REVIEW ARTICLE

CURRENT CONCEPTS

Historical Perspective — Emergence of Influenza A (H1N1) Viruses

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On April 17, 2009, officials at the Centers for Disease Control and Prevention (CDC) confirmed two cases of swine influenza in children living in neighboring counties in California.[1] Here we take a perspective from systems biology to review the series of evolutionary and epidemiologic events, starting in 1918, that led to the emergence of the current swine-origin influenza A (H1N1) strain (S-OIV), which is widely known as swine flu. This article is one of two historical articles on influenza A (H1N1) viruses in this issue of the *Journal*.[2] Our review focuses on the key steps that characterize this viral evolution (Fig. 1).

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EMERGENCE OF A VIRUS

SIMULTANEOUS APPEARANCE IN HUMANS AND SWINE (1918)

Before 1918, influenza in humans was well known, but the disease had never been described in pigs.[3] For pig farmers in Iowa, everything changed after the Cedar Rapids Swine Show, which was held from September 30 to October 5 of that year.[4] Just as the 1918 pandemic spread the human influenza A (H1N1) virus worldwide and killed 40 million to 50 million people, herds of swine were hit with a respiratory illness that closely resembled the clinical syndrome affecting humans. Similarities in the clinical presentations and pathologic features of influenza in humans and swine suggested that pandemic human influenza in 1918 was actually adapted to the pig, and the search for the causative agent began.[5,6]

The breakthrough came in 1931 when Robert Shope, a veterinarian, transmitted the infectious agent of swine influenza from sick pigs, by filtering their virus-containing secretions, to healthy animals.[7] Infectivity of the filtrate was subsequently confirmed by Smith, Andrewes, and Laidlaw,[8] who used the ferret model of influenza infection to document transmissibility for both human and swine viruses.

Shope furthered the notion that the human pandemic strain of influenza A (H1N1) and the infectious agent of swine influenza were closely related by showing that human adult serum could neutralize the swine flu virus.[4] In a mouse model, samples from patients ranging from newborn infants to 76-year-olds were tested for their ability to neutralize a swine influenza virus strain. This work showed that nearly all serum samples from subjects who were at least 12 years of age were able to protect mice from challenge with a virus isolated from pigs in 1930, whereas those from children older than 1 month but under the age of 12 years had no neutralizing antibody.[4] These experiments suggested that the swine influenza virus, or an antigenically similar one, had been in circulation in the human population and had originated from the 1918 pandemic strain. Advanced virologic and molecular studies of viral relatedness support Shope's early hypotheses.[9,10]

Viral adaptation to a new host species is a complex process, involving adapta-

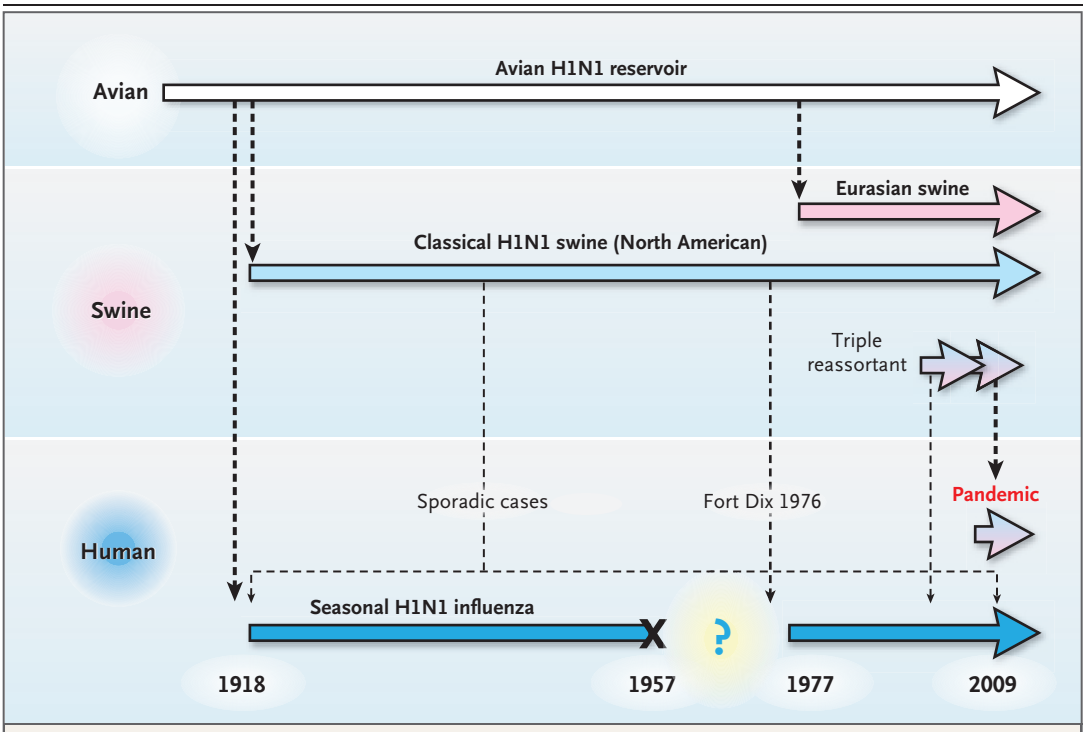

Figure 1. Emergence of Influenza A (H1N1) Viruses from Birds and Swine into Humans.

The diagram shows the important events and processes in the emergence of influenza A (H1N1) viruses during the past 91 years. Avian, swine, and human populations are represented in the top, middle, and bottom of the diagram, respectively. Epidemic or zoonotic viruses are shown as wide horizontal arrows (white for avian viruses, light blue or pink for swine viruses, and dark blue for human viruses). Cross-species transmissions are shown as vertical dashed lines, with thick lines for transfers that gave rise to sustained transmission in the new host and thin lines for those that were transient and resulted in a self-limited number of cases. Principal dates are shown along the bottom of the diagram. The disappearance of H1N1 in 1957 most likely represents competition by the emerging pandemic H2N2 strain in the face of population immunity to H1N1. The reemergence in 1977 is unexplained and probably represents reintroduction to humans from a laboratory source.

tion to new cell-surface receptors,[11] changes in cell tropisms, innate immunity, and mechanisms of transmission.[12] Influenza A (H1N1) virus overcame these barriers in 1918 to emerge from an avian source simultaneously in swine and humans.

ANTIGENIC DIVERGENCE OF HUMAN AND SWINE INFLUENZA (1918–1930)

Shope also discovered that antibody specificity against the 1918 human influenza virus rapidly diverged from that of swine influenza virus. Very young infants, still protected by maternal antibody, and persons over the age of 20 years all had neutralizing antibody against swine influenza but not always against human influenza.[4] Because the presence of antibody against swine influenza followed a much different age distribution from that against human influenza at the time,[4] it was thought that immunity was probably due to exposure to swine influenza in 1918 rather than heterologous antibody cross-reactivity. The absence of antibodies against influenza A (H1N1) swine virus in children born in 1919 or later is evidence that the virus rapidly mutated to a new antigenic variant. Since then, genetic differences in hemagglutinin (HA) show an early divergence between the human and swine viruses.[13]

EVOLUTION OF THE 1918 VIRUS IN HUMANS (1918–PRESENT)

Analysis of full genome sequences of representative influenza A (H1N1) viruses from 17 countries and five continents that were sampled between 1918 and 2006 shows that all eight segments of the virus have had generally congruent patterns

of evolution over time.[14] Thus, human influenza A (H1N1) virus has not acquired new gene segments from avian or other sources. The descent patterns for the genomes have been generally linear, with each new yearly strain successively showing an accumulation of mutations over time. However, there has also been clear phylogenetic evidence of several distinct intrasubtype reassortant events among viruses from various sublineages, so that the overall evolutionary pattern is not truly linear but tightly networked.[14]

INTRASUBTYPIC REASSORTMENT OF HUMAN H1N1 VIRUS (1947)

In 1947, the seasonal vaccine did not provide any protection against influenza. Jonas Salk attributed this finding to changes in the virus that had occurred since the previous year.[15] Vaccine failure, combined with rapid viral dissemination and more severe disease, prompted further study of the genetic characteristics of this virus, which was dubbed "A-prime" to distinguish it from earlier serosubtypes.[15,16] The virus that was responsible for the post–World War II epidemic was found to vary significantly from the 1943 influenza A (H1N1) strain, especially in the HA segment, where five antigenic sites were involved in amino acid changes.[16] The HA segment of the 1947 virus, which was discovered to have emerged through intrasubtype reassortment, was more representative of later HA genotypes, whereas the neuraminidase (NA) segment was conserved, which may have prevented the development of a fully pandemic phenotype.[14]

EXTINCTION OF HUMAN H1N1 VIRUS (1957)

Influenza A (H1N1) abruptly disappeared from humans in 1957 and was replaced by a new reassortant virus that combined genes from the H1N1 strain and an avian virus. This new influenza A (H2N2) strain contained three new segments from the avian source and maintained the other five segments from the H1N1 strain of 1918 lineage.[17] After this pandemic subtype emerged, human influenza A (H1N1) was not detected again until 1977.[18] Reasons for the complete disappearance of this strain in 1957 are not clear, but it is likely that high levels of existing homologous immunity, coupled with a burst of heterologous immunity from the new H2N2 strain, were sufficient to eliminate the virus.[19]

SPORADIC CROSS-SPECIES TRANSFERS (1958—PRESENT)

Serologic evidence of swine flu infection in humans was documented in 1958,[20] and the first isolation of swine influenza virus from a human occurred in 1974 from a patient with Hodgkin's disease who lived on a pig farm.[21] Infection of humans with swine influenza virus is often unrecognized because of its clinical similarity to human disease. A seroprevalence study showed markedly increased odds of elevated antibody against swine influenza A (H1N1) virus in swine workers, as compared with nonexposed control subjects.[22] During the study, one subject was identified with active swine influenza infection. A self-collected nasopharyngeal culture grew a triple reassortant H1N1 isolate (A/Iowa/CEID23/2005)[22] of the genotype known to have circulated in swine in the United States since the late 1990s.[23] Transmission of swine influenza to humans continues sporadically and is related to occupational and environmental exposures, including family members of people in high-risk groups.[24-26]

In January 1976, an outbreak of respiratory disease occurred among soldiers returning to an Army base in Fort Dix, New Jersey. A novel virus H1N1 A/New Jersey/76 was identified as the cause of the epidemic that resulted in serologic evidence of 230 cases and one death.[27] Because of careful characterization of the soldiers and the nature of basic training, the outbreak at Fort Dix provided an ideal setting for investigation and modeling of the epidemic events.[28] The basic reproductive number (R_0) is the number of infections caused by an infected person who is introduced into a completely susceptible population. The estimated R_0 for the Fort Dix swine influenza virus was 1.2, substantially lower than that calculated for human pandemic and seasonal viruses, for which values range from 1.8 to 2.0.[28] Once the virus saturated the tight social-contact structure of the military training base, its transmission potential was insufficient to ignite a larger epidemic in the civilian population at large. The emergence of swine influenza at Fort Dix led to the implementation of a mass vaccination program, which resulted in 40 million civilian vaccinations and 532 cases of the Guillain–Barré syndrome (a rare side effect of influenza vaccination), including 32 deaths.[29]

H1N1 Reemergence in Humans (1977)

Even though human influenza A (H1N1) virus had not circulated since 1957 and the swine influenza A (H1N1) virus that had been identified at Fort Dix did not extend outside the base, in November 1977, the H1N1 strain reemerged in the former Soviet Union, Hong Kong, and northeastern China. This strain affected primarily young people in a relatively mild presentation.[18,30] Careful study of the genetic origin of the virus showed that it was closely related to a 1950 strain but dissimilar to influenza A (H1N1) strains from both 1947 and 1957. This finding suggested that the 1977 outbreak strain had been preserved since 1950.[30] The reemergence was probably an accidental release from a laboratory source in the setting of waning population immunity to H1 and N1 antigens.[19,31]

Seasonal Influenza A (H1N1) (1977–Present)

Each pandemic strain of influenza replaced the previous circulating virus until influenza A (H1N1) reemerged in 1977, when for the first time in known interpandemic influenza history, two serotype A viruses began to cocirculate. Although the peak prevalence of this virus alternates with a more often dominant subtype H3N2, it has nevertheless maintained a continual presence during seasonal epidemics.[32]

Emergence of New H1N1 Strains in Swine (1979–Present)

Influenza A (H1N1) viruses were confirmed to be circulating in the North American pig population as early as 1930 but were not isolated in European pigs until 1976, when a shipment of pigs from the United States to Italy introduced classical influenza A (H1N1) to the continent, where it quickly spread throughout the swine population.[33] A few years later, a new avian-origin influenza A (H1N1) virus was introduced in the European pig population from wild ducks.[34] By 1979, this strain had largely replaced the classical North American A/H1N1 strain.[35,36] In China, similar events have occurred.[37,38] A new triple reassortant swine influenza virus was identified in the North American swine population in 1998.[23,39] Genetic analysis of these viruses revealed a relatively complex genetic makeup, with five gene segments derived from the North American classical A/H1N1 swine virus, but the polymerase gene segments derived from either birds (PA and PB2) or humans (PB1).[40,41]

Sporadic Cross-Species Transmission of Triple Reassortant Virus (1998–2009)

The first recognized case of human disease from a swine influenza triple reassortant influenza A (H1N1) virus occurred in a 17-year-old who had been exposed to pigs at a slaughterhouse in Wisconsin.[42] Investigators have recently reported 11 known human cases of infection with the triple reassortant viruses between 2005 and 2009; most of these patients had been exposed to swine.[41] Given the relative infrequency with which viruses are amplified and characterized from humans with influenza, it is likely that many more cases have occurred.

Reassortment of Two H1 Swine Viruses (2008–2009)

In April 2009, near the end of the usual influenza season in the Northern Hemisphere, the first two cases of S-OIV were identified in the United States.[43] The CDC confirmed that these cases were caused by a genetically similar swine virus that had not been previously identified in the United States.[44] Genetic analysis of the strains showed that they were derived from a new reassortment of six gene segments from the known triple reassortant swine virus, and two gene segments (NA and matrix protein) from the Eurasian influenza A (H1N1) swine virus lineage.[43,45]

Competition between Seasonal and Newly Emerged Viruses

It remains uncertain how forcefully S-OIV will emerge and compete against the currently circulating 1918-derived seasonal H1N1 viruses. The 2009 lineage carries three gene segments that share a common (albeit remote) descent from the 1918 virus with the human seasonal virus: segments encoding for nucleocapsid, nonstructural, and (perhaps most important) HA proteins.[43,45] In studies of human B-cell memory response in survivors of the 1918 pandemic, neutralizing antibody against HA in the recombinant 1918 virus was specific and very long-lasting.[46] Partial heterotypic immunity has been shown in animal models and by somewhat attenuated disease in humans who have had previous influenza infection, especially immunity against viruses contain-

ing similar HA subtypes.[47] Although antibody responses against other viral proteins have not been shown to be important in conferring immunity, responses to NA may provide partial protection and could explain why disease severity in the 1947 influenza epidemic was attenuated in spite of significant changes in the HA protein.[16]

Cell-mediated immunity may also play a role in competition among influenza strains. Although cytotoxic T lymphocytes do not confer clinically significant protection against infection in humans, they can mediate cross-reactive and heterotypic protection in response to conserved viral proteins in mouse models, and reduced viral shedding has been seen in humans, even in the absence of antibodies against HA and NA.[47,48] Cytotoxic T lymphocytes that are generated by seasonal influenza viruses against conserved epitopes might provide heterotypic immune responses that could dampen transmission, even in the absence of measurable antibody protection.

CONCLUSIONS

The emergence of influenza A (H1N1) 91 years ago led to a disastrous global pandemic. That virus is thought to have emerged almost simultaneously from birds into humans and swine. In contrast, S-OIV probably emerged from swine into humans. Although the immediate genetic event that led to the emergence of the new pandemic threat was a reassortment between two influenza A (H1N1) swine viruses, these two viruses were actually the products of at least four independent avian-to-mammalian cross-species transmissions, with at least four previous reassort-

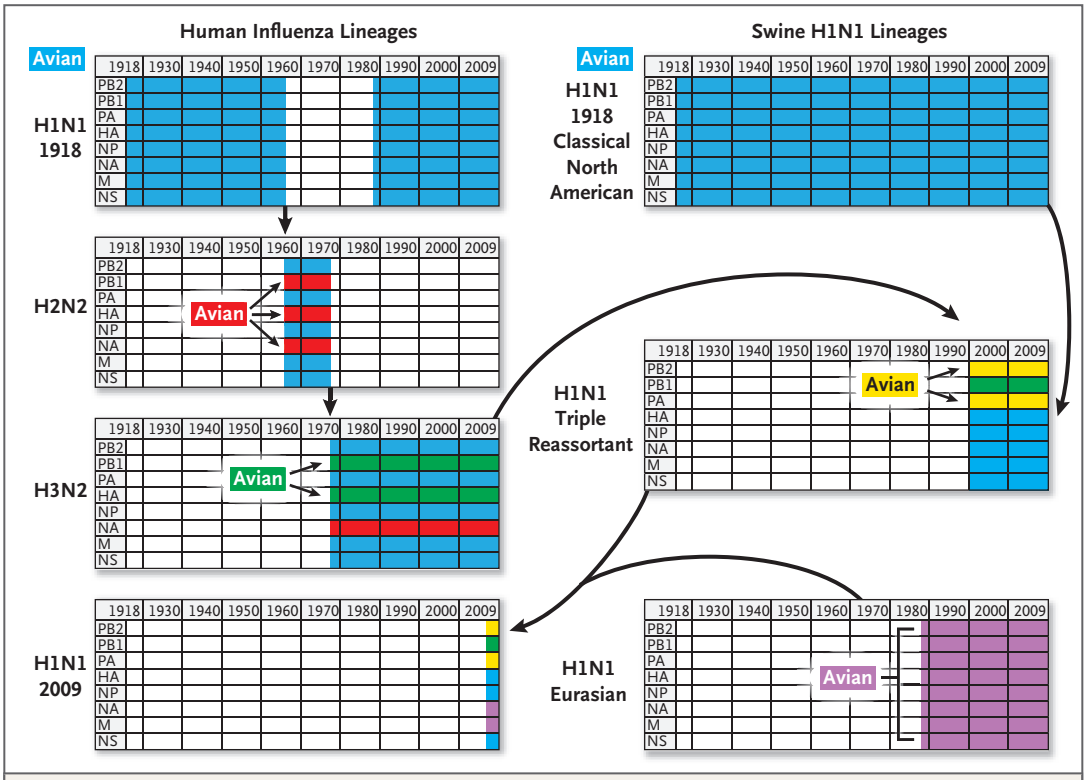

Figure 2. History of Human and Swine Influenza Lineages.

The diagram shows the full genetic history of the swine-origin influenza A (H1N1) virus (S-OIV). Each of the seven charts represents the genetic composition of a particular influenza virus lineage over time. In each chart, gene segments are shown along the left side, and dates from 1918 to 2009 are shown along the top. Color coding shows the avian origins and history of each gene segment in each influenza virus lineage. The influenza virus gene segment reassortments that gave rise to the H2N2 and H3N2 strains of human influenza A are shown on the left side of the diagram, along with human influenza A (H1N1) viruses or their descendants. Swine influenza A (H1N1) viruses are shown on the right side of the diagram.

ments of gene segments among avian, human, and swine-adapted viruses (Fig. 2). One consequence of this intertwined history is that S-OIV shares three gene segments with current seasonal human influenza A (H1N1) virus and three segments with human seasonal influenza A (H3N2) virus. It is not known whether low levels of cross-immunity against historically remote shared epitopes might confer some clinical protection against the newly emerging virus.

The history of influenza A (H1N1) virus is punctuated by frequent, sporadic cross-species transmissions from swine to humans. Although the sporadically transmitted swine viruses are sufficiently pathogenic in humans to cause clinically apparent disease, they are rarely transmitted among humans. Exposure and infection are necessary but not sufficient for a new epidemic virus to emerge; the virus must also adapt and transmit.[12] The one prominent exception to the general rule that these swine viruses are not transmitted among humans was the outbreak at Fort Dix. This virus was never transmitted beyond the military installation, probably because the intrinsic transmissibility of the virus was simply too low. Yet the global response to this outbreak was forceful, especially given that the outbreak self-quenched. The decision to mass-vaccinate the U.S. population resulted in the unfortunately large cluster of Guillain–Barré cases. Perhaps an even more serious consequence was the accidental release of human-adapted influenza A (H1N1) virus from a research study, with subsequent resurrection and global spread of this previously extinct virus, leading to what could be regarded as a "self-fulfilling prophecy" epidemic. The 1998 triple reassortant influenza A (H1N1) swine virus has shown what appears to be a proclivity to jump the species barrier and cause swine-to-human infections.

The emergence of yet another serious global health threat from an animal source highlights the critical need for deeper understanding of zoonotic viruses, including in vivo studies of pathogenesis in animals, field epidemiologic studies, and surveillance in animal populations, along with the development of computational models. The presumptive origins of the S-OIV influenza epidemic outside the United States show the critical importance of international collaboration in efforts to predict and control future pandemic threats.

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