Influenza: The 2009 H1N1 Pandemic And Antiviral Treatment Options

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Abstract

Purpose. To provide an overview of the 2009 H1N1 influenza pandemic and antiviral treatment options for influenza.

Summary. Influenza infection causes significant morbidity and mortality every year. The high mutation rate and segmented nature of influenza virus genome gives rise to high genetic variability which enables the virus to escape antiviral and vaccine interventions. A novel H1N1 strain of influenza virus known as the swine-origin influenza virus has emerged and established itself recently in the population. The result has been the first influenza pandemic to develop in the 21st century. This new H1N1 virus is resistant to the M2 ion channel inhibitors (amantadine and rimantadine), one of the two classes of anti-influenza drugs. Neuraminidase (NA) inhibitors (oseltamivir and zanamivir) became the only treatment options for the novel H1N1 virus. NA inhibitors work by interfering with the cleavage of sialic acid and preventing the release of viruses, thereby preventing further infection. However, an oseltamivir-resistant H1N1 pandemic strain has been identified in patients. Thus, the emergence of antiviral resistance and the limited treatment options available highlight the urgent need for developing new antiviral agents to combat H1N1 infection. In response to this urgent call, the unapproved investigational drug intravenous peramivir was authorized by the FDA for emergency use. In addition, several new drugs for influenza treatment are currently under development.

Conclusion. Understanding the origin, pathogenicity, resistance potentials of influenza viruses, and the availability of new treatment options is crucial for influenza pandemic preparedness.

Introduction

One of the hallmarks of influenza virus is the high genetic variability caused by mutation and reassortment of its segmented viral genome, which contains eight gene segments and coding for ten proteins. This characteristic creates an annual global suspense as the world waits to discover if its new guise will bring an epidemic or a pandemic in the winter ahead. In 2009, we witnessed the emergence of a new strain of influenza, H1N1 swine-origin influenza virus (S-OIV) [1] in the global population as this virus has since spread quickly to many countries [2]. On June 11, 2009, the World Health Organization (WHO) declared a global influenza pandemic which encompassed 70 countries that had reported cases of S-OIV. Between April 15, 2009 and July 24, 2009, as the U.S. Centers for Disease Control (CDC) reported individual cases of confirmed and probable S-OIV infection, a total of 43,771 cases were reported resulting in 5,011 people hospitalizations and 302 deaths [3]. As of January 10, 2010, S-OIV infections resulted in at least 13,554 deaths in more than 208 countries and territories in regions reporting to the WHO [2]. The cases reported most likely represent a substantial underestimation of the total number of cases in the world because of surveillance and laboratory testing biases toward severely ill and hospitalized patients. People with milder influenza-like symptoms often do not seek treatment or are treated but not officially diagnosed with S-OIV infection. Despite this, the novel H1N1 S-OIV has emerged as the dominant strain circulating in the world accounting for 98% and over 71% of specimens reported to the WHO during the periods of December 21, 2009 to January 2, 2010 and August 8, 2010 to August 14, 2010, respectively [4]. In the United States, H1N1 S-OIV accounted for most of the specimens subtyped by the CDC [5]. On August 10, 2010, the WHO announced that the H1N1 influenza event has moved into the post-pandemic period [2].

Vaccination is the primary means of preventing influenza infection, but changes in the antigenic property of the virus can attenuate the effectiveness of the vaccine. The average time frame to produce a new vaccine is 6 months or more, and it may not be feasible to meet the demands of new emerging strains of influenza virus such as the novel S-OIV in a timely manner. Two classes of antivirals, M2 ion channel inhibitors (amantadine and rimantadine) and neuraminidase (NA) inhibitors (oseltamivir and zanamivir), are available to help control influenza
outbreak. Unfortunately, Novel H1N1 viruses that are prevailing in the 2009-2010 influenza season are resistant to M2 ion channel inhibitors leaving NA inhibitors as the only available treatment option. The emergence of oseltamivir-resistant isolates and the limited choice of therapy highlight the need to explore alternative agents that target different stages of the viral life cycle (Figure. 1). To fully prepare for an influenza pandemic, it is crucial to understand the origin, pathogenicity, resistance potentials and treatment options of influenza viruses.

Review

Influenza virus and influenza pandemic

The H1N1 S-OIV that affects humans belongs to the type A influenza virus that is serologically different from type B and C influenza viruses. This is distinguished by the antigenic differences in two viral proteins, the nucleoprotein (NP) and matrix (MA). Influenza A viruses are further identified based on the antigenicity of two surface proteins on the envelope, haemagglutinin (HA) and NA, which mediate virus attachment to the target cells and release of nascent viral particles from the infected cell, respectively [6]. Currently, 16 HA (H1 – H16) and 9 NA (N1 – N9) have been identified. Among the three types of influenza viruses, influenza A and B viruses are associated with significant seasonal morbidity and mortality in humans. Most importantly, the influenza A virus remains an emerging viral disease that affects humans on a worldwide scale and has been responsible for four pandemics in the last century [7].

Influenza pandemic is defined as an outbreak of influenza that spreads through the human population on a global scale. In the last century, influenza pandemic occurred at infrequent and unpredictable intervals, e.g. 1918, 1957, 1968 and 1977 (Table 1). Pandemics usually develop when a new human influenza virus emerges that possesses surface antigens (HA and/or NA) against which humans lack immunity. The change in the genetic makeup of the virus with regard to this antigenic change, also known as antigenic shift, is so great that it is highly unlikely that the new virus has arisen simply by the accumulation of random mutations from the previously circulating virus. Current thought is that antigenic shift arises from reassortment of gene segments from different influenza strains. Reassortment may occur when a host is co-infected with two different influenza viruses. The eight gene segments of each virus will replicate independently and then seemingly assemble randomly. The progeny viruses then contain genetic material from the two parental viruses. In theory, the gene segments from both viruses will reassort freely and give rise to a maximum of 254 (28 – 2) genotypically different reassortants, although not all of these reassortants are capable of replication [6].

HA is a major determinant of host specificity and pathogenicity

The HA surface glycoprotein has two major functions in the influenza virus replication cycle: (1) mediating the initial attachment of the virus to the target cell and (2) initiating the infection process by fusion of the viral envelope with the endosomal membrane. The first function assigns the HA a primary determinant of host specificity because of its role in the binding of the virion to a sugar moiety on the cell surface receptors. The receptor specificity of the influenza virus varies depending on the host from which the virus was isolated. Human influenza viruses preferentially recognize siaiyoligosaccharides terminated by N-acetylsialic acid linked to galactose by the ?2,6 linkage (NeuAc?2,6Gal) [14], the precise sugar moiety found on epithelial cells in the human trachea [15]. However, avian influenza viruses recognize a similar oligosaccharide, but which utilizes an ?2,3 glycosidic linkage to galactose, (NeuAc?2,3Gal ) preferentially binding NeuAc?2,3Gal on the epithelial cells in the intestine of waterfowl, which is the site of replication of avian influenza viruses [14, 16, 17].

At the molecular level, the receptor-binding specificity of influenza viruses is determined by the amino acid signature of the receptor binding site on the HA molecule. For H1 HA, the residues at 190 and 225 (H3 HA numbering) are responsible for the receptor-binding specificity [18]. The H1 HA of human influenza viruses has aspartic acid at positions 190 and 225, which correlates with the preferential binding to a human-type receptor. Avian influenza viruses have H1 HA with glutamic acid at 190 and glycine at 225 and confer binding specificity to an avian-type receptor. The H1N1 S-OIV harbours aspartic acid at both positions suggesting that the virus has a preference to the human-type receptor and can efficiently attach to human cells [19].

The second function of HA is important for virus infectivity and possibly pathogenicity. This involves the activation of HA by proteolytic cleavage and the fusion of an endocytosed virus particle with the endosomal membrane to liberate ribonucleoprotein into the cytoplasm. The HA cleavage site of both the non-avian and the low pathogenic avian influenza viruses have only a single basic arginine residue that is cleaved by trypsin-like proteases in the respiratory and intestinal organs resulting in viral replication being localized to
those organs [20]. However, highly pathogenic avian influenza viruses have multiple basic amino acids at the cleavage site enabling cleavage by ubiquitous proteases in multiple tissues leading to systemic infections. Like all other non-avian influenza viruses, the S-OIV possesses a single arginine [19] limiting it to infection of the upper respiratory tract [1].

**Origin of the novel 2009 H1N1 S-OIV**

Among the hosts that are susceptible to influenza virus infection, pigs have a special role in what appears to be a human-pig-duck triad of influenza ecology [21]. The epithelial cells lining the upper respiratory tract of pigs possess a sugar moiety of both of the aforementioned oligosaccharide linkages [22]. Therefore, pigs can support the growth of viruses of both human and avian origins and act as an intermediate host or “mixing-vessel” that can bridge the human and avian influenza gene pool, potentially generating a pandemic strain. However, there is no direct evidence showing that pigs have played a role in the genesis of any of the pandemics in the last century (Table 1). In the case of S-OIV, it is believed that pigs played a major role in the genesis of the pandemic virus. However, it remains to be discovered if the immediate precursor of the H1N1 S-OIV can be identified in pigs when more epizootiological surveillance is done.

The genetic composition of the S-OIV from the initial cases revealed that the virus is a quadruple reassortant of S-OIV genotypes [1, 19, 23, 24]. It possesses polymerase PB2 and PA genes of North American avian origin, a polymerase PB1 gene of human seasonal H3N2 origin, H1, NP, and non-structural (NS) genes of classical swine H1N1 origin, and N1 and MA genes of Eurasian avian-like swine origin. Although the S-OIV contains genes of swine, human, and avian origin from four different lineages, its genesis has probably resulted from an immediate reassortant event involving two lineages of swine influenza viruses (see below).

All the gene segments described above were established from swine over a period of many years. Specifically, a novel H1N1 virus of avian origin was first identified in pigs in Europe in 1979 and later established as the Eurasian avian-like swine lineage [25]. In the late 1990’s, H1N1 and H1N2 triple reassortants containing PB2 and PA genes from North American avian virus; NP, MA, NS, H1, N1 genes of classical swine origin; and PB1 and N2 genes from seasonal human H3N2 were enzootic in pigs in North America [26]. Therefore, the most likely event that generated the 2009 H1N1 S-OIV was reassortment between an H1N1 Eurasian avian-like swine virus (origin of N1 and MA) and an H1N1/H1N2 triple reassortant virus (origin of PB2, PB2, PA, H1, NP, and NS), both of which are prevalent in pigs [1, 19, 23, 24].

**Antiviral Treatment for Influenza**

Two classes of antiviral medications are approved by the FDA for prophylaxis and treatment of influenza infection: NA inhibitors (oseltamivir and zanamivir) and M2 ion channel inhibitors (amantadine and rimantadine). The adamantanes (amantadine and rimantadine) are only active against influenza A viruses. Due to widespread resistance of the seasonal H3N2 and the 2009 H1N1 pandemic strain, the CDC warned that the adamantanes should not be used as treatment or prophylaxis of influenza infection [27]. Fortunately, the novel H1N1 pandemic strain is susceptible to oseltamivir and zanamivir while the oseltamivir-resistant novel H1N1 strain with H275Y mutation in the NA is still susceptible to zanamivir [28]. The properties and new developments of NA inhibitors are further discussed below.

**NA Inhibitors Targeting Influenza Viruses**

**Recommendations.** NA inhibitors are considered the drug of choice for treatment and prophylaxis of influenza A or B. In the midst of the H1N1 pandemic, the CDC recommended that treatment with oseltamivir or zanamivir should be considered in certain groups of people with suspected or confirmed influenza. These include patients with illness requiring hospitalization and people who are at high risk of complications including children < 2 years of age, adults > 65 years of age, pregnant women, immunosuppressed patients of any age, patients < 19 years of age who are receiving long-term aspirin therapy, and patients who have chronic health conditions [29].

Treatment should be initiated within 48 hours of the onset of illness since viral replication in the respiratory tract peaks at 24 to 72 hours after the onset of illness [30]. Prophylaxis with oseltamivir or zanamivir should be considered for persons at high risk for influenza-related complications and who have had close contact with persons likely to be infected during the infectious period. The infectious period is defined as 24 hours prior to first fever until 24 hours after last fever [29]. In addition, prophylaxis should also be considered for health care workers who have close contact with confirmed or suspected persons during the infectious period. Prophylaxis is not recommended for healthy individuals subject to a potential exposure in the community, school, or camp. This recommendation is based on oseltamivir resistant 2009 pandemic H1N1 influenza isolated from two summer campers who received oseltamivir mass
Mechanism of action. NA inhibitors target the enzymatic function of NA (Figure 1). After replication, NA cleaves the sialic acid from HA and allows progeny virions to be released from the infected cells. These progeny virions will infect new target cells, thereby continuing the viral replication process. NA inhibitors mimic sialic acid natural substrates and competitively bind and inhibit influenza virus NA from cleaving the viral particles from host cells. This process prevents further spread of viral infection to uninfected cells [32].

Pharmacokinetics. Oseltamivir phosphate, a prodrug, is readily absorbed from the gastrointestinal tract after oral administration. It is then hydrolyzed by hepatic esterases to its active form, oseltamivir carboxylate. Protein binding of oseltamivir is low, and oseltamivir is not a substrate of P450 isoenzymes. The half-life of oseltamivir is 6-10 hours. Oseltamivir is excreted primarily via the kidneys, therefore renal dose adjustment is necessary. There is no dose adjustment required for patients who have mild-to-moderate hepatic impairment. However, there is no safety and kinetics data for patients who have severe hepatic impairment [33].

Zanamivir is available as a powder for oral inhalation since it has poor systemic absorption. The onset of action is 10 minutes, and approximately 4% to 17% of the inhaled dose is systemically absorbed. Zanamivir is excreted via the kidneys as an unchanged drug. There is limited protein binding, and its half-life is 2.5-5.1 hours. Renal dose adjustment is not necessary because there is limited systemic absorption. No kinetics data is available for patients who have hepatic impairment [34]. The concentration of zanamivir after oral inhalation is well above the 50 percent inhibitory concentration even for study subjects who inhaled sub-optimally [35].

Efficacy and safety of oseltamivir. A double-blind, randomized placebo controlled, multicenter trial was conducted among 629 healthy adults who were no more than 36 hours past the onset of suspected influenza [36]. Subjects were randomized to oseltamivir 75 mg twice daily, 150 mg twice daily, or placebo. Both oseltamivir treatment groups showed statistically significant reductions in duration of illness by one day compared to placebo. The duration and severity of influenza symptoms were also significantly reduced compared to placebo. Oseltamivir was well tolerated in the study, the most common side effects being nausea and vomiting.

A multi-center randomized controlled trial was conducted in 726 previously healthy adults with less than 36 hours of febrile influenza-like illness [37]. Among 726 patients, 66% had confirmed influenza infection. Patients were assigned to oral oseltamivir 75 mg, oseltamivir 150 mg, or placebo twice a day for 5 days. The median duration of illness was 29 hours shorter in the oseltamivir 75 mg group and 35 hours shorter in the oseltamivir 150 mg group compared to the placebo group (p < 0.02). Oseltamivir was well tolerated in the study. Transient upper gastrointestinal events occurred more frequently in the oseltamivir group than the placebo group but were resolved within 1-2 days of therapy [37]. Moreover, oseltamivir is well tolerated in pediatric patients and is approved for treatment of influenza in children over 1 year of age [38].

Efficacy and safety of zanamivir. A total of 1259 patients with influenza symptoms of less than 48 hours were randomized to receive zanamivir 10 mg twice a day, 10 mg four times a day, or placebo [39]. The number of days to symptom alleviation was reduced by 1 day compared to placebo. Zanamivir also reduced the time to resumption of normal activities. The most common side effects were gastrointestinal related, headaches, nasal signs, and bronchitis.

A meta-analysis was conducted to determine the impact of zanamivir on antibiotic use in 3,815 healthy adults with less than two days of influenza infections [40]. Of the 3,815 patients, 66% had confirmed cases of influenza infection. The patients with confirmed cases of influenza infection were randomized to receive inhaled and intranasal zanamivir (27%), inhaled zanamivir (32%), and placebo (40%), respectively. The results showed that respiratory events leading to antibiotic use occurred in 9% of inhaled and intranasal zanamivir group and 15% of placebo group (p < 0.003), and 13% of inhaled zanamivir group and 18% of placebo group (p < 0.06). There was a reduction in upper and lower respiratory tract events in the intranasal and inhaled zanamivir groups compared to placebo. Inhaled zanamivir showed a reduction in the number of lower respiratory tract events, but the reduction in upper respiratory events did not reach a statistical significance. The study indicated that early treatment with zanamivir could reduce the use of antibiotics [40].

Mechanism of resistance. During the 2007-2008 influenza virus surveillance in Norway, there was an increased level of oseltamivir resistance. Norway had the highest rate of oseltamivir resistance in influenza virus even though its use of oseltamivir was low [41]. While Japan had the highest usage of oseltamivir, the incident of oseltamivir resistance of influenza virus remained low during the 2007-2008 influenza season.
Future Antiviral Development for Influenza

New Route of Administration. Current antiviral treatments are limited to oral or inhalation therapy. The route of administration may be problematic in critically ill patients who are admitted to the intensive care unit (ICU) as evidenced by a recent report of death associated with the use of solubilized zanamivir used in ICU patients outside the U.S [49]. The death was caused by obstruction of the ventilator due to the stickiness of the lactose in the nebulized solution. Therefore, parenteral administration would provide a more rapid and reliable drug delivery to critically ill patients. Parenteral zanamivir was evaluated in a randomized, placebo-controlled, double-blind study [50]. Sixteen healthy subjects received either zanamivir 600mg intravenously or placebo every 12 hours for 5 days beginning 4 hours prior to H1N1 viral inoculation. There were significant reductions in viral shedding, fever, and upper respiratory symptoms in the zanamivir group compared to the placebo group.

The prophylactic and therapeutic efficacy of intravenous zanamivir was evaluated in a macaque model for the highly virulent H5N1 influenza virus [51]. There were reductions in viral load at 10 mg/kg and at 20 mg/kg in both the prophylactic and therapeutic groups. In terms of gross pathology and microscopic pneumonia scores, there was a statistical difference in the prophylactic group but not the treatment group. The differences in efficacy between the two groups might be due to genetic variation in response to viral infection within the macaque model and variable infectivity of the heterogeneous H5N1 influenza virus.

Peramivir is a NA inhibitor of the influenza virus. It has shown activity against influenza A and B, including the H5N1 influenza virus both in vitro and in vivo [52-56]. Compared to zanamivir, peramivir demonstrated a three to four fold increase in activity inhibiting H1N1 and H3N2 influenza viruses in vitro [57]. In a murine model, Banita et al. [54] showed that a single intramuscular injection was comparable to a 5-day course of oral oseltamivir therapy in preventing pathogenicity of H1N1 and H3N2 influenza. In ferrets and mice, there were significant statistical differences in median survival time between the intramuscular peramivir group and the control group [54-56]. Intravenous peramivir is currently an unapproved investigational drug authorized by the FDA for treatment of the novel H1N1 pandemic influenza under the emergency use authorization [58].

New Antiviral Agents. DAS181 is a novel recombinant sialidase fusion protein derived from Actinomyces viscosus fused with a cell surface anchoring sequence [59-61]. It is the first antiviral agent that targets the sialic acid receptors on the host cell. The sialic acid receptor is the initial site of attachment of the influenza virus to the host cell. DAS181 has shown binding activity to sialic acid receptors of both NeuAc2,3Gal and NeuAc2,6Gal linkages [59]. DAS181 works by cleaving off the sialic acid receptors and thereby preventing viral entry into the host cells. In animal models, it showed prophylactic and therapeutic...
efficacy against influenza A and B, including the highly virulent H5N1 avian influenza virus [60, 61].

T-705 is a pyrazine derivative with potent inhibitory activity against the influenza virus [62, 63]. Furuta et al. [64] showed that T-705 targeted the early to middle stage of viral replication rather than the release stage. It selectively inhibits the viral RNA polymerase but does not affect the normal cellular DNA or RNA synthesis processes [64]. In animal studies, it reduced the rate of mortality in mice with H1N1 and H5N1 influenza virus [63, 64].

CS-8958 is a pro-drug of the NA inhibitor of R-125489. It is a long-acting inhaled NA inhibitor with antiviral activity against influenza A and B [65]. A single inhalation of CS-8958 showed a prolonged survival effect that was observed in a murine model. A phase II clinical trial is underway to determine if a single inhalation of CS-8958 is effective for the treatment of seasonal influenza [66].

Combination Therapy. With the emergence of resistant influenza variants and the limited antiviral treatment options, clinicians face the challenge of selecting optimal antiviral therapy. Amantadine and rimantadine were the first line of defense for treatment of community acquired influenza virus infection. However, since resistance develops rapidly to these drugs, the adamantanes are no longer recommended as monotherapy for treatment of influenza infection. Treatment with multiple antiviral agents which target different stages of the viral life cycle is believed to have a synergistic effect and decrease the chance of developing resistance [67].

The combination of amantadine and oseltamivir therapy was shown to reduce the emergence of drug-resistant influenza variants in vitro [67]. Drug-resistant mutations occurred when amantadine and oseltamivir were used in monotherapy, but such mutations were not observed when they were used as combination therapy. Virus production was also reduced when combination therapy was used. In a murine model, the combination of amantadine and oseltamivir therapy provided a higher survivability than monotherapy against the H5N1 influenza virus [68]. Another study also demonstrated that the combination of amantadine and oseltamivir provided 50-60% more protection against H3N2 and H1N1 viruses in vivo [69].

The combination of NA inhibitors (zanamivir, oseltamivir and peramivir) and rimantadine was tested against H1N1 and H3N2 influenza virus isolates [70]. There was a significant reduction in viral production in the combination model compared to when each drug was used alone. Peramivir was the most potent among the NA inhibitors; it required a 10-fold lower dose to produce the same inhibitory effect compared to oseltamivir or zanamivir. There was a synergistic effect when rimantadine was combined with zanamivir, oseltamivir or peramivir in cell culture, but antagonism was also observed at certain drug concentrations [70].

The effect of double combinations of amantadine, oseltamivir and ribavirin on H5N1 influenza virus was tested in mice [71, 72]. The combinations of oseltamivir-ribavirin and amantadine-ribavirin showed an improvement in survival compared to monotherapy with either one of these agents in an amantadine-sensitive virus. Amantadine-oseltamivir, amantadine-ribavirin and oseltamivir-ribavirin combinations showed improvement in body weight and survivability compared to monotherapy. The treatment of an amantadine-resistant virus infection with amantadine-oseltamivir or amantadine-ribavirin was no more beneficial than oseltamivir or ribavirin alone. There was a significant reduction in mortality with oseltamivir-ribavirin treatment of the amantadine-resistant virus infection [71]. Oseltamivir-ribavirin combination treatment also prevented the spread of H5N1 influenza virus to mouse organs as well as a decreased viral load [72].

Conclusion(s)

As we witnessed the antigenic shift of influenza viruses from H3N2 to a novel H1N1 strain in 2009, two recent advances (intranasal live attenuated influenza vaccine and NA inhibitors) have helped us to better prepare for the current pandemic. However, effective new treatments are seemingly elusive given the rapidly evolving nature of the influenza viruses that allows circumvention of current drug and vaccine interventions. Discovery and development of new antiviral compounds and treatment options for influenza viruses are therefore a critical priority in preparing clinicians and researchers to face the public health challenge posed by influenza viruses in the next decade.

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MPSC wrote the sections on the basic science of influenza viruses and the origin of the novel 2009 H1N1 S-OIV. AC wrote the antiviral treatment options for influenza.

References


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Illustrations

Illustration 1

Figure 1. Antiviral agents targeting different stages of the life cycle of influenza virus.
Illustration 2

Table 1. Characteristics of the influenza pandemics in the 20th century.

<table>
<thead>
<tr>
<th>Year</th>
<th>Place of first identification</th>
<th>Virus subtype</th>
<th>Deaths worldwide (estimated)</th>
<th>Deaths in the U.S. (estimated)</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>China, U.S., Europe? [8, 9]</td>
<td>H1N1</td>
<td>20 - 100 million $^a$</td>
<td>600,000</td>
<td>All gene segments are of avian-origin</td>
</tr>
<tr>
<td>1957</td>
<td>Southern China [10, 11]</td>
<td>H2N2</td>
<td>1 – 4 million</td>
<td>69,800</td>
<td>Avian-origin H2, N2, PB1 and the rest from circulating H1N1</td>
</tr>
<tr>
<td>1968</td>
<td>Hong Kong [12]</td>
<td>H3N2</td>
<td>1 million</td>
<td>33,800</td>
<td>Avian-origin PB1, H3 and the rest from circulating H2N2</td>
</tr>
<tr>
<td>1977 $^b$</td>
<td>Northern China [13]</td>
<td>H1N1</td>
<td>0.7 million</td>
<td>N/A</td>
<td>Close resemblance to the H1N1 circulated in the 1950’s</td>
</tr>
</tbody>
</table>

$^a$ Estimates in the 1920’s were 20 million but recently estimates suggest the death worldwide was up to 100 million.

$^b$ May not consider a pandemic by some because it mainly affected children and young adults (< 23 years).
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