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H1N1 Influenza Pandemics: Comparing the Events of 2009 in Mexico with those of 1976 and 1918–1919

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Outbreaks of influenza A (H1N1) of avian- or swine-related origin have substantially impacted human populations. The most dramatic pandemic of influenza H1N1 occurred during 1918–1919 producing significant morbidity and mortality worldwide. In the 20th century, two other major pandemics took place but they were the H2N2 and H3N2 reassorted influenza strains. In 1976, a small outbreak of swine-related H1N1 in the U.S. led to a national scare but without any significant public health impact. More recently, in April 2009, in Mexico, and subsequently worldwide, an influenza (H1N1) triple reassortant strain produced >200,000 laboratory-confirmed cases and resulted in >2000 deaths. In August 2009, WHO declared this outbreak as the first influenza pandemic of the 21st century. It is critical to apply lessons learned during previous pandemics to mitigate the public health impact of the ongoing influenza pandemic in 2009. In particular, it is useful to compare the events in Mexico in 2009 to those during the Spanish influenza pandemic of 1918–1919. © 2009 IMSS. Published by Elsevier Inc.

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Reconstructing the Past of Influenza Pandemics

Influenza viruses are RNA viruses with unstable segmented genomes and multiple wild-animal reservoirs for the occurrence of mutations or genetic reassortment (1–2). The resultant antigenic variability, leading to immunologic susceptibility of human populations, is the reason why influenza viruses represent a constant threat to humans. Indeed, influenza viruses are the most dramatic presentation of the rapid and effective spread of viruses in susceptible human and some animal populations leading to epidemics and epizoonoses, respectively (3). In this manner, influenza viruses produce substantial morbidity and mortality (4). In the natural cycle of influenza transmission there is a dynamic animal reservoir mainly found among wild, migratory waterfowl, with some domestic birds secondarily infected providing a continuous source of new influenza strains. In this manner, there could be genetic reassortment with circulating human strains or simply the avian strain may cross the species barrier to directly affect humans such as occurred in the recent outbreaks of influenza (H5N1) (5). The spread of some of these infections has been facilitated by many aspects of modern life such as travel, population displacement and rapid population growth (6).

The rate of transmissibility of influenza viruses and, hence, their feasibility to cause epidemics and pandemics, relies on their adhesiveness to the respiratory epithelium and their efficiency of transmission through droplets (2). These viruses are highly transmissible from person to person with a basic reproduction number (R_o) ranging between 1.1 and 1.8 and a serial interval of 2–3 days (6). Influenza virus transmission in different geographic settings may be

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explained by environmental factors such as temperature and relative humidity. Low temperatures favor viral shedding and spread of the influenza virus, whereas low relative humidity damages the nasal mucosa and affects mucociliary clearance, thus predisposing to infection during winter months (2).

Over the centuries, it is likely that multiple influenza epidemics and epizoonoses have occurred. In fact, the term influenza takes its name from the interpretation by some of the epidemics of respiratory disease in the Middle Ages that were attributed to the *''influence''* of the position of the stars (7). A historical description of a pandemic that swept Asia, Europe, Africa, and the Americas along trade routes was described in 1580. Since then, at least six pandemics were identified in the 19th century (6). Subsequently, in the 20th century, three pandemics of influenza occurred: the 1918–1919 caused by an avian H1N1 strain, the 1957 caused by a reassortant H2N2 strain, and the 1968 caused by a new reassortant H3N2 strain (8).

The epidemiological signature of influenza pandemics includes a shift from affecting high-risk groups defined by age and comorbidities during seasonal influenza (elderly, children, and those with chronic and cardiac comorbidities) to affecting entire populations through multiple waves of cases producing substantial morbidity and mortality and variability in the seasonality of cases during pandemics (4). Historically, the impact associated with these pandemics resulted not only from pneumonia and influenza per se but also from the exacerbation of cardiopulmonary and other chronic diseases that frequently required hospitalization. This places an overwhelming demand on healthcare settings including outpatient clinics, emergency departments, and hospitals. The combinations of these features explains that the death toll of the influenza pandemics of the 20th century has been estimated at 50 million in 1918–1919, 1–2 million during the Asian influenza pandemic of 1957, and ~700,000 during the 1968 pandemic (8).

The H1N1 Pandemics in 1918–1919, 1976, and 2009

In 1976, an outbreak of influenza H1N1 virus of swine origin at Fort Dix, New Jersey led to a global alert that prompted a nationwide vaccination campaign in the U.S. Fortunately, this outbreak did not achieve the feared catastrophic estimates, causing only a minimal number of cases, including more than 200 soldiers and person-to-person transmissions suspected. Unfortunately, there were many cases of neurological complications associated with the use of a whole-cell vaccine that was developed in an urgent fashion (4). Therefore, the outbreak of influenza H1N1 in 1976 was not considered a pandemic.

Unlike the minimal impact of the 1976 outbreak, the initial wave of cases of influenza A (H1N1) virus in Mexico in April 2009 was more reminiscent of the frightening images seen in historical accounts or medical textbooks of the 1918–1919 pandemic (7,9). By June 11, 2009, 74 nation states have cases with ~27,737 confirmed cases and 141 deaths leading WHO to raise the outbreak to phase 6 (7). Since 1968, 41 years later, this is the next influenza pandemic and the first of this century (3). Major outbreaks have been described on most continents due to its worldwide spread. In dealing with the current pandemic, there are unavoidable epidemiologic similarities with the 1918–1919 pandemic (Figure 1) (3).

When examining the 1918 pandemic, it is important to recognize the significant social, cultural, legal, political, and scientific differences that exist between that period and the present (4). However, some resemblance between these two events is the unexpected emergence of a completely new influenza strain affecting immunologically naïve populations and being transmissible from person-to-person and their seasonality pattern, both arising in early spring of 1918 and 2009, respectively (3). The influenza pandemic of 1918–1919 was notorious for having taken place in three distinct waves. The first wave began during the spring and summer months of 1918 in the northern hemisphere (4,8). Most of the morbidity and deaths associated with this pandemic occurred in the initial 6-month period and particularly affected young adults (15- to 34-year-olds) (4). It is probable that the selective crowding and living conditions of young people, particularly those of World War I soldiers, together with the lack of effective therapy for the bacterial complications of influenza, may account for the high mortality of influenza in young adults at that time (4). In the current 2009 outbreak, it seems that the case-fatality rate seen in Mexico may be due to the host response likely seen during the early 20th century cases, motivated by an exuberant inflammatory cytokine storm (1,3). Strikingly, most of the deaths occurred in a very short time, from early 1918 through 1919. In many countries, the 1918–1919 influenza pandemic had catastrophic effects upon urban populations. Large numbers of sick and frightened people overwhelmed the health care system. In many cities and towns, mortuaries and cemeteries were severely strained by rapid accumulation of corpses of victims (4,8). Yet, most deaths during the ongoing pandemic have spread out over a 5-month period and health care systems in Mexico have suffered moderate strain but never to the degree described during the Spanish flu pandemic (7) (Figure 1). Nonetheless, and similar to the 1918–1919 pandemic, Mexico has seen a second, broader wave that spanned from June to August 2009 in the southern states of the Yucatan Peninsula and Chiapas. Nevertheless, a persistent number of cases have been detected in Mexico from April 2009 through September 2009.

The influenza A (H1N1) strain has been associated with an overall low transmissibility and low case-fatality rate in Mexico (0.6%) (9). The estimated transmissibility of the infection (R_0) ranges from 1.4 to 1.6, which is higher than that of seasonal influenza and lower than the three previous