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Waning protection of influenza vaccine against mild laboratory confirmed influenza A(H3N2) and B in Spain, season 2014–15

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ABSTRACT

Introduction: The 2014/15 influenza season in Spain was dominated by the circulation of drifted A(H3N2) and co-circulation of B viruses. We present the final estimates of influenza vaccine effectiveness (IVE) against confirmed influenza A(H3N2) and B its evolution along the season and with time since vaccination.
Methods: We used data collected on influenza like illness patients (ILI), systematically swabbed for the presence of influenza viruses within the Spanish Influenza Sentinel Surveillance System (SISS) and a restricted observational study (cycEVA). We used a test negative case–control design to compare influenza confirmed cases with negative controls. We estimated the IVE through a logistic regression model adjusting for potential confounders. The evolution of IVE was studied in early and late stages of the epidemic, and in different time intervals between receiving influenza vaccination and the onset of symptoms.
Results: At the end of the season we have found low and moderate IVE point estimates against influenza A(H3N2) and B, respectively, in all ages and target groups for vaccination. An IVE decreased from an early value of 37% to a late of −76% against influenza A(H3N2), and similarly, 84% vs −4% against Influenza B. When the onset of symptoms occurred more than three months after vaccination, the decrease of IVE was slower and milder against influenza B than against influenza A(H3N2). No significant change in the percentage of circulating drifted influenza A(H3N2) strains belonging to the 3c.2a and 3c.3a clades could be identified through the season.
Conclusions: In a season dominated by drifted A(H3N2) circulating virus, the vaccine offered little or no protection against A(H3N2) infection but had a moderate protective effect against influenza B. Efforts should be put in developing influenza vaccines that maintain their protective capabilities throughout the season and could stimulate a potentially broad immune response against diverse influenza strains.

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1. Introduction

Q3 Influenza vaccination is considered the most important intervention towards preventing complications by influenza not only in high-risk groups but also in general population [1,2]. The recommendation for trivalent influenza vaccine for the Northern Hemisphere in the 2014–15 season, included the A/California/7/2009 (H1N1)pdm09, the A/Texas/50/2012 (H3N2) and the B/Massachusetts/02/2012 (Yamagata lineage) strains [3]. The vaccine was offered in Spain to all individuals above 64 years and to those belonging to clinical or professional risk groups [4].

Since the 2008–09 season the (cycEVA) observational case–control study has been monitoring the influenza vaccine effectiveness (IVE) in Spain within the framework of the Influenza Monitoring of Vaccine Effectiveness (I-MOVE) European network. cycEVA has been functioning within the Spanish Influenza Sentinel Surveillance System (SISS), a well-established system of 17 sentinel influenza networks in 17 out of 19 Spanish autonomous regions [5], and has been supplying timely and reliable IVE estimates both during as well as at the end of the season [6–9]. IVE estimates obtained with cycEVA and the entire surveillance system were largely similar [10].

The 2014–15 season in Spain was characterized by the predominant A(H3N2) influenza virus, the majority of which were mismatched with the 2014–15 northern hemisphere A(H3N2) vaccine strain [11].

We present in this paper the final estimates of IVE 2014–15 in Spain obtained using the SISS and the cycEVA study. Moreover, we studied the evolution of the IVE along the season using two strategies. Firstly we compared the IVE estimates in the early and late phase of the epidemic, using both SISS and cycEVA data. Secondly, we studied the effect of time since vaccination (TSV) on the vaccine protection within cycEVA study. Based on the genetic characterization of a representation of detected strains, we tried to provide additional knowledge on the relationship between IVE and circulating strains pattern.

2. Methods

2.1. The study population

We considered as study population all patients with influenza-like illness (ILI) symptoms attending the sentinel physicians (SPs) including generalist doctors and paediatricians integrated in the SISS (788 SPs) or in the six sentinel networks participating in the 2014–15 cycEVA study (174 SPs). In five out of six cycEVA regions all of SPs participate in both cycEVA and SISS studies, whereas in the sixth only 77% of the SPs belonging to SISS are participating in cycEVA. The components and the requirements for the SISS and cycEVA functionality were previously described [6,10,12]. Overall, SPs within SISS systematically swabbed ILI patients and collected demographic, clinical, virological, vaccination, chronic conditions, obesity and pregnancy status data. Several variables are routinely collected for the cycEVA study: number of hospitalizations for chronic condition, SPs visits in the last year, previous influenza vaccination, smoking habit and influenza vaccination date.

During the season, in the SISS the influenza vaccination status was ascertained through a dichotomous variable (yes/no). However, at the end of the influenza epidemic we obtained retrospectively the vaccination date for the immunized patients attending 594 SPs belonging to 14 SISS sentinel networks. This information allowed to check if the patient was correctly immunized, with the administration of the vaccine 14 days or more before the onset of symptoms. Information on vaccination date was obtained for the 93.4% of the patients notified as having received the Influenza vaccine.

2.2. The study design and data analysis

We conducted a test negative case–control study between 8 December 2014 and 19 April 2015 (weeks 50/2014–16/2015). Cases were ILI patients with a Polymerase Chain Reaction (PCR) swab positive for influenza taken less than eight days after onset of ILI symptoms. ILI patients testing negative for all influenza strains were considered controls.

Baseline characteristics of cases and controls were compared using Chi-squared test. We calculated the IVE as (1-OR for vaccination) × 100 and we used logistic regression models to obtain IVE estimates with 95% confidence intervals (95%CI), adjusted by potential confounders collected both by SISS and cycEVA study.

IVE was estimated by virus type/subtype in all ages and in target groups for vaccination. Additionally we studied the IVE within specific age-groups (0–14; 15–64; >64 years), using SISS data.

We performed two sensitivity analyses: (1) Restricting to patients swabbed 4 days or less after symptoms onset; (2) Using SISS data with vaccination date in order to evaluate the potential differences in IVE estimates when considering all patients as correctly vaccinated, and afterwards only patients vaccinated 14 days or more before symptoms onset.

We evaluated the IVE against A(H3N2) and B along the season with SISS and cycEVA data dividing the epidemic season in two phases: an early stage including the epidemic peak (weeks 50/2014–5/2015) and a late stage (weeks 6–16/2015).

Using cycEVA data, IVE was estimated through modelling the TSV as a categorical variable defining three TSV intervals according to the tertiles of the number of days elapsed between vaccination and onset of symptoms: t1 = from the lowest value until the first tertile, t2: between second and third tertile and t3: between the third tertile until the maximum value. We estimated the IVE adjusting for all the variables collected in cycEVA, for each TSV interval and using the non-vaccinated as reference group. We applied a logistic regression model in order to evaluate the differences between the IVE in the first TSV interval (t1), used as reference, and the IVE in the t2 and t3 [13]. All data analysis was conducted using STATA version 13.

2.3. Laboratory methods

Genetic characterization by sequencing the HA1 fragment of the viral hemagglutinin gene was carried out at the WHO National Influenza Centre (Madrid) in a subset of influenza positive samples and/or virus isolates. Phylogenetic analysis of sequences was carried out in order to characterize the specific genetic group of circulating influenza A and B clades. To detect any change in the clades circulating pattern, we analyzed the evolution in time of the overall proportion of discordant strains using the chi-squared for trend.

3. Results

The 2014–15 influenza season peaked in week 5/2015 both at national level and within the regional networks integrated in cycEVA study. The season was dominated by influenza A (61% of the confirmed cases in SISS) with 96% of A(H3N2) among the subtyped A viruses. An increasing influenza B virus circulation was identified towards the end of the epidemic.

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