77768_Auto_Edited-check.docx

WORD COUNT	1867	TIME SUBMITTED	08-SEP-2022 03:45PM
		PAPER ID	90303299

Name of Journal: *World Journal of Virology*

Manuscript NO: 77768

Manuscript Type: LETTER TO THE EDITOR

Global challenge with the SARS-CoV-2 omicron BA.2 (B.1.1.529.2) sub-variant: Should we be concerned?

Roohani J *et al*. SARS-CoV-2 omicron BA.2 and global concern

Abstract

BA.2 is novel omicron offshoot that goes viral. There is limit knowledge regarding this variant of concern. Current evidence suggested this variant is more contagious but less severe than previous severe acute respiratory syndrome coronavirus 2 previous variants. However, there is concern regarding the virus mutations that could be influenced pathogenicity, transmissibility as well as immune evasion.

Key Words: SARS-CoV-2; Omicron; BA.2; B.1.1.529.2

Roohani J, Keikha M. Global challenge with the SARS-CoV-2 omicron BA.2 (B.1.1.529.2) sub-variant: Should we be concerned? *World J Virol* 2022; In press

Core Tip: BA.2 is novel omicron offshoot that goes viral. There is limit knowledge regarding this variant of concern. Current evidence suggested this variant is more contagious but less severe than previous severe acute respiratory syndrome coronavirus 2 previous variants. However, there is concern regarding the virus mutations that could be influenced pathogenicity, transmissibility as well as immune evasion.

TO THE EDITOR

The proliferation of omicron (B.1.1.529) and its global dissemination

On November 25, 2021, 22 patients in Gauteng province, South Africa, were diagnosed with atypical pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Afterward, the Technical Advisory Group of the World Health Organization (WHO) designated the novel SARS-CoV-2 as B.1.1.529 lineage[1]. Omicron has been identified as the fifth variant of concern (VOCs); the B.1.1.529 genome contains over 50 mutations that increase transmissibility, infectivity, immune system evasion, and vaccine inefficacy[2].

In late November 2021, the South African National Institute of Communicable Diseases reported a 22.4% increase in infections with this variant in a single day[1].

Based on a retrospective study conducted in South Africa, the VOC omicron variant significantly increases the risk of reinfection (2.39 ×) compared to the Beta and Delta variants, indicating that this variant has a higher potential to evade the immune system[3]. Belgium, Hong Kong, Israel, Germany, the Netherlands, and the United Kingdom reported the detection of the omicron variant shortly after.

On November 27, due to the omicron variant's spread to more than 50 countries, the United States and Australia banned all transportation to those countries. On November 29, however, the first omicron case in Australia was identified in a traveler to Johannesburg, South Africa (https://www.abc.net.au/news/2021-11-29/nt-covid-outbreakkatherine-traveller-positive-for omicron/100657690). Subsequently, the VOC omicron was identified in populations that were unvaccinated, partially or fully vaccinated, and immune to previous natural infection.

The birth of omicron BA.2 (B.1.1.59.2)

According to the WHO classification, the omicron variant has three-four variants, namely BA.1, BA.1.1, BA.2, and BA.3; nucleotide sequencing analysis revealed that BA.1, BA.1.1, BA.2, and BA.3 subvariants possess 39, 40, 31, and 34 mutations, respectively; All three sub-variants evolved simultaneously in South Africa[4] (Figure 1). According to the hypothesis of Gao *et al*[5], omicron subvariants have emerged in the unvaccinated African population with compromised immune systems; this is because immunocompromised individuals are unable to wane SARS-CoV-2 infection effectively, and they have the best opportunity for multiplication, mutagenesis, and the emergence of new surge variants. Furthermore, animals can act as reservoirs for the evolution of novel variants. Nonetheless, there has been an increase in cases of BA.2 in recent days, to the point where the BA.2 variant is now the most common SARS-CoV-2 variant in most European countries.

BA.2 is also known as the "stealth variant" because it lacks a deletion signature at positions 69-70 that was not detected by the S gene target failure assay; therefore, BA.2 was underestimated with the current reverse transcription polymerase chain reaction

setup, and its detection is only possible *via* whole genome sequencing[6,7]. According to viral genome sequences uploaded to the global GISAID database, the United Kingdom, the United States, Denmark, Germany, and Canada are the five countries with the highest prevalence of BA.2 (https://www.gisaid.org/). By February 18, 2022, BA.2 was reported in 153 countries (https://www.gisaid.org).

The VOC BA.2 is a highly contagious sub-variant

Beginning in 2022, BA.2 has been on the rise in European countries. On January 1, 2022, the prevalence of BA.2 in the United Kingdom was approximately 5%, and it has been steadily rising in recent days[8]. According to preliminary studies conducted in Denmark, the first reports of BA.1 and BA.2 occurred on November 25 and December 5, 2021, respectively. During the 52nd wk of 2021, BA.2 prevalence in Denmark was 20%, while more than 45% of circulating SARS-CoV-2 strains in Denmark during the second week of 2022 were BA.2 lineage[9]. To this end, BA.2 is alarmingly spreading across the globe (Figure 2).

Lyngse *et al*[9] demonstrated that the BA.2 variant was able to infect unvaccinated [odds ratio (OR) = 2.19; 95% confidence interval (CI): 1.58-3.14] and the individuals vaccinated with a third booster (OR = 2.99; 95%CI: 2.11-4.2). According to the Danish Staten's Serum Institute, BA.2 is approximately 1.5 and 4.2 times more contagious than BA.1 and the Delta variant[9,10]. Yu *et al*[11] observed that the neutralizing antibody titer against BA.1 and BA.2 is 23- and 27-fold lower than that of WA1/2020. According to their research, the mean neutralizing antibody titers after the third booster of the BNT162b2 mRNA vaccine were approximately 1.4-fold lower than BA.1, indicating BA.2's capacity to confer neutralizing antibodies and evade humoral immunity[11].

Chen and Wei[10] hypothesized that BA.2 mutations caused the immune evasion ability of BA.2 to be approximately 30% and 17-fold greater than that of BA.1 and the Delta variant and resistant to most MAbs except for sotrovimab. Evidently, BA.2 will quickly become the next dominant global variant. In addition, the United Kingdom Health Security Agency (UKHSA) cautioned that contact tracing data from the United

Kingdom estimates that BA.2 is more likely to infect household contacts than BA.1 (10.3%); UKHSA estimated that the increase in the number of BA.2 patients after a third booster dose vaccination was more significant than that of BA.1 infected population (63% for BA.1 *vs* 70% for BA.2)[12]. According to Covglobe data, the incidence of BA.2 infections has been on the rise since October 2021 and has recently supplanted the VOC B.1.1.529; according to existing databases, BA.2 typically affects younger age groups (Figure 3).

BA.2 variant genome analysis

According to Nextstrain online server data, the omicron variant comprises three distinct branches: 21K (or Pangolin lineage12 BA.1), 21L (or BA.2), and BA.3 of the 21M Omicron clade[4] (Figure 4). BA.2 genome contains 20 shared and six unique mutations in spike (S) protein compared to B.1.1.529 (archetypical) variant; BA.2 has significantly more mutations than BA1; most of these mutations are non-synonymous. By analyzing and comparing the genomes of BA.1 and BA.2, Wiegand *et al*[13] observed that BA.2 possesses the most genetic variation in S protein (24-35 mutations, mean = 30.7) and that the effect of these mutations on virulence, viral transmission, and immune evasion has been identified in previous research. After S, nucleoprotein (N) has the most genetic changes, but the majority of these changes are non-synonymous, affecting the sensitivity and specificity of diagnostic methods[13]. According to the CoronaTrend online server, S, nsp6, and M proteins exhibited the most BA.2 mutations (Figure 5).

Kumar *et al*[4] demonstrated in a recent study that multiple alignments of four omicron sub-lineages revealed that BA.1 comprised 39 mutations, BA.1.1 40 mutations, BA.2 31 mutations, and BA.3 consisted of 34 mutations. BA.1.1 has a single unique mutation of R346K, and BA.2 has eight mutations. Only one unique mutation exists in T19I, L24del (deletion), P25del, P26del, A27S, V213G, T376A, R408S, and BA.3 (R216del). Meanwhile, all sub-variants comprise eleven shared mutations in their second RBD, including G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, and N501Y. By increasing the positive electrostatic surface, these

mutations improve the interaction between the RBD motif and the human angiotensin-converting enzyme 2[4]. They also observed that R400, R490, and R495 mutations in BA.2 formed new salt bridges and hydrogen, resulting in higher viral transmission than BA.1 and BA.1.1 subvariants[4].

Desingu and Nagarajan[14] deduced that the BA.2 lineage consists of five distinct phylogenetically based on the original geographic region, namely Sweden/Denmark, Philippines, Hong Kong, India, and China. They demonstrated that each of these clades exhibits unique mutations, such as the H78Y mutation in Denmark, the substitutions of ORF1a: A2909V and ORF3a: L140F in isolates from the Philippines and Hong Kong, and ORF1a: -3677L, ORF1b: S959P, and ORF7b: H42Y in the Indian subgroup. Each distinct mutation in subpopulations modifies the characteristics of BA.2 in terms of viral transmission, infectivity, disease severity, vaccine efficacy, and clinical outcomes in different geographic regions[14,15]. Recent studies suggest that mutations of P681H, H655Y, and N679K at the furin cleavage site increase the replication of omicron variants and, as a result, the transmissibility of omicron subvariants[4].

Vaccination against the omicron BA.2 sub-variant

The 21L/BA.2 Omicron variant has become predominant even after the third dose of the Pfizer-BioNTech vaccine, according to reports from Denmark (www.news-medical.net/news/20220214/First-survey-on-Omicron-BA2-in-France.aspx). Moreover, on January 26, 2022, Tyra Grove Krause stated, "*There is some evidence that it is more contagious, particularly among the unvaccinated, but it can also infect vaccinated individuals to a greater extent*" (https://www.gavi.org/vaccineswork/stealth-omicron-everything-you-need-know-about-new-ba2-subvariant-coronavirus).

Lyngse *et al*[9] evidenced that the viral load of unvaccinated individuals is significantly greater than that of fully immunized populations. Thus, non-immunized individuals can more effectively release BA.2. Initial UKHSA surveys indicated that the effectiveness of the BA.2 vaccine against symptomatic BA.2 infection was greater than that of the BA.1 vaccine (13% for BA.2 *vs* 9% for BA.1); additionally, a third booster dose

may increase the effectiveness of the BA.2 vaccine (70% for BA.2 *vs* 63% for BA.1)[12,16]. However, Peiris *et al*[17] evaluated the effect of the third dose of BNT162b2 or CoronaVac vaccines against BA.2; they concluded that three doses with BNT162b2 or vaccination with two doses of CoronaVac and a third booster dose with BNT162b2 increased plaque reduction neutralization antibody titer above the threshold for protection against symptomatic BA.2 infection.

Although BA.2 mutations confer resistance to neutralizing antibodies, recent research shows that a third booster causes antibodies to cross-react with the omicron variant[18]. In addition, Lippi *et al*[19] revealed that the third booster vaccination increases neutralizing antibodies against the omicron variant and is a safe strategy until a new, more effective vaccine is introduced.

Further perspective

Despite the recent increase in BA.2 cases, the WHO has not yet given BA.2 a special designation. However, on January 21, the UKHSA designated BA.2 as a "variant under investigation" (https://www.gavi.org/vaccineswork/stealth-omicron-everything-you-need-know-about-new-ba2-subvariant-coronavirus). The WHO official Dr. Maria Van Kerkhove stated that BA.2 is significantly more contagious than BA.1 (https://www.cnbc.com/2022/02/08/who-says-omicron-bapoint2-subvariant-will-rise-globally.html); nonetheless, preliminary studies indicate that there is no difference between BA.2 and BA.1 in terms of hospitalization risk.

The remarkable increase in BA.2 infection cases and the rapidity with which it has spread in a short period of time is perplexing. In addition, intensive care unit admissions and mortality rates are rising, causing worldwide concern in healthcare facilities. According to IDSA, the most effective treatments for SARS-CoV-2 B1.1.529 are monoclonal antibodies such as Sotrovimab, Evusheld, Convalescent sera, and Oxford-AstraZeneca and Pfizer-BioNTech vaccines (https://www.idsociety.org/covid-19-real-time-learning-network/emerging-variants/emerging-covid-19-variants/#). Hand hygiene, physical distance, mask use, and mass vaccination, particularly a third booster

dose, are recommended countermeasures to control the global spread of variant BA.2, as is the consideration of nationwide lockdowns.

77768_Auto_Edited-check.docx

ORIGINALITY REPORT

8%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet	55 words — 3%
2	Philippe Colson, Jérémy Delerce, Mamadou Beye, Anthony Levasseur et al. "First cases of infection with the 21L/BA.2 Omicron variant in Marseille, France", Cold Spring Harbor Laboratory, 2022 Crossref Posted Content	17 words — 1%
3	townhall.virginia.gov Internet	16 words — 1%
4	www.frontiersin.org Internet	16 words — 1%
5	www.journaltocs.ac.uk Internet	16 words — 1%
6	Ting-Yu Yeh, Gregory P. Contreras. " Tajima test accurately forecasts Omicron / COVID-19 outbreak ", Cold Spring Harbor Laboratory, 2021 Crossref Posted Content	14 words — 1%
7	www.news-medical.net Internet	14 words — 1%
8	Perumal A. Desingu, K. Nagarajan. "Omicron BA.2 lineage spreads in clusters and is concentrated in	12 words — 1%

Denmark", Journal of Medical Virology, 2022
Crossref

9 www.biorxiv.org
Internet
12 words — 1%

10 www.science.gov
Internet
12 words — 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS