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LETTER TO THE EDITOR

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The recombinant variants of SARS-CoV-2: Concerns continues amid COVID-19 pandemic

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Dear Editor

In the beginning of 2022, we have highlighted the proposed concept of simultaneous attack of Delta (most deadly) and Omicron (most mutated) in the immunocompromised people, which is an extremely rare event.[1] A combination of the Delta (AY.4) and BA.1 omicron variants has been named as BA.1 x AY.4 recombinant by the World Health Organization, first detected in France in January 2022 and then nicknamed as "Deltacron," and various debates have been held while scientific literature is scanty on this recombinant strain.[2–4] Recently, the World Health Organisation (WHO), in its weekly epidemiological update, has stated the emergence of three recombinant variants of SARS-CoV-2 namely XE (BA.1-BA.2), XF (Delta-Omicron), and XD (Pango lineage, Delta-Omicron) with possibly high rate of transmission that need to be investigated by risk assessment analysis.[5,6] Recombinant strains may emerge when multiple variants infect the same person at the same time. This allows the variants to interact during replication by mixing their genetic materials in the human body, giving rise to new combination. Such events are more likely to happen when viral cases are on higher side and surging rapidly, as COVID-19 cases are again being seen rising after a declining trend. The recombinant strain (XE) is the mutant hybrid of two sublineages (BA.1 and BA.2) of the Omicron variant and was first detected in the United Kingdom (UK) on January 19, 2022. The XE strain has the Spike and structural proteins from BA.2 but the 5′ part of its genome is from BA.1. WHO has warned that the new mutant "XE" variant of Omicron may be more transmissible than any strain of SARS-CoV-2/COVID-19 seen before. A community growth rate advantage of ~10% has been indicated in early data estimation for XE as compared to BA.2, however, such finding need further explorative investigations for knowing the real magnitude of infection. XE has been reported to belong to Omicron variant until significant differences in transmissibility and disease outcome may be seen. [5]

To the surprise of the scientific world, a recent report had preliminarily confirmed that the emergence of Omicron was a result of recombination between the SARS-CoV-2 parent strain (SARS-CoV-2/human/USA/COR-21-434196/2021 (Accession, OL849989)) and B.35 lineage (SARS-CoV-2/human/IRN/Ir-3/2019 (Accession, MW737421)).[7] The UK Health Security Agency (UKHSA) study has revealed two different combinations of Delta and BA.1 (XD and XF). The XD variant, hybrid of Delta and BA.1 sublineage of the Omicron, has been found mostly in France, Denmark, and Belgium. XD contains the S-protein of BA.1 and the genome from French Delta. XF has the Spike and structural proteins from BA.1 but the 5′ part of its genome is from UK Delta. The recombinants containing the spike and structural proteins from a single virus (like XF or XE) may likely act similarly to their parental virus. As per expert virologists, XD variant may be a little more concerning owing to a combination of Delta variant of SARS-CoV-2 and BA.1 sublineage of the Omicron, wherein Delta has been reported to cause severe disease outcome. Presently, there is no evidence that XD (Delta-Omicron) is associated with higher transmissibility or more severe outcomes. Moreover, there is limited data on the status of vaccination of the patients who were found infected with these recombinant strains. Therefore, it becomes early to comment on the effectiveness of the current vaccines, and the severity of disease.

As per reports, the new variant (XE) is 10% more transmissible than the BA.2 lineage of Omicron, which is presently the most dominant strain of the virus. It is also assumed that the new variant such as "XE" may become the most dominant strain in the near future. However, it is too early to ascertain such probability and the assessment of the transmission rate, disease severity, immunity, and vaccine effectiveness for XE require further investigations. Explorative epidemiological investigations, virological and observational studies are required for XD variant to know more about this hybrid strain, especially with regard to transmissibility and disease-causing ability. It is also highly recommended to closely monitor the community growth rates and assess the public health risk associated with these new recombinant variants of SARS-CoV-2. The GISAID identified the SARS-CoV-2 variants from human infections in France, Denmark, and Belgium as XD recombinant strain. The XD infections were noted in all the age groups including pediatric patients, young adults, and people over 60 years of age and both males and females are equally susceptible.[8] The WGS analysis showed that the XD recombinants were increasingly attributed to the AY.4 lineage and GKA clade. The XF recombinant was majorly identified in London, however, one case emerged from the South-East country. The data on the GISAID however reveals that the XF recombinants have no specific age and sex predilections. The XE recombinant was found widely spread throughout London. The BA.2 shows a 75% growth rate in comparison with BA.1. XE was noted to have a 9.8% higher growth rate as compared to the BA.2 sublineage of the Omicron.[9] This suggests that the recombinant viral strains may potentially be more infectious. It was observed that the XE recombinant has three unique mutations (NSP3 C3241T and V1069I, and NSP12 C14599T) that were not seen in both BA.1 and BA.2. The XD recombinant that is majorly confined to France, and first identified in December 2021, has a unique mutation (NSP2: E172D). The XF recombinant shows a breakpoint near the end of NSP3 (nucleotide 5386) unlike the other recombinants. Based on the time of emergence, it appears that the XD emerged first and later followed by XF and XE, the most recent one. The XE recombinant reveals NSP (1–6) mutations of BA.1 and other mutations of BA.2.

The recombinant variants can be detected through phylogenetic profiling and statistical methods. Like, all other SARS-CoV-2 variants, the recombinant variant can be detected through phylogenetic profiling using the sequence from the GISAID. In this direction, Rambaut et al. have proposed a dynamic nomenclature system to assess the SARS-CoV-2 linages through phylogenetic profiling. In this method, maximum likelihood phylogeny was used for phylogenetic profiling.[10] The maximum likelihood approach is a significant one in linkage analysis using in the analysis of reasonable size sequence data which uses the logarithm of the odds score of statistics.[11] At the same time, using another statistical modeling, any virus variant can be detected through the SNV (single-nucleotide variants) calling using variant sequence data of NGS sequencing, and probabilistic clustering was performed with statistical analysis for strand bias in a viral population.[10] Other than these methods, SNP genotyping might be another method that can help to evaluate the recombinant variant like other significant SARS-CoV-2 variants.[12]

A very rapid and high surge in COVID-19 cases was observed worldwide immediately after the emergence of Omicron (B.1.1.529) variant during last week of November 2021. Thereafter, from end of January and early March 2022, a decreasing trend in the number of COVID-19 cases was observed, however, cases were again seen increasing in the next two consecutive weeks, followed by new cases declined again but still, there are nearly 1.5 million new cases being added daily to the total tally of COVID-19 cases.[5,13] As of April 3, 2022, more than 491 million confirmed cases and over 6.1 million deaths have been reported amid the ongoing COVID-19 pandemic.[14] A concern has been raised by the WHO with regard to the recent significant decrease in SARS-CoV-2 testing by many countries, and in such scenario, the collected data to be analyzed are progressively less representative, less timely, and not robust to know the real magnitude of infection by SARS-CoV-2 and its emerging variants at the global level. This is hindering the real-time tracking of the presence of virus, how the virus and its variants are spreading and evolving. Therefore, diagnosis, tracking, and monitoring including genomic surveillance of SARS-CoV-2 and its emerging variants need to be paced up again which would provide sufficient information and data for analyzing the currently evolving and changing scenarios amid the ongoing pandemic and aid in designing and executing effective and timely disease prevention and control strategies to tackle COVID-19. With the emergence of Omicron, simultaneous coinfections of strains/variants are also being identified, and concerns of SARS-CoV-2 variants and evolution occurring in animal reservoirs have been raised as like bird flu (avian influenza) virus after virus spillover to animals and jumping back to humans.[6,13,15–19] A recombinant event between humans and animals harboring SARS-CoV-2 may thus happen that could facilitate to gain mutations to infect more efficiently, for which purpose one health approach needs to be strengthened to limit the chances of animal-humans interfaces and check the emergence of newer variants to some level.[6,20]

Besides booster vaccine shots, advances in modifying and updating existing vaccines, designing new generation vaccines, and finding out more effective drugs and antibodies-based therapies including newer monoclonal antibodies for treating COVID-19 patients are the need of the current time.[21] The continuously emerging variants of SARS-CoV-2 are indicating that vaccines alone could not effectively control the COVID-19 pandemic, and therefore other needful prevention and control measures including public health safety measures are to be implemented appropriately and adequately along with pacing up testing and sequencing across the globe for limiting the spread of SARS-CoV-2 and its emerging variants.

AUTHOR CONTRIBUTIONS

Ranjan K. Mohapatra: Made the first draft. Venkataramana Kandi, Hardeep S. Tuli, and Chiranjib Chakraborty: Updated the manuscript. Kuldeep Dhama: Updated, reviewed, and edited. All authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data Availability Statement is not available.

REFERENCES

1. Mohapatra RK, Tiwari R, Sarangi AK, et al. Twin combination of Omicron and Delta variants triggering a tsunami wave of ever high surges in COVID-19 cases: a challenging global threat with a special focus on the Indian subcontinent. *J Med Virol*2022;94(5):1761-1765.
2. Bolze A, Basler T, White S, et al. Evidence for SARS-CoV-2 delta and omicron-infections and recombination. *medRxiv*. 2022. https://www.medrxiv.org/content/10.1101/2022.03.09.22272113v1
3. Kreier F. Deltacron: the story of the variant that wasn't. *Nature*. 2022;602(7895):19. doi:10.1038/d41586-022-00149-9
4. Wang L, Gao GF. The "wolf" is indeed coming: recombinant "deltacron" SARS-CoV-2 detected. China CDC Weekly; 2022. https://weekly.chinacdc.cn/fileCCDCW/journal/article/ccdcw/newcreate/CCDCW220051.pdf
5. World Health Organization. COVID-19 Weekly Epidemiological Update; 2022. https://deadline.com/wp-content/uploads/2022/03/20220329_Weekly_Epi_Update_85.pdf
6. Mahase E. Covid-19: what do we know about the delta omicron recombinant variant?*BMJ*. 2022;376:o792. doi:10.1136/bmj.o792
7. Liu X, Xiong J, Sun Z, et al. Omicron: a chimera of two early SARS-CoV-2 lineages. *Sig Transduct Target Ther*. 2022;7:90. doi:10.1038/s41392-022-00949-5
8. GISAID. Last accessed: April 7, 2022. https://www.gisaid.org/
9. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1063424/Tech-Briefing-39-25March2022_FINAL.pdf
10. McElroy K, Zagordi O, Bull R, Luciani F, Beerenwinkel N. Accurate single nucleotide variant detection in viral populations by combining probabilistic clustering with a statistical test of strand bias. *BMC Genomics*. 2013;14:501. doi:10.1186/1471-2164-14-501
11. Ott J, Wang J, Leal SM. Genetic linkage analysis in the age of whole-genome sequencing. *Nat Rev Genet*. 2015;16(5):275-284. doi:10.1038/nrg3908
12. Harper H, Burridge A, Winfield M, et al. Detecting SARS-CoV-2 variants with SNP genotyping. *PLoS One*. 2021;16(2):e0243185. doi:10.1371/journal.pone.0243185
13. Bonilla-Aldana DK, Rodriguez-Morales AJ. The threat of the spread of SARS-CoV-2 variants in animals. *Vet Q*. 2021;41(1):321-322. doi:10.1080/01652176.2021.2008046
14. World Health Organization. WHO Coronavirus (COVID-19) Dashboard; 2022. https://covid19.who.int/
15. Du P, Gao GF, Wang Q. The mysterious origins of the Omicron variant of SARS-CoV-2. *Innovation*. 2022;3(2):100206. doi:10.1016/j.xinn.2022.100206
16. Khandia R, Singhal S, Alqahtani T, et al. Emergence of SARS-CoV-2 Omicron (B.1.1.529) variant, salient features, high global health concerns and strategies to counter it amid ongoing COVID-19 pandemic. *Environ Res*. 2022;209:112816. doi:10.1016/j.envres.2022.112816
17. Lennerstrand J, Svensson L, Lundkvist Å. Hur har omikron uppstått och varför sprider den sig så snabbt? [How did Omicron evolve and why does this SARS-CoV-2 variant spread so fast?]. *Lakartidningen*. 2022;119:21242.
18. Sun Y, Lin W, Dong W, Xu J. Origin and evolutionary analysis of the SARS-CoV-2 Omicron variant. *J Biosaf Biosecur*. 2021;4:33-37. doi:10.1016/j.jobb.2021.12.001
19. Wei C, Shan KJ, Wang W, Zhang S, Huan Q, Qian W. Evidence for a mouse origin of the SARS-CoV-2 Omicron variant. *J Genet Genomics*. 2021;48(12):1111-1121.
20. Montagutelli X, van derWerf S, Rey FA, Simon-Loriere E. SARS-CoV-2 Omicron emergence urges for reinforced One-Health surveillance. *EMBO Mol Med*. 2022;14:e15558. https://www.embopress.org/doi/full/10.15252/emmm.202115558
21. Mohapatra RK, Tiwari R, Sarangi AK, Islam MR, Chakraborty C, Dhama K. Omicron (B.1.1.529) variant of SARS-CoV-2: concerns, challenges, and recent updates. *J Med Virol*. 2022;94(6):2336-2342. doi:10.1002/jmv.27633