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Towards the light at the end of the tunnel: Changes in clinical settings and political measures regarding COVID-19 from 2021, and future perspectives in Japan

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Abstract: Japan has faced seven waves of the COVID-19 pandemic since 2020. Due to the less severe Omicron variant and the high rate of vaccination nationwide, the death rate has declined compared to that due to previous variants. In early 2022, current Prime Minister Fumio Kishida devised a new concept entitled "Living with COVID-19", encouraging a new lifestyle of living with SARS-CoV-2. Although treatment and prevention options have increased, the Omicron variant still causes deaths among the most vulnerable population. Before accepting life with SARS-CoV-2, challenges remain, especially with regard to communication, the healthcare system, and vaccination. A society-wide strategy involving multiple stakeholders should be adopted to mitigate the damage and achieve a true world where we are "Living with COVID-19".

***Keywords*:** Omicron variant, living with COVID-19, communication, healthcare system, vaccination

The world has been suffering from the COVID-19 pandemic since the end of 2019, and Japan is no exception. Drastic changes have occurred in epidemiology, virology, public health, and the medical response to COVID-19 (*e.g.*, prevention, diagnosis, and treatment). From a clinician's perspective, this work outlines the changes in and evolution of measures against COVID-19 in Japan from the outbreak of the Delta variant (the 5th wave) to the present outbreak due to the Omicron variant (the 7th wave) (from August 2021 to November 2022).

A summary of changes in public health and political measures

Countries have adopted different policies and philosophies with respect to the pandemic. In the United Kingdom, for example, the government aimed to overcome the pandemic early, and all restrictions regarding COVID-19 were lifted in March 2022 (*1*). In contrast, the Chinese Government has implemented strict regulations known as the "Zero-COVID policy" (*2*). Unlike either of these approaches, Japan has implemented multiple mitigation measures but it has not lifted most COVID-19 restrictions (Figure 1).

Since the time of former Prime Minister Shinzo Abe, Japan has developed a vaccination program as one of its main strategies against the pandemic.

In May 2021, after former Prime Minister Yoshihide Suga initiated the "one million vaccinations per day" campaign during the 4th wave, the number of COVID-19 cases and deaths consequently fell (*3*). Japan faced the 5th wave (late July - early October 2021) during the Tokyo Olympic Games (23rd July - 8th August 2021) due to the Delta variant. The Delta variant was notorious for its high virulence; even young patients occasionally succumbed to severe disease (*4*). Hospitals kept being overwhelmed with many COVID-19 patients, especially patients who were unvaccinated (*5*). The Japanese Government declared a 4th state of emergency (12th Jul 2021-30th Sep 2021) and semi-emergency measures (known as "Man-bo" in Japanese) to reduce the number of cases and severe cases.

Japan is currently facing waves of the Omicron variant, with the 6th in mid-January- early June 2022 and the 7th in early July - early October 2022. The Omicron variant has a higher transmissibility than any previous Variants of Concern (VOCs) (*6*).

In early 2022, under the current Prime Minister Fumio Kishida, the government devised a new concept, "Living with COVID-19", to live with SARS-CoV-2 instead of suppressing it. The decline in mortality among patients with COVID-19 compared to that during the early stages of the pandemic corroborated this approach (*7*).

The government shortened the quarantine period for people who had close contact with COVID-19 patients (July 2022), it subsequently shortened the quarantine

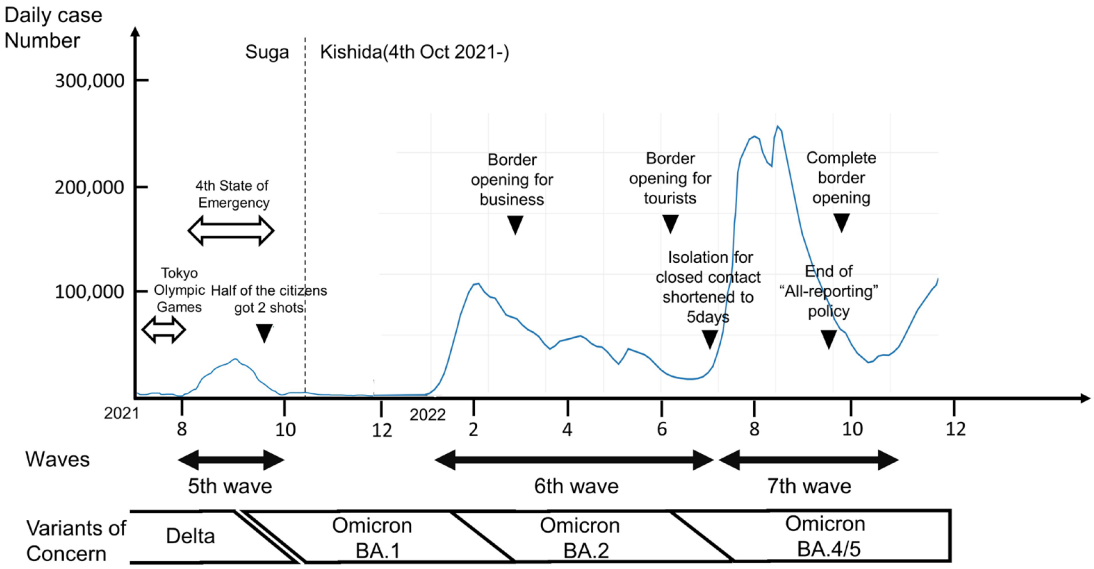

Figure 1. A graph of the daily number of cases from August 2021 to the present. During this period, Japan faced the 5th wave due to the Delta variant and the 6th and 7th waves due to the Omicron variant. The number peaked in August during the 7th wave, preventive measures were gradually implemented. The 8th wave began at the end of November 2022.

period for patients with COVID-19 (September 2022), and it eased restrictions to an extent. In August 2022, Japan's weekly number of newly diagnosed COVID-19 patients was the highest worldwide for four weeks. This is probably a misleading figure because Japan still conducted notifiable disease surveillance to actively diagnose and report cases, whereas other countries reduced the rounds of testing.

In September 2022, the government changed the "all reporting policy" of notifiable disease surveillance of COVID-19 and Japan opened its borders to the outside, shifting toward a world where we are "Living with COVID-19".

Clinical issues

Changes in clinical epidemiology

During the 5th wave, the proportion of severe cases was high mainly because the virulent Delta variant was dominant. Most patients who needed immediate hospitalization were unvaccinated or had an underlying illness. Overloaded hospitals had difficulty promptly receiving patients with severe COVID-19 or who were at high risk of becoming severely ill.

During the 6th and 7th waves, when Omicron was the main variant, the disease was less severe than that due to the Delta variant. The Omicron variant is less virulent than conventional strains and may be less deadly than seasonal influenza (*8*). Patients in critical condition who needed specialized urgent care, such as intubation and extracorporeal membrane oxygenation, were seldom seen (*5*).

However, the number of COVID-19 patients increased more than before, mainly because of the enhanced transmissibility of the Omicron variant. A review indicated that the Omicron variant has a mean primary reproduction number of 8.2, 3.8 times higher than that of the Delta variant (*6*). Most admitted patients are senior citizens, and young patients with mild disease are advised to stay home, even if unvaccinated.

Outside large hospitals, calls for on-site clinics, remote medical interviews, and at-home medical care increased.

The causes of death have also been changed as a consequence. According to a brief report from a national hospital in Tokyo, the leading cause of death during the days of Omicron was exacerbation of pre-hospitalization complications (46%; 11 out of 24 deaths), followed by respiratory failure due to pneumonia (29%; 7/24 deaths.), which was far lower than that during the days of Delta (80%; 16 out of 20 deaths) (*9*)

The aforementioned report implies that succumbing to COVID-19 is less likely but that the virus still causes death among the most vulnerable. Thus, COVID-19 is still a serious threat that cannot be ignored.

Treatment

Emerging evidence has revealed that the pillars for the treatment of COVID-19 include early antiviral therapy, steroids such as dexamethasone for patients needing oxygen, and appropriate anticoagulation (*10*).

For patients in dire need of oxygen, adjunctive immunomodulators such as tocilizumab and baricitinib are also available. Monoclonal antibodies such as

casirivimab/imdevimab and sotrovimab were approved in July 2021 and September 2021, respectively. However, there is a concern that the efficacy of these drugs may decrease with the Omicron subvariants (B1.1.529/BA.2, BA.4, and BA.5.strains) (*11,12*), so these drugs are currently withheld in clinical practice. Available antivirals in Japan are similar to those in the US, such as remdesivir, molnupiravir, and nirmatrelvir/ritonavir, with indicated use for patients with risk factors for severe disease. All of these antivirals and monoclonal antibodies were controlled by the Ministry of Health, Labor, and Welfare when they were first approved, and remdesivir and molnupiravir are now in general distribution. Ensitrelvir is the first-ever Japanese-made oral antiviral granted approval for emergency use in November 2022. The current recommendation is to consider using it for patients with clinical symptoms such as a high fever, bad cough, and severe sore throat (*13*). Further considerations regarding the population to receive this drug should be based on the results of future clinical trials.

Vaccine and pre-exposure prophylaxis

Encouraging vaccines is the most reliable way to prevent severe disease and infection. To date, approved vaccines in Japan include those from Pfizer-BioNTech (approved on February 14, 2021), AstraZeneca (May 21, 2021), Takeda/Moderna (May 21, 2021), and Johnson & Johnson (May 24, 2021). As of November 2022, only the Pfizer-BioNTech and Moderna/Takeda vaccines are publicly used. Omicron-targeting bivalent vaccines, such as the BA.1-targeting bivalent vaccines by Pfizer and Moderna and BA.4/5-targeting bivalent vaccine by Pfizer, were approved by October 2022.

A study has noted the effectiveness of COVID-19 vaccines against symptomatic SARS-CoV-2 infection during periods when Delta and Omicron prevailed in Japan (*14*). Both BA.1- and BA.4/5-targeting vaccines have similar effectiveness against the current dominant subvariant (BA.4/5 (*15*)), so the government, local authorities, and healthcare workers should encourage vulnerable people to receive either instead of waiting for a BA.4/5-targeting vaccine.

Tixagevimab/cilgavimab, a combination of two different monoclonal antibodies, was approved on September 7, 2022 for pre-exposure prophylaxis and treatment of severely immunocompromised patients. Currently, it is not generally distributed and available only for pre-exposure prophylaxis.

Prospects for the future

We discussed what has already been done thus far in Japan. Our philosophy is that every political measure, form of medical care, and public health effort has to target vulnerable people in various ways. Here, from a physician's perspective, is a 3-pronged approach to coping with this pandemic involving communication, the healthcare system, and vaccination.

Communication

Providing citizens with evidence-based information is crucial. Some may believe misinformation without evidence, increasing their mistrust of evidence-based medicine. Mass media such as TV channels, social media, and movie streaming sites are responsible for spreading information. Former President of the United States Donald Trump publicly supported the antimalarial drug hydroxychloroquine, and former President of Brazil Jair Bolsonaro advocated chloroquine, both of which have not proven effective against COVID-19. The government, local authorities, and scientific experts must collaborate to establish an effective and clear message and to proactively combat fake news.

Within the bounds of free speech, every communication must be evidence-based and unbiased. Every disseminator of information should be aware of its responsibility and its possible impact on society. Severe adverse reactions to vaccines should be acknowledged as a fact, but messages should nonetheless support mass vaccination programs because they are absolutely essential to alleviating a pandemic's effects on society.

Various challenges to Japan's healthcare system remain

First, some facilities and clinics still do not accept COVID-19 patients or people with suspected symptoms of COVID-19. Patients in a particular condition (such as pregnant women, newborns, and people who need specialized care) often have difficulty promptly accessing medical care. This is presumably because of a lack of knowledge and experience. Since we face a pandemic, the entire healthcare system must tackle this public enemy.

Most patients infected with Omicron have mild disease, so stratification of healthcare facilities may be effective; clinics and doctors providing at-home care could take on risk-free patients with mild symptoms while referring patients in serious condition to larger hospitals. Testing should be prioritized for vulnerable people to optimize the workforce. The over-the-counter self-antigen test should be encouraged for people without risk of severe disease to reduce unnecessary doctor visits.

Second, the role of surveillance is likely to be affected because notifiable disease surveillance changed dramatically after September 26, 2022. Nowadays, only patients with the following conditions are to be reported: those who are *i*) older than 65 years of age, *ii*) hospitalized, *iii*) with severe disease risk factors and receiving COVID-specific treatment, or *iv*) pregnant. As a result, follow-up with patients who do not fall into these categories through surveillance will be difficult. In medicine, a close eye has to be kept on the unusual

clinical course of unreported cases. Periodic studies of particular populations, such as children, might need to be conducted. In addition, precautions are required for racial and ethnic minorities who are at a greater risk of COVID-19 exposure (*16*). The low severity of the disease and its impact on daily life may cause people to forego testing. As a result, the number of people with undiagnosed "hidden COVID-19" may increase as the infection spreads. "Hidden COVID-19" may trigger an outbreak of varying size in various settings. Therefore, a preemptive policy on preventing infection might be necessary for certain circumstances, and especially where a vulnerable population is involved.

As the government opens the borders, new variants will enter into Japan. In November 2022, there were signs of other outbreaks of BQ.1, BQ1.1, and XBB (recombinants of the BJ.1 and BM1.1.1 lineages) that may negatively affect vaccine effectiveness (*17*). Genetic mutations appear one after another, so quality surveillance should be maintained by enhancing genomic surveillance.

Third, in some medical settings such as nursing homes or remote areas, essential public health supplies to protect healthcare workers tend to run short. The World Health Organization guidelines recommend using droplet and contact precautions (medical masks, gowns, gloves, and eye protection) for all healthcare workers when caring for patients with suspected or confirmed COVID-19 (*18*). The pandemic has revealed longstanding vulnerabilities in the supply chain for essential items. Remedies such as enhancing domestic manufacturing and use of digital technology should soon be implemented.

Fourth, effective antivirals that reduce the proportion of severe cases have been distributed disproportionately. In medically underserved areas such as mountain regions and remote islands, oral antivirals may play a more crucial role than in urban areas, since there may be minimal or no hospital beds. The government and local authorities have to tackle this problem soon to prevent greater disparities in accessing treatment.

Vaccination

Vaccine hesitancy is a significant challenge to ending this pandemic. Multifaceted problems contribute to it, including socioeconomic status, low trust in government, fake news, rumors spread by influential people, and incorrect advice from primary care doctors. Vaccination should be increasingly encouraged since it offers the most robust protection one can have, and especially when preceded by previous infections (i.e., hybrid immunity) (*19*).

Conclusion

We have discussed 3 prongs of a possible approach to end this pandemic. A society-wide strategy involving multiple stakeholders should be adopted to mitigate the damage and achieve a world where we are "Living with COVID-19".

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