〈Review Article〉

Global trends in novel coronavirus infection (COVID-19) and its treatment —Analyses of the background of ivermectin clinical trials—

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The authors collected and analyzed information on the details of the outbreak and global spread (pandemic) of novel coronavirus (SARS-CoV-2) infection (COVID-19) and clinical studies of ivermectin for the prevention and treatment of COVID-19. The time period covered was until the third wave of the epidemic stabilized in February of 2021, which was 15 months after the COVID-19 outbreak in Wuhan, Hubei, China. Review articles were published, in Japanese and English, in this journal.

This review describes the results of data collection and analysis of the global trends of COVID-19 from the fourth to the eighth wave in the ensuing two years and two months. The situations in the United States (most severely affected), Europe and Asia (where different trends were observed among countries), and India and Japan (where unique trends were observed), are also described. In particular, the emergence of variants, the most prominent feature of COVID-19—including subsequent transitions to various lineages, which strongly influence differences in the virulence and infectivity of mutant and subtype strains—is analyzed and described in detail.

As the COVID-19 epidemic progressed, both the infectiousness of COVID-19 and the number of patients increased. However, the pathological course of clinical patients tended to become milder, and the disease prognosis less severe, as patient management improved with the introduction of various therapeutic agents, including rapid detection and increased frequency of testing. Although vaccination of the population progressed rapidly, SARS-CoV-2 mutated just as rapidly, rendering the vaccines less effective in both the prevention and spread of infection. In addition, monoclonal antibody drugs targeting the spike proteins on the surface of SARS-

CoV-2 became less effective due to ongoing mutations involving the target receptors. Novel therapeutic agents continue to be developed, and further improvements in COVID-19 therapy are expected.

The COVID-19 pandemic is currently on a downward trend, and the United States and Japan lifted their emergency pandemic response alerts in May of 2023. The WHO declared the termination of the Public Health Emergency of International Concern for COVID-19 on the 5th of May 2023. It is hoped that no new pandemic waves will appear in the future.

This review provides the necessary background information for the next review by the authors on the clinical trials of ivermectin, by analyzing the status of COVID-19 worldwide and the current status of therapeutic agents being used.

Introduction

The authors have collected and analyzed information on the course of events of the outbreak and global spread (pandemic) of novel coronavirus (SARS-CoV-2) infection (COVID-19) and clinical studies of ivermectin for the prevention and treatment of COVID-19 during the 15 months following the outbreak in Wuhan, Hubei Province, China. The time period covered was up to the point that the third wave of the epidemic subsided in February of 2021. Reviews in both Japanese and English were published in this journal[1,2].

At that time of writing, the SARS-CoV-2 Alpha variant strain (systematic name: B.1.1.7), first detected in the United Kingdom in September of 2020, accounted for 97% of cases in that country and had begun to spread worldwide, replacing the Iota (B.1.526) and Epsilon (B.1.427 / B.1.429) variants in the United States and the B.1.1.214 subtype strain prevalent in Japan[3]. On the other hand, the diversity of COVID-19 virus strains began to become evident[4], with the Beta variant (B.1.351) accounting for 99% in South Africa, the Gamma variant (P.1) accounting for 70% in Brazil, and the Delta variant (B.1.617.2) appearing in India.

Also, by that time, the total number of COVID-19 cases and deaths had already reached more than 100 million and 2.2 million, respectively, in more than 220 countries/regions worldwide[5]. On the other hand, in the United States, where the situation was most severe, the number of new cases, including deaths, was declining rapidly; there was optimism that the COVID-19 pandemic would subside with the cessation of the third wave recorded between October of 2020 and February of 2021. Such optimism was supported by the widespread use of the COVID-19 vaccine, and the use of the antiviral drug remdesivir and the monoclonal antibody combination drug casirivimab/imdevimab, which received an Emergency Use Authorization (EUA)[6] from the U.S. Food and Drug Administration (FDA), and the steroidal drug dexamethasone, which prevented patients with mild to moderate disease from becoming seriously ill. These also saved the lives of patients with severe disease. Some progress was therefore made in the management of

patients with COVID-19.

However, contrary to expectations, the COVID-19 pandemic continued, and by the end of May 2021, as described in detail in this review, three waves of epidemics were observed: an Alpha variant[7] that spread from the United Kingdom to all of Europe and raged in the United States, a Beta variant[8] that spread from South Africa to Europe, Asia, and Oceania but did not reach the level of a large-scale epidemic, and a Gamma variant[9] that caused a fairly large outbreak from Brazil to all of South and Central America.

In India, on the other hand, the epidemic was different, with the first wave of the epidemic occurring over a nine-month period from early May 2020 to late January 2021, caused by mutant strains (B.1.1.32, B.1.1.8, B.1.113, etc.)[10] different from those in other countries. This outbreak peaked at 96,000 new cases per day on the 17th of September, but the subsequent transmission of the third wave of the worldwide epidemic caused by the Alpha variant of British origin was not observed. However, from around the 10th of March 2021, cases of infection with the Delta variant[11] increased rapidly, reaching a peak of more than 410,000 new cases on the 6th of May, and a major fourth wave of the epidemic was observed until the number of cases fell to less than 50,000 by the end of June. The epidemic strain in India (B.1.617.2) was named the Delta variant by the World Health Organization (WHO) on the 31st of May. The spread of the Delta variant from India to the rest of the world was rapid, and the fifth wave, which peaked on the 6th of August with approximately 820,000 cases in the United States and the United Kingdom, continued until mid-October 2021. In Japan, the fifth wave of the epidemic was observed, this time with the Delta variant, coinciding with the Tokyo Olympics and Paralympics.

The subsequent transition from the sixth wave caused by the Omicron variant (B.1.1.529)[12], which began in Zimbabwe/South Africa in mid-November of 2021, to the seventh and eighth waves caused by various lineages of the Omicron variant is described in detail in the text of this review. These waves differed from those caused by the Alpha- and the Delta-variants in that the pathological clinical course was mainly mild, but the infectious capacity was enhanced and the epidemic waves so large that the number of new infections worldwide exceeded 4 million per day.

On the 11th of March 2020, the WHO declared that COVID-19 had reached pandemic status, but on the 14th of September 2022, two years and six months later, the WHO announced[13] that COVID-19 was on a declining trend and that the declaration was expected to be lifted in the near future. However, the number of newly infected cases worldwide was approximately 500,000 per day at the time the seventh wave was in the process of converging, and the situation thereafter remained flat. This did not lead to the lifting of the pandemic declaration. In the winter of 2022–2023, an eighth wave was caused by various lineages of the Omicron variant and it progressed simultaneously with a seasonal influenza epidemic—the global spread of infection had become unpredictable. Additionally, children and susceptible adults were alerted to the possibility of seri-

ous respiratory syncytial virus (RSV) infections. Therefore, the simultaneous outbreaks of three viral respiratory infections were termed “tridemic” or “triple threats”. On the 27th of January 2023, the WHO convened a COVID-19 Emergency Committee based on International Health Regulations to discuss whether or not to declare the pandemic over. However, due to repeated changes in the causative viruses driving the pandemic and the high number of deaths, the committee concluded[14] that it would take several more months of surveillance before officially declaring the pandemic over.

The COVID-19 epidemic has lasted more than three years, despite extensive and diligent efforts—such as antigen testing, vaccinations, antiviral drug therapies, as well as antibody and steroid therapies—being made to prevent the spread of infection and seek a cure. Furthermore, post-COVID/long COVID (post-acute sequelae of COVID-19 or PASC) has been observed[15] in 4.5% of patients infected with the Omicron variant. Although the Omicron variant is considered to be less pathogenic, it, along with other variants, has resulted in pathological sequelae that have become a significant and persistent social problem.

It is not necessary to describe the details of the COVID-19 pandemic in this review, since there are specialized information sources such as the WHO[16] and the database of Johns Hopkins University[17] in the United States. However, the changes in pathogenicity and infectivity of SARS-CoV-2, the status of approval and usage of COVID-19 drugs, and the development of new drugs are all important factors that exert a great influence on the background for the authors’ analysis of the “status of clinical trials of ivermectin against COVID-19” to be described in our subsequent review.

1. Global trends in COVID-19

The virus responsible for the November 2019 outbreak of COVID-19 in Wuhan, Hubei Province, China, was identified to be two strains of SARS coronaviruses belonging to the genus Beta-coronavirus of the family Coronaviridae—the same family as the previous outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)—and was referred to as the Wuhan virus. The WHO prohibits the naming of infectious diseases and pathogens with a person’s or regional name, due to the potential for discrimination and prejudice. On the 7th of January 2020, the Wuhan virus (also called the Chinese Virus in the United States) was provisionally named the 2019 novel coronavirus (2019-nCoV). In response, the national authorities and the press in Japan began to refer to it as the “novel coronavirus”. Subsequently, the International Committee on Virus Classification officially named the virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[18] on the 11th of February that same year. On that same day, the WHO also named[19] SARS-CoV-2 infection as Coronavirus Disease 2019 (COVID-19).

SARS-CoV-2 is an enveloped virus, with a positive-sense, single-stranded RNA genome the size of approximately 30,000 bases—which is extremely large for an RNA virus and easily mutable. Nomenclature for mutant strains has been proposed under eight global clades[20] by the Global Initiative on Sharing All Influenza Data (GISAID). It is an international organization that provides the complete genomic sequence of SARS-CoV-2 as shared information. It follows the rules of global lineage assignment in accordance with PANGO (Phylogenic Assignment on Named Global Outbreak lineages) nomenclature[21] and was developed by a research group in the United Kingdom. On the 31st of May 2021, the WHO published a simplified nomenclature[22] that labels SARS-CoV-2 variants with letters of the Greek alphabet, and further proposed the additional labels "variants of interest (VOI)" and "variants of concern (VOC)". The PANGO strain names and GISAID branch group names are used in epidemiological and molecular biological studies of mutant strains, and a list of names contrasting them with the WHO simplified labels[23] has been published.

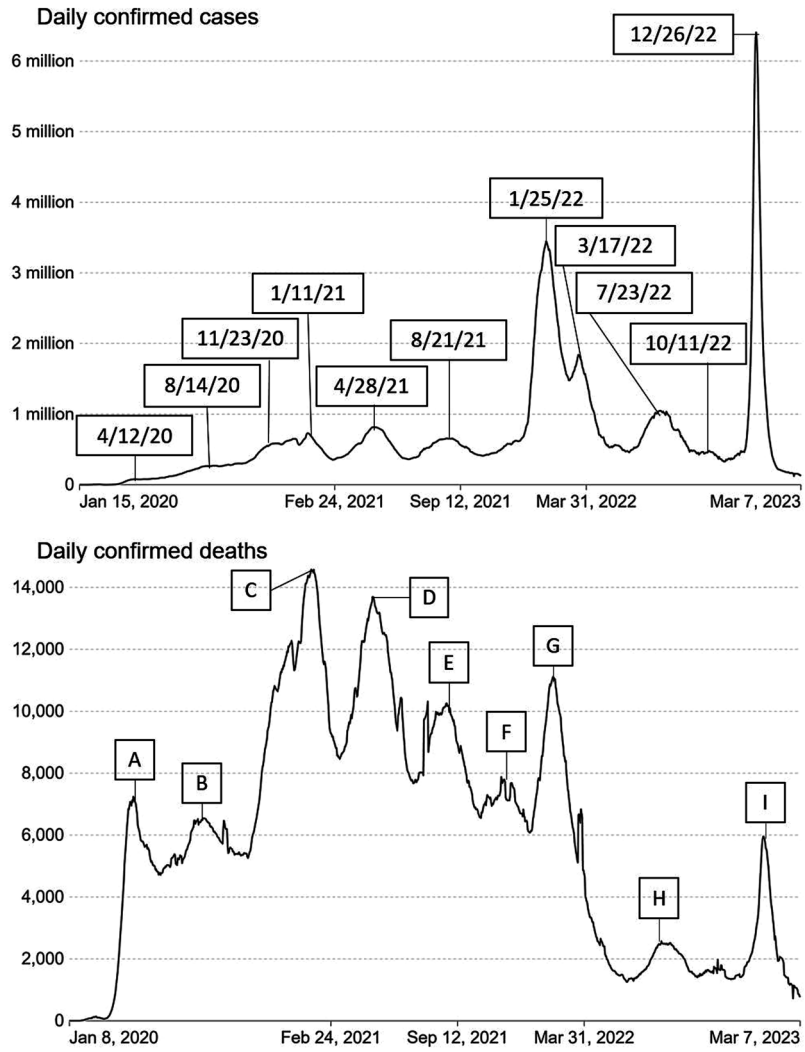
1) COVID-19 epidemic waves caused by SARS-CoV-2 variants

The transition of the COVID-19 epidemic in the world from the first to the eighth wave is shown in Fig. 1, using the Global Change Data Lab (GCDL) database[24] of the United Kingdom, and is based on the WHO COVID-19 dashboard[16]. For the number of new cases and deaths per day, the 7-day average figures are applied in order to provide a bird's-eye view of the 3-year and 3-month endemic period.

The number of newly infected cases remained below 850,000 from the 12th of April 2020 (the peak of the first wave) to the 21st of August 2021 (the peak of the fifth wave). Then, in what has been described as an infection explosion, the number rapidly rose to reach 3.44 million at the first peak of the sixth wave on the 25th of January 2022. After the peak, the number of cases rapidly declined, but began to rise again, reaching the second peak of the sixth wave at 1.81 million on the 17th of March 2022. The number of cases dropped to 500,000 in early May, and the sixth wave appeared to subside. However, in early June, the number of cases began to rise again, and the seventh wave struck. The number of infected cases in the seventh wave increased rapidly, reaching 1.1 million on the 23rd of July (the first peak of this wave), but then also rapidly declined—reaching less than 450,000 on the 22nd of September. Thereafter, another small rise (the second peak) of 480,000 people was recorded on the 11th of October. The number once again dropped to 320,000 on the 5th of November, but this situation did not last. Another upward trend began, exceeding 450,000, and this was the beginning of the eighth wave that began on the 1st of December 2022.

The eighth wave was predicted to peak on the 19th of December 2022, with about 590,000 cases, before being followed by a gradual downward trend and convergence. However, in responding to the criticism by the WHO, China announced on the 14th of January 2023, their number of in-

Fig. 1. Global transition of confirmed cases and deaths of COVID-19 (7-day average)



fected cases and deaths after the 8th of December. Consequently, Fig. 1 shows that the number of newly infected cases peaked on the 26th of December 2022 at more than 6 million, including 5.88 million in China. Since China stopped releasing information on the daily number of new cases and deaths on the 9th of January 2023, the graph in Fig. 1 shows a markedly sharp drop. This steep drop is considered to be hugely artificial and of no scientific significance whatsoever.

The GCDL database allows for a country-specific review of SARS-CoV-2 variants attributable to new infections. The third peak of the third wave (which took place on the 11th of January 2021), recognized at the time of publication of the authors' 2021 review[1], was mainly due to the epidemics of the Epsilon (B.1.427, B.1.429) and Iota (B.1.526)[25] variants in the United States, by outbreaks of the Alpha variant (B.1.1.7) from the United Kingdom in European countries, and the Gamma variant (P.1) in Brazil. The subsequent sharp fourth wave (peaking on the 28th of April

2021), was caused by an epidemic of the Delta variant (B.1.617.2) in India[26]. The gentle fifth wave which occurred between July and October of 2021 (peaking on the 21st of August), shows how several subtypes of the Delta variant raged across the United States. The following small peak in November–December 2021 is also evidence of a small epidemic caused by multiple lineages of the Delta variant in the United States, and several European countries such as Germany, France, and the United Kingdom.

Before the small peak following the fifth wave had fully subsided, an explosive sixth wave of outbreaks—caused by the highly infectious Omicron variant (B.1.1.529)[27], and first detected in South Africa in mid-November—broke out in the United States and European countries (including the United Kingdom, France, Germany, Italy, Spain, and Denmark). In addition, from early January of 2022, the outbreak caused by the Omicron variant spread to Asian countries such as India, Malaysia, and Japan, as well as to Latin American countries such as Brazil and Mexico. The spread of the sixth wave of the epidemic was remarkably rapid. By the 28th of February 2022, the cumulative number of COVID-19 cases worldwide reached 437 million and the cumulative number of deaths 5.99 million.

The first peak of the sixth wave (on the 25th of January 2022), was mainly due to the Omicron variant BA.1 lineage. As shown in Table 1, of the 3.42 million cases worldwide, the United States accounted for 20.1%, or 686,000 cases, and France for 10.1%, or 344,000 cases. The incidence rates in Italy, Germany, and the United Kingdom ranged from 3.1 to 5.1%. In Japan, the incidence rate was 1.3%, in Vietnam 0.5%, and in South Korea it was 0.2%. The second peak (on the 17th of March 2022) was caused mainly by the BA.2 lineage[28]. The composition ratio of this 1.81 million cases peak was quite different from that of the first peak: South Korea showed a sharp increase to 387,000 (21.4%), Vietnam increased to 254,000 (14%), and Germany increased to 220,000 (12.1%), France decreased to 4.0%, Italy showed a slight decrease, the United Kingdom and Japan both showed slight increases, and the United States showed a marked decrease to 33,000 (1.8%).

The first peak of the seventh wave (on the 23rd of July 2022), was caused largely by the Omicron variant BA.5 lineage[29]. While the number of cases in the United States once again increased to 126,000 (12.3% of the world total of 1.03 million), the number of cases in Japan surprisingly jumped to 126,000 (12.2% of the world total). France and Italy also showed slight increases in numbers. On the other hand, South Korea and Vietnam showed a sharp decrease in the number of cases, down to 61,000 (5.9%) and 650 (0.1%), respectively. Germany and the United Kingdom also showed downward trends in case numbers. The second peak of the seventh wave (occurring on the 11th of October 2022) showed only a small number of cases (475,000) worldwide, but the strains caused by this peak were a mixture of BQ.1 and BA.2.75 lineages, in addition to the BA.5 lineage. By country, Germany and France accounted for 21.8% (103,000) and 11.7% (56,000), respectively, of the worldwide total. At the same time, the United States and Japan showed a de-

Table 1. Confirmed cases at the peaks of the 6th and 7th waves of COVID-19 in each country

Peak / Country	6th Wave – 1st *1 Cases (ratio)	6th Wave – 2nd *2 Cases (ratio)	7th Wave – 1st *3 Cases (ratio)	7th Wave – 2nd *4 Cases (ratio)
World	3,420,000 (100.0)	1,810,000 (100.0)	1,030,000 (100.0)	475,223 (100.0)
USA	685,958 (20.1)	32,771 (1.8)	126,397 (12.3)	39,868 (8.4)
France	344,581 (10.1)	72,184 (4.0)	83,365 (8.1)	55,765 (11.7)
Italy	173,006 (5.1)	57,732 (3.2)	79,077 (7.7)	41,180 (8.7)
Germany	121,886 (3.6)	219,774 (12.1)	90,221 (8.8)	103,449 (21.8)
UK	105,469 (3.1)	77,491 (4.3)	16,618 (1.6)	9,547 (2.0)
Japan	44,806 (1.3)	52,220 (2.9)	125,970 (12.2)	31,294 (6.6)
Vietnam	15,785 (0.5)	254,060 (14.0)	650 (0.1)	878 (0.2)
South Korea	7,125 (0.2)	387,279 (21.4)	60,681 (5.9)	21,008 (4.4)

*1 Peak: 1/25/22, Dominant epidemic strain: BA.1 lineage

*2 Peak: 3/17/22, Dominant epidemic strain: BA.2 lineage

*3 Peak: 7/23/22, Dominant epidemic strain: BA.5 lineage

*4 Peak: 10/11/22, Dominant epidemic strain: BA.5 lineage＋BQ.1 lineage＋BA.2.75 lineage

crease in the number of cases, with South Korea also showing a declining trend. Thus, throughout the Omicron variant epidemics, the lineages and the major endemic countries changed.

Table 2 shows the epidemic period and the number of newly infected cases at the peak of each of the above-mentioned first to eighth waves. If the number of new cases at the peak of the first wave caused by the original B.1 strain from Wuhan, Hubei Province, China, is 1.00, then the third peak of the third wave caused by the Alpha variant from England is 7.64, and the fourth wave caused by the Delta variant from India is 9.69. These numbers indicate that the infectivity (spreading power) was gradually enhanced. The Omicron variant of South African origin caused an explosive outbreak of 40.11 in the first peak of the sixth wave. Thus, the Omicron variant was found to have markedly enhanced infectivity. The reason for the low magnification after the second peak of the sixth wave is that nearly 500 million people (6% of the world population) were infected with COVID-19 by the time of the first peak of the sixth wave, and 25–60% of the population (as described below) in the United States and Europe in particular were infected with COVID-19. Therefore, this could be considered as an indication that collective immunity to infection had been established and that the spread of infection had essentially slowed down.

2) Global deaths due to COVID-19

The lower portion of Fig. 1 shows a graph of the number of deaths worldwide due to COVID-19. It also shows a markedly different pattern from that of the number of newly confirmed cases in the upper portion. The dissimilarity is thought to be due to differences in the strength of infectivity and virulence (toxicity) of the variants causing each wave of the epidemic.

Table 2. Transition of the global COVID-19 pandemic

Pandemic	Period (start – end) (M/D/Y)	Peak (M/D/Y)	Confirmed cases at the peak*1	Magnification*2	Epidemic strain
1st Wave	3/18/20 - 4/30/20	4/12/20	85,270	1.00	B.1 (Wuhan Strain)
2nd Wave	5/ 1/20 - 8/25/20	8/14/20	267,040	3.13	
3rd Wave - 1st	10/2/20 - 11/26/20	11/23/20	596,706	7.00	
3rd Wave – 2nd	11/28/20 - 12/28/20	12/20/20	651,381	6.23	
3rd Wave – 3rd	12/30/20 - 2/19/21	1/11/21	744,205	7.64	B.1.1.7 (α variant)
4th Wave	3/ 3/21 - 6/21/21	4/28/21	826,676	9.69	B.1.617.2 (δ variant) Endemic in India
5th Wave	7/ 2/21 - 10/17/21	8/21/21	657,846	7.71	B.1.617.2 (δ variant) Endemic outside of India
6th Wave – 1st	11/ 4/21 - 2/28/22	1/25/22	3,420,000	40.11	B.1.1.529 (ο variant)
6th Wave – 2nd	3/2/22 - 5/8/22	3/17/22	1,810,000	21.23	ο variant BA.2 lineage
7th Wave – 1st	5/28/22 – 9/17/22	7/23/22	1,100,000	12.90	ο variant BA.5 lineage Endemic in Japan/Korea
7th Wave – 2nd	9/18/22 – 10/30/22	10/11/22	482,838	5.66	ο variant BQ.1 lineage Endemic in USA/EU
8th Wave *3	11/6/22 -	12/19/22	588,412	6.90	Endemic of various lineage

*1 Newly confirmed cases: 7-days average

*2 Magnification: Confirmed cases at the 1st wave as 1.00

*3 8th Wave: The indicated peak (12/19/22) does not include Chinese cases
When included Chinese cases, the peak was 12/26/22 (6.41 million cases)

Table 3 shows the results of the analysis of lethality rate, the number of deaths relative to the number of newly confirmed cases, on the peak date of each wave of deaths. The lethality rate was remarkably high at 8.7% in the first wave caused by the Wuhan strain (indicated as **A** in the graph), but it was reduced to 2.5% by the third peak in the third wave (indicated as **C**). This was caused mainly by the Alpha variant of British origin. A further reduction to 1.7% occurred in the fourth wave (indicated as **D**), and was due predominantly to the Delta variant of Indian origin. During the first peak of the sixth wave (indicated as **G**) of the explosive epidemic of the Omicron variant that spread from South Africa to the rest of the world, the lethality rate was remarkably low at 0.4%. Comparing these numbers of new cases and deaths, the differences suggest that the Omicron variant (which caused the global pandemic from early January of 2022) was characterized by remarkably high infectiousness but remarkably low virulence (toxicity) leading to death, and that the primitive Wuhan strain (which caused the initial epidemic) was characterized by low infectiousness but remarkably high virulence (toxicity).

Table 3. Transition of global lethality rate with COVID-19

Pandemic	Peak of deaths	Peak date (M/D/Y)	Deaths/Cases *1	Lethality (%)
1st Wave	A	4/13/20	7,376 /84,864	8.7
2nd Wave	B	8/10/20	6,397/263,009	2.4
3rd Wave – 3rd peak	C	1/26/21	14,859/585,853	2.5
4th Wave	D	4/29/21	13,926/825,914	1.7
5th Wave	E	8/27/21	10,157/656,075	1.5
5th Wave - aftermath	F	12/5/21	8,120/624,817	1.3
6th Wave – 1st peak	G	2/10/22	10,896/2,520,000	0.4
7th Wave – 1st peak	H	8/9/22	2,543/928,037	0.3
8th Wave *2	I	1/8/23	5,963/1,560,000	0.4

*1 Cases: numbers of cases on the peak day of deaths

*2 Peak date for death of 8th wave (1/8/23): includes Chinese cases

3) COVID-19 infection status in countries around the world

The cumulative numbers of confirmed cases and deaths along with the rates of morbidity and lethality of COVID-19 for the top 20 countries in the world as of the 31st of December 2022, are shown in Table 4. The total number of confirmed cases worldwide was calculated to be approximately 665 million, representing 8.3% of the total population of approximately 8 billion people. The total number of deaths was about 6.7 million, and the lethality rate was calculated to be 1.0%. It should be understood that this is an analysis of the global situation excluding China, since it is based on figures prior to the 14th of January 2023 (at which time, China revised and published the number of cases and deaths in response to the WHO's criticisms).

In the United States, which has the largest number of infected persons in the world, the number of confirmed cases reached more than 100 million, or 30.7% of its approximately 335 million population. The number of deaths in the United States is approximately 1.12 million, resulting in a lethality rate of 1.1%—which is higher than the world average. In India, the second largest country based on the number of infected, the number exceeds 44 million. However, with a population of over 1.4 billion people, the morbidity rate is as low as 3.2%, and the lethality rate is calculated to be 1.2% (since the number of deaths is 530,000). In comparison, France, the country with the third largest number of infected cases, 39.3 million people were infected. Nevertheless, France, with a population of 65.5 million, has the highest morbidity rate in the world at 60%. The incidence rate of ten countries, including South Korea, the Netherlands, and Germany, as shown in the footnote of Table 4, is more than 25%. The lethality rate is found to be higher than the world average in eight countries, including Mexico (4.6%), Indonesia (2.4%), and Brazil and Iran (1.9%).

i) Number of infected cases and deaths in the United States

The United States has suffered the most severe health consequences from COVID-19, and the transition of the numbers of confirmed cases and deaths is shown in Fig. 2. The first case de-

Table 4. Global situation of COVID-19
[as of December 31, 2022: top 20 countries]

	Country	Population	Accumulated cases	Morbidity (%)	Accumulated deaths	Lethality (%)
1	USA	334,805,269	102,681,777	30.7	1,118,441	1.1
2	India	1,406,631,776	44,679,905	3.2	530,707	1.2
3	France	65,584,518	39,331,022	60.0	162,042	0.4
4	Germany	83,883,596	37,369,865	44.5	161,465	0.4
5	Brazil	215,353,593	36,357,101	16.9	693,949	1.9
6	Japan	125,584,838	29,299,459	23.3	57,513	0.2
7	Korea	51,329,899	29,116,800	56.7	32,219	0.1
8	Italy	60,262,770	25,143,705	41.7	184,642	0.7
9	UK	68,497,907	24,135,084	35.2	198,937	0.8
10	Russia	145,805,947	21,803,547	15.0	393,762	1.8
11	Turkey	85,561,976	17,042,722	19.9	101,492	0.6
12	Spain	46,719,142	13,684,258	29.3	117,095	0.9
13	Vietnam	98,953,541	11,525,284	11.6	43,186	0.4
14	Australia	26,068,792	11,131,707	42.7	17,052	0.2
15	Argentina	46,010,234	9,963,697	21.7	130,171	1.3
16	Taiwan	23,888,595	8,872,744	37.1	15,273	0.2
17	Netherlands	17,211,447	8,569,228	49.8	22,989	0.3
18	Iran	86,022,837	7,561,213	8.8	144,688	1.9
19	Mexico	131,562,772	7,234,467	5.5	331,099	4.6
20	Indonesia	279,134,505	6,720,181	2.4	160,619	2.4
	World	8,008,468,000	665,273,651	8.3	6,698,268	1.0

Worldometer: COVID-19 Coronavirus Pandemic (https://www.worldometers.info/coronavirus/)

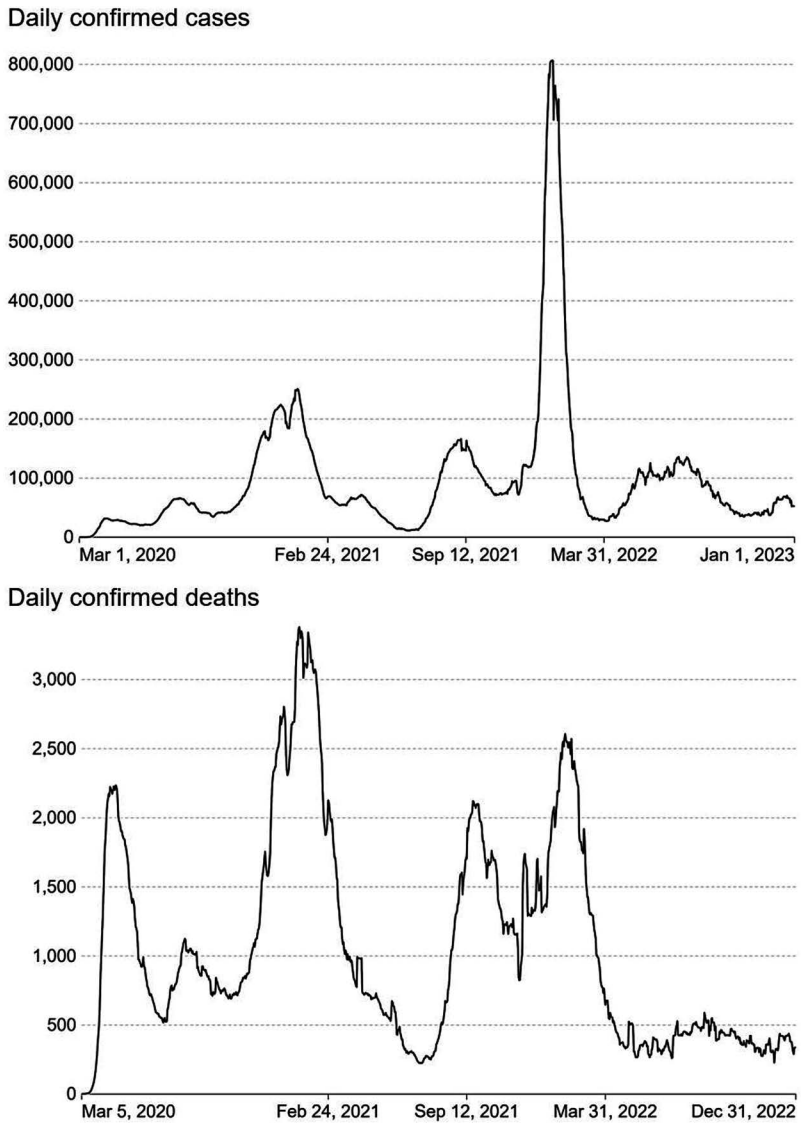
10 countries with >25% morbidity: France, Korea, Netherlands, Germany, Australia, Italy, Taiwan, UK, USA, Spain

8 countries with >1.0% lethality: Mexico, Indonesia, Brazil, Iran, Russia, Argentina, India, USA

tected in the United States was in a person returning from China, just ten days after the Chinese government reported the outbreak in Wuhan City to the WHO on the 11th of January 2020. On the 12th of April—which was at the peak of the first wave of the epidemic—more than 30,000 cases per day were recognized. This was the highest number in the world. The United States recorded the highest number of cases in the second and third waves of the global outbreak, as well as in the fifth wave and the first peak of the sixth wave. On the 12th of January 2022, in particular, near the peak of the first wave of the sixth outbreak, 1.27 million new cases per day (7-day average: 810,000 on the 17th of January 2022) were recorded.

In the United States, the peak day of the number of deaths is observed seven to twenty days after the peak day of the number of newly confirmed cases during each COVID-19 epidemic. Table 5 shows the transition of the lethality rate calculated by dividing the number of deaths on the peak day of deaths by the number of newly confirmed cases on the peak day of newly confirmed cases. The epidemic variants during each epidemic wave are also included in Table 5. The

Fig. 2. Transition of confirmed cases and deaths in the USA (7-day average)



peak date of deaths in the first wave was the 15th of April 2020, with 2,624 deaths. The peak date for newly confirmed cases was the 9th of April, with 36,022 cases, resulting in a lethality rate of 7.3%. In the second wave, there were 1,422 deaths on the 5th of August and 74,944 cases on the 24th of July, with a lethality rate of 1.9%. The highest number of deaths was recorded in the third peak of the third wave on the 20th of January 2021, with 4,389 deaths and a lethality rate calculated to be 1.4%—since there were 302,978 cases on the 8th of January. In the subsequent fifth wave, there were 3,493 deaths on the 16th of September and 235,250 cases on the 3rd of September, resulting in a lethality rate of 1.5%. During the first peak of the sixth wave, there were 4,091 deaths on the 28th of January 2022 and 1.27 million cases on the 12th of January, resulting in a le-

thality rate of 0.3%; in the first peak of the seventh wave, there were 1,174 deaths on the 8th of June and 228,960 cases on the 1st of June, with a lethality rate of 0.5%.

From these results, the original Wuhan strain (B.1), which caused the first wave of the epidemic, was less infectious but significantly more virulent. The Alpha and Delta variants of the fourth and fifth waves, respectively, were more infectious but less virulent, and the Omicron variant BA.1 lineage which caused the first peak of the sixth wave was significantly more infectious but much less virulent. The Omicron variant BA.2.12.1 lineage and the mixed BA.2 lineage of the seventh wave's first peak, as well as the Omicron variant BA.5 lineage[28] and the mixed BA.4 lineage of the seventh wave's second peak, were also considered to have decreased virulence.

In the United States, after the peak of the first peak of the seventh wave, which was dominated by the BA.2.12.1 lineage, the number of newly confirmed cases decreased rapidly, and the BF.7 and BQ.1 lineages, which were derived from the BA.5 lineage, began to increase as the outbreak subsided. In mid-September 2022, when the epidemic began to shift to the second peak of the seventh wave, the BQ.1.1 lineage, the BN.1 lineage derived from the BA.2 lineage, and the XBB lineage, a hybrid between the derived lineages, were all mixed[30,31], but the number of newly confirmed cases did not increase and there was a subsequent lull for about one month. In early November, a major change in the composition of the epidemic lineages was observed: the sum of the BQ.1 and BQ.1.1 lineages exceeded 25%, the BF.7 and BA.4.6 lineages 6–8%, and the BA.5.26, XBB and BN.1 lineages 2%, as the BA.5 lineage decreased to less than 50%. The sum of the BQ.1 and BQ.1.1 lineages exceeded 50% in early December, and the BA.5 lineage[30] accounted for less than 25% of the total.

In the United States, almost all pandemic restrictions were lifted, and life returned to normal

Table 5. Transition of newly confirmed cases and deaths in the USA

Endemic	Peak date of cases (M/D/Y)	Number of cases on the peak date	Peak date of deaths (M/D/Y)	Number of deaths on the peak date	Lethality (%)*1	Dominant epidemic strain in the USA*2
1st Wave	4/9/20	36,022	4/15/20	2,624	7.3	B.1 (Wuhan)
2nd Wave	7/24/20	74,944	8/5/20	1,422	1.9	
3rd Wave-1st	11/20/20	210,214	12/3/20	2,908	1.4	B.1.429 (ε)
3rd Wave-2nd	12/18/20	246,521	12/30/20	3,856	1.6	B.1.526 (ι)
3rd Wave-3rd	1/8/21	302,978	1/20/21	4,389	1.4	
4th Wave	4/9/21	84,418	4/19/21	733	0.9	B.1.1.7 (α)
5th Wave	9/3/21	235,250	9/16/21	3,493	1.5	B.1.617.2 (δ)
6th Wave-1st	1/12/22	1,270,000	1/28/22	4,091	0.3	B.1.1.529 (ο)
6th Wave-2nd	2/28/22	96,900	3/12/22	1,295	1.3	BA.1
7th Wave-1st	6/1/22	228,960	6/8/22	1,174	0.5	BA.2.12.1+BA.2
7th Wave-2nd	7/27/22	240,132	8/3/22	1,055	0.4	BA.5 + BA.4

*1 Deaths on the peak date of deaths/Cases on the peak date of cases

*2 Based on the documents provided by the CDC

in late November of 2022 with less than 40,000 new cases per day. Yet, by the beginning of December, the number of new cases had begun to rise again, indicating the arrival of the eighth wave. The BQ.1 and BQ.1.1 lineages accounted for more than 60% of the total, and the newly emerged XBB.1.5 lineage accounted for 18%, the XBB and BA.5 lineages 5% each, and the BN.1 and BF.7 lineages 3% each, revealing an increasingly complicated aspect in terms of variant lineage compositions of the epidemic.

As a historical, yet oddly appropriate, sidenote, in Europe and the United States, there is a custom of naming creatures that transcend human knowledge after myths and legends. The BA.2.75 lineage is, therefore, also named “Centaurus”, which in Greek mythology is a half-human, half-beast creature in which the neck of a horse is replaced by the upper half of a human body. “Centaurus” is considered the “father” of a race of beastly mythical creatures in Greek mythology. The BA.2.75 lineage is said to be three times more infectious than the BA.5 lineage, so the name may be somewhat fitting. The hybrid lineage XBB, which is the result of the cross-breeding of the BA.2.75 and the BA.2.10.1 lineages, is named “Griffin” (Greek mythology: a monster with the wings and upper body of an eagle and the lower body of a lion). The lineage XBB.1.5 is named “Kraken”, which is the name of a Nordic Sea monster, regarded as a giant octopus or squid, and some believe it to be a real giant squid of modern times—a monster that suddenly pulls an entire cruise ship into the depths of the sea during a peaceful voyage. The BQ.1.1 lineage is also named “Cerberus” (Greek mythology: a dog monster, a guard dog of the underworld, with three dog heads and three serpent tails), which may be reminiscent of a derived virus lineage that has accumulated a variety of mutations. The XBB.1.16 lineage, which has spread around the world since its appearance in early January 2023 and has become a major epidemic strain in India and other countries, is named not after a beast but after an alpha star in the constellation Boötes, Arcturus.

ii) Transition of confirmed cases in five European countries and Russia

In Europe, the number of deaths during the first wave of the COVID-19 pandemic was significantly higher, and there were reports of a shortage of coffins to adequately deal with the increased number of deaths in Italy and Spain. The transition of the confirmed cases in five European countries (the United Kingdom, France, Italy, Spain, and Germany), and in Russia, is shown in Fig. 3. It should be noted that the numbers on the vertical axis showing the number of confirmed cases in each country differ. Also note that the appearances around the third wave (before the 24th of February 2021) and the fifth wave (the 12th of September 2021) are different in each country. There is a date gap in the arrival of the first peak of the sixth wave, as well as marked differences in the presence and intensity of the second peak of the sixth wave. There are also marked differences in the presence and intensity of the first and second peaks of the seventh wave. Even among countries belonging to the same EU group, the status of COVID-19-related

vaccine adherence, patient isolation, social activities such as public dining, and the wearing of masks all differed, along with differences in public commuting restrictions and the acceptance policies of medical facilities for patient admissions may have all influenced the manifestations of the epidemic waves.

Another influencing factor is thought to be due to the virulence (toxicity) of the Omicron variant that caused the sixth wave, which was confirmed to be weak. This, and additional societal measures created to compensate for economic losses, ease restrictions on the behavior of citizens, and improve the movement of people both domestically and abroad all surely played contributory roles. This may have also resulted in the introduction of variants or lineages that were prevalent in regions other than Europe alone. In Russia, it is doubtful whether or not the situation after the sixth wave in January of 2022 has been accurately assessed; therefore, detailed information on the seventh and eighth waves has not been obtained.

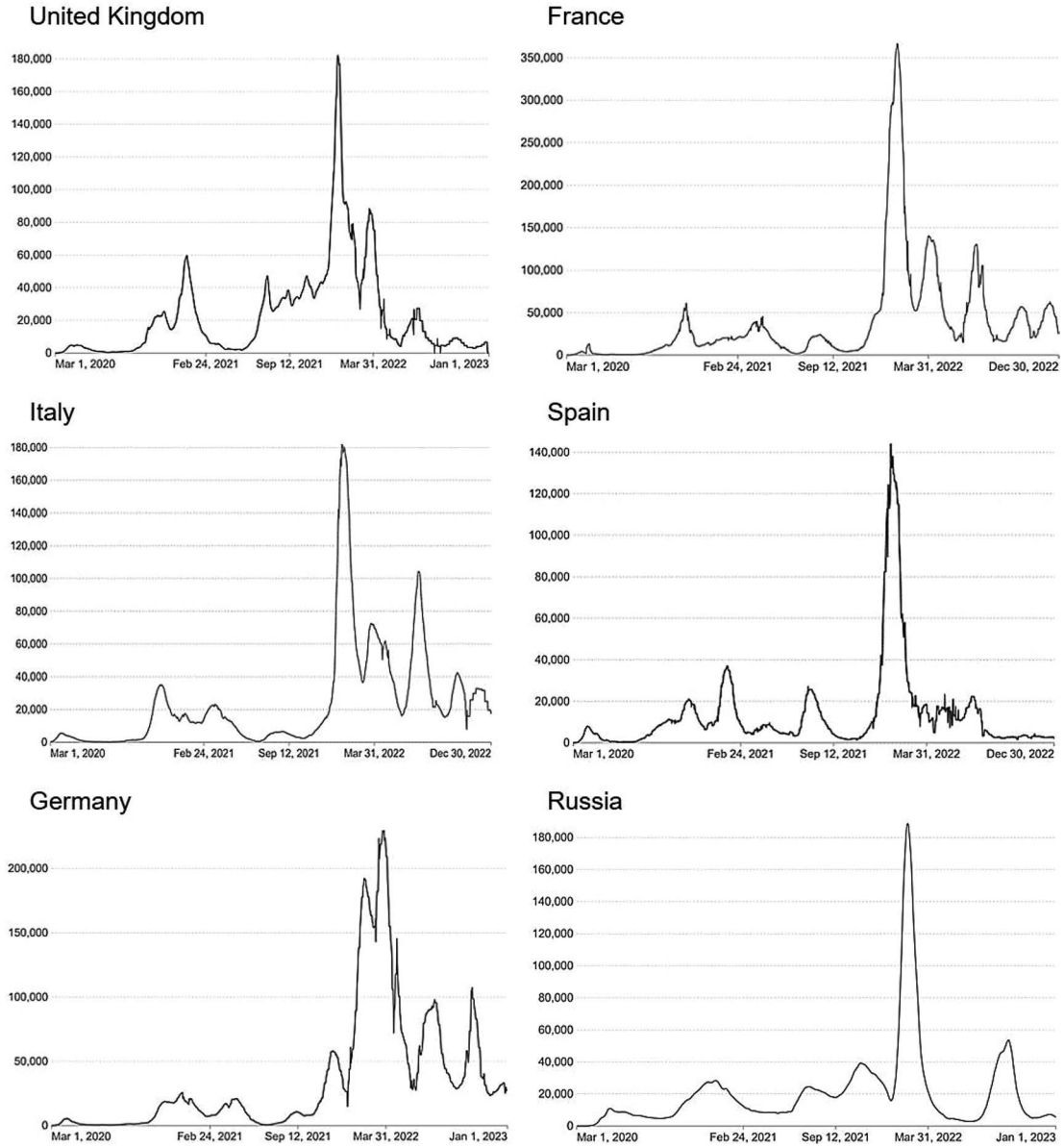
iii) Transition of confirmed cases and deaths in India

India has a population of 1.4 billion, and the COVID-19 epidemic differs greatly from one region to another, such as Uttar Pradesh in the north central region, Maharashtra in the central western region, and Tamil Nadu in the southeastern region. Different measures were taken in different states. Although it may be inappropriate to generalize about all regions in a single figure, this review treats India as a single country, and the number of newly confirmed cases and deaths are shown in Fig. 4.

India was not affected by the first wave of the global COVID-19 epidemic, and a slow epidemic wave with a peak in mid-September was recorded over a 6-month period from mid-June to mid-December of 2020—which corresponded to the period between the global second wave and the second peak of the third wave. As previously mentioned, the prevalent virus during this period were derivatives of the B.1 (B.1.1.32, B.1.1.8, B.1.113, etc.), B.4 and B.6 lineages which differed from those in other countries, but in late December, the Alpha variant of British origin and the Beta variant of South African origin became mixed in the population. By then, however, the outbreak had subsided, thereby avoiding a global third wave of triadic epidemics from early October of 2020 to mid-February of 2021.

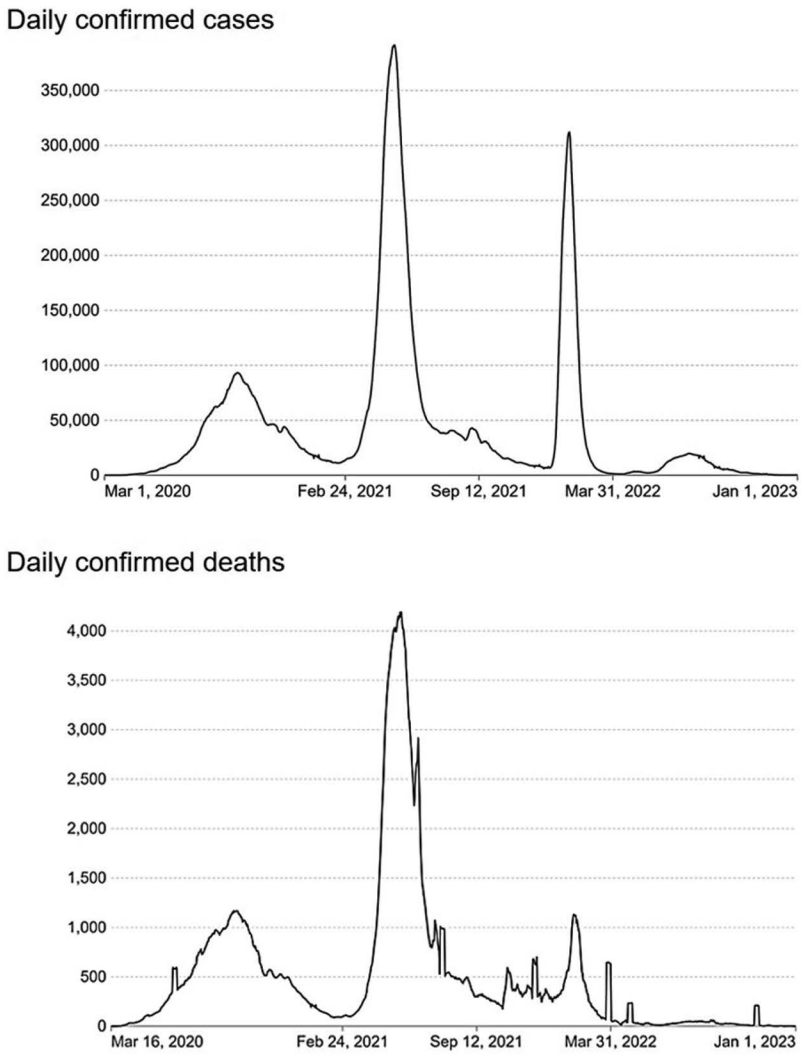
From the beginning of March 2021, the number of cases infected with the Kappa variant (B.1.617.1) began to increase, and this was replaced by the Delta variant (B.1.617.2) in mid-April. The number of the confirmed cases continued to increase rapidly, reaching a peak of 412,000 cases on the 6th of May 2021, and was then followed by a rapid decline to 40,000 cases by late June. Subsequently, the Delta variant spread worldwide, but in India, when the global fifth-wave peak was recorded on the 21st of August 2021, the number of new cases stabilized at 30,000 to 40,000 per day; by the end of November, the number of new cases had dropped further to less than 10,000.

Fig. 3. Transition of newly confirmed cases in 5 countries of EU and in Russia (7-day average)



During the first peak of the global sixth wave caused by the Omicron variant BA.1 lineage, in which the number of newly infected cases increased rapidly from mid-December 2021, India recorded 338,000 new cases at that peak on the 21st of January 2022. However, the subsequent second peak in March of 2022 had less than 2,000 new cases, and the number of new cases had subsided. During the first peak of the seventh wave, 20,000 new cases were recorded on the 20th of July 2022, but by the time of the second peak in early October, the number of new cases was still down to less than 2,500. In the eighth wave after November 2022, the number of new cases

Fig. 4. Transition of newly confirmed cases and deaths in India (7-day average)



had settled even further to less than 500.

The number of deaths from COVID-19 in India correlated with the number of confirmed cases, but the 1,290 deaths on the 15th of September 2020 represented 1.4% of the 90,123 newly confirmed cases—this was a lower rate compared to the global lethality rate of 2.4%. The 4,529 deaths reported on the 18th of May 2021, the peak of the fourth wave, which was mainly in India, represented 1.7% of 267,334 newly confirmed cases, and the 1,733 deaths reported on the 1st of February 2022, the first peak of the sixth wave, represented 1.1% of 161,386 newly confirmed cases at that time—this latter number was an extremely low death rate.

The number of new cases and deaths in India differed greatly between Uttar Pradesh, the state with the largest population in the north-central portion of the country, and Maharashtra, an industrial area in the central-western portion of the country. The reasons for this depended on

whether state governments had implemented measures to prevent the spread of infection or not. This special situation in India will be analyzed in a subsequent review[32] by the authors.

The authors had an opportunity to meet with Mr. Sanjay Kumar Verma, the Indian Ambassador to Japan. We learned that India, with a population of 1.4 billion people, had suffered greatly from the May 2021 outbreak caused by the Delta variant, but that at the time of the January 2022 global outbreak caused by the Omicron variant, the number of new infections in India was only at about 340,000. This is in comparison to the number of approximately 1.36 million new infections in the United States at that time. The number of newly infected cases per million population was 4,004 in the United States and only 238 in India—this is less than one-sixteenth the morbidity rate. Furthermore, the number of new cases per day in India has been kept below 20,000 since then.

In India, the number of new cases of infection continues to increase since March 2023 due to the mitigation of infection control measures, with nearly 1,900 daily cases recorded, and the Omicron variant XBB.1.16 accounted for more than 90% of the cases. The WHO designated[33] this lineage as a Variant of Interest (VOI) on April 17th.

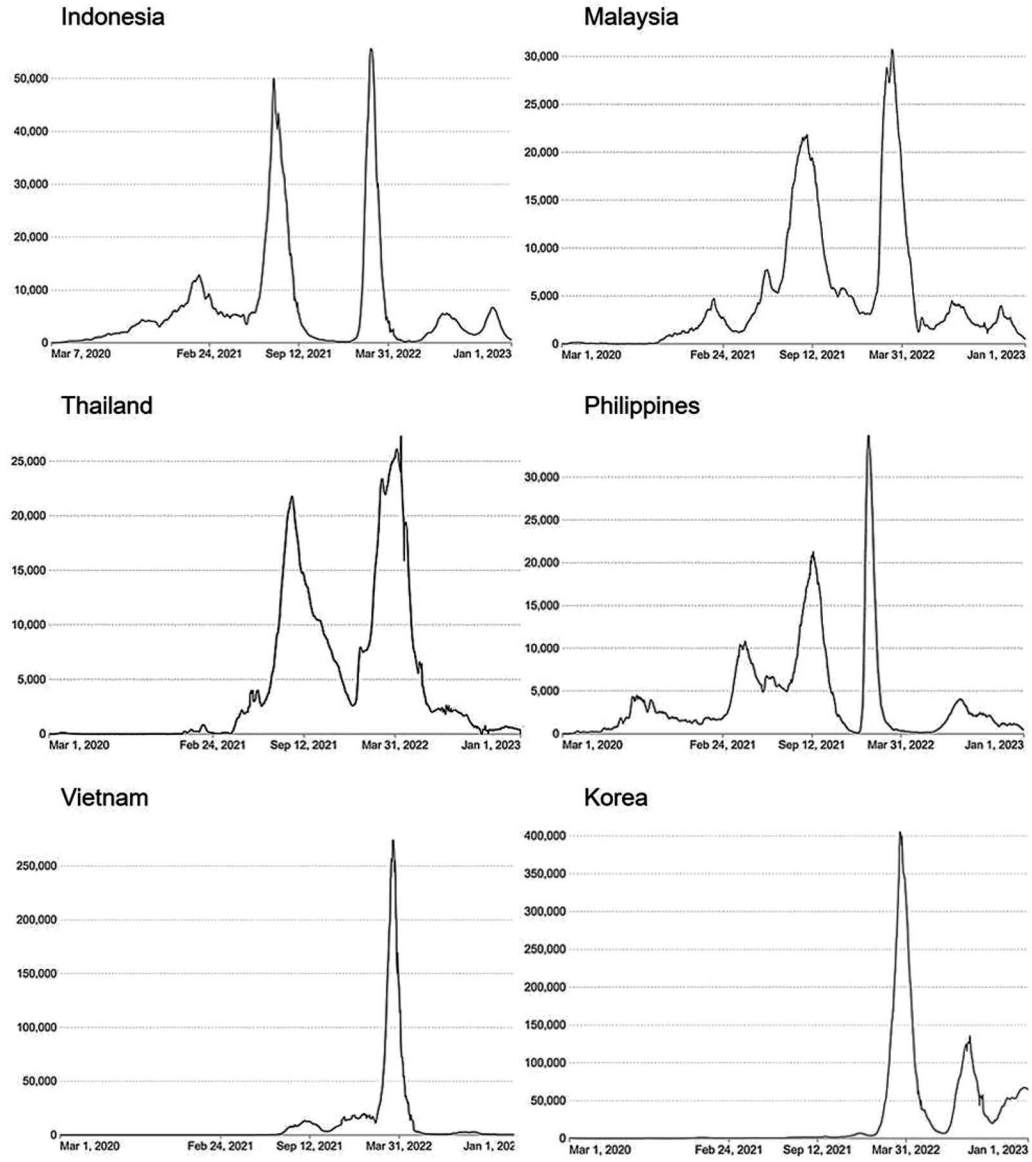
iv) Transition of confirmed cases in six Asian countries

Regarding the situation in Asia other than India, Fig. 5 shows the transition of newly confirmed COVID-19 cases in Indonesia, Malaysia, Thailand, the Philippines, Vietnam, and South Korea. It should be noted that the vertical axis scale numbers on some of the graphs (Vietnam and South Korea) are different from those of the other countries, and the presence or absence of epidemics, as well as the timing of the arrival of each wave is different among the countries—even those located relatively close to each other. These differences in the waves of epidemics among Asian countries are related to the transition of the causative variants of SARS-CoV-2.

Indonesia, with the world's fourth largest population of about 280 million, was spared from the impact of the first global wave. After a small outbreak in the second wave, there was a third wave with a peak of about 13,000 new cases on the 1st of February 2021. The fourth wave, caused by the Delta variant, arrived about two months later from India, and a peak of about 49,000 cases was recognized on the 19th of July 2021. Indonesia was spared from the fifth global wave, but the peak of the sixth wave caused by the Omicron variant BA.1 lineage was observed on the 20th of February 2022 (one month later than the first global peak) with about 56,000 newly confirmed cases. The peak of the seventh wave, caused by the BA.5 lineage, was observed on the 10th of August, with only about 5,500 new cases. The eighth wave, with a peak of 6,645 cases on the 22nd of November, was caused by a mixture of the BA.5 (21%), BQ.1 (24%) and XBB (46%) lineages.

Malaysia, with a population of about 33 million, was spared from the effects of the global first and second waves, but the third wave peaked at about 4,700 cases on the 3rd of February 2021. A small peak of about 7,700 cases in the fourth wave, caused by the Alpha and Beta variants, occurred on the 4th of June. The fifth wave, caused by the Delta variant, peaked at 21,800 cases on the 30th of August, while the sixth wave, caused by the Omicron variant BA.2 lineage,

Fig. 5. Transition of newly confirmed cases in 6 Asian countries (7-day average)



peaked at 30,500 cases on the 10th of March 2022. Subsequently, the seventh wave, with the BA.5 lineage, peaked at 4,300 cases on the 22nd of July, and the eighth wave, with the mixed BA.5 (26%), BA.2.75 (26%), and XBB (38%) lineages, peaked at 3,900 cases on the 9th of November.

Thailand has a population of approximately 72 million, and the COVID-19 epidemic has followed a very similar course to that of Malaysia, with the fifth wave peaking on the 18th of August 2021—with approximately 22,000 cases due to the Delta variant. The sixth wave was a complex epidemic divided into five peaks. The first peak on the 15th of January 2022 was small, consisting of 7,900 cases due to the BA.1 lineage. All of the second peak on the 2nd of March with 23,400

cases, the third peak on the 5th of April with 26,000 cases, the fourth peak on the 24th of April with 19,131 cases, and the fifth peak on the 25th of May with 6,497 cases were due to the BA.2 lineage. The seventh wave showed a gentle peak of about 2,000 cases per day—due to the BA.5 lineage—for 3.5 months from mid-June to late October. The eighth wave showed a maximum of about 700 new cases per day, due to the BA.2.75 lineage.

The Philippines, with a population of approximately 114 million, was spared the first global wave, but the second wave showed a moderate peak of up to 4,400 cases per day over a three-month period from the 20th of July to the 25th of October 2020. The Philippines was also spared from the third wave, but the fourth wave, due to the Delta variant, showed a first peak on the 15th of April 2021 with 10,800 cases, and a second peak on the 10th of June with 6,500 cases. The fifth wave, also caused by the Delta variant, showed a peak of 21,000 cases on the 12th of September. The following sixth wave showed a sharp peak of 34,800 cases on the 17th of January 2022, caused by the BA.2 lineage, and then dropped below 1,000 cases on the 5th of March. During the seventh wave, the first peak of 4,000 cases, due to the BA.5 lineage, was seen on the 11th of August, followed by a second peak of 2,300 cases, due to the BA.2 (48%) and BA.5 (47%) lineages, on the 27th of September. After that peak, from early November to around the 10th of December, there were about 1,000 new cases a day, due to the BA.2 (37%) and XBB (50%) lineages; thereafter, things subsided.

Vietnam and South Korea were significantly less affected by the first through fourth waves of the global outbreak; however, the fifth and sixth waves in Vietnam and the sixth, seventh, and eighth waves in South Korea were remarkable in terms of infection spread. Vietnam has a population of about 98 million, and the gentle fifth wave caused by the Delta variant peaked at 13,000 cases on the 3rd of September 2021, followed by a continuing gentle peak trend, with 10,000–20,000 new cases per day, due to the same variant from mid-November 2021 to early February of 2022. Under such circumstances, a sixth wave explosive outbreak suddenly occurred, with a peak of 273,400 new cases due to the Omicron variant BA.2 (89%) and BA.1 (8%) lineages on the 17th of March. After the steep peak subsided to 4,000 cases on the 5th of May, the number of new cases due to the BA.5 lineage was about 2,000 per day during the seventh global wave. Thereafter, the BA.2 and BA.2.75 lineages appeared at a certain frequency. There has been no eighth wave.

South Korea, with a population of approximately 51 million people, had set up a quarantine system early on in response to the outbreak of COVID-19 in Wuhan, China, and had escaped the effects of the first through fourth waves of the global pandemic. This was achieved due to a high rate of PCR testing and high vaccination rates. However, more than 1,000 cases per day had been recognized since mid-July of 2021. The fifth wave, caused by the late-arriving Delta variant, reached a small peak of 6,850 cases on the 16th of December. The sixth wave arrived in mid-January of 2022 and spread rapidly, reaching a steep peak of 405,000 cases on the 17th of March—due to a mixture of the Omicron variant BA.1 (43%) and BA.2 (56%) lineages. Thereafter, there

was a drop to about 7,000 new cases on the 24th of June. Shortly thereafter, the seventh wave, due to the BA.5 lineage, arrived. This wave reached a peak of 135,300 cases on the 22nd of August, followed by a drop to 20,000 cases on the 11th of October. Following the seventh wave, the number of cases began to increase once again, and an eighth wave was recorded on the 23rd of December, with a peak of 67,300 cases. The eighth wave was due to a mixture of the BA.5 (45%), BA.2.75 (38%), and BQ.1 (13%) lineages.

The five Asian countries shown in Fig. 5, excluding South Korea, are in close proximity to each other, but their COVID-19 epidemics differ markedly. This might be due to differences in public policies to prevent the spread of COVID-19, differences in medical systems, differences in vaccination status, as well as other factors. Even waterfront quarantine policies and operations may have been contributing factors influencing the differences in the presence and extent of transmission from COVID-19-endemic countries (such as Europe, the United States, and India). Vietnam, in particular, has a unique history in that it escaped the outbreak of the Alpha and Delta variants. However, the Omicron variant caused a significantly larger number of new cases in Vietnam than in other countries. Another difference was observed in Vietnam, in that the seventh wave never manifested in the country—yet seventh and eighth waves struck the other countries.

South Korea was the first country in the world to thoroughly strengthen its epidemiology by means of COVID-19 testing using PCR technology. South Korea also took the leading position in the world in terms of vaccination rate. The spread of the Alpha and Delta variants was controlled by securing and managing the use of COVID-19 therapeutic agents at the national level. The outbreak of the Omicron variant, however, could not be controlled, and the sixth wave of outbreaks occurred—recording more than 400,000 new cases per day. This was followed by both the seventh and eighth waves, which also recorded a large number of new cases.

v) Transition of the confirmed cases and deaths of COVID-19 in Japan

Transition of the number of newly confirmed cases and deaths of COVID-19 in Japan is shown in Fig. 6. Comparative analysis of these trends with those of the global epidemic shows considerable differences, reflecting Japan's unique infection control measures. On the 11th of January 2021, corresponding to the peak day of the third wave of the global outbreak, approximately 4,900 new cases and 48 deaths were recorded in Japan—these were due mainly to the B.1.1.214 lineage variant. On the 28th of April, corresponding to the peak day of the fourth global wave, and reflecting the explosive spread of the Delta variant in India, approximately 5,800 new cases and 51 deaths were recorded in Japan—mainly due to the Alpha variant, indicating a small outbreak.

The fifth wave in Japan coincided with the timing of the Tokyo Olympics and Paralympics. The Delta variant caused more than 10,000 new cases per day, reaching a peak of about 26,000 new cases per day on the 20th of August 2021 (four days before the opening of the Paralympics). However, the number of newly confirmed cases rapidly declined thereafter, eventually subsiding in early

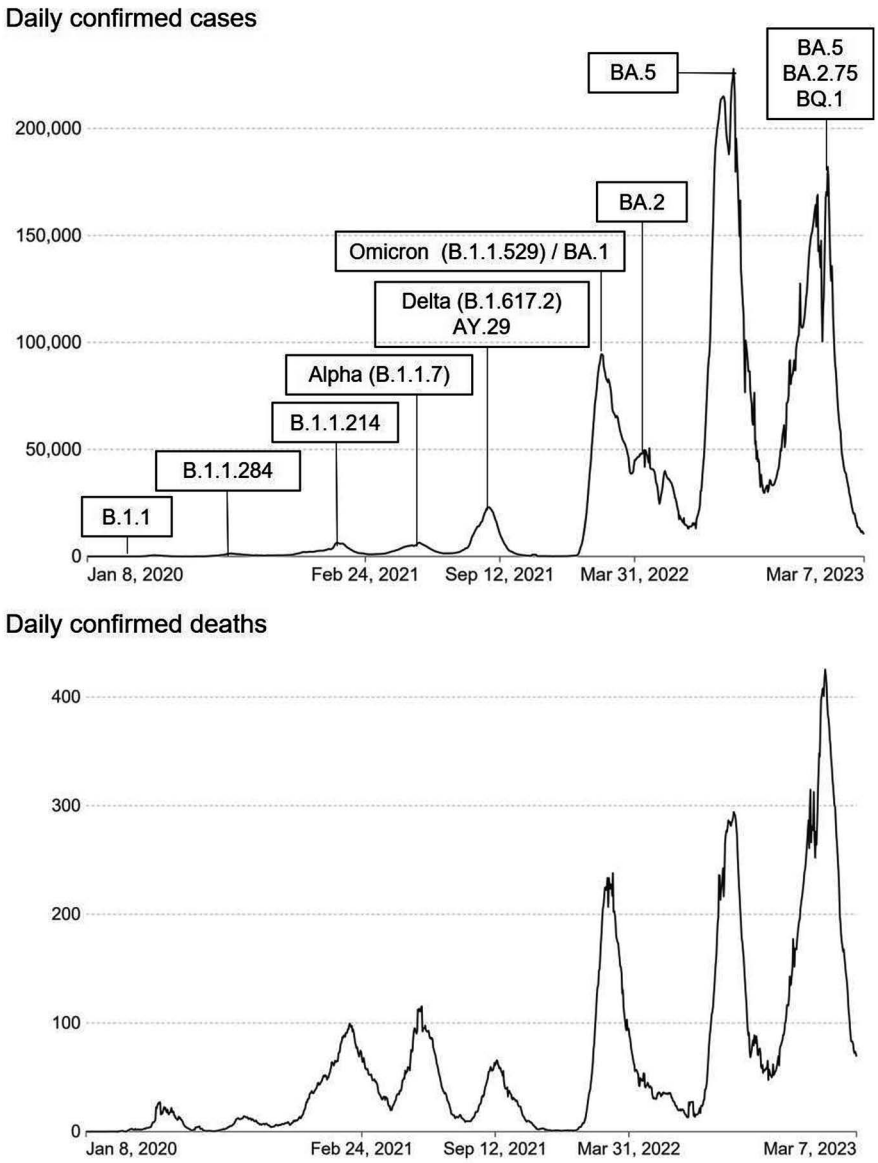
October of 2021. This steep peak of increase and decrease has been commented on as being the result of the success of Japan's COVID-19 countermeasures; in reality, it was a convergence of the spread of infection caused by mutations of the virus that caused the outbreak. The Delta variant AY.29 lineage was the main epidemic strain during this fifth wave, but it was later clarified that the accumulation of mutations leading to the AY.29 lineage damaged the gene for an enzyme that repairs mutations detrimental to the survival (growth) of the virus, with further mutations in the AY.29 lineage resulting in death of the virus. In other words, the AY.29 lineage is considered to be the end of the phylogenetic tree through which the virus evolved by means of mutations.

Another fact demonstrating that the commentary about Japan's COVID-19 countermeasures being successful was incorrect is recognizable by the rapid increase in the number of new cases of the sixth wave caused by the Omicron variant BA.1 lineage (which began in early January of 2022). On the 3rd of February, the peak day of the first peak of the sixth wave, the daily number of newly confirmed cases exceeded 104,000, and on the 22nd of March, it dropped to about 20,000. That number, however, rose again, reaching a peak of about 57,000 during the second peak on the 13th of April and 46,000 during the third peak on the 11th of May—these were mainly due to the BA.2 lineage. The number of deaths corresponding to the peak of the first peak was 322 on the 22nd of February, while that of the second peak was 65 on the 26th of April, and that of the third peak was 50 on the 18th of May. This indicates a decrease in the ratio of deaths to newly infected cases, and suggests that the virulence of the causative virus of COVID-19 decreased over time.

The quiescence of the sixth wave was slow, with the second and third peaks being due to the alternation and complexity (e.g., mixing of the BA.2.12.1 lineage) of the causative lineages. The epidemic was considered to be under control on the 20th of June, when the number of newly confirmed cases fell below 10,000. However, a rapid increase in the number of newly confirmed cases was observed once more in early July, whereupon the seventh wave, the largest wave ever recorded, hit its first peak of about 250,000 cases on the 10th of August and then a second peak of about 260,000 cases on the 19th of August. At the second peak of this wave, Japan had the highest number of newly confirmed cases in the world (South Korea was second with approximately 130,000, and the United States was third with approximately 78,000 cases). The fact that Japan recorded the highest number of cases in the world was surprising. Furthermore, 250,000 new cases per day was an alarming situation, as this was also an indication that 0.2% of the population was infected. Fortunately, although the BA.5 lineage variant that caused the seventh wave of the epidemic was significantly more infectious, its infectious symptoms were limited mainly to inflammation of the pharynx; it rarely caused more severe symptoms such as dyspnea due to inflammation of the lower respiratory tract (as were the cases with the Alpha and Delta variants of the fourth and fifth waves, respectively) and very few patients became seriously ill.

The lethality rates in each wave were calculated from the number of newly confirmed cases and the number of deaths at the peak of the first wave to the second peak of the seventh wave of

Fig. 6. Transition of newly confirmed cases and deaths in Japan (7-day average)



the COVID-19 epidemic in Japan and are shown in Table 6. Referring to the main variant and lineage that caused each epidemic wave, the lethality rate was remarkably high at 4.1% in the first wave caused by the Wuhan strain B.1—the original strain of SARS-CoV-2. The lethality rate was also high at 3.0% in the fourth wave, in which the Alpha variant accounted for 88% of the cases, while the lethality rate was 0.3%, one-tenth of the previous wave, in the fifth wave where the Delta variant accounted for 92% of the cases. Thereafter, the lethality rate was 0.3% in the first peak of the sixth wave, when 96% of the causative virus was the Omicron variant BA.1 lineage. Those in the second and third peaks, where the BA.2 lineage predominated, and in the first

and second peaks of the seventh wave, in which the BA.5 lineage predominated, were remarkably low at 0.1%. However, even though the lethality rate was low, the number of newly confirmed cases was increasing quite remarkably—there was concern that the number of deaths per day might exceed 300 persons. In particular, it is important to note that the cause of death during this time was not due to severe illness caused by COVID-19 itself (such as the worsening of respiratory symptoms), but instead due to the worsening of patients' preexisting disease (which was often the cause of general ill health, due to COVID-19 infection).

The epidemic of the seventh wave subsided rapidly, and the number of newly confirmed cases dropped to about 13,000 on the 10th of October 2022. However, the number began to increase again in late October, and by mid-November, the number of newly confirmed cases exceeded 100,000 per day. This was, again, the highest number in the world, with South Korea occupying second place. This clearly indicated the arrival of the eighth wave. Although BA.5 was

Table 6. Transition of COVID-19 endemic waves in Japan

Endemic	Duration M/D/Y – M/D/Y	Peak date M/D/Y	Cases on the peak date	Deaths on the peak date (peak date)	Lethality*1 (%)	Epidemic variant/lineage
1st Wave	3/23/20 – 5/13/20	4/11/20	701	29 (5/1/20)	4.1	B.1 (Wuhan)
2nd Wave	6/22/20 – 9/23/20	8/7/20	1,605	20 (8/28/20)	1.2	B.1.1.284
3rd Wave	11/2/20 – 2/22/21	1/8/21	7,957	121 (2/10/21)	1.5	B.1.1.214
4th Wave	3/15/21 – 6/21/21	5/8/21	7,238	216 (5/18/21)	3.0	α（88%）
5th Wave	7/5/21 – 10/18/21	8/20/21	25,992	89 (9/8/21)	0.3	α／δ (8%/92%)
6th Wave-1st	1/4/22 – 3/22/22	2/3/22	104,442	322 (2/22/22)	0.3	BA.1/BA.2 (96%/2%)
6th Wave-2nd	3/22/22 – 5/2/22	4/13/22	57,666	65 (4/26/22)	0.1	BA.1/BA.2 (26%/74%)
6th Wave-3rd	5/2/22 – 6/20/22	5/11/22	46,398	50 (5/18/22)	0.1	BA.1/BA.2 (5%/94%)
7th Wave-1st	6/27/22 – 8/15/22	8/5/22	253,392	343 (8/23/22)	0.1	BA.2/BA.5 (3%/95%)
7th Wave-2nd	8/15/22 – 10/11/22	8/29/22	326,090	350 (9/2/22)	0.1	BA.5（98%）
8th Wave	10/17/22 – 2/28/23	12/27/22	281,599	503 (1/15/23)	0.2	BA.5/BA.2.75/BQ.1 (78%/9%/11%)

*1 Lethality: deaths on the peak date/cases on the peak date

the predominant lineage of the eighth wave, a mixture of the BA.2.75 and BQ.1 lineages accounted for about 10% of the cases—thereby complicating the picture. The number of new cases eventually peaked at about 210,000 on the 28th of December, and was then followed by a downward trend.

In Japan, under the "Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases" (abbreviated as "Infectious Disease Law")[34], COVID-19 has been classified as a "new influenza etc." disease[35], which corresponds to a "Class II infectious disease" of high severity in the classification of infectious diseases. As a result, a wide range of measures and regulations were implemented due to the situation of the high lethality rate of 4.1% (as shown in Table 6) caused by the original Wuhan strain (B.1 lineage). These measures continued to be enforced throughout the duration of the low lethality rate of 0.1% caused by the eighth wave epidemic strain (BA.5 lineage). During this period, the exhaustion of medical institutions put under extreme pressure and severe economic losses due to excessive societal measures and regulations were considered to be problematic.

It was argued[36] that the current COVID-19 situation should be treated as a general infectious disease equivalent to a "Class V Infectious Disease", which is the same as a less severe seasonal influenza (under the Infectious Disease Law). Therefore, COVID-19 will be placed into this category of "Class V Infectious Disease" as of May 8, 2023. However, the eighth wave of COVID-19 showed a big surge from mid-October of 2022 to the end of February in 2023 with a major peak of more than 280,000 new cases per day. Even at the end of March 2023, more than 5,000 new cases per day were occurring. The entire nation must be aware that COVID-19 is an infectious disease that is easily changeable, unpredictable, and should not be taken lightly.

vi) Interference with global COVID-19 trend survey

The prevalence of various SARS-CoV-2 variants and lineages, trends in COVID-19 cases worldwide, have been compiled and provided in real time by Johns Hopkins University, the WHO, as well as other organizations and governments. This information is a valuable source and indicator in making infection control policy decisions. However, on the 7th of December 2022, China (the country of origin of COVID-19, and the most populous country in the world) reversed its previous "zero-Covid policy" and lifted strict containment regulations, including urban lockdowns and movement restrictions[37]. As a result, an explosive and serious outbreak of infection occurred, with an estimated 4.8 million new cases and 25,000 deaths per day[38]. However, according to the official announcement by the Chinese government, the number of newly infected people was 3,000 to 4,000 per day and the number of deaths was 1 to 5 per day, and there continued to be a marked discrepancy from the actual reality of the situation. It was assumed that the government was concealing the reality of the situation in order to avoid criticism for its failure in infection control policy. Moreover, since the government has not accurately disclosed the actual re-

ality of the infection situation in China itself, which differed by one full order of magnitude from that of the rest of the world's infection environment, there seems to be no longer any point in analyzing the actual situation of infection in other countries in detail. If China prides itself on being a world power, it should know that the concealment of such a serious matter is a source of ridicule and extreme loss of trust in the world—there is an inherent responsibility to accurately disclose information and cooperate with the rest of the world in controlling the infection.

In response to the extraordinary number of new cases of infection in China, countries around the world have naturally tightened the inspection of travelers entering their countries from China. The Chinese government has raised objections to such measures, calling them unscientific. This type of reasoning, however, is itself not consistent with the methodology or principles of science, because countries around the world need to accurately evaluate and determine the variant/lineage of SARS-CoV-2 entering their borders by travelers from China and prevent the spread of such strains within their own countries. Therefore, rigorous testing is essential. The WHO, which had maintained a tolerant attitude toward China's COVID-19 countermeasures, issued a statement[39] condemning the Chinese government's underestimation of the actual situation in response to its announcement. In response to that statement, the Chinese government changed[40] the total number of deaths since the 7th of December 2022 from 38 to approximately 60,000. No matter what the reason, it is scientifically unacceptable for any government to inflate the official death toll by a factor of 1,600 in response to a condemnation statement.

In addition, a researcher at Peking University estimated that 64% of the Chinese population had been infected with COVID-19 since the 7th of December 2022 suspension of the "zero-Covid policy". This equates to 900 million cases. As shown in Table 4 of this review, the cumulative number of infected people worldwide up to the end of December 2022 was 665 million. Therefore, we must now add about 1.35 times that total number of infected people to this discussion. Even more unreasonably, officials from the Chinese Center for Disease Prevention and Control (CCDC) announced that the actual number of people infected was more than 1.1 billion, or 80% of the nation's population, and that about 12,000 people died in a single week in January of 2023.

According to the announcement on the official website[41] of the CCDC on the 25th of January 2023, the peak number of positive PCR test results was 6.94 million per day on the 22nd of December of the previous year. However, this number dropped to 15,000 on the 23rd of January 2023. The number of outpatients experiencing pyrexia also peaked at 2,867,000 per day on the 23rd of December 2022, but decreased to 63,000 on the 23rd of January 2023. Additionally, the number of hospitalized patients also peaked at 1,625,000 on the 5th of January 2023, but decreased to 248,000 on the 12th of January 2023. The number of severely ill patients decreased from 128,000 on the 5th of January 2023 to 36,000 on the 23rd of January 2023. Similarly, at the beginning of 2023, the number of hospitalized patients who died decreased from 4,273 per day on the 4th of January to 896 per day on 23rd of January, according to the official report. The center

also reported that the outbreak strains in China were of the Omicron variant BA.5.2 and BF.7 lineages, and that no new variant or lineage had been found.

On the other hand, Airfinity, a UK-based health data research institute, published an estimate[38] on the 17th of January 2023, that China's COVID-19 epidemic wave had already peaked, with 4.8 million new cases per day and an estimated maximum daily death toll of 36,000 on the 26th of January 2023. Since the 1st of December 2022, it estimates that 99.5 million people have been infected and 608,000 people have died. The discrepancy from the official announcement of the CCDC mentioned above is large, and there is debate as to which is more credible. It is not possible to add any of the figures to the data compiled by Johns Hopkins University, and the WHO, etc., at this stage.

The accurate investigation of the global trends of COVID-19, which is considered to be the largest pandemic in human history, was obstructed by the concealment of the actual situation in China (where the number of infected people and deaths is expected to be the highest in the world). Valuable and carefully compiled epidemiological data on infectious diseases—acquired at great cost in human suffering and loss of life—have become a collection of meaningless records, making it impossible to discuss the actual situation of the eighth wave of the epidemic of COVID-19 worldwide or use such information for predictive purposes in future epidemics.

2. Trends in COVID-19 Therapeutics

1) Status of COVID-19 therapeutic agents

The status of approval of drugs for the treatment of COVID-19 in the United States, Europe, and Japan, as well as WHO recommendations, are shown in Table 7. The United States Department of Health & Human Services (HHS) issued[42] a "Public Health Emergency (PHE) Declaration" in response to the high number of new cases and deaths in the early years of the disease. In response to this, a number of drugs have been approved as EUA drugs[6] under the jurisdiction of the FDA from early on. Japan has been following the United States in granting special approval for emergency for EUA drugs, and in November of 2022, the MHLW granted special approval for ensitrelvir on its own. The European Medicines Agency (EMA)[43] appears to review and approve COVID-19 drugs, based on different criteria than the WHO and the FDA.

i) Remdesivir

With regard to remdesivir, the WHO in its COVID-19 Treatment Guidelines[44] published on the 20th of November 2020, recommended against its use for the treatment of hospitalized patients, regardless of the severity of symptoms. The reason for this is explained by the fact that in the Solidarity Trial[45] conducted by the WHO itself and in three other randomized comparison trials (RCTs), remdesivir did not provide evidence worthy of recommendation regarding lethality,

Table 7. Approval/authorization of therapeutic drugs for COVID-19

Drug	US FDA	MHLW	EU EMA	WHO
Hydroxy-chloroquine	EUA (2020/3/28) Cancel (2020/6/16)	Against	Not recommend except clinical trial (2020/4/1)	Against (2020/12/17)
Remdesivir	EUA (2020/5/1) NDA (2020/10/22)	SAE (2020/5/7) EI (2022/3/18)	Tentative (2020/7/3) Approval (2022/8/8)	Against (2020/11/20) Conditional recommend (2022/4/22)
Molnupiravir	EUA (2021/12/23) Revise (2022/10/27)	SAE (2021/12/24)	Under investigation (2023/3/13)	Conditional recommend (2022/3/3)
Nirmatrelvir/ritonavir	EUA (2021/12/22) Revise (2022/10/27)	SAE (2022/2/10)	Tentative (2022/1/28) Approval (2022/7/6)	Recommend (2022/4/22)
Ensitrelvir		EA (2022/11/22)		
Bamlanivimab	EUA (2020/11/9) Cancel (2021/4/16)			
Bamlanivimab/etesevimab	EUA (2021/2/9) Halt (2022/1/24)		Withdraw application (2021/11/2)	
Casirivimab/imdevimab	EUA (2020/11/21) Halt (2022/1/24)	SAE (2021/7/19) except Omicron variant	Approval (2021/11/12) Notice (2022/12/9)	Against (2023/1/13)
Sotorovimab	EUA (2021/5/26) Halt (2022/2/23)	SAE (2021/9/27) except Omicron variant	Approval (2021/12/17) Notice (2022/12/9)	Against (2023/1/13)
Tixagevimab/cilgavimab	EUA (2021/12/8) Halt (2023/1/26)	SAE (2022/8/30) except Omicron variant	Approval (2022/3/25) Notice (2022/12/9)	
Bebtelovimab	EUA (2022/2/11) Halt (2022/11/30))			
Regdanvimab			Approval (2021/11/12) Notice (2022/12/9)	
Tocilizumab	EUA (2021/6/24) NDA (2022/12/21)	EI (2022/1/21)	EI (2021/12/10)	Recommend (2021/7/6)
Sarilumab		Off-label use		Recommend (2021/7/6)
Baricitinib	EUA (2020/11/19) Revise (2021/7/28)	EI (2021/4/23)	Withdraw EI-apply (2022/12/7)	Recommend (2022/1/14)
Dexamethasone*1	Within indication	Within indication	NDA-apply (2020/9/2)	Recommend (2020/9/2)
Favipiravir	Under clinical trial	Off-label use Clinical trials suspended		
Ivermectin	Forbid except clinical trial (2021/3/5)	Off-label use Clinical trial completed	Not recommend except clinical trial (2021/3/21)	Not recommend except clinical trial (2021/3/31)
Anakinra	EUA (2022/11/8)		EI (2021/12/20)	
Fluvoxamine				Not recommend except clinical trial (2022/7/14)

*1 WHO: indicated as “systemic corticosteroid”

EUA: emergency use authorization, NDA: new drug application, SAE: special approval for emergency

EA: emergency approval, EI: expanded indication, Tentative; Tentative approval

need for ventilation, improvement in clinical symptoms, or other important clinical outcomes. Even more to the contrary, the U.S. FDA changed the usage of remdesivir for treatment from the previous EUA action to an official New Drug Application (NDA)-approved item on October 22nd of the same year—after receiving data from the manufacturer, Gilead Science, Inc. As a result of this change, remdesivir can still be manufactured, marketed, and clinically used as an approved drug after ending the “EUA item” status in the United States. In addition, on the 21st of January 2022, the drug was approved for use in non-hospitalized adult patients with mild to moderate disease, as well as pediatric patients (age 12 years and older, weighing 40 kg or more). These ap-

provals are in addition to the already existing indication for severely hospitalized patients.

In Europe, clinical use of the investigational drug as "compassionate use" was initiated in April of 2020, and the EMA completed its review in mid-May. It recommended approval to the European Community (EC) on the 25th of June 2020. Based on the recommendation, on the 3rd of July, the EC provisionally approved remdesivir for the treatment of COVID-19 pneumonia in adults and adolescents (age 12 years and older) who are also undergoing oxygen treatment. On November 20th of the same year, the WHO expressed its opposition to the use of remdesivir, but the EMA issued an update to explain the validity of the approval. In January of 2022, the indication expansion for severe COVID-19 not requiring supplemental oxygen treatment, began to be considered. On the 8th of August, the indication was officially approved for use in adults and children (weighing 40 kg or more) in cases with or without the need for supplemental oxygen treatment. The WHO revised its guidelines on the 22nd of April 2022, changing the use of remdesivir from "opposed" to "conditionally recommended".

In Japan, a special approval for emergency was granted on the 7th of May 2020, for administration to patients with moderate disease or worse, requiring oxygen administration. On the 7th of January 2021, administration to patients with moderate disease who do not require oxygen administration, was also approved. Due to the limited supply worldwide, the MHLW purchased the product and distributed it to medical institutions. On August 12th of the same year, the product was covered by insurance and has been in general distribution since the 18th of October. The dosage for adults with pneumonia caused by SARS-CoV-2 (and children weighing 40 kg or more), is 200 mg on the first day, followed by 100 mg on the second and subsequent days. For children weighing at least 3.5 kg and less than 40 kg, the dosage is 5 mg/kg on the first day, then 2.5 mg/kg on and after the second day, given once daily by intravenous infusion. It should be noted that, the total duration of administration should not exceed 10 days. Remdesivir was listed on the National Health Insurance (NHI) drug price list on the 5th of August 2021; a bottle containing 100 mg is priced at 63,342 yen. Since the usual treatment is 5 days, one treatment course per patient will administer a total dose of 600 mg, resulting in drug costs of approximately 380,000 yen (equivalent to $3,472 at the exchange rate on the same day).

ii) Molnupiravir

Molnupiravir[46], developed by Merck & Co., Inc. of the United States, is a prodrug used as an anti-COVID-19 drug. It has oral absorption that gives rise to β-D-N4-hydroxycytidine, which is a nucleoside that inhibits RNA polymerase of SARS-CoV-2. The EUA application was submitted to the U.S. FDA on the 11th of October 2021. The application is based on the results of an interim analysis of a global phase-III study (NCT04575597) conducted in 1,550 adult patients with a confirmed diagnosis of COVID-19 within 5 days of onset of illness, with mild to moderate disease, who were not hospitalized. The results of the interim analysis of 775 patients were pre-

sented on the 5th of August 2021. It showed that patients treated with molnupiravir had an approximately 50% reduction in risk of hospitalization and death compared to those treated with placebo. The interim analysis of the trial conducted at 78 sites in 15 countries, including three sites in Japan, showed that the primary endpoint of hospitalization plus death at 29 days in the molnupiravir group of 7.3% (28 cases/385 cases) was significantly ($p = 0.0012$) lower compared to 14.1% (53 cases/377 cases) in the placebo group. Adverse events were observed in 40% of patients in the placebo group and 35% in the molnupiravir group.

Based on these results, the Independent Data Monitoring Committee recommended early termination of the trial. Merck & Co., Inc. announced that it filed an EUA application at this stage. However, the final results of the trial, which were submitted to the FDA on the 30th of November 2021, showed that the efficacy rate of the primary endpoint, which was estimated at 50% in the interim analysis, had dropped to 30%. This result negated the original "game-changer" expectation, and the Council's vote on the EUA special measure was narrowly approved by a vote of 13 to 10. The EUA approval date was set for December 23rd of that same year, one day after the approval of the nirmatrelvir/ritonavir combination (which was filed late by Pfizer). The National Institutes of Health (NIH), in its COVID-19 treatment guidelines revised[47] on the 24th of February 2022, states that the drug is expected to be effective against the Omicron variant but recommends that it be used only when other treatments are not appropriate, given the low efficacy of the drug.

The EUA special measure for molnupiravir in the United States has been harshly criticized as an example of the collapse of the world's long-established system for reviewing new drug applications. The EUA application for molnupiravir was filed on the 11th of October 2021, but in the press release[48] of the 9th of June 2022 from the HHS, two months before the interim analysis of the clinical trial used in the application conducted on August 5th, it stated that the HHS had made an advance reservation to purchase 1.7 million case doses of the drug for $1.2 billion based on the assumption that the FDA grants EUA or routine approval for the drug. This press release by the HHS, which is the agency with power over the FDA, puts strong pressure on the FDA's review of the drug by making such an announcement before the process is completed. Hence, the press release was criticized for inducing bias into the review process. This is an example of how scientific review for drug approval can be subverted for political purposes.

Even though it has been announced that molnupiravir is approved or licensed for use in 30 countries around the world (including Japan, ten Asian countries such as India, Thailand, and the Philippines, and South Africa), it is interesting to note the different responses in different countries. In Europe, the EMA has been collecting information on molnupiravir since the 25th of October 2021. It issued a warning on the 19th of November for use in the EU as an unapproved drug, and received an application for approval on November 23rd. Despite new data being received and reviewed on the 14th of December 2021, the drug is still unapproved as of the 13th of March 2023. Meanwhile, in the United Kingdom, regulators reportedly granted accelerated approval for the

drug on the 4th of November 2021. On the other hand, according to a Reuters report on the 24th of December, the French government cancelled an order for molnupiravir after discovering that the drug's clinical efficacy was lower than originally reported.

In Japan, Prime Minister Kishida announced on the 12th of November 2021, that a total of 1.6 million case doses were pre-ordered at a cost of around 137 billion yen (equivalent to $1.2 billion), with each case costing around 85,000 yen (equivalent to 745^{00}). With the aim of special approval for emergency at a December 24th Council meeting (the product was already imported in anticipation of its clinical use starting on December 27th), the Council approved the drug as scheduled. The MHLW announced the special approval for emergency purposes on the same day. All of these measures were exceptional, including the importation of the drug product while the approval review was underway, and this was a case in which all the conventional principles and rules for the approval review of new drugs in Japan had been violated. This was a response to a pandemic in which a state of emergency was declared by the government, and it is believed that the government decided that it was not necessary to comply with the conventional principles and rules in terms of national crisis management in order to protect the lives of the people.

The approved molnupiravir 200 mg capsule formulation is to be administered orally at a dose of 4 capsules twice daily, for 5 days, to patients 18 years of age or older who have risk factors for severe infection caused by SARS-CoV-2 and who are otherwise considered to require administration of the drug. The drug is not indicated for use in pregnant women and children under 18 years of age. In Japan, MSD K.K. is the manufacturer and distributor, and Kyorin Pharmaceutical Co., Ltd. is the promotional partner. However, COVID-19 is designated as a Class II infectious disease under the Infectious Disease Law, and the full cost of its treatment is borne by the national treasury. As of the 15th of January 2022, molnupiravir (product name "Lagevrio Capsules 200 mg") is distributed nationwide by the MHLW through approximately 13,000 medical institutions and 12,000 pharmacies registered as distribution sites.

According to the published data[49] of the MHLW, the number of cases in which government-secured molnupiravir was administered, from the start of clinical administration on the 27th of December 2021 to the 15th of September 2022, reached 619,621 cases. The capsules were listed in the NHI Drug Price Standard on the 18th of August 2022, and since the capsules became available for general distribution to medical institutions and pharmacies from the 16th of September, the distribution of the government-secured portion purchased through the registration center was terminated. The daily drug price for an adult dose (800 mg twice daily) is 18,862.4 yen, or 94,312 yen (equivalent to 697^{47}) for a 5-day treatment. The remaining capsules purchased from the government treasury are not allowed to be transferred to other institutions, or disposed of.

Although review regarding the approval of molnupiravir had been underway since the 10th of November, Korea announced that molnupiravir for 242,000 patients had been pre-ordered on the 27th of December 2021. The EUA was issued on the 23rd of March 2022, in response to the emer-

gency situation of the dramatic increase in cases of the Omicron variant. Australia and New Zealand reportedly purchased molnupiravir for 300,000 and 60,000 case doses, respectively. In all of these countries, the existing drug approval system is in a state of collapse, as they are deviating from the normal approval system and making advance reservations to secure their own portion before others. Actions seem to be based on political decisions, without waiting for proper or adequate evaluation of efficacy and safety by their own regulatory authorities. In the Philippines, the first EUA for molnupiravir was issued to Faberco Life Sciences Inc. on the 22nd of December 2021, followed by EUAs to multiple additional companies—one company each day, on January 14th, 24th, and 28th, and two more companies on the 31st of January 2022.

Merck & Co., Inc. announced, in October of 2021, a non-exclusive patent license agreement for pharmaceutical companies wishing to manufacture generic versions of molnupiravir. This was subject to emergency approval by local regulatory authorities, with the aim of accelerating the supply of molnupiravir for low- to middle-income countries around the world. Merck & Co., Inc. has licensed the rights, through the Medicines Patent Pool (MPP), to five companies such as Cipa Limited, Dr. Reddy's Laboratory, Emcure Pharmaceuticals, Hetero Healthcare Labs, and Sun Pharmaceutical Industries. In India, three phase-III clinical trials (involving 1,200 patients) were initiated in May and June of the same year, using domestically produced molnupiravir for COVID-19. In all three trials, the control group was treated with ivermectin, 12 mg for 5 consecutive days, confirming that ivermectin is the standard therapy for COVID-19 in India.

In India, molnupiravir was approved by EUA in December of 2021, but the domestic situation has been complicated. For example, Biophore India, located in New Delhi, announced on the 22nd of January 2022, that it had obtained a license from the MPP for the manufacture of active pharmaceutical ingredients (API) for manufacturing and would supply API not only to India but also to other countries. Currently, more than ten companies, including Optimus Pharma, Zenith, Natco Pharma, Azista Industries, etc., apart from the five companies under contract with Merck & Co., Inc., are manufacturing molnupiravir capsules in India and more than 500 products are being sold by dozens of pharmaceutical companies. A box of 40 capsules of 200 mg oral capsule is priced at 2,400 rupees (about 29^{00}) and can be purchased and taken without a prescription. As mentioned above, the price for one case in Japan (40 capsules of 200 mg oral capsule) is 697^{47}, which is about 24 times the price in India.

Meanwhile, the National Task Force of the Indian Council of Medical Research (ICMR) for COVID-19, which prepares guidelines for COVID-19 treatment in India, issued a statement on the 13th of January 2022, opposing the inclusion of molnupiravir in the guidelines due to safety concerns. The guidelines[50] affected the entire country, making it likely that molnupiravir would no longer be used in India. However, the situation soon changed, and in the Covid Guidelines for India dated February 16, 2022, it was indicated that "usage of molnupiravir in mild to moderate COVID-19 patients without risk factors is strongly opposed, but that it is conditionally recom-

mended as an option only for mild to moderate COVID-19 patients with risk factors (especially obesity) that would make them severely ill and who are vaccinated and treated at home."

According to an announcement on the 3rd of February of 2022 from Merck & Co., Inc., it planned to ship more than 4 million case doses of molnupiravir to more than 25 countries worldwide, including 3.1 million case doses to the U. S. Government (HHS reserved an additional 1.4 million case doses on the 9th of November 2021, for $1 billion) within a short time frame. The company had also announced that it would supply 3 million case doses through UNICEF to 100 low- to middle-income countries around the world in the first half of 2022, and that it planned to manufacture 30 million case doses of molnupiravir by the end of 2022.

In its revised guideline for the treatment of COVID-19 issued on the 3rd of March 2022, the WHO included[51] a chapter on molnupiravir, stating that it should only be recommended for the treatment of non-severe COVID-19 patients (excluding pregnant and lactating women, and children) who are at significantly higher risk of hospitalization. On the 14th of the same month, the WHO also announced that it would conduct a safety study in low- and middle-income countries to investigate the safety of molnupiravir in the treatment of mild-to-moderate COVID-19.

iii) Nirmatrelvir/Ritonavir Combination (Paxlovid®)

Nirmatrelvir [investigational code; PF-07321332 (Pfizer)][52] is a fluorinated peptide analog that inhibits the 3CL protease ($3CL^{PRO}$), known as the main protease, which cleaves between the glutamine and the next amino acid residues of the precursor polyprotein formed by translation from the genomic RNA of SARS-CoV-2 to generate multiple functional proteins. The absence of functional proteins inhibits the replication of SARS-CoV-2. To prevent degradation of nirmatrelvir by CYP3A in the body, ritonavir, which is included in existing anti-HIV drugs, is taken at the same time.

The drug is indicated for the treatment of SARS-CoV-2 infection. The dosage is 300 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days for adults, and children (12 years or older, weighing 40 kg or more), who have risk factors for severe infection and otherwise qualify for treatment with this drug. A patient formulation, Paxlovid Pack® (Paxlovid), consisting of two nirmatrelvir 150 mg tablets and one ritonavir 100 mg tablet, is available.

In the United States, an interim analysis (1,379 of 2,246 targeted patients) of a phase-III trial (NCT04960202) conducted since the 13th of July 2021, showed an 89% reduction ($p<0.0001$) in hospitalization or death in patients with mild to moderate disease within three days of onset. The results were announced on the 5th of November 2021. Based on these results, an EUA application was filed with the FDA on November 17th, and the FDA issued[53] the EUA approval on December 22nd, one day earlier than the previously filed application for molnupiravir. In its December 30th revision of the guideline[54], the NIH noted that the combination drug is expected to be effective in cases of the Omicron variant. It was strongly recommended that ritonavir, which inhibits CYP3A, be used cautiously due to interactions with a wide variety of drugs. On November 18th, the day

after the EUA application was filed, in the United States, the Biden administration announced that it would purchase 10 million case doses of Paxlovid, for $5.3 billion, in the same manner as for molnupiravir.

The European EMA received an Application for Marketing Authorization (AMA) with certain conditions on the 10th of January 2022. It recommended marketing authorization to the EC on January 27th, and issued a marketing authorization valid throughout the EU on January 28th. The United Kingdom Medicines Agency approved the use of Paxlovid on the 1st of January 2022, and stockpiling has reportedly begun. A preliminary order for 500,000 case doses has been placed by Australia. In South Korea, the Ministry of Food and Drug Safety granted emergency approval on the same day after a rapid 5-day review, but fearing criticism announced on the 27th of December 2021 that it had reserved 362,000 case doses of Paxlovid in advance. As outlined above, the securing of Paxlovid has become an important issue for administrations in many countries around the world. Also in Japan, Prime Minister Kishida was working hard to secure the drug, urgently reporting that 2 million case doses had been reserved in advance for national treasury purchase. On the 14th of January 2022, a special approval application was submitted. Paxlovid was then granted a special approval for emergency for the treatment of COVID-19 on the 10th of February 2022.

The Paxlovid packages of the government's treasury purchase were distributed to medical institutions nationwide from the 28th of February, and after the 22nd of April, the MHLW's Novel Coronavirus Infectious Disease Control Headquarters distributed the drug, through registration centers, to medical institutions and pharmacies. The drug was prescribed for the treatment of patients in both inpatient and outpatient settings (including at home care). In particular, since there are many contraindications and precautions against concomitant use of this drug, it is necessary to check all medications being taken by each patient at the time of prescription. According to the MHLW's published data[49], the number of cases in which Paxlovid was administered, from the date of its special approval to the 15th of March 2023, reached 101,464. Then, in an announcement dated the 20th of March 2023, it was notified[55] that the government-secured portion (government-purchased packages) would not be allocated to medical institutions and pharmacies. The reason was because the drug was placed on the NHI drug price list and distributed to the general public from the 22nd of March.

Nirmatrelvir, discovered from peptidomimetics drug exploratory research, is an inhibitor of $3CL^{PRO}$ which excises multiple active proteins from the polyprotein precursors produced by SARS-CoV-2 in cells after infection. The origin of drug exploratory research in this area can be traced back to the structural analysis study[56] of $3CL^{PRO}$ of SARS-CoV in 2003. In a study using crystallized $3CL^{PRO}$ of SARS-CoV-2, existing GC373 and its prodrug GC376 are irreversibly bound[57] to the target cysteine residue at the active center of a protease and inhibitory activity results. Nirmatrelvir is an analog of GC373, in which the aldehyde group covalently bound to the cysteine residue of $3CL^{PRO}$ is replaced by a nitrile group, and shows excellent inhibitory activity.

Nirmatrelvir is metabolized by CYP3A4 *in vivo* after oral administration, but its metabolism is inhibited by ritonavir taken at the same time (nirmatrelvir has been confirmed to exist in its active form in plasma). Although ritonavir has no anti-SARS-CoV-2 activity, its inhibition of CYP3A4 may increase blood levels of various drugs. There are dozens of drugs that are thereby contraindicated or require precautionary measures in order to use. Therefore, when administering ritonavir to patients with underlying medical conditions, it is necessary to take additional measures such as discontinuing routine daily medications that patients require for other underlying conditions.

iv) Ensitrelvir

Shionogi & Co., Ltd. started a phase-I clinical trial[58] of S-217622, an inhibitor of $3CL^{PRO}$ developed in collaboration with the International Institute for Zoonosis Control of Hokkaido University, on the 22nd of July 2021, and a phase- II/III trial[59] on the 27th of September. The study uses a placebo as a control and is designed to evaluate efficacy and safety for oral administration of S-217622, once daily for 5 days, in patients with mild or asymptomatic COVID-19 infection. The antiviral activity of S-217622 against the Omicron variant has been under investigation since the 8th of December 2021. Results were announced on the 20th of December, showing that it has excellent activity to both Omicron and similar existing variants.

On the 7th of February 2022, Shionogi & Co., Ltd. reported[60] the completion of the analysis of the phase-IIa portion (comprised of 69 target cases) of the ongoing phase-II/III clinical trial of S-217622. S-217622 has CYP3A4 inhibitory activity, and unlike nirmatrelvir, which is also a $3CL^{PRO}$ inhibitor, it does not need to be combined with ritonavir (which inhibits CYP3A4) and is administered orally as a single drug. After three doses (i.e., on day 4), viral titers were 60–80% lower than in the placebo group. As for the effect on clinical symptoms, the investigators reported that COVID-19 treatment showed a trend toward improvement in clinical symptoms typically characteristic of COVID-19. No cases of severe disease requiring hospitalization were reported, nor any serious or adverse events requiring discontinuation of the drug.

On the 25th of February 2022, Shionogi & Co., Ltd. submitted[61] an application to the MHLW for manufacturing and marketing approval of S-217622 in Japan. The company had initially hoped to apply under the "Conditional Early Approval System". However, on the 20th of May, the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Pharmaceutical Affairs Law)"[62] was revised and this revision created a new "Emergency Approval System". The company requested urgent approval under this new system. The drug has been given the generic name ensitrelvir, and its fumarate tablet was named, Xocova Tablets 125 mg. The urgent approval request was discussed by the Second Committee on New Drugs held on the 22nd of June. Discussions for approval or disapproval were held at a joint meeting of the Committee and the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council held on the 20th of July. However, the review by the Pharma-

ceuticals and Medical Devices Agency (PMDA) concluded that, although a trend toward a decrease in viral load after drug administration was observed, efficacy for the proposed indication of the drug could not be verified. It was decided that they would continue deliberations following the submission of data from the phase-III portion of the trial, which was still in progress at that time.

Despite the establishment of the “Emergency Approval System”, the drug was not approved at this joint meeting. Discussions were based on conventional deliberation policy by conventional committee members, and it was determined that even though reductions in viral load required for an original antiviral drug were observed, the efficacy results obtained were not based on conventional clinical evaluation methods. The “Emergency Approval” application was rejected. Thereafter, the Japanese Association for Infectious Diseases and the Japanese Society of Chemotherapy submitted a proposal[63] under the names of the presidents of both societies, to the Minister of Health, Labour and Welfare on the 2nd of September. In that proposal, while Japan was under the severe infection environment of the seventh wave of COVID-19, they requested urgent approval of oral drug formulations that could be used for mild cases.

The primary efficacy endpoint of the phase-III clinical trial of ensitrelvir was the time to recovery of five symptoms: (1) malaise or fatigue, (2) feverishness or pyrexia, (3) runny or stuffy nose, (4) sore throat, and (5) cough. The preliminary results of the study demonstrated that the experimental group showed a time reduction of overall symptoms resulting in 167.9 hours of experienced symptoms, compared to 192.2 hours in the placebo group. The PMDA, which conducted the review, concluded that there was sufficient data to infer that the drug was effective. The results were once again submitted to a joint meeting of the Second Committee on New Drugs and the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council, which was held on the 22nd of November 2022, and emergency approval[64] for the drug was granted.

Ensitrelvir is the first oral drug that can be used by patients with mild disease and can also be taken by patients who are not at risk for severe disease. The Japanese government had concluded an agreement with Shionogi & Co., Ltd., to purchase one million case doses of the drug if it is approved. Following the urgent approval of the drug, the MHLW’s Novel Coronavirus Infectious Disease Control Headquarters issued a notice[65] on the distribution of the drug to medical institutions and pharmacies. The drug is the property of the MHLW, and both in-hospital and out-of-hospital prescriptions are registered at the Xocova Registration Center, which has been established on behalf of the MHLW. The distribution of the drug will only be made to medical institutions and pharmacies that have a “record of prescribing Paxlovid”, registered with the “Xocova Registration Center”, established by the Ministry. After the Cabinet meeting on the 13th of December 2022, the Minister of Health, Labor and Welfare announced that a contract for the purchase of an additional 1 million case doses of the drug had been made, and a stockpile of 2 mil-

lion case doses in Japan is said to be ready. According to the MHLW's press release[49], the drug has been administered to 37,198 patients through 3,459 hospitals and 9,159 pharmacies nationwide from the time of its approval, up to the 15th of March 2023. According to Shionogi's press release[66], the drug was listed in the NHI Drug Price Standard on March 15th and began general distribution on March 31st, at a price of 7,407.4 yen per 125 mg tablet. The cost of the drug will be ¥51,851.8 (equivalent to $388[69] at the exchange rate on the same day) per course of treatment. However, since the cost of the drug will, for the time being, be borne by the national treasury, individuals will not have to pay for it.

On the other hand, Shionogi & Co., Ltd. has started the international development of S-217622, and announced that it has been included in the ACTIV-2d program (SCORPIO-HR study; NCT05305547) promoted[67] by the U.S. National Institutes of Health. Based on the results of a phase-II/III study conducted in Japan, the U.S. FDA has approved the study. The study will evaluate the efficacy of a 5-day course of treatment to prevent deterioration in SARS-CoV-2 positive patients with at least one risk factor, starting within 5 days of onset of disease. Approximately 1,700 patients from Europe, North America, South America, Africa, and Asia are expected to be enrolled in the randomized, double-blinded, placebo-controlled study, with a 2 : 1 ratio of patients receiving S-217622 to those receiving a placebo. The company has also announced that it has initiated an efficacy trial for prevention of the disease in family members living with COVID-19 patients, and plans to collect approximately 2,000 patients in Japan and the United States by September of 2023.

v) Monoclonal antibody drugs and others

As a treatment for COVID-19, a neutralizing antibody was developed that specifically binds to the spike protein on the surface of the causative SARS-CoV-2 virus, blocking viral entry into host cells. Several pharmaceutical companies have produced monoclonal antibodies and conducted clinical trials using established monoclonal antibody production methods.

An EUA application, for bamlanivimab (the first monoclonal antibody drug approved by the FDA) was submitted by the Eli Lilly & Co. on the 6th of October 2020. The results used for the approval process were from the interim analysis of a comparative study[68] involving a phase-II/III trial (NCT04427501) that was conducted from the 17th of June 2020. The comparative study analyzed two study arms of bamlanivimab (one alone, and one in combination with etesevimab) in addition to a placebo-controlled arm. The EUA was granted for bamlanivimab monotherapy on the 9th of November 2020. However, as mentioned above, multiple variants of COVID-19 have been attributed to COVID-19 in the United States. Therefore, a single component of bamlanivimab alone is no longer sufficient for therapy. As a result, the FDA issued an EUA on the 9th of February 2021 for combination therapy using bamlanivimab and etesevimab. The EUA for single use bamlanivimab was withdrawn on the 16th of April 2021.

The combination regimen was specified to consist of bamlanivimab 700 mg and etesevimab 1,400 mg, administered intravenously at the same time. Its use in adults (and children weighing 40 kg or more) was also supposed to prevent the onset of disease after exposure to the SARS-CoV-2 virus. However, the NIH issued a recommendation against the use of this combination therapy on the 23rd of December 2021 in its revised guidelines[69]. The basis for this decision was the Omicron variant's mutated spike protein, which renders the combination therapy ineffective. The FDA suspended the EUA on the 24th of January 2022.

The EMA had been reviewing the application for the combination therapy of bamlanivimab and etesevimab (to be used for prevention of disease exacerbation in high-risk COVID-19 patients not requiring supplemental oxygen) since March of 2021. However, due to quality control issues and projected market size issues after launch, Eli Lilly & Co. abandoned development of the project in Europe on the 2nd of November 2021, by withdrawing its application.

The second monoclonal antibody is casirivimab/imdevimab[70], developed by Regeneron Pharmaceuticals Inc., of the United States. Its clinical trial was initiated on the 11th of June 2020, and an application for EUA was filed with the FDA on the 8th of October, using interim analysis results. Its EUA was issued on the 21st of November. In Europe, the marketing authorization application was submitted on the 1st of February 2021. After review by the EMA, a recommendation for authorization was issued to the EC on the 11th of November, and marketing authorization was granted the following day, on November 12th.

In Japan, the drug was referred to as the "cocktail regimen", and evaluation of safety, tolerability, and pharmacokinetics in Japanese adults was conducted from March of 2021. An application for special approval for emergency was filed on the 29th of June, and special approval was granted on the 19th of July. The approved dosage is 600 mg of each drug, as a single intravenous infusion in combination, for mild to moderate patients (adults, and children aged 12 years or older who weigh more than 40 kg) who do not require supplemental oxygen, but who have risk factors for worsening. After special approval, the drug was provided by Chugai Pharmaceutical Co., Ltd. to the MHLW and distributed to eligible medical institutions nationwide. Distribution was through the "Ronapreve Registration Center", under the authority of the MHLW, for use in the treatment of eligible patients as mentioned above. Amid the demand for expansion of the medical care delivery system to cope with the spread of infection in Japan, an application was filed on the 11th of October 2021. This application was based on the results of the COV-2069 and COV-20145 studies conducted overseas, and was for pharmaceutical manufacturing and marketing approval intended for "suppression of onset of SARS CoV-2 infection" and a "single subcutaneous injection". Special approval for emergency was granted for a new "indication" and "dosage and administration" in November of 2021.

However, the FDA suspended the EUA on the 24th of January 2022, because the NIH guidelines recommended against the use of this combination therapy. In Japan, the MHLW's "Guide-

line for the Diagnosis and Treatment of New-type Coronavirus Infections (COVID-19) ", Version 7.0 (issued on February 28, 2022)[71], in the chapter "Neutralizing antibody drugs" in the drug therapy section, states, "There are reports that this drug has reduced neutralizing activity against Omicron variants, and it is not recommended when it is clear that patients are infected with this variant or when there is a high probability that they are infected with this variant". In the public notice of the MHLW issued on the 25th of August 2022, however, this drug is listed first among the eight drugs recommended to be used against COVID-19, as specified by the MHLW and based on the provisions of the "Infectious Diseases Law". No note is made regarding the decreased neutralizing activity of the drug. There is a clear discrepancy between the MHLW guidance and the notification, and there should be concern about the lack of stringency in the handling of drugs with reduced efficacy.

The third, sotrovimab[72], is a spike protein neutralizing antibody created by GSK PLC of the United Kingdom, based on antibodies obtained from a patient infected with the SARS (severe acute respiratory syndrome) in 2003. It recognizes a highly conserved antigenic determinant (epitope) on the SARS-related coronavirus. The epitope does not overlap with the mutated sites of the Omicron variant; therefore, the neutralizing antibody activity is not considered to be reduced. The European EMA initiated its review on the 7th of May 2021, and after a council meeting on the 18th of November that same year, it was recommended that a marketing authorization be issued on December 16th. The EC permitted marketing authorization of the drug on the 17th of December 2021. The U.S. FDA issued an EUA on May 26th of that same year, and the EUA was revised on December 22nd to include an indication for the Omicron variant. In Japan, a special approval for emergency was issued on the 27th of September 2021, for a single 500 mg intravenous infusion. This infusion is indicated for mild to moderate adult patients and children (aged 12 years and older weighing 40 kg or more) with risk factors for deterioration and not requiring oxygen administration.

In the United States, sotrovimab had been used under an EUA based on the NIH guidelines revised on the 24th of January 2022, which stated that the neutralizing activity of sotrovimab against Omicron variant was not reduced. However, the FDA suspended the EUA for sotrovimab on the 23rd of February, because the neutralizing activity of sotrovimab was found to be decreased due to the change of the main epidemic strain in the United States to the BA.2 lineage. In Japan, sotrovimab was also listed as the third monoclonal antibody drug designated by the MHLW; the public notice was issued on the 25th of August 2022, and no further action has since been taken.

The fourth neutralizing antibody drug is tixagevimab/cilgavimab[73], developed by AstraZeneca PLC of the United Kingdom. In the United States, the FDA issued an EUA for its use on the 20th of December 2021. During the clinical development of this drug, efficacy was demonstrated in a placebo-controlled infection prevention study in more than 5,000 adults. These adults were unable to receive any COVID-19 vaccines, due to allergic reactions, and the December 20th EUA

was the first approval that was given, indicated for SARS-CoV-2 post-exposure prevention. In Europe, rolling review by the EMA began on the 14th of October 2021. The EMA eventually recommended marketing authorization on the 24th of March 2022, after successive reviews of quality, safety, clinical pharmacology, clinical trial results, and other well-developed data. In Japan, based on the results of a global phase-III study and a domestic phase-I study, an application for special approval for emergency was filed on the 9th of June 2022. On August 29th of that same year, special approval for tixagevimab/cilgavimab was granted[74] for the treatment of COVID-19 and for the prevention of SARS-CoV-2 onset in individuals prior to any exposure to the virus.

At the time of the FDA's revision of the EUA on the 29th of June 2022, there was no decrease in the neutralizing antibody activity of tixagevimab/cilgavimab against the Omicron variant BA.2, BA.2.12.1, BA.4, and BA.5 lineages; therefore, the drug continued in clinical use. However, on the 6th of January 2023, with an increase of the XBB.1.5 lineage in the United States, its use became problematic as the neutralizing activity of the drug against the lineage decreased. On the 26th of January 2023, the FDA issued a notice[75] that, as a result of its investigation, it would suspend the EUA-based use of the drug until the number of viruses non-susceptible to the drug was reduced to 90% or less.

The U.S. FDA issued an EUA on the 11th of February 2022 for bebtelovimab[76] of Eli Lilly & Co., as the fifth neutralizing antibody drug. No marketing authorization application to the European EMA, nor special approval for emergency to the Japanese MHLW has been submitted to date. Although the drug initially showed no decrease in neutralizing antibody activity against the Omicron variants, as the prevalent strains in the United States changed and the proportion of the BQ.1 and BQ.1.1 lineages increased, the neutralizing activity eventually decreased, and its therapeutic effect became less promising. Accordingly, in an update[77] dated November 30th, the FDA notified that, while the EUA for this drug will continue, it will not permit its use. As a result, the use of all monoclonal antibody drugs against COVID-19 has been suspended in the United States. Use may be permitted again, when the susceptibility of future outbreak strains to neutralizing antibodies is restored.

While the EMA initiated a sequential review of the marketing authorization of tixagevimab/cilgavimab on the 14th of October 2021, the Council began deliberation on regdanvimab. The latter was applied for by Celltrion Inc. of Korea on October 4th and had been under review since the 24th of February 2021. The recommendation for marketing authorization of regdanvimab to the EC was made on November 11th and was granted on November the 12th, 2021. No EUA application to the U.S. FDA, nor special approval for emergency to the Japanese MHLW, has been filed for regdanvimab to date.

The European EMA has issued[78] a warning from the Emergency Working Group on the 9th of December 2022, stating that four monoclonal antibodies (casirivimab/imdevimab, regdanvimab, sotrovimab, tixagevimab/cilgavimab) may be ineffective in the current environment when

used to treat COVID-19 caused by various lineages (BA.4.6, BA.2.75.2, XBB, BQ.1, BQ.1.1, etc.) of the Omicron variant which spread throughout the EU. Instead, it recommended the use of antiviral agents (nirmatrelvir/ritonavir and remdesivir).

Tocilizumab is a monoclonal antibody against the interleukin-6 (IL-6) receptor and is already approved for the treatment of rheumatoid arthritis in the United States, Europe, and Japan. Off-label use of this drug has been attempted since early on, because it has been recognized that although the pathogenesis of COVID-19 begins as a viral infection, as the disease progresses, the immune response becomes abnormally enhanced, resulting in cytokine storm-like symptoms. The U.S. FDA issued[79] an EUA on the 24th of June 2021 and approved (NDA) the drug, for the treatment of adult inpatients, on the 21st of December 2022. In Japan, an additional indication for the treatment of pneumonia caused by SARS-CoV-2, was approved on the 21st of January 2022. The drug is to be administered to hospitalized patients requiring oxygen administration, ventilator management, or external membrane ventilation (ECMO) induction. The dosage and administration of tocilizumab (recombinant humanized form) is 8 mg/kg, once, intravenously, in combination with corticosteroids in adults. If symptoms do not improve, an additional 8 mg/kg dose of tocilizumab can be administered at least 8 hours after the initial dose.

Sarilumab, a monoclonal antibody against the IL-6 receptor, similar to tocilizumab, is used clinically in Japan for the treatment of rheumatoid arthritis. However, following the approval of the intravenous formulation of tocilizumab, it may now be used off-label for the treatment of pneumonia caused by SARS-CoV-2. Since only the subcutaneous formulation of sarilumab is commercially available, and the subcutaneous formulation of tocilizumab is not approved for the treatment of pneumonia caused by SARS-CoV-2, off-label use of the subcutaneous formulation of sarilumab is not recommended. However, the WHO does not distinguish between tocilizumab and sarilumab, and strongly recommends[80] both drugs as "IL-6 receptor blockers" for the treatment of severe COVID-19. This differs from the treatment principles of the U.S. FDA, the European EMA, and the Japanese MHLW.

Baricitinib is a Janus kinase (JAK) inhibitor developed by Eli Lilly & Co. in the United States, for the treatment of rheumatoid arthritis. It has been in clinical use in Japan since September of 2017; its anti-inflammatory action is expected to reduce the hyperinflammatory state and cytokine storm associated with COVID-19. On the 19th of November 2020, the U.S. FDA added[81] an indication for the treatment of pneumonia caused by SARS-CoV-2 (but only in patients requiring oxygen) in combination with remdesivir. On the 28th of July 2021, the U.S. FDA approved baricitinib alone (not in combination with remdesivir), for the treatment of pneumonia caused by SARS-CoV-2 (only in patients requiring oxygen). In Japan, in April of 2021, the additional indication of this same drug for pneumonia caused by SARS-CoV-2 was also formally approved. The dosage and administration instructions stipulate that 4 mg should be administered orally, once daily, to adults, in combination with remdesivir, for a total duration of up to 14 days.

The European EMA initiated its evaluation of baricitinib, for the indication of hospitalized patients requiring oxygen on the 29th of April 2021, but the application was withdrawn on the 7th of December 2022.

vi) Termination of the Declaration of State of Emergency (PHE) in the United States

The HHS declared the COVID-19 outbreak a "public health emergency (PHE)" under the Public Health Service Act on the 27th of January 2020, but announced[82] in a notice dated the 2nd of March 2023 that the declaration would end on the 11th of May 2023. Drugs and vaccines for COVID-19 are EUA items that the FDA has designated in response to the PHE (with the exception of remdesivir, which has been moved from the EUA category to a normally approved, or NDA, item), but the rationale for their authorized use will be lost after the declaration formally ends.

The FDA has established and published[83] in the Federal Register three categories for the 68 guidelines issued under the Declaration: 22 will be discontinued upon termination of the Declaration, another 22 will remain in effect for 180 days after the termination and then discontinued, and an additional 24 will be considered for revision for continuation (another 180-day period). By including the guideline on EUA-measure items in the third category mentioned above, COVID-19 drugs and vaccines can remain available for 6 months and thereafter—under new amended provisions— continue to be used.

In Japan, a number of drugs have been granted special approval for emergency based on EUA actions of the U.S. FDA. The drugs include three antiviral drugs (remdesivir, molnupiravir, nirmatrelvir/ritonavir) and three monoclonal antibody drugs (casirivimab/imdevimab, sotrovimab, Tixagevimab/cilgavimab). All of these drugs will require a formal review on the 8th of November 2023 (which is 180 days from May 11, 2023) if the EUA action is not renewed.

2) Clinical development of new COVID-19 therapeutic agents

While various studies are being conducted worldwide on the efficacy and safety of existing COVID-19 drugs, clinical developments of new drugs are underway, and vigorous reviews[84–87] of their developmental status have been published.

Through the authors' search, there exist 66 compounds in the pipeline, which are listed in Table 8. They are classified by mechanism of action for treatment or prophylaxis against COVID-19. The table does not include vaccines, antibodies, herbal medicines, and other biological products. In particular, clinical trials have been conducted for dozens of monoclonal antibodies, but all the products that were already on the market and widely used are no longer expected to be effective due to mutations in the target viruses (variants/lineages). There is also concern that the development of new products will lose their efficacy in a short period of time. The development of most of these types of products has been suspended.

The compounds listed in Table 8 are candidates to continue clinical development in phase-II

and -III trials, among the approximately 350 substances that have been tested for clinical efficacy against COVID-19.

The main reason that a very large number of candidates have been suspended or terminated in development (since approximately the end of 2021), is evolution of the causative organism SARS-CoV-2 into highly infectious, but less virulent, variants/lineages. Such causative virus variants/lineages have allowed patients to recover in a shorter period of time with milder symptoms. Differences in the improvement of symptoms between patients in the test drug and placebo control groups became difficult to be shown—in some cases, even making it impossible to do so. In addition, the marked increase of vaccination rates (including repeated inoculations) makes it difficult to demonstrate the clinical efficacy of investigational drugs. Furthermore, because of the mild symptoms and rapid recovery from COVID-19, the number of applicants for clinical trials has decreased dramatically. This has also necessitated the withdrawal of many drug development candidates from clinical trials.

The new COVID-19 drugs under development for the treatment of COVID-19 can be categorized according to their mechanism of action. There are a total of 33 antiviral drugs: 13 are cell entry inhibitors, 12 are replication inhibitors, 5 are main protease inhibitors, and 3 are substances that exhibit other actions. The number of drugs related to inflammatory reactions and immunity is

Table 8. Therapeutic drugs for COVID-19 under development

【Antiviral agents: 33 substances】	
Inhibitor of cellular invasion	Alunacedase alfa (P-2), Apabetalone (P-2/3), Bemcentinib (P-2), Brilacidin (P-2), Ensovibep (P-2), Nafamostat (P-3), Niclosamide (P-2/3), PA-001 (P-1), PJS 539 (P-2), Proxalutamide (P-3), SLV213 (P-2), TXA127 (P-2/3), Upamostat (P-2/3)
Inhibitor of viral replication	Azvudine (P-3/4), Bemnifosbuvir (P-3), Clevudine (P-2), Deuremidevir (P-3), Masitinib (P-2), Nitazoxanide (P-3), Opaganib (P-2/3), Pentarlandir (P-2), Plitidepsin (P-2), Sabizabulin (P-3), Silmitasertib (P-2), Zotatifin (P-1)
Inhibitor of 3CL-protease	EDP 235 (P-2), GST-HG171/Ritonavir (P-2/3), PF-07817883/Ritonavir (P-1), Simnotrelvir-Ritonavir (P-2/3), Tafenoquine (P-2)
Others (i.e. visucidal)	Efesovir (P-2), GLS-1200 (P-2), Voxvoganan (P-2)
【Anti-inflammatory/immunomodulating agents: 33 substances】	
Anti-inflammatory activity	Fluoxetine (P-3/4), Fluvoxamine (-2/3), Metformin (P-2/3), Mitoquinone-Mitoquinol (P-1/2), Mosedipimod (P-2), Sabizabilin (P-3), Zegocractin (P-2)
Immunomodulating activity	Abivertinib (P-2), AD17002 (P-2/3), Asapiprant (P-2), Dapansutrile (P-2), Fenretinide (P-2/3), MP1032 (P-2), OP-101 (P-2), Plerixafor-Tacrolimus (P-2), Rintatolimod (P-2), Vidofludimus (P-2/3)
Protection of pulmonary function	Bexotegrast (P-2), Bucillamine (P-3), Deupirfenidone (P-2), Ebselen (P-2), Fostamatinib (P-2/3), Isuzinaxib (P-2), Nezulcitinib (P-1), Olitigaltin (P-3), PUL-042 (P-2), SP16 (P-1/2), TF-0023 (P-2), TM5614 (P-2), Tradipitant (P-3), Zenuzolac (P-2)
Protection of vascular function	Ambrisentan (P-2/3), AV-001 (P-2)

Clinical developments: P-1; phase-1, P-1/2; phase 1/2, P-2; phase-2, P-2/3; phase-2/3, P-3; phase-3, P-3/4; phase-3/4

also 33 in total: 7 substances that exhibit anti-inflammatory effects, 10 immunomodulating substances, 14 substances that protect lung function, and 2 substances that protect vascular function.

Antiviral drugs are effective when administered during the first 72- or 96-hour period when SARS-CoV-2 is infecting and proliferating, but it is impossible to evaluate the true antiviral effect if administered after the proliferation is complete. In actual clinical trials against COVID-19, the administration of the test drug within 72 hours of infection is very rare, and the number of trials completed within 96 hours is also extremely limited. Therefore, to confirm the efficacy of antiviral drugs, it is considered appropriate to evaluate their efficacy in preventing the onset of disease in family members and other close contacts of infected patients, rather than in the course of the disease in infected patients. However, it is necessary to take into consideration that the vaccination status of the target population has a significant influence on the evaluation of the effect of prevention of disease onset.

On the other hand, evaluation of inflammatory reactions and immune-related agents is performed in patients with COVID-19 disease that has progressed to lower respiratory tract disorders. This category comprises cases such as pneumonia, hyperimmune states, and is often based on ICU admission rates, as well as lethality (case-fatality) rates in many severe cases. The sequelae of post-COVID and long-COVID are presumed to be caused by a hyperimmune state, and novel anti-COVID-19 agents are also being evaluated based on their efficacy in treating various sequelae of this process.

Conclusion

The authors published a review article on the COVID-19 pandemic in this journal at the end of March in 2021. At that time, the third wave of the global outbreak was converging, and we had planned to publish a sequel to the review article one year later in hopes of following up on the global trends of the pandemic and the clinical evaluation of ivermectin for COVID-19. However, the sixth wave caused by the Omicron variants that spread from the beginning of the year 2022 was a rapidly and complexly changing day-by-day situation—making it extremely difficult to accurately grasp the global trends. On the 14th of September 2022, two years and six months after the declaration of the pandemic, the WHO announced[13] that COVID-19 had shown a tendency to subside to the point where the declaration was expected to be lifted soon. However, the number of new cases worldwide could not be reduced and soon there was a shift from the seventh wave to the eighth wave. During the seventh wave, the number of newly infected cases in Japan was the largest in the world, followed by South Korea, and the United States. In the case of the United States, which had shown a marked decrease in case numbers (ranking third in the world) the number of cases began to rise once more. All of these factors contributed to making a proper evaluation of the circumstances difficult.

Nevertheless, while referring to the databases of the WHO[16] and Johns Hopkins University[17], it was decided that it would be appropriate to write a sequel to the first review article and cover the interim period up to the end of December 2022. However, on the 14th of January 2023, China released revised numbers of cases and deaths in response to criticism by the WHO, and this made it necessary to further revise the draft creation. The official announcement by China that an estimated 64% of the Chinese population was infected with COVID-19, corresponds to 900 million infected people. Since the cumulative number of infected people worldwide according to the WHO and other data up to that point was approximately 670 million, the addition of China's officially announced figure would increase the cumulative number of patients by approximately 2.4 times; this necessitated a complete change in the discussion points. Furthermore, an official of the Chinese Center for Disease Prevention and Control (CCDC) announced that the actual number of patients was more than 1.1 billion, or 80% of the national population, and that the number of deaths was about 12,000 in one week in January of 2023. This casts doubt on the authenticity of the official Chinese announcement on the 14th of January 2023. Therefore, we concluded that it would be more appropriate to complete this review without including the Chinese data, rather than to be misled by unreliable figures on the number of cases and deaths.

The reasons for the decline in lethality rates as the pandemic progressed, from the first to the third and fourth waves, include the widespread use of PCR testing, increased vaccination rates, as well as advances in treatment with anti-COVID-19 drugs. Direct treatment with antiviral drugs, antibody drugs, anti-inflammatory treatment with steroids, and immunomodulatory drugs have enabled even severely infected patients to be saved. Even more patients have been successfully saved by respiratory management with ventilators and extracorporeal membrane ventilators (ECMO).

Such treatment successes, however, have been accompanied by a situation in which the efficacy of drugs, like antibody drugs, is weakened by mutations of the prevalent virus strain. In such cases, their use is discontinued as a countermeasure, and there have been scattered cases of recurrences/relapses after symptoms have resolved with antiviral drug treatments. In addition, some COVID-19 drugs are contraindicated because of their interactions with a wide variety of drugs used to treat other diseases (comorbidities are a common concern among many patients). Therefore, there is an intense research effort to develop new anti-COVID-19 agents with high safety and efficacy potential, with more than 60 drug candidates currently under clinical evaluation. Many of these candidates are in phase-III clinical trials, and it is hoped that their development will progress smoothly and that a variety of therapeutic agents based on different mechanisms will become available for clinical use.

On the other hand, the COVID-19 vaccine has made great progress, and according to the WHO's tally, 13 billion doses have been administered worldwide by the end of December 2022. This means that 8 billion people worldwide have received an average of 1.6 doses, which is the

achievement of grand-scale social immunity. However, due to the short duration of vaccine-induced immunity and the rapid mutation of the target SARS-CoV-2 virus, protection against infection by vaccination has been incomplete, resulting in renewed and repeated spread of infection. The principle behind vaccination is that although complete protection against infection by vaccination cannot be expected, vaccination can prevent the worsening of symptoms.

There is no doubt that the vaccines are the first line of defense in the prevention of viral infections. For the purpose of preventing COVID-19 infection, vaccines were developed using mRNA encoding the genetic information of the spike protein, which exists on the surface of the virus particles and is involved in binding to human cells (infectivity) and virulence, as the target antigen. These vaccines are based on a completely different principle from conventional vaccine products that use attenuated or inactivated viruses as antigens, and a large-scale clinical trial over a long period of time would normally be required to confirm safety and efficacy. Unexpectedly, however, since the WHO declared COVID-19 a pandemic, and there was an immediate need to take measures to prevent infection, mRNA vaccines were urgently approved in countries around the world. In the process, vaccination coverage and frequency of administration became a matter of competition among countries worldwide.

The variant of SARS-CoV-2 that causes COVID-19 has a mutated spike protein, which is the target antigen of the mRNA vaccines. Since the efficacy of the first mRNA vaccines targeting the original Wuhan strain was reduced, the second mRNA vaccines targeting the mutated alpha and delta variants that were the epidemic strains of the third and fourth waves were developed. Subsequently, the third mRNA vaccines covering the spike protein of the Omicron variant BA.4 and BA.5 lineages were also eventually developed. Because of the short duration of immunity, booster vaccinations are given every 6 or 8 months, and the number of people who have received 4 or 5 doses of the vaccine is increasing. On the other hand, the pathological effects of the spike proteins *in vivo* are gradually being elucidated, and studies on cardiac and nervous system disorders, called spike protein diseases, are underway. A discussion of the history of the development of the vaccine against COVID-19, its widespread use, and its safety and efficacy would require an extensive summary of the data, so the authors will defer that discussion for other reviews. Therefore, more detailed descriptions of the vaccine are omitted from this review.

Three years have passed since the WHO issued the Public Health Emergency of International Concern (PHEIC) declaration on the 30th of January 2020, for the novel coronavirus infection that spread from China. The WHO Director-General's Statement, on the 30th of January 2023, stated that although the situation has improved, compared to the peak of the outbreak caused by the Omicron variant a year ago, there have still been 170,000 deaths worldwide over an eight-week span, resultant sequelae from the infection are still frequent and severe, the virus continues to mutate, and it continues to cause both a high number and high rate of deaths. It was further stated that the situation has not yet reached a point where the declaration can be lifted be-

cause the virus continues to mutate. The statement concludes with seven recommendations from the WHO Director-General for current times. Primary among the recommendations are the promotion of vaccination, improved reporting of surveillance to the WHO by individual countries, and the maintenance of long-term preparatory medical response capabilities. Furthermore, in opening remarks[89] delivered at a March 17th press conference, the Director-General stated that the current situation is the best it has ever been and that there is confidence that the COVID-19 pandemic will end this year. It was also stated that although questions have not been resolved regarding the beginning of the pandemic, the China CDC has provided data on samples taken at the Huanan Seafood Wholesale Market in Wuhan in early 2020 (which have been analyzed by an international group) and expressed regret that this important data should have been shared three years ago but was covered up. The WHO has reiterated the necessity for China to transparently share data, conduct the necessary studies, and share the results.

The words of the Director-General of the WHO in his opening remarks are quoted below as an appropriate conclusion to this review.

> "Understanding how the pandemic began is a moral and scientific imperative, and as we look back to the beginning of this pandemic, we must continue to look forward to strengthening the world's defenses against future epidemics and pandemics. This is something that each country must do together, and no one country can do it alone. We can confront our common threats only through a common response based on a shared commitment to solidarity and equity. This is the pandemic agreement that countries are currently negotiating, an agreement in which countries work together, not competitively, to prepare for and respond to epidemics and pandemics. WHO's role is to help countries implement what they have agreed to. An agreement that captures all the challenges we faced in this pandemic is essential to ensure that the world does not repeat the mistakes made in this pandemic. If we repeat the same mistakes, we will not forgive ourselves, nor will our children and grandchildren. We owe it to ourselves to end this pandemic as soon as possible."

In Japan, COVID-19 has been moved from a strictly regulated Class II infectious disease to a less restrictive Class V infectious disease[36], and in the United States, the "public health emergency declaration"[42] was lifted in early May 2023. In Europe, various restrictions have been lifted in the United Kingdom and France, and in Asia, restrictions have been lifted in India, Vietnam, and South Korea.

Under such circumstances, the Director-General of the WHO stated[90], at a press conference held on the 5th of May 2023, following the results of the deliberations of the COVID-19 Pandemic Emergency Committee held the previous day, that the current COVID-19 situation no longer constituted a public health emergency of international concern (PHEIC), and declared an end to the emergency. It is hoped that a new wave of COVID-19 epidemics will not materialize after

the WHO pandemic declaration is officially terminated.

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Conflict of Interest

None to declare.

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