Omicron: Understanding the Latest Variant of SARS-CoV-2 and Strategies for Tackling the Infection

Sreekanth Reddy Obireddy,*[a, b, c] Ujwala Guntakanti,[b] Anitha Kowthalam,[b] Subha Marata Chinna Subbarao,[b] and Wing-Fu Lai*[a, c, d]

The new variant of concern of SARS-CoV-2, namely Omicron, has triggered global fear recently. To date, our knowledge of Omicron, particularly of how S glycoprotein mutations affect the infectivity of the virus and the severity of the infection, is far from complete. This hinders our ability to treat the disease and to predict the future state of SARS-CoV-2 threats to well-being and economic stability. Despite this, efforts have been made to unveil the routes of transmission and the efficiency of existing vaccines in tackling Omicron. This article reviews the latest understanding of Omicron and the current status of the use of vaccines and drugs for infection control. It is hoped that this article can offer insights into the development of more effective measures to tackle the pandemic.

1. Background

COVID-19 has been a global pandemic, and the situation is worsened recently in South Africa because of the emergence of the Omicron variant (B.1.1.529). In fact, the number of cases reported each day in South Africa had been quite modest until the November 16, 2021 when more than 1000 cases were reported. On November 24, 2021, a report concerning a case of Omicron infection in South Africa was received by the World Health Organization (WHO).[1] Two days later, the first occurrence of Omicron infection was confirmed in Europe. Nine cases were reported in the UK on November 29, 2021. Six of of them were in Scotland.[2] To date, the Omicron infection has spread to different countries, ranging from the Netherlands, France, Germany, and Portugal to Italy.[1] The Omicron variant is highly contagious. This is partially attributed to mutations in the Omicron receptor-binding domain (RBD).[3] These mutations are predicted to favour interactions with ACE2, leading to immunological escape and a higher rate of viral transmission.[3] In fact, the Omicron variant exhibits around 50 mutations in its genome, with more than 30 of these being found in its spike (S) protein.[4,5] Owing to genetic changes of the Omicron variant, the relative effective reproduction number of Omicron over Delta is estimated to be 3.19 times.[6]

In fact, since the start of the pandemic, different types of variants have been reported. Apart from those formerly monitored variants (Table 1),[7] diverse variants of concern (VOCs) of COVID-19 have emerged over the last few years. VOCs refer to variants of SARS-CoV-2 in which alterations in the S protein RBD significantly improve the binding capacity of the virus. They show an increase in the rate oftransmission, a decrease in the susceptibility to neutralization caused by antibodies produced in patient's bodies and an increase in the resistance to existing treatment options (Table 2).[7,8] Apart from VOCs, some variants are designated as variants of interest (VOI), which not only display genetic changes that are predicted or known to influence virus characteristics (including the transmission rate and the severity of the infection caused) but are also thought to show epidemiological impacts to impose an emerging risk to global public health.[7,8] Besides VOCs and VOIs, there are variants designated as "variants under monitoring (VUMs)" (Table 3). These variants are suspected to possess genetic alterations that may alter virus characteristics, yet their phenotypic or epidemiological impact are ill-defined at present, thereby requiring further studies for verification.[7,8]

Previously, the Commonwealth Scientific and Industrial Research Organization (CSIRO) in Australia has declared that variants containing both N501Y (Omicron) and P681R (Delta) mutations do not propagate; however, more studies are still required so that our understanding of the current pandemic can be enhanced. Israel has already reported the first case of Flurona,[9] which is resulted from dual infection caused by the flu virus and SARS-CoV-2.[5,10] In Egypt, a 21-year-old woman has also been tested positive for both SARS-CoV-2 and influenza A (H1N1). Recently, the number of COVID-19 cases in several Asian and European countries (including China and South Korea) has escalated abruptly partly due to the spread of the "stealth" Omicron (BA.2) variant.[11] Along with the possible emergence of Delmicron as recently reported,[5,10] it is unlikely

[a] Dr. S. R. Obireddy, Dr. W.-F. Lai
Department of Urology,
Zhejiang Provincial People's Hospital,
Hangzhou Medical College
Zhejiang, 310012 (P. R. China)
E-mail: sreekanthchem7@gmail.com
[b] Dr. S. R. Obireddy, U. Guntakanti, Dr. A. Kowthalam,
Prof. S. Marata Chinna Subbarao
Department of Chemistry,
Sri Krishnadevaraya University
Anantapur515003 (India)
[c] Dr. S. R. Obireddy, Dr. W.-F. Lai
Ciechanover Institute of Precision and Regenerative Medicine,
The Chinese University of Hong Kong (Shenzhen)
Shenzhen518172 (P. R. China)
[d] Dr. W.-F. Lai
Department of Applied Biology and Chemical Technology,
Hong Kong Polytechnic University
Hong Kong Special Administrative Region (P. R. China)
E-mail: rori0610@graduate.hku.hk

Table 1. Representative examples of variants of SARS-CoV-2 currently designated VOCs and VOIs. Data are obtained from Ref. [7].

Type	WHO label	Pango lineage	GISAID clade	Next strain clade	Additional amino acid changes monitored	Earliest documented samples	Date
VOC	Alpha	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	UK, Sep-2020	18-Dec-2020
	Beta	B.1.351	GH/501Y.V2	20H (V2)	+S:L18F	South Africa, May-2020	18-Dec-2020
	Gamma	P.1	GR/501Y.V3	20J (V3)	+S:681H	Brazil, Nov-2020	11-Jan-2021
	Delta	B.1.617.2	G/478K.V1	21A, 21I, 21J	+S:417N +S:484K	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021
	Omicron	B.1.1.529	GR/484A	21K	–	Multiple countries, Nov-2021	VUM: 24-Nov-2021 VOC: 26-Nov-2021
VOI	Lambda	C.37	GR/452Q.V1	21G	–	Peru, Dec-2020	14-Jun-2021
	Mu	B.1.621	GH	21H	–	Colombia, Jan-2021	30-Aug-2021

Table 2. Representative examples of variants of SARS-CoV-2 currently designated as VUMs. Data are obtained from Ref. [7].

Pango lineage	GISAID clade	Next strain clade	Earliest documented samples	Date
AZ.5	GR	–	Multiple countries, Jan-2021	VUM: 02-Jun-2021
C.1.2	GR	–	South Africa, May 2021	01-Sep-2021
B.1.617.1	G/452R.V3	21B	India, Oct-2020	VOI: 4-Apr-2021 VUM: 20-Sep-2021
B.1.526	GH/253G.V1	21F	USA, Nov-2020	VOI: 24-Mar-2021 VUM: 20-Sep-2021
B.1.525	G/484K.V3	21D	Multiple countries, Dec-2020	VOI:17-Mar-2021 VUM: 20-Sep-2021
B.1.630	GH	–	Dominican Republic, Mar-2021	12-Oct-2021
B.1.640	GH/490R	–	Republic of Congo, Sep-2021	22-Nov-2021

that COVID-19 will end in 2022. In this article, we will first review the latest understanding of Omicron, followed by a discussion of the current status of the use of vaccines and drugs for infection control. It is hoped that this article can offer

Sreekanth Reddy Obireddy completed his PhD in the Department of Chemistry at Sri Krishnadevaraya University, Andhra Pradesh, India. He is currently working as an Academic Consultant at Sri Krishnadevaraya University and as a Visiting Scholar at the Chinese University of Hong Kong (Shenzhen). His research interest lies in the fabrication of polymeric blend matrices for biomedical applications.

Ujwala Guntakanti is currently a PhD student at Sri Krishnadevaraya University, Andhra Pradesh, India. Her research interest lies in the fabrication and characterization of polymer matrices loaded with metal nanoparticles for biomedical and dielectric applications.

Anitha Kowthalam has been working as an Assistant Professor in the Department of Chemistry at Sri Krishnadevaraya University, Andhra Pradesh, India since 2010. Her research interest lies in the development of electrochemical biosensors, in the synthesis of nanocomposites and biomolecules-loaded polymer networks, and in the application of those materials in drug delivery and detection.

Subha Marata Chinna Subbarao obtained her PhD from Sri Krishnadevaraya University. She worked as a Senior Professor at that University. She was in the UK on a Commonwealth Academic Staff Fellowship during 1993–1994, and is currently a UGC-BSR Faculty Fellow on polymer-based drug delivery. She is also the Head, Rector, and Vice Chancellor (I/C) at Sri Krishnadevaraya University.

Wing-Fu Lai is an Honorary Professor at Zhejiang Provincial People's Hospital. He is also an adjunct faculty member in the Department of Applied Biology and Chemical Technology at the Hong Kong Polytechnic University. His research interest lies in the design and engineering of both organic and inorganic materials for encapsulation and controlled release of bioactive agents.

Table 3. Representative examples of formerly monitored variants of SARS-CoV-2. Data obtained from Ref. [7].

Pango lineage	GISAID clade	Next strain clade	Earliest documented samples	Date
AV.1	GR	–	UK, Mar-2021	VUM: 26-May-2021 Reclassified: 21-Jul-2021
AT.1	GR	–	Russian Federation, Jan-2021	VUM: 09-Jun-2021 Reclassified: 21-Jul-2021
P.2	GR/484K.V2	20B/S.484K	Brazil,Apr-2020	VOI: 17-Mar-2021 VUM: 6-Jul-2021 Reclassified: 17-Aug-2021
P.3	GR/1092K.V1	21E	Philippines, Jan-2021	VOI: 24 Mar 2021 VUM: 6 Jul 2021 Reclassified: 17-Aug-2021
R.1	GR	–	Multiple countries, Jan-2021	VUM: 07-Apr-2021 Reclassified: 9-Nov-2021
B.1.466.2	GH	–	Indonesia, Nov-2020	VUM: 28-Apr-2021 Reclassified: 9-Nov-2021
B.1.1.519	GR	20B/S.732A	Multiple countries, Nov-2020	VUM: 02-Jun-2021 Reclassified: 9-Nov-2021
C.36.3	GR	–	Multiple countries, Jan-2021	VUM: 16-Jun-2021 Reclassified: 9-Nov-2021
B.1.214.2	G	–	Multiple countries, Nov-2020	VUM: 30-Jun-2021 Reclassified: 9-Nov-2021
B.1.427, B.1.429	GH/452R.V1	21C	USA, Mar-2020	VOI: 5-Mar-2021 VUM: 6-Jul-2021 Reclassified: 9-Nov-2021
B.1.1.523	GR	–	Multiple countries, May-2020	VUM:14-July-2021 Reclassified: 9-Nov-2021
B.1.619	G	20A/S.126A	Multiple countries, May-2020	VUM:14-July-2021 Reclassified: 9-Nov-2021
B.1.620	G	–	Multiple countries, Nov-2020	VUM:14-July-2021 Reclassified: 9-Nov-2021

insights into the development of more effective measures to tackle the pandemic.

2. Structural Understanding of the Omicron Variant

The Omicron variant can be classified as BA.1, BA.2, and BA.3. The B.1.1.529 variant was identified on November 26, 2021 as a VOC by the Technical Advisory Group on Virus Evolution (TAG-VE)of the WHO.[12] B.1.1.529 was discovered via analysis of genome-sequencing data, in which over 30 alterations were identified in the S protein. The S protein is the viral protein that detects host cells and attacks the host's immune system. Numerous alterations have been discovered in Delta and Alpha strains. They have been found to increase the infectivity of the virus. Omicron is a variant that shows a higher rate of transmission and more resistance to vaccine-elicited antibodies.[2] Different sub-variants of Omicron share over 30 mutations in the S protein,[13] with BA.2 being known as the "stealth" variant owing to its failure to be tracked by using polymerase chain reaction (PCR) tests.[5,14] At this moment, detection of BA.2 (whose transmission rate is 1.5 times higher than that of BA.1[13]) can only be achieved by using the sequencing technology.

Among the mutations found in the genome of the Omicron variant, 12 of them are the same as those found in the Alpha, Beta, Gamma, and Delta variants. These mutations are (△H69, △V70, T95I, G142D, △Y144, △Y145, K417N, T478K, N501Y, D614G, H655Y, and P681H). In earlier studies, all of these mutations have been linked to a higher rate of transmission, higher viral binding affinity, and higher efficiency in immune evasion.[15–18] Regarding the fact that the Omicron variant has the same set of mutations as other VOC variants, it may spread and evade the immune system. In addition, even though 9 distinctive mutations (S:N440K, S:G446S, S:S447N, S:T478K, S:E484A, S:Q493R, S:G496S, S:Q298R, S:N501Y)have been found in the Omicron receptor-binding motif, an extra mutation at S:Y505H has been noted in the motif of certain Omicron variants.[19] Besides the mutations mentioned above, a number of other mutations ((A67V, △V143, △N211, L212I, ins214EPE, G339D, S371L, S373P, S375F, N440K, G446S, S477N, E484A, Q493R, G496S, Q498R, Y505H, T547K, N679K, N764K, D796Y, N856K, Q954H, N969K, and L981F)) have been recognized in the Omicron variant; however, their influence on the survival and infectivity of the virus is still ill-elucidated.[20] Recently, a comparative modelling approach has been adopted by a study to simulate, based on genome-sequencing data, the structures of the RBD and N-terminal domain (NTD) of B.1.1.529 *in silico*.[21] A root mean square deviation (RMSD) difference between the wild type virus and the overlaid B.1.1.529 variant has been estimated to be around 0.835 for the RBD and 0.512 for the NTD. This reveals that secondary structural changes take place and lead to a new way of binding and infection. Clearly the associations between mutations and the properties of the virus are highly complicated. There is a long way to go before we

can fully understand the phenotypic changes of the SARS-CoV-2 virus at the genetic level.

3. Transmissibility and Severity of the Omicron Variant

Mutations in the genome of the Omicron variant appear to affect the infectivity and tropism of the virus. The variant appears to spread less effectively in the lung and more effectively in the bronchus.[22] This is supported by the observation that fewer virus-infected cells have been found in human lung explant cultures grown in the laboratory.[22] The reason underlying the variations in the replication ability of the Omicron variant and Delta variant in the lung and the bronchus has yet to be understood. Nevertheless the binding of a virus to its receptors is important to successful infection.[23] SARS-CoV-2 employs its S protein to recognise and targets ACE2.[24] The S protein has a C-terminal domain which is also known as the RBD.[24,25] It mediates cell-to-cell interactions.[26] It can either be lipid-bound and closely linked in a "closed" state, or be unfolded to expose RBDs to enable, higher receptor affinity and greater access to neutralising antibodies.[17] It is possible that mutations in the S protein, especially the RBD, may result in immunological escape, thereby reducing the effectiveness of existing drugs and vaccines.[27,28] In fact, the Omicron S protein has mutations that match substantially with those mutations that have been found to facilitate SARS-CoV-2 to adapt to mouse hosts.[29] uses ACE2 orthologues successfully to get into host cells.[28]

Despite an increasing understanding of the infection mechanism of Omicron, no data have been available to confirm that infection with Omicron produces more severe disease than infection with other variants. Even though the hospitalisation rate in South Africa has increased upon the emergence of the Omicron variant,[1] this may be due to an increase in the overall infection rate, rather than an increase in the severity of the infection. In fact, a recent study shows that, when comparing with patients infected with other VOCs, those infected with the Omicron variant are much younger, and are less likely to be hospitalized even though the variant leads to a significantly higher vaccine breakthrough rate.[30] At this moment, no evidence is available to show that the symptoms of infection caused by the Omicron variant differ from those caused by other variants of SARS-CoV-2. Nevertheless, all variants are potentially capable of causing serious symptoms or even death. This is particularly true among vulnerable populations. Proper preventive measures are always required.[1]

4. Effectiveness of Existing Vaccines and Diagnosis Tools

Comparing with other strains of concern, the Omicron variant is more likely to re-infect COVID-19 patients.[1] Mutations in the Omicron variant have also been shown to increase the infectivity and immune resistance of the virus.[15–18] An earlier study has demonstrated that a synthetic variant possessing 20 mutations in the S protein can almost completely escape from neutralization in both convalescent and vaccine sera.[31] The

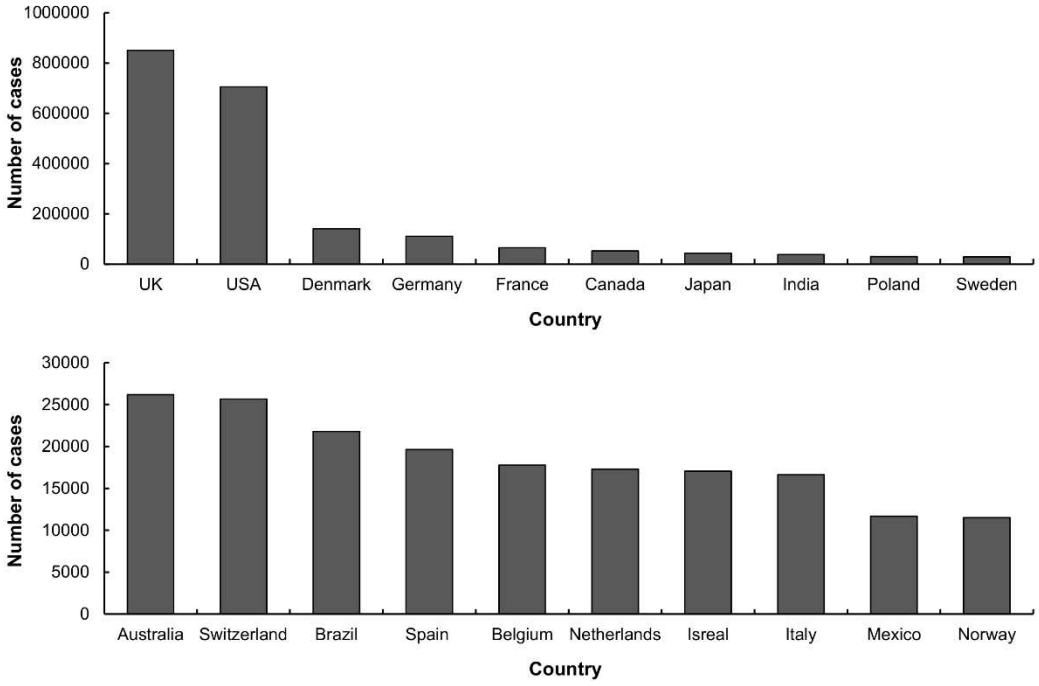

Figure 1. The number of Omicron cases in the first 20 countries that have reported the largest number of cases of Omicron infection. The data are updated to March 21, 2022 and are obtained from Ref. [47].

Omicron variant has many more mutations than this. Its escape from neutralisation is highly possible. Recently, Kannan and co-workers have reported that the mutations in the S protein of the Omicron variant co-evolved at a very high rate with mutations in other parts of the viral genome.[32] This confirms that the Omicron variant may escape from being attacked or recognized by antibodies elicited in an individual due to past infection or vaccination.[32] In fact, vaccines are often designed to target the S protein. Changes in the structure of the S protein of the Omicron variant cause concerns on the effectiveness of an existing vaccine. The situation becomes more complicated by the fact that environmental factors may cause alterations in the S protein structure as well. For example, amino acid variations in the S protein have been found to be at a greater rate among the molnupiravir-treated people.[33] In total 72 changes in the structure of the S protein have been found in 38 individuals having received molnupiravir treatment, even though these alterations may also occur in people administered with a placebo.[33] Last year, the Food and Drug Administration (FDA) considered authorizing certain drugs (such as paxlovid and molnupiravir) under an emergency use authorization (EUA). On November 30, 2021, an FDA advisory group voted 13 to 10 in support of an EUA for molnupiravir.[34]

Apart from the possible impact on the effectiveness of vaccines, mutations in the Omicron variant may affect the accuracy of disease diagnosis, even though their influence on the efficiency of the nucleic acid amplification test (NAAT) for diagnosis seems to be little.[35] S-gene target failure (SGTF) may occur when the Thermo Fischer TaqPath COVID-19 assay is used owing to the deletion of the spike sequence at positions 69 and 70 in the Omicron variant. Concomitant use of multiple tests that examine at least two different parts of the SARS-CoV-2 sequence is, therefore, highly recommended.[35] Right now mutation-specific tests (such as those for E484K/Q, L452R, and N501Y detection) are available in the market. This facilitates the process of variant screening and enhances the efficiency in diagnosing Omicron infection.[35] Despite this, a recent study examining the sensitivity of 7 antigen rapid diagnostic tests (Ag-RDTs) by using samples of patient infected with the Omicron variant revealed a high degree of heterogeneity amongst Ag-RDTs used for Omicron detection.[36] This situation is worsened by the observation that only 50% of the time the tests provide positive results for Omicron infection.[36] Development of more effective tools for Omicron detection is required so that as to more accurate and reliable can be achieved in the clinical setting.

5. Recent Progress in Infection Control

Accompanying with an increase in the knowledge of Omicron infection, several treatment strategies have emerged over the last several months. For instance, treatment with both molnupiravir and nirmatrelvir has been proposed as an effective strategy to tackle Omicron infection.[37] The activity of the S protein has also been shown to be suppressed by using soluble ACE2, which adheres to the RBD and prevents viral entry.[38] Soluble ACE2 has, therefore, emerged as another drug candidate for treating Omicron infection. On top of these agents, corticosteroids and IL6 receptor blockers continue to be effective in controlling severe COVID-19 infection. Other treatment options have been being evaluated to determine if they remain effective to combat the Omicron variant.[1] Despite the recent progress in treatment development as mentioned above, prevention is always better than cure. Vaccination is still the most important way to control Omicron infection and to lower the development of severe COVID-19 symptoms.

WHO is collaborating with technical partners to determine the possible impact of this strain on the effectiveness of the vaccination programmes. Vaccines continue to be crucial for lowering the occurrence of severe symptoms and death, notably those caused by the major circulating strain, Delta. Vaccines currently in use are still effective in preventing serious symptoms and death. Around 50 different mutations have been found in the genome of the variant, including over 30 in the S protein. As far as the development of vaccines is concerned, the S protein, which comes into contact with human cells prior to cell entry, is the main target. Antibodies such asVIR-7831 (sotrovimab) and VIR-7832 show strong affinity to the S protein. This, therefore, raises concerns on the effectiveness of existing measures to tackle Omicron infection. This concern has, however, been ameliorated with the recent observation that people receiving three doses of BNT162b2 can be more effectively protected from infection with the Omicron variant (B.1.1.529 lineage).[40] This is partially because a third dose of BNT162b2 can give a neutralising antibody titre approximately 25-fold higher than that achieved by two doses.[40] Nevertheless, because the majority of the epitopes of CD8+ T cells′ are unaffected by the mutations in the Omicron variant, two doses of the vaccine may still help avoid patients from getting serious symptoms.[40] This has been partially demonstrated by the case of South Africa. Among the cases of Omicron infection admitted to NetCare hospitals in South Africa, 75% of them have not been vaccinated.[41] The symptoms of those unvaccinated patients have been found to be more severe than those vaccinated ones.[41] This demonstrates the protective effect brought about by vaccination against Omicron infection. In fact, the neutralizing activity led by Pfizer 2-dose vaccine sera for the Omicron variant has been shown to be 20–40-fold lower than that for early pandemic viruses.[42] The activity of AZ 2-dose vaccine sera has also been reported to be significantly reduced even to fall below the limit of detection. Yet, regardless of the type of vaccines a person has received, an mRNA booster can always lead to an increase in the neutralising activity. A similar observation has been made by Nemet and colleagues,[43] who evaluated the effectiveness of BNT162b2 against the Omicron variant and found that two doses of BNT162b2 provide little protective action. A third dose greatly increases the neutralising antibody titre even though the protective effect against the Omicron variant is 4-fold less than that against the Delta variant. Recently, Gruell and co-workers have reported that polyclonal sera from people who have received two doses of BNT162b2 show little neutralising activity against the Omicron variant.[44] A considerable rise in the neutralizing activity occurs

in people upon the recipient of an mRNA booster.[44] Receiving three doses of vaccines is clearly one of the possible strategies to tackle Omicron infection in the community,[45] though further studies are needed to determine how long the neutralising activity lasts.[42]

6. Concluding Remarks and Future Outlook

Omicron infection has been regarded as a public health threat because the Omicron variant contains diverse mutations in its genome, leading to changes in its infectivity and reducing the effectiveness of existing measures for infection control.[2] Close monitoring of epidemiological trends for existing VOCs, VOIs, and VUMs may provide insights into possible measures to combat Omicron infection.[46] In addition, early detection of cases of infection is vital so that transmission among the public can be better controlled. Right now it is very likely that the Omicron variant has spread to other places in South Africa or even other countries (Figure 1).[46,47] Despite this, as mentioned earlier in this article, at the moment Omicron infection can still be detected using PCR techniques. Studies developing various diagnosis tools, such as Ag-RDTs, for Omicron detection are ongoing.[1] All these are expected to significantly increase the effectiveness of infection control. Apart from this, antiviral drugs such as paxlovid and molnupiravir are now being considered to be authorized under an EUA by the FDA. These antiviral drugs can be used to treat mild Omicron infection. Severe infection can be treated by using IL6 receptor blockers and corticosteroids. To prevent the development of drug resistance, changing the chemical structure of a drug is one method but this takes time. Another approach is to change the dosage form or to repurpose older antiviral drugs.[48] Obviously there is still a long way to go before we can achieve all these. Collaborative efforts among the scientific, industrial, commercial and public sectors of the society are required. Yet, these efforts are worthwhile and can benefit public health substantially.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: infection control · omicron · SARS-CoV-2 · S glycoprotein · variant of concern

[1] World Health Organization, *"Update on Omicron"*, can be found under https://www.who.int/news/item/28-11-2021-update-on-omicron, **2021**.
[2] I. Torjesen, *Br. Med. J.* **2021**, *375*, n2943.
[3] S. Vardhan, S. K. Sahoo, *Comput. Biol. Med.* **2022**, *144*, 105367.
[4] R. K. Mohapatra, A. K. Sarangi, V. Kandi, M. Azam, R. Tiwari, K. Dhama, *J. Med. Virol.* **2022**, *94*, 1780–1783.
[5] E. Callaway, *Nature* **2022**, *602*, 556–557.
[6] K. Ito, C. Piantham, H. Nishiura, *J. Med. Virol.* **2022**, *94*, 2265–2268.
[7] World Health Organization, *"Tracking SARS-CoV-2 variants"*, can be found under https://www.who.int/en/activities/tracking-SARS-CoV-2-variants, **2021**.
[8] Centers for Disease Control and Prevention, *"SARS-CoV-2 Variant Classifications and Definitions"*, can be found under https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#anchor 1632158885160, **2021**.
[9] R. K. Mohapatra, R. Tiwari, A. K. Sarangi, M. R. Islam, C. Chakraborty, K. Dhama, *J. Med. Virol.* **2022**, https://doi.org/10.1002/jmv.27633.
[10] R. K. Mohapatra, R. Tiwari, A. K. Sarangi, S. K. Sharma, R. Khandia, G. Saikumar, K. Dhama, *J. Med. Virol.* **2022**, *94*, 1761–1765.
[11] F. Rahimi, A. Talebi, B. Abadi, *Int. J. Surg. Pathol.* **2022**, *99*, 106261.
[12] World Health Organization, *"Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern"*, can be found under https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern, **2021**.
[13] F. Rahimi, A. Talebi, B. Abadi, *Int. J. Surg. Pathol.* **2022**, *99*, 106261.
[14] R. K. Mohapatra, S. Kuppili, T. Kumar Suvvari, V. Kandi, A. Behera, S. Verma, E. Z. Kudrat, S. K. Biswal, T. H. Al-Noor, M. M. El-ajaily, A. K. Sarangi, K. Dhama, *Chem. Biol. Drug Des.* **2022**, https://doi.org/10.1111/cbdd.14035.
[15] W. T. Harvey, A. M. Carabelli, B. Jackson, R. K. Gupta, E. C. Thomson, E. M. Harrison, C. Ludden, R. Reeve, A. Rambaut, S. J. Peacock, D. L. Robertson, *Nat. Rev. Microbiol.* **2021**, *19*, 409–424.
[16] A. J. Greaney, T. N. Starr, P. Gilchuk, S. J. Zost, E. Binshtein, A. N. Loes, S. K. Hilton, J. Huddleston, R. Eguia, K. H. D. Crawford, A. S. Dingens, R. S. Nargi, R. E. Sutton, N. Suryadevara, P. W. Rothlauf, Z. Liu, S. P. J. Whelan, R. H. Carnahan, J. E. Crowe Jr., J. D. Bloom, *Cell Host Microbe* **2021**, *29*, 44–57.
[17] J. A. Plante, Y. Liu, J. Liu, H. Xia, B. A. Johnson, K. G. Lokugamage, X. Zhang, A. E. Muruato, J. Zou, C. R. Fontes-Garfias, D. Mirchandani, D. Scharton, J. P. Bilello, Z. Ku, Z. An, B. Kalveram, A. N. Freiberg, V. D. Menachery, X. Xie, K. S. Plante, S. C. Weaver, P. Y. Shi, *Nature* **2021**, *592*, 116–121.
[18] P. Arora, S. Pöhlmann, M. Hoffmann, *Signal Transduct. Target Ther.* **2021**, *6*, 101.
[19] C. T. Ford, D. J. Machado, D. A. Janies, *Front. Virol.* **2022**, https://doi.org/10.3389/fviro.2022.830202.
[20] R. Sarkar, M. Lo, R. Saha, S. Dutta, M. Chawla-Sarkar, *medRxiv* **2021**, https://doi.org/10.1101/2021.12.04.21267284.
[21] A. Khan, H. Waris, M. Rafique, M. Suleman, A. Mohammad, S. S. Ali, T. Khan, Y. Waheed, C. Liao, D. Q. Wei, *Int. J. Biol. Macromol.* **2022**, *200*, 438–448.
[22] K. P. Y. Hui, J. C. W. Ho, M. C. Cheung, K. C. Ng, R. H. H. Ching, K. L. Lai, T. T. Kam, H. G. Gu, K. Y. Sit, M. K. Y. Hsin, T. W. K. Au, L. L. M. Poon, M. Peiris, J. M. Nicholls, M. C. W. Chan, *Nature* **2022**, *603*, 715–720.
[23] P. Han, L. Li, S. Liu, Q. Wang, D. Zhang, Z. Xu, P. Han, X. Li, Q. Peng, C. Su, B. Huang, D. Li, R. Zhang, M. Tian, L. Fu, Y. Gao, X. Zhao, K. Liu, J. Qi, G. F. Gao, P. Wang, *Cell* **2022**, *185*, 630–640.
[24] Q. Wang, Y. Zhang, L. Wu, S. Niu, C. Song, Z. Zhang, G. Lu, C. Qiao, Y. Hu, K.-Y. Yuen, Q. Wang, H. Zhou, J. Yan, J. Qi, *Cell* **2020**, *181*, 894–904.
[25] L. Wu, Q. Chen, K. Liu, J. Wang, P. Han, Y. Zhang, Y. Hu, Y. Meng, X. Pan, C. Qiao, S. Tian, P. Du, H. Song, W. Shi, J. Qi, H.-W. Wang, J. Yan, G. F. Gao, Q. Wang, *Cell Discov.* **2020**, *6*, 68.
[26] C. Toelzer, K. Gupta, S. K. N. Yadav, U. Borucu, A. D. Davidson, M. Kavanagh Williamson, D. K. Shoemark, F. Garzoni, O. Staufer, R. Milligan, J. Capin, A. J. Mulholland, J. Spatz, D. Fitzgerald, I. Berger, C. Schaffitzel, *Science* **2020**, *370*, 725–730.
[27] W. Dejnirattisai, J. Huo, D. Zhou, J. Zahradník, P. Supasa, C. Liu, H. M. E. Duyvesteyn, H. M. Ginn, A. J. Mentzer, A. Tuekprakhon, R. Nutalai, B. Wang, A. Dijokaite, S. Khan, O. Avinoam, M. Bahar, D. Skelly, S. Adele, S. A. Johnson, A. Amini, T. G. Ritter, C. Mason, C. Dold, D. Pan, S. Assadi, A. Bellass, N. Omo-Dare, D. Koeckerling, A. Flaxman, D. Jenkin, P. K. Aley, M. Voysey, S. A. Costa Clemens, F. G. Naveca, V. Nascimento, F. Nascimento, C. Fernandes da Costa, P. C. Resende, A. Pauvolid-Correa, M. M. Siqueira, V. Baillie, N. Serafin, G. Kwatra, K. Da Silva, S. A. Madhi, M. C. Nunes, T. Malik, P. J. M. Openshaw, J. K. Baillie, M. G. Semple, A. R. Townsend, K.-Y. A. Huang, T. K. Tan, M. W. Carroll, P. Klenerman, E. Barnes, S. J. Dunachie, B. Constantinides, H. Webster, et al., *Cell* **2022**, *185*, 467–484.
[28] M. Hoffmann, N. Krüger, S. Schulz, A. Cossmann, C. Rocha, A. Kempf, I. Nehlmeier, L. Graichen, A.-S. Moldenhauer, M. S. Winkler, M. Lier, A. Dopfer-Jablonka, H.-M. Jäck, G. M. N. Behrens, S. Pöhlmann, *Cell* **2022**, *185*, 447–456.
[29] C. Wei, K. J. Shan, W. Wang, S. Zhang, Q. Huan, W. Qian, *J. Genet. Genomics* **2021**, *48*, 1111–1121.
[30] P. A. Christensen, R. J. Olsen, S. W. Long, R. Snehal, J. J. Davis, M. O. Saavedra, K. Reppond, M. N. Shyer, J. Cambric, R. Gadd, R. M. Thakur, A.

Batajoo, R. Mangham, S. Pena, T. Trinh, J. C. Kinskey, G. Williams, R. Olson, J. Gollihar, J. M. Musser, *Am. J. Pathol.* **2022**, *192*, 642–652.
[31] F. Schmidt, Y. Weisblum, M. Rutkowska, D. Poston, J. DaSilva, F. Zhang, E. Bednarski, A. Cho, D. J. Schaefer-Babajew, C. Gaebler, M. Caskey, M. C. Nussenzweig, T. Hatziioannou, P. D. Bieniasz, *Nature* **2021**, *600*, 512–516.
[32] S. R. Kannan, A. N. Spratt, K. Sharma, H. S. Chand, S. N. Byrareddy, K. Singh, *J. Autoimmune Dis.* **2022**, *126*, 102779.
[33] U.S. Food and Drug Administration, *"U.S. Food and Drug Administration, Center for Drug Evaluation and Research, FDA Briefing Document – Antimicrobial Drugs Advisory Committee Meeting, November 30, 2021"*, can be found under https://www.fda.gov/media/154418/download, **2021**.
[34] M. Cully, *"A tale of two antiviral targets – and the COVID-19 drugs that bind them"*, can be found under https://www.nature.com/articles/d41573-021-00202-8, **2021**.
[35] V. M. Ferré, N. Peiffer-Smadja, B. Visseaux, D. Descamps, J. Ghosn, C. Charpentier, *Anaesth. Crit. Care Pain Med.* **2022**, *41*, 100998.
[36] M. Bekliz, F. Perez-Rodriguez, O. Puhach, K. Adea, S. M. Melancia, S. Baggio, A.-R. Corvaglia, F. Jacquerioz-Bausch, C. Alvarez, M. Essaidi-Laziosi, C. Escadafal, L. Kaiser, I. Eckerle, *medRxiv* **2022**, https://doi.org/10.1101/2021.12.18.21268018.
[37] P. Li, Y. Wang, M. Lavrijsen, M. M. Lamers, A. C. de Vries, R. J. Rottier, M. J. Bruno, M. P. Peppelenbosch, B. L. Haagmans, Q. Pan, *Cell Res.* **2022**, *32*, 322–324.
[38] V. Monteil, H. Kwon, P. Prado, A. Hagelkrüys, R. A. Wimmer, M. Stahl, A. Leopoldi, E. Garreta, C. Hurtado del Pozo, F. Prosper, J. P. Romero, G. Wirnsberger, H. Zhang, A. S. Slutsky, R. Conder, N. Montserrat, A. Mirazimi, J. M. Penninger, *Cell* **2020**, *181*, 905–913.
[39] A. L. Cathcart, C. Havenar-Daughton, F. A. Lempp, D. Ma, M. Schmid, M. L. Agostini, B. Guarino, J. Di iulio, L. Rosen, H. Tucker, J. Dillen, S. Subramanian, B. Sloan, S. Bianchi, J. Wojcechowskyj, J. Zhou, H. Kaiser, A. Chase, E. Lauron, M. Montiel-Ruiz, R. Spreafico, J. Noack, N. Czudnochowski, A. Sahakyan, D. Pinto, C. Saliba, E. Delotta, A. Park, E. Cameroni, S. Ledoux, A. Werts, C. Colas, L. Soriaga, A. Telenti, L. A. Purcell, S. Hwang, G. Snell, H. W. Virgin, D. Corti, C. M. Hebner, *bioRxiv* **2022**, https://doi.org/10.1101/2021.03.09.434607.
[40] Pfizer, *"Pfizer and BioNTech Provide Update on Omicron Variant"*, can be found under https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant, **2022**.
[41] Y. Araf, F. Akter, Y. D. Tang, R. Fatemi, M. S. A. Parvez, C. Zheng, M. G. Hossain, *J. Med. Virol.* **2022**, *94*, 1825–1832.
[42] UK. HealthSecurityAgency, *"SARS-CoV-2 Variants of Concern and Variants Under Investigation in England"*, can be found under https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment data/file/1040076/Technical Briefing 31.pdf, **2021**.
[43] I. Nemet, L. Kliker, Y. Lustig, N. Zuckerman, O. Erster, C. Cohen, Y. Kreiss, S. Alroy-Preis, G. Regev-Yochay, E. Mendelson, M. Mandelboim, *N. Engl. J. Med.* **2021**, *386*, 492–494.
[44] H. Gruell, K. Vanshylla, P. Tober-Lau, D. Hillus, P. Schommers, C. Lehmann, F. Kurth, L. E. Sander, F. Klein, *Nat. Med.* **2022**, *28*, 477–480.
[45] Centers for Disease Control and Prevention, *"Updates to the Evidence to Recommendation Framework: Pfizer-BioNTech and Moderna COVID-19 vaccine booster doses"*, can be found under https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-19/06-COVID-Oliver-508.pdf, **2021**.
[46] European Centre for Disease Prevention and Control, *"Guidance for representative and targeted genomic SARS-CoV-2 monitoring"*, can be found under https://www.ecdc.europa.eu/en/publications-data/guidance-representative-and-targeted-genomic-sars-cov-2-monitoring, **2021**.
[47] Statista, *"Number of SARS-CoV-2 Omicron variant cases worldwide as of March 21, 2022, by country or territory"*, can be found under https://www.statista.com/statistics/1279100/number-omicron-variant-worldwide-by-country, **2022**.
[48] O. S. Reddy, W. F. Lai, *ChemBioChem* **2021**, *22*, 939–948.

Manuscript received: March 6, 2022
Revised manuscript received: March 31, 2022
Accepted manuscript online: April 1, 2022
Version of record online: April 19, 2022