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Review:

COVID-19 and Spanish Flu, the Representative Pandemics of the 21st and 20th Centuries

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We are still in the early stage of 21st century and the two pandemics Spanish flu and COVID-19 are the presentative pandemics in 20th and 21st centuries, respectively. The Spanish flu pandemic raged from 1918 to 1920, just after World War I. It was the first influenza pandemic worldwide; since then, humankind has experienced many such pandemics. Spanish flu is caused by a virus. However, since virology was not well established at that time, the new clinical system was needed to cope with "unknown pathogen"; during the pandemic, high infection rates were recorded, but our predecessors managed to somehow tackle the situation. With respect to the ongoing COVID-19 pandemic, both the virus and its genome were clarified quickly. Nonetheless, it has turned out to be quite an intriguing infectious disease, with the high rates in developed countries, such as the US and those in Europe, which have aging societies, and low rates in developing countries such as those in Africa, where the population is largely young. Here, I compared and discuss the two pandemics, COVID-19 and Spanish flu.

Keywords: COVID-19, SARS-CoV-2, vaccine, Spanish flu, influenza

1. Introduction

COVID-19 is a pandemic that broke out in Wuhan, China at the end of 2019 and rapidly spread worldwide (**Fig. 1**). Although almost two years have passed since its emergence, the pandemic is yet be eradicated. The pathogenic virus of COVID-19 belongs to the *Coronaviridae* family and is similar to SARS-CoV, the virus that causes severe acute respiratory syndrome (SARS). Therefore, it was named to "SARS-CoV-2."

Humans have experienced many pandemics, such as plague [1–3], smallpox, influenza [4–6], Japanese encephalitis, tuberculosis [7], and measles [8, 9]. Therefore, the JDR edition "Special Issue on COVID-19 and Historical Pandemics" was planned and the Part 1 was published in January 2021; in addition to COVID-19, various historical infectious disease epidemics are discussed in this special issue. I too contributed a review article to this special issue [7].

Smallpox was eradicated in the 20th century [10, 11], and polio is expected to be eradicated in the near future. However, in developing countries, such as those in Africa or South or Southeast Asia, infectious diseases are major cause of death. In developed countries such as Europe and the US, many infectious diseases outbreaks have declined since World War II, although influenza and food poisonings remain public health problems. In contrast, COVID-19 is a unique infectious disease in that the number of cases in developed countries is higher than that in developing countries. According to the "COVID-19 Weekly Epidemiological Update" released by the World Health Organization (WHO) in mid-September, the cumulative number of COVID-19 cases was 38%, 30%, and 3% in the Americas, Europe, and Africa, respectively, indicating that majority of the cases were in developed countries.

At the time of writing of this article, the COVID-19 pandemic was ongoing, therefore the final pandemic data were unknown. However, more than 230 million cumulative cases and 4.8 million deaths have already been reported worldwide.

About 100 years ago, just after the World War I (WWI), the world had battled the Spanish flu pandemic in 1918–1920, which had spread mainly in Western countries. As mentioned earlier, the COVID-19 virus, SARS-CoV-2, belongs to the *Coronaviridae* family, whereas the influenza virus, the pathogen of the Spanish flu, belongs to the *Orthomyxoviridae* family; in other words, the two viruses belong to different families. Yet, these two pandemics can be considered similar in a way: prominent infectious disease epidemics with a major public health impact on developed countries. In this article, I discuss both of them detail.

2. COVID-19

COVID-19 is a novel coronavirus disease that was first detected in Wuhan, China at the end of 2019 [12–14]. Its virus is similar to SARS-CoV (pathogenic virus of SARS: severe acute respiratory syndrome [15, 16]), and therefore, the International Committee on Taxonomy of Virology (ICTV) named it SARS-CoV-2. It belongs to

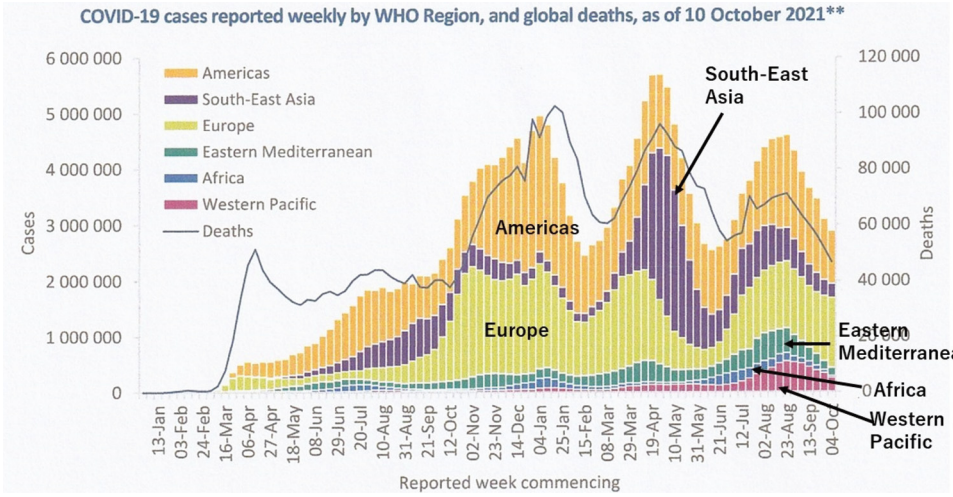


Fig. 1. COVID-19 cases by WHO region reported weekly and global deaths, as of October 10, 2021.

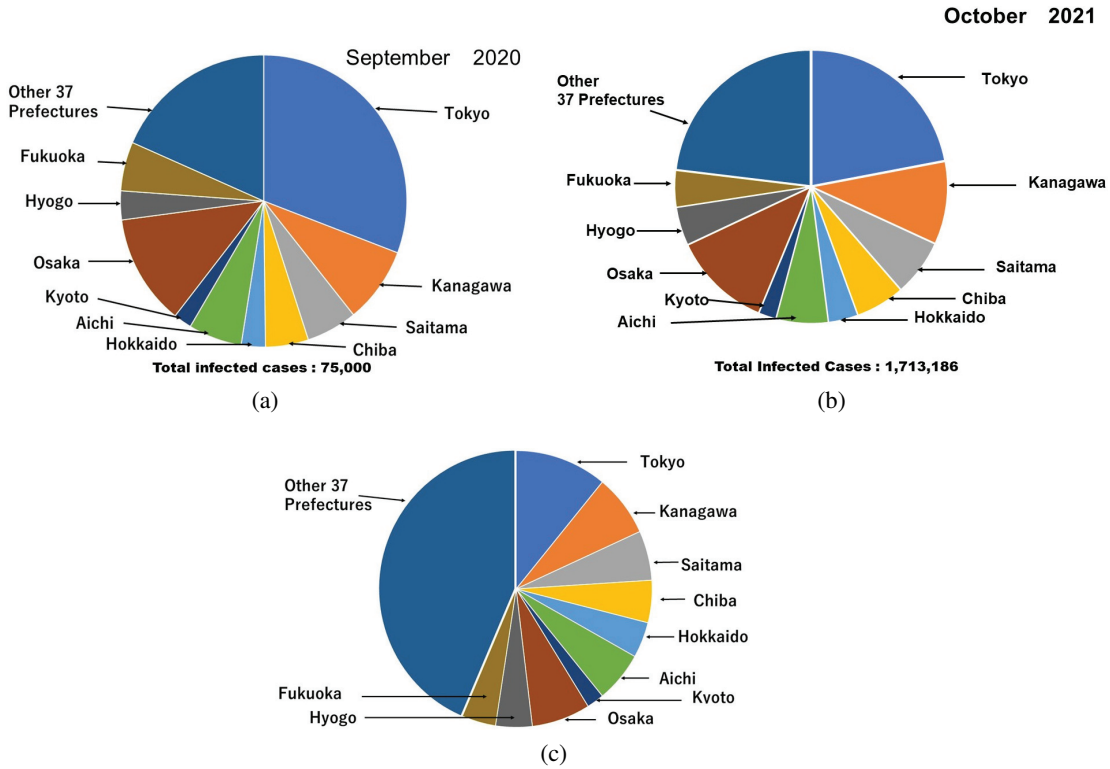


Fig. 2. (a) Cumulative COVID-19 cases in Japan by prefecture in September 2020, (b) cumulative COVID-19 cases in Japan by prefecture in October 2021, (c) population of Japan by prefecture.

Betacoronavius in the family *Coronaviridae*. There are various human pathogenic species in the genus *Betacoronavirus*; before 2019, two species of the genus, namely SARS-CoV [15–17] and MERS-CoV [18] (virus causing Middle East respiratory syndrome) were well known: at the end of 2019, SARS-CoV-2 suddenly emerged.

In Japan COVID-19 into Japan was first detected in Hokkaido at the end of January 2020, and from there, the disease spread nationwide, mainly in 10 prefectures with large cities [7]. In other words, as shown in **Fig. 2(a)**, in September 2020, the number of cases in the Tokyo metropolitan area (Tokyo, Kanagawa, Saitama, and Chiba) accounted for almost half of all cases nationwide, and the 10 prefectures, the Tokyo metropolitan area and additional 6 prefectures with large cities (Hokkaido, Aichi, Kyoto, Osaka, Hyogo, and Fukuoka) accounted for more than 80% of all cases nationwide. In contrast, the vast region including the other 37 prefectures accounted less than 20% of the whole countries as shown in **Fig. 2(a)**.

A year on, in September 2021, there was an approximately 50-fold jump in the total number of cases in Japan,

Table 1. Cumulative COVID-19 cases and deaths by WHO regions, as of October 10, 2021.

WHO region	Population* (in thousand)	Cumulative cases (%)	Cumulative cases per 100,000 population	Cumulative deaths (%)
Global	7,676,965	237,470,988 (100%)	3,093.30	4,846,224 (100%)
Americas	1,009,950	91,325,885 (38%)	9,046.60	2,241,923 (46%)
Europe	930,167	71,863,813 (30%)	7,725.90	1,360,102 (28%)
South-East Asia	2,001,946	43,369,716 (18%)	2,166.40	681,671 (14%)
Eastern Mediterranean	712,276	15,970,239 (7%)	2,242.10	293,568 (6%)
Africa	1,091,759	6,081,759 (3%)	557.1	120,846 (2%)
Western Pacific	1,930,867	8,858,812 (4%)	458.8	148,101 (3%)

*: Obtained from WHO World Health Statistics 2021 [7].

from 75,000 to 1,680,000. Although the number of cases in the metropolitan area increased as matter of course, the cases in local area also increased, therefore, the percentage of the 37 prefectures area has slightly increased as shown in **Fig. 2(b)**, which shows slightly different shape from than in **Fig. 2(a)**. In addition, the distribution of COVID-19 infected persons by prefectures differs from **Fig. 2(c)**, showing that the distribution is unevenly distributed around prefectures with large cities.

The pattern of COVID-19 infected cases in prefecture is different from the population pattern shown in **Fig. 2(c)**, namely COVID-19 cases are maldistributed to mainly prefectures having great cities.

WHO has issued extensive information on COVID-19 including "COVID-19 Weekly Epidemiological Update." **Fig. 1** is a graph obtained from a weekly update in mid-October 2021, showing COVID-19 cases and global deaths. The graph shows that the majority of the cases are from the Americas, Europe and Southeast Asia (mainly India) regions, and very few from Africa. This trend differs from the general trend observed in many other infectious diseases in that such diseases have had a high impact on African countries [19, 20]. I have discussed the high infection rates of malaria and tuberculosis in African countries [7]. However, **Fig. 1** and **Table 1** show the different trends of COVID-19; fewer cases reported in Africa, and high number in Americas and Europe. As shown in **Table 1**, population of Africa region is almost the same as that of Europe or the Americas, but its accumulated number of cases of COVID-19 in Africa is only one tenth that of these two regions. Similarly, the population of the Western Pacific region (WPR), which includes China, is almost double that of the Americas and Europe, but the cumulated number of cases is only 4% of the global total.

Figure 3(a) shows how low China's cumulative number of COVID-19 is compared with the US, European countries, India, and Japan, despite the outbreak occurring in China and the country having the largest population in the world; in fact, in the bars for China, Kenya, Nigeria, and Zambia in the graph can barely even be seen. The values (i.e., the cumulative cases) are 125,115 (China), 251,313 (Kenya), 207,979 (Nigeria),

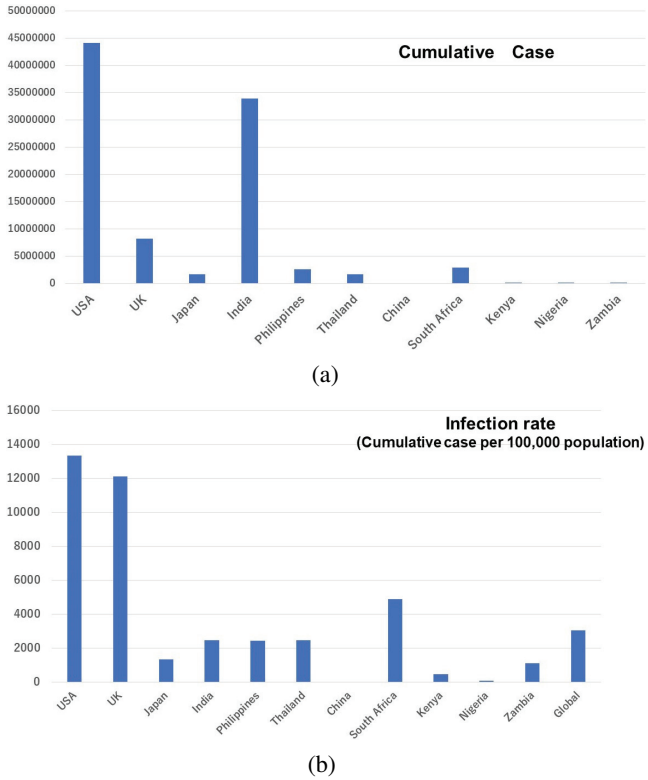
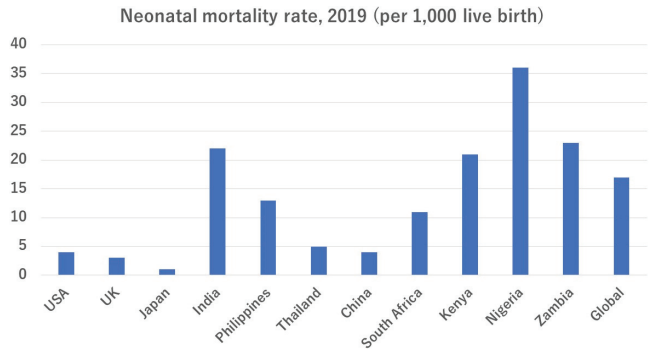
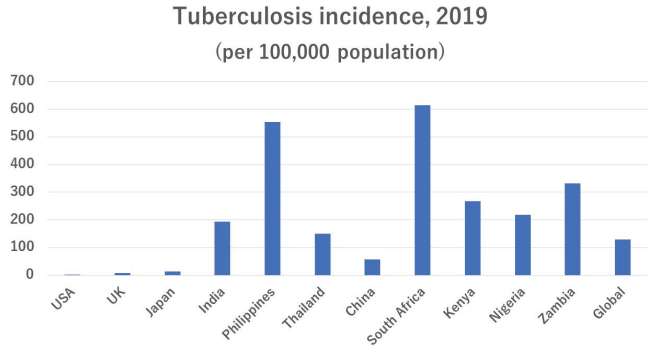


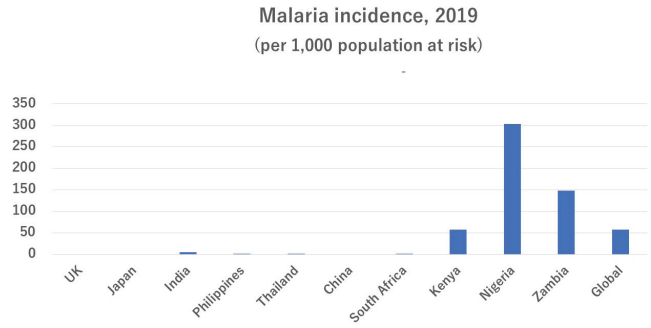
Fig. 3. (a) Cumulative COVID-19 cases in some countries of the different WHO regions, (b) infection rate (cumulative cases per 100,000 population) in some countries of the different WHO regions.



(a) Neonatal mortality per 1,000 live births



(b) Tuberculosis incidence per 100,000 population

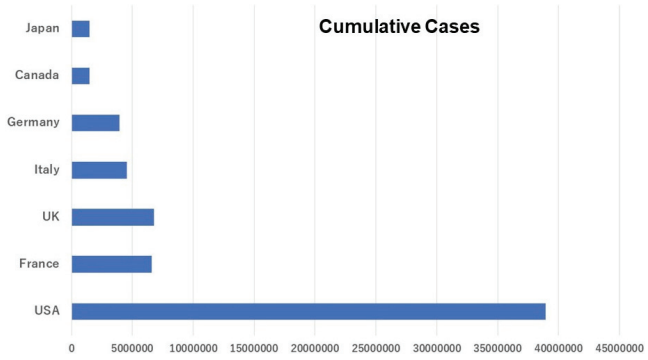


(c) Malaria incidence per 1,000 population at risk

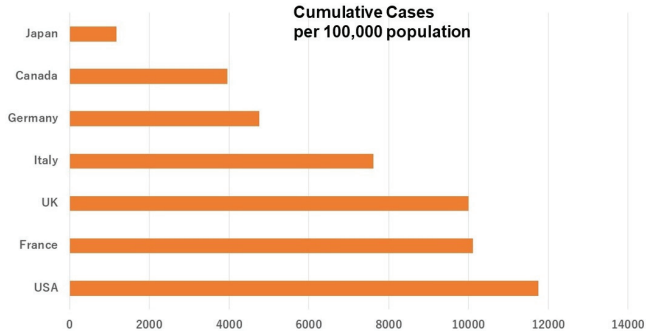
Fig. 4. Health statistics related to infectious diseases [20].

and 209,396 (Zambia), representing only 7.3%, 14.7%, 12.1%, and 12.2% of Japan's cumulative cases, and this is despite the fact that China's population is more than 10 times that of Japan.

Figure 4 shows the neonatal mortality rate **(a)**, tuberculosis incidence **(b)**, and malaria incidence **(c)**, respectively, in accordance with the WHO World Health Statistics 2021 [20]. It can be seen that neonatal mortality and tuberculosis incidence are high in Asia and African regions as shown in **Figs. 4(a)** and **(b)**, while malaria incidence is high in African region as shown in **Fig. 4(c)**. Since neonatal mortality is correlated with infectious diseases, their patterns are similar. In comparison, the prevalence pattern of COVID-19 is completely different, in other words, the shape of COVID-19 in **Fig. 5** contrasts those of the other diseases in **Fig. 4**. The contrast between COVID-19's pattern in the US or UK and countries in other WHO regions can also be seen in the polygonal graph **Fig. 6**.

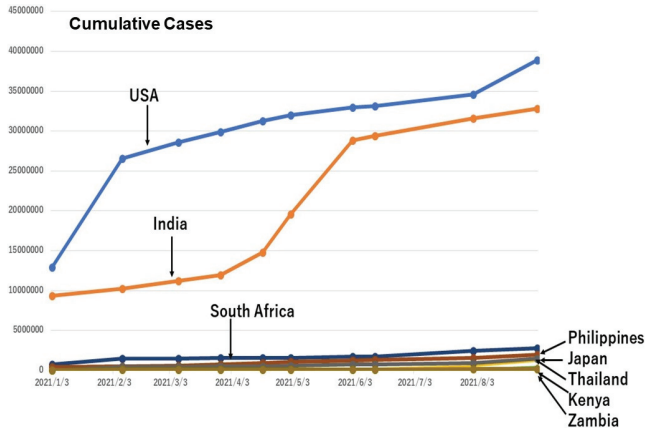


(a)

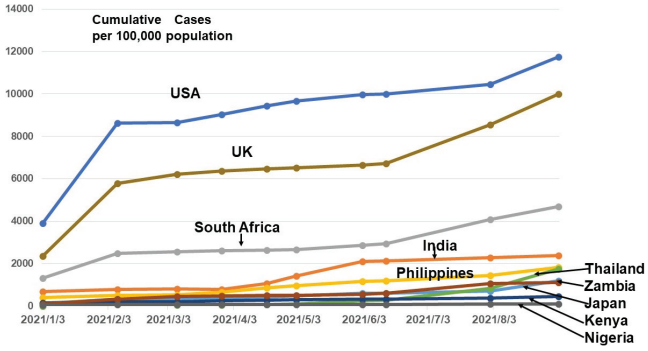


(b)

Fig. 5. (a) Cumulative COVID-19 cases in G7 countries in October 2021, (b) COVID-19 infection rate (cumulative cases per 100,000 population) in G7 countries.



(a)



(b)

Fig. 6. (a) Cumulative COVID-19 cases in the US and some countries of Africa and Asia, (b) COVID-19 infective rate in the US, the UK and some countries of Africa and Asia.

In infectious disease control, improvement of the public health environment is crucial, in particular, the establishment of sanitation infrastructure is necessary. Therefore, infectious diseases occur mainly in the developing countries in Africa or Asia area. However, COVID-19 has spread mainly in the Americas and Europe regions, which include many developed countries. In other words, the COVID-19 pandemic is different from a normal infectious disease pandemic. It is likely to be greatly influenced by adjustments in the sanitation infrastructure system or other factors.

By WHO region, there is a difference in the number of cases between Group 1 (Americas and Europe) and Group 2 (Africa and WPR), suggesting racial differences.

WPR includes Australia and New Zealand as well as Japan and China, but is predominantly East Asia, including Japan, China, and Korea. The inhabitants of East Asia are mainly Mongoloids and their relatives. Residents of Africa are mainly blacks. COVID-19 was confirmed in China at the end of 2019, but as shown in **Fig. 3**, recent cases in China are very few. As shown in **Figs. 5(a)** and **(b)**, cases and infection rates in Japan are the lowest among the G7 countries. In other words, residents of G7 countries other than Japan are Caucasian, while Japanese are mostly Mongoloid.

As shown above, Australia and New Zealand are countries in WPR, in which the COVID-19 cases are lower than other regions. However, residents of Australia and New Zealand are mainly Caucasian, similar to residents in Europe and Americas.

In the case of Australia and New Zealand, however, these two countries being isolated from Europe, the US and Canada, in the South Pacific Ocean, may have contributed to their low number of cases.

In India, as shown in **Fig. 3**, the cumulative number of cases is very high, although the infection rate is not as high due to its large population. India's large number of COVID-19 cases is contrast to that of its Asian counterparts. Thus, the location and inhabitants of the Indian subcontinent need to be considered. The Indian subcontinent locates in the Central Asia, and the main inhabitants are Indo-Aryan descent, similar to those in the Middle East. Therefore, they differ from the East Asian population.

Thus, it is possible that the difference in the COVID-19 infection rate is due to racial difference in particular, difference in some physiological factors may be suggested.

This is a biological race problem, not racial difference between the inhabitants of India and East Asia to understand it.

In India, the cumulative number of cases is high, but the infection rate (cumulative cases per 100,000 population) is not as high, according to the annexed table of the 63rd "COVID-19 Weekly Epidemiological Update" published on November 7, 2021, the infection rate in India is 2,505, while that in the US, the UK, France, Italy, and Germany are 14,441, 14,762, 11,201, 8,330, and 6,793, respectively. The Indo-Aryan race, predominant in India, is closer to the races of Central Asia and the Middle East and different from the Mongoloid and Malay races of East Asia. The infection rates in Middle Eastern countries and some East Asian countries are as follows: Middle East (Iran: 7,253; Iraq: 5,165; Kuwait: 9,625; Saudi Arabia: 1,579) and East Asia (Japan: 1,365; Philippines: 2,582; Thailand: 3,001; Vietnam: 1,209; Korea: 844), in other words, infection rates in Middle Eastern countries are lower than those in Western countries and slightly higher than those in East Asian countries. Because the major ethnic groups in India are similar to those in the Middle East, the infection rate in India is likely to be close to or slightly lower than that in the Middle East.

During this pandemic, virus mutation, especially mutation of the gene encoding its spike protein of the virus, has been a major challenge. WHO has used Greek letters to designate the variants, for example alpha (α: the UK variant) and delta (δ: the Indian variant).

A new variant (omicron: o) was detected in South Africa at the time of writing this article. WHO classified it as "VOC: Variant of Concern," because of a variant necessary of enough care. The α variant was approximately 1.7 times more infectious than the original Wuhan strain and the infection rate of δ variant is has been higher as well.

It is also necessary to take into account the fact that since Wuhan, many young people have had a subclinical COVID-19 infection, even though the incidence and fatality rates among elderly people have been high. All things considered, it is clear that the COVID-19 patterns in developing and developed countries are different, and the disease's overall pattern is different from the usual infectious disease pattern.

Since the publication of the previous issue, "Special Issue on COVID-19 and Historical Pandemics (Part 1)," the number of cases of COVID-19 in Japan has increased significantly. This rapid increase is related to an inadequate clinical system for infectious disease. Malignant tumor, heart disease, and cerebrovascular disease are the major causes of death in Japan. Although the clinical systems for these diseases have considerably improved, the system for infectious diseases remains under developed. Therefore, we are concerned about the hardship of the medical system in this COVID-19 pandemic.

However, the number of COVID-19 cases in Japan is lower than that in Americas or Europe countries. As shown in **Fig. 5**, COVID-19 cases in Japan have the lowest number in the G7 countries. Although the total accumulated cases in Japan are almost same as those of Canada, the population of Japan is larger than that of Canada, approximately 3.3 times, therefore, infection rate (cumulated cases per 100,000 population) of Japan is lower than that of Canada (**Fig. 5(b)**).

After the outbreak in Wuhan, China, at the end of 2019 [12–14, 21, 22], within one month from the first COVID-19 cases, more than 2,000 cases – people living in or visiting Wuhan – were confirmed, and human to human transmission was reported [22]. Many of those who contracted the disease first had visited a live animal market in Wuhan, suggesting that an animal may have trans-

mitted the virus to them [23]. However, it is now believed that the market was not the location of the first zoonotic infection, but rather acted as catalyst for the spread [22].

Various animals have been known as coronavirus hosts. For example, the infectious bronchitis virus, a strain of the avian coronavirus, infects chicken bronchitis leading to high economic loss for the poultry industry [24, 25], while another strain of the same coronavirus has been detected in turkey poults in Europe [25].

Middle East respiratory syndrome (MERS) is an epidemic that originate in Arabian Peninsula in 2012 and then spread to other regions [26, 27]. The pathogen, MERS coronavirus (MERS-CoV) is also a zoonotic virus originates, it is believed to have originated in bats and then transmitted to camel. Human infection is caused mainly through camel with high mortality and morbidity [9, 28].

SARS-CoV (pathogen of SARS; the coronavirus endemic in 2002–2003) is believed to be originated in bats and transmitted to humans via the civet or other animals [29].

SARS-CoV-2 is a coronavirus similar to SARS-CoV, and therefore, bats are considered reservoir. However, the natural ecology of this virus remains unclear. There are various intermediate hosts – pigs, rabbits, monkeys, dogs, sheep, fish, or snakes – before human transmission occur [28, 30–32].

It is thus sufficient to say that coronaviruses have various hosts.

3. Spanish Flu, Spanish Influenza

The Spanish flu from 1918 to 1920 is the largest pandemic in the 20th century, and is believed to have killed 50–100 million people [33–35], the total number of infected is estimated to be one-third of the world's population.

World War I ended in 1918. Several countries – with the Central Powers and the Allied Powers being the two coalitions – fought in the war and the death toll was reported to be 16 million (including 7 million noncombatants). While this figure illustrates the horror of the war, the pandemic that followed was a more horrific disaster.

Though the origin of the name "Spanish flu" is unknown, it is not believed to have originated in Spain. During World War I, Spain was a neutral country, which allowed free information media. Therefore, many people may have heard and obtained the news of the flu pandemic.

Although the location of the first epidemic is unknown, the first case was reported in Kansas by the US Army in March 1918, and the first wave affected various states of the US states and some parts of European. The second wave spread further in the US, Europe, and Asia. The third wave started in January 1919 hitting South-America and Australia, where no influenza pandemic had occurred until the second wave.

Taubenberger and Morens analyzed the differences between three waves and showed that the mortality rate was high in infants, young adults, and elderly people, showing a W-shaped graph [36, 37]. However, in the former year (1911–1918) influenza, U-shaped graph was observed, that is, a high mortality rate in infants and elderly people but low in young adults. Cilek et al. also reported a W-shaped mortality pattern of age groups [38], while Erkoreka compared the death during 1916–1917 flu and 1918 flu in Madrid and Paris [39]. In 1916–1917, a slightly high mortality rate was observed in individuals aged over 45, whereas in 1918 Spanish flu year, a high mortality rate was observed in those in the 25–44 age group. Thus, the physiological effect of the Spanish flu may have been different from that of the influence-like outbreak.

In Japan, Spanish flu was detected in August 1918. The report by Rice and Palmer was based on various Japanese documents, such as the Annual Report of the Central Sanitary Bureau, newspapers, and magazines [40]. The report recorded 21,168,398 cases and 257,363 deaths from Spanish flu in 11 months from September 1918 to July 1919. As the population of Japan at that time was 57,190,355, the infection rate per 1,000 was calculated to be 370.13 (i.e., about 370/1,000). In other words, 37% of country's population was affected by the Spanish flu at that time.

As mentioned above, COVID-19 is a severe disease. The cumulative number of cases in Japan on October 17, 2021 was 1,713,186, and while this number is considered quite high, however, it is much lower than the number of Spanish flu cases recorded in 1918 by Rice and Palmer [40]; according to their report, Japan's infection rate of the Spanish flu in 1918 (for the whole country) was 370.13, while that of COVID-19 was 13.5.

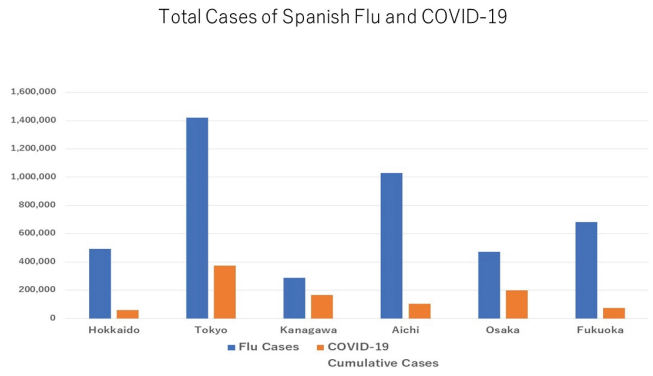
A comparison of Spanish flu and COVID-19 cases in major prefectures (**Fig. 7**) shows a similar pattern. Thus, from this, we can see that the previous generations have battled and borne more severe influenza and pandemics. Influenza has existed throughout human history, for example, the famous ancient Greek physician Hippocrates even described influenza-like symptoms, despite the pathogen not being known at the time. It was not until the 1930s that the influenza virus was finally identified [41–43].

At the end of the 19th, 1892, R. Pfeiffer isolated a bacterium from influenza patient. The bacterium has been named to *Haemophilus influenzae* and thought to be the pathogen of influenza. However, as is known, the influenza pathogen is a virus; the bacterium *H. influenzae* causes meningitis in infants. In other words, during the Spanish flu pandemic from 1918 to 1920, the clinical system had to contend with an unknown pathogen.

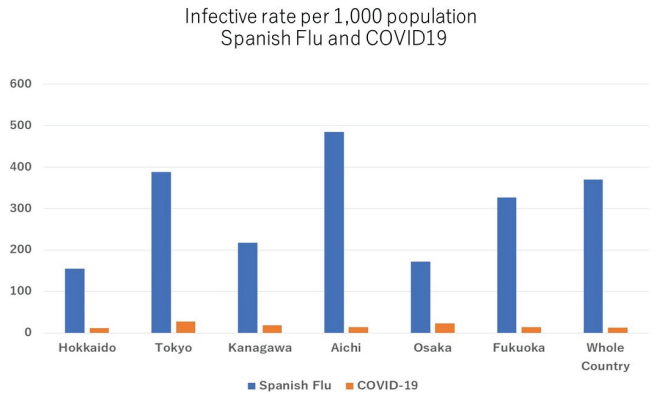
4. Conclusion

Complete eradication of COVID-19 is believed to be difficult.

However, the development of vaccines and therapeutic agents continues to be actively pursued. Conventional vaccination involves the administration (via injection or



(a)



(b)

Fig. 7. (a) Total cases of Spanish flu (from September 1918 to July 1919) and COVID-19 (from January 2020 to October 2021) in Japan, (b) infection rate (cases per 1,000 population) of Spanish flu (from September 1918 to July 1919) and COVID-19 (from January 2020 to October 2021) in Japan.

orally) of antigenic substances such as inactivated vaccines, attenuated vaccines, component vaccines, and toxoids. New biological measures have also been introduced and implemented, namely vaccines containing messenger RNA (mRNA) method [43, 44] and viral vector method. In the beginning, the mRNA vaccine was administered to healthcare workers and elderly people; the later, the viral vector vaccine was introduced for the general public. Initially, the early application of the vaccine had raised concerns about various adverse reactions; however, the possibility of such reactions is rare and improvements are being made.

Because mRNA vaccines are unstable, some kind of an improvement is necessary, which is why lipid nanoparticles are now in practical use [45].

In addition, various drugs against viral pathogens have already been put to practical use. Remdesivir, developed as treatment for Ebola, holds promise as a possible therapeutic option for COVID-19 [46].

The spike protein of SARS-CoV-2 binds to its receptor human ACE2 (angiotensin converting enzyme 2) – thus, the spike protein plays an important role in causing the infection and is considered vital for the development of vaccines and drugs [18, 47, 49].

An antibody cocktail to the spike protein has also been used in the treatment of serious cases via intravenous injections.

Yet, we continue to coexist with these viruses through the development of vaccines and medicines. For the future, it would be beneficial to establish a well-balanced system that enables us to coexist with SARS-CoV-2.

Finally, the hope prevails that we avoid the emergence of a new variant.

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Academic Societies & Scientific Organizations:
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• Society for Antibacterial and Antifungal Agents, Japan (SAAAJ)
• Pharmaceutical Society of Japan (PSJ)