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Original Article

Clinical Manifestations of Influenza A and B in Children and Adults at a Tertiary Hospital in Korea during the 2011–2012 Season

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SUMMARY: This study aims to evaluate and compare the epidemiological patterns and clinical courses of influenza A and B among children and adults. For this purpose, we retrospectively reviewed the medical records of 809 children and 271 adolescents/adults with laboratory-confirmed influenza between October 2011 and May 2012 at a tertiary-care hospital. Children with influenza B presented with high fever (body temperature $>39°C$), sputum production, diarrhea, nausea/vomiting, and myalgia more frequently than those with influenza A. Children with influenza B also showed longer intervals from symptom onset to the initiation of antivirals and higher rates of antibiotic prescription and hospitalization than those with influenza A. Adults aged 20–59 years accounted for approximately 16% and 20% of patients with influenza A and B, respectively. Although clinical manifestations and outcomes were similar between adult patients with influenza A and those with influenza B, influenza B may cause substantial disease burden among not only children but also socially active adults aged 20–59 years.

INTRODUCTION

The annual epidemics of seasonal influenza can affect any age group and result in serious illness or death, particularly in high-risk populations such as adults ≥ 65 years old, children <2 years old, and those with chronic medical conditions at any age. These annual epidemics are estimated to result in 3–5 million cases of severe illness and approximately 250,000–500,000 deaths worldwide (1). Furthermore, influenza has a significant clinical and socioeconomic impact on otherwise healthy children and their household contacts (2).

Predominant clinical manifestations of influenza vary among different age groups. Children tend to present with nonspecific febrile illness such as gastroenteritis or febrile seizure, whereas adults present with typical febrile respiratory illness (3). In general, infection with influenza A virus is known to result in higher rates of hospitalization and mortality than infection with influenza B (4–6). However, further investigation is required to characterize the differences between influenza A and B infections in children and adults with respect to clinical manifestations and outcomes.

The impact of influenza varies from year to year and is dependent on the circulating strains and protective antibody levels in the population. Influenza A and B peaked during the 2011–2012 season; we therefore aimed to describe the epidemiological patterns, baseline characteristics, and clinical courses during this period among a population of children and adults with laboratory-confirmed influenza. In addition, children and adults were separately compared based on the type of influenza.

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PATIENTS AND METHODS

Study design and data collection: The medical records of children, adolescents, and adults diagnosed with laboratory-confirmed influenza between October 2011 and May 2012 were obtained from the outpatient and inpatient departments of the Korea University Guro Hospital and were retrospectively reviewed in the present study.

The Korea University Guro Hospital is a tertiary-care hospital with 1,050 beds and is located in Seoul, Republic of Korea. Selection of patients for testing of influenza was based on the clinical judgment of the clinician. In general, physicians tested for influenza when patients presented with sudden onset of fever of $\geq 37.8°C$ and at least one of the following respiratory symptoms: cough, sore throat, or rhinorrhea/nasal obstruction. Body temperature was the tympanic temperature recorded at presentation or at home in case of prior usage of antipyretics. Patients were defined as laboratory-confirmed influenza cases using multiplex reverse transcription-polymerase chain reaction (Seeplex® RV15 ACE Detection; Seegene, Seoul, Korea) and/or rapid antigen test (Humasis Influenza A/B Antigen Test; Humasis, Anyang, Korea) using nasal/throat swab specimens. Patient data collected included any epidemiological and demographic features, underlying medical conditions, clinical manifestations, radiographic findings, treatments, and/or clinical outcomes. This study was approved by the Korea University Guro Hospital Institutional Review Board (KUGH 13212-001).

Definitions: Children were defined as those aged <14 years and adolescents and adults as those aged ≥ 14 years. Complications were defined as confirmed in-

fluenza infection with organ dysfunction beyond the upper respiratory tract, such as the lower respiratory tract, brain, heart, kidney, and/or muscles. Pneumonia was defined as influenza with pulmonary infiltrates and fever, cough, or abnormal white blood cell count ($>11 \times 10^3$ or $<3 \times 10^3$ cells/μL) (7). Combined bacterial pneumonia was defined as pneumonia with productive cough, leukocytosis ($>15 \times 10^3$ cells/μL), elevated level of serum C-reactive protein (CRP; >60 mg/L), or detection of a bacterial pathogen. Diagnosis of combined bacterial pneumonia involved the identification of the bacterial pathogen using the following laboratory tests performed at some point during the course of influenza: Gram staining and cultures of respiratory tract specimens, blood cultures, urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae*, and acute- and convalescent-phase serological testing for *Mycoplasma pneumoniae*. Primary influenza pneumonia was defined as pneumonia in the absence of leukocytosis, elevated level of serum CRP, or documented bacterial pathogens (8). For hospitalized patients, white blood cell count and serum CRP level determined at the time of documentation of pneumonia were utilized. Febrile convulsion was defined as seizure associated with high fever in the absence of infections of the central nervous system or prior afebrile seizures among children aged >1 month (9). Acute bronchiolitis was diagnosed if wheezing was present along with respiratory symptoms after excluding asthma, chronic obstructive pulmonary disease, and pneumonia (7). Acute kidney injury was confirmed on a decrease in urine output to 0.5 mL/(kg·h) for a duration exceeding 12 h, development of azotemia, or requirement of hemodialysis (10). Influenza encephalitis was diagnosed in patients with laboratory-confirmed influenza on indications of lymphocytic pleocytosis in cerebrospinal fluid along with an altered level of consciousness and focal or diffuse neurological signs and symptoms. Rhabdomyolysis was diagnosed in the presence of the elevated level of serum creatine phosphokinase and myoglobinuria and the absence of myocardial or brain infarction (11).

Statistical analyses: Continuous variables were analyzed using the Student's *t*-test or Mann–Whitney U test, as appropriate. For categorical data, comparisons were performed using the chi-square or Fisher's exact tests. A P value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

RESULTS

Epidemiology and patient characteristics: A total 1,080 patients (809 children and 271 adolescents/adults) were diagnosed with influenza at the Korea University Guro Hospital during the study period. Influenza A was detected in 630 patients (58.3%; 477 children and 153 adults), and influenza B in 450 patients (41.6%; 332 children and 118 adults). The incidence of laboratory-confirmed influenza A increased rapidly among children from week 1 (January 1–7), followed by a rapid increase among adults the following week. Both groups showed a peak at week 4 (January 22–28), with 140 and 42 new cases of influenza A among children and adults, respectively. Following week 4, the incidence of influenza B showed a gradual increase among children at week 6 (February 5–11) and a peak at week 12 (March 18–24), with 62 laboratory-confirmed cases among children. Influenza B peaked 2 weeks later (week 14) among adults, with 21 new patients (Fig. 1).

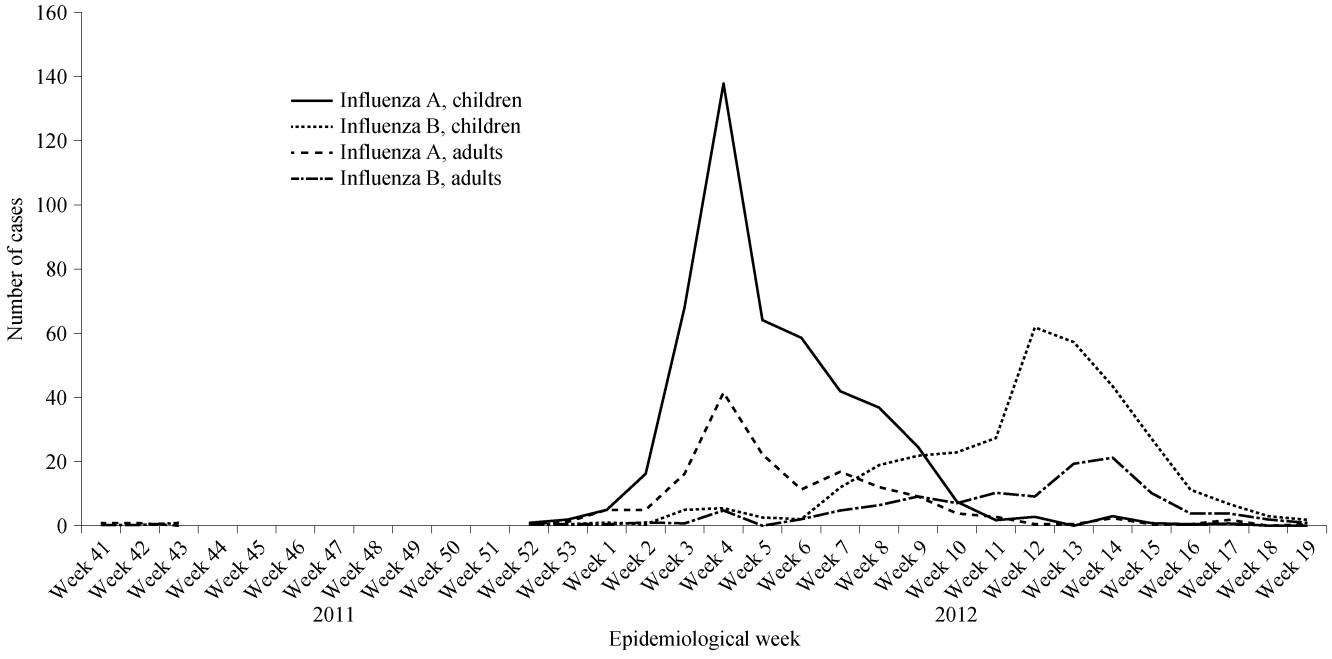

Fig. 1. Epidemiological curve of the incidence of new cases of influenza A and B infections at a tertiary-care hospital in Korea (2011–2012). The incidence of laboratory-confirmed influenza A increased rapidly from week 1 in children, followed by a rapid increase in adults the following week. After week 4, the incidence of influenza B began to increase gradually at week 6 among children and peaked at week 12. In adults, influenza B peaked 2 weeks later.

The frequency of influenza A was higher than that of influenza B among children aged ≤7 years and adults aged ≥20 years. On the other hand, the frequency of influenza B was slightly higher among school-age children of 8–19 years. Among children with influenza A and B, 11.1% (53/477) and 6% (20/332), respectively, were infants aged <1 year. Adults aged 20–59 years accounted for approximately 16% and 20% of patients with influenza A and B, respectively (Fig. 2). The characteristics of children and adult patients with laboratory-confirmed influenza are summarized in Table 1. Univariate analysis revealed that children with influenza A were younger (median age of 4 vs 5 years, $P < 0.01$) than those with influenza B. Significant differences were not observed in sex, rate of influenza vaccination, or prevalence of underlying medical conditions such as bronchial asthma between children with influenza A and those with influenza B. Adult patients with influenza A were

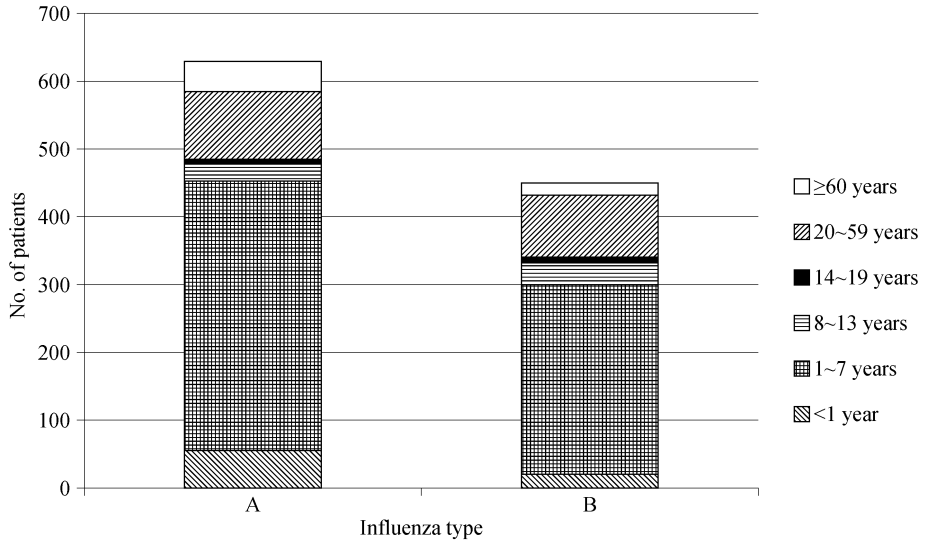

Fig. 2. Proportions of patients in each age group with influenza A or B. Adults aged between 20 and 59 years accounted for approximately 16% and 20% of the patients with influenza A and B, respectively.

Table 1. Baseline characteristics of the patients with laboratory-confirmed influenza A or influenza B

Children[1)]	Flu A (n = 477)	Flu B (n = 332)	P value
Median age in years (IQR)	3 (1.6–4)	4 (2.6–5)	<0.001
Male sex, no. (%)	257 (53.9)	168 (50.6)	0.359
Influenza vaccination received, no. (%)	32 (6.7)	23 (6.9)	0.903
Underlying condition, no. (%)[2)]	5 (1.0)	6 (1.8)	0.359
Bronchial asthma, no. (%)	2 (0.4)	3 (0.9)	0.406
Adolescents and Adults[3)]	**Flu A (n = 153)**	**Flu B (n = 118)**	**P value**
Median age in years (IQR)	42 (31–65)	34.5 (29–51)	0.002
Male sex, no. (%)	9 (38.6)	41 (34.7)	0.519
Current or former smoker, no. (%)[4)]	10 (10.3)	5 (7.9)	0.615
Influenza vaccination received, no. (%)[5)]	24 (32.9)	11 (22.0)	0.189
Underlying medical condition, no. (%)	55 (36.0)	31 (26.3)	0.089
Diabetes	2 (14.4)	7 (5.9)	0.026
Chronic pulmonary disease	17 (11.1)	10 (8.5)	0.472
Chronic cardiovascular disease	10 (6.5)	6 (5.1)	0.615
Neuromuscular disease	3 (2.0)	2 (1.7)	>0.999
Malignancy	9 (5.9)	4 (3.4)	0.402
Pregnancy	7 (4.6)		0.617

[1)]: Children (<14 years of age).
[2)]: Epilepsy (n = 3), intracranial hemorrhage (n = 1), pulmonary tuberculosis (n = 1), meningioma (n = 1), congenital hydronephrosis (n = 1).
[3)]: Adolescents and adults (≥14 years of age).
[4)]: The history of smoking was available in 97 patients with influenza A and 63 patients with influenza B.
[5)]: The vaccination history was identified in 73 adult patients with influenza A and 50 patients with influenza B.

older (median age of 42 vs 34.5 years, $P = 0.002$) and showed a higher frequency of diabetes (14.4% vs 5.9%, $P = 0.026$) than those with influenza B. Other characteristics such as sex, smoking history, rate of influenza vaccination, and prevalence of underlying medical conditions (except diabetes) were not significantly different between adult patients with influenza A and those with influenza B.

Clinical manifestations and radiographic findings: The signs and symptoms at presentation of all patients with influenza A and B are summarized in Table 2. Univariate analysis revealed that children with influenza B experienced fever and respiratory or other symptoms for a longer duration prior to receiving medical attention than those experienced by children with influenza A (mean ± SD, 3.0 ± 2.6 vs 3.6 ± 2.7 days, $P = 0.001$). Symptoms such as high fever of >39°C (35.4% vs 44.0%, $P = 0.014$), sputum production (42.1% vs 50.3%, $P = 0.022$), diarrhea (6.3% vs 10.8%, $P = 0.020$), nausea/vomiting (21.0% vs 27.1%, $P = 0.043$), and myalgia (1.5% vs 5.2%, $P = 0.017$) occurred more frequently among children with influenza B than among those with influenza A. In contrast, significant differences in any symptoms or signs were not observed between the adult patients with influenza A and those with influenza B. In addition, the interval from symptom onset to medical attention was not significantly different between adults with influenza A and those with influenza B (mean ± SD, 3.8 ± 5.4 vs 4.3 ± 5.9 days, $P = 0.540$).

Treatments and clinical outcomes: Statistically significant differences were not observed in the prescription rates of antiviral agents among children (96.9% vs 94.3%, $P = 0.072$) and among adults (93.5% vs 89.8%, $P = 0.278$) with influenza A and influenza B; however, children with influenza B showed longer intervals from symptom onset to the initiation of antivirals (mean ± SD, 2.7 ± 2.7 vs 3.3 ± 2.8 days, $P = 0.002$) and higher antibiotic prescription rates (6.9% vs 11.8%, $P = 0.018$) than children with influenza A. In contrast, significant differences were not observed with respect to the interval from symptom onset to antiviral treatment and antibiotic prescription rates between the adult patients with influenza A and those with influenza B. The rate of hospitalization was significantly higher among children with influenza B than among those with influenza A (4.6% vs 9.0%, $P = 0.011$) but not among adult patients (17.7% vs 11.0%, $P = 0.127$). The dura-

Table 2. Comparison of clinical manifestations and radiographic findings of patients with laboratory-confirmed influenza A and B

	Children[1] (n = 809)			Adolescents and Adults[2] (n = 271)		
	Flu A (n = 477)	Flu B (n = 332)	P value	Flu A (n = 153)	Flu B (n = 118)	P value
Time from illness onset to hospital visit, days (mean ± SD)	3.0 ± 2.6	3.6 ± 2.7	0.001	3.8 ± 5.4	4.3 ± 5.9	0.540
Complaints, no. (%)						
Chills[3]	88 (32.4)	80 (34.8)	0.565	84 (54.9)	71 (60.2)	0.385
Cough	379 (79.5)	265 (79.8)	0.899	135 (88.2)	99 (83.9)	0.303
Sputum	201 (42.1)	167 (50.3)	0.022	97 (63.4)	76 (64.4)	0.864
Sore throat[3]	130 (47.8)	116 (50.4)	0.555	83 (54.3)	67 (56.8)	0.678
Rhinorrhea	328 (68.8)	229 (68.9)	0.949	95 (62.1)	76 (64.4)	0.695
Pleuritic chest pain[3]	1 (0.4)	3 (1.3)	0.240	14 (9.2)	12 (10.2)	0.778
Nausea/vomiting	100 (21.0)	90 (27.1)	0.043	27 (17.7)	25 (21.2)	0.463
Diarrhea	30 (6.3)	36 (10.8)	0.020	6 (3.9)	10 (8.5)	0.115
Abdominal pain[3]	41 (15.1)	36 (15.7)	0.858	11 (7.2)	14 (11.9)	0.187
Headache[3]	22 (8.1)	17 (7.4)	0.771	53 (34.6)	45 (38.1)	0.553
Myalgia[3]	4 (1.5)	12 (5.2)	0.017	68 (44.4)	44 (37.3)	0.236
Clinical findings, no. (%)						
Fever (>39°C)	169 (35.4)	146 (44.0)	0.014	25 (16.3)	23 (19.5)	0.500
Tachypnea	9 (1.9)	10 (3.0)	0.299	25 (16.3)	10 (8.5)	0.056
Crackle	34 (7.1)	16 (4.8)	0.180	16 (10.5)	11 (9.3)	0.757
Wheezing	0 (0.0)	2 (0.6)	0.168	4 (2.6)	5 (4.2)	0.460
Radiographic findings, no. (%)						
Chest X ray examined	224 (47.0)	109 (32.8)	<0.001	100 (65.4)	79 (67.0)	0.784
Presence of pneumonia	9 (1.9)	4 (1.2)	0.448	22 (14.4)	9 (7.6)	0.083
Location of infiltration						
Unilateral	8 (88.9)	3 (75.0)	>0.999	14 (63.6)	5 (55.6)	0.704
Bilateral	1 (11.1)	1 (25.0)		8 (36.4)	4 (44.4)	
Patterns of infiltration						
Interstitial	1 (11.1)	0 (0.0)	0.719	3 (13.6)	1 (11.1)	0.801
Lobar	5 (55.6)	2 (50.0)		12 (54.6)	4 (44.4)	
Patch	3 (33.3)	2 (50.0)		7 (31.8)	4 (44.4)	
Pleural effusion	1 (0.2)	1 (0.3)	>0.999	5 (3.3)	4 (3.4)	>0.999

[1]: Children (<14 years of age).
[2]: Adolescents and adults (≥14 years of age).
[3]: These symptoms were assessed only in children ≥3 years of age (272 children with influenza A and 230 children with influenza B).

tion of hospitalization in children and adult patients were similar irrespective of the influenza type. Influenza-related complications occurred in 43 and 27 children with influenza A (9.0%) and B (8.1%; $P = 0.661$), respectively. Febrile seizure was the most common complication among afflicted children, with incidence rates of 6.5% (31/477) and 6.3% (21/332) among children with influenza A and B, respectively ($P = 0.921$). Status epilepticus was observed in a single child with influenza A. Pneumonia occurred in 1.9% (9/477) and 1.2% (4/332) of children with influenza A and B, respectively ($P = 0.448$). Complications occurred in 17% (26/153) and 9.3% of afflicted adults with influenza A and B, respectively ($P = 0.068$). The most common complication among adults with influenza was pneumonia, which was observed in 14.4% (22/153) and 7.6% (9/118) of individuals with influenza A and B, respectively ($P = 0.083$) (Table 3). Viral pneumonia was diagnosed in 50% (6/12) of children aged <7 years presenting with influenza and pneumonia. In contrast, 75% (12/16) of adults aged ≥60 years presenting with pneumonia were suspected to have contracted bacterial pneumonia (Fig. 3). No children with influenza A or B required mechanical ventilation or experienced shock, and no fatalities developed. Among adults, 4 patients with influenza A (2.6%) and 2 with influenza B (1.7%) required mechanical ventilation, and 1 patient from each group experienced a shock event. A 75-year-old male patient with gastric cancer died of encephalitis and acute kidney injury associated with influenza A infection. Moreover, a 42-year-old male patient with influenza B died of progressive pneumonia and heart failure; the patient was in neutropenic state due to chemotherapy for nasopharyngeal cancer.

Table 3. Treatments and clinical outcomes of patients with laboratory-confirmed influenza A or influenza B

	Children[1] (n = 809)			Adolescents and Adults[2] (n = 271)		
	Flu A (n = 477)	Flu B (n = 332)	P value	Flu A (n = 153)	Flu B (n = 118)	P value
Treatment						
Antiviral treatment	462 (96.9)	313 (94.3)	0.072	143 (93.5)	106 (89.8)	0.278
Time from illness onset to initiation of antivirals days (mean ± SD)	2.7 ± 2.7	3.3 ± 2.8	0.002	3.4 ± 5.4	4.0 ± 6.3	0.417
Antibiotic treatment	33 (6.9)	39 (11.8)	0.018	40 (26.1)	33 (28.0)	0.737
Clinical outcomes hospital admission	22 (4.6)	30 (9.0)	0.011	27 (17.7)	13 (11.0)	0.127
Length of hospital stay, days (mean ± SD)	5.3 ± 1.8	6.3 ± 2.8	0.124	8.1 ± 4.4	10.9 ± 7.6	0.230
Mechanical ventilation	0	0		4 (2.6)	2 (1.7)	0.699
Shock	0	0		1 (0.7)	1 (0.9)	>0.999
Any complication	43 (9.0)	27 (8.1)	0.661	26 (17.0)	11 (9.3)	0.068
Febrile convulsion	31 (6.5)	21 (6.3)	0.921	0	0	
Pneumonia	9 (1.9)	4 (1.2)	0.448	22 (14.4)	9 (7.6)	0.083
Others[3]	2	0		4	2	
Mortality	0	0		1 (0.7)	1 (0.9)	>0.999

[1]: Children (<14 years of age).
[2]: Adolescents and adults (≥14 years of age).
[3]: Acute bronchiolitis (n = 2) for the children with influenza A; syncope (n = 2), acute kidney injury (n = 2), encephalitis (n = 1), and rhabdomyolysis (n = 1) for adults with influenza A; syncope (n = 1) and heart failure (n = 1) for adults with influenza B.

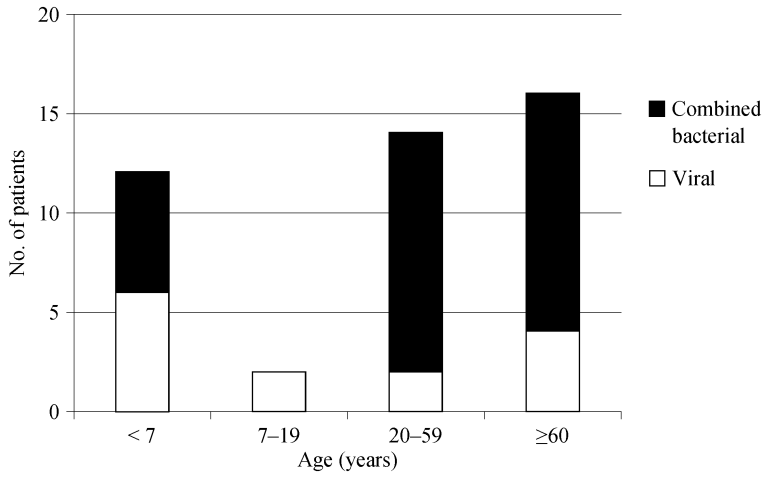

Fig. 3. Number of patients with viral and combined bacterial pneumonia by age group. Fifty percent of children <7 years old with influenza and pneumonia were classified as having viral pneumonia. However, 75% of adults ≥60 years old with pneumonia were thought to have bacterial pneumonia.

DISCUSSION

The epidemiological patterns of influenza A and B observed among children and adults in the present study were consistent with the findings reported by the Korea Centers for Disease Control and Prevention (KCDC) in the Influenza Sentinel Surveillance Report. According to the report by KCDC, influenza A peaked from December 18, 2011 to March 3, 2012, and subsequently influenza B peaked from February 12, 2012 to April 28, 2012. Both the influenza types showed similar activity, and most influenza A infections were attributable to the H3N2 subtype during the 2011–2012 influenza season (12). The present study revealed that the influenza epidemic among children preceded that among adults by an interval of approximately 1 or 2 weeks. This finding supports the hypothesis that children serve as the primary disseminators of influenza among adults and are in agreement with the findings of other studies. Viral shedding is known to persist for a longer duration and with higher titers among children than among adults (13). Principi et al. reported that parents and siblings of influenza-positive children had more respiratory illnesses and required greater medical attention (2). In addition, Reichert et al. showed that the immunization of school-age children against influenza decreased influenza-associated morbidity and mortality among the adult population, suggesting that herd immunity among school children exerts a protective effect, particularly among the elderly (14).

Two previous studies reported that children with influenza B were more likely to present with myalgia or myositis (15,16). In the present analysis, children with influenza B showed a tendency to present with high fever (body temperature $>39°C$, sputum production, diarrhea, nausea/vomiting, and myalgia more frequently than children with influenza A. The rate of hospitalization was also higher among children with influenza B, but the incidence of pneumonia was similar. Among adults, clinical manifestations and outcomes between patients with influenza B and those with A were indistinguishable. The rates of pneumonia and mortality were also similar between adult patients with influenza A and those with B, which is consistent with previous studies (17,18). Gutiérrez-Pizarraya et al. also reported that the rate of pneumonia, admission to the intensive care unit, and mortality were not different between patients with influenza A (H1N1) pdm09 and those with influenza B (19). A previous study suggested that concomitant bacterial pneumonia and myocardial injury contributed to fatal outcomes following influenza B infection (20). Of note, adults aged 20–59 years accounted for 20% of patients with influenza B in the present study, and influenza B infection was not less serious than influenza A infection in this age group. Therefore, influenza B possibly causes substantial burden not only among children but also among the socially active young adults. This is important because influenza epidemics result in substantial workplace absenteeism and reduced productivity. Previous studies reported that mean workplace absenteeism per episode of influenza ranged from 2.8 to 4.9 days (21). Another study that subjectively assessed the performance of individual employees showed that employees returning to work postinfection believed that their work efficiency was only 46% of the maximum (22).

According to the ''Influenza Sentinel Surveillance Report'' by KCDC, the vaccine strain employed during the 2011–2012 season afforded protection against the B/Victoria lineage; however, more than 30% of the circulating influenza B viruses in the Republics of Korea were of the B/Yamagata lineage (12). In the United States, the seasonal trivalent influenza vaccine was matched for the circulating influenza B lineages in only 5 influenza seasons during the period 2001–2010 (23). The cross-protection afforded by immunization with the trivalent influenza vaccine against B strains of the opposite lineage is limited in children (24). A phase-III, randomized, double-blind study showed that compared with the trivalent vaccine, a quadrivalent influenza vaccine provided superior immunogenicity in children aged 3–17 years against alternate-lineage B strains (25). The findings of the present study highlight the need for enhanced protection against both lineages of the influenza B virus through the use of a quadrivalent influenza vaccine, at least in children and young adults.

The present study showed that febrile seizure was the most common complication associated with both influenza A (6.5%) and B (6.3%) infections among children, with statistically significant differences not observed between 2 influenza types. In contrast, several studies reported that influenza A infections were associated with higher incidence of febrile seizures than influenza B infections (9,26,27). A study by Lin et al. reported that 12% of hospitalized children with influenza B infection during the period 2001–2003 presented with neurological manifestations (28). Similarly, Moon et al. reported that febrile seizures occurred in 5.3% (19/355) of hospitalized children with influenza B infection during the 2011–2012 season (29).

The present study has several limitations. Because it is a retrospective study, there is an absence of standardized criteria for the prescription of antivirals or recommendation of hospitalization. Underestimation of the underlying medical conditions is possible owing to limited medical records. In addition, the small number of severe cases, such as patients who required mechanical ventilation, experienced shock, or mortality, is likely to limit the extent of differences detected between the various types of influenza virus. Moreover, vaccine effectiveness was low during the 2011–2012 season; therefore, the clinical outcomes are likely to be different from those of seasons with high vaccine effectiveness (30,31).

The significance of influenza B infections tend to be underestimated, whereas influenza A is considered to represent the main public health burden. The results of the present study demonstrate that clinical manifestations and course of infection were not less serious in adults with influenza B than in those with influenza A; yet, influenza B appeared to be more virulent among children. Thus, influenza B may cause substantial disease burden not only among children but also among socially active young adults. In addition, the use of a quadrivalent influenza vaccine that affords protection against both lineages of the influenza B virus should be considered, particularly among children.

Conflict of interest None to declare.

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