n = 65$	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
HR[b]				
Crude	0.83 (0.53–1.30)	.4100	0.72 (0.44–1.18)	.1910
Adjusted[c]	0.85 (0.54–1.34)	.4970	0.75 (0.46–1.24)	.2610
Multilevel[c,d]	0.94 (0.37–2.38)	.9000	0.84 (0.31–2.26)	.7260
Comparative effectiveness[e]				
Crude	17% (−30 to 47%)	.4100	28% (−18 to 56%)	.1910
Adjusted[c]	15% (−34 to 46%)	.4970	25% (−24 to 54%)	.2610
Multilevel[c,d]	6% (−138 to 63%)	.9000	16% (−126 to 69%)	.7260

[a] International Classification of Diseases, Ninth Revision, Clinical Modification, discharge codes 487–488.89.
[b] Cox regression, week as time at risk.
[c] Adjusted by age, sex, cardiovascular and respiratory drugs dispensed in 2010, travel time to hospital, deprivation, and insurance coverage.
[d] Cox regression multilevel analysis accounting for hospital/health district as shared parameter. $P < .0001$ for between hospital variability.
[e] Comparative effectives estimated as $(1 - \text{HR}) \times 100$.

hospitalization, assuming prescription composition and duration as a proxy for chronic comorbidity [24]. Another contribution of our study includes the specificity of our case definition through confirmation of influenza virus infection in 65 out of 77 hospitalizations.

Other additional limitations must be taken into account. The sensitivity to detect the actual number of influenza-related hospitalizations using hospital discharge records, the redMIVA dataset and data from the ongoing influenza active surveillance study carried out in Valencia may be questioned. We chose to pool the cases confirmed from each of these sources to increase the overall sensitivity of our case definition. In addition, differential case confirmation could have biased our estimates. In this regard, the existence of universal free access to health care of Valencia residents and the adjustment for insurance and hospital, allows us to conclude that this bias, if present, was minimized and taken into account. Moreover, we considered that case confirmation bias could have been introduced if the results obtained in the active surveillance system hospitals had a disproportionate influence on our results. This was not the case, because when we repeated the analysis without the influenza hospitalization detected by this active surveillance system, or excluded the five participating hospitals, the results did not vary substantially and were consistent with the results obtained from the overall cohort (Supplementary Table 2). Our results should be interpreted after accounting for all the previous considerations, but we suggest that case confirmation bias, if present, was not differential, and that despite a possible low sensitivity, the high specificity for case definition supports that our relative estimates were near to the true effect [32].

Hospital admission criteria, the quality of CMBD registers, or the likelihood of specimen sampling for laboratory confirmation of influenza virus is likely to vary between hospitals [33]. In addition, the average socio-economic level of the population living within a hospital catchment area may vary across hospitals. 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. The probability of cases going undetected could be associated with vaccine type. We used multilevel models to account for potential variability between hospitals and found strong evidence for differences in risk of hospitalization for influenza. However, these multilevel analysis results did in fact reinforce our conclusion of no clinically relevant differences between the two adjuvanted vaccines, because the multilevel adjusted estimates obtained were similar to those of the models without the shared-frailty parameter.

The low hospitalization rates for influenza in the age group considered during this A(H1N1)pdm09 predominant influenza season, in comparison with what would have been expected in an H3N2 or B predominant season [17,22,34], limited the power of the analysis to detect significant differences. Nevertheless, our results suggest that this difference, if it did exist, was of minimal clinical relevance.

5. Conclusion

During the 2010–2011 influenza season, we found no differences in the risk of influenza hospitalization in subjects aged ≥65 years vaccinated with MF59-TIV compared with those vaccinated with virosomal-TIV. Similar studies, taking advantage of data routinely collected in the health care process, are warranted. These should be conducted over several influenza seasons to assess comparative vaccine effectiveness and its variability by the degree of antigenic match between vaccine and circulating viruses, type and composition of influenza vaccines, age and risk groups, and predominant circulating influenza strains.

Acknowledgments

We are grateful to Julián Librero for his support and 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; and the Microbiological Surveillance Network in the Valencia Autonomous Community (redMIVA) for their assistance.*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].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.05.070.

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