HUMAN VACCINES & IMMUNOTHERAPEUTICS
2017, VOL. 13, NO. 2, 412–416
http://dx.doi.org/10.1080/21645515.2017.1264829

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RESEARCH PAPER

Costs associated with influenza-related hospitalization in the elderly

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ABSTRACT

Seasonal influenza epidemics remain a considerable burden in adults, especially in those at higher risk of complications. The aim of this study was to determine the costs associated with influenza-related hospitalization in patients aged $\geq$65 y admitted to 20 hospitals from 7 Spanish regions during the 2013–14 and 2014–15 influenza seasons. Bivariate analysis was used to compare costs in vaccinated and unvaccinated cases. Costs were calculated according to the Spanish National Health System diagnosis-related group tables for influenza and other respiratory system conditions (GRD 89 and GRD 101). A total of 728 confirmed influenza cases were recorded: 52.9% were male, 46.7% were aged 75–84 years, and 49.3% received influenza vaccine $\geq$15 d prior to hospital admission. Influenza-related mean hospitalization costs (MHC) were € 1,184,808 in unvaccinated and € 1,152,333 in vaccinated cases (2.75% lower). Influenza vaccination showed significant protection against ICU admission (OR 0.35, 95%CI 0.21–0.59; $p < 0001$); mechanical ventilation (OR 0.56, 95%CI 0.39–0.80; $p = 0.002$); secondary bacterial pneumonia (OR 0.61, 95%CI 0.39–0.98; $p = 0.04$) and a higher degree of dependence (OR 0.74, 95%CI 0.55–0.99; $p = 0.04$). No association was observed for the Charlson comorbidity index or the mean hospital stay. Although influenza vaccination of the elderly may not achieve significant savings in mean hospitalization costs, it may lessen the degree of severity and avoid complications.

KEYWORDS
Influenza; hospitalization; cost; elderly; immunization

Introduction

Every year, seasonal influenza causes a large disease burden with large numbers of influenza infections in all age groups. Influenza is a self-limiting illness, but severe secondary complications may occur and often require hospitalization, overwhelming hospital capacities and resulting in excess influenza-related mortality, especially in the elderly. Population aging is undoubtedly going to be a key demographic challenge in many countries. The latest Eurostat projections (Europop2010) show that, over the next 50 years, population aging is likely to attain unprecedented levels in 31 European countries. This increasing trend to an aging population, low birth rates, and increased life-expectancy highlights the importance of assessing the costs these demographic changes imply.[1]

Vaccination remains the primary means for reducing the burden of influenza yet, despite the availability of immunization strategies, influenza remains a threat, especially for those at greater risk of severe illness such as young children and the elderly. Each year in the US, influenza is associated with approximately 30,000 excess deaths 1,250,000 hospitalizations, and billions of dollars in health care costs.[2,3] The European Centers for Disease Control (ECDC) estimate that nearly 40,000 people in the European Union die prematurely each year due to causes associated with influenza, and that up to 90% of these deaths and nearly 50% of excess hospitalizations occur in persons aged $\geq$ 65 years, especially those with underlying medical conditions.[4,5]

Because the elderly are at increased risk for serious complications due to influenza, they have a high priority in annual vaccination strategies, together with pregnant women, healthcare personnel and people of all ages with underlying comorbidities. Influenza vaccination is recommended annually to ensure an optimal match between the vaccine and the prevailing influenza strains and because, unlike the long-lasting, strain-specific immunity following natural infection, influenza vaccines induce protection of relatively short duration, particularly in the elderly.[6] Annual vaccination is safe and effective and a cost-saving means of preventing and controlling influenza in the elderly. In 2009, the Council of the European Union influenza immunization coverage target for people aged $\geq$65 y was set at 75% by 2014/15, the same goal as applied to all defined target groups.[7] Despite these recommendations, influenza vaccination rates remain limited, even in targeted populations.[8]

Furthermore, most hospitalizations associated with influenza infections are not correctly recorded in the discharge diagnosis, resulting in substantial uncertainty about the magnitude of the clinical and economic burden.[9]

Various factors influence the impact of influenza in the elderly. On the one hand, repeated contact with different

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influenza viruses produces a wide range of immune memory which may be protective but, on the other hand, impaired immunity due to senesce increases susceptibility to influenza. In addition, underlying medical conditions may greatly worsen the disease course. Thus, although morbidity is usually low in the elderly, influenza may occasionally have a severe and complicated clinical course.[10] A study in the elderly by Mullooly et al. found an influenza-associated hospitalization rate of 560 per 100,000 persons in subjects with underlying medical conditions: the rate in healthy persons aged ≥65 y was one third lower.[11] Data from the Spanish Influenza Sentinel Surveillance System (SISS) show cumulative incidence rates in people aged ≥65 y were the lowest of all age groups in the community setting, but that hospitalization rates for severe laboratory-confirmed influenza (SLCI) were the highest, accounting for 59% of all SLCI cases hospitalized and 75% of deaths during 2 influenza seasons (2013–2014 and 2014–2015).[12,13] Excess hospitalization of severe cases during the influenza epidemic season results in greater health costs and a greater work load for hospital services. Reports estimating costs have shown differences between countries, although the magnitude of the economic burden due to influenza excess hospitalizations is of great relevance everywhere.[10,14-16]

The aim of this study was to determine the costs associated with laboratory-confirmed influenza-related hospitalization in patients aged ≥65 y and assess the effect of influenza immunization in reducing costs due to hospitalization.

Results

A total of 728 confirmed influenza cases were recorded, of which 52.9% were male, 46.7% were aged 75–84 years, and 49.3% received influenza vaccine ≥15 d prior to hospital admission.

Overall mean hospital and intensive care unit (ICU) stays were 11.1 d (SD ± 10.8, range 1–138 days) and 8.5 d (SD ± 11.2, range 1–86 days), respectively. Charlson comorbidity index scores were: high comorbidity 59.6%, low comorbidity 26.4%, and 14% had no known comorbidity. Thirty-day mortality was 11.4% (83 cases). Three hundred and 50 9 cases (49.3%) had received seasonal influenza vaccine ≥15 d prior to hospital admission. Influenza immunization significantly protected against ICU admission (OR 0.35, 95%CI 0.21–0.59; $p < 0001$), the need for mechanical ventilation (OR 0.56, 95%CI 0.39–0.80; $p = 0.002$), secondary bacterial pneumonia (OR 0.61, 95%CI0.39–0.98; $p = 0.04$) and the degree of dependence (OR 0.74, 95%CI 0.55–0.99; $p = 0.04$). Total confirmed influenza-related hospitalization costs in the study period were € 2,337,141, with a mean cost per case of € 3,219. Mean hospitalization costs (MHC) € 1,184,808 in unvaccinated cases and € 1,152,333 in vaccinated cases. The cost distribution, derived from laboratory-confirmed influenza, and primary and secondary pneumonia due to confirmed influenza hospitalizations, is shown on Table 1. This difference represents a 2.75% saving (€ 32,475) in hospitalization costs in vaccinated cases. No association was observed for the Charlson comorbidity index or the mean hospital stay. The median age of patients who died was 80 y (range 66–93), with no differences according to gender (50.6% male, 49.4% female): however, there was a significant difference in the proportion of women and men aged <80 y who died (OR 0.28, 95%CI 0.11–0.69; $p = 0.005$). There were no significant differences in people who died according to vaccination status, regardless of age and gender. Total PYLL due to confirmed influenza deaths was 367 years, with a 50% difference between vaccinated and unvaccinated subjects (122.1 vs. 250.1 years). PYLL in unvaccinated women was 149.8 y compared with 23 y in vaccinated women, while in men there was no difference (100.3 vs. 99.1 y respectively). PYLL for males and females according to age group and vaccination status is shown in Table 2.

Table 1. Distribution of costs (€ **2015**) for Confirmed influenza hospitalizations. Influenza seasons 2013–2014 and 2014–2015.

Cause of admission	Admissions	Total Hospitalization cost	Mean cost per case
Influenza	483	1,535,761	3,193
Primary Influenza pneumonia,	160	523,350	3,271
Secondary Influenza pneumonia,	85	278,030	3,271
Total number of cases	728	2,337,141	3,219

Discussion

The clinical and economic burden of influenza is significant, particularly in the elderly who are at greater risk for complications that might require hospitalization and may be fatal.[17] Significant direct healthcare costs are linked with influenza in persons aged ≥ 65 years, driven by substantial numbers of influenza-related hospitalizations, which are increasing as the overall population ages.[8] Moreover, influenza-related hospitalizations in the elderly are

Table 2. Distribution of potential years of lilfe lost (PYLL) caused by laboratory confirmed influenza deaths. Influenza seasons 2013–2014 and 2014–2015.

	Women					Men					Total		
Age group	Deaths in vaccinated n	Deaths in unvaccinated n	PYLL in vaccinated	PYLL in unvaccinated	Total PYLL	Deaths in vaccinated n	Deaths in unvaccinated n	PYLL in vaccinated	PYLL in unvaccinated	Total PYLL	PYLL in vaccinated	PYLL in unvaccinated	Total PYLL
<69	0	0	0	0	0	4	4	52.4	52.4	104.8	52.4	52.4	104.8
70–74	0	7	0	95.2	95.2	5	4	40.5	32.4	72.9	40.5	127.6	168.1
75–79	1	3	8.6	25.8	34.4	2	5	6.2	15.5	21.7	14.8	41.3	56.1
80–84	4	8	14.4	28.8	43.2	7	7	0	0	0	14.4	28.8	43.2
85–89	5	5	0	0	0	0	1	0	0	0	0	0	0
>90	3	5	0	0	0	1	2	0	0	0	0	0	0
	13	28	23	149.8	172.8	19	23	99.1	100.3	199.4	122.1	250.1	372.2

**Value for life expectancy in women was set at 85.6 y and 80.1 for men.[36]

associated with significant disability and impairment of daily activities, with considerable social costs.[19] Although influenza places a considerable burden on patients and society, with indirect costs greatly exceeding direct costs, indirect costs may not be so important in the elderly as they are mostly comprised of work absenteeism and sick leave, which do not occur in the elderly.[20]

Influenza vaccination in the elderly has substantial benefits and has been shown to be cost effective and cost saving.[21] Nichol et al. found a 50% reduction in hospitalizations and a 35% reduction in mortality in people vaccinated against influenza in a study that spanned 3 seasons, and a more recent study found that adherence to seasonal influenza vaccination in the elderly may reduce the risk of severe influenza outcomes.[22,23] Recent Spanish observational studies found that vaccine effectiveness in preventing laboratory-confirmed influenza-related hospitalizations ranged from 31 to 59% in patients aged ≥ 65 y.[24-26] Influenza vaccination policy in most developed countries, therefore, targets people aged ≥65 y as part of the effort to reduce the burden of mortality and disability in this population.

Our study of the direct medical costs of laboratory-confirmed influenza hospitalizations in patients aged ≥65 y in Spain found the mean cost per case was € 3,219, higher than the € 2,490 found in Poland,[14] the € 1,570.3 found in China,[27] or the € 1,270€ (in terms of 2011 purchasing power) reported in Italy.[28] The reduction in cost of 2.5% in vaccinated cases in our study came mainly from the reduction in the ICU stay, sparing mechanical ventilation and preventing secondary bacterial pneumonia. The fact that no association was observed for the Charlson comorbidity index may indicate the success of correct care and close follow up of elderly patients with comorbidities such as CPOD, diabetes or cardiovascular impairment.

Although the highest proportion of cases were in the 75–84 y age group (46.7%) and high proportion of cases presented a high degree of independence in the Barthel score (62.1%), influenza vaccination significantly protected patients with a higher degree of dependence. However, other reports have found that vaccine efficacy in reducing severe complications and mortality declined with increasingly-impaired functional status[29] although our results are in accordance with other studies in the community-dwelling elderly.[30]

This study focused on the direct medical costs of laboratory-confirmed influenza-related hospitalizations in patients aged ≥ 65 y. Future studies should include direct non-medical cost and indirect costs, including transportation, to accurately measure the annual social and economic burden and impact attributed to influenza infections in Spain.

The direct medical costs of laboratory-confirmed influenza-related hospitalizations found in our study indicates a heavy economic burden for the health system. This burden is increased if the patient has underlying medical conditions. Our study highlights the need to develop targeted preventive strategies to increase influenza vaccination coverage in the elderly to reduce hospitalization and its economic burden. The concept of using metrics such as PYLL instead of the number of deaths is often used to quantify the disease burden.[31] We observed an indirect cost-benefit of influenza vaccination, with 50% fewer PYLL, which suggests that greater efforts to improve vaccination of the elderly and their caregivers and healthcare staff should be encouraged.

Vaccines are a cost-effective, core component of any preventive service and vaccination programs use surveillance systems to better understand vaccination coverage and identify strategies to reach those at the highest risk for influenza complications. It is critical to monitor influenza vaccination rates among groups at high risk for developing influenza-related complications to avoid disease onset, and reduce mortality and healthcare costs, since these are the people who have the most serious consequences once infected with influenza.[32]

Although influenza vaccination of the elderly may not achieve significant savings in mean hospitalization costs, it can lessen the degree of severity and avoid complications.

Methods

Study design

We performed a cross-sectional study in patients aged ≥65 y admitted to 20 hospitals from 7 Spanish regions (Andalusia, Basque Country, Catalonia,

Castile and Leon, Madrid, Navarra and Valencia Community) with laboratory-confirmed influenza during 2 influenza seasons; 2013–2014 and 2014–2015. Patients who did not give written consent and residents of nursing homes were excluded. Information on the influenza vaccination status was obtained from vaccination registers, hospital medical records, vaccination cards or primary healthcare records.

Specifically-trained health professionals used a structured questionnaire to collect information by patient interview and review of medical records. The following predisposing characteristics were recorded: age, sex, influenza vaccination status. Variables related to social support were collected (number of general practitioner visits during the last year, number of hospital visits during the last year, and the Barthel index, which has a total score ranging from 0 (complete dependence) to 100 (complete independence), as a measurement of limitations in activity in study patients.[33] Comorbidities were assessed using the Charlson comorbidity index, which assigns a weight to each comorbid condition (0: no comorbidity, 1: low comorbidity, 2: high comorbidity).[34]

The cost-of-illness analysis measured direct health costs, including the cost of hospital admission, using values specified in the Spanish National Health System diagnosis-related group tables for influenza and other respiratory system conditions (GRD 89 and GRD 101)[35] and indirect costs, calculated in potential years of life lost (PYLL). PYLL were calculated by multiplying the number of age-specific deaths attributable to influenza by the difference in standard life expectancy at age of death in 2014 from the mid-point of each age category. Life expectancy, taken from standard life tables of the Spanish Statistical Institute (INE), was 85.6 y in women and 80.1 y in men.[36]

Statistical analysis

Vaccinated and unvaccinated patients were compared using bivariate analysis, taking into account the medical and risk medical conditions and costs. The analysis was performed using the SPSS v.18 statistical package.

Ethical considerations

All data collected were treated as confidential, in strict observance of legislation on observational studies. The study was approved by the Ethics Committees of the hospitals involved (Comité Ético de Investigación Clínica del Hospital Clínic de Barcelona; Comité Ético de Investigación Clínica del Hospital Universitari Mutua de Terrassa; Comité Ético de Investigación Clínica de la Corporació Sanitaria Parc Taulí de Sabadell; Comité Ético de Investigación Clínica del Hospital de Mataró, Consorci Sanitari del Maresme; Comité Ètic d'Investigació Clínica de la Fundació Unio Catalana Hospitals; Comité Ético de Investigación Clínica Área de Euskadi; Comité Ético de Investigación Clínica Área de Salud de Burgos y Soria; Comité Ético de Investigación Clínica Área de Salud de León; Comité Ético de Investigación Clínica Área de Salud Valladolid– Este; Comité Coordinador de Ética de la Investigación Biomédica de Andalucía; Comité Ético de Investigación Clínica del Hospital Ramón y Cajal, Madrid and Comité Ético de Investigación Clínica del Consorcio Hospital General Universitario de Valencia).

Written informed consent was obtained from all patients included in the study.

Abbreviations

aOR	Adjusted odds ratio
CI	Confidence interval
ECDC	European Centers for Disease Control
EU	European Union
GRD	Group related diagnosis
ICU	Intensive care unit
MHC	Mean hospitalization costs
OR	Odds ratio
PYLL	Potential years of life lost
SISS	Seasonal influenza surveillance system
SLCI	Severe laboratory-confirmed influenza

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This study was funded by the National Plan of I+D+I 2008–2011 and ISCIII-Subdirección General de Evaluación y Fomento de la Investigación (Project PI12/02079) and cofounded by Fondo Europeo de Desarrollo Regional (FEDER. Unión Europea. Una manera de hacer Europa), and the Catalan Agency for the Management of Grants for University Research (AGAUR Grant number 2014/ SGR 1403). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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