

〈Review Article〉**Global trends in clinical studies of ivermectin
in COVID-19**

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Response to the initial alarm bells of the Coronavirus infection, which occurred in Wuhan City, Hubei Province, China in November 2019, was delayed as it was announced to be a type of pneumonia of unknown cause. The WHO warned about traveling to China in January 2020. After much urging, the world was finally properly warned, but the Chinese government did not accurately announce the outbreak situation. Consequently, the delaying of the construction of an epidemic prevention system worldwide has resulted in the direst infection circumstances facing the world today. One year has passed since the WHO named the new coronavirus SARS-CoV-2 infection, COVID-19, and it was declared a pandemic on the 11th of March 2020, based on the judgment that it corresponds to “an internationally concerned public health emergency”. Suppression of virus transmission by vaccine has finally begun. To date, the pandemic has affected more than 115 million people and killed more than 2.5 million people in 220 countries/regions around the world. There appears to a potential for control in the near future. However, there is a limit to the supply of vaccines and developed countries are competing to obtain the required amount of vaccination necessary for their own citizens. Although the WHO is trying to secure a certain amount for developing countries, it is predicted that a considerable period of time will be required before COVID-19 becomes controllable.

On the other hand, with regard to therapeutic agents for COVID-19, studies began at an early stage. The therapeutic effects of hydroxychloroquine or chloroquine, lopinavir/ritonavir combination, tocilizumab, interferon β 1, as well as others, were found to have limited efficacies or no effect. Remdesivir improves recovery time by as much as 30% in critically ill patients, but it is not suitable for mild to moderately ill patients—which comprises the majority of infected individuals. Although the

steroid drug dexamethasone is effective in alleviating inflammatory symptoms, its use in mild to moderately ill patients without significant inflammatory symptoms is not recommended. Currently, there are no therapeutic agents available for mildly ill patients who are being treated at home (or in self-isolating accommodations) or for moderately ill hospitalized patients. Nothing is as helpless as a disease without a cure.

In a situation where the number of COVID-19 patients is rapidly expanding, the number of deaths increasing worldwide, hydroxychloroquine, doxycycline, azithromycin, and other drugs are ineffective for therapeutic purposes, an effective treatment method is being sought. An Australian research group reported that ivermectin suppresses SARS-CoV-2 replication in an *in vitro* infection experiment. Ivermectin has been widely used since 1987 for the control of river blindness and lymphatic filariasis, as well as in the treatment of scabies in humans. Because it is an extremely safe and well-known inexpensive drug, it began to be used for the treatment and prevention of COVID-19 in Central and South American countries. One month after the declaration of the pandemic, countries such as Iraq, Egypt, Iran, and India began to register clinical trials with the US clinical trial registration site ClinicalTrials.gov and the WHO's clinical trial registration platform. The publication of the results of the first clinical trial of ivermectin for COVID-19 in the world was an observational study conducted at four related hospitals in South Florida, USA. The mortality rate of 173 patients in the ivermectin group was 15.0%, which was significantly ($p=0.03$) superior to 25.2% of 107 patients in the control group. This result was published as a medRxiv preprint on the 6th of June 2020, but its value was not recognized at the time because it had not yet been peer reviewed. Following peer review, it was published without any changes in the prestigious journal *Chest* on the 13th of October.

Since then, numerous clinical trials have been conducted in various countries around the world. As of the 30th of January 2021, a total of 91 trials in 27 countries has been recorded at these registration sites. There are 43 trials in phase 3 and 27 trials in phase 2, along with 17 observational studies. This includes 80 trials being conducted for therapeutic purposes and 11 for the purpose of preventing the onset of disease in close contacts and healthcare professionals.

Furthermore, by the 27th of February, the results of 42 clinical trials, including approximately 15,000 patients (both registered and unregistered studies) have been subjected to a meta-analysis after exclusion of biasing factors. It was found that 83% showed improvements with early treatment, 51% improved during late-stage treatment, and there was an 89% prevention of onset rate noted. This confirms the usefulness of ivermectin. Since it is a meta-analysis based on 42 test results, it is estimated that the probability of this comprehensive judgment being a mistake is as low as 1 in 4 trillion. In addition, two separate meta-analyses also showed the

usefulness of ivermectin and their conclusions were presented to the WHO and the US FDA with a request for an expansion of the indication of ivermectin in the treatment of COVID-19.

In Japan, Kitasato University has been conducting a doctor-initiated phase 2 clinical trial, since September 2020. However, the progress of the study protocol enrolling a total of 240 patients (120 in the ivermectin group and 120 in the placebo group), has been slow. At this rate, there is concern that the clinical trial will be concluded after a time in which the COVID-19 pandemic converges. Unlike clinical trials conducted by pharmaceutical companies, lack of funds and human resources are the main factors behind the delay in the progress of such clinical trials. Support is being sought on all sides. Ivermectin has been used for more than 30 years with more than 3.7 billion doses dispensed in Africa and Central and South America to control neglected tropical diseases (NTDs). It is also widely used in elderly care facilities to treat scabies in developed countries. Since it has been used so extensively, pharmaceutical companies cannot expect to earn enough money to recover invested funds, even if further development is conducted to obtain an indication for COVID-19.

In this pandemic, which qualifies as an important national security issue requiring multiple state of emergency declarations, there is no therapeutic drug available for treatment or prevention purposes. Ivermectin, which has already been approved and widely used, is found to be effective. Although ivermectin is a potential candidate drug, the current situation is that pharmaceutical companies are not expanding its indications to include COVID-19. Universities and medical institutions unfamiliar with drug development are conducting small-scale clinical trials initiated by doctors. There seems to be a very restricted and uneager approach to the situation.

This review is written with the hope of increasing the understanding and support of all parties, by explaining the current situation in which doctors and researchers all around the world are actively attempting to expand the indication for ivermectin as a therapeutic/preventive drug for COVID-19. It is hoped that ivermectin will be utilized as a countermeasure for COVID-19 as soon as possible.

1. Trends in Novel Coronavirus Infections

1) Outbreak and early spread of novel coronavirus infection

The first case of novel coronavirus infection was confirmed¹⁾ in Wuhan City, Hubei Province, China on the 17th of November 2019 and a warning was issued as a pneumonia of unknown cause. However, it was one and a half months later, on the 31st of December 2020, that Wuhan City authorities reported²⁾ human-to-human transmission to the World Health Organization (WHO). It was confirmed³⁾, on the 7th of January 2020, that the cause was the novel coronavirus.

On the 11th of January, the Chinese government reported to the WHO that the outbreak was related to the South China Seafood market in Wuhan. It was speculated that live wild animals sold in the same market were the source of the infection. The market was closed on the 1st of January, making it impossible to pursue the source of infection. However, samples taken during the previous month showed positive test results. The first cases outside of China were confirmed in Thailand⁴⁾ on the 13th of January, followed by Japan⁵⁾ on the 15th, and South Korea⁶⁾ on the 19th. All of these cases were Chinese patients or travelers from the city of Wuhan. It was therefore concluded that there could be no doubt that the source of this novel coronavirus infection was the area centered on Wuhan.

The WHO published⁷⁾ the Novel Coronavirus (2019-nCoV) Situation Report-1 on the 21st of January, when the number of affected people in China exceeded 250, calling attention to travel to China. The WHO's response at this stage was quick and appropriate. The day prior, a man in the United States who returned from China developed the disease⁸⁾, and the number of affected people in the world was 282 spanning four countries. Subsequently, eight doctors in Wuhan who warned of the outbreak of a new pneumonia at the end of the year were punished by the Chinese authorities for spreading false information. The Chinese government did not accurately announce the situation surrounding the outbreak. Consequently, the construction of a global epidemic prevention system was delayed, leading to the dire infection situation facing the world today.

A week later, in Japan, on the 1st of February, a Hong Kong man who disembarked from the "Diamond Princess" cruise ship on the 25th of January, turned out⁹⁾ to be infected with the novel coronavirus. Despite the ship being suddenly moved to off the coast of Daikoku Pier and placed under quarantine for 14 days, a large infection cluster of more than 700 passengers and crew members eventually manifested on the ship. Under such circumstances, Japan became a seriously infected country. On the other hand, many Japanese companies have branch offices in Wuhan and the emergency evacuation of Japanese residents had become an issue. Negotiations required to evacuate Japanese citizens from Wuhan, which was under lockdown, were difficult. From the first charter flight operated on the 29th of January to the fifth flight on the 17th of February, a total of 829 returnees arrived at Narita Airport where 9 persons (1.1%) tested positive¹⁰⁾ for 2019-nCoV by PCR methods.

Since unknown infectious diseases are spreading internationally and Japan is suffering direct damage, it is necessary to develop domestic laws to deal with such situations. On the 1st of February, the novel coronavirus infection was classified under "designated infectious diseases" (equivalent to class 2) in the "Act on Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Act)". This was enacted by stipulation of a government ordinance¹¹⁾ and as such the novel coronavirus was subject to Article 34 of the Quarantine Law as an infectious agent. By utilization of such designations¹²⁾, it became possible to deny entry to infected individuals and begin other measures such as the hospitalization of infected persons.

Under different circumstances, the transmission to Europe occurred when a group of 30 sightseeing guests departed Wuhan on the 16th of January and made a 9-day tour of Italy, Switzerland, and France on their return trip. One traveler became ill in the city of Rome on the same day, with her condition gradually worsening by the 21st. On the 23rd, two additional travelling companions with this person became ill in the city of Paris and were transported to emergency care facilities. This was the earliest case¹³⁾ that was judged to be 2019-nCoV positive in Europe.

WHO Director-General Tedros visited¹⁴⁾ China on the 27th of January to inspect the status of the novel coronavirus infection. Despite the fact that 2,798 people in 12 countries had been infected and the spread of the infection already predicted, he refrained from declaring a global pandemic due to Chinese government authorities downplaying the situation and being wary of any such declarations. Five days later, on the 1st of February, the infection spread to 24 countries, with about 12,000 infected people confirmed, and the situation worsened rapidly. On the other hand, the crisis management department of the WHO issued, based on past experience with the SARS (2002), Swine Flu (2009) and MERS (2012) epidemics, a notifying document¹⁵⁾. The document stated the need to prepare for the event of the 2019-nCoV infection spreading worldwide.

In the United States, which would later become the world's largest outbreak, the Centers for Disease Control and Prevention (CDC) confirmed¹⁶⁾ the first case of human-to-human transmission in the country on the 30th of January. Then, as early as the 4th of February, the Department of Health & Human Services (HHS) made the decision, in accordance with the provisions of the Federal Food, Drugs and Cosmetics Act, that the novel coronavirus infection developed in Wuhan, China (2019-nCoV) be regarded as an emergency related to national security. As such, an emergency response system regarding the medical system and the supply and demand management of pharmaceutical products needed to be established¹⁷⁾.

This new type of coronavirus was named¹⁸⁾ severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Virus Taxonomy Committee, and the WHO announced¹⁹⁾ on the 11th of February that the SARS-CoV-2 infection was to now be officially named Coronavirus Disease 2019 (COVID-19). At that time, the number of affected people in China had already exceeded 75,000, and the WHO should have declared it a pandemic. Director-General Tedros missed this declaration opportunity and COVID-19 expanded rapidly across the entire world.

On the 20th of February, the world-renowned medical journal The New England Journal of Medicine (NEJM) published a paper²⁰⁾ alerting about the threat of COVID-19 in China and announced its intended cooperation in coping with the future difficulties that the world's medical community would soon be facing as a result. Thereafter, all COVID-19 related papers and articles published in the NEJM and other major medical journals the world over could be read²¹⁾ freely by non-subscribers. On the 28th of February the online edition of the NEJM, Bill Gates himself, under the auspices of the Bill & Melinda Gates Foundation, contributed²²⁾ a perspective article entitled "A Once-in-a-Century Pandemic?", and proposed a list of concrete actions that leaders

should immediately undertake. After enumerating important suggestions, he further stated that “there is no time to waste” as his conclusion.

According to the WHO tally²³⁾ on the 29th of February, the total number of infected people throughout the world reached 85,403. That number included 79,394 in China, 5,304 in another 53 countries, as well as 705 international passengers and crew of the Diamond Princess cruise ship. Further breakdown of the numbers was as follows: Korea 3,150 cases, Italy 888, Iran 388, Japan 230, Singapore 98, the United States of America 62, Germany and France at 57 each, and Spain with 32 cases.

2) COVID-19 pandemic

The WHO, after a period of long hesitation, decided to officially declare the situation a “pandemic”. The number of worldwide countries/regions where COVID-19 infection was confirmed reached 100 on the 8th of March 2020. The cumulative number of infected people²⁴⁾ exceeded 100,000. On the 11th of March, the Director-General recognized that it was a global pandemic and made a declaration²⁵⁾ that it corresponded to an “internationally concerned public health emergency”. When a pandemic is declared, the measures to be taken will differ from country to country, but international tourist restrictions and quarantine systems will invariably be strengthened. Under such conditions, countries much like Japan, which aim to become a tourism-oriented country, will suffer great economic pain as a consequence. In particular, the cumulative number of infected people in China, the country of origin of COVID-19, exceeded 80,000 on the 12th of March. Thereafter, countries around the world began to refuse entry to all travelers from China. It is estimated that the actual number of infected people in China was more than 10 times the number announced and a total of more than 2 billion people traveled during the Chinese New Year (January 25–31), including overseas travel. As a result, the novel coronavirus infection had spread widely both domestically and internationally.

In Japan, on the 13th of March, a “Special Measures for the Novel Coronavirus Infectious Disease” was enacted²⁶⁾ as part of a Supplementary Provisions Article 1–2 of the “Act on Special Measures for Novel Influenza and Others (Act No. 31 of 2012)”. However, by this time, the cumulative number of infected people in Japan had already reached 675. The government established the “Headquarters for Novel Coronavirus Disease Control” as part of the Cabinet Secretariat on the 26th of March and issued the “Basic coping policy for measure against new coronavirus infection” on the 28th of March. This was carried out in order to better enhance cooperation between governmental offices. However, in order to control the spread of infection in Japan and the increase of infected people from abroad, it was necessary to implement emergency measures from the 7th of April to the 6th of May. In Japan, this period also includes a timeframe that spans a traditional long period of sequential national holidays. The state of emergency²⁷⁾ was issued for Tokyo, Osaka, Saitama, Chiba, Kanagawa, Hyogo and Fukuoka.

In the United States, a national state of emergency²⁸⁾ regarding COVID-19 was issued when the cumulative number of infected people in the country exceeded 1,200 and it was reported that there was a heightened sense of caution amongst the population. However, the cumulative number of the infected people, after exceeding 10,000 on the 20th of March, increased rapidly to 31,573 on the 23rd, 51,944 on the 25th, and 68,334 on the 27th. The number continued to rise and eventually exceeded China and Italy when it reached 85,228 on the 28th of March²⁹⁾, becoming the highest in the world.

Thereafter, the number of infected people increased rapidly in the United States and European countries and the cumulative number of infected people worldwide exceeded 750,000 on the 31st of March: 140,640 in the United States, 101,739 in Italy, 85,195 in Spain, 61,913 in Germany, 43,977 in France, and 41,495 in Iran, *etc.* However, in China, the peak of the first wave had already passed, the number of new cases had begun to decline, and the cumulative number of cases had now reached 82,545.

The cumulative number of infected people in the world exceeded 1 million on the 2nd of April, 2 million on the 16th, 3 million on the 28th, 4 million on the 12th of May, and 5 million on the 21st. After that, there were 10 million people on the 29th of June, 20 million on the 11th of August, 40 million on the 20th of October, 60 million on the 1st of December, and over 80 million on the 31st of December 2020. When the state of increase is graphed, a downwardly convex curve is created, but no remarkable plateau is observed. Additionally, it is not possible to clearly distinguish between the first, second, and third waves. Attempts to distinguish and classify the wave pattern tend to reveal a convergence around the 20th of May 20, the second wave beginning around the 15th of June, and the third wave starting around the 20th of October (even before convergence of the second wave). From that point on, the third wave appears to continue until the present day.

COVID-19 had spread to more than 220 countries/regions around the world in a short period of time, affecting 103 million people (morbidity rate of 1.31%) by the 31st of January 2021, of which 2.22 million died (mortality rate of 2.16%), causing catastrophic damage³⁰⁾. Table 1 shows the morbidity as the cumulative number of infected people and the number of deaths or mortality in major COVID-19-infected countries. The most severe situation is in the United States, where the infection rate is equivalent to 1 in 12.5 of the 331 million population. Specifically, 26.67 million people are affected (morbidity rate of 8.1%), 450,000 people have died (mortality rate of 1.7%), and the number of new cases per day, reaching as high as 250,000 at one point in time (but it is now suppressed to 70,000 or less).

The second most impacted region in the world is India, with 10.74 million infected and more than 150 thousand deaths. Brazil is the third most impacted with 9.17 million infected and more than 220 thousand deaths and Russia is fourth with the number of infected people as high as 3.83 million. In Russia, however, the death toll is reported to be limited to 70 thousand. The second

Table 1. Global COVID-19 Affected and Dead Situation [As of the 31st of January 2021]

| Rank | Country | Population* ¹ | Number of affected* ² | Morbidity (%) | Number of deaths* ³ | Mortality (%) |
|------|--------------|--------------------------|----------------------------------|---------------|--------------------------------|---------------|
| 01 | USA | 331,002,651 | 26,675,015 | 8.06 | 450,403 | 1.69 |
| 02 | India | 1,380,004,385 | 10,747,091 | 0.78 | 154,312 | 1.44 |
| 03 | Brazil | 212,559,417 | 9,176,975 | 4.32 | 223,971 | 2.55 |
| 04 | Russia | 145,934,462 | 3,832,080 | 2.63 | 72,697 | 1.90 |
| 05 | UK | 67,886,011 | 3,796,088 | 5.59 | 105,571 | 2.78 |
| 06 | France | 65,273,511 | 3,177,879 | 4.89 | 75,862 | 2.39 |
| 07 | Spain | 46,754,778 | 2,809,021 | 6.01 | 58,573 | 2.09 |
| 08 | Italy | 60,461,826 | 2,541,780 | 4.20 | 88,279 | 3.47 |
| 09 | Turkey | 84,339,067 | 2,470,901 | 2.93 | 25,865 | 1.05 |
| 10 | Germany | 83,783,942 | 2,217,234 | 2.65 | 57,512 | 2.59 |
| 11 | Columbia | 50,882,891 | 2,086,806 | 4.10 | 53,650 | 2.57 |
| 12 | Argentina | 45,195,774 | 1,922,264 | 4.25 | 47,931 | 2.49 |
| 13 | Mexico | 128,932,753 | 1,841,893 | 1.43 | 156,579 | 8.50 |
| 14 | Poland | 37,846,611 | 1,508,679 | 3.99 | 37,082 | 2.46 |
| 15 | South Africa | 59,308,690 | 1,449,236 | 2.44 | 43,951 | 3.03 |
| 16 | Iran | 83,992,949 | 1,411,731 | 1.68 | 57,889 | 4.10 |
| 17 | Ukraine | 43,733,762 | 1,216,278 | 2.78 | 22,628 | 1.86 |
| 18 | Peru | 32,971,854 | 1,133,022 | 3.44 | 40,857 | 3.61 |
| 19 | Indonesia | 273,523,615 | 1,066,313 | 0.39 | 29,728 | 2.79 |
| 37 | Japan | 126,476,461 | 383,083 | 0.30 | 5,546 | 1.45 |
| 83 | China | 1,439,323,776 | 89,430 | 0.01 | 4,636 | 5.18 |
| 86 | Korea | 51,269,185 | 77,850 | 0.15 | 1,414 | 1.82 |
| | Whole World | 7,843,089,447 | 103,112,368 | 1.31 | 2,228,192 | 2.16 |

*¹ Estimated by UN Population Division*² Cumulative number of affected persons*³ Cumulative number of deaths

and third waves of the epidemic are also recognizable in Europe, with a cumulative total of over 3.7 million infected in the UK, 3.1 million in France, 2.8 million in Spain, 2.5 million in Italy and 2.2 million in Germany. These figures have also recorded 50,000–100,000 deaths.

In Table 1 the morbidities of COVID-19 in 19 countries with more than 1 million infected cases are shown. Compared to the global prevalence rate of 1.31%, several countries showed more than tripled rates: the United States at 8.1%, Spain at 6.0%, the United Kingdom at 5.6%, France at 4.9%, Argentina at 4.3%, and Italy at 4.2%. Despite preventive measures such as lockdowns and restrictions on gatherings being taken against the spread of infections in these countries, the continued spread of the infection could not be controlled.

On the other hand, the ratio of deaths among infected people is exceptionally high in Mexico at 8.5% and serious situations exist in Iran, Peru, Italy, South Africa, Indonesia, the United Kingdom, Germany, Colombia, and Brazil where mortality rates of more than 2.5% are recognized.

3) Recent situation in Japan

Japan was impacted by a large third wave where the number of new cases per day exceeded 3,500. Therefore, an emergency declaration was issued on the 8th of January 2021 in Tokyo and its surrounding three prefectures of Chiba, Kanagawa, and Saitama. Then, on the 14th of January, the declaration was expanded³¹⁾ to include Kyoto, Osaka, Tochigi, Gifu, Aichi, Hyogo, and Fukuoka prefectures. The declaration also requested the shortening of business hours for restaurants and encouraged companies to allow their employees to work remotely from home by use of the internet. By the 31st of January, the number of infected people in Japan was at 383,000, the 37th highest in the world, and the number of deaths was kept low at 5,546 (mortality rate of 1.45%). However, it is difficult to prevent the spread of infection over a short period of time, due to the confirmed invasion and existence of mutant strains from overseas. In order to prevent the spread of COVID-19 infection, the government revised the “Act on Special Measures for New Influenza and Others” and its enforcement order. Additionally, an amendment³²⁾ of the “Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Infectious Diseases Control Law)” was carried out. This was followed by a revision³³⁾ of the “Basic Coping Policy for Measures against New Coronavirus Infection” in an attempt to enhance effective countermeasures. Despite these actions, the number of people in the downtown area and the amount of congestion created by public commuting did not decrease as expected. Although the number of new cases has been slowly declining the preparedness of medical facilities and attitudes towards medical care have not been improved.

It is reported that the SARS-CoV-2 mutant strain³⁴⁾, which became apparent in the UK from the beginning of December 2020, has a 1.7 times higher infectivity than the conventional strain. It has already spread to other countries, causing a rapid increase of infected people. According to CDC documents³⁵⁾, the mutant strain was also detected in the United States at the end of December, and British researchers warned that it is not only more infectious but also carries an increased mortality risk. In addition to the mutant strain of the United Kingdom, different types of mutants continued to appear in mid-December in South Africa and subsequently spread to other countries. Other mutants detected in Brazil have moved to both Japan and other European countries in January 2021. The infectivity and pathogenicity of each mutant strain is being investigated³⁶⁾ extensively and the susceptibility of each of the newly developed vaccines is also being examined.

2. Current Status of Therapeutic Agents and Vaccines for COVID-19

1) Search for therapeutic agents and permission for emergency use

The strong infectivity and lack of effective therapeutic agents are the reasons why COVID-19 has continued to spread all over the world for more than one year. However, it is not a fulminant-type of infectious disease that presents with severe symptoms and causes death in a short

amount of time like smallpox or various hemorrhagic fevers. Nevertheless, as COVID-19 symptoms progress, it may cause death by means of serious respiratory failure and thrombosis^{37,38)}. In addition, it is a disease that causes various ongoing prognostic symptoms called “post-acute sequelae of SARS-CoV-2 (PASC)”, or “chronic COVID syndrome (long COVID)”. Manifestations include serious fatigue, alopecia³⁹⁾, cardiovascular disorders⁴⁰⁾, deterioration of memory, and olfactory/taste disorders⁴¹⁾ that may persist for long periods of time even after recovery.

To date, anti-inflammatory treatment of COVID-19 with steroids such as dexamethasone⁴²⁾ has been considered to be effective in alleviating symptoms as symptomatic treatment. No confirmed effective therapeutic drug to suppress SARS-CoV-2 virus proliferation, cell binding or intracellular invasion, has yet been identified and the development of such a compound is desired. However, in order to create a completely new therapeutic drug targeting the SARS-CoV-2 virus, it is necessary to begin with the construction of exploratory systems and make yearly research and development (R&D) plans to evaluate any such drugs. It is not possible to respond to a pandemic of acute illness occurring in hundreds of thousands of patients in such a short period of time.

Therefore, an attempt has been made to search for a chemical entity that has a therapeutic effect or a symptom-relieving effect on COVID-19 from among existing drugs⁴³⁾. The term “repurposing” is used to mean “use for another purpose (indication)” or “off-label use”. Repurposing was attempted more than once in the past. This was the case with the SARS outbreak in 2002 that began in Guangdong, China, and eventually spread to Vietnam and Canada with more than 8,000 infected and more than 770 dead. It was also the case in the Middle Eastern respiratory syndrome (MERS) outbreaks in Saudi Arabia, Jordan, the United Arab Emirates, Qatar and other Middle Eastern countries (including a few cases in France, Germany, and Italy). Attempts were made to treat the outbreaks with existing anti-influenza drugs, but they were met with little success. Attempts⁴⁴⁾ are now being made to search for therapeutic drugs for COVID-19 from amongst other approved drugs.

ClinicalTrials.gov in the United States is a clinical trial registration site operated by the US National Library of Medicine. It is the most trusted and used site in the world because the submitted clinical trial data is examined for its conformity with the requirements provided in the Federal Register⁴⁵⁾ before its citation, and the registered items are updated frequently in real time.

By the 20th of April 2020, there were 605 clinical trials in 557 subjects registered on the site for COVID-19. Among the listings were the following: 79 trials of the antimalarial drugs hydroxychloroquine and chloroquine, 9 trials of the antirheumatic drug tocilizumab, 5 trials of the anti-influenza drug favipiravir, 4 trials of the anti-AIDS combination drug lopinavir/ritonavir, 9 trials of the anti-Ebola hemorrhagic fever drug remdesivir under development by Gilead, 9 trials of the anti-polysclerosis drug interferon β 1, and others. At this time, the subject of this review, 4 clinical trials of ivermectin have been registered: one from the University of Baghdad in Iraq in a study⁴⁶⁾ to investigate the effect of adding ivermectin to a combination of hydroxychloroquine

and azithromycin, and three studies by Tanta University in Egypt to investigate the effect of ivermectin in combination with three different drugs. It was never imagined that more than 50 other trials would also eventually ensue.

Apart from the progress of such clinical trials, the US Food and Drug Administration (FDA) announced on the 28th of March 2020 that the “repurposing” of two drugs was to be carried out. Chloroquine and hydroxychloroquine, were to be made available for use in the treatment and prevention of COVID-19. This was achieved by the granting of special permission under an Emergency Use Authorization (EUA)⁴⁷⁾ process based on the emergency response system under the authority of the U.S. Department of Health and Human Services (HHS). On the same day, the cumulative number of infected people in the United States exceeded that of China and Italy and was the highest in the world. The use of the EUA system was praised. Following that, in the United States, also based on the EUA, remdesivir⁴⁸⁾ on the 1st of May, convalescent patient’s plasma⁴⁹⁾ on the 23rd of August, bamlanivimab, a monoclonal antibody drug jointly developed by Eli Lilly and Abcellera Biologics in Canada on the 9th of November⁵⁰⁾, and an antibody cocktail⁵¹⁾ developed by Regeneron on the 21st of November, all became available for possible use in the treatment of COVID-19. However, the EUA process does not take into consideration or require materials to prove effectiveness and safety. Due to political and economic influences, such investigations are not conducted prior to permission for use being granted. Consequently, it later became apparent that some of the medicines authorized under the EUA did not always produce the expected clinical effects. For hydroxychloroquine and chloroquine, the FDA announced the cancellation of the EUA in a News Release on the 15th of June, less than three months after the EUA was initially issued. Hydroxychloroquine and chloroquine, the lopinavir/ritonavir combination drug, tocilizumab, and interferon β 1 were all found to have limited efficacy as therapeutic agents for COVID-19, based on the results of a large-scale clinical trial referred to as the Solidarity trial⁵²⁾ by the WHO. Although there were previous reports of negative test results regarding the effects of monoclonal antibodies and convalescent patient’s plasma, it has recently been reported that positive results have been obtained in other large-scale trials.

Although dexamethasone is not included in the EUA, its use is recommended by the COVID-19 Treatment Guidelines of the NIH⁵³⁾ and the Infectious Diseases Society of America (IDSA)⁵⁴⁾. The reason why dexamethasone was not designated as part of the EUA is that it is a drug that has already been approved by the FDA, and it is judged that the treatment of lung inflammation in severely ill patients with COVID-19 is already permitted as an “off-label use”. It is further explained that this drug has been widely used as a generic drug for a long time and it was judged that there is no pharmaceutical company that performs the complicated application procedures required to expand the indication of the drug for COVID-19. Hydroxychloroquine has also been used clinically for a long period of time and there are many generic formulations of it available. If it had also been managed as an “off label use” drug, in a similar approach to that used

with dexamethasone, the situation that resulted in the revocation of the EUA designation could have been avoided. There is criticism of hydroxychloroquine being treated differently under the confusion of the emergency circumstances surrounding the pandemic.

A randomized, double-blind, placebo-controlled trial (NCT04280705) on remdesivir was conducted by the Adaptive COVID-19 Treatment Trial (ACTT-1) Study Group. It was organized at 60 facilities in 10 countries. The final result was published⁵⁵⁾ and stated that the average recovery period was 10 days in 541 subjects in the study group and 15 days in 521 subjects in the control group. This indicates that remdesivir was significantly superior ($p < 0.001$) in its desired effects. As a consequence, the FDA changed the handling of remdesivir from EUA-designated to that of an officially approved drug⁵⁶⁾. It should be noted here that EUA designation is valid only under the emergency response system issued by the HHS, and EUA designated medicines cannot be used again under normal circumstances once the designated emergency situation ceases to exist.

2) Vaccine development and clinical use

By the 30th of April 2020, there were 10 clinical trials of vaccines registered at ClinicalTrials.gov. This includes the 3 successfully developed vaccines to date: two mRNA vaccines from Moderna and Pfizer/BioNTech, and one vector vaccine from Oxford University/AstraZeneca. In addition to these three, one vaccine each by a United States and a Canadian venture company, and five other vaccines by Chinese companies, have also been registered. In other areas, as part of a completely new approach, 18 trials were also registered in order to study the clinical effects of convalescent plasma obtained from patients cured of COVID-19.

Vaccine research and development, which is regarded as the most important factor in COVID-19 countermeasures, has progressed smoothly. In the United States, the FDA issued EUA to Pfizer/BioNTech's BNT162b2 on the 12th of December, and to Moderna's mRNA-1273 on the 18th of December. The vaccination process is already underway for medical workers who are at high risk of infection and for the elderly population who are more likely to become seriously ill when infected. In the United Kingdom, AstraZeneca's AZD1222 was approved on the 30th of December and vaccination has already begun. The European Union (EU) approved BNT162b2 on the 21st of December, and mRNA-1273 on the 6th of January 2021. However, the approval of AZD1222 was delayed secondary to problems with supply contracts and approval was not granted until the 29th of January. It has also been reported that Russia and China have begun vaccinations utilizing their own internally developed vaccines and are in fact carrying out "vaccine diplomacy" by supplying their vaccines to other developing countries that have not yet obtained any vaccine supply contracts with the initial three previously mentioned companies above. In response to their own national crisis management, Israel signed a contract to obtain vaccines very early on and publicized their own national vaccination approach; theirs was admirably the fastest

reaction to the crisis throughout the entire world. The WHO aims to purchase a vaccine against COVID-19 through the humanitarian “COVAX” program and supply it to developing countries where vaccines for inoculation are not available. Already, on the 31st of December 2020, the Pfizer/BioNTech vaccines were listed on the emergency drug list, and on the 15th of February, the vaccine manufactured by AstraZeneca/SKBio (Korea) was listed as the second vaccine⁵⁷⁾ for COVID-19.

The FDA issued an EUA⁵⁸⁾ for the third COVID-19 vaccine in the United States on the 27th of February 2021. The EUA allows the Janssen COVID-19 Vaccine (J&J Vaccine) to be distributed in the United State for use in individuals 18 years of age and older. The J&J Vaccine is manufactured using adenovirus type 26 as a vector to deliver a piece of DNA encoding for the spike protein of SARS-CoV-2. Humans can utilize the spike protein produced in the body to make antibodies against the virus. This particular vaccine is characterized by being able to be stored in a normal refrigerator for up to 3 months and stimulate the production of sufficient antibodies in the body with a single inoculation. In terms of safety, no special adverse reactions were observed in about 22,000 inoculations. Its efficacy, in about 19,000 inoculations, suppressed the onset of moderate to severe/critical cases by 67%. Additionally, the vaccine was approximately 77% effective in preventing severe/critical cases 14 days after inoculation and 85% effective in preventing occurrence of the disease by at least 28 days following inoculation.

Vaccine development requires several years of testing to confirm efficacy and safety, as well as evaluate the adequacy and sustainability of any imparted acquired immunity. In principle, it is not possible to develop a vaccine in a short period of time in order to respond to a rapidly out of control pandemic such as COVID-19. Vaccine use was approved as an emergency response given the extraordinary circumstances created under the COVID-19 pandemic. As such, safety and effectiveness have not yet been sufficiently confirmed. It will require an extended amount of time for people around the world to acquire immunity to COVID-19 once vaccination becomes commonplace, and acquired immunity does not always persist for long periods of time. Therefore, it has also been advocated that the development of an effective therapeutic drug for COVID-19 is essential.

Infection with the SARS-CoV-2 mutant, which was 1.7-fold more infectious, was confirmed in the United Kingdom, and a warning was issued⁵⁹⁾ by the European Center for Disease Prevention and Control (ECDC) on the 20th of December 2020. The mutation can be traced back to the 20th of September and it has been reported that it may have contributed to the rapid expansion of the second wave in Europe since October. The emergence and rapid increase of mutant strains have also been observed in South Africa and it is estimated⁶⁰⁾ that the first case can be traced back to October. In Japan, the quarantine was strengthened by designating the United Kingdom, on the 23rd of December, and South Africa, on the 25th of December, as mutant strain endemic countries. On the 28th of December, at the Narita Airport Quarantine Station, a mutant strain was detected in

a patient who had previously stayed in South Africa. In Brazil, a mutant strain was detected around the 20th of December and it was confirmed that the infectivity was rather strong. Subsequently, just such a mutant strain was later brought into Japan⁶¹⁾, detected by quarantine services, by a traveler from Brazil on the 10th of January 2021.

Although there are concerns that the protective effects of the various vaccines against mutant strains will be diminished, Moderna announced⁶²⁾ on the 25th of January that their vaccine maintains its neutralizing activity against both the British and South African mutants. Similarly, Pfizer, jointly with BioNTech, announced⁶³⁾ on the 27th January that they proved *in vitro* that their vaccine demonstrates no changes in effects of antibody production in the presence of key mutations of both the UK and South African mutants. On the other hand, in South Africa, the AstraZeneca vaccine supplied by the United Kingdom was found to have a weakened protective effect against mutant strains; as a result, vaccination with this particular vaccine was suspended⁶⁴⁾ on the 7th of February.

In Japan, the mRNA vaccine by Pfizer/BioNTech was approved⁶⁵⁾ as a special case consideration on the 14th of February. This vaccine also requires special handling in that it must be kept at an ultra-low temperature of -70°C during storage/transfer. Therefore, preparations for inoculation at the municipal level of prefectures are proceeding at a very rapid pace. There is a contract to receive a supply of the vaccine for 72 million people by the end of the year. However, the syringes for the actual vaccination process need to be procured in Japan. Since the vaccine solution remains in the syringe barrel, it is possible to administer 6 doses from a single bottle in Europe and the United States. The Japanese government has been negotiating with Pfizer, because it turns out that each vial can be used to administer only 5 doses in Japan. There is a concern that the initial theoretical 72 million people supply number will actually turn out to be for only 60 million people. Further behind this inconvenience is a long history of unfortunate incidences surrounding vaccines in Japan: involving diphtheria vaccinations in 1948, the pertussis vaccine in the 1970s, the new triple vaccine (MMR) in 1989, and on the human papillomavirus (HPV) vaccine in 2013. In Japan, there have been many negative opinions complaining of side reactions as “vaccine-associated damage”. As a result, the R&D and clinical use of vaccines in Japan are the most delayed, secondary to administrative reasons, among developed countries due to the existence of such disputes. It is said that the inherent vulnerability of this vaccine drug collection problem needs to be significantly announced, discussed, and addressed. It is essential to raise sufficient awareness amongst the public as to the unavoidable risks/benefits of vaccines in the future—especially under such emergency circumstances as this current pandemic. In such times, it is desired to enable rapid R&D and clinical application of vaccine administration in one’s own home country. The Japanese Association for Infectious Diseases has a permanent “vaccine committee” of experts that can be utilized. Such a group can explain⁶⁶⁾ in detail the developmental status, mechanisms of action, efficacy, side reactions, general vaccination procedures throughout Japan, includ-

ing those associated with the COVID-19 vaccine, and play a key role in the process of raising awareness and promoting understanding of vaccines.

On the other hand, regarding the vaccine manufactured by AstraZeneca in the United Kingdom, Phase 1 and Phase 2 trials in Japan have been conducted since the end of August 2020. The inoculation of subjects has been completed. On the 5th of February, a domestic approval application⁶⁷⁾ was submitted. There is a contract to receive a supply of 120 million doses. More than 75% of the undiluted solution will be manufactured by JCR Pharmaceuticals in Japan. Daiichi Sankyo, Meiji Seika Pharma and KM Biologics are scheduled to carry out storage and delivery operations for the filling of vials of undiluted solution. Takeda Pharmaceutical, which develops vaccines manufactured by Moderna, announced⁶⁸⁾ that it started domestic phase 1 and phase 2 trials on the 21st of January. Takeda Pharmaceutical established a contract to receive a supply for 20 million people by June and an additional 5 million people by September (involving two doses). In addition, Takeda plans to produce more than 250 million doses annually in Japan following the technology transfer of the recombinant protein vaccine NVX-CoV2373 being developed by Novavax in the United States. The vaccine is scheduled to begin clinical trials in Japan from around the 20th of February. It is a promising prospect in that it has also shown an 89.3% efficacy in a phase 3 study in the United Kingdom.

On the 9th of February, the Cabinet Secretariat and the Ministry of Health, Labor and Welfare jointly announced⁶⁹⁾ that the government would oversee a wide variety of operations. Among them: the securing of vaccines, the distribution systems, a summary of advance preparations, including examinations, improvement of the inoculation system, needed responses to side reactions, safety measures, and rank vaccinations for use by local governments (such as prefectures) under a program known as “Vaccination for new coronavirus infections”. In addition, on the 12th of February, the Cabinet Secretariat’s Countermeasures Headquarters published a revised version⁷⁰⁾ of the “Basic Coping Policy for Measures against New Coronavirus Infection”. This followed the enactment of the “Special Measures for New Coronavirus Infectious Diseases” on the 3rd of February. The established policy is clearly shown regarding the status of COVID-19 infection in Japan, the status of vaccination, the status of medical institutions, and the problem of preventing further invasion of mutant strains from abroad. In addition to all these measures, the National Institute of Infectious Diseases has also started to provide information⁷¹⁾ entitled “About the New Corona Vaccine”. The goal is to aim for a higher rate of vaccination among the population by widely and accurately disseminating the necessary and appropriate information required by medical professionals and the general public.

Vaccination is the key measure required to curb the spread of COVID-19 infection. The government will set the vaccination cost at the national unified unit price for both the first and second vaccinations while preparing the third supplementary budget for 2020. It was decided to pay 2,070 yen per inoculation and that the entire amount would be borne out by the national treasury.

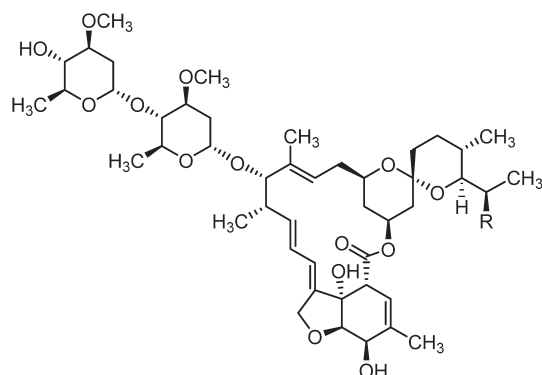
It has already been decided to spend 671.4 billion yen from the reserve fund for the purchase cost of vaccines, and 131.4 billion yen for the purchase cost of special freezers and other incidental costs (such as the construction of an inoculation recording system and to ensure the smooth ongoing operations of the inoculation process). In terms of the 77.6 billion yen to be used for the establishment of the system for local governments, it could be considered a part of the national budget expenditure necessary for ensuring national security. It also serves as a strong reminder as to the huge amount of expenditures required to protect the nation with vaccines. Vaccine-based social defense requires enormous budgetary measures as part of a national strategy, but immunological defense at the individual level also requires high medical costs. For example, it is estimated that the amount of a single dose of a monoclonal antibody will be as much as 250,000 yen. Plasma treatments of convalescent patients require additional screening costs to ensure seronegativity against the potential infusion of pathogens such as HIV, HBV, HCV, syphilis, and even other possible locally transmitted infections. An inexpensive and safe anti-infective drug that can provide therapeutic and prophylactic effects by oral administration is required. Since mild or asymptomatic patients who are being followed up either at homes or in locally designated hotels may suddenly have a change in health status and present with serious symptoms, it further increases the need for such a therapeutic agent.

3. Clinical Trial of Ivermectin for COVID-19

1) From the results of basic research to clinical trial planning

It was confirmed by Caly *et al.* of Royal Melbourne Hospital that ivermectin (Fig. 1), which has been approved by the FDA as an antiprotozoal drug, inhibits⁷²⁾ the growth of the SARS-CoV-2 virus in cultured cells *in vitro*. In the paper published online in “Antiviral Research” on the 3rd of April 2020, they suggested possible clinical efficacy in the use of ivermectin for COVID-19 in humans. One of the co-authors of the paper, Wagstaff of the University of Monash, is a virologist who found⁷³⁾ in 2012 that ivermectin specifically inhibits the enzyme importin α/β , which is involved in the process of translocation into the cell nucleus for HIV and dengue virus replication. It is obvious that they studied the action of ivermectin on the same RNA virus, SARS-CoV-2, and accurately proved SARS-CoV-2 growth inhibition by ivermectin. In response to this *in vitro* finding, clinical trials⁷⁴⁾ of ivermectin and actual clinical use have begun in various countries around the world. To date, more than 100 clinical studies have been conducted.

On the other hand, the IC_{50} concentration in their *in vitro* study to inhibit the growth of SARS-CoV-2 was about $2\mu M$ equivalent to 1,750 ng/mL [molecular weight of ivermectin (B1a component 90%, B1b component less than 10%) is calculated as 873.75]. This is 15 to 30 times higher than the attainable serum concentration by administration of a normal dose of $200\mu g/kg$ body weight (about 50 ng/mL on an empty stomach, and about 130 ng/mL after meals). Much de-

Fig. 1. Structure of ivermectin**Ivermectin**

(22,23-Dihydroavermectin B_{1a}, b)
 B_{1a}; > 80%, B_{1b}; < 20%

bate⁷⁵⁻⁷⁸) subsequently ensued stating that it is impossible to use ivermectin as a therapeutic agent for COVID-19 at its normal dose. In those discussions, it is also argued⁷⁹) that the antiviral action of ivermectin *in vivo* should not only suppress viral replication, but that the involvement of host defense functions should also be considered.

At Kitasato University, a university-wide “COVID-19 Countermeasures Kitasato Project” was established on the 19th of March with the aim of discovery of novel therapeutic agents for COVID-19. In response to the paper by Caly *et al.*, the project has been expanded

to conduct basic studies on the action of ivermectin on the SARS-CoV-2 virus. After obtaining several positive results, the implementation of clinical trials for ivermectin was considered. In that investigation, trends in global clinical trials registered at the US ClinicalTrials.gov are extremely valuable information; following the first registration by Baghdad University in Iraq on the 13th of April, there were three in Egypt, one in India, and two US universities. It was recognized in these doctor-initiated clinical trial protocols that objective items are set for evaluation of outcomes, such as reduction in mortality, shortened length of stay in the intensive care unit, shortened hospital stay, and elimination of the virus. These items are able to be expressed quantitatively. As such, bias can be avoided and real-world evidence obtained.

The cumulative number of people affected by COVID-19 worldwide exceeded 1 million on the 2nd of April 2020, a state of emergency was issued in Japan on the 7th of April, and the total number of people affected by COVID-19 worldwide was 2 million on the 16th of April. Under these circumstances when the pandemic conditions were rapidly worsening, there was illegal use and abuse of ivermectin in South America. It was traded on the black market and people were even taking ivermectin preparations marketed only for animal use. Therefore, the US FDA issued a warning⁸⁰) regarding the danger of using veterinary preparations. The pandemic continued to expand rapidly, with the world's cumulative number of affected people exceeding 3 million on the 28th of April. The situation in the United States also became much worse, leading to more than 1 million cumulative cases and surging deaths.

Kitasato University, based on the judgment that it is necessary to examine the clinical effect of ivermectin to prevent the spread of uncertain COVID-19, asked Merck & Co., Inc. to conduct clinical trials of ivermectin for COVID-19 in Japan. This company has priority to submit an application for an expansion of ivermectin's indications, since the original approval for the manu-

facture and sale of ivermectin was conferred to it. However, the company said that it had no intention of conducting clinical trials. As a result, Kitasato University decided to conduct a doctor-initiated clinical trial, the decision of which was published⁸¹⁾ on the 12th of May. Following the decision to start clinical trials in Japan, the status of clinical trials overseas was extensively investigated. It was then found, somewhat surprisingly, that 14 trials were already registered on ClinicalTrials.gov by the 25th of May. Among them, except for two trials in the United States, all studies were conducted in developing countries with a large number of poor patients. It was also then understood that the use of inexpensive ivermectin to treat COVID-19 could potentially yield significantly great benefits.

However, looking closely at the protocols of the trials in these developing countries, all of them are doctor-initiated. The scales of the trials are small due to a lack of funds. Even if the target patients could be randomized, complete blinding would not be possible due to a shortage of manpower. There are strong tendencies not to employ methods that involve multiple expensive PCR tests. Judgements were made to utilize methods of low cost, such as changes in oxygen demand and the number of days required to improve symptoms. In the case of new drug development conducted by a pharmaceutical company, the cost of clinical trials can be recovered from the sales profit of the new drug after marketing. So, even if it is a costly and labor-intensive investigation, it is actively adopted. However, in doctor-initiated trials it is not possible to hope for cost recovery and the trial is performed in the cheapest possible manner. Although these doctor-initiated trial results may appear at first glance to be of a poor quality and biased (to eyes familiar with the results of company-oriented clinical trials in the clinical development of traditional anti-infective agents), physicians involved in these trials are enthusiastic about avoiding bias and need to understand the attitude of seriously assessing the efficacy and safety of a study drug. It must be appreciated that they are truly striving to treat and prevent the onset of COVID-19 in patients, for non-profit motives.

As already mentioned above regarding the FDA's view on the clinical use of dexamethasone for COVID-19, the use of existing drugs such as ivermectin for diseases other than its approved indications in clinical practice is permitted as "off-label use".

As many clinicians are well familiar with clinical responses (real-world evidence) and understand the actual possibility of off-label use, they naturally wish for approval to be granted for a given disease. However, a particular public law requiring regulators to consider measures for off-label use was enacted in the United States in 2016. In this Act^{82,83)} named the "21st Century Cures Act", "Real world evidence" is stipulated in Section 3022 of Chapter 3 ("Development") as a quasi-Chapter C "Modern Trial Design and Evidence Development" section. A provision of Section 3021 requires that a "Novel clinical design" be devised to justify real world evidence. Thereafter, "real world evidence" obtained from such trials can be aimed at "repurposing" existing drugs. This stipulation warns that one should not disregard evaluations or reviews that adhere to

old-fashioned evidence-based medicine (EBM) that integrates clinical experience. Unfortunately, the law was not enforced due to the change of government in the United States and it is now too late due to the COVID-19 pandemic. This would have otherwise been the most appropriate proof of its legislative significance.

2) Development of clinical trials worldwide

Regarding the treatment of COVID-19, many doctor-initiated clinical trials are being conducted without registering with the official registration sites. The first clinical trial results for ivermectin were reported on a retrospective cohort study conducted at four related hospitals by Rajter and colleagues at the Broward Health Medical Center in South Florida, USA. It was reported in a medRxiv preprint on the 9th of June, and following peer review, published⁸⁴⁾ (without any changes) online on the 13th of October in the prestigious journal *Chest*. The subject of the study was a comparison of mortality between a 173 study group receiving ivermectin and a 107 control group receiving only conventional care (without receiving ivermectin). The mortality rate of the ivermectin group was 15.0%, which showed improvement that was significantly different from 25.2% of the control group ($p=0.03$). Improvements were remarkable in severe cases; the mortality rate of 38.8% in 49 patients treated with ivermectin was found to be significantly different ($p=0.001$) from that of 80.7% in 26 patients without treatment with ivermectin.

The results of the study of Rajter *et al.* being conducted in Florida, where the rates of morbidity and mortality are very high in a country facing the direst pandemic situation in the world, the United States, have great implications. We decided to follow all clinical studies of ivermectin against COVID-19 and explore its potential as a therapeutic agent. The most important source of information was the US ClinicalTrials.gov site, and the WHO database (International Clinical Trial Registry Platform: ICTRP) listing trials registered from around the world. Surprisingly, the ICTRP had already registered 11 studies (5 in India, 2 each in Iran and Spain, and 1 case each in Bulgaria and Nigeria), and 7 of these studies had already begun enrollment of patients. Since then, the number of registrations for both registration sites has been 5 in May, 18 in June, 7 in July, 12 in August, 5 in September, 3 in October, 5 in November, 5 in December, and 8 in January 2021. According to the total up to the 30th of January, there are 57 studies from 21 countries (2 studies were canceled) on the ClinicalTrials.gov site and 36 studies from 6 countries on the ICTRP. In total, 91 studies from 27 countries have been registered. As shown in Table 2, there are 15 studies in India: 10 are in phase 2 or phase 3 clinical trials and 5 are observational studies. 12 of these studies are for the purpose of treatments and the other 3 are for the purpose of preventing the onset of disease in medical staff and family members who came into contact with COVID-19 patients. The next largest number was in Egypt with 12, followed by Iran with 10, Brazil with 7, and Argentina with 5 studies. As shown in Table 1, India has the second highest cumulative number of COVID-19 infections in the world, and Brazil has the second highest number of COVID-

Table 2. Global clinical trials of ivermectin for COVID-19
[As of the 31st of January 2021]

| Country | Registered Studies *1 | Phase of clinical trial | | | | Observational studies | Purpose of studies | | Completed studies |
|--------------|-----------------------|-------------------------|----|----|---|-----------------------|--------------------|-------------|-------------------|
| | | 1 | 2 | 3 | 4 | | Treatment | Prophylaxis | |
| Argentina | 5 | | 2 | 1 | | 2 | 4 | 1 | 4 |
| Australia | 1 | | | 1 | | | 1 | | 0 |
| Bangladesh | 4 | | 2 | 1 | | 1 | 4 | | 2 |
| Brazil | 7 | | 3 | 3 | | 1 | 6 | 1 | 0 |
| Bulgaria | 1 | | 1 | | | | 1 | | 0 |
| Columbia | 4 | | 2 | 2 | | | 3 | 1 | 0 |
| Egypt | 12 | | 1 | 8 | | 3 | 9 | 3 | 2 |
| France | 1 | 1 | | | | | 1 | | 0 |
| India | 15 | | 3 | 7 | | 5 | 12 | 3 | 1 |
| Iran | 10 | | 1 | 9 | | | 10 | | 6 |
| Iraq | 2 | 1 | 1 | | | | 2 | | 2 |
| Israel | 1 | | | | | 1 | 1 | | 0 |
| Italy | 2 | | 2 | | | | 2 | | 0 |
| Japan | 1 | | 1 | | | | 1 | | 0 |
| Lebanon | 1 | | | | | 1 | 1 | | 0 |
| Mexico | 4 | | 1 | 2 | | 1 | 4 | | 1 |
| Nigeria | 1 | | | 1 | | | 1 | | 1 |
| Pakistan | 3 | | 1 | 1 | | 1 | 3 | | 1 |
| Peru | 2 | | 2 | | | | 2 | | 0 |
| Saudi Arabia | 1 | | | | | 1 | 1 | | 0 |
| Singapore | 1 | | | 1 | | | | 1 | 1 |
| Spain | 4 | | 2 | 2 | | | 3 | 1 | 0 |
| Thailand | 1 | | | | 1 | | 1 | | 0 |
| Turkey | 1 | | | 1 | | | 1 | | 1 |
| UK | 1 | | | 1 | | | 1 | | 1 |
| USA | 4 | | 2 | 1 | 1 | | 4 | | 0 |
| Zambia | 1 | | | 1 | | | 1 | | 1 |
| 27 Countries | 91 | 2 | 27 | 43 | 2 | 17 | 80 | 11 | 21 |

*1 Registered at US ClinicalTrials.gov (55 studies) & WHO ICTRP (36 studies)

19 deaths in the world. Therefore, ivermectin is being intensively investigated as a repurposing drug. On the other hand, in Egypt, the cumulative number of affected people is about 40% of that in Japan, and the problem of COVID-19 seems not to be very serious. The mortality rate there, however, is about 5.8%, which is more than double the world average. It can be said with confidence that many studies have been conducted to evaluate ivermectin as a key therapeutic agent in the treatment of COVID-19.

3) Search and analysis of global clinical trial results

The authors planned to summarize these clinical studies of ivermectin in COVID-19, registered worldwide, and describe the results in a review. Writing began in early October 2020 when the second wave of COVID-19 in Japan was appearing to converge, and the cumulative number of patients was starting to settle at about 86,000.

However, the monthly increase (about 17,000 between the end of September and the end of October) rapidly elevated to an increase of 47,000 by the end of November. The cumulative number of patients exceeded 100,000 toward the end of October and this clearly showed the appearance of the third wave. The number of affected people in the world has been steadily increasing. That number exceeded 20 million in early August 2020, and an increase of 10 million was observed over the span of one month. From mid-October, the increasing trend⁸⁵⁾ became even stronger, and the situation began to further worsen to the extent that an increase of 20 million people was now observed over a single month's time. The cumulative number of deaths exceeded 1.25 million, and the increasing trend became stronger from around mid-November, with no sign of convergence.

By the end of October, when the review concept for this article was finalized, 44 studies were registered with ClinicalTrials.gov, and 31 studies were registered with the WHO's ICTRP. However, only 10 studies completed their planned number of cases, and only 7 studies actually published their results. This was less than 10% of the total studies, making it premature to draw conclusions from those published data. In addition, our survey of the clinical studies was limited to those registered with registration sites. Therefore, it was necessary to devise a method for collecting the results of unregistered clinical studies such as the Rajter's team mentioned above. During this period, Andy Crump, the author of a review article⁸⁶⁾ discussing the various effects of ivermectin other than antiparasitic actions, forwarded a draft manuscript by Juan Chamie. The Chamie article described the distribution of ivermectin in Peru and the number of COVID-19 patients and deaths showing the actual situation regarding the widespread use of ivermectin in South America. Next, David Scheim, who has proposed the hypothesis⁸⁷⁾ that ivermectin suppresses peripheral thrombus formation by suppressing the hemagglutination reaction of the SARS-CoV-2 virus, contacted us with his proposal to collaborate with a group considering the clinical indications of ivermectin for COVID-19 in the United States.

4) FLCCC Alliance Activities

In the United States, EUA was given for chloroquine and hydroxychloroquine on the 28th of March. Ten doctors in the field of emergency care medicine, including Paul Marik of the East Virginia Medical School (EVMS) in Virginia, established the Frontline Covid-19 Critical Care Alliance (FLCCC)⁸⁸⁾ on the 5th of March. The purpose of this group was to treat COVID-19 patients with pulmonary inflammation by administering methylprednisolone intravenously, high-

dose vitamin C intravenously, vitamin B1 and low-molecular-weight heparin under a protocol called “MATH+”. Focusing on the excellent results of the clinical study of ivermectin by Rajter *et al.* in South Florida, the FLCCC investigated and analyzed the progress of the clinical studies of ivermectin being conducted in various countries around the world⁸⁹⁾. It was judged that the administration of ivermectin alone was sufficiently effective for the outpatient management and the prevention of onset in close contacts. Based on that decision, the FLCCC established a new protocol⁹⁰⁾ called “I-MASK+” on the 31st of October. It combines a single oral dose of ivermectin with the use of a mask to prevent the spread of the infection. It was reported⁹¹⁾ that ivermectin has the potential to resolve the COVID-19 pandemic worldwide. FLCCC inquired with us about the state of studies on ivermectin on COVID-19 in Japan. After being informed that Kitasato University began a doctor-initiated clinical trial on the 16th of September, the FLCCC requested to work closely by exchanging future information.

FLCCC’s President Pierre Kory was summoned⁹²⁾ as a witness by the Homeland Security and Governmental Affairs Committee of the US Senate on the 8th of December. At that time, he explained the results of the global trials of ivermectin in COVID-19 prevention and treatment, and requested an early expansion of indications for ivermectin to treat COVID-19 in the United States. In particular, Kory complained that ivermectin was listed in the COVID-19 Treatment Guideline⁹³⁾ established by the NIH on the 27th of August. However, the recommendation was negative (against use). The influence of the NIH is so strong in the US that doctors could not even carry out “off-label use” of ivermectin based on an individual patient’s clinical presentation or based on physician discretion. It was insisted that the situation be corrected by the NIH. In order to achieve this change, FLCCC’s Pierre Kory and Paul Marik, along with Andrew Hill, who represents the International Ivermectin Project Team (IIPT), met with the NIH Guidelines Committee on the 6th of January 2021 to discuss the guidelines on ivermectin. They explained the results of the global clinical studies for COVID-19 and recommended that the judgement “against” off-label use be terminated. As a result of subsequent intensive examinations, the NIH announced its revision of the guidelines on the 14th of January. According to the revision⁹⁴⁾, the previous recommendation of “recommends against the use of ivermectin for the treatment” of COVID-19, was revised to a neutral description of “there are insufficient data.....to recommend either for or against the use of ivermectin for the treatment”.

Following this revision, the FLCCC announced⁹⁵⁾ on the 15th of January that ivermectin was “upgraded” in the NIH guidelines under the title “Ivermectin is now one of the treatment options for physicians and prescribers”. Furthermore, in response to the fact that the statement of revision of the guidelines issued by the NIH on the 14th of January contained many factual misunderstandings, a public statement⁹⁶⁾ was issued on the 18th of January. The NIH published the updated COVID-19 treatment guidelines on the 11th of February, with the section on ivermectin have been rewritten in detail. The revision also included the clinical trial results used to review the guidelines.

The recent movement of the Infectious Diseases Society of America (IDSA) is the opposite

of such a revision by the NIH. Their first guideline⁹⁷⁾ issued on the 27th of April 2020 did not mention ivermectin. However, a new recommendation on ivermectin use (created on the 29th of January 2021) was added to the revised edition⁹⁸⁾ published on the 5th of February (Version 3.8.0). There are 19 recommendations. Item 18 is intended for critically ill inpatients and item 19 is intended for outpatients. In their descriptions, the IDSA Committee opposes the use of ivermectin outside of clinical trials, stating that these are “Conditional recommendations,” of “very low certainty of evidence”. This statement has not been corrected in the latest version (Version 3.10.0) issued on the 18th of February, and is inconsistent with the revision of the NIH guidelines. Traditionally, the NIH and the IDSA have coordinated on the diagnosis and treatment of infectious diseases and clinical evaluation methods for anti-infective drugs. The two have also usually carried out their respective activities based on a common approach. It is confusing to show differing guidelines between the NIH (the Governmental research administrative organization) and the IDSA (a specialized academic society). In fact, the recent issuance of the IDSA guidelines following the revision of the guidelines by the NIH, could be considered a fundamental denial of the efforts of the NIH and thereby contribute to a state of increased confusion. Given the problems that occur when clinical physicians do not administer ivermectin in accordance with the IDSA

Table 3. The excerpt of the “Summary of the clinical trials evidence for ivermectin in COVID-19” presented by the FLCCC Alliance as of the 11th of January 2021

as of the 11th of January 2021

Properties of Ivermectin

- 1) Ivermectin inhibits the replication of many viruses, including SARS-CoV-2, influenza, and others;
- 2) Ivermectin has potent anti-inflammatory properties with multiple mechanisms of inhibition;
- 3) Ivermectin diminishes viral load and protects against organ damage in animal models;
- 4) Ivermectin prevents transmission of COVID-19 when taken either pre- or post-exposure;
- 5) Ivermectin hastens recovery and decreases hospitalization and mortality in patients with COVID-19;
- 6) Ivermectin leads to far lower case-fatality rates in regions with widespread use.

Evidence Base Supporting the Efficacy of Ivermectin in COVID-19

Controlled trials studying the prevention of COVID-19 (8 trials completed)

- * 3 RCT's with large statistically significant reductions in transmission rates, a total of 774 patients
- * 5 OCT's with large statistically significant reductions in transmission rates, a total of 2,052 patients

Controlled trials in the treatment of both early and hospitalized COVID-19 patients (19 trials completed)

- * 5 RCT's with large, significant reductions in time to recovery or hospital length of stay, a total of 774 patients
 - * 1 RCT with a large, statistically significant reduction in rate of deterioration/hospitalization, total of 363 patients
 - * 2 RCT's with significant decreases in viral load, days of anosmia, cough, or time to recovery, a total of 85 patients
 - * 3 RCT's with large, significant reductions in mortality, a total of 695 patients
 - * 3 OCT's with large, statistically significant reductions in mortality, a total of 1,688 patients
- [RCT's = randomized controlled trials, OCT's = observational controlled trials). Every clinical trial shows a benefit, with RCT's and OCT's reporting the same direction and magnitude; nearly all are statistically significant.]

Number of Studies and Patients Among the Existing Clinical Trials of Ivermectin in COVID-19

- * 27 controlled trials, including a total of 6,612 patients have been completed using well-matched control groups
- * 16 trials, including over 2,500 patients, are prospective, randomized, controlled studies
- * 11 of the 27 trials have been published in peer-reviewed journals, 3,900 patients, remainder are in pre-print

guidelines, it is necessary to urgently revise such guidelines in accordance with the NIH guidelines.

In addition, the FLCCC Alliance summarizes and publishes the results of research and analysis of clinical trials of ivermectin for COVID-19 conducted worldwide. The first summary was published on the 22nd of December 2020. Its content has been kept up to date in a timely manner, with the addition of further information⁹⁹⁾ on the 11th of January 2021 (at the time of the writing of this review). Since this document summarizes the world situation in a very clear and concise manner, a portion is presented in Table 3. Based on the outcomes in a total of 6,612 patients enrolled in 27 clinical trials (8 for prophylactic and 19 for therapeutic purposes), ivermectin was found to prevent the development of disease in COVID-19-exposed patients, accelerate patient recovery, reduce the need for hospitalization, and reduce mortality. It encourages the clinical use of ivermectin for COVID-19.

Based on the results of such accumulated clinical trials, the FLCCC Alliance issued a public letter¹⁰⁰⁾ requesting a reconsideration of the protocol for the ivermectin clinical trials published by the University of Oxford on the 23rd of January. The letter argues that giving placebos to a control group of patients in trials already making use of existing off-label drugs does not ensure the life and health of clinical trial patients. These types of studies would be in violation of the fundamental principle of the Helsinki Convention. Ivermectin is an off-label drug and has already been shown to be effective in numerous clinical trials for COVID-19. It should be considered as a part of standard treatment. The study design is a placebo-controlled comparative study. Instead of using a placebo, the request was made to change the ethical setting and compare the timing, dose, or duration of treatment of ivermectin in COVID-19.

5) Meta-analysis of clinical trial results

During this COVID-19 pandemic, a major change has taken place in the fields of medical and natural science research in terms of the usual practices of the disclosure of information. It is now required to publish obtained test results as soon as possible. Before this, publishing in print was done in many specialized magazines and academic journals and a form of early publication by online services called advanced online publication, or electronic publishing, was done in a competing fashion. Specialized journals that were only published online without publishing in print were also extensively used and the publication of research results was becoming increasingly diverse. To date, one year has passed since the COVID-19 pandemic was declared. For example, a literature search for COVID-19 and SARS-CoV-2 on PubMed will result in more than 100,000 hits. And many of them are preliminary reports in advance of peer review—called pre-prints. There are first, second, and third epidemic waves all over the world. The rapidly changing areas of vaccine development, the emergence of mutant viruses, the appearance and exit of therapeutic drug candidates, *etc.*, are research results that cannot wait to be published in the traditional print format. The peer-reviewed process itself takes several months to complete. In many cases,

the research results are inevitably published in the form of preprints and then peer-reviewed, whereupon they will then remain as an official treatise.

Most of the clinical trial results of ivermectin for COVID-19 have been published as preprints. About 20 of them have been recognized as official treatises following peer review. Sometimes, the contents of the publication are not changed at all from their preprints, except in the form of some updates. The argument raised from regulatory authorities that preprinted publications do not always provide sufficient evidence is not correct. In fact, some treatises that have been peer-reviewed in advance and later published in print have been withdrawn at a later date. As a final point, it should be remembered that there is a difference in the publication method of a study for the purpose of early publication; the certainty of evidence should be judged by comprehensively evaluating the protocol described in the study, as well as the analysis of the results.

After carefully searching for, organizing, and analyzing the clinical trial results of ivermectin for COVID-19 announced in such preprints, a Twitter account called “@CovidAnalysis” was set up on the web on the 26th of November 2020. In the first edition of this site, meta-analyses of 19 clinical trials (including 8 randomized controlled trials) were displayed in bar graphs and forest charts. These serve as very powerful visual sources of data. On this site, new study results are being added, one by one, from researchers around the world. In such a fashion, the meta-analysis is being repeated and growing at the same time. For example, the second edition was updated to a meta-analysis of 22 trials on the 4th of December. By the sixth edition on the 16th of December, it had been updated to a meta-analysis of 26 studies. The amount of information available from this site is enormous. Medical professionals attempting to use ivermectin clinically for COVID-19 are collaborating together to build a large real-time database. The information on the site has reached its 37th edition¹⁰¹⁾ on the 27th of February 2021. By that time, the meta-analysis has been performed on 14,906 patients in 42 clinical studies (including 21 randomized controlled trials with 2,869 patients). It reported improvements of 83% in early treatment, 51% in late treatment, and 89% in the prevention of onset of disease. Based on the results of these 42 trials, it concludes that the probability of this judgment on ivermectin’s superior clinical performance being false is estimated to be 1 in 4 trillion.

Meanwhile, at IIPT, represented by a WHO consultant Andrew Hill of the Department of Pharmacology at Liverpool University, the results of 18 clinical trials conducted by 40 members from 13 countries (in their own clinical trial organization, totaling 2,282 subjects) were meta-analysed¹⁰²⁾. A report was issued only after carrying out a repeated examination of all the items to be analyzed, as well as the analysis methods to be used. In the meta-analysis of six of these randomized trials (of moderate to severely ill patients), the mortality rate of 14/650 (2.1%) in the ivermectin group was significantly lower ($p=0.0002$) than the mortality rate of 57/597 (9.5%) in the control group. It also confirmed excellent clinical improvement with ivermectin, showing a shorter hospital stay. According to a personal letter from Hill, the IIPT holds regular meetings for

the purpose of accumulating more data. Data was added for about 4,000 cases from six clinical trials on the 5th of February, and approximately 2,200 additional cases are expected by early March. It is predicted that additional clinical trial data for about 5,000 cases will be added by April. Among the source countries/regions of these data, there are ten developing countries and three developed countries (UK, France, and Spain). In the developed countries, clinical trials of vaccines and new antiviral drugs created by advanced science and technology are being conducted and there are no companies/organizations aiming to expand the indications for the repurposing of the existing drug ivermectin. In developing countries, however, enthusiastic studies on ivermectin are being conducted. If ivermectin, which is an inexpensive drug that is easily available, can cope with COVID-19, it has enormous implications for the possible treatment options available to the poorest communities in such countries. Kitasato University, in Japan, is conducting a doctor-initiated clinical trial, and its results, once obtained, will be added to the IIPT analysis.

When the results of such meta-analysis were obtained and collated with the clinical trial information collected so far, the meta-analysis results by more detailed experts were published¹⁰³⁾. Teresa Lawrie of The Evidence-Based Medicine Consultancy Ltd (EBMC), a UK medical statistics consultancy and WHO data analysis consultant, provides a professional meta-analysis in support of FLCCC recommendations. Based on the detailed examination of 15 of the 27 clinical trials covered by the FLCCC (consisting of 6 with low bias and 9 with moderate bias) she reported the meta-analysis results. The results utilize forest plots on mortality, symptom improvement, symptom exacerbation, the required period for recovery, period until PCR becomes negative, the length of hospital stay, the necessity of admission to the ICU or use of a ventilator, and serious side effects. It was concluded that the ivermectin group was superior in all analyzed parameters except for side effects. However, her conclusion was different from that of the NIH committee who performed an evaluation using the same test results.

6) Results of registered clinical trials

As of the end of January 2021, there were 55 clinical studies registered on ClinicalTrials.gov (with 2 exclusions) and 36 other clinical studies registered on the WHO site. This is a total of 91 clinical studies. Among these clinical studies registered (as seen in Table 2), 21 studies have already been completed, and the results of 18 have been published (Table 4). The order of publication in the table is the date of registration, and the study contents, judgment categories, and study results are briefly described. It is noted that most of the 18 studies^{104~121)} have been implemented in developing countries. These are areas where there has been much difficulty with COVID-19 countermeasures. Due to small sizes, some studies were completed in short periods of time. However, it can be said that the earnest desire to complete the studies as quickly as possible also confirms the efficacy of ivermectin in driving the progress of such studies. Of the 18 studies in the table, 13 showed that the ivermectin test group was significantly superior to the control group in

Table 4. Summary of the results of the registered clinical trials

| Registration No. | Main author | Country | Study | Study period | Outcome | Ivermectin group | Control group | Significance |
|----------------------|---------------------|------------|---------------|--------------|-----------------|------------------------|-------------------------|--------------|
| NCT04343092 | Gorial FI | Iraq | Phase 1 | 4/18 – 6/1 | Hospital stay | 7.62±2.75 (16) | 13.22±5.90 (70) | p=0.00005 |
| NCT04381884 | Krolewiecki A | Argentina | RCT Phase 2 | 5/18 – 9/29 | Viral eliminate | 72% (30) | 42% (15) | p=0.004 |
| NCT04390022 | Chaccour C | Spain | RCT Phase 2 | 7/31 – 10/9 | Symptoms | Σ =72 days (12) | Σ =158 days (12) | p<0.001 |
| NCT04392713 | Bukhari KHS | Pakistan | RCT | 3/15 – 6/15 | Viral eliminate | 37/41 (90.2%) | 20/45 (44.4%) | p=0.001 |
| NCT04399746 | Espitia-Hernandez G | Mexico | Pilot study | 5/15 – 6/10 | Symptoms | 0/28 (0.0%) | 7/7 (100%) | |
| NCT04422561 | Shouman WM | Egypt | RCT Phase 3 | 5/31 – 7/27 | Prophylaxis | 15/203 (7.4%) | 59/101 (58.4%) | p<0.001 |
| NCT04425850 | Carvallo HE | Argentina | Observational | 6/1 – 8/10 | Prophylaxis | 0/131 (0.0%) | 11/98 (11.2%) | p<0.0001 |
| NCT04425863 | Carvallo HE | Argentina | Observational | 5/1 – 8/30 | Mortality | 1/167 (0.59%) | National av 2.1% | |
| NCT04434144 | Chowdhury AT | Bangladesh | Observational | 5/2 – 6/5 | Symptoms | 41/60 (63.3%) | 30/56 (53.57%) | |
| NCT04446429 | Cadegiani FA | Brazil | RCT | 6/2 – 12/11 | Hospitalization | 0/110 (0.0%) | 27/137 (19.7%) | p<0.001 |
| NCT04523831 | Mahmud R | Bangladesh | RCT Phase-3 | 6/1 – 9/10 | Symptoms | 111/183 (60.7%) | 80/180 (44.4%) | p<0.03 |
| NCT04591600 | Hashim HA | Iraq | RCT Phase-2 | 6/1 – 10/19 | Symptoms | 3/70 (4.28%) | 7/70 (10.0%) | p>0.05 |
| NCT04646109 | Okumus N | Turkey | RCT Phase-3 | 5/11 – 9/2 | Symptoms | 14/30 (46.7%) | 11/30 (36.7%) | p=0.43 |
| NCT04668469 | Elgazzar A | Egypt | RCT | 6/8 – 10/30 | Symptoms | 193/200 (96.5%) | 124/200 (62.0%) | p<0.001 |
| | | | RCT | | Prophylaxis | 2/100 (2.0%) | 10/100 (10.0%) | p<0.05 |
| IRCT20200408046987N1 | Niaee MS | Iran | RCT Phase-3 | 6/1 – 7/15 | Mortality | 4/120 (3.3%) | 11/60 (18.3%) | p=0.001 |
| IRCT2011122400850N3 | Rezai M | Iran | RCT Phase-3 | 5/21 – 8/22 | Symptoms | 4.1 days (51) | 5.2 days (52) | p=0.018 |
| ISRCTN40302986 | Babalola OE | Nigeria | RCT Phase-3 | 4/23 – 10/6 | Viral eliminate | 5.33 days (42) | 9.15 days (20) | p<0.01 |
| CTRI/2020/06/026001 | Mohan A | India | RCT Phase-3 | 6/25 – | Hospitalization | 2/40 (5.0%) | 6/45 (13.3%) | p=0.27 |

RCT: randomized clinical trials, figure in brackets: number of patients, av: avarage

terms of judgment categories. There are concerns that the scale of the trials, the presence or absence of masking, and the judgment categories are biased. However, in the pandemic conditions of acute diseases such as COVID-19, where a difference between rapid deterioration and improvement of the patient's condition is clear, and the differences from the control group are also clear, it is unlikely that there will be a bias as seen in clinical trials of drugs for normal chronic diseases. As to the concern of “publication bias” (generally described as only positive results being reported and negative results being buried), it is not a likely scenario. All of the enrolled clinical studies shown in Table 4 are doctor-initiated clinical studies. None of these studies are company-oriented studies where there is a reporting obligation to the organization that bears the cost of the trial. Furthermore, some of these trials also include national security implications for the country in question. Therefore, associated publication bias is unlikely. In particular, for clinical trials registered with ClinicalTrials.gov in the United States, it must be taken into account that a report of results¹²²⁾ is required.

7) Unregistered clinical studies and mass distribution of ivermectin

The first clinical study of ivermectin in COVID-19 around the world was a retrospective analysis by Rajter *et al.* in South Florida, USA. It was an observational investigation with the result that ivermectin administration correlates with a reduction of in-hospital mortality due to COVID-19. When these findings spread on the web as a medRxiv preprint in early April of 2020, many clinical studies were then conducted at medical institutions around the world, having difficulty responding to the COVID-19 pandemic, to confirm the therapeutic and preventive effects of

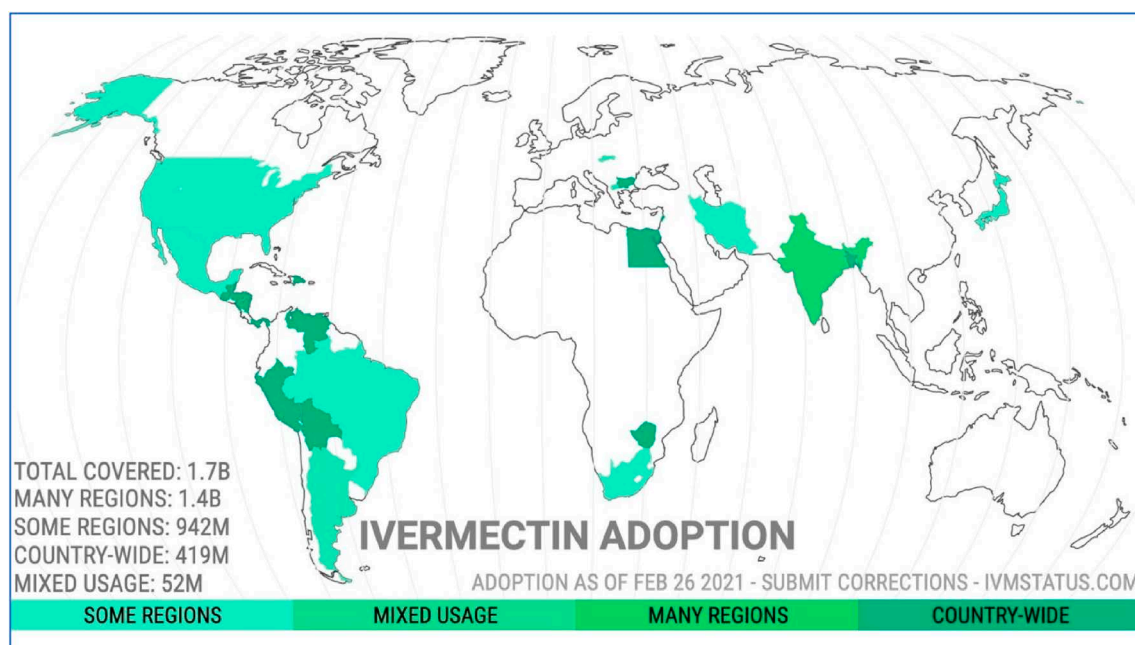
ivermectin. Following the publication of an extensive review of ivermectin's antiviral activity^{123,124)} and a commentary on its clinical application¹²⁵⁾ to COVID-19, many medical facilities around the world began clinical studies under approvals by institutional or regional ethical review boards. Clinical studies that are not registered with the official clinical trial registration sites are now being extensively conducted and the results^{126~132)} reported.

On the other hand, in Peru, the results of *in vitro* studies by Caly *et al.* and the clinical results of Rajter *et al.* were highly evaluated. Consequently, it was decided on the 8th of May to issue treatment guidelines for the administration of two drugs, hydroxychloroquine and ivermectin, in mildly ill patients, and three drugs, hydroxychloroquine, azithromycin and ivermectin, in moderately and severely ill patients with COVID-19. According to a detailed study¹³³⁾ by Chamie-Quintero *et al.*, Peru distributes packs containing ivermectin and other medicines to the public. In the Lima region, where distribution of the packs was delayed, it was confirmed that the infection rate of COVID-19 and mortality rate were significantly higher compared to the other eight regions where packs had been distributed earlier. In Peru, the Ministry of Defense, the Army, the Navy, the Air Force, and the Police have mass-distributed ivermectin through an operation against COVID-19 named "Mega-Operation Tayta (MOT)". These efforts resulted in a decrease in nationwide deaths by one fourteenth (1/14). However, that number started to increase after the distribution was stopped due to a change of government in November. It continued to further rapidly increased by 13 times as of the 1st of December. It is expected that this trend will continue to increase in the future (David Scheim personal communication)¹³⁴⁾. In Bolivia, a neighboring country of Peru, ivermectin for 350,000 people was distributed free of charge from the 12th of May. Paraguay placed restrictions on the sale of ivermectin. In Colombia, advocates sought for policy decisions to prevent ivermectin abuse. It is reported that ivermectin is also distributed in Brazil at the discretion of local governments, although not nationwide.

In the above-mentioned "@CovidAnalysis" meta-analysis site on the web, the world map shown in Fig. 2 was displayed on the summary page (from its 26th edition) on the 5th of February 2021. It indicates countries where ivermectin is being applied as a COVID-19 countermeasure. It illustrates the countries and provides information on each country. Figure 2 quotes the latest version on the 27th of February, notice that Japan was included in the category of "SOME REGIONS" in light green. It was included on the grounds based on an announcement by the Ministry of Health, Labor and Welfare, Japan on the 16th of June 2020. That announcement, in an English guidance document¹³⁵⁾, stated that ivermectin, which is available as a treatment for scabies in Japan, can be used off-label for COVID-19 in the clinical management of COVID-19 patients. However, since its indication has not yet been approved for ivermectin, it has been described that it should be used only after careful consideration by clinicians and patients. In Japan, as of June 2020, regulatory authorities have already approved the off-label use of ivermectin for COVID-19. We will accelerate clinical trials in Japan in order to obtain expanded indications as

Fig. 2. Countries where ivermectin is adopted for COVID-19

[quoted from Covid Analysis Version 37, Feb 27, 2021]

[<https://ivmmeta.com/>]

soon as possible.

The display in Fig. 2 distinguishes between cases (shades of green) where ivermectin is used throughout the country, where it is widely used, where it is used in a limited way, and where it is used in a mixed manner. Table 5 summarizes these distinctions and the conditions of use for each country. Ivermectin is used in the treatment or prevention of COVID-19 in 24 countries around the world. It has already been approved for nationwide use in 14 countries and there is an accumulation of conducted clinical study results for each of these countries. The number of countries has also been increasing since the beginning of 2021.

Ivermectin has already been provided free of charge to endemic areas of two diseases since 1987. The “Mectizan Donation Program; MDP” (in cooperation with the WHO) has distributed¹³⁶⁾ ivermectin to prevent the onset of river blindness and lymphatic filariasis. 300–400 million doses are distributed annually to approximately 70 countries/regions. A total of 3.7 billion doses have been widely distributed over 30 years. Very few serious side effects have been observed, and it is considered to be a drug whose safety has been sufficiently confirmed. Comparing 19 countries participating in the African Program for Onchocerciasis Control (APOC) with 35 countries not participating in it, has yielded interesting results. APOC participating countries were found¹³⁷⁾ to have a COVID-19 morbidity rate 8% lower and a mortality rate 28% lower than those of non-AOPC participating countries. In Africa, the incidence of COVID-19 disease per

100,000 population in countries using ivermectin for preventive chemotherapy (PCT) has been reported¹³⁸⁾. The rate is significantly lower ($p=0.017$) than in countries that do not have PCT. “Mectizan®” is the trade name of the dedicated ivermectin tablet used in the distribution program. Merck’s “Stromectol®” tablet is used for the treatment of fecal nematodes and scabies in the United States and in Japan. For animal treatments, tablets, ointments, liquids, and injections under the trade name “Ivomec®” are used to prevent disease damage caused by parasites and insects. More than 30 years have passed since it was placed on the market, and generic products are also used. Under the situation where ivermectin is distributed to prevent the spread of COVID-19 infection in South America, illegal ivermectin has entered the black market. This includes iver-

Table 5. Global ivermectin adoption for COVID-19 (as of the 26th of February 2021)
<https://ivmmeta.com>

| Country | State | Condition | Data on |
|-----------------|-----------------------|------------------------------|--------------|
| Argentina | mixed usage | | Jan 26, 2021 |
| Bangladesh | country-wide adoption | | |
| Belize | country-wide adoption | used for serious cases | Dec 18, 2020 |
| Bolivia | country-wide adoption | | |
| Brazil | used in some regions | | Jan 26, 2021 |
| Bulgaria | country-wide adoption | | |
| Czech | country-wide adoption | use in hospitalized patients | Mar 3, 2021 |
| Dominican Rep. | country-wide adoption | | Sep 30, 2020 |
| Egypt | country-wide adoption | | Nov 30, 2020 |
| Guatemala | country-wide adoption | | Jan 23, 2021 |
| Honduras | country-wide adoption | | Apr 23, 2020 |
| India | used in many regions | used in many states | |
| Iran | used in some regions | Manufacturing own ivermectin | |
| Japan | used in some regions | *1 & *2 see footnote | Feb 13, 2021 |
| Lebanon | country-wide adoption | | Jan 27, 2021 |
| Mexico | used in some regions | | Dec 29, 2020 |
| Nicaragua | country-wide adoption | | Jan 15, 2021 |
| North Macedonia | mixed usage | | Jan 15, 2021 |
| Panama | country-wide adoption | | |
| Peru | country-wide adoption | | May 8, 2020 |
| Slovakia | mixed usage | only late treatment | Jan 27, 2021 |
| South Africa | used in some regions | must apply approval to use | Jan 27, 2021 |
| USA | used in some regions | | Oct 31, 2020 |
| Venezuela | country-wide adoption | | |
| Zimbabwe | country-wide adoption | | Jan 28, 2021 |

Used in 25 countries: 15 country-wide, 1 many regions, 6 some regions, 3 mixed usage

*1: Nikkei News (Feb 9, 2021)

*2: Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers

Version 2.1 <https://www.mhlw.go.jp/content/000646531.pdf> on June 16, 2020

on page 26: Off-label use of drugs available in Japan:

other drugs (no clinical trials in Japan) ; ivermectin (anthelmintic; indication: scabies)

mectin in injection form, which is used in high concentrations for cattle. It is reported that the preparations contain 0.27% or 1.0% and that polyethylene glycol is used as a base material for such veterinary intended use subcutaneous injections. There was concern about the occurrence of side effects when taking such veterinary intended use injections instead of oral preparations in the United States. The FDA issued an urgent warning letter⁸⁰⁾ stating that “Ivermectin preparations for animals should not be taken”, but detailed background information surrounding the warning was not given. Consequently, the FDA’s warning falsely spread the impression that ivermectin was prohibited for use in COVID-19, causing further confusion.

An interesting expansion of the clinical application of ivermectin can also be seen in the prevention and treatment of COVID-19 in long-term care facilities for the elderly. In such facilities, residents and staff may often be required to take ivermectin in response to outbreaks of scabies. In France¹³⁹⁾, the prevalence of COVID-19 in facilities utilizing ivermectin for such purposes is significantly lower when compared to that of facilities where ivermectin is not taken.

4. Is Ivermectin Not Suitable for COVID-19 Treatment?

Immediately after Caly’s paper was published online, the Mectizan Expert Committee, which runs the MDP, issued a statement¹⁴⁰⁾ that the concentration required to suppress the SARS-CoV-2 virus shown in the *in vitro* experiments was too high when compared to that obtained by the FDA-approved dose. When such a high dose is administered to obtain such a concentration in the body, there are concerns that severe side effects will occur. It was pointed out that since this was such a fundamental finding, it alone was sufficient to justify the ineffectiveness of ivermectin use against COVID-19.

The opinion of Merck has persisted and both the NIH and the IDSA have said that it is the fundamental component comprising the dissenting opinion for the use of ivermectin against COVID-19. The Pan American Health Organization (PAHO), which is the Americas branch of the WHO, also cited⁷⁸⁾ the same statement and opposed the use of ivermectin for COVID-19. The PAHO statement also emphasized that ivermectin is not included in the Solidarity Trial⁵²⁾, an evaluation study of repurposing drugs for COVID-19 being conducted by the WHO. The clinical effect of ivermectin on COVID-19 is manifested, as described in a subsequent statement from the FLCCC, by not only the suppression of SARS-CoV-2 replication, but also in the effects on the binding of the virus to the host cell, as well as effects on the host’s own inflammatory responses. This argument that it is based on such a complex mechanism is not taken into consideration at all, and the argument remains that it is only about the pharmacokinetics/pharmacodynamics (PK/PD) of ivermectin.

It has also been stated that, considering the purpose of MDP activities, if ivermectin is used in large quantities against COVID-19 as an “off-label use”, the market would quickly run out of

ivermectin. The WHO even issued a warning¹⁴¹⁾ that current stock supplies of the drug ivermectin might not remain adequate for patients with fecal nematodes and scabies (the original indications for ivermectin) if the drug is used for other purposes. Furthermore, given the indication of ivermectin use for scabies, the mite that causes scabies might also become more resistant to ivermectin after prolonged exposure to low concentrations of the drug. Therefore, the use of ivermectin in COVID-19 should be kept solely for use against the scabies mite and not be used to potentially contribute to a rise in resistance of the causative organism in the environment.

However, the question has been raised as to whether it is ethically correct to oppose, for such reasons, the use of ivermectin against COVID-19. There are already dozens of clinical trial results that have been accumulated to date that demonstrate that ivermectin is effective against COVID-19. Hundreds of thousands of people worldwide are being infected and thousands continue to die every day. The debate over whether ivermectin is not suitable for COVID-19 treatment has always been taken up at the FLCCC webinar every Wednesday at 7 p.m. (US East Coast Standard Time). It was also discussed at the British Ivermectin Recommendation Development (BIRD) conference, organized by Lawrie of EBMC on the afternoon of the 20th of February (World Standard Time), with attendance of more than 70 ivermectin researchers from around the world. The BIRD conclusions were also submitted to the WHO after a summarization of the opinions from all the participants.

1) Merck Statement and FLCCC Alliance Response

Worldwide, a total of 91 studies, 80 for treatment and 11 for prevention of onset in close contacts, are being conducted in 27 countries. As shown in Table 2, 74 are being carried out in the form of the usual phases of clinical trials, and 17 in the form of observational studies. Looking at the content of these trials, most of them are doctor-initiated clinical trials at the medical institution level, and only one each being conducted by a company in France and in the United States. The first approved company to manufacture and sale ivermectin was Merck & Co. in the United States. If this company had conducted a clinical trial to confirm the efficacy and safety of ivermectin for the recent COVID-19 pandemic, it could have been done in a very short period of time. Then, a necessary and sufficient amount of studies could have been conducted with a large number of cases, consultations and collaborations with regulators—the NIH, CDC and the FDA—carried out smoothly, and an Emergency Use Authorization (EUA) could have been issued much earlier than hydroxychloroquine and remdesivir. Had this happened, it is speculated that the widespread clinical use of ivermectin in the United States could have prevented a large number of affected and fatal cases.

Contrary to such speculation, Merck & Co. released a company statement¹⁴²⁾ dated the 4th of February 2021 stating that “Company scientists continue to carefully examine the findings of all available and emerging studies of ivermectin for the treatment of COVID-19 for evidence of effi-

cacy and safety. It is important to note that, to date, our analysis has identified: (1) No scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies; (2) No meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease; and (3) A concerning lack of safety data in the majority of studies.” This Merck statement cites the package insert for Stromectol®, a product that the company sells, and describes details of the product’s indications and the known adverse events. It might be understandable that Merck has issued this statement with the intention of exempting the company from being liable for any adverse events caused by off-label use of the product for the treatment or prevention of COVID-19. For that purpose, Merck’s statement (regarding the three items described above) would not have caused any extra controversy without a description of the efficacy and safety of ivermectin for COVID-19. It has, however, created a big argument among the scientists involved in COVID-19 clinical studies, leading to controversy over the company’s management stance.

The FLCCC Alliance issued an official statement¹⁴³⁾ on the 7th of February addressing the three items presented by Merck. Such statements are significantly different from the results of ivermectin in terms of the efficacy and safety reported by multiple expert groups around the world, including a meta-analysis of the latest scientific literature. In this controversy, the FLCCC Alliance side has refuted Merck’s allegations by citing recently published papers from eight groups around the world (five of which were published in 2021 and two in November and December 2020), official views issued⁹⁴⁾ by the NIH on the 14th of January, and 16 other papers. However, Merck did not provide any scientific basis to support the three items claimed in their statement. As a consequence, the debate has now gone silent. Regarding the efficacy of COVID-19, it may be argued that there is a disagreement surrounding the scale of individual trials cited as scientific support and that the evaluations of the content of the studies are different. However, regarding the safety of ivermectin, Merck itself has announced on its public relations page that there were very few serious adverse events in the MDP over a period of more than 30 years. So, contradictory points have been raised as to why there are concerns about limited safety in the use of ivermectin for COVID-19.

In addition, regarding the issue that there is no scientific basis for the potential therapeutic effect on COVID-19 from preclinical studies, much evidence is shown in the six papers^{144~150)} of fundamental research presented by the FLCCC Alliance. Furthermore, 13 papers on clinical efficacy and safety also discuss the mechanism of action of ivermectin, which is the basis of clinical efficacy. Therefore, it is natural that there are criticisms that Merck’s claim is misunderstood; it is due to a lack of a sufficient search of existing documents on the topic. On the other hand, there are many opinions surrounding the background of Merck’s statement in that ivermectin competes with their development of MK-4482 (EIDD-2801). This may have been the reason it was eliminated. MK-4482 is a nucleoside analog that suppresses SARS-CoV-2 virus replication like remdesivir. Whereas remdesivir is an injectable drug, MK-4482 is an orally absorbable prodrug capa-

ble to treat mildly ill patients who are treated as outpatients or in their homes. If a therapeutic drug with such characteristics comes to be used clinically, it will become possible to control the COVID-19 pandemic. This would also result in even greater expectations. If both the new drug and ivermectin are used to treat COVID-19, humans around the world will be free from the fear of COVID-19. Ivermectin should not be considered to be in competition with the new drug. In order to respond to the counterarguments published by the FLCCC Alliance, it is necessary for Merck to provide solid evidence and politely justify the company's statements.

Decisions not to conduct clinical trials to expand the indication of ivermectin for COVID-19 are acceptable as a corporate management policy. However, it is not ethically permissible if there is an intention to interfere with the process. In a pandemic that affects more than 100 million people worldwide and kills more than 2.4 million people, many medical professionals around the world are enthusiastically studying ivermectin as a promising therapeutic drug for COVID-19. At the end of their official statement, the FLCCC Alliance quoted the words of the son of the founder of Merck, George W. Merck in 1950, that "Medicine is for the people. It is not for profits".

2) Conflict over clinical data for ivermectin

Under ordinary circumstances, in accordance with the enactment intention^{82,83)} of the "21st Century Cures Act (Public Law 114-255)" promulgated in the United States in December 2016, the expansion of indications for approved drugs such as ivermectin should be carried out in a specific manner. Specifically, under a "novel clinical trial design (Sec. 3021)" established to quickly reflect the "real world evidence; RWE (Sec. 3022)" being recognized in a clinical setting. If the innovator Merck had built a groundbreaking clinical trial design that could evaluate the drug's RWE, things could have turned out differently. If a study had been built based on the evidence accumulated in the 91 registered clinical trials as discussed previously in this report, and the FDA followed up and approved an expanded indication for treatment and prevention of COVID-19, it could have prevented COVID-19 from spreading to 8% of the population in the United States. This could have also avoided the tragedy of the ensuing deaths of hundreds of thousands of people. It is a very unfortunate situation that has been caused by the fact that new concepts in drug evaluation methods suitable for the 21st century have not been realized or carried out. The old-fashioned ways of drug regulation and concepts have not yet been broken through and the consequences have been severe.

In order to ensure the safety and efficacy of medicines, regulators have taken sufficient time and thoroughly deliberated on a huge amount of evidence-based materials under a complete and comprehensive examination system. It stipulates the indication targets and indication methods for the clinical use of the drug. It also recognizes and emphasizes standard precedent. During normal times (or peacetime), not so many people disagree with ideas and practices of such regulators in the review of new medicines for well-known diseases for which therapeutics already exist. How-

ever, in this current time of a raging worldwide COVID-19 pandemic, there are strong opinions that it is impossible to promptly provide effective and safe therapeutic agents with such an outdated examination approach and philosophy. The traditional regulatory concepts that many of the reviewers continue to follow are not keeping adequate pace with modern science and practices and are not able accommodate rapidly developing RWE.

Regulators claim that “there is not enough evidence to accept it,” but the safety level of ivermectin has already been achieved by means of the MDP granting more than 3 billion doses to individuals over 30 years. They argue that there is no clear or sufficient evidence, and that safety assurance when used with COVID-19 patients is inadequate. This is a situation where ethics should be questioned as to whether it is permissible to ban patients whose lives may be able to be saved by administering ivermectin only because absolute safety is not guaranteed. There is a need to state a legitimate reason as to why there is hesitation to use an already effectively confirmed drug such as ivermectin (based on RWE) in patients with COVID-19 who could possibly even expect to be cured with its use.

Regulators argue that existing data on the efficacy of ivermectin for COVID-19 are biased in its study plans and methods, and are insufficient to determine validity. A meta-analysis of 14,906 patients in the 42 clinical trials¹⁰¹⁾ described above has shown sufficient efficacy of ivermectin, with a 1 in 4 trillion chance of the conclusion being a mistake. Yet, it is still considered insufficient evidence. Randomized controlled trials are regarded important by regulators. There are 21 trials employing 2,869 patients out of 42 studies. If regulators argue that studies of this magnitude are inadequate to allow the clinical use of ivermectin in COVID-19, then legitimate and compelling explanations for such judgements should be required.

Both the meta-analysis of 15 clinical studies by Lawrie¹⁰³⁾ of the United Kingdom (who is a consultant for WHO clinical trials) and that of 18 clinical studies¹⁰²⁾ conducted by Hill (who is also a consultant of the WHO) in collaboration with 40 researchers from 13 countries have been carried out. Such analyses have affirmed the effectiveness of ivermectin for COVID-19, after fully analyzing for the bias of beliefs (that ivermectin was effective or that the placebo was ineffective). However, the results of such a meta-analysis are rated as “insufficient data” and “very low certainty” by the panels of the NIH and the IDSA Clinical Evaluation Guidelines Committee. It is requested that the WHO committee responds to the recommendations made by the BIRD team¹⁵¹⁾ submitted at the end of February. Furthermore, the recommendations were also sent to the NIH and the CDC, and it will be noted whether there is a difference in the correspondence between the two. In addition, on the 19th of February, the WHO Working Group was hearing the results of a survey on the rapid decrease in excess mortality and the rapid increase after discontinuation of the mass distribution of ivermectin in Peru¹³⁴⁾. There is also a lot of interest in how the WHO handles such real-world evidence in real time.

5. Domestic Clinical Trial of Ivermectin for COVID-19

Kitasato University has established¹⁵²⁾ the “COVID-19 Countermeasures Kitasato Project” for the purpose of discovery of COVID-19 therapeutic agents in response to the amendment of the “Act on Special Measures for Pandemic Influenza and New Infectious Diseases Preparedness and Response” in Japan. Since the clinical results⁸⁴⁾ in South Florida, USA mentioned above were excellent, and it was thought to be necessary to obtain approval of ivermectin as an indication for COVID-19, it was decided to conduct a doctor-initiated phase 2 clinical trial. In Japan, MSD Co. Ltd., a subsidiary of Merck & Co., Inc. of the United States, is the sole manufacturer and distributor of ivermectin. The company has marketed 3 mg tablets, under the trade name of “Stromectol®”, since 2002 for the treatment of a rare disease, strongyloidiasis. The sale of Stromectol® was transferred to Maruho Co., Ltd. in the April of 2006, and an additional indication for scabies was approved in August of that same year.

MSD Co., Ltd. might have been the best entity to conduct the phase 2 clinical trial aimed at expanding the indication of ivermectin to COVID-19. However, it was reported that Merck & Co., Inc. of the United States had no intention of conducting clinical trials aimed at expanding new indications for ivermectin. It should also be noted that ivermectin has also been sold for more than 30 years with multiple generic products available on the market. At that time, the company was also developing two types of vaccines (V590 and V591) and two therapeutic agents (MK-4482 and MK-7110) against COVID-19. Therefore, in the doctor-initiated phase 2 clinical trial by Kitasato University, “Stromectol®” used for the trial was purchased from Maruho Co., Ltd., and the cost of the clinical trial is covered by the research funding raised by donations collected by the “COVID-19 Countermeasure Kitasato Project”. A fund for “Ivermectin for COVID-19 (Principal Investigator: Kunihiro Yamaoka)” by the Japan Agency for Medical Research and Development (AMED) adopted an open call for participants of the “Research Program on Emerging and Re-emerging Infectious Diseases; Development of Therapeutic Drugs for Novel Coronavirus Infection (COVID-19)”. Unlike clinical trials conducted by pharmaceutical companies, even if the clinical trial is successful and the indication expanded, there is no benefit to be obtained from the results. As such, the recovery of clinical trial costs is not a consideration at all. Therefore, this is a clinical trial with high public interest aimed at alleviating the pain and suffering of patients and saving human lives amidst the devastating COVID-19 pandemic.

In the domestic doctor-initiated clinical trial by Kitasato University, the draft was rewritten several times in consultation with the regulatory authorities with the aim of making sure that the protocol was created perfectly. After finalizing the protocol, it was registered¹⁵³⁾ in the Japan Registry of Clinical Trials (JRCT) on the 16th of September 2020. This domestic registration was automatically registered on the WHO’s clinical trial registration site ICTRP. However, it was required to be registered separately on ClinicalTrials.gov, and the registration was accepted and

listed¹⁵⁴⁾ on the 11th of January 2021. Initially, it was aimed to collect 240 cases by the end of December 2020, but the number of participating subjects was not able to be gathered. Even if the period had been extended by 3 months, the progress still would not have been a smooth process. In advancing clinical trials, in accordance with the “Ministerial Ordinance on Standards for Conducting Clinical Trials of Pharmaceuticals” (called “GCP Ministerial Ordinance”)¹⁵⁵⁾, it is necessary to explain the purpose of the clinical trial to the subjects participating and obtain their consent. However, the regulations are currently set under the assumption that the trial is a company-oriented clinical trial. Hence, the regulations are too complicated to allow for doctor-initiated clinical trials, and it is extremely difficult to obtain participants. The instructions used to obtain the consent of the subjects have at least 18 items that should be included. Such complex explanations, as part of a company-oriented clinical trial, when given to people unfamiliar with the process do not allow for a smooth consent process. Therefore, reaching the planned number of subjects for participation is difficult. In short, the progress of such clinical trials is extremely slow due to insufficient funds and a lack of human resources required to carry them out. Whether it is necessary to conduct clinical trials based on the same concepts (of company-oriented clinical trials) being applied to doctor-initiated clinical trials should be widely discussed in the future. Regarding expanding the indications for compounds for new diseases, it seems that extensive discussion and consideration is needed.

On the other hand, clinical trials of anti-infective drugs in Japan also require strictness in order to be conducted. Therefore, the subjects to be included in such clinical trials are limited to inpatients at medical institutions conducting the clinical trials. However, with regard to COVID-19, the number of affected patients is increasing rapidly, the treatment period is long, there is a high possibility that the symptoms will worsen, and the number of patients accepted is limited due to the current heavy burden on medical institutions. Only very sick and severe (including critically ill) patients are eligible for hospitalization and treatment in Japan. It is inherently built into the system in Japan that mildly ill patients, for whom it is important to prevent exacerbation of symptoms through appropriate management and treatment, are unable to receive inpatient treatment. According to the administrative communication from the Ministry of Health, Labor and Welfare (MHLW), mildly ill persons are to be treated at home or at accommodation treatment facilities without being hospitalized at medical institutions. This response system is handled by the local governments—such as prefectures. The results of numerous clinical trials overseas have confirmed that ivermectin suppresses the worsening of symptoms in mild and moderately ill patients, shortens the recovery period, and prevents the onset of disease in those who are in close contact with affected patients. It was considered necessary to include mildly ill patients in clinical trials in Japan as well. According to the notification¹⁵⁶⁾ from the MHLW’s Countermeasures Headquarters, dated the 2nd of February, it has become possible to administer therapeutic agents to mildly ill patients who are being treated at home or at accommodation facilities. It is hoped

that this mitigation measure will further improve the ultimate progress of delayed clinical trials and allow for the preparation of data on the efficacy of ivermectin necessary for expanding its indication for COVID-19 as soon as possible.

At the House of Representatives Budget Committee on the 17th of February, a proposal regarding ivermectin, which is expected to be effective as a therapeutic drug for COVID-19, was made. The proposal stated that ivermectin “should be maximally backed up in clinical trials so that it can be approved as soon as possible by the government”. The Minister of Health, Labor and Welfare further replied, “It can already be used for off-label use. There is also a way to take it at a medical institution and wait at home.” Following this, the Prime Minister of Japan mentioned that he thinks that the drug is very important for Japan, and that he will do his best to help improve the situation. We should keep observing the types of measures that the department in charge of clinical trials of ivermectin in the MHLW will continue to take or create in the future. The practice of “maximum effort” should not be a long-term examination based on conventional regulatory concepts. The current situation is an issue that asks for a reexamination of the standard attitudes of administrative officers under emergency circumstances.

On the other hand, the most serious problems in COVID-19 patient survivors are sequelae¹⁵⁷⁾ called post-acute sequelae of SARS-CoV-2 (PASC) or long COVID (chronic COVID syndrome). This condition resembles one of fatigue (similar to chronic fatigue syndrome), sleep disorders, headaches, thrombosis, taste disorders, olfactory disorders, palpitations, joint pains, hair loss, dyspnea, chest pains, loss of appetite, diarrhea, vomiting, vascular injury, myocardial infarction, cerebral infarction, *etc.* A variety of sequelae are frequently observed not only in elderly patients, but also in young patients. The nature of this process in some ways resembles chronic lead poisoning in the young that can severely negatively impact the lives of young sufferers well into adulthood—even affecting memory—making it difficult to live normally. According to a report from the US NIH, 30% of cases manifest with sequelae that last for 9 months. If the early administration of ivermectin suppresses the progression of symptoms in COVID-19 patients and allows for early recovery, it is possible to prevent physical damage caused by such sequelae. This could potentially contribute to an improvement in the expected prognosis in this population of patients. Even for young people who are battling with or have survived the COVID-19 infection, reducing the risk of such sequelae will be of great benefit.

6. Conclusion

The effective concentration of ivermectin against SARS-CoV-2 in an *in vitro* experiment⁷²⁾ by Caly *et al.* is as high as 2 μ M; in clinical practice, it is necessary to administer tens of times the normal dose in order to obtain such a blood concentration. Therefore, there are opinions from the IDSA⁹⁸⁾ and others that the therapeutic effect of COVID-19 cannot be expected by the adminis-

tration of the normal dose of ivermectin. However, in actual medical practice, there are many study reports demonstrating that the administration of a normal dose does indeed show a clinical response. As of the 27th of February 2021, the results of 42 clinical studies worldwide have undergone meta-analysis and concluded¹⁰¹⁾ that ivermectin is effective in the treatment and prevention of COVID-19. In the UK, a consensus-based recommendation by 75 healthcare professionals from 17 countries around the world has been carried out and submitted to the WHO to further encourage the issuance of guidelines for the use of ivermectin in the treatment and prevention of COVID-19. We must consider why such a discrepancy is occurring.

The first consideration should be focused on the setting of the sensitivity of the SARS-CoV-2 infection for experimental systems *in vitro*. By use of Vero/hSLAM cells, the antiviral activity of the test drug is reliably measured. The sensitivity setting is set to be as low as possible, because it is necessary to eliminate false-positive samples. If the sensitivity is set high, the number of test drugs (noise) that give a positive reaction increases. Furthermore, if the setting is high, it becomes necessary to set secondary and tertiary tests to exclude false-positive samples. It seems that the sensitivity of the $IC_{50}=2\mu M$ set by Caly *et al.* was appropriate because neither false positives nor false negatives occurred. If the sensitivity of this test is set to 10 or 50 times higher, then changes in the IC_{50} ($IC_{50}=0.2\mu M$, $IC_{50}=0.04\mu M$, respectively) might be expected. Depending on the test cells, viral load, medium composition, and culture conditions, the experimental system *in vitro* can be set in different ways. Therefore, the paper by Caly *et al.* merely indicated that ivermectin was found to *have* anti-SARS-CoV-2 activity *in vitro*—no more, no less. Extrapolating the results to evaluate clinical effects is too much of a leap.

There are *in vivo* infection experiments that can be used to connect *in vitro* experiments to clinical studies. In an *in vivo* infection experiment¹⁵⁸⁾ conducted at the Pasteur Institute in France, they employed the olfactory abnormality in hamsters as an index, along with dosage, in order to determine the equivalent dose that would be needed in humans. It was confirmed that the amount of SARS-CoV-2 virus did not change between groups administered ivermectin and the control. However, a significant decrease in the ratio of IL-6/IL-10 in the lung was observed in the ivermectin group. It has been suggested that ivermectin might be effective on COVID-19 by acting to regulate host inflammatory reactions. As shown in Fig. 1, ivermectin has a macrolide structure. Like other macrolide compounds, it is known to exhibit extremely wide diverse actions¹⁵⁹⁾. Regulation of the host's inflammatory response is one of those diverse effects.

In Japan, in 1994, ahead of the rest of the world, a “Research Group on Novel Action of Macrolides” was established. It was done for the purpose of clarifying actions¹⁶⁰⁾ other than the antibacterial activity of macrolide compounds, such as clarithromycin. The clinical use of several effective macrolide antibiotics for the management and treatment of patients with diffuse lung disease (previously designated as refractory diseases) was established. One such disease is diffuse panbronchiolitis (DPB). DPB causes an obstructive respiratory dysfunction similar to cystic fi-

brosis (CF) (which occurs frequently in Westerners) and has been observed in Japan and East Asia. Although it is a fatal and intractable disease, the long-term administration of low-dose macrolides¹⁶¹⁾ has made it possible to treat and reduced the mortality rate. In elucidating the mechanism of action of macrolides on DPB, novel actions such as chlorine ion channel regulation¹⁶²⁾ and anti-inflammatory actions^{163,164)} were confirmed one after another. Following the elucidation of erythromycin's suppressive actions on the infiltration of macrophages into the endothelium, there were studies that investigated the prevention and treatment of diabetic nephropathy, as well as the treatment of active stage Crohn's disease. Several studies have also been conducted investigating the inhibitory effects of clarithromycin on the production of cytokines. One such study involves the suppression of excessive inflammatory reactions caused by influenza and other chronic otolaryngology diseases. Prior to this, effects such as these that go beyond the antibacterial activity of the macrolide antibiotics could never have been imagined. Additionally, for example, it has been found that erythromycin exhibits prokinetic effects for gastroparesis in diabetic patients. This was discovered to be due to the motilin-like action of a metabolite. A metabolite derivative¹⁶⁵⁾ (which exerted no antibacterial activity) was found to enhance motilin-like activity. By taking advantage of such derivative¹⁶⁵⁾ side effects, a new treatment for constipation in patients with severe diabetes was discovered. The biological reactions of macrolide compounds have been shown to be extremely diverse. Even though some have been elucidated, it is difficult to estimate how many other actions may have not yet been elucidated.

Although clinical trial results have been and continue to be accumulated showing that ivermectin is effective in the treatment and prevention of COVID-19, basic *in vitro* findings that can reasonably explain its effectiveness have not yet been obtained. It is considered that a wide variety of biological activities exhibited by macrolide compounds, such as the above-mentioned actions, at multiple stages could possibly serve to exert an overall and more comprehensive action/effect. Although it must be further elucidated by future studies, clinical efficacy can be determined by investigation of any of the following parameters: (1) antiviral activity, (2) inhibition of the relationship between the virus and the host cell, and (3) actions related to the regulation of host reactions. It is necessary to prove that other effects are being exerted, and it seems that such investigations could be suitable research topics for basic researchers, pharmacological researchers, and clinical researchers to collaborate and elucidate on.

When the effectiveness of ivermectin for the COVID-19 pandemic is confirmed with the cooperation of researchers around the world and its clinical use is achieved on a global scale, it could prove to be of great benefit to humanity. It may even turn out to be comparable to the benefits achieved from the discovery of penicillin—said to be one of the greatest discoveries of the twentieth century. Here, one more use for ivermectin, which has been described as “miracle” or “wonder”¹⁶⁶⁾ drug, is being added. History has demonstrated that the existence of such natural product-derived compounds with such diverse effects is exceedingly rare.

However, in order to pass on to posterity the fact that ivermectin has become widely used to control the world-shattering COVID-19 pandemic, only one simple action is required: the addition of only one word, “COVID-19”, to the 9th item (of the 11 listed) under the “Antiviral” category in the “Ivermectin: The Future” section of the Nobel Lecture’s record¹⁶⁷⁾ entitled “Splendid Gift from the Earth”.

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Conflict of Interest

None to declare.

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