ANALYSIS OF FATAL OUTCOME DUE TO INFLUENZA AND RISK FACTORS ASSOCIATED, ROMANIA, OCTOBER 2009 – MAY 2011

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Abstract: *Background: Limited data are available from Central and Eastern Europe on risk factors for severe complications of influenza. Such data are essential to prioritize prevention and treatment resources and to identify specific priority populations for seasonal influenza vaccination. Objectives: To use sentinel surveillance data to identify risk factors for fatal outcomes among hospitalized patients with severe acute respiratory infections (SARI), and among hospitalized patients with laboratory confirmed influenza. Methods: Retrospective analysis of case-based surveillance data collected from 26 sentinel hospitals in Romania during the 2009/2010 and 2010/2011 winter influenza seasons was performed to evaluate risk factors for fatal outcomes using multivariate logistic regression. Results: During the 2009/2010 and 2010/2011 winter influenza seasons sentinel hospitals reported 661 SARI patients of which 230 (35%) tested positive for influenza. In the multivariate analyses, infection with influenza A(H1N1)pdm09 was the strongest risk factor for death among hospitalized SARI patients (OR:6.6; 95% CI:3.3-13.1). Among patients positive for influenza A(H1N1)pdm09 virus infection (n=148), being pregnant (OR:7.1; 95% CI:1.6-31.2), clinically obese (OR:2.9;95% CI:1.6-31.2) and having an immuno-compromising condition (OR:3.7;95% CI:1.1-13.4) were significantly associated with fatal outcomes. Only 1.7% of SARI patients reported receiving either the 2009 monovalent pandemic vaccine, or the 2010/2011 trivalent seasonal influenza vaccine during the two years of surveillance. Conclusion: Our findings indicate that a substantial number of annual hospitalizations and deaths in Romania may be preventable with influenza vaccination. Hospital-based sentinel surveillance for SARI may provide a mechanism for monitoring the relative severity of influenza seasons, to identify priority populations for influenza vaccination using local data during each influenza season, and during pandemics as well.*

Cuvinte cheie: *gripă, factori de risc, decese, analiză*

Rezumat: *Introducere: În zona centrală şi estică a Europei există disponibile informaţii limitate referitoare la factorii de risc asociaţi cazurilor severe complicate ale gripei. Astfel de informaţii sunt utile în vederea prioritizării resurselor de tratament şi preventive, cât şi pentru identificarea grupelor populaţionale prioritare la vaccinarea antigripală sezonieră. Obiective: Utilizarea datelor din sistemul de supraveghere sentinel pentru a identifica factorii de risc asociaţi cazurilor fatale înregistrate la pacienţii spitalizaţi cu infecţii acute respiratorii severe (SARI) cât şi în rândul pacienţilor spitalizaţi şi confirmaţi prin examene de laborator cu infecţie gripală. Metodă: Analiza retrospectivă a datelor obţinute, caz cu caz, din sistemul de supraveghere sentinelă colectate din 26 de spitale sentinelă din România în perioada 2009/2010 şi 2010/2011, cât şi analiza multivariată şi regresia logistică au fost utilizate pentru evaluarea factorilor de risc asociaţi deceselor înregistrate în cele două sezoane. Rezultate: În perioada sezoanelor gripale 2009/2010 şi 2010/2011 spitalele sentinelă au raportat 661 cazuri de SARI, din care 230 (35%) au fost confirmate ca pozitive pentru infecţia cu virus gripal. Din analiza multivariată a reieşit faptul că infecţia cu virus gripal A(H1N1)pdm09 a fost factorul de risc cel mai mult asociat cu decesul pacienţilor spitalizaţi cu SARI (OR:6.6; 95% CI:3.3-13.1). În rândul pacienţilor cu infecţie cu virus gripal A(H1N1)pdm09 (n=148), sarcina (OR:7.1; 95% CI:1.6-31.2), obezitatea (OR:2.9;95% CI:1.6-31.2) şi imunodepresia (OR:3.7;95% CI:1.1-13.4) au fost semnificativ asociate cu decesul. Numai 1.7% dintre pacienţii cu SARI au declarat că au fost vaccinaţi fie cu vaccin monovalent pandemic 2009, fie cu vaccin trivalent sezonier în cele două sezoane gripale supravegheate. Concluzii: Rezultatele indică faptul că un număr important de spitalizări şi decese anuale pot fi prevenite prin vaccinare. Sistemul de supraveghere bazat pe spitale sentinelă poate fi un mecanism de monitorizare a sezoanelor gripale severe pentru a identifica grupele populaţionale prioritare pentru vaccinarea antigripală, în fiecare sezon gripal, dar şi în timpul unei pandemii.*

INTRODUCTION

Influenza is an acute viral disease of the respiratory tract. On occasions it can produce severe disease through the development of primary viral pneumonia or through increasing host susceptibility to secondary bacterial infections of the lower respiratory tract.(1) Influenza may also exacerbate underlying medical conditions (e.g. pulmonary or cardiovascular diseases), sometimes resulting in hospitalization and death. Very young

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children, the elderly, pregnant women, and persons with chronic medical conditions have traditionally been considered to be at increased risk of influenza-related complications. However, as was evident during the recent 2009 influenza A(H1N1) pandemic, severe complications of influenza may also develop in previously healthy persons.(2,3,4,5,6,7,8)

In 2001, Romania modified its existing respiratory disease surveillance system to establish a sentinel monitoring system for outpatient influenza-like illness (ILI) and acute respiratory infections (ARI) in 21 of its 42 counties. This system utilized a network of general practitioners in each of the 21 counties to identify and collect respiratory specimens for laboratory confirmation of influenza from a subset of outpatients meeting ILI and ARI case definitions. The first evaluation of the Romanian sentinel surveillance system for influenza was performed during July 2009. This evaluation identified a need to broaden the objectives of the national influenza surveillance system in order to better monitor severe influenza and to identify priority populations for influenza vaccination. As a result, Romania implemented sentinel surveillance for hospitalized Severe Acute Respiratory Infections (SARI) in October 2009 with real time RT-PCR (rtRT-PCR) testing of respiratory specimens from hospitalized patients meeting the SARI case definition proposed by the World Health Organization (WHO) Regional Office for Europe.(9) This surveillance also included collection of case-based epidemiological data from all SARI hospitalizations.

To date, limited data are available from Central and Eastern Europe to identify populations at high risk for severe complications of influenza for vaccine prioritization. As a result this paper uses the first two years of hospital-based sentinel surveillance data in Romania to undertake a retrospective study of risk factors for fatal outcomes among SARI patients, and SARI patients that were laboratory-confirmed to have had influenza.

PURPOSE

To use sentinel surveillance data to identify risk factors for fatal outcomes among hospitalized patients with severe acute respiratory infections (SARI), and among hospitalized patients with laboratory confirmed influenza.

METHODS

Selection of sentinel sites

Sentinel SARI surveillance was initiated in twelve hospitals located in five counties in October 2009; Bucharest, Cluj, Constanta, Iasi, and Timiş. The selection of SARI sentinel hospitals was undertaken to represent population centres in Romania. The sentinel hospitals were also selected based on the logistic feasibility to collect, store, and transport specimens to the Reference Laboratory for Influenza located at the Cantacuzino Research and Development of Microbiology and Immunology Institute in Bucharest (Cantacuzino Institute). Within the sentinel hospitals, screening for SARI cases was undertaken in the infectious disease and pediatric wards where the large majority of acute respiratory infections are known to be admitted. In October 2010, 14 hospitals in four additional counties (for a total of 26 sentinel hospitals) were added to the sentinel SARI surveillance network.

Case definition

The clinical case definition for SARI in persons ≥5 years of age was: Onset of measured fever >38°C; and cough or sore throat; and shortness of breath or difficulty in breathing within 7 days prior to hospital admission. For children aged <5 years the WHO Integrated Management of Childhood Illnesses (IMCI) case definitions for pneumonia and severe pneumonia were applied. The IMCI case definition for pneumonia is any child aged 2 months to 5 years with cough or difficulty breathing and breathing faster than 40 breaths/minute (ages 1 – 5 years) or breathing faster than 50 breaths / minute (ages 2 – 12 months). The IMCI case definition for Severe Pneumonia is any child aged 2 months to 5 years with cough or difficult breathing and any of the following general danger signs: unable to drink or breastfeed, vomits everything, convulsions, lethargic or unconscious, or chest indrawing or stridor in a calm child.

Epidemiological data collection

Epidemiological surveillance forms were completed for patients that were identified as SARI cases. SARI patients were followed until time of discharge or death. Completed surveillance forms were subsequently sent to the National Centre for Surveillance and Control of Communicable Diseases from the National Public Health institute, to be validated and entered in the national SARI database. The surveillance forms included data on patient date of birth, sex, residence, date of initial symptom onset, date of first medical encounter and hospital admission, signs and symptoms present on admission, preexisting medical conditions (asthma, chronic pulmonary disease, cardiac disease, diabetes, immuno-compromised status [including patients who have tested positive for Human Immunodeficiency Virus (HIV), patients diagnosed with cancer, and patients who received organ transplants], hepatic disease, renal disease, and clinical obesity), pregnancy status, history of influenza vaccination during the current season, other treatments received, and date of death or discharge.

Respiratory specimen collection, storage, transport and testing

Two swab specimens (one nasopharyngeal and one oropharyngeal) were collected from each patient identified as meeting the SARI case definition during the period between weeks 40/2009 (week beginning October 4, 2009) to week 20/2011 (week beginning May 15, 2011). Specimens were placed in a single vial containing virus transport medium, and stored at 4°C for a maximum of 72 hours before being sent to the Cantacuzino Institute for molecular and virological confirmatory diagnostic testing. At the Cantacuzino Institute the samples were analyzed by rtRT-PCR for influenza A(H1N1)pdm09, seasonal influenza A(H1N1) and A(H3N2), and influenza B using the WHO CDC reagent kit for influenza diagnostics.(9)

Analysis of risk factors associated with fatal outcomes due to SARI and influenza

All patients meeting the case definition for SARI in the sentinel hospitals were included in the risk factor analyses. Descriptive analyses of SARI cases reported by the sentinel hospitals, and the proportion testing positive for influenza were evaluated by influenza type and influenza A sub-type, age groups (0-4, 5-64 and 65+ years), and by week of admission. We conducted bivariate and multivariate regression analyses to evaluate: i) risk factors associated with fatal outcomes in patients hospitalized with SARI, and ii) risk factors associated with fatal outcomes in patients hospitalized with SARI that tested positive for influenza virus infections. When evaluating risk factors for fatal outcomes due to SARI we considered laboratory-confirmed infection with influenza A(H1N1)pdm09, influenza A(H3N2), or influenza type B as independent risk factors for fatal outcomes in comparison to a reference group of influenza-negative persons. In both models, the following exposure categories were analyzed as dichotomous variables: Sex, each of the underlying medical conditions, pregnancy status in women, and anti-viral treatment received following onset of symptoms. Age (in years) and time from onset of symptoms to hospital admission (in days) were analyzed as

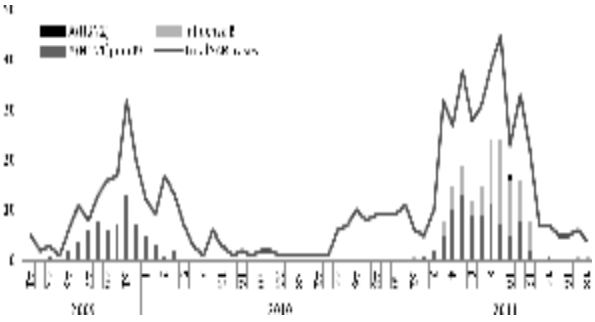
continuous variables. All variables associated with a fatal outcome in the bivariate analyses at a significance level of p <0.25 were included in the multivariate model. Using backward stepwise elimination in the multivariate analyses, variables that were not statistically associated (i.e. p>0.05) with a fatal outcome were excluded, beginning with the variable with the highest p-value. All risk factor analyses were performed with Stata 10.0 (StataCorp, College Station, TX, USA).

RESULTS

A total of 661 patients admitted to the sentinel hospitals between week 40/2009 and week 20/2011 met the case definition for SARI. Fifty-five percent (360/661) of the SARI patients were male and median age was 22 (range 0-86 years). Of the 661 SARI cases, 230 (34.7%) tested positive for influenza; 148 (64.3%) for A(H1N1)pdm09, 81 (35.2%) for influenza B, and 1 (0.4%) for A(H3N2). The increase in SARI cases in both years during the winter months largely correlated with increases in sentinel influenza detections (figure no. 1). Of the 148 influenza A(H1N1)pdm09 viruses detected during the two seasons, 19 (12.8%) were detected in SARI patients aged 0-4 years, 121 (81.8%) in patients aged 5-64 years, and 8 (5.4%) in patients aged 65 years and older. Of the 81 influenza B viruses detected (all during the 2010/2011 winter influenza season) 20 (24.7%) were detected in SARI patients aged 0-4 years, 54 (66.7%) in patients aged 5-64 years, and 7 (8.6%) in patients aged 65 years and older.

During the two years of surveillance 11 (1.7%) of the 648 SARI patients who provided information on their influenza vaccination status reported receiving either the 2009 monovalent pandemic vaccine, or the 2010/2011 trivalent seasonal influenza vaccine that included the A/California/7/2009- like, A(IH1N1)pdm09 component.

Figure no. 1. SARI admissions and influenza detections by week, Romania, 2009/2010 and 2010/2011 winter influenza seasons



Factors associated with fatal outcomes in patients hospitalized with SARI

Of 661 SARI cases, 44 (6.7%) were recorded as fatal. Twenty-seven (61.3%) of the fatal cases were female. Thirty-two (72.7%) of the 44 fatal SARI cases were laboratory-confirmed to have influenza virus infections [29 influenza A(H1N1)pdm09 infections and 3 influenza B infections] indicating the overall case-fatality proportion in the 230 hospitalized SARI patients with laboratory-confirmed influenza to be 13.9% (32 deaths/230 influenza hospitalizations). The case fatality proportion was 19.6% (29 deaths/148 hospitalizations) among hospitalized SARI patients with influenza A(H1N1)pdm09 infections, and 3.7% (3 deaths/81 hospitalizations) among patients hospitalized with influenza B infections. Patients who died were significantly older than patients who were discharged alive, mean age 39.2 years (SD±19.0) versus 25.9 years (SD±24.4) respectively, (p<0.001). In the bivariate analysis (excluding the single influenza A(H3N2) positive case found during the surveillance period), variables significantly associated with a fatal outcome in SARI patients were: female gender (OR 2.0, 95% CI 1.1-3.8; p<0.05), increasing age in years (OR 1.02, 95% CI 1.01-1.03; p<.01), influenza A(H1N1)pdm09 virus infection (OR 8.1, 95% CI 4.2-15.5; p<.001), hepatic disease (OR 5.9, 95 % CI 2.4-15.0; p<.001), clinical obesity (OR 2.9, 95% CI 1.4-5.7; p<.01), pregnancy (OR 4.3, 95% CI 1.5-12.1; p<.05), receiving antiviral treatment (OR 2.1, 95% CI 1.1-3.9; p<.05), and increasing days from symptom onset to hospitalization (OR 1.1, 95% CI 1.04-1.2; p<.01). Other variables included in the multivariate model due to bivariate trends toward significance (p<.25) included influenza B infection, and having asthma, a chronic pulmonary disease, an immune-compromising condition, and chronic renal disease.

In the multivariate logistic regression model, there were 659 SARI cases with complete data on the variables included in the model, and the single influenza A(H3N2) case was again excluded from analysis. The variable most strongly and independently associated with a fatal outcome in these hospitalized SARI patients was having an influenza A(H1N1)pdm09 infection. Other variables significantly and independently associated with a fatal outcome were being pregnant, having hepatic disease, increasing age in years, and increasing time from onset of first symptoms to hospital admission (table no. 1).

Table no. 1. Multivariate analyses of risk factors associated with a fatal outcome among hospitalized SARI patients (n=659)

	Variable (n=659)	Percent with fatal outcome	OR	95% CI	P value
	Influenza A(H1N1)				
	Negative (n=511)	2.9	1.00		
	Positive (n=148)	19.6	6.59	3.31- 13.11	<0.001
Risk	**Pregnancy**				
	No (n=636)	6.1	1.00		
	Yes (n=23)	21.7	4.47	1.40-14.31	0.012
	Hepatic disease				
	No (n=633)	5.8	1.00		
	Yes (n=26)	26.9	3.61	1.26- 10.31	0.017
	Age (years)	-	1.02	1.00-1.03	0.034
	Days from symptoms onset to admission	-	1.12	1.05 - 1.19	0.001

Factors associated with fatal outcomes in SARI patients testing positive for influenza A(H1N1)pdm09 virus infections

Analyses evaluating risk factors for fatal outcomes only among those testing positive for influenza were limited to patients testing positive for influenza A(H1N1)pdm09, as this was the only influenza type or subtype that included an analyzable sample size of fatal outcomes during this time period. Among the 148 SARI patients with laboratory-confirmed influenza A(H1N1)pdm09 virus infections, female gender, having an immuno-compromising condition, having hepatic disease, clinical obesity, pregnancy, receiving antiviral treatment, and increasing days from symptom onset to hospitalization were included in the multivariate model to evaluate risk factors associated with fatal outcomes due to trends toward significance ($p<.25$) for each of these variables in the bivariate analyses. In the multivariate model, pregnancy, clinical obesity, having an immuno-compromising condition, and having hepatic disease were statistically significant and independent risk factors for a fatal outcome (table no. 2).

Table no. 2. Multivariate analyses of risk factors associated with a fatal outcome among SARI patients that were laboratory-confirmed to have influenza A(H1N1)pdm09 virus infections (n=148)

Variable (n=148)	Percent with fatal outcome	OR	95% CI	P value
Pregnancy				
No (n=139)	18.0	1.00		
Yes (n=9)	44.4	7.10	1.62-31.17	0.01
Immuno-compromised				
No (n=636)	6.1	1.00		
Yes (n=23)	21.7	3.74	1.05-13.38	0.042
Hepatic disease				
No (n=135)	17.8	1.00		
Yes (n=13)	38.5	3.43	0.97-12.19	0.057
Obesity				
No (n=112)	17.0	1.00		
Yes (n=36)	27.8	2.89	1.61-31.17	0.01

DISCUSSIONS

In this study we have demonstrated the utility of hospital-based SARI sentinel surveillance data to identify hospitalized patients at risk for fatal illness due to SARI and influenza and to monitor the relative severity of influenza seasons in Romania. We also found that influenza A(H1N1)pdm09 virus infection was a strong independent predictor of fatal outcomes in persons with hospitalized severe acute respiratory infections.

Clinically obese patients, pregnant women, and persons with hepatic diseases and immune-compromising conditions had a higher risk of dying from influenza than other persons hospitalized with influenza virus infections. One in five pregnant women hospitalized with SARI died. However among influenza A(H1N1)pdm09 positive patients, pregnant women were 7 times more likely to die than other patient groups. This is consistent with several other investigations of risk factors associated with influenza A(H1N1)pdm09 virus infections.(2,3,4) These findings also add to the body of literature suggesting that clinical obesity and immune-compromising conditions are risk factors for fatal A(H1N1)pdm09 infections.(5,6) Although influenza B virus infections accounted for 1/3 of the laboratory-confirmed influenza hospitalizations reported over the two seasons, and some deaths as well, they were not significantly associated with fatal outcomes relative to other causes of SARI hospitalizations. This observation is consistent with other estimates that suggest reduced hospitalizations and mortality during seasons where influenza B is the predominant virus in circulation.(7,8)

The case fatality proportion of 19.6% that was observed for hospitalized patients that were laboratory-confirmed to have influenza A(H1N1)pdm09 virus infections was higher than the case fatality proportion of 7% that has previously been reported for hospitalized patients in the United States (10), or than the 14.3% that was reported for critical care patients that were laboratory-confirmed to have influenza A(H1N1)pdm09 virus infections in Australia and New Zealand.(11) While the case fatality proportion may have been higher in Romania, it is also possible that different patterns of hospital care utilization in Romania (e.g. less-severe cases may be relatively less likely to be hospitalized in Romania) may have led to the detection of a relatively greater proportion of severe cases than less severe cases within the Romanian hospital system. Given that only a small subset of all SARI cases were detected and reported within the sentinel hospitals, this also raises the possibility that the sentinel surveillance system may have not detected some less severe cases of hospitalized influenza within the sentinel hospitals.

The information produced from routine SARI surveillance in hospital settings can help to reduce the public misconception that influenza is always a mild disease, which in part may be due to the fact that the outpatient setting has been the traditional focus of influenza surveillance. During both the 2009/2010 and the 2010/2011 season in Romania, influenza was detected in a substantial number of hospitalized SARI patients. Overall one-third of SARI admissions tested positive for influenza during the two seasons. However, during the weeks of peak transmission, influenza was detected in over 50% of SARI patients. Similar peaks in the intensity of influenza circulation in SARI hospitalizations have been observed in Armenia, Georgia, Kyrgyzstan, Republic of Moldova, Russian Federation, and Ukraine.(12)

An additional limitation to this study is that sample sizes of laboratory-confirmed influenza cases were too small to permit age-specific estimation of national influenza hospitalization rates. The addition of new hospitals into the sentinel surveillance system should further increase the sample size and representativeness of sentinel SARI case capture, and the number of influenza hospitalizations identified annually. Although maintaining sentinel surveillance in hospitals can be challenging, these findings do support the notion that sentinel surveillance systems that operate in a manner consistent with recent WHO influenza surveillance recommendations(9) can provide a tool to monitor the severity and relative burden of disease caused by influenza viruses during each influenza season, and during pandemics as well.

CONCLUSIONS

Our findings indicate that a substantial number of annual hospitalizations and deaths in Romania may be preventable with influenza vaccination. Hospital-based sentinel surveillance for SARI may provide a mechanism for monitoring the relative severity of influenza seasons, to identify priority populations for influenza vaccination using local data during each influenza season, and during pandemics as well.

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