Risk Factors and Outcomes of Influenza Infection among Children Presenting with Influenza-Like Illness

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Objective: *Limited data were available to guide management, counseling, and/or diagnostic investigation among children presenting with influenza-like illness (ILI). During a recent period of high influenza activity, we wished to determine the frequency, outcomes, and factors associated with influenza infection among children presenting with ILI.*
Material and Method: *During September and October 2010, children presenting with ILI were enrolled. Nasal swabs were sent for polymerase chain reaction (PCR) to determine the frequency and types of influenza. Information of demographic characteristics, potential risk factors, and short-term outcomes of study participants were collected.*
Results: *Among 300 enrolled subjects, influenza infections were identified in 170 (56.7%) cases; 45.7% (n = 137) were influenza A and 11% (n = 33) were influenza B. Most cases recovered uneventfully with a 3.7% (n = 11) hospitalization rate. Risks for hospitalization did not differ by infection status (2.4% vs. 5.4% between those with and without influenza infection, respectively) or types of influenza infection. Logistic regression analysis indicated that older age, having a household member with acute respiratory illness (ARI) during the previous 7 days, having an underlying co-morbidity, and a history of premature birth were associated with influenza, with adjusted odds ratios and 95% confidence intervals of 1.19 (1.087, 1.30), 3.21 (1.096, 9.424), 2.15 (1.244, 3.728), and 0.08 (0.007, 0.876), respectively.*
Conclusion: *The outcomes of influenza-associated ILI were generally favourable, with no fatalities and 2.4% risk for hospitalization. Among children presenting with ILI, age, household contact with ARI, and co morbidities increased the likelihood of influenza, whereas history of premature birth was negatively associated with influenza.*

Keywords: *Children, Clinical outcomes, Influenza, Influenza-like illness (ILI), Risk factors*

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Human influenza continues to present public health challenges resulting in substantial global burden with large segments of the population infected annually. These challenges relate to the considerable impacts of seasonal influenza infections, uncommon but serious avian influenza A (H5N1), other zoonotic influenza infections, and pandemic (H1N1) 2009 influenza infections. In April 2009, the emergence of a novel swine-origin influenza A H1N1, for which a new standard nomenclature, A(H1N1)pdm09 virus[1] has recently been adopted, was detected and rapidly spread across the globe. Nevertheless, the majority of reports were from industrialized countries where health system infrastructure, access to antiviral agents and/or vaccines, and host nutritional status can substantially differ from developing countries.

Existing evidence indicates that mortality during influenza pandemics can vary widely between countries, with the highest burden in terms of fatality being concentrated in less developed countries[2]. In addition, host nutritional status may influence not only the immune response, but also the genetic make-up of the viral genome[3]. Further, bacterial co-infections may play a significant role in the outcomes of influenza

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pandemic. Unfortunately, data are limited in terms of the natural history, clinical features and outcomes of human influenza in many less developed, resource-limited countries. This information can help prioritize influenza prevention and control strategies. In Thailand, after the first wave of A(H1N1)pdm09 virus in late 2009, the second and third waves of the influenza outbreak continued during the first and third trimesters of 2010. Thailand witnessed a dramatic increase in the number of influenza-like illnesses (ILI) during the period of high influenza activity between August and early November 2010, which overwhelmed the existing health infrastructure.

Numerous studies have demonstrated that young children, especially those younger than 5 years, have increased risk for influenza complications. In addition, these children serve as a reservoir for further spread of the virus[4]. Nevertheless, limited data were available to guide proper management, counselling, and/or diagnostic investigation among children presenting with this condition. Therefore, the objective of this study was to determine the frequency, outcomes, and factors associated with influenza infection among pediatric patients presenting with ILI. This information is essential for guiding prevention and management strategies for human influenza in children during a period of high influenza activity.

Material and Method

During September and October 2010, children presenting with ILI for five or fewer days onset prior to presenting at an outpatient department of Queen Sirikit National Institute of Child Health (QSNICH), were enrolled in the present study. ILI was defined as occurrence of a sudden onset of fever of $\geq$38°C and cough or sore throat in the absence of other diagnoses. Those with a history of influenza vaccination or confirmed influenza infection during the past 12 months were not eligible. Informed consent from subjects and/or their parents/legally-accepted representative (LAR) was obtained prior to the study's implementation. For children 7 years or older, verbal assent was also required prior to study enrollment. After enrollment, each caregiver was interviewed using a structured questionnaire to determine potential risk factors, including age, gender, average household income, maternal education, duration of breastfeeding, day care attendance, exposure to indoor (tobacco smoke) and outdoor pollution (living near congested traffic), underlying disease, crowding index (number of people sleeping in the same room with an index case), and presence of household member with acute respiratory illness during the past one week. After the interview, a nasal swab was obtained from each subject to determine whether influenza infection was the cause. Influenza was confirmed by performing a real-time reverse-transcription-polymerase chain reaction (RT-PCR) at the National Influenza Center, National Institute of Health, Department of Medical Sciences, Ministry of Public Health, Thailand. Positive influenza specimens were further identified based on their hemagglutinin and matrix (M) gene as type A or B. However, they were not further classified by subtype based on the two main surface glycoproteins, hemagglutinin and neuraminidase.

Univariate analysis was conducted to screen for any difference in baseline and clinical characteristics between ILI cases with and without proven influenza infection. Multivariable statistical analysis was employed to adjust for the differences among patients when determining factors associated with influenza infection. Once the result of the PCR became available (within an average of three days), a research nurse contacted caregivers about the test result along with inquiring and recording participants' clinical status after initial visit. Participants were also asked to return to QSNICH if there was any worsening of clinical status.

Results

Among a total of 300 enrolled subjects, influenza infection was identified in 170 (56.7%) cases; 45.7% (n = 137) were influenza A and 11% (n = 33) were influenza B. Ninety-two percent of cases had no documented underlying predisposing condition for influenza complications. The most common co-morbidity was allergic rhinitis (2%), followed by asthma (1.3%), chronic pulmonary disorder (1.3%), and congenital heart disease (1%). Onset of illness in the influenza-infected group appeared to be significantly shorter, with median fever duration prior to seeking medical attention of 1 vs. 2 days (p = 0.006) among those with and without confirmed influenza infection, respectively.

Most cases recovered uneventfully, with 3.7% (n = 11) rate of hospitalization. The authors did not detect any statistical difference in the likelihood of hospitalization by influenza infection status (2.4% vs. 5.4% between those with and without influenza infection, respectively) or types of influenza virus (2.2% and 3% between influenza A and influenza B, respectively).

Univariate analysis indicated that median age,

fever onset, presence of underlying co-morbidity, and household contact with acute respiratory infection (ARI) were significantly associated with influenza infection among those presenting with ILI (Table 1).

Logistic regression analysis indicated that age, having an underlying disease, having a household member with ARI during previous seven days, and history of premature birth were associated with influenza infection with adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of 1.19 (1.087, 1.30), 3.21 (1.096, 9.424), 2.15 (1.244, 3.728), and 0.08 (0.007, 0.876), respectively (Table 2).

Discussion

Influenza virus is a leading cause of ARI worldwide and is associated with significant annual

Table 1. Univariate analysis of clinical and demographic characteristics between ILI cases with and without confirmed influenza infection

	Influenza (n = 170)	Non-influenza (n = 130)	*p*-value
Age in year: median (IQR)	4.84 (3.18)	3.32 (2.98)	<0.001
Monthly household income (Thai baht): median (IQR)	22,830.6 (40,895.17)	18,034.6 (14,809.15)	0.204
Day of fever: median (IQR)	1 (1, 2)	2 (1, 3)	0.006
No. of household members (median)	4 (3, 5)	4 (3, 5)	0.850
No. of people sleeping in the same bedroom with index case mean (SD)	2.27 (0.91)	2.24 (0.83)	0.753
Male n (%)	91 (53.5)	73 (56.2)	0.369
Living in metropolitan area (%)	85 (50.0)	51 (39.2)	0.178
Living near congested traffic n (%)	60 (35.3)	50 (38.5)	0.328
Underlying disease n (%)	19 (11.2)	6 (4.6)	0.031
History of prematurity	1 (0.6)	5 (3.8)	0.057
Household smoking n (%)	82 (48.2)	66 (50.8)	0.375
Household ARI n (%)	67 (39.4)	34 (26.2)	0.011
Exclusive breastfeeding ≥4 months n (%)	139 (81.8)	109 (83.8)	0.377
Day-care attending n (%)	26 (15.3)	17 (13.1)	0.355
Maternal education n (%)			0.833
Less than high school	64 (37.6)	50 (38.5)	
High school	70 (41.2)	55 (42.3)	
College	35 (20.6)	25 (19.2)	
Master or higher	1 (0.6)	0 (0)	
Hospitalization n (%)	4 (2.4)	7 (5.4)	0.218

ARI = acute respiratory infection

Table 2. Logistic regression analysis examining factors associated with influenza infection among children presenting with ILI

Predictors	aORs	95% CI
Age in year	1.190	(1.087, 1.30)
Living in metropolitan areas	1.650	(0.972 ,2.795)
Underlying disease	3.210	(1.096, 9.424)
History of prematurity	0.080	(0.007, 0.876)
Household smoking	0.930	(0.547, 1.565)
Household ARI	2.150	(1.244, 3.728)
Exclusive breastfeeding ≥4 months n (%)	0.870	(0.443, 1.700)
Hospitalization	0.465	(0.098, 2.215)

ARI = acute respiratory infection

morbidity and mortality. In the present study, those with proven influenza infection had significantly shorter duration of fever prior to seeking medical attention than ILI cases caused by other pathogens. This finding may reflect the severity and acuteness of illness compared to non-influenza infection. In addition, we found that children with influenza infection were significantly older than their counterparts. A recent literature in a pediatric population[5] demonstrated that A(H1N1)pdm09 was more likely to affect older children than those affected by seasonal influenza. However, we did not perform further subtyping among influenza A. Therefore, we do not have the data on the proportions of those affected by A(H1N1)pdm09 or H3N2, the two most common strains identified in Thailand during the study period. In addition, for those with a recent history of household contact with ARI, it was twice as likely that their current ILI was due to influenza infection. This finding is consistent with existing literature[6]. For example, a serological survey conducted in Singapore showed that contact with a household member with a recently proven influenza infection increased the risk of influenza seroconversion by a factor of three[7]. A prospective cohort study in the adult population during the 2006/2007 influenza season in Germany indicated that those living with children (who are generally more susceptible to influenza infection than adults) had a three-fold higher risk for influenza seroconversion. The risk is 14-fold higher for those living with three or more children[8]. Although we took into consideration the number of household members as a potential risk factor for influenza infection, we did not stratify them as adults or children.

Of note, the authors found that ILI among children who had a history of premature birth (less than 37 weeks' gestation) were 11-fold more likely to have been infected by pathogens other than the influenza virus. It could be just a chance finding or due to a relatively higher susceptibility of these children to respiratory pathogens other than influenza. This particular finding is unique and requires further supporting evidence for this apparent association. However, most of the existing literature, unlike the present study, focused on hospitalized rather than ambulatory settings. Further, it should also be emphasized that the present study was conducted during a period of unusually high influenza activity. Therefore, the authors cannot be certain that the result can be generalized to a period outside the influenza season.

A few reports in the literature set out to compare clinical characteristics between influenza and other ARI or between A(H1N1)pdm09 and seasonal influenza. There are a few studies reporting significant differences in terms of clinical features that may be useful for differentiating influenza from other respiratory infections or ILI. A prospective study was conducted in England comparing clinical features between adults with and without A(H1N1)pdm09 community-acquired pneumonia (CAP). A multivariate logistic regression model was generated by assigning one point for each of five clinical criteria: age <65 years, mental orientation, temperature $\geq$38.8°C, leukocyte count $\leq 12x10^9$/l, and bilateral radiographic consolidation. A score of 4 or 5 indicated a positive likelihood ratio of 9.0 for predicting A(H1N1)pdm09 influenza-related pneumonia, whereas a score of 0 or 1 yielded a positive likelihood ratio of 75.7 for excluding it[9]. Another retrospective study used multivariate analysis to examine differentiating features of A(H1N1)pdm09 influenza infection among adults presenting with community-acquired pneumonia (CAP). The results demonstrated that age, duration of illness, productive cough, dyspnea, chest pain, and coarse crackles had positive associations with CAP diagnosis. In contrast, a history of sick contact, sore throat, and rhinorrhea were significantly more common among adults with A(H1N1)pdm09 infection[6].

A report from Israel using multivariable analysis to compare clinical features of adults hospitalized with ILI with and without A(H1N1)pdm09 infection demonstrated that age <65 years and cough were independent predictors for A(H1N1)pdm09 infection[10]. Currently, only one study by Michiels et al took into consideration the seasonality of influenza in their analysis. The results showed that during the influenza epidemic, ILI contact, cough, 'expectoration per illness day', nasal symptoms, lack of appetite, and body temperature >37.8°C are the best performing clinical features to discriminate influenza from other ILIs[11]. However, during the pre-and post-influenza epidemic, no prediction rule is helpful for predicting influenza among those younger than 5 years or older than 65 years[11]. Outside an influenza epidemic, the absence of cough and fever (>37.8°C) indicates that influenza is 14-fold less likely to be the source of infection in ILI patients[10]. A study by Ong et al reported that the combination of 'World Health Organization (WHO) ILI criteria' and the 'absence of leukocytosis' has a positive likelihood ratio for predicting A(H1N1)pdm09 and seasonal influenza infections of 7.8 and 9.2, respectively[12]. In general, studies in adult populations suggest that features that

may be useful in distinguishing A(H1N1)pdm09 from seasonal influenza or other ILI include younger age[13], fewer lower respiratory tract symptoms, obesity, pregnancy, presence of underlying predisposing co morbidities[13], and lymphopenia (<900 cell/mm^3)[12].

One retrospective study in Italy among children with ILI indicated that the only significant differences between those with and without proven A(H1N1)pdm09 infection were white blood cell count, relative and absolute lymphocyte count, absolute lymphocyte count z-score, and platelet count. An absolute lymphocyte count <2,556 cells/ml or an absolute lymphocyte count z-score of <0.89 appeared to be useful cut-offs to identify children with A(H1N1)pdm09 infection among children presenting with ILI[14].

Despite several efforts to identify differentiating features of influenza infection that might be useful for clinicians as diagnostic and treatment guides, there is neither a single nor a set of clinical parameters that are useful for distinguishing between overall human influenza (as well as specific types of influenza) and non-influenza ARIs. The above-mentioned studies were conducted in varied settings with different choices of comparison groups and used various combinations of clinical features and different sets of variables in the analyses. With these substantial differences, it is unlikely that there will be any consensus on clinical features that would be useful for distinguishing ARI or ILI caused by influenza from other respiratory pathogens for clinical practice.

During the study period, oseltamivir was generally not prescribed at the initial encounter with ILI cases without laboratory confirmation of influenza in an outpatient setting. Only a few cases received oseltamivir treatment if they had worsening symptoms at follow-up and positive PCR for influenza or have significant predisposing co-morbidities. Of important note, the outcomes of influenza infection in our sample were favorable, with less than a 3% rate of hospitalization and no fatalities. Our findings corroborate existing evidence, suggesting that influenza infections generally cause mild non-specific viral illness indistinguishable from other ILI or ARI[12,15,16]. This information can be useful when counseling parents/caregivers of children presenting with ILI in an outpatient setting. Based on our findings, it appears that the ILI episodes during a high period of influenza activity are more likely to be caused by the influenza virus than other pathogens in the following scenarios: children with ILI whose parent(s) decided that it was severe enough to seek care early (after fever onset of approximately one day), those with a history of household contact with ARI within the previous seven days, those with an underlying predisposing conditions that put them at risk for influenza infection, and those without a history of premature birth. Our findings also suggest that the older the child, the more likely that the ILI episodes are due to influenza infection. In addition, about 96% of these children recovered uneventfully and can be managed in an outpatient setting. The likelihood of hospitalization is lower among those caused by influenza (2.4%) than those with non-influenza infection (5.4%).

Conclusion

During a high period of influenza activity, nearly 60% of ILI cases in children were caused by influenza infection. ILIs caused by influenza appear to have a more acute onset with a shorter duration from fever onset to seeking medical attention compared with ILIs from other causes. The outcomes of influenza infection were generally favorable with low risk of hospitalization. Older age, household contact with ARI, and underlying co-morbidities increased the likelihood of influenza, whereas history of premature birth was negatively associated with influenza among ILI cases.

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Potential conflicts of interest

None

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ปัจจัยเสี่ยงและผลการดำเนินโรคของการติดเชื้อไข้หวัดใหญ่ในเด็กที่มาด้วยกลุ่มอาการคล้ายไข้หวัดใหญ่

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วัตถุประสงค์: เพื่อศึกษาผลการดำเนินโรคและปัจจัยที่สัมพันธ์กับการติดเชื้อไข้หวัดใหญ่ในเด็กที่มากลุ่มอาการคล้ายไข้หวัดใหญ่

วัสดุและวิธีการ: เด็กที่มารับการรักษาด้วยกลุ่มอาการคล้ายไข้หวัดใหญ่ ที่ห้องตรวจผู้ป่วยนอก สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ระหว่างเดือนกันยายน ถึง เดือนตุลาคม พ.ศ. 2553 ได้รับการตรวจหาเชื้อไข้หวัดใหญ่โดยวิธี polymerase chain reaction จากการป้ายน้ำมูกจากโพรงจมูกร่วมกับการเก็บข้อมูลพื้นฐานประชากร, ปัจจัยเสี่ยงและผลการติดตามการรักษาระยะสั้น (ในวันที่ 3-7 หลังเข้าร่วมโครงการ)

ผลการศึกษา: ในอาสาสมัครที่เข้าร่วมโครงการทั้งหมด 300 ราย ตรวจพบการติดเชื้อไข้หวัดใหญ่ 170 ราย คิดเป็นร้อยละ 56.7 โดยพบเป็นสายพันธ์เอ ร้อยละ 45.7 (n = 137), และสายพันธุ์บี ร้อยละ 11 (n = 33) อาสาสมัครเกือบทั้งหมดอาการดีขึ้นจากการรักษาแบบผู้ป่วยนอกโดยพบเพียงร้อยละ 3.7 (n = 11) ที่ต้องเข้ารับการรักษาในโรงพยาบาล โดยไม่พบความแตกต่างของอัตราการนอนโรงพยาบาลระหว่างกลุ่มที่ตรวจพบและไม่พบเชื้อไข้หวัดใหญ่ (อัตราการนอนโรงพยาบาลในกลุ่มที่ตรวจพบและไม่พบเชื้อไข้หวัดใหญ่เท่ากับ ร้อยละ 2.4 และ 5.4 ตามลำดับ) ในกลุ่มที่ตรวจพบว่าติดเชื้อไข้หวัดใหญ่ ไม่พบความแตกต่างของอัตราการนอนโรงพยาบาลระหว่างกลุ่ม ในติดเชื้อสายพันธุ์เอและบี การวิเคราะห์ด้วยวิธี logistic regression analysis พบว่าอายุที่มากขึ้น, ประวัติการมีชนในบ้านมีอาการป่วยของระบบทางเดินหายใจนำมาก่อนภายใน 1 สัปดาห์ก่อน, การมีโรคประจำตัว, และประวัติการคลอดก่อนกำหนดสัมพันธ์กับการติดเชื้อไข้หวัดใหญ่โดยมีค่า adjusted odds ratios และ 95% confidence interval เท่ากับ 1.19 (1.087, 1.30), 3.21 (1.096, 9.424), 2.15 (1.244, 3.728) และ 0.08 (0.007, 0.876) ตามลำดับ

สรุป: การเจ็บป่วยด้วยกลุ่มอาการคล้ายไข้หวัดใหญ่มีการพยากรณ์โรคที่ค่อนข้างดีในเด็ก โดยที่พบมีอัตราการนอนโรงพยาบาลร้อยละ 2.4 และไม่มีผู้ป่วยรายใดเสียชีวิต ปัจจัยที่สัมพันธ์กับการเพิ่มโอกาสการติดเชื้อไข้หวัดใหญ่ในเด็กที่มาโรงพยาบาลด้วยอาการดังกล่าวได้แก่ อายุที่มากขึ้น การมีคนในบ้านมีอาการป่วยของระบบทางเดินหายใจ นำมาก่อนภายใน 1 สัปดาห์, การมีโรคประจำตัว ในขณะที่เด็กที่มีประวัติว่าคลอดก่อนกำหนดจะมีโอกาสการตรวจพบเชื้อไข้หวัดใหญ่น้อยกว่า