REVIEW



Comprehensive estimation for the length and dispersion of COVID-19 incubation period: a systematic review and meta-analysis

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Received: 19 April 2021 / Accepted: 6 August 2021 / Published online: 18 August 2021 © Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract

Purpose To estimate the central tendency and dispersion for incubation period of COVID-19 and, in turn, assess the effect of a certain length of quarantine for close contacts in active monitoring.

Methods Literature related to SARS-CoV-2 and COVID-19 was searched through April 26, 2020. Quality was assessed according to Agency for Healthcare Research and Quality guidelines. Log-normal distribution for the incubation period was assumed to estimate the parameters for each study. Incubation period median and dispersion were estimated, and distribution was simulated.

Results Fifty-six studies encompassing 4095 cases were included in this meta-analysis. The estimated median incubation period for general transmissions was 5.8 days [95% confidence interval (95% CI): 5.3, 6.2]. Incubation period was significantly longer for asymptomatic transmissions (median: 7.7 days; 95% CI 6.3, 9.4) than for general transmissions (P = 0.0408). Median and dispersion were higher for SARS-CoV-2 incubation compared to other viral respiratory infections. Furthermore, about 12 in 10,000 contacts in active monitoring would develop symptoms after 14 days, or below 1 in 10,000 for asymptomatic transmissions. Meta-regression suggested that each 10-year increase in age resulted in an average 16% increment in length of median incubation (incubation period ratio, 1.16, 95% CI 1.01, 1.32; P = 0.0250).

Conclusion This study estimated the median and dispersion of the SARS-CoV-2 incubation period more precisely. A 14-day quarantine period is sufficient to trace and identify symptomatic infections.

Keywords COVID-19 · SARS-CoV-2 · Incubation period · Meta-analysis · Risk assessment · Quarantine period

Abbreviations

WHO World Health Organization COVID-19 Coronavirus disease 2019 SARS-CoV-2 Severe acute respiratory syndrome

coronavirus

SARS Severe acute respiratory syndrome MERS Middle East respiratory syndrome

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Introduction

In December 2019, a cluster of pneumonia cases with unclear pathogenesis was reported in Wuhan, Hubei Province, China. This virus was named by World Health Organization (WHO) as the severe acute respiratory syndrome coronavirus (SARS-CoV-2) and the disease it caused was named as coronavirus disease 2019 (COVID-19) on February 11, 2020 [1]. Consequently, COVID-19 was urgently classified as a Class B communicable disease and managed as a Class A communicable disease in accordance with the Law of the People's Republic of China on the Prevention and Treatment of Infectious Disease [2]. Meanwhile, the



COVID-19 epidemic continued to spread around the globe, with rapid increases in case numbers in European and American countries, and a looming threat in resource-limited settings across Africa [3]. The World Health Organization (WHO) declared a global pandemic on March 11, 2020. As of June 28, the pandemic had spread to 188 countries on six continents, with a total of over 10 million diagnosed cases worldwide [4].

Defining the incubation period of any infectious disease is crucial to evaluate transmission potential, estimate epidemic trends, and inform active monitoring and/or mandatory quarantine policies. The novel pathogenesis of COVID-19 has produced varied epidemiological characteristics from previous coronavirus-derived pulmonary infectious diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). SARS and MERS were rarely transmitted during the asymptomatic period [5, 6]. In contrast, increasing evidence indicates that individuals infected with SARS-CoV-2 could be infectious during the asymptomatic incubation period [7–9]. Thus, knowledge of length and dispersion of incubation period is crucial for SARS-CoV-2 prevention and control. In addition, transmission dynamics models are designed to mimic the spread of SARS-CoV-2 in a nonlinear fashion, and are broadly used for long-term forecasting and evaluating the effect of prevention measures [10]. However, many parameters associated with SARS-CoV-2 transmission are poorly understood, including the incubation period, resulting in a biased prediction [11]. Multiple studies have explored the incubation period for COVID-19, but conclusions remain controversial due to limited sample sizes for each study and considerable heterogeneity between studies [12, 13].

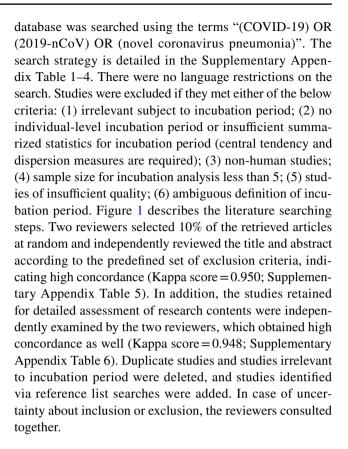
Given the continuing global spread of COVID-19, a further investigation of viral incubation by a systematic review and meta-analysis could provide urgently needed support to improve the understanding of COVID-19 transmission potential and aid prediction and decision-making.

Methods

We carried out this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement. The PROSPERO registration number is CRD42020191038.

Search strategy and selection criteria

In this systematic review and meta-analysis, we searched PubMed, Embase, medRxiv, bioRxiv, and arXiv to identify studies related to COVID-19 published or publicly posted from December 01, 2019 to April 26, 2020 (date of last search) in parallel by two authors (L.W. and Y.L.). Each



Data extraction

From each recruited study, either individual-level incubation period data or summarized statistics for central tendency (mean or median) and dispersion (variance, standard deviation, interquatiles, or range) measures were extracted, as well as population characteristics including sample size, average age, and male proportion. Data were extracted by two independent research coordinators from each publication (L.W., Y.L.); inconsistent inputs were verified and justified by a third author to ensure correctness of data extraction (Y.W.). All literature included in the meta-analysis was labeled as "General Transmissions".

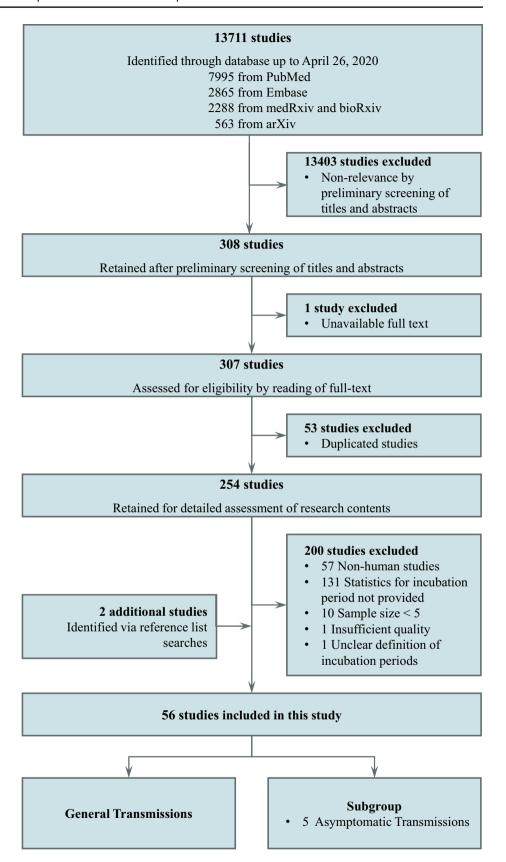
In addition, three publications reported characteristics of incubation among cases infected by asymptomatic or presymptomatic carriers, and additional two studies had a subset of cases infected by carriers in the asymptomatic period [14, 15]; these five studies were grouped and labeled as "Asymptomatic Transmissions".

Quality assessment

The literature quality assessment was evaluated in parallel by two researchers (L.W., Y.L.) according to Agency for Healthcare Research and Quality (AHRQ) guidelines (Supplementary Appendix Table 7). Disagreement between the



Fig. 1 PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Fifty-six studies were included in the meta-analysis. All literature included in the meta-analysis was labeled as "General Transmissions"





two researchers was resolved by consensus and the resolution was confirmed by two senior authors (F.C., Y.W.).

Data synthesis and statistical analysis

Incubation period was assumed to follow a log-normal distribution [16]. Parameters of the log-normal distribution including mean and variation were calculated for each study (Supplementary Appendix Table 8–14). Funnel plots and Egger's tests were used to show the potential publication bias and study heterogeneity. The expected mean of log-scaled incubation period was summarized by meta-analysis followed by exponential calculation to obtain the median of incubation period and the corresponding 95% confidence interval (95%CI). Random-effects meta-analysis was used if P value for heterogeneity test \leq 0.05; otherwise, fixed-effects meta-analysis would be used.

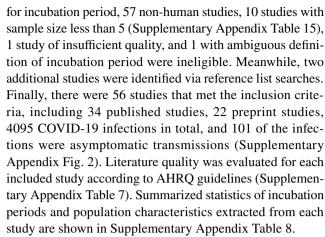
On the other hand, the dispersion for the incubation period was estimated by e^{σ} in which the σ is the estimate of standard deviation of the corresponding log-scaled distribution [17]. Variances of log-scaled incubation period of the recruited studies were assumed to follow the inverse gamma distribution to estimate the expectation value. Bootstrap was used to estimate the corresponding 95% CI of the dispersion.

Furthermore, the distribution of the incubation period was simulated for the general transmissions, and asymptomatic transmissions, respectively. The 1000 posterior means of the log-scaled distribution of incubation period were generated using the Bayesian model that produces probability distribution for each parameter, within R package *bayesmeta* [18]. In addition, the 1000 standard deviations of the log-scaled distribution were generated by Bootstrap sampling. The 1000 means and standard deviations of the log-scaled distribution were used to simulate the distribution of incubation period. The proportion of infections developing symptoms after a certain length of quarantine were estimated; the risk of symptomatic SARS-CoV-2 infections being undetected after a certain length of active monitoring among the active monitoring population was estimated as well [19, 20].

Last, meta-regression was used to explore the association between the age, sex, and median incubation period. All statistical analyses were performed using R software version 3.6.1 (Foundation for Statistical Computing).

Results

Our search retrieved 13,711 records, of which 13,403 were irrelevant to incubation period and were excluded during screening of titles and abstracts (Fig. 1). Fifty-three duplicate studies and 1 study that had no access to full text were removed. By careful screening the full text of the remaining 254 studies, we found that 131 with no summarized statistics

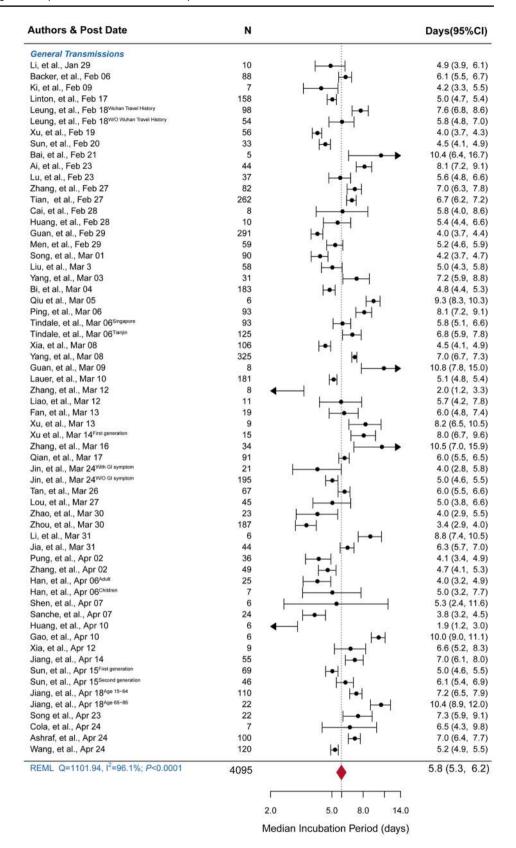


Parameters for log-normal distribution of incubation period were derived for each study (Supplementary Appendix Fig. 1). Across all recruited studies, the median incubation period ranged from 1.9 to 10.8 days; among the five studies had a median of over 10 days, two were from asymptomatic transmissions [7, 21], one from family gathering [22], one from children [23], and one from the elderly [24]. Visual inspection of the funnel plots showed no risk of publication bias, as confirmed by means of the Egger's test (P = 0.2877) (Supplementary Appendix Fig. 2). Due to considerable heterogeneity among studies ($I^2 = 96.1\%$, P < 0.0001), random-effects meta-analysis was used to estimate the median incubation period to be 5.8 days (95% CI 5.3, 6.2) (Fig. 2); the corresponding mean incubation period was 6.9 days. Notably, median incubation period of general transmissions was shorter than that of asymptomatic transmissions (median: 7.7 days; 95% CI 6.3, 9.4; P = 0.0408) (Fig. 3A, Supplementary Appendix Fig. 4). In addition, summarized results of median incubation period for preprint studies without peer-review (median: 6.4 days; 95% CI 5.6, 7.2) showed no difference from that among studies published in scientific journals (median: 5.6 days; 95% CI 5.1, 6.1; P = 0.2045) (Fig. 3B, Supplementary Appendix Fig. 6). No difference was also observed among studies in mainland China (median: 5.9 days; 95% CI 5.4, 6.4) versus those performed in regions other than mainland China (median: 5.4 days; 95% CI 4.3, 6.8; P = 0.6075) (Fig. 3C, Supplementary Appendix Fig. 7). Additionally, rather than solely focusing on the median, the dispersion of the incubation period was studied. Dispersions were estimated as 1.80 (95% CI 1.59, 2.06) for general transmissions, and 1.37 (95% CI 1.24, 1.63) for asymptomatic transmissions, respectively.

For comparison with other viral respiratory infections, the summarized statistics of incubation periods for nine viral respiratory infections were obtained from a previously published systematic review, including measles, adenovirus, respiratory syncytial virus, SARS-CoV, human coronavirus, parainfluenza, rhinovirus, influenza A, and influenza B [17]. In addition, meta-analysis was performed for the



Fig. 2 Forest plot for median incubation period among general transmissions. Studies were ordered by date of post online. Significant heterogeneity was observed among studies ($I^2 = 96.1\%$, P < 0.0001). The random-effects meta-analysis using restricted maximum likelihood (REML) was used to summarize the median incubation period (days) and the corresponding 95% confidence interval (95%CI)





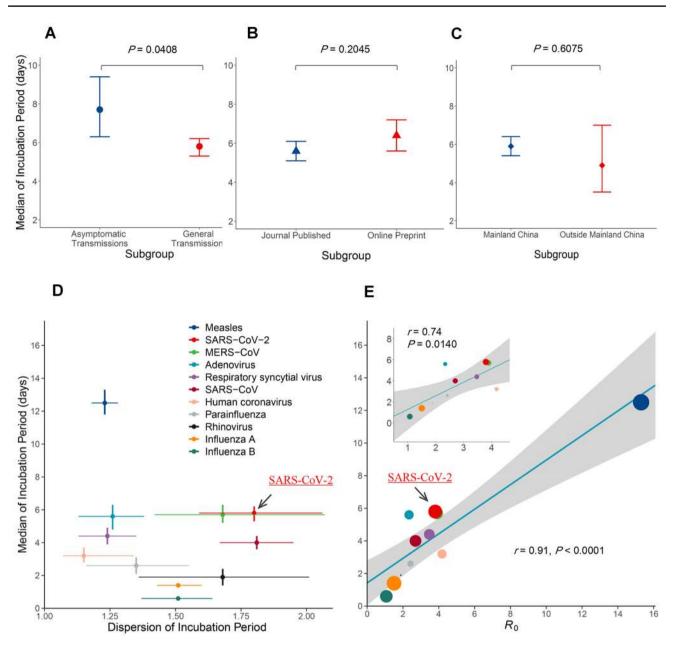


Fig. 3 Subgroup meta-analyses, and comparison for characteristics of incubation period among 11 viral respiratory infections. Subgroup meta-analyses were performed among A General Transmissions versus Asymptomatic Transmissions, B journal-published studies versus preprint studies, and C studies performed in mainland China versus those outside mainland China. Median incubation period between the subgroups was compared using Z test in logscale. Median and disper-

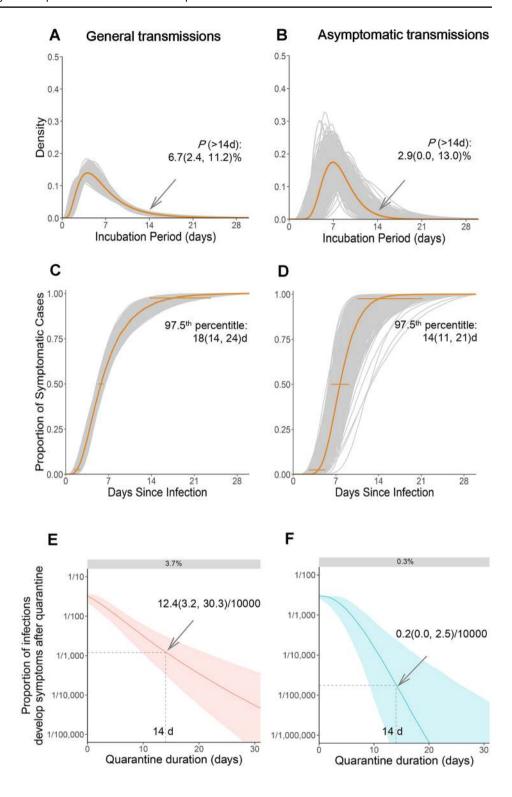
sion of the incubation period, and the corresponding 95% confidence interval for 11 viral respiratory infections are demonstrated (**D**); black arrow highlights the results for SARS-CoV-2. Correlation between the length of incubation period and basic reproductive number (R_0) was evaluated by linear regression (**E**); the correlation was reanalyzed by excluding the results of measles in a sensitivity analysis

incubation period of MERS (Page 44–52 in Supplementary Appendix Material). COVID-19 had a significantly longer incubation period than that of SARS (median: 4.0 days; 95% CI: 3.6, 4.4) (P < 0.0001), but similar to that of MERS (median: 5.7 days; 95% CI: 5.2, 6.3) (P = 0.6392) (Fig. 3D, Supplementary Appendix Fig. 11). Furthermore, among median incubation periods for 11 viral respiratory infections,

SARS-CoV-2 ranked second after measles (Fig. 3D). The dispersion of incubation period of SARS-CoV-2 also ranked second (Fig. 3D). The basic reproductive numbers (R_0) of the assessed respiratory viruses were strongly correlated with the length of incubation period (r=0.91, P<0.0001) and retained statistical significance by excluding one outlier (r=0.74, P=0.0140) (Fig. 3E).



Fig. 4 Distributions of incubation period and risk evaluation for the length of quarantine period. Density distributions of the incubation period for general transmissions (A), and asymptomatic transmissions (B) are shown, respectively; the proportion and the 95% confidence interval (95% CI) of infections having incubation period over 14 days were estimated. Cumulative distributions of incubation period for general transmissions (C), and asymptomatic transmissions (D) are shown, respectively; the 97.5th percentile and the 95% CI were estimated for each distribution. In addition, assuming a 3.7% risk of being infected among the general quarantine population according to the results of Qin et al. study, the risk of having infections develop symptoms after 14-day active monitoring or quarantine was estimated (E). Similarly, assuming that individuals who contacted latent infections during the asymptomatic or presymptomatic period, and 0.3% probability to be infected, the risk of observed asymptomatic transmissions developing symptoms after 14-day quarantine period is shown in (F)



The distribution of incubation period was simulated; 6.7% (95% CI 2.4%, 11.2%) and 1.4% (95% CI 0.1%, 3.6%) of general transmissions had an incubation period over 14 d and 21 d, respectively (Fig. 4A); these proportions reached 2.9% (95% CI 0.0%, 13.0%) and 0.1% (95% CI 0.0%, 2.2%) of asymptomatic transmissions with an incubation period over

14 d and 21 d, respectively (Fig. 4B). The 97.5th percentiles of incubation period in the population of general transmissions, and asymptomatic transmissions were 18 days, and 14 days, respectively (Fig. 4C, D).

A recent literature estimated a series of secondary attack rates in different settings [25]. Assuming a 3.7%



secondary attack rate among the overall close contacts in active monitoring or quarantine, the estimated probability of symptomatic SARS-CoV-2 infections that would be undetected after 14-day active monitoring or quarantine was 12.4 (95% CI 3.2, 30.3) per 10,000 monitored individuals (Fig. 4E). In addition, assuming a 0.3% secondary attack rate among close contacts of asymptomatic index case-patients, the estimated probability of undetected SARS-CoV-2 infections which developing symptoms after 14-day active monitoring or quarantine was 0.2 in 10,000 (95% CI 0.0, 2.5 in 10,000) (Fig. 4F). Furthermore, according to the results of the other epidemiological study of an active monitoring population in China [26], the risks of being infected for the close contacts of symptomatic infections and latent infections were 6.30% and 4.11%, respectively (Page 40 in Supplementary Appendix Material). Under this assumption, about 20 per 10,000 contacts would develop symptoms after 14 days in active monitoring or quarantine; such risk is below 3 in 10,000 for close contacts of asymptomatic index-patients (Supplementary Appendix Fig. 8). Sensitivity analyses considering various settings for the risk of being infected among an active monitoring population were performed as well (Supplementary Appendix Table 17-18). Overall, in the active monitoring population, the risk of developing symptoms after a 14-day quarantine period was about 12 in 10,000, while the risk of close contacts with asymptomatic index-cases developing symptoms after 14-day quarantine period was below 1 in 10,000, which meant only very few

close contacts would get infected from asymptomatic individuals.

Average age and male proportion were extracted from 24 of 56 studies (Supplementary Appendix Table 9). Metaregression incorporating two moderators simultaneously was used to explore the impact of individual characteristics on length of incubation period. A linear relationship was identified between age and log-scaled median of incubation period. Average age per 10-year increments resulted in a 16% increment in median incubation period with adjustment for male proportion (incubation period ratio: 1.16, 95% CI 1.01, 1.32; P = 0.0250) (Fig. 5A). No evidence indicated an association between sex and median of incubation period (P = 0.1315) (Fig. 5B).

Finally, an interactive real-time risk assessment application was developed to provide real-time updates of the risk assessment for symptomatic SARS-CoV-2 infections that would be undetected during active monitoring among active monitoring population with close contacts by setting several crucial parameters (Supplementary Appendix Fig. 12).

Discussion

Increasing evidence supports the transmission potential of SARS-CoV-2 during the latent period [7–9]. Thus, length of incubation period is a crucial parameter to determine the risks for close contacts and guide contact tracing and quarantine policies. The estimated median incubation period in this study was 5.8 days for general transmissions; the estimated

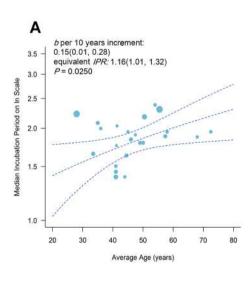
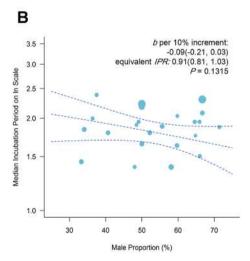


Fig. 5 Meta-regression for the association of average age, male proportion, and median incubation period. The two moderators were evaluated simultaneously in the regression model. **A**, **B** show the scatter plot, the fitted regression lines (straight dash line), and 95% confidence band (dash curves) for average age (**A**) and male proportion (**B**), respectively. Results were described by coefficient (*b*) per



10-year increment in average age, the 95% confidence interval (95% CI), and the P value. Incubation period ratio (IPR), the exponential form of b (e^b), was estimated. IPR > 1 represents relatively increased incubation period, while IPR < 1 represents decreased incubation period



mean incubation was 6.9 days which is 33% longer than the previously frequently adopted value—5.2 mean days as reported by Li [16]. Notably, asymptomatic transmissions appear to have an almost 2-day longer incubation period than general transmissions. Infections contacted with latent infections may have a low viral load that requires a longer incubation to develop symptoms [27, 28]. However, many other factors, such as comorbidities, vitamin D levels and immunity, may pose as factors determining the transmission risk or length of the incubation period [29–31]. More research is needed to verify the mechanism behind the relationship between incubation period and viral load. Of note, large variation of estimates was observed among studies, which indicates a non-negligible heterogeneity in COVID-19 patients. Evolution of SARS-CoV-2 might partially address this heterogeneity [32].

Recently, two meta-analyses of the SARS-CoV-2 incubation period were published as well [33, 34]. However, due to their limited search strategy and inflexible statistical methods, only eight or seven studies were included in their analyses. On the contrary, we screened among over 10,000 literatures to obtain 56 qualified studies, followed by 7 different methods to extract parameters for the distribution of incubation period. We performed a fairly comprehensive estimation with 56 studies included by simulating the distribution of incubation period. Be noted, Qin and his colleagues developed a novel method to estimate SARS-CoV-2 incubation period by renewal process by considering the incubation period as a renewal and the duration between departure and symptoms onset as a forward time [35]. They estimated the SARS-CoV-2 incubation period at 7.76 days [95% confidence interval (CI): 7.02-8.53], which was considerably longer than that in this study and most of the studies included in the meta-analysis. However, the cases with short incubation period, who were infected in Wuhan while first symptoms appeared before departure, were not included in Qin et al. study. Thus, unrepresentative of the population in Qin et al. study, though novel statistical methods applied, might lead to an overestimation of incubation period.

Our study demonstrates that SARS-CoV-2 has a considerably longer incubation period than most types of viral respiratory infections. Notably, a significant positive association between length of incubation period and magnitude of R_0 was observed. This finding indicates viral respiratory infections beyond SARS-CoV-2 may have transmission potential during their incubation period. In addition, SARS-CoV-2 has a high dispersion of incubation period, which increases the difficulty in tracing and controlling for contacts. These unique epidemiologic characteristics partially contribute to today's global spread of COVID-19.

The 14-day quarantine period has been adopted in mainland China and suggested to the international community by WHO [36]. We estimated that 7 out of 100 general infections

and 3 out of 100 infections by asymptomatic transmissions would develop symptoms after 14 days. However, not all the close contacts will be infected in reality; the secondary attack rate was relatively low among close contacts of cases with COVID-19, especially asymptomatic cases whose transmission capacity was limited. In addition, patients with more clinically severe cases or those with symptoms were more likely to infect their close contacts. The mechanism may be that the more severe symptoms COVID-19 cases have, the higher viral load of SARS-CoV-2 and thus the greater transmission capacity. Be noted, the risk for secondary infection was closely related to contact settings. For example, the transmission risk via household contact was higher compared with that via public transportation contact settings [25, 37]. Considering the probability of being infected among contacts in active monitoring or quarantine, about 12 per 10,000 contacts would develop symptoms after 14 days in active monitoring or quarantine; such risk is below 1 in 10,000 for close contacts of asymptomatic index-patients. Assuming the risks of being infected for the active monitoring population having contacts with symptomatic infections and latent infections were 1% in equal, about 3 in 10,000 contacts would develop symptoms after 14 days, which is more than 1.0 in 10,000 reported in Lauer et al. study [19]. Such difference may be attributed to the different estimates of median and dispersion of incubation period, and different definition of close contacts. Although the median incubation period of infections by asymptomatic transmissions was higher than that of general transmissions, the dispersion was relatively lower than that of general transmissions, which resulted in a lower risk of undetected after 14-day quarantine. Overall, the 14-day quarantine or active monitoring policy is sufficient to trace and monitor the persons potentially exposed to SARS-CoV-2. However, precise understanding of the crucial epidemiological parameters related to transmission probability in active monitoring population could aid in further refining the appropriate length of quarantine [38].

In addition, age is likely to have a positive relationship with the length of incubation period, indicating that quarantine period could be justified according to the age. Notably, the result in our study indicated that older adults had a longer incubation period than younger adults, which was consistent with the findings of previous studies [24, 39]. Older adults tend to have more health complications such as respiratory issues and chronic diseases; thus, pre-existing symptoms may mask the onset of COVID-19 symptoms, which could bias the measurement of incubation period. However, the underlying mechanism is unclear and warrants further investigation.

We acknowledge some limitations of this study. First, the sample sizes for asymptomatic transmissions are small, and the results for these subgroups may be less representative.



Second, pre-existing diseases and other important factors, such as vitamin D levels, viral load and contact settings. may pose as factors determining the length of the incubation period. However, these were not further explored in our research, because most studies obtained data from public resources, and the raw data were not provided. In addition, there is a possibility that some data were used repeatedly. Third, 50 of 56 studies were from mainland China; studies from other regions and countries are needed to explore the impact of viral evolution on variation of incubation period and other epidemiological characteristics. Fourth, the massive heterogeneity among the included studies ($I^2 = 96\%$), suggesting underlying confounding factors unexplored. To explore the sources of heterogeneity among the studies, we have performed inverse-variance weighting, random-effects model, stratification analysis, and meta-regression. However, even after a series of subgroup analyses and meta-regression exploration, the major part of heterogeneity is still at large, indicating a major issue of the current COVID-19 epidemiological studies. In addition, precisely estimating the exposure window and time of symptom onset related to SARS-CoV-2 infection could be difficult in practice. Studies used different methods to quantify the uncertainty of incubation period for each individual, which may partially explain the non-negligible between-study heterogeneity. The potential high chance of bias and large variation of each individual study deserve further exploration. Fifth, the R_0 of 11 viral respiratory infections were extracted from the previously published studies, which could be evaluated by systematic review and estimated by meta-analysis in future, to provide a more accurate parameters. Sixth, more studies regarding other mutated variants of SARS-CoV-2 after April 26, 2020 were not included in our study, the topic on how the incubation period will change after the SARS-CoV-2 mutates is very interesting and worthy of further study. Last, knowledge of the risk of being infected among close contacts is limited and may vary due to different definition of close contacts.

Conclusions

In conclusion, this study integrated 56 studies and 4095 COVID-19 infections and estimated the median and dispersion of the SARS-CoV-2 incubation period, both of which ranked second among 11 viral respiratory infections. A long and dispersive incubation period probably partially contributes to the increasing spread of COVID-19 worldwide. Yet, the 14-day quarantine period is sufficient to trace and identify symptomatic infections among an active monitoring population. A certain period of self-isolation after central quarantine can further reduce transmission risk.



Author contributions YW, FC and HS were responsible for initial plan, study design and conducting the study. LW, YL, JC, ZY, LH and YW were responsible for acquisition, analysis, or interpretation of data. YW, LW were responsible for drafting of the manuscript. HS, FC and YW were responsible for critical revision of the manuscript for important intellectual content. LW, YL, RZ, YZ, JC, LH and YW took full responsibility for statistical analysis. F.C. and H.S. provided administrative, technical, or material support. YW, FC and HS obtained funding and conducted the supervision. All authors were involved in editing and approving the manuscript.

Funding This study was funded by the National Natural Science Foundation of China (82041024 to F.C., 82041026 to H.S., 81973142 to Y.W., 81903407 to L.H.). Sponsors had no role in design of the study, collection and analysis of data, or preparation of the manuscript. This study was preprinted at: https://www.medrxiv.org/content/10.1101/2020.06.20.20134387v1.

Declarations

Conflict of interest The authors have no financial interests nor any other conflicts of interest related to this study.

Availability of data, materials and code Additional files available from the corresponding author at fengchen@njmu.edu.cn upon reasonable request.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Written informed consent for publication was obtained from all authors.

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