

Re-Emergence of SARS-CoV-2: Frequent Mutations, Amplified Transmissibility and Immune Elusion

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While the history of coronavirus dates back to 1990, it appeared in China in December 2019, and eight months after the initial outbreak, WHO declared it as a pandemic with the global count of confirmed COVID-19 cases surpassing 27 million and 900,000 reported mortalities.¹ The pandemic of severe acute respiratory syndrome coronavirus, known as SARS-CoV-2 is responsible for grave illness and manifold demises worldwide during the pandemic period. After the first case of COVID in Karachi, Pakistan on 26 February 2020, the virus propagated nationwide and within 45 days there were 4601 confirmed cases of COVID-19 and 66 deaths in Pakistan. According to WHO, Pakistan has reported 1,581,936 cases and 30,664 deaths, despite infrequent testing and underreporting.² After the grave devastation to not only the health situation but also to the economy of countries, the situation improved somewhat after the invention and mass-level dissemination of the COVID-19 vaccine, nonetheless, the hazard continued to exist. The data reports 579 million confirmed cases and 6.4 million deaths globally from May to July 2022, 5–10% undiagnosed cases of acute respiratory infections can still be attributed to coronaviruses.¹

Coronavirus is single-stranded RNA viruses categorized into various families (i.e. Roniviridae,

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Arteriviridae, and Coronaviridae) and genera/variants (i.e. Alpha, Beta, Delta, Gamma and omicron CoV). Among all the genera, Beta-CoV is the most widespread and is further classified into five different lineages. Numerous factors, such as age and gender, pre-existing co-morbidities, immunity level, seasonal variations, and the timing and strength of control measures determine the crescendos of SARS-CoV-2 transmission.³ While the morbidity and mortality of coronavirus decreased after the emergence and wide administration of vaccines, the original virus mutated towards increased pathogenicity, infectivity, transmissibility, and immune escape. These mutations enabled the virus to not only elude vaccines but also dodge a few life-saving medications like monoclonal antibodies. Later on, in 2020, a variant named 'Omicron' appeared and spread globally like wildfire proving to be the worst since the commencement of the epidemic. Since then, five omicron subvariants/lineages BA.1, BA.2, BA.3, BA.4, BA.5 and numerous sublineages BA.1.1, BA.2.12.1, BA.2.11, BA.2.75, and BA.4.6, have been identified. According to the latest reports, amongst all subvariants of the Omicron, the BA.5 exhibited the ability to escape the deactivation by antibodies thus becoming a major cause of coronavirus-related diseases in the majority of the countries in 2022. In the following year, numerous Omicron subvariants were recognized in patients having coronavirus disease i.e. the BA.4 sublineage which then mutated to BA.2 lineage along with the BA.5 sublineages BQ.1.1. and BF.7 Later on, the

BQ.1.1 subvariant propagated swiftly worldwide as the predominant subvariant of coronavirus in the last months of 2022. Subsequently, a new subvariant of the Omicron, known as XBB.1.5. came into the picture at the start of 2023 with an additional spike protein that intensified the ailment due to its enhanced binding capacity to the ACE-2 human cell receptor.^{4,5} Among the presently existing 600 Pango lineages of Omicron, the XBB.1.5 Omicron subvariant was named the 'Kraken' (giant sea monster) due to its markedly enhanced pathogenicity, substantial immune escape, and significant diminutions in the neutralizing capability of serum from vaccinated individuals and those who already had the disease. By the end of 2022, it was estimated that "Kraken" would dominate the European Union and the rest of the world. Similarly, in the United States, the Centers for Disease Control and Prevention (CDC) declared the variant "Kraken" as 'fast spreading virus. During four months till the start of 2023, around 5288 subvariants of Kraken were identified in different countries in total. Then the US suggested to administer booster doses of bivalent vaccination manufactured by BioNTech, Pfizer, and Moderna for all individuals aged 6 months and above after rapid advances in kraken strains.⁶ A report by the CDC suggested that the effectiveness of bivalent vaccine (three 3 months after administration of the vaccine) against Omicron's newly developed strains XBB and XBB.1.5, (among previously vaccinated subjects with monovalent vaccine), was equivalent to that of older ones.⁶ A few studies have reported that these vaccines were found to be effective against the parent SARSCoV-2 virus and the Omicron variant but the effectiveness of vaccines against new strains have not been tested. These might be effective in reducing the mortality caused by newer and lethal strains to some extent but can't entirely be protective in escaping newer strains of the virus. Similarly, no studies exist against the efficacy of antivirals, such as nirmatrelvir/ ritonavir or

remdesivir against the new strains. Hence it is safe to state that along with the previous causes of the emergence of SARSCoV-2, the causes of re-emergence are not only mutating strains of the virus that have amplified infectivity and receptor binding ability, but also that the emerging pathogens causing zoonotic diseases are thrice more influenced by socioeconomic, environmental and ecological factors. Moreover, most people have not received the number of booster doses as per the latest recommendations, to protect against newer strains and re-emergence.

In conclusion, both the global policymakers and scientists should invest time and funds in research to find not only a strong medicine but also a potent vaccine against the new subvariants. Otherwise, these variants may be expected to spread and cause fatalities globally, leading to another pandemic in the coming years.

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