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ORIGINAL ARTICLE

A Case Control Study of the Demographic Characteristics, Risk Factors, Clinical Findings, Treatment and Outcome Among Children 18 Years and Below Who are Confirmed to have Influenza A H1N1/09 Virus

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ABSTRACT

Background: The H1N1/09 virus was reported to be similar to the seasonal flu. However, the World Health Organization (WHO) documented a substantial proportion of patients with H1N1/09 who developed severe illness and death particularly among those with underlying medical conditions.¹ Presently, to our knowledge, there is no data in the Philippines where the demographic and clinical characteristics, risk factors and outcome of children positive for H1N1/09 virus were compared to those with influenza but were negative for H1N1/09.

Objective: The objective of this study was to compare the demographic and clinical characteristics, risk factors, treatment and outcome of the two groups.

Methods: A review was done of the charts of 162 patients who were tested for H1N1/09 virus by RT-PCR assay at the Makati Medical Center from May 5 to July 16, 2009. Demographic characteristics, risk factors, clinical features, treatment and outcomes were compared between the two groups. Categorical variables used between the two groups were compared using Fisher's exact test or Chi square test while quantitative variables were compared using T-test; odds ratio was determined.

Results: A total of 162 patients were included in this study. The largest group of patients positive for H1N1/09 was from the age group of 11-15 years old (35.8%). Risk factors such as travel history and exposure to a confirmed case showed no association to having a positive H1N1/09 test. Clinical features such as fever (100%) and cough (82.1%) were the most common presenting symptoms for both groups. Majority of these patients were given supportive treatment and out of 162 subjects, 91.4 % were treated as outpatient. Clinical outcome showed one mortality from the case group and none from the controls.

Conclusion: Thus, the demographic characteristics and clinical findings were similar for both groups. Future studies are recommended to include those with influenza-like illness not tested for H1N1/09 virus.

INTRODUCTION

In March 2009, an Influenza A virus which emerged from Mexico caused a pandemic and the novel strain was named by the World Health Organization (WHO) experts as the Pandemic H1N1/09.² Similar to the seasonal flu, the virus was transmitted sufficiently by droplets from person-to-person causing community outbreaks and rapid spread regionally. The WHO however, reported that a substantial proportion of H1N1/09 cases developed severe illness, and death occurred among the young and those with underlying medical conditions.¹ Donnelly et al reported that children were twice as susceptible to infection with the pandemic H1N1/09 virus compared to household members aged 19-to-50 years and adults older than 50 years old.³ This finding was consistent with serologic analyses suggesting that there may be some pre-existing pandemic H1N1/09 immune memory in the elderly that are rarely present in children.³

In Asia, the first case was reported on May 1, 2009 in Hong Kong while the first documented case in the Philippines was on May 22, 2009.⁴ In a descriptive observational study done at Makati Medical Center from May 3 to July 4, 2009 (Abad et al 2009), 44.6% of subjects were less than or equal to 18 years of age. Eighty-nine percent of the confirmed cases seen in Makati Medical Center were from the healthy school age and the reproductive age group.⁴ Demographic characteristics were described in patients positive for the H1N1/09 virus. However, no data was available on disease characteristics and outcomes of children negative for the virus. Presenting symptoms and underlying medical conditions of both adults and children were not described separately.

Although studies from other countries revealed that the disease characteristics of the pandemic H1N1/09 virus were similar to those of seasonal influenza strains, the potential effects of this new strain on patients who have underlying medical conditions such as asthma, and the increased susceptibility of

children to the virus, have a substantial impact on public health and finance. Local studies comparing the disease characteristics, risk factors and outcomes among confirmed cases and those with influenza-like illness are lacking.

OBJECTIVES

This study aims to compare the demographic characteristics, clinical features, underlying medical conditions and outcomes in children with H1N1/09 virus with those who tested negative for the virus at the Makati Medical Center. Results of this study hoped to provide necessary information needed to educate the public, to strengthen the role of health care professionals in the prevention against the pandemic H1N1/09 virus and eventually to help in the reduction of hospitalization rate.

MATERIALS AND METHODS

Study Period and Population

This is a case control study conducted among patients of the Makati Medical Center who were tested for H1N1/09 by Real Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), using a nasopharyngeal mucus specimen obtained by swab. RT-PCR samples were sent to the Research Institute for Tropical Medicine (RITM) for testing. Patients included in this study were children aged 18 years old and below who presented with influenza-like symptoms from May 5, 2009 to July 16, 2009. Data were taken from the in-patient medical records and the emergency room logbook. Considered to be confirmed cases were those documented to be positive for the pandemic H1N1/09 virus based on RT PCR assay, while cases tested negative for H1N1/09 virus were used as controls. Subjects however were not followed up to determine possible changes on treatment or possible hospitalization to another institution

Variables of interest

From the medical records, patients' demographic characteristics such as age, gender, nationality, travel history and history of exposure to a confirmed case were noted. Presenting symptoms such as fever, cough, colds, headache, myalgia, rash, diarrhea, vomiting, physical findings, underlying medical conditions, treatment given, and clinical outcome were recorded. Data taken from laboratory-confirmed cases were then compared with those data from the control group.

Statistical Analysis

The qualitative or categorical variables between the group of patients who tested positive for pandemic H1N1/09 and those with influenza-like symptoms, who gave negative results, were compared using Fisher's exact test or Chi square test, whichever was appropriate. The quantitative variables between these groups were compared using the independent T-test. A p value of less than 0.05 was considered to indicate statistical significance. Odds ratio and 95% confidence intervals were also determined.

Scope

This study included patients seen from May 5 to July 16, 2009 only. The duration was based on the dates when nasopharyngeal swab for RT-PCR was being used at the Makati Medical Center. Due to a Department of Health Memorandum on June 24, 2009, regarding the change in the pandemic management strategy from containment to mitigation response,⁴ the use of RT-PCR of nasopharyngeal mucus specimens markedly diminished after July 1, 2009 and its use discontinued after July 16, 2009. Subjects were limited to patients 18 years old and below at the Makati Medical Center - Emergency Room Department and those admitted and considered as probable cases of the pandemic H1N1/09 virus. Admitted probable cases who had influenza-like illness but were not tested for the pandemic H1N1/09 virus were not included in the study.

During the study period, there were 170 patients who were tested for the H1N1/09 virus using the RT-PCR assay. However, eight of the patients who were tested had incomplete data; thus, only a total of 162 patients were included in this study.

Demographic Profile of patients

A total of 162 patients were included during the study period. A total of 109 patients tested positive while 53 patients tested negative. The largest group of patients was from the age group of 16 to 18 years old comprising 35.2% (57) followed closely by the age group 11 to 15 years old which comprised 32.1% (52). The mean age of the study population was 12.24 years. The largest group of patients, who tested positive for H1N1/09 as shown in Table 1, was those aged 11 to 15 years old, comprising 39 patients (35.8%) as compared to the control group wherein most patients were aged 16-18 years (43.4%). There was no significant statistical difference between the mean ages of both groups.

In terms of gender distribution females predominate on both groups; however, no association on gender was shown on H1N1/09 diagnosis.

Table 1. Patient distribution by age group according to result of RT-PCR for H1N1/09 (N = 162)

Age in years	Negative	Positive	Total
	No (%)	No (%)	No (%)
≤ 5	7 (13.2)	8 (7.3)	15 (9.3)
6-10	10 (18.9)	28 (25.7)	38 (23.5)
11-15	13 (24.5)	39 (35.8)	52 (32.1)
≥ 16	23 (43.4)	34 (31.2)	57 (35.2)
Total	53 (32.7)	109 (67.3)	162 (100)
Mean*	12.32	12.20	12.24
Standard Deviation	5.206	4.524	4.742
Sex**			
Female	32 (60.4)	59 (54.1)	91(56.2)
Male	21 (39.6)	50 (45.9)	71 (43.8)

* Independent t-test: p=0.875

** Chi square test: p=0.452: 1.29 (0.63-2.66)

RESULTS

Majority of the patients or 94.4% (153) were Filipinos; other nationalities were Japanese (3.7%), American (0.6%), Thai (0.6%) and Australian (0.6%).

Risk factors

Of the 162 patients studied, 126 (77.8%) had no history of travel to an affected country while 36 patients (22.2%) had traveled one month prior to the onset of the disease. As shown in Table 2, there were a smaller proportion of those who traveled and turned out positive for H1N1/09 (14.7%) when compared to those who tested negative (37.7). The results also showed that the odds of having a positive H1N1/09 test was significantly smaller (OR 0.28) among patients who had a travel history as compared to those who had none.

Table 2. Patient distribution by travel history, according to result of RT-PCR for H1N1/09 (N =162)

	Negative No (%)	Positive No (%)	Total No (%)
Travel History*			
None	33 (62.3)	93 (85.3)	126 (77.8)
With Travel	20 (37.7)	16 (14.7)	36 (22.2)
Exposure to Confirmed Case**			
No	10 (34.5)	27 (47.7)	37 (43)
Yes	19 (65.2)	30 (52.6)	49 (57)

*Chi square test: **p=0.001**; OR 0.28 (0.12-0.65)

** Chi square test: p=0.257; OR 0.58 (0.21-1.62)

76 (46.9%) unknown, n=162

Looking at the history of exposure to a confirmed case only 57% of the patients had close contact with an H1N1/09 case prior to consultation. A smaller proportion (52.6%) of those who tested positive had close contact to a confirmed case as compared to those who tested negative (65.5%).

Seventy-six patients (46.9%) had been in an area where a confirmed case was documented but these patients were unaware of their proximity to the confirmed case. Out of these 76 patients, 52 were

positive for H1N1/09 and 24 were negative for it. There was no association between exposure to close contact and having a positive H1N1/09 test.

Asthma was the most common pre-existing condition for both cases and controls, followed by allergic rhinitis. Only one confirmed case had concomitant pneumonia. This case was a seven-year-old girl who initially complained of difficulty of breathing and was admitted at the pediatric ICU. She was intubated and mechanically ventilated and she eventually died on the 11th hospital day due to severe acute respiratory distress syndrome and pneumothorax. No association was noted between having an underlying medical condition and having H1N1/09.

Table 3. Patient distribution by presence of underlying medical condition, according to result of RT-PCR for H1N1/09; (N = 162)

Underlying Medical Condition	Negative No. (%)	Positive No. (%)	p-value
	Allergic Rhinitis/Rhinitis	0	
Asthma	7 (13.2)	12 (11.0)	0.684**
Pneumonia	0	1 (0.9)	1.000**

¹Fishers exact test: ²Chi square test

Clinical Features:

All subjects presented with fever (100%). The mean day of onset of fever prior to consultation was 1.5 days. A total of 109 subjects who presented with fever were positive for H1N1/09 and 53 were negative. Aside from fever, the top three presenting symptoms for both groups were cough at 82.1% (133), colds at 66.7% (108) and throat pain at 42% (68).

The odds of a patient who presented with cough to be positive for the H1N1/09 test was 2.25 times more than those who had none. Out of 133 patients who presented with cough, 94 tested positive for H1N1/09 while 39 were negative for it. Although most patients also presented with colds (66.7%)

and throat pain (42%), results were not statistically significant.

Other symptoms documented were as follows: headache (19.1%), vomiting (11.73%), myalgia (3.1%), diarrhea (3.1%), dizziness (1.85) and abdominal pain (0.62%). Although gastrointestinal symptoms between the two groups did not show significant statistical difference, those who tested positive for H1N1/09 had more prominent gastrointestinal symptoms such as vomiting and diarrhea than those negative for H1N1/09.

There was one patient in this study who presented with seizure and behavioral changes associated with fever. This patient was a five-year-old girl who initially had fever, cough and colds for four days. However, one day prior to confinement, the patient had seizure episodes. The MRI done on the patient showed focal areas consistent with viral encephalitis and a lumbar tap was negative for bacteriologic and fungal studies. She was admitted at the pediatric ICU and after five days of oseltamivir and antibiotics, patient improved.

Table 6. Patient distribution by presence of fever, according to result of RT-PCR for H1N1/09 (N = 162)

Day of Onset of Fever ¹	Negative	Positive	Total
	No (%)	No (%)	No (%)
0	10 (18.9)	4 (3.7)	14 (8.6)
1	22 (41.5)	67 (61.5)	89 (54.9)
2	8 (15.1)	29 (26.6)	37 (22.8)
3	6 (11.3)	2 (1.8)	8 (4.9)
4	5 (9.4)	5 (4.6)	10 (6.2)
5	1 (1.9)	2 (1.8)	3 (0.9)
6	1 (1.9)	0	1 (0.6)
Mean*	1.64	1.48	1.53
Standard Deviation	1.429	0.929	1.116
Cough**			
No	14 (26.4)	15 (13.8)	29 (17.9)
Yes	39 (73.6)	94 (86.2)	133 (82.1)

* Independent t-test: p=0.448

**Chi square test: p=0.049: OR 2.25 (0.92-5.50)

Figure 1: Clinical Symptoms of patients tested for H1N1/09

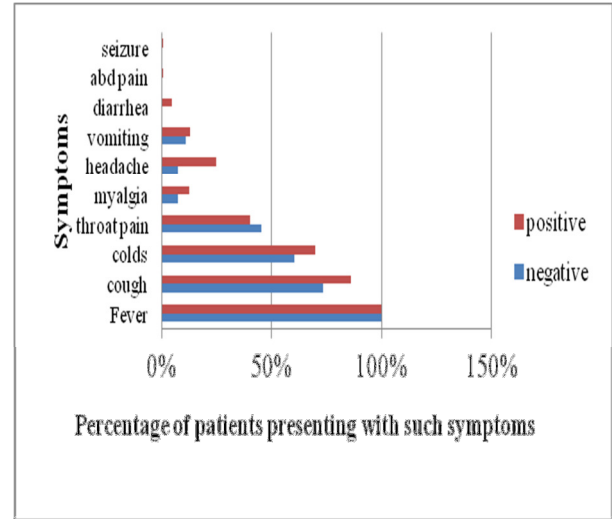


Figure 2: Comparison of treatment given between case and control groups.

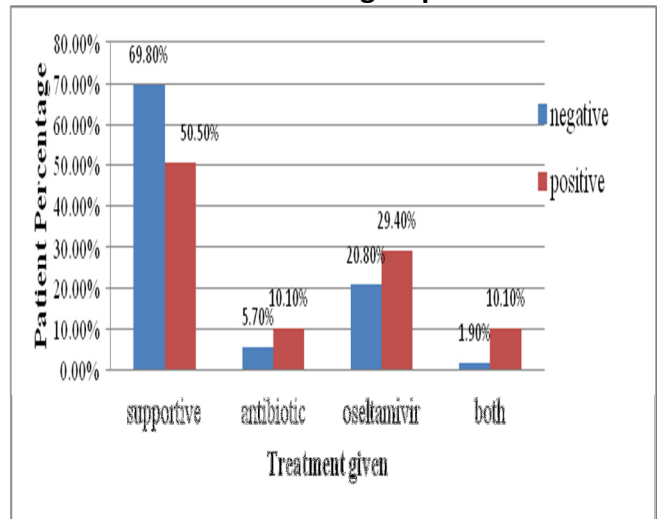


Table 8: Patient distribution by level of medical care, according to result of RT-PCR for H1N1/09; (N = 162)

Level of Medical Care*	Negative	Positive	Total
	No (%)	No (%)	No (%)
Out patient	50 (94.3)	98 (89.9)	148 (91.4)
In patient	3 (7.7)	11 (10.1)	14 (8.6)

* Fisher's exact test: p=0.552: OR 1.87 (0.45-8.89)

On the other hand, the most common and pertinent presenting sign for cases was hyperemic posterior pharyngeal wall at 39.5 % (65). Most subjects had clear breath sounds (159) except for three patients who presented with crackles on physical examination and who were eventually diagnosed to have pneumonia through X-ray findings.

Treatment

Majority (148) of subjects were treated as outpatients. Ninety-two patients were given supportive treatment (56.8%) and of these patients, 55 were positive for H1N1/09 and 37 were negative. There were 43 patients (26.5%) who received oseltamivir alone, 14 (8.6%) patients who received antibiotics alone and 12 patients (7.4%) who received a combination of oseltamivir and antibiotics. Fourteen subjects were admitted and were given Oseltamivir during their confinement. The rest of the patients were given supportive treatment such as decongestants, cough supplements and water therapy.

Clinical Outcome

Majority of patients were seen as outpatients. Of the 148 patients (91.4%) seen as outpatient, 98 (89.9%) turned out positive for H1N1/09 and 50 (94.3%) were negative. Fourteen patients (8.6%) needed hospitalization; of the 14 patients admitted, 11 were positive for H1N1/09 virus. The mean length of stay was 1.45 days. Three of the patients were given oxygen support via nasal cannula due to difficulty of breathing and one patient was intubated due to hypoxemia. Out of 162 subjects, there was one confirmed case who died of pneumothorax, with acute respiratory distress syndrome and respiratory failure. No deaths were seen among the control group.

DISCUSSION

The population involved 162 children who presented with influenza-like symptoms

and who were tested for H1N1/09. A total of 109 patients tested positive for H1N1 while 53 patients tested negative.

The study showed that the largest group of patients noted to be positive for H1N1/09 belonged to the 11 to 15 age group, followed closely by patients aged 16 to 18. The finding was consistent with the initial series done in the United States where majority of confirmed cases were between 10 and 18 years old.⁵ It was concluded that older children may have some pre-existing or cross-reactive immunity to influenza strains from previous seasons which prevented them from being protected against the pandemic H1N1/09 (Barton et al, 2009).⁵ Also, although there was female predominance on both groups in this study, consistent with findings from previous studies, no association on gender and H1N1/09 was shown.

We also found out that majority of patients had no history of travel to an affected country prior to consult. There was also no association between exposure to a confirmed case and having a positive H1N1/09 test. Lessler et al (2009) mentioned that transmission of the H1N1/09 virus is more efficient among schoolchildren than it was in the general population. They also concluded that though the transmission of the pandemic H1N1/09 virus was similar to those of previously observed circulating pandemic and interpandemic influenza viruses, the probability of household transmission was lower than estimates in the case of seasonal influenza.⁶ This suggests that the pandemic H1N1/09 virus was not efficiently transmitted at home, possibly due to decreased susceptibility among older people who may have the immune memory of the virus strain.^{2,6} Also in the same study, within-school reproductive number was estimated to be 3.3, a number noted to be at the high end of the range estimated for pandemic and interpandemic influenza outbreaks.⁶ This may explain the increased number of patients positive for H1N1/09 virus despite low numbers of patients documented to have had direct contact with a confirmed case or those

who had travel history. Considering that a large proportion of patients who were positive for H1N1/09 in this study were school-aged children, patients positive for H1N1/09 virus could have acquired the virus from school. The probability however that the virus had been contracted from other sources cannot be excluded.

As seen in previous studies, asthma remained to be the most common underlying medical condition for both groups. This result however was not statistically significant. Barton et al (2009) showed that asthma was a more significant risk factor for severe disease among children with pandemic H1N1/09 than among those with seasonal influenza.⁵ This was further strengthened by the results gathered by Libster et al (2010), wherein children with asthma or neurologic disorders were noted to have an increased risk in death.⁷ Nichols et al. (2009), studied 13 cases of critically ill children with H1N1/09 and found that rapid screening tests were initially negative in eight out of the 13 children who were eventually admitted at the Pediatric ICU. Eleven out of these 13 children had asthma.⁸ Hence, there is a need for watchful monitoring and a consideration of early use of antiviral medications in all critically-ill children with influenza-like symptoms regardless of test results as well as for those with underlying medical conditions.

For clinical features, all subjects in this study presented with fever. The top five most common presenting symptoms for both groups were fever, cough, colds, throat pain and headache. These findings were consistent with the results shown by Barton et al (2009) wherein presenting features in children with pandemic H1N1/09 and influenza-like illness were noted to be the same.⁵ We, however, found out in this study that children with cough had significantly higher risk (2.25x) of having a positive H1N1/09 test. This was in contrast with the study of Donnelly et al (2009), wherein no symptom was found to be significantly associated with increased infectivity.³ As mentioned previously, although

gastrointestinal symptoms did not show significant statistical difference between the two groups, most patients who presented with vomiting and diarrhea were from the H1N1/09 group. This finding was supported by Libster et al (2010), who concluded that gastrointestinal symptoms were more frequent in patients who were infected only with the H1N1/09 virus than those with other viruses.⁷

Abad et al (2009) stated that the H1N1/09 virus remains susceptible to antiviral drugs such as oseltamivir and zanamivir. This antiviral drug however, is recommended for treatment of severe illness caused by the H1N1/09 virus and for postexposure prophylaxis among high-risk patients.¹³ In the Philippines, oseltamivir is the only available antiviral medication.⁴ Oseltamivir-resistant infection with the pandemic H1N1/09 virus has been described only rarely (Quynh Mai, 2010).⁹

Fourteen patients however, needed hospitalization and one death was reported among the confirmed cases. This patient died of severe pneumonia, pneumothorax with respiratory failure. Libster et al (2010) concluded that the pandemic H1N1/09 was associated with pediatric death rates 10 times the rates for seasonal influenza in previous years. Two-thirds of deaths were attributed to refractory hypoxemia and bacterial co-infection.⁵ Hence, although use of oseltamivir should be restricted to prevent resistant infections, early antiviral therapy should be given as prophylaxis to those with underlying medical conditions and treatment to those suspected of having the disease. The CDC noted that though most infections are mild, research studies done have shown that H1N1/09 virus may infect cells deep in the lungs.

In this study, variables such as underlying medical conditions and indicators of severity of illness were limited. For indicators of severity of illness, variables were limited to level of medical care, use of oxygen and results of complete blood count and chest x-ray, if available. Presence of underlying

medical conditions was not elaborated in relation to its severity. Clinical outcome was based solely on the level of medical care and treatment given upon consultation at the ER. Patients seen as outpatients were not followed-up regarding the progression of disease or possible intake of other medications not previously prescribed or possible hospitalization to another institution during the course of illness. Although these limitations were important, it must be noted that during the study period, the RT-PCR results were released between five days to about a week after specimen had been submitted. Thus, patients who eventually tested positive for H1N1/09 could not have benefited anymore with use of antiviral therapy after the results were released, assuming that the illness had resolved by the time the results were released.

This study is the first local data in the Philippines comparing demographic characteristics, risk factors, clinical features, treatment and outcomes of those confirmed to have H1N1/09 and those who tested negative for it. Majority of the results documented were consistent with international data published. The study was consistent with the conclusion of Barton et al (2009) that demographic characteristics and presenting symptoms of both cases and controls were similar.⁵ In addition, the study showed that patients presenting with cough had significantly higher risk of having a positive H1N1/09 test. Although, underlying medical conditions such as asthma did not show statistical significance, it must be taken into account that most patients who needed hospitalization were known to have asthma. Also, the mortality in the case group showed that the pandemic H1N1/09 was indeed associated with more pediatric deaths than seasonal influenza, hence, the need for watchful monitoring among patients with underlying medical conditions and early initiation of antiviral treatment among those known to have the risk factors. Vaccination is recommended for this potentially fatal but preventable disease.

CONCLUSIONS

This study showed that demographic characteristics, presenting symptoms versus those with influenza-like illness negative for H1N1/09 were similar. In addition, fever and cough showed higher risks of having a positive H1N1/09 test, and gastrointestinal symptoms were noted to be more prominent among the cases than the controls

The disease may be fatal, thus early identification of underlying medical conditions, watchful monitoring and early initiation of antiviral treatment among those known to have the risk factors must be emphasized.

RECOMMENDATIONS

It is recommended for physicians to have a high index of suspicion for H1N1/09 virus on all patients presenting with cough and fever, associated with normal physical findings. Identification of presence of underlying medical conditions should be done in all consults for immediate initiation of antiviral therapy to those considered as high-risk patient. Vaccination is also recommended to all school-aged children and those identified to have risk factors.

Clinical outcomes of this study were based solely from the initial management done at the Emergency Room. Subjects are then recommended to be followed up retrospectively, to determine possible changes on treatment and possible hospitalization to another institution. Future studies are also recommended to include those with influenza-like illness not tested for H1N1/09 virus.

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