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Special Contribution

Pandemic Influenza: A Never-Ending Story

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A novel pandemic influenza emerged in 2009, something that hasn't been seen since 1977. The following issues will be introduced and discussed in this review: the history of influenza pandemics, the emergence of the novel pandemic influenza of 2009, epidemics in the southern and northern hemispheres after the recognition of index cases in the United States, mortality, viral characteristics, prevention in the household setting, clinical aspects, diagnosis, treatment and immunization. Some questions have been answered. However, a number of other questions remain. Scientific research must follow up on these unanswered questions.

Key words: influenza; pandemic; emergence; prevention; treatment

History of pandemics before 2009*

Spanish influenza of 1918 (H1N1)†

More than fourteen influenza pandemics have appeared since 1500. This implies that approximately one pandemic has occurred every 36 years. In the "microbial era" (1876 to present), there were at least six pandemics, one each in 1889, 1918, 1957, 1968, 1977 and 2009. Possibly more pandemics have occurred. However, it is still not easy to document the long history of influenza, because a number of techniques have only been developed recently. Indeed, influenza viruses were not isolated until the 1930s. The characterization of the 1918 pandemic influenza began in 1995 with the identification of a 1918 autopsy and archeological material (Taubenberger and Morens, 2010).

The 1918 pandemic H1N1 viruses killed an estimated 50 million people or more worldwide. Mortality during the 1918 pandemic was concentrated on an unusually young age group. The age group between 20 and 40 years was affected most severely. Despite scientific and technological progress, the reasons for unexpected patterns like this remain obscure to date (Taubenberger and Morens, 2010). The high mortality associated with the 1918 virus appears to have been largely a result of bacterial pneumonia (Morens et al., 2008). Fortunately, the situation has changed completely and antimicrobial agents are available all over the world. Spanish influenza viruses still have an influence on recent epidemics. Seasonal H1N1 [spread before the emergence of 2009 influenza A (H1N1)] acquired polymerase B1 (PB1), polymerase A (PA), nucleoprotein (NP) and N1 genes from 1918 pandemic H1N1 viruses. Similarly, classic swine influenza viruses harbored three segments, PB2, matrix (M) and non-structural (NS), originating from 1918 H1N1 viruses.

Asian influenza of 1957 (H2N2)

This was a descendant of 1918 H1N1, but acquired three novel segments of avian-like HA (H2), NA (N2) and PB1 genes. The mortality rate during this epidemic was as impressive as the pandemic in 1918. After about two years the virus became seasonally epidemic and sporadic, and disappeared

* Table 1.

† H1N1, subtype based on hemagglutinin (HA) and neuraminidase (NA) spikes.

Abbreviations: CDC, Center for Disease Control and Prevention; HA, hemagglutinin; M, matrix; NA, neuraminidase; NP, nucleoprotein; NS, non-structural; PA, polymerase A; PB1, polymerase B1; rRT-PCR, real-time PCR combined with reverse transcription

entirely within 11 years (Taubenberger and Morens, 2009).

Hong Kong influenza of 1968 (H3N2)

Unlike the other two preceding pandemics, H3N2 Hong Kong influenza viruses are still circulating globally. The pandemic of 1968 was modest in its mortality. As in 1957, the epidemic size became smaller and sporadic in its appearance. This virus is a descendant of the H2N2-type virus with two avian-like segments of HA (H3) and PB1. It has been suggested that the relative mildness of the 1968 pandemic resulted in the retention of the NA segment harbored by the strains that had circulated previously. Most of the population had at least partial immunity to this NA (Taubenberger and Morens, 2009).

Russian influenza of 1977 (H1N1)

This reemergence in 1977 is unexplainable and may represent reintroduction to humans from a laboratory source (Zimmer and Burke, 2009).

Emergence of novel influenza A viruses in 2009

From pigs to humans

Before the emergence of novel influenza viruses spreading among humans, there was sporadic infection with triple-reassortant swine influenza A (H1) viruses from pigs to human (one-way flow) in the United States. Eleven cases of sporadic human infections with triple-reassortant swine influenza A viruses, were recognized from December 2005 through February 2009 until just before the epidemic of swine-origin influenza A (H1N1) among humans. Median age was 10 years (from 16 months to 48 years). Nine cases had exposure to pigs. The range of suspected incubation period was 3 to 9 days. Major symptoms were fever (90%), cough (100%), headache (60%) and diarrhea (30%). Four patients were hospitalized and two of these were under invasive mechanical ventilation. All recovered eventually from their illness (Shinde et al., 2009).

Table 1. Influenza history and the advancement of medical technology

Year	Epidemics and other important medical events
1918	Emergence of Spanish influenza (H1N1)
1928	Discovery of penicillin by A. Fleming
1957	Emergence of Asian influenza (H2N2)
1968	Emergence of Hong Kong influenza (H3N2)
1977	Emergence of Russian influenza (H1N1)
1987	Discovery of PCR
2000	Zanamivir (drug infused by inhalation)
2001	Oseltamivir (oral drug)
	General use of antigen detection kits
2009	Emergence of 2009 influenza (H1N1)
2010	Peramivir (drip infusion therapy drug)
	Laninavir (long-acting drug)

Guan et al., 2010; Taubenberger and Morens, 2010.

The severity and main symptoms of this disease seemed similar to that of the novel influenza that emerged and caused a pandemic in 2009.

Among humans

On April 17, 2009, the Center for Disease Control and Prevention (CDC) in the United States determined two cases of febrile respiratory illness occurring in children living in two different counties in southern California. Both of these children were infected with swine influenza A (H1N1) viruses. Neither of these children had contacts with pigs nor with each other. The source of the infection remains unknown. The lack of known exposure to pigs in the two cases increases the possibility that human-to-human transmission of this new influenza virus had occurred. A couple of days later, the CDC reported six additional cases. Four were in California but the other two were in Texas, far from California. These six additional patients were infected by similar strains of swine-origin influenza A (H1N1) viruses identified in the two index cases (CDC, 2009b). As a result, a total of 642 swine-origin influenza cases were identified in 41 states in the United States until May 5. The ages ranged widely, but 60% were 18 years of age or younger. The most common symptoms were fever (94%), cough (92%) and sore throat (66%). Similar to the pig-to-human cases, 25% of patients had diarrhea (Dawood et al., 2009).

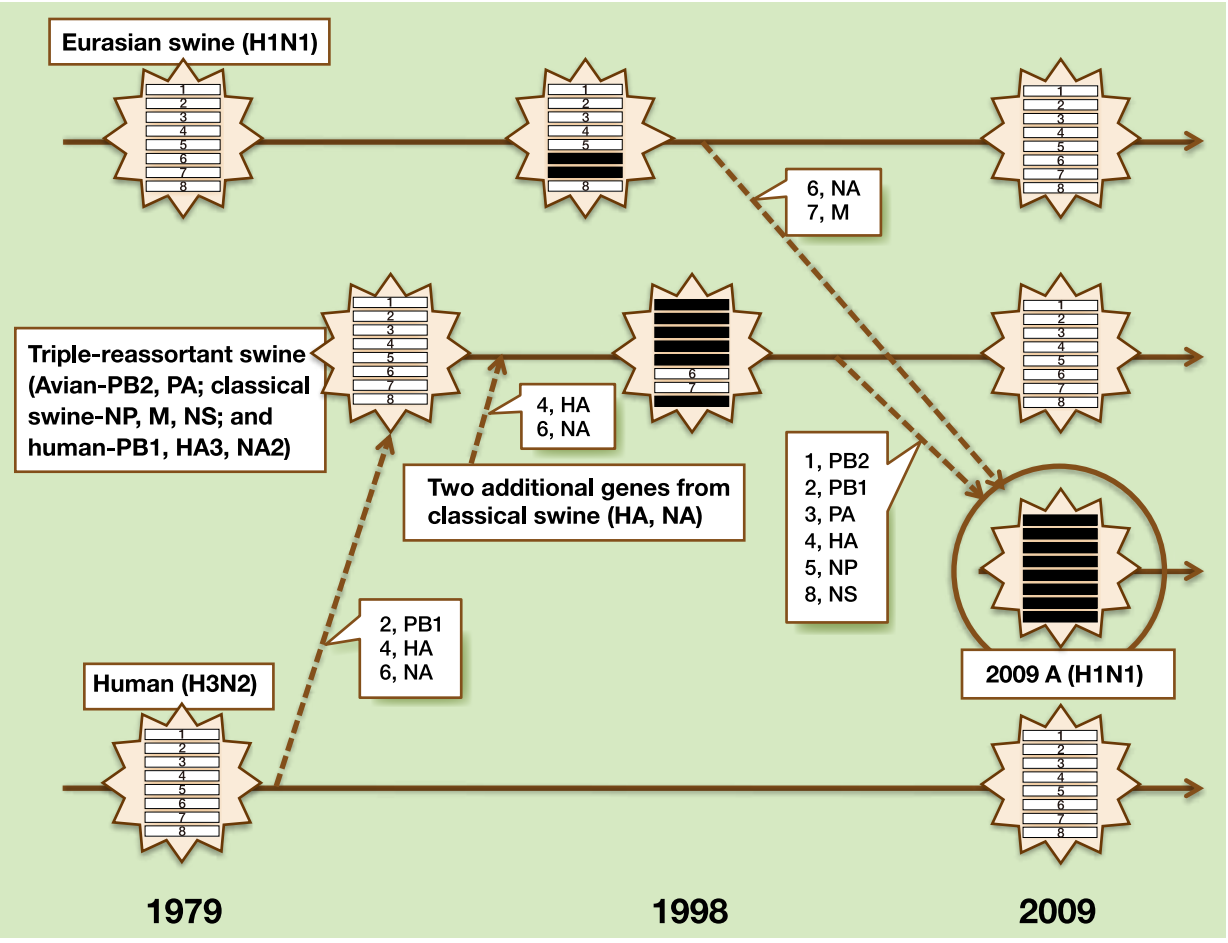

Fig. 1. Reassortment events leading to the emergence of 2009 A(H1N1) virus. Gene segments are indicated by PB2, PB1, PA, HA, NP, NA, M and NS from top to bottom within the viral particles. The 2009 A(H1N1) viruses contained the 6 segments originating from triple-reassortant swine strains (PB2, PB1, PA, HA, NP, and NS) and the 2 from Eurasian swine strains (NA, M). The HA segment of a triple-reassortant swine strain was replaced by the one in a classical swine strain around 1998. H1N1, subtype based on HA and NA spikes; HA, hemagglutinin; M, matrix; NA, neuraminidase; NP, nucleoprotein; NS, non-structural; PA, polymerase A; PB, polymerase B.

Genomic analysis of the 2009 influenza A (H1N1) virus [2009 A(H1N1) virus hereafter] in humans indicates that it is closely related to common reassortant swine influenza A viruses. The segment coding for the polymerase complex (PB2, PB1, PA), HA, NP and NS show high similarity to triple-reassortant swine viruses harbored by North American swine. The reassortment of these three segments was generated in swine around 1990 and infected humans sporadically since then as described above. The segment coding for the NA and M originated from the strains harbored by Eurasian swine (Fig. 1) (Smith et al., 2009; Trifonov et al., 2009).

From humans to pigs

The evolution of influenza A viruses seems to indicate that viruses among pigs change to adapt to humans, and that reversal flow (human-to-pig) doesn't happen. However, a reverse transmission event happened from a human to a pig after the emergence of the swine-origin influenza viruses. In May 2009, 2009 A(H1N1) viruses were confirmed in Thailand from a person who had a history of travel to Mexico. Shortly after this was noted, transmission from humans to pigs was discovered on pig farms (Sreta et al., 2010).

Epidemics in the southern and northern hemispheres

Just after the index cases of novel influenza were recognized in southern California, countries in the southern hemisphere such as Australia were striken by a strong influenza epidemic (Baker, Kelly and Wilson, 2009). This happened four months earlier than the epidemic onset in Japan. In New South Wales the most populous state of Australia, the epidemic lasted from late June to early September (New South Wales Public Health Network, 2009). At least one quarter of the population and one-third of children experienced influenza-like illnesses (Muscatello et al., 2011). The virus affected the younger generation and caused considerable morbidity, 8.5-fold, as compared with seasonal influenza in the previous five seasons (Australian Government Department of Health and Ageing, 2009). However, the fatality rate was not considerably high and even low (0.5–1.5%) for laboratory-confirmed influenza cases caused by the 2009 A(H1N1) virus (Falagas et al., 2011).

The epidemic trend shifted to the northern hemisphere from September to October of that year. Unlike the epidemic in the southern hemisphere, the epidemic size of influenza caused by 2009 A(H1N1) viruses did not seem higher than those of regular seasonal influenza. This lower morbidity in the northern hemisphere is presumably attributed to the new vaccine preparation for this pandemic. Except for the epidemic size, findings are in accordance with those gained during the 2009 winter season in the southern hemisphere. The novel influenza occurred more in the younger generation as compared to the seasonal one (Falagas et al., 2011). Most of the epidemic was caused by 2009 A(H1N1) viruses while a few seasonal viral strains were detected. From April 2009 to June 12, 2010, US-CDC performed antigenic characterization of the 67,022 subtype-A viruses and identified 34 cases of seasonal influenza A (H1N1) (Russian flu type, 0.1%), 72 cases of seasonal influenza A (H3N2) (Hong Kong flu type, 0.1%) and 66,916 cases of the 2009 A(H1N1) virus (99.8%).

Mortality

The World Health Organization stated that an assessment of the severity of a pandemic is complex, and a single assessment of severity may not be relevant or helpful to countries at the global level (World Health Organization, 2009). However, a graded series of responses such as closing schools and other public venues, are required for addressing influenza pandemics. The United States defined the pandemic severity index. It is calibrated to the case fatality ratio. Mild responses are prescribed for a strain resembling seasonal influenza, which kills around 0.1% of infected individuals, whereas stringent measures are implemented for a very severe pandemic with a rate of 2% or more (Lipsitch et al., 2009). A case-fatality ratio of about 0.5% was documented in one report (Nishiura, 2010). However, an estimation of the number of infections is difficult as compared to fatal cases. Indeed, the case fatality ratios were estimated to be 0.4 in the United Kingdom (Pebody et al., 2010) and 0.11 to 0.15 in Germany (Wilking et al., 2010). Similarly, variation could be observed in the fatality ratios per one million inhabitants: 7.6 in the United Kingdom, 3.1 in Germany, 7.0 in the United States, 13.7 in Canada, 3.7 in the Netherlands, 1.8 in Belgium, 4.8 in Austria, 6.3 in Spain, 5.1 in France (Wilking et al., 2010) and 0.7 in Japan (Kamigaki and Oshitani, 2009)

Viral load, shedding/spreaders and stability

The median incubation time was 2 days (range, 1–7) and the duration of fever was typically 3 days (range, 1–11) (Cao et al., 2009). Viral load on the throat swab was inversely correlated with the number of days after the onset of fever. It was maintained at a high level over the first 3 days during the febrile period and then decreased over time. Patients with pneumonia had a higher viral load than those with upper respiratory tract infection (Li et al., 2010).

Median viral shedding time after the onset of symptoms was 6 to 9 days (Cao et al., 2009; Li et al., 2010; Ling et al., 2010). Another meta-analysis

reported that the average duration of shedding over 375 participants was 4.80 days (95% confidence interval: 4.31, 5.29) (Carrat et al., 2008). Independent risk factors for prolonged viral shedding included younger age, male sex and delayed treatment (Cao et al., 2009). Younger patients (< 13 years old) had a longer viral shedding time than older people (≥ 13 years old) (11 days versus 7 days) (Li et al., 2010). Asymptomatic individuals composed one-third of total infections (Carrat et al., 2008), and caused 30% to 50% of secondary infections although symptomatic patients were the main viral spreaders (Carrat et al., 2008). Another report estimated a lower transmission rate from asymptomatic individuals (14%) (Lau et al., 2010).

Influenza virus transmits through droplets (particle diameter, > 5 μm) and direct (physical contact)/indirect contact (hands, instruments, etc.). The knowledge is supported by a number of experimental and epidemiological findings. The transmission through the air-borne route (particle diameter < 5 μm, i.e., transmission over long distance) might be unlikely for human influenza virus infection. Studies examining the particles produced during natural coughing have shown that more than 99.9% of the aerosol volume is composed of particles with a diameter greater than 8 μm (Brankston et al., 2007).

Influenza viruses can survive in and be detected from aerosol for up to 24 h at low levels of relative humidity and 60 min at higher levels. Transmission of viruses has been documented to occur from a surface to the hands of volunteers in sufficient quantities. The contaminated surfaces were capable of supporting viable virus transfer for a substantially long period (up to 2 h). Viruses were detected on 23% and 53% of objects in a day-care center in the autumn and spring, respectively. Approximately 60% of objects swabbed in the homes of sick children were contaminated with viruses. Although direct and indirect contact for viral transmission is important, no study has shown that contact with contaminated surfaces could result in transmission. Further studies should be done (Brankston et al., 2007).

Prevention measures in daily life: wearing masks and washing hands

Killingley and colleagues documented that remarkably little is known about models of transmission of the influenza virus, and understanding the basic science of influenza transmission is key to the development of evidence-based policies for prevention and control of infections. The US Institute of Medicine, the European Center for Disease Control and the World Health Organization have all prioritized understanding the models of influenza transmission as a vital requirement for pandemic planning (Killingley et al., 2011).

Researchers in Egypt have assessed the effect of a hand-hygiene campaign and introduced a randomized control trial at 30 schools over a 12-week period, while 30 different schools acted as controls. School children in the intervention group were required to wash hands twice each day. Incidence of laboratory-confirmed influenza (both A and B strains) was reduced by 50% in the intervention versus control groups ($P < 0.0001$) (Talaat et al., 2011).

Another research group undertook a primary prevention study in the United States. Volunteers were divided into three groups in this study. Volunteers in the first group were assigned to wear surgical masks (daily for 3.5 h on average), while those in the second group wore masks and washed hands. The rest of the volunteers were in the control group. The trial lasted for six weeks. Influenza-like illnesses fell by 35% to 51% in the second group and by 28% to 35% in the first group (Aiello et al., 2010). In households, similar studies have been done. One study reported that intervention within 36 h of symptom onset reduced transmission significantly (adjusted odds ratio 0.33) (Cowling et al., 2009). Another study reported that risk of influenza-like illness was reduced by 60% to 80% in a subgroup of adults who used their masks most of the time (MacIntyre et al., 2009).

Clinical aspects

Infection with the 2009 H1N1 virus causes a broad spectrum of clinical syndromes, from afebrile up-

per respiratory illness to severe viral pneumonia. Fever (>38 ˚C) has been the most frequent symptom (81%–100%) among hospitalized patients. Frequencies of coughing (69%–100%), dyspnea (43%–100%, more in children) and sore throat (4%–31%) follow. Gastrointestinal symptoms (including nausea, vomiting and diarrhea) occur more commonly than in seasonal influenza. Rapid progression is common, typically starting on day 4 to 5 after the onset of illness, and intubation is often required within 24 h after admission (Bautista et al., 2010).

Diagnosis and treatment

In 2009, CDC conducted an evaluation of the rapid tests for influenza diagnosis. The results showed that overall sensitivity was low (40%–69%) among all specimens tested and declined substantially as virus levels decreased. This low sensitivity of the rapid diagnosis system suggests that a negative result could not rule out an infection with novel influenza A (H1N1) virus although a positive result can be used for the deciding to treat. This interpretation suggests that treatment should be considered even in antigen-negative cases, depending on clinical suspicion, underlying medical conditions, severity of illness, and risk of complications. The test of real-time PCR combined with reverse transcription (rRT-PCR) and/or virus isolation should be performed if further definitive determination is required. An M gene can be used for the target of rRT-PCR of influenza A (CDC, 2009a).

We have mainly used two anti-influenza drugs, oseltamivir and zamanivir to date. Both agents inhibit the neuraminidase working process. Detailed knowledge of both pharmacokinetics and pharmacodynamics of oseltamivir after oral administration has been summarized elsewhere (Widmer et al., 2010). Since the outbreak of the 2009 A(H1N1) virus, a number of cases of infections have been reported with oseltamivir-resistant influenza viruses. These strains typically contain a single amino acid substitution at 275 (H275Y) of the viral neuraminidase. The mutation of H275Y could emerge within 48 h therapy (Inoue et al., 2010). The H275Y variant virus can be transmitted, replicated and cause disease (Le et al., 2010). Fortunately, H275Y variants remained mostly susceptible to zanamivir. However, there emerged a 2009 A(H1N1) virus resistant not only to oseltamivir, but to zanamivir in a immunosuppressive host due to allogeneic transplantation. This virus even resisted peramivir (a long acting neuraminidase inhibitor) (van der Vries et al., 2010). These recent increases in drug-resistant influenza virus variants accelerates the need for the development of new drugs targeting other molecules and with different kinetics (Boltz et al., 2010).

Prevention: non-pharmaceutical measures and immunization

It has been recognized that development of strategies for mitigating the severity of a new influenza pandemic is a top global public health priority. Influenza prevention and containment strategies can be considered under the categories of non-pharmaceutical measures, antiviral treatment and vaccine as partly described above. Mathematical models have suggested that school closure can reduce peak attack rates by up to 40%, in which case isolation or household quarantine has a significant impact and that the treatment of clinical cases can reduce transmission. Household-based prophylaxis coupled with reactive school closure could reduce clinical attack rates by 40% to 50% (Ferguson et al., 2006).

Vaccination is the primary strategy for the prevention and control of influenza. Influenza vaccine is trivalent, and formulated to contain three strains representing influenza A (H1N1), A (H3N2) and B. When human 2009 H1N1 viruses were identified in the spring of 2009, vaccine manufacturers were already in the process of annual production of seasonal influenza vaccine for the 2009 to 2010 season. It was then decided that the production of a vaccine against the novel virus would be produced in addition to the seasonal vaccine. For the immediate future, priorities have been established for overcoming the rate-limiting steps in the production of inactivated vaccines (Lambert and Fauci, 2010). The immunogenicity of an influenza vaccine is currently measured by its capacity to induce func-

tional neutralizing HA-specific antibodies in serum, which have been proved to provide acceptable protection against influenza. Healthy adults show 70% to 90% protection against influenza illness upon conventional immunization, if there is a good antigenic match between the vaccine and the circulate influenza strains. However, the protective capacity differs depending on age and health status of population groups. Individuals at the highest risk for severe seasonal influenza infections are the elderly, as well as adults and children suffering of chronic health conditions. Conventional vaccine protects only 50% to 70% of individuals belonging to these population groups. Lower efficacy of vaccination in the elderly might be related to decreased immune function, and the immune systems of small children differs from adults in that they have generated strong immune response through frequent exposure to influenza viruses for many years. The challenge for future manufacturing of inter-pandemic influenza vaccine is concerned with the improvement of immunization strategies for individuals belonging to such high-risk populations (Fichera et al., 2009).

Although an older population has some disadvantage due to the immunological deterioration, they have had the advantage of pre-existing cross-reactive antibodies to 2009 A(H1N1) viruses acquired during the aging process through infection and/or immunizations. On the other hand, persons under 30 years have shown little evidence of cross-reactive antibodies to the 2009 pandemic viruses because the immunization of recent seasonal influenza vaccines induced little or no cross-reactive antibody response to 2009 A(H1N1) viruses (Hancock et al., 2009).

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