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SPECIALTY SECTION

This article was submitted to
Infectious Diseases – Surveillance,
Prevention and Treatment,
a section of the journal
Frontiers in Medicine

RECEIVED 03 August 2022

ACCEPTED 08 September 2022

PUBLISHED 10 October 2022

CITATION

Silva SJRd (2022) The emergence
of new SARS-CoV-2 omicron
subvariants introduces uncertainty
about the end of the COVID-19
pandemic.
Front. Med. 9:1010489.
doi: 10.3389/fmed.2022.1010489

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The emergence of new SARS-CoV-2 omicron subvariants introduces uncertainty about the end of the COVID-19 pandemic

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KEYWORDS

SARS-CoV-2, pandemic, variants of concern, omicron, public health

Background

In late December 2019, health authorities reported a cluster of patients with pneumonia of unknown cause that was epidemiologically linked to a seafood market in Wuhan, Hubei Province, China (1). The etiological agent was identified as a novel coronavirus, eventually named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the respiratory illness was designated as coronavirus disease-2019 (COVID-19) by the World Health Organization (WHO) (2). Since its emergence, the rapid global spread of SARS-CoV-2 has provoked a catastrophic impact in our health and economic systems, causing a devastating pandemic and at the same time testing the resilience of the human population. As of September 5, 2022, more than 604.5 million cases of COVID-19 and 6.4 million deaths have been reported around the world. Most of the cases have been reported by the USA, followed by India, Brazil, and France (3).

The emergence of SARS-CoV-2 has been characterized by the identification of several variants of concern (VOCs) during the pandemic course: alpha (B.1.1.7), beta (B.1.351), gamma (P.1), and delta (B.1.617.2) (4, 5). Over the last 2 years these emerging variants have been associated with an abrupt increase in the number of COVID-19 cases, catalyzing several waves of the pandemic in many countries around the globe (6). More recently, the omicron (B.1.1.529) variant was first reported in Botswana and South Africa at the end of November 2021. After its emergence, this new variant initially named BA.1, spread rapidly across the world and was classified as a VOC by the WHO on 26 November 2021. The BA.1 subvariant rapidly spread around the world and outcompeted other SARS-CoV-2 variants, such as delta variant (7). In a rapidly moving field of study, a cumulative body of findings has demonstrated that the omicron variant is

associated with high transmissibility and less severe illness in the human population, has resistance against most therapeutic antibodies, has robust binding to human ACE2 receptor, and may escape from neutralizing antibody responses in both convalescent and vaccinated individuals (8–11).

However, in the past few months, multiple subvariants (BA.1.1, BA.2, BA.2.12.1, BA.3, BA.4, and BA.5) of the omicron have emerged and raised great concerns to global health (12). These omicron subvariants carry a distinctive constellation of mutations, including several that have been previously determined to be of virological importance to other previous SARS-CoV-2 variants (Figure 1) (13). Among them, BA.2 has recently spread to many countries worldwide (14). Within a short time, research groups around the world have rapidly provided relevant insights about this novel omicron subvariant. Recent progress has shown that the effective reproduction number (R_0) of BA.2 was 1.4-fold higher than that of BA.1 subvariant (7). Immunological studies demonstrated that the immunity induced by most COVID-19 vaccines administered to human populations is not effective against BA.2 subvariant (7). Collectively, *in vitro* and *in vivo* experiments showed that the BA.2 spike confers high capacity to replicate in human nasal epithelial cells and is more pathogenic than the BA.1, as demonstrated in hamsters (7).

As the COVID-19 pandemic progressed, other omicron subvariants are becoming protagonists (Table 1). BA.5 is currently the dominant subvariant in the USA, indicating that this subvariant may have selective advantages when compared to other SARS-CoV-2 omicron variants (15). Moreover, many countries around the world have documented cases associated with the circulation of these novel omicron subvariants.¹ A recent report provided relevant immunological insights in terms of neutralizing antibody titers produced against the Wuhan virus along with omicron subvariants (BA.1, BA.2, BA.2.12.1, BA.4 or BA.5). In that study, Hachmann and colleagues conducted a study including 27 individuals who had been vaccinated and boosted with mRNA vaccine (BNT162b2) and 27 individuals who had been infected with the BA.1 or BA.2 subvariants (12). The results revealed that the omicron subvariants (BA.2.12.1, BA.4, and BA.5) substantially escape neutralizing antibodies induced by previous natural infection and vaccination. Interestingly, the immunological data demonstrated that the neutralizing antibody titers against the subvariants (BA.4, BA.5 or BA.2.12.1) was lower than antibody titers against the BA.1 and BA.2 omicron subvariants (12). Taken together, these findings indicate that the SARS-CoV-2 omicron variant has evolved multiple immune evasion strategies to escape from host the immune response for successful viral replication. This is exemplified due to fact that the omicron spike inefficiently utilizes the TMPRSS2 for cell entry via plasma

membrane fusion. Instead, the omicron variant demonstrates a greater dependency on cell entry via the endocytic route (16).

The widespread dissemination of the SARS-CoV-2 omicron variant has been a devastating threat to pandemic control, indicating that we need to reconsider several features of the virus that had been previously thought to be established. After approximately 2 years and 5 months since the beginning of the pandemic, the emergence of new omicron subvariants introduces uncertainty about the end of the COVID-19 pandemic, at least for now. Although vaccine deployment has contributed to the reduction in the number of hospitalizations and deaths, many countries worldwide have experienced an abrupt increase in the number of COVID-19 cases in the past few months, catalyzing a new wave of the COVID-19 pandemic.

With this in mind, there are some other factors that the healthcare authorities can consider to declare the end of the COVID-19 pandemic: (i) disease severity and mortality due to new SARS-CoV-2 variants and they differ in vaccinated and non-vaccinated individuals. To address this question, recent findings suggested that alpha, beta, gamma, and delta SARS-CoV-2 variants are more serious than the Wuhan virus in terms of hospitalization, intensive care unit (ICU) admission, and mortality (17). In patients with the omicron VOC, the risk of hospitalization or death was considered lower when compared to infected patients with delta variant (18). However, it is important to consider that the high transmissibility and immune evasion properties of the omicron subvariants can lead to an increase in the rate of infection and mortality in older people with comorbidities, as we can see in the case of Japan and China after the emergence of the omicron subvariants (3, 19). While most SARS-CoV-2 variants are linked with breakthrough infections in fully vaccinated individuals, a cumulative body of data has shown that the vaccinated recipients showed a faster clearance time compared to non-vaccinated individuals (20) and reduced risk of death in patients infected with SARS-CoV-2 variants (21). Instead, unvaccinated individuals remained at the highest risk of infection, severe outcomes, and death (21). Therefore, continued efforts to increase vaccination and the establishment of booster campaigns in the human population are of paramount importance to provide protection and overcome the COVID-19 crisis. (ii) How about the authorized antiviral therapies against new omicron variants and comparative efficacy among vaccinated and non-vaccinated individuals. In this way, antiviral drugs and mass inoculations demonstrated a critical role in treating COVID-19 patients, especially to reduce the number of severe cases and deaths (22). According to the Food and Drug Administration (FDA), COVID-19-related therapies include antiviral drugs, immunomodulators, neutralizing antibody therapies, cell therapies, and gene therapies.² Based on the

1 <https://www.gisaid.org/hcov19-variants/>

2 <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>

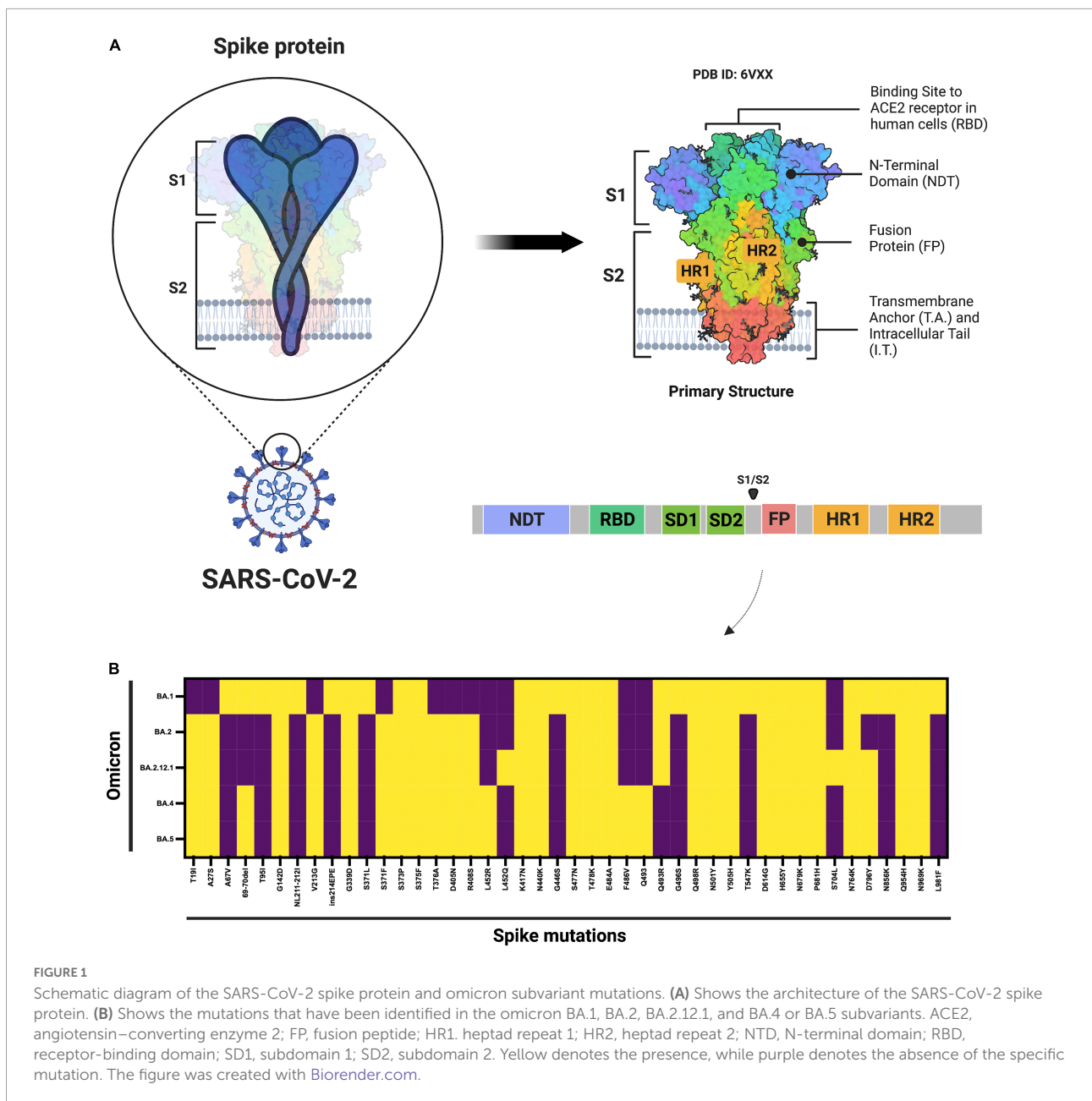


FIGURE 1 Schematic diagram of the SARS-CoV-2 spike protein and omicron subvariant mutations. **(A)** Shows the architecture of the SARS-CoV-2 spike protein. **(B)** Shows the mutations that have been identified in the omicron BA.1, BA.2, BA.2.12.1, and BA.4 or BA.5 subvariants. ACE2, angiotensin-converting enzyme 2; FP, fusion peptide; HR1, heptad repeat 1; HR2, heptad repeat 2; NTD, N-terminal domain; RBD, receptor-binding domain; SD1, subdomain 1; SD2, subdomain 2. Yellow denotes the presence, while purple denotes the absence of the specific mutation. The figure was created with [Biorender.com](https://biorender.com).

ongoing and past pandemic control experiences, some antiviral drugs are questionable for the treatment of patients infected with the omicron VOC and for use in clinical practice (23). Recent studies have shown that the omicron VOC is resistant to most therapeutic monoclonal antibodies (mAbs) (13). In terms of antiviral drugs, recent reports have shown that nirmatrelvir, remdesivir, PF-0730481472, and molnupiravir are effective against infection with the omicron VOC, indicating that these options may be used for clinical practice for the treatment of patients (23, 24). More recently, multiple reports demonstrated that the PAXLOVID™ (oral tablets of nirmatrelvir and ritonavir, a SARS-CoV-2 protease inhibitor)

was able to reduce the risk of hospitalization or death by 89% (within 3 days of symptom onset) and 88% (within 5 days of symptom onset) when compared to the placebo group (25). Despite efforts and recent advances, we need to revise and update frequently the therapeutic arsenal against the SARS-CoV-2 infection based on the past lessons, current experiences, and features of the omicron variant and other SARS-CoV-2 variants. As we have seen for other viruses (e.g., human immunodeficiency virus, HIV), if we create selective pressure on the virus, this can favor the emergence of mutations that help it to survive in the presence of the drug, especially in the case of use of protease inhibitor or viral life cycle inhibitor drugs.

TABLE 1 Characterization of SARS-CoV-2 omicron subvariants.

Omicron lineage	Emergence	Spike mutations	Transmissibility ^a	hACE2 binding	Disease severity	Resistance against therapeutic antibodies and neutralization by convalescent and vaccinated sera
BA.1	South Africa and Botswana, November 2021	A67V 69-70del T95I G142D NL211-212I ins214EPE G339D S371L S373P S375F K417N N440K G446S S477N T478K E484A Q493R G496S Q498R N501Y Y505H T547K D614G H655Y N679K P681H N764K D796Y N856K Q954H N969K L981F	Highly transmissible	Robust binding (13)	Less severe outcomes among infected individuals (11)	Resistance against most therapeutic monoclonal antibodies (mAbs) (26) Escape from neutralizing antibody responses in both convalescent and vaccinated individuals (13, 27)
BA.2	South Africa, December 2021	T19I A27S G142D V213G G339D S371F S373P S375F T376A D405N R408S K417N N440K S477N T478K E484A Q493R Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	The effective reproduction number of BA.2 is 1.4-fold higher than that of BA.1 (7)	BA.2 spike is more fusogenic than BA.1 spike (7) Able to bind to mouse ACE2 with high potency (28)	BA.2 spike-bearing virus is more pathogenic than BA.1 (7)	BA.2 is resistant to BA.1-induced humoral immunity (7) Resistance against most therapeutic monoclonal antibodies (mAbs) (29)

(Continued)

TABLE 1 (Continued)

Omicron lineage	Emergence	Spike mutations	Transmissibility ^a	hACE2 binding	Disease severity	Resistance against therapeutic antibodies and neutralization by convalescent and vaccinated sera
BA.2.12.1	North-America, December 2021	T19I A27S G142D V213G G339D S371F S373P S375F T376A D405N R408S K417N N440K L452Q S477N T478K E484A Q493R Q498R N501Y Y505H D614G H655Y N679K P681H S704L N764K D796Y Q954H N969K	Highly transmissible (30)	BA.2.12.1 exhibits similarities in terms of ACE2-binding affinities to BA.2 (30)	No evidence yet of increased severity	BA.2.12.1 is more resistant (1.8-fold) to sera from vaccinated and boosted individuals than BA.2 (31) BA.2.12.1 and BA.4/BA.5 demonstrate stronger neutralization evasion than BA.2 against the plasma from boosted individuals (30)
BA.4	South Africa, January 2022	T19I A27S Del 69-70 G142D V213G G339D S371F S373P S375F T376A D405N R408S K417N N440K L452R S477N T478K E484A F486V Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	Highly transmissible (30)	BA.4 exhibits similarities in terms of ACE2-binding affinities to BA.2 (30)	No evidence yet of increased severity	Reduced neutralization by serum from triple AstraZeneca or Pfizer vaccinated individual (32) Reduced activity of SARS-CoV-2 therapeutic antibodies against BA.4 (32) More likely to lead to vaccine breakthrough infections among individuals (31) BA.4 demonstrate stronger neutralization evasion than BA.2 against the plasma from boosted individuals (30)

(Continued)

TABLE 1 (Continued)

Omicron lineage	Emergence	Spike mutations	Transmissibility ^a	hACE2 binding	Disease severity	Resistance against therapeutic antibodies and neutralization by convalescent and vaccinated sera
BA.5	South Africa, January 2022	T19I A27S Del 69-70 G142D V213G G339D S371F S373P S375F T376A D405N R408S K417N N440K L452R S477N T478K E484A F486V Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K	Highly transmissible (30)	BA.5 exhibits similarities in terms of ACE2-binding affinities to BA.2 (30)	No evidence yet of increased severity	Reduced neutralization by serum from triple AstraZeneca or Pfizer vaccinated individual (32) Reduced activity of SARS-CoV-2 therapeutic antibodies against BA.5 (32) More likely to lead to vaccine breakthrough infections among individuals (31) BA.5 demonstrate stronger neutralization evasion than BA.2 against the plasma from boosted individuals (30)

^aViral zone (<https://viralzone.expasy.org/9556>).

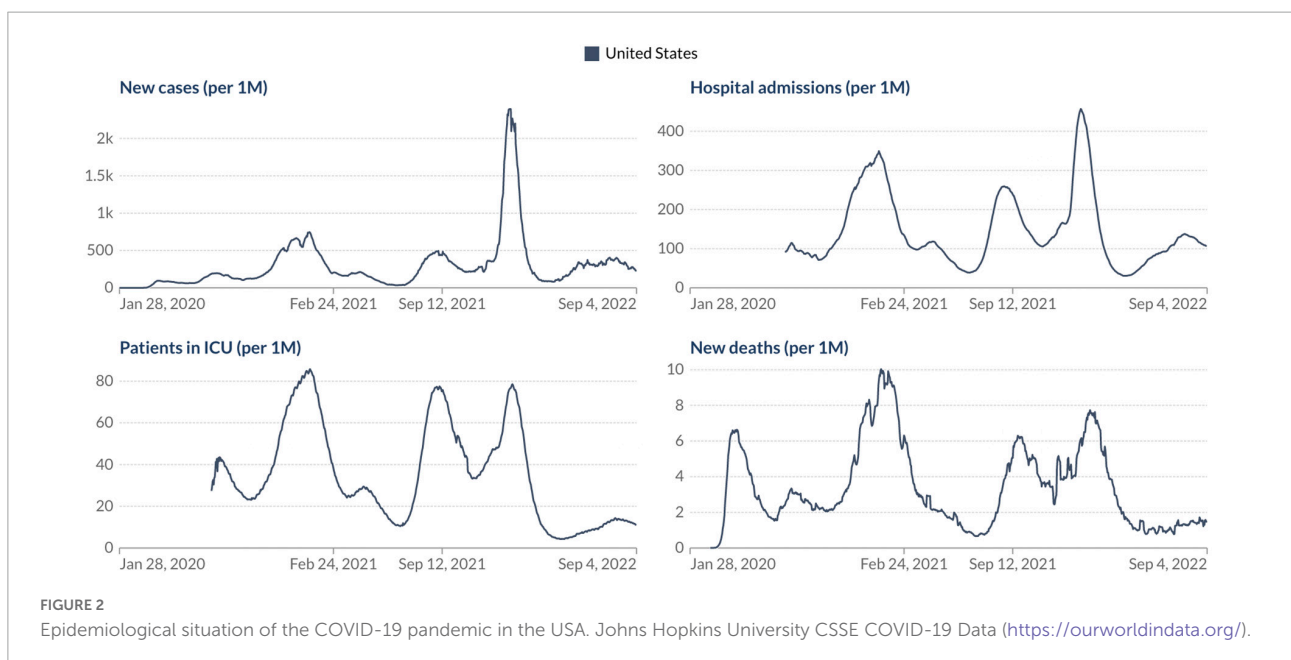


FIGURE 2
Epidemiological situation of the COVID-19 pandemic in the USA. Johns Hopkins University CSSE COVID-19 Data (<https://ourworldindata.org/>).

Final considerations and public health perspectives

Based on our current scenario, what should we expect from our future with SARS-CoV-2? As WHO Director General Dr. Tedros Adhanom Ghebreyesus said, “the pandemic is far from over – and it will not be over anywhere until it’s over everywhere.” Considering all these factors discussed above appears we must take a step back regarding the relaxation of COVID-19 control measures and indicate that it is not yet time to let our guard down in the face of this devastating virus, especially after the emergence of the omicron subvariants. But the good news is if we look at the current epidemiological scenario in the USA, the most affected country during the COVID-19 pandemic. Analyzing the number of confirmed COVID-19 cases, deaths, hospital admissions, and patients in ICU per million people it is evident that we can see a light at the end of the tunnel, but we still have a considerable way to go to see the end of the pandemic phase (Figure 2). What should we expect in the coming months? Different countries around the world will experience the coming phase differently based on some critical factors: vaccine coverage, availability and application of boosters in the human population, dynamics of seasonality, demographics, government policies, and implementation of strategies to reduce the transmission of the virus.

Notably, the SARS-CoV-2 omicron variant will probably not be the last VOC, which suggests that we should prepare for the emergence of new variants that can lead to further immune evasion and render current vaccine ineffective over time. The administration of booster shots using mRNA vaccines as an extra layer of protection will be of paramount importance to overcome the COVID-19 pandemic and combat the impact of further emerging SARS-CoV-2 variants. As with flu, it appears that we should monitor and update the composition of COVID-19 vaccines frequently, as COVID-19 may continue to be an endemic disease in the world. At the same time, we need to

learn to live the new “normal” lifestyle with the hope that SARS-CoV-2 does not bring serious concerns to global health in the near future.

Author contributions

SS conceived the work, wrote the original draft, and reviewed the final manuscript.

Funding

SS is supported by a Postdoctoral Fellowship sponsored by the University of Toronto, Canada. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Figure 1 was created with Biorender.com under academic license.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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