

# The latest Omicron BA.4 and BA.5 lineages are frowning toward COVID-19 preventive measures: A threat to global public health

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## KEYWORDS

B.1.1.529, BA.4, BA.5, coronavirus, COVID-19, Omicron, public health, SARS-CoV-2, SARS-CoV-2 variants

## 1 | BACKGROUND

A cluster of pneumonia cases was reported by the Wuhan Municipal Health Commission, China, Hubei Province, resulting in the identification of a novel coronavirus (SARS-CoV-2).<sup>1</sup> As of September 19, 2022, more than 609 million cases and 6.5 million deaths have been recorded worldwide. The highest number of COVID-19 cases have been recorded in Europe, followed by the Americas, Western Pacific, South-East Asia, Eastern Mediterranean, and Africa regions.<sup>2</sup> As a country, the US contributed the highest number of COVID-19 cases and deaths.<sup>2</sup> SARS-CoV-2 is constantly mutating and dodging antibodies to infect more people. Epidemiologists in South Africa detected the fifth and the latest "variant of concern" (VOC) of SARS-CoV-2. They reported this new variant to the World Health Organization (WHO) on November 24, 2021. This fifth VOC of SARS-CoV-2 contains more than 30 mutations in its viral spike proteins to allow it more transmissibility and infection rates.<sup>1</sup> The WHO named this fifth VOC of SARS-CoV-2 as the Omicron variant (B.1.1.529) on November 26, 2021.<sup>2</sup> Omicron became the leading variant in COVID-19 after its inception. At present, Omicron is the only circulating VOC. Initially, Omicron had three subvariants (e.g., BA.1, BA.2, and BA.3). BA.1 was predominant during the fourth wave of the pandemic in South Africa. However, the global pattern was inconsistent in some other countries. BA.2 variant was responsible for hospitalizations and deaths in most

cases during the Omicron wave in South Africa.<sup>3</sup> Currently, the Omicron variant includes five lineages and some other descendant subvariants.<sup>4</sup> Omicron subvariants that have rapidly spread across the globe.<sup>5,6</sup> Initially, BA.1 and BA.2 were predominant Omicron subvariant worldwide. However, BA.4 and BA.5 variants are now leading in Europe and the United States.<sup>7</sup> The WHO classified BA.4, BA.5, BA.2.12.1, and BA.2.75 as VOC-subvariants under monitoring.<sup>4</sup> The European Centre for Disease Prevention and Control categorized BA.4 and BA.5 as VOC from VOI on May 12, 2022.<sup>8</sup> Therefore, we recommend prioritized monitoring of epidemiology of the COVID-19 pandemic due to Omicron BA.4 and BA.5 subvariants. This article aims to present an update on Omicron BA.4 and BA.5 subvariants of SARS-CoV-2 and their potential impact on global public health. Scientists detected the BA.4 and BA.5 variants from a sample collected from South Africa in early 2022.<sup>9</sup> BA.4 and BA.5 have similarities with parent variants based on their genotype and phenotype as both are subvariants of Omicron. These subvariants have all mutations that Omicron had. The spike proteins of the latest Omicron BA.4 and BA.5 subvariants are identical and more similar to BA.2 than BA.1.<sup>10</sup> The Omicron BA.4 and BA.5 subvariants fueled a surge of cases in South Africa in the spring despite having widespread pre-existing immunity to the virus. The COVID-19 wave due to BA.4 and BA.5 subvariants was not as high as earlier waves, and deaths did not rise as sharply in South Africa.<sup>10</sup>

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## 2 | GENETIC MUTATIONS OF BA.4 AND BA.5

Omicron BA.4 and BA.5 subvariants have similar spike proteins that are most analogous to BA.2. These latest Omicron variants have further spike mutations at positions 69-70del, L452R, and F486V, and there is a wild-type AA at position Q493 like BA.2.<sup>10</sup> Moreover, BA.4 has extra mutations and a triple amino acid deletion at positions N: P151S, ORF7b: L11F, and NSP1:141-143del, respectively, outside the spike protein. However, BA.5 has the M: D3N mutation outside the spike region. Similar to BA.2, BA.5 has additional reversions at ORF6:D61 and nucleotide positions 26,858 and 27,259.<sup>10</sup> Therefore, Omicron BA.4 and BA.5 subvariants have alterations in antigenic characteristics than BA.1 and BA.2. The proxy marker of S-gene fails to identify these lineages due to the 69–70 deletion in the spike region. These two subvariants only differ from each other based on the outside of the spike area.<sup>10</sup>

The BA.4 and BA.5 subvariants have achieved power from biological changes that allow them to infect more people quickly. There are two noticeable mutations in Omicron BA.4 and BA.5 subvariants. The spike mutation at position L452R is responsible for increasing transmissibility. The Delta variant had this mutation. The Omicron BA.4 and BA.5 subvariants can become more contagious due to this mutation because it helps the viral attachment to the human cell. Another vital mutation in BA.4 and BA.5 subvariants is F486V.<sup>10</sup> This mutation occurs in the spike protein region close to the attaching site with the human cell. The idea is that this mutation helps the virus to deceive our immune system. Therefore, these new subvariants of Omicron could be more contagious and capable of escaping the human immune system. Scientists assumed that these new variants have more capacity to infect fully immunized people than the earlier variants and forms of Omicron.<sup>11</sup> Many countries are implementing inadequate measures to control SARS-CoV-2 after 2.5 years since the introduction of the COVID-19 pandemic.<sup>12–16</sup> Therefore, the global population is at risk of getting infected by the Omicron BA.4 and BA.5 lineages.

## 3 | THE PREVALENCE AND DISEASE SEVERITY DUE TO BA.4 AND BA.5

The BA.4 and BA.5 have quickly substituted the BA.2 variant with more than half of sequenced COVID-19 cases in South Africa by early April 2022. Within a couple of months, they have become the leading COVID-19 variants in the world.<sup>17</sup> BA.4 and BA.5 spread more rapidly than BA.2 as our immunity ages. They also have a double benefit of contagiousness and immune escaping power due to their unique mutations. They replaced BA.2 variant and started the fifth wave in South Africa with more than 50% of the new cases.<sup>17</sup> Omicron BA.4 and BA.5 have induced a wave earlier than any previous variants.<sup>18,19</sup> According to the COVID Data Tracker by the Centers for Disease Control and Prevention, Omicron BA.4 and BA.5

subvariants account for about 52% of new cases in the United States.<sup>20</sup> These new subvariants appeared to be overtaking two previous subvariants, BA.2 and BA.2.12.1, in the United States.<sup>11</sup> In Switzerland, the prevalence of BA.5 is much higher, and the spread of BA.4 is comparatively lower.<sup>17</sup> Therefore, all countries will not have a similar effect of BA.4 and BA.5 subvariants at a time.

The COVID-19 symptoms and severity due to BA.4 and BA.5 variants are still not fully known. Omicron BA.4 and BA.5 subtypes are so distinct that scientists have not been able to conclude their COVID-19 symptoms and severity.<sup>10</sup> We do not know whether they can cause more severe diseases than other types or not. Though BA.4 and BA.5 subvariants originated in South Africa, we saw the fifth wave of the COVID-19 pandemic that went away again. However, it did not do as much damage as Omicron did in South Africa. There may be several reasons behind this. One reason might be the mass vaccination and natural immunity from a big Omicron wave in the country.

## 4 | ANTIBODY ESCAPING BY NEW VARIANTS AND IMPACT ON PUBLIC HEALTH

Several studies demonstrated the capacity of avoiding antibodies by the latest Omicron BA.4 and BA.5 triggered by vaccination and earlier Omicron infections.<sup>21–23</sup> Therefore, fully vaccinated populations are at risk of getting multiple Omicron infections. Scientists have claimed that L452R and F486V spike mutations of BA.4 and BA.5 Omicron subvariants are powering them to escape antibodies and infect more people rapidly.<sup>10</sup> Waasila Jassat, an epidemiologist from South Africa, said that “despite high case numbers, South Africa experienced only a small rise in hospitalizations and deaths during its BA.4 and BA.5 wave.” However, the high infection rate due to Omicron BA.4 and BA.5 subvariants might increase the global disease burden. Another study in South Africa observed that BA.4/BA.5 and BA.1 waves had similar risks of severe hospitalization and death. Also, Omicron waves showed a reduced risk of hospitalization and death than earlier waves. In this case, mass vaccination and prior infections were protective against developing severe COVID-19 symptoms.<sup>24</sup> Outside South Africa, the COVID-19 vaccination rate is very high in Portugal. However, the hospitalization and death rates associated with BA.4 and BA.5 subvariants are similar to their first Omicron wave.<sup>17</sup> This might be due to the demographic pattern of Portugal, where older people were infected more by BA.4 and BA.5 variants.

A meta-analysis demonstrated that people aged 70 or above have a higher risk of coronavirus infection and developing severe symptoms than individuals under 70.<sup>25</sup> Therefore, all countries will not face similar prevalence and disease burden due to Omicron BA.4 and BA.5 subvariants. Epidemiologic studies suggest that consecutive COVID-19 waves are converting to milder.<sup>24</sup> However, viruses do not automatically change to become less lethal.<sup>26–29</sup> Therefore, healthcare authorities across the globe need to be more careful about viral mutations and their impact on human health.

## 5 | COVID-19 VACCINES AND ANTIVIRAL AGENTS AGAINST EMERGING VARIANTS

As of September 12, 2022, more than 12 billion vaccine doses have been administered worldwide.<sup>2</sup> Also, 5.3 billion people have got at least one vaccine dose, and 4.9 billion people are fully vaccinated.<sup>2</sup> The role of the COVID-19 vaccines is vital to curb the prevalence and mortality.<sup>30,31</sup> However, corona antibodies last 6–9 months in the human body. There is definite evidence that COVID-19 vaccination reduces the infection rate and disease complications.<sup>30</sup> Studies have shown that hospitalization rate, COVID-19 complications, and mortality rate were lower among the vaccinated population. In South Africa, much lower deaths and hospitalizations occurred in the fifth wave due to BA.4 and BA.5 subvariants.<sup>10</sup> Because of immunity acquired by COVID-19 vaccination and Omicron wave, COVID-19 vaccines reduce disease severity and help to fight the disease well.<sup>10</sup> Some companies are trying to bring a customized vaccine for Omicron. However, it is tough to say whether the vaccine will come before many Omicron mutations. Mass immunization provides a lower infection rate, mild disease complications, and reduced mortality rate. As of January 12, 2022, the WHO included nine different vaccines for emergency use listing for the prevention of COVID-19.<sup>32</sup> At present, two oral antiviral drugs can help to fight mild to moderate COVID-19 by stopping the multiplication of the SARS-CoV-2 virus in the human body. These are paxlovid tablets (nirmatrelvir and ritonavir co-packaged for oral use by Pfizer) and lagevrio (molnupiravir by Merck).<sup>33</sup> Studies showed that nasal delivery of a human antibody (58G6) provides protection against SARS-CoV-2 Delta and Omicron variants.<sup>34</sup> Nitric oxide nasal spray (NONS) may reduce symptoms, severity, and hospitalization rate among mild COVID-19 patients.<sup>35</sup> Also, some studies recommended monoclonal antibodies (mAbs) for high-risk ambulatory COVID-19 patients for better outcomes.<sup>36,37</sup>

## 6 | CONCLUSION

It is difficult to say whether COVID-19 will eradicate from the world.<sup>38,39</sup> Newer Omicron subvariants or other SARS-CoV-2 variants would create an emerging threat to public health. At present, Omicron subvariant BA.2.75 is a dominating strain in India that is spreading to other countries.<sup>40,41</sup> Therefore, the authorities should implement health safety measures and vaccinate the maximum population as early as possible. Also, they can think about customized vaccines for omicron subvariants. These are the options that we can do to be well and protected. We need to wear a face mask. Because we do not know what type of variants we might inhale, the face mask will stop them all. As long as there are new waves, we should wear face masks strictly. The authorities can create more awareness about COVID-19 and increase tests. Because without proper sequencing of the specimen, it is impossible to monitor and understand the nature of the virus.

## AUTHOR CONTRIBUTIONS

Md. Rabiul Islam: Conceptualization; writing–review and editing. Mohammad Shahriar: Writing–original draft. Mohiuddin Ahmed Bhuiyan: Conceptualization; writing–review and editing.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## TRANSPARENCY STATEMENT

The lead author Md. Rabiul Islam affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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