Meta-analysis on Serial Intervals and Reproductive Rates for SARS-CoV-2

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Objective: The aim of this study was to systematically review and meta-analyze all literature reporting the basic reproductive number (R_0), effective reproductive number (R_e or R_t), and the serial interval (SI) values of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection.

Summary Background Data: To assess the rate at which an infectious disease can spread in a population, the 2 measures, R_0 and R_e or R_t, are widely used. One of the parameters which influence the calculations is the SI, the period between symptom onset in an infector and an infectee.

Methods: Web of Science, PubMed, Scopus, and Science Direct searching up to May 10, 2020, was performed. A continuous random-effect model was applied using the DerSimonian-Laird (inverse variance) method. Heterogeneity and publication bias were assessed.

Results: A total of 39 articles met the eligibility criteria. Our results demonstrated the mean SI was 5.45 days, with the 95% confidence interval (CI) of 4.23 to 6.66. Pooled estimates for reproduction rates was 3.14 (95% CI: 2.69–3.59) for R_0 and 3.18 (95% CI: 2.89–3.47) for R_t. Subgroup analysis by geographical region and date of publication revealed variations over both time and geography in calculated R_0 and R_t values. As time has progressed, predicted R_0 and R_t values had decreased globally.

Conclusions: The study findings indicate that one SARS-CoV-2-infected person is likely to infect 3 persons, supporting that COVID-19 is a highly contagious disease. As an essential objective metrics implied in risk assessment for this emerging pandemic, monitoring R_0 and R_e is necessary to indicate the effectiveness or failures of mitigation efforts.

Keywords: coronavirus, meta-analysis, outbreak, reproduction number, SARS-CoV-2, serial interval, transmission

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Funding source: None of the authors have any funding regarding this publication. The authors report no conflicts of interests.

Authors' contributions: M.H., E.T., R.E., M.F., J.D. designed the study; M.H., E.T., R.E. identified and acquired articles and extracted data; M.H., E.T., R.E. performed all data analyses and created the table and figures; M.H., E.T., R.E., M.F., J.D. contributed to data interpretation; E.T., R.E., A.H., D.T., M.F. wrote the first draft; E.T. drafted the final manuscript; all authors critically reviewed and approved the final version of the manuscript.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

ISSN: 0003-4932/20/27303-0416
DOI: 10.1097/SLA.0000000000004400

(*Ann Surg* 2021;273:416–423)

The coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The human-to-human transmission was reported, and the outbreak was declared by the World Health Organization (WHO).[2] As of May 10, 2020, a total of 1,353,919 coronavirus cases, including 80,361 (0.05%) deaths, have been reported in the United States (https://www.worldometers.info/coronavirus/country/us/). The quantification of transmissibility during epidemics is essential to implementing mitigation strategies for public health strategies aimed at mitigation of spread.[3]

An essential aspect of evaluating a viral pandemic is measuring the speed of viral transmission, which is assessed by the basic reproduction number (R_0, pronounced as R naught).[4] R_0, simply put, is the average number of people who become infected by an infectious person.[5] It is a transmissibility estimate used to quantify the successful onward transmission of an infection in a host population.[6] An R_0 value >1 indicates that the number of cases is growing, and the virus will continue to spread among the population, whereas an R_0 value <1 indicates that the number of cases is decreasing and infection rates will decline, stemming or stopping the spread of the virus.[7] However, this estimation is not without limitation. R_0 assumes zero immunity in a population, which means that it cannot reflect changes in time.[8]

The shortcomings of R_0 can be overcome with the use of another metric known as the effective reproduction number (R_e or R_t), which is defined as the number of infections caused by any case and does not assume zero immunity.[9] Both R_0 and R_e are affected by susceptibility (the proportion of a given population that can be infected), infectivity (the ability of a pathogen to establish an infection), and removal (case disappearance by either death or recovery) as described in the Susceptibility – Infectivity – Removal (SIR) model by Kermack & McKendrick.[10] However, R_e is dependent on time and immunity and thus more accurately reflects the current situation.[11] As a result, R_e is better estimated during the latter course of an epidemic when the population has acquired resistance to infection.[8,12]

Two final terms to understand when describing the speed with which an infectious disease spreads in the population are generation time and serial interval (SI).[13] Generation time is defined as the interval between infections in 2 consecutive generations.[14] The SI is the time between the onset of symptoms in a primary case and the onset of symptoms in secondary cases.[15] Together, generation time, SI, and R_0 indicate the risk of an infectious agent concerning epidemic spread.[15–18]

Based on early case counts in Wuhan, China, initial estimates of R_0 for the COVID-19 outbreak were 2.2 and 2.7.[19,20] As the situation progressed worldwide, the exponential growth rate of new cases resulted in different estimates of R_0, which is to be expected as further information is gathered.[8,21] A wide range of methods to

calculate R_0 have been described using the growth rate of the epidemic, the epidemic curve's size, and shape, the final attack rate, or by direct observation of disease transmission from one generation to the next.[22,23] Here, we systematically reviewed the basic reproductive number and the SI of the COVID-19 viral infection in datasets and studies until May 10.

METHODS

Literature Search Strategy

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, http://links.lww.com/SLA/C529) Statement.[24] A comprehensive and systematic search of literature from November 1, 2019, to May 10, 2020, was conducted using the electronic databases Web of Science, PubMed, Scopus, and Science Direct by 2 reviewers (E.T. and R.E.). Our search strategy included the following terms: "Novel coronavirus 2019," "2019 nCoV," "COVID-19," "Wuhan coronavirus," "Wuhan pneumonia," or "SARS-CoV-2" AND "basic reproduction number," "reproduction rate," "R0," "effective reproduction number," or "Re," AND "serial interval." The PubMed function "related articles" was used to extend the search. Additionally, we then performed manual searches of the bibliographies for potentially relevant articles in the references selected.

Study Selection

All article types (eg, full article, abstract, letter) were included if they presented a reproduction number or SI estimate for COVID-19 infection. We did not exclude papers based on language or publication status (preprint or peer-reviewed).

Data Abstraction

Articles meeting the inclusion criteria were abstracted independently by 3 reviewers (MH, ET, RE), who recorded relevant values in a predesigned excel sheet. The results were compared electronically, with discrepancy resolved by referring to the source article. Data on the study characteristics, including the first author's last name, date of publication, journal name, study design, country of the population, time of calculation, and methodology of R_0 calculation, were recorded.

Statistical Analysis

All data analyses were performed using OpenMeta [Analyst][25] and a comprehensive meta-analysis software version 3.0.[26] One-arm meta-analysis was employed to estimate pooled means and standard deviation (SD). Medians and interquartile range were converted to mean and SD using the following formulas: [Mean = (Q1 + median + Q3)/3] and [SD = IQR/1.35], whereas values reported in the articles as 95% CI were converted to SD using the following formula [SD= $\sqrt{N}$ * (upper limit of CI – lower limit of CI)/3.92]. A continuous random-effect model was applied using the DerSimonian-Laird (inverse variance) method.[27,28] Cumulative meta-analysis was carried out to detect temporal changes in the magnitude of effect sizes.

Assessment of Heterogeneity and Publication Bias

Between-study heterogeneity was evaluated using Cochran Q statistic and quantified using I^2 statistics. Articles were considered to have significant heterogeneity between studies when the P value <0.1 or I^2 >50%. Subgroup analysis by ethnicity and date of publication was performed to resolve heterogeneity. Leave-one-out sensitivity analysis was also employed to assess the robustness of the results and to determine further the influence of each study as a source for inter-study heterogeneity. Meta-regression with the random-effects model was conducted using the restricted maximum likelihood algorithm to explore potential sources of heterogeneity. Finally, publication bias was assessed using a funnel plot and quantified Egger linear regression test.[29,30] Asymmetry of the collected studies' distribution by visual inspection or P value <0.1 indicated obvious publication bias.[30] The Duval and Tweedie's trim and fill method's assumption was considered to reduce the bias in pooled estimates.[29]

RESULTS

Study Characteristics for Meta-Analysis

The initial literature search produced 1697 relevant articles. After removing duplicates and primary screening, 145 full-text articles were assessed for eligibility in the meta-analysis. Of these, 106 were excluded due to a lack of sufficient data. Thus, a total of 39 articles published between January 31 and May 7, 2020, were included in the meta-analysis part (Fig. 1). They covered a wide global range, including Asia (China, Korea, Japan, Singapore, and Taiwan), Europe (Germany, Italy, Spain, France, UK, Switzerland), Africa (Nigeria), and the Americas (Canada, Mexico, and Peru). Notably, no studies were identified in the United States.

A total of 18 studies reported data on the SI (Table S1, http://links.lww.com/SLA/C528).[7,9,19–21,31–43] Of those, 14 reported values for both mean and standard deviation and were counted by the software for the calculations of SI. For basic reproduction number, 29 studies, including 39 different datasets, were included.[5–7,9,11,19–23,37,42,44–53] Another 3 studies with 10 datasets reported an effective reproduction number (Table S1, http://links.lww.com/SLA/C528).[8,12,31] Our estimated values for R_t in Louisiana were added in the analysis to compare temporal changes with other studies.

One-Arm Meta-Analysis for a Serial Interval of COVID-19

The overall analysis revealed a pooled mean estimate of 5.45 [95% confidence interval (CI) = 4.23–6.66, $P < 0.001$], with substantial evidence of inter-study heterogeneity (Cochran Q = 719.6, $P < 0.001$, $I^2 = 98.19\%$). Asian studies reported a summary mean of 5.44 (95% CI = 3.87–7.01, $P < 0.001$), whereas SI values for non-Asian articles were 5.43 (95% CI = 4.23–6.66, $P < 0.001$). Articles published early in the outbreak reported a wider confidence interval than the following measures in April: SIs of 6.63 (95% CI = 4.26–9.01, $P < 0.001$) in January–March versus 5.12 (95% CI = 3.86–6.38, $P < 0.001$) in April/May. Stratifying the results by ethnicity and publication date also demonstrated significant heterogeneity (Fig. 2). Sensitivity analysis failed to resolve heterogeneity. The cumulative meta-analysis revealed minimal evidence accumulated after April 1. Meta-regression showed that source and date of publication had no significant influence on calculated pooled estimates (ethnicity: coefficient = 0.49, 95% CI = −1.7 to 2.7, $P = 0.66$; publication date: coefficient = −1.66, 95% CI = −3.9 to 0.58, P = 0.14). For publication bias assessment, remarkable asymmetry, and Egger test ($P = 0.001$) suggested significant bias.

One-Arm Meta-Analysis for the Basic Reproductive Number of COVID-19

Studies reporting basic reproductive numbers analyzed the period between January 10 and April 23. The random-effects summary for the basic and effective reproduction rates was 3.14 (95% CI = 2.69–3.59) and 3.18 (95% CI = 2.89–3.47), respectively. Significant heterogeneity was observed in our results (Cochran Q = 856251.1, $P < 0.001$, $I^2 = 99.9\%$) (Fig. 3).

Subgroup analysis by ethnicity showed studies from Asia to have an overall estimate of 3.00 and a 95% CI of 2.51to 3.50 with heterogeneity ($I^2 = 100\%$, $P < 0.001$). European studies showed a

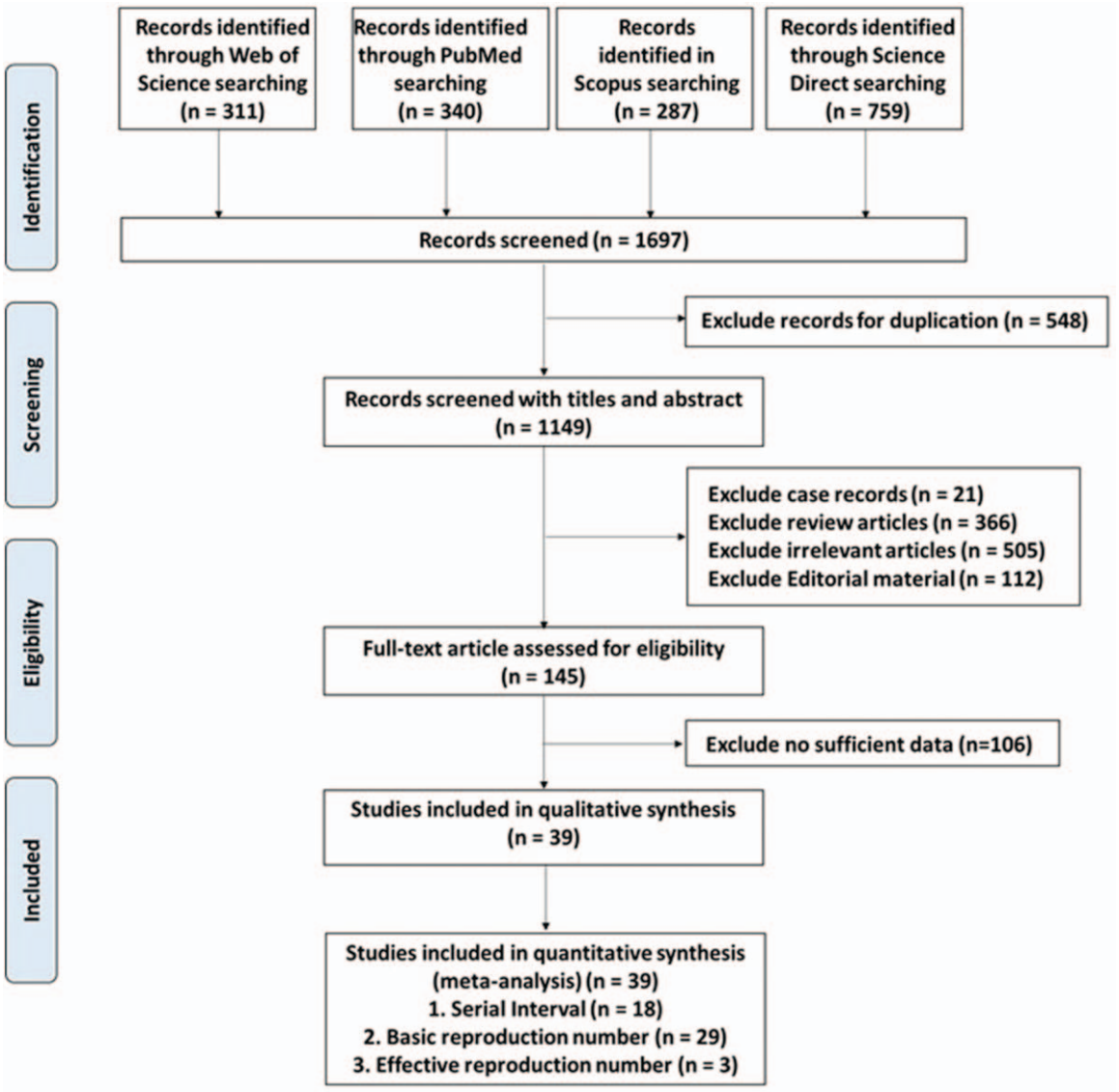

FIGURE 1. Workflow for the selection process of eligible studies.

wider range of R_0: 3.79 (95% CI = 0.89–6.68) with high evidence of inter-study heterogeneity (I^2 = 99.98%, $P < 0.001$). No significant changes were seen in the leave-one-out sensitivity analysis. On stratification by the time of analysis, rather than the date of publication, estimations in January from China and Japan showed a summary of 2.77 (95% CI = 1.73–3.81). Estimations subsequently increased in February from China, Japan, and Italy to 3.79 (95% CI = 3.15–4.43) but declined in calculations during March (estimate = 2.01, 95% CI = 0.92–3.11) and April (estimate = 1.94, 95%CI = 1.92–1.95) in China, Mexico, and the UK. Heterogeneity still existed with I^2 near 100%. Meta-regression analysis showed spatiotemporal variations between studies might not influence the calculated pooled estimates.

One-Arm Meta-Analysis for the Effective Reproductive Number of COVID-19

Temporal screening of the R_t across studies revealed that studies of European origin initially reported very high estimates, ranging from 3.27 to 6.32, with pooled values of 5.18 (3.40–6.96). Estimations of studies gradually declined through March (estimate = 3.98, 95% CI = 3.38–4.58) and April (estimate = 1.01, 95% CI = 0.65–1.38), crossing below 1.0 in May (estimate = 0.92, 95% CI = 0.79–1.05) (Fig. 4). Despite the observed temporal trend on subgroup analysis, heterogeneity was not resolved. One noted difference is the calculated R_t in the 3 included studies performed by 3 different methods: Susceptible-Exposed-Infectious-Hospitalized-Recovered (SEIHR) model, Exponential growth method, and Sequential Bayesian method (Table S1, http://links.lww.com/SLA/C528).

DISCUSSION

Tracing viral transmission rates over time provides objective data on the effectiveness of interventions and can be used to inform decisions regarding adjusting of control efforts such as social restrictions, testing, and contact tracking.[41] The collective goal of these control efforts is to drive down viral transmission rates (R_0 and R_e) to below 1 and, ideally, as close to 0 as possible, to bring the outbreak under control, thereby saving lives and mitigating strain on hospital systems.[21] Here, we sought to

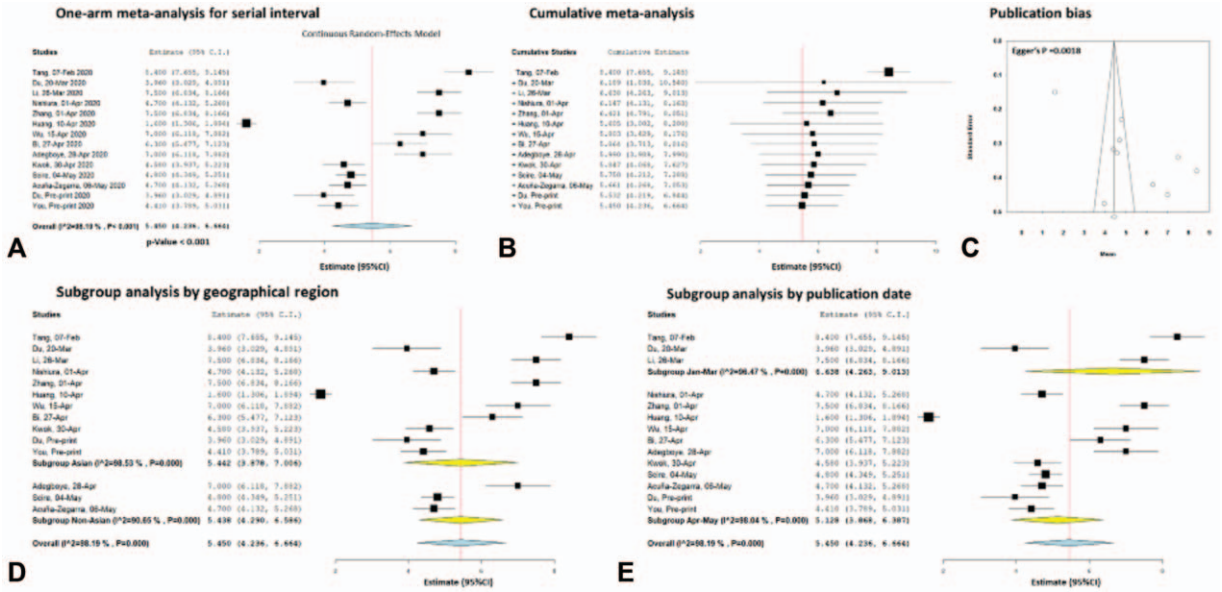

FIGURE 2. One-arm meta-analysis for the serial interval. (A) Forest plot showing the pooled estimate and confidence interval for the serial interval.[7,9,31-35,19–21,36–43] (B) Cumulative meta-analysis showing a temporal trend in literature. (C) Funnel plot showing significant publication bias. (Egger test $P = 0.001$, Begg test $P = 0.66$) (D) Subgroup analysis by geographical region with unsolved heterogeneity. (E) Subgroup analysis by date of publication with unsolved heterogeneity.

systematically examine previously published estimates and measures of COVID-19 spread worldwide to identify the magnitude of transmission chain across different geographic regions and, in comparison, with other viral infections.

Of note, one of the more critical methodological assumptions in the construction of a model for both R_o and R_t is the length of the SI used during the estimation, as it can profoundly impact the model output.[35] Longer SIs have previously been associated with

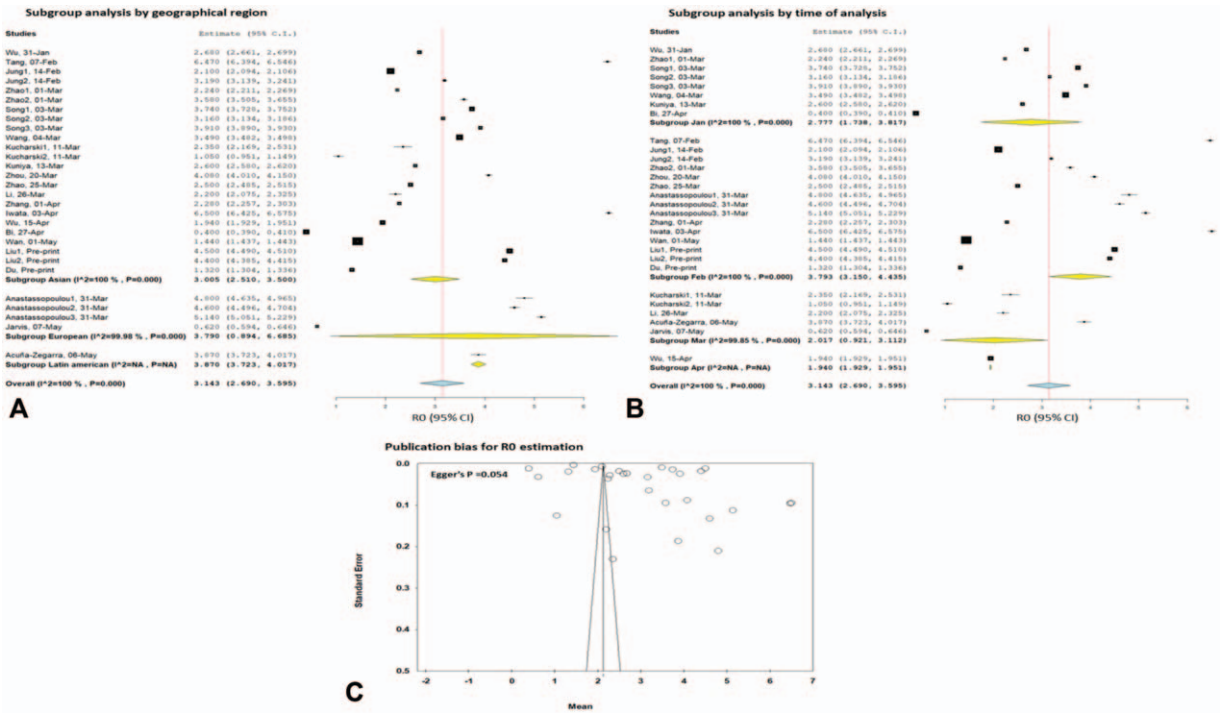

FIGURE 3. One-arm meta-analysis for the basic reproduction number. (A) Forest plot showing the pooled estimate and confidence interval of basic reproductive number stratified by geographical region. (B) Subgroup analysis for by date of publication basic reproductive number. (H) Funnel plot showing publication bias for basic reproductive number.[5–7,9,11,32,34,19–23,37,42,44-58]

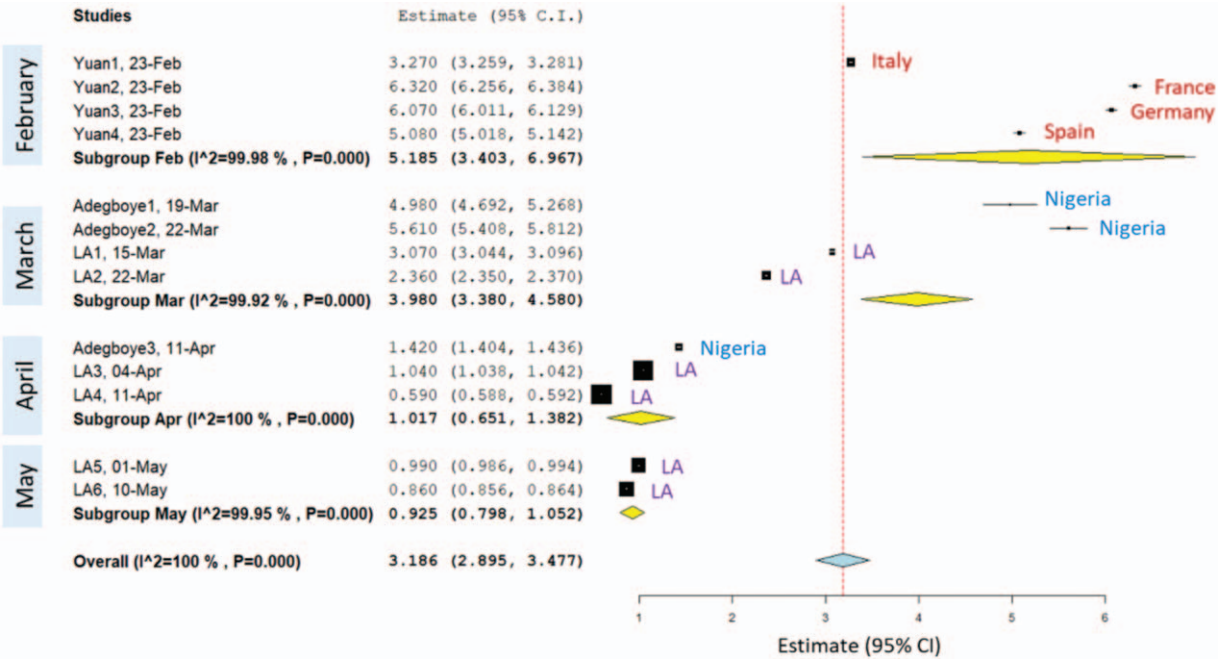

FIGURE 4. One-arm meta-analysis for the time-varying reproduction number. Forest plot showing the pooled estimate and confidence interval of effective reproductive number stratified by timing of study calculation. Spatial origin is shown in the figure.[8,12,31]

higher estimates of R_0 when compared to estimates from the same dataset using shorter SIs.[59] Our meta-analysis for the SI determined the pooled estimate to be 5.45 days (95% CI: 4.23–6.66 days). Longer SIs have previously been associated with higher estimates of R when compared to estimates from the same dataset using shorter SIs.[59] This value is higher than the early result of Li *et al*.[19] One potential explanation is that media portrayals of over-run hospitals and the institution of a stay-at-home order may have led to a later patient presentation. Alternatively, the value could be influenced by testing shortages throughout much of March and into April that existed in Louisiana and across the United States. In other words, symptoms were present, but cases could not be confirmed. On comparison with other viral infection (Fig. 5A), the estimated time between successive cases in a chain of transmission in the current meta-analysis (5.45 days) was shorter than the mean SI for SASR-CoV-1 (8.4 days), measles (14.9 days), and smallpox (22.4 days).[36,60]

For the reproductive number, our literature review found the average overall R_0 to be 3.14 (2.69–3.59). These values exceed WHO estimates, which range from 1.4 to 2.5.[61] Of the reviewed studies, those that used stochastic (ie, random modeling) and statistical methods for deriving R_0 reached reasonably comparable estimates.[51] Studies that utilized mathematical methods produced estimates that are, on average, higher.[21] In more recent studies, R_0 estimates seem to have stabilized around 2 to 3. R_0 estimations provided at later stages can be expected to be more reliable as they are constructed using more case data and include the effect of awareness and intervention.[12] It is worthwhile to note that the WHO estimates are consistently below all published estimates, although the higher end of the WHO range includes the lower end of the estimates reviewed here. Due to insufficient data and short onset time, current estimates of R_0 for COVID-19 are possibly biased. There is also concern that asymptomatic carriers of the virus display no clinical symptoms but are known to be contagious. This population, as well as those with mild disease, may be substantially contributing to propagation.[62]

Pooled estimates of effective reproductive rate showed evidence of time-dependence, as high as 5.18 in February and 3.98 in March, to fluctuate at 1.0 after that. Mitigation measures, social distancing, and stay-at-home orders might lead to a lower incidence of new cases reported. Estimation methods across datasets might also play a role in the heterogeneity of the reproduction rates; those derived using the statistical exponential growth model or Sequential Bayesian approach with a mean R_t of 5.1 and 4.0 were double that calculated by SEIR model (2.5).

Estimated values of the reproduction number for different viruses are summarized from a variety of published sources (Fig. 5B),[63–65] with measles at the highest reproduction rate (15.0) whereas influenza A virus was the least (1.3). For the same coronavirus family, the R_0 for SARS-CoV-1 was 3.1, and MERS-CoV was 4.6. However, the values should be interpreted with caution due to the heterogeneity in the methodology used for R_0 estimation and the different timing along the course of the viral spread.

Our meta-analysis has several potential limitations. First, there was apparent heterogeneity among studies when grouped by geographical region and when grouped temporally. Some articles included in this review did not differentiate between the basic and effective reproductive numbers or state the required population immunity assumptions when reporting the basic reproductive numbers. Therefore, we chose to present summary values for the basic and effective reproductive numbers together to simplify the results. Furthermore, we did not assess included studies for the type or quality of their methodology. We did, however, attempt to control for bias. Lastly, we only included published estimates of the reproductive number, which may not be representative of unpublished reproductive number values.

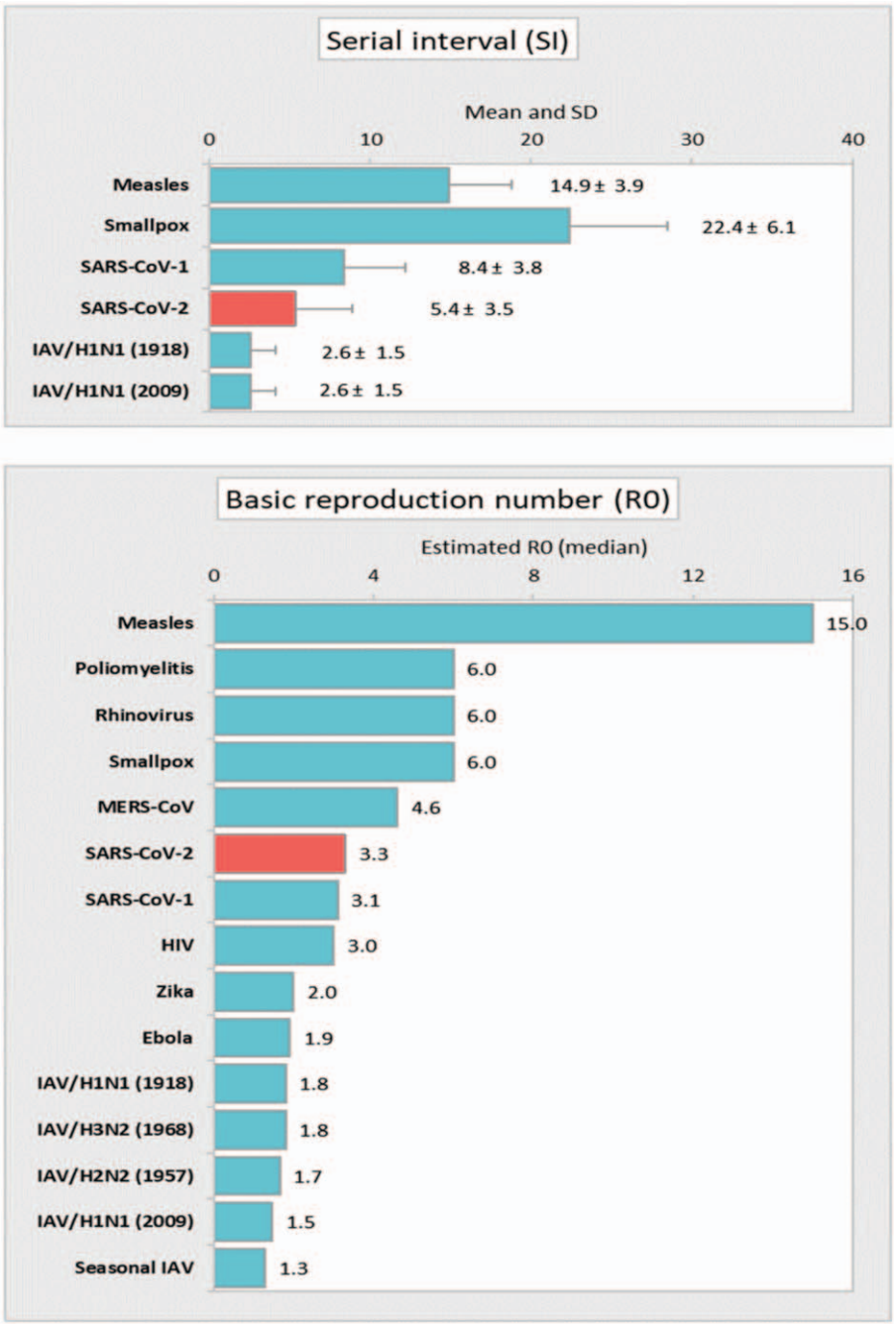

FIGURE 5. Comparison of the serial interval and the estimated reproduction number in different viral infections. (A) Serial interval. Mean and standard deviation are shown. (B) Reproduction number. Bars represented the mean basic reproduction rate. The graph shows how variable estimated values of R_0 varied from virus to virus.[60,66–70] However, the values should be interpreted with caution due to the heterogeneity in the methodology used for R_0 estimation and the different timing along the course of the viral spread. HIV indicates human immunodeficiency virus; IAV, influenza A virus; MERS, middle east respiratory syndrome.

CONCLUSIONS

Our results found that one person is likely to infect 3 persons. Monitoring of R_0 and R_e is crucial objective measures of viral transmission necessary to indicate the effectiveness or failures of mitigation efforts. These measures are not politically motivated and can be used to inform ongoing policy decisions in the interest of public health and to stem the global havoc wreaked by the current pandemic.

ACKNOWLEDGMENT

The authors thank numerous doctors, nurses, government, and civilians working together to fight against the SARS-CoV-2.

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