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Clinical characteristics of adult patients with influenza-like illness hospitalized in general ward during Influenza A H1N1 pandemic 2009/2010

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Klinik erwachsener Patienten, die wegen Influenza ähnlicher Erkrankung auf einer allgemeinen Station während der Influenza A H1N1 Pandemie 2009/10 aufgenommen waren

Zusammenfassung. *Ziel der Studie:* Untersuchung klinischer und labortechnischer Charakteristika von Patienten, die mit einer Influenza A H1N1 Virusinfektion während der 2009/10 Pandemie aufgenommen waren.

Methoden: Prospektive Beobachtungsstudie, die Labor und klinische Parameter von Patienten mit Influenza ähnlicher Erkrankung (ILI), die entweder positiv oder negativ auf Influenza A H1N1 waren, vergleicht.

Ergebnisse: Zwischen 21. Oktober 2009 bis 14. Februar 2010 wurden 196 Patienten mit ILI aufgenommen, von denen bei 66 der Test auf Influenza A H1N1 positiv war. Die Patienten mit der H1N1 Infektion waren jünger (43 Jahre *vs.* 65 Jahre; $P<0{,}01$), waren häufiger schwanger ($P<0{,}01$), und hatten häufiger Allergien ($P<0{,}05$) beziehungsweise Asthma ($P<0{,}01$). Außerdem hatten sie öfter Fieber (91 % *vs.* 72,9 %; $P<0{,}01$) und eine höhere Prävalenz von Kopfweh (31,8 % *vs.* 18,5 %; $P<0{,}05$). Bei den H1N1 positiven Patienten waren die C-reaktiven Protein werte (88 pg/dl *vs.* 126 pg/dl; $P<0{,}01$), die Procalcitoninwerte (0,42 µg/l *vs.* 3,98 µg/l; $P<0{,}05$) und die die Leukozytenzahl (7,4*109/l *vs.* 11,7*109/l; $P<0{,}01$) niedriger – die Troponinwerte (0,162 µ/l *vs.* 0,146 µg/l; $P<0{,}01$) waren vergleichsweise erhöht. Bei den H1N1 negativen Patienten wurden häufiger bakterielle Infektionen beobachtet (68,8 % *vs.* 89,2 %; $P<0{,}05$).

Schlussfolgerungen: In der vorliegenden Studie unterschieden sich Influenza A H1N1 infizierte Patienten von solchen mit ILI ohne H1N1 Infektion in verschiedenen Laborwerten und klinischen Charakteristika. Dies wurde schon von anderen Untersuchern beobachtet. Unsere Studie legen zusätzlich Symptome, wie zum Beispiel eine höhere Inzidenz von Kopfweh, oder höhere Troponin Werte als für eine Infektion mit Influenza A H1N1 typisch nahe.

Summary. *Objective:* To investigate clinical and laboratory features of patients with Influenza A H1N1 virus infection hospitalized during 2009/2010 pandemic. METHODS: Prospective observational study comparing clinical and laboratory characteristics of Influenza A H1N1 positive and negative patients with influenza-like illness (ILI).

Results: From October 21, 2009 to February 14, 2010 196 ILI patients were admitted, of which 66 tested positive for Influenza A H1N1. The patients with H1N1 infection were younger (43 years *vs.* 65 years; $P<0.01$), more patients were pregnant ($P<0.01$), had allergies ($P<0.05$) or, asthma ($P<0.01$). H1N1 positive patients were more often febrile (91% *vs.* 72.9%; $P<0.01$) and had a higher prevalence of headache (31.8% *vs.* 18.5%; $P<0.05$). Lower values of C-reactive protein (88 pg/dl *vs.* 126 pg/dl; $P<0.01$), procalcitonine (0.42 µg/l *vs.* 3.98 µg/l; $P<0.05$), leukocyte count ($7.4*10^9$/l *vs.* $11.7*10^9$/l; $P<0.01$) and higher values of troponin (0.162 µ/l *vs.* 0.146 µg/l; $P<0.01$) were found in H1N1 positive patients. More bacterial infections were found in H1N1 negative group (68.8% *vs.* 89.2%; $P<0.05$).

Conclusions: In this study patients infected with Influenza A H1N1 differed from H1N1 negative ILI patients in several clinical and laboratory characteristics. The same was observed also by other investigators. The results of the study suggest some other specific features, such as a higher incidence of headache and higher values of troponin in Influenza A H1N1 infected patients.

Key words: Influenza, H1N1, troponin, hospital, ILI, clinical characteristics.

Introduction

The 2009/2010 influenza pandemic put a heavy burden on society and the healthcare system. In Slovenia the first

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case of infection with triple-reassortant swine Influenza A H1N1 virus was confirmed on June 19, 2009 in a patient arriving from New York who had influenza-like illness (ILI) [1]. After that the virus spread throughout the country, with the total number of confirmed cases 1,152 by week 23, 2010. The last case was confirmed in week 6, 2010. Nineteen patients died by week 23, 2010 [2, 3].

The novel pandemic influenza is reported to be a mild self-limiting disease similar to seasonal influenza, with the highest incidence rate in younger population and overall fatality less than 0.5% (WHO). However, the disease can have a more destructive course with the possible development of diffuse viral pneumonitis, associated with hypoxemia, ARDS, shock and renal failure. Next to the difference in affected age group some researchers have encountered clinical features that may define the novel influenza as a new clinical entity, e.g. higher risk for pregnant women, more obstetric problems, strong association with obesity, more gastrointestinal symptoms [4–7].

Patients with ILI admitted to adult general ward of the hospital were prospectively studied and their clinical characteristics and the course of illness were evaluated.

Materials and methods

Case definition

Patients with ILI admitted to adult general ward of the Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia between October 21, 2009 and February 14, 2010 were prospectively included in the study. Those admitted directly to the intensive care unit (ICU) or pediatric ward were excluded from the study. Data were collected using a standardized form.

A case of ILI was defined as body temperature ≥37.5°C with symptoms of upper or lower respiratory tract disease (e.g. sore throat, cough, rhinorrhea, nasal congestion). Patients with suspected bacterial infection of the lower respiratory tract during epidemics were considered, until proven otherwise to have co-infection with Influenza A H1N1 virus and they were also included in the study.

Confirmed Influenza A H1N1 infection was defined as ILI and positive real-time reverse transcriptase polymerase chain reaction (rRT-PCR) specific for Influenza A H1N1 virus. In few cases, positive with rRT-PCR for Influenza A, subtype could not be determined. As no other Influenza A virus was present at that time in the region [8], these cases were considered confirmed for further analysis. If rRT-PCR was negative, the diagnosis of Influenza A H1N1 infection was excluded and the case was classified as negative.

A case of bacterial infection was defined either as confirmed or probable. Probable case was defined by the following criteria: C-reactive protein (CRP) ≥ 100 pg/dl or leukocyte count >10.0*10^9/l or procalcitonine (PCT) > 0.5 µg/l or antibiotic therapy on admission. Confirmed bacterial infection was defined by detection of bacteria using standard microbiological tests, in the absence of an alternative explanation and in addition to the above mentioned laboratory parameters for bacterial infection.

The study was approved by the National Medical Ethics Committee.

Laboratory tests

Upon admission laboratory tests including whole blood count, CRP, PCT, hepatic enzymes, lactate dehydrogenase (LDH), creatine kinase, and troponin were performed. All cases of ILI had nasopharyngeal swab taken and were tested for Influenza A H1N1 by rRT-PCR. Samples for detection of bacterial infection were taken when appropriate.

Statistical analysis

Continuous variables were summarized as means ± standard deviation (SD) or medians with interquartile ranges (IQR). For categorical variables, the percentage of patients in each category was calculated. Clinical characteristics were compared between groups of patients using the Mann-Whitney *U* test and independent-samples *T* test. *P* values were considered significant if <0.05 (IBM SPSS statistics, version 18; SPSS).

Results

During the observation period 196 patients with ILI were admitted. Nasopharyngeal swabs tested positive for Influenza A H1N1 virus in 66 (33.6%) patients. The peak of admissions was observed between November 16 and December 20, 2009 (66.7% *vs.* 59.9%) (Fig. 1). Average duration of hospital stay for Influenza A H1N1 positive patients was shorter (median 4 days, range from 1 to 35 days for H1N1 positive *vs.* median 6 days, range from 1 to 65

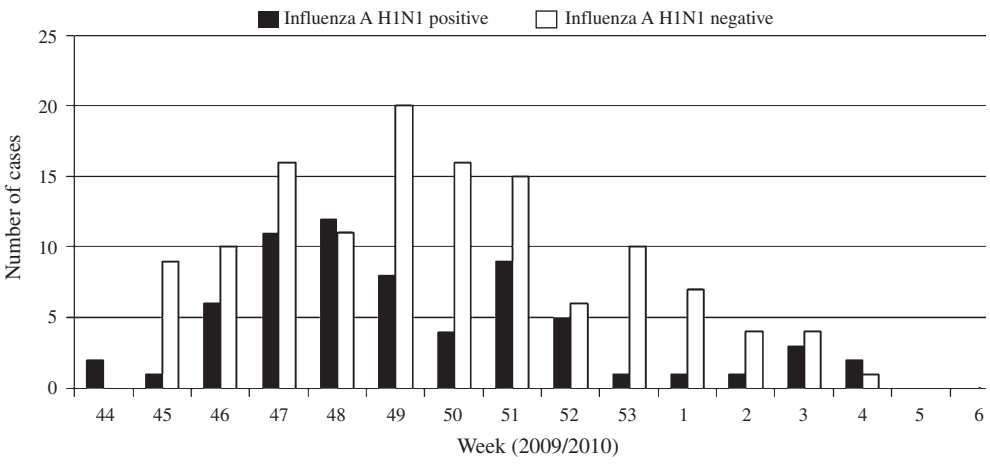

Fig. 1. Weekly number of admitted ILI patients

days for H1N1 negative, $P<0.01$). Patients infected with H1N1 who met the criteria for either probable or confirmed bacterial infection had longer hospital stay than patients with confirmed Influenza A H1N1 infection and no bacterial infection (3.7 days *vs.* 6.7 days; $P<0.05$).

Nine ILI patients died, 2 were Influenza A H1N1 positive: a 54-year-old woman with hypothyroidism and no other preexisting condition and 57-year-old man with decompensated alcoholic liver disease. The mortality rate of H1N1 positive and negative group did not show a significant difference (0.03% *vs.* 0.046%; $P\geq0.05$).

Thirteen patients (7 H1N1 positive, 6 negative) were transferred to ICU; of them, 1 H1N1 positive and 2 negative patients died ($P\geq0.05$). Need for mechanical ventilation due to inability to maintain optimal blood oxygenation with addition of supplementary oxygen alone and secondary bacterial infection with sepsis and hemodinamic instability were the two dominant reasons for the transfer to ICU. The following conditions were documented in H1N1 positive patients transferred to ICU: pregnancy (1), decompensated alcoholic liver disease (1), COPD (1), cardiovascular diseases (2), hypothyroidism (1), diabetes (1) and kidney disease (1). Mean age of patients admitted to ICU was 56.1 *vs.* 48.6 years for those not admitted to ICU ($P\geq0.05$).

Six pregnant women with ILI were admitted, infection with Influenza A H1N1 virus was confirmed in 5. One of them had a miscarriage; the other four did not have any obstetric problems during their hospital stay.

Demographic characteristics of patients are presented in Table 1, medical history and clinical presentation in Table 2, and signs and symptoms together with laboratory tests' in Table 3.

The criteria for probable bacterial infection were met by 44/64 (68.8%) Influenza A H1N1 positive and 116/130 (89.2%) negative patients; $P<0.05$.

Bacteria associated with pneumonia were isolated in 5/63 (7.9%) Influenza A H1N1 positive and 19/128 (14.8 %) negative patients ($P\geq0.05$). *Streptococcus pneumoniae* was the most often detected bacteria (40% *vs.* 47.3%) in both groups, followed by *Haemophilus influenzae* (40% *vs.* 5.3%), *Escherichia coli* (20% *vs.* 0%), *Staphylococcus aureus* (0% *vs.* 15.8%), *Klebsiella pneumoniae* (0% *vs.* 10.5%), *Mycoplasma pneumoniae* (0% *vs.* 10.5%), *Legionella pneumophila* (0% *vs.* 5.3%) and *Streptococcus pyogenes* (0% *vs.* 5.3%).

All ILI patients received oseltamivir (75 mg bid) at admission; if rRT-PCR was negative, treatment was stopped. The average duration of treatment was 4.6 ± 1.1 days (median 5; range from 0 to 7 days) for H1N1 positive patients and 1.2 ± 1.6 days (median 1; range from 0 to 16) for negative patients. Five patients received the first dose on the second day and 4 on the third day after admission. The treatment of patients in the study is presented in Table 4.

Table 1. Demographic characteristics

	Influenza A H1N1 positive group ($n=66$)	Influenza A H1N1 negative group ($n=130$)	*P*
Male sex – No. (%)	33 (50.0)	67 (51.5)	NS
Age (years)			
Mean ± SD	43 ± 17	65 ± 20	<0.01
Median ± IQR	39 ± 23	70 ± 28	
Range	17–87	17–100	
Age group – No. (%)			
≤24	9 (13.6)	3 (2.3)	
25–64	50 (75.8)	50 (38.5)	
≥65	7 (10.6)	77 (59.2)	

NS–non-significant.

Table 2. Medical history and clinical presentation

Characteristic	Influenza A H1N1 positive group ($n=66$)	Influenza A H1N1 negative group ($n=130$)	*P*
Medical history – No./No. of all patients with available data (%)			
Pregnancy	5/33 (15.2)	1/63 (1.6)	<0.01
Allergy	12/60 (20)	10/115 (8.7)	<0.05
Asthma	10/66 (15.2)	5/126 (4)	<0.01
COPD	4/66 (6.1)	12/126 (9.5)	NS
Other pulmonary disease	11/66 (1.5)	8/126 (6.3)	NS
Cardiovascular disease	10/66 (15.2)	66/126 (52.4)	<0.01
Kidney disease	3/66 (4.5)	2/126 (1.6)	NS
Clinical symptoms – No./No. of all patients with available data (%)			
Fever before admission (≥38.0°C)	51/56 (91)	78/107 (72.9)	<0.01
Headache	21/66 (31.8)	22/119 (18.5)	<0.05
Myalgia	19/66 (28.8)	27/119 (22.7)	NS
Arthralgia	11/66 (16.7)	25/119 (21)	NS
Chills	24/66 (36.4)	36/121 (29.8)	NS
Dispnoe	22/66 (33.3)	43/122 (35.2)	NS
Pleuritic pain	9/66 (13.6)	12/121 (9.9)	NS
Diarrhea	10/66 (15.2)	14/121 (11.6)	NS
Cough	59/66 (89.4)	96/123 (78)	NS

[1]lung cancer, NS – non-significant.

Discussion

During Influenza A H1N1 pandemics in 2009/2010 196, adult ILI patients were admitted to our ward; 66 suffered from Influenza A H1N1 infection. Admission rate for the whole country cannot be calculated because the cumulative number of all admitted patients in Slovenia is not available. Mortality rate (0.03%) for hospitalized patients, with confirmed Influenza A H1N1 infection is comparable to data available from WHO and does not change with H1N1 negative patients [4]. Since patients admitted directly to ICU are not included in the study, the overall mortality rate is probably underestimated, as other sources state that mortality rate of patients in ICU is significantly higher (14–36%) [4]. This mortality rate is in accordance with mortality rate of H1N1 patients transferred from normal ward to ICU.

Table 3. Clinical findings and results of the tests upon admission

Characteristic	Influenza A H1N1 positive group ($n=66$)	Influenza A H1N1 negative group ($n=130$)	*P*
Clinical signs - No./No. of all patients with available data (%)			
Body temperature (°C)			
Mean ± SD	37.5 ± 1.0	37.2 ± 0.9	<0.05
Fever (≥38.0°C)	23/65 (35.4)	26/127 (20.4)	<0.05
Hypoxemia[1]	14/65 (21.5)	44/129 (34.1)	NS
Abnormal pulmonary auscultation[2]	36/61 (58.9)	91/124 (73.4)	<0.05
Clinical signs – mean ± SD (No. of all patients with available data)			
Respiratory rate (per min)	26 ± 7 (40)	27 ± 9 (82)	NS
Systolic pressure (mmHg)	129 ± 26 (64)	126 ± 24 (128)	NS
Pulse (per min)	103 ± 25 (65)	95 ± 18 (129)	NS
Laboratory findings – mean ± SD (No. of all patients with available data)			
CRP – pg/dl	88 ± 77 (63)	126 ± 96 (130)	<0.01
PCT - µg/l	0.42 ± 0.74 (33)	3.98 ± 14.30 (67)	<0.05
Leukocyte count – 10^9/l	7.4 ± 4.0 (64)	11.7 ± 6.1 (127)	<0.01
<4.0 - no. / no. of all patients with available data (%)	15/64 (23.4)	8/127 (6.3)	<0.01
>10.0 - no. / no. of all patients with available data (%)	15/64 (23.4)	71/127 (55.9)	<0.01
Band neutrophil - %	4 ± 7 (35)	6 ± 8 (114)	NS
Hemoglobin – g/l	128 ± 20 (64)	126 ± 20 (126)	NS
Platelet count – 10^9/l	201 ± 96 (63)	223 ± 119 (126)	NS
<140 - No. / No. of all patients with available data (%)	16/63 (25.4)	21/126 (16.7)	NS
Urea – mmol/l	6.0 ± 5.0 (60)	9.9 ± 7.7 (126)	<0.01
Creatinine - µmol/l	90 ± 53 (62)	109 ± 70 (125)	<0.01
Potassium – mmol/l	4.1 ± 0.5 (60)	4.2 ± 0.5 (124)	NS
Sodium – mmol/l	139 ± 3 (60)	139 ± 5 (124)	NS
ALP[3] - µkat/l	1.19 ± 0.57 (50)	2.62 ± 11.65 (99)	<0.05
AST[4] - µkat/l	1.69 ± 4.97 (50)	0.84 ± 0.98 (102)	NS
ALT[5] - µkat/l	0.80 ± 1.03 (50)	0.71 ± 0.93 (102)	NS
γGT[6] - µkat/l	0.90 ± 1.37 (49)	1.0 ± 1.20 (101)	NS
AST > 0.58 or ALT > 0.74 or γGT > 0.92 - No./No. of all patients with available data (%)	28/49 (57.1)	55/100 (55)	NS
LDH[7] - µkat/l	4.94 ± 5.99 (39)	4.43 ± 2.69 (66)	NS
Creatinine kinase - µkat/l	42.82 ± 178.33 (22)	3.86 ± 7.02 (35)	NS
Mioglobin - µg/l	345 ± 1203 (23)	129 ± 123 (38)	NS
Troponin - µg/l	0.162 ± 0.63 (36)	0.146 ± 0.584 (66)	<0.01
Abnormalities on chest radiograph - no./no. of all patients with available data (%)[7]	29/57 (50.9)	70/116 (60.3)	NS

[1]blood oxygen saturation of less than 91% measured by pulse oxymeter; [2]most frequent abnormal breath sounds were inspiratory crackles (49.2%; 37.7% *vs.* 54.8%) and expiratory wheezing (5.9%; 9.8% *vs.* 4%), combination of both was present in 11.4% (11.5% *vs.* 11.3%); [3]alkaline phospathasis; [4]aspartat aminotransferase; [5]alanine aminotransferase; [6]γ-glutamyltransferase; [7]the abnormalities were most often located in two or less lobes (91.3%) and pleural effusion was found in 7.1%; NS – non-significant.

Most (66.7%) H1N1 positive patients were admitted between week 47 and 51; this is slightly later than the peak of confirmed cases in Slovenia and other countries of EURO region of WHO [9]. On average, H1N1 positive patients had shorter hospital stay, which indicates a relatively mild disease and quick recuperation. Longer hospital stay of H1N1 positive patients with probable bacterial infection is expected, since bacterial infection is a known complication of influenza.

Sexes were equally distributed among H1N1 positive and negative patients (50% *vs.* 51.5%). Mean age was lower in H1N1 positive patients (43 years *vs.* 65 years); this feature was also noticed by other researchers [4, 6, 10, 11]. Younger age is presumed to be a risk factor, as young

Table 4. Treatment of the patients included in the study

Characteristic – no./ no. of all patients with available data (%)	Influenza A H1N1 positive group ($n=66$)	Influenza A H1N1 negative group ($n=130$)	*P*
Oseltamivir	62[1]/64 (96.9)	96/127 (75.6)	<0.01
Antibiotic	35/61 (57.4)	113/127 (89)	<0.01
Supplementary oxygen	30/63 (47.6)	75/126 (59.5)	NS
ICU admission	7/66 (10.6)	6/130 (4.6)	NS

[1]2 patients did not receive therapy because of a less than 24 hour stay and 1 patient was already receiving oseltamivir prior to admission; NS – non-significant.

people do not have cross-protective antibodies derived from lifelong exposure to antigenically related influenza viruses [4, 12]. Contributing factors are also a higher degree of close social contacts with a wider variety of people in younger population, higher likeliness for travel to foreign countries and visiting areas with high concentration of people (e.g. hotels, airports, bars, nightclubs, malls). Our H1N1 positive patients were older in comparison to other studies; however, mean age was in agreement with findings of WHO [4, 11, 13–16]. The reason for this may be the exclusion of pediatric patients.

Fever and cough were the most frequent symptoms in ILI patients. Fever was reported more often by H1N1 positive patients (91% *vs.* 72.9%; $P<0.01$), with similar numbers found in literature, 87.3–95.9% [13, 14, 18, 19]. Incidence of headache was also higher in H1N1 positive group (31.8% *vs.* 18.5%; $P<0.05$). Other symptoms (cough, myalgia, arthragia, chills, dispnoa, pleuritic pain, gastrointestinal symptoms) did not differ between the two observed groups of ILI patients. Body temperature measured upon admission was higher in H1N1 positive patients (37.5°C *vs.* 37.2°C; $P<0.05$), and was the only sign that showed differences between the two groups.

The number of pregnant women among ILI patients in the study (6.3% of all women) was low, however, most of them (5/6) belonged to H1N1 positive group. Association between H1N1 infection and pregnancy was also noticed by WHO [4]. One H1N1 positive pregnant woman in the study had a medically unexplained miscarriage on the second day after admission. Complications of pregnancy related to H1N1 infection were described by other authors as well [17, 18].

History of drug allergies or asthma was more common in H1N1 positive patients; the same is reported by other researchers [4, 19]. Other chronic pulmonary diseases (e.g. COPD) were equally distributed between the two groups. Cardiovascular disorders were found mainly in H1N1 negative patients. As the incidence of cardiovascular diseases increases with age, the finding of this study may be related to the higher age of H1N1 negative patients.

Both groups had elevated levels of CRP and PCT; however, the levels were higher in H1N1 negative group. This is probably related to bacterial infection which was, according to the criteria in the study, more frequent in H1N1 negative patients. Mean white blood cell count was lower in H1N1 positive patients and significantly more H1N1 positive patients had leucopenia, a feature also observed in the Chinese study (23.4% in Slovenian and 21.4% in Chinese patients) [15]. Troponin level was higher in H1N1 positive patients; the values were in the so-called grey-zone and cannot be interpreted as a reliable marker of higher viral tropism for myocardial cells. In literature two studies preformed prior to Influenza A H1N1 pandemic on 30 and 152 patients with Influenza infection did not find any patients with an increased troponin level [19, 20].

The study is limited by the relatively small group of patients and missing data in spite of the prospective design of the study. Nevertheless the data collected allow some statistically significant conclusions and some of the findings add to the knowledge on clinical presentation of Influenza A H1N1 infection.

Conclusion

Influenza A H1N1 is a disease with some characteristics different for Influenza A from seasons before and these were also observed in the study (younger age of affected patients, pregnancy as a risk factor). Most often reported symptoms and signs are those found also in patients with Influenza A. Laboratory tests routinely done did not disclose any new insights; however, higher troponin levels were observed in our patients, a feature not reported before by other researchers. Further investigation of this feature could provide new data on the Influenza A H1N1.

Conflict of interest
None.

References

1. Prvi primer okužbe z virusom nove gripe v Sloveniji. IVZ. [Internet]. 2009 [cited 2010 Jun 6]. Available from: http://www.ivz.si/Mp.aspx?ni=78&pi=6&_6_id=428&_6_PageIndex=1&_6_groupId=-2&_6_newsCategory=IVZ+kategorija&_6_action=ShowNewsFull&pl=78-6.0.
2. Announced number of new and cumulative confirmed fatal 2009 pandemic influenza A (H1N1) cases in EU and EFTA countries, as of Week 17 - 2010. ECDC. [Internet]. 2010 [cited 2010 Jun 6]. Available from: http://ecdc.europa.eu/en/healthtopics/H1N1/Pages/Reported_number_of_new_and_cumulative_confirmed_fatal_cases.aspx.
3. FluNet. WHO. [Internet]. [cited 2010 Jun 13]. Available from: http://gamapserver.who.int/GlobalAtlas/DataQuery/viewData.asp.
4. Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, Uyeki TM, Zaki SR, Hayden FG, Hui DS, Kettner JD, Kumar A, Lim M, Shindo N, Penn C, Nicholson KG. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 2010;362(18):1708–19.
5. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, Gubareva LV, Xu X, Bridges CB, Uyeki TM. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;360(25):2605–15.
6. Crum-Cianflone NF, Blair PJ, Faix D, Arnold J, Echols S, Sherman SS, Tueller JE, Warkentien T, Sanguineti G, Bavaro M, Hale BR. Clinical and epidemiologic characteristics of an outbreak of novel H1N1 (swine origin) influenza A virus among United States military beneficiaries. Clin Infect Dis. 2009;49(12):1801–10.
7. Poggensee G, Gilsdorf A, Buda S, Eckmanns T, Claus H, Altmann D, Krause G, Haas W. The first wave of pandemic influenza (H1N1) 2009 in Germany: From initiation to acceleration. BMC Infectious diseases. 2010;10:155.

8. Pandemic (H1N1) 2009 - update 86. WHO. [Internet]. 2010 [cited 2010 Jun 13]. Available from: http://www.who.int/csr/don/2010_02_5/en/index.html.
9. FluNet. WHO. [Internet]. [cited 2010 Jun 16]. Available from: http://gamapserver.who.int/GlobalAtlas/DataQuery/viewData.asp.
10. Dee S, Jayathissa S. Clinical and epidemiological characteristics of the hospitalised patients due to pandemic H1N1 2009 viral infection: experience at Hutt Hospital, New Zealand. N Z Med J 2010;123(1312):45–53.
11. Scriven J, Mcewen R, Mistry S, Green C, Osman H, Bailey M, Ellis C. Swine flu: Birmingham experience. Med J Aust. 2010;192(2):84–6.
12. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. Lancet 2010;375(9720):1100–8.
13. Babek A, Akhtar R, Fadaei Nobari R. Epidemiological and clinical characteristics of Influenza A (H1N1) V infection in Isfahan, Iran, July-October 2009. 20th European congress of clinical microbiology and infectious diseases Vienna, Austria, 2010 Apr 10-13. Clinical microbiology and infection. 2010; Vol. 16, Supp 2, page S711.
14. Ataman Hatipoglu C, Mutlu AG, Bulut C, Altun S, Erdinc FS, Tuncer Ertem G, Kinikli S, Oral B, Tulek N, Demiroz AP. Evaluation of epidemiological, clinical and laboratory characteristics of pandemic influenza A (H1N1) case in a tertiary hospital in turkey. 20th European congress of clinical microbiology and infectious diseases Vienna, Austria, 2010 Apr 10-13. Clinical microbiology and infection. 2010; Vol. 16, Supp 2, page S675.
15. Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, Liang ZA, Liang L, Zhang SJ, Zhang B, Gu L, Lu LH, Wang DY, Wang C. Clinical features of the initial cases of 2009 pandemic Influenza A (H1N1) virus infection in China. N Engl J Med 2009;361(26):2507–17.
16. Echevarría-Zuno S, Mejía-Aranguré JM, Mar-Obeso AJ, Grajales-Muñiz C, Robles-Pérez E, González-León M, Ortega-Alvarez MC, Gonzalez-Bonilla C, Rascón-Pacheco RA, Borja-Aburto VH. Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. Lancet 2009;374(9707):2072–9.
17. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, Louie J, Doyle TJ, Crockett M, Lynfield R, Moore Z, Wiedeman C, Anand M, Tabony L, Nielsen CF, Waller K, Page S, Thompson JM, Avery C, Springs CB, Jones T, Williams JL, Newsome K, Finelli L, Jamieson DJ. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. J Am Med Assoc 2010;303(15):1517–25.
18. Toal M, Agyeman-Duah K, Schwenk A, Yoong W. Swine flu and pregnancy. J Obstet Gynaecol 2010;30(2):97–100.
19. Ison MG, Campbell V, Rembold C, Dent J, Hayden FG. Cardiac findings during uncomplicated acute influenza in ambulatory adults. Clin Infect Dis 2005;40(3):415–2.
20. Greaves K, Oxford JS, Price CP, Clarke GH, Crake T. The prevalence of myocarditis and skeletal muscle injury during acute viral infection in adults: measurement of cardiac troponins I and T in 152 patients with acute influenza infection. Arch Intern Med 2003;163(2):165–8.
21. Situation update in the European Region: overview of influenza surveillance. WHO. [Internet]. [Cited 2010 Jun 16]. Available from: http://www.euro.who.int/Document/CSR/EuroFlu_Situation_update_40-09.pdf.
22. Writing Committee of the WHO. Clinical Aspects of Pandemic 2009 Influenza. N Engl J Med 2010;362:1708–19.
23. Akinci E, Kayaaslan BU, Yetkin MA, Yilmaz S, Aliravci D, Yildiz S, Ulgen F, Eren SS, But A, Yilmaz GR, Bodur H. Evaluation of H1N1 pandemic influenza cases in an infectious diseases clinic. 20th European congress of clinical microbiology and infectious diseases Vienna, Austria, 2010 Apr 10-13. Clinical microbiology and infection 2010;16(Supp. 2):S711.
24. Kalpakou G, Stravopodis P, Aggelopoulou V, Litrokapis M, Verikou M, Gouga D, Koutroubi A, Bourinaris T, Sidirokastriti O, Spinou M. Clinical features of patients with confirmed infection form A/H1N1 virus. 20th European congress of clinical microbiology and infectious diseases Vienna, Austria, 2010 Apr 10-13. Clinical microbiology and infection 2010;16(Supp. 2):S675.
25. Rodriguez C, Cordova E, oviedo G, Cornistein W, Noel A, Vazquez L. Clinical and epidemiological characteristics of outpatients with influenza-like ilness during influenza A H1N1 pandemic in Buenos Aires, Argentina. 20th European congress of clinical microbiology and infectious diseases Vienna, Austria, 2010 Apr 10-13. Clinical microbiology and infection 2010;16(Supp. 2):S305.
26. Trifonov V, Khiabanian H, Rabadan R. Geographic dependence, surveillance, and origins of the 2009 influenza A (H1N1) virus. N Engl J Med 2009;361(2):115–9.
27. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, Gubareva LV, Xu X, Bridges CB, Uyeki TM. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;360(25):2605–15.
28. Louie JK, Acosta M, Jamieson DJ, Honein MA and Group, California Pandemic (H1N1) Working. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med 2010;362(1):27–35.
29. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, Louie J, Doyle TJ, Crockett M, Lynfield R, Moore Z, Wiedeman C, Anand M, Tabony L, Nielsen CF, Waller K, Page S, Thompson JM, Avery C, Springs CB, Jones T, Williams JL, Newsome K, Finelli L. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010; 303(15):1517–25.