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Review Article

# The Future of the COVID-19 Pandemic: Insights from the Human Coronaviruses Found before 2019

Michiaki Masuda

*Department of Microbiology, Dokkyo Medical University School of Medicine, Tochigi, Japan*

**Summary**

At the end of December 2019, epidemic cases of pneumonia of unknown cause in Wuhan, China were reported to the World Health Organization (WHO). A novel species of coronavirus was identified as the causative agent and named SARS coronavirus type 2 (SARS-CoV-2) because its genome sequence was found to be similar to that of SARS coronavirus (SARS-CoV), which caused the outbreak of severe acute respiratory syndrome (SARS) from 2002 to 2003. The WHO has designated the official name of SARS-CoV-2 infection as coronavirus disease 2019 (COVID-19) and declared it a pandemic on March 11, 2020. As of this writing (March, 2022), there are about 480 million people who have been infected with SARS-CoV-2 and more than 6 million killed worldwide, and the pandemic is inflicting a huge negative impact on various aspects of human life. Six species of coronavirus, which cause human diseases, had been identified before the outbreak of COVID-19. Four of them cause the common cold, and the other two cause severe respiratory disease with high case fatality rates. In this paper, the possible origins and phylogenetic properties of these human coronaviruses are summarized, and the future of the COVID-19 pandemic will be speculated based on the characteristics of pre-existing human coronaviruses.

**Key Words**: COVID-19, human coronavirus, SARS-CoV-2, zoonotic infection, viral evolution

## Introduction

On December 1, 2019, a patient developed pneumonia of unknown cause in Wuhan, China[1]. Since then, similar cases had continued to increase in Wuhan[1] and were officially reported to the World Health Organization (WHO) on December 31[2]. Meanwhile, a Chinese research group revealed by analyzing the specimens collected from a patient on December 30 that the causative agent was a novel coronavirus (CoV)[3]. By January 10, 2020, the entire genome sequence of the virus was determined and found to be similar to that of SARS-CoV[4], which caused the severe acute respiratory syndrome (SARS) from 2002 to 2003. As a result, the International Committee on Taxonomy of Viruses (ICTV) named the new virus as SARS-CoV type 2 (SARS-CoV-2), and the WHO designated the official name of SARS-CoV-2 infection as CoV disease 2019 (COVID-19), declaring it a pandemic on March 11[2]. About two years later, at the time of writing this article (March 2022), the cumulative number of infected people in the world is about 480 million, and the death toll is over 6 million.

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Reprint requests to: Michiaki Masuda
m-masuda@dokkyomed.ac.jp
Department of Microbiology, Dokkyo Medical University School of Medicine, Mibu, Tochigi 321-0293, Japan

**Table 1** Human pathogenic coronaviruses isolated and identified so far.

| Genus | Species | First identified in | Natural host | Intermediate host | Disease |
|---|---|---|---|---|---|
| Alphacoronavirus | Human coronavirus 229E | 1966 | Bats | Camelids? | Common cold |
| | Human coronavirus NL63 | 2004 | Bats | Unidentified | Common cold |
| Betacoronavirus | Human coronavirus OC43 | 1967 | Rodents | Bovines | Common cold |
| | SARS coronavirus | 2003 | Bats | Palm civets | Severe acute respiratory syndrome (SARS) |
| | Human coronavirus HKU1 | 2005 | Rodents | Unidentified | Common cold, pneumonia |
| | MERS coronavirus | 2012 | Bats | Dromedary camels | Middle East respiratory syndrome (MERS) |
| | SARS coronavirus 2 | 2020 | Bats | Pangolins? | Coronavirus disease 2019 (COVID-19) |

At the same time, Japan is amid the sixth wave of the outbreak, and its enormous impact on social life and the economy is continuing.

Prior to the outbreak of COVID-19, six species of CoVs responsible for human diseases had been identified. In this article, I would like to outline the origin and evolution of SARS-CoV-2 by comparing it with those pre-2019 human CoVs (HCoVs) and speculate the future of the COVID-19 pandemic.

## Probable Zoonotic Origin of HCoVs Including SARS-CoV-2

Official classification of viruses is determined by ICTV based on molecular biological properties such as the structure of virus particles and the similarity of the nucleotide sequences of viral genomes. Viruses in family *Coronaviridae* have a single-stranded RNA genome in the nucleocapsid and the lipid bilayer envelope on the surface, and are divided into two subfamilies, *Letovirinae* and *Orthocoronavirinae*. The latter includes more than 40 species of viruses that can infect mammals and birds, and is further divided into four genera; alpha, beta, gamma and delta. There are six species of HCoVs isolated and identified before 2019 (Table 1), and two of them are classified as alphacoronavirus whereas the other four belong to betacoronavirus. From the viewpoint of viral pathogenicity, four species of HCoVs, 229E, OC43, NL63 and HKU1, mainly cause common cold with benign prognosis whereas the other two cause severe respiratory diseases with high case fatality rates (CFRs). One of the highly pathogenic HCoVs is SARS-CoV identified in 2003 as the cause of SARS originated in Guangdong Province, China, in 2002. The other one is MERS-CoV identified in 2012 as the cause of Middle East respiratory syndrome (MERS), which originated in the Middle East region centering on Saudi Arabia. It is generally understood that those six HCoVs were generated by zoonotic transmission of ancestral CoVs from the natural host animals, such as bats and rodents, to humans either directly or through other animals (Table 1).

SARS-CoV-2, which causes COVID-19, was identified in 2020 as the seventh pathogenic HCoV. Its genome sequence was found to be 79.6% and 89.1% similar to those of SARS-CoV and bat-derived SARS-like CoV (SL-CoV), respectively[3]. In addition, a higher similarity (96.1%) was found between SARS-CoV-2 and RaTG13 CoV isolated from a wild bat in Yunnan Province in China[5]. More recently, it has been reported that the genome sequences of the bat CoVs designated as BANAL found in northern Laos are more similar to that of SARS-CoV-2 than RaTG13 is. It was also shown that the amino acids in the receptor binding site of the spike (S) protein of BANAL CoVs are almost identical to that of SARS-CoV-2[6]. Moreover, it was experimentally demonstrated that the S protein of a BANAL CoV can facilitate the viral entry into human cells by using the same receptor, ACE2, as SARS-CoV-2[6]. Therefore, it is strongly suggested that bats are involved in the emergence of SARS-CoV-2 and that the BANAL CoV may be the most closely related ancestor. Although additional studies are necessary, it is very much likely that bats were involved in the emergence of SARS-CoV-2.

## Mutation of Coronavirus Genome

The human genome is comprised of the chromosomal double-stranded DNA. On the other hand, the nucleic acids comprising viral genomes vary, i. e., DNA or RNA, and single-stranded or double-stranded. The CoV genome consists of a single-stranded RNA molecule built up with approximately 30,000 bases, and its replication is catalyzed by RNA-dependent RNA polymerase (RdRp) whose gene is encoded in the viral genome. Generally, genome replication of RNA viruses is said to make more errors, or mutations, than that of DNA viruses partly due to the low fidelity of RdRp. Particularly, frequent mutations are anticipated in replication of CoV's large genome and might negatively affect virus propagation. To circumvent this problem, CoV has evolved to make an enzyme called nsp14 that contributes to correction of RdRp's errors[7]. The nsp14 has an exonuclease activity for removing the nucleotides misincorporated by RdRp during viral RNA synthesis and enables proofreading. Thanks to nsp14, the error rate of CoV genome replication is reduced by 1/20, resulting in the mutation probability of about 1 in 1,000,000 for each base per genome replication[8]. If one parent virus with a 30,000-base genome produces about 1,000 progeny viruses by single round of replication, the progeny population will always contain mutated viruses[8]. Some of these progeny viruses have mutations that are detrimental to their growth, and they are culled out and disappear. On the other hand, those mutants that happen to acquire mutations favorable for proliferation will survive and become dominant in the virus population. Therefore, the observed speed of virus mutation can be influenced not only by the biochemical properties of RdRp and nsp14, but also by the selective pressure from the host and the environment in which the virus propagates.

## Biological Clock of Viral Evolution

The genome mutation speed can be used to estimate when viruses with different genome sequences diverged from a common ancestor. For example, if the genome of a certain virus, whose mutation speed is estimated to be 1 base per month, differs from that of the reference virus by 120 bases, it is estimated that those viruses diverged about 10 years ago. Thus, by utilizing the mutation rate as a biological clock, it is possible to trace the evolution of viruses. In using the clock, however, it should be taken into consideration that its speed might not be constant but could be affected by various factors. For example, the mutation rate might be higher shortly after cross-species transmission because there is a strong selective pressure for adapting to a new host. When the virus is successfully adapted to the new host, additional mutations may become unnecessary, and the mutation rate can be lowered. Therefore, it is generally important to analyze viral mutations for a sufficiently long period for determining how fast the biological clock is ticking.

Of the four genera of CoVs, alphacoronavirus and betacoronavirus infect mammals, while gammacoronavirus and deltacoronavirus mainly infect birds. It is estimated that these genera diverged from the common ancestral virus about 300 million years ago[9], consistent with the time of separation between mammals and birds in animal evolution. Therefore, it is likely that CoVs have co-evolved with the host animals. In addition, CoVs are thought to have evolved by cross-species transmission from one host animal to another followed by adaptation to the new host through genetic mutation.

## Suggested Derivation of Common-cold HCoV OC43 from Bovine CoV, Which may have Caused the Russian Cold Pandemic in 19th Century

It is estimated that HCoVs are responsible for 10-15% of common cold cases only second to rhinovirus responsible for 30-50% cases[10]. So far, four species of HCoVs, namely, 229E, NL63, OC43 and HKU1, have been identified as causes of common cold and are detected all over the world (Table 1). The former two are classified as alphacoronavirus and the latter two as lineage A of betacoronavirus (Table 1 and Fig. 1). Phylogenetic analysis based on the entire genome sequences reveals that for each common-cold HCoV, evolutionarily related animal CoV can been found (Fig. 1).

For example, HCoV OC43 discovered in the 1960s[11] is evolutionarily close to bovine CoV (BCoV) (Fig. 1), which causes respiratory tract infection in cattle[12-14]. As it also causes severe diarrhea in newborn calves[12,14], posing a problem in the livestock industry, BCoV sam-

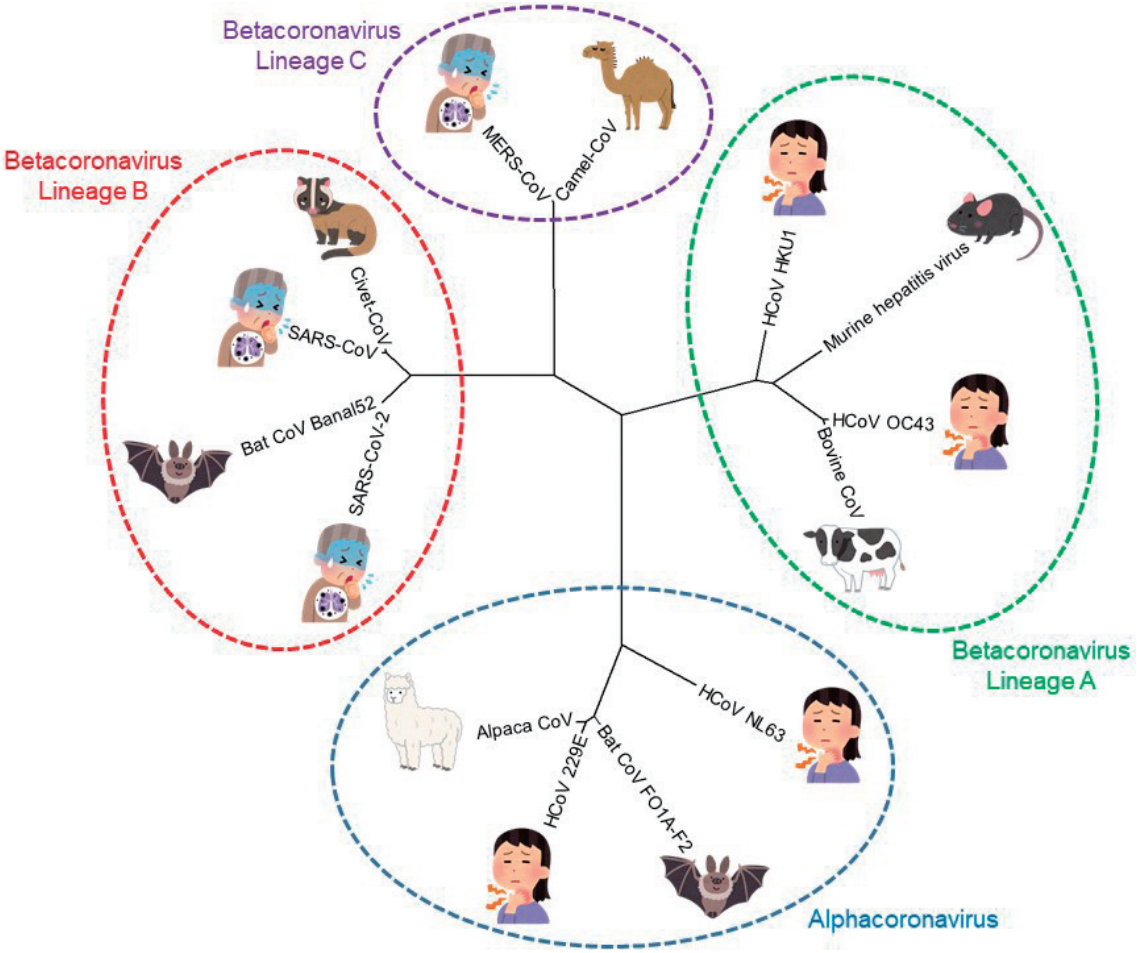


**Figure 1** Phylogenetic tree of HCoVs and their putative ancestral animal CoVs. Complete genome sequences of SARS-CoV-2 (Genbank accession no. NC_045512), as well as 4 common cold HCoVs, 229E (NC_002645), OC43 (NC_006213), NL63 (NC_005831), and HKU1 (NC_006577), 2 highly pathogenic HCoVs, SARS-CoV (NC_004718) and MERS-CoV (NC_019843), and 7 animal CoVs, alpaca CoV CA08-1/2008 (JQ410000), BCoV ENT (NC_003045), bat CoV FO1A-F2 (KT253270), murine hepatitis virus A59 (NC_048217), civet CoV SZ3 (AY304486), camel CoV KSA-CAMEL-363 (KJ713298) and bat CoV BANAL-20-52/Laos/2020 (MZ937000), were aligned and trimmed by Clustal Omega (https://www.ebi.ac.uk/Tools/msa/clustalo/) and TrimAl (http://phylemon.bioinfo.cipf.es/), respectively. By using the generated data, the evolutionary history was inferred by using the Maximum Likelihood method and General Time Reversible model[56]. The tree with the highest log likelihood is shown. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using the Maximum Composite Likelihood (MCL) approach, and then selecting the topology with superior log likelihood value. A discrete Gamma distribution was used to model evolutionary rate differences among sites (5 categories ( + G, parameter = 1.6388)). The rate variation model allowed for some sites to be evolutionarily invariable ([ + I], 12.78% sites). The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. This analysis involved There were a total of 36118 positions in the final dataset. Evolutionary analyses were conducted in MEGA11[57].

ples have been isolated and reposited for many years. Based on the nucleotide sequence analysis of the spike (S) protein gene of those BCoV samples, whose date of isolation was known, the mutation rate was calculated to be approximately $4 \times 10^{-4}$ substitutions per site per year[15]. According to this mutation rate, the time of divergence between BCoV and HCoV OC43 was estimated to be around 1890, suggesting the possibility that zoonotic transmission of BCoV to human took place about 130 years ago. Zoonotic transmission of BCoV to human may not be too rare an event because a pediatric diarrhea case has been reported in which

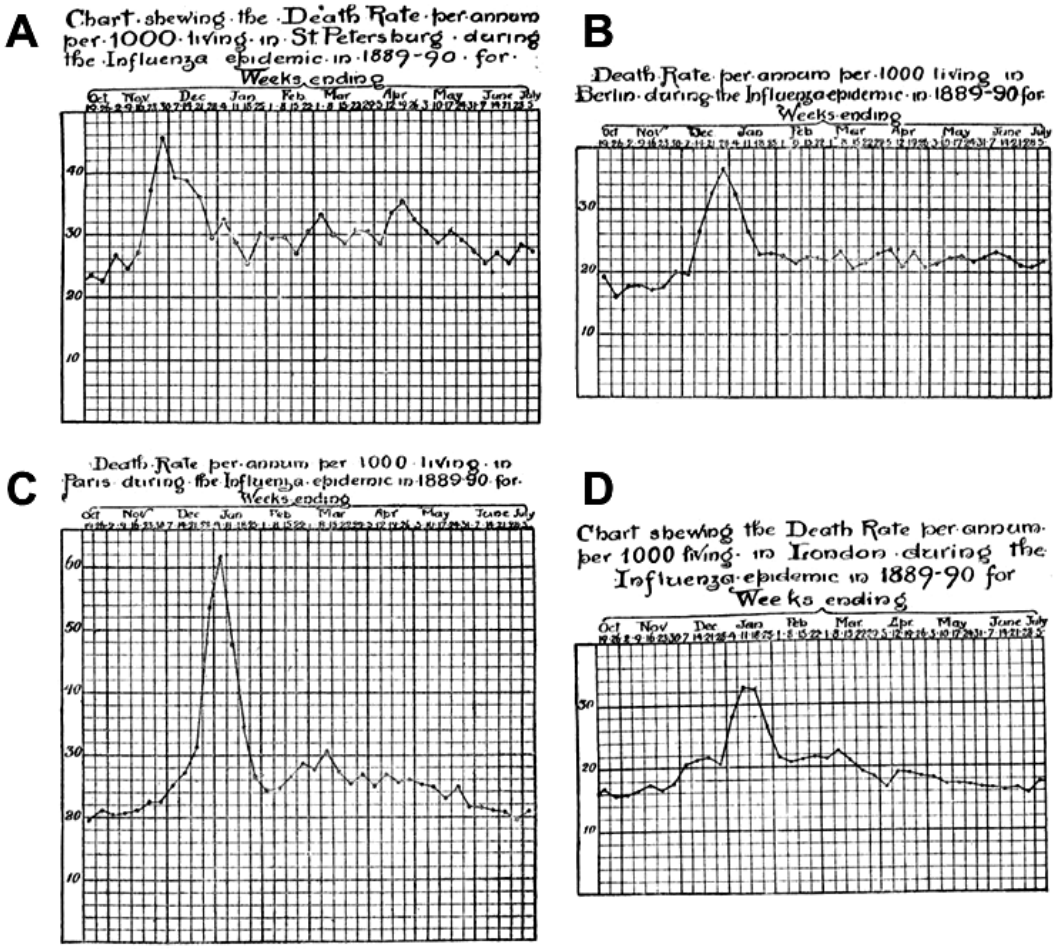


**Figure 2** Graphs of deaths per 1,000 people in major cities during the Russian cold pandemic[17]. The peaks of death toll in St. Petersburg **(A)**, Berlin **(B)**, Paris **(C)** and London **(D)** were in the last week of November 1889, the last week of December, the first week of January 1890, and the second week of January, respectively, demonstrating that the endemic area expanded from Russia to the west. In each city, only a single peak was observed, and the epidemic period appears to have been only up to 2 months.

BCoV was isolated from feces of the patient[16]. The estimated time of the zoonotic transmission of BCoV to human around 1890 coincides with the period of the Russian cold pandemic from 1889 to 1891. The Russian cold has historically been considered as an influenza pandemic, and a British doctor, Richard Sisley, described the situation at that time in his book[17]. It seems that flu-like cases first became apparent in 1889 in Central Asia of the inland Russia and spread to Western Europe in 1890 in the order of Germany, France and England. At major cities, a surge of excess deaths were recorded for one to two months (Fig. 2). Then, the outbreak spread to the United States and Asia, arriving in Japan around April 1890[18]. Description on the situation in Japan at that time can be found in the official report on the Spanish flu compiled by the Hygiene Bureau of the Japanese Ministry of Home Affairs in 1922[18]. The record says, "Various schools had to be closed due to a large number of patients. There is no doubt that the disease has caused significant damage not only to health but also to education" comparable to the drastic influence of COVID-19 on school education. The description also suggests that the Russian cold may have affected many children and young people. In those days, the elderly population was small, and the aged patients may not have been conspicuous. Nonetheless, it seems to be comparable to the current situation that many children and young people are found to be infected with the Omicron strain of SARS-CoV-2. Although there was no technology of vaccination or antiviral medication, the Russian cold epidemic in Japan subsided after a few months, and the world-

wide pandemic appears to have ended in 1891. It is reasonable to speculate that zoonotic infection of BCoV to human developed into the Russian cold pandemic and that the virus was finally adapted to human, becoming established as common-cold HCoV OC43.

## Emergence and Evolution of Other Common-cold HCoVs

Like OC43, HCoV 229E is a common-cold virus found in the 1960s[19]. Search and analysis of the CoV RNA in the feces of bats in Ghana revealed presence of the virus whose genome sequence was similar to that of 229E[20]. By tracing back the evolutionary clock based on the sequence data, it was estimated that the bat CoV and HCoV 229E diverged about 200 years ago. Later, CoVs with genome sequences more similar to that of the 229E were found in other bats and alpacas (Fig. 1)[21,22], and it is possible that these animals became intermediate hosts for zoonotic infection to human, although it is unknown exactly when it took place and whether there was any pandemic of respiratory disease at that time. Through adaptation to the human hosts, the zoonotic virus possibly became established as HCoV 229E.

Similar analysis suggests that HCoV NL63[23], which belongs to alphacoronavirus, and the CoV found in bats in the Appalachian Ridge of the United States diverged from a common ancestor about 500 to 800 years ago[24]. It is unclear whether the zoonotic infection to human occurred directly from the Appalachian bats or indirectly via some other animals that served as the intermediate hosts. The HCoV HKU1[25] belongs to the lineage A of betacoronavirus (Fig. 1). The natural host of the lineage A virus is thought to be rodents rather than bats. Therefore, the rodent CoV transmitted to human directly or via some intermediate host is likely the origin of HKU1. Although the exact timing of the zoonotic infection to human is unknown, analysis of mutations in the S protein gene suggests that the common ancestor of extant HKU1 strains existed in the 1950s[26]. Due to the limited number of HKU1 strains subjected to the analysis, it is possible that the variation of the S gene sequences is underestimated, and that the zoonotic infection occurred further back in time. For both NL63 and HKU1, it is unclear whether there was any disease pandemic that might correspond to the initial timing of zoonotic transmission to humans.

It should be mentioned that genome variations in different species and strains of CoVs involve not only point mutations, but also genome recombination between co-infected viruses. Therefore, it must also be considered that the generation of each common-cold HCoV may have involved multiple ancestral viruses rather than a single event of zoonotic transmission of one kind of virus.

## Where did SARS-CoV and MERS-CoV Come from?

SARS is a severe pneumonia (CFR: 10%) that originated in Guangdong Province, China in 2002. Via Hong Kong where multiple guests were infected at a hotel, it was spread all over the world. Approximately 8,000 infected people were confirmed in 29 countries around the world, and nearly 800 died. Its etiological agent, SARS-CoV which belongs to the lineage B of betacoronavirus, was identified in 2003[4]. At first, CoV whose genome sequence was similar to that of SARS-CoV was found in masked palm civets sold at a live animal market in Guangzhou, China[27]. Then, viruses whose genome sequences were remotely similar to that of SARS-CoV were found in wild bats[28,29]. Thus, it was the previous consensus that SARS-CoV originated from bats and transmitted to humans through civets as the intermediate host. More recently, SL-CoV that shares the structure of an accessory gene, ORF8, with SARS-CoV and civet CoV was found in bats in China[30,31]. Therefore, alternative possibility is that the bat SL-CoV was transmitted to humans and civets independently. Molecular evolution analysis estimated the time of divergence between SARS-CoV and the bat SL-CoV was in the range of 4 to 17 years before the SARS epidemic[32-34]. Unlike COVID-19, SARS outbreak did not become a pandemic and ended in less than a year, although there were sporadic cases of laboratory infections after 2003[35,36].

MERS-CoV, which belongs to the lineage C of betacoronavirus, was identified in 2012 as the cause of MERS[37]. MERS is prevalent in the Middle East region centering on Saudi Arabia, and 2,585 cases had been confirmed with 931 fatalities (CFR: 35%) as of September 2021. Like SARS-CoV, the natural host of MERS-

CoV is thought to be wild bats, but it seems to have exploited dromedary as the intermediate host for zoonotic transmission to humans[38]. MERS-CoV also seems to efficiently cause human-to-human transmission, represented by the MERS outbreak in South Korea in 2015 with 186 laboratory-confirmed cases and 38 fatalities[39]. The outbreak involved a number of hospital infection events but was ended by strict infection control strategies. Currently, there are sporadic cases of MERS found mostly in the Middle East with no sign of spreading to other areas.

Although both SARS-CoV and MERS-CoV are highly pathogenic in human hosts, it is fortunate that neither SARS nor MERS have developed into a pandemic like COVD-19. The exact reason for the failure of those viruses to cause pandemic hasn't been elucidated. It is possible that the species barrier between their natural host animals and human might be relatively high, and they may not have been able to evolve through subtle mutations to obtain such a high level of human-to-human transmissibility as common-cold HCoVs and SARS-CoV-2. However, we should keep it in mind that various CoVs still exist in wild bats and other animals and that they could serve as the natural reservoir of highly pathogenic human pathogens.

## How Could We Estimate the Virulence of SARS-CoV-2?

At the time of writing this article, more than two years have already passed since the declaration of the COVID-19 pandemic. However, it is still unclear when the pandemic will end. In contrast, the Russian cold pandemic which began in 1889 appears to have ended in about two years. In those days, even the existence of viruses as a pathogenic entity was not yet known, and reasonably, there was no advanced medical technology available, such as diagnosis by PCR and prevention by vaccination. Based on an assumption that the Russian cold was caused by zoonotic BCoV, it might as well be said that people in the 19th century were quite adept, in a sense, in controlling the CoV pandemic compared with us in the 21st century. Of course, even if CoV is responsible for both the Russian cold and COVID-19, it does not warrant the direct comparison of these pandemics in the same line. Biological factors, such as differences in transmissibility and replication competency of the viruses and properties of the host immune responses against the virus are important factors that determine the virulence. In comparing the Russian cold and COVID-19, differences in the social factors, such as population densities, proportion of elderly people and frequency of cross-border global human migration, should also be taken into consideration. In addition, a large number of asymptomatic and mild cases of SARS-CoV-2 infection, which could not be found for Russian cold in 19th century, can now be diagnosed by PCR and the antigen tests. Therefore, it would be meaningless to simply compare the apparent CFR of the Russian cold and that of COVID-19. In order to estimate the virulence of SARS-CoV-2, it appears more realistic to understand the ongoing adaptation of SARS-CoV-2 to human and compare its CFR with those of the common cold CoVs in today's same social settings. Those analysis may also provide useful insights into the argument whether COVID-19 should be classified as the category II infectious disease of the Japanese Infectious Diseases Control Law or as the category V infectious disease.

## Adaptation of SARS-CoV-2 to Human

As mentioned above, it is plausible that zoonotic BCoV, which may have caused the Russian cold pandemic, evolved into common-cold HCoV OC43 through adaption to human. Similarly, other common-cold HCoVs 229E, NL63 and HKU1, are likely derived from animal coronaviruses and adapted to human. Adaptation of zoonotically infected animal viruses to human hosts has been documented for other viruses, such as influenza virus and human immunodeficiency virus, as well[40]. The major factor that determines successful adaptation of the virus is whether it can efficiently be transmitted from human to human and replicate well in the human body. In addition, if a sufficiently large number of hosts are immunized by natural infection or vaccination, the virus that can avoid their immunity will be more advantageous for propagation in the population. Therefore, it is not surprising that enhancement of transmission, replication and immune evasion is observed in the course of viral adaptation. At the time of writing this article, Japan is in the midst of the sixth wave of the COVID-19 outbreak due to the Omicron mutant variant of SARS-CoV-2. This mutant

strain is reported to cause human-to-human infection more efficiently compared to the Delta variant, which caused the fifth wave in Japan[41]. It is also reported that the effects against the Omicron strain of vaccination and certain therapeutic antibodies have diminished[42]. On the other hand, several studies suggest that the virulence of the Omicron variant is attenuated compared with the previous strains[43-45]. In fact, a cohort study in England indicated that the risk of severe outcomes, such as hospitalization and death, is substantially lower for Omicron than for Delta[46]. These observations could be explained by the animal studies showing that the Omicron variant appears to have a reduced affinity to the lower respiratory tract than the previous strains[42]. That is, once the Omicron variant reaches the upper respiratory tract, it can replicate at the site and cause symptoms, such as runny nose and sore throat, and it doesn't have to go down to the lungs for efficient replication. If a virus only has to travel from the nose or throat of an infected person to the other person's nose or throat, the virus would have an advantage for human-to-human transmission over the lung-tropic virus. Therefore, it is possible that the Omicron variant has become more competent in propagating in the human community at the price of compromising its ability to cause severe disease of the lower respiratory tract. In other words, SARS-CoV-2 may be in the process of evolving from the pneumonia virus to the attenuated common-cold virus.

## SARS-CoV-2 in Comparison to the Common Cold CoVs

Even if SARS-CoV-2 is attenuated and the CFR is lowered, the actual number of fatal cases may not necessarily be decreased because the elevated transmissibility could drastically increase the total number of infected people. That is, the apparent virulence of the virus can be influenced not only by the biological properties of the virus itself, but also by social factors such as frequency of human-to-human contacts and the level of medical service systems. Thus, it is generally difficult to define virus virulence only from a virological point of view. For example, HCoV-HKU1 (Table 1), generally designated as a common-cold virus, was originally isolated from a 71-year-old male patient hospitalized for pneumonia in 2004[47]. Also, HCoV-HKU1 was retrospectively detected in the clinical specimens collected in 2003 from a 35-year-old pneumonia patient with no underlying disease[47]. In addition, fatal cases of pneumonia caused by HCoV-HKU1 have been reported[48,49]. Therefore, HCoV-HKU1 could cause pneumonia even in a young healthy individual and could be lethal despite its label as a common-cold virus. Quite a few cases of severe or fatal pneumonia of "unknown etiology" may have actually been caused by HCoV-HKU1 and possibly by other common cold HCoVs. Since four common cold HCoVs are detected all over the world including Japan, they can be regarded as "pandemic" viruses in a sense. However, since there has been no systematic effort made to detect them by PCR or the antigen test, it is practically impossible to evaluate their potential pathogenicity or CFR accurately.

SARS-CoV and MERS-CoV with their high CFRs can easily be discriminated from the common-cold HCoVs. However, SARS-CoV-2 doesn't appear to be in the same category as these highly pathogenic viruses. Since the majority of people infected with SARS-CoV-2, especially the Omicron strain, are reported to have mild symptoms or be asymptomatic, it seems that the line for distinguishing the common-cold HCoVs and SARS-CoV-2 is drawn only arbitrarily, but not objectively.

## How Could Immunity Play a Part in Controlling COVID-19?

When the mRNA vaccines against SARS-CoV-2 were put into use, it was categorically and optimistically stated that the pandemic of COVID-19 would end if herd immunity was to be established. However, it has long been known that life-long immunity cannot be generated against common-cold HCoVs. For example, a previous study showed that volunteers challenged with common cold HCoV 229E were shown to maintain protective immunity for a limited period of time and that they could be re-infected after a year although the symptoms were none or mild[50]. Comparably, the currently available SARS-CoV-2 vaccines appear to require serial booster vaccinations for maintaining high levels of antibody titers. Since the vaccines are designed based on the S gene sequence of the original Wuhan strain, it is not surprising that they demonstrate limited effects against mutant strains,

such as Omicron. Although the vaccination may have a certain level of efficacy in preventing aggravation of COVID-19, it cannot be expected to prevent SARS-CoV-2 infection per se. Even if the vaccination rate reaches 100%, SARS-CoV-2 will unlikely be eradicated, but rather the emergence and propagation of novel mutant strains, which avoid the vaccine-induced immunity, might end up being enhanced. Results from a previous epidemiological survey in Beijing showed that most people are naturally infected with all four common-cold HCoVs by the age of 14, and more than 70% of adults have significant levels of antibodies against them[51]. Since the common-cold HCoVs can be detected all over the world, the immunological status of people is likely similar in other regions including Japan. It is plausible that thanks to the immunological memory acquired in the childhood from natural infection with the common-cold HCoVs, many of us are spared from severe pneumonia which these viruses might potentially cause. Cases of SARS-CoV-2 infection in children are usually mild or asymptomatic with CFR of essentially zero. The natural infection with the apparently attenuated strain of SARS-CoV-2 might lead to formation of the solid immunological memory, which could protect them from the severe or fatal case of COVID-19 even if they are re-infected at older ages. Of course, it goes too far to say that children and young people are encouraged to get infected with SARS-CoV-2 because their risks of aggravation and sequelae cannot completely be denied. However, in light of the pathogenicity of SARS-CoV-2, especially the Omicron strain, it does not seem appropriate to be occupied with the stereotyped idea that the virus infection is the absolute evil. Depriving the chance of SARS-CoV-2 infection in childhood more than necessary might lead to loss of the opportunity for acquiring the immunological memory in a natural way. For example, in China where the extremely strict zero SARS-CoV-2 policy has been in effect, the number of COVID-19 cases is now increasing abruptly. As for SARS-CoV-2, it seems to be inevitable to take controlling measures on the premise that we have to live with them. For that purpose, it may be realistic to wisely tolerate some cases of infection while developing the appropriate medical system.

## What Could We Envision for the Future of COVID-19 from the Viewpoint of Viral Evolution?

If we are destined to live with SARS-CoV-2, the biggest concern would be the emergence of a highly pathogenic mutant whose CFR can be as high as those of SARS-CoV and MERS-CoV. How realistic might that scenario be? So far, the major pandemic strains of SARS-CoV-2 has shifted from the original Wuhan strain → Alpha strain → Delta strain → Omicron strain, and each transition seems to have been associated with increased transmissibility and enhanced immune evasion. As mentioned above, these relatively fast changes in the biological properties through mutations likely represent adaptation of the zoonotic virus to the human hosts and will continue until SARS-CoV-2 evolves into a genuinely human-adapted virus. In the course of the evolution, it is reasonable to expect that the mutation rate and the genome diversity within the same strain will decrease as the adaptation to a new host species is accomplished. If the genomic diversity of Omicron or the following mutant strain, which will potentially emerge, is comparable to those of common cold HCoVs, the findings could imply that the evolution of SARS-CoV-2 from bat CoV to human CoV is approaching the final stage and that the chances of SARS-CoV-2 suddenly turning into a highly pathogenic virus might be negligible. The advanced genome analysis technology detects and identifies new variants of SARS-CoV-2 one after another. Genome sequence data of millions of SARS-CoV-2 samples determined all over the world are being cumulatively registered in the international databases such as GISAID. Although these advanced technologies represent scientific progress, the obtained data ironically appear to be exploited for emphasizing that the end of the COVID-19 pandemic would be further ahead rather than for fastening it. It is expected that the compiled data wisely utilized in combination with the clinical information and comparison with the common cold HCoVs may provide useful insights into not only the evolution of SARS-CoV-2 but also the strategy for building the global consensus on the end of the COVID-19 pandemic.

## Conclusion

Viruses, especially pathogenic ones, are thought to be troublesome for humans. However, humans, as well as various other organisms, have undergone co-evolution with viruses. In fact, there are remnants of viral genes (endogenous viruses) in our chromosomes as well[52]. Our immune system also seems to have evolved partly through exposure to a variety of viruses[53-55]. In other words, from the perspective of the evolution of living creatures, coexistence with viruses is inevitable. State-of-the-art technologies provide massive scientific information about viruses. For tackling the problem of infectious disease, however, other factors in different dimensions should also be considered. Thus, declaration of the end of COVID-19 pandemic will require the global consensus with political, economic, and cultural factors, in addition to scientific evidence, considered. At the same time, the declaration should not unnecessarily be delayed by the influence from commercialism or expedience. The COVID-19 pandemic is not only a contemporary problem, but also a problem that could affect the future of children and young people, who will lead the next generation society. Thus, how we could minimize the negative impact of the pandemic especially on education is an important issue. One hundred years later, people might compare us struggling against COVID-19 today and the 19 th century humans, who managed to terminate the Russian cold pandemic in 2 years, and ask who were more successful. Just like the risk of COVID-19 aggravation is different from person to person, there are considerable diversities between nations and individuals in the idea of how the COVID-19 problem should be handled. With those differences kept in mind, it is our mission to promote cooperation, but not confrontation, at both local and global levels for overcoming the pandemic in a timely manner.

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