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November 14, 2022

Dear editors,

Please find enclosed our manuscript, entitled **Lineage frequency time series reveal elevated levels of genetic drift in SARS-CoV-2 transmission in England**, which we are submitting for consideration as a Research Article in eLife. In this manuscript, we address the question of how stochasticity in transmission affected the SARS-CoV-2 pandemic.

Stochasticity in transmission, such as due to superspreading, affects disease transmission and evolution. However, except for in some specific scenarios, it has been challenging to quantify more generally using traditional methods of contact tracing. We harness **the large quantities of sequencing data generated during the pandemic to estimate the strength of stochasticity in transmission by studying the fluctuations in the abundance of genetically similar groups of sequences** (“lineages”) over time**.** In contrast to more commonly used phylogenetic methods for inferring stochasticity from sequence data, **our method directly accounts for sampling noise, can work for pathogens with low mutation rates, and can be more scalable to large numbers of sequences**.

Our results reveal that there was consistently more stochasticity in SARS-CoV-2 transmission in England than expected based on the number of infected individuals. **The magnitude of stochasticity is not easily explained by superspreading estimates from contact tracing.** As a potential additional explanation, we connect our results to transmission networks with community structure, which can generate increased stochasticity in transmission dynamics. **This suggests that new models will be needed for explaining the high levels of stochasticity in SARS-CoV-2 transmission.**

We believe that this work will be of broad interest for researchers in infectious disease epidemiology, population genetics, and evolutionary biology. Suggested senior editors include Molly Przeworksi and George Perry, reviewing editors include Armita Nourmohammad, Richard Neher, Caroline Colijn, Graham Coop, Guy Sella, and Mashaal Sohail, and reviewers include Katia Koelle, Richard Neher, Trevor Bedford, Dan Weissman, Oliver Pybus, Joshua Plotkin, Michael Lassig, and Michael Desai.

Sincerely,

QinQin Yu and Oskar Hallatschek

(on behalf of co-authors Joao Ascensao, Takashi Okada, Olivia Boyd and Erik Volz)