ORIGINAL ARTICLE

Influenza vaccine effectiveness for the elderly: a cohort study involving General Practitioners from Abruzzo, Italy

L. MANZOLI[1][2], P. VILLARI[3], C. GRANCHELLI[4], A. SAVINO[5], C. CARUNCHIO[6], M. ALESSANDRINI[7], F. PALUMBO[1],
C. DE VITO[3], F. SCHIOPPA[1], F. DI STANISLAO[8], A. BOCCIA[3]

[1] Section of Epidemiology and Public Health, University "G. d'Annunzio" of Chieti; [2] Regional Health Care Agency, Abruzzo Region
(ASR-Abruzzo); [3] Section of Clinical Medicine and Public Health, Department of Experimental Medicine and Pathology, University
"La Sapienza," Rome; [4] Local Health Unit (ASL) of Pescara; [5] Local Health Unit (ASL) of Chieti; [6] "Camillo De Lellis" Foundation
for Clinical Research, Pescara; [7] Department of Prevention of the Abruzzo Region; [8] University of the Marche Region, Italy

Key words

Summary

Introduction. *In all Italian regions influenza vaccine is routinely administered to the elderly population. However, vaccination impact has been rarely evaluated because of the high costs of conventional cohort investigations. A promising low-cost alternative approach uses administrative discharge data to derive vaccine effectiveness indicators (hospitalizations and/or deaths) and involves General Practitioners (GPs) to document the exposure. We conducted a cohort analysis using such approach to assess influenza vaccine effectiveness and to investigate the feasibility and validity of that methodology for routine vaccine evaluation.*

Methods. *During October 2006, all GPs from two Local Health Units (LHUs) were requested to indicate immunization status of all their patients in a specific form containing patient's demographic records. Immunization status information were also*
collected from Prevention Departments. Main outcomes were hospitalizations for influenza and/or pneumonia. Analyses were based upon random-effect logistic regression.

Results. *Of a total of 414 GPs assisting 103,162 elderly, 116 GPs (28%) provided data on 32,457 individuals (31.5%). The sample was representative and had an overall 66.2% vaccination rate. During the first semester 2007, the hospitalization rate was low in the sample, with only 7 elderly patients admitted for influenza and 135 for pneumonia. At either bivariate or multivariate analysis, vaccination did not significantly reduce the risk of in-hospital death, influenza or pneumonia admission.*

Discussion. *The study had minimal costs, recruited a large and representative sample size, and had no evidence of a substantial selection bias. Administrative and GP's data may be successively pooled to provide routine assessment of vaccination effectiveness.*

Introduction

Influenza epidemics are one the major causes of excess mortality [1-3] and hospitalization [4] worldwide. Annual vaccination has shown to be safe and effective in children [5], adults [6] and elderly [7], and it is still considered the most effective tool to prevent and controlling influenza epidemics [8]. Because elderly are at higher risk of serious complications [9], vaccination is recommended for subjects aged 65 years or more in several countries including Italy [10].

Despite routine and free-of-charge administration of influenza vaccine to the elderly population in all regions of Italy, its impact and effectiveness have been rarely evaluated [11, 12] because of the high costs and logistic complications of conventional cohort investigations [13]. A promising low-cost alternative approach to evaluate vaccination impact uses administrative discharge data to derive an indicator of vaccine effectiveness (hospitalizations and/or deaths) and involves General Practitioners (GPs) in the assessment of the exposure [12, 14-16]. We carried out a cohort analysis involving a large sample of GPs from the Abruzzo Region of Italy in order to assess influenza vaccine effectiveness in reducing hospitalizations due to

influenza, and to investigate the feasibility and validity of such a methodology for routine vaccine evaluation.

Methods

The study was carried out in two Local Health Units (LHU) of the Abruzzo Region of Italy – Chieti and Pescara – in which a total of 414 GPs have to care 103,162 elderly persons.

Using the Regional register, updated in October 2006, we extracted data on age, gender, name, fiscal and GPs codes for each citizen. Through linkage with GP code, we sent to all resident GPs an invitation letter (including the aims of the study and the instructions, and the permission granted by the main regional GP's association – FIMMG) and a specific form, which contained his/her patient's demographic data and a space to cross for each patient in case of vaccination. To participate, a GP had to compile and send back the form via electronic or regular mail. Information on immunization status were also collected on site from LHU Departments of Preventive Medicine, where elderly patients may also receive flu vaccine (< 1500 vaccinations yearly).

Elderly people received commercially available vaccines containing WHO recommended influenza virus strains: A/New Caledonia/20/99-like (H1N1), A/Wisconsin/67/2005-like (H3N2), B/Malaysia/2506/2004-like [10]. Vaccines were administered in a single intramuscular dose of 0.5 ml, containing at least 15 μg of hemagglutinin antigen per strain.

Outcomes were all-cause in-hospital mortality and hospital ordinary admissions for influenza and/or pneumonia recorded in the first semester of 2007, as extracted from routine discharge data (ICD-9-CM codes 480.0 through 487.8 in any diagnosis field [12, 14, 17]). It was not possible to assess total and influenza-related mortality because data from the Regional Registry on Mortality are not updated (currently, data are available up to the year 2003).

Random-effect logistic regression was used to evaluate the risk of admission for vaccinated versus unvaccinated individuals, using the GP as a cluster and adjusting for age, gender, LHU and number of hospitalizations in 2006.

The study protocol was approved by the local Ethical Committee and by the main regional GP's Associations (FIMMG and SIMG).

Results

As shown in Table I, 116 GPs out of a total of 414 (28.0%) provided data on their patients and were thus included in the study. Excluding errors and missing data (n = 242), the final sample was composed by 32,457 elderly individuals (31.5% of the population potentially available). The sample was virtually identical to the general population of the selected LHUs in terms of gender and age distribution, but differed slightly in vaccination coverage (66.2% in the sample; 67.0% overall).

Concerning hospitalizations, during the first semester 2007 in the selected LHUs only 21 older patients were admitted for influenza (0.20 x 1000 inhabitants); 624 for pneumonia (6.05 x 1000 – Table I). The hospitalization rate for influenza was similarly low in the sample (0.22 x 1000) and even lower for pneumonia (4.16 x 1000). In hospital deaths for any cause were 1080, and mortality rates were comparable in the two groups of patients.

Compared to vaccinated subjects, those unvaccinated were significantly older (mean ages 74.4 ± 7.5 and 76.6 ± 7.2 years respectively; p < 0.001), but similar in gender (males 43.4% vs 42.9%, respectively). The mean all cause hospitalization rate in 2006, which may be considered a raw proxi for baseline health, was slightly higher among vaccinated subject (0.14 vs 0.12, p < 0.001), but more than 80% of individuals in both groups were not hospitalized in the previous year.

The low hospitalization rate for influenza or pneumonia is clearly related to the low circulation of influenza viruses during the study period. Therefore, it was not surprising to find no significant differences between vaccinated and unvaccinated elderly in the risk of death, influenza and pneumonia admission at both bivariate and multivariate analyses (Tab. II).

Discussion

In Italian Regions, educational interventions together with economical incentives are used every year to increase the rate of influenza vaccination, which is recommended and administered to more than two thirds of the total elderly population [10, 18]. The impact of these vaccination campaigns, however, has been rarely evaluated [11, 12], most probably because of the high-costs and complexities of a traditional cohort study, which is typically based upon a direct assessment of the exposure (vaccine administration) and outcomes (influenza cases, clinically or laboratory confirmed) by trained investigators [7]. The alternative approach of this study used GP's declarations to evaluate the exposure and administrative discharge data to measure vaccine efficacy in

Tab. I. Comparison between the sample and the general elderly population.		
	Overall population [1]	Sample
N. of GPs	414	116
N. of elderly persons	103,162	32,457
Male gender, %	43.2	43.4
Mean age (± SD)	75.8 (7.4)	75.8 (7.4)
Influenza vaccination coverage, % [2]	67.0	66.2
N. admissions for influenza in the first semester of 2007 (rate x 1000 inhabitants) [3]	21 (0.20)	7 (0.22)
N. admissions for pneumonia in the first semester of 2007 (rate x 1000 inhabitants) [4]	624 (6.05)	135 (4.16)
N. of in-hospital all-cause deaths in the first semester of 2007 (rate x 1000 inhabitants) [5]	2,463 (33.97)	1,080 (38.56)

[1] Elderly population of the two Local Health Unit participating in the study (Chieti and Pescara, Italy). [2] Author's personal data. [3] ICD-9-CM codes 487.0-487.8 in any diagnosis field. [4] ICD-9-CM codes 480-486 in any diagnosis field. [5] Out of a total of 28,006 admissions.

Tab. II. Comparison between vaccinated and unvaccinated elderly subjects.

	Vaccinated (n = 21,496) %	Unvaccinated (n = 10,961) %	Adjusted OR (95% CI) *
Admissions due to influenza	0.01	0.04	0.41 (0.09-1.89)
Admissions due to pneumonia	0.46	0.33	1.22 (0.82-1.80)
All-cause in-hospital mortality	3.69	3.94	1.03 (0.78-1.36)

* Random-effect logistic regression, adjusting for age, gender, LHU and number of hospitalizations in the previous year (influenza admission estimate is adjusted for age only to reduce overfitting, but it was non-significant with any combination of covariates). OR = Odds Ratio. CI = Confidence Intervals.

reducing hospitalizations. Clearly, the use of electronic datasets makes it possible to obtain data rapidly and efficiently on large populations [16, 19]. By contrast, GP's declaration may be less reliable than that of more motivated professional researchers, and hospitalizations are a less valid outcome as compared to clinically- and especially laboratory-confirmed influenza cases [5].

Relying on GPs voluntary minimal effort, this study had very low costs (< € 15,000), recruited a large and representative sample size (31.5% of the population), had a very positive feedback from GPs. A relevant exposure misclassification seems unlikely because of the absence of incentives and the great attention paid by GPs in reporting Registry errors (74% of all GPs reported at least one error). Also, previous studies using electronic datasets showed a misclassification rate of immunization status lower than 3% [19].

Concerning the outcome evaluation, the use of hospital admission as an indicator of influenza vaccine effectiveness can be challenged because of potential ICD-9-CM under-coding and because the proportion of total influenza cases being hospitalized may vary (admission depending on factors other than just disease severity) [3, 7]. It is to note, however, that in a meta-analysis on influenza vaccine efficacy for the elderly, eight of the nine cohorts assessing both clinically confirmed respiratory illness/pneumonia and hospitalizations showed concordant results for these outcomes [7]. Influenza surveillance data [20] confirmed the absence of a large epidemic during 2007 as emerged from administrative discharge data, suggesting that the low number of influenza admissions detected in our study may have not been caused by a substantial ICD-9-CM under-coding, but rather by a low circulation of influenza viruses in the study period. The absence of a significant under-reporting is also supported by the observation that the mean number of diagnosis codes in ordinary admissions from Abruzzo (2.42) is greater than the National average (personal communication from the National Agency for Regional Healthcare Services – AGENAS).

We found no effect of vaccination on the likelihood of hospitalizations due to influenza or pneumonia in any age-class (data not shown). Theoretically, this may be related to the fact that the H1N1 vaccine strain used in Central Italy during the 2006-07 season did not perfectly match the circulating H1N1 virus (A/Solomon Islands/3/06 [20]), but it is apparent that the scarce number of influenza cases in this season did not allow any meaningful evaluation of vaccination effectiveness.

Such finding, however, does not invalidate study methodology, but it may rather support its validity. Indeed, the use of a cohort design to evaluate influenza vaccine efficacy has been challenged, mainly because of the selection of frailty individuals among the unvaccinated (especially over 70 years of age), which would lead to an overestimation of vaccine effectiveness [21, 22]. In addition, it has been suggested that the use of non specific outcomes (such as all-cause mortality) may increase the degree to which the above frailty selection bias exaggerate vaccine benefits [21]. Finally, beyond health status or demographic characteristics, it has been hypothesized the existence of a residual "unmeasured" confounder, which may contribute to inflate effectiveness estimates [17, 21]. Such biases would be apparent from the analysis of pre-post or non epidemic seasons [21, 22]. Despite our study was not designed to address this specific question (which emerged after the beginning of the study), no vaccine effect was detected in a non-epidemic season, and there was no evidence of frailty selection among vaccinated, who were two years older on average but they had similar in-hospital mortality and all-cause admissions rates (in both 2006 and in 2007 years). Therefore, our analysis which, however, is limited by the inclusion of only "measured" confounders (with a raw proxi of baseline co-existing conditions) tends to support the recent extensive multi-seasonal studies by Nichol et al. [17] and Groenwold et al. [15] suggesting the substantial validity of cohort design in assessing the efficacy/effectiveness of influenza vaccination.

Conclusions

In conclusion, although the scarcity of influenza cases impaired vaccine effectiveness evaluation, the simple methodology using routine GP's and administrative discharge data for the assessment of vaccination impact minimized costs, permitted a large-scale evaluation with an optimal feedback by General Practitioners, and had no evidence of a substantial selection bias. If combined with other sources of data that are necessary to reduce the likelihood of typical administrative data collection biases (surveillance data to evaluate ICD-9-CM under-coding and mortality registries to provide external outcomes validation), the adopted cohort design involving GPs is promising and may deserve application as a routine healthcare evaluation instrument and an effective tool to enhance GP's informatics use and research participation.

References

[1] Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. *Mortality associated with influenza and respiratory syncytial virus in the United States.* JAMA 2003;289:179-86.

[2] Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. *Impact of influenza vaccination on seasonal mortality in the US elderly population.* Arch Intern Med 2005;165:265-72.

[3] Foppa I, Hossain M. *Revised estimates of influenza-associated excess mortality, United States, 1995 through 2005.* Emerg Themes Epidemiol 2008;5:26.

[4] Simonsen L, Fukuda K, Schonberger LB, Cox NJ. *The impact of influenza epidemics on hospitalizations.* J Infect Dis 2000;181:831-7.

[5] Manzoli L, Schioppa F, Boccia A, Villari P. *The efficacy of influenza vaccine for healthy children: a meta-analysis evaluating potential sources of variation in efficacy estimates including study quality.* Pediatr Infect Dis J 2007;26:97-106.

[6] Villari P, Manzoli L, Boccia A. *Methodological quality of studies and patient age as major sources of variation in efficacy estimates of influenza vaccination in healthy adults: a meta-analysis.* Vaccine 2004;22:3475-86.

[7] Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. *The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature.* Ann Intern Med 1995;123:518-27.

[8] Nichol KL. *Efficacy and effectiveness of influenza vaccination.* Vaccine 2008;26(Suppl 4):D17-22.

[9] Cox NJ, Subbarao K. *Influenza.* Lancet 1999;354:1277-82.

[10] Ministero della Salute. P*revenzione e controllo dell'influenza.* Available at: http://www.ministerosalute.it/dettaglio/pdPrimoPiano.jsp?id=320&sub=5&lang=it. Last access February 2009.

[11] Gasparini R, Lucioni C, Lai P, Maggioni P, Sticchi L, Durando P, et al. *Cost-benefit evaluation of influenza vaccination in the elderly in the Italian region of Liguria.* Vaccine 2002;20:50-4.

[12] Valent F, Schiava F, Gnesutta D, Brianti G, Barbone F. *Valutazione dell'efficacia della vaccinazione antinfluenzale nell'anziano in Friuli-Venezia Giulia.* Epidemiol Prev 2005;29:195-203.

[13] Hak E, Wei F, Grobbee DE, Nichol KL. *A nested case-control study of influenza vaccination was a cost-effective alternative to a full cohort analysis.* J Clin Epidemiol 2004;57:875-80.

[14] Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. *A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom General Practice Research Database.* J Infect Dis 2004;190:1-10.

[15] Groenwold RHH, Hoes AW, Hak E. *Impact of influenza vaccination on mortality risk among elderly.* Eur Resp J 2009 Feb 12 [epub ahead of print].

[16] Rota MC, Bella A, Ciofi degli Atti M, de Mei B, Giannitelli S, Salmaso S. *FLU-ISS: il sistema di sorveglianza sentinella dell'influenza.* In: *Rapporto Osservasalute, 2006.* Milan: Prex 2006, pp. 51-5.

[17] Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. *Effectiveness of influenza vaccine in the community-dwelling elderly.* New Engl J Med 2007;357:1373-81.

[18] Sticchi L, Gasparini R, Icardi G, Durando P, Ansaldi F, Crovari P. *Copertura vaccinale antinfluenzale.* In: *Rapporto Osservasalute, 2006.* Milan: Prex 2006, pp. 44-5.

[19] Nordin J, Mullooly J, Poblete S, Strikas R, Petrucci R, Feifei W, et al. *Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 Health Plans.* J Infect Dis 2001;184:665-70.

[20] Centro Interuniversitario di Ricerca sull'Influenza e le infezioni virali (CIRI). Available at: www.influciri.it. Last access February 2009.

[21] Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. *Mortality benefits of influenza vaccination in elderly people: an ongoing controversy.* Lancet Infect Dis 2007;7:658-66.

[22] Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. *Evidence of bias in estimates of influenza vaccine effectiveness in seniors.* Int J Epidemiol 2006;35:337-44.

■ Correspondence: Lamberto Manzoli, Section of Epidemiology and Public Health, University "G. d'Annunzio" of Chieti, via Vestini 5, 66013 Chieti, Italy - Tel. +39 347 4727282 - E-mail: lmanzoli@post.harvard.edu.