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Effectiveness of subunit influenza vaccination in the 2014–2015 season and residual effect of split vaccination in previous seasons

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ABSTRACT

Background: In Navarra, Spain, subunit vaccine was first used in the 2014–2015 season, whereas trivalent split-virion influenza vaccines had been used in previous seasons. We estimate the effectiveness of the subunit vaccine in the current season and split vaccine in the two previous seasons against laboratory-confirmed influenza in the 2014–2015 season.
Methods: Patients with influenza-like illness hospitalized or attended by sentinel general practitioners were swabbed for influenza testing. The previous and current vaccine status of laboratory-confirmed cases was compared to test-negative controls.
Results: Among 1213 patients tested, 619 (51%) were confirmed for influenza virus: 52% influenza A(H3N2), 46% influenza B, and 2% A(H1N1)pdm09. The overall effectiveness for subunit vaccination in the current season was 19% (95% confidence interval [CI]: −13 to 42), 2% (95%CI: −47 to 35) against influenza A(H3N2) and 32% (95%CI: −4 to 56) against influenza B. The effectiveness against any influenza was 67% (95%CI: 17–87) for 2012–2013 and 2013–2014 vaccination only, 42% (95%CI: −31 to 74) for 2014–2015 vaccination only, and 38% (95%CI: 8–58) for vaccination in the 2012–2013, 2013–2014 and 2014–2015 seasons. The same estimates against influenza A(H3N2) were 47% (95%CI: −60 to 82), −54% (95%CI: −274 to 37) and 28% (95%CI: −17 to 56), and against influenza B were 82% (95%CI: 19–96), 93% (95%CI: 45–99) and 43% (95%CI: 5–66), respectively.
Conclusion: These results suggest a considerable residual protection of split vaccination in previous seasons, low overall effectiveness of current season subunit vaccination, and possible interference between current subunit and previous split vaccines.

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1. Introduction

The fact that influenza vaccines are commercialized annually without efficacy evaluations has given rise to interest in post-commercialization effectiveness studies. The majority of influenza vaccines available in recent decades have been trivalent inactivated split-virion vaccines produced from egg-grown viruses whose membrane is disrupted by detergent treatment. Subunit vaccines only contain purified hemagglutinin and neuraminidase from which other virus components have been removed [1]. Split-virion and subunit vaccines contain similar amounts of hemagglutinin [2]; however, differences in protection could not be accounted for by differences in serum hemagglutination inhibition titers, since multiple immune mechanisms can confer protection against influenza [3–6]. Split-virion vaccines usually contain more internal proteins, which may be important for cellular immune responses [7]. These responses, directed toward internal proteins such as nucleoprotein, polymerases and matrix proteins, have been associated with clearing influenza infection [8]. An experimental study has correlated reduction of viral replication and protection from disease with pre-existing cellular immunity [9], but more information is needed about whether differences in cellular immune responses translate into differences in influenza vaccine effectiveness.

The composition of the trivalent influenza vaccines for use in the 2014–2015 influenza season in the northern hemisphere included an A/California/7/2009(H1N1)pdm09-like, an A/Texas/50/2012(H3N2)-like, and a B/Massachusetts/2/2011-like virus [10]. The A(H1N1) component has remained unchanged since 2010; the A(H3N2) component can be considered unchanged since the 2012–2013 season given that A/Texas/50/2012 is an A(H3N2) virus antigenically like the cell-propagated virus A/Victoria/361/2011; and the trivalent influenza vaccine has contained the B/Yamagata-lineage since the 2012–2013 season [10,11].

In Navarra, Spain, the trivalent split-virion influenza vaccines were used annually in the influenza vaccination program until the 2013–2014 season, while subunit influenza vaccines were used for the first time in the 2014–2015 season [12]. The aim of this study was to estimate the effectiveness of subunit vaccination in the current season and of split-virion vaccination in the two previous seasons in preventing laboratory-confirmed influenza in the 2014–2015 season.

2. Methods

2.1. Study population

This study was performed in Navarra, a region in northern Spain. The Regional Health Service provides health care, free at point of service, to 96% of the population. The Navarra Ethical Committee for Medical Research approved the study protocol.

The seasonal vaccination campaign took place from 13 October to 28 November 2014. Every year the trivalent inactivated non-adjuvant vaccine was recommended and offered free of charge to people aged 60 years or older and to those with risk factors or major chronic conditions; the criteria for vaccination have remained unchanged in the last four influenza seasons. Unlike previous seasons when split-virion vaccine had been used (Vaxigrip, Sanofi Pasteur MSD), in the 2014–2015 season an influenza subunit vaccine produced in cell culture (Optaflu, Novartis) was offered for people aged 18 years and over, and an egg-grown influenza subunit vaccine (Chiroflu, Novartis) was offered to those younger than 18 years [12]. Other people were also vaccinated if they paid for the vaccine in drugstores.

Influenza surveillance was based on automatic reporting of cases of medically-attended influenza-like illness (MA-ILI) from all primary healthcare centers and hospitals. ILI was considered to be the sudden onset of any general symptom (fever or feverishness, malaise, headache, or myalgia) in addition to any respiratory symptom (cough, sore throat or shortness of breath). A sentinel network composed of a representative sample of primary healthcare physicians, covering 18% of the population, was asked to take double swabs, nasopharyngeal and pharyngeal, after obtaining verbal informed consent, from all their patients diagnosed with ILI whose symptoms had begun less than five days previously. The protocol for influenza cases in hospitals establishes early detection and nasopharyngeal and pharyngeal swabbing of all hospitalized patients with ILI. Swabs were analyzed by real-time reverse-transcription polymerase-chain-reaction (RT-PCR). Strains selected among culture-positive samples with representation of each week and virus type/subtype were sent to the National Influenza Center–Madrid laboratory for complete genetic characterization.

2.2. Study design and statistical analysis

We carried out a test-negative case-control study in the population covered by the Navarra Health Service. Healthcare workers, persons living in nursing homes, and children under six months of age were excluded. The study period started after the end of the vaccination campaign and included the weeks between the first and the last virus detection. This period was defined from 1 December 2014 (week 49) to 26 April 2015 (week 17) for the analysis of all influenza cases, from 1 December 2014 to 5 April 2015 for influenza A(H3N2) cases, and from 22 December 2014 to 26 April 2015 for influenza B cases.

The cases were MA-ILI patients in primary healthcare or in hospitals who were confirmed for influenza virus by RT-PCR, and the controls were MA-ILI patients who tested negative for influenza virus. Their influenza vaccination status for the current and two previous seasons was obtained from the regional vaccination register [13]. Subjects were considered to be protected starting 14 days after vaccine administration. Two cases and five controls who received the split influenza vaccine in the 2014–2015 season were excluded from the analysis.

Percentages were compared by the χ^2 test. The preventive effect of current and previous vaccination on laboratory-confirmed influenza was evaluated in four categories: unvaccinated in all three seasons, any previous dose of split vaccine only, current-season subunit vaccine only, and any previous dose of split vaccine and current-season subunit vaccine. In some analyses one and two previous doses of split vaccine were considered as separate categories. Logistic regression was used to calculate the odds ratios (OR) with their 95% confidence intervals (CI), adjusting for sex, age group (<5, 5–14, 15–44, 45–64, 65–84, and ≥85 years), any major chronic condition (heart disease, respiratory disease, renal disease, cancer, diabetes mellitus, cirrhosis, dementia, stroke, immunodeficiency, rheumatic disease, and body mass index ≥40 kg/m^2), three-week period of sample collection, and healthcare setting (primary healthcare and hospital). Separate analyses were done by type/subtype of influenza and healthcare setting. The interaction term of prior-season split vaccination and current-season subunit vaccination was evaluated. Some analyses included the number of

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