



# Severe acute respiratory infections (SARI) from influenza in adult patients in Chile: the experience of a sentinel hospital

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## ABSTRACT

**Objective.** To 1) describe clinical characteristics of adult patients in Chile with severe acute respiratory infections (SARI) associated with influenza viruses, and 2) analyze virus subtypes identified in specimens collected from those patients, hospital resources used in clinical management, clinical evolution, and risk factors associated with a fatal outcome, using observational data from the SARI surveillance network (SARInet).

**Methods.** Adults hospitalized from 1 July 2011 to 31 December 2015 with influenza-associated SARI at a SARI sentinel surveillance hospital in Santiago were identified and the presence of influenza in all cases confirmed by reverse transcription polymerase chain reaction (RT-PCR), using respiratory samples.

**Results.** A total of 221 patients (mean age: 74.1 years) were hospitalized with influenza-associated SARI during the study period. Of this study cohort, 91.4% had risk factors for complications and 34.3% had been vaccinated during the most recent campaign. Pneumonia was the most frequent clinical manifestation, occurring in 57.0% of the cohort; other manifestations included influenza-like illness, exacerbated chronic bronchitis, decompensated heart failure, and asthmatic crisis. Cases occurred year-round, with an epidemic peak during autumn–winter. Both influenza A (H1N1pdm09 and H3N2) and B virus co-circulated. Critical care beds were required for 26.7% of the cohort, and 19.5% needed ventilatory assistance. Multivariate analysis identified four significant factors associated with in-hospital mortality: 1) being bedridden (adjusted odds ratio (aOR): 22.3; 95% confidence interval (CI): 3.0–164); 2) admission to critical care unit (aOR: 8.9; CI: 1.44–55); 3)  $PaO_2/FiO_2$  ratio < 250 (aOR: 5.8; CI: 1.02–33); and 4) increased serum creatinine concentration (> 1 mg/dL) (aOR: 5.47; CI: 1.20–24). Seasonal influenza vaccine was identified as a significant protective factor (aOR: 0.14; CI: 0.021–0.90).

**Conclusions.** Influenza-associated SARI affected mainly elderly patients with underlying conditions. Most patients evolved to respiratory failure and more than one-quarter required critical care beds. Clinical presentation was variable. Death was associated with host characteristics and disease-associated conditions, and vaccine was protective. Virus type did not influence outcome.

## Keywords

Influenza, human; respiratory tract infections; adult; hospitalization; risk factors; fatal outcome; Chile.

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Influenza has a high burden of disease and mortality worldwide, especially among groups at increased risk for complications, such as children under 5 years old, the elderly, pregnant women, and individuals with chronic medical conditions (1–6). Influenza prevention requires periodic vaccination campaigns designed according to the virological information gathered at different sentinel points. Knowledge gained from pandemics in the past led to the development of the World Health Organization (WHO) Global Pandemics Preparedness Plan at the beginning of the 21<sup>st</sup> century (7). This plan was designed to help countries prepare for influenza virus pandemics like the ones experienced in 2009, when timely detection of the emergent virus failed, impeding the effectiveness of mitigation measures (8, 9). One result of this experience was the development of an active surveillance network to monitor admitted patients with severe acute respiratory infections (SARI) in sentinel hospitals that includes appropriate sampling, laboratory testing, and early online reporting. The SARI surveillance network (SARInet) has been operating in various countries in Latin America and the Caribbean since 2011; in Chile, it includes six hospitals in different geographic regions (north, central, and south). Ongoing efforts to strengthen surveillance are focused on 1) detection of new emerging respiratory viruses; 2) analysis of the circulation of different influenza types and subtypes; 3) facilitation of vaccine composition; and 4) evaluation of vaccine and antiviral therapy effectiveness to help prevent death or complications (10). Using the observational data collected through SARInet, this study aimed to 1) describe clinical characteristics of adult patients in Chile with influenza-associated SARI, and 2) analyze virus subtypes identified in specimens collected from those patients, hospital resources used in clinical management, clinical evolution, and risk factors associated with a fatal outcome.

## MATERIALS AND METHODS

### Study design

This descriptive observational study used data from the SARI surveillance network complemented by information obtained from reviews of individual medical records. The researchers

identified adult patients hospitalized with influenza-associated SARI between 1 July 2011 and 31 December 2015 at Hospital Militar, a SARI sentinel surveillance hospital in the metropolitan area of Santiago, Chile.

### Inclusion/exclusion criteria, case definition, and laboratory testing

SARI cases were identified using the following standard case definition: measured/reported fever plus respiratory symptoms associated with tachypnea ( $\geq 30$  breaths/minute) and/or low pulse oximetry (blood oxygen saturation  $< 90\%$  while breathing ambient air). However, fever was a conditional inclusion criterion, left to the discretion of the physician in charge of case recruitment, due to the older age of the study cohort, as described in more detail below.

Nasopharyngeal swab specimens collected from patients that met the SARI criteria were analyzed first by direct immunofluorescence (IF) for eight different viruses: influenza A and B, parainfluenza 1–3, respiratory syncytial virus, metapneumovirus, and adenovirus. Samples positive for influenza or negative for all respiratory viruses were processed further at the national reference laboratory (*Instituto de Salud Pública de Chile*), using reverse transcription polymerase chain reaction (RT-PCR) to detect influenza A or B and perform viral subtyping. All adult patients with SARI and influenza, based on molecular detection methods, were included in the study. Cases with incomplete information or readmissions were excluded.

### Clinical characterization, management, and outcome

For each case, demographic and other information, including data on smoking; influenza vaccination (based on self-report or relative's information); epidemiological week of admission; domiciliary oxygen use; residence in long-term care facilities; comorbidities; symptoms and signs at admission (e.g., cough, sputum, obstructive symptoms, rhinorrhea, headache, myalgia); systolic ( $< 90$  mmHg) or diastolic ( $< 60$  mmHg) hypotension; initial laboratory evaluation (hemoglobin concentration; leukocyte, lymphocyte, and platelet count; erythrocyte sedimentation rate (ESR); plasmatic lactic dehydrogenase (LDH); albumin; blood urea

nitrogen (BUN); serum creatinine concentration; and C-reactive protein (CRP) concentration); and presence or absence of pneumonia (as interpreted by the physician in charge or based on the radiologist report). Pneumonia was classified as lobar or interstitial. Blood cultures were requested based on the discretion of attending physicians. Clinical presentation was classified in the following mutually exclusive groups: influenza-like illness (ILI) (no pneumonia, decompensated heart failure, or asthma); asthma (signs of obstruction without pneumonia or cardiovascular collapse); chronic bronchitis exacerbation (positive history, increased cough, sputum or dyspnea, and no pneumonia); pneumonia (as detected by chest x-ray); and cardiovascular decompensation (heart failure diagnosed by physical examination). Data on variables associated with disease management (need for invasive or noninvasive mechanical ventilation; corticosteroid use (systemic or inhaled); vasoactive drugs; antiviral (oseltamivir); and antibiotic compounds prescription) were also obtained. Site of hospitalization (critical care or general ward beds) was also recorded, along with the CURB-65 pneumonia severity score (11), and outcome at discharge (deceased or alive).

### Statistical analysis

Risk or protective factors associated with death or critical care unit (CCU) admission were identified by odds ratio (OR) calculations. Continuous variables were transformed to categorical variables to facilitate OR estimations. Factors identified by univariate analysis ( $P < 0.10$ ) were integrated in a multivariate analysis by binary logistic regression.

### Ethics approval

This study was approved by the Hospital Militar Institutional Review Board and, as a retrospective analysis of the data, deemed exempt from the informed consent requirement. Patient anonymity was assured during the analysis.

## RESULTS

From 1 July 2011 to 31 December 2015 (4.5 years), 1 637 adult patients with SARI were admitted to Hospital Militar, and 1 583 (96.7%) were tested for influenza using IF. Of the 1 583 cases tested, 110

were positive for influenza (6.9%) and 102 were positive for other viruses (6.4%). Of the 110 cases positive for influenza based on IF, 108 were confirmed by RT-PCR. The RT-PCR testing, which included 1 282 of the 1 371 cases with initially negative results, using IF (93.5%), detected 117 additional cases of influenza infection. The IF sampling was incomplete due to rejection of the nasopharyngeal swab or a premortem condition. The RT-PCR processing was incomplete due to failure to deliver respiratory samples to the reference lab. Of the 225 adult patients admitted to Hospital Militar for SARI that were also found to experience influenza-associated SARI events, two (0.9%) were missing relevant data and were therefore excluded from the study, and two others were admitted twice, resulting in a final count of 221 patients.

### General features

Characteristics of the study cohort included older age (mean age: 74.1 years); prevalence of smoking (previous or current); chronic diseases or conditions, especially pulmonary (38.9%), cardiovascular (28.1%), and neurological (26.2%), and diabetes mellitus (24.4%) (Table 1). No cases of influenza were detected among pregnant women. Of all the variables, only age and tobacco smoking showed statistically significant differences by gender. Female patients were older (mean age of 77.7 years versus 69.4 years in males;  $P < 0.001$ ), and male patients smoked more (18.6% versus 8.3% in females;  $P < 0.05$ ). Risk factors for complications associated with influenza infections, other than pregnancy (older age; chronic heart, lung, or liver conditions; cancer; immunosuppression; and obesity), were present in almost all patients (91.4%). Bedridden patients (17.6%) and residents of long-term care facilities (5.4%) were also identified, suggesting a potentially frail elderly study population. Approximately one-third (34.3%) of the study cohort reported receiving the seasonal influenza vaccine during the most recent vaccination campaign (23 of the 221 cases had no information for this variable) (Table 1).

### Clinical presentation

Cough was the most common symptom in patients admitted for influenza-associated SARI (reported by 93.2%)

**TABLE 1. General characteristics of a group of adult patients admitted for influenza-associated severe acute respiratory infections (SARI) at Hospital Militar ( $n = 221$ ), Santiago, Chile, 2011–2015**

Characteristic	Result
Average age in years (range)	74.1 (22–99)
Age $\geq 65$ years (%)	167 (75.6)
Female (%)	124 (56.1)
Former smoker (%)	61 (27.6)
Current smoker (%)	28 (12.7)
Consumed alcohol (%)	5 (2.3)
Had a chronic disease or condition (%)	
Chronic obstructive pulmonary disease (COPD)	70 (31.7)
Asthma	18 (8.1)
Any respiratory condition	86 (38.9)
Heart disease	62 (28.1)
Chronic neurological disease	58 (26.2)
Diabetes mellitus	54 (24.4)
Chronic kidney disease or dialysis	15 (6.8)
Cancer	14 (6.3)
Immune suppression from disease or drugs	11 (5.0)
Obesity	7 (3.2)
Liver disease	5 (2.3)
Bedridden (%)	39 (17.6)
Long-term care resident (%)	12 (5.4)
Home oxygen user (%)	18 (8.1)
Pregnant (%)	0 (0.0)
Had a risk condition <sup>a</sup> (%)	201 (91.4)
One risk factor	42 (19.0)
Two risk factors	82 (37.1)
$\geq 3$ risk factors	78 (35.3)
Received seasonal influenza vaccine (%)	68 (34.3) <sup>b</sup>
Mean length of stay in days (range)	10.9 (1–64)

**Source:** Prepared by the authors based on the study data.

<sup>a</sup> Older age, chronic disease condition(s), cancer, immune suppression, or obesity.

<sup>b</sup> Of patients with available information (23 cases had no information for this variable).

(Table 2). More than one-quarter of the study cohort (25.8%) had no fever. Other hallmark symptoms of influenza, such as myalgia, and those corresponding to upper respiratory viral infections (e.g., rhinorrhea and odynophagia), were relatively infrequent in this patient group (10.4%–22.6%). More than half (56.1%) of the patients presented obstructive bronchial signs, and about one-quarter (26.7%) had systolic or diastolic hypotension (Table 2). Bronchial obstructive signs were significantly associated with chronic obstructive pulmonary disease (COPD) or asthma (OR: 5.2; CI: 2.8–9.9;  $P < 0.0001$ ). About two-thirds of the patients were admitted at their first consultation (142 or 64.3%), with 62 (28.1%) admitted at the second consultation and the rest (17 or 7.7%) admitted after three to five visits.

Many patients did not present with the full array of SARI inclusion criteria. Low

pulse oximetry was the most common finding (65.2%). Tachypnea was detected in  $< 30\%$  of patients (Table 2). A high percentage of patients had partial respiratory failure (71.9%) and 29 patients (13.1%) had global respiratory failure (Table 2). The latter condition was significantly associated with chronic lung conditions (OR: 3.7; CI: 1.6–8.5;  $P = 0.02$ ). A low  $\text{PaO}_2/\text{FiO}_2$  ratio ( $< 250$ ) was frequent but not predominant (44.8%).

Laboratory evaluation showed a low frequency of leukocytosis (30.3%), thrombocytopenia (15.8%), hyponatremia (12.7%), and hypoalbuminemia (18.6%) (Table 2). Frequently presented conditions included lymphopenia (49.8%), altered kidney function parameters (50.7%), increased LDH plasmatic concentration (36.7%), and high CRP values ( $> 10$  times the upper-normal value) (43.9%).

Only about half (57.0%) of the patients had pneumonia as a clinical presentation,

**TABLE 2. Clinical characteristics of a group of adult patients admitted for influenza-associated severe acute respiratory infections (SARI) at Hospital Militar (n = 221), Santiago, Chile, 2011–2015**

Clinical characteristic	No. of patients (%)
Symptom	
Cough	206 (93.2)
Fever	164 (74.2)
Myalgia	50 (22.6)
Rhinorrhea	28 (12.7)
Odynophagia	23 (10.4)
Bronchial obstructive signs	124 (56.1)
Systolic (< 90 mmHg) or diastolic (< 60 mmHg) hypotension	59 (26.7)
Tachypnea ( $\geq$ 30 breaths/min)	57 (25.8)
Tachycardia (> 100 heartbeats/min)	113 (51.1)
Low pulse oximetry (blood oxygen saturation < 90%, ambient air)	144 (65.2)
Low PaO <sub>2</sub> /FiO <sub>2</sub> ratio (< 250)	99 (44.8)
Partial respiratory failure	159 (71.9)
Global respiratory failure	29 (13.1)
No arterial gases taken	33 (14.9)
Leukocytosis (white blood cell count > 12 000 $\mu$ L)	67 (30.3)
Lymphopenia (blood count < 1 000/ $\mu$ L)	110 (49.8)
Low platelet count (< 150 000/ $\mu$ L)	35 (15.8)
Hypoalbuminemia (< 3.5 g/L)	41 (18.6)
Hyponatremia (< 135 mEq/L)	28 (12.7)
Increased plasmatic lactic dehydrogenase (> 250 UI/L)	81 (36.7)
Increased blood urea nitrogen (BUN) concentration (> 20 mg/L)	112 (50.7)
Increased serum creatinine concentration (> 1 mg/dL)	83 (37.6)
Increased C-reactive protein (> 100 mg/L; > 10 times upper-normal value)	97 (43.9)
Clinical presentation	
Influenza-like illness	25 (11.3)
Asthmatic crisis	14 (6.3)
Decompensated heart failure	15 (6.8)
Community-acquired pneumonia	126 (57)
Exacerbated chronic bronchitis	24 (10.9)
Other <sup>a</sup>	17 (7.7)
CURB-65 severity score	
0	17 (7.8)
0–2	135 (61.1)
$\geq$ 3	84 (38.0)

**Source:** Prepared by the authors based on the study data.

<sup>a</sup> Decompensated lung fibrosis, pneumonia mixed with myocardial infarction.

with the rest presenting with ILI (11.3%), decompensated heart failure (6.8%), asthmatic crisis (6.3%), exacerbated chronic bronchitis (10.9%), and other conditions (e.g., decompensated lung fibrosis, pneumonia mixed with myocardial infarction) (Table 2). Of those with pneumonia, 77 (61.1%) had a chest x-ray with a consolidated pattern, and 49 (38.9%) had an x-ray with an interstitial pattern. Scores for the CURB-65 criteria spanned the full range of possible results (0 to 5); 7.8% of patients had zero points. Blood cultures were requested for 171 patients (77.4%) and six (3.5%) cases were positive (two for *Streptococcus pneumoniae*, two for *Staphylococcus*

*aureus*, one for *Haemophilus influenzae*, and one mixed infection—*Escherichia coli* and *Pseudomonas aeruginosa*—in a patient with acute leukemia, pancytopenia and pneumonia). Gender analysis did not show any differences other than more male patients with increased serum creatinine concentrations (52.7% versus 29.2% in female patients;  $P = 0.001$ ) and high CRP levels (> 100 mg/dL) (53.8% versus 38.8% in female patients;  $P = 0.03$ ).

### Seasonal viral subtype distribution

Influenza-associated SARI cases were distributed throughout the year, with an

epidemic peak during autumn–winter (Figure 1). Cases were also detected in summer months (December to March in the Southern Hemisphere) (Figure 1). During the study period, influenza A cases predominated over influenza B events, with 173 (78.3%) versus 48 (21.7%) respectively. Except for one case, all influenza A cases were subtyped. For the whole group, influenza A belonging to H3N2 subtype predominated (123 cases or 55.7%), with nearly equal distributions for influenza A(H1N1pdm09) (49 cases or 22.2%) and influenza B events (48 cases or 21.7%). Annual incidence analysis showed co-circulation of the three viral types/subtypes, except for year 2012, when influenza A(H1N1pdm09) events were not detected (Figure 2).

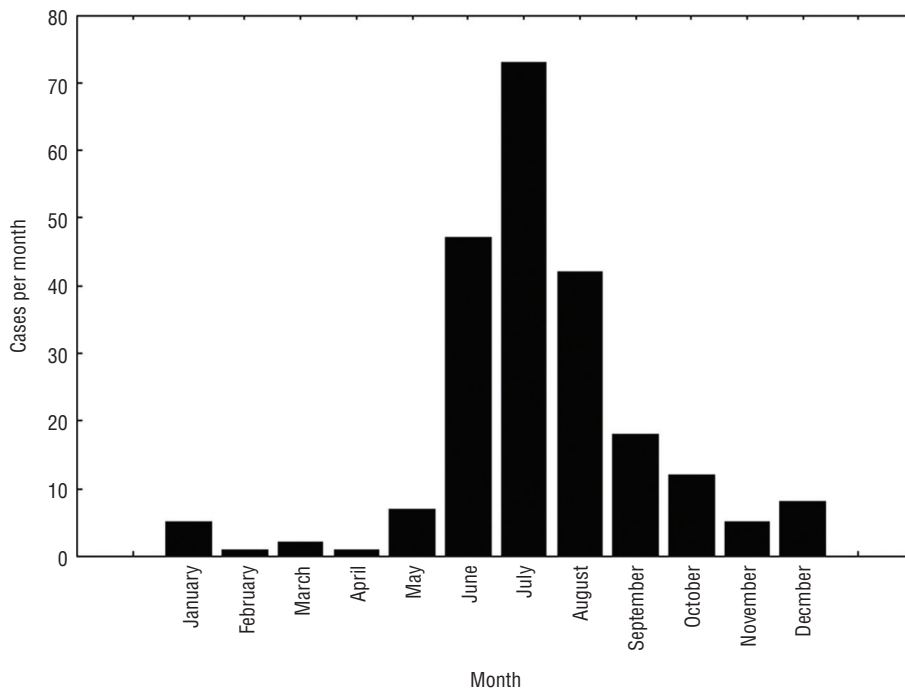
### Management and outcome

The majority of the study cohort survived (195 cases or 88.2%), 25 patients died (11.3%), and one patient (0.5%) was transferred without follow-up information.<sup>7</sup> Mean length of stay (LOS) was 10.9 days (range: 1–64 days). LOS surpassed one week in 112 cases (50.7%) and two weeks in 41 cases (18.6%).

Most patients (162 or 73.3%) were managed in general wards, with the remainder—59 or 26.7%—sent to the CCU (intensive or intermediate care beds). Invasive mechanical ventilation was required by 20 patients (9.0%) and another 23 required noninvasive mechanical ventilation (10.4%). Thus, 19.5% needed some form of ventilatory assistance. Vasoactive drugs were applied to 21 patients (9.5%). Most patients received topical bronchodilators by nebulizers (207 cases or 93.7%), and systemic corticosteroids were frequently applied (141 cases or 63.8%). Simultaneous antiviral and antibiotic therapy were prescribed almost universally (193 cases or 87.3%). Exclusive antiviral use (15 cases or 6.8%) or antibiotic therapy (10 cases or 4.5%) was uncommon. Only one patient (0.5%) did not receive antimicrobial treatment; two other cases (0.9%) had no information for the variable. Only two patients (0.9%) required renal replacement therapy.

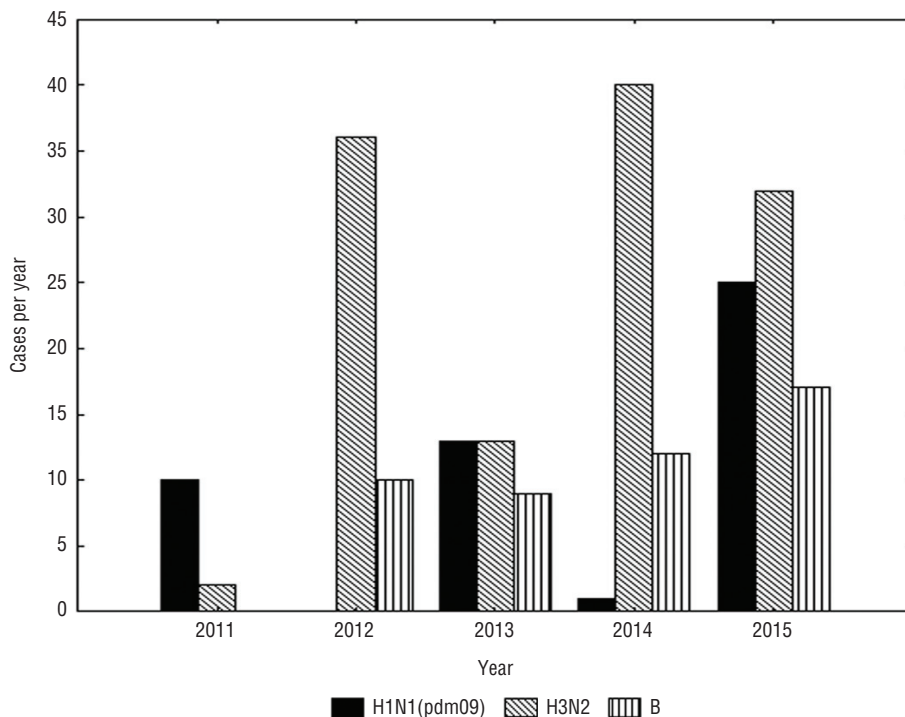
<sup>7</sup> As the univariate analysis was limited to patients with a known mortality outcome, this loss to follow-up reduced the patient count for the model to 220 (versus 221 for the total study cohort).

**FIGURE 1. Distribution of influenza-associated severe acute respiratory infections (SARI) cases by month of symptom onset in a group of adult patients admitted at Hospital Militar (n = 221), Santiago, Chile, 2011–2015**



Source: Prepared by the authors based on the study data.

**FIGURE 2. Annual distribution of influenza-associated severe acute respiratory infections (SARI) cases by viral type/subtype in a group of adult patients admitted at Hospital Militar (n = 221), Santiago, Chile, 2011–2015**



Source: Prepared by the authors based on the study data.

**Risk factors for a fatal outcome**

In the univariate analysis, several factors were associated with in-hospital mortality, including preadmission conditions (being bedridden), disease-associated conditions (respiratory failure, renal failure, higher CURB-65 severity score, admission to CCU, use of vasoactive drugs, ventilatory assistance, increased LDH plasmatic levels, low platelet count, hypoalbuminemia, and lobar pneumonia) (Table 3). Patients that were vaccinated during the most recent vaccination campaign and those that initiated oseltamivir during the first three days following symptom onset were less likely to have a fatal outcome. Age, comorbid conditions, viral type or subtype, and high CURB-65 severity score were not linked to a fatal outcome. A multivariate analysis was performed using binary logistic regression, incorporating the significant factors identified from the univariate analysis and relevant variables for appropriate adjusting (gender, age, presence of any risk factor, and infection with influenza A(H1N1pdm09)). Redundant variables for severity (low albumin concentration, increased LDH levels, ventilatory assistance, and use of vasoactive drugs) were excluded. Bacteremia was also excluded from the model, due to the low number of cases. Multivariate analysis identified four factors statistically associated with a fatal outcome: being bedridden (aOR: 22.3); admission to CCU (aOR: 8.9); PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 250 (aOR: 5.8); and increased creatinine concentration (> 1 mg/dL) (aOR: 5.47) (Table 3). Seasonal influenza vaccine was identified as a protective factor (aOR: 0.14).

**Comparison of vaccine composition with viral circulation**

Type and subtype distribution allowed for comparison of the vaccine composition with circulating influenza viruses. Information about vaccine composition was provided by the national reference laboratory. Annual comparison analysis was performed from April through March of the following year. Of the 68 patients in the study cohort that had received the seasonal vaccine, a total of 40 (58.8%) had an influenza virus type/subtype with a composition similar to the vaccine. The remaining patients who received the seasonal

**TABLE 3. Analysis of factors affecting mortality in a group of adult patients admitted for influenza-associated severe acute respiratory infections (SARI) at Hospital Militar, Santiago, Chile, 2011–2015**

Factor	Mortality outcome		Odds ratio	CI <sup>b</sup>	P
	Deceased (No./n <sup>a</sup> )	Alive (No./n)			
Univariate analysis (n = 220) <sup>c</sup>					
Female gender	15/25	109/195	1.18	0.5–2.7	0.7 <sup>d</sup>
Age ≥ 65 years	20/25	147/195	1.3	0.46–3.6	0.6 <sup>d</sup>
Any risk condition <sup>e</sup>	24/25	177/195	2.4	0.3–19	0.38 <sup>d</sup>
Bedridden	11/24	28/192	4.9	2–12	< 0.001 <sup>d</sup>
Admission to critical care unit	12/25	46/195	3.0	1.3–7.0	0.009 <sup>d</sup>
Low PaO <sub>2</sub> /FiO <sub>2</sub> ratio (< 250)	19/23	79/176	5.8	1.9–17.8	0.001 <sup>d</sup>
Low platelet count (< 150 000/μL)	10/25	25/194	4.5	1.8–11.1	< 0.001 <sup>d</sup>
Hypoalbuminemia (< 3.5 g/L)	11/25	30/179	3.9	1.6–9.4	0.001 <sup>d</sup>
Increased serum creatinine concentration (> 1 mg/dL)	16/25	66/185	3.2	1.3–7.7	0.006 <sup>d</sup>
Increased plasmatic lactic dehydrogenase (> 250 UI/L)	15/25	65/181	2.7	1.13–6.3	0.021 <sup>d</sup>
Increased plasmatic lactic dehydrogenase (> 500 UI/L)	7/25	9/181	7.4	2.4–22	< 0.001 <sup>d</sup>
Vasoactive drug requirement	8/25	12/195	7.2	2.6–19	< 0.001 <sup>d</sup>
CURB-65 score ≥ 2 points	22/25	119/193	4.5	1.3–15	0.01 <sup>d</sup>
Ventilatory assistance (invasive or noninvasive)	13/25	29/195	6.2	2.6–14	< 0.001 <sup>d</sup>
Pneumonia with consolidated pattern	15/25	61/195	3.3	1.4–7.7	0.004 <sup>d</sup>
Antiviral therapy within three days of symptom onset	7/23	107/184	0.31	0.12–0.80	0.012 <sup>d</sup>
Pandemic influenza A(H1N1pdm09) virus	8/25	40/195	1.8	0.7–4.5	0.19 <sup>d</sup>
Bacteremia	2/21	4/149	3.8	0.65–22	0.11 <sup>d</sup>
Seasonal vaccine	2/20	66/177	0.19	0.04–0.83	0.015 <sup>d</sup>
Multivariate analysis (n = 220)			aOR <sup>f</sup>	CI	P
Male gender			0.44	0.1–1.9	0.267 <sup>g</sup>
Age ≥ 65 years			1.43	0.17–12.1	0.74 <sup>g</sup>
Any risk condition <sup>e</sup>			6.74	0.23–191	0.26 <sup>g</sup>
Bedridden <sup>h</sup>			22.3	3.0–164	0.002 <sup>g</sup>
Admission to critical care unit <sup>h</sup>			8.9	1.44–55	0.019 <sup>g</sup>
Low PaO <sub>2</sub> /FiO <sub>2</sub> ratio (< 250) <sup>h</sup>			5.8	1.02–33	0.047 <sup>g</sup>
Low platelet count (< 150 000/μL)			3.3	0.68–15	0.136 <sup>g</sup>
CURB-65 score ≥ 2 points			0.37	0.04–2.8	0.347 <sup>g</sup>
Pneumonia with consolidated pattern			0.55	0.13–2.3	0.412 <sup>g</sup>
Antiviral therapy within three days of symptom onset			0.53	0.12–2.3	0.397 <sup>g</sup>
Pandemic influenza A(H1N1pdm09) virus			2.65	0.54–13	0.229 <sup>g</sup>
Increased serum creatinine concentration (> 1 mg/dL) <sup>h</sup>			5.47	1.20–24	0.028 <sup>g</sup>
Seasonal vaccine <sup>h</sup>			0.14	0.021–0.9	0.04 <sup>g</sup>

**Source:** Prepared by the authors based on the study data.

<sup>a</sup> Number of patients with available information for variable.

<sup>b</sup> CI: 95% confidence interval.

<sup>c</sup> Limited to patients with known mortality outcome so excluded one person from the study cohort who was transferred out of Hospital Militar and lost to follow-up.

<sup>d</sup> Based on chi-square test with contingency tables.

<sup>e</sup> Older age, chronic disease condition(s), cancer, immune suppression, or obesity.

<sup>f</sup> aOR: adjusted odds ratio.

<sup>g</sup> Based on binary logistic regression.

<sup>h</sup> Significant variables associated with mortality in the multivariate analysis.

influenza inoculation (28 cases or 41.2%) had a virus type/subtype with a composition that was different from the vaccine. As only two vaccinated patients died (one with a circulating influenza type/subtype matching the composition of the vaccine, and one with a circulating type/subtype that differed from it), further analysis to compare the impact of vaccine composition on mortality could not be performed. A detailed antigenic/vaccine matching analysis was not performed.

## DISCUSSION

Sentinel surveillance of SARI at Hospital Militar demonstrated that despite a seasonal distribution, influenza was a near-permanent cause of hospital admissions year-round, in Chile's temperate climate. This pattern reinforces the need for suspicion, diagnosis, and appropriate treatment of this viral infection beyond assumed timeframes (autumn–winter). In this study, SARI affected mainly elderly,

frail patients, and more than one-quarter of them required intensive or intermediate care beds. Moreover, in-hospital mortality was significant (10%) and LOS prolonged. These findings underscore the extent of the influenza disease burden and the need for additional public health efforts to prevent it.

Three factors appeared to have magnified the consequences of influenza in the study cohort: 1) low coverage of the influenza vaccine, 2) host characteristics,

and 3) disease-associated conditions. Low coverage of the influenza vaccine (only 34.3%) decreased the preventive effect of seasonal vaccination—a strategy that has been shown to have a profound impact on vulnerable populations and reduce hospitalizations among elderly patients and those with diabetes mellitus, cancer, or dialysis. Seasonal vaccination also reduces mortality in the same groups (2; 12–15). More than 90% of the patients in this patient group had indications for influenza seasonal vaccination, but influenza vaccine uptake was low, and after multivariate analysis the vaccine turned out to be a significant protective factor for in-hospital mortality. Influenza vaccines are offered free in Chile through the expanded program on immunization, and nationwide vaccination campaigns are carried out annually before the start of the influenza season. To the best of the authors' knowledge, these results are the first to demonstrate a protective effect from influenza vaccine uptake in SARI patients admitted to hospitals in Chile. It seems clear that, based on these study results, Chile should continue to increase influenza vaccine coverage. Host characteristics influenced severity and the need for CCU intensive or intermediate care beds and/or ventilatory assistance. This means that influenza affects hospitals by increasing not only the number of hospitalizations but also the demand for highly complex resources, amplifying its disease burden. Data on these factors have been previously reported (16), but the proportions of patients needing ventilatory support in this study were higher. Disease-associated conditions affecting the influenza outcome in this study included antiviral use, which was reported in almost all of the identified SARI patients (although timeliness of use was suboptimal in nearly half of them). As shown consistently in large observational studies, early initiation of antiviral therapy (within 3–4 days of first symptoms) had a protective effect on hospital mortality (16–18). This same effect was observed in this study, in the univariate analysis. However, the fraction of patients in this study without antiviral therapy was low (< 10%, and only two of them died), limiting the ability to draw statistical conclusions.

The widely used tool for measuring pneumonia severity, the CURB-65 score (11), showed limitations in this study,

with the SARI events that were analyzed scoring few points in a significant proportion of the study cohort. This limitation can be attributed to three factors: 1) the exclusion of pulse oximetry (an important tool for identifying patients at risk) in the CURB-65 score; 2) the low percentage of patients with tachypnea ( $\geq 30$  breaths/minute) in this study (< 30%); and 3) the relatively low frequency of hypotension in patients with viral respiratory illnesses (about 16%–21%) versus bacterial invasive diseases (31%) (19–21). Based on this study, it appears that some SARI events are not appropriately identified by the classical CURB-65 score. Therefore, using this tool to develop clinical decision rules could lead to underestimation of the seriousness of influenza-related symptoms—and the need for hospitalization—by health providers. This could be an important factor to consider in Chile, where management of community-acquired pneumonia in elderly patients in Chile is based on the CURB-65 score and admission of those with lower scores ( $\leq 1$ ) is discouraged.

Another important finding in this study was that some SARI patients had no fever, which may have been related to the older age of the study cohort, as elderly people may not experience a rise in body temperature. This phenomenon has important implications for appropriate recognition of SARI-affected patients. The authors believe fever should not be a SARI criterion for surveillance purposes if other criteria are present to ensure appropriate recognition of every case and the disease burden associated with respiratory viruses.

In this study cohort, a wide array of clinical presentations was observed, including pneumonia, asthmatic crisis, ILI, chronic bronchitis exacerbation, decompensated heart failure, and other conditions, underscoring the broad spectrum in which influenza must be prevented, suspected, diagnosed, and treated (22–25). In addition, in this patient group, pneumonia presented with both consolidated and interstitial lung patterns, demonstrating once again that x-ray findings are not associated with specific etiologies. For example, in a recent report, viral etiologies were associated with lung x-ray consolidation (59% of cases) as well as infiltrates (42%). On the other hand, bacterial-only events showed infiltrates in 31% of patients (26).

Lymphopenia (< 1 000/ $\mu$ L) and increased CRP in plasma (> 10 times the

upper-normal value) have been previously described in the literature, demonstrating the systemic involvement of influenza infection (16, 20). In this study, altered renal function was frequently detected, but non-stringent criteria (“above normal values”) were used. In addition to dehydration, several mechanisms have been identified in patients suffering from acute renal failure during influenza infection, including rhabdomyolysis, hemolytic uremic syndrome, acute glomerulonephritis, disseminated intravascular coagulation, and acute interstitial nephritis (27). In this study, two patients with renal failure (0.9% of the study cohort) presented with acute glomerulonephritis (reported elsewhere (27)) and required renal replacement therapy.

Several in-hospital mortality risk factors for severe influenza requiring hospital admission have been described. They include delayed medical attention; lung, kidney, liver, or cardiovascular disease; cancer chemotherapy; increased BUN or creatinine concentration; a high Simplified Acute Physiology Score (SAPS) or Sequential Organ Failure Assessment (SOFA) score; age > 65 or > 80 years; admission to the intensive care unit (ICU); development of acute respiratory distress syndrome (ARDS); bilateral lung involvement; mechanical ventilation requirement; superinfection; corticosteroid use; and pregnancy (28–34). The in-hospital risk factors found in this study cohort included admission to critical care beds; low PaO<sub>2</sub>/FiO<sub>2</sub> ratio; and high creatinine concentration. Being bedridden was another identified risk factor and to some extent a proxy of older age and severe comorbidities; 28% of bedridden patients in the study cohort died. No association was found between influenza virus type and mortality, suggesting that viral type/subtype does not play a role in the final outcome of influenza-associated SARI in the elderly, frail population in Chile.

## Limitations

This study had several limitations. First, the study cohort was highly homogeneous for several variables, which impeded statistical comparisons. For example, most patients were elderly, so there were not enough younger people in this patient group to investigate if older age was linked to a higher mortality rate. The use of antivirals by most of the patients in this group created the

same type of limitation. Second, the search for viral or bacterial coinfection was mainly restricted to blood cultures, which led to another study limitation. No systematic search for respiratory viral coinfection was attempted, except during year 2015, when this type of coinfection was detected in 12% of the study cohort (manuscript in preparation), and neither pneumococcal urinary antigen nor serological studies for atypical agents were routinely included during the whole study period. However, blood cultures were collected from 77.4% of patients and only a small fraction (3.5%) were positive for bacterial species, including *Staphylococcus aureus* and *Streptococcus pneumoniae* and, in one case, bacteremic *Haemophilus influenzae*, all of which have been found to be associated with influenza infection in previous studies (35, 36). Viral-viral coinfection appears to be low in adults with asthma attacks or acute exacerbations of chronic bronchitis (24), so it seems unlikely that other, unexplored viral etiologies

influenced severity or outcomes in the study cohort. On the other hand, bacterial-viral coinfection rates in adult patients with pneumonia ranged from 3%–17% in previous studies (22, 23, 26), so the frequency of this type of coinfection could have been higher than estimated through blood cultures in this study. Unfortunately, the extreme age of the patients in the study cohort, which led to limited comprehension and cooperation, hampered the collection of adequate bronchial samples for investigation of bacterial causes by sputum cultures. Another limitation was that chest x-rays were not systematically evaluated by different observers, a strategy that could have changed the frequency of pneumonia associated with influenza in this patient group.

### Conclusions

These study results indicate that influenza is a relevant cause of admissions for SARI, especially among elderly frail

patients, and requires intensive care resources. Pneumonia is not the only form of clinical presentation, and influenza-related admissions, associated with every viral type and subtype, occur year-round. In this study, 1 out of 10 admitted patients had a fatal outcome related to host characteristics (being bedridden) and disease-associated conditions/variables (admission to CCU, low PaO<sub>2</sub>/FiO<sub>2</sub> ratio, and increased serum creatinine concentration). The widely used CURB-65 severity score did not predict an adverse outcome or the virus type or subtype. A seasonal vaccine was protective, so efforts should be intensified to increase population coverage.

**Conflicts of interest.** None.

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## RESUMEN

### La infección respiratoria aguda grave asociada a la gripe en pacientes adultos en Chile: experiencia de un hospital centinela

**Objetivos.** 1) Describir las características clínicas de los pacientes adultos con infección respiratoria aguda grave relacionada con virus gripales en Chile, y 2) analizar los subtipos de los virus identificados en las muestras recogidas de estos pacientes, los recursos hospitalarios empleados en el tratamiento clínico, la evolución clínica y los factores de riesgo asociados a un desenlace mortal, mediante los datos de observación de la red de vigilancia de las infecciones respiratorias agudas graves (SARInet).

**Métodos.** Se identificaron los adultos hospitalizados entre el 1 de julio del 2011 y el 31 de diciembre del 2015 con infección respiratoria aguda grave relacionada con la gripe en un hospital de vigilancia centinela de esta afección en Santiago y se confirmó la presencia de gripe en todos los casos por medio de la reacción en cadena de la polimerasa con transcriptasa inversa realizada en muestras de las vías respiratorias

**Resultados.** Un total de 221 pacientes (con una media de edad de 74,1 años) fueron hospitalizados con infección respiratoria aguda grave relacionada con la gripe durante el período de estudio. En esta cohorte de estudio, 91,4 % presentó factores de riesgo de complicaciones y 34,3 % había recibido la vacuna en la campaña más reciente. La neumonía fue la manifestación clínica más frecuente y afectó a 57,0 % de la cohorte; otras manifestaciones fueron el síndrome gripal, la bronquitis crónica exacerbada, la insuficiencia cardíaca descompensada y la crisis asmática. Los casos se presentaron durante todo el año y alcanzaron un pico epidémico durante el otoño y el invierno. Tanto el virus de la gripe de tipo A (H1N1pdm09 y H3N2) y tipo B circularon simultáneamente. En 26,7 % de la cohorte se precisaron cuidados intensivos y en 19,5 % fue necesario recurrir a la respiración asistida. El análisis multifactorial detectó cuatro factores fundamentales relacionados con la mortalidad hospitalaria: 1) la postración (razón de posibilidades ajustada [ORA]: 22,3; intervalo de confianza [IC] de 95 %: 3,0–164); 2) la admisión en la unidad de cuidados intensivos (ORA: 8,9; IC: 1,4–55); 3) un coeficiente  $PaO_2/FiO_2$  inferior a 250 (ORA: 5,8; IC: 1,02–33), y 4) una mayor concentración de creatinina sérica ( $> 1$  mg/dL) (ORA: 5,47; IC: 1,20–24). Se determinó que la vacuna contra la gripe estacional era un factor protector significativo (ORA: 0,14; IC: 0,021–0,90).

**Conclusiones.** La infección respiratoria aguda grave asociada a la gripe afectó a pacientes predominantemente ancianos con afecciones subyacentes. La mayoría de los pacientes evolucionó en una insuficiencia respiratoria y más de una cuarta parte precisó cuidados intensivos. El cuadro clínico fue variable. La mortalidad estuvo relacionada con las características del huésped y los trastornos relacionados con la enfermedad, y la vacuna tuvo un efecto protector. El tipo vírico no influyó en los desenlaces.

#### Palabras clave

Gripe humana; infecciones del sistema respiratorio; adulto; hospitalización; factores de riesgo; resultado fatal; Chile.

**RESUMO****Infecção respiratória aguda grave (SARI) decorrente da influenza em pacientes adultos no Chile: experiência de um hospital-sentinela**

**Objetivo.** Descrever as características clínicas de pacientes adultos com infecção respiratória aguda grave (SARI) associada ao vírus da influenza e analisar os subtipos virais identificados em amostras coletadas destes pacientes, os recursos hospitalares empregados no tratamento clínico, a evolução clínica e os fatores de risco clínicos associados a um desfecho fatal, a partir de dados observacionais da rede de vigilância de SARI (SARInet) no Chile.

**Métodos.** Foram identificados os adultos hospitalizados com SARI associada a influenza em um hospital-sentinela de vigilância de SARI, em Santiago, de 1o de julho de 2011 a 31 de dezembro de 2015. A ocorrência de influenza foi confirmada em amostras respiratórias em todos os casos com a reação em cadeia da polimerase via transcriptase reversa (RT-RCP).

**Resultados.** Ao todo, 221 pacientes (idade média de 74,1 anos) foram hospitalizados com SARI associada a influenza no período de estudo. Nesta coorte, 91,4% apresentavam fatores de risco para complicação e 34,3% haviam sido vacinados na última campanha de vacinação. Pneumonia foi a manifestação clínica mais frequente, ocorrendo em 57,0% da coorte. Outras manifestações foram doença gripal, bronquite crônica exacerbada, insuficiência cardíaca descompensada e crise asmática. Os casos estiveram distribuídos ao longo do ano, com pico epidêmico no outono-inverno. Houve circulação simultânea dos vírus da influenza A (H1N1pdm09 e H3N2) e B. Leitos de terapia intensiva foram necessários em 26,7% da coorte e suporte ventilatório, em 19,5%. Na análise multivariada, quatro fatores importantes associados à mortalidade hospitalar foram identificados: estar restrito ao leito (odds ratio ajustado [ORaj] 22.3; intervalo de confiança de 95% [IC 95%] 3.0–164); ser admitido na unidade de terapia intensiva (ORaj 8.9, IC 95% 1.4 4–55); relação PaO<sub>2</sub>/FiO<sub>2</sub> <250 (ORaj 5.8; IC 95% 1.02–33) e aumento da creatinina sérica (>1 mg/dl) (ORaj 5.47; IC 95% 1.20–24). A vacinação sazonal contra influenza foi identificada como importante fator de proteção (ORaj 0.14; IC 95% 0.021–0.90).

**Conclusões.** A SARI associada a influenza acometeu sobretudo pacientes idosos com doenças preexistentes. A maioria dos pacientes evoluiu com insuficiência respiratória e mais de um quarto precisou de cuidados intensivos. O quadro clínico foi variável. Morte foi associada às características do hospedeiro e problemas relacionados à doença. A vacinação teve efeito protetor e o tipo viral não influiu no desfecho.

**Palavras-chave**

Influenza humana; infecções respiratórias; adulto; hospitalização; fatores de risco; evolução fatal; Chile.