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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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,

pharyngitis, expectoration, dyspnoea, bronchitis/bronchiolitis) and other symptoms (gastrointestinal symptoms, conjunctivitis, adenopathy and otitis/earache); and the median number of symptoms at clinical presentation, between non-vaccinated and vaccinated patients, overall and separately within each age group and by virus (sub)-type. We applied the Student's *t*-test, the Wilcoxon rank-sum test, and the chi-square test, to compare means, medians and, respectively, proportions between non-vaccinated and vaccinated patients. We finally fitted logistic regression models to estimate the odds of presenting with each symptom among vaccinated vs. non-vaccinated influenza patients, adjusting by age group, virus (sub)type and season.

All analyses were performed by using STATA version 11.2 (STATA Corp., TX, USA). All statistical tests were two-sided, and considered as significant for $p < 0.05$.

2.5. Ethical Aspects and consent

An oral informed consent was obtained by the GP from each study participant at the moment of consultation and before swab taking, upon providing detailed information on the aims and objectives of influenza surveillance. The consent was given orally and recorded in the data collection form accompanying the swab. All forms were anonymized by the laboratories before being sent to the GROG network coordination. In accordance with the laws and regulations in force in France, obtaining an oral informed consent is sufficient to include patients into epidemiological studies based on anonymized data collected during routine influenza surveillance activities, and no further approval of an Ethics Committee is required for the retrospective analysis of such data.

3. Results

A total of 2277 respiratory samples were taken from ARI patients aged 65 years or older who consulted their GP during 2003–2014 (average number of samples per season = 228, range 111–345). Overall, 675 respiratory samples tested positive for influenza (IDR 29.6%), of which 290 among non-vaccinated ARI patients and 385 among vaccinated ARI patients (corresponding to an IDR of 29.5% and 29.8% respectively, p for difference = 0.875) (Table 1). Vaccinated patients were significantly older than unvaccinated patients (mean age: 75.4 vs. 71.4, $p < 0.001$) and influenza was more frequent in women in both groups (sex ratio (M/F): 0.75 in non-vaccinated and 0.89 in vaccinated, $p = 0.285$). The IDR tended to decrease with age among non-vaccinated ARI patients, while there was no such trend among vaccinated ARI patients.

The A(H3) viruses caused the majority of influenza cases during the study period (55.1%), followed by influenza B (22.9%) and A (H1) (10.3%) (Fig. 1). Only two vaccinated patients were co-infected with two viruses (AH3 and B): both were aged 65–69 years and were swabbed during the 2012–2013 season. Globally, in patients 65 years or older, the proportion of influenza cases that were caused by A(H1) was higher among non-vaccinated vs. vaccinated patients (13.5% vs. 7.8%, p-value 0.017), while there were no significant difference for A(H3N2) and B. The distribution of influenza cases in terms of virus (sub)-type also differed by age group: the proportion of cases caused by the A(H3) subtype increased with age (47.1% among those aged 65–69 years, 58.2% among those aged 70–74 years, and 60.4% among those aged 75 + years, p-value 0.007), while an opposite trend was observed for A(H1) (14.7%, 9.4% and 6.8%, p-value 0.013) and, although not significantly, for influenza B as well (26.9% 21.8% and 20.0%, p-value 0.171). Twelve patients were co-infected with influenza and another respiratory virus, of which six among non-vaccinated and six among vaccinated patients.

Table 1
Number (and proportions) of respiratory samples that tested positive for influenza among non-vaccinated and vaccinated ARI patients, overall and by age group (65–69 years, 70–74 years, 75 + years). *Source:* GROG influenza sentinel surveillance network, France, 2003–2004 to 2013–2014 (2009–2010 excluded).

Season	All ages (65 + years)			65–69 years			70–74 years			75 + years		
	Non-vaccinated	Vaccinated	Total	Non-vaccinated	Vaccinated	Total	Non-vaccinated	Vaccinated	Total	Non-vaccinated	Vaccinated	Total
2003–2004	6 (14.0%)	20 (29.4%)	26 (23.4%)	2 (13.3%)	4 (18.2%)	6 (16.2%)	3 (20.0%)	9 (40.9%)	12 (32.4%)	1 (7.7%)	7 (29.2%)	8 (21.6%)
2004–2005	10 (17.2%)	38 (33.3%)	48 (27.9%)	3 (14.3%)	10 (27.0%)	13 (22.4%)	4 (23.5%)	8 (25.0%)	12 (24.5%)	3 (15.0%)	20 (44.4%)	23 (35.4%)
2005–2006	9 (12.9%)	8 (7.9%)	17 (9.9%)	4 (11.4%)	2 (6.1%)	6 (8.8%)	3 (21.4%)	2 (5.9%)	5 (10.4%)	2 (9.5%)	4 (11.8%)	6 (10.9%)
2006–2007	22 (20.0%)	35 (20.7%)	57 (20.4%)	9 (20.5%)	9 (19.6%)	18 (20.0%)	4 (13.3%)	13 (27.7%)	17 (22.1%)	9 (25.0%)	13 (17.1%)	22 (19.6%)
2007–2008	23 (22.3%)	32 (22.2%)	55 (22.3%)	9 (20.5%)	10 (32.3%)	19 (25.3%)	11 (30.6%)	4 (12.9%)	15 (22.4%)	3 (13.0%)	18 (22.0%)	21 (20.0%)
2008–2009	49 (35.5%)	60 (29.0%)	109 (31.6%)	21 (42.9%)	15 (29.4%)	36 (36.0%)	15 (33.3%)	15 (24.6%)	30 (28.3%)	13 (29.5%)	30 (31.6%)	43 (30.9%)
2010–2011	30 (27.8%)	28 (25.5%)	58 (26.6%)	21 (36.2%)	6 (20.7%)	27 (31.0%)	3 (14.3%)	7 (29.2%)	10 (22.2%)	6 (20.7%)	15 (26.3%)	21 (24.4%)
2011–2012	40 (36.4%)	66 (43.7%)	106 (40.6%)	17 (37.8%)	17 (38.6%)	34 (38.2%)	10 (38.5%)	14 (45.2%)	24 (42.1%)	13 (33.3%)	35 (46.1%)	48 (41.7%)
2012–2013	65 (43.0%)	61 (47.7%)	126 (45.2%)	29 (42.6%)	20 (57.1%)	49 (47.6%)	17 (53.1%)	12 (42.9%)	29 (48.3%)	19 (37.3%)	29 (44.6%)	48 (41.4%)
2013–2014	36 (38.7%)	37 (36.6%)	73 (37.6%)	22 (46.8%)	10 (35.7%)	32 (42.7%)	7 (33.3%)	9 (39.1%)	16 (36.4%)	7 (28.0%)	18 (36.0%)	25 (33.3%)
Total	290 (29.5%)	385 (29.8%)	675 (29.6%)	137 (32.2%)	103 (28.9%)	240 (30.7%)	77 (30.0%)	93 (27.9%)	170 (28.8%)	76 (25.2%)	189 (31.3%)	265 (29.3%)
p-Value[a]	0.875			0.330			0.589			0.060		

ARI: acute respiratory infection.
[a] The p-values are for the comparison of total percent of specimens testing positive for influenza among non-vaccinated vs. vaccinated patients, overall and within each age group.

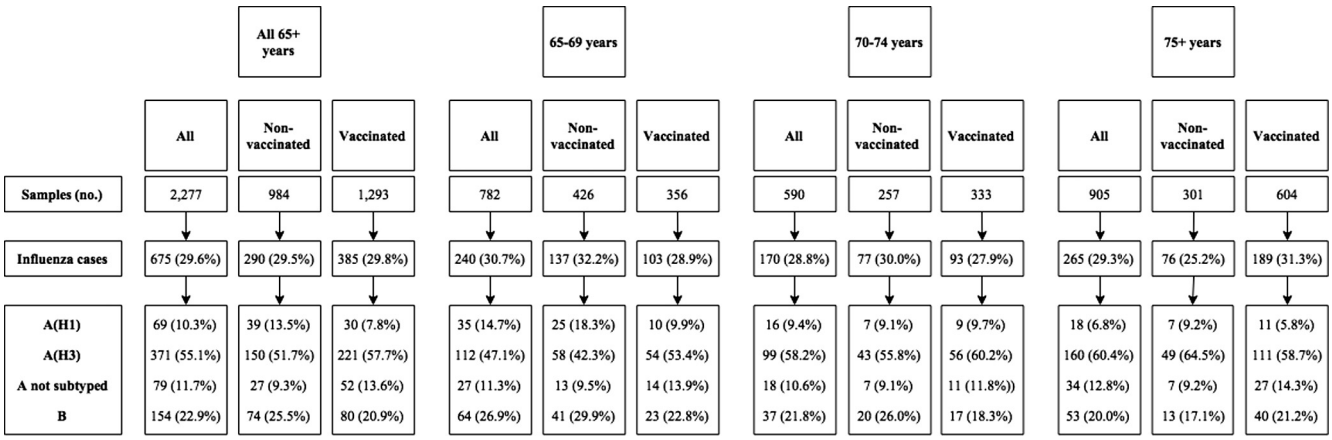

Fig. 1. Number of respiratory samples taken, and influenza cases that were caused by each virus (sub)type, among non-vaccinated and vaccinated patients aged 65–69 years, 70–74 years, or 75+ years (the numbers of influenza cases caused by each virus (sub)type do not sum up to the total number of influenza cases among vaccinated patients aged 65–69 years because we excluded two patients that were co-infected with A(H3) and B virus strains). *Source*: GROG influenza sentinel surveillance network, France, 2003–2004 to 2013–2014 (2009–2010 excluded).

There were few, not clinically relevant (although statistically significant) differences in the clinical presentation of non-vaccinated and vaccinated influenza patients at the time of the enrolment interview (Table 2). In univariate analysis, vaccinated influenza patients were significantly less likely to present with myalgia (72.4% vs. 80.3%), shivering (64.3% vs. 72.9%) and headache (61.7% vs. 70.9%), and had an average maximum temperature lower by 0.1 degree (38.9 °C vs. 39.0 °C) than non-vaccinated patients. There were no statistically significant differences in age group-specific comparisons, with two exceptions: vaccinated patients aged 65–69 years presented more frequently with cough (96.1% vs. 87.5%), and the average maximum temperature was higher among non-vaccinated patients aged 70–74 years (39.1 °C vs. 38.9 °C). Moreover, the difference in the frequency of a symptom between non-vaccinated and vaccinated patients very seldom exceeded 10% in age group-specific comparisons: this happened for dyspnoea in the age group 65–69 years (more frequent among vaccinated patients, 24.5% vs. 13.5%), and shivering and headache in the age group 75+ years (both were more frequently reported by non-vaccinated influenza patients: 65.3% vs. 54.1% the former, 64.0% vs. 53.2% the latter). The mean number of days between onset of symptoms and consultation with a GP and the median number of symptoms at consultation did not differ by patient's vaccination status, neither overall nor within any age group. Six patients overall were referred to the hospital (0.9%), equally distributed between non-vaccinated and vaccinated patients (results not shown).

We reported in Table 3 the comparison of the clinical presentation of non-vaccinated and vaccinated influenza patients infected with the different virus (sub)-types. The average maximum temperature was higher among non-vaccinated vs. vaccinated influenza patients infected with any influenza virus (sub)-type, significantly so ($p < 0.05$) for A(H1) and B. The delay between onset of symptoms and consultation with a GP was significantly longer only among non-vaccinated vs. vaccinated patients infected with the A(H1) virus (2.1 vs. 1.4, $p < 0.05$). Vaccinated patients were less likely to present with myalgia (69.7% vs. 80.0%) and headache (62.0% vs. 72.7%) when infected with the influenza A(H3) virus, and with shivering (57.7% vs. 77.8%) and headache (56.3% vs. 72.6%) when infected with influenza B virus. Instead, they were significantly more likely to present with gastrointestinal symptoms (23.3% vs. 5.1%) when infected with the A(H1) virus. The median number of symptoms at consultation did not significantly differ by vaccination status among patients infected with any influenza virus.

After adjusting by age group, virus (sub)type and season, the odds of presenting with headache was significantly reduced among vaccinated vs. non-vaccinated influenza patients (OR 0.69, 95%CI 0.48–0.98) (Table 4). The odds of presenting with any of the other symptoms did not significantly differ by vaccination status.

4. Discussion

We sampled 2277 individuals aged 65 years or older who consulted a general practitioner because of ARI during ten influenza seasons (2003–2014) in France: 56.8% of them had been vaccinated against influenza. We calculated the influenza detection rate, and determined what was the most frequently detected virus (sub)-type among vaccinated and non-vaccinated influenza patients, in the whole study sample and by age group (65–69 years, 70–74 years, 75 years or older). We then compared the clinical presentation of vaccinated and non-vaccinated influenza patients, overall and separately by age group and virus (sub)-type (A(H1), A(H3) and B).

We found that the IDR did not differ between vaccinated and non-vaccinated ARI patients. IDR tended to decrease with age among non-vaccinated patients: this finding has been reported by other authors [13,14], and suggests that ARI may be increasingly due to causes other than influenza as people get older. IDR among vaccinated patients tended to slightly exceed that among non-vaccinated individuals in the oldest age group (75 years or older). Elderly people are more likely to receive the vaccine when suffering from underlying chronic conditions, i.e. when being at risk of developing influenza-related complications [15–17]. Therefore, a tentative explanation for this finding is that vaccinated elderly people tend to consult a GP less frequently (compared to non-vaccinated individuals) when they have a relatively mild clinical presentation, and more frequently when they have symptoms suggestive of influenza (as this represents a potentially life-threatening condition in this population).

A delay in consulting the GP might be due to either a more severe illness at onset of symptoms, because of the inability to travel to the GP's practice [18], or to the subsequent worsening of an illness that was relatively mild at onset. In our study, the difference was only significant among patients infected with the A(H1) (sub)-type (i.e. sixty-nine patients overall). It might be speculated that the vaccine is able to mitigate the severity of influenza caused by the pandemic strain only: this is consistent with Belongia et al. [5], which showed a higher vaccine effectiveness against A(H1)

Table 2
Frequency of symptoms of influenza patients according to vaccination status and age group (65–69 years, 70–74 years, 75+ years). *Source*: GROG influenza sentinel surveillance network, France, 2003–2004 to 2013–2014 (2009–2010 excluded).

	All influenza patients			65–69 years			70–74 years			75+ years		
	Non-vaccinated (n = 290)	Vaccinated (n = 385)	p-Value	Non-vaccinated (n = 137)	Vaccinated (n = 103)	p-Value	Non-vaccinated (n = 77)	Vaccinated (n = 93)	p-Value	Non-vaccinated (n = 76)	Vaccinated (n = 189)	p-Value
M/F ratio	0.75	0.89	ns	0.77	1.11	ns	0.77	1.30	ns	0.67	0.65	ns
Age (mean)	71.4	75.4	**<0.05**	66.6	66.9	ns	71.7	71.9	ns	79.6	81.8	**<0.05**
Days before consultation (mean)	1.8	1.6	ns	1.9	1.7	ns	1.9	1.8	ns	1.7	1.5	ns
Sudden onset	81.4%	83.3%	ns	80.7%	85.0%	ns	82.7%	83.5%	ns	81.3%	82.3%	ns
Temperature max (°C)	39.0	38.9	**<0.05**	39.0	38.9	ns	39.1	38.9	**<0.05**	39.1	38.9	ns
No. symptoms (median, IQR)	7 (6–8)	7 (5–8)	ns	7 (6–8)	7 (6–8)	ns	7 (6–8)	7 (6–8)	ns	7 (5–8)	6 (5–8)	ns
General infection symptoms:												
Fever	95.5%	94.5%	ns	97.1%	93.2%	ns	94.8%	95.6%	ns	93.3%	94.7%	ns
Asthenia	81.7%	82.0%	ns	83.2%	84.5%	ns	81.8%	87.1%	ns	78.9%	78.1%	ns
Myalgia	80.3%	72.4%	**<0.05**	86.1%	85.4%	ns	79.2%	77.4%	ns	71.1%	62.8%	ns
Shivering	72.9%	64.3%	**<0.05**	75.2%	74.5%	ns	76.4%	74.1%	ns	65.3%	54.1%	ns
Headache	70.9%	61.7%	**<0.05**	75.9%	68.9%	ns	68.8%	71.0%	ns	64.0%	53.2%	ns
Respiratory symptoms:												
Cough	90.0%	91.4%	ns	87.5%	96.1%	**<0.05**	92.2%	93.5%	ns	92.1%	87.8%	ns
Rhinitis	75.4%	72.7%	ns	78.1%	78.6%	ns	75.3%	82.8%	ns	70.7%	64.4%	ns
Pharyngitis	51.9%	50.5%	ns	51.5%	53.5%	ns	55.3%	53.9%	ns	49.3%	47.3%	ns
Expectoration	29.0%	33.8%	ns	31.0%	36.1%	ns	20.0%	29.5%	ns	34.2%	34.6%	ns
Dyspnoea	19.3%	24.0%	ns	13.5%	24.5%	ns	24.3%	28.6%	ns	26.7%	21.6%	ns
Bronchitis/bronchiolitis	18.6%	19.4%	ns	16.5%	15.7%	ns	18.4%	15.1%	ns	22.4%	23.7%	ns
Other symptoms:												
Gastrointestinal symptoms	12.2%	10.9%	ns	14.8%	15.5%	ns	11.7%	9.7%	ns	8.0%	9.0%	ns
Conjunctivitis	8.6%	5.7%	ns	10.9%	8.0%	ns	4.3%	2.7%	ns	8.8%	5.8%	ns
Adenopathy	4.3%	4.5%	ns	5.4%	2.7%	ns	6.7%	8.8%	ns	0.0%	3.5%	ns
Otitis/earache	3.1%	1.6%	ns	3.7%	2.9%	ns	3.9%	1.1%	ns	1.3%	1.1%	ns

IQR: inter-quartile range.
Bold is for statistically significant findings.

Table 3
Frequency of symptoms of influenza patients according to vaccination status and virus (sub)type: A(H1), A(H3), A not subtyped, B. *Source*: GROG influenza sentinel surveillance network, France, 2003–2004 to 2013–2014 (2009–2010 excluded).

	A(H1)			A(H3)			B		
	Non-vaccinated (n = 39)	Vaccinated (n = 30)	p-Value	Non-vaccinated (n = 150)	Vaccinated (n = 221)	p-Value	Non-vaccinated (n = 74)	Vaccinated (n = 80)	p-Value
M/F ratio	1.27	0.76	ns	0.69	0.99	ns	0.69	0.87	ns
Age (mean)	69.4	72.8	**<0.05**	72.6	76.2	**<0.05**	70.1	74.4	**<0.05**
Days before consultation (mean)	2.1	1.4	**<0.05**	1.7	1.6	ns	1.9	2.0	ns
Sudden onset	84.6%	93.3%	ns	82.7%	86.4%	ns	76.7%	71.4%	ns
Temperature max (°C)	39.2	38.8	**<0.05**	39.1	39.0	ns	39.0	38.8	**<0.05**
No. symptoms (median, IQR)	7 (5–8)	7 (6–8)	ns	7 (6–8)	7 (5–8)	ns	7 (6–8)	7 (5–8)	ns
General infection symptoms:									
Fever	92.1%	93.3%	ns	95.3%	95.9%	ns	95.9%	90.0%	ns
Asthenia	79.5%	80.0%	ns	81.3%	81.9%	ns	81.1%	83.5%	ns
Myalgia	76.9%	80.0%	ns	80.0%	69.7%	**<0.05**	82.4%	71.3%	ns
Shivering	64.9%	83.3%	ns	72.5%	64.6%	ns	77.8%	57.7%	**<0.05**
Headache	53.8%	56.7%	ns	72.7%	62.0%	**<0.05**	72.6%	56.3%	**<0.05**
Respiratory symptoms:									
Cough	84.6%	90.0%	ns	91.3%	91.4%	ns	94.5%	90.0%	ns
Rhinitis	79.5%	60.0%	ns	75.3%	70.0%	ns	71.2%	77.5%	ns
Pharyngitis	42.1%	50.0%	ns	51.3%	45.7%	ns	50.0%	55.0%	ns
Expectoration	35.9%	41.4%	ns	29.0%	29.1%	ns	29.0%	33.3%	ns
Bronchitis/ bronchiolitis	17.9%	20.7%	ns	20.0%	15.9%	ns	17.1%	28.2%	ns
Dyspnoea	16.7%	37.5%	ns	21.8%	23.7%	ns	18.4%	19.1%	ns
Other symptoms:									
Gastrointestinal symptoms	5.1%	23.3%	**<0.05**	11.3%	7.7%	ns	15.5%	11.3%	ns
Conjunctivitis	11.8%	0.0%	ns	9.8%	4.9%	ns	6.0%	6.8%	ns
Adenopathy	5.6%	4.0%	ns	2.5%	2.0%	ns	6.7%	9.5%	ns
Otitis/earache	7.7%	3.4%	ns	2.7%	0.9%	ns	0.0%	2.5%	ns

IQR: inter-quartile range.
Bold is for statistically significant findings.

Table 4
Odds ratio, 95% CI and p-value from logistic regression models using vaccination status as predictor, each symptom as outcome, and age group, virus (sub)type and season as adjusting variables. *Source*: GROG influenza sentinel surveillance network, France, 2003–2004 to 2013–2014 (2009–2010 excluded).

Outcome	OR (95% CI)	p-Value
General infection symptoms:		
Fever	0.74 (0.35–1.56)	ns
Asthenia	1.12 (0.73–1.70)	ns
Myalgia	0.77 (0.52–1.13)	ns
Shivering	0.80 (0.56–1.16)	ns
Headache	0.69 (0.48–0.98)	**<0.05**
Respiratory symptoms:		
Cough	1.32 (0.75–2.31)	ns
Rhinitis	0.95 (0.65–1.38)	ns
Pharyngitis	0.99 (0.71–1.37)	ns
Expectoration	1.10 (0.78–1.56)	ns
Dyspnoea	1.59 (0.88–2.89)	ns
Bronchitis/bronchiolitis	0.92 (0.61–1.38)	ns
Other symptoms:		
Gastrointestinal symptoms	0.95 (0.58–1.55)	ns
Conjunctivitis	0.93 (0.56–1.54)	ns
Adenopathy	1.34 (0.84–2.12)	ns
Otitis/earache	0.52 (0.19–1.37)	ns

Bold is for statistically significant findings.

than A(H3N2) and B. However, more evidence is needed to confirm or refute this hypothesis.

Vaccinated elderly outpatients with laboratory-confirmed influenza had a slightly milder illness compared to non-vaccinated patients of the same age. In particular, vaccinated patients had a slightly reduced maximum temperature and presented less frequently with systemic symptoms like myalgia, shivering and headache, compared to non-vaccinated patients. The observed effect appeared to vary across age groups and virus (sub)types: influenza vaccine effectiveness is known to vary from season to season and by age group and virus (sub)-type [19–21], and this variability might extend to its ability to mitigate symptoms of influenza. After simultaneously adjusting by age group, virus (sub)type and season, however, the only statistically significant difference emerged for headache, which was less frequent among vaccinated vs. non-vaccinated patients.

Our results are consistent with previous studies reporting limited or no efficacy of the influenza vaccine in reducing illness severity at onset of symptoms [6,17]. Van Wormer et al. examined 399 community-dwelling individuals aged 65 years or older infected with influenza between 2007 and 2011 in the US, and found a mildly reduced self-reported influenza severity score among vaccinated vs. non-vaccinated patients, thereby confirming our findings. Unlike our study, Van Wormer et al. found a reduction in the frequency of respiratory symptoms (cough and sore throat) in addition to feverishness among vaccinated vs. non-vaccinated patients. Differences in the age distribution of included patients and in the proportion of cases caused by the different virus (sub)-types (Van Wormer et al. also included cases from the 2009–2010 pandemic season) may help explain these discrepancies. Petrie et al. compared health status at enrolment by vaccination status in 588 adults with laboratory-confirmed influenza and found that vaccinated patients self-reported a modest, but significantly better health score [17]. Finally, influenza vaccination did not reduce the risk of hospital admission among patients with vaccine failure in the US during 2004–2013 [22], although it appeared to improve the prognosis of hospitalized influenza patients during the season 2013–2014 in Spain [23].

Our study relies on a wide community dwelling database that originate from a representative network of sentinel primary care practitioners spread over the whole French territory, which differs from studies focusing on the frequency of complications (admission to ICU and influenza-related death) among hospitalized influenza patients [8]. Each influenza case was virologically confirmed and vaccination status was documented. ARI is a very sensitive case definition for influenza surveillance [24,25], weakening the selection bias of a too strict case definition. Finally, the inclusion of data from a countrywide influenza surveillance system during ten seasons enabled us to conduct analyses stratified by age group and virus (sub)-type.

Our study has several limitations, the most important of which lies in how the study sample was assembled. We compared the severity of symptoms among unvaccinated vs. vaccinated ARI outpatients who consulted their GP. As a consequence, we may have missed the subset of influenza patients with a more severe illness at onset of symptoms who went directly to the hospital. If these were more represented in the unvaccinated group, the ability of the vaccine to mitigate influenza symptoms among elderly populations may indeed be higher than we were able to observe in our study sample. Although not conclusive, some of our findings (e.g. the decrease of IDR with age among the non-vaccinated group, or the higher proportion of cases caused by AH3 among non-vaccinated vs. vaccinated patients aged 75+ years) can be interpreted as supporting this alternative hypothesis. Moreover, included subjects were not followed-up with regard to the possible occurrence of complications, and no information was available on the final burden of disease, which may be lower among vaccinated patients. Only six patients were hospitalized following the encounter with the GP; however, it might be possible that vaccinated or non-vaccinated patients subsequently visited their GP or a hospital emergency room because of severe and/or complicated illness. Comparability of vaccinated and non-vaccinated patients may be questioned as very little is known about the propensity to seek care of each group and the propensity of the GPs to swab ARI patients according to their vaccine status. Circulation of minor antigenic variants different from the vaccine strains occurred several times during the study period (Supplementary Table 1); however, antigenic characterization was not performed for the majority of positive influenza samples, therefore we were unable to evaluate the impact of antigenic vaccine mismatches on our results. No information was available on co-morbidities and prior vaccination status. Finally, in France, the 2009 pandemic A(H1) virus has completely replaced the pre-pandemic strain since 2009; however, the small number of patients infected with this virus subtype (39 not-vaccinated and 30 vaccinated patients) prevented from conducting an analysis stratified by strain (i.e. pre-pandemic vs. post-pandemic).

5. Conclusion

In conclusion, we found that, in the small population of elderly outpatients presenting influenza disease despite vaccination, the influenza vaccine is modestly associated with a less severe clinical presentation of influenza at disease onset, reinforcing the need of influenza vaccines providing better protection.

Declaration of interest

SC, HB, JMM declare having no conflicts of interest.

ID declares that their institutions received grants from several pharmaceutical companies on matters relating to influenza surveillance and burden of illness due to influenza and its prevention.

JMC declares having received support for travel to meetings and their institutions received grants from several pharmaceutical companies on matters relating to influenza surveillance and burden of illness due to influenza and its prevention.

AM declares having received support for travel to meetings and their institutions received grants from several pharmaceutical companies on matters relating to influenza surveillance and burden of illness due to influenza and its prevention; she is a member of the Scientific Board of GEIG.

BL declares having received travel grants to attend meetings from ROCHE, BioMérieux and Seegene; he is a former member of ESWI, and a member of the Scientific Board of GEIG and GII.

SvdW was vice-president of the GROG network from 2004 to 2014; she is a member of ESWI and of the Scientific Board of GEIG.

Authors' contributions

Conceived and designed the experiments: AM ID BL.
Performed the experiments: AM ID SC.
Analysed the data: AM ID SC.
Contributed reagents/materials/analysis tools: JMM SvdW BL.
Wrote the first draft of the manuscript: AM ID SC.
Contributed to the writing of the manuscript: AM ID SC BL.
Agree with manuscript results and conclusions: AM ID SC HB JMM SvdW JMC BL.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.02.067.

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