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Correspondence

Emergence of Omicron sub-variant BA.2: Is it a matter of concern amid the COVID-19 pandemic?

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Dear Editor

The appearance of the SARS-CoV-2 Omicron variant (B.1.1.529) has been recognized as a severe threat despite many countries' best attempts to limit the so-called COVID-19 pandemic [1]. The Omicron variant was first discovered in Botswana, South Africa, and further designated as VOC (Variant of Concern) by the World Health Organization (WHO) on November 26, 2021 [1,2]. According to current statistics, the Omicron variant is a significantly altered strain with more than 30 mutations compared to other VOC like Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2). Therefore, scientists were concerned about the larger frequency of mutations in the Omicron variant. Higher transmissibility, decreased vaccination effectiveness, and an increased risk of reinfection are issues related to new variants of SARS-CoV-2 [2], which the scientific communities have raised over the last few months [1–3].

According to recent computational analysis along with sequencing analysis, the Omicron variant has been divided into three sublineages, namely BA.1 (B.1.1.529.1), BA.2 (B.1.1.529.2), and BA.3 (B.1.1.529.3) [4,5]. It has been estimated through the sequencing data that the sub-lineage BA.1 has spread to over 130 nations and is distinguished by a large number of alterations, including 37 mutations in the spike protein (S protein) of the receptor-binding domain (RBD) [6]. According to the WHO, BA.1 seems to be more likely to infect and reproduce in the upper respiratory tract. However, it is important to note that the Delta variant usually infects and multiplies in the lower part of the respiratory tract. Such differences among the Delta and Omicron variants may account for the higher transmissible nature of the BA.1 sublineage as well as the reason that it appears to cause less severe illness than the Delta variant [6].

However, in the wake of the emergence of BA.1 (B.1.1.529.1), a sublineage of the Omicron variant, BA.2 (B.1.1.529.2), was assigned as a variant under investigation (VUI) by the UK Health Security Agency (UKHSA) on January 19, 2022, given its widespread distribution across the countries. In England, 1,072 genomically validated cases of BA.2 have been documented as of January 24, 2022 [7]. Furthermore, the WHO reports that the BA.2 sub-variant of Omicron has been found in 57

countries. (BBC News, <https://www.bbc.co.uk/news/health-60233899>). In addition, BA.2 sub-lineage has been found responsible for more than half of all sequenced Omicron infections in several countries. The sharp rise in documented cases of the BA.2 sub-variant has been considered abnormal in several regions. According to the Statens Serum Institut (SSI) in Denmark, BA.2 infections accounted for nearly half of all recorded COVID-19 cases in January 2022. Interestingly, India is another country where BA.2 sub-variant quickly displaces the Delta and Omicron BA.1 (B.1.1.529.1) variants. According to Dr. Meera Chand, COVID-19 director at the UKHSA, BA.2 infections are rising quicker in Germany than the BA.1 and Delta variant. (BBC News <https://www.bbc.co.uk/news/health-60233899>).

According to the UKHSA, BA.2 has a higher growth rate than BA.1 around England. However, during the early investigations, growth rates might be overstated, but there is a sharp increase in the “apparent growth advantage,” which is a concern of the coming time. Meanwhile, contact tracing data shows that BA.2 infected persons are more likely to infect household contacts than BA.1 infected people. However, there is presently no evidence on the severity of the BA.2 sub-lineage as per data of FDA [6,8].

As per the statement of Professor Wendy Barclay, Head, Department of Infectious at Imperial College London, there is still a scarcity of information on the BA.2 sub-lineage, and several aspects are unresolved. Still, this sub-lineage has similar abilities as BA.1, with many mutations in the S-protein, which may prevent the immune system from recognizing the virus. She speculated that due to the acquisition of a huge number of modifications by the BA.1 sublineage, its capabilities to infect and propagate have been hampered. On the other hand, with fewer alterations, BA.2 may have achieved a better equilibrium with antibody evasion while preserving high transmissibility [6,9].

According to the Tokyo Medical and Dental University, community transmission of BA.2 is underway, stating a sample case of a COVID-19 patient without any travel history or contact with an infected person. However, it is unknown if BA.2 will become more prevalent among the infections caused by the Omicron strain in Japan, likewise several other countries. Even though the number of BA.2 cases is presently small, the

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health ministry's COVID-19 advisory board of Japan concluded on Wednesday, February 10, 2022, that the country should be on high alert about the virus, warning that it might re-ignite a sharp rise in new cases of COVID-19. (The Japan Times, <https://www.japantimes.co.jp/news/2022/02/10/national/science-health/stealth-omicron-subvariant-spreads-japan/>).

Researchers are still attempting to figure out what caused BA.2 to spread so quickly. Some of their assumptions state that because many of the mutations in BA.2 occur in sites of the virus that the immune system prefers to attack, alterations that conceal those sites may allow the virus to avoid detection. With 31 mutations in the spike protein, BA.2 has fewer mutations than BA.1, which has 37 mutations in S-protein [6]. In addition, it is essential to consider that T19I, L24S, P25del, P26del, A27S, V213G, T376A, and R408S are ten unique mutations found in the BA.2 sublineage of the Omicron variant [5], which may give an advantage in the fast transmission of BA.2 sublineage of the Omicron variant over the other sublineages of this variant. In addition, some scientists believe that BA. 2 sublineage should not be considered as an Omicron variant due to the distinct mutations and characteristics of this sublineage. However, the BA.2 sublineage of the Omicron variant can be considered as new VOC as BA.1, and BA.2 have been shown as distinct from each other on the evolutionary tree (Fig. 1). (Science Insider, <https://www.science.org/content/article/sudden-rise-more-transmissible-form-omicron-catches-scientists-surprise>).

Some of the questions are yet to be resolved by scientific communities, such as how the subvariants or sublineages were born. According to Andrew Rambaut, an evolutionary biologist at the University of Edinburgh, viral evolution in a single immunocompromised patient is one of the theories which can explain the evolution of the sub-variants. One plausible reason is the long-term infection that can produce a lot of diversity in the viral strain within a single individual. This can lead to compartmentalization in a single individual. Hence, different variants can emerge in different parts of the body simultaneously. In addition, both variants of the Omicron strain could have also evolved in animals infected with human-adapted SARS-CoV-2, then spread back into people (Science Insider, <https://www.science.org/content/article/sudden-rise-more-transmissible-form-omicron-catches-scientists-surprise>).

Furthermore, the ability of the sub-lineage BA.2 to reinfect spontaneously recovered and vaccinated persons have yet to be determined.

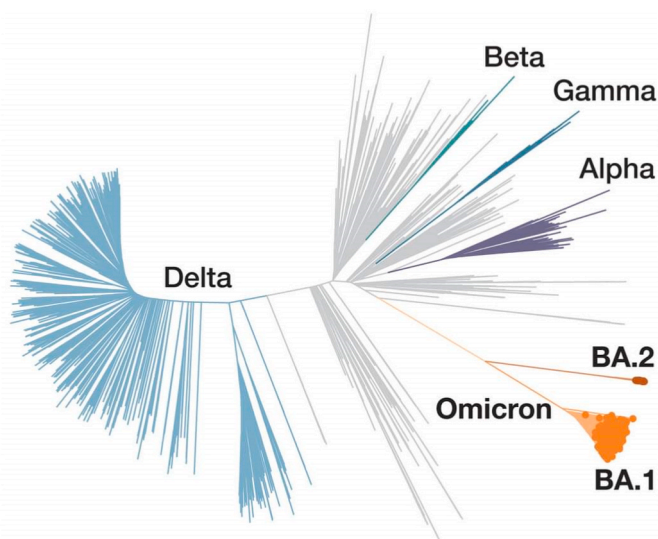


Fig. 1. A representation of distinct evolution of sublineage BA.2 (B.1.1.529.2) from the sublineage BA.1 (B.1.1.529.1) of Omicron variant, Alpha, Beta, Gamma, and Delta variants. In the future, the sublineage BA.2 may be considered as distinct VOC (Variant of Concern) due to its distinct mutations. Adapted from (Science, <https://www.science.org/content/article/sudden-rise-more-transmissible-form-omicron-catches-scientists-surprise>).

Moreover, it is unknown if BA.2 differs sufficiently from BA.1 to elicit reinfections in those who have already been infected with BA.1. In other words, experts aren't sure if one can be infected with the sublineage BA.2 after being infected with the sub-lineage BA.1 (<https://www.vox.com/22923891/omicron-subvariant-ba2-coronavirus>).

The most important aspect is the effectiveness of the available vaccines in providing protection against the sublineage BA.2 of the Omicron variant. Vaccine efficacy against symptomatic infection caused by BA.2 was not shown to be significantly lower in early investigations when compared to BA.1. Vaccine efficacy against symptomatic infection was recorded 9% and 13% for BA.1 and BA.2 sublineages, respectively, at least 25 weeks following two doses of the vaccine [6]. Further 63% enhancement for BA.1 and 70% increase for BA.2 have been recorded at two weeks when given with a third or booster dose. Meanwhile, the UKHSA has said that there is no evidence of the severity of disease caused by Omicron BA.2 sublineage at this time [6–8].

Furthermore, researchers suggest that it is critical to remember that the BA.2 lineage does not appear to induce more severe illness; thus, there is no need to be concerned. It's worth noting that having subgroups of the same variant is not uncommon - it's the nature of a virus that may evolve and has as many human hosts as Omicron does. Vaccines still provide immunity against severe infection and, as per the research, potentially contain the transmission, so it's critical to get them when they are provided. (Aljazeera, <https://www.aljazeera.com/features/2022/2/7/is-the-omicron-subvariant-ba-2-more-transmissible>).

In conclusion, it can be stated that it is too early to provide concrete evidence about the plausible threats associated with the emergence of sublineage BA.2 of the Omicron variant. Moreover, the actual number of COVID-19 cases due to the sublineage BA.2 may be higher than the documented figures as there are several countries that don't have provisions of sample sequencing regularly. Hence, it will be early to state the emergence of the BA.2 sublineage as a severe threat during this ongoing pandemic. Moreover, the exact figure is yet to be drawn; but it can be stated very clearly that the vaccination programs should continue to provide booster doses [10], especially in developing countries like India, Africa, Bangladesh, where vaccination coverage is seriously lower as compared to developed countries as many studies have clearly shown that the three doses or booster doses of the vaccines provide a substantial amount of immunity to reduce the risk of hospitalizations.

Ethical approval

This article does not require any human/animal subjects to acquire such approval.

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Author contributions

Manish Dhawan: Conceptualization, Data Curation, Visualization, Writing - Original Draft, Writing - review & editing. **Priyanka:** Conceptualization, Writing - Original Draft, Writing - review & editing. **Om Prakash Choudhary:** Supervision, Writing - Original Draft, Writing - review & editing. All authors critically reviewed and approved the final version of the manuscript.

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Guarantor

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Data statement

The data in this correspondence article is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature.

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All authors report no conflicts of interest relevant to this article.

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