

Review

Not peer-reviewed version

COVID-19 and COVID-19 Vaccine in Japan—A Review from a General Physician's Perspective

[Hiroshi Kusunoki](#) *

Posted Date: 26 May 2023

doi: 10.20944/preprints202305.1835.v1

Keywords: COVID-19; SARS-CoV-2; vaccines; breakthrough infection; hybrid immunity; SARS-CoV-2 antibody



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Review

COVID-19 and COVID-19 Vaccine in Japan—A Review from a General Physician's Perspective

Hiroshi Kusunoki

Department of Internal Medicine, Osaka Dental University, 8-1 Kuzuhahanazonocho, Hirakata, Osaka 573-1121, Japan; kusunoki1019@yahoo.co.jp

Abstract: More than 3 years have passed since the emergence of COVID-19. On May 8, 2023, COVID-19 in Japan was downgraded to Category 5 by the Infectious Disease Control Law. In Japan, at the beginning of the COVID-19 pandemic in 2020, cases of infection and deaths from severe disease were few compared with those of Western countries. However, in the medical field, screening for COVID-19 was given top priority, resulting in confusion and proving disadvantageous for many patients, also the overreaction to COVID-19 as the most important issue in society can be attributed largely to statements by infectious disease experts. In addition, the mRNA vaccine emerged in 2021, and most of the population was vaccinated up to two times within a short period of less than 1 year because infectious disease experts strongly promoted vaccination. After 2022, when vaccination progressed, and the Omicron strain, which is an attenuated strain, became the mainstay of the SARS-CoV-2, the number of severe cases of COVID-19 decreased significantly; however, the number of infected people increased dramatically instead. A significant portion of the population is thought to have hybrid immunity due to vaccination plus natural infection and maintains high antibody titers. Henceforth, additional vaccination should be given preferentially to those who will benefit most from it. Conversely, measures against COVID-19 caused serious damage to the economy and society. Policies that not only address countermeasures against infection, but also those that encompass the economy and society as a whole are necessary.

Keywords: COVID-19; SARS-CoV-2; vaccines; breakthrough infection; hybrid immunity; SARS-CoV-2 antibody

Introduction

On May 8, 2023, COVID-19 in Japan was downgraded to a Category 5 disease, the same status as seasonal influenza, based on the Infectious Diseases Control Law. Since the first cases were reported in Japan, the COVID-19 pandemic has been called the “the coronavirus catastrophe,” and states of emergency and semi-emergency coronavirus measures were declared several times causing great confusion in the lives of the Japanese people.

The SARS-CoV-2 will continue to exist, and the prevalence will repeat, and some state that the coronavirus catastrophe is not over; however, society appears to be regaining its composure. In this article, the author would like to review the “the coronavirus catastrophe” that lasted >3 years in Japan from the perspective of a general physician, introducing cases that appeared in the Japanese national examinations and cases the author has experienced. In addition, the author would like to emphasize that the purpose of this report is not to criticize or slander any particular individual or group, but only to review the facts, although the author will introduce many individual statements and internet articles because all of them were trying to communicate and act on what they believed to be right at the time.

First, let us look at a question from the 116th Japanese National Medical Examination F55, which was administered in February 2022.

A typical case of COVID-19 severe pneumonia as considered by the general public

(116th Japan's National Medical Examination F55)

【Current medical history】

A 76-year-old man was brought in through ambulance for dyspnea. Eight days ago, fever and dry cough began, and since that evening, he complained of difficulty in breathing even at rest. His wife noticed that he was losing consciousness and requested an ambulance. His wife had a sore throat and low-grade fever 2 weeks ago; however, they have improved. His smoking history is 20 cigarettes/day from 20 to 63 years of age. Awareness was JCS III-100; height 163 cm; weight 65 kg; temperature 37.7°C; heart rate 80/min, steady; blood pressure 104/64 mmHg; respiratory rate 24/min; SpO₂ 93% (mask with reservoir 10 L/min under oxygen administration); and no abnormal heart sounds. Coarse crackles were heard in the lower thoracic region on the bilateral dorsal surfaces.

【Blood findings】

Red blood cell count 4.7 million/mL, Hb 14.2 g/dL, White-cell count 4,800/ μ L, Platelet count 10,000/ μ L, PT-INR 2.4 (standard 0.9-1.1).

【Blood biochemistry findings】

LD was 629 U/L (reference 120–245), urea nitrogen 23 mg/dL, creatinine 0.9 mg/dL, blood glucose 128 mg/dL, and CRP 10 mg/dL.

【Arterial blood gas analysis (mask with reservoir 10 L/min oxygen administration)】

pH 7.40, PaCO₂ 42 Torr, PaO₂ 64 Torr, HCO₃⁻ 24 mEq/dL.

ECG: normal sinus rhythm.

Chest radiograph (A) and chest CT (B) are shown separately (Figure 1).

PCR test for SARS-CoV-2 using saliva was positive. Which two options are appropriate at this time?

- a. Ventilatory management
 - b. Antifibrotic drug administration
 - c. Bronchoscopic lung biopsy
 - d. Corticosteroids
 - e. Oral cyclophosphamide
-

The correct answers are a. Ventilatory management and d. Corticosteroids, which are appropriate at this time. The patient was presenting with dyspnea, fever, and dry cough, which are symptoms that are commonly associated with COVID-19. The PCR test for SARS-CoV-2 using saliva was positive confirming the diagnosis. The patient had a low oxygen saturation level (SpO₂ 93%) despite oxygen administration indicating hypoxemia. Coarse crackles were heard in the lower thoracic region on the bilateral dorsal surfaces, and chest imaging reveals bilateral ground-glass opacities and consolidations, which are typical findings of COVID-19 pneumonia. The patient has an elevated PT-INR level of 2.4, which indicates a coagulopathy. This may be associated with the hyperinflammatory state induced by COVID-19, which can lead to a prothrombotic state. Given the severity of the patient's symptoms and the hypoxemia, ventilatory management is appropriate, which may include non-invasive ventilation, high-flow nasal cannula, or mechanical ventilation.

Corticosteroids are recommended in the treatment of severe COVID-19 pneumonia, as they have been shown to reduce mortality and the need for mechanical ventilation in hospitalized patients. The patient's CRP level of 10 mg/dL indicates a high level of inflammation, which further supports the use of corticosteroids. Antifibrotic drug administration, bronchoscopic lung biopsy, and oral cyclophosphamide are not appropriate at this time, as supporting their use in the management of COVID-19 pneumonia has no evidence.

This case is a typical example of severe pneumonia caused by COVID-19 and is the very image that many Japanese have of what happens when COVID-19 becomes severe. Many students may have felt that this case had something in common with that of Mr. Ken Shimura, a very famous comedian in Japan who died in March 2020 due to severe COVID-19 pneumonia because he was an older adult and had a history of smoking.

The correct answers, a. Ventilatory management and d. Corticosteroids, are commonly used as symptomatic therapy in cases of cytokine storm caused by acute respiratory distress syndrome (ARDS) even if not caused by COVID-19 or before the appearance of COVID-19. Therefore, it can be

answered with medical knowledge prior to the COVID-19 pandemic and not a question that deals with matters that are medically new.

Although such a case of severe pneumonia leading to ARDS is similar to a typical case of COVID-19 that the public had in mind, the case was actually a small fraction of the actual PCR-positive cases in Japan in the early stage of the COVID-19 pandemic.

COVID-19 pneumonia cases that were actually common in early stages of the COVID-19 pandemic in 2020

Thus, what were the actual typical cases in the early stages of the COVID-19 pandemic in 2020? The author personally wore personal protective equipment (PPE) and examined patients with fever and collected PCR specimens at a fever outpatient clinic during the early stages of the COVID-19 pandemic in 2020. The author remembers that the rate of positive PCR tests for COVID-19 was quite low during this period; however, if a patient had even a slight fever (around 37°C) or common cold symptoms, he or she was unconditionally sent to the fever outpatient clinic. This was done to minimize the occurrence of COVID-19 clusters in the hospital; however, until PCR-negative results were confirmed, normal testing and medical treatment were postponed, and considering that most cases were PCR-negative for COVID-19, many of the cases were a great disadvantage to most patients. The following are the COVID-19 cases that the author experienced in a fever outpatient clinic. In each case, pneumonia was observed on chest CT, but the disease resolved spontaneously without special treatment, and no sequelae occurred.

Case 1: 47-year-old female

【Current medical history】

She had cough and low-grade fever of 37°C since August 10, 2020. She had a sore throat, but no olfactory or gustatory symptoms. She came to the outpatient clinic for fever on August 14, 2020, pedaling a bicycle under the scorching sun.

【Contact history】

Mother (who does not live with the patient but lives nearby) has had fever since July 30. The mother tested positive for SARS-CoV-2 PCR on August 4. The father, whom the mother was caring for, also tested positive for PCR.

【Life history】

She is single and lives alone with no one living with her. She shares a bath with her 95-year-old grandmother (needs nursing care) who lives in a house away from hers.

【Medical history】 Breast cancer: under hormone therapy, lung metastasis.

【Blood findings】 WBC 3370/ μ L, AST 38 U/L, ALT 55 U/L, LDH 225 U/L, ALP 110 U/L, γ -GTP 101 U/L, CRP 1.07 mg/dL.

The patient was a middle-aged woman with an underlying breast cancer and poor liver function due to fatty liver. She was undergoing hormone therapy. Despite this, she was in good general health and even pedaling her bicycle under the scorching sun during the hot summer season. However, CT revealed a clear image of pneumonia (Figure 2). This circular infiltrate shadow is often called the marimo sign in Japan because it resembled the marimo (a type of freshwater green alga named for its ability to form spherical aggregates) found in Lake Akan, Hokkaido, Japan. The patient was hospitalized, but did not require any specific treatment, and at the 3-month follow-up, the pneumonia disappeared.

Case 2: 55-year-old female

【Current medical history】

She had fever in the 37°C range and headache since January 2, 2021, temperature of 38°C since January 5, SARS-CoV-2 PCR test result on January 6 was negative. Her son and husband were SARS-CoV-2 PCR positive. The PCR was retested on January 8, but the result was negative. Although antipyretics were used, general fatigue, fever, and

headache persisted. On January 13, the third PCR test result was negative; however, the fever and fatigue persisted.

【Family and contact history】

January 1, 2021: Her son returned home from Tokyo for New Year. On January 2, he had fever. On January 7, the SARS-CoV-2 test result was positive. After recuperating at a hotel from January 10 to 18, he was confirmed negative and returned to society.

The husband also tested positive for SARS-CoV-2 PCR on January 7. After recuperating at a hotel from January 11 to 16, he was confirmed PCR negative and returned to society.

【Blood findings】 WBC 5040/ μ L, CRP 0.07 mg/dL.

This case was clinically COVID-19, although repeated PCR test results were negative because the chest CT showed a clear image of pneumonia and a clear family history of infection was present (Figure 3).

The patient was clinically thought to have COVID-19; however, as a definitive diagnosis could not be made through PCR testing, the patient was followed up without hospitalization and without specific treatment, and at the 2-month follow-up, the pneumonia image on CT disappeared. This case is educational and demonstrates that false-negative PCR tests do occur.

Cases of patients seen in an outpatient clinic for fever but not COVID-19

COVID-19 PCR-negative cases were the most common in fever outpatient clinics in 2020. Some of the cases treated in the fever outpatient clinic and diagnosed with other diseases are shown in Table 1, including heart failure in the older adults and urinary tract infections, which, if left untreated, could be more lethal than COVID-19.

Table 1. Cases of patients seen in an outpatient clinic for fever but not COVID-19.

Case s	Chief complaint	Body temperature	WBC (/ μ L)	CRP (mg/dL)	Diagnosis
80 F	Cough	unknown	7350	0.04	Heart failure
25 M	Fever, dry cough, sore throat	39°C range	8900	11.46	Bronchial pneumonia
68 M	Fever	39°C range	11610	18.65	Pyelonephritis
56 F	Sub fever	unknown	5810	5.52	Pelvic tumor
19 M	Fever, right lower abdominal pain	38°C range	7710	7.42	Appendicitis

In all cases, other tests and medications were postponed until the PCR test results were known. A case of appendicitis presented with typical right lower abdominal pain, yet the previous physician only performed a COVID-19 PCR test because of fever, delaying the diagnosis for more than 2 weeks. This case would have been diagnosed and treated immediately before the appearance of COVID-19.

Because these cases were in general hospitals, appropriate treatments were taken after COVID-19 PCR negativity was confirmed. However, in many small- and medium-sized hospitals and clinics, priority was given to the COVID-19 PCR test, which has a low pre-test probability, and waiting for the results delayed the treatment of more serious diseases, to the detriment of patients, and increased the burden on medical personnel.

During the first year of the COVID-19 pandemic in 2020, unlike in western countries, few febrile patients in Japan actually tested positive for COVID-19 through PCR. Among all COVID-19-infected patients, the overwhelming majority had mild symptoms and were cured without sequelae without any specific treatment even if pneumonia was revealed on chest computed tomography (CT) as described above.

Factor X of Japan in early stages of the COVID-19 pandemic in 2020

The first state of emergency was declared in Japan in April 2020, when the cumulative number of cases was extremely low compared with those of western countries, and the lives of the Japanese people were severely restricted. In response to the recommendation of infectious disease experts that the government should take a cautious approach to unknown infectious diseases, the government took the extremely bold step of severely restricting the private rights of the citizens.

Why were there fewer cases of COVID-19 infection and less severe cases in Japan than in western countries? In response to this question, Nobel Prize laureate Dr. Shinya Yamanaka pointed to not only the efforts of the Japanese health authorities and the Japanese people to self-refrain from outings, the lack of close contacts, such as handshaking and kissing, compared with Westerners, public health programs, such as BCG inoculation against tuberculosis during childhood but also the Japanese people's genetic resistance to SARS-CoV-2. The possibility that Japanese people are genetically resistant to SARS-CoV-2 or have already acquired resistance to SARS-CoV-2 through infection with other similar viruses was considered. These factors were collectively referred to as "Factor X," which caused a great deal of controversy (1).

Some specialists clearly stated that the fact that the Japanese are more resistant to COVID-19 than Westerners is only nothing but an illusion (2) and that Factor X does not exist (3-4).

However, compared with western countries, fewer people are infected with COVID-19 and less severe disease in Japan. This phenomenon was seen not only in Japan but throughout the Western Pacific region, from East Asia to Australia, including New Zealand, in the total infected cases and deaths caused by COVID-19 (Figure 4). Ethnic and genetic backgrounds, lifestyles, cultural backgrounds, and medical conditions in Western Pacific region, where fewer people are infected with COVID-19 compared with western countries, vary greatly from country to country. Although the definitive facts regarding Factor X are still unknown, is there really no biological difference compared with Western countries, where the infection spread rapidly and caused incomparably much more serious deaths than in the Western Pacific region? Whether denying Factor X outright as "nothing but an illusion" and causing anxiety among the general public is appropriate for a scientist is debatable.

Emergence of mRNA vaccines and Omicron strain

The mRNA vaccine was widely expected to be a game changer for the COVID-19 pandemic and was rapidly promoted for vaccination. However, this vaccine had the disadvantage of causing a high rate of adverse reactions such as fever. The following is a question from D8 of the 116th National Dental Examination administered in January 2023.

(116th Japan's National Dental Examination D8)

() is one of the major side effects of COVID-19 vaccination. What goes in ()?

- a. Cough
 - b. Fever
 - c. Loss of taste
 - d. Smell disturbance
 - e. Sore throat
-

Of course, the correct answer is b. Fever. It was known from an early stage that COVID-19 vaccination causes a high rate of fever. But why were so many people vaccinated in such a short period of time? One of the reason is that the entire country, based on the recommendations of infectious disease experts, promoted the extremely high efficacy of the mRNA vaccine and promoted the expansion of vaccination.

In addition to Prime Minister Kishida, other intellectuals who greatly influenced national policy making appeared in online video distributions promoting the expansion of vaccination. A prominent specialist introduced an article showing the high efficacy of mRNA vaccines (6) in an Internet article and appeared in an Internet video himself strongly promoting vaccination (7-9).

The mRNA vaccine was shown to be effective in preventing the onset and severity of disease in Japan (10-13), and vaccination was considered a form of compassion for others to prevent the spread of infection, giving rise to the catchphrase, "Vaccines given for compassion for others" (14).

By the end of 2021, more than 70% of the Japanese population had completed up to the second dose of mRNA vaccination. With the expansion of vaccination, the rate of severe pneumonia, indicated at the beginning of this article, appeared to have decreased. Then, from the end of 2021 to the beginning of 2022, SARS-CoV2 was rapidly replaced by the attenuated Omicron strain, which greatly accelerated the decrease in the rate of severe cases. However, as the Omicron strain became the predominant strain, the virus, although attenuated, became more infectious and spread rapidly. In other words, COVID-19 is no longer a rare infectious disease, but a very common disease that many people in Japan are commonly infected with and recover from. Therefore, most of the COVID-19 cases in Japan were infected with the Omicron strain after most of the population had been vaccinated up to the second dose. Here, the author wants to present a case experienced in early 2022, when the Omicron strain became the predominant strain.

Case 3: 73-year-old male**【Current medical history】**

On the evening of February 5, 2022, a man fell and fractured his mandible and maxilla. He was referred to our hospital's Oral Surgery Department by a dentist of a local doctor and was urgently hospitalized.

【Life history】

He lives alone and has no roommate.

Smoking history: 20 cigarettes/day x 50 years, current smoker

Medical history: No family doctor, no medication.

【Blood findings】 WBC 7960/ μ L, ALP 115 U/L, γ -GTP 77 U/L, CRP 3.29 mg/dL.

On February 9, PCR test result for SARS-CoV-2 was positive. Surgery at the hospital was cancelled, and the patient was discharged from the hospital and placed in a hotel for recuperation. During the hotel stay, the patient had a slight fever in the 37°C range, but no symptoms, such as cough or respiratory distress, were observed. The PCR test was repeated on February 21, and the results were confirmed negative. On February 28, the recuperation of this patient was lifted.

Chest CT showed emphysematous and old inflammatory changes that may have been present prior to SARS-CoV-2 infection (Figure 5), although this case shares similarities with the case in the national examination at the beginning of this article in which the patient was an older adult man with a history of heavy smoking. Although the risk of serious illness appears to be high, the symptom of COVID-19 was only a mild common cold. However, the patient was forced to recuperate in a hotel without undergoing oral surgery, which he could have undergone. Thus, after SARS-CoV-2 was replaced by the Omicron strain, the symptoms of COVID-19 were either asymptomatic or extremely mild; however, once a positive test was confirmed, patients had to be quarantined for a certain period of time and were at a disadvantage because they could not receive necessary medical care. At approximately this time, a growing consensus exists that, as with influenza, the status of COVID should be lowered to Category 5 based on the Infectious Disease Control Law and that isolation measures should be relaxed so that patients could be treated at general medical facilities.

Acquisition of hybrid immunity

As COVID-19 infection after vaccination, or the so-called breakthrough infection, spread, hybrid immunity through vaccination plus natural infection attracted much attention. Mr. Yasutoshi Nishimura, who appeared in the media daily as a Minister in charge of the COVID-19 measure under the Yoshihide Suga administration, contracted COVID-19 on an overseas business trip to Southeast Asia in September 2022 as Ministry of Economy, Trade and Industry (METI) Minister. Mr. Nishimura's statement that he was infected with COVID-19 when he dined without a mask and his antibody titer was elevated, and that he was thinking of postponing his fourth mRNA vaccine, was covered in a weekly article (15).

The article criticized Mr. Nishimura for saying that no scientific basis exists for his statement that antibody titers increase without masks during dinners, but a scientific basis exists for the increase in SARS-CoV2 antibody titers due to hybrid immunity caused by natural infection after vaccination.

It has been reported that SARS-CoV-2 antibody is markedly elevated through vaccine plus natural infection (16-18). We recently reported that antibody titers increased markedly after natural infection with COVID-19 after two or more doses of vaccine, and some cases had antibody titers that remained high for 6 months to 1 year (19). We present two cases in which the PCR was not tested; however, the patients were considered to have been naturally infected and continued to have high levels of SARS-CoV-2 antibody titers for a long time. (Figure 6A, B)

Table 2 shows 17 cases of spontaneous COVID-19 infections after receiving two or more doses of vaccines (Table 2). All patients were infected with COVID-19 after two or three doses of the vaccine, and all of them were either asymptomatic or showed very mild symptoms. Some of them were not counted as infected people because PCR tests were not performed. Nine of them had antibody titers of more than 40,000 AU/mL after spontaneous infection, and two of them maintained antibody titers in the 10,000 AU/mL range even after >6 months had passed since infection (19).

Hybrid immunity offers protection against COVID-19 infection and is reported to persist for a relatively long time (between 6 and 8 months) (20,21). A systematic review of recent studies has also shown that individuals with hybrid immunity are more protected against the Omicron variant than those with only a history of infection suggesting that individuals with hybrid immunity may not require a booster dose immediately (22). In Japan, most cases of SARS-CoV-2 infection occurred after two or more doses of vaccine. In such cases, as shown in our previous report (19), the post-infection antibody titer increased markedly, and the high antibody titer may have continued for a long period of time (>6 months).

Table 2. Cases of spontaneous COVID-19 infection after 2 or more doses of vaccine (from Reference 19, additional data are contained).

	1st Ca se	2nd vaccin ation date	3rd vaccin ation date	Date of infection	Post- infectio n antibod y test date①	Post- infectio n antibod y titer① (AU/mL)	Post- infectio n antibod y test date②	Post- infectio n antibod y titer② (AU/mL)	Post- infectio n antibod y test date③	Post- infectio n antibod y titer③ (AU/mL)
36 M	4/30/2 021	5/21/2 021		1/17/2022 ※	2/7/2022	>40000.0	8/16/2022	31409.9	11/15/2022	22684.0
65 M	4/27/2 021	5/18/2 021	2/7/2022	4/2/2022	4/20/2022	>40000.0	10/4/2022	15769.9	12/27/2022	12379.0
45 M	5/6/20 21	5/27/2 021		8/3/2022	9/20/2022	>40000.0	12/23/2022	19533.0		
68 M	July 2021	Aug 2021	April 2022	Aug 2022#	11/1/2022	>40000.0	12/20/2022	39247.6	2/14/2023	>80000.0
63 M	4/28/2 021	5/19/2 021	2/4/2022	8/20/2022	11/4/2022	43907.1				
44 M	7/24/2 021	8/21/2 021	7/16/2022	8/9/2022	11/10/2022	17451.4				
27F	4/30/2 021	5/21/2 021		1/22/2022	2/7/2022	>40000.0				
23F	5/26/2 021	6/18/2 021	3/11/2022	Aug 2022	11/28/2022	>80000.0				
24F	April 2021	5/14/2 021	1/15/2022	Aug 2022	11/28/2022	36446.4				

23F	7/24/2021	8/21/2021	4/22/2022	8/12/2022	12/1/2022	36292.0
35F	April 2021	May 2021		1/10/2022	1/24/2022	18907.4
28F	8/27/2021	9/17/2021	4/9/2022	12/14/2022	1/6/2023	45218.1
25F	April 2021	Aug 2021	May 2022	Aug 2022	11/29/2022	37648.8
23F	7/24/2021	8/21/2021	4/22/2022	8/12/2022	12/1/2022	27238.4
23F	July 2021	8/13/2021	3/19/2022	Sep 2022	12/2/2022	>80000.0
63F	5/14/2021	6/4/2021	3/14/2022	11/9/2022	12/5/2022	31879.8
40F	3/26/2021	4/16/2021	12/17/2021	1/1/2023	2/2/2023	27849.0
	021	021	021		5/1/2023	18024.8

※ No fever, only mild cold symptoms, PCR test was not conducted. # No symptoms due to concentrated contact only, PCR test was not conducted.

Therefore, judging that additional vaccination is unnecessary because the antibody titers have remained high is reasonable for Mr. Nishimura, who has been following up SARS-CoV-2 antibody titers after infection. However, the entire population have no opportunities to follow up antibody titers similar to that of Mr. Nishimura, and in reality, many people have received additional vaccinations even though their antibody titers have remained high due to hybrid immunity. In our study in a private clinic in Wakayama Prefecture, we have observed actual cases of post-vaccination COVID-19 infection and additional vaccination despite markedly elevated antibody titers (22). Table 3 shows four cases of spontaneous infection after the third dose of vaccine. All of them maintained high levels of antibody titers. However, despite maintaining high levels of antibody titers, they had received the fourth dose of vaccine (22).

Table 3. Participants who were infected after the third dose of vaccine (modified from Reference 23).

Cas e	1st vaccination date	2nd vaccination date	3rd vaccination date	Date of infectio n	Days from 3rd vaccinatio n to infection	Post- infection antibody test date	Post- infection antibody titer (U/mL)	Number of days from infection to antibody titer measurement	4th vaccinatio n date
65F	6/22/2021	7/13/2021	2/21/2022	3/29/2022	36	4/12/2022	20500	14	8/3/2022
75M	6/26/2021	7/17/2021	3/5/2022	8/8/2022	156	8/26/2022	41000	18	8/26/2022
71F	7/10/2021	7/31/2021	3/10/2022	8/10/2022	153	8/26/2022	9840	16	8/26/2022
71F	Unknown	Unknown		3/11/2022	31	4/25/2022	63400	45	8/3/2022

2/8/2022

The Ministry of Health, Labour and Welfare (MHLW)'s view was that if a person becomes infected after completing the initial vaccination, one tentative guideline for the interval between recovery of physical condition and the next vaccination was 3 months (24). In addition, the MHLW has stated that additional vaccination with the Omicron strain-compatible bivalent vaccine can be given regardless of the period of time since the infection.

In response to this view of the MHLW, a famous specialist recommended an additional vaccination around 3 months after infection, even if the patient has already been infected (25). He also recommended that those who had severe disease when first infected with COVID-19 are more likely to be severely ill when re-infected, and he repeatedly recommends additional vaccinations to prevent severe disease when re-infected (26).

However, as our previous report showed, in the case of hybrid immunization, antibody titers may remain high for 6 months to 1 year or more, and whether additional vaccination is necessary even in such cases is questionable. Although antibody titers will gradually decline in the case of hybrid immunization, the patient may be infected again during the period when sufficient antibody titers are maintained, and antibody titers will be boosted again. In addition to the induction of antibodies, the effect of natural immunity is considered significant regarding hybrid immunity. As for the natural immunity after COVID-19 infection, the effects of CD4⁺ T cells, CD8⁺ T cells, and memory B cells have been shown to be maintained for more than 8 months (27,28). Studies in Qatar have also shown that the natural immune protection against the SARS-CoV-2 infection wanes over time; however, the prophylactic effect against the severe disease forms of COVID-19 remains strong (29). Although measuring antibody titers and prioritizing those with low antibody titers for booster vaccination, rather than blindly recommending booster vaccination to the entire population is desirable, seeing how the finances, personnel, time, and educational costs can be afforded may be difficult.

Changes in COVID-19 Measures and Events in Japan

The image of COVID-19 countermeasures by infectious disease experts is shown in Figure 7A. Since the early days of the 2020 pandemic, cases of severe pneumonia requiring ventilators, such as the case in the national examination described at the beginning of this article, were the tip of the iceberg in terms of the total number of COVID-19-infected patients. These severe cases were mainly treated by emergency physicians or intensivists at large medical institutions. They feared that the progression of COVID-19 severe pneumonia would be rapid that the number of severe cases would exceed their capacity, and they complained of the risk of medical collapse. Although the number of people infected overall was low, human and material support for the treatment of these severe cases should have been given top priority; however, the infectious disease experts recommended that the government and administration declare states of emergency and semi-emergency coronavirus measures. They recommended that general public citizens self-refrain from outing, taking thorough infection control measures using masks, temperature checks, and acrylic plates, promoting vaccination, and expanding PCR tests. The main focus was on reducing the size of the base of the iceberg. Although these measures to restrict people's private rights caused serious damage to the society and economy, they may have had some effect in terms of reducing the number of deaths caused by COVID-19. Conversely, we general physicians were treating mainly mild cases and PCR-positive but asymptomatic patients, and many of them may not have realized the seriousness of the infectious disease called COVID-19. However, many of these general physicians may also have been exhausted as they were busy preventing cluster outbreaks in their own facilities.

What happened after the Omicron strain becomes the main strain in 2022? After the Omicron strain became the main strain, the base and size of the iceberg itself increased to an incomparable extent compared with that of the early stage of the COVID-19 pandemic; however, as indicated by the lighter color in the figure, the pathogenesis of the disease became weaker and milder for many people (Figure 7B). The rate of severe cases at the tip of the iceberg has also decreased considerably.

In response, many people have suggested that COVID-19 should be downgraded to category 5 under the Infectious Disease Control Law, and that it should be treated at ordinary medical facilities, eliminating the need for isolation and the tracking of persons in close contact with the disease.

In contrast, infectious disease specialists still insisted that if the total number of COVID-19 infections increases, a risk of an increase in the number of severe cases, risk of mutating and becoming highly toxic again, certain number of sequelae occurring even with the Omicron strain, and higher mortality rate than with influenza will exist and the fact that severe cases and deaths have occurred even among young people and children. The government was reluctant to lower COVID-19 to category 5 status.

As the number of infected people continued to increase even after two or more vaccinations and the reality of severe adverse reactions to the vaccine became clear, more and more people began to question the words and actions of these infectious disease specialists. In addition, many people who had experienced COVID-19 infection themselves, their families, or others around them, and felt that they had been treated with surprisingly mild illnesses, began to question the continuation of the intensive measures that had been taken up to that point.

A famous expert pointed out that Japan may continue to experience a large-scale spread of COVID-19 because the number of people who retain immunity through natural infection is low compared with those in other countries (30). Assuming this point is correct, the only way for COVID-19 to become an endemic phase in Japan, where the N antibody possession rate (with a history of natural infection) is as low as 40%, is for more of the population to acquire hybrid immunity through natural infection. The number of deaths due to COVID-19 will probably increase during this process, particularly among the older adults in the later stages of life. However, considering that the average age of deaths due to COVID-19 in Japan is close to the average life expectancy of Japan as a whole, and that the late older adults have a higher probability of death due to various factors (31), the extent of the impact of COVID-19 on the overall population, including the number of excess deaths, will be uncertain. Conversely, the impact of COVID-19 on the elderly may still be significant. When the older adults are affected by COVID-19, even after recovery, the risk of frailty and aspiration pneumonia is increased, and life expectancy is worse (32-34). Frailty caused by COVID-19 pandemic is also a problem due to the older adults being afraid of contracting COVID-19, refraining themselves excessively, and staying at home. Taking well-balanced measures while keeping an eye on the situation will be necessary.

One reason COVID-19 was difficult to treat as a common cold was that the problem of sequelae could not be underestimated; the long-term sequelae of COVID-19 were termed long COVID and greatly feared. In a cross-sectional study using questionnaires and electronic medical records, more than half of the patients reported prolonged COVID symptoms of varying severity 1 year after the onset of COVID-19 (35).

The enrollment of participants for this study took place in 2020, in the early stages of the pandemic, in which the disease was considered quite different from the current one caused by the Omicron strain. In addition, as the authors also state in the article, selection bias may have influenced participants' willingness to participate, and recall bias may have played a role in the severity of sequelae; those with long COVID were more likely to participate in a survey regarding COVID-19 sequelae, and conversely, those without long COVID are more likely to be uninterested in the study and consequently may not have participated.

With approximately 40% of the entire population already infected, imagining that more than half of the patients have sequelae and that such a study would overestimate the prevalence of sequelae of COVID-19 even among the general public is difficult.

A study that also used a questionnaire reported that more than one-fourth of patients who recovered from COVID-19 had at least one symptom at 6, 12, 18, and 24 months after the onset of COVID-19, although the disease was mild in the acute phase, and that a small number of COVID-19 patients have mild but persistent symptoms in the long term (36).

This study may be affected by similar selection bias and other factors; however, if such a study is widely reported, some citizens may still think that the sequelae occur at a very high rate and are

quite serious, which may cause adverse effects, such as excessive self-restraint. Thus, the publication should be done with caution.

Postscript

This article reviewed the author's memorable cases and changes in Japan's COVID-19 during the 3 years of the COVID-19 pandemic. After reading this article, some may be uncomfortable with this article and say, "The only reason you can write like this is that you happen to have only seen mild cases. Particularly during the fifth wave caused by the Delta strain around the time of the Tokyo Olympics in the summer of 2021, many really serious cases were present that medical care collapsed." Others, while not denying the contents of the article in general, may not agree with them because they themselves were affected by COVID-19 and experienced really painful symptoms, suffered from the sequelae, or had someone around them who did. The author, of course, does not deny such views. This article is merely a report of the author's own limited experience and honest opinion. The author does not consider COVID-19 to be something to be taken lightly and does not deny all the positive aspects of COVID-19 vaccine. The author is convinced that many infectious disease specialists had the courage to speak out and act with real sincerity in times of global pandemic, and the author is filled with great respect and gratitude for their efforts.

The infectious disease experts motivated the government, public administrators, and health authorities to take action, and the public's voluntary self-restraint may have saved lives. The COVID-19 pandemic was a very bold attempt to greatly restrict the people's private rights in the name of a cautious response to an unknown infectious disease and semi-mandate the use of vaccines and masks through peer pressure. Many people still believe that such attempts have kept the number of COVID-19 cases and deaths low in Japan without strict lockdown, and the author has no intention of denying such perspective.

However, it is undeniable that aspects of excessive behavior that resulted from giving top priority to the recommendations of infectious disease specialists who consider infection control measures to be of the highest priority exist. In addition, the public took excessive self-restraint and infection control measures, which led to various problems, such as the promotion of semi-mandatory vaccinations at workplaces and schools against vaccinations that were supposed to be optional, numerous troubles over the wearing of masks, and an increase in frailty due to excessive self-restraint among the elderly. The damage to society as a whole could have been mitigated if policies that looked at not only the actual situation of infectious diseases but also the economy and society as a whole (which would have been extremely difficult) had been adopted. Conversely, a certain number of people, who have a negative view of the words and actions of infectious disease specialists who are biased against infection control, and their opinions may have a point and should be listened to (37).

In addition, while COVID-19 sequelae are important, vaccine sequelae are also important. After vaccination, the development of herpes virus (38) and herpes zoster virus (39), autoimmune diseases (40,41), thrombotic thrombocytopenia (42), nephrosis (43,44), nephritis (45,46), myocarditis, and pericarditis (47-52) have been reported. The relationship between these pathologies and vaccines will require clarification in the future.

High antibody titers due to hybrid immunity persist for a fairly long period of time in previously infected people, and considering the immune dynamics of each individual and the risk of severe disease when administering additional vaccinations, rather than blindly promoting vaccination to the entire population, would be beneficial from the perspective of cost effectiveness.

What we have learned from this pandemic is the importance of taking a clear perspective of not only medical treatment but also the entire social system, and the need for the ability to evaluate real events and data with careful observation and discernment. Reaffirming the importance of these matters will surely be useful in the next era of pandemics. In addition, Japanese people still have a tendency to prioritize the eyes of those around them and peer pressure rather than rational judgment, not only in the case of this infectious disease pandemic. Although mentally easier, the risk that everyone may take extremely inefficient and uneconomical actions and that everyone may suffer as a result should be recognized.

Finally, the author sincerely hopes that the Japanese society will return to its pre-2019 state after the downgrading of COVID-19 to a Category 5 disease.

References

1. <https://asia.nikkei.com/Business/Science/Yamanaka-on-COVID-19/Uncovering-Japan-s-coronavirus-X-factor-matters-to-the-world>
2. Shukan Bunshun 2020.8.13.p148-153
3. <https://www.jmedj.co.jp/journal/paper/detail.php?id=15375>
4. <https://bunshun.jp/articles/-/42157>
5. <https://bungeishunju.com/n/n339bef1e0c6b>
6. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* 2020 Dec 31;383(27):2603-2615.
7. <https://news.yahoo.co.jp/byline/kutsunasatoshi/20210120-00217893>
8. https://www.kantei.go.jp/jp/headline/kansensho/vaccine_arch.html
9. <https://twitter.com/kutsunasatoshi/status/1552908712800423942>
10. <https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10966-covid19-71.html>
11. <https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10614-covid19-55.html>
12. <https://www.niid.go.jp/niid/ja/2019-ncov/2484-idsc/10757-covid19-61.html>
13. Arashiro T, Arima Y, Muraoka H, Sato A, Oba K, Uehara Y, Arioka H, Yanai H, Kuramochi J, Ihara G, Chubachi K, Yanagisawa N, Nagura Y, Kato Y, Ueda A, Numata A, Kato H, Ishii K, Ooki T, Oka H, Nishida Y, Stucky A, Smith C, Hibberd M, Ariyoshi K, Suzuki M. Coronavirus Disease 19 (COVID-19) Vaccine Effectiveness Against Symptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection During Delta-Dominant and Omicron-Dominant Periods in Japan: A Multicenter Prospective Case-control Study (Factors Associated with SARS-CoV-2 Infection and the Effectiveness of COVID-19 Vaccines Study). *Clin Infect Dis.* 2023 Feb 8;76(3): e108-e115.
14. <https://www.facebook.com/fukuokaitv/videos/%E6%80%9D%E3%81%84%E3%82%84%E3%82%8A%E3%83%AF%E3%82%AF%E3%83%81%E3%83%B3-%E3%82%AB%E3%83%83%E3%83%97%E3%83%AB%E7%AF%87-15%E7%A7%92/540124383727813/>
15. https://www.news-postseven.com/archives/20230228_1844673.html?DETAIL
16. Walls, A.C.; Sprouse, K.R.; Bowen, J.E.; Joshi, A.; Franko, N.; Navarro, M.J.; Stewart, C.; Cameroni, E.; McCallum, M.; Goecker, E.A.; et al. SARS-CoV-2 breakthrough infections elicit potent, broad, and durable neutralizing antibody responses. *Cell* 2022, 185, 872–880.e3.
17. Sarrigeorgiou, I.; Moschandreou, D.; Dimitriadis, A.; Tsinti, G.; Sotiropoulou, E.; Ntoukaki, E.; Sotiropoulou, E.; Ntoukaki, E.; Eliadis, P.; Backovic, M.; et al. Combined monitoring of IgG and IgA anti-Spike and anti-Receptor binding domain long term responses following BNT162b2 mRNA vaccination in Greek healthcare workers. *PLoS ONE* 2022, 17, e0277827.
18. Desmecht, S.; Tashkeev, A.; El Moussaoui, M.; Marechal, N.; Perée, H.; Tokunaga, Y.; Fombellida-Lopez, C.; Polese, B.; Legrand, C.; Wery, M.; et al. Kinetics and Persistence of the Cellular and Humoral Immune Responses to BNT162b2 mRNA Vaccine in SARS-CoV-2-Naive and -Experienced Subjects: Impact of Booster Dose and Breakthrough Infections. *Front. Immunol.* 2022, 13, 863554.
19. Kusunoki, H.; Ohkusa, M.; Iida, R.; Saito, A.; Kawahara, M.; Ekawa, K.; Kato, N.; Yamasaki, K.; Motone, M.; Shimizu, H. Longitudinal Changes in IgG-Type SARS-CoV-2 Antibody Titers after COVID-19 Vaccination and a Prominent Increase in Antibody Titers When Infected after Vaccination. *Vaccines* 2023, 11, 860.
20. Hall, V.; Foulkes, S.; Insalata, F.; Kirwan, P.; Saei, A.; Atti, A.; Wellington, E.; Khawam, J.; Munro, K.; Cole, M.; et al. Protection against SARS-CoV-2 after COVID-19 Vaccination and Previous Infection. *N. Engl. J. Med.* 2022, 386, 1207–1220.
21. Sidik, S.M. COVID vaccine plus infection can lead to months of immunity. *Nature* 2022.
22. Bobrovitz, N.; Ware, H.; Ma, X.; Li, Z.; Hosseini, R.; Cao, C.; Selemon, A.; Whelan, M.; Premji, Z.; Issa, H.; et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: A systematic review and meta-regression. *Lancet Infect. Dis.* 2023.

23. Kusunoki H, Ekawa K, Ekawa M, Kato N, Yamasaki K, Motone M, Shimizu H. Trends in Antibody Titers after SARS-CoV-2 Vaccination-Insights from Self-Paid Tests at a General Internal Medicine Clinic. *Medicines (Basel)*. 2023 Apr 20;10(4):27.
24. <https://www.cov19-vaccine.mhlw.go.jp/qa/0028.html>
25. <https://news.yahoo.co.jp/byline/kutsunasatoshi/20230103-00329974>
26. <https://news.yahoo.co.jp/byline/kutsunasatoshi/20230429-00347557>
27. Dan, J.M.; Mateus, J.; Kato, Y.; Hastie, K.M.; Yu, E.D.; Faliti, C.; Grifoni, A.; Ramirez, S.I.; Haupt, S.; Frazier, A.; et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science* 2021, 371, eabf4063.
28. Crotty, S. Hybrid immunity: COVID-19 vaccine responses provide insights into how the immune system perceives threats. *Science* 2021, 372, 1392–1393.
29. Chemaitelly, H.; Nagelkerke, N.; Ayoub, H.H.; Coyle, P.; Tang, P.; Yassine, H.M.; Al-Khatib, H.A.; Smatti, M.K.; Hasan, M.R.; Al-Kanaani, Z.; et al. Duration of immune protection of SARS-CoV-2 natural infection against reinfection. *J. Travel Med.* 2022, 29, taac109.
30. <https://www.m3.com/news/iryoishin/1133025>
31. <https://president.jp/articles/-/53323?page=4>
32. <https://twitter.com/aquariusmed/status/1641732605539418113?ctx=HHwWWgoDUlejGzcgtAAAAAA>
33. <https://gemmed.ghc-j.com/?p=52573>
34. Ciarambino T, Crispino P, Minervini G, Giordano M. COVID-19 and Frailty. *Vaccines (Basel)*. 2023 Mar 7;11(3):606. doi: 10.3390/vaccines11030606.
35. Imoto W, Yamada K, Kawai R, Imai T, Kawamoto K, Uji M, Kanda H, Takada M, Ohno Y, Ohtani H, Kono M, Hikiishi A, Eguchi Y, Namikawa H, Kawaguchi T, Takeya H. A cross-sectional, multicenter survey of the prevalence and risk factors for Long COVID. *Sci Rep.* 2022 Dec 27;12(1):22413.
36. Morioka S, Tsuzuki S, Maruki T, Terada M, Miyazato Y, Kutsuna S, Saito S, Shimanishi Y, Takahashi K, Sanada M, Ashida S, Akashi M, Kuge C, Osanai Y, Tanaka K, Suzuki M, Hayakawa K, Ohmagari N. Epidemiology of post-COVID conditions beyond 1 year: a cross-sectional study. *Public Health*. 2023 Mar;216:39-44.
37. <https://www.yomitv.jp/ZpkJU>
38. Navarro-Bielsa A, Gracia-Cazaña T, Aldea-Manrique B, Abadías-Granado I, Ballano A, Bernad I, Gilaberte Y. COVID-19 infection and vaccines: potential triggers of Herpesviridae reactivation. *An Bras Dermatol*. 2023 May-Jun;98(3):347-354.
39. Iwanaga J, Fukuoka H, Fukuoka N, Yutori H, Ibaragi S, Tubbs RS. A narrative review and clinical anatomy of herpes zoster infection following COVID-19 vaccination. *Clin Anat.* 2022 Jan;35(1):45-51. doi: 10.1002/ca.23790. Epub 2021 Oct 1.
40. Safary A, Esalatmanesh K, Eftekharsadat AT, Jafari Nakjavani MR, Khabbazi A. Autoimmune inflammatory rheumatic diseases post-COVID-19 vaccination. *Int Immunopharmacol.* 2022 Sep;110:109061.
41. Shakoort MT, Birkenbach MP, Lynch M. ANCA-Associated Vasculitis Following Pfizer-BioNTech COVID-19 Vaccine. *Am J Kidney Dis.* 2021 Oct;78(4):611-613.
42. Favaloro EJ. Laboratory testing for suspected COVID-19 vaccine-induced (immune) thrombotic thrombocytopenia. *Int J Lab Hematol.* 2021 Aug;43(4):559-570.
43. Thappu S, Thalappil SR, Abbarh S, Al-Mashdali A, Akhtar M, Alkadi MM. Minimal change disease following the Moderna COVID-19 vaccine: first case report. *BMC Nephrol.* 2021 Nov 11;22(1):376.
44. Ma Q, Li X, Xu G. New-Onset and Relapsed Membranous Nephropathy post SARS-CoV-2 and COVID-19 Vaccination. *Viruses.* 2022 Sep 28;14(10):2143.
45. Schaubsluger T, Rajora N, Diep S, Kirtke T, Cai Q, Hendricks AR, Shastri S, Zhou XJ, Saxena R. De novo or recurrent glomerulonephritis and acute tubulointerstitial nephritis after COVID-19 vaccination: A report of six cases from a single center. *Clin Nephrol.* 2022 May;97(5):289-297.
46. Morimoto N, Mori T, Shioji S, Taguchi T, Watanabe H, Sakai K, Mori K, Yamamura A, Hanioka A, Akagi Y, Fujiki T, Mandai S, Mori Y, Ando F, Susa K, Iimori S, Naito S, Sohara E, Ohashi K, Uchida S. Rapidly progressive IgA nephropathy with membranoproliferative glomerulonephritis-like lesions in an elderly man following the third dose of an mRNA COVID-19 vaccine: a case report. *BMC Nephrol.* 2023 Apr 24;24(1):108.

47. Morgan MC, Atri L, Harrell S, Al-Jaroudi W, Berman A. COVID-19 vaccine-associated myocarditis. *World J Cardiol.* 2022 Jul 26;14(7):382-391.
48. Nassar M, Nso N, Gonzalez C, Lakhdar S, Alshamam M, Elshafey M, Abdalazeem Y, Nyein A, Punzalan B, Durrance RJ, Alfshawy M, Bakshi S, Rizzo V. COVID-19 vaccine-induced myocarditis: Case report with literature review. *Diabetes Metab Syndr.* 2021 Sep-Oct;15(5):102205.
49. Le Vu S, Bertrand M, Jabagi MJ, Botton J, Drouin J, Baricault B, Weill A, Dray-Spira R, Zureik M. Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines. *Nat Commun.* 2022 Jun 25;13(1):3633.
50. Furqan M, Chawla S, Majid M, Mazumdar S, Mahalwar G, Harmon E, Klein A. COVID-19 Vaccine-Related Myocardial and Pericardial Inflammation. *Curr Cardiol Rep.* 2022 Dec;24(12):2031-2041.
51. Fazlollahi A, Zahmatyar M, Noori M, Nejadghaderi SA, Sullman MJM, Shekarriz-Foumani R, Kolahi AA, Singh K, Safiri S. Cardiac complications following mRNA COVID-19 vaccines: A systematic review of case reports and case series. *Rev Med Virol.* 2022 Jul;32(4):e2318.
52. Foltran D, Delmas C, Flumian C, De Paoli P, Salvo F, Gautier S, Drici MD, Karsenty C, Montastruc F. Myocarditis and pericarditis in adolescents after first and second doses of mRNA COVID-19 vaccines. *Eur Heart J Qual Care Clin Outcomes.* 2022 Mar 2;8(2):99-103.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.