Review Article

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COVID-19 and the 1918 influenza pandemics: a concise overview and lessons from the past

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Abstract: The coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first reported in December, 2019, in Wuhan, China. Even the public health sector experts could not anticipate that the virus would spread rapidly to create the worst worldwide crisis in more than a century. The World Health Organization (WHO) declared COVID-19 a public health emergency on January 30, 2020, but it was not until March 11, 2020 that the WHO declared it a global pandemic. The epidemiology of SARS-CoV-2 is different from the SARS coronavirus outbreak in 2002 and the Middle East Respiratory Syndrome (MERS) in 2012; therefore, neither SARS nor MERS could be used as a suitable model for foreseeing the future of the current pandemic. The influenza pandemic of 1918 could be referred to in order to understand and control the COVID-19 pandemic. Although influenza and the SARS-CoV-2 are from different families of viruses, they are similar in that both silently attacked the world and the societal and political responses to both pandemics have been very much alike. Previously, the 1918 influenza pandemic and unpredictability of the second wave caused distress among people as the first wave of that outbreak (so-called Spanish flu) proved to be relatively mild compared to a much worse second wave, followed by smaller waves. As of April, 2021, the second wave of COVID-19 has occurred around the globe, and future waves may also be expected, if the total population of the world is not vaccinated. This article aims to highlight the key similarities and differences in both pandemics. Similarly, lessons from the previous pandemics and various possibilities for the future course of COVID-19 are also highlighted.

Keywords: pandemic, COVID-19, influenza pandemic, SARS-CoV-2

1 Introduction

In the 21st century, emerging viral infections are among the greatest challenges in the public health sector [1]. Among these are zoonotic viruses, which jump to humans from other mammals. By crossing species barriers, coronaviruses have infected the human population for the third time in the 21st century. In December, 2019, in China, a novel coronavirus provisionally named 2019-nCoV was identified in individuals linked to the seafood market in China. In January, 2020, the virus was identified as SARS-CoV-2 [2]. On February 11, 2020, the World Health Organization (WHO) named the outbreak COVID-19. The patient with confirmed COVID-19 displayed distinctive respiratory symptoms, such as dry cough, fever, myalgia (lung damage), and other signs including nasal congestion, aches and diarrhea [3]. Like the SARS outbreak in 2002 and MERS in 2012, SARS-CoV-2 is another coronavirus that emerged in the human population causing severe respiratory disease [4]. As of June, 2020, the WHO reported millions of laboratory-confirmed cases with more than a million deaths globally.

Coronaviruses are RNA viruses that circulate among mammals, such as bats and humans, causing hepatic, enteric, neurologic and severe respiratory diseases [5,6]. The six coronavirus species that infect humans are HKU1, NL63, OC43, 2293, SARS-CoV and MERS-CoV [7]. The last two viruses (SARS-CoV and MERS-CoV) have a zoonotic origin and have resulted in severe outbreaks in 2002 in China and 2012 in the Middle East [8–12]. SARS-CoV-2 is now considered to be the seventh species of coronavirus

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to infect humans. The genome of the novel coronavirus has now been sequenced, which represents more than 75% genetic similarity to SARS-CoV [13]. Further exploration of the epidemiological characteristics of COVID-19 is critical for developing and implementing effective control strategies.

Both SARS and MERS infect the human population, but in different ways. COVID-19 shows distinct epidemiological, pathogenetic, and clinical features compared to SARS and MERS, so it is difficult to predict the COVID-19 situation from the data available. SARS-CoV-2 has a fatality rate of 2.3%, which is much lower than that of SARS (9.5%) and even lower than that of MERS (34.4%). However, it has higher transmission rate than SARS and MERS.

On the other hand, the influenza pandemic can be a good comparative model and could be used to prepare for the future course of COVID-19. In the 20th century, there were eight influenza pandemics, and 3 of them occurred after 1918 (1957, 1968 and 2009) [14,15]. By highlighting the key differences and similarities in the epidemiology of the influenza and coronavirus pandemics, we can envision various possibilities for the future course of COVID-19. We have summarized some differences and similarities of these pandemics in Tables 1 and 2 and Figure 1. Similarly, the comparative mortality rate of both pandemics has been represented in Tables 3–7. As the second wave of COVID-19 has started globally and with more severity, which also happened in the 1918 influenza pandemic, lessons need to be learned from that pandemic. The lack of strong health care facilities, malnutrition, improper hygiene, and less responsible attitudes toward proper care and management (e.g., not following standard operating procedures) of disease in various areas of the world might result in greater severity of the pandemic [16]. Since more waves of COVID-19 are expected based on the previous influenza pandemic, we are highlighting a few aspects of both pandemics.

2 Origin of influenza in 1918 and COVID-19

The 1918–1919 flu was the most disastrous pandemic in human history, with the projected number of deaths ranging from 20 to 150 million [17,18]. There is still disa-

Table 1: Common features between the 1918-19 influenza and COVID-19

Common features	1918-19 influenza and COVID-19
Causative agent	RNA virus
Mode of transmission	Aerosol or droplet infection, touching infected surfaces
Symptoms	Fever, mild illness, tiredness, shortness of breath, aches and pains
Preventive measures	Social distancing, wearing masks, avoid touching people and surfaces, staying home
Epidemic or pandemic	Pandemic
Disease type	Zoonotic diseases

Table 2: Differences between the 1918-19 influenza and COVID-19

Differences	1918-19 influenza	COVID-19
Origin	Many theories but mostly say USA	China
Strain of virus	H1N1	SARS-CoV-2
Mostly effected age group	20–40 years	Over 60
Incubation period	Average 1 to 2 days	Average 5–6 days, can be up to 14 days
Total deaths	50 million	2,901,600

greement regarding the name given to that pandemic. Since the beginning, because of the misinformation of the virus origin, the pandemic has been called "Spanish flu". Despite the name, little information about the consequences and course are available regarding a Spanish origin [19,20]. After 90 years, virologists and epidemiologists globally agreed that the virus did not originate in Spain. Some theories indicate that the virus probably started in British Army camps in mainland Europe in 1916–1917. However, others consistently date its appear-

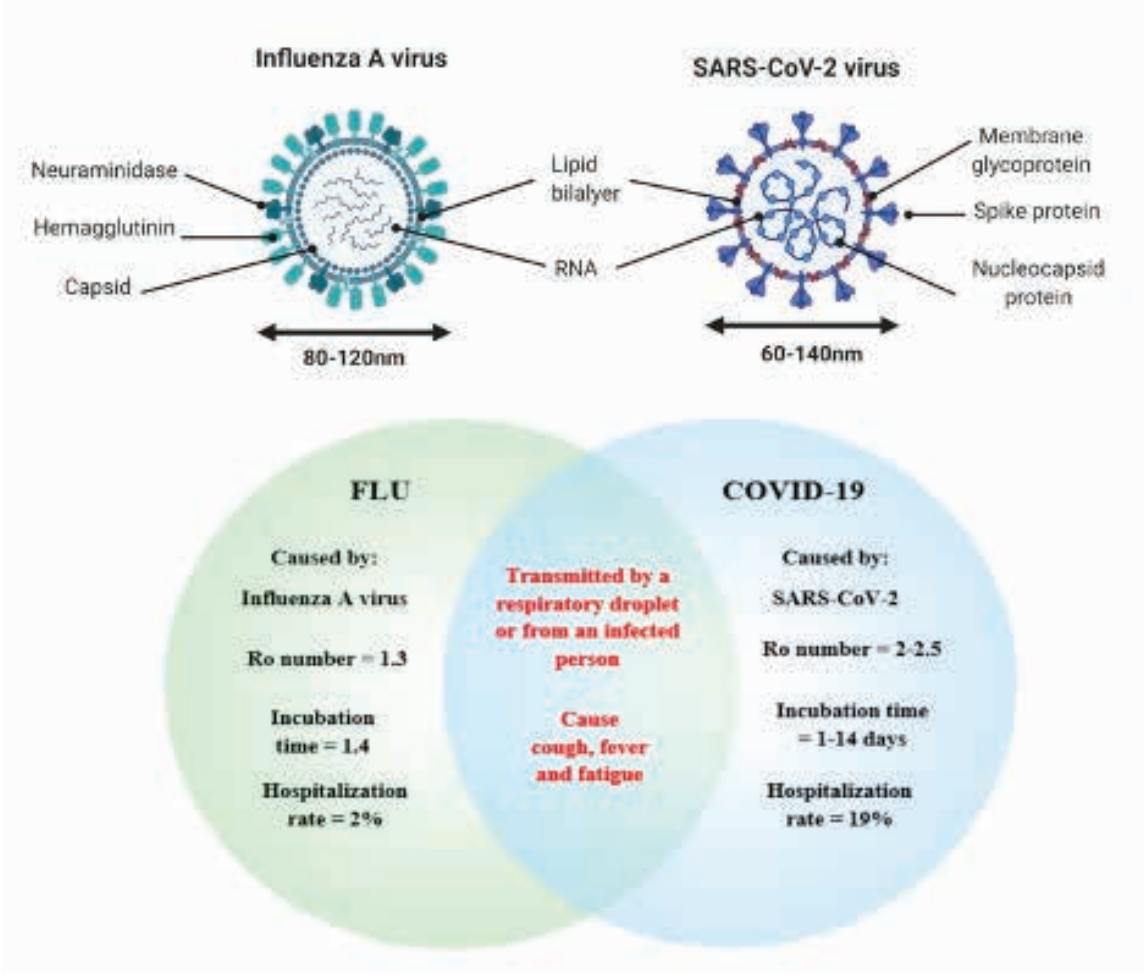

Figure 1: A comparison of influenza A virus and SARS-CoV-2 along with the diseases they cause i.e. flu and COVID-19.

Table 3: Comparative mortality rate of the 1918-19 influenza and COVID-19 (up to April 7, 2021): Africa

Country	Total population 1918–19	Published death rate from 1918 flu (per 1,000)	Total population 2021	Published death rate from COVID-19 (per 1,000)
Gambia	211,000	~50	2,468,006	0.067
Ghana	2,298,000	~40	31,564,990	0.024
Kenya	2,596,000	40	54,669,365	0.041
Nigeria	18,631,000	30	210,008,723	0.010
Sierra Leone	1,541,000	30	8,100,074	0.010
South Africa	6,769,000	43.97	59,877,996	0.885

The source of the data was World Health Organization, an article published by Johnson and Mueller [17] and Google (Worldometer 2020).

Table 4: Comparative mortality rate of the 1918-19 influenza and COVID-19 (up to April 7, 2021): the Americas

Country	Total population 1918–19	Published death rate from 1918 flu (per 1,000)	Total population 2021	Published death rate from COVID-19 (per 1,000)
Argentina	8,517,000	1.20	45,511,967	1.24
Brazil	26,277,000	6.00	213,712,338	1.57
Canada	8,148,000	6.25	37,994,490	0.60
Mexico	14,556,000	23.00	129,964,977	1.57
Uruguay	1,439,000	1.40	3,482,929	0.34

The source of the data was World Health Organization, an article published by Johnson and Mueller [17] and Google (Worldometer 2020).

Table 5: Comparative mortality rate of the 1918-19 influenza and COVID-19 (up to April 7, 2021): Europe

Country	Total population 1918–19	Published death rate from 1918 flu (per 1,000)	Total population 2021	Published death rate from COVID-19 (per 1,000)
Austria	6,131,445	3.00	9,045,631	1.055
Denmark	3,010,000	3.50	5,807,787	0.418
Ireland	4,280,000	4.04	4,979,804	0.949
England & Wales	34,020,000	~4.90	68,158,309	1.861 (UK)
Finland	3,120,000	5.80	5,547,325	0.155
France	32,830,000	3.90	65,384,318	1.494
Germany	58,450,345	3.70	83,989,395	0.930
Italy	36,280,000	11.00	60,393,531	1.860
Norway	2,580,000	5.70	5,453,693	0.125
Portugal	6,010,000	9.70	10,173,859	1.660
Russia	184,000,000	5.00	145,982,499	0.695
Spain	20,880,000	12.00	46,768,680	1.625
Sweden	5,810,000	5.41	10,147,504	1.338
Switzerland	3,880,000	6.00	8,703,085	1.198

The source of the data was World Health Organization, an article published by Johnson and Mueller [17] and Google (Worldometer 2020).

ance in the United States Army training camps to about 1918. Even more recent data shows that the disease could have appeared in New York City [21].

Coronaviruses, on the other hand, have infected the human population by crossing the species barrier for the third time in the 21st century. In December, 2019, in China, a novel coronavirus, provisionally named as 2019-nCoV, was identified in individuals and linked to the seafood market of China [3]. Much information about the origin and form of transmission still needs to be identified. Similarity of the SARS-CoV-2 to bat coronaviruses indicates that the primary reservoirs of the virus are bats. Previously, SARS-CoV and MERS-CoV were transmitted to humans from exotic animals (through the seafood market) and camels, respectively. However, the primary hosts were bats in both cases. The spread of SARS-CoV-2 from bats directly or via other routes should be studied to explain the pattern of zoonotic transmission.

Table 6: Comparative mortality rate of the 1918-19 influenza and COVID-19 (up to April 7, 2021): Oceania

Country	Total population 1918–19	Published death rate from 1918 flu (per 1,000)	Total population 2021	Published death rate from COVID-19 (per 1,000)
Australia	5,304,000	2.8	25,726,041	0.035
Fiji	164,000	52.0	901,419	0.002
New Zealand	1,158,000	<20.0	5,002,100	0.005
Tonga	23,000	42.0–84.0	105,695	—
Western Samoa	36,000	220.0	198,414	—

The source of the data was World Health Organization, an article published by Johnson and Mueller [17] and Google (Worldometer 2020).

Table 7: Comparative mortality rate of the 1918-19 influenza and COVID-19 (up to April 7, 2021): the Asia

Country	Total population 1918–19	Published death rate from 1918 flu (per 1,000)	Total population 2021	Publish death rate from COVID-19 (per 1,000)
Japan	55,033,000	~6.70	126,178,877	0.073
Philippines	10,151,000	8.00	110,695,150	0.127

The source of the data was World Health Organization, an article published by Johnson and Mueller [17] and Google (Worldometer 2020).

3 Biological comparison of the 1918 influenza and COVID-19

Both influenza and SARS-CoV-2 contain RNA as their genetic material. RNA viruses are known for accumulating mutations with their multiplication, as they lack proofreading ability during replication [22]. Such mutation may lead to significant variation in the pathogenicity and drug resistance [23]. Distinctively, the genetic material of the influenza virus is organized in segmented chunks [24]. This idiosyncrasy can be associated with the trading of RNA segments with other influenza viruses, leading to rapid evolution [25]. The influenza viruses also circulate more in winter than in other seasons. As the strains of influenza circulate, they oscillate between the Northern and Southern Hemispheres' winter season and mutate rapidly [26]. Such capacity to quickly adapt is responsible for the new vaccines that must be produced annually against new strains emerging in a particular region.

Coronaviruses, on the hand, can proofread their copied RNA to fix the inadvertent errors occurring during replication, which is one possible reason for their relatively lower mutation rate. From the very first reported sequences of SARS-CoV-2 in Wuhan, China, to the sequences reported from the United States, less than 10 mutations in about 30,000 potential loci in the genome have been observed, despite the fact that the virus has traveled around the globe, with various generations of human hosts [27–30]. Unlike coronaviruses, errors per cycle of replication have been observed 6.5 times more often in the influenza viruses that are independent of entire genome-segment swaps [31]. This relative stability of the SARS-CoV-2 genome can predict that future peaks of COVID-19 are unlikely to happen due to natural variations. The seasonality of COVID-19 is also unknown currently. COVID-19 has successfully been spread in several climates; hence, it is unlikely that a decline in disease rate can be associated with warm weather, but a decline could occur as a result of various strict non-pharmaceutical interventions. Conclusively, the fluctuations in COVID-19 cases are unlikely to be similar to the influenza waves in 1918. Rather, COVID-19 continues to circulate among non-immune populations globally. For example, the lower mutation rate in coronaviruses compared to that in influenza virus might not contribute to a surge of cases in the same population, because after a population becomes infected with coronavirus, unlike with influenza virus, immunity develops.

4 Demographical comparison of the 1918 influenza and COVID-19

There was no vaccine for the 1918 influenza virus; however, several vaccines approved by the Food and Drug Administration (FDA) are available for COVID-19. The unavailability of antibiotics to treat secondary bacterial infections basically made the 1918 influenza more lethal. Therefore, the only solution was isolation, quarantine and use of disinfectants. The 1918 flu pandemic ended in the summer of 1919, which could be linked to fewer deaths and higher immunity levels [16]. Since the world was at war in 1918, soldiers were considered to spread the virus globally [32]. Up to November, 2020, more than 52 million people had confirmed COVID-19 infections worldwide, with more 1.2 million deaths reported. The total world population was about 1.8 billion in 1918. The estimate of 50 million deaths indicates that the 1918 influenza killed 2.7% of the world population.

The current world population is about 8 billion, with an overall lower death rate from COVID-19. The lower rate is likely to be related to greater awareness about viruses, improved health care facilities, and COVID-19 being less lethal than the 1918 influenza. The health care facilities were impacted in 1918 not only by the pandemic but also by mass casualties and war injuries; many medical staff were stationed with troops, and physicians themselves were infected with the influenza virus.

5 Comparison of the 1918 influenza and COVID-19 based on pathogenesis

On the basis of the cells being infected, COVID-19 could be divided into three phases representing different disease stages [32].

5.1 Phase 1: The symptomatic state (initial 1–2 days of infection)

The SARS-CoV-2 targets and replicates in the epithelial cells of the nasal cavity. Angiotensin-converting enzyme-2 (ACE2) is the major receptor for SARS-CoV-2 [33–35]. It has been reported that the primary infected cells in the conducting airways are the ciliated cells [36,37]. There is a confined spread of the virus with limited innate immune response. Virus can be detected by nasal swabs at this phase. Despite the low viral load, individuals can still be infected. The viral load can be predicted by using real-time reverse transcription-polymerase chain reaction (RT-PCR).

5.2 Phase 2: Upper and conducting airways response

In this phase, the virus further spreads and moves down the respiratory tract, and a stronger response is triggered. The SARS-CoV-2 can be clinically apparent in this phase. The C-X-C motif chemokine 10 (CXCL10) level can be predictive of the clinical course [38]. The infected epithelial cells become the major source of beta and lambda interferon [39]. In about 80% of the cases, the disease is restricted to the upper conducting airways, and these patients can be monitored with conventional symptomatic treatment.

5.3 Phase 3: Hypoxia and progression to acute respiratory distress syndrome (ARDS)

More than 20% of the infected individuals can progress to this phase. The overall mortality rate is approximately 2%, but this varies with age. At this phase, the virus enters the lungs and infects alveolar type 2 cells. The infected alveolar cells tend to be peripheral and subpleural [40,41]. The virus propagates inside type 2 cells, and as a result, a significant number of viral particles are released. Consequently, the cell undergoes apoptosis. The released viral particles infect type 2 cells of the adjacent units. The precursors of type 1 cells are type 2 cells, and this series of events is shown in the murine model of influenza pneumonia [41,42]. Elderly people are at high risk because of their weak immune response and impaired ability to repair the damaged epithelium. This basically allows the propagation of viruses to the gas exchange unit [43]. Despite rapid progress in the understanding of COVID-19 pathogenesis, it is not yet fully explained. However, viral entry is the same for both SARS-CoV and SARS-CoV-2.

5.4 Pathogenesis of the 1918 influenza in reconstructed 1918 virus

To gain insight into the pathogenesis of the 1918 flu, the reconstructed 1918 virus was injected in mouse and non-human primate models [44–46]. In the infected animal models, virus propagated at a high rate and migrated throughout the respiratory tract. Severe lung

damage, such as extensive edema and hemorrhagic exudates, was shown in the virus-infected models, which eventually led to acute respiratory distress and death [45]. A high titer of 1918 virus was observed in upper and lower respiratory tracts. The molecular mechanism of the 1918 virus was also studied in non-human primates, which showed a high expression of the genes involved in innate immune response [45]. Moreover, the 1918 virus triggered fewer type 1 interferon genes, which led to more viral replication [45]. This uncontrolled innate immune response has also been shown in mouse models [46]. This data suggest that vigorous innate response is a hallmark of high influenza viral infection.

6 Epidemiologic similarities and differences between the 1918 flu and COVID-19

Even though influenza and coronaviruses are different, both pandemics share several significant similarities. First, they both were novel pathogens to which the world had little or no immunity, making people susceptible to infection. Second, their mode of transmission was the respiratory route by droplets and smaller aerosols. Asymptomatic transmission is a contributing factor in both viruses. Both the viruses infected millions of individuals worldwide. There are a few differences, such as the average incubation period for influenza is 1–4 days, whereas it is 2–15 days for COVID-19 [47]. This longer incubation period allows the virus to spread silently without being detected, and this results in an initial complexity before an individual becomes aware of possible infection [48,49]. The asymptomatic fraction could be another important element in both infections. The asymptomatic fraction for coronavirus may not yet be completely explained, but health care professionals have stated that 25% cases could be asymptomatic [49].

A number of studies have described a mutual mean for an asymptomatic fraction of 16% (45 to 28%) [50]. Both viruses could lead to asymptomatic infection; however, the asymptomatic infection rate could be higher for COVID-19 than for influenza. Another significant concern is the time period for pre-symptomatic viral shedding in infected people. A recent study suggested that the viral load is elevated at the symptom onset, indicating that infection could be at peak before the occurrence of symptoms and, hence, lead to substantial pre-symptomatic transmission [51]. A study of SARS-CoV-2 in hospitalized patients showed that out of 27 patients who were asymptomatic during initial testing, symptoms appeared in 24 individuals after 4 days, supporting the potential for several days of pre-symptomatic infection [52].

With the 1918 virus, research revealed that infection peaked 1 to 2 days after the onset of symptoms, showing less pre-symptomatic shedding for the influenza pandemic as compared to that of SARS-CoV-2 [53]. All these factors lead to virus transmission. One method to quantify viral transmission could be finding the basic reproductive number (R0) for that virus. The R0 is considered the average number of new viral infections resulting from one infected individual in a total vulnerable population [54].

The R0 varies by a factor that influences the contact rate among individuals, such as the number of lockdowns proposed to drive the R0 below 1. An R0 below 1 indicates the outbreak is shrinking rather than expanding, because each infected individual is infecting less than 1 person. R0 could not be affected by herd immunity, no matter whether produced by immunization or natural infection [54]. Immunity of the population can influence an outbreak if the R0 is below 1 [55]. The R0 during the initial pandemic course was estimated to be 2.0 to 2.5 for SARS-CoV-2 [56]. However, one study revealed that the R0 value for SARS-CoV-2 could have been higher in several regions; the R0 was problematic because of the difficulties in detecting and testing infected individuals [57].

The R0 for SARS-CoV-2 is not the same for each person; it is different with the natural inconsistency in viral infection by infected individuals. The average R0 value is not a purely biological quantity; it relies on behavior and contacts. For example, R0 for SARS-CoV-2 could be greater in densely populated areas, such as large cities. Moreover, some studies indicate that a few individuals are superspreaders, as shown in cases of MERS-CoV and SARS-CoV [58,59]. The countries in the studies were able to keep their R0 for SARS-CoV-2 less than 1 with mitigation measures, but as these mitigation measures were increased, the R0 in a particular region could increase to 1 or above, eventually leading to infection reappearance over time. The R0 of influenza pandemics has varied, but showed consistency at approximately 2 or less, which suggests that the influenza viruses of past pandemics were more transmissible than SARS-CoV-2 [60].

7 Conclusion

Exploring important differences and similarities in the epidemiology of the 1918 influenza and COVID-19 pan-

demics could help provide numerous possible scenarios for the future course of the current pandemic. We have highlighted the key resemblances and differences in several aspects of both pandemics. COVID-19 could be a part of the future; however, social distancing (physical distance of 1.5 meter), use of masks and gloves, extensive testing, hospital preparation and vaccine development are needed for the timely management of the disease [61,62]. The most urgent need is to vastly increase the information about the genomic sequencing of coronavirus, so that mutations can be tracked efficiently and vaccines can be updated accordingly [63]. Similarly, lessons need to be learned from past pandemics.

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