Turkish Journal of Medical Sciences

Volume 42 | Number 3 Article 9

1-1-2012

Risk factors and prognosis in children hospitalized due to pandemic H1N1 influenza A virus infection in Ankara, Turkey*

MEDİNE AYŞİN TAŞAR

YILDIZ BİLGE

ÖZGE UYSAL SOYER

ŞÜKRAN YILDIRIM

MUSTAFA TAŞAR

See next page for additional authors

Risk factors and prognosis in children hospitalized due to pandemic H1N1 influenza A virus infection in Ankara, Turkey*

Authors
MEDİNE AYŞİN TAŞAR, YILDIZ BİLGE, ÖZGE UYSAL SOYER, ŞÜKRAN YILDIRIM, MUSTAFA TAŞAR, and FATMA İNCİ ARIKAN

TÜBİTAK

Original Article

Turk J Med Sci
2012; 42 (3): 433-440
© TÜBİTAK
E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1011-1308

Risk factors and prognosis in children hospitalized due to pandemic H1N1 influenza A virus infection in Ankara, Turkey*

Medine Ayşin TAŞAR[1], Yıldız DALLAR[1], Özge UYSAL SOYER[1], Şükran YILDIRIM[1], Mustafa TAŞAR[2], Fatma İnci ARIKAN[1]

Aim: To describe the demographic characteristics and clinical features in children with influenza A (H1N1) virus infection and to identify risk factors for severe disease or poor prognosis. Following the first tourist-imported case in Turkey on 16 May 2009, the influenza A (H1N1) virus has spread throughout the country.

Materials and methods: Children under 18 years of age who were hospitalized for at least 24 h with an influenza-like illness and who had confirmed influenza A (H1N1) virus infection were included in the study. Demographic factors, clinical signs and symptoms, laboratory results, radiographic findings, treatments, and follow-up periods were noted.

Results: During the period of October to December 2009, 126 [63.5% males, median age: 3 years (range: 0.1-9 years)] children with cases of influenza A (H1N1) virus infection were hospitalized. Fever (95.2%), cough (84.1%), rhinorrhea (70%), and dyspnea (63.5%) were the most common presenting symptoms. A total of 46 patients (36.4%) had chronic underlying medical conditions, with asthma being the most common (21.4%). During hospitalization, durations of oxygen requirement and wheezing were longer in patients with chronic respiratory disease. Duration of oxygen requirement and tachypnea decreased if oseltamivir was initiated within 48 h (P = 0.006 and 0.033, respectively). No risk factor was defined for hospitalization longer than 4 days.

Conclusion: In our cohort, influenza A (H1N1) virus infection did not appear to cause severe disease. Asthma was a significant risk factor for severe disease. Delayed (>48 h) initiation of antiviral therapy might have contributed to an increase in morbidity, which suggests the importance of timely administration of antiviral treatments.

Key words: Pandemic H1N1 influenza A, oseltamivir, prognosis, asthma

Ankara'da Pandemik İnfluenza A virüs enfeksiyon nedeniyle hastaneye yatırılan çocuklarda risk faktörleri ve prognoz

Amaç: Türkiye'de ilk vaka 16 Mayıs 2009' da bir turistte saptandıktan sonra influenza A (H1N1) virüsü tüm ülkeye yayıldı. Bu çalışmanın amacı H1N1 virüs enfeksiyonlu çocuklarda demografik faktörleri, klinik özellikleri ve şiddetli hastalık veya kötü prognoz için risk faktörlerini tanımlamaktır.

Yöntem ve gereç: İnfluenza benzeri hastalığı olan ve H1N1 enfeksiyonu doğrulanmış 18 yaş altı çocuklar çalışmaya alındı. Demografik faktörler, şikayet ve bulgular, laboratuar sonuçları, tedavi ve izlemleri kaydedildi.

Bulgular: Ekim-Aralık 2009 döneminde, 126 çocuk H1N1 [% 63,5 erkek, yaş: 3 yıl (0,1 - 9)] enfeksiyonu nedeniyle hastaneye yatırıldı. En sık başvuru şikayetleri ateş (% 95,2), öksürük (% 84,1), burun akıntısı (% 70), ve solunum sıkıntısı (% 63,5) idi. Hastaların % 36,4 `ünün süregen hastalığı mevcuttu; en sık astım (% 21,4) saptandı. Hastanede yatış süresi, oksijen ihtiyacı süresi ve hışıltı süregen akciğer hastalığı olanlarda daha uzun saptandı. Oseltamivir tedavisi ilk 48 saat

Received: 22.12.2010 – Accepted: 05.05.2011

[1] Department of Pediatrics, Ankara Research and Education Hospital, Ankara - TURKEY
[2] Department of Radiology, Gülhane Military Medical Academy, Ankara - TURKEY
Correspondence: *Medine Ayşin TAŞAR, Department of Pediatrics, Ankara Research and Education Hospital, 06030 Ankara - TURKEY*
E-mail: aysintasar@yahoo.com

* This abstract was presented at the 30th EACII Congress in İstanbul, Turkey.

içinde başlananlarda oksijen ihtiyacı süresi ve takipne daha az bulundu (P = 0,006 ve 0,033). Dört günden daha uzun hastanede yatış için risk faktörü saptanmadı.

Sonuç: Bu çalışmada, H1N1 virüs enfeksiyonu şiddetli hastalık nedeni olarak saptanmadı. Astım şiddetli hastalık için belirleyici bir etken olarak bulundu. Antiviral tedavinin geç başlanması (>48 saat) artmış hastalık riski ile beraber olabilir; bu nedenle şiddetli hastalık riski antiviral tedavinin zamanında başlanması ile azaltılabilir.

Anahtar sözcükler: Pandemik influenza A (H1N1), oseltamivir, prognoz, astım

Introduction

In late April 2009, a novel influenza virus led to human infection in Mexico. A public health emergency of international concern was declared by the World Health Organization (WHO) on 25 April 2009 (1). Over the following weeks, the virus spread rapidly to all regions of the world. Consequently, WHO declared a phase 6 pandemic on 11 June 2009 due to evidence of community-level transmission in multiple countries globally (2). Despite the rapid spread of the pandemic influenza A (H1N1) virus (1,2), most cases did not have a serious disease course. In the United States and Canada, about 2%-5% of people with laboratory-confirmed infection required hospitalization (3). Between one-half and two-thirds of hospitalized cases had comorbidities such as asthma, other chronic respiratory diseases (CRDs), diabetes, and autoimmune disorders (3,4). Fatalities due to pandemic influenza A (H1N1) virus did occur (5). Based on seasonal influenza data, children under the age of 5 years and especially those under the age of 2 years, as well as those with underlying chronic conditions, are at a substantially higher risk of hospitalization compared to older or otherwise healthy children. Pulmonary complications such as bronchitis or pneumonia, neurological complications such as encephalitis or encephalopathy, and a sepsis-like syndrome in neonates have been reported even in previously healthy children (6,7).

Since the first tourist-imported case in Turkey on 16 May 2009, pandemic influenza A (H1N1) virus has spread throughout the country, affecting mainly young adults and children. In this article, we present our experience with children hospitalized due to pandemic influenza A (H1N1) virus infection. Our aim was to describe the demographic characteristics, clinical features, and markers of disease severity in children with pandemic influenza A (H1N1) virus infection. Our secondary aim was to identify risk factors for severe disease or poor outcome.

Materials and methods

Children under 18 years of age who were hospitalized for at least 24 h with an influenza-like illness and who had pandemic influenza A (H1N1) virus infection as confirmed by a real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay between October and December 2009 at the Ankara Training and Research Hospital, Ankara, Turkey, were included in the analysis. A probable case of pandemic influenza A (H1N1) virus was defined as a person with high fever (≥38 °C) and/or at least 2 acute respiratory symptoms with epidemiological criteria listed in the case definition protocol published by WHO (8). The hospital provides medical services to a population of 953,000 inhabitants, mainly a low-income community.

We used a questionnaire addressing demographic factors (age, sex, weight, height, and underlying medical conditions), information about a possible epidemiological link to a pandemic influenza A (H1N1) virus case, and clinical signs and symptoms. Underlying CRDs were further investigated. The diagnosis of asthma was made by a history of intermittent wheezing and the presence of reversible airway obstruction as defined by at least a 12% improvement in forced expiratory volume in 1 s (FEV1) following bronchodilator administration and therapeutic response to antiinflammatory medications according to international guidelines (GINA). The diagnoses of bronchopulmonary dysplasia and bronchiectasis were made by computed tomography of the lung. We noted laboratory test results, radiographic findings, treatments, and follow-up periods. The chest X-rays of the patients were evaluated by a radiologist who was blinded to the history and clinical evaluation of the patients. We did not include children admitted more than 3 days before the onset of influenza-like symptoms, since the disease was considered incidental to their admission.

Respiratory samples (nasopharyngeal and nasal swabs) were tested for pandemic influenza A (H1N1) virus with RT-PCR at the Refik Saydam National Public Health Agency in Ankara. The "in house" real-time RT-PCR protocol and reagents were supplied by the Centers for Disease Control and Prevention (Atlanta, GA, USA). The QIAamp Viral RNA Mini Kit (QIAGEN, Valencia, CA, USA) or the High Pure Viral RNA isolation kit (Roche Applied Science, Penzberg, Germany) was used for RNA extraction. Real-time RT-PCR was performed on an ABI 7000 and/or 7500 (Applied Biosystems, Foster City, CA, USA). The NA, HA, and M genes of the index case were partially sequenced and analyzed with CLC Main Workbench Software 4.1.1 (CLCbio, Aarhus, Denmark).

Oseltamivir was used as antiviral therapy in age-appropriate doses. The study was approved by the Local Ethics Committee of the Ankara Training and Research Hospital.

All data analyses were conducted using SPSS for Windows, version 15 (SPSS Inc., Chicago, IL, USA). We compared the categorical variables using the chi-square test and the others using the nonparametric Mann-Whitney U test. We compared the demographic characteristics of patients with or without chronic lung disease. Binary logistic regression was used to determine risk factors associated with an increased hospitalization period. Variables that were associated with the outcomes in the univariate analysis at a P-value of less than 0.25 were examined in the multivariate logistic regression models. A forward likelihood ratio (LR) modeling strategy was used. The effect of the risk factors was measured using odds ratios (ORs) and 95% confidence intervals (CIs). A value of $P < 0.05$ was considered statistically significant.

Results

During the period of October-December 2009, there were 126 (63.5% males) confirmed patients with pandemic influenza A (H1N1) virus infection hospitalized at our institution. The median age of patients was 3 years (range: 0.1-9 years). Nasopharyngeal swabs of 2 neonates presenting with fever were positive for pandemic influenza A (H1N1) virus.

The sources of the pandemic influenza A (H1N1) virus infections were diverse, including family history of influenza-like illness in 41.3%, nosocomial infection in 3.2%, and travel abroad in 1.6% of the patients.

Fever or history of fever (95.2%), cough (84.1%), rhinorrhea (70%), and dyspnea (63.5%) were the most common presenting symptoms of infection (Table 1). Convulsions were seen in 14 patients (11.1%), including febrile seizures (8.3%). A diagnostic work-up was done for 3 patients, and central nervous system imaging and cerebrospinal fluid analysis were within normal limits. All patients with seizures recovered fully and had no neurologic sequelae at discharge.

In the study population, growth percentiles were within the 5th to 95th percentiles except in 1 child aged 6 years and diagnosed with infantile spasm, for which systemic corticosteroid had been used for the last 3 months. The physical examinations revealed a median respiratory rate of 34 (30-40)/min and a median heart rate of 127 (110-138)/min. The main findings in the respiratory system were wheezing (24.6%), crackles (41.3%), and both wheezing and crackles (11.3%). Respiratory distress in the form of tachypnea (respiratory rate > 2 SD of age-specific normal limits) and suprasternal, intercostal, and subcostal retractions was detected in 80 (63.5%) children.

Table 1. Symptoms at admission in children with pandemic influenza A (H1N1) virus (n = 126).

	Number of cases	%
Fever	120	95.2
Cough	106	84.1
Rhinorrhea	88	70.0
Dyspnea	80	63.5
Sore throat	35	27.8
Headache	35	27.8
Myalgia	24	19.0
Vomiting	17	13.5
Seizures	14	11.0
Diarrhea	6	4.8
Abdominal pain	5	4.0

A total of 46 patients (36.5%) had chronic underlying medical conditions (Table 2). CRDs [23.4%; asthma (n = 27), bronchopulmonary dysplasia (n = 2), and bronchiectasis (n = 1)] were the most common accompanying chronic diseases, followed by neurologic diseases [6.4%; cerebral palsy (n = 5), meningomyelocele (n = 1), hydrocephaly (n = 1), and Duchenne muscular dystrophy (n = 1)] and cardiovascular diseases [3.1%; congenital heart diseases (n = 3) and acute rheumatic fever (n = 1)].

In the laboratory evaluation, the median white blood cell count was 9000 (6200-11,900)/μL, hemoglobin concentration 12.0 (11.2-13.0) g/dL, and erythrocyte sedimentation rate 14 (5.5-27.5)/h. Chest radiography was done on 96 patients, and 25 of them were normal. The main radiologic findings were interstitial infiltration (n = 28), hilar lymph node enlargement (n = 19), and lobar consolidation (n = 5).

When patients were grouped based on the presence of CRD, patients with CRD were older than those without CRD [median age of 6 (3-10) years vs. 2 (0.1-7) years, respectively; P = 0.003] (Table 3). Even though the onset of symptoms before admission did not differ between groups, physical examination findings differed in the respiratory system. Crackles alone were observed in children without CRD, while wheezing was most commonly seen in patients with CRD. Respiratory distress was more prominent in children with CRD compared to children without CRD [29 (96.7%) vs. 51 (63.8%), respectively; P < 0.001], but chest X-ray findings were similar (data not shown). During the hospitalization period, durations of oxygen requirement and wheezing were longer in patients with CRD.

The median time from onset of illness to antiviral treatment was 2 days (range: 1-13). Oseltamivir was used as antiviral therapy after respiratory samples were taken in all patients and it influenced the morbidity of the pandemic influenza A (H1N1) virus infection (Table 4). The duration of oxygen requirement and tachypnea decreased if oseltamivir was initiated within 48 h of the onset of symptoms compared to patients whose therapy was initiated ≥48 hours after onset (P = 0.006 and 0.033, respectively). In 15% of patients, side effects due to oseltamivir were observed as diarrhea (13.5%) and vomiting (1.6%).

Table 2. Underlying medical conditions of the patients.

	n (%)
Chronic respiratory disease	**30 (23.8)**
Asthma	27 (21.4)
(Asthma + idiopathic thrombocytopenic purpura)	
Bronchopulmonary dysplasia	2 (1.6)
Bronchiectasis	1 (0.8)
Neurologic disease	**8 (6.4)**
Cerebral palsy	5 (4.0)
Meningomyelocele	1 (0.8)
Hydrocephaly	1 (0.8)
Duchenne muscular dystrophy	1 (0.8)
Cardiovascular disease	**4 (3.1)**
Congenital heart diseases	3 (2.3)
Acute rheumatic fever	1 (0.8)
Diabetes mellitus	**1 (0.8)**
Fructose intolerance	**1 (0.8)**
Henoch-Schönlein purpura	**1 (0.8)**
Mucopolysaccharidosis	**1 (0.8)**
Total	**46 (36.5)**

Table 3. Demographic, clinical, and laboratory features of patients with and without chronic respiratory disease.

	Whole group (n = 126)	Chronic respiratory disease (+) (n = 30)	Chronic respiratory disease (-) (n = 96)	P
Age (years)*	3 (0.1-9)	6 (3-10)	2 (1-7)	**0.003**
Sex (male) (%)	80 (63.5)	18 (60)	62 (64.6)	>0.05
Onset of symptoms (days)*	2 (1-2)	2 (1-3)	1.5 (1-2)	>0.05
Influenza vaccination, current season (%)	8 (6.3)	6 (20)	2 (2.1)	**<0.001**
Fever (%)	120 (95.2)	28 (93.3)	92 (95.8)	>0.05
Cough (%)	106 (84.1)	28 (93.3)	78 (81.3)	>0.05
Physical examination				
Respiratory rate/min*	34 (30-40)	32 (30-36)	36 (30-40)	>0.05
Heart rate/min*	127 (110-138)	121 (102-138)	128 (114-138)	>0.05
Crackles (%)	52 (41.3)	-	52 (54.2)	**<0.001**
Wheezing (%)	31 (24.6)	23(76.7)	8 (8.3)	**<0.001**
Crackles + wheezing (%)	14 (11.1)	7(23.3)	7(7.3)	**<0.001**
Respiratory distress (%)	80 (63.5)	29 (96.7)	51 (53.1)	**<0.001**
Respiratory insufficiency (%)	6 (4.8)	2 (6.7)	4 (4.2)	>0.05
Total leukocyte count ($\times 10^3$/L)*	9 (6.2-11.9)	6.7 (4.8-12)	9.2 (6.7-11.9)	>0.05
Erythrocyte sedimentation rate (mm/h)*	14 (5.5-27.5)	9 (2-18)	15.5 (7-33)	**0.026**
Follow-up period				
Duration of O_2 requirement (days)*	2 (0-3)	3 (2-4)	0 (0-3)	**<0.001**
Duration of tachypnea (days)*	2 (1.5-4)	2 (2-3.5)	2 (1-4)	>0.05
Duration of wheezing (days)*	2 (0-4)	3 (2-5)	1 (0-3)	**0.007**
Duration of hospitalization (days)*	4 (3-6)	4 (3-6)	4 (3-5)	>0.05

*median (interquartile range)

Table 4. The effect of initiation of antiviral therapy on morbidity.

	<48 hours	≥48 hours	P
Duration of O_2 requirement (days)*	1 (0-3.0)	3 (1.5-4.0)	**0.006**
Duration of tachypnea (days)*	1.5 (0.3-3.0)	2 (2.0-3.8)	**0.033**
Duration of wheezing (days)*	2 (0-3.0)	3 (0-5.0)	>0.05
Duration of hospitalization (days)*	4 (3.0-5.3)	4.5 (4.0-6.0)	>0.05

*median (interquartile range)

The median time of hospitalization was 4 (range: 3-6) days. Logistic regression analysis was done to determine risk factors associated with hospitalization of ≥4 days. Sex, respiratory distress at admission, concomitant chronic disease, concomitant CRD, smoke exposure, and initiation of antiviral therapy within 48 h of onset of symptoms were included in the regression model. None of these factors were associated with longer hospitalization periods.

Our 2 patients with severe chronic neurologic disease died. A 16-year-old boy with Duchenne muscular dystrophy was diagnosed with pandemic influenza A (H1N1) virus infection and pneumonia. He was treated with oseltamivir and ceftriaxone for 5 days and he needed mechanical ventilation. Due to the increased severity of his respiratory distress, he died 20 days after hospitalization. A 15-month-old girl with hydrocephalus, a ventriculoperitoneal shunt, and growth retardation was admitted due to cough and fever over the previous 10 days and was diagnosed with pandemic influenza A (H1N1) virus infection and pneumonia. She was treated with oseltamivir and ceftriaxone for 7 days. Due to the increased severity of her respiratory distress and the expanded infiltration revealed in a chest X-ray on day 8, her antibiotic regimen was changed to imipenem and vancomycin, but she did not recover and died on the same day.

Discussion

In 2009, the H1N1 influenza virus caused a pandemic, creating public apprehension and a socioeconomic burden, especially on health care systems. This necessitated the sharing of experiences in different countries during this pandemic with emphasis on severe/hospitalized patients. In this study, we reviewed our patients with pandemic influenza A (H1N1) virus infection hospitalized in a tertiary care center, which also served as a primary and secondary care facility during the pandemic.

The rate of hospital admission due to pandemic influenza A (H1N1) virus was highest among children less than 5 years old in both Chicago and New York (9,10). In Canada, the mean age of children hospitalized because of pandemic influenza A (H1N1) was 6.4 years, versus 3.3 years because of seasonal influenza. We observed that our hospitalized patients with the pandemic influenza A (H1N1) virus were younger compared to the Canadian data (11). However, community epidemiologic data are essential to assist in interpreting the observed difference in the ages of children admitted to hospital.

Recent data support the development of neurological complications in children in association with the pandemic influenza A (H1N1) virus in the United States. In the United States, it was reported that the H1N1 influenza virus caused acute encephalopathy and encephalitis without leading to mortality and sequelae (7). Convulsions with or without fever were seen as a presenting symptom in 11% of our patients. The incidence rate of gastrointestinal symptoms such as diarrhea among confirmed cases in children was found to be 23%. The frequency of diarrhea ranged from 17% in Cyprus to 36% in Canada and 42% in the United States (11-13).

Because all of our patients were hospitalized, compliance with oseltamivir treatment was high (100%). Furthermore, side effects, seen in 15% of all cases, were nausea and vomiting, the most common side effects reported in the literature (14,15). In a recent study on school-aged children in the United Kingdom, in which children received oseltamivir as influenza prophylaxis, the rate of adverse effects was much higher, with 40% of the students developing gastrointestinal symptoms and 18% developing mild neuropsychiatric side effects such as poor concentration, sleeping problems, bad dreams, and strange behavior (16). No patient in our series presented any of the neuropsychiatric side effects described in that report. This might be attributed to the younger age of the subjects in our study, who may have been unable to express their complaints properly.

Asthma has been identified as a significant risk factor for the pandemic influenza A (H1N1) virus requiring hospital admission, present at 21%-30% in other studies (9,10). Surveillance for pediatric deaths associated with the pandemic influenza A (H1N1) virus in the United States declared that asthma or reactive airway disease was a part of the underlying condition in only 3 of 36 children who died of pandemic influenza A (H1N1) virus. Furthermore, all of these children also had neurologic impairment

(17). Our experience suggested that asthma was a more significant risk factor for pandemic influenza A (H1N1) virus infection requiring hospitalization (21.4%). O'Riordan et al. stated that even mild persistent asthma could be a risk factor for hospitalization due to pandemic influenza A (H1N1) virus infection, and the risk was also higher compared to infection with a seasonal influenza virus (11).

Furthermore, they reported that more than 50% of the children with asthma admitted to their hospital for pandemic influenza A (H1N1) virus infection presented with evidence of pneumonia, with or without bronchospasm, compared to those admitted for seasonal influenza. We cannot estimate the rate of admission to the hospital because of pandemic influenza A (H1N1) virus without population-based epidemiologic data. This is an area for imminent future research.

CRD and neurodevelopmental disorders were the most commonly reported conditions in a national survey investigating mortality due to pandemic influenza A (H1N1) virus infection in England. The median age of patients was 8 (range: 2-19, n = 25) in those with neurodevelopmental disorders. As age increased, asthma and chronic obstructive respiratory disease were the major risk factors for mortality (18). Our 2 patients with severe chronic neurologic disease died.

Delays in the prescription of antiviral drugs emerged from studies of hospitalized patients in the United States and England (13,18). An analysis of 272 inpatients with pandemic influenza A (H1N1) virus infection in the United States suggested that use of antiviral drugs confers a survival benefit, particularly when they are started within 2 days of the onset of illness (13). In England, antiviral treatment was given within 48 h of the onset of symptoms in only 9% of patients and delayed treatment led to an increase in mortality (18). However, in another study in the United States, the duration of critical illness did not differ between early- and late-onset treatment groups (19). In this study, we showed that antiviral treatment within 48 h of disease onset decreased morbidity in terms of the durations of oxygen requirement and tachypnea.

In our cohort, the pandemic influenza A (H1N1) virus infection did not appear to cause severe disease, and the majority of pediatric cases had a mild clinical course. Treatment with antivirals appeared to not have any major adverse effects. Asthma was a significant risk factor for severe disease among children with pandemic influenza A (H1N1) virus. Delayed (≥48 h) initiation of antiviral therapy might have contributed to an increase in morbidity, which suggests the importance of timely administration of antiviral treatments.

References

1. Chan M. World now at the start of 2009 influenza pandemic. WHO Press Release; 2009. Available from: URL: http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html.
2. World Health Organization. Influenza A (H1N1): WHO announces pandemic alert phase 6, of moderate severity. WHO Press Release; 2009. Available from: URL: http://www.euro.who.int/en/what-we-publish/information-for-the-media/sections/press-releases/2009/06/influenza-a-h1n1-who-announces-pandemic-alert-phase-6,-of-moderate-severity.
3. Centers for Disease Control and Prevention. Hospitalized patients with novel influenza A (H1N1) virus infection - California, April-May, 2009. Morb Mortal Wkly Rep 2009; 58: 536-41.
4. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009; 360: 2605-15.
5. European Center for Disease Prevention and Control (ECDC). ECDC situation report. Influenza A (H1N1)v infection. 2009 May. Available from: URL: http://ecdc.europa.eu/en/healthtopics/Documents/090502_InfluenzaAH1N1_Situation_Report_0800hrs.pdf.
6. American Academy of Pediatrics. Influenza. In: Pickering LK, editor. Red Book: 2009 report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2009. p.400-12.
7. Centers for Disease Control and Prevention. Neurologic complications associated with novel influenza A (H1N1) virus infection in children - Dallas, Texas, May 2009. Morb Mortal Wkly Rep 2009; 58: 773-8.
8. World Health Organization. Pandemic (H1N1) 2009. 2009 Nov. Available from: URL: http://www.who.int/csr/disease/swineflu/en/index.html.

9. Centers for Disease Control and Prevention. 2009 pandemic influenza A (H1N1) virus infections - Chicago, Illinois, April-July 2009. Morb Mortal Wkly Rep 2009; 58: 913-8.

10. New York City Department of Health and Mental Hygiene. 2009 New York City Department of Health and Mental Hygiene health alert #27: pandemic (H1N1) 2009 influenza update, revised reporting requirements and testing procedures, July 8, 2009. Available from: URL: http://www.nyc.gov/html/doh/downloads/pdf/cd/2009/09md27.pdf.

11. O'Riordan S, Barton M, Yau Y, Read SE, Allen U, Tran D. Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. CMAJ 2010; 182: 39-44.

12. Koliou M, Soteriades ES, Toumasi MM, Demosthenous A, Hadjidemetriou A. Epidemiological and clinical characteristics of influenza A (H1N1)v infection in children: the first 45 cases in Cyprus, June-August 2009. Euro Surveill 2009; 14(33): pii=19312.

13. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med 2009; 361: 1935-44.

14. Food and Drug Administration. Tamiflu pediatric adverse events: questions and answers. 2009. Available from: URL: http://www.fda.gov/Drugs/DrugSafety/rketDrugSafetyInformationforPatientsandProviders/ucm107840.htm.

15. Prober CG. Antiviral therapy for influenza virus infections. Semin Pediatr Infect Dis 2002; 13: 31-9.

16. Kitching A, Roche A, Balasegaram S, Heathcock R, Maguire H. Oseltamivir adherence and side effects among children in three London schools affected by influenza A (H1N1)v, May 2009 - an internet-based cross-sectional survey. Euro Surveill 2009; 14(30): pii=19287.

17. Centers for Disease Control and Prevention. Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection - United States, April-August 2009. Morb Mortal Wkly Rep 2009; 58: 941-7.

18. Donaldson LJ, Rutter PD, Ellis BM, Greaves FEC, Mytton OT, Pebody RG et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ 2009; 339: b5213.

19. Lockman JL, Fischer WA, Perl TM, Valsamakis A, Nichols DG. The critically ill child with novel H1N1 influenza A: a case series. Pediatr Crit Care Med 2010; 11: 173-8.