The Response to Novel Influenza A (H1N1) Epidemic in Taiwan and Analysis of the Initial 61 Confirmed Cases

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Overview of the novel influenza A (H1N1) epidemic and pandemic response

Mexico and the southwestern part of the United States of America have reported serial outbreaks of novel influenza A (H1N1) since this April. As of April 24, 2009, there were clusters reported from 3 cities in Mexico and 8 confirmed cases of novel influenza A (H1N1) infection. The novel influenza A (H1N1) virus was made up with four gene components of North American swine influenza virus, North American avian influenza virus, human influenza virus and European-Asian swine influenza virus. It was resistant to amantadine and rimantadine but sensitive to Tamiflu (oseltamivir) and Relanza (zanamivir).

In response to the epidemics occurred in the United States of America and Mexico, Taiwan Centers for Disease Control (Taiwan CDC) immediately proceeded with multiple activities outlined in the "Strategic Pandemic

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Influenza Preparedness Plan". The main framework for the plan includes 4 major strategies and 5 lines of defense. The World Health Organization (WHO) published the case definitions for infection with novel influenza A (H1N1) virus on April 26, 2009. Immediately afterwards, Taiwan CDC announced the inclusion of human infections with novel influenza A (H1N1) virus in the list of Category I Notifiable Infectious Disease. All medical institutes are required to report such cases to local health authorities or to Taiwan CDC within 24 hours. The WHO's emergency committee decided to raise the influenza pandemic alert level to phase 4 on April 28, 2009. Simultaneously, Taiwan established the Central Epidemic Command Center (CECC) as planned in response and its first meeting was organized by the Minister of Health, Ching-Chuan Yeh. Border monitoring for disease is the first and foremost task in disease control and prevention in Taiwan. Therefore, in addition to the fever screening, we began to carry out onboard quarantine inspection on all certain flights from the United States and Mexico at Taoyuan International Airport. During April 29-May 19, 2009, there were 236 flights that came directly from the US or Canada, carrying 43,948 passengers (including 73 passengers who traveled to Mexico). Onboard quarantine identified 22 (0.05%) passengers with fever and 34 (0.08%) with respiratory symptoms. There were also 26 fever travelers identified and 15 self-reported illness at fever screening station. On April 30, WHO further raised influenza pandemic alert level to phase 5. We also set up the Notifiable Infectious Disease Reporting System and the Real-time Outbreak and Disease Surveillance System to timely monitor domestic cases and epidemic situation. In addition, the laboratory testing system has also been set up to conduct testing rapidly and accurately.

On May 1, the first case of novel influenza A (H1N1) was confirmed in Hong Kong. Since the Taiwanese travelers of the same flight had entered Taiwan, CECC tracked down those sitting within three rows in front and three rows behind and gave them antiviral drugs and urged them to conduct quarantine at home.

In light of vaccination is the most effective method for prevention and control of influenza, at 7pm in Taiwan on May 4, 2009, the Taiwan CDC and representatives from ADImmune Corporation and the National Health Research Institutes attended the cross-national teleconference organized by the International Federation of Pharmaceutical Manufacturers & Association (IFPMA). The conference invited all major vaccine manufacturers around the world to discuss plans to produce novel influenza A (H1N1) vaccine with the WHO. This conference was held weekly and Taiwan CDC also attended it routinely.

In the mid-May, there were outbreaks of novel influenza A (H1N1) in the Kansai region in Japan and the magnitude expanded quickly. Since the number of Taiwanese travelers to Japan was quite large, CECC advised people planning to visit Japan to pay attention to disease prevention. From the midnight of May 19, in place with more comprehensive unusual notification onboard quarantine measure, onboard quarantine inspection of certain flights was suspended. From May 18 to 22, the Minister of Health, Ching-Chuan Yeh led a team to attend the 62nd World Health Assembly (WHA) conference in Geneva. This was the first time that Taiwan attended the conference as an observer. Many issues about novel influenza A (H1N1) were discussed during the conference and the meeting duration was shortened due to the pandemic.

On May 20, the first imported case of novel influenza A (H1N1) who came from the United States was identified by fever screening at Taoyuan International Airport and the pandemic alert level in Taiwan was raised to level 2. In addition to the continuation of border quarantine and contact tracing, CECC also exchanged the most update information with other countries by IHR focal point on the aspect of case tracing.

Keywords: Novel influenza A (H1N1), influenza pandemic, onboard quarantine, Tamiflu (oseltamivir)

Case definitions for infection with novel influenza A (H1N1) virus

According to the Infectious Disease Control Act of Taiwan, anyone who meets the epidemiological and clinical criteria of novel influenza A (H1N1) infection is regarded as a case under investigation and should be reported to Taiwan CDC immediately. Epidemiological criteria include an epidemiologic link to a confirmed or probable case in the past 7 days, or a travel history to endemic countries in the past 7 days. In the beginning of this epidemic, only the United States and Mexico were listed as endemic countries. The list then gradually expanded to include many Asian and European countries as the epidemic evolves. Clinical criteria are the presence of acute febrile respiratory tract illness, ranging from mild influenza-like illness to severe pneumonia. Throat/nasal swab and blood samples should be taken from every case reported. Throat/nasal swabs will be sent for real-time RT-PCR and virus isolation. Serological tests will be performed on blood samples. If a throat/nasal swab specimen was tested positive for influenza A virus by real-time RT-PCR but negative for human H1 and H3, the case will be defined as a “probable” case of novel influenza. Novel H1N1 specific primers will be used to confirm the diagnosis. In our current laboratory

system, a confirmatory diagnosis can be made within 12 hours after the specimen is obtained. All the intervention below will be initiated after a case is confirmed. The ability of rapid diagnosis enables timely, targeted intervention, which conserves both time and resources.

During April 27 to June 19, human infected with novel influenza A (H1N1) virus was listed along with Category I Notifiable Infectious Diseases. 1363 cases under investigation were reported to the National Notifiable Disease Reporting System (Figure 1). Ninety percent (n=1240) of them were reported by hospitals. Ten percent (n=123) were reported by airport quarantine. Among the cases reported by hospitals, 49 turned out to be confirmed cases of novel influenza A (H1N1) infection, giving a confirmation rate of 4%. Among the cases reported by airport quarantine, 12 were confirmed and the confirmation rate was 9%. Ninety-four percent of the cases under investigation had travel history to endemic countries, with the most were China (n=278, 20%), the United States (n=242, 18%) and Thailand (n=203, 14%).

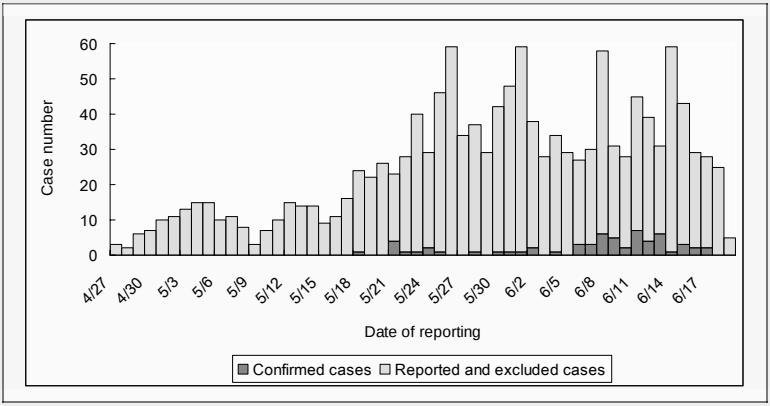

Figure 1. Epidemiological curve of novel influenza A (H1N1) infection as category I notifiable infectious disease by date of reporting, 2009/4/27-2009/6/19

Confirmed novel influenza A (H1N1) cases: management and contact investigation

Once the diagnosis of novel influenza A (H1N1) infection has been confirmed, the medical and public health system will work together for intervention. As for medical care, all confirmed cases will be admitted to negative pressure wards of designate hospitals in the corresponding region. Anti-viral medications will be prescribed and infection control measures will also be implemented. Taiwan CDC has set up the discharge criteria for confirmed cases admitted. Patients will be sampled after their clinical symptoms have improved. Real-time RT-PCR will be performed on these samples. Patients are ready for discharge once the virus load decreased to undetectable.

Taiwan CDC has established a Communicable Disease Medical Network, which has 25 designated response hospitals in the six regions all over Taiwan. The designated hospitals offer high quality medical care to all confirmed cases admitted. Regional directors of the Communicable Disease Medical Network are responsible for the allocation of medical resources, as well as supervision of clinical management of patients.

In the public health system, local health bureaus will perform case investigation, contact tracing and post-exposure prophylaxis under the supervision of Taiwan CDC. Contacts are classified as household contacts and aircraft contacts. Household contacts are those who live or spend more than 8 hours a day with a confirmed case. Aircraft contacts are passengers who sit within three rows in front or three rows behind (7 rows) the confirmed case who was infectious during the flight and did not wear a surgical mask. After receiving the flight number, date and seat number of a

confirmed case, Taiwan CDC will ask the airline company to provide the passenger list. Every passenger on the list will be checked by National Immigration Agency to see if they have entered Taiwan. If so, we will search the National Household Registration System for their contact information including address and telephone number. The contact information will be given to local health bureaus to perform case and contact investigation. At the same time, the date, number and seat number of the involved flight will be released to the mass media. Passengers sitting within three rows in front or three rows behind are encouraged to identify themselves voluntarily through our 24-hour hotline 1922. More than 400 contacts of the first 19 confirmed cases were investigated. It is noteworthy that many of the contacts reported voluntarily through 1922. Because the address obtained from the National Household Registration system may not be the current residence of the contacts, voluntary reporting of the contacts can speed up contact tracing and is also resources-saving.

It has been proved that antiviral chemoprophylaxis given within 48 hours after the contact with a confirmed case has 70-90% efficacy in preventing influenza illness. As we learn more about the nature of novel influenza A (H1N1) infection, Taiwan CDC's policy for chemoprophylaxis also adjusted. In the first three weeks of this epidemic (April 27-May 15), 10-day chemoprophylaxis with oseltamivir was given to all household and aircraft contacts. In the following months (May 16-June 19), the decision for chemoprophylaxis was made by regional directors of the Communicable Disease Medical Network. The decision was determined by the contact duration, intensity as well as the presence of risk factors such as chronic

illness that may increase the risk of severe illness. In this period of time, most of the contacts given chemoprophylaxis are household contacts. Aircraft contacts were considered to have lower risk of infection because none of them had become confirmed case in previous investigations.

Clinical characteristics of confirmed cases with novel influenza A (H1N1) infection

As of June 19, there were 61 confirmed cases with novel influenza A (H1N1) infection. Among them, 2 were indigenous and 59 were imported, including 28 (46%) from Thailand, 24 (39%) from the United States, 3 (5%) from Philippines, and 1 each from Australia, Canada, China, and Republic of Honduras. It is obvious that the origin of importation of novel influenza A (H1N1) infection follows the pattern of international epidemics; for instance, in the initial period from May 18 to May 31, 9 of 15 confirmed cases had traveled to the United States; later from June 1 to June 15, more than half of confirmed cases (28/46) had traveled to Thailand. The median age was 22 years (range: 3-57 years); 29 were male and 32 were female. Sixty percent of confirmed cases were aged 20-30 years, and most of them were students (Figure 2). This age distribution was associated with that majority of our cases were imported. From cases investigation, only 3 (4.9%) had underlying diseases: 2 had asthma and 1 had systemic lupus erythematosus. One (1.6%) had received seasonal influenza vaccination in the past year.

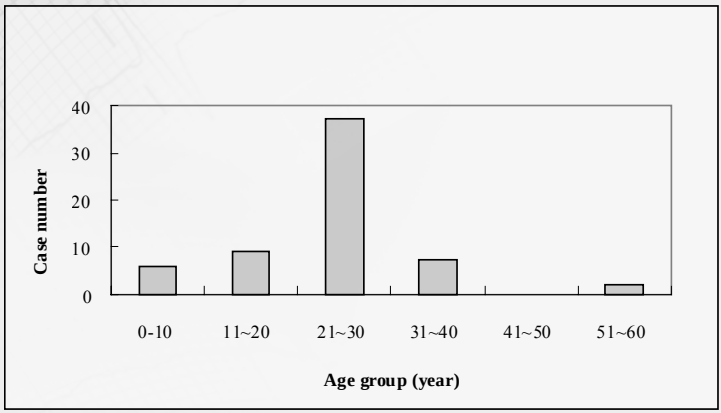

Figure 2. Age distribution of confirmed cases with novel influenza A (H1N1) infection in Taiwan, 2009/5/20-2009/6/19

For clinical manifestations, 82% cases had fever. The proportion of fever was lower than United States, Canada and Japan, which might possibly result from our active case detection and early diagnosis of patients with minor symptoms in several clusters (Table 1). In addition, about 15-25% patients in western countries had gastrointestinal (GI) symptoms. However, only 3-5% of our cases had GI symptoms, the similar feature as Japan's report, in which 2-6% patients had GI symptoms. Further study will be necessary to define whether the virus has different impact on clinical manifestations in different races.

All patients had been isolated and treated with oseltamivir, and 63.9% patients received the drug within 48 hours after onset of symptoms. All had minor symptoms and none developed severe nervous or respiratory complications or died.

Table 1. Clinical features of patients with confirmed novel influenza A (H1N1) virus infection

Clinical symptoms	USA, n=642	Canada, n=173	Japan, n=217	Taiwan, n=61
Age (median, range),	20 years (0.25 -81)	22 years (1-61)	16 years (1-69)	22 years (3-57)
Fever	94%	87%	95%	82%
Cough	92%	87%	59%	82%
Sore throat	66%	48%	39%	39%
Rhinorrhea	-	27%	33%	38%
Diarrhea	25%	23%	6%	5%
Vomiting	25%	15%	2%	3%
Headache	-	38%	13%	23%
Malaise/fatigue	-	35%	31%	31%
Myalgia	-	35%	19%	30%
Arthralgia	-	13%		5%

For those initial 40 cases with follow-up result, the median hospital stay were 6 days (range: 3-11 days), and the median interval between symptoms onset and negative follow-up RT-PCR result were 6 days (range: 3-13 days). The relevance of clinical symptoms, treatment and follow-up RT-PCR results showed that regardless of whether they had symptoms at the time of specimen collection, more than 70% patients had negative RT-PCR results after 7th day of symptoms onset, which indicated low transmission risk. Similarly, more than 70% patients had negative RT-PCR result after 5th day of oseltamivir treatment. For those 15 patients with fever at admission, about 70% had negative RT-PCR result after 3rd day of defeverence (Table 2). However, we did not have patients without antiviral treatment as a control group; based on the above data, it is still inconclusive if antiviral therapy could shorten the time of negative conversion of RT-PCR and the recovery.

Table 2. Follow-up RT-PCT results of initial 40 confirmed cases with novel influenza A(H1N1) infection

Cumulative no. (%)	Interval		
	Symptom onset to negative RT-PCR (n=40)	Treatment to negative RT-PCR (n=40)	Defeverence to negative RT-PCR (n= 15)
1st day			3(20.0%)
2nd day		3(7.5%)	10(66.7%)
3rd day	1(2.5%)	15(37.5%)	11(73.3%)
5th day	16(40.0%)	29(72.5%)	12(80.0%)
7th day	29(72.5%)	36(90.0%)	14(93.3%)

Conclusion

Since the novel influenza A (H1N1) outbreak had spread to the rest of the world, the WHO raised the level of influenza pandemic alert to phase 6 and declared a pandemic of moderate severity on June 12, 2009. According to the epidemiology of novel influenza A (H1N1), its severity seemed as modest as seasonal influenza. CECC decided to remove novel influenza A (H1N1) from the Category I Notifiable Infectious Disease and included it in list of Category IV Notifiable Infectious Disease reported as influenza complications. Only the novel influenza A (H1N1) -infected cases with complications of respiratory system, nervous system, myocarditis, secondary bacterial infection or other severe diseases should be reported. In addition to continuously pay attention to the incidence of severe cases, the mortality rate and the prognosis, CECC has planned to integrate the community surveillance of the novel influenza A (H1N1) virus and the National Health Insurance database to monitor the development of the epidemic timely and more closely. Further, CECC will continue to pay

close attention to the epidemics in the Southern hemisphere, begin the preparedness and purchase of vaccine, and recruit experts of working groups to assist the government and medical systems in order to be prepared for the future epidemics and ensure the health of the people in Taiwan.

Acknowledgment

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