Clinical differences of influenza subspecies among hospitalized children

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Abstract

Aim: Clinical findings, mortality, and morbidity rates differ among influenza subspecies. Awareness of these differences will lead physicians to choose the proper diagnostic and therapeutic strategies and to foresee possible complications. The aim of this study was to evaluate the clinical differences of influenza subspecies among hospitalized children.

Material and Methods: Hospitalized children with proven influenza infection by polymerase chain reaction on nasopharyngeal swab specimens in our clinic, between December 2013 and March 2016, were enrolled. These children were divided into 3 groups as Influenza A/H1N1 (n=42), Influenza A/H3N2 (n=23), and Influenza B (n=35).

Results: The median age of the children was 51.5 months (range, 3-204 months). The most common presenting symptoms were fever (n=83), cough (n=58), and difficulty in breathing (n=25). The most common non-respiratory findings were lymphadenopathy (n=18) and gastrointestinal system involvement (n=17). Sixty-two percent of the patients (n=62) had chronic diseases. H1N1 and H3N2 were significantly more common among patients with chronic neurologic disorders and renal failure, respectively. Leukopenia (n=32) and thrombocytopenia (n=22) were the most common pathologic laboratory findings. Neutropenia, elevated CRP levels, and antibiotic use were significantly more common among patients with H1N1 infection. Seven patients were transferred to the intensive care unit with diagnoses of acute respiratory distress syndrome (n=4), encephalitis (n=2), and bronchiolitis (n=1). Two patients with chronic diseases and H1N1 infection died secondary to acute respiratory distress syndrome.

Conclusions: Influenza A/H1N1 infection represented more severe clinical disease. (Turk Pediatri Ars 2017; 52: 15-22)

Keywords: Influenza, influenza A/H1N1, influenza A/H3N2 and Influenza B

Introduction

Influenza is a significant acute respiratory tract disease that affects 5-20% of the world population and is characterized by high morbidity and mortality, especially in high-risk groups (1). In the United States of America (USA), approximately 250,000-500,000 cases of seasonal influenza are reported each year and about 200,000 of these patients require hospitalization (2). In children and patients with chronic disease, the attack rate may reach up to 40% during outbreaks (3). The agents that lead to morbidity in humans are mostly influenza A and B (4). However, influenza A is mostly responsible for seasonal epidemics and worldwide pandemics.

When the statistics of pandemic influenza in years were examined, it was observed that the clinical pictures, and morbidity and mortality rates showed variance between influenza subtypes (5-7). In the years during which the H3N2 type was generally predominant, the rates of pneumonia and mortality rates were reported higher compared with H1N1 epidemics (8). Studies reported that central nervous system (CNS) findings were mostly related with influenza A and myositis and digestive system symptoms were observed more frequently in influenza B infections (9-11). Knowledge of these clinical differences will be helpful for physicians to predict complications that may occur in relation with influenza. In this study, we aimed to compare the clinical pictures and

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complications of influenza subtypes by examining the clinical and laboratory findings of patients who presented to our clinic with respiratory tract infection findings, hospitalized, and were found to have influenza.

Material and Methods

This study is a retrospective archive screening study. Using polymerase chain reaction (PCR), influenza and non-influenza respiratory viruses were studied in nasopharyngeal swab samples of 3263 patients who presented to our Pediatric Emergency Outpatient Clinic between December 2013 and March 2016 and followed up in the emergency room. Influenza virus was found in 161 of these subjects (4.9%) and non-influenza respiratory tract virus was found in 1314 (40.3%).

One hundred patients who were found to have influenza virus in the viral respiratory tract panel examination and hospitalized after a 24-hour follow-up period in the emergency room because of different causes were included in this study. The age, sex, presentation symptoms, physical examination findings, laboratory results [complete blood count, C-reactive protein (CRP), procalcitonin (PCT), viral PCR examination result on respiratory tract swab sample], presence of antiviral drug use, hospitalization status, hospitalization period, and complications were recorded by retrospectively examining the patient files, computer records, and discharge summary epicrisis reports. The subjects were divided into three groups as influenza A/H1N1, influenza A/H3N2, and influenza B.

Nasopharyngeal swab samples were obtained by rotating swabs 360° after entering into both nostrils and proceeding up to the nasopharyngeal area in order to detect viruses leading to respiratory tract disease. After the swabs were closed in covered boxes containing transport medium (Virocult, Medical Wire & Equipment, UK), full nucleic acid extraction was performed using an EZ1 virus mini kit V2.0 (Catalog number: 955134, Qiagen, Germany) in the virology laboratory. An FTD Respiratory Pathogens 21 kit (Fast-track diagnostics Ltd. Malta), which has the ability to differentiate influenza A (H3N2 and H1N1) and influenza B, was used with real-time and multiplex PCR to detect respiratory tract pathogens in the Rotor-Gene Q platform (Qiagen, Germany).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL,

USA) version 21 package program. Normality was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Data were given as median, minimum-maximum, frequency and percentage. Measurable data that did not show normal distribution were compared using the Kruskal-Wallis test in independent groups. Categorical data were evaluated using the Chi-square test and Fisher's exact test. A p value of <0.05 was considered significant.

Ethics committee approval was obtained from Istanbul University Faculty of Medicine Ethics Committee for this study (2016: 1479).

Results

One hundred patients with a median age of 5.5 months (range, 3-204 months) the majority of whom were male (65%) were included in the study. The clinical and laboratory characteristics of the patients are shown in Table 1. When examined by age group, eight patients were in the 0-6 years age group, 18 patients were in the 6 months-12 years age group, 35 patients were in the 2-5 years age group, and 39 patients were aged more than five years. Although patient distribution and influenza subtypes showed difference by years, congestion of patients was generally observed most frequently between the months of January and March (Figure 1).

Eighty-three percent of the patients presented with fever. Other presenting symptoms included cough (58%), respiratory distress (25%), sore throat (18%), rhinorrhea (18%), vomiting-diarrhea (17%), hoarse voice (8%), headache (6%), seizure (6%), redness in the eyes (4%), and eruption (4%). Two of the patients who had seizure were healthy previously and had a positive history of febrile convulsion. The remaining four patients had epilepsy. Although presentation because of fever and seizure was observed more frequently in patients who were found to have H1N1 infection, the difference was not statistically significant.

The median time period of symptoms was found as three days (1-13). There was no difference between the different influenza subtypes in terms of the time period of symptoms before presentation. The most common finding on physical examination was oropharyngeal hyperemia with a rate of 63%. Pathologic respiratory sounds were present in 29% of patients, postnasal discharge was present in 28%, and tachypnea was present in 20%. The most common non-respiratory findings included enlarged lymph nodes in the cervical region (18%)

Table 1. Clinical and Laboratory Characteristics of Patients with Influenza (4-204)

Sex [female, number, (%)]	35 (35)
Age group (number, %)	
0-6 months	8 (8)
6 months-2 years	18 (18)
2-5 years	35 (35)
>5 years	39 (39)
Symptom at the time of presentation (number, %)	
Fever	83 (83)
Cough	58 (58)
Respiratory distress	25 (25)
Sore throat	18 (18)
Nasal discharge	18 (18)
Vomiting-diarrhea	17 (17)
Hoarse voice	8 (8)
Headache	6 (6)
Seizure	6 (6)
Redness in the eyes	4 (4)
Eruption	4 (4)
Period of symptoms [days, median (range)]	3 (1-13)
Presence of chronic disease (number, %)	62 (62)
Neurologic disease	16 (16)
Metabolic disease	14 (14)
Asthma	10 (10)
Chronic renal failure	6 (6)
Chronic liver disease	5 (5)
Congenital heart disease	4 (4)
Malignancy	3 (3)
Diabetes mellitus type 1	1 (1)
Congenital neutropenia	1 (1)
Familial Mediterranean fever	1 (1)
Juvenile idiopathic arthritis	1 (1)
Pathological finding on PALG (number, %)	44 (44)
Paracardiac infiltration	32 (32)
Increased aeration	7 (7)
Ground-glass appearance	4 (4)
Pleural effusion	1 (1)
Laboratory [median (range)]	
Leukocyte count (/mm ³)	6 550 (1 900-30 610)
Neutrophil count (/mm ³)	3 585 (400-26 650)
Lymphocyte count (/mm ³)	1 895 (400-6 800)
Hemoglobin (gr/dL)	12 (7.4-14.6)
Platelet count (/mm ³)	210 650 (19100-602000)
CRP (mg/L)	6.9 (0.1-86.7)
PCT (ng/mL)	0.33 (0.01-2.90)
Oseltamivir use (number, %)	45 (45)
Period of oseltamivir use [days, median (range)]	5 (5-14)
Period of antibiotic use [days, median (range)]	7 (3-21)
Hospitalization period [days, median (range)]	5 (2-94)

CRP: C-reactive protein; PALG: postero-anterior lung graphy; PCT: procalcitonin

Figure 1. Distribution of the influenza subtypes by seasons

and gastrointestinal findings (17%). Influenza-related CNS involvement was present in seven patients who were healthy previously [encephalopathy (3%), febrile convulsion (2%), Guillain-Barré syndrome (2%)]. Other findings included myositis (6%), conjunctivitis (4%), eruption (4%), hepatitis (2%), and myocarditis (1%). Although enlarged lymph nodes and nervous system involvement were observed with a higher frequency in patients who were positive for H1N1, the difference was not statistically significant. All patients with neurologic symptoms who were healthy before the influenza infection recovered without sequela.

Sixty-two percent of the patients had chronic diseases including most commonly neurologic diseases [epilepsy (7%), cerebral palsy (5%), neuromotor retardation (4%)], metabolic disease (14%), asthma (10%), chronic renal failure (6%), chronic liver disease (5%), congenital heart disease (4%), malignancy (3%), diabetes mellitus type 1 (1%), familial Mediterranean fever (1%), juvenile idiopathic arthritis (1%), and congenital neutropenia (1%). Seventy percent (70.2%) of the patients who had chronic disease were aged more than two years. H1N1 positivity was found with a significantly higher frequency in patients who had chronic neurologic disease and H3N2 positivity was found with a significantly higher frequency in patients with chronic renal failure ($p=0.007$ and $p=0.032$, respectively) (Table 2).

When evaluated in terms of laboratory findings, the most common pathologic findings at the time of presentation were leukopenia (32%) and thrombocytopenia (22%). Anemia was present in 17% of patients, neutropenia in 16%, and leukocytosis was present in 7%. Neutropenia was statistically significantly more frequent in patients with H1N1 positivity compared with the other patients ($p=0.021$) (Table 2). At the time of presentation, the median CRP value was found as 6.9 mg/L (range, 0.1-86.7 mg/L) and the median PCT value was 0.33 ng/mL (range, 0.01-2.9 ng/mL). In patients who were found to have H1N1 infection, the

Table 2. Comparison of the clinical and laboratory findings of patients in terms of different influenza subtypes

	Influenza A/H1N1 (n=42)	Influenza A/H3N2 (n=23)	Influenza B (n=35)	p
Age [months, median (range)]	50 (3-158)	58 (5-204)	65 (3-178)	0.066 ^b
Presence of chronic disease^a	26 (61.9)	15 (65.2)	21 (60)	0.92 ^c
Neurologic disease	12 (28.6)	0	4 (11.4)	0.007 ^d
Metabolic disease	7 (16.7)	4 (17.4)	3 (8.6)	0.51 ^d
Asthma	0	4 (17.4)	6 (17.1)	0.058 ^d
Chronic renal failure	1 (2.4)	4 (17.4)	1 (2.9)	0.032 ^d
Cronic liver disease	3 (7.1)	1 (4.3)	1 (2.9)	0.20 ^d
Congenital heart disease	1 (2.4)	0	3 (8.6)	0.68 ^d
Symptom at the time of presentation (n, %)				
Fever	39 (92.9)	17 (73.9)	27 (77.1)	0.079 ^c
Cough	22 (52.4)	15 (65.2)	21 (60)	0.57 ^c
Respiratory distress	11 (26.2)	5 (21.7)	9 (25.7)	0.91 ^c
Sore throat	6 (14.3)	6 (26.1)	6 (17.1)	0.48 ^c
Nasal discharge	10 (23.8)	5 (21.7)	3 (8.6)	0.19 ^d
Vomiting-diarrhea	7 (16.7)	5 (21.7)	5 (14.3)	0.75 ^c
Seizure	5 (11.9)	0	1 (2.9)	0.096 ^d
Non-respiratory findings (n, %)				
Lymphadenopathy	9 (21.4)	4 (17.4)	5 (14.3)	0.71 ^d
Neurologic	4 (9.5)	1 (4.3)	2 (5.7)	0.68 ^d
Myositis	3 (7.1)	1 (4.3)	2 (5.7)	0.89 ^d
Eruption	2 (4.8)	1 (4.3)	1 (2.9)	0.42 ^d
Conjunctivitis	2 (4.8)	1 (4.3)	1 (2.9)	0.24 ^d
Hepatitis	1 (2.4)	1 (4.3)	0	0.49 ^d
Myocarditis	0	0	1(2.9)	0.39 ^d
Laboratory (n, %)				
Leukocytosis	4 (9.5)	2 (8.7)	1 (2.9)	0.41 ^d
Neutropenia	11 (26.2)	0	5 (14.3)	0.021 ^d
Leukopenia	15 (35.7)	7 (30.4)	10 (28.6)	0.78 ^c
Anemia	11 (26.2)	1 (4.3)	5 (14.3)	0.070 ^d
Thrombocytopenia	10 (23.8)	6 (26.1)	6 (17.1)	0.67 ^c
Increased CRP	28 (66.7)	10 (43.5)	13 (37.1)	0.026 ^c
Increased procalcitonin	5 (11.9)	2 (8.7)	2 (5.7)	0.63 ^d
Radiologic finding (n, %)	24 (57.1)	7 (30.4)	13 (37.1)	0.070 ^c
Antibiotic use (n, %)	30 (71.4)	12 (52.2)	12 (34.3)	0.005 [#]
Hospitalization in intensive care unit (n, %)	4 (9.5)	2 (8.7)	1 (2.9)	0.48 ^d
Mortality	2 (4.8)	0	0	0.24 ^d

^aPatients with chronic diseases (n=62); comparison of patients with malignancy (n=3), diabetes mellitus type 1 (n=1), congenital neutropenia (n=1), familial Mediterranean fever (n=1), and juvenile idiopathic arthritis (n=1) could not be performed because they had inappropriate numbers for statistical comparison.

^bKruskal-Wallis test; ^cPearson's Chi-square test; ^dFisher's exact test

CRP level at the time of presentation was statistically significantly higher compared with the other patients (p=0.026) (Table 2). Postero-anterior lung radiography revealed pathologic findings in 44% of patients includ-

ing paracardiac infiltration (32%), increased aeration (7%), ground glass appearance (4%), and pleural effusion (1%). Although pathologic findings were observed with a higher frequency on postero-anterior lung ra-

Table 3. Clinical characteristics of patients hospitalized in the intensive care unit

Sequence	Age/Sex	Chronic disease	Symptoms	Diagnosis	Influenza type	ICU hospitalization period (days)	Mechanical ventilation	Antiviral treatment/duration	Final status
1	50 months/M	Malignancy	Fever, cough, respiratory distress	Pneumonia/ARDS	H3N2	4	-	-	Discharge
2	112 months/M	-	Fever, somnolence	Encephalopathy	H1N1	4	-	Oseltamivir 7 days	Discharge
3	55 months/M	Chronic liver disease	Fever, respiratory distress	Pneumonia/ARDS	H1N1	10	4	-	Mortality
4	8 months/	-	Fever, respiratory distress	Acute bronchiolitis	H3N2	3	-	Oseltamivir 5 days	Discharge
5	59 months/M	Metabolic disease	Fever, respiratory distress	Pneumonia/ARDS	H1N1	76	76	Oseltamivir 14 days	Mortality
6	46 months/M	Neurologic disease	Fever, somnolence, seizure	Encephalopathy	Influenza B	7	-	-	Discharge
7	29 months/M	Chronic lung disease	Fever, respiratory distress	Pneumonia/ARDS	H1N1	14	9	Oseltamivir 10 days	Discharge

ARDS: acute respiratory distress syndrome; ICU: intensive care unit

diographs in the H1N1 group, the difference was not statistically significant.

Oseltamivir treatment was given to 45 patients for a median period of 5 days (5-14 days). Antibiotic use was found in 54 patients with a median period of 7 days (3-21). Antibiotic use was found with a significantly higher frequency in patients with H1N1 positivity compared with the other patients ($p=0.005$) (Table 2). The median disease period was found as 10 days (range, 5-28 days) in all patients. During the follow-up period, seven patients were hospitalized in the intensive care unit (ICU) [acute respiratory distress syndrome (ARDS, $n=4$), encephalitis ($n=2$), bronchiolitis ($n=1$)] (Table 3). Although the frequency of H1N1 ($n=4$) was high among patients who were hospitalized in the neonatal intensive care unit, the difference was not statistically significant. Two patients, one with glutaric aciduria type 1 and one with chronic liver disease died of ARDS. H1N1 was positive in both patients.

Discussion

Influenza virus, which is a significant agent of respiratory tract infections, frequently leads to an acute and self-limiting disease in previously healthy children; it may cause high morbidity and mortality in children with chronic disease and in children aged below 2 years. In the 2003-

2008 National Surveillance Assessment of the USA, it was reported that hospitalization because of influenza in childhood occurred most commonly below the age of two years and especially below the age of six months (9). The Centers for Disease Control and Prevention reported that children below the age of two years carried risk in terms of the development of complications and recommended that they should be vaccinated (12). In our study, the majority of patients who were hospitalized because of influenza were above the age of 2 years in contrast to the literature information. This finding seemed to be related with the fact that our clinic is a tertiary healthcare institution and has a high rate of chronic disease in the group aged >2 years. It is known that influenza A virus causes hospital presentation with a higher frequency, especially in children aged below one year (9, 13). Similarly, the ages of patients who were found to have influenza A infection were younger in our study, but the difference was not statistically significant.

The clinical findings of influenza virus are variable and frequently characterized by cough and sore throat accompanying suddenly developing fever, headache, and myalgia. Higher fever, febrile convulsion, enlarged lymph nodes, a higher rate of gastrointestinal involvement and a lower rate of respiratory findings may be observed in children because they have not been exposed to the virus before (14). This causes difficulty in

the diagnosis and increases unnecessary antibiotic use (14). In a study of 353 pediatric patients with confirmed influenza infection, fever was reported with a rate of 95%, cough as 77%, and coryza was reported as 78% (15). In the same study, headache (26%) and myalgia (7%) were reported more rarely. Gastrointestinal symptoms including vomiting, diarrhea, and abdominal pain may be observed with varying frequencies during the course of influenza infection. According to a meta-analysis compiled by Minodier et al. (16), this rate ranged between 2.8% and 30.9% for influenza A infection.

There are also studies stating that abdominal pain and gastrointestinal symptoms are observed more frequently during influenza B infection (17). Although the pathophysiology of this state has not been elucidated fully, detection of viral RNA in stool suggests direct invasion by the virus and there are also publications proposing that the immune reaction created by growing viruses in lung mucosa might lead to gastrointestinal findings (18, 19). In our study, gastrointestinal symptoms including vomiting-diarrhea were found with a rate of 17%, and no significant difference was found between H1N1, H3N2, and influenza B subtypes in terms of the frequency of gastrointestinal symptoms.

Similarly, there are studies showing that myositis is observed more frequently in influenza B and H3N2 infections (9, 11). In another study in which 10 patients with acute benign childhood myositis in our clinic were examined, influenza B was detected in six patients and influenza A was detected in four (20). In our study, patients with influenza who were hospitalized were examined and myositis was found with rate of 6%; no difference was found in terms of influenza subtypes.

One of the most important non-respiratory findings of influenza is CNS involvement. Different neurologic findings, mainly including febrile convulsion, encephalopathy, encephalitis, aseptic meningitis, Guillain-Barre syndrome, extrapyramidal system involvement, and myelitis may be observed (21). In a study of 842 children with laboratory-confirmed influenza infection, the frequency of neurologic complications was reported as 4/100,000 person-year (21). However, it has been reported that the frequency of neurologic complications is increased in patients with chronic neurologic diseases. In a study in which the clinical findings in influenza A and B infections were compared, CNS involvement was found significantly high in the influenza A group (9). In our study, H1N1 positivity was more frequent in patients who were previously healthy and who had CNS

involvement, but a statistically significant difference was not found when compared with the other influenza subtypes. In the group with chronic neurologic disease, H1N1 positivity was found more frequently. When examined in terms of other chronic diseases, it was found that influenza B infection occurred more frequently and the complication rate was higher in individuals with chronic lung disease, chronic heart disease or immune system problems (9, 22). However, it is not known why influenza B virus leads to more serious findings in these patient groups. Similarly, influenza B was found with a higher frequency in patients with asthma in our study, though statistical significance was not shown.

Among patients with chronic renal failure, H3N2 was found with a higher frequency ($p=0.032$). During influenza infection, different hematologic findings, especially including reduction in bone marrow series may be observed (23). It is thought that hematologic findings occur as a result of cell migration from the circulation to tissues, cell death by way of necrosis or apoptosis, and suppression of hematopoiesis in the bone marrow (24). In the literature, there are different publications related with the hematologic findings of influenza subtypes.

In a study conducted in Japan in which 196 adult influenza cases were evaluated, the prevalence of leukopenia was found higher in patients with H3N2 positivity (11). In H1N1 infection, lymphopenia is generally observed in the first 1-3 days and neutropenia is observed after the fifth day. This is thought to be related with cell migration from the circulation to the infected respiratory mucosa during infection (25). It has been reported that hemophagocytosis, which develops during influenza infection, causes reduction in bone marrow cell series (26). In our study, the most commonly observed abnormal laboratory findings included leukopenia and thrombocytopenia, in accordance with the literature. When the influenza subtypes were compared, presence of neutropenia was found with a significantly higher frequency in the H1N1 group.

The causes of mortality related with influenza mainly include pneumonia, ARDS, and encephalopathy (27). Although the H1N1 subtype has generally been associated with more severe clinical prognosis, the frequency of complications and mortality rates may show variance in different patient groups during epidemics (28). In our study, a total of seven patients, two of whom were healthy previously, were hospitalized in the intensive

care unit during the follow-up period because of ARDS (n=4), encephalopathy (n=2), and bronchiolitis (n=1). H1N1 was found positive in four of these patients. In addition, increased CRP and increased antibiotic use rates were found significantly more frequently in patients who were infected with H1N1.

In light of these findings, it can be stated that the clinical picture of H1N1 infection is more severe. It was observed that clearance of viral load was delayed and proinflammatory cytokines increased in the nasopharyngeal samples of patients who developed ARDS or died following H1N1 infection, but a correlation between viral load and disease severity has not been reported (29). Mortality is still high despite appropriate treatment in patients who develop ARDS (30). In our study, mortality occurred in two patients following H1N1-related ARDS.

In conclusion, influenza is characterized by various findings in childhood, and clinical differences may be observed between the subtypes. Awareness of these differences will prevent unnecessary investigations and antibiotic use by enabling better diagnosis of influenza cases, especially during the months when influenza infections are observed more frequently. Detection of influenza subtype will enable prediction of complications including ARDS and encephalopathy, which might have a fatal prognosis.

Ethics Committee Approval: Ethics committee approval was received for this study from İstanbul University School of Medicine Ethic Committee.

Informed Consent: Informed consent was not obtained due to retrospective nature of this study.

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References

1. American Academy of Pediatrics. Influenza. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, (eds). Red Book: 2015 Report of the Committee on Infectious Diseases. 30th ed. American Academy of Pediatrics. Elk Grove Village, IL 2015.p.476.
2. Xu J, Kochanek KD, Murphy SL, Tejada-Vera B. Deaths: Final Data for 2007. Natl Vital Stat Rep 2010; 58: 1-19.
3. Monto AS, Kioumehri F. The Tecumseh study of respiratory illness, IX: Occurrence of influenza in the community, 1966-1971. Am J Epidemiol 1975; 102: 553-63. [\[CrossRef\]](#)
4. Petric M, Comanor L, Petti CA. Role of the laboratory in diagnosis of influenza during seasonal epidemics and potential pandemics. J Infect Dis 2006; 194: S98-110. [\[CrossRef\]](#)
5. Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. J Infect Dis 2006; 194: S82-91. [\[CrossRef\]](#)
6. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289: 179-86. [\[CrossRef\]](#)
7. Çiftçi E, Tuygun N, Özdemir H, et al. Clinical and epidemiological features of Turkish children with 2009 pandemic influenza A (H1N1) infection: experience from multiple tertiary paediatric centres in Turkey. Scand J Infect Dis 2011; 43: 923-9 [\[CrossRef\]](#)
8. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004; 292: 1333-40. [\[CrossRef\]](#)
9. Daley AJ, Nallusamy R, Isaacs D. Comparison of influenza A and influenza B virus infection in hospitalized children. J Paediatr Child Health 2000; 36: 332-5. [\[CrossRef\]](#)
10. Hu JJ, Kao CL, Lee PI, et al. Clinical features of influenza A and B in children and association with myositis. J Microbiol Immunol Infect 2004; 37: 95-8.
11. Masahide K, Watanabe A, Aizawa H. Differences in clinical features between influenza A H1N1, A H3N2, and B in adult patients. Respirol 2003; 8: 231-3. [\[CrossRef\]](#)
12. Centers for Disease Control and Prevention (CDC). Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices-United States, 2013-2014. MMWR Recomm Rep 2013; 62: 1-4
13. Glezen WP, Taber LH, Frank AL, Gruber WC, Piedra PA. Influenza virus infections in infants. Pediatr Infect Dis J 1997; 16: 1065-8. [\[CrossRef\]](#)
14. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med 2006; 355: 31-40. [\[CrossRef\]](#)
15. Silvennoinen H, Peltola V, Lehtinen P, Vainionpää R, Heikkinen T. Clinical presentation of influenza in unselected children treated as outpatients. Pediatr Infect Dis J 2009; 28: 372-5. [\[CrossRef\]](#)
16. Minodier L, Charrel RN, Ceccaldi PE, et al. Prevalence of gastrointestinal symptoms in patients with influenza, clinical significance, and pathophysiology of human influenza viruses in faecal samples: what do we know? Virol J 2015; 12: 215. [\[CrossRef\]](#)
17. Lennon DR, Cherry JD, Morgenstein A, Champion JG, Bryson YJ. Longitudinal study of influenza B symptoma-

- tology and interferon production in children and college students. *Pediatr Infect Dis* 1983; 2: 212-5. [\[CrossRef\]](#)
18. Wiwanitkit V. Diarrhoea as a presentation of bird flu infection: a summary on its correlation to outcome in Thai cases. *Gut* 2005; 54: 1506. [\[CrossRef\]](#)
 19. Wang J, Li F, Wei H, Lian ZX, Sun R, Tian Z. Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation. *J Exp Med* 2014; 211: 2397-410. [\[CrossRef\]](#)
 20. Akturk H, Uysalol M, Salman N, et al. Benign acute childhood myositis associated with influenza: A cluster of cases from a single centre in the 2013-2014 cold season. *Hong Kong J Emerg Med* 2016; 23: 186-91.
 21. Newland JG, Laurich VM, Rosenquist AW, et al. Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. *J Pediatr* 2007; 150: 306-10. [\[CrossRef\]](#)
 22. Brocklebank JT, Court SD, McQuillin J, Gardner PS: Influenza-A infections in children. *Lancet* 1972; 2: 497-500. [\[CrossRef\]](#)
 23. Cao B, Li XW, Mao Y, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *N Engl J Med* 2009; 361: 2507-17. [\[CrossRef\]](#)
 24. Lewis DE, Gilbert BE, Knight V. Influenza virus infection induces functional alterations in peripheral blood lymphocytes. *J Immunol* 1986; 137: 3777-81.
 25. Sharon N, Talnir R, Lavid O, et al. Transient lymphopenia and neutropenia: pediatric influenza A/H1N1 infection in a primary hospital in Israel. *Isr Med Assoc J* 2011; 13: 408-12.
 26. Beutel G, Wiesner O, Eder M, et al. Virus-associated hemophagocytic syndrome as a major contributor to death in patients with 2009 influenza A (H1N1) infection. *Crit Care* 2011; 15: R80. [\[CrossRef\]](#)
 27. Glezen WP, Payne AA, Snyder DN, Downs TD. Mortality and influenza. *J Infect Dis* 1982; 146: 313-21. [\[CrossRef\]](#)
 28. Huang SS, Banner D, Fang Y, et al. Comparative analyses of pandemic H1N1 and seasonal H1N1, H3N2, and influenza B infections depict distinct clinical pictures in ferrets. *PLoS One* 2011; 6: e27512. [\[CrossRef\]](#)
 29. To KK, Hung IF, Li IW, et al. Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. *Clin Infect Dis* 2010; 50: 850-9. [\[CrossRef\]](#)
 30. Streng A, Prifert C, Weissbrich B, Liese JG; Bavarian PICU Study Group on Influenza and Other Viral ARI. Continued high incidence of children with severe influenza A(H1N1) pdm09 admitted to paediatric intensive care units in Germany during the first three post-pandemic influenza seasons, 2010/11–2012/13. *BMC Infect Dis* 2015; 15: 573. [\[CrossRef\]](#)