Relative instantaneous reproduction number of Omicron SARS-CoV-2 variant with respect to the Delta variant in Denmark

Kimihito Ito1 | Chayada Piantham2 | Hiroshi Nishiura3

1International Institute for Zoonosis Control, Hokkaido University, Sapporo, Japan
2Graduate School of Infectious Diseases, Hokkaido University, Sapporo, Japan
3Graduate School of Medicine, Kyoto University, Kyoto City, Japan

Correspondence
Kimihito Ito, International Institute for Zoonosis Control, Hokkaido University, Sapporo 0010020, Japan.
Email: itok@czc.hokudai.ac.jp

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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% confidence interval [CI]: 2.82–3.61) times greater than that of Delta under the same epidemiological conditions. The proportion of Omicron infections among all SARS-CoV-2 infections in Denmark was expected to exceed 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
epidemiology, evolution, SARS coronavirus

1 | INTRODUCTION

Since its designation as a variant of concern by the World Health Organization on November 22, 2021, 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.

Datasets from countries with the early spread of Omicron suggest that Omicron is more transmissible than the Delta variant. Pulliam et al.3 found that Omicron had a substantial ability to evade immunity from prior infections with other variants or vaccination.

Kuhlmann et al.4 reported that Omicron infected individuals who were fully vaccinated and those who had additional booster shots. Rössler et al.5 found that titers of sera from vaccinated individuals to neutralize Omicron was much lower than any other analyzed variants.

Using frequencies of nucleotide sequences of Omicron and other variants identified in Gauteng province, South Africa, Nishiura et al.6 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.

As of December 7, 2021, a total of 758 Omicron cases were confirmed in Denmark.7 Given high coverage of COVID-19...
vaccination in the country. 76% of these Omicron patients had received two doses of vaccination and an 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 the 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 2021.8

In our previous paper, we have developed a method to estimate the relative instantaneous reproduction number, $R_{0}^*$, of a variant with respect to (w.r.t.) another variant using time series of the numbers of observations of each variant.9 The $R_{0}$ 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.10 By estimating the $R_{0}^*$ of Omicron w.r.t. Delta, we compare the effective reproduction number of Omicron with that of Delta in Denmark.

2 | METHOD

The $R_{0}^*$ of Omicron w.r.t. Delta was calculated using the method proposed by Ito et al.9 Briefly, the $R_{0}^*$ of Omicron w.r.t. Delta at calendar time $t$ is defined as the $R_{\text{Omicron}}(t)/R_{\text{Delta}}(t)$, where $R_{\text{Omicron}}(t)$ and $R_{\text{Delta}}(t)$ are instantaneous reproduction numbers of infections by Omicron and Delta at calendar time $t$, respectively.11 Assuming that $R_{0}^*$ 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 $t$, $q_{\text{Omicron}}(t)$, can be represented as

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

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 $t_{\text{Omicron}}$ with a frequency at $q_{\text{Omicron}}(t_{\text{Omicron}})$. 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 $q_{\text{Omicron}}(t)$ in $N(t)$ trials, the $R_{0}^*$ of Omicron w.r.t. Delta, which is equal to 1 + s, can be estimated by maximizing the likelihood function of the binomial distribution.

3 | 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.10 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.12 The remaining seven 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 Table S1.

The $R_{0}^*$ 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 follow a lognormal distribution with a mean of 4.7 days and a standard deviation of 2.9 days.13 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 Denmark (Table S1). 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 $R_{0}^*$ of variants circulating in Denmark w.r.t. Delta from November 1, 2021 to January 8, 2022. The population average of $R_{0}^*$ w.r.t. Delta remains around one until the end of November since most of the SARS-CoV-2 infections were that of Delta. The population average of $R_{0}^*$ 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 Denmark 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 threefold within a matter of a month.

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

| Parameter | Estimated values | 95% CI         |
|-----------|-----------------|----------------|
| $R_{0}^*$ 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] |

Abbreviations: CI, confidence interval.
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. The proportion of Omicron infections among all SARS-CoV-2 infections in Denmark was expected to 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 threefolds 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. 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. 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 the 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 the 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 $R_0$ of Omicron w.r.t. Delta might have been overestimated. Given the high WGS rate in Denmark, 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 findings.

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CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Kimihito Ito and Chayada Piantham collected data and conducted estimation. Hiroshi Nishiura addressed public health implications. Kimihito Ito, Chayada Piantham, and Hiroshi Nishiura wrote the paper.

DATA AVAILABILITY STATEMENT
Table S1 contains all data needed to reproduce the result of this study.

ORCID
Kimihito Ito http://orcid.org/0000-0003-4986-1795
Chayada Piantham https://orcid.org/0000-0003-2813-3676
Hiroshi Nishiura https://orcid.org/0000-0003-0941-8537

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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