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Pandemic influenza: certain uncertainties

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SUMMARY

For at least five centuries, major epidemics and pandemics of influenza have occurred unexpectedly and at irregular intervals. Despite the modern notion that pandemic influenza is a distinct phenomenon obeying such constant (if incompletely understood) rules such as dramatic genetic change, cyclicity, "wave" patterning, virus replacement, and predictable epidemic behavior, much evidence suggests the opposite. Although there is much that we know about pandemic influenza, there appears to be much more that we do not know. Pandemics arise as a result of various genetic mechanisms, have no predictable patterns of mortality among different age groups, and vary greatly in how and when they arise and recur. Some are followed by new pandemics, whereas others fade gradually or abruptly into long-term endemicity. Human influenza pandemics have been caused by viruses that evolved singly or in co-circulation with other pandemic virus descendants and often have involved significant transmission between, or establishment of, viral reservoirs within other animal hosts. In recent decades, pandemic influenza has continued to produce numerous unanticipated events that expose fundamental gaps in scientific knowledge. Influenza pandemics appear to be not a single phenomenon but a heterogeneous collection of viral evolutionary events whose similarities are overshadowed by important differences, the determinants of which remain poorly understood. These uncertainties make it difficult to predict influenza pandemics and, therefore, to adequately plan to prevent them.

"The certainty of uncertainty is the only kind of certainty."John Allen Paulos [1]

Pandemic and epidemic influenza have been appearing unexpectedly for at least 500, and possibly 1000 or more, years [2–10]. Varying pandemic features include generation by different viral genetic mechanisms, association with mammalian epizootics/enzootics, occurrence at irregular intervals, and differences in when they recur, who they attack, and their clinical severity [6]. Such significant variations suggest a need to reconsider what is known about, and what remains to be learned about, the nature, characteristics, and behavior of influenza pandemics as infectious disease phenomena.

In examining the rich and complex historical information about influenza, it should be borne in mind that the virologic data only reaches back to the 1930s and that inconclusive archeoserological data reach back only a few decades before that. Influenza historians must

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accept provisional—and unprovable—assumptions that diseases documented in earlier eras as having characteristic clinical and epidemiological features of influenza were in fact influenza and not diseases caused by different known or extinct infectious agents.

Such issues become more problematic as one goes back further in time to eras in which medical concepts were less well developed and in which surviving epidemic accounts were fewer and more isolated in time and place. A related problem is that with only scattered accounts, we cannot be sure that influenza, had it occurred, would have been recognized as a distinct disease of interest, recorded in enough detail that we could recognize it now, and be preserved over centuries and millennia. The historical record might thus be potentially biased by the "loss" of important epidemic/pandemic information.

As a rough guide to evaluating the evidence examined here, it can be generally said that until the early 1500s, there was little or no appreciation that the epidemic disease we now identify as influenza was a distinct and periodically recurring disease—those epidemics that were recorded, usually by chroniclers or monks, tended to be recorded in a similar formulaic/non-specific fashion that might omit features we now consider pathognomonic or distinctive; until the mid-1700s, influenza was not viewed as being a distinct clinical–pathological–epidemiological entity; until the 1830s, there were few reliable measurements of influenza mortality rates, age-specific mortality rates, or case-fatality rates; and until the late 1800s, influenza morbidity rates were generally not calculated. It is important to realize that, lacking modern concepts and knowledge, observers in earlier eras might not have been able to describe the occurrence of influenza in the way we would describe it, or be able to recognize or rule it out, today. This places a burden on us to objectively evaluate imperfect evidence in light of modern knowledge that was not known at the time the evidence was originally recorded.

WHAT WE KNOW ABOUT PANDEMIC INFLUENZA

Influenza pandemics have been occurring for at least five centuries

"Pandemic" (from the Greek, "of all the people") generally refers to the widespread occurrence of a disease over one or more regions of the world. In recent decades, it has sometimes been applied more specifically to the global spread of influenza viruses that contain novel hemagglutinin [HA] genes [6,10–12]. Influenza pandemics also can be described by their geographic extension as trans-regional (affecting two or more adjacent regions of the world, e.g. Africa and Europe), inter-regional (affecting two or more nonadjacent regions of the world), or global [6].

As noted above, possible influenza pandemics of the pre-virology era, identified by contemporary observers and by historians applying clinical and epidemiologic criteria, cannot always be confirmed because historical reports are incomplete, of variable quality, mostly limited to European sources, and unverifiable by modern virologic criteria (Tables 1–4; Figures 1–3). Moreover, if "mild" pre-modern influenza pandemics had occurred, they might not have been recognized or documented, potentially biasing historical perception toward greater pandemic explosiveness or severity.

In the first of four empirically designated historical periods (1194 BC to 875 AD; Table 1), evidence for pandemic influenza is insufficient because of imprecise clinical and epidemiologic descriptions and limited ability to detect trans-regional spread of disease. The "Plague of Athens," which spread to Europe from the Middle East and Africa in 430 BC, is an exception, but it probably was not influenza [13].

Between 876 AD and 1491 AD, many explosive pan-European or local epidemics of febrile coughing disease have been attributed by historians to influenza (Table 2; Figure 1) [2,14–77], but European contact with the outside world remained so limited that pandemic spread, had it occurred, might not have been appreciated. Such widespread epidemics were nevertheless considered sufficiently important to be specifically named, for example, in 1307 AD *le tac* (French, the sound of a coughing "hack"), in 1327 AD *slaedán* (Irish, "prostration"), and in 1357 *influenza di freddo* (Italian, "influence of the cold") or *una influenza* [16,75,78]. Evidence consistent with influenza in the Dark and Middle Ages includes characteristic signs and symptoms, pulmonary involvement, broad, explosive, and directional geographic spread, high attack rates, and elevated mortality in the elderly and debilitated, in infants and small children, and in pregnant women (Table 2) [2–5,14,17,71,74,75,79–82]. Although with one possible exception in 1414 [30], epidemic involvement beyond Europe was not documented; historians have speculated that some influenza epidemics in this era were true pandemics. These include, for example, the epidemics of 876–877 and 927—both of which arrived in Italy and spread northward, a pattern later described for known pandemics (see below)—and the widespread European epidemics of 1173, 1311, and 1386–1387 [3–5,33,51,65,77,83,84].

Between 1492 and 1728 (Table 3; Figure 2), a period of European exploration and colonization, trans-regional, inter-regional, and global pandemics were documented by printed reports and by a burgeoning medical literature. Three 16th century pandemics, separated by 47-year and 23-year intervals, respectively, preceded a 147-year pandemic-free period (1581–1728). Recurrent epidemics of a mysterious new disease called "sweate" ("English sweating sickness"; *sudor anglicus*), appearing between 1485 and 1551, have been plausibly attributed to influenza [85,86]. During this time, independently occurring epidemics and trans-regional pandemics appeared in the newly discovered Western Hemisphere [31].

Between 1729 and the present, influenza pandemics returned in force and exhibited a variety of epidemic characteristics discussed below. Because the pandemics of 1889 and thereafter have been well studied and considerable information about them is widely available in most medical libraries [6,87,88], we do not address the modern era but instead emphasize the less well-appreciated occurrences of influenza between 1729 and 1888 (Table 4; Figure 3).

The basic clinical picture of pandemic influenza has not changed for centuries

Common features include abrupt febrile onset, cough, myalgia, malaise, and prostration [3,5,33,51,89–94]. These symptoms generally resolve in about 1week but occasionally are complicated by miscarriage, premature labor, infant death, maternal death, and severe or fatal pneumonia in the elderly and debilitated [2–5,14,17,43,71,74,75,78–82,95]. Pulmonary involvement was documented as early as 1400 and possibly centuries earlier [51,77,82].

When influenza autopsies began to be reported in the early 1700s, they generally revealed characteristic features of tracheitis and severe purulent pneumonia [22,96–98]. The clinical picture of pandemic influenza and its complications as recorded 500 and more years ago is typical of pandemic influenza in 2011 [93,94].

Most basic epidemiologic features of pandemic influenza have not changed for centuries

Including directional geographic spread, explosiveness with high attack rates, and increases in population mortality.

An association between human population movement and pandemic/epidemic spread was noted early on (Table 2), for example, an epidemic that followed Carolman's army across Europe in 876–877 [3–5,77] and an epidemic associated with European travel during the "new century celebrations" of 1400 [82]. At the local level, observers repeatedly noted 4-week to 6-week prevalences within, and rapid spread of influenza between, major cities, followed by directional spread outward into surrounding towns, and from there to villages and farms [67].

Pandemic origin in Asia or Eastern Russia with westward spread to Europe has been noted repeatedly for more than 500 years. The origins of several other pandemics have been linked to the Western Hemisphere (e.g. 1761), or have not been localized [99]. For example, the origin of the 1918 pandemic has been attributed to, among other locations, China, the USA, and France, largely on the basis of circumscribed outbreaks of severe/fatal pneumonias within the 2 years before spring 1918, considered to be consistent with influenza complicated by secondary bacterial infection [100–103]. All three 16th century pandemics arrived in Mediterranean Europe from the southeast trade routes and spread northwesterly. Two hundred years later, the pattern changed dramatically: pandemics apparently originating in Asia in 1729, 1733, 1781, 1833–1836, and 1889 spread westward through Russia and into northern Europe and then spread southward, the last of these (1889) being mapped with some precision (Figure 4) [104,105].

This reversed European directionality corresponds roughly in time to the establishment of the Hanseatic League and the rapid expansion of cities along the northern European Baltic coast, including St. Petersburg, possibly providing efficient new overland and Baltic Sea routes of population movement. Global spread of the 1957 pandemic was primarily by shipping routes and, to a lesser extent, by air routes [106–108]. In contrast, the pandemics of 1968 and 2009 followed airline routes, representing ever more modern means of efficient population movement. But even such earlier pandemics as those of 1782 (before clipper ships) and 1918 (before commercial air travel) spread almost as rapidly as the recent pandemics of 1957, 1968, and 2009. It has now become possible to follow country-to-country importations in "real time" using molecular virologic techniques [109–111].

Influenza has long been considered the most explosive of the epidemic diseases. In ancient times, apparent influenza was described as a "cough which spread like the plague" (in 927 AD [4,71]), an "evil and unheard of cough" that "affected everyone far and near" (in 1173–1174 [50,76]), and a catarrh "with rapid diffusion to the head and chest" [14] that "raged universally" (in 1327–1328 [47]). It caused attack rates allegedly as high as 90%

[14,81,112], so that “hardly anyone remained healthy” (in 1386–1387 [14]), and in 1729, it “spread from Russia like a hurricane” [92].

In addition to explosiveness, pandemic influenza was shown centuries ago to cause mortality in the elderly and debilitated [113], in infants and small children [82], and in pregnant women [95]. It was repeatedly associated with increases in burials or with increased population mortality [2–5,14,17,43,71,74,75,78–82,95]. Mortality peaks were reported as early as the 14th century [16] and quantified with vital registration data as early as 1558 [67,95]. In the 19th century, more sophisticated independent calculations estimated adult influenza case-fatality rates of 2% or higher [2,3,66,80,81,92], although the figures could well have been unknowingly inflated by incomplete recognition of milder cases. The most significant cause of death in the 1889 and 1918 pandemics appears to have been bacterial pneumonia. Evidence suggests that this may also have been true in earlier pandemics, and it seems to have remained at least partly true in the pandemics of the antibiotic era, that is, 1957, 1968, and 2009 [114–122].

With the exception of certain unexplained epidemiologic features of the 1918–1919 pandemic, discussed in the next sections, the basic epidemiologic features of pandemic influenza appear unchanged from those of 500 and more years ago [93,94].

Pandemic/epidemic and panzootic/epizootic influenza have co-existed for centuries

In the 20th and 21st centuries, concentrated pig farming has led to the establishment of separate American (human virus-descended) and European (avian virus-descended) lineages of H1N1 swine viruses, of swine lineages of H3N2 and various swine–human reassortant viruses [123,124], and of swine infections with human influenza viruses. A 1976–1977 “swine flu” outbreak in humans quickly disappeared following limited person-to-person spread [125–127], but the 2009 H1N1 pandemic—caused by an antigenically related virus [128]— spread quickly and globally. Its history and genetic makeup as a lineal descendent of a number of reassortments between avian, human, and swine viruses (Figure 5) suggest a significant risk of future swine virus epidemics/pandemics. The 2009 swine influenza pandemic [111,128] has established that mammals may serve as intermediate hosts (“mixing vessels”) [129,130] for pandemic generation, an idea long suggested by the frequent close association of epizootics with epidemics [6].

In earlier eras, when they were ubiquitous in virtually all rural and urban settings, horses may have played a role in influenza virus maintenance and evolution analogous to that of pigs in the modern era. Today, H3N8 (equine-2) influenza viruses circulate enzootically in horses but rarely cause human disease, whereas H7N7 (equine-1) viruses have rarely been detected in recent decades and may have become extinct [131]. However, from 1648 until 1917, many if not most major influenza pandemics/epidemics were preceded by [38,48,132–140], or less often followed by (e.g. in 1776, 1780, and 1831 [81,141–145]), epizootics of equine influenza.

By our calculations, which are undoubtedly not comprehensive given that many influenza accounts have probably not been identified, or have been lost, of the 112 years in the 200-year period between 1688 and 1888 in which either significant influenza epidemics/

pandemics or equine epizootics were documented in Europe, combined equine epizootics/human epidemics were documented in 67 years; equine epizootics only in 25 years, and human epidemics only in 20 years [146]. The pattern in the Western Hemisphere during the same interval differed in degree: of the 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. Large-scale equine influenza epizootics or panzootics that overshadowed concurrent human influenza were recognized in 1727, 1750, 1760, and 1872 [146].

An explosive 1872–1873 Western Hemispheric equine panzootic [140,142,146,147] was strongly associated temporally and geographically with widespread outbreaks of fatal influenza-like poultry disease, which also killed turkeys, ducks, geese, herds of swine, and, allegedly, forest deer [146]. This panzootic was further associated with limited outbreaks of mild human influenza (which was popularly known as “the zooty” [140,143,147,148], of uncertain relationship to true epidemic influenza recognized some months later [71,146]). For the next 30 years, equine epizootics were common across the USA. With the exception of major outbreaks in 1880–1881 and 1900–1901, however, they tended to be local, to affect mostly young horses, and to feature much lower attack rates [144,145]. The last widespread equine influenza epizootic in the USA occurred in the winter of 1915–1916, concurrent with a major epidemic season [149]. It appears that at least during the 270-year period from 1648 to 1917, influenza was almost as much a global equine disease as it was a global human disease [146].

Cases of canine and feline influenza associated with equine or human outbreaks have been described for centuries [38,135,139,140,150,151]. Widespread outbreaks of canine and feline influenza may have occurred during the 1782 influenza pandemic [152], which also was associated with epizootic equine disease. A substantial canine outbreak was seen during an 1851–1852 Australian epidemic as well [153]. Horse-to-dog transmission of influenza has affected racing greyhounds for more than a century [146], and canine H3N8 epizootics have recently resulted in enzootically stable transmission between dogs [154]. Clearly, other mammals have long been involved in influenza virus circulation; their possible role in pandemic generation or in viral maintenance and evolution are poorly understood.

WHAT WE DO *NOT* KNOW ABOUT PANDEMIC INFLUENZA

How and why do influenza pandemics emerge?

Pandemics have resulted from importation of avian genes into human-adapted viruses via gene reassortment (1957 and 1968 [155,156]), by human adaptation of viruses previously adapted to other mammals (2009 [128]), and possibly from the *de novo* adaptation of an avian-like virus to mammals (1918 [157,158]). We do not understand the basic mechanisms of how these viruses emerge, including how, where, when, how quickly, and under what circumstances the host-switching processes occur. We also do not know whether human adaptation occurs directly and immediately, or gradually in human or intermediate hosts [159]; nor do we know the characteristics of viral “fitness valleys” between donating and accepting hosts [160,161].

Although the origin of the 1918 pandemic virus has not been fully resolved, it has an avian-like genome and may have been derived from an avian virus in the decade before 1918 [157,158]. Alternatively, it may have evolved in swine prior to its emergence [162]. There has also been concern that the H5N1 HPAI virus, circulating since 1996, is similarly evolving in the direction of human adaptation [163]. But poultry influenza outbreaks have never been known to cause more than a limited number of human "spillover" cases. In the 1557 and 1580 influenza pandemics (called in German *Hühnerweh*, or "chicken malady," ostensibly because croupy human coughs sounded like those of ill chickens), poultry epizootics were not to our knowledge documented [51,164]. When poultry epizootics consistent with avian influenza were eventually described, for example, a 1789 epizootic in Northern Italy [165], they were not associated with pandemics, major epidemics, or significant human-to-human transmission.

The once comfortable notion that pandemics are generated only by antigenic shift (insertion by genetic reassortment of a new HA subtype) has become increasingly problematic. A novel evolutionary mechanism was discovered in 2003 when a prevailing H3N2 virus acquired, by intra-subtypic reassortment, an antigenically variant H3 to which population immunity was incomplete [166,167]. Genetic evidence suggests that 1918 H1N1 and 1968 H3N2 viral descendants have evolved by frequent intra-subtypic reassortment as well, not only in the H1N1 era (e.g. 1947 and 1951) [168] but also in the H3N2 era (e.g. 1997 and 2003) [166,169]. Although typically we do not refer to such events as pandemics [12], some appear to meet standard definitions of the term on the basis of their rapid global spread [10,12]. The 2009 H1N1 pandemic, which followed reassortment of two well-established swine-adapted viruses, represents yet another complex and novel pathway to pandemic generation [10,111,128]. Influenza viruses evolve by a number of different mechanisms in a number of different hosts, and they can easily cross species barriers, which suggest many different potential pathways to pandemic emergence, none of which are understood.

Why do influenza pandemics differ in severity?

For 500 years, observers have documented significant differences in the severity of influenza pandemics. Unrelated to the basic symptomatology of typical cases (apparently unchanged over many centuries), pandemic influenza severity has usually been measured by mortality, which is influenced by such variables as (i) the age and health structure of the population; (ii) the variable presence of residual protective immunity in older age cohorts; (iii) the case incidence of potentially fatal complications (predominantly bacterial pneumonia); and possibly, (iv) inherent differences in the ability of influenza viruses to cause infrequent but severe or fatal complications (pathogenicity), such as primary viral pneumonia or viral potentiation of secondary bacterial pneumonia.

Obviously, demographic factors alone influence influenza mortality, including age-related susceptibility to influenza complications and different levels of immunity related to exposures to viruses circulating in earlier eras. Although the pandemic(s) of the 1830s, of 1889, and of 1918 were similar in their pathologic picture and relatively high mortality—including evidence for, or consistent with, deaths from secondary bacterial pneumonia—"mild" pandemics with mild recurrences were documented in, for example, 1761–1762,

1775, and 1781–1782. The latter pandemic is said to have been associated with protection of persons previously infected in both 1732–1733 and 1775 [6,170,171]. Such protection also was suggested for the pandemics of 1831–1837 and 1847–1848 based on prior infections around 1782 [3,172,173], but without accurate incidence data, such claims remain unsubstantiated. Information on human protection from prior influenza exposures has occasionally been supplemented by similar information about horses, for example, that horses experiencing influenza in the years before 1760 were protected during a 1760 epizootic [135]. Data from the 1918 pandemic suggest decreased incidence in persons older than about 60–65 years (alive during the pandemic eras of the 1830s and 1840s [6,8]), but mortality in this age group was still elevated by a high case-fatality rate that was largely attributable to a high incidence of complicating pneumonias [99]. Notably, with or without protection from disease based on prior exposures, in the pandemics of the earlier centuries mentioned above, in every case there seemed to have been increases in mortality of the elderly, and usually the other noted risk groups as well. Such elevated mortality in the key risk groups has been seen in virtually all pandemics, whether mild or severe.

For unknown reasons, apparent protective effects were also seen in 1957 [174–176]; in the subsequent era of H3N2 circulation because of immunity to previously circulating H2N2 viruses [11,177–179]; in the era of the 1977 return of H1N1 viruses by prior infection with H1N1 and—paradoxically—H3N2 viruses [180]; and in 2009 by residual H1N1 viral immunity induced by long-ago exposures to 1918-descended human viruses and possibly also by vaccine-induced immunity [181–184]. Based on mortality rates, these latter pandemics are essentially indistinguishable from severe endemic seasonal influenza and probably would not have been recognized as pandemics in the pre-virologic era [10,11]. To our knowledge, the only pandemic in the last 280 years without evidence of, or claims for, pandemic-to-pandemic protection is that of 1889, at which time incident cases seem to have been unaffected by pre-exposure to the pandemics of the 1830s or of 1847–1848; and in turn, exposure during the 1889 pandemic seems not to have protected individuals against the next pandemic in 1918.

Although influenza pandemics have appeared and peaked in all seasons, European accounts spanning 500 years suggest that pandemic influenza has rarely ever caused high mortality in the summer months. Of the 16 pandemics noted between 1510 and 2009, the eight associated with significant increases in mortality all peaked in the winter months. Of the other eight ostensibly milder pandemics, only two (in 1775 and 1968) peaked in the winter months. The remaining six milder pandemics either peaked in summer (1510, 1580) or arrived in spring and spread more slowly over the summer, sometimes returning in the fall or winter to produce low or moderate numbers of deaths (1761, 1782, 1957, 2009).

This suggests that seasonal timing of pandemic appearance could be a determinant of severity. It might be speculated that arrival and spread of a pandemic virus in the summer months, when bacterial pneumonias of any cause are less frequent, provide an opportunity for a new virus to create significant population immunity without producing substantial mortality. When a new pandemic virus arrives or peaks in the winter months, on the other hand, substantial mortality from secondary bacterial pneumonia may occur. Possible examples of the latter may include the pandemic of 1557, which appeared in Europe in June,

spread rather slowly, but recurred to cause substantial mortality in the winter of 1557–1558. Similarly, in 1918 a new pandemic virus appears to have caused moderate attack rates but low mortality in a few northern European countries in July and August 1918, only to return globally in the fall and winter of 1918–1919 to cause higher attack rates with significant mortality. These speculations do not explain the anomalous mild pandemics of 1775 and 1968, both of which peaked in winter. Despite extremely high attack rates, the 1775 pandemic, which followed an earlier pandemic by 13 years, is probably the mildest on record, whereas the 1968 pandemic reflected a second "update" by reassortment of the 1918 virus. Conceivably, the "founding" viruses causing these mild pandemics were of such low pathogenicity (e.g. because of pre-existing NA-based immunity as shown in 1968 [177–179]) that although fully capable of spreading explosively, they could not cause substantial mortality, even in the winter.

An exception to the usual demographic pattern of influenza deaths occurred in the pandemic of 1918–1919, which featured an enormous mortality peak in persons 20 to 40 years of age due to an unexplained high incidence of secondary bacterial pneumonia and empyema [8], but without causing an increased pneumonia case-fatality rate. The cause of this pneumonia-associated mortality peak remains unknown and is the subject of continued speculation. Although 1918–1919 mortality was low in children 5 to 15 years old—characteristic of all influenza pandemics and epidemics—it appears to have been significantly higher in this age group than in the moderately severe pandemic of 1889–1890 [8], perhaps suggesting greater inherent viral pathogenicity, or greater viral-bacterial co-pathogenicity. Several different mechanisms have been hypothesized for enhanced pathogenicity in viral–bacterial co-infections, including enhanced bacterial colonization and spread resulting from viral damage to respiratory epithelial cells, viral-induced immunosuppression, and effects of bacterial proteases on viral activation [115,185]. The high mortality rate in humans infectedwithH5N1HPAI virus (59%, World Health Organization, 7 March 2011, http://www.who.int/csr/disease/avian_influenza/country/cases_table_2011_03_07/en/index.html) suggests extreme virulence. However, this virus has not become pandemic, and it remains unclear whether or not it is inherently capable of doing so [6].

Pandemics are thus of variable severity, and severity appears not to be related strictly to the source of the pandemic virus or the means of its generation. Other factors such as pre-existing partial immunity, seasonal timing, and inherent viral properties may all play important roles. The relationship between different viral evolutionary mechanisms and the production of pandemics of variable severity is obscure [159,186]. Presumably complex/polygenic viral determinants underlie some of pandemic influenza's severity, but it seems clear that variation in pandemic mortality is a complex product of interactions between multiple poorly understood viral, host, and environmental factors.

Why do influenza pandemics recur, and why do they recur in differing patterns?

Even when transmitted quickly and efficiently, pandemic influenza has seemed unable, at least in the last 200 years, to infect an entire population at one time. Historically, pandemic influenza usually recurs at least once before settling into a familiar pattern of annual/seasonal endemicity. But it also has done so with very different recurrence patterns (Figure

6). Such patterns include explosive and largely annual seasonal recurrences and waves (a term we apply to pandemic recurrences of significant mortality within a 9-month interval, to distinguish them from the annual/seasonal recurrences that pandemics seem always to initiate). The 1889 pandemic appeared in most places in winter (Northern Hemisphere), recurring annually and largely seasonally until as late as 1894 [8,187], the annual seasonal recurrences being referred to at the time as waves. In the 1918–1919 pandemic, most countries experienced, within an interval of 9 months or less, one occurrence and one recurrence, whereas a few (mostly Northern European) countries experienced two recurrences, and others experienced only one recurrence or, rarely, none [6,99,102]. As noted elsewhere [88], historical clustering of pandemics at intervals of 2 to 4 years (e.g. in 1729/1732 and 1830/1833/1836) might have represented expected but “delayed” recurrences of single pandemic viruses in eras of lower population density and slower travel.

Pandemics have appeared at all times of year. In the last century, at least, they have tended to recur with increasing seasonality as they give way to initial and subsequent recurrences, settling within a few years, at most, into annual seasonal (winter) endemicity in temperate climates. The determinants of these patterns remain to be fully elucidated [169] but may well be related to an increasing tendency for almost all respiratory viral diseases to prevail in temperate climates during winter months [188,189]. This seasonal tendency decreases in proximity to the equator, consistent with the century-old notion that respiratory agents are stabilized by more favorable winter conditions, for example, cooler temperatures and lower humidity [188,190].Additional winter seasonal factors may include lower nasal epithelial temperatures, which favor virus survival, less efficient indoor ventilation, and more intense and prolonged indoor crowding. It seems probable that many if not most “waves” (rapidly successive recurrences) are the products of either regional variability in viral introduction and explosiveness [106,191,192], or the action of environmental conditions upon new viruses beginning to circulate at seasonally unfavorable times [193]. Some recurrent “waves” of influenza mortality have been associated with very low-incidence rates of influenza; apparently, low-incidence “waves” of high case-fatality result from the relative confinement of secondary bacterial pneumonias to the winter months [191]. Waves of influenza incidence and waves of influenza mortality may thus be two different phenomena.

Confusingly, influenza’s familiar seasonal recurrence pattern seems to have developed only gradually over the past 300 years. Until the early 1700s, influenza pandemics and major epidemic recurrences were detected in Europe about as often in the spring–summer months (April–September) as in the fall–winter months (October–March; Figures 1 and 2) and often occurred in association with equine epizootics, which themselves tended to occur in spring and fall. Conceivably, in the era before modern heating, cold weather may have placed such significant limits on human and equine movement that person-to-person and horse-to-horse spread was “forced” into the otherwise environmentally unfavorable late spring to early fall months. Determinants of influenza seasonal patterns remain obscure.

Do influenza pandemics occur in fixed geographic patterns?

As noted, geographic directionality has long been recognized as a feature of pandemic influenza, including frequent attribution of pandemic origin to Asia, westward spread to

Europe, directional spread within Europe, and acceleration of spread by contemporary means of mass population movement. Since 1889, all influenza pandemics have been global. However, it is important to remember that in earlier eras, pandemics were not always observed globally. Not only were pandemics before 1889 variable in their geographic extension (Figures 1–3) but beginning around or just before the 17th century until 1889—a period during which otherwise global pandemic spread was repeatedly documented—the Western Hemisphere seems to have charted its own endemic/epidemic/pandemic and epizootic influenza course. In 1647—a time when influenza was relatively silent elsewhere in the world [31,194,195]—a trans-regional pandemic spread from New England to the tip of South America, a pattern repeated in 1697–1698 and 1719–1720 (Figure 2). In 1761, within a year of a major equine influenza epizootic, an American-origin pandemic has been said (with questionable documentation, however) to have been exported to Europe, causing an inter-regional pandemic abroad [31,81,196].

Between 1789 and 1889, the Western Hemisphere exhibited an influenza occurrence pattern seemingly disconnected from Europe and the rest of the world (Figures 2 and 3),without detected pandemic activity even during the deadly and otherwise global pandemics of the 1830s and of 1847–1848 [71]. Thus, until 1889, influenza pandemicity seems to have existed on a continuum of geographic extension, including regional, trans-regional, interregional, and global pandemicity, an epidemiological feature that may hold important clues to influenza evolution but as yet remains unexplained. Although our understanding of influenza epidemiology leads us to expect that future influenza pandemics will continue to spread globally, by failing to understand determinants of past geographic restrictions, we may be missing important clues that could help us prevent or control pandemics of the future.

Why do pandemic viruses disappear, and why are they replaced?

History suggests that pandemic viruses appear, remain pandemic as they recur for one to a few years, thereafter become endemic/seasonal for variable periods, and eventually are replaced by new pandemic viruses [197]. However, the necessity of “viral replacement” was called into question in 1977 when a naturally “extinct” descendant of the 1918 H1N1 pandemic virus suddenly reappeared after a 20-year absence and re-established first pandemic and then seasonal circulation [10,198]. The 1977 H1N1 virus and the 1968 H3N2 pandemic virus have co-circulated without evidence of imminent extinction for 33 years [6], leaving a trail of population immunity directed against four of the five influenza surface proteins known to have ever been incorporated into human viruses (H1, H3; N1, N2).

In 2009, with the emergence of the swine-origin H1N1 pandemic virus, global co-circulation of three evolutionarily and antigenically distinct descendants of the 1918 founding virus began. It is not known whether there is a limit to how many type A influenza viruses of different or highly variant antigenic subtypes can co-circulate or whether co-circulation of multiple viruses might protect against the emergence of new pandemics. Moreover, it is still unclear whether the 2009 pandemic H1N1 virus will lead to the extinction of seasonal H1N1 and/or H3N2 viruses or whether it will continue to co-circulate with them. Influenza experts have long speculated that only certain influenza A subtypes (e.g. H1, H2, and H3) can cause

pandemics and that they do so cyclically, their successive replacement driven by the eventual dying out of human populations exposed to particular viruses in early life [199–201].

This begs an additional question of whether, as has been claimed dogmatically for centuries, influenza pandemics occur in recognizable cycles. Aware that ancient observers had posited 100-year cycles [3], in 1792 Anthony Fothergill proposed 31-year influenza cyclicity [202]. Soon thereafter, 10-year cycles were suggested, first by Noah Webster (in 1799 [31]) and again in 1841 by Theophilus Thompson [81]. The latter idea persisted well into the 21st century [7]. From the vantage point of 2011, however, we are not able to identify either cyclic pandemic patterns or effects of global population growth on pandemic frequency (Figure 7).

In considering the historical record of influenza pandemics—including the past 93 years in which four pandemics and at least five pandemic-like events have been associated with moderate or low mortality—it is worth noting a 147-year period without evident pandemic activity (1581–1728), as well as a similar 245-year span of relative silence (928–1173) in the era before pandemic documentation (Figure 1). Were pandemics absent during the 17th century? A 1657–1658 epidemic associated with equine disease involved most of Europe but produced relatively low attack rates [203]. A brief 1675–1676 European summer epidemic, and a non-directional 1709–1710 epidemic concentrated in Central Europe, represent the only other documented major influenza activity during this 147-year period. Curiously, from 1581 to 1693, nine of 11 major epidemics for which seasonality can be reliably documented appeared in the summer months, several in association with equine epizootics (Figure 2).

It is arguably as important to understand long periods without recognized pandemics as it is to understand how pandemics occur in the first place. Are there determinants of post-pandemic “stability” that prevent or delay new pandemics, and is stability a desirable state given that the cumulative seasonal mortality caused by successive years of antigenic drift may eventually exceed the mortality caused by new pandemics [10,11,197]? How and why do pandemic eras end? Do influenza viruses exhaust their repertoires of antigenic drift or acquire mutations limiting their ability to replicate or be transmitted efficiently? Are some pandemics stochastic events unrelated to previous pandemic eras? Could post-pandemic stability be maintained by high vaccination rates against multiple HAs or conserved cross-reacting epitopes? We have almost no information to answer any of these questions about pandemic appearance, disappearance, or replacement.

Summary

> ***“[E]ach [influenza] epidemic has presented some special [epidemiologic] phenomenon, each form has constituted, as it were a sort of morbid individuality.”Robley Dunglison, 1842*** **[204]**

Influenza seems for at least five centuries to have remained a clinically distinct and pathologically stable disease. However, its appearance in pandemic form, its patterns of pandemic recurrence, the stability of its endemic persistence, its eventual disappearance, and

its ability to cause fatalities all appear to be highly complex and poorly understood processes. Trans-regional, inter-regional, and global influenza pandemics, as well as major and often highly fatal regional epidemics, have occurred unexpectedly after short or long intervals, have arisen from different genetic mechanisms, have had unpredictable mortality impacts on different population age cohorts, have varied greatly in recurrence patterns, have been followed soon thereafter by new pandemics or have faded into long-term endemicity, have been caused by viruses that evolved singly or in co-circulation with other pandemic viral descendants, and have often involved significant transmission in, or establishment of viral reservoirs within, other animal hosts. Our limited understanding of pandemic influenza is being repeatedly shaken by unanticipated events that expose fundamental gaps in scientific knowledge.

A new picture of pandemics seems to be developing. Characteristically, unique epidemic eras are initiated by the sudden explosive appearances of founding viruses such as, perhaps, those of the 1830s, of 1889, and of 1918. This is followed by rapid adaptation to endemic/seasonal circulation. Subsequently, secondary pandemics and pandemic-like events may result from such successful evolutionary achievements of the founding virus as subtypic and intra-subtypic reassortment, drift with and without selective sweeps, and complex interchanges with mammalian-adapted viruses. In addition to current concerns about potential human adaptation of avian influenza viruses, in 2011 we are now pondering the implications of co-circulation of descendants of three different pandemic influenza A viruses themselves descended from one 1918 founding progenitor virus [10], a phenomenon that would have been unthinkable to most experts only a few decades ago.

Perhaps all that can be said with certainty about influenza pandemics is that they represent brief moments in which particularly fit viruses temporarily get a step or two ahead of the human population whose growing immunity will inevitably slow them down and lead to their demise. Despite the persistent modern notion that pandemic influenza is a distinct phenomenon obeying invariant if poorly understood rules, the historical evidence suggests that pandemics are instead a heterogeneous collection of viral adaptational events, the determinants of which are probably highly complex and remain obscure. Such uncertainties make it difficult to predict the occurrence of, and the severity of, pandemics and therefore to adequately prevent and control them. Planning for the worst while hoping for the best, health authorities risk creating public confusion and the perception of “crying wolf.” Ongoing and emergency planning is essential to pandemic containment, yet in recent decades, public health authorities have been repeatedly criticized for over-reacting to pandemics that either failed to materialize or were less severe than was predicted. For public health decision-makers, the dilemma remains constant because the determinants of influenza pandemics remain hidden. With human influenza, the only certain thing seems to be uncertainty.

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Abbreviation used

HPAI	highly pathogenic avian influenza
HA	hemagglutin

REFERENCES

1. Paulos, J. Preface. Irreligion. New York: Hill and Wang; 2008. p. ix-xvii.
2. Schnurrer, F. Chronik der Seuchen, in Verbindung mit den gleichzeitigen Vorgängen in der physischen Welt und in der Geschichte der Menschen. Tübingen: Osiander; 1823. p. 1825
3. Parkes, E. Influenza. In: Reynolds, J., editor. A System of Medicine. Vol. Vol. I, Part 1. London: MacMillan and Company; 1866. p. 27-50.
4. Wilson, J.; Da Costa, J. INFLUENZA. In: Wilson, J.; Da Costa, J., editors. A Treatise on the Continued Fevers. New York: William Wood & Company; 1881. p. 10-45.
5. Clemow F. Epidemic influenza. Proceedings of the Society of Medical Officers of Public Health. Public Health. 1889–1890; 2:358–367.
6. Taubenberger JK, Morens DM. Pandemic influenza—including a risk assessment of H5N1. Revue Scientifique et Technique. 2009; 28:187–202. [PubMed: 19618626]
7. Dowdle WR, Schild GC. Influenza: its antigenic variation and ecology. Bulletin of the Pan American Health Organization. 1976; 10:193–195. [PubMed: 187273]
8. Morens DM, Fauci AS. The 1918 influenza pandemic: insights for the 21st century. The Journal of Infectious Diseases. 2007; 195:1018–1028. [PubMed: 17330793]
9. Zimmer SM, Burke DS. Historical perspective—emergence of influenza A (H1N1) viruses. The New England Journal of Medicine. 2009; 361:279–285. [PubMed: 19564632]
10. Morens DM, Taubenberger JK, Fauci AS. The persistent legacy of the 1918 influenza virus. The New England Journal of Medicine. 2009; 361:225–229. [PubMed: 19564629]
11. Noble, G. Epidemiological and clinical aspects of influenza. In: Beare, A., editor. Basic and Applied Influenza Research. Boca Raton, FL: CRC Press; 1982. p. 11-50.
12. Morens DM, Folkers GK, Fauci AS. What is a pandemic? The Journal of Infectious Diseases. 2009; 200:1018–1021. [PubMed: 19712039]
13. Morens DM, Littman RJ. “Thucydides Syndrome” reconsidered: new thoughts on the “Plague of Athens”. American Journal of Epidemiology. 1994; 140:621–628. [PubMed: 7942762]
14. Valesco de, Taranta. Practica Valesci de Tharanta, que alias Philoniumdicitur. Lyon: Mathias Huss; 1490. Decatarrho Prognosticatio. In Valesco de Taranta.
15. Benedetti, A.; Aemilianus, Q. De observatione in pestilentia. Venetiis: Joannes & Gregorius de Gregoriis, de Forlivio; 1539.
16. Buoninsegni, D. Historia Fiorentina. Fiorenza: Giorgio Marescotti; 1581.
17. Pasquier, É. Les recherches de la France d’Estienne Pasquier: augmentées par l’autheur en ceste dernière édition de plusieurs beaux placards & passages, & de dix chapitres entiers, dont le contenu se void au fueilley suivant. Paris: Laurent Sonnius; 1617. p. 493-495.
18. Fonseca, A. De Epidemia febrili grassante in Exercitu Regis Catholici in inferiori Palatinatu, Anno 1620 & 1621. Tractatus, in quo febris malignae essentia, causæ, signa diagnostia, & prognostica, & methodus curatiua Philosophice & Medice elucidantur. Mechliniae: apud Henricum Jaye; 1623.
19. Schneideri, CV. De Catarris, Quo agitur de Speciebus Catarrhorum, & de Osse Cuneiformi, per quod Catarrhi decurrere singuntur. D. Tobiae Mevii: Wittbergae; 1660–1662.
20. de Mézeray, F-E.; Lewis, XII.; King, LVI. A General Chronological History of France, Beginning Before the Reign of King Pharamond, and Ending with the Reign of King HENRY the Fourth: Containing both the Civil and the Ecclesiastical Transactions of that Kingdom. Translated by John Bulteel, Gent. Vol. 1683. London: Thomas Basset, Samuel Lowndes, Christopher Wilkinson, William Cademan, Jacob Tonson; 1510. p. 548
21. Targioni Tozzetti, G. Brevi Notizie Intorno alle Infreddature Epidemiche. In: Targioni Tozzetti, G., editor. Prima Raccolta Di Osservazioni Mediche. Firenze: Stamperia Imperiale; 1752. p. 174-176.

22. Morgagni, J. Epistola Anatomico-Medica XIII: Verba siunt pauca de Catarrho, plura de Oculorum Affectibus. In: Morgagni, G., editor. De Sedibus, Et Causis Morborum Per Anatomen Indagatis Libri Quinque. Venetiis: Remondiniana; 1761. p. 96-108.
23. Boissier de la Croix de Sauvages, F. Nosologie méthodique, ou distribution des maladies en classes, en genres et en espèces, suivant l'esprit de Sydenham,&la méthode des botanistes. Lyon: Tome quatrième. Jean-Marie Bruyset; 1772.
24. Boissier de la Croix de Sauvages, F. Nosologia Methodica sistens Aegritudines Morbos Passiones ordine artificiali ac naturali. Castigavit emendavit auxit Icones (Iam V.) Etiam ad naturam Pictas. Tome, II., editor. Lipsiae: E. B. Schwickerti; 1791.
25. Boissier de la Croix de Sauvages, F. Nosologia Methodica sistens Aegritudines Morbos Passiones ordine artificiali ac naturali. Castigavit emendavit auxit Icones (Iam V.) Etiam ad naturam Pictas. Tome, III., editor. Lipsiae: E. B. Schwickerti; 1795.
26. Boissier de la Croix de Sauvages, F. Nosologia Methodica sistens Aegritudines Morbos Passiones ordine artificiali ac naturali. Castigavit emendavit auxit Icones (Iam V.) Etiam ad naturam Pictas. Tome, IV., editor. Lipsiae: E. B. Schwickewrti; 1796.
27. Épidémies, PerkinsJ. Extrait d'unmémoire redigé par M. Perkins, médecin de Boston, sur la nature & l'origine des fièvres catarrhales épidémiques, & remis a la Société par M. Franklin. Histoire [et mémoires] de médecine de la Société royale de médecine. Année 1776. 1779:206–212.
28. Saillant, C-J. Tableau historique et raisonné des épidémies catarrhales, vulgairement dites la grippe; depuis 1510 jusques & y compris celle de 1780, avec l'indication des traitemens curatifs & des moyens propres à s'en préserver. Paris: Didot jeune; 1780.
29. Grant, W. Observations on the Late Influenza, the Febris Catarrhalis Epidemica of Hippocrates, as It Appeared at London in 1775 & 1782. London: T. Cadell; 1782.
30. Nikon Ruskaja Letopis po Nikonovu spisku. Sv. III., část V., Část pjataja C' 1407 po 1462 goda. V Sanktpeterburge: Pri imperatorskoj Akademii Nauk; 1789. Nikon [1414]; p. 51-55.
31. Webster, N. A Brief History of Epidemic and Pestilential Diseases; with the Principal Phenomena of the Physical World, which Precede and Accompany Them, and Observations Deduced from the Facts Stated. Vol. Vol. I. Hartsford, CT: Hudson & Goodwin; 1799.
32. de Villalba, J. Epidemiologia española; ó, Historia crónologica de las pestes, contagios, epidemias y epizootias que han acaecido en España desde la venida de los cartagineses, hasta el año 1801. Con noticia de algunas otras enfermedades de esta especie que han sufrido los españoles en otros reynos, y de los autores nacionales que han escrito sobre esta materia, así en la península como fuera de ella. Mateo así en la península como fuera de ella. Madrid: Mateo Repullés; 1802.
33. Zeviani, GV. Memorie di Matematica e di Fisica. Vol. 11. Modena: Societa Italiana delle Scienze; 1804. Sul catarrho epidemico opuscolo; p. 476-530.
34. Schnurrer, F. Geographische Nosologie; oder die Lehre von den Veränderungen der Krankheiten in den verschiedenen Gegenden der Erde, in Verbindung mit physischer Geographie und Natur-Geschichte des Menschen. Stuttgart: Steinkopf; 1813.
35. Sprengel, KPJ.; Jourdain, A-J-L. Histoire de la médecine, depuis son origine jusqu'au dix-neuvième siècle. Tome troisiéme. Paris: Deterville; 1815. Translator.
36. Most, GF. Influenza Europaea, oder die grösseste Krankheits-Epidemie der neuern Zeit. Hamburg: Perthes und Besser; 1820.
37. Fodéré, F. Leçons sur les épidémies et l'hygiène publique, faites à la Faculté de médecine de Strasbourg. Tome, III., editor. Paris: Levrault; 1822.
38. Forster, T. Illustrations of the Atmospherical Origin of Epidemic Diseases, and of Its Relation to Their Predisponent Constitutional Causes, Exemplified by Historical Notices and Cases, and on the Twofold Means of Prevention, Mitigation, and Cure, and of the Powerful Influence of Change of Air, as a Principal Remedy. To which are Appended, Popular Rules for the Maintenance of Health. 2nd edn.. Chelmsford: Meggy & Chalk; 1829.
39. Naumann, M. Handbuch der medicinischen Klinik. Erster Band. Berlin: August Rücker; 1829.
40. Martiny, E. Die Influenza oder Grippe, eine Contagiös-epidemische Krankheit; in Hinsicht ihrer Geschichte, ihrer Entstehung und Verbreitung, ihres Wesens, Verlaufs und ihre Behandlung, für Aerzte und Laien geschildert. Weimar: Bernhard Friedrich Voigt; 1835.

41. Gluge, G. Die Grippe oder Influenza. Eine historisch-pathologische Abhandlung. In: Hecker, JFC., editor. Neue wissenschaftliche Annalen der gesammten Heilkunde. Dritter Band. Berlin: Th[eodor] Ch[ristian] Friedr[ich] Enslin; 1836. p. 129-171.
42. Schweich, H. Die Influenza. Ein historischer und ätiologischer Versuch. Berlin: Theodor Christian Friedrich Enslin; 1836.
43. Most, G. Influenza. In: Most, G., editor. Encyklopädie der gesammten medicinischen und chirurgischen Praxis, mit Einschluss der Geburtshülfe, der Augenheilkunde und der Operativchirurgie Im Verein mit mehreren praktischen Ärzten und Wundärzten. Zweiter Band. Hyalitis - Zymosis. Leipzig: FA Brockhaus; 1837. p. 253-255.
44. Haeser, H. Historisch-pathologische Untersuchungen. Als Beitrage zur Geschichte der Volkskrankheiten. Dresden: Gerhard Fleischer; 1839. p. 1841
45. Villani, M. D'un singolare accidente ch'avvenne in questi paesi. In: Dragomanni, FG., editor. Cronica di Matteo Villani A Miglior Lezione Ridotta Coll'Ajuto De'Testi A Penna. Vol. Vol. II. Firenze: Sansone Coen; 1846. p. 110-111.
46. Canstatt, C. Influenza. In: Canstatt, C., editor. Die specielle Pathologie und Therapie; vom klinischen Standpunkte aus bearbeitet. Band II. Abt. 2. Erlangen: Ferdinand Enke; 1847. p. 659-677.
47. O'Donovan, J., editor. Annals of the Kingdom of Ireland, by the Four Masters, from the Earliest Period to the Year 1616. Vol. Vol. I. Dublin: Hodges, Smith & Co.; 1848. Anonymous. The age of Christ, 1328; p. 536-543.
48. Glass, T. 7. Dr. Thomas Glass, of Exeter. [1775]. In: Thompson, T., editor. Annals of Influenza or Epidemic Catarrhal Fever in Great Britain from 1510 to 1837. London: Sydenham Society; 1852. p. 96-102.
49. White, W. 9. Dr. W. White. [1775]. In: Thompson, T., editor. Annals of Influenza or Epidemic Catarrhal Fever in Great Britain from 1510 to 1837. London: Sydenham Society; 1852. p. 105-107.
50. de Diceto, R. Ymagines historiarum. AD. 1174. Prevalence of coughs. In: Stubbs, W., editor. Radulfi de Diceto Decani Lundoniensis Opera. Vol. Vol. I. London: Her Majesty's Stationery Office; 1858. p. 379-398.
51. Corradi, A. Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850. Parte Prima. Dalle Prime Memorie Fino al 1500. Bologna: Gamberini e Parmeggiani; 1865.
52. Corradi A. L'influenza od epidemica di febbre catarrale dell'anno 1580 in Italia con nuovi documenti illustra. Annali Universali di Medicina. 1866; 198:3–78.
53. Corradi A. L'influenza od epidemica di febbre catarrale dell'anno 1580 in Italia con nuovi documenti illustra. Annali Universali di Medicina. 1866:515–544.
54. Corradi, A. Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850. Parte Seconda. Dal 1501 a tutto il 1600. Bologna: Gamberini e Parmeggiani; 1867.
55. Corradi, A. Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850. Parte 1–2, Appendice. Bologna: Gamberini e Parmeggiani; 1867.
56. Corradi, A. Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850. Parte Terza. Dall'Anno 1601 al 1700. Bologna: Gamberini e Parmeggiani; 1870.
57. Corradi, A. Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850. Parte IV.a. Dall'Anno 1701 al 1850. Bologna: Gamberini e Parmeggiani; 1876.
58. Corradi, A. Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850. Parte IV. (Disp. 2a). 1802–1833. Bologna: Gamberini e Parmeggiani; 1877.
59. Corradi, A. Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850. Parte IV. (Disp. 3a). 1833–1850. Bologna: Gamberini e Parmeggiani; 1880.
60. Corradi, A. Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850. Vol. Vol. III. Bologna: Gamberini e Parmeggiani; 1892. Appendice. Parte I. Sino al 1600.
61. Corradi, A. Appendice. Parte II. Dal 1601 in poi con altre Aggiunte. Vol. Vol. III. Bologna: Gamberini e Parmeggiani; 1892. Annali delle epidemie occorse in Italia dalle primememorie fino al 1850.
62. Corradi, A. Annali delle epidemie occorse in Italia dalle prime memorie fino al 1850. Vol. Vol. VIII. Bologna: (postumo). Indici. Gamberini e Parmeggiani; 1894.

63. Aitken, W.; Clymer, M. Influenza. In: Aitken, W.; Clymer, M., editors. The Science and Practice of Medicine. Vol. Vol. I. Philadelphia: Lindsay & Blakiston; 1872. p. 705-710.
64. Tuetey, A., editor. Anonymous. Journal d'un bourgeois de Paris 1405 –1449. Publié d'après les manuscrits de Rome et de Paris. Paris: H. Champion; 1881.
65. Hirsch, A. Influenza. In: Hirsch, A., editor. Die allgemeinen acuten Infektionskrankheiten vom historischgeographischen Standpunkte und mit besonderer Berücksichtigung der Aetiologie. Zweite, vollständig neue Bearbeitung. Stuttgart: Ferdinand Enke; 1881. p. 5-40.
66. Thompson, T.; Symes Thompson, E. Influenza or Epidemic Catarrhal Fever. An Historical Survey of Past Epidemics in Great Britain from 1510 to 1890. London: Percival & Co.; 1890.
67. Creighton, C. Influenza. In: Creighton, C., editor. A History of Epidemics in Great Britain from AD 664 to the Extinction of Plague. Cambridge: University Press; 1891. p. 397-413.
68. Creighton, C. Influenzas and epidemic agues. In: Creighton, C., editor. A History of Epidemics in Great Britain, Vol. II. From the Extinction of Plague to the Present Time. Cambridge: University Press; 1894. p. 300-433.
69. Ruhemann, J. Die Influenza im Winter 1889–1990. Leipzig: Thieme; 1891.
70. Wolff, J. Die Influenza-Epidemie, 1889 –1892. Stuttgart: Ferdinand Enke; 1892.
71. Finkler, D. Influenza. In: Stedman, T., editor. Twentieth Century Practice: an International Encyclopedia of Modern Medical Science by Leading Authorities of Europe and America. Vol. Vol. XV. New York: William Wood & Company; 1898. p. 3-249.
72. Mousson-Lanauze J-B-O-P. Une épidémie de grippe à la Renaissance. Paris médical. 1921; 43:227–228. (annexe).
73. Laubié A. Deux épidémies de grippe au XV^{ème} siècle. La maladie du taq et la maladie de ladendo. Gazette hebdomadaire des sciences médicales. 1924; 14:438–439.
74. Brown M. Historical medicine: early epidemics of influenza in America. Medical Journal and Record. 1932; 135:449–451.
75. Townsend J. History of influenza epidemics. Annals of Medical History. 1933; 5:533–547.
76. Anderson, A.; Anderson, M.; Dickinson, W., editors. The Chronicle of Melrose. From the Cottonian Manuscript, Faustina B. IX in the British Museum. London: Percy Lund, Humphries & Co.; 1936. Anonymous. [Anno…1173].
77. Annals of Fulda [Annales Fuldenses]. Manchester: Reuter T, Translator,Manchester University Press; 1992. Anonymous.
78. Crookshank, F. Influenza: Essays by Several Authors. London: Heinemann; 1922.
79. Petit, A. Grippe. In: Tome, XIX., editor. Dictionnaire des sciences médicales, par une société de médecins et de chirurgiens. Paris: GOM-GYP. C-L-F Panckoucke; 1817. p. 351-367.
80. Ozanam, J-A-F. Maladies épidémiques. I. Fièvre catarrhale. In: Tome, I.; Ozanam, J-A-F., editors. Histoire médicale, générale et particulière, des maladies épidémiques, contagieuses et épizootiques, qui ont régné en Europe depuis les temps les plus reculés jusqu'à nos jours. 2nd édn. Paris: Tous les Librairies pour la Médecine; 1835. p. 92-218.
81. Thompson, T. Influenza. In: Tweedie, A., editor. A System of Practical Medicine. Diseases of the Organs of Respiration. Philadelphia: Lea and Blanchard; 1841. p. 313-333.
82. Maréchal, F.; Didion, J. Tableau historique, chronologique et médical des maladies endémiques, épidémiques et contagieuses qui ont régné à Metz et dans le Pays-Messin depuis les temps les plus réculés jusqu'à nos jours. Deuxième partie. Metz: Jules Verronnais; 1863.
83. Bouquet, M. Recueil des historiens des Gaules et de la France. Tome, huitième, editor. Vol. 38. Aux depens des libraires associés: Paris; 1752. p. 245
84. Gluge, G. Die Influenza oder Grippe, nach den Quellen historisch-pathologisch dargestellt. Minden: Ferdinand Essmann; 1837.
85. Hecker, JFC. The sweating sickness. In: Hecker, JFC., editor. The Epidemics of the Middle Ages. Third edn. London: TrüCbner & Co.; 1859.
86. Hamer W. The Milroy Lectures on epidemic disease in England—the evidence of variability and persistency of type. Lancet. 1906; 1:569–574.
87. Leichtenstern, O. Influenza und dengue. In: Nothnagel, H., editor. Cholera asiatica und Cholera nostras, von C Liebermeister. Influenza und Dengue, von O Leichtenstern. Der Keuchhusten, Der

Bostock'sche Sommerkatarrh, das sogenannte Heufieber, von Georg Sticker. Wien: Alfred Hölder; 1896.

88. Morens DM, Taubenberger JK. Understanding influenza backward. Journal of the American Medical Association. 2009; 302:679–680. [PubMed: 19671909]
89. Anonymous. On the influenza of 1847. British and Foreign Medico-Chirurgical Review. 1849:90–112.
90. Thompson, T. Annals of Influenza or Epidemic Catarrhal Fever in Great Britain from 1510 to 1837. London: Sydenham Society; 1852.
91. Crawfurd, R. Plague and Pestilence in Literature and Art. Oxford: Clarendon Press; 1914.
92. Clarkson F. The history of influenza. Canadian Medical Monthly. 1920; 4:59–63.
93. Morens DM, Taubenberger JK, Folkers GK, Fauci AS. Pandemic influenza's 500th anniversary. Clinical Infectious Diseases. 2010; 51:1442–1444. [PubMed: 21067353]
94. Morens DM, North M, Taubenberger JK. Eyewitness accounts of the 1510 influenza pandemic in Europe. Lancet. 2010; 376:1894–1895. [PubMed: 21155080]
95. Short, T. A General Chronological History of the Air, Weather, Seasons, Meteors, &c. in Sundry Places and Different Times; More Particularly for the Space of 250 Years. Together with Some of Their Most Remarkable Effects on Animal (Especially Human) Bodies, and Vegetables. London: Two Volumes. Longman, T; Millar, A; 1749.
96. Lieutaud, J. La suette. In: Lieutaud, J., editor. Précis de la médecine pratique, contenant l'histoire des maladies, & la manière de les traiter; avec des observations & remarques critiques sur les points les plus intéressans. Paris: Vincent; 1761. p. 41-43.
97. Falconer, W.; Broderip; Davis, JF.; Cam, TC.; Haygarth, J. An Account of the Epidemic and Catarrhal Fever, Commonly Called the Influenza, as It Appeared at BATH in the Winter and Spring of the Year 1803. Bath: Cruttwell; 1803. Dobson.
98. Mojon, B. Memoria sopra l'epidemia catarrale che ha regnato in Parigi nell'inverno dell'anno XI. Genova: Società medica di Emulazione; 1803.
99. Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. Emerging Infectious Diseases. 2006; 12:15–22. [PubMed: 16494711]
100. Abrahams A, Hallows N, French H. A further investigation into influenzo-pneumococcal and influenzo-streptococcal septicaemia: epidemic influenzal "pneumonia" of highly fatal type and its relation to "purulent bronchitis". Lancet. 1919; 1:1–10.
101. Opie E, Freeman A, Blake F, Small J, Rivers T. Pneumonia at Camp Funston. Report to the Surgeon-General. Journal of the American Medical Association. 1919; 72:108–116.
102. Jordan, E. Epidemic Influenza: A Survey. Chicago: American Medical Association; 1927.
103. Oxford JS, Lambkin R, Elliot A, Daniels R, Sefton A, Gill D. Scientific lessons from the first influenza pandemic of the 20th century. Vaccine. 2006; 24:6742–6746. [PubMed: 17069939]
104. Clemow F. The recent pandemic of influenza: its place of origin and mode of spread. Lancet. 1894; 1:139–143.
105. Clemow, F. Influenza. In: Clemow, F., editor. The Geography of Diseases. Cambridge: University Press; 1903. p. 187-203.
106. Langmuir, A.; Serfling, R.; Sherman, I.; Dauer, C. The Epidemiology of Asian Influenza 1957–1960. A Descriptive Brochure. Washington, DC: U.S. Department of Health Education and Welfare, Public Health Service, Communicable Disease Center; 1960. Center for Disease Control, Epidemiology Branch.
107. Loosli C, Langmuir A, Fukumi H, Horowitz A, Soloviev VD, Payne M-M. Global epidemiology; epidemiology of Asian influenza, with special emphasis on the United States. American Review of Respiratory Disease. 1961; 83:2–14. [PubMed: 13758900]
108. Pyle, G. The Diffusion of Influenza: Patterns and Paradigms. Totowa, NJ: Rowan & Littlefield; 1986.
109. Valli MB, Meschi S, Selleri M, et al. Evolutionary pattern of pandemic influenza (H1N1) 2009 virus in the late phases of the 2009 pandemic. PLoS Currents: Influenza. 2010; 2 RRN1149.

110. Lemey P, Suchard M, Rambaut A. Reconstructing the initial global spread of a human influenza pandemic: a Bayesian spatial-temporal model for the global spread of H1N1pdm. PLoS Currents: Influenza. 2009; 1 RRN1031.
111. Smith GJ, Vijaykrishna D, Bahl J, et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature. 2009; 459:1122–1125. [PubMed: 19516283]
112. de Konigshoven, Jacobi. [Jakob Twinger von Königshofen] Die Alteste Teutsche so wol Allgemeine Als Insonderheit Elsassische und Strassburgische Chronicke von Jacob von Königshoven. Priestern in Strassburg. Von Anfang der Welt biss ins Jahr nach Christi Geburth MCCCLXXXVI [1386] beschrieben an jetzo zum ersten mal heraus undmit historischen Anmerkungen in Truck gegeben. In: Schilter, n; Johann, D[SchilteroJo(annis)].; Jo(annis), Schiltero, editors. Chronicon Universale #x00026; Alsaticum Jacobi de Konigshoven, Presbyteri ad D. Thomæ Argentorah an 1386. Nunc primum Editium. Strassburg: Josias Städel; 1698.
113. Whytt R. An account of the epidemic distemper at Edinburgh, and several other parts in the South of Scotland, in autumn 1758. Medical Observations and Inquiries by a Society of Physicians. 1758; 2:187–202.
114. Mulder, J.; Hers, J. Influenza. Groningen: Wolters-Noordhoff Publishing; 1972.
115. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. The Journal of Infectious Diseases. 2008; 198:962–970. [PubMed: 18710327]
116. Gill JR, Sheng ZM, Ely SF, et al. Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. Archives of Pathology & Laboratory Medicine. 2010; 134:235–243. [PubMed: 20121613]
117. Brundage JF, Shanks GD. What really happened during the 1918 influenza pandemic? The importance of bacterial secondary infections. The Journal of Infectious Diseases. 2007; 196:1717–1718. [PubMed: 18008258]
118. Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerging Infectious Diseases. 2008; 14:1193–1199. [PubMed: 18680641]
119. Shanks GD, Mackenzie A, McLaughlin R, et al. Mortality risk factors during the 1918–1919 influenza pandemic in the Australian army. The Journal of Infectious Diseases. 2010; 201:1880–1889. [PubMed: 20450336]
120. Klugman KP, Astley CM, Lipsitch M. Time from illness onset to death, 1918 influenza and pneumococcal pneumonia. Emerging Infectious Diseases. 2009; 15:346–347. [PubMed: 19193293]
121. Chien Y-W, Klugman KP, Morens DM. Bacterial pathogens and death during the 1918 influenza pandemic. The New England Journal of Medicine. 2009; 361:2582–2583. [PubMed: 20032332]
122. Chien Y-W, Klugman KP, Morens DM. Efficacy of whole-cell killed bacterial vaccines in preventing pneumonia and death during the 1918 influenza pandemic. The Journal of Infectious Diseases. 2010; 202:1639–1648. [PubMed: 21028954]
123. Brown IH. The epidemiology and evolution of influenza viruses in pigs. Veterinary Microbiology. 2000; 74:29–46. [PubMed: 10799776]
124. Dunham EJ, Dugan VG, Kaser EK, et al. Different evolutionary trajectories of European avian-like and classical swine H1N1 influenza A viruses. Journal of Virology. 2009; 83:5485–5494. [PubMed: 19297491]
125. Gaydos JC, Top FH Jr, Hodder RA, Russell PK. Swine influenza A outbreak, Fort Dix, New Jersey, 1976. Emerging Infectious Diseases. 2006; 12:23–28. [PubMed: 16494712]
126. Sencer D, Millar J. Reflections on the 1976 swine flu vaccination program. Emerging Infectious Diseases. 2006; 12:29–33. [PubMed: 16494713]
127. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. Clinical Infectious Diseases. 2007; 44:1084–1088. [PubMed: 17366454]
128. Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. Science. 2009; 325:197–201. [PubMed: 19465683]

129. Scholtissek C, Burger H, Bachmann PA, Hannoun C. Genetic relatedness of hemagglutinins of the H1 subtype of influenza A viruses isolated from swine and birds. Virology. 1983; 129:521–523. [PubMed: 6623931]

130. Webster R, Bean W, Gorman O, Chambers T, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiological Reviews. 1992; 56:152–179. [PubMed: 1579108]

131. Horimoto T, Kawaoka Y. Pandemic threat posed by avian influenza A viruses. Clinical Microbiology Reviews. 2001; 14:129–149. [PubMed: 11148006]

132. de Solleysel, J. Le Parfait Mareschal, Qui Enseigne A Connoistre La Beauté, La Bonté, Et Les Defauts Des Chevaux, Les Signes & les Causes des maladies: les moyens de les prévenir, leur guerison, & le bon ou mauvais usage de la Purgation & de la Saignée. La maniere de les conserver dans les Voyages, de les nourit & de les penser selon l'ordre. La Ferrure sur les desseins des Fers, qui rétabliront les méchans pieds, & conserveront les bons. Ensemble Un Traité du Haras, pour élever de beaux& de bons poulains; & les Préceptes pour bien Emboucher le Chevaux: Avec les Figures necessaires. neuvième, édn; Tome, Premier, editors. Bruxelles: Lambert Marchant; 1691.

133. Huxham, J. De Aëre et Morbis Epidemicis, Anno MDCCXXIX [1729]. In: Huxham, J., editor. Observationes de Aere et Morbis Epidemicis, Ab Anno MDCCXXVIII [1728] Ad Finem Anni MDCCXXXVI [1736], Plymuthi factæ. Londini: S. Austen; 1739. p. 27-77.

134. Whytt, R. Appendix. An account of an epidemic distemper at Edinburgh, and several other parts in the South of Scotland, in the autumn of 1758; in a letter to Dr. [John] Pringle. In: Whytt, R., editor. Observations on the Dropsy in the Brain. Edinburgh: John Balfour; 1758. p. 159-171.

135. Bissett, C. An Essay on the Medical Constitution of Great Britain. To Which are Added Observations on the Weather, and the Diseases which Appear in the Period Included Betwixt the First of January 1758, and the Summer Solstice in 1760. Together with a Narrative of the Throat Distemper, and the Miliary Fever, which were Epidemical in the Duchy of Cleveland, in 1760. Likewise, Observations on the Effects of Some Antihelminthics, Particularly the Great Bastard, Black Hellibore, or Bear's-Foot. Bissett, C., editor. London: A. Millar, D. Wilson; 1762.

136. Burne J. Dispensary reports. The present influenza. London Medical Gazette. 1831; 8:430–432.

137. Hingeston J. Of the late influenza. London Medical Gazette. 1833; 12:199–201.

138. Forry S. On the epidemic influenzas, with special reference to the now prevailing epidemic catarrhal fever. New York Journal of Medicine. 1843; 1:64–79.

139. Fleming, G. Animal Plagues: Their History, Nature, and Prevention. London: Chapman and Hall; 1871.

140. Law, J. Influenza in horses. In: Commissioner of Agriculture. , editor. Report of the Commissioner of Agriculture for the Year 1872. Washington, DC: US Government Printing Office; 1874. p. 203-248.

141. Husard J-B. Épizootie catarrhale de 1776. Journal de médecine, chirurgie, pharmacie, etc. 1780; 54:333–337.

142. Judson A. History and course of the epizoötic among horses upon the North American continent in 1872–73. Public Health Papers and Reports. 1873; 1:88–109.

143. Hutton T, Galen Treichler G, Seip G, et al. On the epidemic influenza. The Medical and Surgical Reporter. 1873; 28:275–281.

144. Tibbals, N. Appendix. Report on diseases of horses. In: Board of Health of the City of New Haven. , editor. The Fifth Annual Report of the Board of Health of the City of New Haven 1877. New Haven, CT: Tuttle, Morehouse & Taylor; 1878. p. 65-67.

145. Soper G. Influenza in horses and in man. New York Medical Journal. 1919; 109:720–724.

146. Morens DM, Taubenberger JK. Historical thoughts on influenza viral ecosystems, or behold a pale horse, dead dogs, failing fowl, and sick swine. Influenza and Other Respiratory Viruses. 2010; 4:327–337. [PubMed: 20958926]

147. Judson, A. Report on the origin and progress of the epizootic among horses in 1872, with a table of mortality in New York. Illustrated with maps. In: Board of Health of the Health Department of the City of New York. , editor. Third Annual Report of the Board of Health of the Health Department of the City of New York, April 11, 1872, to April 30, 1873. New York: D. Appleton and Company; 1873. p. 250-291.

148. Tyrrell G. The epidemic influenza. Pacific Medical and Surgical Journal. 1873; 7:213–225.

149. Mathers G. The streptococcus in acute epidemic respiratory infection of horses, so-called equine influenza, stable fever, shipping fever, equine typhoid fever, contagious pleuropneumonia, etc. The Journal of Infectious Diseases. 1918; 22:74–79.

150. Rutty, J. A Chronological History of the Weather and Seasons, and of the Prevailing Diseases in Dublin, with Their Various Periods, Successions, and Revolutions, during the Space of Forty Years. With a Comparative View of the Difference of the Irish Climate and Diseases, and Those of England and Other Countries. London: Robinson and Roberts; 1770.

151. Trombone-Zymosis; Ripley, G.; Dana, C., editors. The American Cyclopaedia: a Popular Dictionary of General Knowledge. Vol. Vol. XVI. New York: D. Appleton and Company; 1876. Anonymous. Veterinary science; p. 331-336.

152. Barrier, C. De la maladie des chiens. In: Tome, V.; deuxième, édn; Chabert, P.; Flandrin, P.; Huzard, J-B., editors. Instructions et observations sur les maladies des animaux domestiques. Paris: Huzard; 1804. p. 123-148.

153. Parkes, E. Influenza. In: Reynolds, J.; Hartshorne, H., editors. System of Medicine. Vol. Vol. I. Philadelphia: Henry C. Lea's Son; 1880. p. 33-47.

154. Crawford PC, Dubovi EJ, Castleman WL, et al. Transmission of equine influenza virus to dogs. Science. 2005; 310:482–485. [PubMed: 16186182]

155. Scholtissek C, Rohde W, Von Hoyningen V, Rott R. On the origin of the human influenza virus subtypes H2N2 and H3N2. Virology. 1978; 87:13–20. [PubMed: 664248]

156. Kawaoka Y, Krauss S, Webster RG. Avian-to-human transmission of the PB1 gene of influenza A viruses in the 1957 and 1968 pandemics. Journal of Virology. 1989; 63:4603–4608. [PubMed: 2795713]

157. Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. Characterization of the 1918 influenza virus polymerase genes. Nature. 2005; 437:889–893. [PubMed: 16208372]

158. Rabadan R, Levine AJ, Robins H. Comparison of avian and human influenza A viruses reveals a mutational bias on the viral genomes. Journal of Virology. 2006; 80:11887–11891. [PubMed: 16987977]

159. Taubenberger JK, Kash JC. Influenza virus evolution, host adaptation and pandemic formation. Cell Host & Microbe. 2010; 7(6):440–451. [PubMed: 20542248]

160. Dugan VG, Chen R, Spiro DJ, et al. The evolutionary genetics and emergence of avian influenza viruses in wild birds. PLoS Pathogens. 2008; 4:e1000076. [PubMed: 18516303]

161. Parrish CR, Holmes EC, Morens DM, et al. Cross-species virus transmission and the emergence of new epidemic diseases. Microbiology and Molecular Biology Reviews. 2008; 72:457–470. [PubMed: 18772285]

162. Smith G, Bahl J, Vijaykrishna D, et al. Dating the emergence of pandemic influenza viruses. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106:11709–11712. [PubMed: 19597152]

163. Peiris JS, de Jong MD, Guan Y. Avian influenza virus (H5N1): a threat to human health. Clinical Microbiology Reviews. 2007; 20:243–267. [PubMed: 17428885]

164. Sennerto, D. De Catarrho & Tussi epidemia. In: Sennert, D., editor. De Febribus Libri IV. Wittbergæ: Zachariam Schurerum; 1619. p. 1055-1064.

165. Baronio, G. Essai sur lamaladie épizootique qui a regné sur les volailles, dans la Lombardie, pendant l'été de 1789. In: Tome, IV.; deuxième, édn; Chabert, P.; Flandrin, P.; Huzard, J-B., editors. Instructions et Observations sur les maladies des animaux domestiques. Paris, An X: Huzard; 1802. p. 207-225.

166. Holmes EC, Ghedin E, Miller N, et al. Whole-genome analysis of human influenza A virus reveals multiple persistent lineages and reassortment among recent H3N2 viruses. PLoS Biology. 2005; 3:e300. [PubMed: 16026181]

167. Memoli MJ, Jagger BW, Dugan VG, Qi L, Jackson JP, Taubenberger JK. Recent human influenza A/H3N2 virus evolution driven by novel selection factors in addition to antigenic drift. The Journal of Infectious Diseases. 2009; 200:1232–1241. [PubMed: 19743921]

168. Nelson MI, Viboud C, Simonsen L, et al. Multiple reassortment events in the evolutionary history of H1N1 influenza A virus since 1918. PLoS Pathogens. 2008; 4:e1000012. [PubMed: 18463694]

169. Rambaut A, Pybus OG, Nelson MI, Viboud C, Taubenberger JK, Holmes EC. The genomic and epidemiological dynamics of human influenza A virus. Nature. 2008; 453:615–619. [PubMed: 18418375]

170. Gray E, Anderson, Murray. An account of the epidemic catarrh, of the year 1782. Medical Communications. 1784; 1:1–70.

171. Carmichael, SmythJ. Remarks on the influenza of the year 1782. Medical Communications. 1784; 1:71–85.

172. Brown. The Medical Magazine. Vol. 11. Boston: Allen and Ticknor; 1833. Influenza [Part I]; p. 674-676.

173. Marc-d'Espine J. De la grippe à Genève, comparée aux épidémies de grippe qui ont visité cette ville précedement. Gazette médicale de Paris. 1848:372–375. 385–388.

174. Chin T, Foley J, Doto I, Gravelle C, Weston J. Morbidity and mortality characteristics of Asian strain influenza. Public Health Reports. 1960; 75:149–158. [PubMed: 19316351]

175. Slepushkin A. The effect of a previous attack of A1 influenza on susceptibility to A2 virus during the 1957 outbreak. Bulletin of the World Health Organization. 1959; 20:297–301. [PubMed: 13651915]

176. Henle W, Lief F. The broadening of antibody spectra following multiple exposures to influenza viruses. American Review of Respiratory Disease. 1963; 88:379–386. [PubMed: 14064952]

177. Roden A. National experience with Hong Kong influenza in the United Kingdom, 1968'69. Bulletin of the World Health Organization. 1969; 41:375–380. [PubMed: 5309441]

178. Monto A, Kendal A. Effect of neuraminidase antibody on Hong Kong influenza. Lancet. 1973; 1:623–625. [PubMed: 4121842]

179. Yamane N, Odagiri T, Arikawa J, Kumasaka M, Ishida N. Effect of specific immunity to viral neuraminidase on subsequent influenza virus infection in man. Microbiology and Immunology. 1979; 23:565–567. [PubMed: 491992]

180. Sonoguchi T, Naito H, Hara M, Takeuchi Y, Fukumi H. Cross-subtype protection in humans during sequential, overlapping, and/or concurrent epidemics caused by H3N2 and H1N1 influenza viruses. The Journal of Infectious Diseases. 1985; 151:81–88. [PubMed: 3965596]

181. Hancock K, Veguilla V, Lu X, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. The New England Journal of Medicine. 2009; 361:1945–1952. [PubMed: 19745214]

182. Wei CJ, Boyington JC, Dai K, et al. Cross-neutralization of 1918 and 2009 influenza viruses: role of glycans in viral evolution and vaccine design. Science Translational Medicine. 2010; 2 24ra21.

183. Kash JC, Qi L, Dugan VG, et al. Prior infection with classical swine H1N1 influenza viruses is associated with protective immunity to the 2009 pandemic H1N1 virus. Influenza and Other Respiratory Viruses. 2010; 4:121–127. [PubMed: 20409208]

184. McCullers JA, Van De Velde LA, Allison KJ, Branum KC, Webby RJ, Flynn PM. Recipients of vaccine against the 1976 "swine flu" have enhanced neutralization responses to the 2009 novel H1N1 influenza virus. Clinical Infectious Diseases. 2010; 50:1487–1492. [PubMed: 20415539]

185. Peltola V, McCullers J. Respiratory viruses predisposing to bacterial infections: role of neuraminidase. The Pediatric Infectious Disease Journal. 2004; 23(Suppl)(1):S87–S97. [PubMed: 14730275]

186. Bastien N, Antonishyn NA, Brandt K, et al. Human infection with a triple-reassortant swine influenza A(H1N1) virus containing the hemagglutinin and neuraminidase genes of seasonal influenza virus. The Journal of Infectious Diseases. 2010; 201:1178–1182. [PubMed: 20199242]

187. Lubinski H. Statistische Betrachtungen zur Grippepandemie in Breslau 1918-22. Zentralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten. 1923–1924; 91:372–383.

188. Shaman J, Kohn M. Absolute humidity modulates influenza survival, transmission, and seasonality. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106:3243–3248. [PubMed: 19204283]

189. Lofgren E, Fefferman NH, Naumov YN, Gorski J, Naumova EN. Influenza seasonality: underlying causes and modeling theories. Journal of Virology. 2007; 81:5429–5436. [PubMed: 17182688]

190. Lowen AC, Palese P. Influenza virus transmission: basic science and implications for the use of antiviral drugs during a pandemic. Infectious Disorders Drug Targets. 2007; 7:318–328. [PubMed: 18220963]

191. Trotter Y, Dunn F, Drachman R, Henderson D, Pizzi M, Langmuir A. Asian influenza in the United States, 1957–1958. American Journal of Hygiene. 1959; 70:34–50. [PubMed: 13670166]

192. Dauer C, Serfling R. Mortality from influenza 1957–1958 and 1959–1960. American Review of Respiratory Disease. 1961; 83:15–28.

193. Dunn F. Pandemic influenza in 1957: review of international spread of new Asian strain. Journal of the American Medical Association. 1958; 166:1140–1148. [PubMed: 13513331]

194. Zuelzer, W. Influenza. In: Acute Infectious Diseases, von Ziemssen, H.; Buck, A., editors. Cyclopædia of the Practice of Medicine. Vol. Vol. II. New York: William Wood and Company; 1875. p. 515-538.

195. Winthrop, J. The History of New England from 1630–1649. Vol. Vol. II. Boston: Little, Brown and Company; 1853. p. 378-381.

196. Gilchrist, E. Observations on the catarrhal epidemic of 1762. In: Gilchrist, E., editor. Essays and Observations, Physical and Literary. Read before the Philosophical Society in Edinburgh, and Published by Them. Vol. Vol. III. Edinburgh: John Balfour; 1771. p. 409-424.

197. Morens DM, Taubenberger JK, Fauci AS. The 2009 H1N1 pandemic influenza virus: what next? MBio. 2010; 1(4) e00211-10.

198. Nakajima K, Desselberger U, Palese P. Recent human influenza A (H1N1) viruses are closely related genetically to strains isolated in 1950. Nature. 1978; 274:334–339. [PubMed: 672956]

199. Francis T. On the doctrine of original antigenic sin. Proceedings of the American Philosophical Society. 1960; 104:572–578.

200. Kilbourne, E. Epidemiology of influenza. In: Kilbourne, E.; Bean, W., editors. The Influenza Viruses and Influenza. New York: Academic Press; 1975.

201. Hilleman MR. Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control. Vaccine. 2002; 20:3068–3087. [PubMed: 12163258]

202. Fothergill A. An account of the epidemic catarrh, (termed influenza), as it appeared at Northampton, and in the adjacent villages, in 1775; with a comparative view of a similar disease, as it was observed in London, and its environs, in 1782. Memoirs of the Medical Society of London. 1792; 3:30–43.

203. Willis, T. Febris Catarrhalis, Anno 1658. medio Vere, Epidemicæ descriptio, prid. Calen. Junii habita. In: Willis, T., editor. Opera Omnia. Tomus Prior. De Febribus. Caput XVI. De Febribus Epidemicis. Genevae: Samuelem de Tournes; 1680. p. 209-222.

204. Dunglison, R. 2. Epidemic Acute Bronchitis. The Practice of Medicine or, a Treatise on Special Pathology and Therapeutics. Vol. Vol. I. Philadelphia: Lea and Blanchard; 1842. p. 265-269.

205. Jack W. A note on the history of influenza. Glasgow Medical Journal. 1919; 91:1–24.

206. How Achilles and Agamemnon quarelled over Briseis, and how Thetis persuaded Zeus to support her son. Book I. The Iliad. New York: Thomas Nelson and Sons, Ltd; 1938. Homer.

207. Diodorus Siculus. Bibliotheca Historica, lib xiii, C. 45; lib. xiv, C. 70, 71.

208. Smallman-aynor, M.; Cliff, A. War Epidemics. An Historical Geography of Infectious Diseases in Military Conflict and Civil Strife, 1850–2000. Oxford: Oxford University Press; 2004.

209. de Mussis, J.; Muratori, LA. Chronicon Placentinum [Piacenza] ab anno CCXXII [222]. usque ad annum MCCCCII [1402]. Milano: Societas Palatina; 1730. [column 546].

210. Valeriola, F. Loci medicinae communes, tribus libris digesti. Appendix. Cap. II. Lugduni [Leiden]: Haeredes Sebastiani Gryphii; 1562. p. 45

211. Ripperger, A. Die Influenza; ihre Geschichte, Epidemiologie, Aetiologie, Symptomatologie und Therapie sowie ihre Complicationen und Nachkrankheiten. München: Lehmann; 1892.

212. Sydenham, T. Observationes Medicae circa Morboram Acutorum Historiam et Curationem. Londini: Gualteri Kettilby; 1676.

213. Heberden, W. Medical Transactions. Second edn. Vol. Vol. I. London: Royal College of Physicians of London; 1772. The epidemical cold, in June and July, 1767; p. 437-441.

214. Fothergill, J. A Sketch of the Late Epidemick Disease as It Appeared in London. London: Anonymous; 1775.

215. Hamilton, R. A Description of the Influenza; with Its Distinction and Method of Cure. London: J. Johnson; 1782.

216. Haygarth, J. 10. Dr. Haygarth, of Chester. [1775]. In: Thompson, T., editor. Annals of Influenza or Epidemic Catarrhal Fever in Great Britain from 1510 to 1837. London: Sydenham Society; 1852. p. 108-111.

217. Haygarth, J. 6. Dr. John Haygarth. Of the manner in which the Influenza of 1775 and 1782 spread by contagion in Chester and its neighborhood. In: Thompson, T., editor. Annals of Influenza or Epidemic Catarrhal Fever in Great Britain from 1510 to 1837. London: Sydenham Society; 1852. p. 191-199.

218. Clendinning J. Notice of the influenza of January and February, 1837. London Medical Gazette. 1837; 19:780–784.

219. Moore, V. Influenza. In: Moore, V., editor. The Pathology and Differential Diagnosis of Infectious Diseases of Animals. Ithaca, NY: Taylor & Carpenter; 1906. p. 440-445.

220. Taubenberger JK, Hultin JV, Morens DM. Discovery and characterization of the 1918 pandemic influenza virus in historical context. Antiviral Therapy. 2007; 12:581–591. [PubMed: 17944266]

221. Arbuthnot, J. An Essay Concerning the Nature of Aliments, and the Choice of Them, According to the Different Constitutions of Human Bodies. In which the Different Effects, Advantages and Disadvantages of Animal and Vegetable Diet, are Explained…. London: J Tonson; 1732.

222. Arbuthnot, J. An Essay Concerning the Effects of Air on Human Bodies. London: J & R Tonson & S Draper; 1751.

223. Jones A. Observations on the influenza or epidemic catarrh, as it prevailed in Georgia during the winter and spring of 1826. The Philadelphia Journal of the Medical and Physical Sciences. 1826; 13(4) new series No. 7 1–30.

224. Steer M. Cenni sull'epidemia detta Influenza o Grippe. Annali Universali diMedicina. 1833; 47:19–50.

225. Anonymous. The influenza. Lancet. 1837; 1:621–622.

226. Anonymous. Geschichte der Grippe mit näherer Rücksicht auf ihre geographische Richtung und ihr Vorkommen in Wien. (Neue Folge der) Gesundheits-Zeitung (Wien). 1837; 1:145–151. 155–156.

227. Mojon B. Note sur la grippe qui a régné à Paris en 1803. Gazette Médicale de Paris. 1837; 15:162–164.

228. Lessing, M. Handbuch der Geschichte der Medizin. Berlin: August Hirschwald; 1838.

229. Begin, É-A. Lettres sur quelques phlegmasies muqueses épidémiques qui ont régné depuis deux siècles dans le nord-est de la France. Metz: Verronais; 1841.

230. Hernandez-Morejon, A. Epidemiología. In: Hernandez-Morejon, A., editor. Bibliotheca escojida de medicina y cirujía ó coleccion de las mejores obras de esta extranjero, y de otras originales. Madrid: Jordan é Hijos; 1846. p. 61-68.

231. Hancock, T. INFLUENZA (epidemic catarrh). In: INFLUENZA-RAPE, Forbes, J.; Tweedie, A.; Conolly, J.; Dunglison, R., editors. The Cyclopedia of Medicine: Comprising Treatises on the Nature and Treatment of Diseases, Materia Medica and Therapeutics, Medical Jurisprudence, etc, etc. Vol. Vol. III. Philadelphia: Lea & Blanchard; 1847. p. 17-26.

232. Peacock, T. On the Influenza, or Epidemic Catarrhal Fever of 1847–1848. London: Churchill; 1848.

233. Biermer, A. Influenza; Grippe; epidemisches Katarrhfieber. In: Virchow, R., editor. Handbuch der speciellen Pathologie und Therapie. Band V. Abth. 1, 4te. Lieferung. Erlangen: Ferdinand Enke; 1865. p. 592-634.

234. Brochin, H. Grippe. In: Tome, X.; GOU-GRO, Dechambre, A., editors. Dictionnaire encyclopédique des sciences médicales. Quatrième série. F-K. Paris: G. Masson; 1884. p. 713-749.

235. Kusnezow, A.; Herrmann, F. Influenza. Eine geschichtliche und klinische Studie. Wien: Šafář; 1890. [Kuznetsov ACh, German FL].

236. Sisley, R. Epidemic Influenza: Notes on Its Origin and Method of Spread. London: Longmans, Green, and Company; 1891.

237. Tarchetti, P. Rivista storico-clinica delle principali epidemie d'influenza dal secolo XVI al nostri giorni. Allesandria: G Panizza; 1892.

238. Hinsdale, G. Contributions to Medical and Biological Research, Dedicated to Sir William Osler. Vol. Vol. II. New York: Paul B. Hoeber; 1919. Epidemics of influenza in 1647, 1789-90 and 1807, as Recorded by Noah Webster, Benjamin Rush, and Daniel Drake; p. 721-730.

239. Rahts C. Die Influenza-Epidemie des Winters 1893/94 im Deutschen Reiche. Arbeiten aus dem Kaiserlichen Gesundheitsamte. 1896; 12:423–448.

240. Serfling R, Sherman I, Houseworth R. Excess pneumonia-influenza mortality by age and sex in three major influenza A2 epidemics, United States, 1957-58, 1960 and 1963. American Journal of Epidemiology. 1967; 86:433–441. [PubMed: 6058395]

241. Ailing D, Blackwelder W, Stuart-Harris C. A study of excess mortality during influenza epidemics in the United States, 1968-76. American Journal of Epidemiology. 1981; 113:30–43. [PubMed: 7457477]

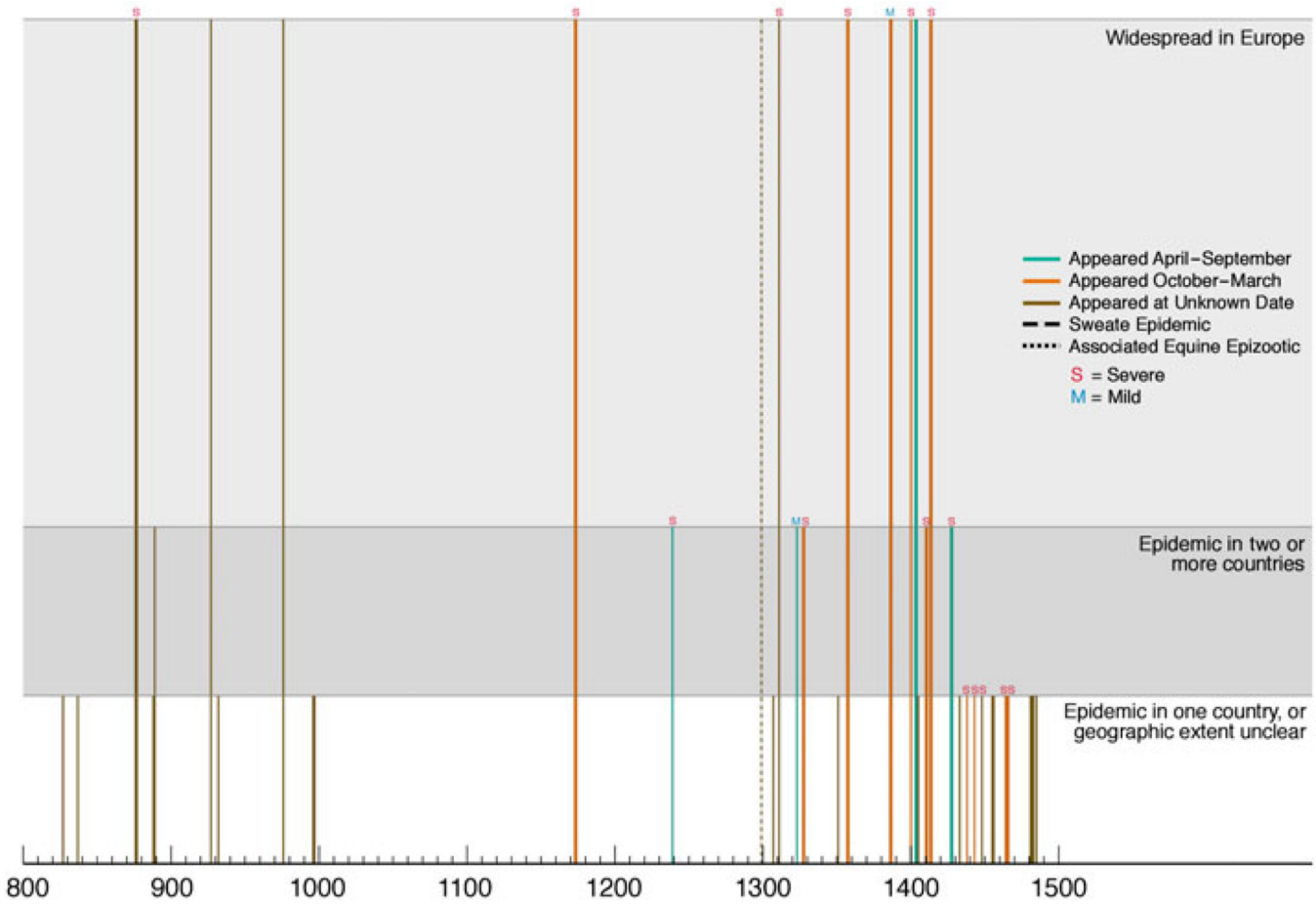

Figure 1.

European epidemics of probable influenza during the period of European monastic and court chronicles, 876–1491AD.On the *y*-axis, influenza activity is recorded according to apparent degree of geographic extension, as determined by historians and historical documents [2–6,13,14,17,18,22–28,30–33,35–37,39–44,46–68,71,74–76,78–82,84,87,90–92,95,97,104,133,170,194–196,205–212,215,218,219,221–238]. Such determinations may only be rough approximations. Disease severity as reported by contemporary observers is characterized as “mild” (M) or “severe” (S). In most instances, these designations have not been established by either reliable mortality or case-fatality data. Unlettered epidemics/pandemics reflect insufficient information about disease severity. Also plotted is the first sweate epidemic of 1485

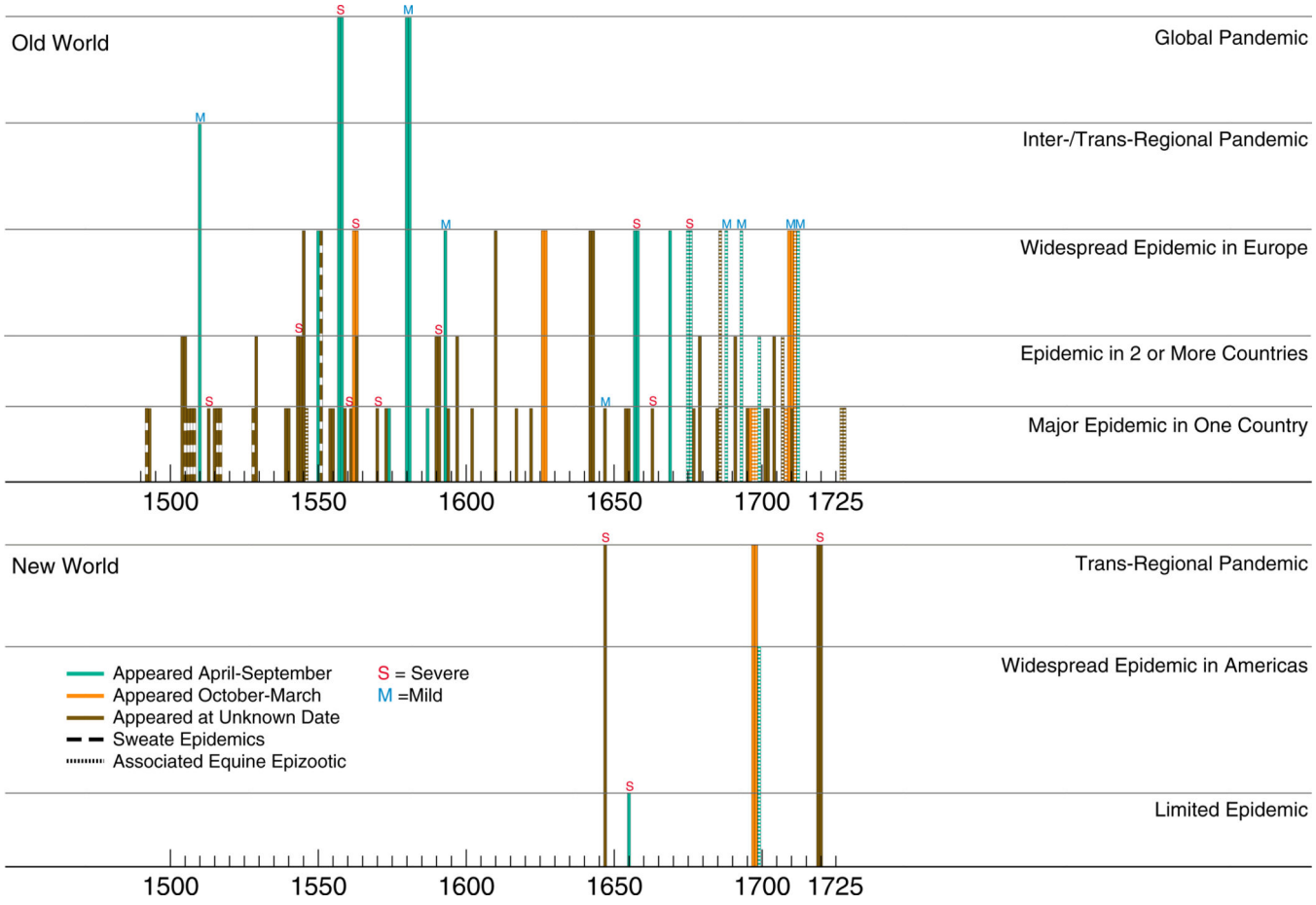

Figure 2.

Old World (top panel) and New World (bottom panel) pandemics and epidemics of probable influenza, 1492–1728. On the *y*-axis, influenza activity is recorded according to apparent degree of geographic extension, as determined by historians and historical documents [2–6,13,14,17,18,22–28,30–33,35–37,39–44,46–63,65–68,71,74–76,78–82,84,87,90–92,95,97,104,133,170,194–196,205–212,215,218,219,221–238]. Such determinations may only be rough approximations. Disease severity as reported by contemporary observers is characterized as “mild” (M) or “severe” (S). In most instances, these designations have not been established by either reliable mortality or case-fatality data. Unlettered epidemics/pandemics reflect insufficient information about disease severity. Also plotted are the sweate epidemics of the early 16th century

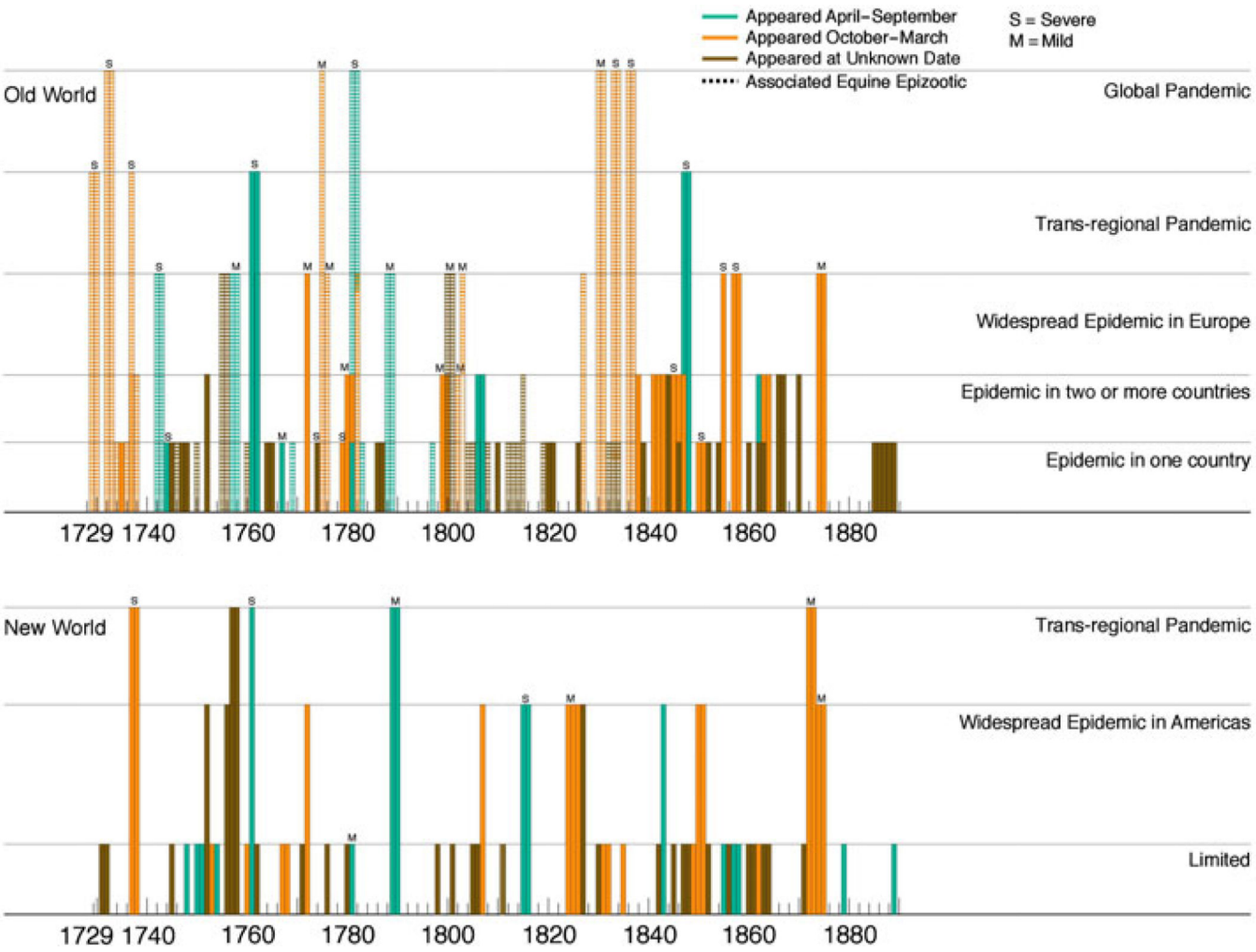

Figure 3.

Old World (top panel) and New World (bottom panel) pandemics and epidemics of probable influenza, 1729 to 1888. On the *y*-axis, influenza activity is recorded according to apparent degree of geographic extension, as determined by historians and historical documents [2–6,13,14,17,18,22–28,30–33,35–37,39–44,46–63,65–68,71,74–76,78–82,84,87,90–92,95,97,104,133,170,194–196,205–212,215,218,219,221–238]. Such determinations may only be rough approximations. Disease severity as reported by contemporary observers is characterized as “mild” (M) or “severe” (S). In most instances, these designations have not been established by either reliable mortality or case-fatality data. Unlettered epidemics/pandemics reflect insufficient information about disease severity

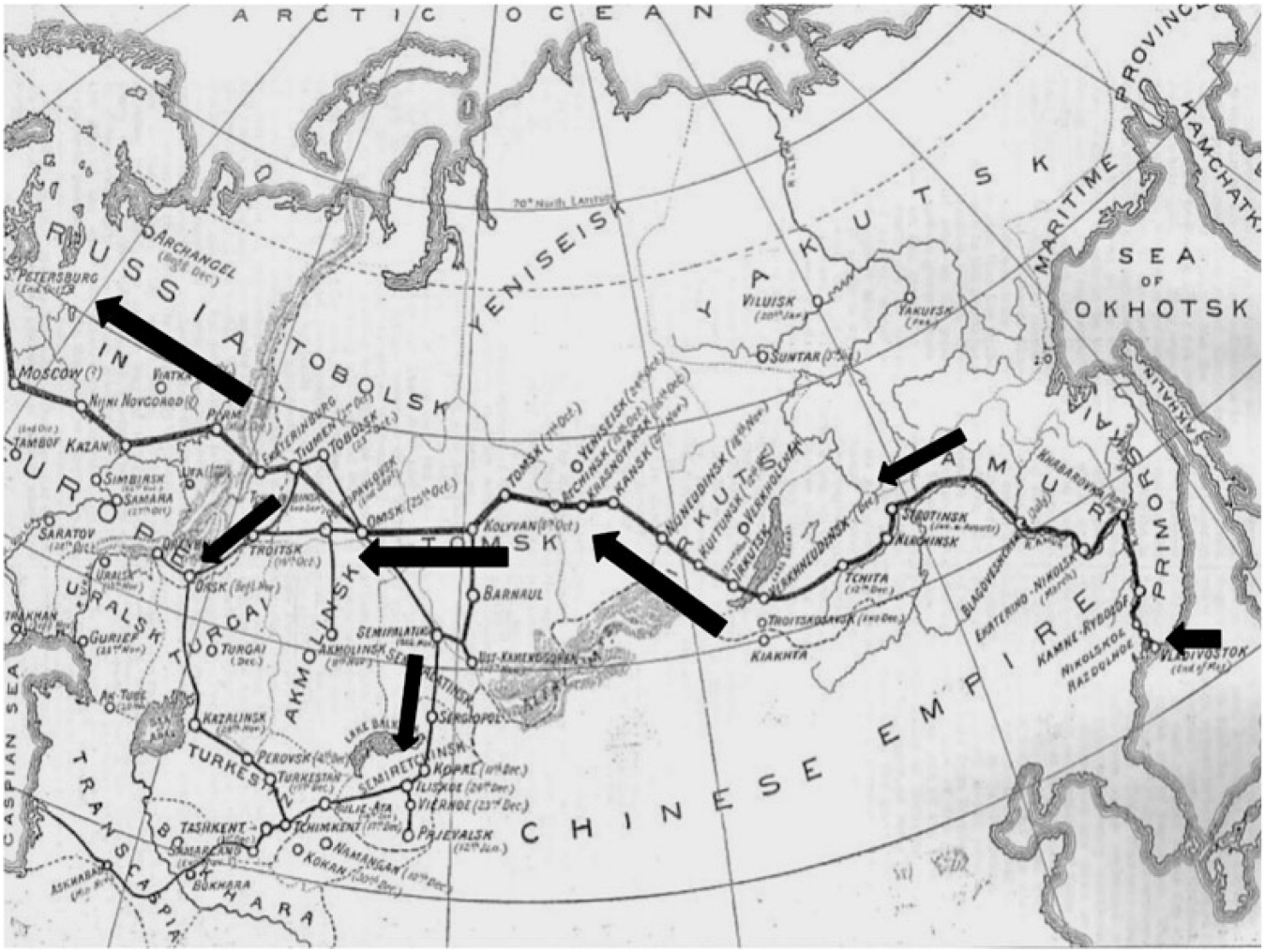

Figure 4.

The 1889 influenza pandemic was tracked globally as it first appeared and then spread quickly, in this case from East to West (Asia to Europe), similar to the rapid spread of modern pandemics [104,105]. Figure adapted from Clemow [5]

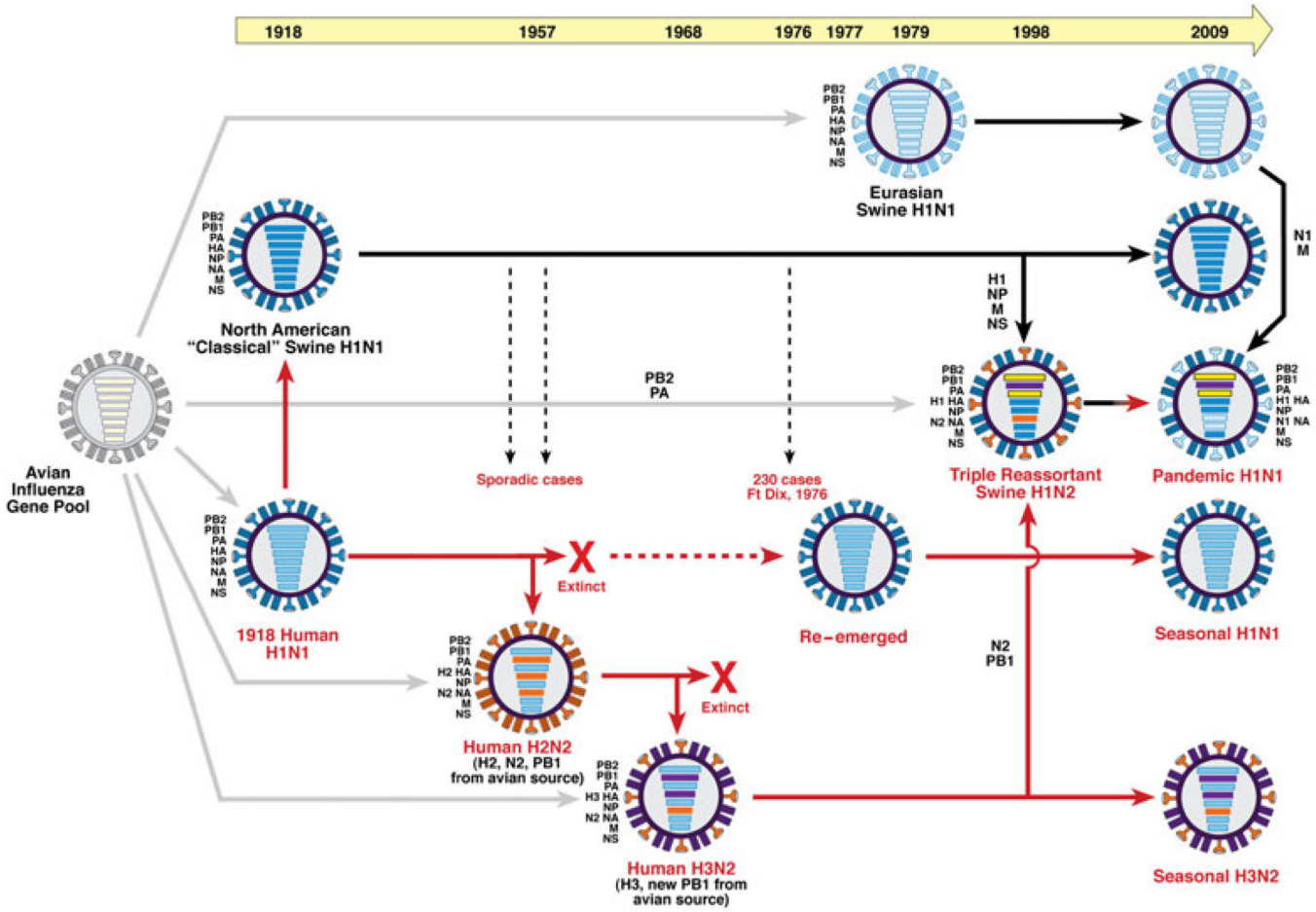

Figure 5.

Genetic relationships between human and swine influenza viruses, 1918–2010; adapted from Morens *et al.* [10]

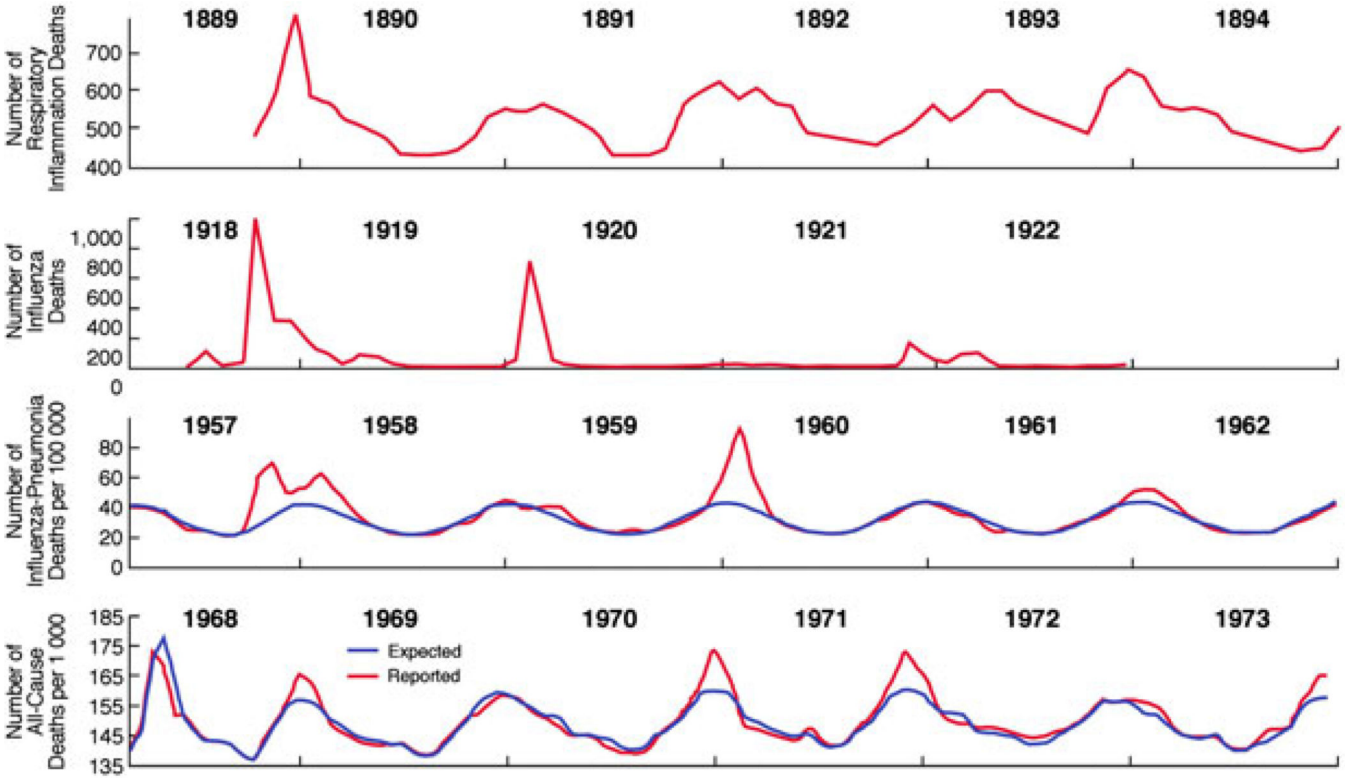

Figure 6.

Secular patterns of mortality increases over the first 5 years after pandemic appearance, in four influenza pandemics appearing between 1889 and 1968. The four panels are adapted from different data sources and cannot be compared for purpose other than examining appearance/recurrence patterns. The top panel represents data from Germany [239]. The second panel represents data from Breslau (now Wrocław, Poland), from Lubinski [187]. In the bottom two panels, representing the 1957 [240] and 1968 [241] pandemics in America, data on mortality increases are displayed as rising above the expected background

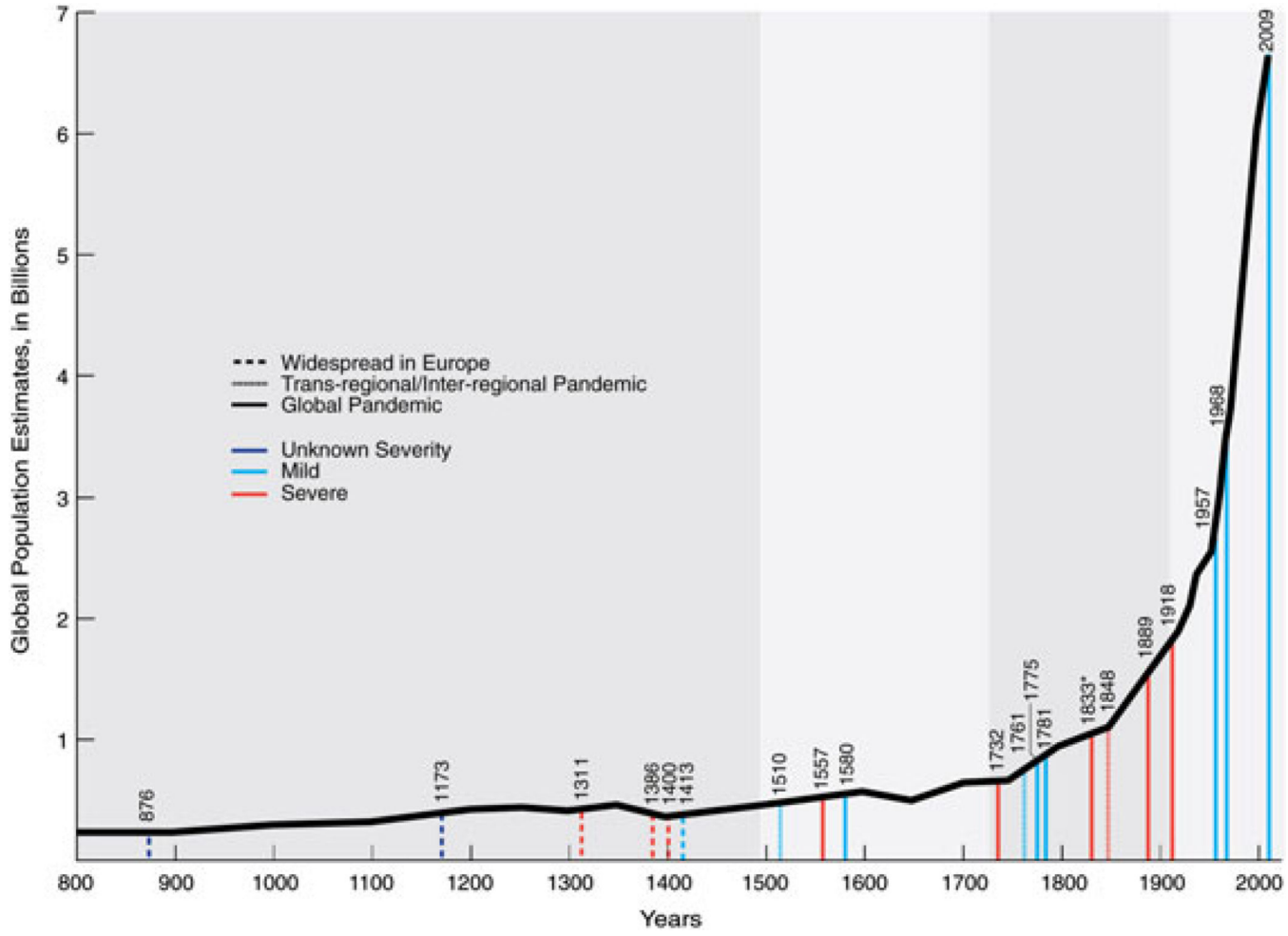

Figure 7.

Pandemic occurrence by estimated global population, 800–2009 AD. European-wide epidemics are included for the period when pandemics may not have been recorded, from 800–1491 AD (see text). *For 1833, see text discussion on different pandemics versus "waves" between 1830 and 1837

Table 1

Ancient epidemics (1194 BC to 875 AD) suggested by historians as having been caused by influenza; in no case have we found other than vague and circumstantial evidence

Date	Described	Reference
Ancient, undated	Mentioned by Hebrew writers	[205]
1194–1184 BC	Trojan war; 9-day epidemic; horses/dogs affected	[68,90,92,206]
713 BC	Host of Sennacherib, Assyrian epidemic in 185 000 men	[92]
430–425 BC	The “Plague of Athens” described by Thucydides	[13]
415 BC	Fatal epidemic in the Athenian army in Sicily	[3,5,207]
393 BC	Epidemic during the Carthaginian siege of Syracuse	[75]
212 BC	Epidemic during the Second Punic War	[208]
591–592 AD	Epidemic “extreme cough” over “the whole earth”	[71]

Table 2

Significant events recorded during European epidemics of influenza-like illness occurring in the period in which epidemics were documented in monastic and court records, 876–1491 AD

Date	Described	References
876	European-wide epidemic of fatal coughing disease; followed population movement; associated with deaths of birds and dogs	[3–5,77]
1357	Use of the term “influenza”	[16]
1386–1387	Catarrh “with rapid diffusion to the head and chest”; mortality in elderly and debilitated	[5,14,16,71,209]
1400	Infants at risk	[14,82]
1413–1414	Maternal hemorrhage, premature labor, and abortion; mention of disease in Russia	[17,30,71]

Table 3

Significant events recorded during European influenza pandemics and major epidemics, 1492–1728 AD

Date	Described	References
1510	Inter-regional pandemic	[6,33,71,81,210]
1557–1558	Global pandemic; origin in Asia	[6,65,211]
	Southeast to northwest directionality in Europe	[46,81,87]
	Recurrences associated with mortality peaks (1558–1561)	[67,95]
	Mortality peaks occur first in larger towns, later in smaller cities; still later in countryside	[67]
1580	Global pandemic; ≈6-week disease prevalences in large urban centers	[67,95]
1647	Regional pandemic in Western Hemisphere; equine influenza epizootics associated with epidemic	[4,31,71,92,95,194,195]
1675	Fatal influenza pneumonia documented by Sydenham	[212]
1693	Decreased attack rates in the elderly	[90,212]
1712	European epidemic proceeding from North to South	[31,65,71,194]

Table 4

Significant events recorded during European influenza pandemics, 1729–1889 AD

Date	Described	References
1729–1730	Autopsy of Roman cardinal who died of influenza	[22]
1775	Pandemic with very low mortality	[49,81,90,213,214]
1781–1782	First “Russian Katarrh” or “Russian disease”	[170,215]
	Persons infected in 1732–1733 or in 1775 may have been partially protected; increasing disease severity during pandemic progression?	[170]
1782	Recommendation for patient isolation	[216,217]
1802	Tracheal involvement said to be critical in severe cases	[97]
1827	Influenza not spread by blood transfusion	[3]
1833–1837	Quantification of adult influenza case fatality (not age-adjusted) at ≈2%	[80,81,92]
1836–1837	Influenza deaths associated with pre-existing bronchial conditions	[218]
	Influenza mortality associated with cardiac disease	[218]
1847	Extreme mortality in the eldest elderly	[68,173]
1872–1873	Equine panzootic in Western Hemisphere is followed by human cases and fatal avian epizootic	[6,146]
1889	Comprehensive histopathology/bacteriology in an influenza pandemic	[219,220]