COMPARISONS OF THE CLINICAL FEATURES AND OUTCOMES OF CHILDREN PRESENTING WITH INFLUENZA-LIKE ILLNESSES, INCLUDING A(H1N1) PDM09 AND SEASONAL INFLUENZA, IN A UNIVERSITY HOSPITAL, THAILAND

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Abstract. In Thailand, during the A(H1N1)pdm2009 pandemic, 82% of fatal cases did not received the specific treatment within 48 hours of the onset of symptoms. Specific diagnostic tests, especially RT-PCR, were not available throughout the country. To assist early clinical diagnosis and treatment, this study compared the clinical features and treatment outcomes of children presenting with influenza-like illness (ILIs). These included confirmed cases of A(H1N1)pdm2009, as well as seasonal influenza and cases for which no cause could be specified**.** The medical records of patients aged less than 15 years with ILIs, who had RT-PCR performed for influenza virus between May 2009 and December 2011 at Srinagarind Hospital, were reviewed. Clinical features, chest radiographs and treatment outcomes were compared between those positive for A(H1N1)pdm2009, and those with seasonal influenza and/or the unspecified causes group. In 179 complete medical records, 27.4% were positive for A(H1N1)pdm2009, 13.4% for seasonal influenza and the cause of illness in the remainder was unspecified. Both A(H1N1)pdm2009 and seasonal influenza viruses infected older children more than did the unspecified group (group median ages 96, 48 and 24 months, respectively). Sore throat, headache and myalgia were significantly more frequent in the A(H1N1)pdm2009 group than in the other two groups (p <0.001). Half of all children had pneumonia but there were no significant differences among groups. There was no mortality in this study. In conclusion, sore throat, headache and myalgia were the significant clinical features suggestive of A(H1N1)pdm2009 infection in children and might be helpful indicators prompting early administration of specific treatments in the settings where definitive laboratory tests are not available.

Keywords: influenza-like illness, A(H1N1)pdm2009, seasonal influenza, Thailand

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INTRODUCTION

Before the World Health Organization (WHO) announced the emergence of an H1N1 2009 influenza [A(H1N1)pdm09] pandemic to the highest level of 6 in June

2009 (Chan, 2009; WHO, 2009a), Thailand was affected and the first two imported cases of A(H1N1)pdm09 were detected on May 12, 2009 (Ungchusak *et al*, 2012). National surveillance data indicate that Thailand had three waves of this infection between May 2009 and December 2010, during which a total of 234,050 suspected cases were reported. Of these, 47,433 cases were laboratory-confirmed to be due to A(H1N1)pdm09. There were 347 deaths (Ungshusak *et al*, 2012). Worldwide, young children and adolescents experienced the highest rates of infection (Bautista *et al*, 2010).

The clinical features of A(H1N1) pdm09 infection were reported to be similar to those of seasonal influenza, but most of these reports concerned adult patients (O'Riordan *et al*, 2010; Ahmed *et al* 2011; Al-Mahrezi *et al*, 2012 ;Yang *et al*, 2012). Fatalities were significantly greater in high risk patients such as those with obesity, asthma, an immunocompromised state and pregnancy (Bautista *et al*, 2010). In 49% of fatal cases reported from Thailand, however, the patients did not belong to any high-risk group. Specific therapy was initiated within 48 hours of the onset of symptoms in only 18% of fatal cases (Bunthi *et al*, 2013).

During the pandemic period, clinical practice guidelines were rapidly implemented in all health care centers across Thailand. A real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay was adopted to be the standard for laboratory diagnosis. This specific test was available only in large health-care centers, however, thus leading to delays in diagnosis for the majority of patients. Consequently, the Ministry of Public Health of Thailand (MOPH) rescinded the initial policy and recommended that suspected A(H1N1)pdm09 patients should be treated immediately on the basis of clinical presentations rather than waiting for laboratory findings (Ungchusak *et al*, 2012).

Studies of this novel influenza in children in Thailand are few, particularly in the comparison of clinical features between the A(H1N1)pdm09 serotype and other influenza-like infections. Therefore, this study was conducted to seek clinical and demographic features that might be useful in distinguishing influenza from other influenza-like illnesses (ILIs) in children as an aid to early diagnosis and treatment and hence improved outsomes.

MATERIALS AND METHODS

A retrospective analysis of the clinical data from the medical records of children who presented with influenza-like illness at Srinagarind Hospital, Khon Kaen University, Thailand from May 2009 to December 2011 was conducted. Inclusion criteria were children aged less than 15 years from whom nasopharyngeal swabs for A(H1N1)pdm09 and other influenza viruses had been tested using RT-PCR. Children who later had final diagnoses other than respiratory infections and had incomplete medical record data were excluded. Children with influenza-like illness (ILIs) were defined as those who presented with fevers more than 38°C and had a cough or a sore throat and might include runny nose, myalgia, vomiting and diarrhea. The demographic data, clinical features, chest radiological findings and clinical outcomes were reviewed and compared among groups of children positive by RT-PCR for A(H1N1)pdm09, positive for seasonal influenza, and a group for whom RT-PCR could not specify a cause for the ILI. The real time RT-PCR assays were performed at the laboratory accord-

ing to the protocol recommended by the US-CDC protocol for real time RT-PCR for swine influenza A (H1N1) (WHO, 2009b).

All statistical analyses were performed using the STATA statistical software version 12.0 (Stata Corp, College Station, TX). The Bonferroni adjustment test was used for multiple comparisons among patient groups. A $p<0.05$ was accepted as statistically significant. This study was approved by the Khon Kaen University Ethics Committee for Human Research (Number: HE 551193).

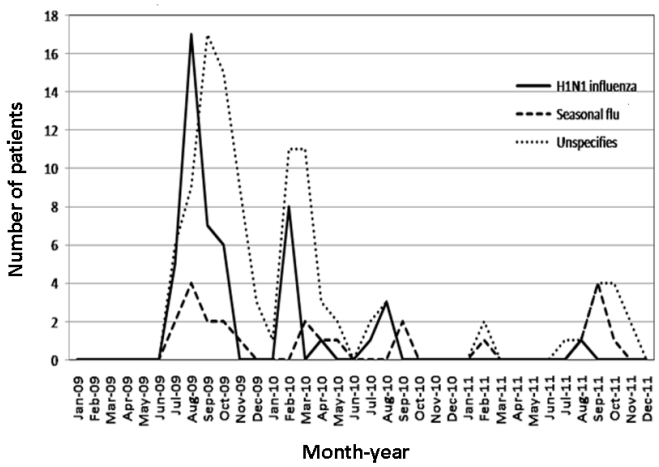

Fig 1–Numbers of H1N1 2009, seasonal influenza and unspecified groups during the study period.

RESULTS

Nasopharyngeal swabs from 451 children with ILIs were analyzed using RT-PCR. Two hundred and seventy-two children were subsequently excluded due to incomplete medical record data and incompatible clinical symptoms and diagnoses. A total of 179 children (median age 36 months: range 6-168 months) were included for the review. Of these, 106 (59.2%) were males. RT-PCR was positive for A(H1N1)pdm09 in 49 children (27.4%) and for seasonal influenza in 24 children (13.4%). RT-PCR did not indicate a diagnosis for the remaining 106 cases (the unspecified group).

Children in the unspecified group were significantly younger with a median age of 24 months compared with 96 and 48 months in the A(H1N1)pdm09 and seasonal influenza groups ($p<0.001$). One hundred and fourteen children (63.7%) had no underlying disease while asthma was the only significant preexisting condition in the A(H1N1)pdm09 group when compared with the other two groups ($p=0.047$). The history of household contact of A(H1N1)pdm09 was only 24.5% in this group but significantly higher than the other two groups ($p=0.007$) (Table 1).

During the two years of the study period, the prevalence of all ILIs peaked during the rainy (June-October) and winter seasons (January-March). Numbers of patients were 3-4 fold greater in the year of the A(H1N1)pdm09 pandemic than in the second year of the review (Fig 1).

All children presented with high grade fever and had mean body temperatures of 38.8°C, (SD 0.9), with no significant differences among groups (Table 2). Among ILI symptoms, 95.5% had cough and 79.9% rhinorrhea. These were the common presenting symptoms in all children and no significant differences existed among groups. Respiratory distress was found in 24.6%,with no significant differences among groups, however, the children in the unspecified group had significantly faster respiratory rates with a median of 32 time per minute, range 20-80, $p=0.0027$. Although sore throat was a complaint in only 27.4% of all children, it was found to be significantly higher in the A(H1N1)pdm09 group than in the

Table 1
Demographic data, preexisting conditions and history of H1N1 contact (N=179).

Demographic data	Total n=179	H1N1 influenza n=49	Seasonal influenza n=24	Unspecified group n=106	p-value		
					Three groups	H1N1 and seasonal influenza	H1N1 and unspecified group
Male, no. (%)	106 (59.2)	26 (53.1)	14 (58.3)	66 (62.3)	0.553	>0.999	0.556
Age, months							
Median, range	36 (0.5-168)	96 (2-171)	48 (2-169)	24 (0.5-168)	<0.001	0.257	<0.001
Mean, SD	58 (54.2)	89.6 (56.7)	67.5 (56.4)	41.9 (45.4)	<0.001	0.115	<0.001
Body weight, kg (median, range)	13.5 (2.7-74)	24.5 (3.2-70)	14.5 (4.9-59)	11.3 (2.7-74)	<0.001	0.132	<0.001
Weight for age > P90th, no. (%)	32 (17.9)	10 (20.4)	2 (8.3)	20 (18.9)	0.412	0.412	>0.999
Preexisting conditions, no. (%)							
No underlying disease	114 (63.7)	30 (61.2)	13 (54.2)	71 (67)	0.457	>0.999	0.97
Asthma	19 (10.6)	9 (18.4)	0 (0)	10 (9.4)	0.047	0.05	0.23
Allergic rhinitis	3 (1.7)	2 (4.1)	0 (0)	1 (0.9)	0.363	0.632	0.374
Bronchopulmonary dysplasia	5 (2.8)	2 (4.1)	0 (0)	3 (2.8)	0.832	0.632	>0.999
Cardiac diseases	6 (3.4)	0 (0)	0 (0)	6 (5.7)	0.167	-	-
Malignancies	14 (7.8)	0 (0)	6 (25)	8 (7.5)	0.001	<0.001	0.096
Others	23 (12.8)	8 (16.3)	4 (16.7)	11 (10.4)	-	-	-
History of H1N1 contact, no. (%)	22 (12.3)	12 (24.5)	3 (12.5)	7 (6.6)	0.007	0.484	0.006

Table 2
Clinical manifestations.

Clinical manifestations	Total *n*=179	H1N1 influenza *n*=49	Seasonal influenza *n*=24	Unspecified group *n*=106	*p*-value		
					Three groups	H1N1 and seasonal influenza	H1N1 and unspecified group
Body temperature, °C							
Mean (SD)	38.8 (0.9)	38.8 (0.9)	38.7 (0.9)	38.8 (1)	0.8143	>0.999	>0.999
Onset of symptoms, days							
Median (range)	3 (1-21)	2 (1-21)	4 (1-9)	3 (1-14)	0.0094	0.019	0.075
Respiratory symptoms							
Respiratory rate, tpm							
Median (range)	30 (20-80)	28 (20-77)	28 (20-72)	32 (20-80)	0.0027	0.488	0.0018
Respiratory distress, no. (%)	44 (24.6)	11 (22.4)	5 (20.8)	28 (26.4)	0.781	>0.999	>0.999
Desaturation, no. (%)	9 (5)	1 (2)	2 (8.3)	6 (5.7)	0.374	0.478	0.668
Sore throat, no. (%)	49 (27.4)	25 (51)	3 (12.5)	21 (19.8)	<0.001	0.006	<0.001
Cough, no. (%)	171 (95.5)	48 (97.9)	24 (100)	99 (93.4)	0.231	>0.999	0.518
Rhinorrhea, no. (%)	143 (79.9)	34 (69.4)	19 (79.2)	90 (84.9)	0.081	0.764	0.054
Gastrointestinal symptoms, no. (%)							
Nausea, vomiting	51 (28.5)	11 (22.4)	7 (29.2)	33 (31.1)	0.536	>0.999	0.534
Diarrhea	44 (24.6)	8 (16.3)	6 (25)	30 (28.3)	0.273	0.76	0.222
Abdominal pain	2 (1.1)	0 (0)	0 (0)	2 (1.9)	>0.999	>0.999	>0.999
Dehydration	98 (54.7)	21 (42.9)	13 (54.2)	64 (60.4)	0.125	0.728	0.086
Systemic symptoms, no. (%)							
Headache	21 (11.7)	14 (28.6)	0 (0)	7 (6.6)	<0.001	>0.999	0.002
Myalgia	21 (11.7)	14 (28.6)	3 (12.5)	4 (3.8)	<0.001	0.276	<0.001
Drowsy	38 (21.2)	12 (24.5)	4 (16.7)	22 (20.8)	0.732	0.9	>0.9

Table 3
Chest x-ray findings of the study populations.

Chest x-ray findings	Total *n*=149	H1N1 influenza *n*=43	Seasonal influenza *n*=18	Unspecified group *n*=88	*p*-value		
					Three groups	H1N1 and seasonal influenza	H1N1 and unspecified group
Normal, no. (%)	55 (30.7)	19 (38.8)	9 (37.5)	27 (25.5)	0.187	0.188	>0.999
Interstitial infiltration, no. (%)	75 (41.9)	15 (30.6)	7 (29.2)	53 (50)	0.028	0.05	>0.999
Patchy infiltration, no. (%)	17 (9.5)	7 (14.3)	2 (8.3)	8 (7.5)	0.435	0.388	0.946
Pleural effusion, no. (%)	2 (1.1)	2 (4.1)	0 (0)	0 (0)	0.165	>0.999	>0.999

other two groups ($p < 0.001$). Association of gastrointestinal and systemic symptoms was present in low prevalence in all groups. In the latter class of symptoms, headache and myalgia were significantly more frequent complaints in the A(H1N1) pdm09 group compared with the other two groups ($p < 0.001$). The A(H1N1) pdm09 group presented to the hospital earlier than the other two groups with the median time after onset of symptoms of two days (range 1-21, p=0.0094) (Table 2).

Chest x-rays were performed in 149 cases (83.2%) which showed abnormal findings in 94 cases (69.2%). Interstitial infiltration was the most common radiographic finding in 75 cases, or 41.9%, and was significantly higher in the unspecified group as compared with the other two groups (p=0.028) (Table 3).

For the treatment and clinical outcomes, the A(H1N1)pdm09 cases had less severe clinical manifestations and fewer required hospitalization than in the other two groups (61.2% *vs* 91.6% *vs* 78.3%; p=0.0084) (Table 4). Respiratory failure requiring mechanical ventilation was required in 7 cases (3.9%); 2 in the A(H1N1)pdm09 group and 5 in the unspecified group. There was no significant difference among groups in terms of the need for mechanical ventilation, oxygen therapy or the prescription of antibiotics. Pneumonia was the most common complication found in 92 cases (51.4%), however, there were no statistically significant differences between all the recorded complications among groups and no mortality in this study (Table 4).

DISCUSSION

This study showed that influenza, both A(H1N1)pdm09 and seasonal viruses, infected older children significantly

Table 4
Clinical outcomes and complications of the study populations.

Outcomes	Total *n*=179	H1N1 influenza *n*=49	Seasonal influenza *n*=24	Unspecified group *n*=106	*p*-value		
					Three groups	H1N1 and seasonal influenza	H1N1 and unspecified group
Admission, no. (%)	135 (75.4)	30 (61.2)	22 (91.6)	83 (78.3)	0.008	0.03	0.056
Length of admission, days median (range)	3 (1-30)	3 (1-23)	3.5 (1-30)	3 (1-13)	0.938	>0.999	>0.999
Mechanical ventilation, no. (%)	7 (3.9)	2 (4.1)	0 (0)	5 (4.7)	0.865	>0.999	>0.999
Oxygen therapy, no. (%)	14 (7.8)	3 (6.1)	2 (8.3)	9 (8.5)	0.925	>0.999	>0.999
Oseltamivir usage, no. (%)	134 (74.8)	42 (85.7)	20 (83.3)	72 (67.9)	0.035	>0.999	0.046
Antibiotic usage, no. (%)	73 (40.8)	19 (38.8)	14 (58.3)	40 (37.7)	0.169	0.236	>0.999
Complications, no. (%)							
None	71 (39.7)	22 (44.9)	9 (37.5)	40 (37.7)	0.688	>0.999	0.796
Pneumonia	92 (51.4)	24 (49)	9 (37.5)	59 (55.7)	0.257	0.712	0.878
Bacterial co-infection	3 (1.7)	1 (2)	1 (4.2)	1 (0.9)	0.363	>0.999	>0.999
ARDS	1 (0.6)	0 (0)	1 (4.2)	0 (0)	0.134	0.22	0.658
Bronchitis	3 (1.7)	1 (2)	0 (0)	2 (1.9)	>0.999	>0.999	>0.999
Sinusitis	1 (0.6)	0 (0)	1 (4.2)	0 (0)	0.134	0.5	0.658
Otitis media	1 (0.6)	0 (0)	1 (4.2)	0 (0)	0.134	0.5	0.658
Sepsis, DIC	1 (0.6)	0 (0)	0 (0)	1 (0.9)	>0.999	>0.999	>0.999
Seizure	1 (0.6)	1 (2)	0 (0)	0 (0)	0.408	0.632	>0.999
Croup	3 (1.7)	1 (2)	0 (0)	2 (1.9)	>0.999	>0.999	>0.999
Others	9 (5)	2 (4.1)	4 (16.7)	3 (2.8)	0.028	>0.999	0.176

more frequently than unspecified respiratory infections (medians of four and two years, respectively). Among the influenza-like symptoms; sore throat, headache and myalgia were the significant presenting symptoms in A(H1N1)pdm09 cases compared with other causes. Pneumonia was the most common complication found in about half of all children presenting with ILI, but there were no significant differences between the three groups.

In the recent years, the clinical features of A(H1N1)pdm09 have been reported from around the world with a wide variety of manifestations ranging from mild upper respiratory infection to fulminant pneumonia or ARDS which can lead to death. Children and young adults were reported to have the highest attack rate (Bautista *et al*, 2010). The epidemic data in this study showed a similar pattern to previous epidemiological studies from Thailand in that most respiratory pathogens, *ie*, RSV, rhinovirus, infect children at a peak in rainy and winter seasons (Sunakorn *et al*, 1990; Suwanjutha *et al*, 1990; Teeratakulpisarn *et al*, 2007). This obliges pediatricians or physicians to differentiate the causative organisms before prescribing specific treatments to prevent overuse. This study found similar results to those previous reports from Thailand in that influenza, especially A(H1N1)pdm09, infected older children and that unspecified causes were more commonly responsible for infection in younger children (Bumpenkiatikul *et al*, 2012; Udompornwattana *et al*, 2012). These unspecified causative pathogens might be RSV, rhinovirus or other respiratory viruses common in young children. Unfortunately, it was a limitation of this study that the confirmatory tests were not routinely available during the study period.

With regard to clinical manifestations, this study found that sore throat, headache and myalgia were significant helpful complaints to increase the suspicion of A(H1N1)pdm09 infection. These findings are similar to those previously reported both from pediatric and adult patients (Ahmed *et al*, 2011; Al-Mahrezi *et al*, 2012; Bumpenkiatigul *et al*, 2012). Gastrointestinal symptoms such as diarrhea were also reported to be significant complaints in adult patients (Ahmed *et al*, 2011; Al-Mahrezi *et al*, 2012). In contrast, in these pediatric patients, GI symptoms were not shown to be helpful because they were the common manifestations of most respiratory infections. Sixteen percent of the A(H1N1)pdm09 group in this study had diarrhea and it was not significantly different as compared with the other respiratory infections. Nevertheless, the history of H1N1 exposure was also found to be significant useful information in this study. This finding was similar to a previous report on adult patients from Oman (Al-Mahrezi *et al*, 2012).

Pneumonia was the common complication in the present study, occurring in more than half of all cases but without statistically significant differences among groups. There was no mortality in this study with regard to pre-existing conditions. This outcome might be due to early detection and oseltamivir treatment within 48 hours of onset in the A(H1N1)pdm09 group. These treatment results were similar to the previous report during the first wave of the H1N1 pandemic in Thailand (Udompornwattana *et al*, 2012).

During the first pandemic year, mortality due to A(H1N1)pdm09 infection was reported to be 10-fold higher than that due to seasonal influenza (Libster *et al*, 2010). Therefore, the World Health Organization recommended that antivi-

ral treatment be administered as early as possible to any patient with confirmed or suspected influenza who was at high risk or presented with severe symptoms (WHO, 2010). The pneumonia-associated case fatalities reported in adult patients from Thailand, however, showed that 46% had no identified risk factors (Bunthi *et al*, 2013). In Thailand, the influenza confirmatory test is not available throughout the country, so the Ministry of Public Health modified the WHO recommendation, proposing that suspected influenza patients be given oseltamivir immediately on presentation rather than waiting for laboratory results (Ungchusak *et al*, 2012). To avoid the over prescription of oseltamivir to pediatric patients, this study adds more clinical information that A(H1N1)pdm09 significantly infected older children (>2 years) and caused more significant systemic symptoms such as headache and myalgia than did other viruses. Another limitation of this study was the incomplete clinical outcomes because one-fourth of infected children were treated as outpatients and they were lost to followed-up.

In conclusion, A(H1N1)pdm09 significantly infected older children, who had higher prevalence of sore throats, headaches and myalgia than did children with other respiratory pathogens. This information should be useful for early intervention in children suspected of A(H1N1)pdm09 infection in settings where definitive diagnostic tests are not available.

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