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Influenza A(H1N1)pdm09 and Postpandemic Influenza in Lithuania

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Abstract: The objective of this study is to describe the clinical and epidemiological characteristics of patients hospitalized in Lithuania who are infected with influenza A(H1N1)pdm09 and to compare pandemic A(H1N1) pdm09 infection with postpandemic.

In total, 146 subjects hospitalized with influenza A(H1N1) pdm09 were identified from 2009–2011. There were 53 during the initial pandemic wave in the summer of 2009, 69 during the peak pandemic period, and 24 during the "postpandemic" period that we included in this study. There were 22 subjects who died after laboratory confirmation of influenza A(H1N1)pdm09.

No deaths were documented during the first wave. Subjects presenting during the peak of pandemic influenza had a greater incidence of fever (100% vs 77.4%; p<0.001), dry cough (95.7% vs 82.7%; p=0.01), and vomiting (26.1% vs 1.9%, p<0.001) as compared with patients infected during the first wave. The rate of bacterial pneumonia was 18.8% (13/69) during the peak pandemic period and 12.5% (3/24, p=0.754) during the postpandemic period. None of the postpandemic influenza subjects' intensive care unit stays were due to pneumonia.

The hospitalized early 2009 H1N1 pandemic cases and postpandemic cases were milder compared with those at the peak of pandemic activity.

Keywords: Complications; Epidemiological characteristics; Influenza A(H1N1)pdm09; postpandemic influenza

1 Introduction

An influenza pandemic occurs when the human population is infected with an antigenically new influenza virus that readily spreads from person to person. Over the past three centuries, there have been at least 10 global influenza pandemics, three of them in the last century: pandemic influenza A (H1N1) in 1918; A (H2N2) in 1957; and A (H3N2) in 1968. The 1918 H1N1 influenza pandemic was among the most severe, with influenza-attributed mortality estimates exceeding 50 million people [1]. Comparatively, the 1957 and 1968 influenza pandemics were less lethal. The pandemic that began in April 2009 was even less severe. Since April 2009, various countries, both in Europe and worldwide, have experienced one or more waves of the influenza A(H1N1)pdm09 activity, with notable differences in both incidence and the number of reported deaths between countries [2]. The risk groups affected by the pandemic were different from those normally affected by inter-pandemic or seasonal influenza. Whereas both seasonal and pandemic influenza produce more severe illness among those with chronic medical conditions, pandemic influenza also seems more severe in persons with obesity, diabetes, who are pregnant, and who have other co-morbid conditions. It has remained unclear whether pandemic influenza A(H1N1)pdm09 infection differs substantially from postpandemic influenza in its presentation and clinical course. Comparing the epidemiological characteristics of influenza A(H1N1) pdm09 pandemic and postpandemic is important to help contextualize clinical considerations and to prepare for the next pandemics.

The objective of this study is to describe the main clinical and epidemiological characteristics of patients hos-

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pitalized because of influenza A(H1N1)pdm09 infection in Lithuania and how pandemic and postpandemic influenza A(H1N1)pdm09 infection clinically differ.

2 Methods

2.1 Study subjects and design

We defined a study subject as an person who presented for the hospitalization in Lithuania with influenza-like illness and laboratory-confirmed influenza A(H1N1)pdm09 virus. We also divided study subjects into three groups: those who presented during the initial months of the pandemic (June 16–September 15, 2009) ("first wave"), those presenting during the peak months of pandemic activity (November 1, 2009 and January 31, 2010) ("peak") and those who presented during the following influenza season in the post-pandemic period (January 1, 2011 and May 15, 2011), ("postpandemic"). We also included subjects who died after laboratory confirmation of influenza A(H1N1)pdm09 and subsequently to admission to any Lithuanian hospital. Twenty-two of the 23 subjects who died were included in our analysis. We excluded one of these 23 subjects from our analysis because of missing data. Study subjects who presented during first wave were those admitted to any Lithuanian hospital. All study subjects who presented during either the peak of the pandemic or the postpandemic period were admitted to the Infectious Diseases and Tuberculosis Hospital Affiliate of Vilnius University Hospital Santariskiu Klinikos. This hospital is the reference center for adult infectious diseases in the Vilnius district and serves a population of 809,000, which is 27% of the nation's total population. When the influenza A (H1N1) pandemic started in April 2009 and the first persons with influenza were detected in Europe (the earliest validated date of onset of influenza in any person in Europe was April 19, 2009), a case-based reporting system was implemented by the European Centre for Disease Prevention and Control (ECDC). European Union and European Economic Area (EU and EEA) countries started to submit detailed case-based reports to ECDC from May 5, 2009 to September 22, 2009. The case-based reporting system was rapidly implemented in Lithuania. As the pandemic clinical activity accelerated, the individual case-reporting became impossible to sustain. Individual case reporting was therefore suspended and a new approach designed to more efficiently collect and aggregate data was implemented. Figure 1 shows laboratory-confirmed influenza activity and Figure 2 contrasts aggregated influenza-like illness activity with timing of fatal cases.

Nasopharyngeal swab specimens were collected at admission from subjects with influenza-like illness. The real-time reverse transcriptase polymerase chain reaction (RT-PCR) was performed using assay kits provided by the World Health Organization (WHO). Testing was performed at the National Public Health Surveillance Laboratory of Lithuania. Vilnius Regional Bioethics Committee approved the study protocol; this was deemed the minimal risk and the written consent was waived.

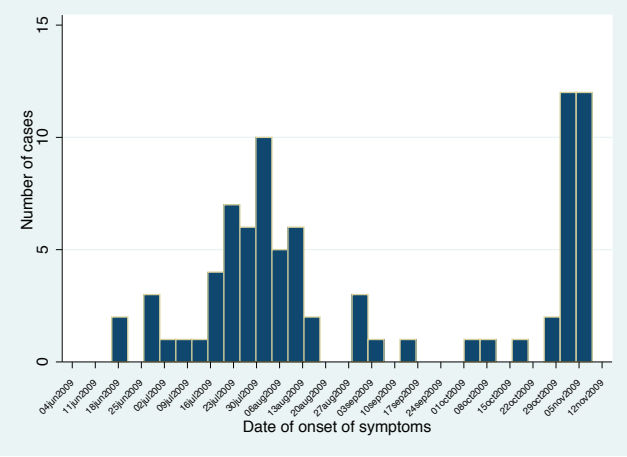

Figure 1: Epidemic curve: start of influenza pandemic in Lithuania, the first wave and beginning of the second wave (individual, case - based reporting).

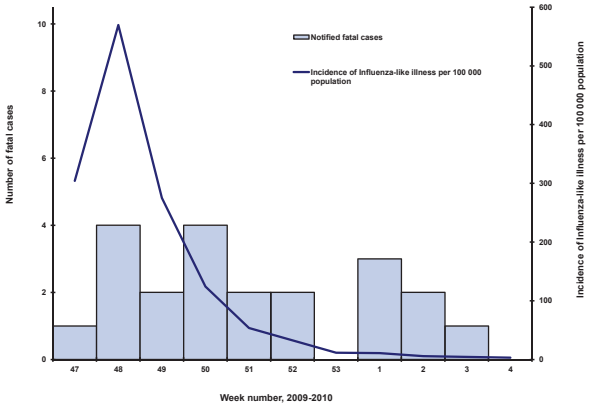

Figure 2. Incidence of influenza-like illness and number of fatal cases from week 47 of 2009 to week 4 of 2010 (aggregate reporting).

2.2 Data collection

The WHO "new" pandemic strain influenza A(H1N1) pdm09 case summary form for case-based data collection was used for first wave of subjects [3]. The variables for the characterization of the cases were: age, sex, travel-association, possible exposure, outcome at last assessment (alive or dead), dates (notification, onset of symptoms, treatment started and death), laboratory tests, clinical presentation, underlying conditions, complications, antiviral treatment and prophylaxis, seasonal influenza vaccination status, and hospitalization. We used the WHO "new" influenza A(H1N1)pdm09 case summary form for subject data collection for reporting those who died. To characterize subjects presenting during the peak and the postpandemic period, we abstracted data from subjects' medical records into the variables noted above. We defined fever as an axillary temperature ≥37.5°C. The definition of community-acquired pneumonia was based on the current Lithuanian Pulmonologists and Allergologists Society guidelines [4]. Viral pneumonia was defined as the presentation with acute respiratory distress syndrome and diffuse infiltrates involving two or more lobes on chest X-ray. The exposure was defined as a contact with a possible source of infection (confirmed or probable Influenza A(H1N1)pdm09 case) within a distance appropriate for conversation in the 7 days before onset of illness. Hospital admission, microbiologic testing criteria, and treatment decisions including antibiotics prescription, were not standardized and were made by an attending physician.

3 Statistical methods

Descriptive statistics and bivariate analyses were conducted. Categorical data were analyzed using Fisher's exact test. Wilcoxon's rank-sum test was used for continuous variables. Data for continuous variables are reported as median (range) and for categorical variables as percentages. All p values reported are two-sided, and a p value of less than 0.05 is considered significant. Statistical analyses were performed with Stata, (version 11, StataCorp, TX, USA).

4 Results

4.1 Epidemiological characteristics

In Lithuania, the first study subject with 2009 pandemic influenza A/H1N1 presented on June 18, 2009, in week 25. This subject was a Lithuanian citizen who returned from India. Following this initial case, a wave of additional subjects also presented during the summer evidencing local human-to-human influenza transmission (Figure 1). During the entire official pandemic period (week 18/2009 to week 32/2010), we identified two waves of pandemic influenza disease. The peak of the morbidity during the first wave was observed in week 32 (2-8 August), 2009 (Figure 1) and during the second wave in week 48 (22-28 November), 2009 (Figure 2). The first person who died was reported on November 17, 2009 and the last, on February 17, 2010.

During the first pandemic wave in the summer of 2009, 53 subjects with influenza A (H1N1)pdm09 were identified. During the peak period, the first subject with pandemic influenza A (H1N1)pdm09 virus infection was admitted to the Infectious Diseases and Tuberculosis Hospital Affiliate of Vilnius University Hospital Santariskiu Klinikos on November 4, 2009 and the last one on January 21, 2010. In all, 196 patients with influenza like illnesses were hospitalized during this period in this hospital. This group of patients comprised 26.7% (196/735) of all hospitalized patients during the peak period. Nasopharyngeal swab samples to detect influenza virus were taken from 191 of these 196 patients. Influenza A(H1N1) pdm09 was confirmed for 69 (36%) of patients included in our "peak" subject sample. Seasonal influenza A (H1N1) was confirmed for 21 (11%) patients, but no influenza B was detected. During the "postpandemic" period, from January 1 to May 15, 2011, 24 patients qualified for inclusion in our study.

None of the patients had received the *pandemic* influenza vaccine. The vaccination rate with seasonal influenza vaccine was 5.7% (3/53) in the first wave group, 2.9% (2/69) in the pandemic peak group, 4.2% (1/24) in the postpandemic group and 4.5% (1/22) in the group that died. The only subject (1/53, 1.9%), who was vaccinated with pneumococcal vaccine presented during the first wave. Only one subject received antiviral chemoprophylaxis in the 14 days prior to clinical presentation; this patient

presented with influenza and was hospitalized during the postpandemic period.

In total, 39 of 52 first-wave subjects (75%) during the 7 days prior to the onset of symptoms had been in an area where other people with influenza A (H1N1)pdm09 virus had been identified. Influenza exposure in the 7 days before onset of illness to persons with confirmed or probable influenza A(H1N1)pdm09 during the first wave was reported for 16 of 51 (31.4%) patients. Reliable data to inform the duration of the incubation period were available for only 15 study subjects. The median duration of the incubation period (time of exposure to time of symptom onset) for these 15 subjects was 4 days (range, 2-15). During the pandemic peak, there was an increase in the proportion of subjects who reported an exposure in the 7 days before illness onset. Exposure was reported for 44 of 69 subjects (63.8%) during the peak pandemic period versus only 16 of 51(31.4%) during the first wave, p=0.001. In the postpandemic group, the proportion of subjects reported as exposed was similar to that during the pandemic peak. A total of 15 of 24 (62.5%) subjects reported exposure to influenza A (H1N1)pdm09 in the postpandemic influenza group. Among the patients who died, exposure to a confirmed or probable "new" influenza A(H1N1)pdm09 case during the period of 7 days before the onset of illness was reported in only 1 patient of 22 (4.5%). During the peak of the pandemic, none of 22 subjects who died had recently traveled abroad.

Only one of 53 first wave subjects (1.9%) was a health care worker who had recurrent direct contact with patients. None of the 22 subjects who died was a healthcare worker.

4.2 Demographic data

The majority of the study participants in all four groups were young (median age <40 years, 7-70 years old). The baseline demographic data and comorbid conditions are summarized in Table 1. The 22 subjects who died with pandemic influenza, were older than those who survived (median 40.5 years vs median 25 years; p =0.001). Those who died were mostly male (68.2%) and had pre-existing conditions putting the individuals at risk for serious complications (72.7%) (Table 1). The most common co-morbidity was underlying cardiovascular disease in the group that died: 22.7%, compared with 2.9% for survivors of influenza A(H1N1)pdm09 during the peak of the pandemic group (p=0.008). Of all pregnant women who contracted influenza A(H1N1)pdm09 virus during the pandemic in Lithuania, 1 (14.3%) died (Table 1). A total of 11 of the 69 (15.9%) hospitalized during the peak period were smokers, and 40 of 69 (58%) were nonsmokers; no smoking history was collected for the remaining 18 of 69 (26.1%) A(H1N1)pdm09 influenza subjects.

Table 1: Baseline demographic characteristics and pre-existing conditions of patients with influenza A(H1N1)pdm09 infection.

Study characteristic	Wave 1 pandemic n=53	Peak pandemic n=69	p^a	Post-pandemic n=24	p^b	Pandemic Mortality n=22	p^c
Demographic characteristics							
Age, mean (SD), years	25.5 (11.6)	28.5 (11.6)	0.159	31.4 (12.2)	0.300	38.2 (12.9)	0.001
Age, median, years	23	25	0.137	28.5	0.083	40.5	0.001
Age min - max, years	7-62	18-67	-	18-70	-	13-62	-
Sex, male, n (%)	24 (45.3)	33 (47.8)	0.780	13 (54.2)	0.593	15 (68.2)	0.096
Pre-existing conditions							
n (%)	9 (17.0)	20 (29)	0.123	0	0.003	8 (72.7)	0.514
COPD	5 (9.4)	5 (7.2)	0.745	0	0.323	2 (9.1)	>0.999
Cardiovascular diseases	2 (3.8)	2 (2.9)	>0.999	0	>0.99	5 (22.7)	0.008
Diabetes mellitus	1 (1.9)	3 (4.3)	0.632	0	0.566	2 (9.1)	0.591
Chronic CNS diseases	No data	5 (7.2)	0.066	0	0.323	No data	-
Pregnancy	1 (3.5)	7/36 (19.4)	0.014	0	0.175	1/7 (14.3)	>0.999
Other	6(11.3)	0		0	-	6 (27.3)	<0.001

COPD = chronic obstructive pulmonary disease; CNS = central nervous system;
p^a – Pandemic influenza cases during the first wave: Pandemic influenza cases during the peak of pandemic
p^b – Pandemic influenza cases during the peak of pandemic: Postpandemic (2011) influenza A(H_1N_1) cases
p^c– Pandemic influenza cases during the peak of pandemic: Cases that died with pandemic influenza

5 Clinical presentation

The presenting signs and symptoms of influenza are summarized in Table 2. The most frequent were fever and dry cough in all three study groups, except among the cases that died, where shortness of breath stood out as a leading symptom. These symptoms were followed in frequency by sore throat, headache and myalgia. Subjects presenting during the peak of pandemic influenza had the greater incidence of fever (100% vs 77.4%; $p<0.001$), dry cough (95.7% vs 82.7%; $p=0.01$), and vomiting (26.1% vs 1.9%, $p<0.001$) as compared with subjects during the first wave of pandemic influenza. The frequency of most signs and symptoms was similar in subjects during the peak of pandemic and postpandemic influenza patient groups. The frequency of productive cough (50% vs 5.8%; $p=0.001$), shortness of breath (84.2% vs 21.7%; $p<0.001$), arthralgia (26.7% vs 2.9%; $p=0.008$) and altered consciousness (46.2% vs 10.1%; $p=0.005$) were higher among those who died vs those who survived during the peak of pandemic group.

6 Complications and outcome

One or more complications of pandemic influenza developed in 27 of 69 (39.1%) subjects during the peak of the pandemic (Table 3). The rate of complication in subjects with risk factors for complications such as COPD, cardiovascular diseases, diabetes mellitus, chronic CNS diseases, or pregnancy was 50% (10/20), as compared with those having no risk factors for influenza complications, at 34.7% (17/49, $p=0.283$). The most frequent complication was bacterial pneumonia (13/69, 18.8%). None of the subjects had clinical features and signs of primary influenza pneumonia upon chest X-ray examination. Four (80%) of 5 subjects with chronic obstructive pulmonary disease (COPD) developed an exacerbation of their COPD, despite having a stable chest X-ray. A total of seven of 69 (10.1%) subjects developed encephalopathy: two of them presented with coma (2.9%), four with somnolence (5.8%) and one with delirium (1.4%). The cause of encephalopathy for five of 69 subjects was influenza infection. One previously healthy pregnant woman (1/7, 14.3%) had a

Table 2: Presenting symptoms of patients with influenza A(H1N1)pdm09 and postpandemic (2011) influenza

Study characteristic	Wave1 pandemic A(H1N1) n=53	Peak pandemic A(H1N1) n=69	p[a]	Postpandemic (2011) A(H1N1) n=24	p[b]	Pandemic Mortality A(H1N1) n=22	p[c]
Symptoms n (%)							
Fever (≥ 38ºC)	41(77.4)	69(100)	<0.001	24(100)	>0.999	20/21(95.2)	0.233
Runny nose	33(62.3)	26(37.7)	0.007	5(20.8)	0.019	3/15(20.0)	0.192
Sore throat	41(77.4)	46(66.7)	0.196	16(66.7)	0.039	7/13(53.8)	0.528
Dry cough	43(82.7)	66(95.7)	0.010	22(91.7)	0.456	14/18(77.8)	0.031
Productive cough	9(17)	4(5.8)	0.047	3(12.5)	0.284	8/16(50)	0.001
Dyspnea	7(13.2)	15(21.7)	0.224	3(12.5)	0.324	16/19(84.2)	<0.001
Vomiting	1(1.9)	18(26.1)	<0.001	6(25.0)	0.917	1/13(7.7)	0.281
Diarrhea	1(1.9)	3(4.3)	0.449	0	0.299	0/13	>0.999
Headache	39(73.6)	45(65.2)	0.323	18(75.0)	0.377	10/16(62.5)	0.838
Myalgia	35(66%)	46(66.7)	0.942	14(58.3)	0.462	8/16 (50)	0.212
Arthralgia	22(41.5)	2(2.9)	<0.001	3(12.5)	0.072	4/15(26.7)	0.008
Altered consciousness	1(1.9)	7(10.1)	0.068	1(4.2)	0.675	6/13(46.2)	0.005
Arterial hypotension	No data	1(1.4)	-	2(8.3)	0.162	No data	-
Fever and dry cough	No data	66(95.7)	-	22(91.7)	0.601	No data	-
Fever, dry cough and sore throat	No date	46(66.7)	-	15(62.5)	0.711	No data	-
Fever, dry cough, sore throat, myalgia and headache	No date	24(34.8)	-	5(20.8)	0.204	No data	-

p^a – Pandemic influenza cases during the first wave: Pandemic influenza cases during the peak of pandemic
p^b – Pandemic influenza cases during the peak of pandemic: Postpandemic (2011) influenza A(H_1N_1) cases
p^c – Pandemic influenza cases during the peak of pandemic: Cases that died with pandemic influenza

Table 3: Complications, outcomes, laboratory values and treatment among patients with influenza A(H1N1)pdm09 or postpandemic 2011 influenza

Variable	Peak pandemic influenza A(H_1N_1) n=69	Postpandemic (2011) Influenza A(H1N1) n=24	p
Complicated influenza, n (%)	27 (39.1)	9 (37.5)	0.888
Bacterial pneumonia	13 (18.8)	3 (12.5)	0.754
Encephalopathy	5(7.2)	1(4.2)	0.652
Exacerbations of COPD	4/5 (80)	-	–
Acute renal failure	2(2.9)	0	>0.999
Admitted to ICU	9 (13.0)	2 (8.3)	0.722
Acute respiratory failure	6 (8.7)	2 (8.3)	>0.999
Need for mechanical ventilation	2 (2.9)	0 (0)	>0.999
Laboratory values, n (%)			
Leukopenia (leukocyte count <4x10^9/l)	6 (8.7)	8 (33.3)	0.007
Leukocytosis (leukocyte count >10x10^9/l)	7 (10.1)	3 (12.5)	0.714
Anemia (Hb <100g/l)	7 (10.1)	1 (4.2)	0.675
ESR increase (>30 mm/h)	13 (18.8)	5 (20.8)	>0.999
CRP >10mg/l	28 (40.6)	11 (45.8)	0.653
CRP increase due to influenza	11/52 (21.2)	6(25)	0.708
Median (minimal - maximal), (mg/L)	23 (15 -37)	31.0 (27 -54)	-
CRP increase due to complications	17 (24.6)	5 (20.8)	0.706
Median (minimal - maximal), (mg/L)	97 (18 -450)	62 (35-104)	-
CXR performed, n (%)	56 (81.2)	23 (15.8)	0,105
CXR diagnosed as pneumonia	13/56 (23.2)	3/23 (13.0)	0,372
Treatment			
Received antiviral after admission, n (%)	66 (95.6)	24 (100.0)	0.283
Treatment started within 48 hours from symptom onset, n (%)	44/66 (66.7)	14/24 (58.3)	0.465
Received antibiotics, n (%)	42 (60.9)	14 (58.3)	0.827
Patients treated: for complications,	17/42 (40.5)	5/14 (35.7)	>0.999
for influenza	25/42 (59.5)	9/14 (64.3)	<0.001

antiviral = oseltamivir; COPD = chronic obstructive pulmonary disease; CXR = chest radiograph; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; Hb = hemoglobin; ICU = intensive care unit;

threat of miscarriage because of her influenza. The other complications included bacterial meningitis 1 (1.4%), bacterial otitis 1 (1.4%), urinary tract infection (without bladder catheter) 1 (1.4%), post-infectious polyneuropathy 1 (1.4%). Nine of 69 (13%) subjects during the peak period were admitted to the intensive care unit (ICU). Acute respiratory failure developed in six subjects (8.7%) as did altered consciousness; these were the most frequent reasons for ICU admission, followed by acute renal failure for two subjects (2.9%).

The frequency of complications in the postpandemic influenza group was similar to the subjects with pandemic influenza during the peak of pandemic (37.5% vs 39.1%; p=0.89) (Table 3). Three subjects (12.5%) with bacterial pneumonia were observed among 24 subjects with postpandemic influenza. One subject (4.2%) developed encephalopathy resulting from influenza and another, influenza meningoencephalitis (4.2%). None of these subjects had primary influenza pneumonia, bacterial meningitis, urinary tract infections, acute renal failure, or acute post-infectious polyneuropathy. Two of 24 (8.3%) study subjects required ICU care for an acute respiratory failure from influenza bronchitis; interestingly, both had normal chest x-rays and blood tests.

The median ICU length of stay was 2 days (range, 1-17 days) for the peak of pandemic group versus 2.5 days (range, 1-4 days) for the postpandemic influenza group. Of the 20 subjects who died, 18 (90%) developed pneumonia. Primary influenza pneumonia was diagnosed in 15 of 19 ubjects (78.9%) and secondary bacterial pneumonia in

9 of 18 subjects (50%) of those who died. Other complications, such as renal failure, were reported for one subject (4.5%) and general weakness for five subjects (22.5%). Of the 53 subjects observed during the first wave of influenza pandemic, only one (1.9%) developed pneumonia.

7 Laboratory findings

Blood test abnormalities were found in 30 of 69 (63.5%) influenza A(H1N1)pdm09 subjects during the peak of the pandemic (Table 3). None of the six (8.7%) subjects with leukopenia developed the bacterial complications of influenza. Of the 11 subjects with elevated C-reactive protein (CRP) resulting from influenza, 3 (27.3%) had pre-existing conditions that placed them at increased risk for influenza complications. Bacterial cultures were taken from 14 of 69 (20.3%) subjects. Blood cultures were obtained from 8 (11.6%) subjects, cerebrospinal fluid (CSF) cultures from 5 (7.2%) patients, urine cultures from 2 (2.9%) subjects, fecal cultures from 2 (2.9%) subjects, and nasopharyngeal cultures from 5 (7.2%) subjects. *S. aureus* grew from one sputum culture and *S. pyogenes beta haemolyticus* from 2 asopharyngeal cultures. Blood test abnormalities were found in 17 (70.8%) subjects with post-pandemic influenza. Leukopenia was more common among individuals with postpandemic influenza than those with influenza A(H1N1)pdm09 during the peak of the pandemic (33.3% vs 8.7%; p=0.007). None of the subjects with leukopenia in the postpandemic influenza group had bacterial complications of influenza. Leukocytosis was found in 12.5% of postpandemic influenza patients; all of them had bacterial pneumonias. All bacterial cultures obtained from 4 of 24 (16.7%) subjects were negative: 1 culture from blood, 1 from cerebrospinal fluid, 1 from feces, and 1 from the nasopharynx.

CSF was analyzed in 5 of 69 subjects in the peak pandemic activity group. Only one subject who presented with bacterial meningitis had abnormal CSF: neutrophilic pleocytosis of 240/mm^3, protein level of 9.2 g/l, glucose level of 0.3 mmol/l. In the postpandemic influenza group lumbar puncture was performed for 1 of 24 subjects and that CSF analysis showed lymphocytic pleocytosis of 347/mm^3, 1.5 g/l of protein and 2.6 mmol/l of glucose.

8 Treatment

Of the 53 first wave subjects, 23 (43.3%) received antiviral treatment upon the hospital admission. Oseltamivir was used for 15 subjects and rimantadine for 5 subjects. Antiviral treatment was started in 11 out of 20 (55%) subjects within 48 h from the onset of influenza symptoms. Antibiotics were given to 16 (30.2%) of the 53 first-wave subjects.

Only 4 of 69 (5.8%) subjects in the pandemic peak group received antiviral drugs prior to their hospital admission. Only one subject received rimantadine, one received zanamivir, and two, oseltamivir. Data on the treatment with antivirals and antibiotics after the admission of subjects with influenza A (H1N1)pdm09 during the peak of pandemic and postpandemic influenza period are shown in Table 3. All subjects who received antivirals were treated with oseltamivir upon their hospital admission. Oseltamivir 75 mg twice daily was given to 64 patients (97%). An increased dosage (150 mg twice daily) was used in the remaining subjects. Median duration of antiviral treatment was 5 days (minimal 2 days, maximal 15 days). More than half of the subjects in the pandemic peak group (25; 59.5%) were treated empirically with antibiotics, with only influenza symptoms and no signs of bacterial complications. The antibiotics used were penicillin G (23 patients; 54.8%), followed by ampicillin (8 subjects; 19%), ceftriaxone (7 subjects; 10.1%), amoxicillin/clavulanic acid (3 subjects; 7.1%), vancomycin (2 subjects; 4.8%), and imipenem/cilastatin (1 subject; 2.4%).

None of the subjects in the postpandemic influenza group received antiviral treatment before admission. The median duration of treatment was 4 days (minimal 3 days, maximal 16 days). Oseltamivir 75 mg twice daily was given to 22 subjects (91.7%) and 150 mg twice daily to 2 (8.3%) subjects. Antibiotics were given to 14 subjects (58.3%): ampicillin (9 subjects; 64.3%), ceftriaxone (5 subjects; 35.7%), penicillin G (2 subjects; 14.3%), and vancomycin (1 subject; 7.1%).

Median time from symptom onset to hospitalization was 4.5 days (minimal 0, maximal 12 days) in the group that died. Seven of 18 evaluable subjects who died were admitted to the hospital 5 to 7 days from symptom onset, but 6 were admitted on day 3 or 4 after symptom onset. All 18 evaluable subjects who died received oseltamivir, but only one of these subjects started oseltamivir treatment within the first 48 h from the symptom onset. Of the 22 subjects who died, 20 (90.9%) received antibiotic therapy.

The median hospital length of stay for subjects with influenza A(H1N1)pdm09 during the pandemic peak and postpandemic period was 6 days (minimal 2 days, maximal 37 days) and 5 days (minimal 3 days, maximal 18 days), respectively (p=0.17).

We compared subjects from the peak wave of influenza who did (n=25) or did not (n=27) receive antibiotics as part of their hospital influenza care (Table 4). Subjects

who received antibiotics were more likely to have underlying COPD (5; 20% vs 0%; p=0.02), and shortness of breath (7; 28% vs 1; 3.7% p=0.022) as compared with those who did not. Subjects who received antibiotics had a longer hospital length of stay than those who did not (6.76 days vs 5.04 days; p=0,026). The laboratory values and antiviral treatment characteristics were similar in both study groups (Table 4).

9 Discussion

9.1 Epidemiology

Lithuania experienced two waves of pandemic influenza during the summer and autumn in 2009. The European Union (EU) reached the peak of laboratory confirmed 2009 pandemic influenza activity during the summer wave in week 25 [2]. The first subject with influenza A(H1N1)pdm09 in Lithuania presented as the summer

Table 4: Comparison of frequency of selected study characteristics in treated with antibiotics for influenza patients group with patients group not received antibiotics

Study characteristic	Patients treated with antibiotics for influenza n=25	Patients not treated with antibiotics n=27	p
Age, median, (years)	25	22	0.733
Minimal – maximal, (years)	18-67	18-57	
Sex: (male)	10(40%)	14(51.9%)	0.392
Preexisting conditions, n (%)	8 (32)	8 (29.6)	0.853
COPD	5 (20)	0	0.020
Pregnancy	2 (8)	4 (14.8)	0.670
Symptoms n (%)			
Fever (≥38ºC)	20 (80)	16 (59.3)	0.105
Dry cough	24 (96)	26 (96.3)	0.105
Dyspnea	7 (28)	1 (3.7)	0.022
Vomitting	4 (16)	9 (33.3)	0.149
Headache	16 (64)	19 (70.4)	0.625
Altered consciousness	1 (4)	4 (14.8)	0.352
Length of hospital stay (days)			
Mean	6.76	5.04	0.026
Median (minimal – maximal)	4 (2-7)	5 (2-8)	-
Complicated cases, n (%)	5 (20)	5 (18.5)	1.00
COPD exacerbations, n (%)	4 (16)	0	0.047
Encephalopathy, n (%)	1 (4)	4 (14.8)	0.352
Threat of fetal loss, n (%)	0/2	1/4 (25)	>0.999
Admitted to ICU, n (%)	0	4 (14.8)	0.112
Laboratory values, n (%)			
Leukopenia	2 (8)	4 (14.8)	0.670
ESR increase	5 (20)	1 (3.7)	0.094
CRP increase	8 (32)	3 (11.1)	0.065
Mean, (mg/L)	24.13	25.33	0.801
Median (minimal – maximal)	22 (15-37)	26 (20-30)	
CXR performed, n (%)	23 (92)	17 (63)	0.013
CXR diagnosis of pneumonia	0	0	-
Treatment			
Antiviral treatment after hospitalization, n (%)	24 (96)	26 (96.3)	1.00
Antiviral treatment within			
48 h from symptom onset, n (%)	16 (66.7)	18 (69.2)	0.846
Duration of treatment (days) Mean			
Median (minimal – maximal)	4.21	4.12	0.848
	4 (2-7)	4 (1-15)	-

antiviral = oseltamivir; COPD = chronic obstructive pulmonary disease; CXR = chest radiograph; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ICU = intensive care unit

wave in EU reached its peak. The peak of the morbidity in Lithuania during the first wave was observed in week 32, ie, 7 weeks later than other EU countries. In Europe, countries hosting major hubs for international travel (eg, France, UK) reported infections earlier than countries with less international traffic. In Lithuania, the pandemic infections were reported much later. The first case of pandemic influenza in a traveler returned from India was diagnosed on the June 26, 2009. The earlier cases were mainly among travellers (75%) who returned from the infected areas, so their basic descriptive variables reflected the characteristics common to an average traveler. Exposure to confirmed or probable pandemic influenza A (H1N1) during the first influenza wave in the 7 days before illness onset was reported in 31.4% of subjects. This proportion increased to 63.8% for subjects during the pandemic peak. No deaths were documented during the first wave. These data suggest that throughout the first wave there was also a high incidence of asymptomatic and mild infections, and that few infections were reported.

Since the beginning of November, a sustained local spread of pandemic influenza virus within the country was documented. In total, 69,000 influenza cases were reported during the peak of the pandemic [5]. The laboratory-confirmed pandemic influenza occurred in 810 patients in Lithuania during the pandemic peak, from week 47 of 2009 to week 4 of 2010 [6].

Influenza pandemics usually cause more widespread disease and higher mortality as compared with seasonal influenza [7]. The 2009 pandemic has resulted in relatively few deaths in comparison with the pandemics of the 20th century. The rates of hospitalization and fatal cases during the H1N1 influenza pandemic have varied widely according to country [7,8]. According to the systematic review study of Khandaker et al, the overall case fatality rate among laboratory-confirmed cases of the influenza A(H1N1)pdm09 was 2.9% [7]. The case fatality rate for symptomatic illness in the USA has been estimated to be 0.048% [9] and 0.026% in the United Kingdom [10]. In Lithuania 23 fatal cases associated with laboratory-confirmed influenza A(H1N1)pdm09 cases were reported. Overall mortality was 6.9 (95% CI: 4.4 to 10.3) per one million inhabitants [6]. During the peak of pandemic 36% of hospitalized subjects had laboratory-confirmed A(H1N1) pdm09 infection, similar to that reported for Norway [11].

9.2 Demographics

The median age in our study was 20 to 30 years, younger than the median age for the subset that died. This is in agreement with most of the previous studies [12–15]. If younger individuals' exposure to influenza virus was more likely to be a novel influenza virus A(H1N1) than that of older ones with more years to develop protective immunity, they will have had less protective immunity than older adults to various influenza strains [16]. We found that the majority of the subjects who died were male, had more comorbidities, especially heart diseases, and were older. At least one underlying medical condition was reported for 73% of lethal cases. In total, 27% of deaths during the pandemic were in entirely healthy young adults and outside the traditional risk groups. In our study, all of the patients who died were under the age of 65 years, whereas most of the deaths caused by seasonal influenza occurred in individuals over 64 years of age who also had one or more chronic underlying medical conditions. The global study of influenza H1N1 2009 proved that although older adults may have a lower risk of infection, they have a significantly higher risk of death if they are infected [17]. Some studies reported that the mean age of subjects increased with severity of disease [14,18–20] and is the highest in lethal cases group [18,21]. Most studies report that fatal cases were disproportionately male [18,22], as were the individuals with pneumonia and admitted to ICU [8]. The reasons for the gender difference in disease severity may relate to underlying conditions, especially cardiovascular diseases, that are more common among the men. Similarly, the proportion of smokers could be higher among the men, placing them at greater risk for complications.

The risk groups affected by the pandemic differed from those affected by the seasonal influenza. During seasonal influenza, those who experience severe disease usually belonged to specified clinical risk groups [23]. Whereas both viruses mainly caused a severe disease among those with chronic medical conditions, the pandemic virus seems to have a predilection for pregnant women. In total, 19.4% of hospitalized women during pandemic peak were pregnant. One pregnant woman died during the peak of the pandemic. The increased risk for severe influenza among pregnant women should be emphasized, and vaccination should be noted for these women.

The hospitalized postpandemic influenza subjects had no comorbidities. One of the reasons could be that the general practitioners had learned a lot from the first year of influenza pandemic and they were more attentive, especially that there was a high risk for influenza complications subjects. Oseltamivir or zanamivir was given to the majority of subjects with influenza-like symptoms in the ambulatory setting, usually free of charge.

9.3 Clinical presentation

We found that fever and dry cough were the most common clinical features. These results are in concordance with most previous reports [7,13,15,24,25]. As suggested by Khandaker et al, fever and cough were the most sensitive predictors for 2009 pandemic H1N1 influenza [7]. This is similar to that reported for seasonal from other strains [26]. The subjects presenting during the first wave of pandemic had less severe disease as compared with the subjects during the peak of pandemic. Fewer subjects had fever, vomiting, altered consciousness, and only 1 of 53 (1.9%) developed pneumonia. According to Bin et al, the early cases of pandemic H1N1 influenza were mild, subjects were young and none of them had evidence of severe respiratory illness [27]. Severe cases and deaths occurred during the pandemic peak. We hypothesize that naturally occurring antigenic drift, ie, maturation and adaptation of the new influenza virus circulating over several weeks within the non-immune population, could offer one explanation for this observation of changing disease severity. The hospitalized pandemic influenza subjects and postpandemic subjects had a similar presentation with the most common symptoms of fever, dry cough, muscle pain, sore throat and headache. All of these symptoms occurred together in 34.8% of the peak pandemic cases but only in 20.8% of postpandemic cases. In the study by Shiley et al, fewer A(H1N1)pdm09 influenza subjects had headache and sore throat: 27% and 24% [25]. The principal clinical findings preceding death were productive cough, shortness of breath, and altered consciousness. These findings are similar to the findings of other studies [7,19,21]. Our study indicates that those patients with comorbidities had increased risk for pandemic influenza complications as compared with those without comorbidities (50% vs. 34.7%).

9.4 Complications and outcome

Pneumonia was the most frequent complication in all study groups except the earlier cases; the highest rate of pneumonia (90%) occurred among those who died. Primary viral pneumonia was diagnosed more frequently than bacterial in cases that died: (79% vs 50%, p=0.065). Several reports indicate that primary influenza pneumonia is associated with a high mortality rate [13,17,21,22,28]. Compromised pulmonary function could be best explained by the rapidly developing progressive hypoxemia caused by direct alveolar damage by virus [20]. Some authors have suggested that bacterial pneumonia has been less prevalent in influenza A(H1N1)pdm09 infection than during previous influenza pandemics [28]. The study of Sullivan et al [29] revealed bacterial coinfection in 29% of fatal cases with the predominance of *S. pneumonia*. In the study of Lee et al, the rate of bacterial pneumonia was 28% among the fatal cases [30]. Surprisingly, no viral pneumonia was found in subjects hospitalized at the Vilnius Infectious Diseases and Tuberculosis Hospital during the peak of pandemic and among the subjects with postpandemic influenza. In total, 18.8% of subjects developed pneumonia during the peak of the pandemic, and half of these were dyspneic and more than third visited the ICU; none died. Unfortunately, we did not identify the causative pathogens of pneumonias. Blood and sputum cultures were obtained from only 4 of 13 patients. *S. aureus* growth was documented in one sputum culture. Recent Lithuanian data showed a rate of pneumonia of 49.5% among hospitalized adult subjects [5]. Among hospitalized A(H1N1)pdm09 influenza subjects presented by Louie et al, 66% had pneumonia and 31% were admitted to the ICU [31]. In all, 12.5% of postpandemic influenza subjects developed bacterial pneumonia for which the clinical course was less severe, compared with the disease in the peak pandemic group. None of the subjects' ICU stay was due to pneumonia.

Pandemic (H1N1) virus infection can cause neurologic complications, affecting both the peripheral and central nervous system. Neurologic complications are uncommon but include encephalopathy, meningoencephalitis, transverse myelitis, and Guillain Barr**é** syndrome. In our study, 10.1% of peak pandemic influenza subjects and 8.4% of postpandemic subjects developed neurologic complications. For five (7.2%) pandemic influenza subjects, encephalopathy was caused by influenza virus. Three of 5 subjects had their CSF examined and no abnormalities were found: the CSF cultures were negative. All of those 5 subjects were young (age range 18-27 years) and had no comorbidities; they presented with encephalopathy on admission. Four of them required ICU care. According to Khandaker et al, [7] encephalopathy was present in 7.7% of the H1N1 pandemic influenza cases admitted to ICU. One subject developed influenza meningoencephalitis in the postpandemic influenza group. Unfortunately, the CSF was not tested for influenza virus. Babamahmoodi et al described a case of influenza meningoencephalitis with positive H1N1 RNA in CSF [32]. Our study and previous reports [32,33] emphasize the importance of considering CNS complications in pandemic or seasonal influenza, and of considering influenza in every case of aseptic meningoencephalitis during epidemics or pandemics.

Our subjects requiring ICU admission during the pandemic peak dwarfed that of the Brandsaeter BJ et al [11] study from Norway (13% vs 27%). Severe pneumonia and encephalopathy were the main reasons for ICU admission. The number of patients admitted to the ICU during the postpandemic period was lower than during the peak of pandemic activity. The hospitalization was also longer for the peak pandemic group (6 vs. 5 days). Although pandemic and postpandemic influenza presented with similar symptoms, the complications of postpandemic influenza were less severe compared with the peak of the pandemic. This could be explained by the development of population immunity to the virus resulting from the widespread infection and exposure during the pandemic period. Surprisingly, two other studies found that hospitalized subjects with influenza A(H1N1)pdm09 infection were more severely ill in the postpandemic season [34,35].

9.5 Treatment

Recent reports suggested that early treatment within 2 days after the onset of symptoms with oseltamivir was statistically associated with the lower risk for ICU admission and lethal outcome in hospitalized influenza A(H1N1) pdm09 subjects [5]. The proportion of treated subjects with oseltamivir was very high in the peak of pandemic and postpandemic groups (95.6% and 100%, respectively), and more than half of them (66.7% and 58.3%) received antivirals within 48 hours from symptom onset. In some studies, these proportions among hospitalized pandemic influenza subjects were lower [11,13,36].

In our study, the rate of antibiotic misuse for influenza subjects was quite high, as 59.5% of subjects with no signs of bacterial infection were given antibiotics. We believe that slightly elevated CRP (less than 30 mg/l) without leukocytosis and an increase of erythrocyte sedimentation rate (ESR) may not be an imminent indication of bacterial complications; therefore, the initiation of empiric antibiotic therapy can be safely delayed. Yun TJ et al [24] reported that elevated CRP combined with a lack of leukocytosis or elevated ESR may be typical in patients with influenza infection, and that these findings could help to rule out bacterial pneumonia. As shown in our study, dyspnea in conjunction with a stable chest X-ray and normal values of blood parameters does not indicate the need for antibiotics. Shortness of breath could be associated with exacerbation of COPD or influenza bronchitis. Our data show that treatment with antibiotics for influenza subjects does not improve recovery.

There were some limitations in this study. Only subjects from Vilnius district were included in this analysis. The Infectious Diseases and Tuberculosis Hospital Affiliate of Vilnius University Hospital Santariskiu Klinikos provide health care services to about 30% of the total population of Lithuania. Therefore, it is possible that our findings cannot be generalized to the entire population of hospitalized subjects with pandemic influenza in Lithuania. Another study in Kaunas, the second largest city of Lithuania revealed a similar pattern of influenza symptoms and complications rate [5]. As this study is retrospective, measurements, hospital admission, bacteriological culturing criteria, and treatment decisions, including antibiotics, could not be standardized and were made at the discretion of each attending physician. Subjects during the first pandemic wave period were more often admitted with less severe disease as a result of increased awareness and concerns for more serious disease from pandemic influenza.

10 Conclusions

In conclusion, Lithuania experienced two waves of pandemic influenza during summer and autumn 2009. Each wave presented a different epidemiological and clinical profile. The early influenza A(H1N1)pdm09 cases and postpandemic cases were milder compared with those at the peak of pandemic activity; fever and cough were the most prevalent clinical symptoms; shortness of breath, productive cough, altered consciousness with signs of pneumonia on chest X-ray were the principal clinical symptoms in those who went on to die, especially among individuals at risk for influenza complications. The highest rate of viral and bacterial pneumonias was among those who died.

Abbreviations

CNS, central nervous system;
CSF, cerebrospinal fluid;
COPD, chronic obstructive pulmonary disease;
ECDC, European Centre for disease Prevention and Control;
ESR, erythrocyte sedimentation rate;
EU, European Union;
ICU, intensive care unit;
WHO, World Health Organization.

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