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

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Evolution of new variants of SARS CoV-2 during the pandemic: mutation limited, or selection limited? REVIEW 7 July 2023

GENERAL:

The author's sophisticated analysis of epidemiological models of SARS CoV-2 viral infection offer valuable insights into the complexity of the COVID-19 pandemic. The need for accurate lessons learned from COVID-19 pandemic is vital for the medical-science community to learn and offer guidance in dealing with future pandemic preparedness.

RECOMMENDATIONS

There are a number of issues that require clarification. Definition of the concepts and simplification of the presentation of the models is recommended to allow all readers and non-experts in mathematical modeling of viral infection to properly understand and benefit from this review.

Revision of Title

The title assumes that the evolution and emergence of new SARS CoV-2 variants is limited to one of two mutually exclusive processes-mutation versus selection. It is understood that survival advantage of mutations and selective pressure of new variants are the drivers of evolution, but it is neither intuitively obvious nor necessarily valid to assume that the limitation on "evolution of new SARS CoV-2 variants" is dominated exclusively by one or the other processes.

Presentation of the Concept

Genetic variation rather than use of the term mutation. The authors do not differentiate between mutation rate and viral recombination

The mutation rate (base pair substitution, deletions due to infidelity in RNA dependent RNA polymerase) of the entire SARS-CoV-2 genome, estimated from the related mouse hepatitis virus (MHV) to be 10–6 nucleotides per cycle, or 4.83 × 10–4 subs/site/year, is similar or slightly lower, that observed for influenza and other common RNA viruses. It is now widely accepted that viral recombination (exchange of genetic sequences by cross over or re-assortment during coinfection) is the main driver of new SARS CoV-2 variants during the pandemic, which have been tracked in real-time by over 15 million genome sequence submissions in EpiCoV database of the global initiative sharing of all influenza data

(GSAID).

The validity and relevance of mathematical models of "SARS CoV-2 evolution" may in deed be dependent on the different infection waves and the extent of compliance with testing, isolation, vaccination during different phases/stages of the COVID-19 pandemic which were implemented to varying extents in different human populations even within the same geographical region or demographic group.

The convergent evolution of the SARS CoV-2 Spike protein occurred at specific amino acid residues across the different variants of concern (alpha, beta, gamma, delta). In February 2020 and May 2020, aspartate to glutamate at the spike protein position 614 (D614G variant led to B.1.1.7 (also known as the UK variant) and B.1.351 (also known as the South African variant) of greater transmissibility. The delta variants which associated with increased transmissibility and COVID-19 severity in October 2020 carried critical mutations such as D614G, L452R, P681R, and T478K in the S-protein. In the third year of Pandemic, the evolution of omicron in November 2021 acquired additional group of mutations at different amino acid residues, namely R346, K444, N450, N460, F486, F490, Q493, and S494. Omicron subvariants in 2022 and 2023 gave rise to antibody immune escape, high transmissibility and fortunately have been associated with asymptomatic or mild COVID-19 illness.

Definition and clarity on the selective pressures. Differ according to the resources in different populations of the world and the vaccination coverage (i.e 30% in Africa vs 70-90% in EU, USA and much of Asia)

The major selective pressure on the survival of new variants within different human host populations is immunity from natural infection and/or vaccination. The second, selective pressure is human behavior. Political and social factors negatively impacted public health measures to reduce transmissibility by social distancing, wearing of facial masks and self- isolation after positive SARS CoV-2 diagnostics.

Role of the animal reservoir or lack of

The SARS CoV-2, hCoV-19/Wuhan/WIV04/2019, and influenza are both zoonotic respiratory infections. Although the animal reservoir was the most likely origin of the SARS CoV-2 ancestral strain, the SARS CoV-2 VOCs emerged in human populations, not animal reservoirs. In the case of influenza variants, the direct circulation in intermediate mammalian host plays a major role in the seasonal influenza outbreaks. So far, the SARS CoV-2 so show limited circulation in animal reservoirs. Although aerosol spread from viral loads in upper respiratory epithelial cells is predominant host tropism there is curious evidence of SARS CoV-2 in waste water and during the severe COVID-19 associated with delta variant, virus was detected in blood tissues of some patients. Thus, the assumptions and use of models for evolution of SARS CoV-2 variants versus influenza strains should be discussed.

The underlying assumption in this review of “either mutation or selective pressure as limiting factor” in the author's epidemiological models of SARS-CoV-2 infection, requires reconsideration.

The appropriateness of the SIR model for COVID-19 pandemic is questionable?

SARS CoV-2 infection flared up as epicenters at different times in different populations throughout the globe. The classical

assumptions of a) constant homogenous mixing of infected (I), susceptible (S) and recovered (R) individuals and b) fraction of susceptible population decreasing toward zero may not apply in the COVID-19 pandemic. Whether the SIR model can take into account surges of COVID-19 from individuals re-infected with new SARS CoV-2 variants is an open question?

The discussion on page 18 should list take home messages and conclusions. The reader is left without a definite guidance on the calculated slope of incidence curves of the new SARS CoV-2 variant waves and why they “contradict the mutation-limited paradigm and support the selection-limited paradigm”?