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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Hybrid SARS-CoV-2 variants

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Dear Editor,

In December 2019, discovery of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2] critically changed the collective mindset about future emergence of an infectious agent with potential to cause an outbreak. The unprecedented spread of SARS-CoV-2 to more than 200 countries in five continents within less than three months in 2020 convinced the World Health Organization to reclassify the epidemic outbreak to a pandemic [3], a classification which has been current when we wrote this letter in mid-April 2022. The global case numbers due to the coronavirus disease 2019 (COVID-19) have been increasing with more than 6.1 million deaths recorded. As the pandemic progressed, distinct peaks of the COVID-19 case numbers coincided with circulation of the genetically evolved SARS-CoV-2 variants in many countries [4,5]. Managing the COVID-19 pandemic, overshadowed by continuously evolving SARS-CoV-2 variants, has been challenging and negatively affected the international healthcare institutions. Thus, understanding the biological rationale for the virus to evolve so rapidly is important for the management of future outbreaks.

SARS-CoV-2 hybrids

Viruses use two major mechanisms to undergo genetic alterations and generate new variants. The first is mainly driven by random occurrence of point-mutations. Many SARS-CoV-2 variants—for example, Alpha, Beta, Gamma, Mu, Delta, and Omicron—have emerged because of point-mutations [5,6]. The second mechanism is "recombination" whereby RNA viruses exchange large segments of genetic material, not necessarily "reciprocally" [7]. Examples of RNA viruses that frequently undergo recombination are coronaviruses, influenza virus, and the human immunodeficiency virus [8]. Recombination was confirmed previously among the viral lineages of MERS-CoV, the coronavirus agent causing the Middle East Respiratory Syndrome [9,10]. By analogy, emergence of the hybrid SARS-CoV-2 variants are expected, though RNA viruses generally are thought to undergo point-mutations more frequently than recombination [7].

The RNA-proofreading enzymes of the RNA viruses are found to be inefficient, thus causing a high rate of errors and low viral fidelity [11]. Coronaviridae however are an exception [11]. Therefore, point-mutations would be a less efficient mechanism to generate new SARS-CoV-2 variants than recombination. Nevertheless, initial high circulation of SARS-CoV-2 and high COVID-19 case numbers worldwide helped the virus to generate successful variants by point mutations. Similarly, observation of several peaks of the COVID-19 cases in five continents during the pandemic suggests that the virus generated highly transmissible and successful variants without gradually losing survival benefits which are expected to occur because of accumulation of deleterious missense mutations. Because recombination mostly occurs between distinct lineages of a virus with more infectious traits and coincides with circulation of highly transmissible viral variants, SARS-CoV-2 is thus highly likely to undergo, and benefit from, recombination as it keeps circulating and evolving. However, the genetic diversity observed in the SARS-CoV-2 genome is less than those of other RNA viruses [12].

An example of a highly transmissible SARS-CoV-2 variant is the Omicron variant detected in South Africa [13,14]. Alpha and Delta variants similarly circulated successfully. Finally, emergence and cocirculation of BA.1 and BA.2, as closely related strains of Omicron, facilitated formation of the hybrid strains following coinfection cases. For example, 47 cases were reported as BA.2-positive shortly after infection with BA.1 in Denmark, thus facilitating occurrence of recombination between the two viral strains [15]. Therefore, the continuity of the pandemic peaks partially armed the new highly transmissible variants to circulate simultaneously. Although early to conclude, we speculate that the new hybrid forms of SARS-CoV-2 followed circulation of Omicron and circulation of the Omicron subvariants that caused high COVID-19 hospitalizations in European and American countries.

At the beginning of the COVID-19 pandemic, the possibility of recombination among SARS-CoV-2 variants was questioned [16], and the role of recombination and emergence of new, hybrid viral lineages were not seriously considered. However, generation of the hybrid virus strains should now be considered as a potential mechanism that could aggravate the pandemic by increasing the number of COVID-19-positive cases. Until April 2022, three recombinant forms of the Omicron variants were identified. These include XD, XF, and XE. XD is thought to have resulted from recombination between Delta and the BA.1 lineage of

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Omicron. XF is a recombinant of BA.1 and the U.K. Delta variants. Interestingly, following the 2022 case surges in the U.K., the U.K. Health Security Agency reported several hybrid forms of SARS-CoV-2 rapidly circulating in the community. The World Health Organization highlights the emergence of the XE variant as a hybrid of the two Omicron subvariants, BA.1 and BA.2 (also termed stealth Omicron). Although the pathological characteristics of XE are not well understood yet, XE is thought to be tenfold more contagious than BA.2. Notwithstanding the mechanisms by which viruses achieve genetic diversity, viral genetic alterations precede evolutionary fitness, including resistance to antiviral drugs or vaccines, high infectivity and transmissibility, immune evasion, and high virulence because deleterious genetic alterations fail to dominate and propagate with the virus [7].

In conclusion, large-scale sequencing projects and alternatively fast and affordable analytical technologies will be valuable for monitoring the progression of the mutated and recombinant SARS-CoV-2 variants globally.

Ethical approval

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

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Author contribution

Farid Rahimi: Conceptualization, data curation, writing – review & editing. **Amin Talebi Bezmin Abadi:** Conceptualization, data curation, writing – original draft, writing – review & editing. All authors critically reviewed and approved the final version of the manuscript before submission.

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