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Does seasonal vaccination affect the clinical presentation of influenza among the elderly? A cross-sectional analysis in the outpatient setting in France, 2003–2014

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ABSTRACT

Vaccine-induced protection against influenza is not optimal, however it has been suggested that the vaccine may reduce the severity of symptoms among those who develop illness despite being vaccinated. We tested this hypothesis within a countrywide, sentinel general practitioners-based surveillance system in France. We included 2277 individuals aged 65 years or older (of whom 1293 had been vaccinated against influenza, 56.8%) who consulted a general practitioner because of an acute respiratory infection (ARI) during 2003–2014. All patients were taken a nasopharyngeal swab, and information was collected on demographic characteristics and symptoms at disease onset. All specimens were tested for respiratory viruses and, if positive for influenza, the virus type and subtype were determined. We compared the average maximum temperature and the frequency of each symptom, between non-vaccinated and vaccinated influenza patients. We then used logistic regression models to calculate the odds of presenting with each symptom between vaccinated vs. non-vaccinated patients, adjusting by age group, virus (sub)type and season. Overall, 675 ARI patients (29.6%) tested positive for influenza. The A(H3) virus caused the majority of cases (55.1%), followed by influenza B (22.9%), A not-subtyped (11.7%), and A(H1) (10.3%) viruses. Compared to non-vaccinated influenza patients, those who had been vaccinated had a slightly reduced maximum temperature and presented less frequently with myalgia, shivering and headache. In stratified analyses, the observed effect was limited to patients infected with A(H3) or type B viruses. After adjusting by age group, virus (sub)type and season, the difference remained statistically significant only for headache, which was less frequent among vaccinated individuals (odds ratio 0.69, 95% confidence intervals 0.48–0.98). In conclusion, the vaccine was found to be modestly associated with less severe clinical presentation of influenza among the elderly. Our findings reinforce the need for influenza vaccines providing better protection.

1. Introduction

The purpose of influenza vaccination is to prevent influenza illness, complications and severe outcomes among subjects who come into contact with the virus. Elderly people are the main population targeted by influenza vaccination campaigns as they are a high-risk population for severe complications (like bacterial pneumonia, exacerbation of chronic obstructive pulmonary disease, or decompensation of chronic underlying conditions) that may result

Abbreviations: ARI, Acute Respiratory Infection; GP, General Practitioner; GROG, Regional Groups for the Surveillance of Influenza; ICU, Intensive-Care Unit; IDR, Influenza Detection Rate; NIC, National Influenza Centre; RT-PCR, Reverse Transcriptase Polymerase Chain Reaction.

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in hospitalization, admission to an intensive-care unit (ICU), and eventually influenza-associated death [1]. The more concerned individuals are those suffering from chronic co-morbid conditions such as diabetes, heart failure or asthma. In a recent meta-analysis [2], the influenza vaccine was found effective in preventing laboratory-confirmed influenza among community-dwelling elderly people, however its ability to confer protection is far from optimal and convincing evidence for protection in adults aged 65 years or older is still lacking [3]. In particular, the vaccine effectiveness is frequently below 50% [4] as it critically depends on how well it matches the circulating strains [5].

Surprisingly, very few studies have addressed the question of whether the vaccine mitigates influenza severity among those who develop the illness despite being vaccinated. The self-scored severity of influenza at time of enrolment was reduced among vaccinated vs. non-vaccinated elderly individuals (aged 65 years or older) who sought care for an acute respiratory infection (ARI) during the period of influenza activity (December to May) in four consecutive seasons in the US [6]. Castilla et al. found that the vaccine did not affect hospitalization rates among laboratory-confirmed influenza cases, but was effective in reducing the risk of ICU admission and death among hospitalized patients, during the 2010–2011 season in Spain (which was dominated by the A(H1) pandemic virus strain) [7]. Conversely, Arriola et al. could not detect any difference in disease severity among hospitalized influenza patients by vaccination status during the A(H3)-dominated 2012–2013 season in the US, except for a shorter length of ICU stay among vaccinated vs. non-vaccinated patients aged 50–64 who were treated with antivirals [8].

The vaccine may affect both the clinical presentation of influenza at onset of symptoms and the likelihood of developing later complications that could result in hospitalization or influenza-related death. Here, we compared the symptoms at onset of illness among vaccinated and non-vaccinated elderly outpatients (aged 65 years or older) with laboratory-confirmed influenza reported to a countrywide, sentinel general practitioners-based surveillance system in France during ten influenza seasons.

2. Materials and methods

2.1. The GROG influenza surveillance system

The GROG (Regional Groups for the Surveillance of Influenza) is a French countrywide surveillance network for influenza and ARI, based on clinical and virological data collected from sentinel general practitioners (GP) and paediatricians from October through April. The GROG surveillance was established in 1984 [9] and discontinued at the end of the influenza season 2013–2014; in its last season of activity, it included over 500 physicians distributed throughout the country.

Each sentinel practitioner was requested to take a nasopharyngeal swab and to collect demographic and clinical information (including symptoms suggestive of influenza, underlying chronic conditions, and influenza vaccination status) from a subset of ARI patients (selected by purposive sampling) presenting within 48 h of onset of symptoms. The ARI case definition in use within the GROG was as follows: sudden onset of illness AND at least one general sign or symptom suggestive of an acute infectious disease (fever, asthenia, myalgia, headache, etc.) AND at least one respiratory sign or symptom (cough, rhinitis, pharyngitis, dyspnoea, etc.).

2.2. Inclusion and exclusion criteria

We included in the present study all ARI patients swabbed from the season 2003–2004 through 2013–2014 (except 2009–2010) aged 65 years or older and with known influenza vaccination status at the moment of the enrolment interview. A patient was considered vaccinated if he/she had received the seasonal influenza vaccine at least 15 days before the date of onset of ARI symptoms; patients vaccinated since less than 15 days were considered as non-vaccinated ($n = 1$). Information on the vaccination date was not available for 237 patients. In France, the uptake of influenza vaccine among the elderly usually reaches 50% at the end of October [10]. Moreover, by mid-November the vaccine is already delivered to $\geq$80% of those who purchase it during the season [11]. Based on this, patients who declared being vaccinated but with missing information on date of vaccination were included in the study and considered as vaccinated if the date of ARI onset was after November 30th ($n = 215$), while those with date of ARI onset before December 1st or unknown ($n = 22$) were excluded from the study.

We also excluded from the study database all ARI patients who had taken antivirals during the fourteen days before the onset of symptoms ($n = 7$) and those who tested positive to type C influenza virus ($n = 1$). Patients co-infected with an influenza virus and another respiratory virus ($n = 12$) or with two different influenza viruses ($n = 2$) were left in the database, but the latter were not included when performing analysis stratified by virus (sub)type.

2.3. Laboratory diagnosis

Nasopharyngeal swabs were prepared for shipping by using a triple packaging system at the GP's practice (according to the international guidelines for the transport of infectious substances, category B, classification UN 3373) and transported by post to the French National Influenza Centre (NIC; Institut Pasteur, Paris, or Hospices Civils, Lyon) or to one of the regional laboratories collaborating with the GROG network.

All specimens were tested for respiratory viruses and, if positive for influenza, the virus type and subtype (for most influenza A cases) were determined. Until the 2008–2009 influenza season, enzyme immunoassays were mostly used to determine the virus type (A, B or C), and the identification of the virus subtype was performed by isolation in cell culture, followed by a hemagglutination inhibition test using specific polyclonal sera. Since the 2009 pandemic, real time reverse transcriptase polymerase chain reaction (RT-PCR) has become widespread and quickly supplanted the techniques previously used for virus detection and (sub)typing [12].

2.4. Statistical analysis

We calculated the number of non-vaccinated and vaccinated ARI patients who were swabbed, and the proportion of those who tested positive for influenza (referred to as "influenza detection rate" – IDR - henceforth), in each season and during the whole study period, overall and by age group (65–69 years, 70–74 years, 75 years or older). We also calculated the proportion of laboratory-confirmed influenza cases (among non-vaccinated and vaccinated patients, overall and within each age group) that were caused by each of the following virus (sub)-types: A(H1), A(H3), A not subtyped, and B. The 2009 pandemic A(H1) influenza virus has completely replaced the previously circulating seasonal A (H1) strain in France since its appearance; in what follows, A(H1) will therefore refer to the pre-pandemic strain for the seasons 2003–2004 through 2008–2009, and to the 2009 pandemic strain from the season 2010–2011 onwards.

We compared the male/female ratio, the mean age, the mean delay (days) between onset of symptoms and consultation with a GP, the average maximum temperature (°C), the frequency of sudden onset, general infection symptoms (fever, asthenia, myalgia, shivering, headache), respiratory symptoms (cough, rhinitis,