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Research Article

Influenza Hospitalizations Averted by Vaccination in a General University Hospital, 2015-2017

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ABSTRACT

From a hospital point of view, the goal of influenza vaccination programs is to reduce the serious influenza-associated disease outcomes in high-risk patients. Our aim was to estimate the influenza hospitalizations averted by vaccination. We used existing real-time electronic hospital clinical records and a CDC model to assess the impact of vaccination. The number of influenza hospitalizations averted per season by vaccination ranged from 5.4 to 8.3 in a young population and from 38.5 to 42.8 in the elderly. The influenza coverage ranged from a low of 3.4% in oncologic young patients to a high of over 40% in chronic lung or mentally ill elderly patients. However, the highest influenza hospitalizations averted were observed in oncologic or cardiac elderly patients, and the highest prevented fraction of 52.2% was determined in the elderly. Influenza vaccination programs at a hospital need some expansion to produce substantial health benefits and efficiency.

INTRODUCTION:

Since the 1990s, people 60 years of age and older in Catalonia have been recommended to receive annual influenza vaccination as well as those at high risk for developing influenza-associated disease outcomes or those who might spread infection to high-risk persons.[1] Each year, seasonal influenza is estimated to affect 5-10% of the world's population, resulting in between 350,000 and 700,000 infections in Catalonia, as well as causing significant costs to health care.[2] Most people who get the flu will have mild illness, not need medical care or antiviral drugs, and recover in less than two weeks without hospital stay.[3] Some people, however, are more likely to get influenza complications or may experience a worsening of their condition triggered by influenza that can result in hospitalization and sometimes premature death. [3,4] These high-risk patients for influenza complications or serious influenza-associated diseases usually have the following chronic conditions: neurological or neurodevelopmental conditions, including disorders of the brain, spinal cord, peripheral nerve, and muscles such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury; chronic lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis; heart diseases such as congenital heart disease, congestive heart failure, and coronary artery disease; blood disorders such as sickle cell disease; endocrine disorders such as diabetes mellitus; kidney disorders; liver disorders; metabolic disorders such as inherited metabolic disorders and mitochondrial disorders; weakened immune system due to disease or medication such as HIV or AIDS, cancer, or chronic steroid use; people younger than 19 who were receiving long-term aspirin therapy; and those with extreme obesity, including a body mass index (BMI) of 40 or more.[3]

In Catalonia, influenza immunization of the elderly should be systematically provided in primary health care units, but immunization of people at high risk for developing influenza-associated disease outcomes is misleading and they would likely benefit from an organized hospital immunization program. Influenza immunization is not universally provided. From a hospital point of view, the goal of influenza vaccination programs should be to reduce the serious influenza-associated disease outcomes in high-risk patients. Therefore, estimating the averted influenza burden as a result of vaccination would allow for a clear understanding of the value of immunization programs in hospitals and the areas where improvements could lead to the greatest benefits for patient safety. The objectives of our study are to estimate the direct effect of influenza vaccination in terms of influenza coverage, the averted number of influenza hospitalizations, and their prevented fraction over two recent influenza seasons by age and morbidity group at a teaching hospital.

MATERIAL AND METHODS

STUDY DESIGN

This cross-sectional study was conducted in accordance with the Declaration of Helsinki and institutional standards and was approved by the Institutional Review Committee at the University Hospital of Bellvitge (HUB), L'Hospitalet, Spain. Written informed consent of all patients was not required.

Potential participants were identified by a daily review of electronic clinical records provided by the Central Computer Department at HUB. Patients who fulfilled the inclusion criteria were included in the study.

SETTING AND STUDY POPULATION

This study was conducted during the two recent influenza seasons (from October 2015 to March 2016 and from October 2016 to March 2017) at HUB, a Catalan acute-care hospital setting with 800 beds.

Inpatients older than 18 years were eligible; an inpatient was considered a person who stayed for one or more nights in a hospital to receive medical care. Patients were considered immunized against seasonal influenza if at the time of the study they presented a seasonal immunization electronic registry/card with the exact date of immunization. Exclusion criteria included children, inpatients younger than 65 without chronic medical illnesses, inpatients hospitalization <1 night, and patients who visited as outpatients or were admitted to the emergency room.

SAMPLE SIZE

This study was designed to estimate the number of averted influenza hospitalizations as a pilot study because such estimation has never been done in a specific hospital in our region. Thus, no estimation of sample size was performed.

OUTCOMES

The primary outcome was to determine the influenza hospitalizations averted expressed as the number of hospitalizations due to influenza avoided by immunization in a general university hospital during two recent influenza seasons according to age and morbidity. The secondary outcomes were influenza coverage by age and morbidity and prevented fraction of influenza hospitalization expressed as the proportion of hospitalizations due to influenza avoided by immunization. Two different inpatient populations were analyzed according to age defined as 18 to 64 and the elderly as 65 or older.

In this study, the burden is defined in terms of influenza hospitalizations, vaccine coverage, and the estimated averted burden of influenza-related outcomes. We estimated the fraction of influenza hospitalizations averted and prevented using several steps. First, we estimated the number of outcomes that occurred in each season by age and morbidity group using local surveillance data (electronic hospital clinical records) as a primary input. The vaccine effectiveness was obtained from the CDC estimates by age group, but not for high-risk patients.[5] We then computed intermediary inputs such as the rates of influenza hospitalization among inpatients for each month of each season while accounting for the vaccination coverage and disease occurrence and used these rates to project the burden of influenza that would have occurred in the absence of vaccination. The difference between the estimated number of outcomes with and without vaccination equaled the burden averted by vaccination. Each season's model was developed according to the CDC model stratified by month to accommodate time-sensitive patterns of vaccination coverage and disease occurrence and was built to reflect the length of each season as 6 months for seasons 2015-2016 through 2016-2017 (October through March). We defined the prevented fraction as the proportion of averted outcomes out of potential outcomes in the absence of vaccination.[3,5]

Therefore, we present averted influenza burden not only in terms of absolute numbers, but also in terms of the prevented fraction for two age categories: 18-64 and 65 and older. This approach estimates only the direct effects of vaccination to vaccines and does not reflect the indirect impact of vaccination or how the underlying attack rates and disease transmission patterns would have changed in the complete absence of vaccination.

DATA SOURCES

We used data on the rates of reported influenza-associated hospitalizations from electronic hospital clinical records to estimate the averted seasonal number of influenza hospitalizations and prevented fractions from 2015 to 2017.

The electronic clinical records have been the only data source that may provide timely real-time tracking of influenza hospitalizations in our hospital since 2010, when the system was implemented. The electronic clinical records receive clinical data from the hospital as well as from primary health care. However, the main diagnosis and procedures have been specified in each hospitalization only since 2015. This is why we could not reconstruct the previous seasons' epidemiological curves of prior influenza coverage. Our department conducts surveillance for different infectious diseases in inpatients through the electronic clinical records. The coverage of inpatients' electronic clinical records is almost 100% based on monthly and age-specific hospitalization reporting. We obtained estimates of the reported rates of influenza hospitalizations across two age groups for the two most recent seasons with complete clinical data.

Because electronic influenza diagnosis records only hospitalizations confirmed by influenza laboratory test, we needed to account for underreporting. Underreporting occurs when a patient is suffering from influenza but it is not tested or is a false negative due to a low sensitivity test used or its timing. To account for underreporting, we adjusted the electronic clinical records estimate by applying a hospitalization underreporting multiplier of 2.7 (CI 1.7-4.5) for both seasons.[6] Thus, we estimated the number of influenza hospitalizations by applying a ratio of observed cases to hospitalizations adjusted by a factor of 2.7.

Vaccine effectiveness (VE) is the percentage reduction in the risk of influenza illness that is attributable to vaccination. We do not have real-time or retrospective local, regional, or national data about VE. Therefore, we used the US estimates as the only timely estimates available by age groups, but not for high-risk patients because they were unavailable.[7]

STATISTICAL ANALYSIS

Baseline characteristics were described by frequencies and compared using Pearson $\chi 2$ test or Fisher's exact test as appropriate for categorical variables. Influenza coverage was described as the proportion of the inpatients who received influenza vaccination in each current season with its 95% confidence intervals (95% CI). All statistical tests were two-tailed and a P value ≤0.05 was considered statistically significant. Statistical analysis was performed using PASW version 18 (SPSS, Chicago, IL, USA).

RESULTS

Vaccination status was ascertained in 14,249 of 16,126 inpatients (88.4%), so the overall eligible population was 7,368 inpatients from the 2015/2016 season and 6,881 from the 2016/2017 season. The gender ratio of males to females was 1:3. The patients were mainly older than 65 (64.3%) with cancer (35.2%), chronic digestive disorder (10.4%), chronic cardiovascular disease (9.5%), or without any chronic condition (16.4%). The distribution of gender, age, and main diagnosis by influenza season is shown in Table 1, and no significant differences (P>0.05) were observed.

Table 1. *Description of participants by influenza season (n=14,249)*

Variables	*N (%)*	*2015-2016*	*2016-2017*
Gender			
Male	8,136 (57.1)	4,259 (57.8)	3,874 (56.3)
Female	6,113 (42.9)	3,109 (42.2)	3,007 (43.7)
Age			
<65 years	5,083 (35.7)	2,613 (35.5)	2,470 (35.9)
≥65 years	9,166 (64.3)	4,755 (64.5)	4,411 (64.1)
Main diagnosis			
Chronic pulmonary disease	700 (4.9)	320 (4.3)	380 (5.5)
Chronic hepatic disease	230 (1.6)	93 (1.3)	137 (2.0)
Cancer	5,010 (35.2)	2,636 (35.8)	2,374 (34.5)
Diabetes mellitus	192 (1.3)	83 (1.1)	109 (1.6)
Chronic cardiovascular disease	1,347 (9.5)	781 (10.6)	566 (8.2)
Chronic renal disease	1,106 (7.8)	609 (8.3)	497 (7.2)
Chronic neurological illness	960 (6.7)	465 (6.3)	495 (7.2)
Chronic digestive disease	1,488 (10.4)	734 (9.9)	754 (11.0)

Mental illness	198 (1.4)	127 (1.7)	71 (1.0)
Chronic osteoarticular disease	682 (4.8)	321 (4.4)	361 (5.2)
No chronic conditions	2,336 (16.4)	1,199 (16.3)	1,137 (16.6)

Influenza coverage in the 2015/2016 season was 15.2% (95% CI: 14.4-16.0), with a significant increase (P<0.05) to 18.2% (95% CI: 17.3-19.1) in the 2016/2017 season. The highest influenza coverage observed in both seasons was in elderly, diabetic, chronic pulmonary or cardiovascular patients (Table 2). No significant difference was observed according to gender in any influenza season.

Table 2. *Description of influenza coverage (n=14,249)*

	Influenza season 2015-2016		***Influenza season 2016-2017***	
	Influenza coverage (95% CI)	***P value***	***Influenza coverage (95% CI)***	***P value***
Age				
18-64 years	7.1 (6.1-8.1)	<0.001	7.2 (6.2-8.2)	<0.001
≥65 years	21.9 (20.7-23.1)		27.5 (26.2-28.8)	
Gender				
Male	14.5 (13.5-15.5)	0.861	16.9 (15.8-18.0)	0.326
Female	14.7 (13.6-15.9)		18.1 (16.8-19.4)	
Pathology				
Chronic pulmonary disease	19.7 (15.8-23.6)	<0.001	30.3 (25.1-35.5)	<0.001
Chronic hepatic disease	8.1 (3.3-12.9)		7.5 (2.5-12.5)	
Cancer	11.2 (9.9-12.5)		13.9 (12.6-15.2)	
Diabetes mellitus	21.2 (11.1-31.1)		20.6 (13.5-27.7)	
Chronic cardiovascular disease	19.4 (17.4-21.4)		23.2 (20.7-25.7)	
Chronic renal disease	18.8 (15.7-21.9)		15.9 (12.7-19.1)	
Chronic neurological disease	18.5 (15.1-22.0)		16.0 (12.7-19.3)	
Chronic digestive disease	12.7 (10.3-15.1)		19.2 (16.3-22.1)	
Mental illness	9.4 (4.3-14.5)		17.1 (8.3-25.9)	
Chronic osteoarticular disease	11.7 (8.5-14.9)		9.7 (6.3-13.1)	
No chronic conditions	20.2 (17.4-23.0)		30.4 (26.7-34.1)	
Total	15.2 (14.4-16.0)		18.2 (17.3-19.1)	

Stratifying influenza coverage by age groups (Table 3), young adult patients with chronic medical conditions were consistently less likely to develop influenza irrespective of the underlying disease than the elderly. The influenza coverage rate in middle-aged adults was higher than 10% only in diabetics in the 2015/2016 season and in chronic hepatic disease and chronic pulmonary disease in the 2016/2017 season. In the elderly, this rate was higher than 30% only in mentally ill patients in the 2015/2016 season and higher than 40% in chronic lung or mentally ill patients in the 2016/2017 season. No subjects received the influenza vaccination during hospitalization according to the hospital administrative data.

Overall, the estimated number of influenza hospitalizations averted was 95 in two influenza seasons, ranging from 5.36 to 8.34 in middle-aged adults and from 38.52 to 42.78 in the elderly. The highest number of influenza hospitalizations averted was estimated in cancer and cardiac elderly inpatients in both seasons. Thus, the largest total number of averted hospitalizations occurred among adults older than 64.

Table 3. *Influenza coverage and influenza hospitalizations averted according to influenza season, main diagnosis, and age (n=14,249)*

		Influenza season 2015-2016			***Influenza season 2016-2017***		
		Influenza coverage (95% CI)	***Total population***	***Number of averted influenza cases***	***Influenza coverage (95% CI)***	***Total population***	***Number of averted influenza cases***
18-64 years	Chronic pulmonary disease	7.0 (2.8-11.2)	104	0.28	11.7 (5.9-17.5)	120	0.28
	Chronic hepatic disease	4.9 (0.2-9.6)	51	0.11	12.5 (4.4-20.6)	64	0.15
	Cancer	3.4 (2.3-4.5)	1,062	1.92	4.7 (3.5-5.9)	1,016	4.38
	Diabetes mellitus	16.7 (4.5-28.9)	43	0.17	5.0 (0.1-11.8)	38	0.09
	Chronic cardiovascular disease	7.6 (5.3-9.9)	352	1.07	9.5 (6.8-12.2)	248	1.04
	Chronic renal disease	8.7 (5.1-12.3)	232	0.56	4.3 (1.7-6.9)	234	0.55
	Chronic neurological disease	6.3 (2.9-9.7)	192	0.34	2.8 (0.6-5.0)	218	0.51
	Chronic digestive disease	4.7 (2.5-6.9)	324	0.45	4.1 (2.0-6.2)	338	0.79
	Mental illness	3.8 (1.1-7.5)	103	0.11	7.7 (0.5-14.9)	52	0.12
	Chronic osteoarticular disease	5.6 (2.2-9.0)	150	0.28	2.8 (0.1-5.5)	142	0.33
	Total	**5.3 (4.4-6.2)**	**2,613**	**5.36**	**5.4 (4.5-6.3)**	**2,470**	**8.34**
≥65 years	Chronic pulmonary disease	26.8 (21.4-32.2)	216	4.92	42.4 (35.3-49.5)	260	2.82
	Chronic hepatic disease	14.3 (3.7-24.9)	42	0.43	0	73	0
	Cancer	17.7 (15.6-19.9)	1,574	15.49	21.3 (19.3-23.3)	1,358	12.0
	Diabetes mellitus	26.7 (10.9-42.5)	40	0.58	27.9 (18.4-37.4)	71	0.87
	Chronic cardiovascular disease	25.1 (22.5-27.7)	429	19.24	32.1 (28.6-35.6)	318	7.96

	Chronic renal disease	25.0 (20.7-29.3)	377	6.94	26.6 (21.2-32.0)	263	2.46
	Chronic neurological disease	26.5 (21.5-31.5)	273	5.63	27.3 (21.8-32.7)	277	2.53
	Chronic digestive disease	19.2 (15.4-23.0)	410	5.78	32.3 (27.7-36.9)	416	4.55
	Mental illness	33.3 (14.4-52.2)	24	0.58	44.4 (21.4-67.4)	19	0.29
	Chronic osteoarticular disease	16.8 (11.8-21.8)	171	2.60	16.4 (10.4-22.4)	219	0.87
	No chronic conditions	20.2 (17.4-23.0)	1,199	11.42	30.4 (26.7-34.1)	1,137	6.57
	Total	**21.9 (20.7-23.1)**	**4,755**	**38.52**	**27.5 (26.2-28.8)**	**4,411**	**42.78**

Influenza vaccine effectiveness (2015-2016 season) was 36.5% in patients 18 to 64 years of age and 41.8% in those 65 and older. Influenza vaccine effectiveness (2016-2017 season) was 33.4% in patients 18 to 64 years of age and 20.9% in those 65 and older.

The relatively low number of averted serious influenza cases in middle-aged patients in both seasons reflects the low intensity or virulence of the season and the fact that fewer cases can be prevented when the underlying incidence is low. Indeed, in the elderly, the number of averted outcomes was 5 to 7 times higher than in the middle-aged patients with low vaccine effectiveness but with the highest attack rate and virulence of all the seasons.

The prevented fraction increased over time and age and was higher in the last season and in the elderly inpatients. The prevented fraction in influenza season 2015/2016 ranged from 10.3% to 25% in the middle-aged or elderly patients and in influenza season 2016/2017 ranged from 21.9% to 52.2%, respectively.

DISCUSSION

The health benefits of influenza vaccination have not traditionally been evaluated in Catalonia, and no specific data about vaccine effectiveness stratified by age group or comorbidity is available in this region. To our knowledge, this is the first study from one hospital to estimate the burden of influenza hospitalization averted and its prevented fraction in adults in this area. Based on the bed capacity of this general university hospital and the latest influenza activity, an immunization program could have averted up to 52.2% of admissions in the elderly and 25.0% of admissions in non-elderly adults.

Influenza activity in the 2015-2016 season peaked in weeks five to seven of 2016; the influenza A(H1N1) pdm09 virus predominated followed by type B influenza viruses. However, hospitalizations were observed between middle-aged adults suffering the A(H1N1) pdm09 subtype. Our findings on the number of middle-aged patients admitted to the hospital support the epidemiological data.[1,8,9]

Influenza activity in the 2016/2017 season started early in week 46 of 2016; the influenza A viruses (H3N2) predominated with hospitalizations and severe outcomes in adults over 65 years, overwhelming some hospitals. Recent vaccine effectiveness estimated for all age groups against A(H3N2) subtype from Europe (38%, 95% CI: 21-51) were consistent with estimates from Canada (42%, 95% CI: 18-59) and the United States (43%, 95% CI: 29-54) earlier in the season. However, some information about different age groups and high-risk patients is still misleading in Europe.[1,8,9] Current seasonal influenza vaccines are only moderately protective, and vaccines eliciting broader and more durable immunity are therefore needed.[4]

The findings from this study demonstrate that elderly inpatients and those with chronic disease at particular influenza risk remain under-immunized. While it is difficult to compare vaccination rates across studies due to different methodologies, information biases, and selected populations, the vaccination rates for influenza estimated in this study appear incomparable to estimates obtained previously.[10-12]

In our study, the overall influenza coverage was lower than 20%, with low vaccine effectiveness in both seasons and both age groups. However, 95 hospitalizations were averted in the 6-month periods of the two influenza seasons, and the prevented fraction ranged from 10% to 52.2%. The influenza coverage among hospitalized adults is low in our study but quite similar to 15% of surgical patients,[13] 19% among inpatients under the age of 65 in France,[14] 22.1% of adults aged 15-59 years with any chronic condition,[15] and 35% of Medicare pneumonia inpatients.[16] In high-risk conditions, there was lower coverage of influenza rates in adults younger than 60 years than in children.[15,17] However, our influenza coverage greatly differs from the 47% of adults with chronic diseases or high-risk persons in Australia18 or the 57.2% of inpatients in South Korea.[19]

In Catalonia, where influenza immunization is not universal, since 2006, there has been a significant decrease in the influenza immunization rate from 74.2% to 56% of the general population.[20,21] In 2015, this national coverage rate was quite different according to age, ranging from 29.5% in people aged 60 to 64 to 74.4% in those 75 years or older.[21] Our results suggest that immunization among hospitalized adults with or without chronic diseases remains far below the Healthy People 2020 target of 70% for the annual vaccination of adults against seasonal influenza. More effort is needed to reach the Healthy People 2020 targets, and immunization during hospital admission could lead to an incremental benefit. Ensuring that all people who visit a health care provider during the influenza season even upon hospital admission receive a vaccination recommendation could increase both influenza vaccination rates and the averted influenza rate. In Catalonia, influenza immunization should be universally recommended to all patients being treated by general practitioners, but its recommendation during hospital admission, emergency room consultation, or outpatient visit is usually not considered.

It is likely that barriers from the patient, provider, and system level could explain the under-immunization rate.[22] The occasional fear or worry that is experienced by a patient during his or her hospital stay due to the main diagnosis or procedure, as well as patient misconceptions, their reluctance for inpatient vaccination, and the relationship established with the medical specialist may influence low admission and low accessibility to primary health care after hospitalization. Providers or medical specialists from the hospital often deprioritize preventive health care such as immunizations in favor of managing more acute issues, so immunization is not discussed with patients during their hospital stays and vaccination is not ordered. Sometimes providers present doubts about immunization safety to inpatients, even though no strong evidence of increased risk for adverse outcomes was found in comparisons of patients who received influenza vaccines during a surgical hospitalization and those who did not.[13] On the other hand, different locations between hospitals and primary health care services diminishes patients' accessibility. Finally, system-level barriers could be the logistic pathway to patient attendance.

In our study, we found that the elderly has a greater tendency to be vaccinated in consonance with other studies,[23] likely because it is universally recommended. Fewer provider and system barriers exist (physician education, physician reminders, and annual general practitioner economic milestones) and greater demand for vaccinations from the elderly community could lead to more vaccine accessibility (such as generous hours and months for vaccination in the primary health care system during the influenza season).

These data indicate multiple missed opportunities for vaccination and the need to increase the routine assessment of targeted adult vaccination needs and vaccination with necessary vaccines in the hospital environment. However, the influenza vaccine is not the only inadequate vaccine in adults, as compliance for most routinely recommended vaccines is also quite low (such as tetanus diphtheria and pneumococcal vaccine in the elderly). Thus, more adult immunization strategies need to be developed, established, and promoted.

The usage of real-time electronic clinical records in this study provided validated data about the determination of vaccination status, demographic characteristics, and the identification of high-risk inpatient conditions. In fact, the electronic clinical records avoided recall bias as vaccination coverage was not subjected to self-reporting; in other studies, the influenza coverage rate was much lower when only the registered immunizations were considered.[24] In addition to the electronic medical records, an immunization campaign should be in place during hospitalization based on embedded orders in the electronic medical record to facilitate ordering vaccinations by providers, daily reminders from ward clerks, and standing orders for influenza vaccination on discharge as is done in the UK.25 In fact, our hospital has a laboratory-confirmed surveillance system but no standard immunization program is in place to expand the high-risk inpatient or outpatient influenza coverage.

This study's findings are subject to at least four limitations. First, the general university hospital sample excluded inpatients from private hospitals and those in residence, which might result in an underestimation or overestimation of the vaccination coverage levels. Second, the information about immunization coverage was from primary health care, but we ignored other sources of immunization (including workplaces, outpatient private clinics, health insurance, travel clinics, and private hospitals). Catalonia's national health service has a usage rate of 78% (5.8 million), and 70% of the population visits at least once a year, but only 5.8% of Catalonians had one hospital stay in the prior 12 months.[21] Third, when the vaccination was not recorded, it was defined as not administered, so underestimation of vaccination may have occurred. Finally, we did not have access to previous influenza vaccine administration in previous seasons as the electronic system had just been established for the first studied season. Previous influenza administration has often been considered a main predictor of current influenza coverage.

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BIOGRAPHICAL SKETCH

Dr. Masuet-Aumatell is a medical doctor in a university hospital with more than 15 years of experience on immunization and epidemiology. She is also a medical teacher in the Universitat de Barcelona on Epidemiology and Preventive Medicine.

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