นิพนธ์ต้นฉบับ

Viral Pathogens of Influenza–Like Illness and Clinical Presentation in Thai Children during the 2009 Pandemic Influenza A (H1N1)

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บทคัดย่อ : ไวรัสที่ทำให้เกิดอาการคล้ายไข้หวัดใหญ่ในเด็กและอาการแสดงในช่วงที่มี pandemic H1N1

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วัตถุประสงค์

1. เพื่อศึกษาว่าไวรัสชนิดใดที่ทำให้เกิดอาการคล้ายไข้หวัดใหญ่ในเด็ก

2. เพื่อศึกษาถึงอาการของการติดเชื้อไวรัสแต่ละชนิดและศึกษาว่าช่วงอายุและฤดูใดที่พบไวรัสเหล่านี้ได้บ่อย

วิธีการศึกษา

ในระยะที่มีการระบาดของเชื้อไวรัส H1N1 ได้มีการเฝ้าระวังการติดเชื้อไวรัสไข้หวัดใหญ่ในเด็กอายุ 0-15 ปีโดยการทำ throat swab สัปดาห์ละ 10 คน โดย throat swab จะถูกส่งโดยกระบวนการที่ได้รับการรับรองมาตรฐานไปที่กรมวิทยาศาสตร์การแพทย์เพื่อทำ real-time PCR

ผลการศึกษา

พบว่าผลการเพาะเชื้อคนไข้จำนวน 259 ราย พบว่าร้อยละ 50 พบเชื้อไวรัส โดยพบเชื้อไวรัส H1N1 ร้อยละ 28 เชื้อ RSV ร้อยละ 24 และเชื้อ parainfluenza ชนิดที่ 1 ร้อยละ 12 ตามลำดับโดยในเด็กอายุน้อยกว่า 2 ปีพบเชื้อ RSV มากที่สุด ในช่วงเด็กอายุ 2 ถึง 15 ปีพบเชื้อ parainfluenza ชนิดที่

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1 มากที่สุด และเชื้อ influenza และเชื้อ RSV พบได้บ่อยที่สุดในฤดูฝน การทดสอบโดยวิธี multivariate analysis พบว่า positive predictor ของ การติดเชื้อ influenza คืออาการเจ็บคอ (OR = 2.380, 95% CI = 1.121-5.055), ขณะที่การติดเชื้อ RSV สัมพันธ์กับอาการน้ำมูกไหล (OR = 5.155, 95% CI = 1.153-23.048)

สรุป

ระหว่างที่มีการระบาดของเชื้อ H1N1 การติดเชื้อ influenza พบได้บ่อยในช่วงเด็กอายุ 2 – 15 ปี อย่างไรก็ตามในเด็กที่อายุน้อยกว่า 2 ปี เชื้อไวรัสที่พบได้บ่อยที่สุดคือเชื้อ RSV จากการศึกษาพบว่าอาการเจ็บคอสัมพันธ์กับการติดเชื้อ influenza virus มากกว่าเชื้อชนิดอื่น

Objective : **To identify the viral pathogen associates with ILI in children. And secondary aim is to determine age group and season associated with viral pathogen and clinical presentations of ILI due to specific viral pathogens.**

Method : **Virological influenza surveillance was conducted by collecting throat swab specimens for viral culture in children 0-15 years who came to hospital with ILI during pandemic H1N1. ILI criteria is fever > 38°C with cough or sore throat.**

Result : **259 throat samples were collected and 130 (50%) were positive for virus: 28% for Influenza A (H1N1) virus, 24% for respiratory syncytial virus (RSV), 12% for parainfluenza type 1, 8% for influenza A (H3), 7% for adenovirus, 5% for human metapneumovirus, 3% for influenza B, 3% for parainfluenza type 3, 1.5%for parainfluenza type 2. RSV is most common detected in children < 2 years and influenza virus is most common detected in children 2-15 years. Influenza and RSV were most detected during rainy season. In multivariate analysis, positive predictor of influenza infection was sore throat (OR = 2.380, 95% CI = 1.121-5.055), whereas runny nose (OR = 5.155, 95% CI = 1.153-23.048) was associated with RSV infection.**

Conclusions : **Influenza positive cases were more frequent among children aged 2- 15 years old during pandemic H1N1. However, in children < 2 years, the dominant virus is RSV. ILI may be difficult to distinguish on clinical presentations. We found patient with influenza infection was associated with sore throat more than other virus.**

Introduction

In April 2009, a new influenza A(H1N1) virus was reported from the United States and Mexico and spread rapidly worldwide including Thailand[1-2]. It is reported that between 3 and 5 million cases of severe influenza disease occur each year[3] In most people, the infection results of fever, cough, sore throat, headache, and malaise (tired, no energy); some people also may develop nausea, vomiting, and diarrhea[6]. Influenza-like illness (ILI) is the criteria by World Health Organization (WHO) to identify case. The definitions have been used worldwide for influenza surveillance which is fever (> 38°C) with cough or sore throat[7] in every age group.

Previous studies found Influenza was detected 30-50% in adult patient with ILI. Bellei N. et al found Influenza was detected in 30.9% in adult with ILI, rhinovirus in 19.% and other respiratory viruses in 13.7%[8]. Hasman H. et al found that influenza A virus infections were most common (50%) in adult with ILI, followed by human respiratory syncytial virus (HRSV) 16% and human parainfluenza viruses (HPIV) 5.8%[9]. Most of the studies found peak of the influenza infection in winter season.[10-12]

The clinical presentation of influenza in children varies in different age groups and overlaps with the presentations of other viral illness because a variety of viral pathogens can cause influenza-like illness. Since 2003, a virological surveillance network has been implemented across the country by the National Institute of Health (NIH) of Thailand. Throat samples are collected from children with ILI in sentinel sites. Prapokklao Hospital is one of the sentinel sites in this surveillance network which is the tertiary hospital in Chantaburi Province situated in the eastern Thailand about 245 km from Bangkok. We have no regularly throat swab to identify the organism due to the high cost of investigation. We use influenza-liked illness criteria to identify and treat patient. The primary aim of this study was to identify the viral pathogen associates with influenza-liked illness in children during the pandemic. A secondary aim was to determine the distribution of age groups and seasons associated with viral pathogen and identify the clinical predictors of influenza-like illness due to specific viral pathogens.

1. Methods

We conducted a surveillance in children 0-15 years who came to hospital with influenza-like illness at Prapokklao hospital from September 2009 to August 2010 which is during pandemic H1N1 in Thailand. The surveillance was done at least 10 children per week. The criteria for influenza-like illness is fever > 38°C with cough or sore throat. Children were excluded if disease duration was > 3 days at the time of evaluation. Throat specimens were collected from the patients by a well- trained laboratory assistant. The specimens were immediately inserted into viral transport media

and kept frozen at –70° C. The specimens were transported weekly to the Thai NIH influenza laboratory in Bangkok for viral identification by real-time PCR method and viral confirmation at a WHO Collaborating Center for Reference and Research on Influenza. The Thai NIH has participated in the WHO influenza laboratory network as a national influenza center since 1972.

1.1 Statistical methods

Frequencies and proportions were used for the descriptive statistics. Univariate and multivariate analysis were performed to determine the clinical predictors of culture-confirmed influenza infection. Univariate analysis included chi-square test and Odds ratio (OR) with 95% confidence interval (CI). Forward stepwise logistic regression analysis was conducted only on the variables that reached statistical significance at the 0.05 level with univariate analysis. The accuracy of clinical diagnosis on the basis of influenza-like illness definition was determined by sensitivity, specificity and positive and negative predictive value. All the calculation were performed by using SPSS 10.0 software.

2. Results

Throat samples were collected from 259 cases of children with ILI during this period. 137 are boys and 122 are girls. 130 (50%) were culture positive for virus: 37 for Influenza A (H1N1) virus, 32 for respiratory syncytial virus, 16 for parainfluenza type 1, 11 for influenza A (H3), 10 for adenovirus, 7 for human metapneumovirus, 5 for influenza B, 4 for parainfluenza type 3, 2 for parainfluenza type 2. Six (4.6%) mixed infection were detected including 1 adenovirus plus respiratory syncytial virus, 1 influenza A (H1N1) plus adenovirus plus respiratory syncytial virus, 1 influenza virus A (H1N1) plus parainfluenza type 3, 1 influenza B plus adenovirus, 1 parainfluenza type 1 plus adenovirus, 1 parainfluenza type 3 plus adenovirus.

Age and seasonal distribution

Age distribution and positive samples is shown in table 1. Among children aged under 24 months, RSV is the most common detected virus caused ILI. Among children aged from 2 years until 15 years, Influenza is the most common detected virus caused ILI.

Seasonal distribution of viruses was shown in table 1 and figure 1. Influenza and RSV was most frequently detected during rainy season (June to October). The peak of influenza virus and RSV detections coincided with the peak of clinical incidence of ILI.

Table 1 age and seasonal distribution of viruses

	Number of samples collected (n=259)	Respiratory syncytial virus (n=34)	Influenza (n=56)	Parainflu-enza (n=25)	Human metapneu-movirus (n=7)	Adenovirus (n=15)	Number (%) culture positive
Age Infant (1-23 months)	79	18	7	11	2	6	44 (55%)
Preschool children (2-5 years)	68	13	17	10	2	7	49 (72%)
Child (6-12 years)	83	3	25	3	3	2	46 (43%)
Adolescent (13-15 years)	29	0	7	1	0	0	8 (27%)
Season Summer season (April to May)	48	0	7	8	0	3	37.5%
Rainy season (June to October)	120	22	37	8	6	5	78(65%)
Winter season (November to February)	91	12	12	9	1	7	41(45%)

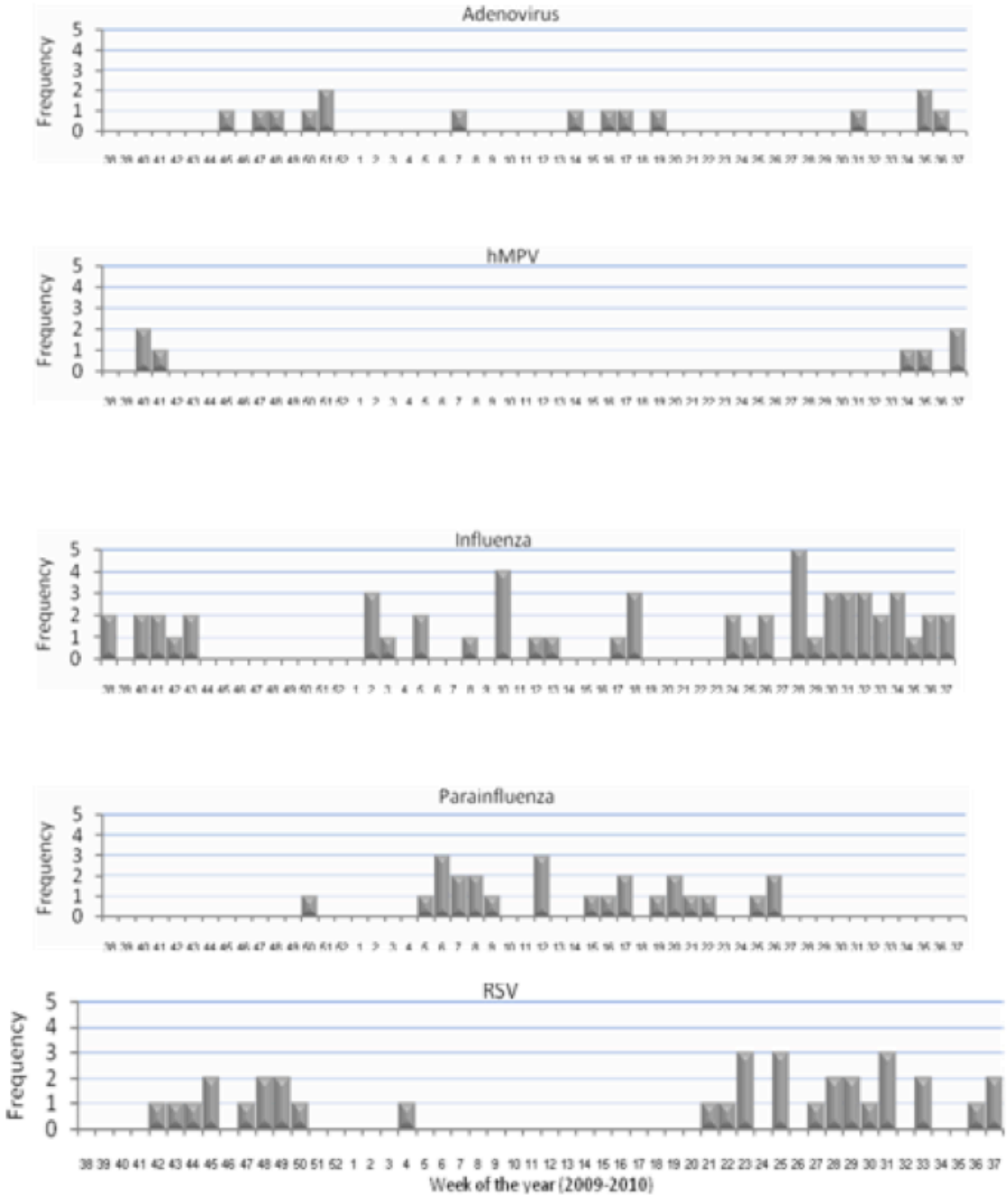

Figure 1 seasonal distribution of viruses

Clinical presentations and viral pathogen

Clinical presentations and viral pathogen was presented in table 2. Univariate and multivariate analysis was performed for Respiratory syncytial virus and Influenza virus were shown in table 3 and table 4. Most patients with ILI presents with cough. In multivariate analysis, positive predictor of influenza infection was sore throat (OR = 2.380, 95% CI = 1.121-5.055), whereas runny nose (OR = 5.155, 95% CI = 1.153-23.048) was associated with respiratory syncytial virus infection. We found no difference in gastrointestinal symptoms in the proportions of ILI patients by types of virus.

Discussion

This study summarizes the surveillance and report the etiology of Influenza-like illness and the clinical presentations in Thai pediatric patients from September 2009 to August 2010. In our study revealed that viral pathogens was detected 50% of the 259 samples. We report the significant differences in the age distributions of influenza virus and other viruses for ILI. Our data showed that the respiratory viruses detected most often were influenza virus, RSV virus, and parainfluenza virus accounting for 28%, 24%, and 12% respectively. Among children aged under 12 years old, Influenza, RSV, and parainfluenza virus accounted for minimum 60% of pathogens identified in samples. This is in agreement with results by Hasman[9], who reported that influenza A virus infections were most common (50%), followed by RSV (16%) and parainfluenza virus (5.8%). Influenza positive cases were more frequent among children aged between 2 and 15 years old during pandemic H1N1 virus. However, in children under 2 years, the dominant virus is RSV. Most culture negative cases were in Adolescent may be explained by acquired partial immunity in previous years via prior natural exposure.

The proportions of the viruses changed over the season. Our pediatric patients were at increased risk of acquiring the influenza virus during June to October 2009. RSV virus peak activity was concurrent with the influenza season. This is consistent to the previous studies in tropical countries which showed that the RSV and Influenza circulated in the community during rainy season and winter[8, 10-11] especially end of rainy season to beginning of winter season. This is different from the studies in the western countries which showed that the RSV and Influenza are winter illness[13-14].

Table 2 clinical presentations and viral pathogen

Clinical symptoms	Respiratory syncytial virus (n=34)	Influenza (n=56)	Parainfluenza (n=25)	Human metapneumovirus (n=7)	Adenovirus (n=15)
Cough	34	55	24	7	15
Sore throat	12	42	12	3	10
Runny nose	32	44	18	5	11
Headache	8	42	11	4	5
Muscle ache	2	31	7	1	4
Fatique	0	0	0	0	0
Nausea	3	12	4	0	1
Vomit	8	17	6	3	5
Diarrhea	3	1	3	1	2

Table 3 clinical presentations associated with respiratory syncytial virus infection

Clinical symptoms	Univariate analysis		Multivariate analysis	
	Odds ratio	95% CI	Odds ratio	95% CI
Cough	3.151	0.398-24.945	-	-
Sore throat	0.421	0.199-0.89	1.067	0.450-2.533
Runny nose	8.000	1.867-34.280	5.155	1.153-23.048
Headache	0.166	0.072-0.380	0.369	0.143-0.953
Muscle ache	0.084	0.020-0.350	0.163	0.034-0.774
Fatique	0.778	0.358-1.690	-	-
Nausea	0.448	0.130-1.536	-	-
Vomit	0.681	0.294-1.580	-	-
Diarrhea	1.355	0.371-4.950	-	-

Table 4 clinical presentations associated with Influenza virus infection

Clinical symptoms	Univariate analysis		Multivariate analysis	
	Odds ratio	95% CI	Odds ratio	95% CI
Cough	3.151	0.398-24.945	-	-
Sore throat	3.278	1.687-6.372	2.380	1.121-5055
Runny nose	1.727	0.855-3.489	-	-
Headache	2.438	1.243-4.740	1.230	0.461-3.285
Muscle ache	2.517	1.378-4.598	1.762	0.836-3.711
Fatique	2.350	1.085-5.089	2.221	0.967-5.101
Nausea	1.513	0.719-3.185	-	-
Vomit	1.015	0.533-1.932	-	-
Diarrhea	0.199	0.026-1.529	-	-

The data we have presented here suggest that in Thailand, the clinical presentation of influenza including H1N1 was similar to that of the other viruses that were circulating during the pandemic. Therefore, ILI may be difficult to distinguish on the the basis of symptoms alone from symptomatic infections caused by other respiratory viruses. Almost all pediatric patients with ILI presented with cough. However, our study found runny nose was associated with respiratory syncytial virus infection and sore throat was associated with influenza virus infection. Although there have been many reports of a higher proportion of pH1N2 ILI patients with gastrointestinal symptoms 15-16. We found no difference in gastrointestinal symptoms in the proportions of ILI patients by types of virus. In agreement of previous study found diarrhea was inversely associated with influenza virus infection[17].

There are limitations to our ILI surveillance. First is the potential for sampling and selection bias. So our results may not be representative of the entire population of Thailand. Second is the small number of cases of influenza that could be analyzed, which limits the power to detect differences in clinical presentation. However, one advantage provided by sentinel surveillance systems is the ability to identify increasing trends in the number of patients seeking medical attention due to ILI symptoms and fewer resources than a population-based study require.

Influenza-like illness circulation will continue to be monitored throughout Thailand, to determine when the novel influenza virus reach epidemic levels and detect any further changes in the viral distribution pattern in the

different season.

In conclusion, Influenza positive cases were more frequent among children aged between 2 and 15 years old during pandemic H1N1 virus. However, in Infant under 2 years, the dominant virus is RSV. ILI may be difficult to distinguish on the the basis of clinical presentations. We found patient with influenza viral infection was associated with sore throat more than other virus. However, clinical presentation and viral pathogens need further study.

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