16 March 2022

Dear Editor,

Please find enclosed, our manuscript entitled "*Regional importation and early asymmetric within-country spread of SARS-CoV-2 variants of concern in the Netherlands*", which we would be grateful for your consideration for publication at eLife.

Blanket travel bans have been imposed by many countries during the COVID-19 pandemic to deter the introduction of novel SARS-CoV-2 variants. However, such travel restrictions can cause further burden on lives during the pandemic, especially when imposed on low- and middle-income countries, disincentivising countries from sharing their surveillance data. The recent emergence of the Omicron variant of concern (VOC) from Southern Africa in November 2021 also led to reactionary targeted flight bans by multiple countries including the Netherlands. Yet, that did not deter Omicron from rapidly becoming the dominant variant circulating the Netherlands by December 2021.

By analysing over 39,000 SARS-CoV-2 sequences collected in the Netherlands and their phylogenetically closest genomes sequenced overseas in this study, we showed that regional travel in Europe posed far greater importation risks of VOCs in a country like the Netherlands with minimal travel restrictions to and from neighbouring countries. In fact, we show that all four VOCs (i.e. Alpha, Beta, Gamma and Delta) that circulated in the Netherlands in 2020-2021 were introduced into the Netherlands before targeted flight restrictions were imposed on countries where these variants first emerged. After the implementation of these targeted travel restrictions, sustained foreign introductions of VOCs originated mostly from neighbouring countries around the Netherlands.

We also found that immediately after the respective introductions of Alpha and Delta, the initial within-country spread of these variants were consistently concentrated in the more populous regions of the Netherlands with greater international connectivity. These early-spread regions then acted as the transmission source for the rest of the country. Given that countries are beginning to scale down SARS-CoV-2 surveillance efforts, our findings highlight the importance of maintaining robust surveillance, especially in these regions of early-spread, for continued detection of future VOC introduction.

This work provides important empirical evidence on the extent to which travel bans may or may not curb future variant introductions and could help shape future policies regarding emerging variants. Additionally, we identified key regions in the Netherlands, and by

extension for most other European or high-income countries as well, where surveillance should be maintained to acquire timely actionable information on variant introductions. This work and the methodology used here should appeal to a wide audience including clinicians, virologists, epidemiologists, and public health experts working on COVID-19 research and outbreak control.

Thank you for your consideration and we look forward to your decision.

Sincerely,
Alvin X. Han