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Article

Tracing the international arrivals of SARS-CoV-2 Omicron variants after Aotearoa New Zealand reopened its border

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In the second quarter of 2022, there was a global surge of emergent SARS-CoV-2 lineages that had a distinct growth advantage over then-dominant Omicron BA.1 and BA.2 lineages. By generating 10,403 Omicron genomes, we show that Aotearoa New Zealand observed an influx of these immune-evasive variants (BA.2.12.1, BA.4, and BA.5) through the border. This is explained by the return to significant levels of international travel following the border's reopening in March 2022. We estimate one Omicron transmission event from the border to the community for every ~5,000 passenger arrivals at the current levels of travel and restriction. Although most of these introductions did not instigate any detected onward transmission, a small minority triggered large outbreaks. Genomic surveillance at the border provides a lens on the rate at which new variants might gain a foothold and trigger new waves of infection.

At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, Aotearoa, New Zealand, closed its borders in order to quell the addition of further outbreaks in the community[1,2] (March 2020). These border control measures greatly limited arrivals and required those who were able to enter to spend at least 14 days at a dedicated managed isolation and quarantine (MIQ) facility upon arrival[3]. Due to its geographical isolation, the New Zealand border was able to be tightly regulated. Coupled with a stringent local response (including stay-at-home orders, contact tracing, and isolation of cases[4]), this strategy resulted in the elimination of COVID-19 in New Zealand by May 2020[5,6]. This elimination phase, which lasted until late 2021, saw several small but quickly contained outbreaks, which leaked from MIQ facilities, cargo vessels, and other channels through the border[3]. Between May 2020 and July 2021, the country recorded a total of only 1390 cases and five deaths. Real-time genomic surveillance played a pivotal role in sustaining this state of elimination[3,7].

The border restrictions remained until the trans-Tasman travel 'bubble' opened in April 2021, enabling quarantine-free travel between New Zealand and Australia (Fig. 1), which at the time was also pursuing an elimination strategy[8,9]. However, the travel bubble was suspended in July 2021 due to Australia's difficulty in controlling the emergent Delta variant of concern (VoC). Shortly afterwards, the Delta variant entered the New Zealand community; it likely leaked from a MIQ facility via a traveller from Australia[10]. Unlike previous variants, Delta spread widely and quickly and was unable to be fully controlled, thus leading New Zealand (following a nationwide vaccine rollout, Fig. 1) to abandon its elimination strategy in favour of suppression by early October 2021[11]. By early 2022, the even-more infectious Omicron VoC (BA.1 and BA.2) had entered the community and quickly outcompeted Delta as it had done globally[12–14]. Border controls were gradually relaxed and the MIQ system was abandoned in favour of pre-departure and on-arrival testing. In the first half of 2022, New Zealand recorded ~1.2 million COVID-19 cases.

Unlike other severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, Omicron includes multiple subvariants, termed BA.1–BA.5. Omicron variants are characterised by at least 50

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estimated average detection lag of 19 days between lineages being introduced into the community and then being detected, but this estimate could be further improved by subsampling global genomes that are more closely related to community cases, or by including even more locally acquired genomes in the analysis. This framework is based on real-time genomic surveillance coupled with Bayesian phylogenetic inference. Recent computational advancements - such as the BICEPS, ORC, and online packages for BEAST 2[26–28]—have made rapid Bayesian phylogenetic inference on large genomic datasets more feasible.

We showed that the first quarter of 2022 was characterised by the introduction, and widespread transmission, of Omicron BA.1 and BA.2 into the country (Fig. 2), while the second quarter was characterised by multiple introductions of BA.2.12.1, BA.4 and BA.5. We estimated at least six (for BA.1) and 27 (BA.2.12.1) introductions of each variant (Fig. 3). The preponderance of recent introductions were of the BA.2.12.1 and BA.5 variants, reflecting trends in overseas 'feeder' countries. This may also reflect their higher transmissibility and ability to evade immunity. Community introductions of Omicron variants surged after the New Zealand borders reopened in March 2022, and grew roughly linearly with the daily international arrival rate. Under the current border settings where arrivals are required to be vaccinated and self-test on arrival, we estimated there is approximately one transmission event into the community for every 5000 passenger arrivals into the country (Fig. 6). Epidemiological models from earlier in the year predicted that a second wave was likely to arise in August or September 2022 due to the nation's waning population immunity, but they noted that a variant with a growth advantage could bring that wave forward[29,30]. It turned out that BA.4 and BA.5 were the new variants that caused the wave, with case data showing a peak of the second wave, dominated by BA.5, occured in mid-July with cases now declining.

Congruent with previous phylodynamic studies worldwide, we found that while some introductions into the country triggered widespread outbreaks, around half of the introductions did not instigate any detectable onward transmission at all (Fig. 4)[2,23,31–37]. This speaks to the highly stochastic nature of disease transmission[38] and emphasises how a greater rate of international travel, and therefore a greater rate of viral importation (Fig. 6), leads to a higher chance of a large community outbreak being triggered. Among these introductions were three large outbreaks with over 100 samples, associated with at least two superspreader events: a wedding for BA.1 (Fig. S2) and a music festival for BA.2 (Fig. S3). However, despite the prevalence of Omicron in New Zealand, we did not detect any infections originating from the community to the rest of the world (only from the community to the border). This contrasts with a recent study in Brazil which estimated around one export event to the rest of the world for every 10 introductions[36], as well as studies performed in Colombia[14], Jordan[33], Rwanda[37], Belarus[39] and Europe[40]. This discrepancy is perhaps due to the small population size of New Zealand at a global scale (five million people), and comparatively low global sequencing rates.

Although the existing literature on COVID-19 phylodynamics is vast[41], we believe this study is among the first to directly link temporal viral introduction rates to international traveller arrival rates. This link is intuitive and likely to generalise to other parts of the world, but is more readily established in nations where travel across the border is highly regulated[33]. Prolonged genomic surveillance throughout the border reopening has placed Aotearoa, New Zealand, in an excellent position to study this system.

The analyses performed here come with their limitations. First, due to the overwhelming availability of both global genomic data on the GISAID as well as local New Zealand data produced here, subsampling was necessary. Our methodologies are only as powerful as their subsampling strategies, which are in turn only as powerful as the underlying processes by which infections are detected and then sequenced by COVID-19 surveillance programmes, both locally and globally. Second, the pool of genomic sequences is not a representative sample of the global pandemic due to the wide disparity in real-time genomic sequencing outputs across different parts of the world[7,42]. Finally, the reliability of the epidemiological annotations of New Zealand cases into community and border is contingent on the New Zealand Ministry of Health's internal protocols, which are beyond our control and have varied in quality during different stages of the pandemic. Still, with these caveats noted, we believe our results are robust and are generally consistent with previous studies.

Overall, we have demonstrated how pathogen surveillance at the border can measure the effectiveness of border control measures and provide advance warning of potential outbreaks. This approach is not restricted to COVID-19—it can also be applied to seasonal influenza virus, respiratory syncytial virus, or the ongoing global monkeypox outbreak[43], for example. As new pathogens continue to emerge around the world, monitoring their global transmission and tracing their arrival into unexposed communities remain important tasks for genomic surveillance.

Method

Genomic sequencing and epidemiology

For cases reported between 8 December 2021 and 15 June 2022, ~0.8% of all COVID-19 cases were referred to the Institute of Environmental Science and Research, New Zealand. In brief, viral extracts were prepared from respiratory tract samples in which SARS-CoV-2 was detected by rRT-PCR. Extracted RNA was subjected to whole-genome sequencing using the Oxford Nanopore Technologies R9.4 chemistry by following the Midnight protocol v6[44], which contains a 1200-bp primer set tiling the SARS-CoV-2 genome. Consensus genomes were generated through a standardised pipeline (https://github.com/ESR-NZ/NZ_SARS-CoV-2_genomics) based on the original ARTIC bioinformatics pipeline (https://artic.network/ncov-2019/ncov2019-bioinformatics-sop.html; v1.2.1). Genomes were designated into lineages using Pangolin version 4.0.6[45]. Here we report high-quality genomes which have less than 10% ambiguous characters. Recombinant Omicron genomes - XE ($n = 1$), XAG ($n = 1$) and XAC ($n = 4$)—were detected at low frequencies but were not included in this study.

We estimated the number of community cases belonging to each variant (Fig. 2; bottom left panel) using a multinomial model. In this model (*nnet* package[46]), the variant associated with each sequenced case was treated as a response variable and the report date and district health board of that case were set as predictors. We used the fitted model to predict the proportions of each variant for a given district health board and date, and then multiplied these values by the corresponding reported case numbers to estimate the total number of cases for each variant. Growth advantages per day of BA.4 and BA.5, relative to BA.2, were estimated using a multinomial logistic regression model, as described by[18], from public data that is the 7-day rolling average of variant counts.

We use two distinct definitions of COVID-19 hospitalisations throughout this article. These definitions and data were provided by the New Zealand Ministry of Health. First, hospitalisations *for* COVID-19 (as shown in the middle panel of Fig. 1) are determined by evaluating clinical codes entered in the National Minimum Dataset (NMDS) for hospitalisations nationwide and excluding hospitalisations that are highly unlikely to be related to COVID-19. The NMDS provides a robust estimate of hospitalisations for COVID-19, however, there is often a delay before data are finalised. This delay can vary but can be approximately 60 days or more. Second, hospital admissions *with* COVID-19 (as detailed in Omicron genomics and sampling) included individuals who tested positive for COVID-19 in the seven days prior to admission or whilst in hospital; excluding hospitalisations that were admitted and discharged within 24 h, and those where admitted was highly unlikely to be related to COVID-19 infection. This dataset