Reproduction Numbers of SARS-CoV-2 Variants: A Systematic Review and Meta-analysis

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Abstract

The COVID-19 pandemic continues to pose substantial risks to public health, worsened by the emergence of SARS-CoV-2 variants which may have a higher transmissibility and reduce vaccine effectiveness. We conducted a systematic review and meta-analysis on reproduction numbers of SARS-CoV-2 variants and provided pooled estimates for each variant.

Main Text

Globally, five variants of concern (VOC) and two variants of interest (VOI) of SARS-CoV-2 have been identified by 25 January 2021 [1]. These SARS-CoV-2 variants might spread more easily or cause more severe infections as compared to the prototype virus [2] and might be able to escape the pre-existing immunity elicited by prior infection or vaccination [3] As of 25 January 2021, the Alpha, Beta, Gamma, Delta, and Omicron VOC have been reported in 202, 153, 114, 205, and 175 countries and territories, respectively [4].

The basic reproduction number (R_0) is a key epidemiological metric that denotes the average number of new infections caused by an infected case in a fully susceptible population. R_0 describes the intrinsic transmissibility of an epidemic. The effective reproduction number (R_e) denotes the average number of new infections caused by an infected case after accounting for population immunity and the effect of control measures. R_e is often used to characterize the instantaneous transmissibility of an epidemic and monitor the effectiveness of public health interventions. Reliable estimates of R_0 and R_e for SARS-CoV-2 variants are essential to adjusting the public health and social measures (PHSMs) against the outbreaks caused by these variants. For example, the relaxation of PHSMs for reopening societies becomes feasible when R_e is lower than 1, whereas the activation of PHSMs may be necessary to suppress the new outbreak when R_e is higher than 1. In this report, we performed a systematic review and meta-analysis to synthesize the evidence from published estimates of R_0 and R_e for the SARS-CoV-2 variants (e.g., Alpha, Beta, and Delta).

Methods

Search Strategy and Selection Criteria

All searches were carried out on 10 January 2022 in PubMed for articles published from 1 January 2020 to 10 January 2022. We included all relevant English articles published at peer reviewed journals, with 2 additional articles recommended by experts. Our search terms for reproduction numbers of SARS-CoV-2 variants include (#1) "COVID-19" OR "SARS-CoV-2" OR "2019-nCoV" OR "coronavirus"; (#2) "reproduct* number" OR "reproduct* ratio" OR "reproduct* rate"; and (#3) "variant" OR "mutation" OR "lineage" OR "amino acid substitution". Our final search term was #1 AND #2 AND #3. After reading the abstract and full text, we included the studies that provide the information about the uncertainties and estimation periods for the estimated reproduction numbers. Although systematic reviews,

meta-analysis, and unrelated studies (e.g., wild-type, simulation, modelling, virology, vaccine, diagnosis, clinical trials) were excluded from our analyses, we included the relevant studies mentioned in these reviews.

Data Extraction

All data were extracted independently and transformed into a standardized form by 2 co-authors (C. L. and C. W.). Conflicts over the inclusion of studies and retrieving the estimates of relevant parameters were resolved by another co-author (Z. D.). We extracted the estimations on the basic reproduction number R_0 and the effective reproduction number R_e of SARS-CoV-2 variants, including the corresponding 95% confidence interval (CI) or the 95% credible interval (CrI). We also collected several useful information including the studied location from each selected study (see Supplementary Materials for details).

Statistical Analysis

We used the I^2 index to categorize all identified studies into three levels of heterogeneity and a random-effects model to perform the meta-analysis.

Results

We in total identified 122 studies by searching PubMed and also included 2 additional studies recommended by experts. Of these, 2 duplicates were removed and 55 irrelevant studies were excluded through title and abstract screening, leaving 67 studies for the full-text assessment. A total of 24 of them were finally included in this review, which provides 7 R_0 estimates and 62 R_e estimates. Detailed selection process is illustrated in **Figure S1**. The reported variants include Alpha, Beta, Delta, Epsilon, Eta, Gamma, Iota, Kappa, Zeta, R.1, B.1.1.519, B.1.1.222, N501Y, and D514G. The Alpha variant was analyzed in most studies. As to the studied locations, one study [5] analyzed data from 64 countries, and the remaining studies mainly analyzed the UK, India, Japan, the US, Denmark, Switzerland, China, Mexico, Norway, Canada, Germany, Netherlands, and South Africa (**Table S1**).

High heterogeneity was reported among the included studies ($I^2 = 96\%$, $p<0.01$, and $\tau^2 = 0.10$) (**Figure S2**). Using the random-effects model, we estimated that the Delta variant has the highest transmissibility, with the pooled estimates of R_0 and R_e as 5.94 (95% CI: 5.19 to

6.68) and 1.54 (95% CI: 1.27 to 1.81), respectively (**Figure 1**). The pooled estimate of R_e is 1.37 (95% CI: 1.24, 1.50) for the Alpha variant during the study period from September 2020 to June 2021 (**Table S1**). The relative change in the basic or effective reproduction number for SARS-CoV-2 variants other than the Alpha variant as compared to the Alpha variant is shown in **Figure 1C**. Similarly, the pooled estimates of R_0 and R_e with the uncertainties were also obtained for other variants.

To explore the potential association between the study location and the estimated reproduction number, we conducted the meta-regression analysis for the Alpha variant because of the large sample size (**Figure S3** and **Figure S4**). We found that the study location was associated with the reported R_e in the meta-analysis by including country as a categorical variable (*p*=0.0523) (**Figure S4**). This may be because of the country-specific differences in the vaccine rollout rates, travel restrictions, usage of face masks, and other mitigation strategies.

The serial interval denotes the time interval between symptom onsets of the infector and the infectee in a transmission pair [6], which is often used as a key metric for estimating reproduction numbers. As such, we extracted the serial interval estimates for each variant if they are mentioned in the identified studies. For the Alpha variant, we found that the serial interval was considered to be 4.8 (95% CI: 3.5 to 5.9) days in Japan, 5.2 (standard deviation = 4) days in the US, and 4.0 (95% CI: 1.5 to 7.8) days in the UK (**Table S2**). In contrast, the Delta variant often had a shorter serial interval, which was estimated to be 1.4 (95% CI: 1.3 to 12) days in Japan and 2.3 (95% CI: 1.4 to 3.3) days in China. The incubation period was estimated to be 4.4 (95% CI: 3.9 to 5) days for the Delta variant (**Table S2**).

Discussion

The continuous emergence of new SARS-CoV-2 variants substantially increases the uncertainty in the future of the COVID-19 pandemic [7]. Throughout the pandemic, governments have primarily relied on non-pharmaceutical interventions and more recently mass distribution of vaccines to slow down transmission and reduce mortality [8]. Meanwhile, the constantly evolved SARS-CoV-2 variants through mutation and immune selection have been circulating all over the world. More drastic measures may be needed to suppress the spread of variants with a higher transmissibility.

COVID-19 pandemic response requires constant, systematic and rigorous assessment of the transmission risks of new variants. Reliably estimating the basic reproduction number (R_0) and effective reproduction number (R_e) for each variant of SARS-CoV-2 is critical to adjust the intensity of non-pharmaceutical interventions and the schedule of vaccination rollout [9] In this report, we performed a systematic review and meta-analysis to synthesize the evidence from the published estimates of R_0 and R_e for all major SARS-CoV-2 variants before the dominance of the Omicron variant in the US and European countries.

The study has several limitations. First, some studies might have used the data from the same sources, leading to double counting in the pooled estimates. Second, some factors potentially correlated with estimates of the basic reproduction number such as contact patterns and climatic factors were not included in this study because of data availability. Third, we only study reproduction numbers to assess the transmissibility of SARS-CoV-2 variants. There are other studies of transmission advantage using other metrics, which were not included in our study. Fourth, most of the eligible studies in our review do not account for the immunity waning and re-infection, which could impact the comparison of basic and effective reproduction numbers. And the reproduction numbers could also vary widely depending on the study location, the study period, vaccine rollout, travel restriction, mask use, human behavior, and effectiveness of other mitigation strategies. The pooled basic or effective reproduction numbers reflect an overall trend and should be interpreted cautiously, in particular it would be preferable to use local estimates to guide local control measures. Fifth, the publication bias is possible in our review, given that many preprints of SARS-CoV-2 variants remain to be under review, which could have accurate estimates of reproduction numbers but not included in our study.

In conclusion, multiple estimates of the reproduction number have been published for 14 SARS-CoV-2 variants. Study location was indicated to be associated with the reported estimates of the effective reproduction number. Reliable estimates of reproduction numbers in an epidemic will affect the assessment-impact of mitigation efforts and the potential need for introduction or re-introduction of public health and social measures.

NOTES

Author Contributions

ZD, CL, CW, and BJC: conceived the study, designed statistical and modelling methods, conducted analyses, interpreted results, wrote and revised the manuscript; EHYL, PW, XX, LW, YB, LX and MX: interpreted results and revised the manuscript.

Competing interests

BJC reports honoraria from AstraZeneca, Sanofi Pasteur, GSK, Moderna and Roche. The authors report no other potential conflicts of interest. BJC, CL, CW, EHYL, MX, PW, YB, ZD, and LX report funding from AIR@InnoHK administered by Innovation and Technology Commission of the Hong Kong SAR Government.

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Figure 1. Reproduction number estimates for multiple variants of SARS-CoV-2 virus.

(A) Pooled estimates of effective reproduction numbers, with detailed studied periods of each variant specified in Table S1. (B) Pooled estimates of basic reproduction numbers. (C) Relative change in reproduction number estimates for variants other than the Alpha variant as compared to the Alpha variant. The dots and error bars demonstrate the estimated mean and 95% confidence interval, respectively.

Figure 1