

Approaching Challenges Posed by SARS-CoV-2 Genetic Variants

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In this new collection of the most viewed and cited papers, one of the Editor's chosen articles, published in *Pathogens* in 2021, addressed the impact and the concerns relating to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants [1]. SARS-CoV-2, which caused the pandemic of coronavirus disease 2019 (COVID-19), is an RNA virus discovered in December 2019 in Wuhan, China. Since then, the virus has spread worldwide with 6.61 million deaths reported by November 13, 2022 (<https://www.worldometers.info/coronavirus/>, accessed on 13 November 2022), a figure that is probably underestimated.

Vaccines have been the most effective intervention for the control of COVID-19, which, together with improved virus infection diagnostics, epidemiological surveillance, and treatment, have reduced disease prevalence and symptomatology (Figure 1). However, as reviewed by Janik et al. [1], the appearance of new genetic variants of concern and interest constitutes a challenge for disease prevention and control (Figure 1). Variants with higher transmissibility, and reduced effectiveness of neutralizing antibodies and other immune protective mechanisms in response to infection and/or vaccination, have affected virus detection and surveillance with increased severity of disease symptomatology and reduced effectiveness in disease treatment and vaccine efficacy [1].

Using the terms "SARS-CoV-2" plus "variants" to perform a search up to the date of November 11, 2022, PubMed recorded 1847 articles published in 2021 and 4529 articles published in 2022. These numbers highlight and support the relevance of the study of emerging SARS-CoV-2 genetic variants. The topics focused on emerging SARS-CoV-2 genetic variants and addressed in these publications include new treatment interventions (e.g., [2,3]) and vaccine formulations (e.g., [4,5]); virus detection tools (e.g., [6,7]); study of host–virus molecular interactions (e.g., [8–10]); virus infection, transmission, and lethality in vaccinated and non-vaccinated individuals (e.g., [11,12]); mechanisms of virus evolution and the emergence of new genetic variants (e.g., [13–18]); and vaccination efficacy and new strategies (e.g., [19–25]).

Despite important advances in the characterization, surveillance, and prevention of emerging SARS-CoV-2 variants, challenges in other areas need to be considered for effective prevention and control of these genetic variants. Based on existing information, these challenges include the possible role of domestic and wild animal species in the appearance and transmission of new virus genetic variants, with impacts on both human and animal health (e.g., [26–29]), differences in the impact of environmental factors on virus persistence and transmission (e.g., [30,31]), and the still questioned role of arthropod vectors in virus transmission (e.g., [32–34]).

Understanding genetic variability in SARS-CoV-2 and the functional implications of these mutations is important to understand the impact of new variants on virus infection and transmission, evasion of protective immune response, and disease severity. This information is also relevant for the design and implementation of personalized medical interventions and more effective vaccines. To approach these challenges, traditional well developed and novel challenging tools could be used.



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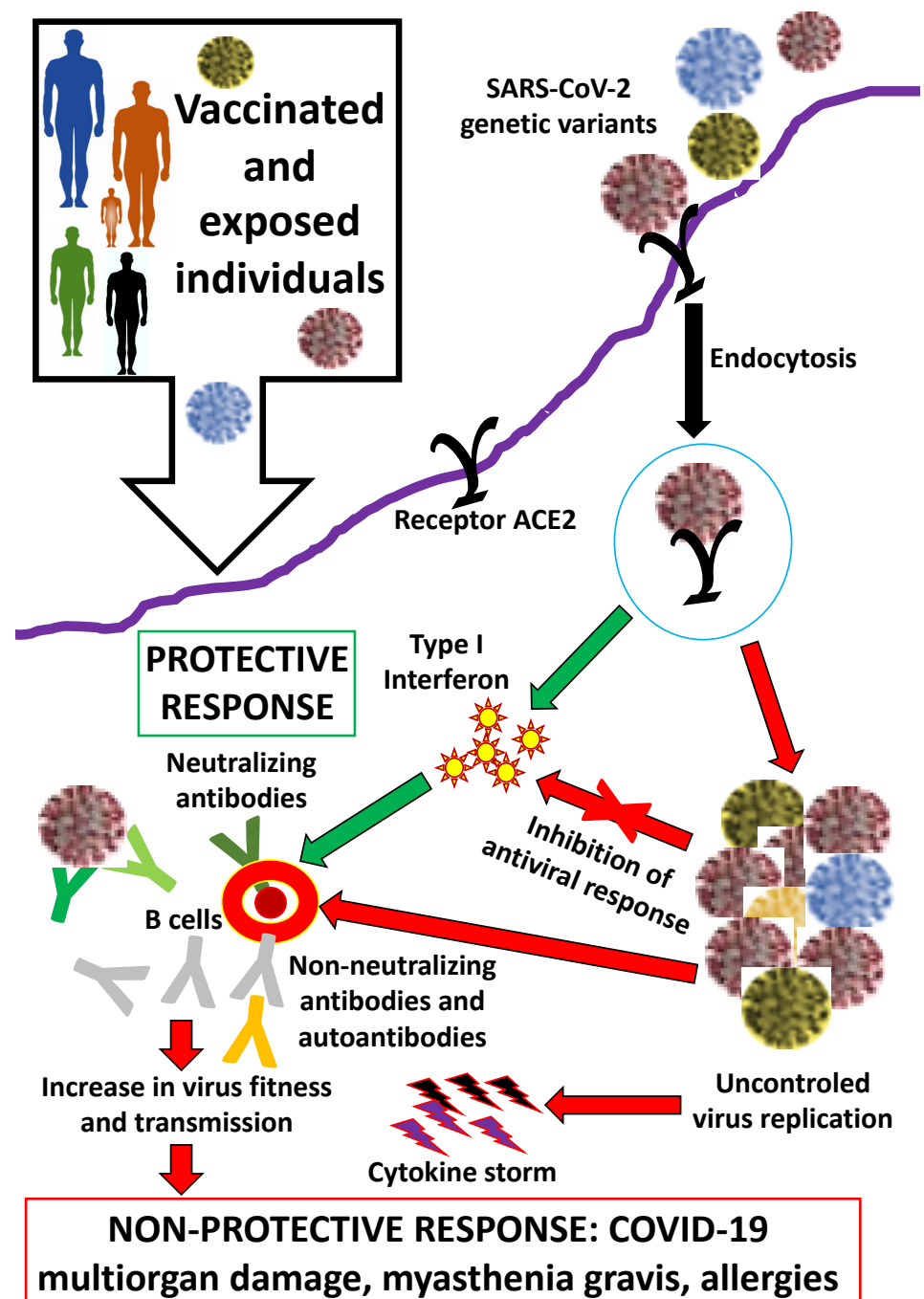


Figure 1. Impact of SARS-CoV-2 genetic variants on individual's protective responses to coronavirus infection and vaccination and non-protective responses associated with COVID-19 prevalence and severity.

Among novel tools, the quantum mechanisms may be considered to understand SARS-CoV-2 evolution and the appearance of new genetic variants and the design of vaccine protective antigens [35]. For example, quantum genetics could be applied to study virus evolution as proposed by Baianu [36] regarded as a "multi-scale process which is initiated by underlying quantum (coupled) multi-molecular transformations of the genomic and interactomic networks, followed by specific phenotypic transformations at the level of organism and the variable biogroupoids associated with the evolution of species which are essential to the survival of the species". Regarding SARS-CoV-2, various quantum approaches have been proposed to study virus–host interactions [37–39]. For vaccine development, quantum vaccinology and vaccinomics approaches could be applied for

the identification and combination of protective epitopes alone or in combination with post-translational modifications, such as glycans in chimeric antigens, to enhance vaccine efficacy against multiple virus genetic variants [40–46].

In conclusion, although the COVID-19 pandemic has been controlled, the appearance of new SARS-CoV-2 genetic variants is still possible, and a One Health multidisciplinary approach is required to be better prepared for the prevention and control of these viruses. Surveillance and timely communication of genetic analyses using validated and innovative quantum approaches is important to get ahead of the new virus variants. Vaccine design and implementation also needs innovation using quantum and other approaches to better protect against new emerging virus genetic variants.

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References

1. Janik, E.; Niemcewicz, M.; Podogrocki, M.; Majsterek, I.; Bijak, M. The Emerging Concern and Interest SARS-CoV-2 Variants. *Pathogens* **2021**, *10*, 633. [\[CrossRef\]](#)
2. Dehghani, J.; Movafeghi, A.; Mathieu-Rivet, E.; Mati-Baouche, N.; Calbo, S.; Lerouge, P.; Bardor, M. Microalgae as an efficient vehicle for the production and targeted delivery of therapeutic glycoproteins against SARS-CoV-2 variants. *Mar. Drugs* **2022**, *20*, 657. [\[CrossRef\]](#)
3. Shang, W.; Dai, W.; Yao, C.; Xu, L.; Tao, X.; Su, H.; Li, J.; Xie, X.; Xu, Y.; Hu, M.; et al. In vitro and in vivo evaluation of the main protease inhibitor FB2001 against SARS-CoV-2. *Antivir. Res.* **2022**, *208*, 105450. [\[CrossRef\]](#)
4. Kim, W.S.; Kim, J.H.; Lee, J.; Ka, S.Y.; Chae, H.D.; Jung, I.; Jung, S.T.; Na, J.H. Functional expression of the recombinant spike receptor binding domain of SARS-CoV-2 Omicron in the periplasm of *Escherichia coli*. *Bioengineering* **2022**, *9*, 670. [\[CrossRef\]](#)
5. Hu, Q.; Zhao, Y.; Shaabani, N.; Lyu, X.; Powers, C.; Sun, H.; Cruz, V.; Stegman, K.; Xu, J.; Fossier, A.; et al. Chimeric mRNA based COVID-19 vaccine induces protective immunity against Omicron and Delta variants. *Mol. Ther. Nucleic Acids* **2022**, *30*, 465–476. [\[CrossRef\]](#)
6. Wallace, Z.S.; Davis, J.; Niewiadomska, A.M.; Olson, R.D.; Shukla, M.; Stevens, R.; Zhang, Y.; Zmasek, C.M.; Scheuermann, R.H. Early detection of emerging SARS-CoV-2 variants of interest for experimental evaluation. *Front. Bioinform.* **2022**, *2*, 1020189. [\[CrossRef\]](#)
7. Yang, J.; Barua, N.; Rahman, M.N.; Li, C.; Lo, N.; Yeong, K.Y.; Tsang, T.F.; Yang, X.; Cheung, Y.Y.; Tsang, A.K.L.; et al. Rapid SARS-CoV-2 Variants Enzymatic Detection (SAVED) by CRISPR-Cas12a. *Microbiol. Spectr.* **2022**, e0326022. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Dacon, C.; Peng, L.; Lin, T.H.; Tucker, C.; Lee, C.D.; Cong, Y.; Wang, L.; Purser, L.; Cooper, A.J.R.; Williams, J.K.; et al. Rare, convergent antibodies targeting the stem helix broadly neutralize diverse betacoronaviruses. *Cell Host Microbe* **2022**, S1931-312800523-6. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Villar, M.; Urrea, J.M.; Rodríguez-Del-Río, F.J.; Artigas-Jerónimo, S.; Jiménez-Collados, N.; Ferreras-Colino, E.; Contreras, M.; de Mera, I.G.F.; Estrada-Peña, A.; Gortázar, C.; et al. Characterization by quantitative serum proteomics of immune-related prognostic biomarkers for COVID-19 symptomatology. *Front. Immunol.* **2021**, *12*, 730710. [\[CrossRef\]](#)
10. Pacheco-Olvera, D.L.; Saint Remy-Hernández, S.; García-Valeriano, M.G.; Rivera-Hernández, T.; López-Macías, C. Bioinformatic analysis of B- and T-cell epitopes from SARS-CoV-2 structural proteins and their potential cross-reactivity with emerging variants and other human coronaviruses. *Arch. Med. Res.* **2022**, *53*, 694–710. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Zali, A.; Khodadoost, M.; Gholamzadeh, S.; Janbazi, S.; Piri, H.; Taraghikhah, N.; Hannani, K.; Looha, M.A.; Mohammadi, G. Mortality among hospitalized COVID-19 patients during surges of SARS-CoV-2 alpha (B.1.1.7) and delta (B.1.617.2) variants. *Sci. Rep.* **2022**, *12*, 18918. [\[CrossRef\]](#)
12. Woodbridge, Y.; Amit, S.; Huppert, A.; Kopelman, N.M. Viral load dynamics of SARS-CoV-2 Delta and Omicron variants following multiple vaccine doses and previous infection. *Nat. Commun.* **2022**, *13*, 6706. [\[CrossRef\]](#)
13. Magiorkinis, G. On the evolution of SARS-CoV-2 and the emergence of variants of concern. *Trends Microbiol.* **2022**, S0966-842X(22)00291-8. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Safari, I.; Elahi, E. Evolution of the SARS-CoV-2 genome and emergence of variants of concern. *Arch. Virol.* **2022**, *167*, 293–305. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Alkhatib, M.; Svicher, V.; Salpini, R.; Ambrosio, F.A.; Bellocchi, M.C.; Carioti, L.; Piermatteo, L.; Scutari, R.; Costa, G.; Artese, A.; et al. SARS-CoV-2 variants and their relevant mutational profiles: Update summer 2021. *Microbiol. Spectr.* **2021**, *9*, e0109621. [\[CrossRef\]](#) [\[PubMed\]](#)

16. Vöhringer, H.S.; Sanderson, T.; Sinnott, M.; De Maio, N.; Nguyen, T.; Goater, R.; Schwach, F.; Harrison, I.; Hellewell, J.; Ariani, C.V.; et al. COVID-19 Genomics UK (COG-UK) Consortium*, Birney, E.; Volz, E.; Funk, S.; Kwiatkowski, D.; Chand, M.; Martincorena, I.; Barrett, J.C.; Gerstung, M. Genomic reconstruction of the SARS-CoV-2 epidemic in England. *Nature* **2021**, *600*, 506–511, Erratum in *Nature* **2022**, *606*, E18. [\[CrossRef\]](#)
17. Chavda, V.P.; Patel, A.B.; Vaghasiya, D.D. SARS-CoV-2 variants and vulnerability at the global level. *J. Med. Virol.* **2022**, *94*, 2986–3005. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Johnson, B.A.; Menachery, V.D. A new tool to probe SARS-CoV-2 variants. *Science* **2021**, *374*, 1557–1558. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Gao, F.X.; Wu, R.X.; Shen, M.Y.; Huang, J.J.; Li, T.T.; Hu, C.; Luo, F.Y.; Song, S.Y.; Mu, S.; Hao, Y.N.; et al. Extended SARS-CoV-2 RBD booster vaccination induces humoral and cellular immune tolerance in mice. *iScience* **2022**, *25*, 105479. [\[CrossRef\]](#)
20. Yuan, M.; Wang, Y.; Lv, H.; Tan, T.J.C.; Wilson, I.A.; Wu, N.C. Molecular analysis of a public cross-neutralizing antibody response to SARS-CoV-2. *Cell Rep.* **2022**, 111650. [\[CrossRef\]](#)
21. Mistry, P.; Barmania, F.; Mellet, J.; Peta, K.; Strydom, A.; Viljoen, I.M.; James, W.; Gordon, S.; Pepper, M.S. SARS-CoV-2 variants, vaccines, and host immunity. *Front. Immunol.* **2022**, *12*, 809244. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Singh, D.D.; Parveen, A.; Yadav, D.K. SARS-CoV-2: Emergence of new variants and effectiveness of vaccines. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 777212, Erratum in *Front. Cell. Infect. Microbiol.* **2022**, *12*, 885482. [\[CrossRef\]](#)
23. Zeng, B.; Gao, L.; Zhou, Q.; Yu, K.; Sun, F. Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: A systematic review and meta-analysis. *BMC Med.* **2022**, *20*, 200. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Huang, X.; Kon, E.; Han, X.; Zhang, X.; Kong, N.; Mitchell, M.J.; Peer, D.; Tao, W. Nanotechnology-based strategies against SARS-CoV-2 variants. *Nat. Nanotechnol.* **2022**, *17*, 1027–1037. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Kingstad-Bakke, B.; Lee, W.; Chandrasekar, S.S.; Gasper, D.J.; Salas-Quinchucua, C.; Cleven, T.; Sullivan, J.A.; Talaat, A.; Osorio, J.E.; Suresh, M. Vaccine-induced systemic and mucosal T cell immunity to SARS-CoV-2 viral variants. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2118312119. [\[CrossRef\]](#)
26. Sharun, K.; Dhama, K.; Pawde, A.M.; Gortázar, C.; Tiwari, R.; Bonilla-Aldana, D.K.; Rodriguez-Morales, A.J.; de la Fuente, J.; Michalak, I.; Attia, Y.A. SARS-CoV-2 in animals: Potential for unknown reservoir hosts and public health implications. *Vet. Q.* **2021**, *41*, 181–201. [\[CrossRef\]](#)
27. Gozalo, A.S.; Clark, T.S.; Kurtz, D.M. Coronaviruses: Troubling Crown of the Animal Kingdom. *Comp. Med.* **2022**. [\[CrossRef\]](#)
28. Shehata, A.A.; Attia, Y.A.; Rahman, M.T.; Basiouni, S.; El-Seedi, H.R.; Azhar, E.I.; Khafaga, A.F.; Hafez, H.M. Diversity of coronaviruses with particular attention to the interspecies transmission of SARS-CoV-2. *Animals* **2022**, *12*, 378. [\[CrossRef\]](#)
29. Maurin, M.; Fenollar, F.; Mediannikov, O.; Davoust, B.; Devaux, C.; Raoult, D. Current status of putative animal sources of SARS-CoV-2 infection in humans: Wildlife, domestic animals and pets. *Microorganisms* **2021**, *9*, 868. [\[CrossRef\]](#) [\[PubMed\]](#)
30. de la Fuente, J.; Armas, O.; Barroso-Arévalo, S.; Gortázar, C.; García-Seco, T.; Buendía-Andrés, A.; Villanueva, F.; Soriano, J.A.; Mazuecos, L.; Vaz-Rodrigues, R.; et al. Good and bad get together: Inactivation of SARS-CoV-2 in particulate matter pollution from different fuels. *Sci. Total Environ.* **2022**, *844*, 157241. [\[CrossRef\]](#)
31. Meyerowitz, E.A.; Richterman, A.; Gandhi, R.T.; Sax, P.E. Transmission of SARS-CoV-2: A review of viral, host, and environmental factors. *Ann. Intern. Med.* **2021**, *174*, 69–79. [\[CrossRef\]](#)
32. de la Fuente, J.; Mera, I.G.F.; Gortázar, C. Challenges at the host-arthropod-coronavirus interface and COVID-19: A One Health approach. *Front. Biosci. (Landmark Ed.)* **2021**, *26*, 379–386. [\[CrossRef\]](#)
33. Nekoei, S.; Khamesipour, F.; Benchimol, M.; Bueno-Marí, R.; Ommi, D. SARS-CoV-2 Transmission by arthropod vectors: A scoping review. *Biomed. Res. Int.* **2022**, *2022*, 4329423. [\[CrossRef\]](#)
34. Higgs, S.; Huang, Y.S.; Hettenbach, S.M.; Vanlandingham, D.L. SARS-CoV-2 and arthropods: A review. *Viruses* **2022**, *14*, 985. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Löwdin, P.O. Quantum genetics and the aperiodic solid: Some aspects on the biological problems of heredity, mutations, aging, and tumors in view of the quantum theory of the DNA molecule. *Adv. Quantum Chem.* **1966**, *2*, 213–360.
36. Baianu, I. Quantum genetics and quantum automata models of quantum-molecular evolution involved in the evolution of organisms and species. *Nat. Prec.* **2012**. [\[CrossRef\]](#)
37. Hwang, S.; Baek, S.H.; Park, D. interaction analysis of the spike protein of delta and omicron variants of SARS-CoV-2 with hACE2 and eight monoclonal antibodies using the fragment molecular orbital method. *J. Chem. Inf. Model.* **2022**, *62*, 1771–1782. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Genovese, L.; Zaccaria, M.; Farzan, M.; Johnson, W.; Momeni, B. Investigating the mutational landscape of the SARS-CoV-2 Omicron variant via Ab initio quantum mechanical modeling. *bioRxiv* **2021**, *152*, 1–16. [\[CrossRef\]](#)
39. Gómez, S.A.; Rojas-Valencia, N.; Gómez, S.; Cappelli, C.; Restrepo, A. The role of spike protein mutations in the infectious power of SARS-COV-2 variants: A molecular interaction perspective. *ChemBiochem* **2022**, *23*, e202100393. [\[CrossRef\]](#)
40. de la Fuente, J.; Contreras, M. Vaccinomics: A future avenue for vaccine development against emerging pathogens. *Expert Rev. Vaccines* **2021**, *20*, 1561–1569. [\[CrossRef\]](#)
41. Campos, D.M.O.; Silva, M.K.D.; Barbosa, E.D.; Leow, C.Y.; Fulco, U.L.; Oliveira, J.I.N. Exploiting reverse vaccinology approach for the design of a multiepitope subunit vaccine against the major SARS-CoV-2 variants. *Comput. Biol. Chem.* **2022**, *101*, 107754. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Galili, U. Increasing efficacy of enveloped whole-virus vaccines by *in situ* immune-complexing with the natural anti-gal antibody. *Med. Res. Arch.* **2021**, *9*, 2481. [\[CrossRef\]](#) [\[PubMed\]](#)

-
43. De la Fuente, J.; Gortázar, C.; Cabezas-Cruz, A. Immunity to glycan α -Gal and possibilities for the control of COVID-19. *Immunotherapy* **2021**, *13*, 185–188. [[CrossRef](#)] [[PubMed](#)]
 44. Galili, U. Host synthesized carbohydrate antigens on viral glycoproteins as “Achilles’ heel” of viruses contributing to anti-viral immune protection. *Int. J. Mol. Sci.* **2020**, *21*, 6702. [[CrossRef](#)]
 45. Galili, U. Amplifying immunogenicity of prospective Covid-19 vaccines by glycoengineering the coronavirus glycan-shield to present α -gal epitopes. *Vaccine* **2020**, *38*, 6487–6499. [[CrossRef](#)]
 46. Chen, J.M. SARS-CoV-2 replicating in nonprimate mammalian cells probably have critical advantages for COVID-19 vaccines due to anti-Gal antibodies: A minireview and proposals. *J. Med. Virol.* **2021**, *93*, 351–356. [[CrossRef](#)]