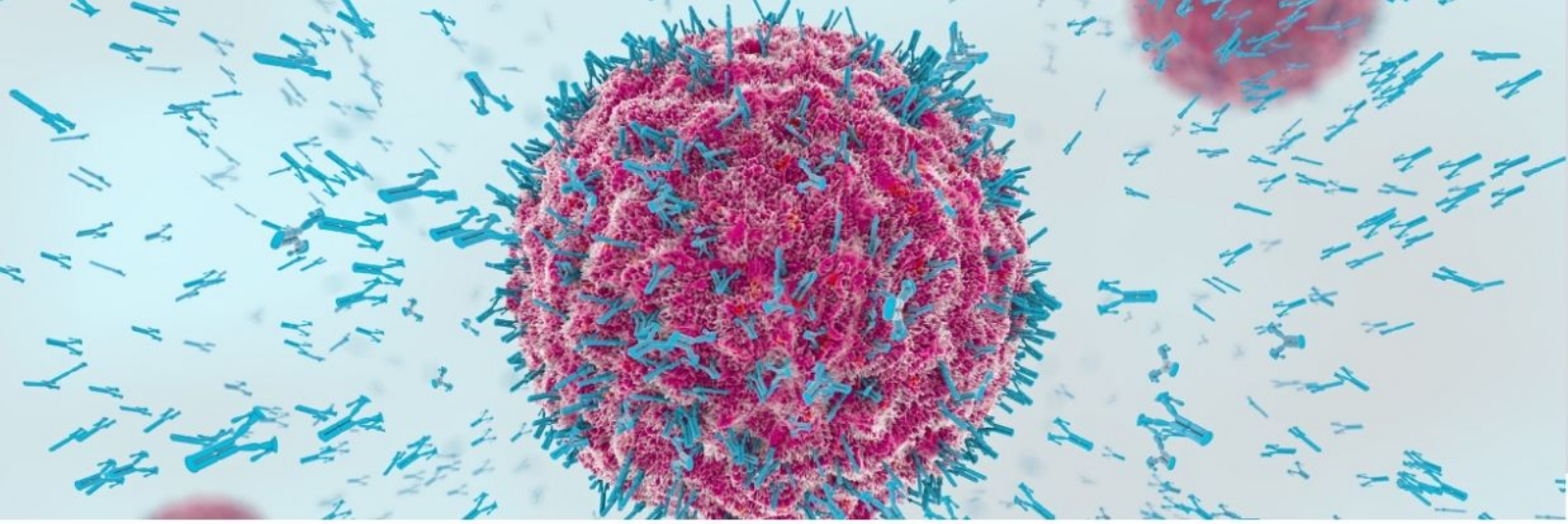

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Relative Instantaneous Reproduction Number of Omicron SARS-CoV-2 variant with respect to the Delta variant in Denmark

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Abstract

The Omicron variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become widespread across the world in a flashing manner. As of December 7, 2021, a total of 758 Omicron cases were confirmed in Denmark. Using the nucleotide sequences of the Delta and Omicron variants registered from Denmark in the GISAID database, we found that the effective (instantaneous) reproduction number of Omicron is 3.19 (95%CI 2.82–3.61) times greater than that of Delta under the same epidemiological conditions. Proportion of Omicron infections among all SARS-CoV-2 infections in Denmark was expected exceed the 95% on December 28, 2021 with a 95% CI from December 25 to December 31, 2021. Given that the Delta variant or variants less transmissible than Delta are dominant in most countries, the rapid increase in Omicron in the virus population may be observed as soon as the Omicron is introduced. Preparing proactive control measures is vital, assuming the substantial advantage of the transmission by Omicron.

Keywords: SARS coronavirus < Virus classification, Epidemiology, Evolution

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Introduction

Since its designation as a variant of concern (VOC) by the World Health Organization (WHO) on November 22, 2021 (World Health Organization, 2021a), the Omicron variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become widespread across the world in a flashing manner. As of December 14, 2021, Omicron has been confirmed in 76 countries (World Health Organization, 2021b).

Datasets from countries with early spread of Omicron suggest that Omicron is more transmissible than the Delta variant. Pulliam et al. found that Omicron had substantial ability to evade immunity from prior infections with other variants or vaccination (Pulliam et al., 2021). Kuhlman et al. reported that Omicron infected individuals who were fully vaccinated and those who had additional booster shots (Kuhlmann et al., 2021). Rössler et al. found that titers of sera from vaccinated individuals to neutralize Omicron were much lower than any other analyzed variants (Rössler, Riepler, Bante, Laer, & Kimpel, 2021). Using frequencies of nucleotide sequences of Omicron and other variants identified in Gauteng province, South Africa, Nishiura et al. estimated that the reproduction number of Omicron was 4.2 times (95% confidence interval (CI): 2.1, 9.1) greater than that of the Delta variant (Hiroshi Nishiura et al., 2021).

As of December 7, 2021, a total of 758 Omicron cases were confirmed in Denmark (Espenhain et al., 2021). Given high coverage of COVID-19 vaccination in the country, 76% of these Omicron patients had received two doses of vaccination and additional 7.1% had three doses. The daily number of newly diagnosed cases in Denmark is swiftly growing. It is natural to think of this increase in the number of SARS-CoV-2 infections as the result of a rapid increase in the proportion of Omicron among the SARS-CoV-2 population in Denmark. Denmark is one of the countries having highest whole genome sequencing (WGS) capacities for SARS-CoV-2. As of December 17, the WGS rate of the country was 0.572 sequence per confirmed cases for the 48th week (from November 29 to December 5) of 2021 (Danish Covid-19 Genome Consortium, 2021).

In our previous paper, we have developed a method to estimate the relative instantaneous reproduction number, R_{RI}, of a variant with respect to (w.r.t.) another variant using time series of the numbers of observations of each variant (Ito, Piantham, & Nishiura, 2021).The R_{RI} of a target variant w.r.t a baseline variant is defined as the ratio of the effective reproduction number of the target variant to that of the baseline variant. In this Short Communication, we apply the method to the nucleotide sequences of the Delta and Omicron variants registered from Denmark in the GISAID database (Shu

& McCauley, 2017). By estimating the R_{RI} of Omicron w.r.t. Delta, we compare the effective reproduction number of Omicron with that of Delta in Denmark.

Result

As of December 18, 2021, the GISAID database has a total of 61,372 records of nucleotide sequences that were collected and submitted from Denmark (Shu & McCauley, 2017). Of these, 61,093 sequences were assigned to PANGO lineages corresponding to Delta and 272 sequences were assigned to those of Omicron in the metadata provided by the GISAID database (Rambaut et al., 2020). The remaining 7 sequences were assigned to lineages other than Delta or Omicron and these were ignored in the subsequent analyses. The date of sample collection of the earliest Omicron sequence was November 22, 2021. The information on dates of sample collection and PANGO lineages of these sequences are provided in Supplementary Table 1.

The R_{RI} of Omicron w.r.t. Delta in Denmark was estimated to be 3.19 (95% CI 2.82–3.61) (Table 1), assuming that serial intervals follows a log-normal distribution with a mean of 4.7 day and a standard deviation of 2.9 day (H. Nishiura, Linton, & Akhmetzhanov, 2020). Namely, it is expected that the effective reproduction number of Omicron at a time point is 3.19 greater than that of Delta under the same epidemiological conditions.

Figure 1 shows frequencies of Omicron and Delta variants estimated from the dates and lineages of SARS-CoV-2 samples registered from Demark (Supplementary Table 1). It is expected that the proportion of infections by Omicron among SARS-CoV-2 infections in Denmark will exceed 95% on December 28, 2021 with a 95% CI from December 25 to December 31, 2021.

Figure 2 shows the population average of R_{RI} of variants circulating in Denmark w.r.t. Delta from November 1, 2021 to January 8, 2022. The population average of R_{RI} w.r.t. Delta remains around one until the end of November, since most of SARS-CoV-2 infections were that of Delta. The population average of R_{RI} suddenly increases around the middle of December, due to the replacement of circulating viruses from Delta to Omicron. It is expected that the proportion average of transmissibility of SARS-CoV-2 viruses circulating in Demark on January 1, 2021 is 3.15 (95% CI: 2.76–3.59) times greater compared to the situation where only Delta was circulating in the population. This means that, if epidemiological conditions are unchanged, the effective reproduction number of SARS-CoV-2 infections will increase more than three folds within a matter of a month.

Discussion

We have estimated the effective (instantaneous) reproduction number of Omicron as 3.19 (95% CI 2.82–3.61) times greater than that of Delta under the same epidemiological conditions. Proportion of Omicron infections among all SARS-CoV-2 infections in Denmark was expected exceed 95% on December 28, 2021 with a 95% CI from December 25 to December 31, 2021. The effective reproduction number of SARS-CoV2 infections in Denmark was expected to increase more than three folds from December 1, 2021 to January 1, 2020, if epidemiological conditions are unchanged.

Our estimates from Danish data were consistent with the other one from Gauteng, South Africa (Hiroshi Nishiura et al., 2021). Theoretically, the enormous advantage of transmission can stem from two independent factors, (i) intrinsically greater transmissibility of Omicron compared to that of Delta, and (ii) substantial capacity of Omicron variant to escape from existing population-level immunity conferred either naturally or by vaccination. While (i) is not refuted, multiple studies demonstrated that the Omicron variant escapes from human immunity more efficiently than Delta (Kuhlmann et al., 2021; Pulliam et al., 2021; Rössler et al., 2021). While vaccination coverage in South Africa was approximately 30% with DNA vaccine (AstraZeneca vaccine) and the remainders were thought to have acquired infection naturally, more than 70% of Danish population was fully vaccinated partly using mRNA vaccines. The value of the present short communication is that the replacement of Delta by Omicron is seen at a comparable speed even in such a setting, and thus, other countries with widespread use of mRNA vaccine should recognize the substantial risk of immune evasion.

The estimates obtained in this study are completely based on the nucleotide sequences submitted to the GISAID database from Denmark. One of the possible limitations of this study is reporting bias. If the reporting of Omicron is prioritized in WGS analyses in the country, the R_{RI} of Omicron w.r.t. Delta might have been overestimated. Given high WGS rate in Denmark (Danish Covid-19 Genome Consortium, 2021), however, the extent of reporting bias may be minimal. Evaluation of similar datasets (e.g. S-gene deletion data) would be useful for validating our finding.

Method

The R_{RI} of Omicron w.r.t. Delta was calculated using the method proposed by Ito et al. (Ito et al., 2021). Briefly, the R_{RI} of Omicron w.r.t. Delta at calendar time t is defined as the $R_{Omicron}(t)/R_{Delta}(t)$, where $R_{Omicron}(t)$ and $R_{Delta}(t)$ are instantaneous

reproduction numbers of infections by Omicron and Delta at calendar time t, respectively (Fraser, 2007). Assuming that R_{RI} of Omicron w.r.t. Delta has a constant value of $1+s$ over time and that no lineages other than Omicron or Delta is circulating in the population, the frequency of Omicron in the population at time t, $q_{Omicron}(t)$, can be represented as

$$q_{Omicron}(t) = \frac{\sum_{j=1}^{l} g(j)\,(1+s) q_{Omicron}(t-j)}{1+s\sum_{j=1}^{l} g(j) q_{Omicron}(t-j)}, \#$$

where $g(j)$ is the probability mass function of serial intervals of which values are small enough to be neglected for $j<1$ and $j>l$.

Suppose that Omicron was introduced in the population at time $t_{Omicron}$ with a frequency at $q_{Omicron}(t_{Omicron})$. Let $N(t)$ be the number of sequences of either Omicron or Delta at calendar time t. Assuming that the Omicron sequences are sampled following a binomial distribution with probability $q_{Omicron}(t)$ in $N(t)$ trials, the R_{RI} of Omicron w.r.t. Delta, which is equal to $1+s$, can be estimated by maximizing the likelihood function of the binomial distribution.

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Data Availability

Supplementary Table 1 contains all data needed to reproduce the result of this study.

Conflict of Interest

We declare that there is no conflict of interest.

Author Contribution

KI and CP collected data and conducted estimation. HN addressed public health implications. KI, CP, HN wrote the paper.

Figures

Figure 1. Estimated frequencies of Omicron and Delta variants in Demark from November 1, 2021 to January 8, 2022. Circles and triangles represent observed frequency of sequences assigned to Omicron and Delta in the GISAID database from November 1 to December 9, 2021. Solid lines indicate the maximum likelihood estimates of frequencies of Omicron (red) and Delta (blue) variants. Dashed lines represent predicted frequencies of Omicron (red) and Delta (blue) in Demark from December 10, 2021 to January 8, 2022. Dotted lines show 95% CI lower and upper bounds of estimated and predicted variant frequencies.

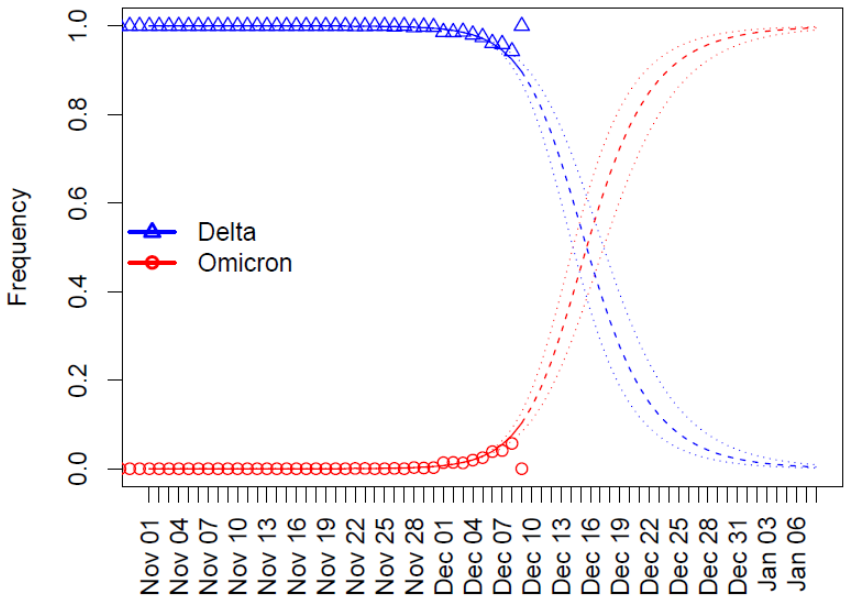

Figure 2. Population average of R_{RI} of variants circulating in Demark w.r.t Delta from November 1, 2021 to January 8, 2022. The solid line (until December 9) and dashed line (from December 10) indicate the maximum likelihood estimates, and dotted lines represent its 95% CI.

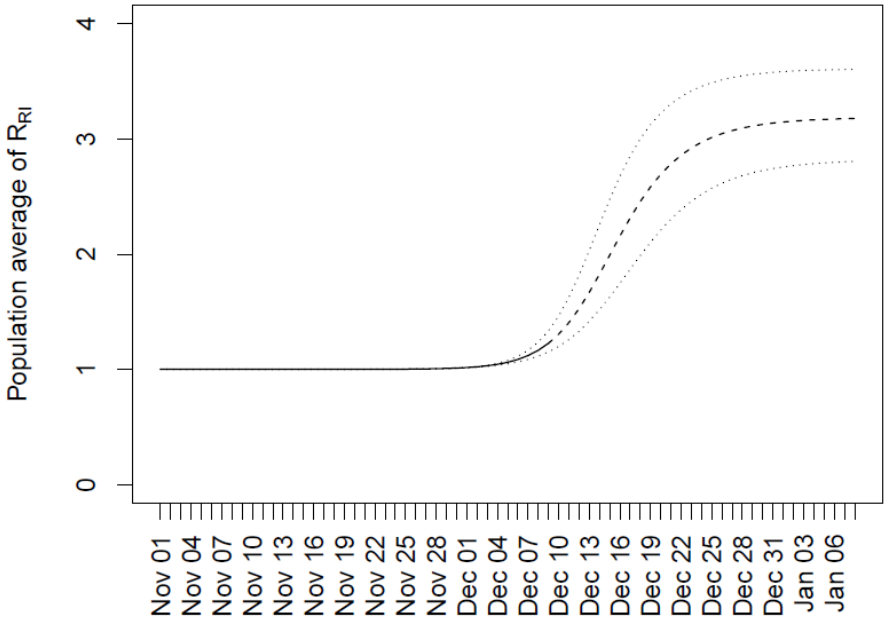

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Table 1. Estimated values of parameters and their 95% CIs

Parameter	Estimated values	95% CI
R_{RI} of Omicron w.r.t Delta	3.19	[2.82, 3.61]
Frequency of Omicron on November 22, 2021	0.0080	[0.00044, 0.0014]