

Peer Review

Review of: "Evolution of New Variants of SARS-CoV-2 During the Pandemic: Mutation-Limited or Selection-Limited?"

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This manuscript presents an ambitious and conceptually provocative attempt to distinguish mutation-limited from selection-limited dynamics in the emergence and spread of SARS-CoV-2 variants, using publicly available epidemiological and genomic surveillance data. A major strength is its hypothesis-driven structure: the authors clearly articulate competing evolutionary models, derive qualitative testable predictions, and evaluate them against real-world data across multiple countries. The integration of simulation outputs with empirical pattern analysis (timing of variant invasion, wave structure, slope correlations, lag distributions) provides a coherent narrative challenging the widely assumed “new variant causes new wave” paradigm. The consistent observation that variant invasions typically occur during low-incidence phases, along with weak correlations between variant proportion and early wave slope, offers non-trivial support for a context-dependent, selection-limited interpretation.

However, several methodological and inferential limitations warrant caution. The operational definitions of “origin,” “invasion,” and “wave” are somewhat arbitrary and could materially affect classification outcomes; formal sensitivity analyses using alternative thresholds would strengthen robustness. The reliance on reported case data (subject to testing variability, behavioral changes, reporting artifacts, and policy effects) complicates interpretation of incidence slopes as direct transmission proxies. The correlation analyses are simple and do not control for confounders such as vaccination coverage, mobility, seasonality, non-pharmaceutical interventions, or prior immunity levels. The simulations are qualitative and based on simplified assumptions (e.g., absence of cross-immunity in the mutation-limited model), which may bias the contrast between paradigms. Importantly, rejecting a strictly mutation-limited model does not automatically establish that evolution is predominantly selection-limited without formal comparative model fitting or likelihood-based model selection. Finally, policy conclusions regarding

lockdown inefficacy and limited impact on variant emergence extend beyond the strength of the presented evidence and should be framed more cautiously.

Declarations

Potential competing interests: No potential competing interests to declare.