Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The recently emerged BA.4 and BA.5 lineages of Omicron and their global health concerns amid the ongoing wave of COVID-19 pandemic – Correspondence

Dear Editor

Recently, researchers in South Africa have identified two game-changing lineages of the Omicron variant called BA.4 and BA.5, reflecting continuous emergence and evolution of Omicron, and due to which resurgence of COVID-19 cases are noticed again in South Africa [1]. The BA.4 and BA.5 lineages were first detected from specimens collected in January and February 2022 in South Africa. Since then, these lineages have also been found in other parts of the globe and now have been detected in multiple countries. The fourth COVID-19 wave of South Africa was mainly due to three Omicron lineages (BA.1, BA.2 and BA.3). In late 2021, BA.1 (Omicron) ousted the most deadly Delta variant and became a dominating variant which was then replaced by BA.2 lineage of Omicron in March 2022 to become the most dominant variant worldwide as of late April 2022 [2,3]. In the meantime, multiple new subvariants/sub-lineages of Omicron have emerged and some of them, mainly BA.2.11 (France), BA.2.12.1 (the USA) and BA.4/5 (South Africa) are dominating BA.2 in several countries [4]. Apart from these, recombinant/hybrid variants of SARS-CoV-2 (XD, XE, XF) have also been identified, of which XE (BA.1/BA.2 recombinant form) is posing to have comparatively higher adverse impacts and global health concerns amid the ongoing COVID-19 pandemic [5–8].

The two new lineages of Omicron (BA.4 and BA.5) have rapidly replaced BA.2 and initiated the fifth wave in South Africa from April 2022 and onwards, reaching to an account of more than 50% of sequenced cases [9]. According to GISAID, the number of BA.4 and BA.5 cases is rising worldwide. The percentages of sequences for BA.4 and BA.5 have reached 35% and 20%, respectively by the end of April 2022 in South Africa. As per ECDC, BA.5 accounted to ~37% of the positive cases in Portugal as of May 8, 2022 [10]. These growth rates suggest that BA.4 and BA.5 variants may be more transmissible than the other Omicron lineages [9]. The enhanced growth rate of BA.4 and BA.5 may be due to their ability to evade immune protection induced by prior virus infection and/or vaccination [10]. However, there is no research data available yet regarding diseases severity for BA.4 and BA.5 lineages as compared with other variants of SARS-CoV-2. The greatest proportion of these cases is recorded by South Africa, however BA.4 has also been detected in Austria, the UK, the USA and Denmark while BA.5 is detected in Germany, Portugal, the UK and the USA. Hence, these variants may cause a significant overall increase in COVID-19 cases in the coming time owing to their predicted higher transmissibility. Recently, these two sub-lineages (BA.4 and BA.5) have been re-categorised as variants of concern (VOC) by ECDC, which were designated as variant of interest (VOI) previously (ECDC, 2022). Keeping this in mind, ECDC has suggested a second mRNA COVID-19 booster dose for adults above 60 years [10]. Omicron as VOC includes BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages as well as BA.1/BA.2 circulating recombinant XE variant [11].

The recent BA.4 and BA.5 lineages have emerged with changes (L452R and F486V mutations in S-protein RBD) relative to BA.1 (Omicron). The BA.4 and BA.5 S-proteins are identical with BA.2 (Omicron) except for the addition of 69–70 deletion, F486V and L452R [9]. Both of these contain the amino-acid substitutions L452R, F486V, and R493Q in S-protein RBD compared to BA.2. The BA.4 and BA.5 lineages carry F486V mutation in S-proteins, which is responsible for infection. Furthermore, BA.4 and BA.5 lineages have their ability to evade immune responses. It is still not clear whether these newly emerged lineages will cause much hospitalization, however, it may reduce harm to people with acquired higher immunity induced from previous Omicron infection and (or) vaccination. A study suggested that another newly emerged sub-lineage BA.2.12.1 has the ability to evade antibodies triggered by previous infection with Omicron and vaccination [12].

Yamasoba et al. (2022) have evaluated the sensitivity of these novel subvariants to eight therapeutic monoclonal antibodies (mAbs) (bebtelovimab, bamlanivimab, cilgavimab, casirivimab, sotrovimab, imdevimab, etesevimab, and tixagevimab), wherein BA.4 and BA.5 exhibited higher resistance to cilgavimab as compared to BA.2 [4]. As several key mutations are observed in the S-proteins of the emerging SARS-CoV-2 variants, rapid evaluation of the efficiency of therapeutic mAbs against the novel variants need urgent attention. Khan et al. (2022) have tested the neutralizing immunity of vaccinated and unvaccinated individuals previously infected with Omicron/BA.1 [13]. The newly emerging sub-variants of the Omicron (BA.4 and BA.5), which have almost replaced all the previous variants appear to be a potential threat to global healthcare. The effectiveness of the current vaccines against infections with the Omicron sub-lineages thus far has not completely been encouraging. Previous studies have shown that the neutralizing antibodies (nAbs) produced against infection with the Omicron variant could be sufficient only to avoid severe infection with the other sub-lineages. Similarly, a recent study has attempted to find out the efficacy of nAbs after BA.4 and BA.5 infections among both vaccinated and unvaccinated people. This study included unvaccinated people who were infected with the BA.4 and BA.5 sublineages, and those individuals who developed breakthrough infections after being vaccinated with Pfizer BNT162b2 or Johnson and Johnson Ad26.CoV vaccines. It was observed that there was a significant drop (>7-fold) in the nAbs titres against the newer sub-lineages as compared to the previous sub-lineage (BA.1). These results point to the fact that the newer sub-lineages may potentially harbor unique mutations, and therefore, an infection with such newer lineages of Omicron variant may cause clinical infection even among the vaccinated people.

To understand which new variants will dominate in future, Chen et al. (2022) have developed Persistent Laplacian-based deep learning

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models by evaluating variant infectivity [14]. The study suggested that BA.3, BA.4, BA.5, BA.2.11 and BA.2.12.1 are more contagious than BA.2. The recently evolved lineages namely BA.4 and BA.5 are about 36% more infectious than BA.2. The emerging reports of increasing infections with the BA.4 and BA.5 are reflecting that these two lineages may possibly replace the previous BA.1, BA.2, and BA.3 lineages, and may become the new dominating lineages of Omicron variant in the near future. Moreover, the immune escape of these two newly identified lineages considered as VOC, combined with the waning of immune response to COVID-19 vaccination may predispose people to infection with BA.4, and BA.5 sub-lineages. Therefore, it can be presumed that the future COVID-19-related increase in the cases, and global multiple waves of infections may be inevitable.

It is encouraged to remain vigilant for BA.4 and BA.5 lineages of Omicron. The sensitive and representative testing as well as continuous monitoring and genomic surveillance of SARS-CoV-2 and its emerging variants, mutants and lineages are highly essential for early detection of any variant and in estimating the contribution and impact of these variants to the ongoing viral circulation amid the ongoing COVID-19 pandemic. The close epidemiological monitoring of newly emerging variants and lineages is also recommended for any observed increase in severe disease outcomes, such as increase in hospitalization or ICU admissions. The evaluation of effectiveness of vaccines and antibodies-based therapies against these newly emerged variants/lineages is also essential along with designing and developing of next generation vaccines, more effective updated vaccines and newer mAbs in order to check the spread of continuously evolving and emerging newer SARS-CoV-2 variants and lineages.

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Guarantor

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