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# Influenza vaccine effectiveness in an Italian elderly population during the 2016-2017 season

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**Abstract**

Interim analyses of the 2016-17 influenza vaccine effectiveness showed variable results depending on timing of the analysis and geographical setting. We conducted a population-based retrospective cohort study based on the analysis of health-related administrative data to assess the effectiveness of the 2016-17 influenza vaccine among the elderly population of a north-eastern Italian area. Data on 64854 subjects ≥65 years of age were analyzed up to April 30, 2017. The influenza vaccine was administered to 53% of the elderly population. No significant effect was observed on the likelihood of Emergency department visits, hospitalizations, or deaths from pneumonia and influenza.

**Key words**

- influenza vaccine
- effectiveness
- Italy
- cohort study
- administrative data

## INTRODUCTION

The health consequences of influenza during the 2016-17 season have been relevant from the public health perspective. Data from 17 European countries or regions participating in the EuroMOMO project (http://www.euromomo.eu/index.html) suggested a pattern of excess all-cause mortality among the elderly population in the first weeks of 2017, estimated approximately 200,000 excess deaths In 9 EU countries reporting hospital data, 7400 hospitalized cases of influenza were reported to the European Centre for Disease Prevention and Control (ECDC), half of which were in intensive care units [1].

In Italy, 230 serious influenza cases were reported and 68 of them died in the 2016-17 season. Median age of those cases was 72 and almost all had at least one pre-existing comorbidity [2]. According to 531 Italian general practitioners, the incidence of the influenza syndromes among the elderly population was 0.36 per 1000 patients [2].

The Italian Ministry of Health recommended to vaccinate all the population ≥65 years of age, in addition to those affected by various chronic conditions, pregnant women in the third trimester during the influenza season, physicians and healthcare workers and other selected workforce groups [3]. The National Vaccination Plan in force in 2016 set the goal for the minimum vaccination coverage among the elderly and the other high-risk groups at 75% [3] . Nonetheless, in the 2016-17 season, the overall Italian coverage among the elderly was 52% [4].

Interim estimates of the effectiveness of the 2016-17 influenza vaccination published for North America (Canada as of January 16, 2017 [5] and USA as of February 4, 2017 [6]) showed a protective effect against the laboratory-confirmed disease. Using a test-negative design, the Canadian study reported an overall vaccine protection of 42% (95% Confidence Interval: 18-59) against influenza A(H3N2) in the general population, with geographical variation that could reflect genetic heterogeneity in circulating A(H3N2) variants [5]. In the USA, overall protection was 48% (37 to 57) against influenza A and B and 43 (29 to 54) against influenza A(H3N2) in the general population, although the estimated effectiveness was compatible with much smaller or even no effects in the elderly subgroup [6].

In Asia, an interim analysis with test-negative design conducted in South Korea as of January 7, 2017 showed no significant effect of the vaccine against either influenza A or influenza A(H3N2) [7].

In Europe, an interim analysis conducted in the elderly population of Stockholm County and Finland showed a vaccine effectiveness of approximately 50% during the first weeks, which declined to 30% as of January 2017 [8]. Aminoacidic substitutions in the 3C.2a1 and 3C.2a subclades of influenza A(H3N2) viruses might have been responsible for viral antigenic change and for the observed vaccine effectiveness drop [8].

Another study in Spain showed no significant protective effect of the vaccine against laboratory-confirmed

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influenza A(H3N2) [9], either in the hospital and in the primary care setting, as of January 31, 2017.

Since no data are available on the effectiveness of the 2016-17 influenza vaccine at the end of the season in an Italian setting, we conducted a research to investigate the 2016-17 influenza vaccine effectiveness in the north-eastern Italian area around the city of Udine.

## METHODS

This population-based retrospective cohort study was based on the health-related administrative data of subjects living in the area of the Azienda Sanitaria Universitaria Integrata di Udine, (37 municipalities with approximately 250,000 inhabitants), in the North-East of Italy. In particular, subjects ≥65 years of age, born before December 31, 1951, alive and residing in the study area as of October 1, 2016 were included in the cohort.

For each cohort subject, various health databases were linked at the individual level through an anonymous univocal stochastic key: the vaccination database, to assess whether the study subjects had been vaccinated during the 2016-17 influenza season, the residential history database, to assess losses to follow-up, the Emergency Department (ED), the Hospital Discharge (HD), and the mortality databases to assess health outcomes. For all the residents in the study area, the vaccination database contains information on the date of influenza vaccination and type of vaccine, as well as information on pneumococcal vaccinations. Two types of influenza vaccines were used in the elderly in the study area: the intradermal vaccine, recommended by the local health Authority in most cases and generally administered by General Practitioners to their elderly patients, and the tetravalent vaccine, recommended for healthcare workers and high-risk groups of patients.

For each study subject, observation started on October 1, 2016, whereas the follow-up ended when the subject moved out of the study area, died from any cause, had the outcome of interest, or April 30, 2017, whichever came first. Exposure to the influenza vaccine was assessed from October 1 and December 31, 2016. The statistical significance of the associations between vaccination status and subject characteristics was assessed through the chi-square test for categorical variables and t-tests for continuous variables. P-values <0.05 were considered statistically significant.

Three outcomes of interest were investigated through 3 distinct survival analyses: a) ED visits for pneumonia and influenza (ICD-9-CM 480-488) occurring between November 1, 2016 and April 30, 2017; b) hospitalizations with admission date between November 1, 2016 and April 30, 2017 and any discharge diagnosis with ICD-9-CM code 480-488; c) death from pneumonia and influenza (ICD-9 480-488) between November 1, 2016 and April 30, 2017. Cohort enrolment and follow-up are summarized in *Figure 1*.

Vaccine effectiveness was assumed to start 14 days after administration. For each outcome. we built a multivariate Cox regression model including influenza vaccination as a time-varying independent variable, with a 14-day lag, and the following potential confounders: subject's age in year, sex, previous pneumococcal vaccination (at least one dose of either the conjugate vaccine PCV13 or the polysaccharide vaccine PPSV23) and a numeric comorbidity score developed by Gagne et al., based on previous hospitalization diagnoses, combining conditions from the Charlson and Elixhauser measures, and performing well in mortality prediction [10-12]. The associations were expressed through the Hazard Rations (HR) with 95% Confidence Intervals (95%CI).

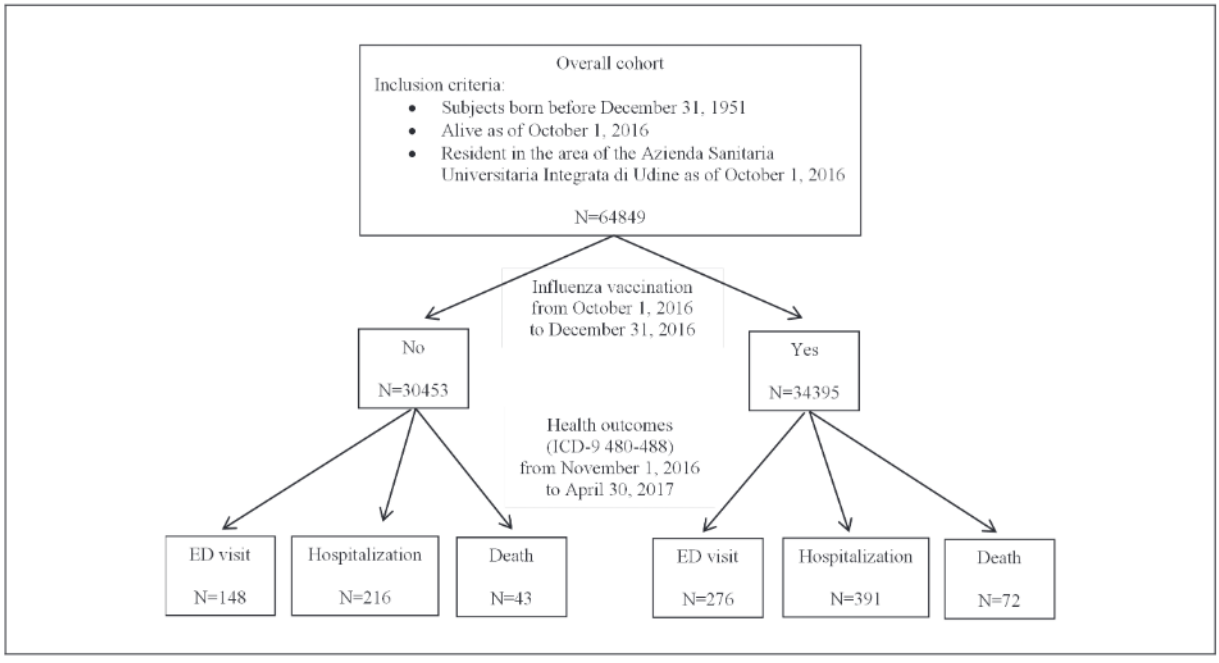


**Figure 1**
Summary of the cohort enrolment and follow-up.

Stratified analyses by influenza vaccine type were also conducted.

To rule out the possibility of residual confounding due to age and comorbidity, we compared hospitalizations with discharge diagnosis ICD-9-CM code 480-488 occurring between May 1, 2016 and September 30, 2016 (i.e., a period with no influenza activity and no vaccine effect), in subjects who were subsequently vaccinated and in those who were not: under the hypothesis that our regression model completely adjusts for confounding, the application of the same model outside the influenza period should estimate no risk difference between the two groups.

All the analyses were conducted with SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

### *Compliance with Ethical Standards*

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This article does not contain any studies with human or animal subjects performed by any of the authors. Since this analysis was based on anonymous administrative data, patient informed consent and Ethical Committee approval were not required in Italy.

## RESULTS

The cohort included 64854 elderly subjects. Of them, 53.0% were administered the influenza vaccine in the 2016-17 season. The characteristics of the study cohort are shown in *Table 1*. The frequency of vaccination increased with increasing age, from less than 40% in subjects 65-69 to almost 70% in those ≥80, and was a little more likely among women than among men. The comorbidity score was, on average, higher among the vaccinated subjects than among the others. Subjects who were vaccinated against pneumococcus were vaccinated against influenza much more frequently than the others. All the differences in the distribution of patient's characteristics and outcomes between vaccinated and non-vaccinated subjects were statistically significant. The intradermal vaccine was by far the most commonly used type (N = 30 743, 89.4%), followed by the quadrivalent flu vaccine (N = 3494, 10.1%).

The study population contributed to 13,393,335 days of observation in the analysis of ED visits (on average,

**Table 1**
Characteristics of the study cohort and outcomes

| | Vaccination status | | | |
|---|---|---|---|---|
| | **Non-vaccinated (N = 30 456)** | **Vaccinated (N = 34 398)** | **Total** | **p-value** |
| *Age category (years)* | | | | <0.0001 |
| 65-69 | 10 761 (62.7%) | 6398 (37.3%) | 17 159 | |
| 70-74 | 7500 (50.8%) | 7268 (49.2%) | 14 768 | |
| 75-79 | 5594 (41.6%) | 7840 (58.4%) | 13 434 | |
| 80-84 | 3311 (35.8%) | 5932 (64.2%) | 9243 | |
| 85-89 | 1953 (31.7%) | 4199 (68.3%) | 6152 | |
| ≥90 | 1337 (32.6%) | 2761 (67.4%) | 4098 | |
| *Sex* | | | | <0.0001 |
| Female | 18 105 (48.2%) | 19 468 (51.8%) | 37 573 | |
| Male | 12 351 (45.3%) | 14 930 (54.7%) | 27 281 | |
| *Pneumococcal vaccine* | | | | <0.0001 |
| Yes | 555 (5.9%) | 8902 (94.1%) | 9457 | |
| No | 29 901 (54.0%) | 25 496 (46.0%) | 55 397 | |
| *Gagne comorbidity score (mean ± standard deviation; median)* | 0.2 ± 0.8; 0 | 0.3 ± 1.0; 0 | 64 849 | <0.0001 |
| ED visit | | | | <0.0001 |
| No | 30 308 (47.0%) | 34 122 (53.0%) | 64 430 | |
| Yes | 148 (34.9%) | 276 (65.1%) | 424 | |
| Hospitalization | | | | <0.0001 |
| No | 30 239 (47.1%) | 34 004 (52.4%) | 64 243 | |
| Yes | 217 (35.5%) | 391 (64.4%) | 611 | |
| Death | | | | 0.0396 |
| No | 30 412 (47.0%) | 34 326 (53.0%) | 64 738 | |
| Yes | 44 (37.9%) | 72 (62.1%) | 116 | |

206.5 days per person), 13 385 632 days in the analysis of hospitalizations (on average, 20.4 per person), and 13 424 224 days in the analysis of deaths (on average, 207 per person). All the outcomes were observed more frequently among subjects who had been vaccinated against the flu: ED visits for pneumonia and influenza were observed in 0.5% of non-vaccinated and in 0.8% of vaccinated subjects; hospitalizations in 0.7% and1.1%, respectively; deaths in 0.1% and 0.2%, respectively (all p-values < 0.0001). After adjusting for sex, age, and comorbidity score, none of the outcomes was significantly associated with the influenza vaccination *(Table 2)*. The HR for ED visits for pneumonia and influenza was 1.13 (0.91-1.40); the HR for hospitalizations was 1.11 (0.93-1.33); the HR for deaths was 1.05 (0.70-1.58). Age and comorbidity score were significantly associated with all outcomes: for each increasing year, the HR was 1.09 (1.08-1.10) for ED visit, 1.10 (1.09-1.11) for hospitalization, and 1.19 (1.16-1-22) for death; for each comorbidity score unit increase, the HR was 1.38 (1.31-1.45) for ED visit, 1.45 (1.39-1.50) for hospitalization, and 1.35 (1.23-1-42) for death. No significant associations were observed between outcomes and pneumococcal vaccination status: among vaccinated subjects, HR was 1.01 (0.76-1.34) for ED visit, 0.96 (0.75-1.22) for hospitalization, and 0.83 (0.46-1.57) for death.

In the additional analysis of hospitalizations occurring from May to September, 186 hospitalizations were recorded in the cohort, much less than during the following influenza season. Hospitalizations were slightly more common among subjects who were subsequently vaccinated (0.32%) than among the others (0.25%, p-value of chi-square test 0.0693). However, after adjusting for sex, age, and comorbidity, multivariate Cox regression analysis did not show any increased likelihood of hospitalization in the cohort of subjects who were subsequently vaccinated (HR = 0.87, 95%CI: 0.65-1.17).

When analyzing the effectiveness of the tetravalent and of the intradermal vaccine separately, adjusting for sex, age, Gagne's comorbidity score, and pneumococcal vaccination, none of the outcomes was significantly associated with influenza vaccination, except hospitalizations for pneumonia and influenza, that were 47% more likely among subjects who received the tetravalent vaccine as compared with those who were not vaccinated (p = 0.0501, *Table 2*)

## DISCUSSION

In this north-eastern Italian study, we could not show any protective effect of the influenza vaccine in the 2016-17 season. Our results may depend on some degree of outcome misclassification, since we do not known whether the ED visits, hospitalizations, and deaths that were coded as "pneumonia and influenza" had been confirmed by virology. However, a cohort study conducted in the broader Italian region Friuli Venezia Giulia, that included our study area and used the same sources of information, found a significantly reduced mortality among vaccinated patients as compared to the others during the 2014-15 season [13], suggesting that outcome misclassification in the present cohort should not have heavily affected the results.

Confounding due to age and comorbidity seems to be adequately controlled for by the multivariate models we used in the primary analyses, since no excess risk of hospitalization was observed in the vaccinated group when analogous models were applied out of the influenza season. However, some residual confounding might exist in the sub-analysis on the tetravalent vaccine, which showed a borderline significant increased risk of hospitalization among vaccinated subjects. The Local Health Agency recommended the tetravalent vaccine to be used in high-risk patient categories, among whom age and hospitalization-based comorbidity scores may not be sufficient proxies for the underlying health status. In fact, previous cohort studies conducted in this area indicated that general practitioners' data collected ad hoc may be more sensitive in detecting comorbidities than hospital discharge data [14]. Unfortunately, general practitioners' data have not yet been integrated into the health information system used for the present analyses.

In our study, the lack of protective effect of the vaccine may be due to the mutations of the circulating virus during the 2016-17 season, which might have reduced the vaccine effectiveness. In Italy, in fact, influenza A(H3N2) (mostly belonging to the3C.2a1 subclade) was detected in 88% of the positive specimen collected in the 2016-17 season; however, several clusters characterized by aminoacidic substitutions in the haemagglutinin HA have been identified, in particular the N121K, T135K, and I140M substitutions [15], whose impact on the antigenic characteristics is unclear. Aminoacidic substitutions in influenza A(H3N2) viruses might have explain the vaccine effectiveness drop throughout the

**Table 2**
Association between influenza vaccination and Emergency Department (ED) visits, hospitalizations, and deaths due to influenza and pneumonia (ICD-9 480-488) in the 2016-17 influenza season in the area of Udine, Italy

| | Outcome | | |
|---|---|---|---|
| | ED visit | Hospitalization | Death |
| | HR[1] (95% CI) | HR[1] (95% CI) | HR[1] (95% CI) |
| Influenza vaccination (any *vs* no vaccination) | 1.13 (0.91-1.40) | 1.11 (0.93-1.33) | 1.05 (0.70-1.58) |
| Influenza vaccination (intradermal *vs* no vaccination) | 1.11 (0.95-1.48) | 1.11 (0.92-1.34) | 1.02 (0.67-1.54) |
| Influenza vaccination (tetravalent *vs* no vaccination) | 0.81 (0.46-1.41) | 1.47 (1.00-2.15) | 1.12 (1.03-1.54) |

[1]Hazard ratios are estimated by Cox proportional hazard models in which the independent variable vaccination is treated as a time-varying variable with a 14-days lag. All hazard ratios are adjusted for sex, age, comorbidity score, pneumococcal vaccination.

2016-17 season observed among some Northern-European elderly populations [8]. Recently, results of a multicenter hospital-based test-negative design case-control study conducted in the 2016-17 season in 27 hospitals from 10 countries including Italy confirmed low vaccine effectiveness among the elderly [16]. Public health professionals must be aware that influenza vaccine effectiveness can vary depending on the predominant circulating viruses and should be prepared to implement measures to support and treat people who get the disease.

***Author's contribution statement***

Francesca Valent conceived and designed the study, analyzed the data and wrote the article; Tolinda Gallo conceived the study and critically revised the article.

***Conflicts of interest***

None.

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