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Clinical characteristics of patients hospitalized with severe respiratory illness during influenza seasons in the cities of Bogota and Manizales, Colombia 2000-2006

Características clínicas de pacientes hospitalizados con enfermedad respiratoria severa durante temporadas de influenza en las ciudades de Bogotá y Manizales, Colombia 2000-2006

Karol Cotes, José Moreno-Montoya, Alexandra Porras-Ramírez, Alejandro Rico-Mendoza and Fernando de la Hoz-Restrepo

Departamento de Salud Pùblica, Facultad de Medicina.Universdiad Nacional de Colombia. Bogotá, Colombia. karpatri@hotmail.com, josemorenomontoya@gmail.com, aporraslu@yahoo.es, aricomendoza@gmail.com, fpdelahozr@unal.edu.co

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ABSTRACT

Objective Identifying clinical factors associated with respiratory tract diseases during human influenza circulation seasons in children aged less than two years old and adults aged over 65 years in two hospitals in the cities of Manizales and Bogota, Colombia.
Methods A retrospective case study in patients hospitalized with acute respiratory illness was carried out during influenza circulation seasons from 2000 to 2006 in Bogota and Manizales. Complication frequency was studied, including death, and its relationship with baseline diseases.
Results 535 children under two years of age and 288 adults over 65 years old were studied. 38.9 % of the children and 27 % of the adults had at least one complication. The presence of underlying disease in children was associated with complications such as hospital death (OR=16.5; 4.7-57.7 95%CI), being admitted to an intensive care unit (OR=6.3; 3.5-11.3 95%CI), respiratory distress needing FIO2> 40 % (OR=2.4; 1.6-3.7 95 %CI), mechanical ventilation (OR=2.4; 1.6-3.7 95 %CI) and multilobar pneumonia (OR=2.1; 1.3-3.4 95 %CI). This association remained after adjusting for confounding factors such as age and socioeconomic status, whilst such relationship was not observed in older adults.
Conclusion Children with underlying chronic diseases were more susceptible to clinical complications during influenza seasons. Those under 6 months of age were

particularly prone to dying or being admitted to an ICU. These results suggested that vaccination policies need to be adjusted.

Key Words: Respiratory tract diseases, influenza A virus, complications, risk factors, respiratory insuficiency (*source: MeSH, NLM*).

RESUMEN

Objetivo Identificar factores clínicos y sociodemográficos asociados a enfermedad respiratoria severa durante las temporadas de circulación de influenza
Métodos Se realizó un estudio de casos retrospectivo en pacientes hospitalizados por enfermedad respiratoria aguda durante las temporadas de circulación del virus de la influenza del año 2000 al 2006 en tres hospitales de Bogota y Manizales. Se estudio la frecuencia de complicaciones, incluyendo la muerte, y su relación con la presencia de enfermedades de base.
Resultados Se estudiaron 535 niños menores de dos años y 288 adultos mayores de 65 años. En los niños, la presencia de una enfermedad de base se relacionó con complicaciones como la muerte hospitalaria (OR=16,5 IC 95 % 4,7-57,7), , el ingreso a UCI (OR=6,3 IC 95 % 3,5-11,3), dificultad respiratoria que ameritaba uso de ventilación mecánica (OR= 2,4 IC 95 % 1,6-3,7),) y, la neumonía multilobar (OR=2,1 IC 95 %1,3-3,4),.Esta asociación se mantenia después de ajustar por factores de confusion como edad y estrato socioeconomico. En los adultos mayores no se observó esta relación.
Conclusiones Durante las temporadas de influenza los niños con enfermedad crónica presentan una enfermedad más severa. Los niños menores de 6 meses, que no son objeto de vacunación, mostraron tener mayor frecuencia de complicaciones importantes como la muerte y el ingreso a UCI Es necesario por tal razón tener en cuenta este aspecto para el ajuste en las medidas de prevención y control tales como la vacunación.

Palabras Clave: Virus de la influenza A, neumonía, insuficiencia respiratoria, factores de riesgo (*fuente: DeCS, BIREME*).

Influenza virus infection is a major cause of acute respiratory illness and complications since such infection can lead to hospitalisation or death, especially in populations such as children under two years of age, people aged over 65 or individuals suffering certain chronic diseases (1). The virus has a distinct pattern of movement in tropical and subtropical regions but is often associated with rainy seasons and the impact of such movement on morbidity and mortality has been less studied than in temperate zones (2).

The factors which have usually been associated with increased risk for influenza are mainly age (being over 65 years of age, or less than 2 years) and having suffered from some chronic diseases such as lung or

heart disease. The Advisory Committee for Immunization Practices (ACIP) has identified certain clinical conditions that increase the risk for acquiring influenza complications such as asthma, chronic lung disease, chronic cardiovascular disease and metabolic or endocrine disorders (3). A recent study in a tropical country found that social status and overcrowding were associated with complications related to influenza-like illness (4).

The influenza virus can be complicated in people having risk factors or extreme ages of life and may lead to pneumonia or exacerbation of underlying medical conditions (heart or lung disease). It has also been associated with encephalopathy, transverse myelitis, Reye's syndrome, myositis, myocarditis and pericarditis, including asthma (3-5).

Colombia has a sentinel surveillance system for the circulation of respiratory viruses and some studies have been crried out regarding influenza and its relationship to severe disease (6-8). However, as in many tropical countries, some aspects regarding the epidemiology of seasonal influenza are still unknown, especially the clinical consequences of infection by the virus in the general population in high risk patients. A recent study found that mortality could become increased in seasons having the largest circulation of influenza virus in Colombia, including pneumonia and cardiovascular disease in patients older than 60 years; the influenza A virus showed a pattern of seasonal movement (9).

This article presents the results of a study of patients hospitalised in Manizales and Bogota for acute respiratory disease during seasonal influenza seasons from 2000 to 2006 to help improve knowledge about the consequences of influenza infection in Colombia.

METHODS

Type of study

This was a retrospective case study of patients who had been hospitalised for acute respiratory illness during seasonal influenza virus circulation between 2000 and 2006. The medical records of children under two years of age and people aged over 65 were reviewed in three hospitals in Colombia: a paediatric hospital in the city of Manizales, located in the west of the central part of Colombia (420,000 inhabitants) and two general hospitals in Bogotá (the capital, 8,840,116 population according to the latest census). The study

was submitted to each hospital's scientific committee and the confidentiality of the information collected was respected.

Definition of flu season

The concept used by Chiu and Cabbage in a study of influenza-related hospitalisations in children in Hong Kong was applied for defining the seasons.10 This study defined a season as a circulation period having two or more consecutive weeks where at least 4 % of the annual number of diagnoses confirmed for influenza virus were registered (regardless of type or subtype) and less than 2 % of the annual number positive for respiratory syncytial virus (RSV). This criterion was applied in two ways; the first identified two consecutive weeks where the sum of positive diagnoses for both influenza and RSV complied with the percentage required by the criterion and an alternative approach was applied to each week.

The flu seasons corresponded to the following months during the study period: April, May and June (2000), August, September and October (2002) October and November (2003), April and May (2004); September October and November, September, October and November (2006). None of the criteria used could be configured during 2001.

Study population

The medical records of 535 children younger than 2 years old from selected schools were studied and those of 288 adults aged over 65 who were hospitalised with a diagnosis associated with acute respiratory illness during seasonal influenza virus circulation between 2000 and 2006. The number of children in Manizales represented 65.4 % and 34.6 % in Bogota (19.8 % in Hospital Simon Bolivar, 14.8 % in the Police Hospital). The number of adults represented 60.1 % in the Simon Bolivar Hospital and 39.9 % in the Police Hospital.

Selection criteria for the medical records

The medical records of patients who had the following characteristics were included: being aged less than two or older than 65, hospitalisation during the influenza seasons described above and having a discharge diagnosis within the following International Code of Diseases categories (version 10, ICD 10): J100, J101, J108, J110, J111, J180, J181, J189, J218, J219, J22, J128 and J19. The following were also included for children under two years: J04, J05, J06, J12, J13, J14, J15, J16, J17, J18, J20 and J21. J44, J440, J441, J448 and J449 were included for older adults.

Clinical histories where the outcome was unclear, where the patient had been transferred to hospital or because the parents had decided that a child should leave a hospital without the consent of the treating physician were excluded. Cases where health status was unclear on discharge were also excluded.

Definition of outcomes

The outcomes considered were the presence of complications during hospital treatment and death. The complications studied were: empyema, multilobar pneumonia, cardiac complications, gastrointestinal complications, neurological complications, respiratory distress that warranted >40 % FIO2, pleural effusion, worsening of underlying disease, secondary bacterial pneumonia, admission to intensive care unit (ICU), use of mechanical ventilation and acute otitis media. Only the information recorded in the medical history was used to define the presence of these events.

Defining exposure

The presence of underlying chronic diseases and hospital deaths were defined as exposures of interest. These were divided into those identified as high risk by the ACIP and those not included in this definition. According to the ACIP, high-risk chronic diseases include chronic cardiovascular disease, chronic lung disease (with or without asthma), asthma without other chronic lung diseases, metabolic or endocrine disorders, immunosuppression, aspirin therapy, haemoglobinopathies and renal disease. All other chronic diseases, including malnutrition, were considered in the second category.

The presence of these events was defined according to that recorded in the medical history. Other exposures considered were social security affiliation considering that the poor were not affiliated with the category of greatest exposure, the hospital and a patient's gender and age. All such data were drawn from the clinical history.

Recording information

Six trained interviewers (two per hospital) collected information from the medical records (each survey team consisted of a health professional, doctor or senior nurse and a technician). The collection form included demographic variables such as age, gender, health social security system membership status, place of birth and place of residence; clinical variables

included symptoms on admission, presumptive diagnoses and final diagnoses, days of hospitalisation, history of hospitalisation for acute respiratory disease (ERA) and acute diarrhoeal disease (ADD) during the last twelve months, the presence of underlying disease and the presentation of the complications mentioned in the case definition.

Treatment and data analysis

The frequency of complications, deaths and number of days' hospitalisation among patients was compared with underlying diseases and those without it. Events' results were compared regarding age, gender and social security affiliation. Means and percentages were compared and 2 by 2 tables were constructed for calculating the odds ratios (OR) and their respective 95 % confidence intervals.

The data was processed using Epi-info 3.2 (11) and Stata 10 software (12). Logistic regression models were used to adjust the effect of the presence of underlying diseases on complications and death for the other covariates listed.

RESULTS

Children aged less than two years

The study included 535 patients; average age was 8 months and 53.6 % were male. 18.3 % were affiliated to the contributory regime (the regime where their parents would have had to have been formally employed people, pensioners, retirees and independent workers who were able to pay) (13); 21.5 % belonged to the subsidised regime (people lacking the ability to pay and who qualify for subsidies). 45.4 % were uninsured or "linked" to the system (people lacking the ability to pay, outside the system who are entitled to subsidised health services provided by government entities) (13). 14.8 % were in special schemes.

The common symptoms were cough (67.6 %), followed by fever (61.2 %), respiratory distress (24.6 %), rhinorrhoea (23.3 %), gastrointestinal symptoms (15.8 %), vomiting (7.2 %) and diarrhoea (8.35 %) and dyspnoea (8.22 %). The commonest presumptive and definitive diagnoses were pneumonia (47.2 %) followed by bronchiolitis (18.8 %) and broncobstructive syndrome (7.2 %).

About 27 % (n=142) of the patients had at least one underlying disease; 58 of these (40.8 %) had at least one disease belonging to a group defined by the ACIP as high risk and for whom vaccination was recommended (Table 1). Malnutritioin was the underlying disease in 21 of 142 (14 % or 3.9 % of all the children studied). Their vaccination background could not be obtained from the clinical records.

The average length of hospital stay was 6.7 days (1 to 14 days range). Average days' stay was significantly higher among children having underlying diseases (8.8 days) than among those not suffering from these diseases (5 days) ($p<0.001$). This difference was also presented by age, where children under 6 months stayed longer in hospital (6.8 days) than those aged 6 to 24 months (5.3 days) ($p<0.001$).

Table 1. Underlying diseases in 142 children in the study, Colombia, 2000-2006

Disease group	Diseases	Cases (%)
Considered high risk by ACIP[a]		58
Cardiovascular chronic heart disease	Atrial septal defect (ASD), ventricular septal defect (VSD), congenital heart disease, mitral insufficiency, cardiomegaly, heart failure, patent ductus arteriosus, tricuspid insufficiency	25 (43.1)
Chronic lung diseases (with or without asthma)	Bronchopulmonary dysplasia, pulmonary hypertension, pulmonary malformation	29 (50)
Asthma without other chronic lung diseases	Asthma	3 (5.1)
Metabolic or endocrinal disorders	Hyperglycemia, adrenal hiperplasia, congenital hypothyroidism	6 (10.3)
Immunosuppression	HIV	3 (5.1)
not considered high risk by ACIP		84
nutritional disorders	Chronic malnutrition, Kwashiorkor type chronic malnutrition, chronic malnutrition severe malnutrition, marasmus type	21 (25)
CNS disorders	Epilepsy seizure syndrome, West's syndrome, sequelae of hypoxic ischemic encephalopathy, autism	13 (15.5)
Congenital malformations	Down's syndrome, cleft palate, Rubinstein's syndrome, left hemihypertrophy, neurofibromatosis	7 (8.3)
digestive disorders	Gastroesophageal reflux (grade II, III, IV, V), gastric ulcer	20 (23.8)
History of prematurity		8 (9.5)
Others	Hypertension, anemia, craneosinotosis, overinfected scabies, extravagant TBC, hialiana membrane, inguinal hernia	19 (22.6)

[a] No patients had three conditions considered by the ACIP as being at high risk (aspirin therapy, hemoglobinopathies and renal disease)

Thirty-nine percent of hospitalized children (n=208) had at least one complication; the most frequent complication was respiratory distress which merited >40 % FIO2 occurring in 125 children (23.4 %), followed by multilobar pneumonia in 98 patients (18.3 %) and admission to an ICU in 56 children (10.5 %). There were 19 deaths (3.6 % death-case ratio). Children with underlying disease became complicated more frequently than children without any underlying disease (2.3 OR; 1.5-2.4 95 %CI).

Significant statistical associations were found between having an underlying disease and complications such as death (16.5 OR;, 4.7-57.7 95 %CI), being admitted to an ICU (6.3 OR; 3.5-11.3 95 %CI), respiratory distress warranting >40 % FIO (2.4 OR; 1.6-3.7 95 %CI), requiring mechanical ventilation (4.3 OR; 2.0-9.9 95 %CI), multilobar pneumonia (2.1 OR; 1.3-3.4 95 %CI). After adjusting for possible confounding variables (age and health social security system affiliation), the relationship between death ($p<0.001$) or admission to an ICU ($p<0.05$) with the presence of underlying diseases was observed. The state of social security affiliation was also associated with admission to an ICU (2.5 OR; 1.3-4.9 95 %CI).

Table 2 shows the association between complications and the presence of underlying disease divided into two groups; one was composed of those considered by ACIP as being at high risk for influenza complications and the other by underlying diseases not considered by the ACIP. The magnitude of the associations was stronger with diseases in the ACIP group even though there was also a strong association with the groups of diseases not considered by the ACIP.

Older adults

288 subjects aged between 65 and 99 years old were studied. The average and median age was 73 years; 53.6 % were male. Regarding social security affiliation, 11.5 % were uninsured, 15.6 % were subsidised, 12.5 %, were in the contributory scheme and 60.4 % were in a special scheme.

The most frequent symptoms were dyspnea (51.5 %) followed by fever (32.4 %), cough (24.7 %) and respiratory distress (23.3 %). The most frequent clinical diagnoses were definitely suspected or chronic obstructive pulmonary disease (exacerbated COPD) (50.1 %) followed by pneumonia (38.6 %) and bronchitis (12.9 %); 258 (89.6 %) of the patients had at least one underlying disease.

Length of hospital stay averaged 8.8 days (median 7 days), ranging from 1 to 45 days. Average length of hospital stay was 9 days amongst patients having an underlying disease while the mean was 5.6 ($p<0.05$) for those without it. As many as 27 % of these patients had some type of complication. The most frequent complication was respiratory distress (>40 % FIO2) found in 35 patients (12.2 %), followed by the death of 28 patients (9.7 %), pleural effusion in 27 patients (9.4 %) and multilobar pneumonia in 24 patients (8.4 %). There were no statistically significant associations between the occurrence of adverse outcome and underlying disease.

Table 2. Association between underlying disease (ACIP high risk disease and non ACIP underlying disease) and clinical complications in children Colombia, 2000-2006

ACIP high risk diseases *cf* healthy children				Non ACIP underlying diseases *cf* healthy children			
Outcome	No. of cases/ total cases	OR (95%CI)	OR 95%CI adjusted by hospital, age and affiliation scheme	outcome	No. of cases/ total cases	OR (95% CI)	OR 95%CI adjusted by hospital, age and affiliation scheme
Any complication				Any complication			
Previously healthy	131/393			Previously healthy	131/393	2.2 (1.3-3.5)	3.1 (1.8- 5.3)
		2.6 (1.5-4.6)	3.8 (2.0- 7.4)				
ACIP high risk disease	33/58			Non ACIP underlying disease	44/84		
Death				Death			
Previously healthy	3/393			Previously healthy	3/393		
		27.1 (7.2-101.8)	30.0 (7.4-120.9)			10 (2.4-4.8)	10.6 (2.6- 42.9)
ACIP high risk disease	10/58			Non ACIP underlying disease	6/84		
Admission to ICU							
Previously healthy	20/393			Previously healthy	20/393		
		9.1 (4.4-18.4)	1.2 (5.1- 25.1)			4.7 (2.4-9.5)	5.3 (2.5-11.3)
ACIP high risk disease	19/58			Non ACIP underlying disease	17/84		
Respiratory distress warranting >40% FIO2							
Previously healthy	74/393			Previously healthy	74/393		
		2.8 (1.6-5.1)	4.1 (2.1- 8.1)			2.2 (1.3-3.6)	2.9 (1.6-5.6)

ACIP high risk diseases *cf* healthy children				Non ACIP underlying diseases *cf* healthy children			
Outcome	No. of cases/ total cases	OR (95%CI)	OR 95%CI adjusted by hospital, age and affiliation scheme	outcome	No. of cases/ total cases	OR (95% CI)	OR 95%CI adjusted by hospital, age and affiliation scheme
ACIP high risk disease	23/58			Non ACIP underlying disease	28/84		
Use of mechanical ventilation							
Previously healthy	12/393			Previously healthy	12/393		
		6.6 (2.7-16.1)	7.4 (2.9-19.3)			2.8 (1.1-7.6)	3.1 (1.2-8.5)
ACIP high risk disease	10/58			Non ACIP underlying disease	7/84		
Multilobar pneumonia							
Previously healthy	59/393			Previously healthy	59/393		
		1.8 (0.9-3.4)	2.2 (1.15- 4.5)			2.4 (1.4-4.1)	3.1 (1.7-5.6)
ACIP high risk disease	14/58				25/84		

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pneumonia in 24 patients (8.4 %). There were no statistically significant associations between the occurrence of adverse outcome and underlying disease.

DISCUSSION

A high frequency of complications was found in children hospitalised during influenza seasons in Colombia (38 %) which was within the limits found in the literature (2 % to 60 %). Such wide variability may be explained by differences in the rate of the complications studied, the diversity of influenza viruses involved in the seasons analysed and differences in hospitals' infection management protocols (14-17). It is most likely that many differences between studies were due to the strains' virulence being different since the same strain can circulate for several consecutive years and therefore be associated with being benign or more tables associated with more severe disease, thereby significantly changing their antigenic characteristics.

Pneumonia was the most frequent clinical diagnosis; the literature has reported differences in frequencies related to clinical diagnosis or in hospitalised patients, but pneumonia has higher overall frequency during seasonal influenza (18). Moreover, the international literature reports fthat bronchiolitis usually occurs more frequently in infections caused by respiratory syncytial virus (RSV). Such predominance of pneumonia in bronchiolitis in this study suggested that influenza infection predominated over infection with other viruses in enrolled patients.

Underlying disease in older adults was remarkably high and about 90% of patients had at least one chronic underlying disease. The percentage of underlying diseases was quite high compared to other studies, such as Glezen's where frequency was 60 % (19). The high frequency of older people who are hospitalised for recrudescence of chronic obstructive pulmonary disease also suggested that the criterion for selecting the influenza seasons was adequate. Most elderly patients hospitalised during the study period had a diagnosis of exacerbated COPD (~60 %) which has also been reported in other studies as a characteristic regarding the impact of seasonal influenza on the elderly's health (20-22).

This study had some limitations; one of the most important ones being that it could not be established whether all patients included in the

retrospective study actually had active infection caused by the influenza virus. It is possible that influenza viruses circulate along with other respiratory viruses, which would hamper attributing all the complications and deaths found in the study to flu virus infection. However, surveillance data from the Colombian National Institute of Health's virology laboratory has shown that RSV circulates at different times to that for the influenza virus and that the frequency of other viruses causing severe respiratory disease is relatively low. For example, adenovirus and parainfluenza virus frequency in the same monitoring system was less than 5 % for the 10 years studied (6-8).

Another limitation concerned the representativeness of such data for Colombia. Until this study was conducted, the respiratory virus monitoring system in Colombia only systematised samples collected from two sites in the country, Bogota and Manizales, both located on the central mountain range in climatic and geographic conditions which are different to the country's other regions. Although studying several outbreaks of influenza in Colombia has shown that the circulation of influenza viruses, particularly influenza A H3N2, is usually national with a few weeks between different regions, there is no guarantee that the results of this study, especially the percentage of cases which die, can be generalised to other regions where access to health services and healthcare quality may be different.

There was a significant frequency regarding children having underlying diseases (26.5 %) which also came within the limits reported by other studies (8 % to 40 %) (23-34). However, a significant percentage of these diseases (59 %) was not considered high risk by ACIN for complications from influenza. However, these children were also more likely to develop complications and die during hospitalisation, this being found infrequently in the literature (27). This is important for clinical management, suggesting that patients having underlying diseases other than those identified by the ACIN, including malnutrition, should also be included in the priority groups for annual vaccination against influenza.

This study has shown that a large number of people requiring hospitalisation for respiratory illness during influenza virus circulation-dominated seasons have severe underlying diseases, suffer major complications during hospitalisation and about 4 % may die. This reinforces the need for vaccination against influenza in the region's tropical and

intertropical countries, placing special emphasis on such risk groups and prospectively strengthening surveillance of influenza-associated clinical events ♣

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