Dear Editors,

Please find attached our manuscript entitled “Local-Scale Phylodynamics Reveal Differential Community Impact of SARS-CoV-2 in Metropolitan US County” that we are submitting to *Science Translational Medicine.* We’d greatly appreciate your consideration of our manuscript for publication.

Since the initial detection of SARS-CoV-2 in Washington State (WA) in early 2020, genomic epidemiology has played a crucial role in estimating new introductions and community transmission throughout the US, and has motivated rapid public health interventions. While previous genomic epidemiology studies of SARS-CoV-2 have focused on a global, countrywide, or statewide level, the majority of transmission is driven by infections and movement at a local scale, where even neighboring regions in the same municipality can have vastly different epidemic dynamics on the backdrop of prevalent structural inequities. The lack of finescale investigation into local dynamics and the interplay between SARS-CoV-2 transmission and socioeconomic inequities has left local health departments to design interventions with limited information.

In the submitted manuscript, we fill this gap by analyzing epidemiologic, demographic, and genomic data sampled between February 2020 and March 2022 jointly with cell phone mobility data to investigate fine scale spatiotemporal SARS-CoV-2 transmission dynamics in King County, Washington, a diverse, metropolitan US county. We employ an approximate structured coalescent approach to model transmission within and between North King County and South King County, two regions marked by differences in mobility, median income, household size, and occupation.

Our phylodynamic analyses reveal that following stay-at-home orders, the epidemic trajectories of North and South King County diverged, revealing important differences in the role of importations and persistence of local viral transmission. We estimate that about 35% of new cases in North King County can be attributed to introductions instead of local spread while only about an average of 25% of new cases were estimated to be from introductions in South King County, and discover that introductions often drive transmission at a local level, even when local spread alone would be insufficient to produce an exponentially growing epidemic. We also find that South King County experienced a more modest and less sustained reduction in mobility following stay-at-home orders than North King County, while also bearing more socioeconomic inequities that might contribute to a disproportionate burden of SARS-CoV-2 transmission. Overall, our findings suggest a role for local scale phylodynamics in understanding the heterogeneous transmission landscape.

We believe our results have vital implications for informing equitable allocation of public health resources in metropolitan areas of socioeconomic and epidemic heterogeneity. We have already seen the impact of our work by continuously sharing our results with public health partners, including Public Health Seattle King County and the Washington State Department of Health. This study also highlights the importance of ongoing robust genomic surveillance at the local level to monitor COVID-19 transmission in the face of rapidly emerging variant lineages. To our knowledge, our study is the most detailed and comprehensive phylodynamic analysis examining SARS-CoV-2 transmission at a local-scale and the impact of social inequities on differential epidemic dynamics. We thank you for your consideration.

Yours sincerely,

Miguel Paredes, Nicola Müller, and Trevor Bedford on behalf of all co-authors who have all reviewed the manuscript

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