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2009 Pandemic Influenza A (H1N1): Diagnosis, Management, and Prevention— Lessons Learned

Kristin A. Swedish

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Abstract The 2009 pandemic influenza A (H1N1) was responsible for the first influenza pandemic of the 21st century. The virus— a previously unknown triple-reassortant virus containing segments of avian, human, and swine origins— generally caused mild disease. Unlike seasonal influenza, 2009 pandemic influenza A (H1N1) primarily affected adults 18 to 64 years of age. During the course of the pandemic, public health officials tried to facilitate diagnostic procedures and share information about treatment modalities globally. Efforts to contain the spread of 2009 pandemic influenza A (H1N1) included personal protective mechanisms and the 2009 H1N1 vaccine, which was not produced quickly enough or in large enough quantities. The lessons learned from this pandemic should be applied to ensure better preparedness in case of future pandemics.

Keywords Influenza A · H1N1 · Pandemic · Influenza vaccines

Introduction

Prior to being declared a global, phase 6 pandemic on June 11, 2009, more than 30,000 cases of 2009 pandemic influenza A (H1N1) had been reported in 74 countries. At that time, the World Health Organization (WHO) was concerned by the virus's rapid spread throughout the world and its potential for severe disease, particularly in developing countries [1]. The 2009 pandemic influenza A (H1N1) virus was an influenza strain previously unknown to humans, a unique triple-reassortant combination of avian, human, and swine viral gene segments [2••]. When the pandemic was declared, 2009 pandemic influenza A (H1N1) was exhibiting a unique epidemiological factor that signified a potential for severe disease: its targeting of younger persons, particularly those with underlying medical conditions.

However, 14 months later, the WHO declared 2009 pandemic influenza A (H1N1) to be in post-pandemic period: "the new H1N1 virus has largely run its course" [3]. The feared high level of global morbidity and mortality never materialized because of rapid global response and several viral factors. The WHO-mandated enhanced surveillance and reporting of the pandemic provided necessary and timely information worldwide [4]. The virus never mutated to become more virulent, as was originally feared [3]. Widespread antiviral resistance did not develop, despite several reports of patients with oseltamivir-resistant strains of 2009 pandemic influenza A (H1N1) [5–8], most of which were associated with oseltamivir treatment and prophylaxis. Finally, the influenza A (H1N1) 2009 monovalent vaccines were highly immunogenic, with more than 90% of adults and children vaccinated developing protective antibody levels [9••].

The 2009 Pandemic Influenza A (H1N1) Virus

Influenza A is a single-stranded RNA virus from the family Orthomyxoviridae. Its viral genome consists of eight gene segments, each of which can individually exchange with gene segments from other influenza A viruses, causing antigenic shift. Two gene segments code for the two cell-

K. A. Swedish (✉)
Department of Preventive Medicine,
Mount Sinai School of Medicine,
One Gustave L. Levy Place, Box 1043,
New York, NY 10029, USA
e-mail: Kristin.Swedish@mssm.edu

surface proteins that characterize influenza A subtypes, hemagglutinin (HA) and neuraminidase (NA). HA is necessary for viral binding and entry into host cells; NA enables the release of newly formed viruses. Both proteins elicit immune responses in the host. New strains of influenza A are created by changes in the cell-surface proteins. Of the 16 different possible subtypes for HA and nine for NA, only three HA (H1, H2, and H3) and two NA (N1 and N2) have been found in human influenza viruses [10•, 11].

The 1918 influenza pandemic was caused by an H1N1 influenza A virus. During the same time period, swine were infected with a respiratory illness resembling human influenza. The 1918 H1N1 virus continued to circulate in the swine population for many decades following, and is known as "classical swine influenza" [12]. Around 1998, the classical swine influenza virus reassorted with a human seasonal H3N2 and a North American avian influenza A virus to form a triple-reassortant swine influenza virus that subsequently circulated in the swine population [2••]. The first documented human infection with triple-reassortant swine influenza was noted in December 2005, with 10 additional sporadic cases reported through February 2009 [13].

In April 2009, 2009 pandemic influenza A (H1N1) was identified as a previously undescribed triple-reassortant H1N1 virus. Six of its gene segments were from the known triple-reassortant H1N1 virus. Gene segments 1 and 3 were of North American avian origin, segment 2 was of human seasonal H3N2, and segments 4, 5, and 8 were of North American classic swine origin. The remaining segments 6 and 7 were from the Eurasian swine genetic lineage that had previously not been reported outside of Eurasia [2••].

Epidemiology

The Centers for Disease Control and Prevention (CDC) estimates that between 43 million and 88 million cases of 2009 pandemic influenza A (H1N1) occurred in the United States between April 2009 and March 13, 2010. About 8,720 to 18,050 deaths related to 2009 pandemic influenza A (H1N1) occurred in the same period [14•]. Internationally, the WHO estimates that between 20% and 40% of the population in some areas have been affected by 2009 pandemic influenza A (H1N1) [3].

In the United States, the majority of 2009 pandemic influenza A (H1N1) cases (~ 58%), hospitalizations (~ 58%), and deaths (~77%) occurred in the 18- to 64-year-old age group [14•]. A meta-analysis demonstrated that throughout the Northern Hemisphere, young and middle-aged adults (aged 20–65) accounted for the majority of reported 2009 pandemic influenza A (H1N1) cases (13%–87%), hospitalized patients (15%–72%), intensive care unit (ICU) admissions (50%–59%), and fatalities (50%–92%) [15••]. A similar trend was evident in the Southern Hemisphere. A study of 722 confirmed patients admitted to the ICU in Australia and New Zealand found that nearly 93% were less than 65 years of age [16].

Patients hospitalized with 2009 pandemic influenza A (H1N1) frequently had underlying medical conditions. Common types of comorbidity included respiratory diseases (asthma, chronic obstructive pulmonary disease), cardiovascular disease, chronic neurological disease, and diabetes [15••]. Pregnant women accounted for 9% of patients admitted to the ICU in Australia and New Zealand [16], and 5% of all reported 2009 pandemic influenza A (H1N1) deaths in the United States between April and December 2009 [17•]. Obesity has been found to be associated with increased hospitalization rates, ICU admissions, and deaths due to 2009 pandemic influenza A (H1N1) while controlling for chronic medical conditions that tend to be associated with obesity, indicating that obesity alone was a risk factor [18•].

Diagnosis

Clinically, 2009 pandemic influenza A (H1N1) causes symptoms similar to seasonal influenza. Patients typically present with fever, cough, sore throat, and rhinorrhea. Gastrointestinal symptoms, including nausea, vomiting, and diarrhea, have occurred more frequently with 2009 pandemic influenza A (H1N1) than with seasonal influenza. Up to one third of 2009 pandemic influenza A (H1N1) infections have been mild, causing an afebrile upper respiratory illness. However, fulminant viral pneumonia has developed in severe cases, resulting in up to 72% of ICU admissions for 2009 pandemic influenza A (H1N1) [19••].

Following the virus's identification in April 2009, the CDC modified their real-time polymerase chain reaction (RT-PCR) assays in order to adequately detect 2009 pandemic influenza A (H1N1). These assays were quickly published on the WHO web site to facilitate diagnostic testing worldwide [20]. The WHO designated RT-PCR as the method of choice for 2009 pandemic influenza A (H1N1) detection [21]. In May 2009, the Food and Drug Administration (FDA) began granting Emergency Use Authorizations (EUAs) for several RT-PCR assays to be used in the diagnosis of 2009 pandemic influenza A (H1N1) [22].

However, RT-PCR is not commercially available. The more widely available commercial diagnostic tests— rapid influenza diagnostic tests and direct immunofluorescence assays (DFAs)— proved to be less effective than RT-PCR.

Rapid influenza diagnostic tests, point-of-care tests that provide results in 15 minutes or less, have sensitivities for 2009 pandemic influenza A (H1N1) that range from 10% to 70%, with very high specificity (> 95%). DFAs, which take between 1 and 4 hours to process, have sensitivities for 2009 pandemic influenza A (H1N1) ranging from 47% to 93%, with very high specificity (>96%) [23•].

During the initial stages of the epidemic, the CDC recommended laboratory testing for 2009 pandemic influenza A (H1N1) in patients with an acute febrile respiratory illness or sepsis-like syndrome, especially those severe enough to require hospitalization or considered high-risk for complications. However, because of the inadequacy of commercially available diagnostic tests, public health laboratories quickly became overwhelmed with requests for RT-PCR diagnostic testing [20]. This prompted the CDC to limit testing recommendations during the 2009–2010 influenza season to hospitalized patients with suspected influenza; patients for whom a diagnosis of influenza would inform decision-making related to clinical care, infection control, or management of close contacts; and patients who died of a suspected influenza-related acute illness [23•]. The CDC has not yet released its recommendations for diagnostic testing during the 2010–2011 influenza season.

Management

During the 2009–2010 influenza season, the CDC recommended initiating prompt antiviral treatment for patients with suspected or confirmed 2009 pandemic influenza A (H1N1) with severe illness, requiring hospitalization, or at risk of severe disease. The virus is resistant to the adamantine class of antivirals, but is sensitive to the neuraminidase inhibitors oseltamivir and zanamivir [24•]. Although there were rare occurrences of oseltamivir-resistant 2009 pandemic influenza A (H1N1) strains [5–8], these strains remained sensitive to treatment with zanamivir [20].

The recommended treatment for 2009 pandemic influenza A (H1N1) is 5 days of oseltamivir or zanamivir, initiated ideally within 48 hours of illness onset. However, even when initiated after 48 hours after onset, antiviral treatment was shown to reduce mortality in hospitalized patients [24•]. Studies of the effectiveness of antiviral treatment on morbidity and mortality were not conclusive because of their lack of comparison data. However, a meta-analysis of studies of more than 3,000 patients with 2009 pandemic influenza A (H1N1) demonstrated that over half received antiviral treatment, usually with oseltamivir. The majority of the treated patients were in the hospital or ICU [25•]. A study of ICU patients in Mexico demonstrated that survivors were more than eight times more likely to have been treated with oseltamivir or zanamivir than nonsurvivors [26].

During the course of the pandemic, the FDA approved several EUAs for oseltamivir and zanamivir that relaxed distribution and dispersal regulations. Under the EUAs, oseltamivir was authorized to treat and prevent 2009 pandemic influenza A (H1N1) in children under 1 year of age. The EUAs authorized the use of both oseltamivir and zanamivir for adult and pediatric patients whose symptoms began more than 48 hours previously. Finally, the EUAs authorized public health authorities to distribute oseltamivir and zanamivir without all of the FDA-required prescription label information [27]. In October 2009, an investigational neuraminidase inhibitor, peramivir, received an EUA for intravenous administration in both adult and pediatric patients [28]. These EUAs expired when the Public Health Emergency determination for 2009 pandemic influenza A (H1N1) expired on June 23, 2010 [27].

Prevention

Even before the identification of the 2009 pandemic influenza A (H1N1) virus, public health officials were encouraging the implementation of preventive measures to control the spread of the virus, particularly hand washing and staying home from work when ill. According to national polls from April through June 2009, most Americans heeded that advice. The majority noted washing their hands or using hand sanitizer more frequently (59%–62%), 55% had made preparations to stay home if s/he or a family member were sick, and 35% to 38% noted taking steps to avoid being near someone with flulike symptoms [29••]. Surveys in Hong Kong during the same period indicated that citizens abroad were also following public health advice, washing their hands more frequently (74%) and wearing face masks in public when experiencing influenza-like symptoms (89%) [30].

Studies have demonstrated that nonpharmaceutical interventions are effective at reducing the incidence of influenza. College students cluster-randomized to use face masks and alcohol-based hand sanitizer during 6 weeks of the 2006–2007 season showed significant reductions in influenza-like illness compared to control college students [31•]. A study of health care workers randomly assigned to surgical mask or N95 respirator during the 2008–2009 influenza season demonstrated that both masks provided comparable protection against influenza [32]. School closure, an intervention used frequently at the outset of the 2009 pandemic influenza A (H1N1) pandemic, was shown to be less effective at decreasing the attack rate [33].

Vaccination against 2009 pandemic influenza A (H1N1) proved to be the ideal prevention strategy. Immunogenicity

studies demonstrated that a single dose of 2009 H1N1 vaccine produced a protective immune response in the majority of adults and children 10 years and older, with children 6 months to 9 years requiring a second dose. Four manufacturers were licensed to produce monovalent, unadjuvanted 2009 pandemic influenza A (H1N1) vaccines on September 15, 2009 [34]. However, uncertainties about the supply and demand for the vaccine caused the CDC's Advisory Committee on Immunization Practices (ACIP) to initially recommend prioritizing vaccination for five target groups: pregnant women, caretakers of infants younger than 6 months of age, health care and emergency medical services personnel, people between the ages of 6 months and 24 years old, and those between the ages of 25 and 64 years with high-risk medical conditions. It was recommended to delay vaccinating people 65 and older because of their decreased risk of infection [35•].

The American public was wary about the 2009 pandemic influenza A (H1N1) vaccine. Although many felt that it was safe, only half of Americans polled between July and October 2009 planned to get vaccinated when it became available. Polls showed that people were concerned about the safety of the vaccine and did not trust public health officials to provide correct information about vaccine safety. Once the vaccine became available, manufacturing delays caused significant supply and demand mismatch in some areas. By early November 2009, only 7% of high-priority adults were actually vaccinated [29••]. By February 2010, about 124 million doses of 2009 H1N1 vaccine had been distributed in the United States. The median vaccine coverage was reported to be 36.8% among children 6 months to 17 years, 20.1% for adults 18 and older, and 33.2% for people in the ACIP initial target group [36].

The WHO and the FDA recommended including a 2009 pandemic influenza A (H1N1) virus be included as one of the three strains in this year's seasonal influenza vaccine. The virus (A/California/7/2009 H1N1-like) is the same vaccine virus that was used in the 2009 pandemic influenza A (H1N1) monovalent vaccine [37]. The CDC recommends that all persons 6 months of age and older receive the seasonal influenza vaccine annually, with enhanced focus on those at higher risk for influenza-related complications [9••].

The delays in 2009 pandemic influenza A (H1N1) monovalent vaccine availability could have had serious consequences had the virus been more virulent or if it had required two doses to produce sufficient immunity [20]. Globally, the supply of 2009 pandemic influenza A (H1N1) monovalent vaccine was not sufficient to meet the WHO's goal of producing enough to vaccinate two billion people within 6 months after the vaccine became available. The 2009 pandemic influenza A (H1N1) vaccine was not available in developing countries until January 2010 because of limited supply. Significant challenges remain in the vaccine production process in order to optimize production capacity and to support the rapid production of pandemic vaccines [38•].

Conclusions

The 2009 pandemic influenza A (H1N1) caused the first influenza pandemic of the 21st century. Although it caused significant morbidity and mortality globally, it was not as virulent as originally feared. International collaboration facilitated the rapid spread of knowledge, technology, and surveillance that helped slow the initial spread of the virus. However, the pandemic highlighted areas in which public health officials were unprepared. Vaccine development depends upon growing the virus in eggs, which is a timely and unpredictable process that delayed production of the 2009 pandemic influenza A (H1N1) vaccine. Additionally, there were not enough suppliers to produce the vaccine in sufficient quantities. By the time the vaccine was available, the public was skeptical about its safety and efficacy. Also, precursors of the 2009 pandemic influenza A (H1N1) virus had circulated in swine for many years. Improved surveillance of the swine population could have alerted public health officials to the disease before it emerged. Better surveillance of animal health may help predict the next influenza with pandemic potential before it infects humans. The lessons learned from this pandemic will help public health officials worldwide be better prepared for the next infectious disease emergency.

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