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Incubation Period of Severe Acute Respiratory Syndrome Novel Coronavirus 2 that Causes Coronavirus Disease 2019: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has currently become a major global public health problem. The prevalence of COVID-19 has increased rapidly worldwide. Because there is no effective COVID-19 vaccine available yet, it is increasingly important to understand the average incubation period of severe acute respiratory syndrome novel coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, to design appropriate preventive and control strategies.

Objective: This systematic review and meta-analysis was designed to estimate the pooled average incubation period of SARS-CoV-2, the virus that causes COVID-19.

Methods: We conducted a systematic electronic web-based search of online databases, including PubMed, Google Scholar, Embase, and the World Health Organization Hinari portal. We included peer-reviewed research studies written in the English language on the incubation period of SARS-CoV-2 using pre-defined quality and inclusion criteria. STATA version 15 statistical software was used to analyze the data. Joanna Briggs Institute critical appraisal quality assessment tool for observational studies was utilized to evaluate the included studies. We extracted relevant data and presented in a tabular form. The I² test was used to assess heterogeneity across studies. funnel plot asymmetry and Egger tests were used to check for publication bias. The final effect size was determined by applying a random-effects model.

Results: Our search identified 206 studies, amongst which 18 studies, representing 22,595 participants were included in the final analysis. The pooled average incubation period of SARS-CoV-2 was 5.7 days (95% CI, 5.1–6.4). Subgroup analyses by geographic location showed that the pooled average incubation period of SARS-CoV-2 was 6.1 days (95% CI, 5.34–6.94) in China and 4.54 (95% CI, 3.9–5.2) in other countries (Singapore, South Korea, and globally).

Conclusions: The pooled average incubation period of SARS-CoV-2 was about 6 days. The longest incubation period was observed in China. Global health initiatives as well as local health planners should consider this average incubation period when designing optimal prevention and control strategies for SARS-CoV-2. (Curr Ther Res Clin Exp. 2020; 81:XXX–XXX)

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Introduction

The incubation period of an infectious disease is the time period from the initial exposure to the infectious agent until the appearance of the signs and symptoms of the disease. It varies from person to person, and the distribution tends to be right-skewed.1,2 This major biological parameter is a part of the case definition of coronavirus disease 2019 (COVID-19) and is used to determine the...
duration of quarantine and to inform policy decisions when mathematical modeling is used.\textsuperscript{1}

COVID-19 is a new infectious disease caused by severe acute respiratory syndrome - novel coronavirus 2 (SARS-CoV-2), which was first recognized as an outbreak of an unknown respiratory illness in Wuhan, China.\textsuperscript{1,4} SARS-CoV-2 is a deadly novel virus that is a member of the coronaviridae family and has a crown-like appearance when viewed with an electron microscope. It can infect various vertebrates and cause disease of the lung, gastrointestinal system, liver, and nervous system.\textsuperscript{5,6} COVID-19 was declared a global health emergency and pandemic by the World Health Organization (WHO) on March 11, 2020.\textsuperscript{7} According to WHO Situation Report-103, as of May 2, 2020, there were 3,267,184 cases and 229,971 deaths globally attributable to COVID-19. Patients with COVID-19 may exhibit the symptoms of severe pneumonia and severe acute respiratory distress. However, many patients exhibit mild symptoms resembling a simple upper respiratory tract infection or may even be completely asymptomatic.\textsuperscript{8} Some experts have estimated that up to 50% patients may be asymptomatic carriers.\textsuperscript{9}

Transmission of SARS-CoV-2 is mainly through respiratory droplets produced by the coughing and sneezing of an infected individual. A healthy person may get exposed to these droplets directly or indirectly from a contaminated surface.\textsuperscript{5} Asymptomatic patients may be infectious and symptomatic patients may be infectious for as long as symptoms last.\textsuperscript{10} Previous studies have described the variability in the incubation period of the Middle East respiratory syndrome coronavirus.\textsuperscript{11–15}

The incubation period is believed to be a function of the initial infective dose, speed of replication of the pathogen within the host, and the host defense mechanisms.\textsuperscript{10} Estimation of the incubation period of a novel pathogen is vital for prevention and control; for example, to determine the appropriate duration of quarantine or observation of an exposed individual.\textsuperscript{16} Different studies have revealed that the incubation period of SARS-CoV-2 varies across different countries; the incubation period ranges from 1.8 to 12.8 days (mean) in China, 4 days (median) in Singapore, 3.6 days (median) in South Korea, and 4.9 days (median) globally.\textsuperscript{17–21}

Because there is no effective COVID-19 vaccine available yet, the responses to this pandemic are dependent on prevention and control modalities. Therefore, information about the incubation period is needed to decide on the length of quarantine. Additionally, this information could be useful for contact tracing. To date, data about the average incubation period of COVID-19 are inconsistent and vary greatly across publicly available literature. Therefore, this systematic review and meta-analysis was designed to estimate the pooled incubation period of SARS-CoV-2.

**Methods**

**Search strategies**

Articles reviewed in this meta-analysis were accessed through electronic web-based database searches and reference list reviews in the English language. We followed the Preferred Reporting Items of Systematic Reviews and Meta-Analysis Protocols checklist guidelines.\textsuperscript{22} This study was not preregistered. The electronic databases searched were PubMed; Google Scholar; Embase; and the WHO\textsuperscript{23} database portal for low-to-middle income countries that includes the Web of Science, Scopus, African Index Medicus, Cumulative Index to Nursing and Allied Health Literature, WHO Institutional Repository for Information Sharing, and African Journals Online databases. Besides, we found related articles available in institutional repositories and by reviewing the reference lists of already identified journal articles. The key terms utilized in the database searches were incubation period, COVID-19, and novel coronavirus-2. These search terms were predefined to allow a comprehensive search strategy that included all fields within the records and Medical Subject Headings terms. This study also used the Boolean operator (within each axis we combined the key words with the "OR" operator and then linked the search strategies for the two axes with the "AND" operator) to search for the specific incubation period in each country. Searches were conducted from April 15, 2020, to May 2, 2020. Potentially relevant studies were identified using the search strategy, retrieved, and managed using Endnote X8 software (Clarivate Analytics, Philadelphia, Pennsylvania).

**Inclusion and exclusion criteria**

The inclusion criteria used were: all articles published only in the English-language, full-text articles published globally in 2020. With regard to studies published in peer-reviewed journals or found in grey literature, all observational study designs (ie, cross-sectional, case-control, and cohort), studies involving human beings, and studies reporting the incubation period of SARS-CoV-2 were eligible for inclusion in this systematic review and meta-analysis. Studies with no accessible full text after using all the Preferred Reporting Items of Systematic Reviews and Meta-Analysis Protocols search strategies and studies not reporting a specific incubation period for SARS-CoV-2 were excluded from this systematic review and meta-analysis.

**Outcome measurements**

The primary outcome of this review was the incubation period of SARS-CoV-2 in human beings. It was defined as the time interval between the exposure and onset of symptoms.\textsuperscript{17} The incubation period was reported as a mean value with a CI or range, and the SE was calculated from a 95% CI. In case of studies that reported only a median with an interquartile range (IQR), the median value was transformed to a mean value and the IQR was transformed to the SE.\textsuperscript{24,25}

**Data extraction**

We used 2 steps for screening. Firstly, we screened the titles and abstracts based on the criteria set in the protocol. Secondly, we identified potentially relevant articles using titles and abstracts for further rescreening of the content of the full article. The relevance of the articles was evaluated based on their topic, objectives, and methodology as listed in the abstract. In addition, the abstracts were also assessed for agreement with the inclusion criteria. When it was unclear whether an abstract was relevant, it was included for retrieval. At this stage, articles deemed irrelevant or beyond the scope of the study were excluded and the full text of the relevant article downloaded for a detailed review. Data were extracted by following the Joanna Briggs Institute data extraction format,\textsuperscript{26} which includes the first author, year of publication, country, study design, mean or median with 95% CI or IQR, range, and sample size.

**Risk of bias assessment**

The risk of bias in included studies was assessed using the 10-item rating scale developed by Hoy et al\textsuperscript{27} for observational studies. Sampling, data collection, reliability and validity of study tools, case definition, and study periods were assessed. Each study was categorized as having a low risk of bias (Yes answers to domain questions) or a high risk of bias (No answers to domain questions). Each study was assigned a score of 1 (Yes) or 0 (No) for each domain, and these domain scores were summed up to provide an overall study quality score. Scores of 8 to 10 were considered as having a low risk of bias, 6 to 7 as having a moderate risk, and 0
to 5 as having a high risk (see supplemental appendix). Two independent reviewers (GM and GD) critically appraised each article. Disagreements between the 2 reviewers were resolved by discussion. If not, a third reviewer (GT) was involved to resolve the disagreement between the 2 independent reviewers. For the final risk of bias classification, discrepancies between the reviewers were resolved via consensus.

**Data processing and analysis**

Information on the study characteristics (i.e., time frame, study location, sample size, and mean and median incubation period with 95% CI) was extracted for each study using a Microsoft Excel (Redmond, Washington) spreadsheet template. These data were then transferred to STATA version 15 software (StataCorp LLC, College Station, Texas) for the final analyses. Heterogeneity across the studies was assessed using the inverse variance ($I^2$) and Cochran Q statistics with 25% as low, 50% as moderate, and 75% as severe heterogeneity. A value of $I^2 > 75$ was considered to indicate severe heterogeneity in the studies. The DerSimonian and Laird random-effects model was used for the heterogeneity analysis. Subgroup and sensitivity analyses were performed using the country, sample size, and risk of bias, and a forest plot was used to show the findings. Furthermore, we used funnel plot asymmetry and Egger test to check for publication bias.

**Results**

**Identification and description of studies**

The database search and desk review yielded a total of 206 articles that were found in the above listed electronic sources.

After reviewing the titles and abstracts, we excluded 46 articles due to duplication. Moreover, 138 articles were excluded due to irrelevance, and 4 additional articles were excluded because 3 of them did not report the outcome of interest, whereas 1 article was outdated and concerned other coronaviruses (Figure 1).

**Characteristics of included studies**

In this review, only 1 included study was a prospective study, whereas the rest used a retrospective study design. All of the included studies were conducted in 2020. Overall, 18 studies with a total of 22,595 patients were evaluated to estimate the pooled average incubation period. In this review, only 3 countries were represented. Among these studies, 14 were from China, 1 from Singapore, 1 from South Korea, and the remaining 2 were conducted globally. The sample size of the studies ranged from 17 to 8866. Regarding the incubation period, the shortest average incubation period of 1.8 days and the longest of 12.8 days were reported from China (Table 1).

**Risk of bias assessment of included studies**

In this review, we assessed the risk of bias in each of the original studies by the risk-of-bias assessment tool by Hoy et al (see Supplemental Table 1). Among the included studies, our summary assessment showed that 4 (22.22%) studies had a high risk of bias, 1 (5.56%) had a medium risk, and the remaining 13 (72.22%) had a low risk of bias (Table 1).
Table 1
Characteristics of studies included in a systematic review and meta-analysis of the incubation period of severe acute respiratory syndrome novel coronavirus 2 that causes coronavirus disease 2019.

| No. | Reference | Publication year | Country   | Sample size | Study design     | Mean (SE) | Risk of bias |
|-----|-----------|------------------|-----------|-------------|------------------|-----------|--------------|
| 1   | Guan W, et al | 2020   | China     | 1099        | Retrospective    | 7.5 (0.181) | High         |
| 2   | Qin J, et al | 2020   | China     | 1211        | Prospective      | 8.62 (0.39) | High         |
| 3   | Lauer SA, et al | 2020 | China     | 181         | Retrospective    | 5.1 (0.36)  | Low          |
| 4   | Linton NM, et al | 2020 | Global    | 158         | Retrospective    | 5 (0.24)   | Low          |
| 5   | Pung R, et al | 2020   | Singapore | 17          | Retrospective    | 4.33 (0.587) | High        |
| 6   | Li Q, et al  | 2020   | China     | 425         | Retrospective    | 5.2 (0.92)  | Low          |
| 7   | Guan W, et al | 2020   | China     | 1099        | Retrospective    | 4.33 (0.113) | Medium      |
| 8   | Backer JA, et al | 2020 | China     | 88          | Retrospective    | 6.4 (0.663) | Low          |
| 9   | Song R, et al | 2020   | China     | 24          | Retrospective    | 12.8 (0.58) | Low          |
| 10  | Leung C | 2020   | China     | 175         | Retrospective    | 1.8 (0.47)  | Low          |
| 11  | Leung C | 2020   | China     | 175         | Retrospective    | 7.2 (0.612) | Low          |
| 12  | Jin X, et al | 2020   | China     | 74          | Retrospective    | 4.67 (0.35) | Low          |
| 13  | Qian G-Q, et al | 2020 | China     | 91          | Retrospective    | 5.67 (0.4)  | High         |
| 14  | Yang Y, et al | 2020   | China     | 8,866       | Retrospective    | 4.8 (0.025) | Low          |
| 15  | Tian S, et al | 2020   | China     | 262         | Retrospective    | 6.7 (0.76)  | Low          |
| 16  | Jiang X, et al | 2020   | Global    | 49          | Retrospective    | 4.9 (0.31)  | Low          |
| 17  | Ki M, et al  | 2020   | South Korea | 22         | Retrospective    | 3.6 (0.426) | Low          |
| 18  | Zhang J, et al | 2020   | China     | 8579        | Retrospective    | 5.2 (1.73)  | Low          |

Figure 2. Forest plot to show the average incubation period of severe acute respiratory syndrome novel coronavirus 2 that causes coronavirus disease 2019.

Pooled average incubation period of SARS-CoV-2

Overall, the pooled incubation period of COVID-19 was 5.7 days (95% CI, 5.1–6.4) (Figure 2). The shortest (3.1 days) and longest (12 days) average incubation periods were reported by studies conducted in South Korea and China, respectively. The $I^2$ statistic for heterogeneity indicated that the studies differed significantly ($I^2 = 97.2%$; $P < 0.05$). Theoretically, we expected large differences in the study settings and socioeconomic contexts; therefore, we fitted a DerSimonian and Laird random-effects model to estimate the pooled average incubation period of SARS-CoV-2.

Subgroup and sensitivity analyses

Subgroup analyses by country revealed that the pooled incubation period of SARS-CoV-2 in China was 6.1 days (95% CI, 5.34–6.94), whereas it was 4.54 days (95% CI, 3.9–5.2) in other countries (Singapore, South Korea, and globally). Despite the subgroup analyses, the results still demonstrated that the heterogeneity across the studies was significant (Table 2).

A leave-1-out sensitivity analysis was performed by the deletion of 1 category using country, sample size, and risk of bias. The average incubation period of SARS-CoV-2 was longer in China (6.14 days) compared with other countries (4.54 days); however, the heterogeneity was not statistically significant ($P = 0.36$). We also found that the average incubation period was not robust over the sample size. Additionally, there was a statistically significant heterogeneity in the incubation period by sample size and risk of bias (Table 2).

Publication bias

Despite the apparent asymmetry of the funnel plot, Egger test was not statistically significant and this indicated that there was no publication bias in estimating the overall average incubation period of SARS-CoV-2 ($P = 0.172$) (Figure 3).

Discussion

The current COVID-19 pandemic is creating a health catastrophe and economic crisis in the world. SARS-CoV-2 is highly contagious and there is no vaccine or established treatment yet.
Therefore, knowledge about the incubation period of SARS-CoV-2 is very important to design appropriate preventive and control strategies. In this systematic review and meta-analysis, the overall pooled average incubation period of SARS-CoV-2 in 22,595 patients derived from 18 available published articles across the globe was 5.7 days (95% CI, 5.1–6.4). This estimate is a little higher than that of other coronaviruses, such as SARS-CoV (4.4 days) and Middle East respiratory syndrome coronavirus (5.5 days). This study also compared the average incubation period of SARS-CoV-2 at the country level. The subgroup analysis by country revealed that a longer incubation period was observed in China, amounting to 6.1 days (95% CI, 5.34–6.94), whereas it was 4.54 days (95% CI, 3.9–5.2) in other countries (Singapore, South Korea, and globally).

This result has significant implications for the current prevention and control practices for SARS-CoV-2. The overall influence of isolation and contact tracing is uncertain and highly dependent on the number of asymptomatic patients. Patients with few or no symptoms are estimated to be as high as 80%, which complicates the prevention and control practices. COVID-19 is clinically diverse, transmittable during the incubation period, and viral loads have been found to be similar in symptomatic and asymptomatic patients. A study from China determined that the incubation period was infectious and confirmed that COVID-19 was contagious from 9 days before the onset of clinical illness.

This evidence contradicts the isolation and contact tracing guidelines developed by the WHO and implemented by many member states, which state that “contact of a COVID-19 case is any person who has had contact with a confirmed or probable COVID-19 case during the 2 days before and the 14 days after the onset of symptoms.” There is a risk of missing plenty of secondary cases during this range of the incubation period.

This meta-analysis revealed that the pooled mean incubation period of COVID-19 was 5.7 days (95% CI, 5.1–6.4). Hence, the current 14-day quarantine policy and contact-based surveillance protocol should be revised and shortened to 7 days, accompanied with longer passive monitoring to track potential asymptomatic positively skewed and false negative cases. In addition, the close contacts of confirmed case patients should be traced, quarantined, and tested starting 5 days before the onset of symptoms.

### Limitations of the study

We only included studies from peer-reviewed English-language journals, which may have restricted our findings. The lack of variability and even representation in the studies that were included in this meta-analysis means that some people with the disease may have been missed. Moreover, the data were obtained from only a few countries. Therefore, the findings of this study should be interpreted after considering these analytical limitations as well as the limitations of the original studies.

### Conclusions

The pooled average incubation period of SARS-CoV-2 was about 6 days. A longer incubation period was observed in China. Global health initiatives as well as local health planners should design their prevention and control strategies based on the estimated incubation period of SARS-CoV-2. Further studies should be conducted to understand to what extent COVID-19 cases are infectious during the incubation period.

### Supplemental Table 1. Risk of bias assessment of the eligible articles determined by using the tool developed by Hoy et al.

| Risk | Bias | Mean (95% confidence interval) | F (%) | Heterogeneity test P value |
|------|------|-------------------------------|-------|---------------------------|
| Low  | Medium risk | 4.33 (4.11–4.55) | 95.5 | < 0.001 |
| Bias | High risk  | 6.59 (5.10–8.07) | 94.5 | |

* Singapore, South Korea, and global.

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### Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.curtheres.2020.100607.

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