The 1918 Influenza Pandemic: Back to the Future?

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Abstract

Background: It is just over a century since the 1918 flu pandemic, sometimes referred to as the “mother” of pandemics. This brief retrospective of the 1918 pandemic is taken from the viewpoint of the current SARS-CoV-2/COVID-19 pandemic and is based on a short lecture given during the 2021 Virtual Congress of the ERA-EDTA. **Summary:** This review summarizes and highlights some of the earlier pandemic’s salient features, some parallels with today, and some potential learnings, bearing in mind that the flu pandemic occurred over 100 years ago at a time of major turmoil during the climax to WWI, and with limited medical expertise and knowledge, research facilities, or well-structured and resourced healthcare services. While there is little or no information on renal complications at the time, or an effective treatment, some observations in relation to COVID-19 and vaccination are included. **Key Messages:** Lessons are difficult to draw from 1918 other than the importance and value of non-pharmaceutical measures to limit viral transmission. While the economic impact of the 1918 pandemic was significant, as it is now with COVID-19, subsequent economic analysis has shown that protecting public health and preserving economic activity are not mutually exclusive. Both

H1N1 and SARS-CoV-2 viruses are neurotropic and may cause chronically debilitating neurological diseases, including conditions such as encephalitis lethargica (still debated) and myalgic encephalomyelitis (chronic fatigue syndrome), respectively. Although coronavirus and influenza viral infections have some similarities, they are certainly not the same, as we are realising, and future infectious pandemics may still surprise us, but being “forewarned is forearmed.”

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While the present does not repeat the past,
the past can enlighten the present
*Adapted from Timothy Snyder, Richard Levin
Professor of History at Yale University*

Introduction

Influenza mortality in 1918 was unprecedented and although the final figure is still argued about, it was probably in excess of 50 million attributable deaths worldwide, and over half a million in the United States alone [1], equivalent to over 2 million for today’s US population, with 1% of those infected dying (case-fatality ratio) [2]. While there are many social and cultural differences from today, there was already widespread travel in 1918 by land (motor car, bus, and train) and sea, although no aviation; there was also rapid communication by telegraph, local,

national and international newspapers, although no radio or television; and already large mixed populations in high urban concentrations – all factors that facilitate the spread of a contagious disease like influenza.

An Historical Perspective

The “Spanish flu,” as it became known, overtook war as a cause of death at the close of WWI and may even have contributed to its ending. It was called “flu”, although its exact nature was not really clear even then and until much later. Something very like flu, at least as it was described, probably first appeared around 1510, although some authorities have suggested that it was described much earlier, in the mid-12th century, and was referred to as the “sweating sickness” [3]. As such, it is described in some detail in an account by Jhon Caius (John Keys) a physician, and later President of the Royal College of Physicians, in 1552 [4]. However, there is some doubt as to what this actually was and it probably covered a number of different causes of a contagious fever, although not particularly confined to crowded and unsanitary towns or cities, but also common among more rural populations, and perhaps a rat-borne viral infection – hantavirus has been suggested (for which bats can also be a host, as has been speculated on for the source of SARS-CoV-2 [5]). It was known to be seasonal, although more common in the summer, rather than winter, and it seemed to occur more frequently in the rich than the poor, and with a high mortality, especially in young adults. Symptoms were mainly of widespread aches and pains with headache, sweating, fever, and delirium. Later in the 17th and 18th centuries, there were several epidemics of a similar illness, but accompanied by major respiratory symptoms and the term “influenza” in Italian, from the Latin *influentia*, meaning “influence” or “visitation”, was coined. The physician Thomas Sydenham, known as the “English Hippocrates”, writing in 1679 gives a detailed account of a seasonal and epidemic respiratory illness occurring in winter and very like flu, but which he likened to “hooping cough” in children [4]. An early epidemiological study carried out by the Royal College of Physicians in England in 1780 identified one such epidemic of this flu-like illness that spread rapidly from Newcastle to London [3].

By the middle of the 19th century, influenza was recognized as widespread throughout Europe and data began to be collected on it as an important cause of death: average annual death rates per 100,000 population attributed to influenza for England and Wales in the 1840s were

Fig. 1. Adapted from reference [3] showing reported death rates per 100,000 population in England and Wales attributed to influenza from the 1840s to the 1950s and showing the peak during the 1918 pandemic; the inset (adapted from reference [6]) illustrates the 3 waves of infection during 1918 from spring, when large-scale infections first appeared and death rates were relatively modest, to the second autumn wave when deaths from infection increased dramatically, and the following spring when death rates began to fall and the pandemic slowly subside. Mortality from influenza by age is typically “U-shaped” (highest in the very young and the very old), but during the second wave in 1918, it was “W-shaped” with a peak mortality in young adults [6].

around 1,500 (for a population of 18 million) with an epidemic jump in 1847 to almost 10,000 (Fig. 1). However, the first recorded influenza pandemic was from 1889 to 1892, known as the “Russian flu” and became prevalent throughout Europe and North America, and probably spread originally from Western Siberia [3]. This established influenza as we know it today, with regular and limited seasonal outbreaks, until the 1918 pandemic. Figure 1 shows estimated deaths in England and Wales from influenza from 1840 to 1950, with the peak of the pandemic in 1918-19, and also illustrating the 3 waves of infection that occurred in 1918 – spring, autumn, and the following spring – before eventually fading away to become epidemic and seasonal again, typically in the late autumn and early winter, as now [3, 6].

Some Parallels between Influenza and COVID-19

As to its origins in 1918, this is still widely debated and there was probably no single country as the source of spread. The term “Spanish flu” is, of course, unfair, and a

Fig. 2. Worldwide patterns of influenza spread in 1918 adapted from reference [12] and the Africa Center for Strategic Studies showing at least 2 infection epicentres, the US and Europe, with relative sparing of countries such as Australia and New Zealand that could only be reached by a long sea voyage.

Fig. 3. Comparison of a typical large (mainly military) hospital (left) set up to accommodate cases of influenza in 1918 with the Nightingales emergency hospital (right) "built" in matter of days in London in anticipation of increasing numbers of severe COVID-19 cases requiring mechanical ventilation.

misnomer. Spain was a neutral country and journalists were free to report the beginnings of the pandemic, unlike the combatant nations that all enforced heavy censorship, fearing public alarm and of giving comfort to the enemy. However, cases in large numbers began to be described in the Midwest of the USA, mainly in military barracks for young army recruits before their transfer overseas to France, as well as cases in France on the Western Front, which caused significant problems for the fighting strength of both opposing armies [7, 8]. Pioneer neurosurgeon Harvey Cushing was a medical army officer in France at the time and he describes troops with epidemic "grippe", a term Osler [9] had also used (in his famous textbook *The Principles and Practice of Medicine*). Cushing [10] also describes his own affliction with what may very well have been post-influenza Guillain-Barré syndrome, which has been reported recently as a sequel of COVID-19 infection [11].

Patterns of worldwide spread are shown in Figure 2 [12]; the main affected countries are similar to what has

been seen with COVID-19, though perhaps more widespread globally, and with relatively isolated countries like Australia and New Zealand somewhat spared, although less so now because of air travel [13]. In 1918 special multi-bedded "fever" hospitals were soon established, initially for infected troops who had become ill while in their crowded dormitories or confined on troopships crossing the Atlantic to France. Figure 3 shows a typical photograph of such a facility (left) and how it compares with the first Nightingale emergency hospital (right) set up in London in just 9 days with almost 3,000 intensive care beds for anticipated COVID-19 cases.

Mask-wearing was the only form of protection available in 1918 and was standard among medical personnel and soon became widespread in public, but the masks were flimsy and worn more in the mistaken belief that they protected the wearer from infection, rather than that they might reduce the spread of infection. However, as with COVID-19, many people opposed wearing masks and protest meetings were held that only served to spread

the infection, as well as rumours and quack remedies for protection by wearing camphor ball necklaces (reminiscent of the posies worn during earlier plague epidemics¹), gargling, eating onions, fumigation and the use of carbolic spray (cf. recommendations of disinfectant and UV light for COVID-19). Despite the risks, large gatherings and “parties” were often encouraged to gain immunity; the reasoning being similar to the earlier and dangerous practice of variolation for protection against a serious bout of small pox (rather than the safer inoculation with cowpox introduced by Edward Jenner in 1796). The mortality from seasonal influenza is now generally quite low (<0.3% [13]), and it is often considered a mild infection, except in the very young and very old or infirm. In contrast, mortality in 1918 was around 3% overall, rising to almost 10% or higher in some places during the second wave, which caused death mainly among young adults (25–40 years), who accounted for 40% of fatalities [14]. This seems surprising, given the demographics of seasonal flu today, but has been attributed to residual immunity in the elderly at the time, a generation exposed as children to the 1890 pandemic mentioned earlier, and probably due to a closely related influenza virus; as well as the serious complication in many of those younger adults with first infections of secondary bacterial pneumonia and sepsis, and no effective treatments. However, why this was so prominent during the second, but not the first or third waves of infection is still unclear; it may have been due to the explosive spread of infection during the second autumn wave and an increased viral load, or the virus may have mutated to become more pathogenic. As already mentioned, influenza mortality today is <0.3% compared with current estimates of around 2% for COVID-19 [13]. But it is known that patients with chronic kidney disease tend to be older and at increased risk of a severe illness from influenza, which is why annual vaccination is generally recommended. The situation with COVID-19 in chronic kidney disease is similar and also potentially very serious with one series reporting a mortality of over 40% [15]. (These figures are for until now unvaccinated patients.)

Many of the leading scientists involved in trying to understand and combat the infection in 1918 were based in the USA and mainly at the Rockefeller Institute, which had been founded only 20 years before. William Welch

(1850–1934) had helped to create the Rockefeller Institute with the philanthropist John D. Rockefeller and was one of the first to recognize in 1918 the significance of what he considered to be a new infection that he likened to plague. Scientists at the time understood and accepted the germ theory of disease developed by Robert Koch (1843–1910) and Louis Pasteur (1822–1895) half a century earlier; they could identify and grow bacteria, and were also aware of agents causing infection that could be filtered (“filterable viruses”) and were not simple toxins. Paul Ehrlich (1854–1915) had coined the term “magic bullet” for treatments that could kill infectious pathogens. There was already an appreciation of the immune system and how it might be manipulated to protect and treat some infections with the development of antibacterial vaccines and antisera. However, it was also recognized that vaccines and antisera can only work against a specific causal agent or toxin that had to be known and identified, which was the problem for the cause of influenza. Paul Lewis (1879–1929), with Simon Flexner (1863–1946), had identified a virus as the cause of poliomyelitis in monkeys 10 years earlier and produced an effective vaccine in monkeys [16], although it would take much longer to develop a vaccine for humans. Rufus Cole (1872–1966) had successfully produced a pneumococcal vaccine that proved effective in some patients with influenza and secondary bacterial pneumonia [17]. However, much of the early focus on the causal agent for influenza was another bacterium, rather than a virus, *Haemophilus influenzae*, originally known as Pfeiffer’s bacterium, which had been isolated by Richard Pfeiffer (1858–1945) during the 1890 influenza pandemic, and hence its later name. It was found frequently in patients with influenza, although not in all cases, and attempts to immunize against it or produce an antiserum had failed. In fact, Osler considered it an association only and “constantly with us”, and an unlikely cause of influenza [9].

While it is generally believed that in 1918 the main cause of death was secondary bacterial infection with pneumonia [14], death was often rapid, occurring within 3–5 days in many cases, and it is possible that something very similar to a “cytokine storm” occurred [18], as is seen in fatal cases of COVID-19 infection, and that this contributed to the high death rate in young adults who were capable of mounting a more aggressive immune response to the virus [19]. Heliotrope (“lavender”) cyanosis, indicating profound hypoxia, was a universally fatal sign and is repeatedly referred to in the descriptions of cases reported during the second wave of infection, again mainly in young adults, and heralded by so-called ma-

¹ Children’s popular rhyme songs during the Plague; Ring a Ring o’ Roses, A pockets full of posies, Atischoo, atischoo, We all fall down, and during the 1918 pandemic; I had a little bird, its name was Enza, I open up the window and “in flu” Enza.

Fig. 4. Portraiture of example patients with severe influenza infection showing the facial signs of Heliotrope cyanosis and Mahogany spots – see text for details (adapted from reference [20]).

hogany spots over the cheeks with a flushed appearance [20] (Fig. 4). Viral as well as bacterial pneumonia occurred and subsequent studies of archived post-mortem tissue have been able to detect viral antigen [1]. Similar examples of pathology of the lung with COVID-19 infection have been described, together with bacterial superinfection in cases of severe disease and with a much poorer outcome [21, 22]. There are no descriptions available in 1918 of any associated renal involvement, but this is probably because recognizing renal dysfunction was still rudimentary at the time and that the pulmonary pathology was such a dominant clinical feature; but even today, renal complications of influenza are uncommon [23]. In contrast, it soon became apparent that SARS-CoV-2 infection is associated with acute kidney injury, initially attributed to severe pneumonia with acute respiratory distress syndrome and the recommendation to restrict intravenous fluids [24]. However, it soon became clear that the virus is renotropic and targets epithelial cells expressing angiotensin-converting enzyme 2, the receptor mediating viral entry and infection, including in renal tubular cells and causing direct cellular injury [25].

Large doses of quinine and aspirin were often the mainstays of drug treatment at the time, but administered at doses likely to cause toxicity, including deafness; aspirin toxicity may have been a contributory factor to the high mortality [26]. Again, Osler had warned of this and described the risk of “profound prostration” with the incautious use of aspirin, although he recommended strychnine during recovery as a cardiac stimulant [9].

It was again Paul Lewis who proposed that the most likely cause of influenza was a virus and not a bacterium, but he was unable to isolate it and produce a vaccine, as he had done so successfully for polio. It was left to Lewis’ sometime assistant and protégé Richard Shope (1901–1966) to isolate the virus much later, then known as swine

influenza, in 1936 and to demonstrate that it was the likely cause of the 1918 pandemic [27]. This was later identified as H1N1 virus and its related strains named according to the surface-expressed haemagglutinin (H) and neuraminidase (N) proteins (cf. SARS-CoV-2 spike protein) [28].

There have been 3 pandemics since 1918, two with different strains of the virus, the last one in 2009 with what was a similar H1N1 strain to the 1918 pandemic [1]. Animal reservoirs for influenza viruses are pig and wildfowl [29] and, as also seems possible, if contentious, for coronavirus [5]. Asian live-poultry or “wet markets” are still an important possible source of new virus strains. These markets also sell meat from other wild animals (some that can be intermediate viral hosts from, e.g., bats and pangolins [5]) and could potentially cross-contaminate.

The main routes of viral transmission for both influenza and COVID-19 seem similar, although for COVID-19 it is mainly via droplets and aerosols, rather than fomites (inanimate surfaces) [30]; direct patient contact might also be important for COVID-19 [31]. So far it seems that complications of infection are more likely in the elderly than in the very young, but as we learn more about COVID-19, it is becoming apparent that all age groups can contract COVID-19 and become seriously ill, and there is growing concern at what is being described as “long COVID”, a debilitating state of chronic ill-health following recovery from acute infection [13]. Risk and comorbidities associated with more severe infection and a poorer clinical outcome are similar for both influenza and COVID-19, including obesity and underlying cardiovascular or pulmonary disease, as well as premature birth in pregnant women [29].

An interesting and perhaps important retrospective and historical aside is that US President Woodrow Wilson contracted influenza while in Paris following the Armistice and during the Versailles Treaty negotiations. He had what may have been one of more small strokes, which were probably related to the infection (cf. COVID-19) that left him severely incapacitated. However, this was kept a secret for fear of compromising the negotiations, but historians believe that it probably resulted in the unopposed harsh demands for war reparations made by the allies, especially France, which may have led eventually to WWII [8].

Consequences, Measures, and Lessons

The pandemic compounded the economic losses of WWI. Unlike the economic upswing of a war-time economy itself, and the further post-war rebound in eco-

Fig. 5. Adapted from reference [34] showing a comparison of peak mortality between the cities of Philadelphia and St Louis: The former delayed its “lock-down” measures, whereas the latter acted promptly and maintained NPI for longer – see text for details. NPI, non-pharmaceutical interventions.

economic growth that can occur, as seen after WWII, there was an estimated 7% drop in overall economic activity from 1918 to 1920. This is similar to estimates for COVID-19 and economic activity did seem to recover significantly after the pandemic and during the boom years of the 1920s until the onset of the Great Depression in 1929 [32]. Measures to contain the infection in 1918 relied on social distancing and quarantine, as now. It became clear that large gatherings must be avoided, indeed banned, and schools closed, with enforced reporting of cases of infection and their quarantine [33]. The latter probably had a smaller impact on infection spread than the former. However, since this was not imposed in a uniform manner, it is possible to compare how these measures were put in place in different cities, their duration, and effect on peak mortality rates. For example, it became clear that a city in the USA such as Philadelphia that delayed introducing these restrictions and allowed large gatherings to continue, when compared with St Louis, a city that rapidly introduced containment measures within a few days of being alerted to new cases, experienced a much higher death rate [34] (Fig. 5). Also, the duration of these measures was important: the longer the better [35]. While the effect of reducing peak mortality may have risked another wave of infections once social distancing measures were eased, and until there had been sufficient infections to confer some degree of “herd immunity”, which at that time was only possible through being infected (rather than vaccination), it did mean that hospital services were more likely to cope with a slow easing of restrictions, and infections

may have proved milder or easier to manage with the available medical support.

An interesting recent economic analysis from data available from 1918, and in light of the debate over a choice between preserving health or preserving the economy, is that while there was clearly a significant economic impact of the pandemic, those cities that “locked-down” sooner and for longer not only experienced a lower mortality overall, but also had better maintained levels of employment-related economic activity [36]. However, what does seem crucial today is the need for financial support from governments in the short-term to sustain a healthy workforce in readiness for the pandemic’s ending. Moreover, the experience of 1918 serves to emphasize the importance and value of non-pharmaceutical interventions (NPI) and that they may need to be maintained for longer periods to match with available medical services, including personnel. Assisting the population financially helps to ensure that these measures can be put in place and continued, and that livelihoods and the economy can be supported until recovery.

We have been fortunate in developing several effective vaccines against COVID-19 in record time, which has depended not only on exploiting advances in molecular and cell biology, but also on a reassuring ability and willingness of scientists, industry, and government to co-operate [37]. These vaccines may provide the level of herd immunity we need to limit the spread of infection and end the current pandemic. However, this still depends on viral infectivity and the initial or baseline R number, the number of secondary cases generated by one primary infection in an at-risk population, as well as the efficacy of the vaccine. With the currently most effective COVID-19 vaccines, the herd immunity threshold is estimated to be around 70% of the population, but if new variants of the virus become more infectious, this threshold will increase [38]. Until the virus slows its rate of pathogenic mutation, non-pharmaceutical intervention will need to stay in place in some form and reapplied when necessary. Having learnt some of the lessons from 1918 in pandemic preparedness, the response to the last H1N1 outbreak in 2009 was quite effective [31], but for some reason we have been slower off the mark with COVID-19, despite repeated warnings that another pandemic was very likely to occur, and our earlier and recent experiences with SARS (SARS-CoV-1), MERS-CoV, Ebola, and Zika viral epidemics. No doubt future historians will provide explanations in due course.

The Longer Term

The influenza pandemic had burnt itself out by 1920 and what followed were sporadic seasonal cases, but there were subsequent large-scale epidemics in 1957 (H2N2 or Asian flu), 1968 (H3N2 or Hong Kong flu) and in 2009 (H1N1 or Swine flu). Annual flu vaccination, despite the potential for viral mutations and need to adapt vaccines, has proved effective in reducing seasonal infection rates and deaths from influenza, especially in the elderly and in those with significant comorbidities. There are now several reports that flu vaccination itself offers some protection against COVID-19 [39, 40], which may be the result of a more general priming or boost to the immune system [41].

The main late and long-term health consequence attributed to an influenza infection before and during the 1918 pandemic was encephalitis lethargica or "sleepy sickness" [42] and brought to public attention by the 1990 film "Awakenings" and the dramatic benefits of L-DOPA treatment [43]. While the link to the 1918 influenza pandemic is still disputed, the timing and epidemiology are difficult to ignore and although so far no H1N1 virus material has been isolated from historical brain tissue or CSF, no alternative causal agent has been identified [44]. Could this neurological complication or something similar follow infection with COVID-19? This is speculative, but it is worth noting that anosmia is almost a cardinal sign of early COVID-19 infection, suggesting that the virus is neurotropic, and there has been at least one case report of COVID-19-associated encephalitis [45]. However, neurological and musculoskeletal involvement may be more insidious, resulting in a syndrome very like chronic fatigue syndrome (myalgic encephalomyelitis) [46]. More neuropsychiatric complications following COVID-19 infection are becoming evident and cannot be explained by prolonged social isolation [47]. Osler [9] could have been describing COVID-19 when writing about influenza and remarking that "convalescence requires careful management, and it may be weeks or months before the patient is restored to full health" and that "depression of spirits following the disease is one of its most unpleasant and obstinate features". Moreover, there seem to be broader multiorgan consequences of COVID-19 that are beginning to be recognized, with increased disease rates for diabetes, cardiovascular events, chronic kidney and chronic liver disease [48], and that this applies across the age spectrum for a variety of other clinical sequelae [49].

Conclusion

Finally, it is instructive to look back and consider some of the parallels between 1918 and 2020 and to learn a few practical lessons from an earlier time, despite the many intervening years, and the scientific and technical progress we have made since then. One striking difference today from 1918 is the way in which it has been possible to disseminate so rapidly and freely clinical observations and research findings on COVID-19, and to test and validate quickly potential therapies. This is a tribute to the wider scientific community and its willingness to co-operate, share, and organize when necessary. But it could be that these advances have been offset to some extent by the greater freedom of travel and the inroads made into parts of the world and their animal habitats that have been relatively isolated until now. This highlights once again the importance of our environment, a theme of the 58th ERA-EDTA Congress, and how we should respect and nurture it carefully, and to prepare ourselves not only for the long-term health consequences of COVID-19, but also to ensure that our public health services are better prepared and equipped for the next (inevitable) pandemic.

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References

- 1 Taubenberger JK, Kash JC, Morens DM. The 1918 influenza pandemic: 100 years of questions answered and unanswered. *Sci Transl Med*. 2019;11(502):eaau5485.
- 2 Morens DM, Taubenberger JK, Fauci AS. A centenary tale of two pandemics: the 1918 influenza pandemic and COVID-19, part I. *Am J Public Health*. 2021;111(6):1086–94.
- 3 Gale AH. *Epidemic diseases. First. Harmondsworth*. Middlesex: Penguin Books; 1959.

- 4 Major RH. [Classic Descriptions of Disease](#). 3rd. Springfield, Illinois: Charles C. Thomas; 1965.
- 5 Wacharapluesadee S, Tan CW, Maneeorn P, Duengkae P, Zhu F, Joyjinda Y, et al. Evidence for SARS-CoV-2 related coronaviruses circulating in bats and pangolins in Southeast Asia. [Nat Commun](#). 2021;12(1):972.
- 6 Taubenberger JK, Morens DM. Influenza: the mother of all pandemics. [Emerg Infect Dis](#). 2006;12(1):15–22.
- 7 Spinney L. [Pale rider: the spanish flu of 1918 and how it changed the world](#). 1st. London: Vintage; 2018.
- 8 Barry JM. [The great influenza: the story of the deadliest pandemic in history](#). 2nd. New York: Penguin Books; 2018.
- 9 Osler SW. [The principles and practice of medicine](#). 11th. D. Appleton-Century Company; 1916.
- 10 Cushing H. [From a surgeons journal 1915–1918](#). 1st. London: Constable and Co., Ltd.; 1936.
- 11 Filosto M, Piccinelli SC, Gazzina S, Foresti C, Frigeni B, Servalli MC, et al. Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. [J Neurol Neurosurg Psychiatry](#). 2021; 92(7):751–6.
- 12 Patterson KD, Pyle GF. The geography and mortality of the 1918 influenza pandemic. [Bull Hist Med](#). 1991;65(1):4–21.
- 13 da Costa VG, Saivish MV, Santos DER, de Lima Silva RF, Moreli ML. Comparative epidemiology between the 2009 H1N1 influenza and COVID-19 pandemics. [J Infect Public Health](#). 2020;13(12):1797–804.
- 14 Liang ST, Liang LT, Rosen JM. COVID-19: a comparison to the 1918 influenza and how we can defeat it. [Postgrad Med J](#). 2021;97(1147): 273–4.
- 15 Gibertoni D, Reno C, Rucci P, Fantini MP, Buscaroli A, Mosconi G, et al. COVID-19 incidence and mortality in non-dialysis chronic kidney disease patients. [PLoS One](#). 2021; 16(7):e0254525.
- 16 Flexner S, Lewis PA. Experimental epidemic poliomyelitis in monkeys. [J Exp Med](#). 1910; 12(2):227–55.
- 17 Cole R, Moore HF. The production of anti-pneumococcal serum. [J Exp Med](#). 1917;26(4): 537–61.
- 18 Watanabe T, Kawaoka Y. Pathogenesis of the 1918 pandemic influenza virus. [PLoS Pathog](#). 2011;7(1):e1001218.
- 19 McCullers JA. Insights into the interaction between influenza virus and pneumococcus. [Clin Microbiol Rev](#). 2006;19(3):571–82.
- 20 Abrahams A, Hallows N, French H. A further investigation into influenza pneumococcal and influenza-streptococcal septicaemia: epidemic influenzal “pneumonia” of highly fatal type and its relation to “purulent bronchitis. [Lancet](#). 1919;1:1–11.
- 21 Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. [Lancet](#). 2020;396(10247):320–32.
- 22 Feldman C, Anderson R. The role of co-infections and secondary infections in patients with COVID-19. [Pneumonia \(Nathan\)](#). 2021; 13(1):5.
- 23 Watanabe T. Renal complications of seasonal and pandemic influenza A virus infections. [Eur J Pediatr](#). 2013;172(1):15–22.
- 24 Wan ER, Unwin R, Walsh SB. COVID-19 2020: the experience of a London teaching hospital’s nephrology service. [Kidney Blood Press Res](#). 2021;46(2):137–41.
- 25 Fan C, Lu W, Li K, Ding Y, Wang J. ACE2 expression in kidney and testis may cause kidney and testis infection in COVID-19 patients. [Front Med](#). 2021;7:563893.
- 26 Starko KM. Salicylates and pandemic influenza mortality, 1918–1919 pharmacology, pathology, and historic evidence. [Clin Infect Dis](#). 2009;49(9):1405–10.
- 27 Shope RE. Influenza: history, epidemiology, and speculation. [Public Health Rep](#). 1958; 73(2):165–78.
- 28 Reid AH, Fanning TG, Hultin JV, Taubenberger JK. Origin and evolution of the 1918 “Spanish” influenza virus hemagglutinin gene. [Proc Natl Acad Sci U S A](#). 1999;96(4):1651–6.
- 29 Short KR, Kedzierska K, van de Sandt CE. Back to the future: lessons learned from the 1918 influenza Pandemic. [Front Cell Infect Microbiol](#). 2018;8:343.
- 30 Horoho S, Musik S, Bryant D, Brooks W, Porter IM. Questioning COVID-19 Surface Stability and Fomite Spreading in Three Aero-medical Cases: a Case Series. [Mil Med](#). 2020; 186(7–8):e832–5.
- 31 Wang Q, Zhang T, Zhu H, Wang Y, Liu X, Bai G, et al. Characteristics of and public health emergency responses to COVID-19 and H1N1 outbreaks: a case-Comparison Study. [Int J Environ Res Public Health](#). 2020;17(12): 4409.
- 32 De Santis RA, der Veken WV. Macroeconomic risks across the globe due to the Spanish flu. [SSRN Electron J](#). 2020;2466:31.
- 33 Markel H, Lipman HB, Navarro JA, Sloan A, Michalsen JR, Stern AM, et al. Nonpharmaceutical interventions implemented by US cities during the 1918–1919 influenza pandemic. [JAMA](#). 2007;298(6):644–54.
- 34 Hatchett RJ, Mecher CE, Lipsitch M. Public health interventions and epidemic intensity during the 1918 influenza pandemic. [Proc Natl Acad Sci U S A](#). 2007;104(18):7582–7.
- 35 Bootsma MC, Ferguson NM. The effect of public health measures on the 1918 influenza pandemic in US cities. [Proc Natl Acad Sci U S A](#). 2007;104(18):7588–93.
- 36 Correia S, Luck S, Verner E. Pandemics depress the economy, public health interventions do not: evidence from the 1918 flu. [SSRN Electron J](#). 2020;468:56.
- 37 Gilbert S, Green C. [Vaxxers](#). London: Hodder & Stoughton Ltd; 2021.
- 38 Horton R. [The Covid-19 Catastrophe](#). 2nd. Cambridge, UK: Polity Press; 2021.
- 39 Wilcox CR, Islam N, Dambha-Miller H. Association between influenza vaccination and hospitalisation or all-cause mortality in people with COVID-19: a retrospective cohort study. [BMJ Open Respir Res](#). 2021;8(1):e000857.
- 40 Conlon A, Ashur C, Washer L, Eagle KA, Hofmann Bowman MA. Impact of the Influenza Vaccine on COVID-19 Infection Rates and Severity. [Am J Infect Control](#). 2021;49(6): 694–700.
- 41 Debisarun PA, Struycken P, Domínguez-Andrés J, Moorlag SJCFM, Taks E, Gössling KL, et al. The effect of influenza vaccination on trained immunity: impact on COVID-19. [medRxiv](#). 2020;2020;22.
- 42 Macnalty AS. A lecture on encephalitis lethargica in England. [Br Med J](#). 1926;1(3416): 1073–6.
- 43 Hoffman LA, Vilensky JA. Encephalitis lethargica: 100 years after the epidemic. [Brain](#). 2017;140(8):2246–51.
- 44 McCall S, Vilensky JA, Gilman S, Taubenberger JK. The relationship between encephalitis lethargica and influenza: a critical analysis. [J Neurovirol](#). 2008;14(3):177–85.
- 45 Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. [Brain Behav Immun](#). 2020;88:945–6.
- 46 Komaroff AL, Bateman L. Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? [Front Med](#). 2021;7:606824.
- 47 Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. [Lancet Psychiatry](#). 2021;8(2):130–40.
- 48 Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. [BMJ](#). 2021;372:n693.
- 49 Daugherty SE, Guo Y, Heath K, Dasmariñas MC, Jubilo KG, Samranvedhya J, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. [BMJ](#). 2021;373:n1098.