

Original Article

Early experience of the pandemic influenza H1N1 2009 epidemic in Taiwan

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Abstract

Background: A novel influenza H1N1 began in March 2009, rapidly spread, and then became a pandemic outbreak. Diagnosis by polymerase chain reaction result was not always available because of a surge in workload and therefore clinical diagnosis became important. However, clinical differences between the patients infected by the novel H1N1 virus and those infected by the influenza-like non-novel H1N1 have not been reported. This study was conducted to compare the demographic background, clinical manifestations, and laboratory findings between novel H1N1 influenza infections and other non-novel H1N1 infections.

Methods: At an early stage of H1N1 spread, cases presenting with influenza-like symptom and travel or contact history were quarantined into infection disease-designated hospitals in Taiwan. Data on consecutive patients under investigation for infection with novel influenza A (H1N1) were collected between April 29 and June 19, 2009. The data set consisted of clinical manifestations, plain chest radiography, hematological results, and biochemical findings. Testing of nasopharyngeal swab samples by reverse transcription polymerase chain reaction was used to detect H1N1.

Results: Overall, 166 cases were collected. Among these individuals, there were 14 confirmed H1N1 cases. The clinical manifestations of the H1N1 cases included fever in 13 patients (92.9%), followed by cough, rhinorrhea, a sore throat, myalgia, headache, malaise, abdominal tenderness, and diarrhea. Leukopenia was present in nine patients (64.2%) and lymphocytopenia was present in five (35.7%). The duration of virus shedding was 7.0 ± 1.8 days. When compared with the non-H1N1 cases by multiple logistic regression analysis, cases infected by the novel H1N1 virus were more likely to be younger than 20 years [Odds ratio (OR) = 27.7, 95% confidence interval (CI) = 1.3–597.8, $p = 0.034$], have traveled from the US (OR = 14.5, 95% CI = 2.1–101.4, $p = 0.007$) or Thailand (OR = 56.7, 95% CI = 4.6–700.6, $p = 0.002$) and to have presented with myalgia (OR = 8.5, 95% CI = 1.4–52.0, $p = 0.021$) or leukopenia (OR = 17.4, 95% CI = 3.4–90.5, $p = 0.001$).

Conclusion: When a patient presents with influenza-like acute febrile respiratory illness symptoms and is young in age, has a travel history involving an affected area, and is suffering from myalgia or leukopenia, physicians should be alerted to the possibility of novel H1N1 virus infection.

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Keywords: H1N1 subtype; Influenza a virus; Risk factors; Signs and symptoms

1. Introduction

Novel influenza A (H1N1) is a new triple-reassortant virus,^{1–3} which contains genes from human, swine, and avian influenza A viruses; this virus first caused illness in Mexico⁴ and the United States⁵ during March and April of 2009. It was quickly determined that the virus was spreading

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from person to person. The virus then spread quickly from country to country. By June 11, 2009, nearly 30,000 confirmed cases had been reported in 74 countries. As a result, the World Health Organization (WHO) decided to raise the level of the influenza pandemic alert from Phase 5 to Phase 6.⁶ By August 1, 2010, it was estimated that over 214 countries and overseas territories or communities had reported laboratory confirmed cases of pandemic influenza H1N1 2009 and infection had caused at least 18,449 deaths.⁷

On April 27, 2008, the Department of Health in Taiwan, in conjunction with the Center for Disease Control and Prevention, Taiwan (CDC, Taiwan), began implementing measures to limit the spread of the novel H1N1 influenza in Taiwan.⁸ Airport checkpoints, where temperature checks were carried out and health declarations filled in, were set up to screen people coming into Taiwan. Travelers arriving from abroad with a fever or flu-like symptoms (cough, sore throat etc.) were asked to wear N-95 masks and were sent immediately to a designated hospital for quarantine and further diagnosis. Travelers who did not have a fever or symptom were asked to check their body temperature each morning and night for 7 days. If they developed fever or influenza-like symptoms during this time, they were asked to wear N-95 masks and report to a designated hospital for further diagnosis and quarantine immediately. Individuals who had been in contact with those quarantined cases and developed fever or influenza-like symptoms were also quarantined.

In this study, we analyzed the characteristics, initial clinical symptoms, physical examination results, and laboratory findings of patients sent to the designated infectious disease control hospital, the Taipei City Hospital, Heping branch, for quarantine procedures.

2. Methods

Between April 29 and June 19, 2009, 166 consecutive cases were quarantined and investigated for novel influenza A (H1N1) infection at the Heping branch of Taipei City Hospital. After a physician's diagnosis that the individual was a "person under investigation", the cases were quarantined in a negative-pressure isolation facility at the Heping branch. The definition of a "person under investigation" was based on the guidance established by the CDC, Taiwan, including the clinical criteria for an acute febrile respiratory illness, the clinical criteria for an influenza-like-illness {defined as fever [temperature of 100°F (37.8°C) or greater] and a cough and/or a sore throat in the absence of a known cause other than influenza}, or pneumonia; in addition there were also epidemiological criteria including close contact with or travel to area with confirmed or probable cases of H1N1.⁹ Baseline and daily clinical data, including demographical information, travel history, exposure history, symptoms and signs, comorbidities, and laboratory information were obtained during the patients' quarantine in the hospital. The initial investigation consisted of a local examination of the ears, nose, and throat, palpation of the bilateral nuchal areas, a complete blood panel including differential counts, serum biochemical studies

including blood sugar, renal and liver functions, a C-reactive protein assay, and plain chest radiography. Analysis of each patient's nasopharyngeal swab samples by reverse transcription polymerase chain reaction (RT-PCR) was conducted by a laboratory at the CDC, Taiwan. Molecular tests were carried out for influenza A/B and subtyping tests were used to identify pandemic H1N1, seasonal H3N2 and seasonal H1N1. Detection of other respiratory pathogens was not performed. All patients were placed in negative-pressure isolation facilities initially, and treated with oseltamivir thereafter (orally twice a day for 5 days in a dosage based on body weight, according to the manufacturer's recommendations). During quarantine, serial routine examinations, such as body temperature, blood pressure, respiratory rate, heart rate, and O₂ saturation were recorded. Among the 166 cases, 14 patients were confirmed to be cases of human infection with novel influenza A (H1N1). The confirmed cases were defined as any case with a laboratory confirmation by RT-PCR carried out at the CDC, Taiwan using a rapid SYBR green I RT-PCR method.¹⁰ The primers used for pandemic influenza strain H1N1 detection in the SYBR green I assay were designed by the Taiwan CDC and based on the sequence of strain A/California/04/2009. The primers were SWH1LF (5'-ATTACTGGACACTAGTAGAGC-3') and SWH1LR (5'-GCATTTCTTTCCATTGCGAA-3'), which amplify a 97-bp fragment within the hemagglutinin gene. The assay was performed using the Roche LightCycler and LightCycler RNA master SYBR green I kit. The detection limit of the assay was at least 10 copies/mL of the hemagglutinin gene. The high sensitivity of fluorogenic 5' nuclease assays means that special precautions must be taken to avoid false-positive amplifications. A false-negative result may occur if inadequate numbers of organisms are present in the specimen because of improper collection or poor transport/handling; furthermore, such a result may occur if an excess of DNA/RNA template is present in the reaction mix.

RT-PCR was also used to analyze serial sampling of the nasopharynx to assess viral shedding by the confirmed cases during their quarantine. A second nasopharyngeal sampling for RT-PCR was decided on by the doctor after the symptoms and signs had subsided. If the sample was positive, another sampling was done again 48 hours later. The criteria for discharge from quarantine were two successive negative PCR results for influenza from nasopharyngeal swabs taken at least 24 hours apart. This study was approved by the institutional review board of Taipei City Hospital.

3. Statistical analysis

The analysis of the data was carried out using a statistical software package (SPSS, version 13.0; SPSS; Chicago, IL). Descriptive statistics are presented as numbers of cases, percentages, and means with standard deviation. Fisher's exact test was used to evaluate the significance of any differences. Furthermore to the descriptive analyses, multiple logistic regression analysis using the stepwise method was used to evaluate the risk indicators for being infected by novel H1N1 influenza virus.

4. Results

4.1. Patients and travel history

A total of 14 confirmed cases of human infection with the outbreak strain of novel influenza H1N1 virus were identified by RT-PCR (Table 1); one was a Thai national (patient No. 6) and all the others were Taiwan citizens. All the confirmed cases were travelers except for patient No. 11. Seven cases (50%) reported that they had traveled from the US and four cases (35.7%) reported that they had traveled from Thailand, all within 7 days before the onset of illness. One confirmed case had a history of travel to Central America. The one indigenous case was found to have had close contact with patient No. 10, who was a family member. Furthermore, patients No. 8, 9, and 12 were members of the same family, which was a different family from that of patient No. 10. None of the 166 patient case histories indicated a disease that might cause an increase or decrease in the patients' white cells or thrombocytes, such as a bone marrow disease or the use of specific medication (e.g. corticosteroid, lithium, or beta-adrenoceptor agonists).

4.2. Demographic and clinical features

The age of patients with confirmed novel H1N1 infection ranged from 8 years to 57 years (mean age: 23.6 ± 12.2 years) (Table 1). A total of 42.9% of patients were of the ages 0–20 years, and only 7.1% of patients were 41 years old (Table 2). Seven were men and seven were women. The most common symptoms were fever, cough, and rhinorrhea, as shown in Table 1. No cases were reported to have chills, dizziness, or remarkable gastrointestinal symptoms, such as diarrhea, nausea and/or vomiting.

The nasal mucosa, pharyngeal wall, and the tonsil area demonstrated mild hyperemia or an inflammatory reaction with moisture on the mucous membrane in all of the cases except the oropharynx of two cases (patients No. 4 and 5). There was no lymphadenopathy in the nuchal areas, including submental, submandibular, and upper, middle, or lower cervical lymph nodes, in any of the cases. One case was found to have redness of the eye (conjunctivitis). One case had rhonchi in chest when auscultation was performed, but this showed up as normal by chest radiography. One patient showed abdominal tenderness, but no diarrhea was found (Table 1).

4.3. Laboratory analyses

In terms of our H1N1 cases, leukopenia (a white-cell count of less than $5.0 \times 10^3/\mu\text{L}$) was found in nine cases (64.2%), with a mean leukocyte count of 4.6 ± 1.3 (range = $3.0\text{--}8.21$) $\times 10^3/\mu\text{L}$. Lymphopenia (a total lymphocyte count of less than $8.0 \times 10^3/\mu\text{L}$ or less than 15% lymphocytes in the total white-cell count) occurred in 35.7% of cases, with a mean lymphocyte count of 1.0 ± 0.4 (range = $0.4\text{--}1.7$) $\times 10^3/\mu\text{L}$. Thrombocytopenia (a total

Table 1
Characteristics, symptoms, signs and laboratory findings of the 14 patients with novel H1N1 infection who were quarantined at the Heping branch of Taipei City Hospital

| No./Sex/ Age in yr | Date of illness onset | Travel history | Contact | Fever | Cough | Rhinorrhea | Sore throat | Myalgia | Throat | Conjunctivitis | Leukopenia ^a | Lymphopenia ^b | Duration of virus shedding (d) |
|-----------------------|--------------------------|-----------------|----------|---------|---------|------------|----------------|---------|-----------|----------------|-------------------------|--------------------------|--------------------------------------|
| 1/M/33 | May 30 | US | - | + | + | + | - | + | Congested | No | No | No | 11 |
| 2/M/9 | May 29 | US | - | + | + | - | - | - | Congested | No | No | Yes | 6 |
| 3/M/24 | May 31 | US | - | - | - | + | + | + | Congested | No | Yes | No | 6 |
| 4/M/19 | June 7 | Thailand | Plane | + | + | - | + | + | n.p. | No | No | No | 7 |
| 5/F/23 | June 8 | Thailand | - | + | + | + | + | + | n.p. | No | Yes | No | n.a. |
| 6/M/31 | June 7 | Thailand | - | + | - | + | - | - | Congested | Yes | No | Yes | 8 |
| 7/M/30 | June 11 | Thailand | - | + | - | - | - | - | Congested | No | Yes | No | 6 |
| 8/F/18 | June 11 | US | - | + | + | + | + | + | Congested | No | Yes | Yes | 6 |
| 9/M/8 | June 11 | US | - | + | + | + | + | - | Congested | No | Yes | No | 6 |
| 10/F/57 | June 10 | US | - | + | + | - | + | + | Congested | No | Yes | No | n.a. |
| 11/F/25 | June 13 | No | +Pt 10 | + | + | + | - | - | Congested | No | Yes | No | n.a. |
| 12/F/15 | June 13 | US | +Pt 8, 9 | + | + | + | - | - | Congested | No | No | No | n.a. |
| 13/F/32 | June 15 | US | - | - | - | - | + | + | Congested | No | Yes | Yes | n.a. |
| 14/F/21 | June 16 | Central America | - | - | + | + | - | + | Congested | No | Yes | Yes | n.a. |
| Total (n/%) | | | | 11/78.6 | 10/71.4 | 9/64.3 | 8/57.1 | 8/57.1 | 12/85.7 | 1/7.1 | 9/64.2 | 5/35.7 | 7.0 ± 1.8* |

* A p value <0.05.

^a Leukopenia was defined as a white-cell count of less than $5.0 \times 10^3/\mu\text{L}$.

^b Lymphopenia was defined as a total lymphocyte count of less than $8.0 \times 10^3/\mu\text{L}$ or less than 15% lymphocytes in the total white-cell count. F = female; M = male; n.a. = not available; n.p. = nothing particular; Pt = patient; US = United States.

Table 2
Comparison between H1N1 influenza A (H1N1) infection cases and non-H1N1 cases

| Variables | H1N1 (n = 14) No (%) | Non-H1N1 (n = 152) No (%) | p |
|--------------------------------|-------------------------|------------------------------|---------|
| Age | | | |
| 0–20 yr | 6 (42.9) | 17 (11.2) | 0.021* |
| 21–30 yr | 5 (35.7) | 57 (37.5) | |
| 31–40 yr | 2 (14.3) | 36 (23.7) | |
| >41 | 1 (7.1) | 42 (27.6) | |
| Sex | | | |
| Female | 7 (50.0) | 71 (46.7) | 1.000 |
| Male | 7 (50.0) | 81 (53.3) | |
| Travel history | | | |
| US | 8 (57.1) | 29 (19.1) | <0.001* |
| Thailand | 4 (28.6) | 10 (6.6) | |
| Others | 2 (14.3) | 113 (74.3) | |
| Symptoms | | | |
| Fever | 13 (92.9) | 105 (69.1) | 0.069 |
| Myalgia | 8 (57.1) | 41 (27.0) | 0.029* |
| Productive cough | 5 (35.7) | 25 (16.4) | 0.137 |
| Conjunctivitis | 1 (7.1) | 1 (0.7) | 0.164 |
| Dizziness | 0 (0.0) | 20 (13.2) | 0.223 |
| Diarrhea | 0 (0.0) | 14 (9.2) | 0.220 |
| Infiltrate on chest radiograph | 0 (0.0) | 16 (10.5) | 0.365 |
| Leukopenia ^a | 9 (64.3) | 16 (10.5) | <0.001* |

Other variables included: contact history, chills, malaise, headache, sore throat, rhinorrhea, nasal obstruction, sneezing, cough, nonproductive cough, dyspnea, nausea and vomiting, abdominal tenderness, nose, throat, neck, lung, lymphopenia, thrombocytopenia, and C-reactive protein. These variables demonstrated no significant difference.

Statistics were obtained by Fisher's exact test.

* A *p* value <0.05.

^a Leukopenia was defined as a white-cell count of less than $5.0 \times 10^3/\mu\text{L}$. No = number.

platelet count of less than $150.0 \times 10^3/\mu\text{L}$) was not found, with the patients having a mean thrombocyte count of 209.1 ± 42.6 (range = 154.0 – 313.0) $\times 10^3/\mu\text{L}$. The definitions of leukopenia, lymphopenia, and thrombocytopenia were the same as in previous literature.¹¹ The mean C-reactive protein was 6.5 ± 6.8 (range = 0.0 – 21.0) mg/L. The patients' renal function tests, liver function tests, and chest radiographs were all normal. The O₂ saturation of these patients was measured during quarantine. The lowest O₂ saturation measured had a mean of $96.1 \pm 1.2\%$ (range = 95 – 98%). Viral shedding (from the first day of illness to the day of the first negative PCR result of two consecutively negative PCR tests) lasted a mean of 7.0 ± 1.8 days.

4.4. Treatment and outcome

All patients including the children in our study were treated with oseltamivir orally twice daily for 5 days using a dose based on body weight according to the manufacturer's recommendations (for adults who were >40 kg, 75 mg twice daily; for children who were: ≤15 kg, 30 mg twice daily; >15–23 kg, 45 mg twice daily; >23–40 kg, 60 mg twice daily; >40 kg, 75 mg twice daily). No patient required

Table 3
Logistic regression analysis relating to H1N1 reverse transcription polymerase chain reaction positivity by associated variables using forward conditional methods

| Characteristics | Adjusted OR | 95% CI | p |
|-------------------|-------------|-----------|-------|
| Age | | | |
| >41 yr | 1 | | 0.624 |
| 31–40 yr | 2.1 | 0.1–39.1 | 0.529 |
| 21–30 yr | 2.5 | 0.1–45.3 | 0.034 |
| 0–20 yr | 27.7 | 1.3–597.8 | |
| Traveling history | | | |
| Others | 1 | | |
| US | 14.5 | 2.1–101.4 | 0.007 |
| Thailand | 56.7 | 4.6–700.6 | 0.002 |
| Symptoms | | | |
| Myalgia (Y/N) | 8.5 | 1.4–52.0 | 0.021 |
| Leukopenia (Y/N) | 17.4 | 3.4–90.5 | 0.001 |

Initial variables include: age, travel history, fever, myalgia, dizziness, productive cough, diarrhea, conjunctivitis, and leukopenia.

CI = confidence interval; N = no; OR = Odds ratio; US = United States; Y = yes.

supplemental oxygen or intubation. The lowest O₂ saturation for the H1N1 cases was not statistically different from that of the non-H1N1 cases (*p* = 0.302). At the time of writing, all 14 patients had been discharged after a policy change by the CDC, Taiwan on June 19, 2009, namely that there was no need to isolate patients if there were no serious complications,¹² since WHO considered H1N1 to be a moderate form of influenza. The outcome was that all patients were discharged from quarantine without mortality or morbidity.

4.5. Risk indicators for being infected by novel H1N1 influenza virus

Analysis using Fisher's exact test found that age, travel history, myalgia and leukopenia were significantly different between the H1N1 and non-H1N1 groups, as shown in Table 2. Table 3 shows the risk indicators for H1N1 cases by logistic regression analysis. A greater risk was found among the age group younger than 20 years [Odds ratio (OR) = 27.7, 95% confidence interval (CI) = 1.3–597.8, *p* = 0.034] and among those who had traveled from the US (OR = 14.5, 95% CI = 2.1–101.4, *p* = 0.007) or Thailand (OR = 56.7, 95% CI = 4.6–700.6, *p* = 0.002). Patients presenting with myalgia symptoms (OR = 8.5, 95% CI = 1.4–52.0, *p* = 0.021) seemed to have a greater risk of being infected with H1N1. Furthermore, initial laboratory findings of leukopenia (OR = 17.4, 95% CI = 3.4–90.5, *p* = 0.001) were associated with a higher risk of being infected with H1N1.

5. Discussion

To our knowledge, this is the first study comparing the clinical and laboratory differences between H1N1 and influenza-like non-novel H1N1 cases. We identified the characteristics of H1N1 patients in the early phase of disease spread. It has been shown that, in the community, the triad of

fever, respiratory symptoms (cough, sore throat, or nasal symptoms), and constitutional symptoms (headache, malaise, myalgia, sweats/chills, or fatigue) has a sensitivity of 60% if influenza was known to be present in the community.¹³ However, to guide isolation policy and therapy, a definitive diagnosis of influenza as the causative organism is often needed. RT-PCR is accurate; however, it is expensive, needs 4–24 hours,^{13,14} and is only available by means of a sophisticated laboratory that can perform the procedure. When there is a pandemic, the laboratory may not be able to tolerate the testing load. The rapid influenza diagnosis test is a timely method but relatively inaccurate, as it has a low sensitivity (11.1–69%).^{15–17}

In our study, 42.9% of H1N1 infected cases were 20 years of age or less, in agreement with various previous series.^{1,18,19} Specifically, persons younger than 21 years have a higher odds ratio of being infected by H1N1 virus. In a US school in New York, all H1N1 cases were students, with the exception of one student teacher aged 21 years.²⁰ The same phenomenon was found in 1977, when Russian influenza mainly affected individuals aged 14–20 years. It is possible that the H1N1 circulating at present (a swine-origin triple-reassortant influenza virus) has enough antigenic similarity to related H1N1 influenza strains of the past to allow older individuals exposed to the virus to be protected if they had been infected previously.²¹

Recent evidence suggests that transmission of influenza occurs over short distances rather than over long distances and occurs predominantly by the droplet and contact routes (within 3 feet), rather than by aerosol.^{13,22} Travel history to a highly affected area, such as the US or Thailand, was strongly correlated with H1N1 infection in our series ($p < 0.001$). Those who had traveled from Thailand had an odds ratio of 56.7 (95% CI = 4.6–700.6) of being H1N1 infected, whereas those who had traveled from the US had an odds ratio of 14.50 (95% CI = 2.1–101.4) of being H1N1 infected. The airport check point for fever identified a group of students who were returning from Thailand on June 9, 2009 as having fever and other symptoms. Three of them were confirmed to be victims of the H1N1 novel virus infection after quarantine and examination. Taiwan CDC reported this event to the WHO and the Thailand government. Although Thailand was not categorized as an “at-risk” country during this early phase, nevertheless confirmed cases of H1N1 from Thailand were reported frequently during June, 2009 by Taiwan CDC.²³ Moreover, the cumulative confirmed cases (518) from Thailand were higher in number compared to other nearby countries such as Philippines; the Republic of Korea; and Malaysia as of June 19, 2009.²⁴

Myalgia usually involves the long muscles of the back and the extremities. Cytokines are responsible for the muscle ache. Myalgia is present in 39% of influenza patients.^{25,26} Previous H1N1 series have reported myalgia with a range from 30% to 59%.^{1,18,19,27,28} In our series, myalgia was found in 57.1% of H1N1 cases and was the only significant symptom that differentiated these cases from the non-H1N1 group. Logistic regression showed it to be a predictor of H1N1 cases, with an

odds ratio of 8.5 (95% CI = 1.4–52.0). However, several studies have found that symptoms and signs have a relatively poor predictive value during an influenza outbreak.^{29–31} Monto et al.³² reported that fever and cough occurred more frequently among influenza patients involved in the clinical trials of one antiviral agent, but these results may not apply directly to a primary care setting because they represent pooled findings across several epidemics. Fewer of our patients had a cough (71.4%) or a sore throat (57.1%), rhinorrhea (coryza) (64.3%), and none had diarrhea, compared to larger case series that have been reported.^{1,18,19} However, none of the above symptoms show a statistically significant difference between the H1N1 and non-H1N1 cases.

It is very unusual that, compared to other studies, none of our cases reported gastrointestinal symptoms, such as diarrhea (range = 25–41%) and/or vomiting (range = 13–25%).^{1,18,19} However, a series in Singapore also reported no diarrhea among their first 10 cases.²⁷ The information from People Republic of China³³ also showed that among their cases, only 2.8% have diarrhea and 1.9% had nausea and/or vomiting, which was much lower than in other countries.

In our study, a patient with leukopenia had higher odds of being a H1N1 case, with the mean leucocyte count for the patients being $4.6 \pm 1.3 \times 10^3/\mu\text{L}$ (range = 3.0–8.2). Similar findings have been found in other studies of influenza.³⁰ Nonetheless, this is quite different from novel H1N1 cases reported in Singapore, where there was a leucocytosis rate of 30% and a mean leucocyte count of 7.8 (range 5.1–14.7) $\times 10^3/\mu\text{L}$.²⁷ Although the etiology of leukopenia is not known, it has been associated with a poor prognosis during avian H5N1 infection.³⁴ This blood test is not a routine test that might be performed regularly outside of a hospital setting overseas, but it can be easily and quickly obtained in Taiwan.

Our first patient had detectable virus in a nasopharyngeal swab until Day 11 from their illness onset, after completion of 5 days of oseltamivir and the resolution of the fever and respiratory symptoms. Two other patients still had detectable virus in their nasopharyngeal swabs by RT-PCR on Days 7 and 8 of their illness, respectively. The mean duration of virus shedding was found to be 7.0 ± 1.8 days (Table 1). Although the reported mean duration of viral shedding has been presented as 4.8 days in other studies of influenza, several studies have reported viral shedding as late as Days 8–10 and involving 20–30% of cases.³⁵ A series of novel H1N1 infections reported from Singapore had findings similar to ours.²⁷ Because this new virus has been shown to be sensitive to oseltamivir,¹ our observation that some patients had prolonged viral shedding is intriguing. One possibility is that standard viral culture detects “live virus” whereas the RT-PCR method may not. Another possibility is that this may be due to a higher false positive rate for the influenza RT-PCR assay compared with viral culture,³⁶ but it could also suggest the possibility of more prolonged viral shedding from this new influenza A (H1N1). This could potentially result in longer duration of infectivity and this possibility might aid the emergence of oseltamivir resistance. There have been a total of 313 cases of resistant H1N1 reported across the world up to

October 27, 2010.³⁷ Monitoring for resistance to oseltamivir started in July 2009 in Taiwan; however, no strains resistant to oseltamivir were detected until two separate cases on Oct. 20, 2009 and Oct. 27, 2009 were identified.³⁸ Furthermore, the published meta-analysis of the duration of virus shedding³⁵ has been mainly collected from studies where healthy volunteers had been inoculated, which is different from a naturally acquired influenza virus infection. Further studies are underway to delineate these concerns.

There are limitations that affect this hospital-based case control study. Most important, although statistically significant for both the Fisher's exact test and logistic regression, only 14 H1N1 cases were part of our study. Therefore, there may be bias in estimating the prevalence of patient characteristics because of the low numbers.

In conclusion, since novel H1N1 is pandemic at this time and has been reported to have considerable mortality and morbidity in Mexico, physicians dealing with patients who are younger in age, have a history of travel to an affected area, have myalgia, and have laboratory finding showing leukopenia should take greater care with these individuals.

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