Influenza epidemiology—past, present, and future

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In April 2009, Mexican, American, and Canadian authorities announced that a novel influenza virus with pandemic potential had been identified in large segments of the population. Within weeks, it became apparent that the world was dealing with the first influenza pandemic in >40 yrs. Despite the unpredictable nature of influenza severity and spread in the pandemics of the 20th century, understanding the epidemiology of the past pandemics and current influenza pandemic will help prepare physicians, hospitals, and governments to predict and prepare for the subsequent waves and subsequent pandemics. We present a summary of the biology that predisposes influenza to cause sudden pandemics, as well as a summary of the epidemiology of the 20th century pandemics. We also report on the epidemiology, disease severity, and risk factors for severe disease and intensive care admission from the first wave of the current pandemic (April–August 2009). Last, we provide a mathematical model based on transmission dynamics of the H1N1 influenza virus that may provide some guidance in terms of disease incidence and hospital impact. (Crit Care Med 2010; 38[Suppl.]:e1–e9)

KEY WORDS: influenza; epidemiology; pandemic; H1N1; severity; mortality; hospitalization

As the world was preparing for a pandemic influenza in 2008 caused by H5N1—the bird flu, a highly lethal but non-human-to-human transferrable influenza that raged through Southeast Asian countries, Egypt, and other countries—H1N1, the swine flu, emerged. It appeared first in Mexico and quickly, over the course of 3 months, was reported from practically all countries, regardless of the season. As of October 11, 2009, which was the end of the first wave of this epidemic and the beginning of the second wave, close to 400,000 laboratory-identified H1N1 influenza cases and >4735 deaths had been reported to the World Health Organization. In addition to the human costs, the economic burden of the H1N1 influenza is substantial and an additional load on the present brittle world economy. In Mexico alone, at the beginning of the epidemic, every day led to a loss of $57 million, and the World Bank estimates that the pandemic may cost as much as $3 trillion.

Despite the progress in molecular biology and vaccine research, the production of H1N1 vaccine is still occurring in chicken eggs, with a substantial delay in the production of adequate amounts of vaccine material for the entire world's population. In addition, the research on adjuvant treatment has been slow, which also contributes to the paucity of our defense tools. Luckily, the H1N1 virus is not highly pathogenic; therefore, the number of deaths and severe diseases has been of low magnitude. In addition, the H1N1 is slow in acquiring resistance to oseltamivir; to date, only approximately 30 strains were reported as oseltamivir-resistant, allowing for effective treatment if therapy is started early in the course of the disease.

The H1N1 flu is not limited to humans and has been reported in herds in Canada, Norway, and sporadically in the United States, defining this virus as zoonosis, or rather humano-zoonotic. In this article, we describe some of the epidemiologic features of H1N1 and make some predictions regarding its second wave.

Influenza: Virology, Antigenic Evolution, and Ecology

Influenza viruses are members of the orthomyxovirus viruses that encode a segmented RNA genome. There are three groups of influenza virus: influenza A, influenza B, and influenza C (1, 2). Influenza B and C viruses are associated with low-level sporadic disease and limited outbreaks and are never causes of pandemic influenza (2). On the other hand, influenza A is responsible for most seasonal influenza and all known pandemics (2). Only influenza A is discussed here.

Influenza A virus contains an RNA genome comprising eight RNA segments encoding 11 genes. Of these, the hemagglutinin (HA), which binds to the cellular receptor sialic acid, and neuraminidase (NA), which cleaves sialic acid residues from budding viruses, are of particular importance to the epidemiology of influenza (1–3). Other genes, including nucleoprotein, M1 (matrix), M2 (ion pore), NS1, NS2, PA, PB1, PB1-F2, and PB2, encode for proteins critical for structure, reproduction, and virulence, and may also be used as diagnostic targets by polymerase chain reaction or antigen detection (e.g., M1 or nucleoprotein) and may be studied to predict virulence in certain nonhuman hosts (2–4).

HA and NA genes encode surface proteins that are involved in attachment to and budding of the virus from host cells. They are the primary antigenic proteins of the virus. Fifteen serologically distinct HA and nine distinct NA proteins have

been identified and are sequentially named H1, H2, H3, and so on, and N1, N2, and so on (2, 3). Of these, only H1, H2, and H3 in combination with N1 and N2 typically cause disease in humans (1). The remaining tend to be zoonotic, causing disease in fowl and nonhuman mammals (1, 2). The human specificity is largely attributable to the receptor specificity of hemagglutinin to target structures of sialic acid present in human cells (1). Both these surface proteins undergo significant variation over the course of their replication and during repeated epidemics as a result of influenza's error-prone RNA polymerase (1, 3, 5–7). Over the course of epidemics, insertions, deletions, and changes in the sequence of these genes result in polymorphisms of NA and HA structures, although they are of insufficient magnitude to change their antigenic nomenclature; these polymorphisms are termed antigenic drift (1, 3, 7). In other words, despite these mutations, the primary antigenic properties of the NA or HA protein in question are still maintained (e.g., H1), but these mutations result in partial loss of host immunity within a given population (2, 8). Antigenic shift, which may result in pandemic spread because of lack of partial immunity within the population, occurs when a sufficiently antigenically distinct HA (with or without a new NA) emerges (1, 6). Antigenic shift may occur either as a result of a reassortment event between human-adapted influenza and animal-adapted strains within a coinfected host, resulting in a progeny virus capable of sustained human transmission, or if a new human-adapted HA arises when an animal or avian influenza A virus is transmitted without reassortment from an animal reservoir to humans (1, 3, 4). Neither the HA nor the NA needs to be "numerically" different from the antigens circulating seasonally. The only prerequisite for antigenic shift (and therefore a potential for pandemic spread) is that little or no immunity from previous influenza infections or vaccination exists in the population. For example, the 2009 pandemic H1N1 strain is significantly antigenically different from the previous circulating strains (including "seasonal" H1N1) (9).

The sustained survival of influenza within a population and its epidemic potential are entirely dependent on the evolution of its HA and NA genes. As population immunity increases as a result of natural infection or vaccination, anti-genic shifts sufficient to negate preexisting host immunity drive continued sporadic and epidemic infection but are insufficient to generate pandemics (1, 3, 6–8, 10). Antigenic shift, however, produces a virus to which preexisting immunity is very low or absent, thereby exposing a very large susceptible population, potentially resulting in a pandemic.

Influenza ecology is complicated by the presence of avian and mammalian clades of virus, relaxed host specificity, and the aforementioned antigenic evolution. Several avian species serve as large reservoirs for influenza A viruses (1, 3). In general, these viruses appear to be in evolutionary stasis with their hosts and tend to cause asymptomatic infections. However, certain viruses that cause asymptomatic infection in shorebirds or waterfowl can cause fatal infection in other avian species, such as domestic poultry (1). Avian species are poorly adapted to human infection because their hemagglutinins typically do not have high affinity for mammalian sialic acid residues. As a result of this, avian-adapted viruses cannot cause sustained human outbreaks or pandemics without appropriate spontaneous genetic alterations that result in human host adaptations (1, 3). Avian viruses can infect a limited range of other mammals, including seals, whales, horses, and pigs (1). Pigs may be readily infected with both avian and mammalian strains because of the presence of both avian-like and mammal-like sialic acid residues in their tracheal epithelium (1). Pigs, therefore, may serve as a reservoir for intermingling and reassortment of mammalian and avian species, potentially resulting in antigenic shift. This potential for the pig to function as a "mixing vessel" has been one of the reasons for the significant interest in China and Southeast Asia as a source of past and future pandemics, where intermingling of humans, domestic fowl, and pigs occurs at an intensity not seen anywhere else on earth. Pigs also serve as reservoirs for swine influenza. Classic swine influenza causes mild influenza-like illness in pigs and, because the virus is mammalian, it can be transmitted to humans (1, 3). However, infections are typically limited to persons with close contact to pigs and do not result in large-scale outbreaks or pandemics. Despite the swine HA or NA gene segments of swine influenza viruses that have adapted to human hosts by genetic rearrange-ments, the use of the term "swine influenza" in not appropriate.

Epidemiology of Seasonal (Inter-Pandemic) Influenza

The incidence of seasonal influenza typically increases in the late autumn and begins to decline in mid spring. In the Northern hemisphere, this corresponds to November through March; in the Southern Hemisphere, this corresponds to April through September (1, 6). In tropical countries, influenza occurs sporadically throughout the year, but more so in the rainy periods (1, 3, 6, 8). Localized outbreaks of seasonal influenza also occur in inter-pandemic years, particularly when strains of virus penetrate communities with little or no preexisting immunity to the circulating virus. The reason for seasonality remains unclear. Because the primary mode of transmission is by large droplet aerosols, increased crowding in the colder months, the return to schools and university dormitories, and the start of military recruit courses have been suggested as contributing factors (1–3, 6). Fomites may serve as a secondary mode of transmission, and it has also been suggested that the higher intensity of sterilizing ultraviolet light in the summer months may serve to reduce the environmental burden of virus. Dry environments, such as those that prevail during the winter months, are also known to increase transmission for unknown reasons (6). Higher serum vitamin D levels and other immunomodulating factors associated with ultraviolet light levels have also been suggested as factors influencing influenza attack rates (8). The intensity of seasonal influenza varies from year to year and largely depends on the size of the susceptible population, which in turn depends on the degree of antigenic drift that has occurred in the previous seasons (6, 11). Both previous natural infections and vaccination reduce the susceptible host population dramatically if neutralizing antibodies to the virus are present, but a significant antigenic drift results in a more susceptible population and a correspondingly higher incidence of disease (3). Other factors, including overcrowding, crowded sleeping arrangements, and unhygienic living conditions with poor access to hand hygiene, can contribute to localized pockets of increased incidence (3, 6). This partially explains the higher incidence of seasonal influenza observed

in colleges, individuals living in low socioeconomic conditions, daycare centers, and military settings.

All immunologically susceptible individuals exposed to seasonal influenza may become infected. Average attack rates during epidemics range from 10% to 20% but may be as high as 40% to 50% in particularly susceptible populations (1, 3). The attack rate is typically highest in school-age children and daycare populations (1–3, 7). This probably represents the higher intensity of transmission behaviors in this population and a relatively low rate of immunity. In seasonal outbreaks, age-specific incidence generally follows a predictable course, with children being affected early in epidemics, followed by their adult caregivers, and, last, the elderly (1). Although immunity is the major factor in incidence of disease, severity and morbidity of seasonal influenza are dependent on several host factors. The average influenza mortality in developed countries is approximately 12 in 100,000 persons, but certain populations experience significantly higher morbidity and mortality from seasonal influenza (6). These include those at the extremes of age, with a particularly steep increase in age-specific mortality after 64 yrs of age, and those with asthma and other chronic pulmonary diseases, cardiovascular diseases, diabetes, liver cirrhosis, immunodeficiency states, hemoglobinopathies, malignancy, and renal dysfunction (2, 3, 7, 12, 13).

Outbreaks of interpandemic influenza generally follow a predictable course. They begin abruptly, peak within 2 to 3 wks, and have a total duration of 5 to 10 wks. This pattern is also typically observed with pandemic influenza, although a much higher incidence is typically noted, and second or subsequent waves of similar duration and intensity are commonly observed (1–3, 6).

Epidemiology of Past Pandemics

Three major pandemics were recorded in the 20th century: the 1918 to 1919 pandemic (H1N1), the 1957 to 1958 pandemic (H2N2), and the 1968 pandemic (H3N2) (1). Each had a unique epidemiologic pattern and origin.

1918 to 1919 Pandemic: H1N1 "Spanish" Influenza

The geographic origin of the 1918 pandemic virus remains unclear. According to medical historians and despite the pandemic's name, the most probable origin is either China or in military camps in the United States soon after the return of soldiers from the European front (1, 4, 14, 15). What is more certain is the phylogenic origin of the virus, elucidated through sequencing of the virus found in human tissues preserved from 1918. Using drift modeling, it appears that the ancestor virus first penetrated mammalian hosts (pigs) between 1882 and 1913, and the 1918 pandemic virus originated from a human/swine H1N1 reassortment event that led to an effective human transmission in approximately 1915 (16). However, the earliest reliable description of the 1918 pandemic influenza was in military camps during March 1918, although recent reports also suggest a first wave in New York in February to April 1918 (15). Most accounts suggest that this "first wave" had a relatively low incidence of nonsevere clinical disease with a limited spread. In August 1918, the disease pattern suddenly changed, with widespread reports of severe influenza compatible clinical disease that emerged simultaneously in North America, Africa, and Europe (1). The global "second wave" peaked in October 1918, when school absenteeism was approximately 40% according to some reports (17). This wave was followed by a smaller "third wave" in February 1919 (17). Although the attack rates and age-specific incidence rates of this pandemic did not differ significantly from subsequent pandemics, this pandemic was characterized by its particularly high rates of morbidity and mortality, especially among young adults (1, 17). The reason for the high mortality rates remain unclear, although recent analysis of genetic reconstruction of the 1918 strain suggest that the virus itself was more virulent and had a propensity to cause viral pneumonia, as well as a clinical picture compatible with a "cytokine storm" (1, 4, 18, 19). Controversy remains regarding whether the virus itself, or its strong association with postviral bacterial pneumonia, was the major cause of death in 1918 (19, 20). The overall evidence today supports that both mechanisms, direct viral virulence and postviral superinfection, played major roles in causing the high mortality. The exact molecular mechanisms behind the hypervirulence are not fully known, but *in vitro* genetic recombinants of H1N1 1918 and modern seasonal strains support an important role of the genes PB1, NA, and HA in the virulence of the 1918 virus in animal models (4, 18, 19). It has also been suggested that the NS1 protein of the 1918 strain had the ability to inhibit interferon activity, leading to more severe viral infection (4).

1957 to 1958 Pandemic: H2N2 Asian Influenza

This pandemic was somewhat better characterized than the 1918 pandemic because of more reliable intercontinental communication and the ability of laboratories to isolate the virus in cell cultures. It appears the virus originated in Guizhou, China, in approximately February 1957, and spread rapidly throughout that country (1). The epidemic reached Hong Kong in April 1957, and the causative virus was definitively isolated in Japan in May 1957. The virus was unique in the human population because of the presence of different HA and NA antigens. Until then, the major circulating strains were descendants of the 1918 H1N1 strain. By November 1957, the outbreak reached pandemic proportions (1). In the Northern Hemisphere, peak incidence occurred in October and a second wave was observed in January 1958. Like other influenza epidemics, age-specific attack rates were highest in children aged 5 to 19 yrs and, although excess mortality was noted in both waves, no 1918-like excess mortality among younger adults was observed (1). Studies similar to those that established the origin of the 1918 pandemic virus support the notion that the H2N2 virus originated from a single reassortment even between avian H2N2 and human H1N1 (1).

1968 Pandemic: H3N2 Hong Kong

The Hong Kong influenza pandemic was first noted in Hong Kong in July 1968 (1) and appeared to spread globally somewhat more slowly than the previous pandemics, reaching the United States in December 1968/January 1969 and Europe 1 yr later. This pandemic had the lowest excess mortality of the 20th century influenza pandemics, probably because of partial immunity to the N2 component of the virus from previous circulating H2N2 in much of the population (1). Interestingly, the H2N2 virus became extinct after the emergence of H3N2 in the human population, an observation further supporting cross-immunity. Like the H2N2

virus, the H3N2 virus appears to have originated from a reassortment between avian H3-containing viruses and the human H2N2 (1).

Epidemiology of the 2009 H1N1 Pandemic

In April 2009, near-simultaneous reports surfaced of an epidemic of severe influenza-like illness in various parts of Mexico and a report of influenza infection in three children in the southwest United States caused by an H1N1 strain of influenza closely related to domestic swine influenza (21). None of the children had exposure to swine, and sequencing of the isolated virus later confirmed that all the Mexican cases were caused by the same novel H1N1 strain. Although the misnomer "swine flu" was initially used, the virus was clearly capable of human-to-human transmission and was later more appropriately named swine-origin H1N1 influenza virus, human-adapted swine H1N1 influenza virus, novel H1N1, or 2009 H1N1 (contrasting it from 1918 H1N1).

Origins

Despite modern epidemiologic techniques and communication, the true geographic origin of the novel H1N1 virus remains a mystery and is of limited relevance. Although the virus appears to have emerged first in Mexico (more specifically in San Luis Potosi) in late February 2009 (personal communication, Celia Alpuche, Mexican Institute of Diagnostic and Epidemical Reference, Mexico City, Mexico), this likely represents the first large-scale transmission of this virus, which is readily supported by the nature of subsequent global outbreaks, with initial cases having exposure or links to Mexico. However, like the 1918 pandemic, the novel H1N1 strain or a similar swine-adapted virus may have been circulating at low levels among humans for months, or less likely years, before February 2009; it also may have been circulating among mammals (pigs) for years earlier. Molecular analysis suggests that the common ancestor to the human 2009 pandemic H1N1 probably emerged in humans between August 2008 and January 2009, whereas the nearest common ancestor in pigs has probably been circulating in pigs for at least a decade (22–24). Because worldwide pandemic influenza surveillance has focused on Asian avian strains,

little work was performed to identify and type strains circulating in pigs, leading to the likelihood that a closely related ancestor swine H1N1 virus existed long before its emergence as a human-adapted strain in February 2009. Unlike other influenza viruses, the genetic origin of this virus is better understood. Complete sequence analysis reveals that the virus is a triple-reassortment virus, with elements originating from multiple established swine viruses (22, 25, 26). Although Eurasian swine, North American swine, avian, and human components are included in the genome, these components were already present in ancestor triple reassortment swine viruses. Therefore, the virus certainly originated from pigs and has likely emerged as a result of reassortment between swine-adapted viruses containing human and avian elements (23). Lack of systematic swine surveillance allowed for the undetected persistence and evolution of this potentially pandemic strain to evolve for many years.

2009 H1N1 Pandemic: Descriptive Epidemiology of the "First Wave"

As noted, the epidemic was first described in Mexico in April 2009 (26–28). The first wave of the epidemic followed the course typical to influenza, with exponentially increasing incidence from April 9 to April 24, peaking on April 26, and declining rapidly to effectively zero by May 25 (29). The duration of the first wave, therefore, was approximately 12 wks. The confirmed rate of infection was approximately five per 100,000 but is presumably much higher in reality, because many individuals had subclinical disease and therefore were not tested (29). Age-specific incidence of confirmed cases was highest among children aged 0 to 14 yrs (29). Age-specific confirmed case mortality of 55.7% suggested higher mortality rates among adults aged 30 to 59 yrs, although this case fatality rate is likely to have been grossly inflated by biased sampling (29).

After World Health Organization notification of the increased incidence of influenza cases in Mexico, countries worldwide implemented enhanced surveillance. Subsequently, outbreaks of 2009 H1N1 were reported in Canada, the United States, the Middle East, East Asia, and Europe (30–32). The first appearance of cases outside of Mexico corresponded with travel to

Mexico, supporting the notion that Mexico was the initial site of sustained human-to-human transmission (26, 33–35). In Canada, the epidemic followed a course similar to that in Mexico, beginning in mid April, peaking on June 10, and effectively disappearing by early July for a total duration of approximately 11 wks (30, 36). In the United States, the epidemic reached a peak approximately June 20 and a nadir approximately August 25 before increasing again (31). The situation in Europe mirrored that in North America with the outbreak starting slightly later (late April) and reaching a nadir in 10 to 12 wks (32). The global spread of influenza was very rapid, touching every country by early July.

Contrary to countries in the Northern Hemisphere, some countries in the Southern hemisphere reported somewhat later appearance of the virus (early to mid June in New Zealand and Australia; late June in South Africa), with somewhat longer duration in the Southern autumn. The wave lasted approximately 18 wks in Australia and 13 wks in New Zealand and South Africa (37–40).

Early during the enhanced surveillance for influenza, patient characteristics could be accurately pinpointed. These data indicated that patients at greatest risk for infection were younger, primarily younger than 20 yrs of age, with no sex predilection, and with relatively low rates of morbidity and mortality (29–31, 35, 41–43).

Attack Rates and Estimates of True Incidence

Worldwide, confirmed attack rates were highest in younger age groups, and the average age of cases increased over the course of the epidemic, as was typical of previous influenza outbreaks (33, 42, 44, 45). It became clear during the early part of the pandemic that the case severity, hospitalization, and mortality rates were low, lower than seasonal influenza in some countries, but excess hospitalizations were noted throughout the affected areas because of the very high incidence of disease (30–32). Although diagnostic testing was used extensively in developed countries, attack rates and true incidence are difficult to ascertain because of under-testing of less symptomatic cases and the lack of a reliable method for the retrospective serological diagnosis of H1N1 infection. Therefore, the incidence of laboratory-confirmed cases or even clinical
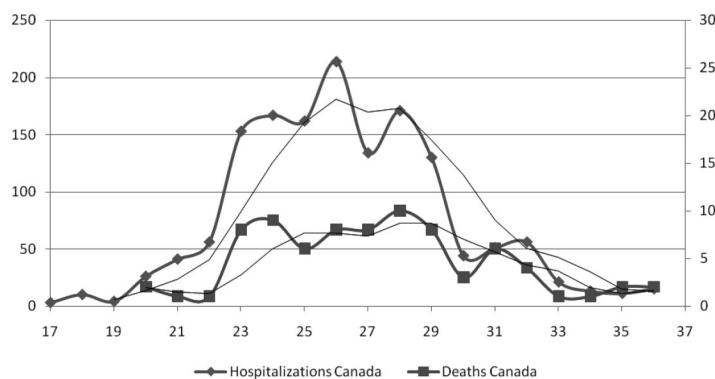
Figure 1. Total hospitalizations (*left axis*) and deaths (*right axis*) by epidemic week, starting April 26, 2009 (week 17), in Canada. Data from FluWatch (30).

Table 1. Select characteristics of patients with laboratory confirmed H1N1 2009 influenza in Canada

	Total Cases, n = 7107	Hospitalized, n = 1504	Admitted to ICU, n = 295	Deaths, n = 76
Females, %	51.9	51.4	56.3	60.5
Median age	18	23	37	50
Aboriginal status, %	12.5	17.5	15.3	11.8
Comorbidities, %	39.2 (728/1859)	58.5 (576/988)	68.6 (151/220)	78.9 (45/57)
Pregnancy, %	5.0 (87/1724)	28.1 (77/274)	19.7 (15/76)	28.6 (4/14)

Data from FluWatch (30).

cases represent a gross underestimation of the total cases because most were minimally symptomatic, and serological studies were severely hampered by serological cross-reactivity with vaccine and seasonal strains. Although reference level serologic tests can differentiate between pandemic H1N1 and infection or vaccination with other H1N1 viruses, these are not practical or cost-effective to use outside of research settings. Estimates of attack rate and incidence can be made using epidemiologic techniques and mathematical modeling on the basis of epidemic curves. These are discussed later.

Co-Circulation of Other Influenza Viruses

Co-circulation of other influenza viruses is important for two reasons. When a single strain of influenza is circulating, anti-viral susceptibility is usually predictable. For example, seasonal H3N2 strains are widely susceptible to neuraminidase inhibitors, whereas seasonal H1N1 strains are resistant (31). However, if co-circulation is occurring, it may be impossible to provide definitive therapy before genotyping. Second, when co-circulation is occurring, reassortment between viruses is possible, potentially leading to new, more virulent, or more resistant viruses.

During the first wave of the H1N1 pandemic, the presence of co-circulating virus was variable from country to country. In much of the temperate Northern Hemisphere, minimal or no co-circulation occurred with H1N1 2009 (30, 31). In the United States, where a second wave has begun, >99% of circulating viruses are H1N1 2009 (31), and in Canada >97% of influenza viruses circulating are H1N1 2009 as of mid-October (36). In the Southern Hemisphere, in countries outside of the Americas, reports of co-circulation were more common during the first wave. Australia (40, 46), New Zealand (46, 47), and South Africa (46, 48) all reported significant co-circulation with H3N2 for significant parts of the first wave. However, as the epidemic unfolded, H1N1 2009 virtually replaced all other influenza A types and became the dominant strain circulating globally (32).

Epidemiology of Resistance to Adamantanes and Neuraminidase Inhibitors

Two classes of drugs are available for the treatment of influenza A. Adamantanes (amantadine and rimantadine) function by inhibiting the ion pump M2, thus interfering with viral cell invasion, and neuraminidase inhibitors (oseltamivir, zanamivir, peramivir), which prevent neuraminidase activity, thereby preventing release of infectious virus particles from infected cells (2). Well defined mutations in the M2 gene or

NA gene confer resistance to these agents. Resistance to adamantanes is class-specific, whereas resistance to oseltamivir does not typically confer resistance to zanamivir (49). Surveillance is ongoing worldwide to detect the early development of resistance in the H1N1 2009 pandemic strain. To date, virtually all H1N1 2009 pandemic strains have been resistant to adamantanes (31). More than 10,000 viruses have been tested for resistance to oseltamivir worldwide and <1% have been found to be resistant. As of October 14, 2009, 31 cases of oseltamivir-resistant H1N1 2009 infections have been reported, and all had the H275Y mutation conferring resistance (30, 31). No strain to date has been resistant to zanamivir (30–32).

Second Wave in the Northern Hemisphere

Whereas pandemic activity is currently subsiding in the Southern Hemisphere, a second wave of H1N1 influenza has begun in some areas of the Northern Hemisphere. In particular, the United States and parts of Europe are reporting increasing incidence since early September 2009 (30). Mexico reports a second epidemic wave started in early October (30). Population demographics and severity have been similar to those observed in the first wave, with the virus primarily affecting children and young adults in the early phase of the epidemic; low morbidity and mortality rates continue to be reported in most populations (31). Between August 30 and October 3, 2009, the United States reported a total of 3874 laboratory-confirmed, influenza-associated hospitalizations, with 240 laboratory-confirmed H1N1 2009-associated deaths (31). In Canada, where activity was lower than in the United States, 50 hospitalizations and six deaths were reported in the same period, although some deaths are likely attributable to illness during the first wave (30). Influenza activity during this second wave is >99% attributable to H1N1 2009 and remains generally susceptible to oseltamivir (31).

Severe Respiratory Infection

Severe respiratory infection is variably defined in the literature. Tangible definitions include case hospitalization rates, case mortality rates, and case intensive care unit (ICU) admission rates. Because total cases cannot be determined reliably, and testing practices change over the
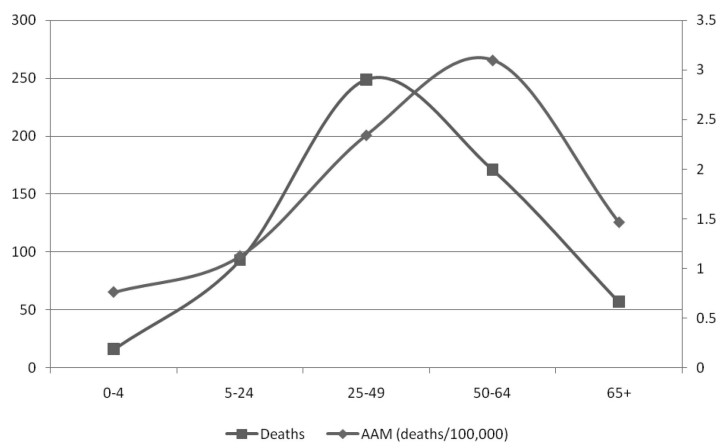
Figure 2. Total deaths (*left axis*) and age-adjusted mortality (*AAM, right* axis) by age category in the United States. The highest age-adjusted mortality was in the 50- to 64-yr group, whereas the highest absolute mortality was in the 25- to 49-yr group. Data from Centers for Disease Control and Prevention, Atlanta, Georgia (31).
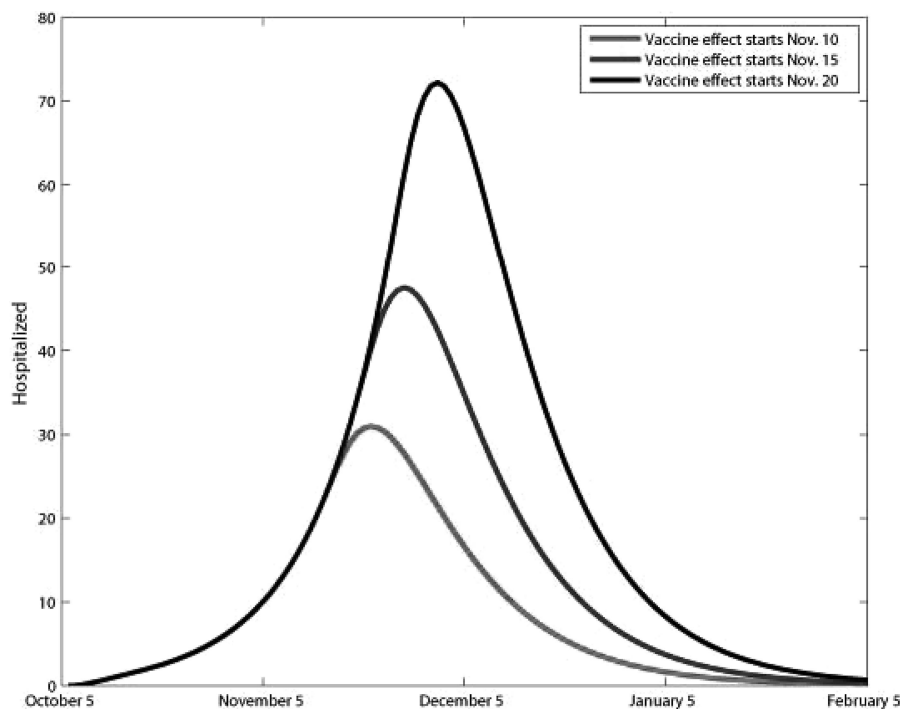

Figure 3. Number of hospitalized individuals in Manitoba (population 1.1 million) according to various vaccine effect start times. Numbers assume a 10% seroprevalence before the wave.

course of the epidemic, it is impossible to determine true rates. However, most cases resulting in hospitalization will be investigated and total laboratory-confirmed influenza hospitalizations, ICU admissions, and deaths provide an epidemiologic surrogate for severe infections. By mid-September, Canada had recorded 1459 hospitalizations, of which 288 (19.7%) were ICU admissions and 76 (5.2%) resulted in death (30). Both admission and, to a lesser extent, deaths were strongly associated with the influenza epidemic curve, accelerating in mid-

June. Deaths were somewhat spread out across the epidemic, mostly as a result of intensive care practices and prolonged aggressive care before death (Fig. 1). Similar observations were noted in the United States, with 9079 hospital admissions by September 3, of which 593 (6.5%) resulted in death (31).

Demographics and Risk Factors for Severe Infections

The demographics of severe infection differ somewhat from those of uncompli-

cated infection. Overall illness with 2009 H1N1 seems to be in keeping with seasonal influenza, affecting primarily children and young adults, affecting males and females equally, and showing minimal predilection for people with underlying comorbidities. Contrary to that, severe illness shows a unique age, gender, and risk-factor predisposition (50–53). The proportion of female patients affected, the median age, and the proportion of cases with underlying medical conditions increased with severity of illness (Table 1). In a recent publication, 98.2% of critically ill patients with H1N1 2009 had at least one comorbidity (52). Those comorbidities most frequently reported were chronic lung disease (41.1%), obesity (33.3%), hypertension (24.4%), diabetes (20.8%), immunosuppression (19.6%), neurologic disease (15.5%), cardiac disease other than hypertension (14.9%), and pregnancy (7.7%) (52). In addition, certain populations, including aboriginals, were at high risk for severe disease in several countries (30, 39, 52). Age distribution of death also was not typical to interpandemic influenza. The age distribution of population-adjusted mortality in laboratory-confirmed influenza H1N1 2009 is skewed to middle-aged individuals, rather than the very young and very old, creating a more *W*-shaped mortality curve reminiscent of the 1918 H1N1 pandemic (Fig. 2).

Modeling the Next Wave

To provide information on the impact of the second wave of influenza, models can be constructed using known characteristics of transmission (e.g., reproductive number) and estimated rates of severe illness, ICU admissions, and deaths. One such model is presented here.

The modeling component of this study is based on the design and use of a new deterministic compartmental model for the transmission dynamics of H1N1 in the population. The total population of individuals in the province of Manitoba is split into a number of mutually exclusive compartments depending on their infection (or risk of infection) status. We consider 15 compartments of the following: susceptible individuals, vaccinated individuals, latently infected individuals, infectious individuals without disease symptoms, high-risk symptomatic individuals in the early stage (first 2 days) of infection, low-risk symptomatic individuals in the early stage (first 2 days) of
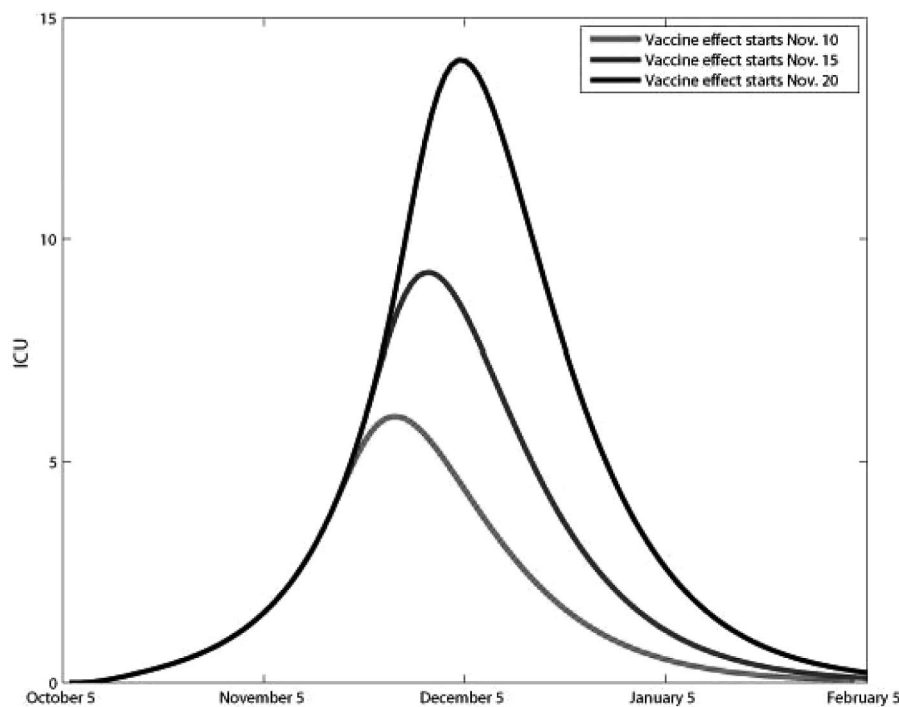
Figure 4. Number of intensive care unit (*ICU*) admissions in Manitoba (population 1.1 million) according to various vaccine effect start times. Numbers assume a 10% seroprevalence before the wave.
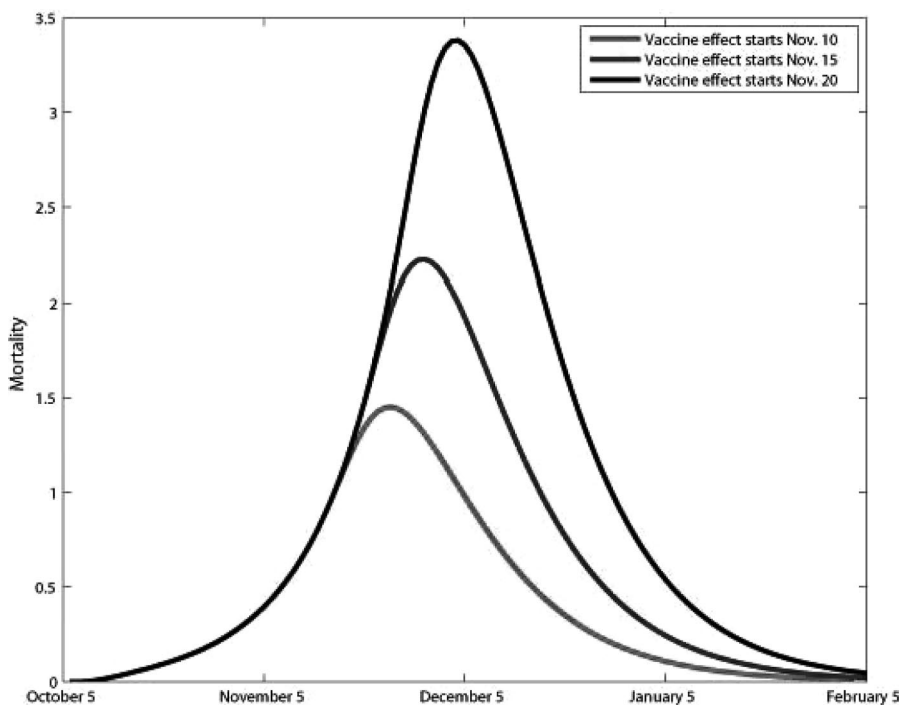

Figure 5. Modeled mortality in Manitoba (population 1.1 million) according to various vaccine effect start times. Numbers assume a 10% seroprevalence before the wave.

infection, high-risk symptomatic individuals in the later stage of infection, low-risk symptomatic individuals in the later stage of infection, high-risk treated infected individuals, low-risk treated infected individuals, high-risk hospitalized individuals not in the ICU, low-risk hospitalized individuals not in the ICU, high-risk hospitalized individuals in the ICU, low-risk hospitalized individuals in the ICU, and recovered individuals. The model takes the form of the deterministic system of nonlinear differential equations, similar to those for pandemic avian influenza (54–56).

The model is parameterized using epidemiologic and demographic data for the province of Manitoba, Canada, but should allow for approximate estimates to be extrapolated to other regions. For comparison, the population of Manitoba is approximately 1.1 million.

Main modeling assumptions include second wave begins first week of October 2009; high-risk individuals more likely to have severe illness develop, require hospitalization, and ICU admission in comparison to low-risk individuals; mass vaccination commences October 26, 2009 (vaccine efficacy ≈80%); at least 10% to 20% of the total population have previous immunity (attributable to first-wave infection); first wave reproduction number is approximately 1.3, as reported by others (57–60); and the R0 of the second wave is higher (1.9 before vaccine effect).

Figure 3 depicts the time series of the number of hospitalized individuals; the scenario is that 10% of the total population are assumed to have infection-acquired immunity for various times when the vaccine impact takes effect. It is evident that the peak, which is expected to occur at the end of November or early December, increases with increasing duration of time before the vaccine impact is felt. Furthermore, the figure shows that the pandemic would run until late January or early February 2010. It also demonstrates dramatically the impact that timely vaccination can have on the course of the pandemic. Similar plots are depicted for the ICU admissions (Fig. 4) and H1N1-induced mortality (Fig. 5). This study estimates that where 10% of the total population has previous immunity, the province of Manitoba could have between 946 and 2223 hospitalizations, 194 and 459 ICU cases, and 45 and 108 H1N1-induced mortalities, depending on when the vaccine impact occurs. However, simulating a similar scenario in which population immunity resulting from the first wave is higher at 20% predicts a lower disease burden: 436 to 849 hospitalizations, 90 to 175 ICU admissions, and 21 to 41 deaths. In summary, this study projects that the burden of the second wave of the H1N1 pandemic could be at least three times that of the first wave, and that the second wave may last until early 2010. In the absence of serological surveys, it is difficult to predict the seroprevalence of disease after the first wave, but studies in New Zealand have predicted a seroprevalence after the first wave to be between 10% and 20%

(39). The simulation results obtained are sensitive to changes in the parameters and initial values used, and although the simulations provide some idea of the outcome of various scenarios, caution should be used in interpreting the results.

CONCLUSION

The first influenza pandemic of the 21st century has provided us with insight into the fundamental epidemiologic characteristics of influenza and has afforded us a much greater understanding of the impact of pandemic influenza on the healthcare system and on individuals. Although the reasons for the enormous variability of influenza pandemic severity and spread remain elusive, it is certain that anunderstanding of the basic epidemiologic principles, pathophysiology, and natural history of this pandemic, as well as those of history, will serve to help all physicians—from the ICU to the hallways of public health—provide the best possible individual and population-level interventions to reduce the impact of this truly formidable pathogen. In addition to presenting data on the impact of previous pandemics and the first wave of the current pandemic, we also have used a deterministic compartmental model for the transmission dynamics of H1N1 in the population to predict the impact of the next wave. Our predictions suggest that vaccination and existing natural immunity from the first wave will have a significant impact on the disease and severe disease incidence and that the peak is likely to occur approximately in early December 2009. The wave is expected to last into early 2010.

ACKNOWLEDGMENTS

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