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BRIEF REPORT

Reproduction Numbers of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variants: A Systematic Review and Meta-analysis

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The coronavirus disease 2019 (COVID-19) pandemic continues to pose substantial risks to public health, worsened by the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants that 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.

Keywords. COVID-19; SARS-CoV-2; reproduction number; systematic review; meta-analysis.

Globally, 5 variants of concern and 2 variants of interest of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been identified since 25 January 2021 [1]. These SARS-CoV-2 variants might spread more easily or cause more severe infections compared with the prototype virus [2] and might be able to escape the preexisting immunity elicited by prior infection or vaccination [3]. As of 25 January 2021, the Alpha, Beta, Gamma, Delta, and Omicron variants of concern 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 (eg, Alpha, Beta, 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 (eg, 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 coauthors (C. L. and C. W.). Conflicts over the inclusion of studies and retrieving the estimates of relevant parameters were resolved by another coauthor (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. We also collected 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 3 levels of heterogeneity and a random-effects model to perform the meta-analysis.

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RESULTS

We identified 122 studies in total by searching PubMed and 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 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, 1 study [5] analyzed data from 64 countries, and the remaining studies mainly analyzed the United Kingdom, India, Japan, the United States, Denmark, Switzerland, China, Mexico, Norway, Canada, Germany, Netherlands, and South Africa (Table S1).

High heterogeneity was reported among the included studies (I^2 = 96%, $P < .01$, and $\tau^2 = .10$) (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: 5.19–6.68) and 1.54 (95% CI: 1.27–1.81), 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 with 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 = .0523) (Figure S4). This may be because of the country-specific differences in the vaccine rollout rates, travel restrictions, use 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 4.8 (95% CI: 3.5–5.9) days in Japan, 5.2 (standard deviation = 4) days in the United States, and 4.0 (95% CI: 1.5–7.8) days in the United Kingdom (Table S2). In contrast, the Delta variant

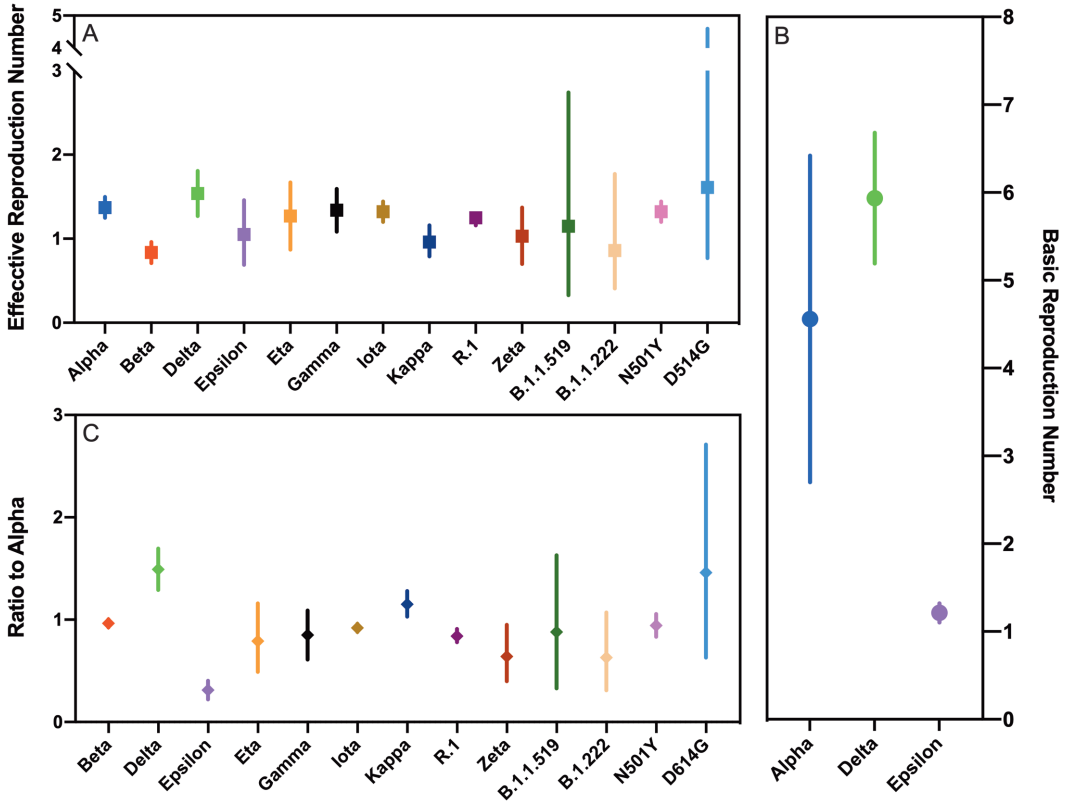

Figure 1. Reproduction number estimates for multiple variants of SARS-CoV-2 virus. (*A*) Pooled estimates of effective reproduction numbers, with detailed studied periods of each variant specified in Table S1. (*B*) Pooled estimates of basic reproduction numbers. (*C*) Relative change in reproduction number estimates for variants other than the Alpha variant compared with the Alpha variant. The dots and error bars demonstrate the estimated mean and 95% confidence interval, respectively.

often had a shorter serial interval, which was estimated to be 1.4 (95% CI: 1.3–12) days in Japan and 2.3 (95% CI: 1.4–3.3) days in China. The incubation period was estimated to be 4.4 (95% CI: 3.9–5) 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 coronavirus disease 2019 pandemic [7]. Throughout the pandemic, governments have primarily relied on nonpharmaceutical interventions and, more recently, mass distribution of vaccines to slow down transmission and reduce mortality [8]. Meanwhile, the constantly evolving 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.

Coronavirus disease 2019 pandemic response requires constant, systematic, and rigorous assessment of the transmission risks of new variants. Reliably estimating the basic R_0 and R_e for each variant of SARS-CoV-2 is critical to adjust the intensity of nonpharmaceutical 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 United States and in 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 studied 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 reinfection, 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Z. D., C. L., C. W., and B. J. C. conceived the study, designed statistical and modelling methods, conducted analyses, interpreted results, and wrote and revised the manuscript; E. H. Y. L., P. W., X. X., L. W., Y. B., L. X., and M. X. interpreted results and revised the manuscript.

Acknowledgments. All data were collected from open sources, with a detailed description in the Methods section. Code used for data analysis is freely available upon request.

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References

1. Tracking SARS-CoV-2 variants. Available at: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. Accessed 17 September 2021.
2. Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. **2021**. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html. Accessed 18 May 2021.
3. Garcia-Beltran WF, Lam EC, St Denis K, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. Cell **2021**; 184:2523.
4. Variants of concern SARS-CoV-2 comparison January 2021. Available at: https://www.statista.com/statistics/1206597/coronavirus-new-variants-comparison/. Accessed 4 February 2022.
5. Campbell F, Archer B, Laurenson-Schafer H, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as of June 2021. Euro Surveill **2021**; 26. Available at: http://dx.doi.org/10.2807/1560-7917.ES.2021.26.24.2100509.
6. Ali ST, Wang L, Lau EHY, et al. Serial interval of SARS-CoV-2 was shortened over time by nonpharmaceutical interventions. Science **2020**; 369:1106–9.
7. Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature **2021**. Available at: http://dx.doi.org/10.1038/s41586-021-03324-6.
8. Lai S, Ruktanonchai NW, Zhou L, et al. Effect of non-pharmaceutical interventions to contain COVID-19 in China. Nature **2020**. Available at: http://dx.doi.org/10.1038/s41586-021-03324-6 .
9. Novel coronavirus (2019-nCoV) situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed 30 March 2020.