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Pneumonia Caused by Influenza Virus in Hospitalized Patients Study of the Direct Costs in a Public Hospital of the Autonomous City of Buenos Aires

Neumonía por virus de influenza hospitalizada Estudio de costos directos en un hospital público de la Ciudad Autónoma de Buenos Aires

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ABSTRACT

Introduction: Influenza-associated hospitalization is one of the most severe consequences of the infection caused by this virus. There is no local information on the costs of the hospitalization impact.

Objectives: To determine the structure of direct costs of patients hospitalized for influenza pneumonia in a public hospital of the City of Buenos Aires in 2022.

Materials and methods: We analyzed patients hospitalized for influenza pneumonia in 2022. Diagnosis was made through a viral panel (polymerase chain reaction [PCR]) on respiratory specimens, with negative SARS-CoV2 results. Direct costs were determined from the perspective of the funder, based on medication costs and the clinical hospitalization and emergency department cost modules provided by the Government of the City of Buenos Aires (GCBA) as of April 2023, with a peso/dollar exchange rate of 210.78.

Results: 7 patients were admitted: median age, 72 years (interquartile range [IQR] 67.5-75); male gender, 57%; 85% smokers (50% former smokers, 45 pack-years). All patients met the criteria for influenza vaccination, but only 28.5% had actually been vaccinated the previous year. A high prevalence of comorbidities was determined: Charlson index median of 5 (IQR 4-7); 85% cardiovascular diseases, 28.5% alcoholism, 28.5% diabetes, 28.5% asthma/COPD (chronic obstructive pulmonary disease) and 14.8% neoplasms. The median duration of emergency room hospitalization was 1 day (IQR 0.5-1), and 7 days in the general ward (IQR 4.5-12). The case-fatality rate was 14.8%. The direct cost was US$2,663.19 per patient (IQR 1878.28-3974.54). The direct non-modular cost was 26.76% of the total cost (IQR, 16.71-33.44): 25% for medications and 75% for studies.

Conclusion: Patients hospitalized for influenza pneumonia were men over 70 years old, with a high burden of comorbidities. Although they all met the criteria for vaccination, only a minority had been vaccinated. The direct cost from the funder's perspective was US$ 2,663 per patient. This is the first study on direct costs of influenza pneumonia in hospitalized patients to be conducted in our country. National policy measures must be maximized to ensure higher vaccination coverage for at-risk populations.

Key words: Influenza; Pneumonia; Hospitalizations; Direct cost; Expenses

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RESUMEN

Introducción: La hospitalización por influenza es una de las consecuencias más graves de la infección por este virus. No hay información local de costos del impacto de su hospitalización.

Objetivos: Determinar la estructura de costos directos de los pacientes hospitalizados por neumonía por influenza en un hospital público de la ciudad de Buenos Aires en 2022.

Materiales y métodos: Se evaluaron pacientes hospitalizados por neumonía por influenza en 2022. El diagnóstico se hizo por panel viral (PCR) en especímenes respiratorios y negatividad SARS-CoV2. Se determinaron los costos directos desde la perspectiva del financiador, según costos de medicamentos y la modulación de internación clínica y guardia del Gobierno de la Ciudad de Buenos Aires a abril de 2023, a una cotización oficial venta con paridad peso/dólar de 210,78.

Resultados: Se internaron siete pacientes: edad 72 años mediana (RIQ 67,5-75); género masculino 57 %; 85 % tabaquistas (50 % ex, 45 paq-años). Tenían criterio de vacunación antigripal 100 % de los pacientes, pero solo 28,5 % la habían realizado el año previo. Se determinó alta prevalencia de comorbilidades: índice Charlson 5 mediana (RIQ 4-7): 85 % cardiovasculares, enolismo 28,5 %, diabetes 28,5 %, asma/EPOC 28,5 % y neoplasia 14,8 %. La duración de la internación en guardia fue un día de mediana (RIQ 0,5-1), siete días en sala general (4,5-12). Tasa de casos fatales 14,8 %. El costo directo fue 2663,19 dólares/paciente (RIQ, 1878,28-3974,54). El costo directo no modulado fue 26,76 % del total (RIQ, 16,71-33,44): 25 % por medicamentos y 75 % por estudios.

Conclusión: Los pacientes hospitalizados por neumonía por influenza fueron hombres, mayores de 70 años con alta carga de comorbilidades, y, aunque tenían indicación de vacunación; una minoría la realizó. El costo directo desde la perspectiva del financiador fue de 2663 dólares/paciente. Es el primer estudio de costos directos en nuestro país de neumonía por virus de influenza hospitalizada. Se deben extremar las medidas de políticas nacionales para asegurar una mayor cobertura vacunal a la población de riesgo.

Palabras clave: Influenza; Neumonia; Hospitalizaciones; Costo directo; Gastos

Influenza is an acute respiratory disease caused by influenza viruses.[1] It can affect both the upper and lower respiratory airways and is accompanied by systemic signs and symptoms such as fever, headache, myalgia, and asthenia.[1] It typically presents in outbreaks every fall/winter season, with varying degrees of spread and severity. This leads to significant morbidity and mortality in at-risk populations.[1] Influenza viruses belong to the *Orthomyxoviridae* family and are single-stranded RNA viruses. They are classified into three types: A, B, and C, based on the antigenic characteristics of their nucleoprotein and matrix protein.[1] Influenza A virus is further subdivided into several subtypes based on surface hemagglutinin (H) and neuraminidase (N).[1] There are 18 different H subtypes and 11 N subtypes of influenza A, but only subtypes H1, H2, H3, N1, and N2 have been associated with epidemics in humans, like the most recent pandemic in 2009/2010 (H1N1).[1]

Less than 30% of acute community-acquired pneumonias in adults are of viral origin.[2] The most common viral genera are influenza A, parainfluenza, respiratory syncytial virus, rhinovirus, metapneumovirus, coronavirus, and adenovirus.[2]

Globally, between 3 to 5 million people get severely ill from influenza viruses each year.[3-5] Annually, between 290,000 and 650,000 people die from severe forms of influenza infection.[3-5] The identified risk factors are the severity of the infection leading to hospitalization, age over 65 or under 5 years, and immunosuppressed patients.[3-5] Between 2009 and 2010, the H1N1 pandemic also reached Argentina. The peak incidence of cases occurred in the winter of 2009.[6] A total of 12,477 cases were confirmed, and 685 patients died (0.5% case-fatality rate).[6] The fatality rate was higher among hospitalized patients (9%), and the associated risk factors were pre-existing chronic respiratory diseases (asthma and COPD), obesity, pregnancy,

human immunodeficiency virus (HIV), age under 5 and over 45 years, and pre-existing heart disease.[7]

In Argentina, up until week 44 of 2022, 2,700 patients had been hospitalized, with 122 deaths (mainly from H3N2 and then H1N1).[8] 82% of hospitalized patients were unvaccinated. 88% of unvaccinated patients had comorbidities, and the two affected age groups were children under 9 years old and adults over 45 years old.[8] 11 people died in the city of Buenos Aires in 2022, and most of them were over 80 years old.[9] Paradoxically, the influenza vaccine is included in the Argentina's National Vaccination Program for at-risk populations free of charge, yet vaccination coverage is still poor.[10]

In our country, there is no information available on the direct cost of hospitalization for influenza-related pneumonia.

OBJECTIVE

The objective of this study is to describe the direct cost of hospitalization for pneumonia caused by the influenza virus and to determine its structure in a public hospital in the City of Buenos Aires in 2022.

MATERIALS AND METHODS

The medical records of patients hospitalized for influenza pneumonia in all areas of the Hospital General de Agudos Dr. J. M. Ramos Mejía of the Autonomous City of Buenos Aires (CABA) from January 1, 2022, to December 31, 2022 were reviewed.

The influenza diagnosis was made through a viral panel of PCR on respiratory specimens, with negative SARS-CoV2 results. The pneumonia diagnosis was based on a combination of clinical symptoms and the presence of pulmonary opacities in chest imaging studies (X-ray and high-resolution computed tomography without contrast). The Charlson Comorbidity Index was calculated to assess the number of comorbidities of each patient.[11-12]

The study included adults over 18 years of age. Direct costs were determined from the perspective of the funder, based on medication costs and the clinical hospitalization and emergency department cost modules for Public Hospitals provided by the Government of the City of Buenos Aires as of April 2023.[13-14] The cost module for inpatient care in isolation for infectious disease was 56,750 pesos (US$269.23) per day; for emergency care with diagnostic studies, the cost was 13,853 pesos (US$65.72), and the cost for critical emergency care without mechanical respiratory assistance was 78,194 pesos (US$370.97).[13] Each module included a predetermined number and type of services (biochemical tests, imaging, electrocardiogram, spirometry, mechanical respiratory assistance, oxygen, disposable materials, medications, etc., as well as proportional costs related to salaries, taxes and fees, administrative charges, equipment amortization, food and laundry costs, etc.). When an additional consultation or diagnostic procedure was made, or if some treatment (e.g., medications) outside the module was performed, the cost was determined from the funder's perspective based on the KAIROS Pharmaceutical Manual and the service fee schedule provided by the Government of the City of Buenos Aires.[14] All patients were treated within 48 hours of the onset of respiratory symptoms with antibiotics, oseltamivir (75 mg every 12 hours for 5 days), and oxygen therapy.

Due to the fluctuations in the peso/dollar exchange rate, results will be reported in U.S. dollars. The exchange rate used for cost calculation was the official selling rate of Banco Nación as of April 1, 2023 (210.78 pesos = 1 dollar).

Descriptive statistics was used. For quantitative variables with a non-Gaussian distribution, the median was used as the central measure, and the interquartile range (IQR 25%-75%) as the measure of dispersion. For variables with a Gaussian distribution, the mean was used as the central measure, and the standard deviation as the measure of dispersion. Percentages were used for qualitative variables.

RESULTS

During the year 2022, 7 adult patients were hospitalized, all of them in general wards. The median age was 72 years (IQR 67.5-75); 57% were male; 85% were smokers (50% former smokers, 45 pack-years) and 42% had social health insurance (n=3).

All patients met the criteria for influenza vaccination, but only 28.5% (n=2) had been vaccinated the previous year. Similarly, only 28.5% (n=2) had completed the pneumococcal vaccination schedule.

A high prevalence of comorbidities was determined in all the patients: Charlson Index median of 5 (IQR 4-7); 85% cardiovascular diseases, 28.5% alcoholism, 28.5% diabetes, 28.5% asthma/COPD and 14.8% neoplasms.

Arterial blood gas on admission showed a pH of 7.38 (IQR 7.34-7.4), $PaCO_2$ of 46 mmHg (37.5-51), and a median PO_2 of 54 mmHg (50-67).

Only one patient died, resulting in a case-fatality rate of 14.8%).

Direct cost analysis

The median duration of hospitalization in an emergency room was 1 day (IQR 0.5-1), and 7 days in the general ward (4.5-12). No patients were referred to the Intensive Care Unit. The case-fatality rate was 14.8% (n=1).

The final cost per patient was US$2,663.19 (IQR 1,878.28-3,974.54), and the total cost for the 7 patients was US$21,803.84.

The direct non-modular cost was 26.76% of the total cost (IQR, 16.71-33.44). 25% of these non-modular costs were for medications, and 75% for studies (Figure 1).

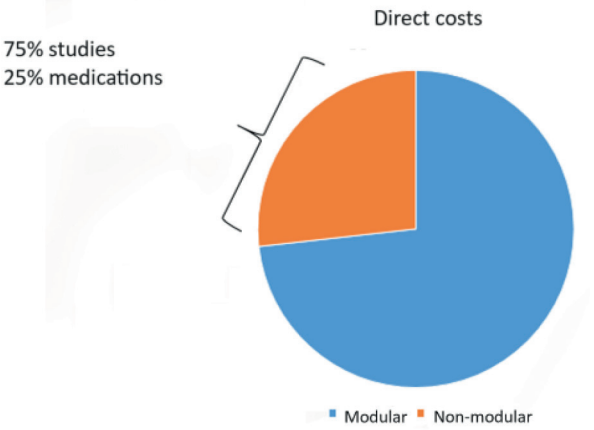

Figure 1. Total direct cost structure.

TABLE 1. Demographic data

Age (median and IQR 25-75%), years	72 (67.5-75)
Masculine gender, %	57
Smokers, former smokers, %	50
Packs-year (median and IQR 25-75%)	45 (35-70)
Social Health Insurance, %	42
Criteria for influenza vaccination, %	100
Influenza vaccine administered, %	28.5 (n = 2)
Pneumococcal vaccine administered,%	28.5 (n = 2)
Charlson Index, (median and IQR 25-75%)	5 (4-7)
Comorbidities, %	
Cardiovascular	85
Alcoholism	28.5
Diabetes	28.5
Asthma/COPD	28,5
Neoplasm	14.8
Arterial blood gas on admission (median and IQR 25-75)	
pH	7.38 (7.34-7.4)
PaO_2, mmHg	54 (50-67)
$PaCO_2$, mmHg	46 (37.5-51)
Deceased patients, %	14.8 (n = 1)

DISCUSSION

The direct cost of hospitalization for influenza pneumonia in a public hospital of the Autonomous City of Buenos Aires has been determined. In a sample of seven patients, mostly male and in their eighth decade of life, with a high prevalence of comorbidities and a significant smoking load, all the patients met the criteria for influenza vaccination, but less than a third had actually been vaccinated. The total direct cost was US$2,263 per patient, with one day spent in the emergency room

and seven days in the general ward. One-quarter of the cost was non-modular and was mainly related to various requested studies.

In the latest 2023 Epidemiological Bulletin of the Ministry of Health of the Nation, between weeks 1 and 48 of the year 2023, 1,052,718 cases of influenza-like illness (ILI) were reported in the Clinical Surveillance component of the National Health Surveillance System (NHSS), with an accumulated incidence rate of 2,256.4 cases per 100,000 inhabitants.[8] If we compare the number of ILI notifications in the first 48 weeks of the 2014-2023 period, we can observe that the highest number of notifications was recorded in 2022 (with 1,287,058 cases), followed by years 2016 and 2017.[8]

On the other hand, in a study on the incidence of community-acquired acute pneumonia in three Latin American cities (General Roca in Argentina, Rivera in Uruguay, and Concepción in Chile), Lopardo et al determined that 30.8% of the patients with that condition had previous coverage only for the influenza vaccine, and 17.5% for the 23-valent pneumococcal vaccine at least once.[15] At least one comorbidity was present in 82.4% of the patients, and two comorbidities in 48%.[15] Cardiovascular diseases were the most common (43.6%), followed by smoking (37.3%), diabetes mellitus (16%), and COPD (15.2%).[15] These results are very similar to those found in our study, where all of the patients should have received both vaccines previously, but only 28.5% did. Our sample also presents a high burden of comorbidities and recognized risk factors: the eighth decade of life, high Charlson Index, cardiovascular diseases (85%), smoking (85%), alcoholism (28.5%), diabetes (28.5%), asthma/COPD (28.5%), and neoplasms (14.8%).

In our study, all patients met the criteria for influenza vaccination, but only 28.5% (n=2) had been vaccinated the previous year. There is much evidence regarding the effectiveness of the annual influenza vaccine among at-risk respiratory patients in preventing severe acute respiratory and non-respiratory events.[16-35] Vasileiou et al conducted a meta-analysis of the effectiveness of the vaccine in people with asthma, where they determined that it prevents 59-78% of acute asthma episodes that lead to emergency visits and/or hospitalizations.[16] Acute asthma episodes can be triggered by infectious agents, among other multiple causes.[17] 80% of said causes are of viral etiology (rhinovirus, influenza, parainfluenza, adenovirus, coronavirus).[18] The Global Initiative for Asthma (GINA) recommends an annual vaccine for patients with moderate to severe asthma (Evidence C), which can be administered along with the COVID-19 vaccine.[17] In relation to patients with COPD, exacerbations are very important events in the progression of the disease, not only deteriorating the patients' quality of life but also being associated with increased morbidity and mortality.[19] In terms of etiology, a smaller fraction is due to viruses of similar viral genera associated with exacerbations in asthma.[19-20] In recent years, more attention has been paid to other complications of systemic inflammatory damage, such as the development of cardiovascular and cerebrovascular events associated with systemic inflammation from exacerbations, not necessarily synchronous with the acute respiratory episode.[21-22] Thus, extrapulmonary complications have been described in the following months, such as myositis, heart conditions (pericarditis, myocarditis), and central nervous system conditions (Reye syndrome, Guillain-Barré syndrome, and transverse myelitis with serotype A and encephalitis with serotype B).[1] In a series of 25,857 cases of moderate COPD exacerbations, Donaldson et al found that the risk of acute myocardial infarction doubles in the first five days post-exacerbation, and the risk of stroke increases by 40% in the first ten days.[21] Kunisaki et al conducted a post-hoc analysis of the SUMMIT study including 16,485 patients and determined that the risk of a cardiovascular event increased approximately tenfold in the first 30 days after a severe exacerbation and remained up to 20% higher after one year.[22] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) suggests that patients should be vaccinated annually (Evidence B).[19] This is based on the reduced rate of lower respiratory tract infections requiring hospitalization, being more effective in the elderly, and co-administered with the pneumococcal and COVID-19 vaccines.[19] In Taiwan, Huang et al determined in a multivariate logistic regression analysis that influenza vaccination is associated with a reduced risk of respiratory failure (adjusted OR [odds ratio] 0.87, 95% CI [confidence interval] 0.79-0.96).[23] In China, Bao et al found that the influenza vaccine once a year reduces exacerbations ($p = 0.0001$) and shows a trend toward reducing hospitalizations ($p = 0.09$).[24] Huang et al have shown that it reduces the risk of ischemic heart

attacks by 26% in the vaccinated COPD population (OR 0.746; 95% CI, 0.595–0.937).[25] The Argentinian Association of Respiratory Medicine has recommended the influenza vaccine for patients with asthma and COPD, following the guidelines of the Ministry of Health of the Nation, the CDC (Centers for Disease Control and Prevention), the GEMA (Spanish Guidelines for Asthma Management), and the GESEPOC (Spanish COPD Guidelines).[26-29]

The GEMA have determined the different components of direct and indirect costs of asthma in healthcare, which can be extrapolated to other respiratory diseases.[30] They report forty-seven recommended characteristics to be used when conducting a study of costs.[30] This study complies with those recommendations. A mixed methodology has been used to determine direct costs: cost modules provided by the GCBA (top-down method) and, in addition to the review of each medical record, paying for the patient's expenses outside the cost modules (bottom-up method). In our study, primary data were directly collected from the medical records, which adds a valuable detail.[30] As previously mentioned, we conducted the study of costs from the perspective of the funder (GCBA) within the setting of a general acute care public hospital, therefore the conclusions can only be extrapolated to that specific health system. Cost comparison between countries or direct extrapolation is not recommended, as cost structure varies from country to country due to the different health systems. However, this comparison can give us an idea of the magnitude of the problem and the qualitative weight of each variable.[30]

By associating the costs of the influenza infection with the vaccination status, Nichol et al had demonstrated three decades ago the cost-effectiveness of influenza vaccination in individuals over 64 years old within a private health system in the United States. They found reductions in hospitalization costs by 47-66% ($p<0.005$), respiratory events by 37% ($p<0.05$), congestive heart failure events by 43% ($p<0.05$), and mortality by 39-54%[31]. They estimated annual savings of US$117 in direct expenses per patient and total annual savings of US$5 million.[31] Another study on the subject by Wongsurakiat et al in a underdeveloped country demonstrated that in patients with COPD, the impact of influenza vaccination is associated with lower consumption of health and economic resources in the more severe forms of the disease.[32] Hughes et al estimated in a theoretical model in the United States that increasing the influenza vaccine coverage would reduce the rate of minor respiratory infections and additional hospitalizations.[33] Many studies have been published on patients with a high burden of cardiovascular disease, especially coronary disease, and the effect of the influenza vaccine in reducing cardiovascular risk.[34-35] A meta-analysis and systematic review of four randomized controlled prospective trials and twelve observational studies demonstrated that the influenza vaccine reduced the relative risk of major cardiovascular events by 12% (95% CI, 0.80-0.94, $p<0.001$), overall mortality by 25% (95% CI, 0.60-0.93, $p=0.01$), and cardiovascular mortality by 18 % (95% CI, 0.80-0.84, $p<0.001$) in patients with cardiovascular disease.[34] A study conducted after the cited meta-analysis, involving 2,571 patients across eight countries who had experienced an acute myocardial infarction or were at high coronary risk, who had been followed for one year, demonstrated that the influenza vaccine reduced the incidence of a composite cardiovascular event by 28% (hazard ratio [HR] of 0.72, 95% CI, 0.52–0.99, $p=0.040$).[35] Overall mortality was reduced by 41% (HR 0.59, 95% CI, 0.39–0.89, $p=0.010$), and cardiovascular mortality was also reduced by 41% (HR 0.59, 95% CI, 0.39–0.90, $p=0.014$).[35] Despite the short- and medium-term respiratory and systemic damage caused by the influenza infection, and considering only direct costs, knowing that indirect costs are significantly higher, it seems paradoxical that vaccination coverage is so poor in our country, where the influenza vaccine is included in the Argentinian National Vaccination Program for at-risk populations free of charge.[10] In 2021, a report by the National Immunization Commission showed that only 32.9% of healthcare workers, 30% of adults over 65 years old, 9% of pregnant women, and less than 5% of children between 6 months and 2 years had received the full vaccination schedule.[10] In fact, in our study, only 28.5% ($n=2$) of the patients had received the influenza vaccine in the previous year, despite all of them having the indication to do so.

Among the limitations of this study, it can be said that data collection from medical records was retrospective. Another limitation is that extrapolating the conclusions to other healthcare systems in our country or other regions (external validity)

is not advisable due to the previously mentioned differing cost structures. No indirect costs were evaluated (which are presumed to be higher than direct costs based on previously reviewed literature); and costs were not determined from other perspectives (for example, patient or societal perspectives). While costs were initially calculated in pesos, the currency instability and devaluation experienced by our country in recent times led us to report the results in dollars. Finally, the cost modules used by the GCBA did not allow breaking down the internal cost structure to determine which variables have been considered and to what extent. It should also be noted that at the time of conducting the study, the exchange rate gap between the official and parallel dollar rate was significant. If a higher dollar parity value were used, it would likely reduce the cost in dollars.

To conclude, the direct cost of hospitalization for influenza pneumonia in a public hospital of the Autonomous City of Buenos Aires has been determined. The study was conducted on a sample of predominantly male patients in their eighth decade of life, with a high prevalence of comorbidities and smoking load. All patients met the criteria for influenza vaccination, but less than a third had been vaccinated. The total cost per patient was US$2,263, considering one day in the emergency room and seven days in the general ward. One quarter of the cost was non-modular, being particularly related to the tests requested.

It is imperative that measures should be maximized to ensure higher vaccination coverage for at-risk populations. We would like to emphasize the need to incorporate this type of studies in the hospital setting so as to collect data that will allow for a better management of the available resources. Including cost-related issues in all sectors involved can contribute to a more efficient management of resources, enabling better planning, organization, and systematization of patient care, thereby improving service production and quality with the same budget or even a lower one. Ensuring that the influenza vaccine (which is public and free) reaches all at-risk populations in a timely and appropriate manner is of utmost importance in terms of the healthcare system to reduce the number of hospitalizations and mortality, both of which can be prevented, along with their associated costs.

Conflict of interest:
Dr. Martin Sívori has participated in continuous medical education programs for Glaxo SmithKline, Astra Zeneca, Sequirus, ELEA, Pfizer and SANOFI.

Dr. Daniel Pascansky has participated in continuous medical education programs for Glaxo SmithKline, Astra Zeneca, Sequirus, ELEA, and SANOFI.

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