Influenza Pandemic Epidemiologic and Virologic Diversity: Reminding Ourselves of the Possibilities

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The 2009 influenza A (H1N1) pandemic serves as a stark reminder of the inherently unpredictable nature of influenza virus. Although most planning centered on the potential emergence of a wholly new influenza A subtype of avian origin causing the next pandemic, a very different scenario occurred: a mammalian-adapted reassortant variant of a familiar subtype caused the first pandemic of the 21st Century. This pandemic also reminds us of the variability possible with respect to the epidemiology of pandemic influenza, the effects of population immunity to novel influenza strains on age-specific morbidity and mortality, and the potential importance of domestic animals in the ecology of influenza and the formation of new virus strains with pandemic potential. Future pandemic preparedness planning should include addressing gaps in influenza surveillance among nonhuman mammalian species at the animal human interface as part of pandemic risk assessment.

The unexpected origin and subtype of the first influenza pandemic virus of the 21st Century, an influenza A (H1N1) reassortment between North American and Eurasian–lineage swine influenza virus strains of the same subtype as circulating human seasonal influenza A (H1N1), provide another humbling example of the capacity of influenza virus to surprise and of the immense range of possibilities of the virus[1]. Before the 2009 pandemic, a principle planning assumption included that the next pandemic would be caused by a completely novel influenza A subtype, most likely of avian origin. In addition, it was assumed that most of the population would be immunologically naive to this virus, but the virus traveled at record speed to all regions of the world [3–4]. Within 1 month of the initial case identification, 32 countries had reported human cases of 2009 H1N1, and 1 month later, by 15 June, 76 countries had reported cases to the World Health Organization (WHO) [5].

Watching in real time the emergence of a novel pandemic strain has understandably renewed interest in swine influenza and highlighted gaps in influenza surveillance in swine and other mammalian populations where influenza is endemic. Although not new conceptually, a human pandemic caused by a nonhuman mammalian-adapted virus was, until now, only theory, as the pandemics characterized since the advent of modern virology were all caused by the acquisition of new avian genes by a previously circulating human virus [6], and the 1918 pandemic strain is thought to have emerged likely in total from birds [6–7]. The 2009 pandemic was another apt lesson in pandemic preparedness, prompting reconsideration of a wider range of likely scenarios in planning for future pandemics and risk assessment.

Of the 11 proteins coded for by the 8 RNA gene segments of influenza A virus strains, a strain-specific
antibody against the hemagglutinin (HA) surface protein is most important for protection against infection [8]. Antibodies against different subtypes of HA confer little to no protection against an influenza A virus of a different subtype. And antibodies against a certain strain of an influenza A subtype can produce different degrees of cross-reactive antibodies against other strains of the same subtype depending on how closely related the HAs are in terms of antigenicity [9–11]. The degree of genetic distance between the HAs of existing human strains compared to novel influenza virus strains provides important information regarding the likely similarity between strains. However, specific serologic studies using human serum from a wide age range, as was done with the emergence of the 2009 H1N1 [4], must be included in the risk analysis of any novel strain to fully understand population and age group immunity.

The 1918 pandemic was caused by an influenza A (H1N1) virus that later contributed 5 of its 8 genes, combined with 3 avian influenza virus genes, to generate the 1957 Asian influenza (H2N2) virus. This reassortment event was followed by a replacement of the H2 HA and the PB1 gene with avian H3 HA and PB1 genes to create the 1968 Hong Kong influenza (H3N2) virus [6]. Multiple reassortment events, including avian, human, and swine influenza A virus strains, then occurred, from which the 2009 H1N1 virus emerged [12]. The mechanisms by which the pandemic strains evolved from the 1918 virus differ, as did the epidemiology of disease caused by them. The likely ancestor of the 2009 H1N1 virus HA gene is the 1918 virus, which is thought to have entered both pigs and human populations from birds at approximately the same time [7]. This 1918 virus HA then evolved separately in humans and pig populations, diverging both antigenically and genetically. However, the H1 HA in swine-origin influenza virus strains maintained some significant antigenic similarities to the original 1918 virus [13]. These antigenic similarities between the 1918 virus and the 2009 H1N1 resulted in long-term immunity against infection with 2009 H1N1 for many persons born before about 1947, as demonstrated by laboratory studies and by epidemiologic studies showing decreased risk of 2009 H1N1 infection among older adults compared to younger age groups [4, 14]. This immunologic memory in older adults affected the unique epidemiologic characteristics of the 2009 pandemic and resulted in substantially lower impact in the older US adult population as compared to prior pandemics and to seasonal influenza. The “reemergence” of the H1 HA from a nonhuman mammalian-adapted virus has highlighted the necessity of better understanding the diversity of influenza virus strains circulating in other mammalian species. We review the epidemiologic characteristics of the most recent 4 pandemics (1918, 1957, 1968, and 2009) and discuss consideration of future influenza pandemic risk assessment and novel influenza A surveillance given the diversity of H1 and H3 virus strains and other novel influenza A subtypes circulating in nonhuman mammalian populations that may pose a pandemic threat.

GEOTEMPORAL SPREAD

After its initial recognition in North America, the 2009 Pandemic Influenza A (H1N1) virus (2009 H1N1) rapidly spread throughout the world. The first identified cases had their illness onset in late March 2009 and were confirmed as 2009 H1N1 on 15 and 17 April 2009 [15]. Cases were then rapidly confirmed in Mexico and Canada, quickly followed by reports from Europe, South America, Asia, New Zealand, and Israel [16]. By 29 April 2009, the WHO had declared a phase 5 pandemic alert (sustained outbreaks in at least 2 countries in one WHO region, pandemic imminent), followed by phase 6 (pandemic in progress with sustained outbreaks in countries in at least 2 WHO regions) on 11 June 2009 [17].

Initial reports from Mexico included large numbers of severe illnesses and deaths [18]. However, as more epidemiologic data on the clinical spectrum of illness became available from multiple countries, including Mexico, the relatively low risk of severe illness or death from this new pandemic strain as compared to prior pandemics became apparent. Estimated case fatality ratios have ranged from 0.048% to 1.23% [19–20], with lower-than-expected numbers of deaths in part due to relative sparing of adults 65 years and older, a contributing factor being immunity via their previous exposure to the 1918 virus [4]. The immunity in older adults, however, appears to have had little to no effect on the spread of the virus, with the 2009 H1N1 virus spreading efficiently and resulting in large outbreaks in the Southern Hemisphere as early as 3 months after the first detection of the virus [3, 21].

While many temperate Southern Hemisphere countries had outbreaks consistent with or slightly earlier than their typical seasons, the United States and Canada experienced two distinct waves of influenza activity, the first occurring from May to July 2009 and the second from September through December, with activity peaking in the United States during the week of 24 October 2009. Activity continued throughout the winter and spring 2010, but at much lower levels [22]. This contrasts with the 1957 and 1968 pandemics, each of which started in Asia and spread globally. In 1957, the pandemic was first identified in Hong Kong in May, while the first cases in the United States were discovered a month later. The US epidemic accelerated once school began in September, a pattern repeated in the 2009 pandemic. This was followed by a subtle early spring wave, with an absence of widespread outbreaks but with a clear rise in excess mortality [23]. There was thought to be very little pre-existing immunity to the 1957 H2N2 virus [24], which resulted from the reassortment between the drift variant of the 1918
H1N1 virus and an avian virus replacing both the HA and the neuraminidase (NA) 1918 genes with the HA and NA genes from the avian virus. The lack of immunity in the population to the H2 HA and N2 NA contributed to the 1957 pandemic’s severity and widespread illness across age groups.

The 1968 pandemic likely originated in southern China, was first identified in Hong Kong in July, and caused the first outbreaks in the United States in late October 1968 [25]. However, neither preceding summer nor subsequent winter or spring waves were detected during the 1968–1969 influenza season. A possible contributing factor may have been preexisting immunity to the N2 NA among most of the population, which was unchanged from the Asian Flu H2N2 virus. The resulting immunity against the NA, while not as protective as immunity to the HA protein, likely reduced the severity of disease caused by the new H3N2 virus [9].

**MORBIDITY AND MORTALITY**

The Centers for Disease Control estimated that, from April 2009 through mid-March 2010, ~60 million Americans had been infected with the pandemic H1N1 2009 virus [26–27]. This equates to an ~17% attack rate, similar to the 21% attack rate estimated for the 2009 pandemic based on antibody testing of serum samples from persons in the Pittsburg, Pennsylvania area [28] and close to the 15% estimated attack rate during the first season of the 1968 pandemic [29]. Unlike 1968, however and very similar to 1957, the age-specific attack rates in 2009 were highest in the young and generally decreased with age [28, 30–31]. In contrast, in 1968, age-specific attack rates were relatively constant, with a small decline in the 15–35 year age group [32].

Age-specific mortality also differed among the pandemics (Table 1). Although precise comparisons of age group and overall mortality among the 4 most recent pandemics is not possible given differences in methods used to estimate influenza-related deaths, overall patterns and relative impact can be compared. Age-specific mortality from the 1918 pandemic produced a W-shaped curve, with increased mortality among young children and young adults and a smaller increase in deaths among elderly persons; 99% of 1918 pandemic influenza-related deaths are thought to have occurred among those <65 years of age. Age-specific mortality in 1957 followed the U-shaped curve of seasonal influenza, with the majority of those killed being ≥65 years of age [35]. This contrasts with 1968, when approximately half of the deaths were among those <65 years of age, and the 2009 H1N1 pandemic, where preliminary estimates suggest that approximately 87% of the deaths occurred among persons <65 years of age (Table 1)[26–27]. This high proportion of deaths in younger ages is likely attributable in part to preexisting immunity against 2009 H1N1 among many older adults and is in stark contrast to seasonal influenza, in which ~90% of deaths typically occur among those ≥65 years of age [36].

**SIGNIFICANT PAST GENETIC EVENTS AND THEIR IMPLICATIONS**

The 2009 H1N1 pandemic virus descended indirectly from the 1918 pandemic virus. The 1918 virus is thought to have entered human and swine populations at approximately the same time from an avian host, but then it evolved along different trajectories in pigs and people such that the virus strains diverged genetically and antigenically, forming a classical swine influenza A (H1N1) virus lineage in pigs. During 1997–1998, the classical swine H1N1 virus, which to that point had not undergone any reassortment events since its introduction in approximately 1918, reassorted with the H3N2 human virus and an avian virus, creating a new lineage of triple reassortant virus strains with classical swine H1 and N1 genes. This swine triple reassortant has subsequently circulated widely among North American pig

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**Table 1. Estimated Number and Proportion of Deaths in Persons <65 Years of Age in the United States During Pandemic and Nonpandemic Periods.**

<table>
<thead>
<tr>
<th>Influenza Season</th>
<th>Total Number of Estimated Influenza Deathsa</th>
<th>Proportion (%) of Deaths in &lt;65 Year Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918 H1N1 Pandemic [33]</td>
<td>546,000b</td>
<td>99</td>
</tr>
<tr>
<td>1957–1958 H2N2 Pandemic [33]</td>
<td>66,000b</td>
<td>36</td>
</tr>
<tr>
<td>1968–1969 H3N2 Pandemic [33]</td>
<td>16,400b</td>
<td>48</td>
</tr>
<tr>
<td>Nonpandemic (Seasonal) Influenza Average 1976/1977–2002/2003 [34]</td>
<td>22,461c</td>
<td>11</td>
</tr>
<tr>
<td>2009–2010 H1N1 Pandemic [26–27]</td>
<td>11,687d</td>
<td>87</td>
</tr>
</tbody>
</table>

a The methods of estimating influenza deaths between pandemics and for seasonal influenza have varied over time. Estimates are not directly comparable but are included to illustrate the wide range in potential impact.
b Estimated excess pneumonia and influenza deaths attributed to influenza [33].
c Estimated excess respiratory and circulatory deaths attributed to influenza [34].
A number of other reassortant virus strains with human influenza virus–lineage H3 and H1 HAs also emerged among North American swine, contributing further to the substantial increase in the genetic heterogeneity among swine influenza virus strains circulating since 1998 compared to 1918–1997, when only one lineage of influenza virus is known to have circulated in North American swine herds [1, 12]. Thus, the most significant occurrence in the genetic history of the 2009 pandemic might prove to be the triple reassortant event in swine, which produced a number of antigenically divergent progeny available for adaptation to circulation in humans or for further reassortment with other virus strains of avian or mammalian origin. Figure 1 shows the close evolutionary relationship between North American swine lineage virus strains and the pandemic strain. The nucleotide sequences coding for the hemagglutinin protein for the 2009 H1N1 pandemic virus strains can be seen originating from the same common ancestor as those from the North American swine virus strains and not from those of the human seasonal group.

The swine-origin triple-reassortant virus strains, with their apparent increased capacity for reassortment, may represent an important source for the emergence of other novel influenza A virus strains. Other lineages of virus strains that are currently or have caused identified outbreaks in pigs include the avian lineage H1N1 virus strains widely circulating among pigs in Europe and Asia, which are antigenically distinct from both circulating human H1N1 virus strains and North American swine-lineage virus strains, and an H2N3 virus, which caused outbreaks in at least 2 US pig herds in 2006 [38]. These H2N3 virus strains had avian HA and NA genes but contained internal genes from the North American swine-lineage triple-reassortant virus strains [38]. Other influenza A virus strains of avian origin have also been shown to cause sporadic illness in humans and pigs, including H4N6, H9N2, and H5N1 [39–41]. In addition, both North American and Eurasian avian lineages of H7 virus strains have caused illnesses in humans [42].
CONCLUSION

The 2009 pandemic, the cause of which was a new reassortant of a familiar subtype (H1N1) and not a wholly new subtype, highlights the labile nature and adaptive capacity of influenza virus strains and the importance of animals in human influenza ecology. The signal should be clear: the potential emergence of reassortant influenza virus strains is evolving along a different genetic path from the H3 HA in human virus strains, resulting in genetic and antigenic divergence [44]. Thus, H3 virus strains in pigs may, in time, represent another potential source for an H3 subtype influenza A virus with the potential to cause widespread outbreaks in humans. Although the recognized capacity for pigs to serve as a mixing vessel for the generation of reassortant influenza virus strains [45] highlights the importance of swine in influenza ecology, mammalian-adapted virus strains in other species along with avian influenza virus strains that have shown the potential to infect humans should not be ignored as a potential threat to human health. As new virus strains with pandemic potential are identified, assessment of population-based immunity along with the virus’s genetic and antigenic characteristics is critical for understanding the potential impact on different age groups.

Other nonhuman mammalian-adapted virus strains are additional potential sources for the next pandemic. An equine H3N8 virus that circulates widely in horses, for example, recently jumped species, causing outbreaks and establishing a new H3N8 lineage among domestic dogs [43]. Both the equine and canine H3N8 virus strains are antigenically and genetically distinct from human H3 virus strains. No human infections from either the canine or equine H3N8 virus strains have been reported. However, their mammalian origin, their antigenic and genetic dissimilarity from known human H3 virus strains, and close human contact with these animals suggest that these virus strains may also have the potential to cause illness in humans. Figure 2 shows a distant common ancestry for circulating human seasonal H3 virus HA genes and the equine and canine H3 HAs, indicating wide genetic, and likely antigenic, difference between the human H3 virus strains and the canine and equine H3 virus strains. In addition, the H3 HA introduced in 1997–1998 from the human population into swine influenza virus strains is evolving along a different genetic path from the H3 HA in human virus strains, resulting in genetic and antigenic divergence [44]. Thus, H3 virus strains in pigs may, in time, represent another potential source for an H3 subtype influenza A virus with the potential to cause widespread outbreaks in humans. Although the recognized capacity for pigs to serve as a mixing vessel for the generation of reassortant influenza virus strains [45] highlights the importance of swine in influenza ecology, mammalian-adapted virus strains in other species along with avian influenza virus strains that have shown the potential to infect humans should not be ignored as a potential threat to human health. As new virus strains with pandemic potential are identified, assessment of population-based immunity along with the virus’s genetic and antigenic characteristics is critical for understanding the potential impact on different age groups.

References


