A Novel Influenza A H1N1 Clinical Manifestations in Patients at Chiang Mai University Hospital

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Objective: *To describe the clinical manifestations of patients affected with a novel influenza A (H1N1 2009) during the pandemic*

Material and Method: *A retrospective study was conducted in patients with influenza-like illness receiving care at Chiang Mai University Hospital between June 1 and September 30, 2009. The inclusion criteria were as follows 1) patients had influenza-like illness that was defined as fever, with cough and/ or sore throat, 2) detection of influenza A H1N1 2009 by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swabs or throat swabs.*

Results: *Among 278 patients, 150 patients (54.0%) were male and the mean age was 21.4 $\pm$ 13.1 years (range 1-74). Eighty-seven patients (31.3%) were in age group 15-19 years. Fifty-eight patients (20.9%) had underlying diseases and asthma was the most common health problem. The presenting symptoms were cough (dry or productive) (248 patients, 89.2%), fever $\geq$ 38.0°C (229 patients, 82.4%), sore throat (195 patients, 70.1%), rhinorrhea (126 patients, 45.3%) and myalgia (113 patients, 40.6%). Five patients had co-infection at admission, three patients had dengue hemorrhagic fever, one patient had mycoplasma infection, and the other one with Acinetobacter lwoffii bacteremia. One hundred forty four patients (51.8%) received oseltamivir. Two hundred seventy two patients (97.8%) recovered without complications. One pregnant-woman developed severe pre-eclampsia five days after the first symptom, one patient developed Guillain Barre syndrome 10 days after the first symptoms. Four patients died, all had pneumonia.*

Conclusion: *Younger people were more likely to be infected with influenza A H1N1 2009. The clinical manifestations were similar to the seasonal influenza. However, the mortality rate was much higher, particularly in patients who developed pneumonia. In this study, all patients who died had existing underlying medical conditions.*

Keywords: *Novel influenza A (H1N1), Clinical manifestations*

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A novel influenza A (H1N1) was recognized in April 2009 in Mexico and caused human diseases mainly respiratory illness throughout the world[1]. The World Health Organization (WHO) declared a pandemic stage of novel influenza A (H1N1) on June 11, 2009[2]. This was the first pandemic influenza since 1968, with illnesses occurring outside the influenza season[3]. It caused unusual clinical patterns in which the younger age groups experienced more severe symptoms than older people. As of August 1, 2010, there were more than 214 affected countries and at least 18,449 deaths due to this pandemic H1N1 influenza. These numbers underestimated the actual numbers as many infections and deaths were not tested or recognized as influenza related[4]. In Thailand, as of July 31, 2010, there were 37,496 confirmed cases and 235 deaths[5].

Currently, as pandemic H1N1 virus has spread to all countries, many people in all age groups have some immunity to the new virus, resulting in no large or unusual summer outbreak has occurred in either the northern or southern hemispheres. Seasonal influenza A (H3N2) and influenza B viruses are also being reported in many countries. Therefore, WHO declared a post-pandemic stage on August 10, 2010. The pandemic pattern is transitioning to a seasonal pattern of influenza. It is expected that this new virus will remain for many years[6].

The present study aimed to describe the clinical manifestations of patients affected with

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influenza A H1N1 2009 receiving care at Chiang Mai University (CMU) Hospital, in the northern part of Thailand, during the pandemic stage.

Material and Method

A retrospective study was conducted among patients with influenza-like illness at Chiang Mai University Hospital between June 1 and September 30, 2009. The inclusion criteria were: 1) patients who had an influenza-like illness which was defined as body temperature of 38.0°C or greater or patients who had no fever but received an antipyretic drug within 4-6 hours, with cough and/ or sore throat and 2) detection of influenza A H1N1 2009 by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swabs or throat swabs. During the first phase of the pandemic in Thailand (May to mid July, 2009), the RT-PCR was performed to detect new cases to prevent transmission to others. In the later phase (after mid July 2009) when the virus had already spread throughout the country, the RT-PCR was performed to detect patients who required hospitalization or who had severe diseases such as dyspnea, syncope, hypotension, or alteration of consciousness. For those who were healthcare workers (HCWs), RT-PCR was performed in all cases to prevent transmission to other HCWs or patients.

Clinical data were retrospectively collected using a pre-printed data collection form. The present study was approved by the Faculty of Medicine, Chiang Mai University Ethical Committee.

Statistical analysis

Clinical data were presented in numbers (percent), mean and standard deviation (SD) and range. Comparisons between patient groups were performed using Student's t-test, Mann-Whitney U test, Chi-square test or Fisher's exact test as appropriate. Variables with a p-value < 0.10 from univariable analysis were then tested in multivariable models. All statistical analyses were performed using Stata statistical software version 10.0 (Stata Statistical Software; Release 10.0, Stata Corporation, College Station, TX, 2007). A two-sided test at a p-value of < 0.05 was used to indicate statistical significance.

Results

Demographic data

During the study period, there were 12, 236 patients with influenza-like illness receiving care at CMU Hospital (Fig. 1). RT-PCR from nasopharyngeal swabs or throat swabs was performed in 1,029 patients (8.4%). It was positive for novel influenza A (H1N1) in 395 patients (38.4%), influenza A H3N2 in two patients (0.2%), and influenza B in one patient (0.1%). The first confirmed case was reported on June 14, 2010. She was a college student who had just come back from the United States two days before having symptoms.

Among the 395 patients with positive RT-PCR for novel influenza A (H1N1), 40 patients had no medical records available for review and 77 patients had no relevant clinical information recorded. Therefore, only 278 patients were included in the analysis. One hundred fifty patients (54.0%) were male. The mean age was 21.4 ± 13.1 years (range 1-74). Eighty-seven patients (32.3%) were in the 15-19 year age group (Fig. 2). One hundred nine patients (39.2%) were students or college students. One hundred sixty patients (57.6%) had the illness in July 2009.

Fifty-eight patients (20.9%) had underlying diseases of which asthma was the most common. Two patients had body mass index ≥ 30 kg/m^2 (Table 1). Seventeen patients had H1N1 pneumonia,

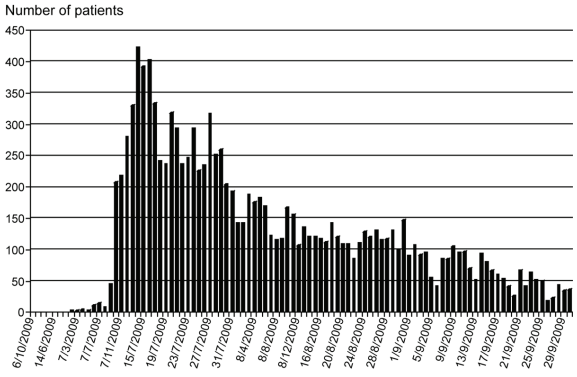

Fig. 1 Number of patients with influenza-like illness receiving care at Chiang Mai University hospital

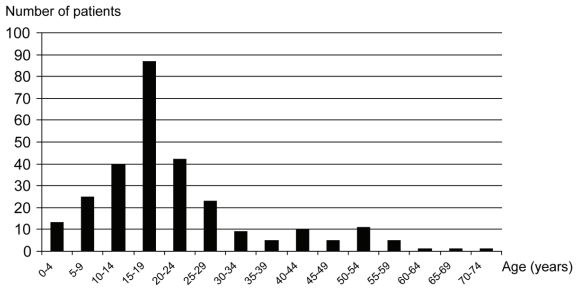

Fig. 2 Number of patients infected with novel influenza H1N1by age-group

Table 1. Demographic data of 278 patients infected with novel influenza H1N1

Characteristics	Number (%) or mean ± SD
Male	150 (54.0)
Age (years)	21.4 ± 13.1
Occupation	
Students and college students	109 (39.2)
Healthcare personnel	23 (8.3)
Physicians	10 (3.6)
Pharmacist	1 (0.4)
Nurse	7 (2.5)
Nurse assistant	2 (0.7)
Medical students	3 (1.0)
Others	5 (1.8)
Unspecified	141 (50.7)
Underlying diseases	58 (20.9)
Asthma	17 (6.1)
Hypertension	10 (3.6)
Diabetes	4 (1.4)
Chronic kidney diseases	3 (1.1)
Chronic obstructive pulmonary diseases (COPD)	2 (0.7)
Human immunodeficiency virus (HIV) infection	1 (0.4)
Congestive heart failure	1 (0.4)
Cirrhosis	1 (0.4)
Pregnancy	1 (0.4)
Postsplenectomy	1 (0.4)
Others	17 (6.1)
Body weight* (kg)	49.3 ± 19.4 (range 5.2-115)
Body mass index** (kg/m^2)	22.5 ± 4.3 (range 15.1-34.2)
< 18.50 (underweight)	4 (12.1)
18.50-24.99 (normal range)	23 (69.7)
25.00-29.90 (overweight)	4 (12.1)
≥ 30.00 (obesity)	2 (6.1)

* Data available from 154 patients
** Data available from 32 patients

eight of them (47.1%) had underlying diseases that included chronic kidney disease (3 patients), diabetes (2 patients), congestive heart failure (1 patient), dilated cardiomyopathy (1 patient), asthma (1 patient), cirrhosis (1 patient), valvular heart disease (1 patient) and bronchopulmonary dysplasia (1 patient). Three patients had more than one underlying medical illnesses.

Clinical manifestations

Among 278 patients included in the analysis, the mean duration from the first symptom to hospital visit was 2.2 ± 2.1 days (range 1-21, median 2) (Table 2). One patient reported a history of rhinorrhea without influenza-like illness for almost three weeks.

Five patients had co-infection with other pathogen at admission, three had dengue hemorrhagic fever, one had mycoplasma infection, and one had *Acinetobacter lwoffii* bacteremia.

Investigation

Laboratory findings are shown in Table 3. Seventeen patients had pneumonia had abnormal chest radiography and included 11 patients had bilateral interstitial infiltration, three patients had right lower lung interstitial infiltration, one patient each had right perihilar infiltration, right lower lung alveolar infiltration, and bilateral alveolar infiltration.

Treatment

One hundred seventeen of the 278 patients (42.1%) needed hospitalization. Four patients were admitted to the intensive care unit due to respiratory failure. All four had pneumonia.

Table 2. Clinical manifestations of 278 patients infected with novel influenza H1N1

Clinical manifestations	Number (%) or mean ± SD
Body temperature (°C)	38.5 ± 1.03
37.3-37.9	17 (6.1)
38.0-38.9	115 (41.4)
≥ 39.0	114 (41.0)
Dry or productive cough	248 (89.2)
Sore throat	195 (70.1)
Runny nose/Rhinorrhea	126 (45.3)
Myalgia	113 (40.6)
Headache	98 (35.3)
Nausea/vomitting	39 (14.0)
Shortness of breath	33 (11.9)
Sneezing	31 (11.2)
Diarrhea	27 (9.7)
Conjunctivitis	9 (3.2)
Alteration of consciousness (drowsiness)	3 (1.1)
Duration from onset to hospital visit* (days)	
Mean	2.2 ± 2.1
Median	2
< 3	191 (70.2)
3-5	71 (26.1)
> 5	10 (3.7)

* Data available from 272 patients

Table 3. Results of laboratory tests of 278 patients infected with novel influenza H1N1

Laboratory tests	Number (%) or mean ± SD
Hemoglobin (g/dL)	12.9 ± 1.7
White blood cell count (cells/mm^3)	
Mean*	6,753 ± 2,449
Range	55-19,560
< 4,000 cells/mm^3	12 (3.4)
> 10,000 cells/mm^3	12 (3.4)
Absolute lymphocyte count (cells/mm^3)	
Mean	1,252 ± 894
Range	121-5,868
Platelet count (/mm^3)	
Mean**	204,000 ± 63,585
Range	21,400-9,450,000
AST > 40 U/L***	13 (33.3)
ALT > 40 U/L***	7 (17.9)

* Did not include 1 patient who had white blood cell count 55 cells/mm^3

** Did not include 1 post-splenectomized patient who had platelet count 9,450,000 /mm^3

*** Data available from 39 patients

One hundred forty four of the 278 patient (51.8%) received oseltamivir and 97 of these 144 were hospitalized. The duration from the first symptoms to receiving oseltamivir was 3.1 ± 2.5 days (median 2, range 1-20). Inpatients received oseltamivir 3.0 ± 2.5 days after the first symptoms (median 2, range 1-20). Outpatients received oseltamivir 3.2 ± 2.6 days after the first symptoms (median 2, range 1-15). Overall, 76 patients (27.3%) received oseltamivir within 48 hours after the first symptoms.

Outcomes

Two hundred seventy two patients (97.8%) recovered without complications. One pregnant woman developed severe pre-eclampsia five days after her first symptoms. One patient developed Guillain Barre syndrome 10 days after her first symptoms. She also developed respiratory failure and required a respirator. Four patients died (1.4%). The first case was a 1-year-old boy, who had bronchopulmonary dysplasia. He had pneumonia and died from respiratory failure. The second case was a 24 year-old male, who had chronic kidney disease and hypertension. He had pneumonia and died from severe metabolic acidosis. The third case was a 57 year-old male, who had pre-existing dilated cardiomyopathy and cirrhosis. He had pneumonia and received oseltamivir 20 days after the first symptoms. He died from *Pseudomonas aeruginosa* septicemia during the course of hospitalization. The fourth case was a 40 year-old female, who had valvular heart disease and required warfarin therapy. She had clinical improvement after receiving oseltamivir. However, she developed intracerebral hemorrhage from warfarin overdose. The mortality rate was 23.5% among the patients who had pneumonia.

One hundred thirty four patients (49.6%) had clinical resolution without antiviral therapy. Available data from 127 patients demonstrated that fever disappeared in 4.3 ± 1.9 days (median = 4).

Of the 144 patients who received oseltamivir, 97 inpatients and seven outpatients had available data on defervescence. The duration from receiving oseltamivir to defervescense was 1.7 ± 1.0 days (median 2, and range 0-5). Patients who received oseltamivir within and after 48 hours had similar defervescense time. (2.3 ± 1.5 days vs. 1.6 ± 1.0 days, respectively, p-value 0.13). Fifty-one patients (49.0%) defervesced within 48 hours after receiving oseltamivir. (Fig. 3). The three patients who had dengue hemorrhagic fever co-infection had longer defervescense time

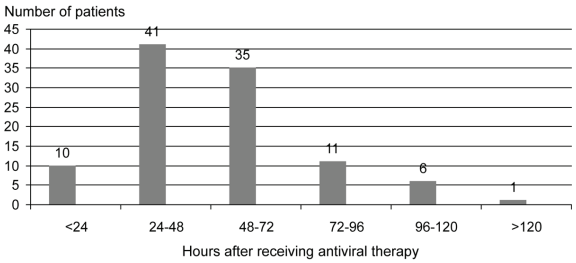

Fig. 3 Duration of defervescense in 104 patients who received antiviral therapy

(day 5-6 after the first symptoms) despite having received oseltamivir.

Discussion

As influenza virus is easily transmitted through droplet or close contact. It is not surprisingly that the majority of patients were students and college students. During the first phase of the pandemic, the schools and colleges were in session. The patients' ages ranged from 1-74 years. However, 82.7% of the presented patients aged < 30 years. This result corresponded with other reports from Mexico[7], USA[8], and China[9], where younger people were more likely to get infected. Partial immunity to this novel influenza virus in adults older than 60 years may explain this phenomenon[10].

Clinical manifestations were similar to seasonal influenza[11]. These were acute fever, cough, and sore throat. In the present study, the majority (96.3%) had fever for less than five days before seeking medical care. Headache and myalgia, which were also reported in seasonal influenza[11,12], were found in 40% of the presented patients. Dyspnea was found in 11.9% of the presented patients and in 64.7% among patients who had pneumonia. This corresponded to reports from the USA, in which the study population were hospitalized patients[8, 13] (Table 4).

Sixteen percent of the presented patients and 47% of those who had pneumonia had underlying medical conditions. Previous reports found that

Table 4. Comparisons of characteristics of patients infected with novel influenza H1N1 from various countries

Characteristics	Mexico[7] (n = 18)	USA[8] (n = 272)	China[9] (n = 426)	This study (n = 278)
Study population	Hospitalized patients with pneumonia	Hospitalized patients	Quarantined patients	Outpatients and hospitalized patients
Male (%)	50	51	53.8	54.0
Age (years) (median)	38	21	23.4	18.0
Patients with underlying diseases (%)	44.4	73	7.2	20.9
Clinical manifestations (%)				
Body temperature ≥ 38.0°C	100	95	36	82.4
Dry or productive cough	100	88	69.5	89.2
Sore throat	NA	31	36.6	70.1
Runny nose/ Rhinorrhea	28	38	23.7	45.3
Shortness of breath	100	60	NA	11.9
Conjunctivitis	NA	NA	2.8	3.2
Diarrhea	22	24	2.8	9.7
Nausea/vomiting	NA	29	1.9	14.0
Headache	22	34	19.5	35.3
Myalgia	44	36	10.1	40.6
Laboratory tests (mean ± SD)				
Hemoglobin (g/dL)	NA	NA	13.51 ± 1.48	12.9 ± 1.7
White blood cell count (cells/mm^3)	6,000	NA	3,440 ± 220	6,753 ± 2,449
Absolute lymphocyte count (cells/mm^3)	850	NA	1,399.34 ± 776.73	1,252 ± 894
Platelet count (/mm^3)	NA	NA	201,200 ± 59,000	204,000 ± 63,585
AST > 40 U/L (%)	NA	44	10.1	33.3
ALT > 40 U/L (%)	NA	45	8.8	17.9

NA = not available

patients who had BMI > 30 kg/m^2 were at risk of developing severe pneumonia[8,13,14]. One report from the USA found that 29% of pneumonia patients had BMI > 30 kg/m^2. However, because of the lack of data on weight and height in many patients in the present study, the authors could not demonstrate this effect.

The mean white blood cell count in the present study was in the normal range (6,753 $\pm$ 2,449 cell/mm^3) which differed from the report from China, which was 3,440 $\pm$ 220 cell/mm^3. One of the presented patients who was on chemotherapy and had white blood cell count of 55 cells/mm^3 was excluded from the analysis. The platelet count was in normal range, except for thrombocytopenia in the three patients who had co-infections with dengue hemorrhage fever. Chest radiograph showed mostly bilateral interstitial infiltration patterns in patients who had pneumonia. Almost 50% had clinical resolution without antiviral therapy. However, since the present study included only patients who sought medical care, and RT-PCR in the later phase of the pandemic was performed only in those who were hospitalized, there were many patients who did not seek medical care and who were never tested or recognized as cases of influenza. Thus, the presented number may underestimate the actual number of patients who resolved without antiviral therapy.

One hundred forty four patients received oseltamivir. Fifty-one percent of the patients defervesced within 48 hours after the initiation of treatment, even though the medicine was started more than 48 hours after the onset of illness.

The mortality rate in the present study was 1.4%, which was much higher than that of seasonal influenza[15]. However, it may be difficult to compare the mortality rate in novel influenza with that of seasonal influenza, because not all patients who got sick with seasonal influenza sought medical care and fewer patients who got sick received antiviral treatment. The mortality rate in the present study was lower than reports from the USA and Argentina[8,16], due to the severity of illness in patients included in those studies. All four deaths occurred in patients who had underlying medical conditions, which were similar to seasonal influenza in which patients at risk of developing severe diseases had underlying medical illnesses[14,17]. However, the authors cannot conclude that patients who had underlying diseases were more likely to have unfavorable outcome, due to the small number of deaths. Epidemiologic studies reported that although older people were less likely to be infected with novel influenza, the case-fatality ratio was higher. The case-fatality ratio was 6% among adults aged > 50 years, whereas it was 1-2% among children[10,18].

Three patients who had co-infections with dengue hemorrhagic fever. All patients had serologic study confirmation. All presented with fever, cough and/or sore throat, and myalgia. They had high-grade fever even after 3-4 days of oseltamivir treatment. This finding should raise the awareness of physicians who take care of patients in endemic areas of tropical diseases.

One patient developed Guillain Barre syndrome (GBS) 10 days after the first onset of respiratory illness and after a complete course of oseltamivir. The incidence of GBS was 1-2 patients/ 100,000 population[19]. It may follow infections particularly those caused by *Campylobacter jejuni*. There were also reports of GBS following influenza virus infection or influenza virus vaccination[19]. Report of GBS following novel influenza was rare[20]. In children, neurological manifestations associated with novel influenza included encephalitis and seizure[21].

Limitation

The present study does have several limitations. Firstly, this is a retrospective study; therefore, there were incomplete data due to the nature of the study. Thirty percent of patients had no medical records or clinical data available. Secondly, the guideline for performing RT-PCR was not consistent throughout the study period, which resulted in heterogeneity of the study population. Generalization to all patients who had a novel influenza A (H1N1) infection needed to be interpreted with caution.

Conclusion

People aged < 30 years were predisposed to be infected with influenza A H1N1 2009. The clinical manifestations were similar to those of the seasonal influenza. The symptoms may resolve without antiviral therapy. The mortality rate was much higher than that of seasonal influenza, particularly in patients who developed pneumonia. All deaths in the present study occurred in patients with underlying medical conditions. Eighty-six percent of patients had fever resolution within 72 hours. Co-infections with other pathogens should be considered when the response was delayed or the manifestation included unexpected features.

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Potential conflicts of interest

None.

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ลักษณะทางคลินิกของผู้ป่วยไข้หวัดใหญ่ชนิดเอเอชหนึ่งเอ็นหนึ่งสายพันธุ์ 2009 ที่เข้ารับการรักษาในโรงพยาบาลมหาราชนครเชียงใหม่

รมณีย์ ชัยวาฤทธิ์, นิพพิชฌน์ พรหมมี, เฉลิม ลิ่วศรีสกุล, เพณณินาท์ โอเบอร์ดอร์เฟอร์, นนทกานต์ นันทจิต, ชายชาญ โพธิรัตน์

วัตถุประสงค์: *เพื่อรวบรวมข้อมูลอาการทางคลินิกของผู้ป่วยไข้หวัดใหญ่ชนิดเอเอชหนึ่งเอ็นหนึ่งสายพันธุ์ 2009*
วัสดุและวิธีการ: *การศึกษาย้อนหลังในผู้ป่วยที่มาตรวจด้วยอาการคล้ายไข้หวัดใหญ่ที่โรงพยาบาลมหาราชนครเชียงใหม่ตั้งแต่วันที่ 1 มิถุนายน พ.ศ. 2553 ถึง 30 กันยายน พ.ศ. 2553 เกณฑ์การคัดเลือกผู้ป่วยประกอบด้วย 1) มีอาการคล้ายไข้หวัดใหญ่ ได้แก่ ไข้ ไอ และ/หรือเจ็บคอ 2) ตรวจพบสารพันธุกรรมของเชื้อไวรัสไข้หวัดใหญ่ ชนิดเอเอชหนึ่งเอ็นหนึ่งสายพันธุ์ 2009 จากสิ่งส่งตรวจจากโพรงจมูกหรือคอ*
ผลการศึกษา: *ผู้ป่วยทั้งสิ้น 278 ราย เป็นเพศชาย 150 ราย (ร้อยละ 54.0) เพศหญิง 128 ราย (ร้อยละ 46) อายุเฉลี่ย 21.4 ± 13.1 ปี (พิสัย 1-74 ปี) ผู้ป่วย 87 ราย (ร้อยละ 31.3) อายุระหว่าง 15-19 ปี ผู้ป่วย 58 ราย (ร้อยละ 20.9) มีโรคประจำตัวอยู่เดิม และโรคหอบหืดเป็นโรคที่พบได้บ่อยที่สุด อาการนำที่พบได้บ่อยได้แก่ ไอ (ร้อยละ 89.2) ไข้ (ร้อยละ 82.4) เจ็บคอ (ร้อยละ 70.1) มีน้ำมูก (ร้อยละ 45.3) และปวดเมื่อยกล้ามเนื้อ (ร้อยละ 40.6) ผู้ป่วย 5 ราย มีการติดเชื้ออื่นร่วมด้วยเมื่อรับไว้ในโรงพยาบาล ได้แก่ ไข้เลือดออก 3 ราย ติดเชื้อไมโคพลาสมา 1 รายและติดเชื้อ Acinetobacter iwoffii 1 ราย ผู้ป่วย 144 ราย ได้รับยาต้านไวรัส oseltamivir ผู้ป่วย 272 ราย หายโดยไม่มีภาวะแทรกซ้อน หญิงตั้งครรภ์ 1 ราย เกิดภาวะ pre-eclampsia และผู้ป่วย 1 รายเกิดภาวะ Guillain Barre syndrome ผู้ป่วย 4 รายเสียชีวิตจากปอดอักเสบ*
สรุป: *ผู้ป่วยติดเชื้อไวรัสไข้หวัดใหญ่ชนิดเอเอชหนึ่งเอ็นหนึ่ง 2009 ส่วนใหญ่มีอายุน้อย อาการ และอาการแสดงไม่แตกต่างจากไข้หวัดใหญ่ตามฤดูกาลแต่มีอัตราการเสียชีวิตที่สูงกว่า สาเหตุของการเสียชีวิตเกิดจากปอดอักเสบ ผู้ป่วยที่เสียชีวิตทุกรายมีโรคประจำตัว*