CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will vaccinate their patients against influenza, suspect influenza in patients with respiratory symptoms, and use antiviral drugs appropriately

MICHAEL G. ISON, MD, MS*
Divisions of Infectious Diseases and Organ Transplantation, Departments of Medicine and Surgery, Northwestern University Feinberg School of Medicine; Director, Transplant and Immunocompromised Host Infectious Diseases Service, Northwestern University Comprehensive Transplant Center, Chicago, IL

NELSON LEE, MD
Division of Infectious Diseases, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong

Influenza 2010-2011: Lessons from the 2009 pandemic

ABSTRACT

Much was learned about the diagnosis, management, and pathogenesis of influenza from the 2009 pandemic of influenza A (H1N1). This knowledge can be applied to the management of people affected by seasonal infection and to future pandemics.

KEY POINTS

In the H1N1 pandemic, proportionally more children and younger adults were infected and had serious disease than in the seasonal epidemic. Older people were relatively spared from infection, but if infected they had high rates of serious disease as well.

Groups at risk of serious complications from seasonal or pandemic influenza include the very young, the very old, pregnant women, and those with chronic medical conditions.

Currently available rapid antigen detection tests have limitations; molecular tests such as polymerase chain reaction are the optimal diagnostic method and are now more widely available.

Early diagnosis and treatment are associated with better outcomes in influenza-infected patients, particularly those needing hospitalization.

It is critical to continue aggressive vaccination and diligence in diagnosing and treating influenza to mitigate the continued threat of this important infection.

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Fortunately, the 2009 pandemic of influenza A (H1N1) was less severe than some earlier pandemics, in part thanks to advances in our ability to diagnose influenza, to treat it, and to quickly activate the public health and industry infrastructures to mitigate such a pandemic.

In this article, we present lessons learned from the 2009 pandemic, which may allow clinicians to better prepare for the upcoming influenza seasons.

FOUR PANDEMICS IN THE LAST 100 YEARS

Influenza causes annual epidemics of varied severity and risk of death. In the United States, these seasonal epidemics are estimated to account for more than 200,000 hospitalizations[1] and 1.4 to 16.7 deaths per 100,000 persons (3,349 to 48,614 deaths) each year, mostly in the elderly.[2]

The past 100 years have seen four influenza pandemics[3,4]: H1N1 in 1918, H2N2 in 1957, H3N2 in 1962, and H1N1 in 2009. With each pandemic came a spike in hospitalization and death rates in addition to a higher proportion of deaths in people under the age of 65,[3] although the relative impact varied widely with the different viruses.[3,5]

After the 1918, 1957, and 1962 pandemics, the rates of hospitalization and death decreased, although still varying from year to year, and the pattern of who developed seri-

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ous disease returned to normal, with the very young, those with underlying medical conditions, pregnant women, and those age 65 and older being at risk.[3,5,6] Whether the situation in the current postpandemic period will evolve similarly remains uncertain; however, it is believed that the 2009 H1N1 virus will continue to circulate among other established viruses in the community.

THE 2009 PANDEMIC H1N1 VIRUS CAME FROM PIGS, NOT BIRDS

In the late winter and early spring of 2009, H1N1, a novel strain of influenza A, was recognized to have caused outbreaks of respiratory illness in Mexico and southern California.[7,8] The virus spread rapidly, and with the aid of global air travel it reached nearly every country in the world within several weeks.[4,9]

The virus was of swine origin, having six genes of North American swine virus lineage and two genes of Eurasian swine virus lineage.[10] Although classic teaching suggested that pandemics were caused by "new" viruses, typically of avian origin,[11] antigen mapping has clearly shown that swine viruses are antigenically significantly divergent from human viruses,[14] but are more adapted than avian viruses for human transmission.[10,12,13]

Little antigenic drift has occurred since the beginning of the outbreak. Nearly all isolates seen to date are antigenically similar to the A/California/7/2009 strain that was selected for pandemic influenza vaccines worldwide and that is now included in the vaccine for seasonal influenza for 2010-2011.[4,6,15]

The virus appears to replicate more efficiently in the lungs and lower airways than seasonal H1N1 and H3N2 viruses, but generally lacks many of the mutations associated with greater pathogenicity in other influenza viruses.[4,10,16]

PANDEMIC H1N1 DISPROPORTIONATELY AFFECTED THE YOUNG

Most infections caused by the 2009 influenza A (H1N1) pandemic virus were acute and self-limited, similar to seasonal influenza.[4] Asymptomatic infection has been demonstrated from serologic surveys.[17,18]

Notably, many older people had preexisting antibodies that cross-reacted with the novel 2009 pandemic virus, which is antigenically related to but highly divergent from the 1918 pandemic H1N1 virus.[14] This phenomenon may explain why older people were relatively protected against contracting the virus, while younger people, who lacked these antibodies, were more likely to be infected.

A number of studies, using various methods, suggest that each person infected goes on to infect 1.3 to 1.7 other people, a rate called the *basic reproduction number* or R0. This rate is comparable to that for seasonal influenza and is higher in more crowded settings.[4,19] Seroprevalence studies suggest that there was significant geographic variability in the proportion of the population affected during the first and second waves of the pandemic.[4,20,21]

Risk factors for complications or severe illness include age younger than 5 years, pregnancy, morbid obesity, and chronic medical conditions. Interestingly, although people 65 years of age and older had the lowest rate of infection, they had high case-fatality rates if they became sick.[4,22–25] However, in up to 50% of patients with severe disease, no conventional risk factor could be identified.[4,22]

Many patients with H1N1 who need to be hospitalized are younger adults with viral pneumonia

Hospitalization rates varied widely by country but were generally highest in those under the age of 5; 9% to 31% of hospitalized patients required intensive care, and 14% to 46% of those receiving intensive care died.[4]

Overall, the case-fatality rate was less than 0.5%, but ranged from 0.0004% to 1.47%.[4] The lowest case-fatality rates were in Japan, where early diagnosis and treatment are credited, in large part, for such exceptional outcomes.[26]

The incubation period of pandemic H1N1 influenza is 1.5 to 3 days but may be as long as 7 days.[4] This virus causes a spectrum of clinical syndromes that range from afebrile upper respiratory illness to fulminant viral pneumonia.[4] As with seasonal influenza, most patients present with fever, sore throat, and cough. Gastrointestinal symptoms including nausea, vomiting, and diarrhea are more common than with seasonal influenza.[4,27,28]

The viral kinetics of H1N1 are similar to those of seasonal influenza in ambulatory pa-

tients, although some reports suggest that the duration of viral shedding may be slightly longer.[28]

Most patients who needed to be hospitalized presented late after symptom onset with viral pneumonia, which was sometimes may be accompanied by severe hypoxemia, acute respiratory distress syndrome, shock, and renal failure.[29,30] Viral loads were very high in those needing intensive care, and virus shedding longer than 5 days, particularly in the lower respiratory tract, was documented despite antiviral therapy.[29] Fewer patients were hospitalized for other indications, including exacerbation of underlying medical conditions (especially asthma or chronic obstructive pulmonary disease) and bacterial pneumonia, which might be explained by the different profiles of patients with pandemic vs seasonal influenza.[4,31–33]

In severe cases, a number of laboratory abnormalities were common at presentation, including lymphopenia and elevations in levels of serum aminotransferases, lactate dehydrogenase, creatine kinase, and creatinine.[4]

SEASONAL INFLUENZA: USUALLY ACUTE AND SELF-LIMITED

Most seasonal influenza infections are acute and self-limited. Risk factors for complications or severe illness include age 2 years or younger, age 65 years or older, pregnancy, and chronic medical conditions.[5,30,34]

Secondary bacterial infections occur at a rate similar to that during the pandemic.[4,19] The prevalence of bacterial superinfection is about 5% to 15%, depending on the virus, the local prevalence of bacterial pathogens, and the tests used to diagnose the infections.

Hospitalization rates in the United States average 0.052% but range from 0.0115% for ages 5 to 49 to 0.773% for ages 85 and older.[35] Death rates range from year to year from 0.0014% to 0.0167%.[2] Indications for hospital admission include viral pneumonia, bacterial pneumonia, and exacerbation of underlying medical conditions, especially asthma or chronic obstructive pulmonary disease. Exacerbation of underlying lung disease appears to be a more common indication for admission in patients with seasonal infection than with pandemic infection.[5,30–34]

PCR is highly sensitive and specific, and, where available, is now the test of choice

CLINICAL DIAGNOSIS OF INFLUENZA IS UNRELIABLE

Clinical diagnosis of influenza is unreliable, particularly in patients requiring hospitalization.[36] The wide clinical spectrum of influenza infection overlaps with those of other common respiratory viral or bacterial infections. In hospitalized patients, the diagnosis is further confounded by underlying conditions, immunosuppression, and extrapulmonary complications.

Thus, up to half of cases may go unrecognized.[31,33,36] Clinicians should consider influenza as a potential cause of or contributor to any hospitalization whenever influenza is circulating in the community (ie, during seasonal peaks or pandemics).

Diagnostic tests

Several diagnostic assays are commonly used.[37,38]

Rapid antigen tests generally have low sensitivity, in the range of 50% to 60%, particularly for the 2009 A (H1N1) virus. Therefore, a negative test result does not exclude infection and should be interpreted with caution. Newer technologies are being developed that may improve the diagnostic yield of these assays.[4,37–39]

Immunofluorescence antigen tests, when performed on nasopharyngeal aspirates or on flocked swabs, are very sensitive for seasonal influenza. However, their sensitivity is lower for 2009 H1N1 influenza.[40]

In general, the sensitivity of antigen assays depends on where the specimen is collected (nose, throat, or lower respiratory tract—eg, tracheal aspirates, bronchoalveolar lavage), the collection method (conventional vs flocked swabs, nasopharyngeal aspirate and wash, bronchoalveolar lavage), the assay type, the virus, and the viral burden at the time of testing (the longer the time, the lower the viral load).[40,41]

Viral culture is 100% specific and more sensitive than antigen assays, but it takes 2 to 3 days to run, limiting its usefulness in guiding patient management.

Polymerase chain reaction (PCR) is highly sensitive and specific and, where available, is now the test of choice.[40] In addition, it can be

performed on a wide range of specimens, and subtype-specific PCR assays may provide immediate information on virus subtypes, which may have therapeutic implications. Expanded assays can detect a wider range of pathogens, such as respiratory syncytial virus, although these assays are typically used in selected patients, such as those requiring intensive care or those who are immunocompromised.

Consider sampling the lower airway

In patients with 2009 H1N1 viral pneumonia, up to 19% may have had negative upper respiratory tract samples but detectable virus in the lower airways. Therefore, obtaining a lower respiratory tract specimen for testing should be considered, whenever possible, in cases of suspected influenza pneumonia.[4,42,43]

Similarly, when monitoring clearance of the virus in cases of influenza pneumonia, clinicians should remember that the upper respiratory tract may become negative earlier than the lower airways. Active viral replication may continue in the lungs despite apparent clearance in the upper airways.[29,43,44]

Relapsed disease and viral replication have been documented when antiviral drugs are discontinued early, even when upper tract shedding is no longer measurable.[29,45,46] Nonetheless, no study has compared the risk of transmission in patients who remain PCR- or culture-positive for a prolonged time. In theory, those who are culture-positive could transmit infection. Clinicians should consult with local infection-control clinicians to determine the duration of isolation for individual patients.

DRUG THERAPY FOR INFLUENZA INFECTION

Antiviral drugs that are active against influenza are:

- The neuraminidase inhibitors oseltamivir (Tamiflu), zanamivir (Relenza), and peramivir (commercially available only in Japan and South Korea)[47]
- The adamantanes amantadine (Symmetrel) and rimantadine (Flumadine)[48]
- Ribavirin (Rebetol).[49]

The neuraminidase inhibitors and adamantanes are generally well tolerated. These classes of drugs have been reviewed extensively elsewhere.[47,48] The oral agents may be challenging to administer to patients who cannot swallow and in those with critical illness or gastrointestinal dysfunction. Some studies have shown reasonable absorption of oseltamivir given by nasogastric tube in critically ill patients.[50]

Inhaled zanamivir, taken via a proprietary "Diskhaler" device, requires the patient to inspire deeply and may induce bronchospasm, which could be problematic in those with underlying airway diseases such as chronic obstructive pulmonary disease or asthma.[47] Nebulization of the commercially available preparation has been reported to cause ventilator dysfunction and even death, so this should not be done.[51]

Antiviral therapy efficacious only if started early in ambulatory adults and children

Several large prospective studies in ambulatory adult and pediatric patients have clearly shown that antiviral therapy can reduce the duration of symptomatic illness due to influenza by up to 2 days if started within 48 hours of symptom onset.[47,52] In fact, the earlier these drugs are started, the better the clinical outcome.[47] Further, starting antiviral therapy early is associated with lower rates of hospitalization, death, and complications requiring antibiotics.[47] Recent data from Japan also suggest that such early therapy may be partially responsible for the low death rate in that country during the recent pandemic.[26]

In pneumonia cases, viral replication may continue in the lungs despite apparent clearance in the upper airways

Given the evidence of efficacy, antiviral drugs should be considered in all patients with risk factors for severe disease. Antiviral drugs are also appropriate in patients without specific risk factors because of the risk of progression to severe disease in these patients, especially in the context of pandemic H1N1 influenza.[38,53,54] Further, therapy is associated with symptomatic improvement and reduced infectious complications even in patients without risk factors for severe disease.[55] Such early therapy may also have a positive impact on secondary infections among contacts.[55]

Antiviral therapy recommended in hospitalized patients with influenza

Clinical studies of the treatment of hospitalized influenza patients are limited, with few

prospectively conducted studies. Because of differences in clinical course and viral kinetics in hospitalized patients and emerging data in these patients, the ambulatory treatment data and paradigms likely do not apply to hospitalized adults.[29,43,44,56–59]

To date, only four prospective, randomized clinical trials have been completed in hospitalized patients with severe influenza, and only one has been published.[60–63] These studies indicate that combination therapy, higher doses, and intravenous therapy may have a role in this unique population.[60–63]

Several large observational cohort studies suggested that clinical and virologic outcomes were better in hospitalized patients who received antiviral treatment.[4,29,31,33,42,56–58,64,65]

For seasonal influenza, antiviral drugs accelerate the decline in viral load, shorten the duration of viral shedding,[29] and reduce hospital length of stay[66] and risk of death.[33,57,67] Their impact appears to be greatest if they are started early, but efficacy was still observed if they were started up to 4 days after illness onset, as viral replication continues longer in hospitalized patients. The benefit may be greater in immunocompromised patients, preventing progression to pneumonia and improving survival.[46,68]

Antiviral drugs can shorten flu symptoms by up to 2 days if started within 48 hours of symptom onset in ambulatory patients

In pandemic H1N1 influenza, data suggested that timely antiviral treatment was associated with enhanced viral clearance and improved survival in hospitalized patients. Unfortunately, many patients had a delay before starting antiviral therapy.[4,29,64]

Higher-dose oral therapy has been advocated for severely ill patients, although evidence is lacking at the moment. A recently completed study in Southeast Asia shows that prospective studies in adults are needed to document a benefit of such higher-dose therapies before they are widely accepted as standard practice.[4,63] This study found that clinical and virologic outcomes in severely ill patients were no better with oseltamivir in higher doses than in standard doses.[63] Whether this study can be generalized to US populations is not clear, since viral dynamics differ by virus type, clinical care (especially referral patterns and timing) may be different in Southeast Asia, and children predominated in this study.

Ongoing studies will, we hope, demonstrate if intravenous therapy (eg, peramivir, zanamivir) is better than oral therapy for such patients. This is especially important, since oral therapy may result in adequate blood levels in many patients.[51]

In the United States, many patients with febrile respiratory illnesses were hospitalized and started on antibacterial drugs, but antiviral drugs were not given or initiation of these drugs was delayed.[64] Influenza should be suspected as a cause of fever or respiratory symptoms, including pneumonia, in any hospitalized patient when influenza is circulating in the community. Antiviral therapy should be started empirically and should not be delayed while awaiting test results.[64] Further, much like with bacterial pneumonia, testing may be erroneously negative or unavailable until progression has occurred. Therefore, antiviral therapy should be initiated early in any patient in whom influenza is included in the differential diagnosis.

Should a longer course of therapy be considered? Prolonged viral shedding has clearly been documented in patients infected with the pandemic 2009 A (H1N1) virus, and in hospitalized or immunocompromised adults with seasonal influenza.[29,44,46,68–71] Given the current information and the lack of prospective studies comparing 5 days vs a longer course of therapy, 10 days of therapy has been suggested for patients with severe pandemic H1N1 infection requiring hospitalization (particularly if they are treated with corticosteroids or require intensive care) or who are immunosuppressed.[4,72] Longer therapy may be necessary and should be guided by virologic monitoring, optimally of the lower respiratory tract if easily accessible.

For hospitalized patients with seasonal influenza virus infection, the optimal duration of treatment has not been established, but a prolonged course seems reasonable for immunocompromised patients.[46,54]

For patients who do not have a clinical response or who have a relapsing or prolonged virologic course, isolates should be assessed for emergence of resistance.[54,73]

Antiviral resistance

Antiviral resistance (**TABLE 1**) is an emerging issue among circulating viruses (in which case

TABLE 1

Antiviral resistance among circulating influenza viruses

VIRUS	RESISTANCE TO ADAMANTANES	RESISTANCE TO NEURAMINIDASE INHIBITORS
Seasonal A/H1N1	Rare	100% (NA mutation H275Y)[a]
Pandemic A/H1N1	99.7% (M2 mutation S31N)	Rare
Seasonal A/H3N2	~100% (M2 mutation S31N)	Rare
A/H5N1 Clade 1	~100% (M2 mutation S31N)	Rare
A/H5N1 Clade 2.1	80%	Rare
A/H5N1 Clade 2.2	Rare	Rare
A/H5N1 Clade 2.3	Rare	Rare

[a] Resistance emerged during the 2007-2008 influenza season; resistance was rarely discovered previously.

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it is called primary resistance). It also occasionally occurs during antiviral prophylaxis or treatment (in which case it is called secondary resistance). This topic has been reviewed extensively elsewhere.[74]

Sporadic cases of resistance to neuraminidase inhibitors were recognized in the 2009 influenza A (H1N1) and avian H5N1 infections, typically in viruses with the H275Y mutation.[4,75] Risk factors for the emergence of resistance are high viral load and prolonged shedding, as is common in children and immunocompromised patients, and exposure to low drug concentrations, such as during the course of prophylactic antiviral therapy.[45,74,76–78] Clinical evidence suggests that strains with the H275Y mutation are transmissible, can cause disease similar to that of wild type virus, and are resistant to oseltamivir but remain susceptible to zanamivir.[45,74–76,79]

Tests for resistance are not widely available. When testing is considered, robust testing methods that can detect resistance to a wide range of mutations, not just H275Y, should be used.[74] If resistance is considered, the patient should be managed in collaboration with a specialist in infectious disease.

Since resistance may be recognized midseason, national health authorities monitor data on resistance and update it for clinicians regularly (see **www.cdc.gov/flu/** and **www.who.int/csr/disease/influenza/en/**).

LESSONS LEARNED AND FUTURE DIRECTIONS

We were very fortunate that the recent pandemic was relatively mild compared with earlier pandemics. Nonetheless, it has provided a number of useful lessons to guide clinical care of patients with influenza and to focus future research efforts.

Suspect flu as a cause of fever or respiratory symptoms in any hospitalized patient during flu season

Vaccination. Both seasonal and pandemic influenza vaccines are safe and offer effective protection. Unfortunately, a vaccine against a pandemic virus is not likely to be available during the first wave of a pandemic. Improved surveillance may identify a potential pandemic threat sooner and allow earlier preparation of vaccines. Novel strategies, such as adjuvants, cell culture instead of eggs, and a wider array of rapidly growing seed strains may allow for faster responses to future pandemics.[80]

Since the overall impact of vaccination may be limited by low vaccination rates in the community and in health care professionals, strategies to improve their vaccination uptake and the benefits of universal vs targeted vaccination warrant further study. The critical role of vaccination is unquestioned, and many groups are now calling for mandatory influenza vaccination of health care workers, with rare exceptions.[81–85] Further, current guidelines recommend influenza vaccination for all people without contraindications 6 months of age and older.[6]

Infection control remains an important intervention in the control of influenza. While there continues to be some disagreement about the relative contribution of aerosols in the transmission of influenza, recent data suggest that N95 respirators offer little advantage over properly worn surgical masks for seasonal influenza.[86,87] Nonetheless, infectious aerosols may be generated during certain clinical procedures, such as resuscitation, intubation, bronchoscopy, sputum suction, high-flow oxygen therapy, and bilevel positive airway pressure ventilation, and most experts would recommend the use of N95 respirators in addition to standard precautions.[88]

Antiviral drugs will continue to play a significant role in the management of influenza, given the inherent limitations of vaccines. Expanded, early use of these agents, particularly in high-risk patients and those requiring hospitalization, may result in improved clinical outcomes. If influenza is suspected in such individuals, antiviral drugs should be started immediately and discontinued only if active infection is ruled out or an alternative diagnosis is established, such as respiratory syncytial virus infection. Since humans are not colonized with influenza, broad empiric use of anti-influenza antiviral drugs is unlikely a major contributor to the emergence of resistance.

The optimal duration and route of delivery of antiviral drugs need to be clarified through prospective controlled studies.

The current pandemic also highlights the need for better antiviral therapies for seriously ill patients. Novel antiviral drugs should be developed to allow for the use of antiviral combinations. Such combinations may reduce the emergence of resistance, as is the case with other viral infections in which resistance emerges quickly with monotherapy, and would improve the ease of selecting therapy if strains of various susceptibility patterns are circulating. The optimal role of antibody-based therapies warrants further study.[89,90]

Antiviral therapy should be initiated early in hospitalized patients in whom influenza is considered

Testing. Since rapid antigen assays have limited sensitivity and since samples obtained from the upper tract may be negative in patients with pneumonia, robust molecular testing strategies are preferred. Sampling of the lower airways is critical to rule out influenza in patients with pneumonia with negative upper tract samples.

The pathogenesis of influenza also needs more study. It is now recognized that both uncontrolled viral replication and hyperactivated cytokine and chemokine responses contribute to disease manifestation of severe influenza infection, and that the degree of severity varies with different viruses (eg, pandemic H1N1 vs highly pathogenic avian H5N1).[91] Understanding the relative effect of antiviral and anti-inflammatory interventions on clinical outcomes may allow more tailored therapy depending on the pathogenesis of future pandemics.

Animal hosts. The current pandemic clearly shows the importance of influenza viruses within animals. Efforts to improve our surveillance of viral disease in a wide range of animal species and studies to understand the pathogenesis and antigenic changes of influenza in animal hosts are critical.[92]

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***ADDRESS**: Michael G. Ison, MD, MS, Department of Medicine, Infectious Diseases Division, 645 North Michigan Avenue Suite 900, Chicago, IL 60611; e-mail mgison@northwestern.edu.*