Dear Editor,

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 \_\_\_, reviewing editors include \_\_\_, and reviewers include \_\_\_.

Sincerely,

QinQin Yu

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

Notes:

How will your work make others in the field think differently and move the field forward?

* Found that genetic drift was consistently elevated between 1 and 2 (or 3) orders of magnitude, low levels of Ne, even when the number of positives was high
* Not easily explained by offspring number variance
* We propose some ways how genetic drift can be elevated: jackpot events that result from deme structure rather than superspreading

Briefly

* New method to account for sampling noise in inferring genetic drift and selection
* Can infer how the strength of genetic drift changes over time and space

How does your work relate to the current literature on the topic?

* Current work inferring super spreading through contact tracing
* Current work on inferring evolutionary dynamics of new variants
* Current work on inferring effective population sizes, selection, and deme structure

Who do you consider to be the most relevant audience for this work?

* Population geneticists, infectious disease epidemiologists

Have you made clear in the letter what the work has and has not achieved?

* Has achieved: developed and tested new method for inferring effective population size
* Has not achieved: application to more messy systems, have not figured out why genetic drift is elevated