

Historical thoughts on influenza viral ecosystems, or behold a pale horse, dead dogs, failing fowl, and sick swine

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Objectives To understand human influenza in a historical context of viral circulation in avian species, mammals, and in the environment.

Design Historical review.

Setting Global events in a variety of circumstances over more than 3,000 years time.

Sample Comprehensive review of the historical literature including all major publications on pandemic and panzootic influenza.

Main Outcome Measures Influenza pandemics, panzootics, major epidemics and epizootics, and instances of interspecies transmission of influenza A.

Results Extensive documentation of human and animal influenza over many centuries suggests that influenza A viruses have

adapted to a variety of species and environmental milieu and are capable of switching between many different hosts under widely varying circumstances.

Conclusions The genetic elements of influenza A viruses circulate globally in an extensive ecosystem comprised of many avian and mammalian species and a spectrum of environments. Unstable gene constellations found in avian species become stable viruses only upon switching to secondary hosts, but may then adapt and circulate independently. It may be desirable to think of influenza A viruses as existing and evolving in a large ecosystem involving multiple hosts and environments. Implications for understanding human influenza are discussed.

Keywords Equine, history, influenza.

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The importance of understanding how pandemic influenza A viruses (IAV) emerge, and the nature of their relationship with IAV of birds and mammals, has been emphasized by the 2009–2010 H1N1 swine-origin influenza pandemic, and by 13 years of enzootic/epizootic/human “spill-over” circulation of highly pathogenic H5N1 avian IAV (HPAI) that have not yet, despite grave concerns, become pandemic. The threat of animal influenza is, however, not new [Figure 1, references (1, 2)]. Thousands of possible outbreaks, spanning centuries, and even millennia have been reported but never examined systematically. Lacking such organized historical information, in this brief review we nevertheless draw attention to events, themes, and trends in the occurrence of (apparent) non-human influenza as reported in scientific and non-scientific sources up to the beginning of the “microbial era”.³ In doing so, we attempt to broaden the picture of influenza and to suggest that it is useful to view influenza viruses as existing and circulating

within a large complex ecosystem which includes not only wild waterfowl, but also various other avian and mammalian hosts and environmental milieus.

Current understanding of influenza as an avian enzoonosis

All pandemic influenza viruses, like those of 1918, 1957, 1968, and 2009, ultimately acquired some or all of their gene segments from the avian IAV gene pool.⁴ Additionally, zoonotic infections with both low pathogenicity (LPAI) and HPAI viruses have sporadically occurred.⁵ Diverse IAV are widely distributed in their natural reservoir, numerous wild avian species – especially the aquatic *Anseriformes* and *Charadriiformes* waterfowl – around the world,^{6–10} where they infect predominantly the lower intestinal tract^{9,11} and are transmitted via the fecal-oral route. Although not reservoir hosts of avian IAV, domesticated



Figure 1. *The Race Track (Death on a Pale Horse)*, by Albert Pinkham Ryder (1847–1917), ca. 1896, oil on canvas, Cleveland Museum of Art. Katherine Anne Porter's (1890–1980) classic novella *Pale Horse, Pale Rider*,² which describes both the 1918 death of her lover and her own near death from influenza has fixed in the imagination of many readers an association between the chilling biblical imagery of the “pale horse” (*Revelation* 6:8) and the enormous death toll of the 1918–1919 pandemic.

Galliformes (e.g., chickens, turkeys, quails) are susceptible, after adaptation, to infection with wild bird-derived IAV.^{12,13} Avian IAV are antigenically and genetically diverse; all 16 identified hemagglutinin (HA) and nine neuraminidase (NA) subtypes have been identified in a great variety of combinations.^{8,9,14} The existence of a large number of different HA–NA subtype combinations, without evidence of genetic linkage among the specific segments, indicates that mixed IAV infection and reassortment in wild birds is extremely common^{15,16}, and it further suggests that in wild birds IAV exist as transient genome constellations.¹⁵ It is also likely that IAV can be maintained in the environment, e.g., in pond water and mud;^{17–19} the significance of this in relation to the complex ecobiology of IAV is still poorly understood¹⁴ but remains an important subject for further research.

As will be discussed, IAV maintained in wild birds have frequently switched to such new hosts as horses, swine, humans, and most frequently domestic poultry. But the mechanisms by which avian IAV cross species barriers, whether causing “dead-end” infections or onward transmission in the new hosts, are largely unknown. Stable host switching likely involves acquisition of numerous mutations, depending on the virus and the host species^{12,13,20} and is likely achieved by a variety of different evolutionary pathways, leading to different sets of genetic changes in each such event. Because adaptation to a new host seems to limit return to the wild bird IAV gene pool,^{13,21} emergent viruses that begin as transient gene constellations in their natural avian hosts must go on to evolve as distinct

and stable eight-segment genome configurations within the new host.^{5,15} Although the historical record is silent on the question, similar mechanisms may well have been causing influenza viral emergences for many centuries.

Influenza infections in animals: historical background

A major problem with review of the historical literature for evidence of animal influenza is that the further one goes back in time, the more difficult it becomes provisionally to identify influenza. Before the 16th century, epidemics of all kinds were usually recorded by laymen without medical vocabularies, and without appreciation of etiology, pathogenesis, natural history, distinctive/pathognomonic signs, or any of the modern ways in which we now diagnose, identify, and classify specific diseases. Even such distinct diseases as measles and smallpox were long confused with each other.

Human influenza can nevertheless be provisionally recognized historically when there is evidence of such unmistakable clinical and epidemiologic features as explosive epidemic febrile coughing that kills the young, the old, the infirm, and pregnant women. Looking for historical evidence of animal influenza is more complicated. Until the late 1700s, there were no veterinarians or veterinary schools, and until the late 19th century no organized poultry industry. Reports of animal diseases generally came as anecdotes or “asides” from physicians, farmers, or interested citizens; diseases we now recognize to be of different etiologies were frequently confused with each other, and until the 20th century many believed that what we now know to be different diseases based on their different etiologies were instead single diseases whose manifestations differed under the influence of various ill-defined environmental, or telluric/atmospheric/climatic influences. The quality of this patchwork animal disease record remains poor until the late 19th century. Reference works on the historical occurrences of human and animal influenza are widely available,^{1,22–39} including an important multivolume series begun by Corradi⁴⁰ but often depend for primary source material on subjective and unscientific information such as speculative epidemic/epizootiologic treatises, eye witness accounts, diaries, and hearsay.

Claims for animal influenza in the ancient literature

The classical literatures of Greece, Rome, and other ancient civilizations, as well as records from the Dark and Early Middle Ages, are packed with reports of human and animal disease outbreaks. In most cases, the diseases in question are so vaguely described that identification with

modern diseases is difficult or impossible. For example, Homer's *The Iliad* describes an epidemic of 9-day duration at the beginning of the Trojan War (ca. 1194 BC) that first affected horses and dogs, then men. Some 19th- and 20th-century observers considered this disease to be influenza,^{31,41,42} even though *The Iliad* does not mention cough or typical epidemiologic features. On similarly shaky ground is the description by veterinary physician Absyrtus of an alleged equine influenza epizootic in 330 AD.⁴³

A major epidemic of influenza-like disease followed Carolman's (Charlemagne's) army across Europe in 876–877, having first arrived in Italy to spread northward, a directional pattern that was documented repeatedly for certain influenza pandemics occurring between 1510 and 1761, and also killing dogs and birds.^{44,46} Another epidemic “cough that spread like the plague”⁴⁴ in 927 AD [but long confused by scholars with an epidemic 100 years earlier, in 826–827 AD⁴⁵] again first struck Italy and spread northward to affect the whole European continent, and again caused illness and death in humans, dogs, and birds.^{29,32} Scholars have speculated that this was the first recorded pandemic of influenza, a possibility consistent with its appearance in southern Europe and its rapid spread northward.

The emphasis in these early accounts on horses, birds, and dogs is curious but inconclusive in implicating influenza. Domestic animals like horses and dogs were ubiquitous and probably suffered from many endemic and some epidemic illnesses that were considered indistinguishable from each other at the time. It would not be surprising if,

during epidemic prevalences, coincidental observations of clinically similar illnesses in domestic animals would be noted by observers who lacked a scientific understanding of infection. References to avian deaths might also reflect formulaic Greek literary traditions attributing bird deaths to epidemics of any sort, or arguments favoring miasmatic spread. While tantalizing, many references to deaths of birds and domestic animals associated with possible human influenza outbreaks in the ancient literature are ultimately inconclusive.

Influenza in the middle ages

Although some historians consider the first influenza pandemic to have occurred earlier [frequently mentioned candidates include the European epidemics of 927, 1173 and 1386–1387^{5,45}], there is little doubt that the three pandemics of the 16th century, occurring in 1510, 1557, and 1580, ushered in a major influenza pandemic era (Figure 2). Although several writers commented non-specifically about ill animals,^{43,47} to our knowledge none of them reported specific influenza-like illnesses in large domestic animals. A curious footnote was however recorded by Daniel Sennert (1572–1637), the physician who first scientifically described scarlet fever, in noting that: “...names applied to [the 1580 pandemic disease] included febrile catarrh, suffocating fever, epidemic catarrh, coughing epidemic, [and] contagious headache. The Germans called [it] ‘the chirp’, the sheep cough, the sheep disease, [and] the chicken malady, because sick persons were suffering [as with] the coryza of chickens” [(48); Figure 3]. The identity of the disease

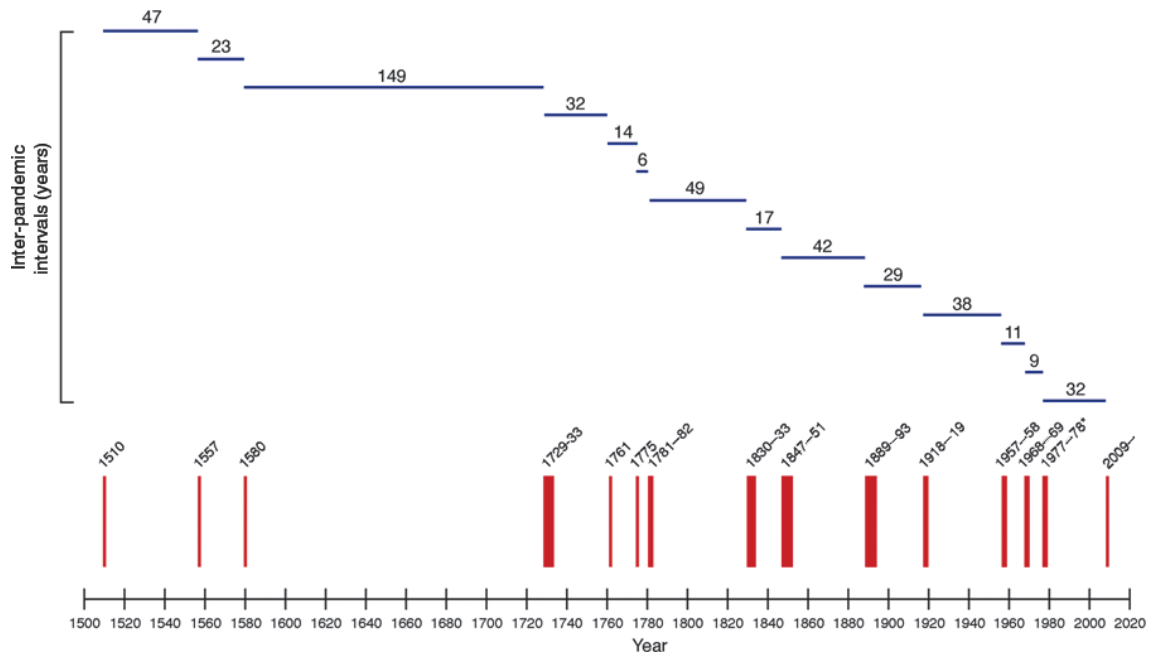


Figure 2. Influenza pandemics since 1510 [modified from (5)].

CAPUT XVII.

De Catarrho & Tussi epidemia.

IN Februm Malignarum catalogo merito & illa adscribitur, quæ cum catarrho & tussi epidemia, anno 1580. sub Syrii ortum, maximè autem circa novilunium æquinoctii autumnalis, totam penè Europam, imò ferè omnes mundi regiones pervagata est, & hinc inde varia nomina accepit. Appellabatur enim catarrhus febrilis, febris catarrhosa, febris suffocativa, catarrhus epidemius, tussis epidemia, cephalalgia contagiola. Germani nominabant den Zey / den Schaffshustē / die Schaffranckheit / das Hinerwehe / quod ægri instar gallinarum coryzâ vexarentur.

Figure 3. The first page of Chapter 17, “On the catarrh and coughing epidemic”, in Daniel Sennert’s account of the 1580 influenza pandemic.⁴⁸ Sennert refers obliquely to a “coryza of chickens”, but it is not known whether avian influenza occurred during the pandemic.

causing “chicken coryza” noted in 1580 is not known, although the same term had been used at the time of the 1557 pandemic, possibly in referring to croup-like respiratory signs in children.⁴⁹ Neither HPAI nor Newcastle disease was recognized until more than 300 years later. We are unaware of other reports of similar avian illnesses in the voluminous literature on the 1580 pandemic which, however, has rarely been examined systematically, and never to our knowledge for evidence of animal disease.

An association between human and equine influenzas, 1648–1916

An H7N7 equine IAV was first isolated during a 1956 epizootic⁵⁰ but is now likely extinct;⁵¹ an H3N8 equine IAV, detected in the early 1960s⁵² still circulates enzootically to cause significant disease and economic burden.⁵³ Equine H3N8 viruses can infect humans experimentally,⁵⁴ and it has been noted by several groups that human birth cohorts from the late 19th century, particularly those born before about 1893, demonstrated serologic reactivity with equine H3N8 viruses many decades later.⁵⁵

Before the virologic era, equine epizootics highly suggestive of influenza were documented repeatedly, beginning in

1299 with an equine epizootic⁴³ coincident with a widespread European influenza epidemic. In this epizootic: “the horse carried his head drooping, would eat nothing, and ran from the eyes”.²² Twenty-nine years later, in 1328, an equine epizootic in Yemen, later attributed to influenza,^{1,56} coincided with a major European epidemic of apparent influenza. In 1404, yet another equine epizootic was associated with a major European influenza epidemic.^{34,38,45}

Between 1581 and 1728, a 147-year period in which pandemic influenza seemingly disappeared,⁵ countless local and regional influenza outbreaks were documented in Europe, the New World, and elsewhere. During this time, a close temporal–geographic association between equine and human influenza-like disease activity began to be documented in hundreds of medical, epidemiologic, and other publications. The first well-documented occurrence in the Renaissance followed a modest 1647–1648 human outbreak at the end of the Thirty Years’ War in Spain, in French soldiers in Germany, and in their cavalry horses.^{1,23,43} A decade later, in 1657–1658, one of the era’s most significant European influenza epidemics caused high human mortality [Oliver Cromwell (1599–1658) apparently died of it] accompanied by cases of influenza-like illnesses in horses.³⁵

From 1658 until the early 20th century, outbreaks consistent with equine influenza were associated with major human outbreaks, epidemics, and pandemics more often than not. Considering several hundred published reports of major influenza occurrences between 1688 and 1888 that we have examined (obviously subject to errors related to, among other things, the possibility of not recognizing outbreaks that occurred), and considering only those with reasonably complete historical information, by our count there were 112 (of 200) years in which either significant epidemics/pandemics or equine epizootics of apparent influenza were documented in Europe. Of these 112 years, combined equine epizootics/epidemics were documented in 67; equine epizootics only in 25; and epidemics only in 20. The pattern in the western hemisphere during the same interval was somewhat different: of 56 years in which human or equine influenza was documented, both horses and humans were involved in 21 years; humans only in 25 years, and horses only in 10 years.

Regardless of geographic locale, equine influenza typically appeared about 3 weeks before human influenza,^{42,57} a pattern first noted in 1688 in England and Ireland.⁴³ But in a few instances, this pattern was reversed, e.g., in 1776 and 1780 human outbreaks preceded equine outbreaks.^{31,42,43,47,57} Commenting on a 1688 influenza epidemic, one chronicler wrote: “...an epidemic catarrh followed all over Europe, beginning among horses and ending with men as is frequently the case”,⁵⁷ then observed the same pattern five and again 10 years later [1693 and

1698^{1,57}]. Well before the year 1700, a strong association between human and equine influenza had been widely observed and widely accepted as a typical pattern of influenza occurrence.

Although these were non-pandemic years, the equine association appears to have been about as strong during major (e.g., European-wide) epidemics as during more local outbreaks. When the next pandemic appeared (in 1729), equine cases were again seen.⁵⁸ It was also noted that older horses and horses that had had influenza in the past were often immune.⁵⁹ With better epizootic documentation, and occurring with or without coincident epidemics, it was eventually noted, between 1815 and 1873, that major equine epizootics occurred in almost exact 4-year cycles,⁶⁰ presumably reflecting equine birth cohort susceptibility. Moreover, it came to be understood that although human non-pandemic influenza in this era was often a seasonal (winter) event, when epidemics were associated with equine epizootics they tended to occur in the spring or fall, the usual seasons in which equine influenza prevailed. Conceivably, during the warmer months horses and humans alike were more likely to be traveling and moving about in agricultural work, and thereby more likely to acquire and transmit influenza.

In 1727, a year of low-level endemic and epidemic influenza in Europe, an apparently new phenomenon was documented: an extremely explosive equine epizootic that far overshadowed the associated epidemic. Large scale European equine epizootics or panzootics recurred in 1750 and 1760.^{1,41,60,61} In 1750: "About the middle or latter end of December, the most epidemic and universally spreading disease among horses that anyone living remembered [and] analogous to [human epidemic] influenza...now particularly attacked the horses...[and] spread through all England in almost an instant, and...raged in Denmark at the same time...there was scarce an instance of a horse in town or country but had it...It vanished about the middle of January [1751]"⁶¹

The 1872 western hemispheric equine panzootic

The most explosive equine panzootic ever documented was first recognized in pastured horses in three farm communities north of Toronto in late September, 1872, at a time when human influenza was not prevalent.^{43,60} From Toronto, it spread quickly along rail lines, with separate paths going eastward into Upstate New York and westward into Michigan, radiating outward from these new foci in every direction, eventually spreading via shipping routes to the Caribbean and Central America. By some accounts, the panzootic stopped at Panama, where there were no horses.⁶² Ill horses exported to Europe were quarantined in port; although enzootic and epizootic equine influenza prevailed in Europe that year, principally in England and

Germany, there is no good evidence of importation from America.

Horses, mules, and circus/menagerie zebras were all affected, and there were numerous outbreaks and single cases of mild influenza in humans as well, often linked to equine exposures.⁶³ National epidemics of influenza in 1873 and 1874 that seemed to spare old people were linked by some physicians to the equine epizootic,⁶⁴ but as mild seasonal influenza had already been prevailing in some locales in late 1872, a causal association is speculative. The human form of the epizootic disease became popularly known throughout the United States as the "epizooty" or "zooty";⁶³ a term that ended up as a plot device in a famous novel published exactly a century later.⁶⁵

Onset of the disease in horses was acute with fever and a "short, dry, husky cough"^{43,66} followed within about 2 days by loosening cough, nasal discharge, swollen eyelids, labored breathing, loss of appetite, increased thirst, painful swallowing, weakness, dullness, and prostration. Complications included pneumonia and dropsy: "oedematous swellings of the limbs, beneath the chest and belly, and in the lower part of the head".⁴³ Necropsies of horses that died acutely revealed evidence consistent with primary viral pneumonia in some instances and secondary bacterial pneumonia in others.⁴³ Almost all urban epizootics were explosive with urban attack rates approaching 100%. The death rate was in the range of 2%, including not only acute deaths from pneumonia but also dropsical complications, the latter occurring in about 1–15% of surviving horses and associated with a fatality rate of 20–50%. Dropsy appeared as a "trailing" epizootic about 3 weeks after the peak of epizootic influenza; it predominated in some cities, but not in others, and was widely observed to occur in older horses that had been overworked or poorly cared for when ill with influenza (*The Chicago Daily Tribune*, 14 and 15 November 1872).

The 1872 panzootic literally shut down the United States for several weeks, preventing travel, transportation, mail delivery, and delivery of goods and provisions. Truck deliveries ground to a halt as winter approached, causing coal prices to skyrocket across the nation (*The Chicago Daily Tribune*, 17 November 1872; *The New York Times*, 27 November 1872). Physicians were unable to reach their patients (*The New York Times*, 16 November 1872). Fire stations around the country either brought in oxen from the countryside or trained teams of young men to pull fire wagons. Nevertheless, a fire in Boston's financial district got out of control, and much of the city burned down on 9 November [Figure 4; (67)], allegedly in part because slower moving fire wagons drawn by teams of young men could not respond quickly enough (*Boston*, 11 November 1872). Equine epizootics were common across the United States for the next 30 years, but with the exception of major epizootics in 1880–1881 and 1900–1901, they tended



Figure 4. The Boston fire of 9 November 1872 burned down much of the financial district of Boston.⁶⁷ Among other factors, the devastation of the fire has been attributed to the ongoing influenza panzootic (*Boston*, 11 November 1872). Because most of the equine work force was incapacitated, fire stations throughout the United States recruited teams of men to pull fire wagons. The slow response times of the Boston teams are believed by many to have led to the fire getting out of control. Above, onlookers on Devonshire Street assemble around Steamer Number 10, from the Fire House on Mount Vernon Street. At far right a fireman with a hose sprays the ruins.

to be local, to affect mostly young horses, and to feature much lower attack rates.^{68,69} One of the last widespread equine influenza epizootics in the United States occurred in the winter of 1915–1916, concurrent with a major epidemic season.⁷⁰

Were the countless reports of influenza-like diseases in horses, recorded over centuries, really influenza? We are unaware of pathological material available before modern times that might answer this question definitively. Circumstantial but arguably strong evidence for equine influenza includes the consistency of clinical signs, the temporal–geographic association with human influenza, high explosivity and rapid horse-to-horse spread – with increased explosivity in crowded stables – and a consistent incubation period for both equine and human secondary cases. Eighteenth and nineteenth century authorities believed the two diseases were the same disease and believed them to be transmitted in both directions. The infrequency in the differential diagnosis of other clinically consistent respiratory diseases of high explosivity is also of note.

At a time when horses were ubiquitous in virtually all rural and urban settings, it is thus conceivable that they played a role in influenza virus maintenance and evolution analogous to that of pigs in the modern era. Although the cause of the 1889 influenza pandemic is unknown, various archeological data suggest the possibility of an H3 HA, and possibly also an N8 NA.^{54,55,71–73} Equine influenza-like disease was common in the 1889 pandemic, but the virus clearly spread globally by means of person-to-person spread.⁷⁴ The possibility that the 1889 pandemic was

caused by an H3N8 equine influenza virus that had become adapted to humans, and which then spread pandemically, is highly speculative but cannot yet be ruled out. Alternatively, if the 1889 pandemic virus was truly of H3N8 subtype, it is conceivable that, in a manner analogous to the persistent “classical” swine H1N1 virus derived from the 1918 pandemic virus, it was at some point transmitted from humans to horses and the virus or some of its gene segments may persist in horses today.

Influenza in dogs, cats, and other mammals

Influenza-like illnesses in dogs and cats, apparently acquired from either horses or, less commonly, humans, have been reported for centuries during epidemics and equine epizootics,^{1,62} probably representing in most instances occasional “dead-end” host transmission. Apparent canine influenza was reported, for example, during the 1675–1676, the 1760, and the 1767 epidemics/equine epizootics,^{1,43,57,59,61} and substantial outbreaks of possible influenza in dogs were seen during the 1782 pandemic, anecdotally associated with transmission to parrots,⁷⁵ and the Australian epidemic of 1851–1852.⁷⁶ Similar canine and feline illnesses and deaths were reported frequently in the 1872 equine panzootic as well and have more recently been reported in the 2009 H1N1 pandemic. Influenza cases and deaths in racing greyhounds have been recognized for over a century (*The San Francisco Call*, 11 November 1901;



Figure 5. During a 1900–1901 equine influenza epizootic, the US champion racing greyhound *For Freedom* died of “an attack of the epizooty, which is prevalent here among horses” (*The San Francisco Call*, 11 November 1901).

Figure 5). Equine H3N8 viruses have recently become stably adapted to dogs⁷⁷ and are now evolving in dogs by antigenic drift,⁷⁸ establishing another extra-avian IAV reservoir. Different lineages of this virus are now spreading internationally,⁷⁹ a situation without recognized precedent in the historical literature. Other species such as large cats, ferrets, minks, seals, and other mammals have also occasionally been infected.

Influenza in pigs

Despite the strong historical association between human and equine influenza, and the extensive documentation of many swine diseases over several centuries,^{1,33} including swine outbreaks in association with poultry outbreaks, we have been unable to identify any epizootics that appear highly consistent with swine influenza until the fall wave of the 1918 influenza pandemic.⁸⁰ At that time, the pandemic virus seems to have been transmitted from humans to pigs, thereby splitting off into two lineages, one human, the other porcine, from which viral descendants were isolated in the 1930s.^{81,82} These viral lineages persist today, having both contributed genes to the 2009 H1N1 reassortant pandemic virus.⁸³ Conceivably, in the modern era, pigs have replaced the once ubiquitous horse as a secondary extra-human mammalian influenza reservoir.

Numerous influenza subtypes isolated from pigs cause either enzootic infections or self-limited outbreaks globally. Since 1998, several lineages of triple reassortant viruses containing genes from “classical” swine H1N1, human H3N2, and avian influenza viruses have emerged to cause enzootic disease in pigs in the United States and elsewhere.^{84,85} Other fully avian or human IAV-derived viruses, or reassortant viruses containing genes of avian, swine, and/or human IAV origin, have been associated with less widespread disease in swine, e.g., H1N1, H1N2, H1N7, H2N3, H3N1, H3N2, H3N3, H4N6, and H9N2 subtypes.⁸⁶ Equine H3N8 viruses were recently isolated from pigs in China without evidence of stable host switching.⁸⁷

In the late 1970s, yet another H1N1 lineage emerged to cause enzootic disease in Eurasia by genomic adaptation of an avian IAV.^{88–90} Still in circulation, this virus played a reassortment role in the emergence of the 2009 pandemic H1N1 virus,⁹¹ which caused swine outbreaks in many places around the world⁹² after apparent back transmission from humans to pigs. The history, genetic makeup, and behavior of this virus⁴ suggest significant risk of future swine virus epidemics/pandemics. Other swine-adapted IAV have caused zoonotic infections of at least 50 humans, with seven fatalities, between 1958 and 2005,⁹³ including a 1976 outbreak at Fort Dix, New Jersey, associated with human-to-human transmission, in which classical swine H1N1 infected 230 soldiers and caused one death.⁹⁴

Because pigs are susceptible to infection with both avian and human IAV strains,^{10,88} they have been considered a possible intermediate host (“mixing vessel”) for the generation of IAV of pandemic potential.^{10,95} This dual susceptibility was previously attributed to the presence of both sialic acid (SA)- α 2,3-galactose (“avian-like”) and SA- α 2,6-galactose (“human-like”) linkages on the glycocalyx of epithelial cells lining the swine upper airway and trachea.⁹⁶ However, recent lectin histochemistry studies have shown little SA- α 2,3-galactose in the upper airway,⁹⁷ thus swine likely have an SA receptor pattern similar to that of humans.^{98,99}

Influenza in poultry

In the past decade, many documented human infections with avian IAV have occurred, prominently in association with H5N1 HPAI epizootics in Eurasia and Africa.¹⁰⁰ H5N1 HPAI viruses initially caused a 1996 poultry epizootic in southern China, followed within a year by a Hong Kong epizootic that caused 18 human cases and six deaths.^{101,102} H5N1 strains continued to circulate thereafter in China, reappeared in epizootic form in 2003, and then spread widely,¹⁰³ resulting in the appearance and spread of genetically and antigenically diverse strains, including reassortants with other avian IAV.¹⁰⁴ The H5N1 panzootic is unique in causing the deaths from infection and culling of millions of poultry in 64 countries on three continents,¹⁰⁵ and in producing, since 2003, 499 human spill-over cases with 295 deaths in 15 countries (WHO, as of 8 June 2010), and rare instances of self-limited human-to-human transmission.¹⁰⁶ The H5N1 panzootic is also unique in causing infections and deaths in numerous wild bird species¹² and occasional infections of wild and domestic mammals.^{107,108}

In 2003, an H7N7 HPAI virus caused a poultry epizootic in the Netherlands and spread regionally. Before the epizootic was contained, at least 86 poultry workers and three of their contacts had become infected and developed conjunctivitis with or without influenza-like illnesses; one of them died.¹⁰⁹ Similarly, two persons developed influenza conjunctivitis during an outbreak of H7N3 HPAI in Canada in 2004.¹¹⁰ During the past decade, at least eight other major poultry epizootics have occurred, caused either by novel emerging H5 or H7 subtype HPAI viruses, or in one instance by an H9N2 LPAI virus,¹² leading to occasional human infections.¹⁰⁹

Did human infection with avian IAV occur before the virologic era? As noted earlier, the vague references to bird deaths and disappearances during historical influenza epidemics, and the curious passage of Sennert noting “coryza of chickens” in the 1580 pandemic,⁴⁸ are of uncertain meaning. An oft-cited fatal 1776 poultry epizootic associated with an influenza pandemic was probably not of influenza origin⁴³ and was not fatal to humans, nor were other temporally

associated poultry outbreaks that were consistent with influenza such as one that spread across Northern Italy in 1789.¹¹¹ In any case, the historical record indicates that poultry influenza outbreaks have never been shown to cause more than a limited number of human spill-over cases.

H5N1 (then called “fowl plague”) was recognized as a disease entity in 1878¹¹² and between 1901 and 1903 was shown to be caused by a filterable agent.^{113–116} Epizootiologic links were soon made to transmission from pet birds to humans, and to epizootics of pneumo-enteritis in pigs,¹¹⁵ although it is not certain that these diseases were influenza. Fowl plague virus was identified as influenza A in 1955.¹¹⁷ Isolation of IAV from wild ducks in 1974⁷ led to the realization that wild aquatic birds are the natural reservoir for IAV.¹⁰

With this historical picture in mind, it is curious to note that between 15 November and 15 December 1872, 6 years before the recognition of “fowl plague”, an explosive, fatal, and still mysterious epizootic in poultry, prairie chickens, turkeys, ducks, and geese occurred over much of the populated United States in temporal–geographic association with the panzootic of equine influenza that had just begun.^{43,60} First recognized in Poughkeepsie, New York, on 15 November (*The New York Times*, 16 November 1872), whole flocks were usually struck simultaneously, with fatality at or near 100%. Prominent features included upper respiratory signs of “a cold or influenza”, slimy discharge emitted from the beak, dark streaks in the neck, “dizziness” or “staggering fits”, crawling away from the flock into holes or corners, and in most cases death within 12–18 hours (*The [New York] World*, 17 November 1872; *The New York Herald*, 18 November 1872; *The Iowa State Reporter*, 20 November 1872; *The Janesville [Wisconsin] Gazette*, 22 November 1872).

Concentrated mostly in the Northeast and Midwest, the epizootic spread outward with tremendous speed from the upper Hudson River area of New York State. According to the newspapers, it “follow[ed] in the tracks of the dread [equine] Epizootic” (*The Richwood [Ohio] Gazette*, 28 November 1872), allegedly spreading “all over the country” by 19 November (*Indiana Progress*, 21 November 1872) and without exception occurring in locales that were or had been experiencing equine influenza. Outbreaks in poultry often occurred immediately after they had been allowed to roost or peck in stables that held ill or recently ill horses (*The New York Herald*, 19 November 1872; *The [Baltimore] Sun*, 21 November 1872; *The Janesville [Wisconsin] Gazette*, 27 November 1872; *The [Davenport, Iowa] Daily Gazette*, 28 November 1872).

The epizootic poultry disease – amply recorded in the national press, but apparently not studied scientifically – could have been caused by other agents. “Chicken cholera” (linked to *Pasteurella multocida* in 1878) was well known in 1872 but was considered to be a different disease than the

1872 epizootic disease (*The [New York] World*, 19 November 1872). Newcastle disease was not recognized until 1926, does not seriously affect horses, pigs, or humans, and in any case seems somewhat less consistent with epizootic features described in 1872. The consistent clinical features and epidemiologic evidence, coupled with a remarkable temporal–geographic association between equine influenza and poultry outbreaks of an explosive and fatal illness, appear consistent with influenza transmission. Although “back-transmission” of a mammalian-adapted influenza virus to an avian host would seem unlikely based on current (but limited) understanding of IAV host switching, it is noteworthy that both classical swine H1N1 and the 2009 H1N1 pandemic virus have caused symptomatic epizootics in turkeys;^{118,119} 138 years after it occurred, the poultry epizootic associated with the 1872 equine influenza epizootic remains a mysterious footnote in the ever mysterious history of influenza.

Conclusions

Although IAV are rightly considered to be avian viruses resident in a large reservoir comprised of many species of wild waterfowl and shorebirds, they are uniquely promiscuous in undergoing an extraordinary degree of genetic change within their primary hosts, and within the host’s aquatic environment – comprised of water, mud, and organic material – and they frequently switch hosts to infect many other avian and mammalian species. The genetic elements of IAV circulate globally in an extensive ecosystem comprised of many avian and mammalian species and a spectrum of environments around the world. In their natural reservoirs, IAV can be thought of not as stable viral entities but as transient genome constellations.¹⁵ Genomic stability seems to be an unnatural state and may be only attainable when an eight-gene segment constellation finds its way into an “unnatural” secondary host. What IAV can do when they become stabilized by adaptation is not fully explored, but the breadth of the viral repertoire is inferred by the historical literature suggesting viral infection of, adaptation to, and onward transmission by a variety of hosts including humans, horses, pigs, dogs, and domestic poultry. It may be desirable to more broadly conceive of IAV as being adapted not just to a few avian reservoir hosts but to a complex environment populated by many different species in a variety of stabilizing environmental milieux. The historical literature on influenza, though frustrating in its general lack of corroboration by modern scientific methods, suggests that IAV may be more evolutionarily flexible than we have realized. It would not be surprising if additional secondary reservoir hosts were involved in viral maintenance, evolution, and transmission. Influenza history suggests that there is still much to learn, and many surprises probably still await us.

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