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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Implications of the SARS-CoV-2 subvariants BA.4 and BA.5

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Dear Editor,

The monkeypox outbreak in Europe in early May 2022 [1] attracted the focus of the news and social media, and the global healthcare authorities. Concurrently, the newly emerged SARS-CoV-2 subvariants BA.4 and BA.5 (sublineages of Omicron B.1.1.529) have caused a new surge of the COVID-19 hospitalizations across the world after the BA.1 and BA.2 subvariants receded in March 2022 [2,3]. The initial outbreak by the highly transmissible SARS-CoV-2 Omicron variant in November 2021 in South Africa prompted the World Health Organization to classify Omicron as a new variant of concern [4]. Emergence and global dissemination of the Omicron variant then surprised many, while emergence of the divergent Omicron sublineages, including BA.1, BA.2.12.1, BA.2, BA.4, and BA.5, was also unexpected but understandable because of the natural viral biology [5].

The SARS-CoV-2 Omicron subvariants share many point-mutations (e.g., G339D, S375F, E484A, N501Y, H655Y, and L452R) and other genetic variations. In particular, F486V and L452R substitutions are found specifically in the BA.4 and BA.5 subvariants; these are thought to help the virus evade the immune responses established due to neutralizing antibodies [6], thus reinfecting those who previously suffered COVID-19 or were vaccinated [7,8]. Therefore, BA.4 and BA.5 are more transmissible and expected to be more contagious than BA.1, BA.2, or BA.2.12.1, causing high hospitalization rates [9]. These characteristics have implications for the global management of the COVID-19 pandemic.

BA.4 and BA.5 were initially reported in January and February 2022 and dominated over the BA.2 subvariant by early April 2022 in South Africa [10]. By the end of July 2022, four out of the six WHO regions witnessed sharp rises in new COVID-19 infections, possibly by BA.4 or BA.5 subvariants [11]. Given the rising trend of new cases and enhanced infectivity of the subvariants, BA.4 and BA.5 are anticipated to swiftly progress into all WHO regions [12]. Months of steadily controlling the pandemic by vaccination campaigns and epidemiological countermeasures allowed return to normalcy and decreased the global mortality rates. Thereafter, epidemiological restrictions were gradually eased or lifted. The highly transmissible nature of the BA.4/BA.5 subvariants coinciding with the public sense of normalcy facilitated high hospitalizations and fatalities among vulnerable individuals. Indeed, summer vacation in the northern hemisphere means that many individuals will take part in outdoor activities and mass-gatherings in enclosed spaces. The winter season in the southern hemisphere means that many individuals will be confined indoors, in closed spaces. Thus, many will be at high risk of exposure to BA.4/BA.5 irrespective of the season. Additionally, a large proportion of individuals will have reduced immunity against SARS-CoV-2. Relaxation of epidemiological countermeasures, including face-masking and physical distancing, and low immune response increase the chance of reinfection with BA.4 or BA.5.

Vaccine inequity is a grave problem because it provides an appropriate means for the BA.4 and BA.5 subvariants to circulate more efficiently in human hosts, accumulate new mutations, propagate, achieve the best fitness, cause more infections or reinfections, and increase the mortality rate among the vulnerable or immunocompromised individuals. More than 63% of the world population are fully vaccinated (mainly in high-income and upper middle-income countries); the average immunization rate in low-income countries is about 13%. Immunization boosters using updated vaccine formulations are now necessary to surpass ineffective vaccines [13].

Lastly, monitoring the recombination patterns of the viral variants and subvariants is necessary to track how the sublineages evolve and adapt. This monitoring is necessary also for formulating new vaccines. Epidemiological countermeasures, including face-masking, physical distancing, strict cross-border controls, and prevention of mass-gatherings and festivals should be reimplemented. If relaxation of the restrictions (the normalcy) continues, high hospitalizations in September and October 2022 will increase the healthcare burden and

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stretch hospital care and resources globally.

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