Vaccine 32 (2014) 5447–5454

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 12 August 2014

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),