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LETTER TO THE EDITOR

Global threat from novel SARS-CoV-2 variants, BF.7, XBB.1.5, BQ.1, and BQ.1.1: variants of concern?

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Dear Editor,

Globally, the recent surge in COVID-19 cases in China and the United States of America (USA) was brought about by the novel BF.7 and XBB.1.5 variants that have garnered considerable public attention [1]. Commonly reported symptoms are illustrated in Fig. 1.

Since its first report in late 2021, the Omicron variant has mutated into several variants, such as BA.5, which in turn forms BA.5.2.1.7, also known as BF.7 [2]. Compared to Omicron (average reproduction number or $R_0 = 5.08$), BF.7 ($R_0 = 10–18.6$) [2] had the greatest capacity for infection, owing to its rapid transmissibility, short incubation period, and a greater propensity to affect individuals previously COVID-19 positive, vaccinated, or both [3].

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Such a rapid infection rate, usually within hours, makes detection using quantitative real-time polymerase chain reaction (qRT-PCR) daunting [2]. The immune evasion ability of BF.7 has been reported and has been associated with the R346T mutation in the SARS-CoV-2 spike protein [4]. This evasion has been validated by testing BF.7 in the sera obtained from triple-vaccinated healthcare workers and patients infected with the Omicron BA.1 and BA.5 variants during the pandemic [5].

In vitro studies revealed a 4.4-fold reduction in neutralization ($p < 0.0001$) in BF.7 compared to the original D614G variant, which explains its potential to replace the already dominant sublineages in the US and UK populations [6]. Furthermore, BQ.1 and BQ.1.1, other Omicron sublineages, were found to have approximately 10.4 ($p < 0.0001$) and 10.7-fold ($p < 0.0001$) reduction in neutralization [5].

XBB.1.5 is regarded as a hybrid of pre-existing BA.2.10.1 and BA.2.75 variants [7]. Preliminary studies on the XBB.1.5 variant underscore its higher infectivity, rapid transmission, and immune evasion capacity than other Omicron sublineages, especially in populations not previously exposed to omicron variants [1]. However, there is a paucity of evidence supporting the higher infectivity rates and immune evasion capacity of variant XBB.1.5, and the surge in infections is heavily dependent on the geographical and immunological landscape, vaccination coverage, and governmental norms. The receptor-binding domain (RBD) of the XBB.1.5 variant demonstrates rare mutations, such as F486P and G252V, which account for its adherence to host cells and potential immune evasion. However, its contribution to disease severity and mortality must be determined [1, 8]. Additionally, in order to address the potential of immune evasion of any novel variant, the authors believe that all potential antigenic sites and/or epitopes must be identified and then tested for immune evasion in their respective

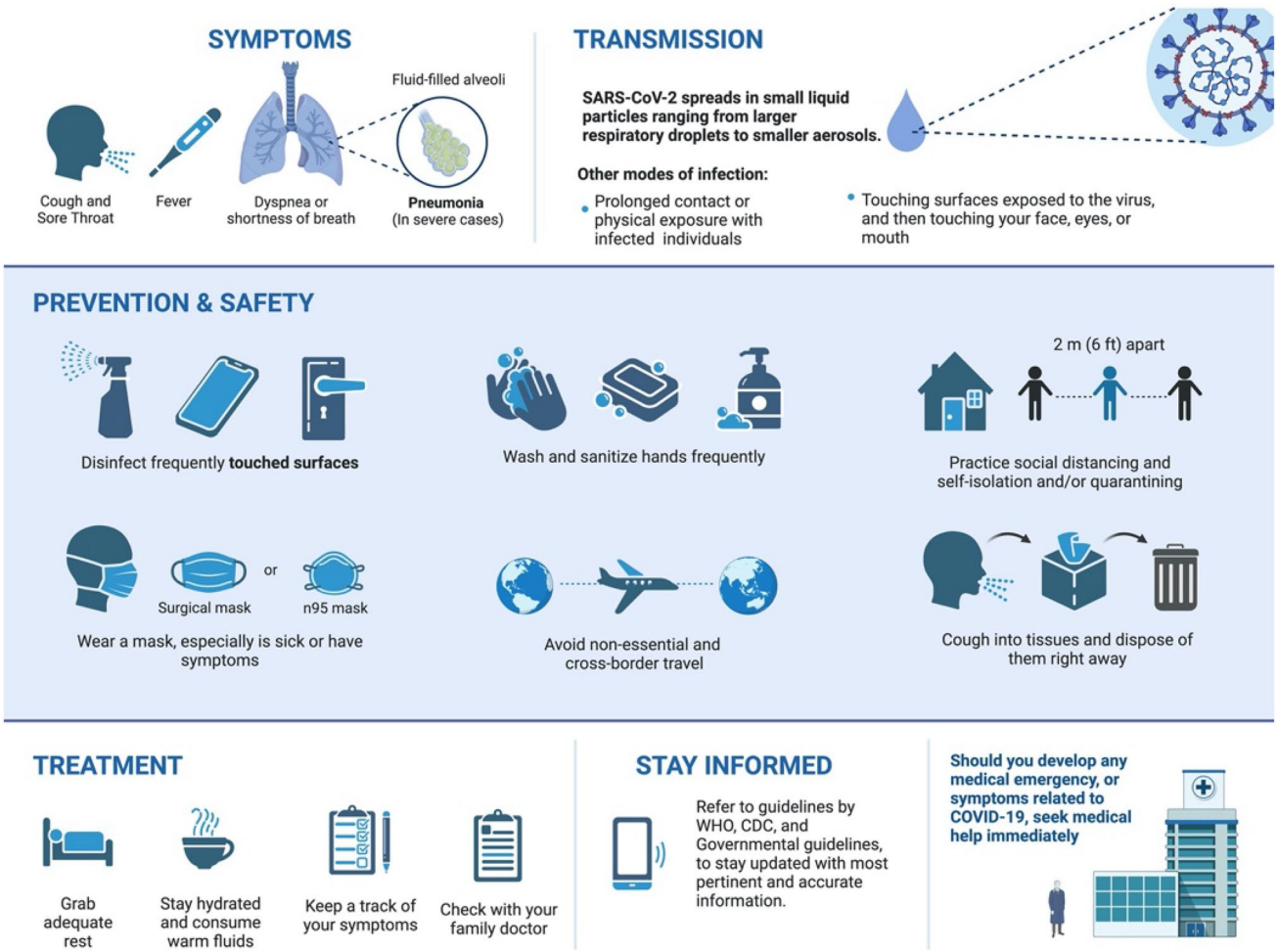

Fig. 1 Common symptoms, transmission, precautions, and treatment suggested for novel SARS-CoV-2 variants

populations, owing to differences in population immunity. Figure 2 elucidates the factors that favor the newer variants of SARS-CoV-2.

Immunization and vaccine booster doses, especially in vaccination drives, confer protection to a large population against the current and upcoming variants, thereby reducing the number of hospitalizations, disease severity, fatalities, and long-term complications [1]. With the immunity waning rapidly, recurrent booster doses have been advised, thereby defeating the rationale of vaccine development and vaccination. This necessitates the development of newer drugs, vaccines, and monoclonal antibodies, targeting newer omicron variants and subvariants.

Novel drugs, therapies, and biologics, including monoclonal antibodies (mAbs) effective against Omicron, such as Bebtelovimab, Casirivimab, and Bebtelovimab + Etesevimab, as well as the United States COVID-19 panel recommended mAbs, including Sotrovimab, Bamlanivimab + Etesevimab, and Casirivimab + Imdevimab, could be employed [7].

However, vaccines can include mRNA, inactivated or attenuated strain, and protein-based adjuvant vaccines. However, the development of vaccines targeting pan-beta and human endemic coronaviruses, such as conservative S2-targeting vaccines, RBD-dimeric vaccines, and mosaic RBD nanoparticle vaccines, can confer relatively long-term protection because of their ability to induce broad-spectrum neutralizing antibodies, leading to pan-CoV immunity, even against potential future strains [1]. As the protection conferred by the immune system follows a time-dependent reaction pattern following contact with the antigen, parameters, such as the onset of immunity, duration of immunity, and waning period, must be considered while evaluating the efficacy of the vaccines. Compared to the original monovalent BNT162b2 vaccine, the bivalent BA.4/5 vaccine [9] presents a higher immunogenic potential against the Omicron subvariants and the current variant BQ.1.1 [10]. Additionally, the devising of an adequate immunization scheme is of paramount importance to confer optimal protection against these novel variants.

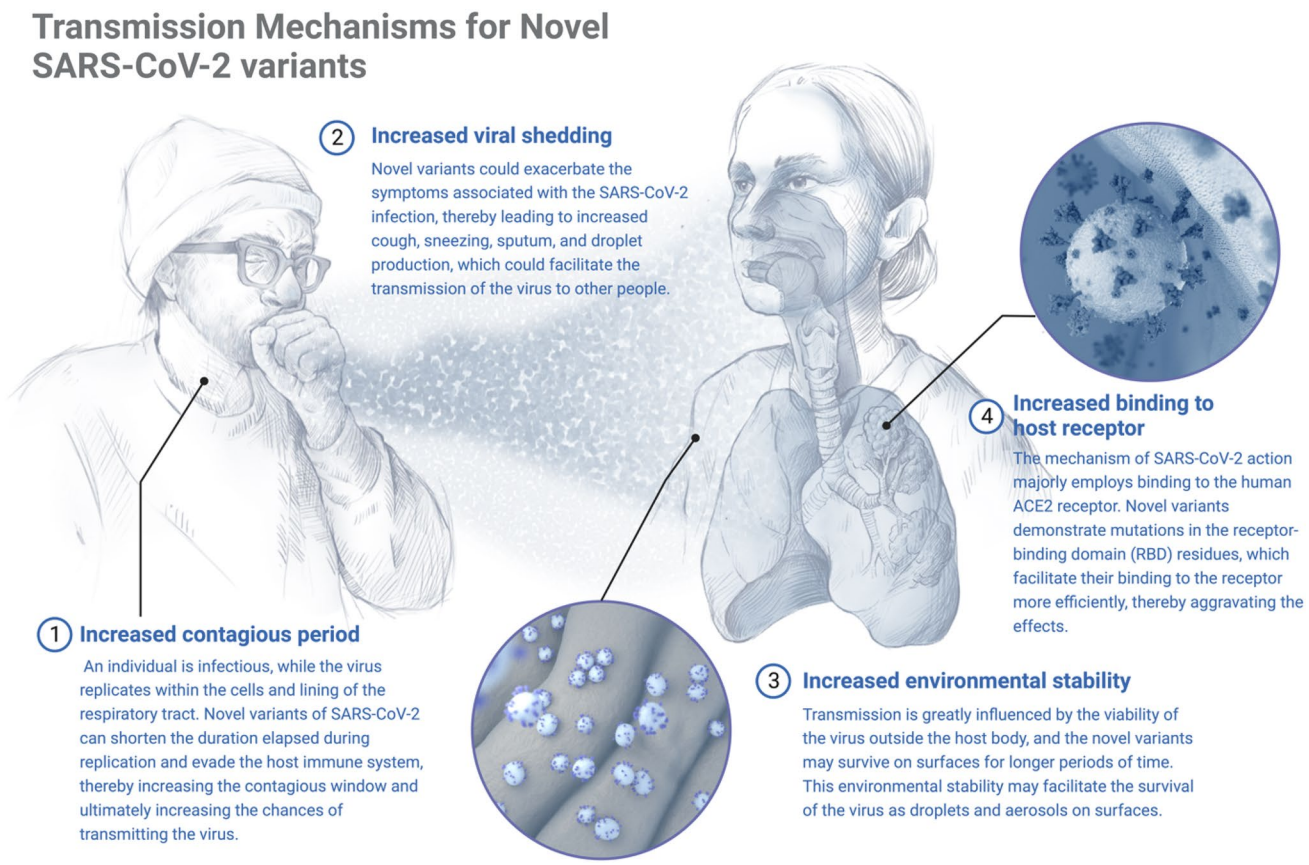

Fig. 2 Mechanisms by which the mutations in newer SARS-CoV-2 variants favor them

As most cases are mild, it is recommended for government and healthcare agencies to devise a new measuring stick to gauge the severity of the COVID wave by enumerating moderate to severe cases or those demanding oxygen supply, mechanical ventilation, and/or mass hospitalization, rather than simple active cases. Additionally, mass vaccination drives and the test-track-treat-vaccinate strategy should be adopted to curtail outbreaks during the festive season.

The authors believe that mitigation steps can include the development of immunotherapeutic agents, and repurposing pre-approved antiviral drugs could be imperative in combating novel variants. Additionally, centralized surveillance and monitoring systems, reporting hierarchy, databases, genomic libraries, rapid testing facilities, pharmacogenomic modeling centers, and pharmacovigilance centers to monitor and report drug reactions could be institutionalized. Furthermore, the emphasis on formulating pre-existing drugs and immunotherapeutic agents into novel dosage forms, such as a polypill with multiple pharmacophores, could help frog-leap research to combat a multitude of viral and zoonotic diseases. Pets and other animal vectors need to be monitored and reported owing to their ability to propagate variants while exerting evolutionary stress that would lead to mutations and their potential to act as zoonotic viral reservoirs. Additionally, public education via mass media can be reinstated to ensure compliance with government mandates and public safety norms. These procedures could serve as a springboard for mitigating the risk stemming from the newer variants of SARS-CoV-2.

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