H1N1 Influenza: A Viral Infection

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Abstract

The outbreak of Influenza H1N1 on 11 June 2009 caught attention worldwide. H1N1 influenza is a subtype of Influenza A. There are several serious outbreaks of H1N1 influenza which occurred in the history in 1918, 1957, 1968 and 2009. H1N1 influenza is caused by influenza viruses, which are small RNA that will infect many mammals, including humans, birds, and swine. The deadly virus contains two types of protein on its surface which are hemagglutinin (H) and neuraminidase (N). Hemagglutinin binds to its receptor, sialic acid on the host cell surface. Neuraminidase cleaves the sialic acid receptor and then release progeny virus from the cell surface that has been infected by the virus. The common symptoms of patients with H1N1 influenza are difficulties in breathing, cough, headache, tiredness, sore throat, vomiting and diarrhoea. The preventive measures that can be taken for H1N1 influenza include getting vaccinated, practising proper and frequent hand washing, avoiding close contact with sick people, wearing a facemask, and practising a healthy lifestyle. The treatment of the H1N1 influenza involves drugs such as Tamiflu® (oseltamivir) and Relenza® (zanamivir).

Introduction

A Brief Swine Flu History and Overview

The beginning of a global influenza A (H1N1) is marked on June 11, 2009, over last two years ago. The director general of World Health Organization (WHO) declared that the status of the influenza A (H1N1) pandemic had reached phase 6, which is active transmission on a global scale since the last 1968 Hong Kong Flu (Yamada, 2009). This global pandemic has challenged the medical world and the people in general. What is H1N1? When did the first outbreak happen? The answers to these questions could arm us with proper knowledge on how to fight and prevent this deadly disease from arising again in the next wave of the pandemic.

What is influenza A (H1N1)?

The influenza viruses are small RNA viruses that infect many mammals, including humans, birds, and swine. Influenza A (H1N1) is a subtype of Influenza Virus. Some strains are endemic in humans like the influenza A (H1N1) and the seasonal flu. Some are endemic in pigs (swine influenza) and some are in birds (avian influenza). This deadly virus can be subdivided according to the two proteins found on the surface of the virus: hemagglutinin (H) and neuraminidase (N). All of the influenza strains contain these two protein structures, however, they vary from strain to strain in terms of the structure of the proteins. Each strain is assigned an H and an N numbers based on how many protein structures they contain.

When did the first outbreak happen?

1918-1920 Flu Pandemic (subtype H1N1)

The 1918 flu pandemic which is also known as Spanish Flu has been cited as the most devastating pandemic recorded in world history. The influenza killed 50-100 million people worldwide. The flu killed so many people because of its cytokine storm on the body. The patient will have difficulty breathing and dies.

1957-1958 Asian Flu Pandemic (subtype H2N2)

At the start of May 1957, former Director-General of WHO, Dr Lee Jong-wook stated that the WHO received news of extensive influenza epidemics in East Asia. The Asian Flu was identified as a completely new virus subtype, a form of avian influenza which is normally found in wild ducks and had crossed with a human virus. It was named H2N2; the H and N numbers designate the proteins on the outside of the virus that bind to target cells in the victim (Szczechaski, 2009). Since influenza is a sloppy sort of virus, it easily recombines and mutates - and human immune systems cannot always keep pace.

According to the Johns Hopkins School of Public Health, the Asian Flu killed almost 2 million people around the globe, including some 69,800 in the United States. It was most deadly for the elderly.

1968-69 The Hong Kong Flu Pandemic (subtype H3N2)

The H3N2 flu strain was first detected in Hong Kong in July of 1968; the illness spread explosively in Hong Kong's tightly-packed population, but the death rate was very low. It is believed that people who survived the 1957-58 Asian Flu pandemic had developed resistance to the H2N2 virus responsible for the outbreak (Lee, 2005). However, 10 years later the virus mutated by changing its H antigen - the hemagglutinin - and enough people's immune systems were fooled by the change of the new H3N2 subtype (Lee, 2005). The virus likely combined and incubated in pigs, which then transferred it to human carriers. World-wide, an estimated 500,000 people died in the
Hong Kong Flu pandemic. Again, the elderly were the 
hardest hit.

2009 Influenza A Pandemic (subtype H1N1) 
In April 2009, the Mexican Secretariat of Health 
anounced an outbreak of a novel H1N1 swine 
influenza virus, which has then caused a global 
pandemic (Wenzel, 2009). In the affected patients, a 
novel swine origin influenza A (H1N1) virus (S-OIV) 
with molecular features of North American and 
Eurasian swine, avian, and human influenza viruses 
was found (Padilla et. al, 2009). Experts writing in the 
August issue of The New England Journal of Medicine 
stated that the initial outbreak began in the state of 
Veracruz, Mexico, with evidence that there had been 
an ongoing epidemic for months before it was officially 
recognized as such (Padilla et. al, 2009). The Mexican 
government closed most of Mexico City’s public 
and private facilities in an attempt to contain the spread of 
the virus; however, it continued to spread globally, and 
clinics in some areas were overwhelmed by infected 
persons (Padilla et. al, 2009). On June 11, 2009, the 
World Health Organization (WHO) and the U.S. 
Centers for Disease Control and Prevention (CDC) 
stopped counting cases, declared that the status of the 
influenza A (H1N1) pandemic, moving the alert level to 
phase 6, marking the first global pandemic since the 
1968 Hong Kong flu (Yamada, 2009). According to the 
latest WHO statistics in July 2010, the virus has killed 
more than 18,000 people since it appeared in April 
2009, however they stated that the total mortality 
(including deaths unconfirmed or unreported) from the 
H1N1 strain is unquestionably higher (WHO, 2010).

Epidermiology

Cause Of Disease
Influenza A H1N1 is also known as swine flu. A highly 
contagious form of influenza seen in swine is caused 
by a virus of the family Orthomyxoviridae (Kimura K et 
al, 1998). Orthomyxoviridae have two major envelope 
glycoproteins which are hemagglutinin and 
neuraminidase. Hemagglutinin binds to its receptor, 
sialic acid on the host cell surface. Neuraminidase 
cleaves the sialic acid receptor and then release 
progeny virus from the cell surface that has been 
infecte by the virus (Couch, B. Robert, 1996).

Entry of Virus
The newly synthesized virus has glycoprotein on its 
surface that contains N-acetylneuraminic acid. This 
structure is susceptible to self agglutination by 
hemagglutinin. The neuraminidase acts on the 
N-acetylneuraminic acid residues in mucus to produce 
liquefaction. This liquefied mucus will spread the virus 
through respiratory tract (Elsevier Ltd, 2006). This 
proves that this RNA virus can cause respiratory 
disease in human. This is the first symptom without 
fever in which an individual can be suspected to have 
the influenza (CDC, 2010).

The first strain seen in Mexico is termed as novel 
H1N1 flu because it has two main surface antigens 
which are hemagglutinin type 1 and neuraminidase 
Type 1 (Medicine Net, Inc., 2011). Recent study 
shows the eight RNA strands from H1N1 flu have one 
strand derived from human flu strains, two from avian 
(bird) strains, and five from swine strains (Heinen, P., 
2003). There are three genera of influenza virus that 
can cause flu to human, two of them cause influenza 
in pigs where influenza A is the common one 
(Kothawala, H et al, 2006).

In the past, swine flu does not infect people and 
human cases are rare. It only infects a person that has 
direct contact with pigs. But, presently the outbreak is 
different because the swine flu has changed in many 
ways. This is the reason why it can be spread from 
one person to another person that has even no 
contact with pigs (Daniel J DeNoon, 2011).

There is no proof suggesting the routes of 
transmission other than a direct contact. This means 
that one person can spread the virus to another. 
Human to human transmission can occur through 
coughing or sneezing of the infected people 
(GlobalSecurity.org, 2011). Other than that, this virus 
can also be transmitted if a person is in contact with 
contaminated surface that is exposed to the virus such 
as handles, doorknobs, counters and telephones 
(Northwest Territories Health and Social Sciences, 
2009).

According to the hypothesis published in the PLoS 
Currents: Influenza website, the authors from the 
Mount Sinai School of Medicine, New York, said that 
aerosol transmission is acutely sensitive to relative 
humidity and temperature, while contact transmission 
is not. The experiments done by them showed that 
contact route was neither affected by humidity nor by 
temperature (The Hindu, 2009).

Another study stated that influenza virus is completely 
blocked at warm or humid conditions. But, the 2009 
H1N1 influenza virus continued to spread in spring 
and summer months in northern hemisphere. This 
contradicts the fact that low temperature and humidity 
favours transmission of influenza.

Signs and symptoms

Generally, symptoms of H1N1 flu in people are similar 
to the symptoms of regular human seasonal influenza
including fever, muscles or body aches, lack of appetite and coughing. Some people with H1N1 have also reported runny nose, sore throat, headaches, fatigue, nausea, vomiting and diarrhea (U.S. Department of Health & Human Services, 2011). However, the signs and symptoms might differ between adults and children. In adults, emergency warning signs that need urgent medical attention are having difficulty in breathing or shortness of breath, pain or pressure in the chest or abdomen, sudden dizziness, confusion, severe or persistent vomiting and flu-like symptoms that improve but then return with fever and worse cough (CDC, 2009). Meanwhile, symptoms in children suspected with H1N1 include breathing difficulties, bluish skin colour, not drinking enough fluids and not waking up or not interacting. A child might also be so irritable that the he does not want to be held, unable to eat and also having no tears when crying (CDC, 2009). Individuals who experience flu-like symptoms should immediately contact their physicians and health care professionals, as Swine Flu is a highly contagious disease. People who believe they are infected with H1N1 should avoid going out in public unless absolutely necessary (Medicine Net, Inc., 2009). People with flu-like illness should stay at home except to get medical care or other necessities.

**Treatment**

The treatment of H1N1 influenza A virus is through antiviral drugs. The H1N1 influenza A virus strain which emerged and was isolated in 2009 showed resistance to adamantanes but is susceptible to neuraminidase inhibitors, oseltamivir and zanamivir (Hayden, F.G. & Pavia, A.T., 2006). Thus, during the pandemic, treatment with oseltamivir (trade name Tamiflu®) or zanamivir (trade name Relenza®) is recommended for people with suspected or confirmed influenza who require hospitalization (Centers for Disease Control and Prevention, 2010). However, as the use of oseltamivir becomes more widespread, there is increased resistance among H1N1 virus isolates towards oseltamivir, while most remained susceptible to zanamivir (Hayden, F.G. & Pavia, A.T., 2006).

The formulation of oseltamivir (Tamiflu®) as capsules or oral suspension is FDA-approved for the treatment of uncomplicated acute influenza in patients 1 year and older who has showed symptoms not more than two days. An Emergency Use Authorization (EUA) was also issued by the FDA, authorizing treatment with oseltamivir for patients less than 1 year old with 2009 H1N1 influenza. Similarly, zanamivir (Relenza®), formulated as oral inhalation is FDA-approved for treatment of influenza in patients but for 7 years old or older. Both oseltamivir and zanamivir have EUA from the FDA authorizing treatment for 2009 H1N1 influenza patients who have been symptomatic for two days and sick enough, requiring hospitalization (CDC, 2009).

Besides that, during the pandemic, an unapproved investigational neuraminidase inhibitor, peramivir was issued an EUA by the FDA for intravenous (IV) administration after a public health emergency was declared (Birnkrant, D. & Cox, E, 2009). Under the EUA, treatment using peramivir for adult patients was approved if patient is non-responsive towards oral or inhaled antiviral therapy; if drug administration other than IV is not possible; or due to other circumstances, the clinician concludes that IV therapy is appropriate. Treatment for paediatric patients was also approved for they fit either of the first two criteria (CDC, 2009). The Centers for Disease Control and Prevention (CDC) distributes peramivir directly to a hospital after the request from a licensed clinician is verified (Birnkrant, D. & Cox, E, 2009). However, it is important that health care providers recognise that peramivir is an unapproved drug authorised for use only because of and during the 2009 H1N1 public health emergency (Birnkrant, D. & Cox, E, 2009).

The dosage of both Tamiflu® and Relenza® is divided into treatment and prophylaxis of influenza. This is shown in the table below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamiflu®</td>
<td>75mg once daily</td>
<td>75mg once daily</td>
</tr>
<tr>
<td>Tamiflu®</td>
<td>75mg once every other day</td>
<td>75mg once every other day</td>
</tr>
<tr>
<td>Tamiflu®</td>
<td>75mg once daily for 5 days</td>
<td>75mg once daily for 5 days</td>
</tr>
<tr>
<td>Tamiflu®</td>
<td>75mg once daily for 2 days</td>
<td>75mg once daily for 2 days</td>
</tr>
<tr>
<td>Tamiflu®</td>
<td>75mg once daily for 7 days</td>
<td>75mg once daily for 7 days</td>
</tr>
<tr>
<td>Relenza®</td>
<td>75mg once daily</td>
<td>75mg once daily</td>
</tr>
<tr>
<td>Relenza®</td>
<td>75mg once daily for 5 days</td>
<td>75mg once daily for 5 days</td>
</tr>
<tr>
<td>Relenza®</td>
<td>75mg once daily for 2 days</td>
<td>75mg once daily for 2 days</td>
</tr>
</tbody>
</table>

However, for renally impaired patients with creatinine clearance of 10-30mL/min the dosage of Tamiflu® need to be adjusted. For these patients, the use of Tamiflu® for treatment is reduced to 75mg once daily for 5 days. Meanwhile, in prophylaxis, it is reduced to 75mg once every other day or 30mg once daily (Genentech USA, Inc, 2011). Tamiflu® is contraindicated in patients with known serious hypersensitivity to oseltamivir or any components of Tamiflu® (Genentech Usa, Inc, 2011). For Relenza®, it is contraindicated in patients with history of allergic reaction to any ingredient of Relenza®, including lactose (GlaxoSmithKline, 2010). Relenza® is also not recommended for patients with underlying airways disease (GlaxoSmithKline, 2010). Some side effects of the use Tamiflu® include serious skin or hypersensitivity reaction (Genentech USA, Inc, 2011). For both Tamiflu® and Relenza®, their use should be discontinued if allergic-like reactions occur or are suspected (Genentech USA, Inc, 2011) (GlaxoSmithKline, 2010). Influenza patients receiving both these drugs should also be monitored for...
abnormal behaviours. This is because the use of these two drugs may cause neuropsychiatric events, such as increased risk of seizures, confusion or abnormal behaviour, particularly in paediatric patients early in their illness (Genentech USA, Inc., 2011) (GlaxoSmithKline, 2010). However, patients taking Relenza® need to be cautious if bronchospasm develops because it is serious and some fatal cases have occurred. It is thus not recommended in individuals with underlying airways disease because it is not proven effective in such patients (GlaxoSmithKline, 2010).

The adverse reactions involving the use of Relenza® in treatment studies include sinusitis and dizziness whereas prophylaxis studies reveals fever or chills (or both), arthralgia and articular rheumatism (GlaxoSmithKline, 2010). On the other hand, treatment studies of Tamiflu® showed adverse reactions to be nausea and vomiting while nausea, vomiting, diarrhoea or abdominal pain are seen in prophylaxis studies (Genentech USA, Inc, 2011).

**Prevention**

There are numerous preventive measures that can be taken or practised by the public in order to prevent H1N1 infection. One of the best ways to prevent the H1N1 swine flu infection is by vaccination. According to Center for Disease Control and Prevention (CDC, 2011), pregnant women, children younger than 5 years old, elderly people, caregiver, health care workers, and people who are suffering from chronic health disorder such as asthma, diabetes, or weakened immune system are the most susceptible populations to get this infection. Hence, they are encouraged to get the flu vaccine at least once a year. Besides, minimizing or avoiding exposure to the virus is also a good way to prevent any flu diseases. Thus, people are advised to practise good health habits and to take everyday preventive actions such as washing their hands frequently and properly with soap and water, avoiding close contact with sick people, staying at home when having flu-like illnesses, covering their mouth and nose with a tissue or handkerchief when coughing, sneezing or having nasal secretion to keep from spreading the flu viruses to others (Medicine Net, Inc., 2011). They are also advised to avoid crowds, limit contact as much as possible and to stay home for at least 24 hours after they are free of fever or signs of fever without taking any fever-reducing medicine (CDC, 2011).

Furthermore, wearing a facemask and respirator may also provide protection to both infected and uninfected people since they can prevent the spread of infected droplets from one person to another. A facemask creates a physical barrier between the mouth and nose of the wearer and potential contaminants. Meanwhile, the respirator is designed to protect the wearer from breathing in very small particles, which might contain viruses. The facemask and respirator must be worn properly. Avoid reusing the mask or respirator and discard it correctly, by placing it in a plastic bag and putting it in the trash (U.S. Department of Health & Human Services, 2011).

**Acknowledgement**

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**References**

3. Centers for Disease Control and Prevention (2009) Updated Interim Recommendations for the Use of

Illustrations

Illustration 1

Table 1: Antiviral medication dosing recommendations for treatment and chemoprophylaxis of 2009 H1N1 infection. (Extracted from product information for Tamiflu® and Relenza®) (CDC, 2009).

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment (5 days)</th>
<th>Chemoprophylaxis (10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 mg twice daily</td>
<td>75 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>Body Weight (lbs)</td>
<td></td>
</tr>
<tr>
<td>15 kg</td>
<td>33 lbs</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>15 kg to 23 kg</td>
<td>33 lbs to 51 lbs</td>
<td>45 mg twice daily</td>
</tr>
<tr>
<td>23 kg to 40 kg</td>
<td>51 lbs to 88 lbs</td>
<td>60 mg twice daily</td>
</tr>
<tr>
<td>40 kg</td>
<td>88 lbs</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Age Group</td>
<td>Zanamivir Dose</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td><strong>Children 3 months to 12 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/dose twice</td>
<td>3 mg/kg/dose once per day</td>
</tr>
<tr>
<td><strong>Children 0 to 3 months</strong></td>
<td>3 mg/kg/dose twice daily</td>
<td>Not recommended unless situation judged critical due to limited data on use in this age group</td>
</tr>
<tr>
<td><strong>Zanamivir</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>10 mg (two 5-mg inhalations) twice daily</td>
<td>10 mg (two 5-mg inhalations) once daily</td>
</tr>
<tr>
<td><strong>Children (7 years or older for treatment, 5 years for chemoprophylaxis)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg (two 5-mg inhalations) twice daily</td>
<td>10 mg (two 5-mg inhalations) once daily</td>
</tr>
</tbody>
</table>
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