Clinical Presentations of Pandemic 2009 Influenza A (H1N1) Virus Infection in Hospitalized Thai Children

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Background: *A novel influenza A (H1N1) virus of swine origin caused human infection and acute respiratory illness in Mexico during the spring of 2009. After that, the virus spread globally, resulting in the influenza pandemic.*
Objective: *To observe the clinical manifestations of the 2009 pandemic influenza A (H1N1) and the epidemic waves of hospitalized children for a period of one year.*
Material and Method: *A prospective observational study of children under eighteen years old, confirmed having the 2009 pandemic influenza (H1N1) infection by real-time reverse-transcription-polymerase-chain-reaction (RT-PCR), admitted at Queen Sirikit National Institute of Child Health, Bangkok, Thailand during one year, from 1st June 2009 to 31st May 2010.*
Results: *A total of 83 pandemic influenza infected children were admitted during a one-year period. There were two waves of epidemic outbreak, the first wave from June to August 2009 and the second wave from January to February 2010. There were 47 cases of males (56.6%), with the highest attack rates among children 1-5 years of age (48.2%). The youngest case was a 29-day old girl. The correct provisional diagnosis of pandemic influenza infection are 39.5%, the other initial diagnosis are pneumonia, bronchiolitis, tonsillitis, encephalitis, and dengue infection. Most patients coming for care had typical, influenza-like symptoms with fever (98.8%), cough (92.6%) and rhinorrhea (74.1%). Systemic symptoms are frequent. Gastrointestinal symptoms (including vomiting (46.9%) and diarrhea (24.7%)) occur more commonly than seasonal influenza. Pneumonia is the most common complication (43.2%); other complications include bronchiolitis, hemoptysis, acute respiratory distress syndrome (ARDS) and encephalitis. In one case, a seven year old girl suffered from ARDS, sepsis, multi-organ dysfunction syndrome and ventilator associated pneumonia, but survived with some neurological sequelae. Radiographic findings included diffuse interstitial, alveolar infiltrates and some in lobar distributions. Apart from oseltamivir, the other antibiotics included ceftriaxone, cefotaxime, amplicillin and azithromycin, were added for pneumonia. All patients in the present study survived.*
Conclusion: *The burden and character of pandemic influenza infection in developing countries are still incompletely understood. Early therapy with oseltamivir in severely ill patients, without waiting for laboratory confirmation for diagnosis, will save patients from severe complications.*

Keywords: *Pandemic influenza, Pneumonia*

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A novel influenza A (H1N1) virus of swine origin caused human infection and acute respiratory illness in Mexico in the spring of 2009[1,2]. After that, the virus spread globally, resulting in the influenza pandemic. In Thailand, the first confirmed case of pandemic 2009 H1N1 virus infection was reported in May 2009[3]. Pandemic 2009 H1N1 virus derived six genes from triple-reassortant North American swine virus lineages and two genes from Eurasian swine virus lineages[4]. Reassortment has not occurred with human influenza viruses to date. The level of pulmonary replication of the 2009 H1N1 virus has been higher than that of seasonal influenza A (H1N1) viruses in experimentally infected animals[5-7]. Studies of hemagglutinin-receptor binding indicates that the 2009 H1N1 virus is well adapted to mammalian hosts and binds to both α 2,6-linked cellular receptors (as do seasonal influenza viruses) and α 2,3-linked receptors[8], which are present in the conjunctivae, distal airways, and alveolar pneumocytes. The 2009

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H1N1 virus shows increased *ex vivo* replication in human bronchial epithelium, compared with a seasonal influenza virus[9] and is also characterized by increased replication and pathological changes in the lungs of nonhuman primates and increased replication in *ex vivo* human lung tissues[6]. Such observations may help explain the ability of the virus to cause severe viral pneumonitis in humans.

Objective

To observe the clinical and pulmonary manifestations of the 2009 H1N1 virus infection and the epidemic waves of the hospitalized children with pandemic 2009 H1N1 virus infection.

Material and Method

A prospective observational study for the clinical aspects and management of children under 18 years old, confirmed for the 2009 H1N1 virus infection by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) from nasopharyngeal aspirates or swabs, admitted at Queen Sirikit National Institute of Child Health (QSNICH), Bangkok, Thailand. The duration of study was from 1st June 2009 to 31st May 2010, for a period of 1 year.

Results

A total of 83 children infected by the 2009 H1N1 virus were admitted during the 1 year period (1st June 2009-31st May 2010). There were 2 waves of epidemic outbreak of pandemic 2009 influenza A (H1N1). The first wave was from June to August 2009 for the period of 3 months and the second wave was from January to February 2010 for the period of 2 months. There were sporadic cases between each epidemic outbreak (Fig. 1).

There were 47 cases of males (56.6%), with

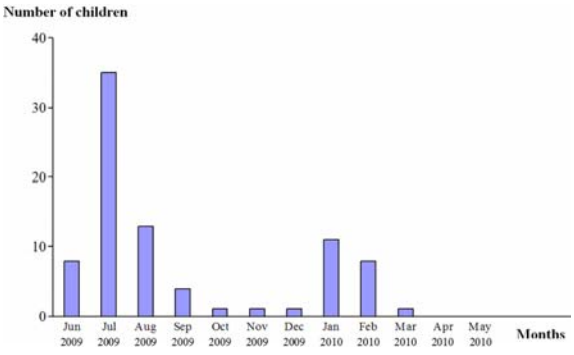

Fig. 1 Patients with pandemic 2009 H1N1 virus infection by month (n = 83)

the highest attack rate among children 1-5 years of age (48.2%). The youngest case was a 29 day old girl who came in with pneumonia and nonspecific symptoms. The correct provisional diagnosis of the 2009 H1N1 virus infection is 39.5%. The other initial diagnoses on admission are pneumonia (35.8%), bronchiolitis (4.9%), tonsillitis (2.5%), encephalitis (2.5%) and dengue fever (1.2%). There were 6 cases (7.4%) with an initial diagnosis of unspecific fever. Most patients coming for care have typical influenza-like illness, with fever (98.8%), cough (92.6%), rhinorrhea (74.1%), dyspnea (32.1%) and sore throat (16.1%). Systemic symptoms were frequent. Gastrointestinal symptoms, including vomiting (46.9%), diarrhea (24.7%) and abdominal pain (7.4%) occurred more commonly than seasonal influenza. Pneumonia was the most common complication of the 2009 H1N1 virus infection. Other complications included bronchiolitis, hemoptysis, acute respiratory distress syndrome (ARDS), sinusitis and encephalitis. One case of a 7 year old girl infected by 2009 H1N1 virus suffered from ARDS, sepsis, multi-organ dysfunction syndrome and ventilator associated pneumonia, but survived with some neurological sequelae. There were 3 cases of encephalitis presenting with drowsiness and seizure.

Approximately one quarter (25.9%) of patients with 2009 H1N1 virus infection, who were hospitalized, had coexisting medical conditions. Underlying conditions that are associated with complications from 2009 H1N1 virus infection include asthma (6.2%), allergic rhinitis (4.9%), congenital heart disease (3.7%), Thalassemia (3.7%), G6PD deficiency (2.5%), etc (Table 1). Radiographic findings of 35 cases (43.2%) with complicated pneumonia included perihilar infiltrate (42.9%), diffuse mixed interstitial (45.7%) and alveolar (22.9%) infiltrates, lobar consolidation (5.7%) and atelectasis (5.7%) (Table 2).

Almost all patients (91.4%) were treated with the neuraminidase inhibitor oseltamivir (Tamiflu). The other antibiotics include ceftriaxone, cefotaxime, azithromycin, and ampicillin were added on for treatment of complicated pneumonitis. Approximately one quarter (25.9%) of patients, who had complicated pneumonitis, need oxygen therapy. The ARDS case need high frequency oscillator ventilation for respiratory support. All patients in the present study survived.

Discussion

There were 2 waves of epidemic outbreak of pandemic 2009 influenza A (H1N1) in the present study. The first wave in June to August 2009 was similar to

Table 1. Epidemiologic features, preexisting conditions, clinical status and complications in children hospitalized with 2009 H1N1 virus infection

Variable	No.(%)
Age (Yr) (n = 83)	
< 1	7 (8.4)
1-5	40 (48.2)
6-10	26 (31.3)
11-15	9 (10.8)
16-20	1 (1.2)
Male sex	47 (56.6)
Preexisting condition (n = 81)	
AR	4 (4.9)
Asthma	5 (6.2)
TB	1 (1.2)
CLD	1 (1.2)
CHD	3 (3.7)
Thalassemia	3 (3.7)
G6PD deficiency	2 (2.5)
Down syndrome	1 (1.2)
Signs and symptoms (n = 81)	
Fever	80 (98.8)
Cough	75 (92.6)
Rhinorrhea	60 (74.1)
Sore throat	13 (16.1)
Dyspnea	26 (32.1)
Headache	12 (14.8)
Myalgia	12 (14.8)
Abdominal pain	6 (7.4)
Vomiting	38 (46.9)
Diarrhea	20 (24.7)
Drowsy	25 (30.9)
Seizure	1 (1.2)
Complications (n = 81)	
Pneumonia	35 (43.2)
Bronchiolitis	2 (2.5)
Sinusitis	3 (3.7)
OM	1 (1.2)
ARDS	1 (1.2)
Hemoptysis	3 (3.7)
Encephalitis	3 (3.7)
Oxygen supplementation	21 (25.9)
Use of mechanical ventilation	1 (1.2)

AR: allergic rhinitis, TB: tuberculosis, CLD: chronic lung disease, CHD: congenital heart disease, OM: otitis media, ARDS: acute respiratory distress syndrome

Table 2. Chest x-rays finding in pneumonia complicated children hospitalized with 2009 H1N1 virus infection (n = 35)

CXR finding	No. (%)
Perihilar infiltration	15 (42.9)
Interstitial infiltration	16 (45.7)
Patchy infiltration	8 (22.9)
Consolidation	2 (5.7)
Atelectasis	2 (5.7)

the global pandemic[4,10]. The second wave from January to February 2010 was due to antigenic drip of pandemic 2009 H1N1 virus.

The highest attack rate was among children age 1-5 years old (48.2%). The attack rate in infants was only 8.4%, which is different from Argentina with the highest attack rate in infants (60%)[11]. One case of a 29-day old newborn contracted from her mother during the postpartum period, but suspected transplacental transmission of the 2009 H1N1 virus was reported from Thailand[12]. The correct provisional diagnosis of 2009 H1N1 virus infection is high (39.5%) due to QSNICH being the referral center, so many cases were already confirmed for influenza infection by RT-PCR or rapid influenza antigen assay. However, the wide clinical spectrum of 2009 H1N1 virus infection and its features that overlapped with those of other common infections, sometimes led to misdiagnosis[13]. Infection with the 2009 H1N1 virus caused a broad spectrum of clinical syndromes, ranging from afebrile upper respiratory illness to fulminant pneumonia and ARDS[14]. Most patients had typical influenza-like illness (ILI) with fever, cough, rhinorrhea and sore throat[2,11,14-17]. Gastrointestinal symptoms (including nausea, vomiting, and diarrhea) occurred more commonly than in seasonal influenza[10,18]. The principal clinical syndrome leading to hospitalization and intensive care was diffuse pneumonia, ARDS, encephalitis, which is similar to the other reports[19-21]. The 2009 H1N1 virus infection can cause severe, prolonged exacerbation of asthma. Among hospitalized patients with 2009 H1N1 infection a history of asthma was reported in 6.2%, less than that reported from California, USA (24%)[22]. Radiographic findings of complicated pneumonitis were compatible with viral pneumonia, but in some cases lobar consolidation could be from bacterial coinfection[19,20,23].

The currently circulating 2009 H1N1 virus is susceptible to the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza), but is almost always resistant to amantadine and rimantadine[6,10]. Therapy with a neuraminidase inhibitor is especially important for patients with underlying risk factors. In the present study, almost all patients treated with oseltamivir, only

some patients did not get oseltamivir due to the patients recovering before the laboratory confirmed for 2009 H1N1 infection.

Conclusion

A large amount of information about the natural history and clinical management of 2009 H1N1 virus infection has been obtained in a short period of time, but considerable gaps remain. The burden and character of pandemic influenza infection in developing countries are not still fully understood. Pneumonia is the major complication for hospitalization especially in high risk groups. Available findings highlight the importance of early use of oseltamivir and antibiotics in the treatment of serious cases and of the potential value of influenza and pneumococcal vaccines for prevention.

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Potential conflicts of interest

None.

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อาการแสดงของผู้ป่วยไข้หวัดใหญ่สายพันธุ์ใหม่ 2009 (เอช1 เอ็น1) ในเด็กไทย

สรศักดิ์ โล่ห์จินดารัตน์, ธัญญณัฐ บุนนาค

ภูมิหลัง: *ไข้หวัดใหญ่สายพันธุ์ใหม่ ชนิดเอ (เอช1 เอ็น1) ที่ได้รับสารพันธุกรรมมาจากหมู ทำให้เกิดการติดเชื้อของระบบหายใจในประชากรของประเทศแมกซิโก ตั้งแต่ฤดูใบไม้ผลิของปี พ.ศ. 2552 หลังจากนั้นเชื้อไวรัสนี้ได้มีการระบาดใหญ่ลุกลามไปทั่วโลกอย่างรวดเร็ว*

วัตถุประสงค์: *เพื่อสังเกตอาการแสดงของผู้ป่วยไข้หวัดใหญ่สายพันธุ์ใหม่ 2009 ที่มารับการรักษาแบบผู้ป่วยในและติดตามระลอกของการระบาดใหญ่เป็นระยะเวลานาน 1 ปี*

วัสดุและวิธีการ: *เฝ้าติดตามลักษณะทางคลินิกของผู้ป่วยเด็กอายุน้อยกว่า 18 ปี ได้รับการยืนยันว่าป่วยด้วยไข้หวัดใหญ่สายพันธุ์ใหม่ 2009 โดยวิธี RT-PCR รับการรักษาแบบผู้ป่วยใน ณ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี กรุงเทพฯ ระหว่างวันที่ 1 มิถุนายน พ.ศ. 2552 ถึง 31 พฤษภาคม พ.ศ. 2553 เป็นเวลา 1 ปี*

ผลการรักษา: *ผู้ป่วยไข้หวัดใหญ่สายพันธ์ใหม่ที่เข้ารับการรักษาจำนวน 83 ราย ในระยะเวลา 1 ปี มีการระบาดใหญ่เป็น 2 ระลอก โดยระลอกแรกในช่วงเดือนมิถุนายน ถึง สิงหาคม พ.ศ. 2552 และในระลอกที่ 2 ในช่วงเดือนมกราคม ถึง กุมภาพันธ์ พ.ศ. 2553 เป็นเพศชาย 47 คน (56.6%) กลุ่มอายุที่มีผู้ป่วยจำนวนสูงสุดคือ 1-5 ปี (48.2%) ผู้ป่วยที่มีอายุน้อยที่สุดคืออายุ 29 วัน ผู้ป่วยที่ได้รับการวินิจฉัยถูกต้องตั้งแต่แรกรับคิดเป็นร้อยละ 39.5 สำหรับการวินิจฉัยเบื้องต้นในผู้ป่วยรายอื่นๆ ได้แก่ ปอดอักเสบ หลอดลมฝอยอักเสบ ต่อมทอนซิลอักเสบ ไข้สมองอักเสบ และไข้เลือดออก ผู้ป่วยส่วนใหญ่มาด้วยอาการของไข้หวัดใหญ่ คือ ไข้ (98.8%) ไอ (92.6%) และน้ำมูก (74.1%) อาการทางระบบทางเดินอาหารได้แก่ อาเจียน (46.9%) และท้องเสีย (24.7%) พบได้บ่อยกว่าผู้ป่วยไข้หวัดใหญ่ตามฤดูกาล ภาวะแทรกซ้อนที่พบบ่อยที่สุด คือ ปอดอักเสบ สำหรับภาวะแทรกซ้อนอื่นๆ ได้แก่ หลอดลมฝอยอักเสบ ไอเป็นเลือด ARDS และสมองอักเสบ รายงานผู้ป่วยหญิงอายุ 7 ปี มาด้วยภาวะ ARDS, muti-organ dysfunction syndrome และ ventilator associated pneumonia ได้รับการรักษาจนรอดชีวิต แต่มีภาวะแทรกซ้อนทางสมอง ภาพรังสีทรวงอกที่พบได้แก่ interstitial, alveolar และ lobar infiltrations ยาต้านไวรัสหลักที่ใช้คือ oseltamivir สำหรับยาปฏิชีวนะอื่นที่ใช้รักษาภาวะปอดอักเสบได้แก่ ceftriaxone, cefotaxime, ampicillin และ azithromycin ในการศึกษานี้ไม่มีผู้ป่วยเสียชีวิต*

สรุป: *ผลกระทบและลักษณะของการระบาดใหญ่ไข้หวัดใหญ่สายพันธุ์ใหม่ 2009 ในประเทศที่กำลังพัฒนายังไม่ได้ข้อสรุปที่แน่ชัด อย่างไรก็ตามในช่วงที่มีการระบาดของโรคในชุมชนการรักษาโดย oseltamivir ในผู้ป่วยหนักตั้งแต่ระยะแรกของโรคสามารถลดความรุนแรงของโรคและภาวะแทรกซ้อนลงได้*