

ORIGINAL ARTICLE

## CLINICAL PROFILE AND OUTCOME OF PEDIATRIC PATIENTS WITH REVERSE TRANSCRIPTION-POLYMERASE CHAIN REACTION (RT-PCR)-CONFIRMED INFLUENZA A (H1N1)

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**ABSTRACT**

**Background:** The World Health Organization declared on June 11, 2009 the first pandemic of the 21<sup>st</sup> Century caused by the novel Influenza A (H1N1) virus. The virus was observed to be clinically similar to the seasonal influenza, in which case, patients recover even without medical treatment. The virus affected the younger age group even those who are healthy, which make it different from seasonal flu.

**Objective:** The study aimed to describe the clinical profile and outcome of pediatric patients with Reverse Transcription-Polymerase Chain Reaction (RT-PCR)-confirmed Influenza A (H1N1).

**Methodology:** Pediatric patients of the Lung Center of the Philippines seen from May 1 to July 31, 2009 for Influenza-like illness upon presentation and confirmed to have Influenza A (H1N1) virus through Reverse Transcription-Polymerase Chain Reaction (RT-PCR) assay were included in the study. Charts of patients were reviewed. Information from patients was obtained using the WHO Case Summary Form and the National Epidemiology Center Initial Screening of Influenza A (H1N1) form. The patient's demographic data, clinical characteristics, co-morbid conditions, vaccination, clinical course, complications, anti-viral medications received and adverse reactions, and over-all outcome were noted, as well as, exposure to confirmed cases and history of travel.

**Results:** Out of the 243 RT-PCR-confirmed patients, 71.6% (n=174) came from the adolescent age group, with a median age of 13 years old. A predominance of male patients (57.2%) was noted. Fever (92%), cough (83.1%), nasal congestion (52.7%) and sore throat (35%) were the most common presenting signs and symptoms. Bronchial asthma (14.4%) was the leading co-morbidity present and pneumonia was the most common complication. Eight patients (3.3%) were hospitalized during the course of the disease. All RT-PCR-confirmed Influenza A (H1N1) patients recovered and no mortality was noted.

**Conclusions:** In this study, majority of the RT-PCR-confirmed Influenza A (H1N1) patients were characterized by self-limited, uncomplicated, and febrile respiratory illness, who all recovered with minimal complications.

## INTRODUCTION

In June 11, 2009 World Health Organization (WHO) Director General Margaret Chan declared a pandemic alert level 6 due to the spread and outbreak of the Influenza A (H1N1) virus in at least two countries within the WHO region.<sup>1</sup> The epidemic was caused by the swine-origin Influenza A (H1N1) virus (S-OIV) which was said to be made up of the HA gene derived from the 1918 swine flu virus and other genes from human, avian and Eurasian swine influenza viruses.<sup>2</sup> The virus has initially affected the United States and Mexico (North America), which were the epicenters of the pandemic, and has increasingly spread in Europe, Latin America, Australia, and the South East Asian region.<sup>3</sup> Aside from the fact that the virus can be easily transmitted, it showed clinical similarity to seasonal influenza wherein majority of patients recovered and survived even without medical treatment.

As of October 25, 2009, WHO reported nearly 440,000 of laboratory-confirmed cases of Influenza A (H1N1) virus and 5700 mortalities in 180 countries, with the number of cases continuing to increase in Central America and the tropical regions of Asia.<sup>3,4</sup> Notably, the proportion of cases in Asia that are related to seasonal influenza A (H3N2) continue to decline globally while the proportion related to the pandemic H1N1 in 2009 virus increases.<sup>5</sup> Meanwhile, in the WHO geographic map of Influenza Activity, the Philippines did not show any available information as regards Influenza A (H1N1) disease activity.

In the Philippines, the Department of Health (DOH), which heads the task force for the Pandemic Response to Influenza A (H1N1) virus, started its screening late April 2009 with the first RT-PCR-confirmed Influenza A (H1N1) case reported on May 22, 2009. The first patient was a ten-year old girl who presented with an influenza-like illness after arriving from the United States along with her family.<sup>6</sup> On June 14,

2009, the first community outbreak was declared in Jaen, Nueva Ecija, after ten grade school pupils were found to be positive for the virus. Since then, the confirmed cases have continued to grow in number, again, with a great majority recovering with minimal medical intervention. The initial responses have focused on early detection of cases and containment of the virus. However, with the continuing spread of the virus, earlier strategies have become less feasible. It has been recommended that mitigating measures should be implemented to minimize the continuing growth of the pandemic.

This study aimed to describe the clinical profile and outcome of pediatric patients with Reverse Transcription-Polymerase Chain Reaction (RT-PCR)-confirmed Influenza A (H1N1) from May 1 to July 31, 2009 at a DOH-designated Sub-national Referral Center for Infectious Diseases. This study also aimed to provide medical practitioners with the clinical and epidemiologic data necessary for early recognition of the disease and its proper management.

## METHODOLOGY

This descriptive, retrospective study reviewed the records of pediatric patients with Influenza A (H1N1) virus.

Pediatric patients (0-to-18 years old) of the Lung Center of the Philippines who were seen from May 1 to July 31, 2009 for Influenza-like illness and were confirmed to have Influenza A (H1N1) virus through Reverse Transcription-Polymerase Chain Reaction (RT-PCR) assay of their nasal swab were included in this study. The nasopharyngeal swab specimens were sent to the Research Institute for Tropical Medicine (RITM) for testing and confirmation.

Data was gathered using the Case Report Form for Initial Screening of Influenza A (H1N1) and the National Surveillance Network Case Report Form from the National Epidemiology Center of the Philippines. These forms were accomplished during the patient's initial

consultation and prior to the nasopharyngeal swab. Information in the said forms include demographic data, signs and symptoms and date of onset, presence of co-morbidities, history of exposure to a confirmed or suspected case of Influenza A (H1N1) virus, exposure to animals that maybe infected with the virus or travel to a country with known cases of Influenza A (H1N1) virus, intake of any antiviral medications prior to consult and history of influenza vaccination. This study, likewise, utilized the WHO Influenza A (H1N1) Case Summary Form which was used to determine the severity and clinical characteristics of the Influenza A (H1N1) confirmed cases. Additional data included in this form were presence of complications developed during the course of the disease, anti-viral medications received and adverse reactions, if any, and patient's over-all outcome. Patients who were positive for Influenza A (H1N1) were notified and given anti-viral medications according to the prescribed dose by the Department of Health.

On follow-up, outcome was noted using the WHO Influenza A (H1N1) Case Summary Form. A follow-up consult when the period for quarantine was completed by the patient: 21 days for patients below 12 years of age; and 10 days for patients above 12 years of age. The patients who did not have any out-patient information were followed-up through telephone for verification.

## RESULTS

A total of 243 patients were included in this study. Majority of the patients who sought consult in the adolescent age group (10-18 years old), comprising 71.60% as shown in Table 1. A male predominance was noted among those screened and diagnosed. Due to the location of the Lung Center of the Philippines which is in Quezon City, a large number of the subjects came from that area, comprising 58.85% (n=143). 19.34% came from the rest of Metro Manila, while 21.81% came from outside Metro Manila.

Onset of influenza-like illness was observed to occur between 1 to 3 days prior to consultation in 67.1% (n=163) of the confirmed cases. Seventy-two patients (29.6%) sought consultation within one week from the onset of illness and a total of 12 patients sought consultation beyond seven days from the onset of signs and symptoms.

**Table 1. Demographic data of patients with RT-PCR confirmed Influenza A (H1N1)**

AGE	Male (n=139)	Female (n=104)	TOTAL% (n=243)
0 – 12 months	0	2	2 (0.82%)
2 3 years	6	1	7 (2.88%)
4– 5 years	3	4	7 (2.88%)
6– 9 years	36	17	53 (21.81%)
10– 18 years	94	80	174 (71.60%)

Subjects who were RT-PCR positive for Influenza A (H1N1) had fever, cough, nasal congestion and sore throat (Table 2). Two patients had seizure and exhibited altered consciousness at the height of fever. There was no recurrence in the illness upon follow-up.

Pulmonary disease was the most important co-morbid condition noted. 186 (76.5%) patients received anti-viral therapy while 11 patients (4.5%) received prophylaxis.

During the course of the disease, some complications such as pneumonia and bronchial asthma (Table 5) developed mostly among patients in the school age group (Tables 4.1 and 4.2). Despite the complications, all of the patients recovered fully.

The subjects who had positive RT-PCR positive showed a history of exposure to either a confirmed case or suspected case of Influenza A (H1N1). Travel to an area with confirmed cases of the disease also configured in 11.5% of the subjects (Table 7).

**Table 2. Symptoms exhibited at consult by confirmed H1N1 patients**

Signs & Symptoms	H1N1 Positive (n= 243)	%
fever	224	92.2%
cough	202	83.1%
nasal congestion	128	52.7%
sore throat	85	35.0%
headache	43	17.7%
myalgia	27	11.1%
vomiting	19	7.8%
diarrhea	9	3.7%
nausea	4	1.6%
difficulty of breathing	4	1.6%
conjunctivitis	2	0.8%
seizures	1	0.4%
nose bleeding	1	0.4%
altered consciousness	1	0.4%

**Table 3. Co-morbid Conditions of Influenza A (H1N1) Patients**

Co-morbid Conditions	H1N1 Positive (n=243)	%
Pulmonary disease (i.e. asthma, TB,)	35	14.4%
Cardiac disease (i.e. congenital, acquired)	2	0.8%
Nephrotic Syndrome	1	0.41%
Immunocompromised Biliary Atresia s/p Liver Transplant	1	0.41%

**Table 4. Adverse Events in patients who received antiviral medications**

Classification	No. of patients	%
Gastrointestinal (i.e. nausea, vomiting, diarrhea)	26	10.7%
Respiratory (i.e. cough, dyspnea)	8	3.3%
Nervous System (i.e. headache, dizziness)	5	2.1%

**Table 5. Complications which developed during the course of the disease**

Complications	H1N1 Positive (n=243)	%
Clinical Pneumonia	29	11.9%
Radiographic Pneumonia	12	41.4%
Bronchial Asthma in Exacerbation	2	0.8%

**Table 6. Demographic profile of RT-PCR patients who developed pneumonia**

AGE	Male (n=17)	Female (n=12)	TOTAL % (n=29)
0– 12 months	1	0	3.44%
2– 3 years	0	0	0
4– 5 years	4	0	13.8%
6– 9 years	7	9	48.3%
10– 18 years	5	3	27.6%

**Table 7. History of exposure/possible Exposure of RT-PCR Positive Patients**

Type	H1N1 Positive (n= 243)	%
Exposure to a confirmed case of Influenza A (H1N1) virus	67	27.6%
Exposure to a suspected case of Influenza A (H1N1) virus	56	23.0%
Exposure to an animal confirmed or suspected to have Influenza A (H1N1) virus	3	1.2%
Exposure / with travel history to an area with confirmed cases of Influenza A (H1N1) virus	28	11.5%

## DISCUSSION

Since the outbreak of the novel Influenza A (H1N1) virus, much attention has been given to determining its origin, mode of transmission, detection and affectation in the human population. In the Philippines, the first case of Influenza A (H1N1) virus was a pediatric patient, who presented with fever and cough and had a travel history to a country with confirmed Influenza A (H1N1) cases. Since then, the pediatric age group had been monitored especially when the number of symptomatic patients increased during the resumption of classes early this year. The initial responses had focused on early case detection and containment of the virus. Later on, there was a shift to mitigating measures to minimize the continuous spread of the virus.

By analyzing the outbreak in Mexico City, early data on international spread and viral diversity made it possible to conduct early assessment on the transmissibility and severity of the disease, followed by epidemiologic analysis of confirmed cases. According to an initial report made on the clinical manifestations of 642 confirmed Influenza A (H1N1) virus cases in the United States, patients ranged from 3 months to 81 years in age with 60% of patients below 18 years old and only 5% above 50 years old.<sup>3</sup>

Therefore, younger populations were much more susceptible than the elderly, however, presence of co-morbid conditions in both age groups put them at a high-risk for mortality. The same report showed that the most common presenting symptoms were fever (94%), cough (92%) and sore throat (66%); 25% of patients had diarrhea and 25% had vomiting, both of which are rarely seen in the seasonal flu.<sup>3</sup>

In comparison with other epidemiologic studies done, the mean age group of those who were RT-PCR positive for Influenza A (H1N1) was similar to that found in this study, the adolescent age group. The virus can easily be transmitted through regular contact with classmates and peers in a school setting and even outside the school.

Local data from the DOH in July 2009 show that most cases range from 5 months to 79 years old, with 18 years old as the median age. Most was said to belong to the pediatric age group of 10-19 years old, with majority of the cases being males, coming from National Capital Region (NCR), Regions III, IV-A and VIII.<sup>7</sup> Cases from the NCR mostly came from Quezon City, Manila, Paranaque and Pasig.

In an analysis done on RT-PCR confirmed cases in the Japanese pediatric age group belonging to 16 prefectures in Kobe City and Osaka, from May 9, 2009 to June 4, 2009, a total of 401 laboratory-confirmed cases of Influenza A (H1N1) virus were reported.<sup>9</sup> Reflecting the outbreaks in high schools described above, confirmed cases in the age group of 15-19 years accounted for 64% (n=256) of all cases, followed by 10% (n=40) of cases in the age group of 10-14 years. Males accounted for 63% (n=254) and females for 37% (n=147) of all diagnosed cases.<sup>8</sup> In this study, similarly, the mean age group was 13 years old with relatively a larger number of males (56.2%) screened and diagnosed with the virus in comparison with those of the females (43.8%).

Since this Novel Influenza A (H1N1) virus is likened to the seasonal flu, presenting signs and symptoms are indistinguishable. As with other studies, the most frequent signs and symptoms would be fever, cough, sore throat and nasal congestion. In an epidemiologic analysis done on a total of 182 RT-PCR confirmed cases in Colombia from May 2, 2009 to July 16, 2009, the presenting clinical symptoms noted were fever (84.8%) followed by cough, sore throat and nasal discharge.<sup>10</sup> Thirteen cases (6%) reported diarrhea and five cases (2%) had nausea. The findings of diarrhea and vomiting in patients with seasonal flu are uncommon as compared to those diagnosed with Influenza A (H1N1) virus. Similar findings as to signs and symptoms were also documented in this study, with fever, cough, nasal congestion and sore throat as the most common.

Most confirmed cases of Influenza A (H1N1) virus infection have been characterized by self-limiting, uncomplicated febrile respiratory illness and symptoms similar to those of seasonal influenza. However, some healthy patients diagnosed with the disease would develop severe complications requiring hospitalization. Respiratory co-morbidities pose the greatest risk for pediatric patients as these may lead to chronic medical conditions.

In this study, a number of patients were found to have respiratory co-morbidities, with bronchial asthma as the leading condition. Viral respiratory infections may lead to pneumonia, as seen in 29 (11.9%) of the RT-PCR confirmed patients and these in turn may lead to patients requiring hospitalization as was documented. Patients requiring hospitalization in this study were mostly due to pneumonia and required intravenous medications and monitoring.

In a study done in the United States on all Influenza A (H1N1) patients who required hospitalization, 45% (n=122/272) of the patients belonged to the pediatric age group.<sup>10</sup> The clinical features of patients who were

hospitalized were similar to those reported during peak periods of seasonal influenza with an acute respiratory illness. Symptoms at presentation included fever and cough. Diarrhea and/or vomiting was seen in 39% (n=106/272) of the hospitalized patients, 42% (n=45/106) of whom were pediatric patients.<sup>10</sup> Similarly, bronchial asthma was the most common underlying condition seen among all hospitalized pediatric patients.

Notable in the data gathered is the history of exposure to confirmed or suspected cases or history of travel to a country with known cases, among those symptomatic patients who tested positive for Influenza A (H1N1) virus, only 63.4% had a travel history or history of known exposure either to a confirmed or suspected case. In a secondary school located in Toulouse, France, a confirmed outbreak of Influenza A (H1N1) was reported in June 2009.<sup>11</sup> On investigation, none of the students or staff had a history of travel after June 1 to countries affected by the pandemic or has had been in contact with a confirmed case.<sup>11</sup> However, it was reported that some of the children's parents/relatives worked for international firms and may have been exposed to probable cases and some parents/relatives travelled to areas with known cases.

In a study done in London from April-May 2009 documenting oseltamivir adherence and side effects in children, 53% (n=45/85) reported adverse drug reactions specifically, gastrointestinal side effects.<sup>12</sup> The same was documented in this study, followed by respiratory and nervous system side effects respectively. These signs and symptoms were observed only after intake of oseltamivir, either as prophylaxis or as recommended treatment.

It is said that the only way to control this pandemic is through large scale immunization. Vaccine production is well underway, with the pediatric population at the forefront to receive this. In a study done in the United States by the

Center for Disease Control and Prevention, immunization with the seasonal influenza vaccine was found to confer little or no serum cross-reactive antibody response to Influenza A (H1N1).<sup>13</sup> In the study, only a modest increase in cross-reactive antibody response was detected in serum samples of 45 children between the ages of 6 months and 59 months who received 2008-2009 seasonal influenza vaccine.<sup>13</sup> It remains clear that optimal protection against this virus for children will be achieved through development of a strain-specific vaccine.

The present Influenza A (H1N1) vaccine is now available and is being administered in the United States to 5 initial target groups, namely, (1) pregnant women, (2) persons who live with or provide care for infants aged <6 months, (3) health-care personnel, (4) persons aged 6 months–24 years and (5) persons aged 25-64 years with underlying medical conditions. Plans of expanding beyond the initial target groups are to be made once a steady supply of vaccines are made available. Countries capable of launching large-scale studies have already come up with information regarding this virus and how it continues to affect people of different regions, those financially capable have started producing vaccines to contain this disease.

### CONCLUSIONS /RECOMMENDATIONS

In conclusion, majority of the RT-PCR confirmed Influenza A (H1N1) pediatric patients were characterized by self-limiting, uncomplicated, febrile respiratory illness and made an over-all recovery with minimal complications. Monitoring outbreaks from different parts of the country will provide sufficient information to formulate conclusions regarding this influenza pandemic and how to properly manage it. Vaccination, once made available, should be mandatory to be administered to all.

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