Review of: "Evolution of new variants of SARS-CoV-2 during the pandemic: mutation-limited or selection-limited?"

Kenneth Lundstrom

Potential competing interests: No potential competing interests to declare.

What is behind the novel emerging SARS-CoV-2 variants?

Kenneth Lundstrom

PanTherapeutics, Lutry, Switzerland

Abstract

The emerging SARS-CoV-2 variants have presented a significant impact on the efficacy of current COVID-19 vaccines and the future development of novel vaccines. The origin of new SARS-CoV-2 variants has been investigated using simulation data by Bajpai and Watve on 125 new variants from 64 countries, which has been verified by three hypotheses based on the evasion of the immune system by the new variants (hypothesis 1), random appearance of mutations (hypothesis 2), and a combination of immune evasion and infection advantage for variant selection (hypothesis 3). The simulation data supports hypothesis 3.

Bajpai and Watve further present a comparison of variants of other viruses such as influenza A virus, rhinoviruses, poxviruses, and polioviruses. Although some similar patterns are claimed for the emergence of variants for influenza A virus and coronaviruses but not poxviruses and polioviruses the comparison is questionable due to the differences in the genomic composition and the immunogenic properties of each virus type.

Introduction

The engineering of safe and efficacious vaccines against SARS-CoV-2 presented a real game changer in saving millions of lives and allowing the COVID-19 pandemic to be declared endemic [1]. Unfortunately, but not unexpectedly, mutations were discovered in the SARS-CoV-2 genome, leading to the emergence of novel SARS-CoV-2 variants, which posed the risk of enhanced transmissibility and pathogenicity [2]. It also raised the fear of reduced protection of existing COVID-19 vaccines against novel variants [3]. Recently, Bajpai and Watve discussed the evolution of novel variants of SARS-CoV-2 occurring during the COVID-19 pandemic in their publication in Qeios [4]. Three possible hypotheses were laid out for the spread of emerging SARS-CoV-2 variants. One possibility (hypothesis 1) is the evasion of the immune system by novel variants. Related to this is the random appearance of mutations, which rather leads to an advantage of a specific variant than an evasion of the immune system (hypothesis 2). The third possibility (hypothesis 3) comprises a combination of immune evasion and infection advantage for variant selection.

Simulation Data from Studies on Novel Variants

Although simulation data cannot be used for quantitative predictions, they can provide some limited insight into the patterns of quantification. Based on data from 125 new SARS-CoV-2 variant waves from 64 countries none aligned with the expectations related to hypothesis 1. Instead, there was an indication of an invasion of new variants before the new wave occurred. Moreover, the waves were completed without emergence of any new variant in 27 cases. These findings demonstrated that at least one of three patterns contradicted the statements of hypothesis 1. As new waves are not dependent on the presence of new variants or the variants causing new waves, the authors claim that hypothesis 1 can be rejected [4].

In the case of hypothesis 2, the new invading variant should be either directly proportional to the viral population present or it should remain constant over time. Therefore, according to hypothesis 2, the emergence of a new variant within a given time interval should be proportional to the area under the incidence curve or remain constant over time.

According to hypothesis 3, a new wave of a variant leads to the increase in the incidence of earlier variants but the new variant can also replace existing variants without causing a wave. As new waves can emerge without the detection of the invasion of new variants, these are unlikely to invade at the peak or early after the peak of earlier waves. Therefore, new variants can only occur after a relatively long time. The simulation results presented by Bajpai and Watve support hypothesis 3.

Comparison to Other Viral Infections

The authors also compare the concept of new variants for other types of viruses such as influenza A virus, common cold viruses (rhinoviruses), poxviruses, and polioviruses [4]. Although some similar patterns have been observed for the emergence of variants for influenza A virus and coronaviruses but not for poxviruses and polioviruses, it is questionable how useful such a comparison can be as these viruses are quite different from SARS-CoV-2 and coronaviruses in general. Briefly, the single-stranded RNA (ssRNA) positive-sense genome of SARS-CoV-2 is approximately 29-30 kb in length [5] and possesses a proofreading activity [6]. Although SARS-CoV-2 is an enveloped virus containing the envelope (E) and membrane (M) proteins, the main protein of immunogenic relevance and the target for most COVID-19 vaccines is the spike (S) protein [7]. In contrast, the influenza A virus envelope contains two prominent membrane proteins, hemagglutinin (H) and neuraminidase (N) [8], which play a key role in immune evading of existing vaccines by the combination of different types of H and N variants. Moreover, the influenza A virus genome is negative sense ssRNA composed of eight RNA segments. Rhinoviruses, which are known to cause the common cold, are small non-enveloped RNA viruses belonging to the picornavirus family [9], which both from genetic and immunological aspects anticipate different scenarios compared to SARS-CoV-2. In the case of poxviruses, their large double-stranded DNA genome and complex protein structure present completely different challenges [10]. Finally, polioviruses carry a ssRNA genome and a simple nonenveloped icosahedral structure resembling more rhinoviruses than coronaviruses [11]. Bajpai and Watve also claim that the mutation rates are unlikely to show significant differences for different types of viruses [4]. However, this is incorrect. Although exact measurements might be difficult to establish, DNA viruses show a lower rate of 10^{-8}-10^{-6} substitutions/nucleotide/cell compared to 10^{-6}-10^{-4} substitutions/nucleotide/cell for RNA viruses. For SARS-CoV-2 a

mutation rate of 10^{-5}-10^{-3} substitutions/nucleotide/cell has been described despite its proofreading activity [6]. For these reasons, comparative studies on viruses with major differences in genomic composition and immunologic properties are not very fruitful.

Lockdown and New Variants

The discussion of lockdown measurements is to some extent misplaced. Although Bajpai and Watve admit that the lockdown strategy was effective in reducing transmission at the early stages of the COVID-19 pandemic, they suggest that lockdown efforts are unlikely to be effective against new variants and that the appearance of new variants is not only caused by mutations. The efficacy of existing vaccines and continuous re-engineering of vaccines to address the shortcomings in protection against new variants are important factors in making future lockdowns unnecessary. To my knowledge, health authorities have not recommended lockdowns after the emergence of new SARS-CoV-2 variants.

Conclusions

Although direct quantitative predictions are not possible based on simulation models, the study by Bajpai and Watve [4] has generated some interesting and important results, providing a better understanding of the origin of new variants of SARS-CoV-2. Among the three hypotheses presented and tested by simulation, the conclusion is that hypothesis 3, a combination of immune evasion and infection advantage for variant selection, showed the best fit with the obtained simulation results. Bajpai and Watve further compared the emergence of new variants of influenza A virus, rhinoviruses, poxviruses and polioviruses to coronaviruses, which is questionable due to the substantial differences in the genetic composition and immunogenic properties of each virus group.

References

1. *It's (Finally) Time to Stop Calling It a Pandemic: Experts (2023). WebMD Health News. www.webmd.com/covid/news/20230317/time-to-stop-calling-it-a-pandemic (Accessed on August 24, 2023).*

2. *Lundstrom, K. (2023). Role of Nucleic Acid Vaccines for the Management of Emerging Variants of SARS-CoV-2. In SARS-CoV-2 Variants and Global Vulnerability (Eds. Chavda, V., Uversky, V.N.) Apple Academic Press, Palm Bay, FL, USA, in press.*

3. *Chenchula, S., Karunakaran, P., Sharma, S. & Chavan, M. (2022). Current evidence on efficacy of COVID-19 booster vaccination against the Omicron variant: A systematic review. J Med Virol 94, 2969-2976.*

4. *Baipai, S. & Watve, M. (2023). Evolution of ne variants of SARS-CoV-2 during the pandemic: mutation-limited or selection-limited. Qeios LLA6AO.*

5. *Brant, A.C., Tian, W., Majerciak, W., Yang, W. & Zheng, Z.-M. (2021). SARS-CoV-2: from its discovery to genome structure, transcription, and replication. Cell Bioscience 11, 136.*

6. *Deval, J. & Guard-Levin, Z.A. (2022). Opportunities and Challenges in Targeting the Proofreading Activity of SARS-*

CoV-2 Polymerase Complex. Molecules 27, 2918.

7. *Yao, H., Song, Y., Chen, Y., Wu, N., Xu, J., Sun, C., Zhang, J., Weng, T., Zhang, Z., Wu, Z., Cheng, L., Shi, D., Lu, X., Lei, J., Crispin, M., Shi, Y., Li, L. & Li, S. (2020) Molecular Architecture of the SARS-CoV-2 Virus. Cell 183, 730-738.*

8. *Dou, D., Revol, R., Ostbye, H., Wang H. & Daniels, R. (2018). Influenza A Virus Cell Entry, Replication, Virion Assembly and Movement. Front Immunol 9, 1581.*

9. *Boncristiani, H.F., Criado, M.F. & Arruda, E. (2009). Respiratory Viruses. Encyclop Microbiol (3rd Edition) 500-518.*

10. *Hughes, A.L. Irausquin, S. & Friedman, R. (2010). The evolution biology of pxviruses. Infect Genet Evol 10, 50-59.*

11. *Minor, P.D. (1996). Poliovirus biology. Structure 4, 775-778.*