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Waning protection of influenza vaccination during four influenza seasons, 2011/2012 to 2014/2015

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ABSTRACT

Background: Concerns have been raised about intraseasonal waning of the protection conferred by influenza vaccination.
Methods: During four influenza seasons, we consecutively recruited individuals aged 18 years or older who had received seasonal influenza vaccine and were subsequently admitted to the hospital for influenza infection, as assessed by reverse transcription polymerase chain reaction. We estimated the adjusted odds ratio (aOR) of influenza infection by date of vaccination, defined by tertiles, as early, intermediate or late vaccination. We used a test-negative approach with early vaccination as reference to estimate the aOR of hospital admission with influenza among late vaccinees. We conducted sensitivity analyses by means of conditional logistic regression, Cox proportional hazards regression, and using days between vaccination and hospital admission rather than vaccination date.
Results: Among 3615 admitted vaccinees, 822 (23%) were positive for influenza. We observed a lower risk of influenza among late vaccinees during the 2011/2012 and 2014/2015A(H3N2)-dominant seasons: aOR = 0.68 (95% CI: 0.47–1.00) and 0.69 (95% CI: 0.50–0.95). We found no differences in the risk of admission with influenza among late versus early vaccinees in the 2012/2013A(H1N1)pdm09-dominant or 2013/2014B/Yamagata lineage-dominant seasons: aOR = 1.18 (95% CI: 0.58–2.41) and 0.98 (95% CI: 0.56–1.72). When we restricted our analysis to individuals aged 65 years or older, we found a statistically significant lower risk of admission with influenza among late vaccinees during the 2011/2012 and 2014/2015 A(H3N2)-dominant seasons: aOR = 0.61 (95% CI: 0.41–0.91) and 0.69 (95% CI: 0.49–0.96). We observed 39% (95% CI: 9–59%) and 31% (95% CI: 5–50%) waning of vaccine effectiveness among

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participants aged 65 years or older during the two A(H3N2)-dominant seasons. Similar results were obtained in the sensitivity analyses.
Conclusion: Waning of vaccine protection was observed among individuals aged 65 years old or over in two A(H3N2)-dominant influenza seasons.

1. Introduction

Influenza vaccine administration is universally recommended for certain groups at risk of severe outcomes [1]. The effectiveness of influenza vaccines is moderate [2,3], and potential waning of this moderate effect has been reviewed [4–6].

During the 2011/2012 European influenza season, patients belonging to target groups for vaccination experienced a reduction of vaccine protection against influenza A(H3N2) virus infection [7]. A similar effect during the same season was reported by other authors [8–10]. Similar results were reported in the United Kingdom of possible waning protection against infection with type A(H3N2) influenza during the 2012/2013 season [11]. One study using pooled data collected during five consecutive influenza seasons in Europe reported waning of the protection conferred by the influenza vaccine to prevent medically attended illness with laboratory confirmed infection with A(H3N2) and B/Yamagata lineage influenza viruses in outpatients [12]. Similar results have been reported in a study during 4 consecutive influenza seasons in the United States [13].

In most published studies, the main exposure variable has been defined as the number of days elapsed between vaccination date and symptoms onset date [7–9,12,13]. Since this definition is related with the definition of the outcome variable, the validity of a reported waning effect of influenza vaccination using this covariate (days between vaccination and symptom onset) should be interpreted with caution [14,15].

Since 2010, the Valencia Hospital Network for the Study of Influenza (VAHNSI) has conducted a prospective, hospital-based, active surveillance study in Valencia, Spain. We ascertain hospital admissions with influenza infection by reverse transcription polymerase chain reaction (RT-PCR) using pharyngeal and nasopharyngeal swabs, and we obtain vaccination data from the Valencia Region Vaccine Information System (VRVIS) [16]. This ongoing study has provided the opportunity to investigate whether influenza vaccine effectiveness waned in accordance with the calendar period of vaccination during four influenza seasons.

2. Methods

2.1. Study population

The VAHNSI study methods have been previously described [16]. During four influenza seasons, we identified patients who were consecutively admitted to the hospital with complaints that could be related to recent influenza infection. The number of participating hospitals varied by season, according to the available funds. The Ethics Research Committee of the *Centro Superior de Estudios en Salud Pública* approved the study protocol.

Using incidence-density sampling [17], we enrolled all consecutively admitted patients aged 18 years or older who were non-institutionalized, residents for at least 6 months in the recruiting hospitals catchment area, not discharged from a previous admission episode in the past 30 days, with length of hospital stay less than 48 h, who reported an influenza-like illness (ILI) defined as one systemic symptom (fever or feverishness, headache, malaise, or myalgia) and one respiratory symptom (cough, sore throat, or shortness of breath) within 7 days of admission. All enrolled participants provided written informed consent. We collected sociodemographic and clinical information by interviewing patients or by consulting clinical registries and we obtained nasopharyngeal and pharyngeal swabs from all patients. Influenza infection was ascertained by RT-PCR at the study reference laboratory following World Health Organization (WHO) laboratory guidelines for the diagnosis and characterization of influenza viruses [16,18].

The current analysis was restricted to individuals who belonged to target groups for vaccination and who had received the seasonal influenza vaccine more than 14 days before the onset of ILI. We decided to include only vaccinated patients, from which we could obtain their vaccination date from the population-based registry VRVIS, in order to avoid possible heterogeneity introduced by the uncertainty vaccination status among unvaccinated individuals.

2.2. Vaccination and seasons

Each hospital provides care to a defined population who are entitled to free health care. Each individual has a unique identification number that is linked to the VRVIS, inpatient and outpatient clinical records, and sociodemographic information [19]. Influenza vaccines were offered free of charge to participants older than 6 months with high-risk conditions and to those 60 years or older with or without high-risk conditions. Information on the vaccine administered to all patients included in the study, in addition to the date of vaccination, was obtained from the VRVIS.

2.3. Statistical analysis

2.3.1. Outcome and exposure

The outcome variable was hospital admission with RT-PCR-confirmed influenza. Main exposure variable was the date of vaccination. Calendar date of vaccination was grouped in tertiles to report results by comparison of late and early vaccination. Participants who were vaccinated during the first tertile were considered early vaccinees and those vaccinated in the third tertile, late vaccinees.

We used a multivariable logistic regression to explore the impact of those factors possibly related to early or late vaccination such as age, number of chronic medical conditions, smoking status, socioeconomic level, recruiting hospital, and previous season vaccination. Covariates with $p < 0.05$ were included in our final model to estimate the waning effect.

2.3.2. Waning effect

We considered waning vaccine protection to be present when the adjusted odds ratio (aOR) of hospital admission with influenza for late versus early vaccination was less than 1 and the aOR with 95% confidence interval (CI) did not include the unity.

The aOR of being positive for influenza was estimated using multilevel models [20]. The following variables were used as fixed effects: age, sex, smoking status, socioeconomic level, number of chronic medical conditions, days from onset of symptoms to swab collection, number of hospitalizations in the previous 12 months, number of outpatient visits in the previous 3 months, and epidemiological week of admission. Hospital was included in the model as a random effect. Age was divided into deciles and modeled using