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BMJ Open

The incubation period of COVID-19 – A rapid systematic review and meta-analysis of observational research

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039652
Article Type:	Original research
Date Submitted by the Author:	22-Apr-2020
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Keywords:	Epidemiology < INFECTIOUS DISEASES, EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES

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TITLE PAGE

Title: The incubation period of COVID-19 – A rapid systematic review and meta-analysis of observational research

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Word Count: 3156

Key words: “COVID-19”; “Incubation period”; “Meta-analysis”

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ABSTRACT

Objectives: The aim of this study was to conduct a rapid systematic review and meta-analysis of estimates of the incubation period of COVID-19.

Design: Rapid systematic review and meta-analysis of observational research

Setting: International studies on incubation period of COVID-19

Participants: Studies were selected for meta-analysis if they reported either the parameters and confidence intervals of the distributions fit to the data, or sufficient information to facilitate calculation of those values. Twenty studies selected for initial review, 8 of these were shortlisted for meta-analysis. Final estimates conducted on meta-analysis of 7 studies.

Primary outcome measures: Parameters of a lognormal distribution of incubation periods.

Results: The incubation period distribution may be modelled with a lognormal distribution with pooled mu and sigma parameters (95% confidence intervals) of 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55) respectively. The corresponding mean (95% confidence intervals) was 5.8 (5.01, 6.69) days. It should be noted that uncertainty increases towards the tail of the distribution: the pooled parameter estimates (95% confidence intervals) resulted in a median incubation period of 5.1 (4.5, 5.8) days, whereas the 95th percentile was 11.6 (9.5, 14.2) days.

Conclusions: The choice of which parameter values are adopted will depend on how the information is used, the associated risks and the perceived consequences of decisions to be taken. These recommendations will need to be revisited once further relevant information becomes available. Finally, we present an RShiny app that facilitates updating these estimates as new data become available.

Key words: “COVID-19”; “Incubation period”; “Meta-analysis”

ARTICLE SUMMARY

Strengths and limitations of this study

- This study provides a pooled estimate of the distribution of incubation periods which may be used in subsequent modelling studies or to inform decision-making
- Several studies used data that was publicly available, therefore there is potential that some the data may be used for more than one study.
- This estimate will need to be revisited as subsequent data become available.
- We present an RShiny app to allow the meta-analysis to be updated with new estimates

INTRODUCTION

Reliable estimates of the incubation period are important for decision making around the control of infectious diseases in human populations. However, incubation periods are expected to vary across individuals within the population. A single measure of central tendency (i.e. mean or median) does not adequately represent this variation accurately.[1] Therefore, it is critically important to understand the variation in incubation periods (i.e. the distribution) within the population.

Knowledge of the incubation period distribution can be used directly to inform decision-making around infectious disease control. For example, the maximum incubation period can be used to inform the duration of isolation, or active monitoring periods of people who have been at high risk of exposure. Knowledge of the incubation period, coupled with estimates of the latent period, serial interval or generation times, may help infer on the duration of the pre-symptomatic infectious period, which is important in understanding both the transmission of infection and opportunities for control.[2] Finally, decision making in the midst of a pandemic often rely on predicted events, such as daily number of new infections, from mathematical models. Such models rely on key input parameters relevant to the transmission of the specific infectious disease. It is important that input parameters into such models are as robust as possible. Given that some models fit data to many parameters, only some of which are specifically of interest but all of which are interdependent, output estimates may be compared to the robust estimates as part of the validation of the model. However, to date, many COVID-19 models have used input values from a single study. The decision on which study to use may vary from model to model. Earlier work has shown that for models of respiratory infections, statements regarding incubation periods are often poorly referenced, inconsistent, or based on limited data.[3]

We hypothesized that a pooled estimate of the distribution of incubation periods could be obtained through a meta-analysis of data published to date. Therefore, the aim of this study was to conduct a rapid systematic review and meta-analysis of estimates of the incubation periods of COVID-19, defined as the period of time (in days) from virus exposure to the onset of symptoms. Specifically, we aimed to find a pooled estimate for the parameters of an appropriate distribution that could be subsequently used as an input in modelling studies and that might help quantify uncertainty around the key percentiles of the distribution as an aid to decision making.

MATERIALS AND METHODS

For the purpose of this study we followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[4] The outcome was defined as the time in days from the point of exposure, (in this case, infection) to the onset of clinical signs; all observational studies were included in the analysis. Finally, the population was confirmed infected individuals, where an exposure time could be ascertained with some degree of certainty and precision.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Search methodology, initial screening and categorisation

A survey of the literature between 1 December 2019 and 8th April 2020 for all countries was implemented using the following search strategy. Publications on the electronic databases PubMed, Google Scholar, MedRxiv and BioRxiv were searched with the following keywords: “Novel coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR “COVID-19” AND “incubation period” OR “incubation”. The dynamic curated PubMed database “LitCovid” was also monitored, in addition to national and international government reports. No restrictions on language or publication status were imposed so long as an English abstract was available. Articles were evaluated for data relating to the aim of this review, and all relevant publications were considered for possible inclusion. Bibliographies within these publications were also searched for additional resources. The initial searches were carried out by three of the investigators (ÁC, KH, FB). Authors of studies were contacted only to clarify reporting queries.

Study appraisal and selection of meta-analysis

Studies were selected for meta-analysis if they reported either the parameters and confidence intervals of the distributions fit to the data, or sufficient information to facilitate calculation of those values. Specifically, this included studies that reported: the point estimate and confidence intervals or standard errors of each parameter; the mean and standard deviation on the original (non-transformed) scale with confidence intervals; the mean and one or more percentiles of the distribution (with confidence intervals); or two or more percentiles of the distribution (with confidence intervals). Studies were excluded if they described the distribution (e.g. with mean, median, percentile) but did not report any uncertainty around that figure. The selection of studies to include in the meta-analysis was conducted by the primary author (CMA).

Data extraction

On initial appraisal, it was apparent that the majority of studies fitted a lognormal distribution to the data. Earlier work has shown that this distribution is appropriate for many acute infectious diseases.[3, 5] Therefore, the study proceeded as the meta-analysis (pooled estimate) of the parameters of this distribution.

A variable (X) has a lognormal distribution when the log-transformed values follow a normal distribution with mean, mu, and variance, sigma^2, i.e.:

ln(X) ~ N(mu, sigma^2)

Methods exist for the meta-analysis of studies that combine a mix of log transformed and non-transformed data.[6] In this case we opted to transform data, where possible to the log-transformed scale, and obtain a pooled estimate of both mu and sigma.

Calculation of distribution parameters from each study

Where the values for each parameter (mu and sigma) were available from the studies, along with corresponding confidence intervals/standard errors, these were extracted as reported. In the remaining studies, the values were calculated where possible from the information presented.

Calculation of mu and sigma from studies reporting the mean and standard deviation of the lognormal distribution on the original scale.

The mu and sigma parameters of the original lognormal distribution were calculated as:

$$mu = \ln(m) - \frac{sigma^2}{2}$$

$$sigma = \sqrt{\ln\left(\frac{v}{m^2} + 1\right)}$$

Where v = variance (= sd^2), and m = the mean of the distribution on the original (i.e. non-log transformed) scale.

Similarly upper and lower confidence intervals of mu and sigma were found by substituting the upper and lower bounds of the mean or standard deviation (from the original scale) into the equation above, one at a time, whilst holding the value for the other parameter constant (as the point estimate for that parameter).

Calculation of mu and sigma from studies reporting mean and percentiles on the original scale

Where studies reported the results as the mean and 95th percentile on the original scale, the "lognorm" package in R was used to calculate the original values of mu and sigma and corresponding standard errors or confidence intervals.[7]

Calculation of variance of mu and sigma

For studies reporting confidence intervals, the standard error was calculated as (upper bound – lower bound)/(2 x 1.96)

Meta-analysis

A random effects meta-analysis was conducted in R-studio Version 1.2.5033,[8] using the "metafor" package,[9] of the mu and sigma parameters of the lognormal distribution, specifying the point estimate and the standard error using "yi" (i.e. the point estimate) and "sei" (i.e. the standard error) arguments. Forest plots were produced using the same package. Quantitative estimates of bias were obtained using the Egger's test and funnel plots. Heterogeneity was quantified using the *I2* statistic and investigated by conducting subgroup analyses of the dataset.

Calculation of the se of the mean and sd on the original scale from pooled estimates of mu and sigma

The mean and standard deviation of the pooled estimate were converted to the original (i.e. non-log transformed) scale as:

$$\text{Mean} = e^{\left(mu + \frac{sigma^2}{2}\right)}$$

$$\text{SD} = \sqrt{e^{(2 \times mu + sigma^2)} \times e^{(sigma^2 - 1)}}$$

The upper and lower confidence intervals were found by substituting, one at a time, the upper and lower bounds for mu and sigma and recalculating the subsequent figures for mean and SD.

The resulting distribution was plotted using the "ggplot2" package in R.[10] In addition, the distributions for studies that did not fit a lognormal distribution, but that reported the parameters of an alternative distribution fitted were also plotted alongside the pooled lognormal distribution.

Finally, an R Shiny app was created which allows the meta-analysis estimates to be updated as new data become available.

RESULTS

After initial search and selection of relevant papers and removing duplicates, 20 studies were available for appraisal.

- Two papers were removed as they dealt with specific cohorts of cases – young adults [11] and children.[12]
- One study was removed since only the abstract was in English and there was not enough detail to extract the relevant results.[13]
- Several papers were removed since they contained insufficient data or methods description to facilitate their inclusion:
    - One study was removed since there was not enough detail in the paper to determine whether new parameters were being estimated or whether the parameters quoted were input values for their model.[14]
    - Five papers were removed since the data were largely descriptive, with no confidence intervals reported.[15-19]
    - One study was removed because the error terms associated with the mean, median and percentiles were not reported and there was not enough information presented to recover the parameters of the lognormal distribution.[20]

Of the shortlisted studies (n=10), six reported lognormal distributions as best fitting the data. [21-26] Of the remaining 4, one reported that several distributions were trialled but it was not clear which distribution was used for the final estimates.[27] However, these authors provided raw data which we used to fit the parameters of the lognormal distribution using the “rriskDistributions” package.[28] The remaining 3 studies reported that either Weibull or gamma distributions fitted the data better. Of these, 1 study also presented the results of a log normal distribution fit to the data,[29] facilitating its inclusion in the subsequent analysis. The final two studies reporting a Weibull [30] and a gamma distribution [31] were removed from further analysis at this stage, however, those distributions were plotted over the final distribution to evaluate the impact of removing those studies. The values extracted from each study are shown in Table 1.

Table 1. Study size and extracted data for the lognormal mu and sigma parameters from the 8 studies that were used for meta-analysis.

Author	n	mu	se	sigma	se
Backer et al., 2020	88	1.796	0.077	0.349	0.045
Lauer et al., 2020	181	1.621	0.064	0.418	0.069
Li et al., 2020	10	1.425	0.240	0.669	0.141
Bi et al., 2020	183	1.570	0.245	0.650	0.167
Jiang et al., 2020	40	1.530	0.066	0.464	0.046
Linton et al., 2020	158	1.611	0.070	0.472	0.048
Zhang et al., 2020	49	1.540	0.092	0.470	0.072
Ma et al., 2020	587	1.857	0.024	0.547	0.023

The initial pooled estimate of mu from this dataset (i.e. dataset 1, n=8 studies) was 1.65 (1.55, 1.76) and the pooled estimate of sigma was 0.47 (0.41, 0.54). The I^2 values were 78% and 59% for mu and sigma respectively. Egger's tests for mu and sigma were not statistically significant; p=0.11 and p=0.31 for mu and sigma respectively. However, evaluation of the funnel plots (Figures S1 and S2 Supplementary Material) suggests the potential for bias associated with one of the studies included in the analysis.[25] Evaluation of the meta-analyses results for mu demonstrated that two studies were responsible for much of the heterogeneity in the analysis of this value. In particular, the values reported by Ma et al. [25] and

Backer et al. [29] were higher than the estimates from other studies. Both studies were further evaluated to determine whether these differences may have been due to methodological differences. The Backer et al. [29] study was subsequently excluded since it appeared that the exposure window was somewhat imprecisely defined which would have biased this estimate upwards. Conversely, the study reported by Ma et al. [25] used only patients where the exposure window was 3 days or less, with the majority of those of a 1-day duration. The meta-analysis was repeated with the Backer et al. [29] study removed (i.e. dataset 2, n=7 studies). The resulting pooled estimates were 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55), whilst the I^2 values were 78% and 28% for mu and sigma respectively. Figures 1 and 2 show the resulting forest plots for the meta-analyses of mu and sigma respectively from dataset 2 (n=7), that is the 8 studies from which the parameters were extracted, minus the Backer et al. [29] estimate.

<Figure 1 here>

<Figure 2 here>

Figure 3 shows the resulting density plot of the pooled distribution. Figure 4 shows the cumulative density function plot of the same (pooled distribution). In this instance, all possible combinations of distributions across the 95% confidence intervals of the estimates of each of the mu and sigma values are plotted on the same graph. Table 2 shows the percentiles and corresponding confidence intervals of the pooled lognormal distribution.

<Figure 3 here>

<Figure 4 here>

Table 2. Percentiles of the pooled log normal distribution after simulating all possible combinations of mu and sigma within the 95% confidence intervals of the pooled estimates of both parameters. The

median days for each percentile are shown along with the minimum and maximum values for that percentile.

Percentile	Median (days)	min	max	Difference (max – min)
0.025	1.92	1.54	2.38	0.84
0.05	2.24	1.83	2.75	0.92
0.1	2.69	2.24	3.23	0.99
0.25	3.64	3.12	4.25	1.13
0.5	5.1	4.53	5.75	1.22
0.75	7.15	6.13	8.34	2.21
0.9	9.69	8.06	11.6	3.54
0.95	11.6	9.49	14.2	4.71
0.975	13.6	10.9	16.9	6

Figure 5 shows the cumulative density function plots of the pooled lognormal distribution along with the estimates from the original studies. Finally, Figure 6 shows the probability density function of the pooled lognormal distribution, plotted alongside the two studies that could not be included in the final meta-analysis due to the fact that they fit alternative distributions to the data.

<Figure 5 here>

<Figure 6 here>

DISCUSSION

For the purpose of this study we defined incubation period as the time in days from the point of COVID-19 exposure to the onset of symptoms. Figure S3 (Supplementary Material) shows a schematic of this time period with respect to other key parameters influencing COVID-19 transmission. Studies to determine incubation period are likely most precise during the early phase of the outbreak, before the pathogen is widespread.[21] During this early phase, exposure windows can be determined with some confidence. Most studies achieved this by conducting the analysis based on travellers from an epicentre of infection (Wuhan) to another country/region that was free from infection at that time point or in the very early stages of the outbreak.

By definition, the required case data for the determination of individual incubation periods needs to include both exposure (window) and onset of symptoms. Precisely estimating these events can be difficult. Symptom onset is based on case recall, whereas exposure is determined either from: movement history, thereby providing a window prior to movement of potential exposure, or a known window of exposure (from earliest to latest) to a confirmed case (close contact). However, exposure and/or symptom onset are rarely observed exactly. The methods used to deal with this include restricting the analysis to data from patients where the exposure window could be narrowed to a short window (e.g. <3 days); taking a median point from the exposure window to determine the exposure timepoint. Alternatively, Linton et al.[24] included left exposure dates as parameters to be fitted in the model.

After the initial meta-analysis we decided to remove the Backer et al.[29] study from the pooled estimate. The estimates from that study were found to be shifted considerably to the right compared to other estimates. Examination of that study identified that many of the patients had long exposure windows which would be expected to bias the estimate upwards. Interestingly, that study conducted an additional subset analysis of patients whose exposure windows were well defined and for these data, the mean incubation period dropped from 6.4 to 4.5 days. However, it is interesting to note that Ma et al.[25] restricted their analysis to patients with a 3-day exposure window and still found a mean incubation period of 7.4 days. Since this study had the largest sample size (n = 587), it has a significant impact on the estimation of the lognormal parameters. Repeating the meta-analysis with both the Backer et al.[29] and Ma et al.[25] studies removed results in values of 1.58 (1.51, 1.64) and 0.47 (0.42, 0.53) respectively. With both of these studies removed the I^2 values drop to 0% for both parameters. The corresponding mean and median are 5.48 days and 4.85 days respectively. Interestingly, removing this study also increases the precision of the estimate of the value for mu.

One of the weaknesses of our approach is that we extracted and analysed the parameters of the lognormal distribution independently. However, in reality the parameters and the initial distribution that they are fitted to are linked. We were unable to include two studies that did not fit lognormal distributions to the data. However, Figure 6 demonstrates that the impact of removing these studies is likely to be small since they are similar to the pooled estimate, with one falling to the left of the pooled estimate, and the other falling to the right. Ideally, we would have fit distributions to the raw data available from each of the studies, in a way that facilitated the distributions to vary across studies. Such an approach was taken by Lessler et al.[3] in reviewing acute respiratory viral infections. However, the raw data were not available in all cases for the studies that we examined. Another limitation is that many of the papers included in this study used publicly available data to estimate incubation period. Therefore, there is a reasonable chance that several of the analyses have re-used at least some of the same data. In these cases, the studies would not be independent of each other.

It is worth noting that the parameter values from our meta-analysis are somewhat higher than previously used in modelling studies. For example, Ferguson et al.[32] used a mean of 5.1 days for incubation period, citing two previous studies.[24, 31] Mean incubation period from our meta analysis was 5.8. Tuite et al.[33] on the other hand, used an incubation period of 5.0 days citing the study by Lauer et al.[22] . This figure, (5.0 days) was the median incubation period reported from that study,[22] which is much closer to the median estimate of 5.1 days from our meta analysis.

It is reasonable to assume that the incubation period estimated here should be relatively generalizable across different populations: unlike parameters such as serial interval for example, incubation period depends only on the interaction between the virus and the host, which is expected to be similar across populations, and not on behavioural factors such as frequency of contacts which might be expected to vary across different countries. However, there is potential for a number of biases in these data which may impact on their external validity: In order to accurately estimate incubation period, it is possible that well characterized cases which may be preferentially chosen to reduce the impact of prolonged exposure windows. It is possible that such cases could be biased towards more severe cases. In that case, the estimate for incubation period could be biased downwards, since it is possible that the incubation period could be shorter in more severely affected individuals. Furthermore, these well characterised cases may not have been representative of all cases (often male, often younger,[29]), highlighting the need for information on incubation period from older people, people with comorbidities, from women and those with mild symptoms. These findings are mostly based on studies from Chinese patients. Whilst the incubation period for a given set of circumstances should be similar across different populations, there may be factors that might impact on incubation period, such as infectious dose for example that might vary between populations (and possibly within populations over the course of the outbreak) meaning that the resulting distribution may vary for different populations, or potentially at different stages of the outbreak. Finally, incubation periods may be different for people of different ages.[11]

Based on available evidence, we find that the incubation period distribution may be modelled with a lognormal distribution with pooled mu and sigma parameters of 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55) respectively. It should be noted that uncertainty increases towards the tail of the distribution (Figure 4 and Table 2). The choice of which parameter values are adopted will depend on how the information is used, the associated risks and the perceived consequences of decisions to be taken. The corresponding mean was 5.8 days and the median was 5.1 days. These recommendations will need to be revisited once further relevant information becomes available. Finally, we present an R Shiny app which facilitates users to update these estimates as new data become available https://mcaloon-ucd.shinyapps.io/shiny2/.

Funding: All investigators are full-time employees (or retired former employees) of University College Dublin, the Irish Department of Food and the Marine or University of Nottingham. No additional funding was obtained for this research.

Author contributions: CMA conducted the eligibility screening of shortlisted studies, extracted the data and conducted the analysis with input from all authors; ÁC, KH and FB conducted the initial literature searches; CMA and SM completed the initial drafts of the manuscript; MG and LOG reviewed the statistical methods; All authors read and approved the final manuscript.

Data statement: The data for the meta-analyses are presented as part of the manuscript (Table 2).

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Patient and public involvement statement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

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Figure 1. Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal distribution of incubation period.

Figure 2. Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal distribution

Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period with mu = 1.63 and sigma = 0.50

Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.

Figure 5. Cumulative distribution function of pooled lognormal distribution for incubation period and original input studies.

Figure 6. Probability density function of pooled lognormal distribution for incubation period and studies (n=2) not included in the meta-analysis because of the distribution used.

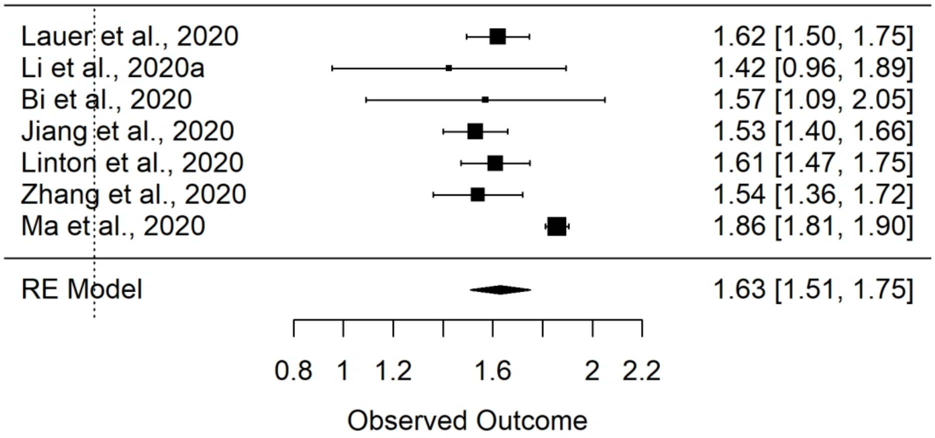

Figure 1. Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal distribution of incubation period.

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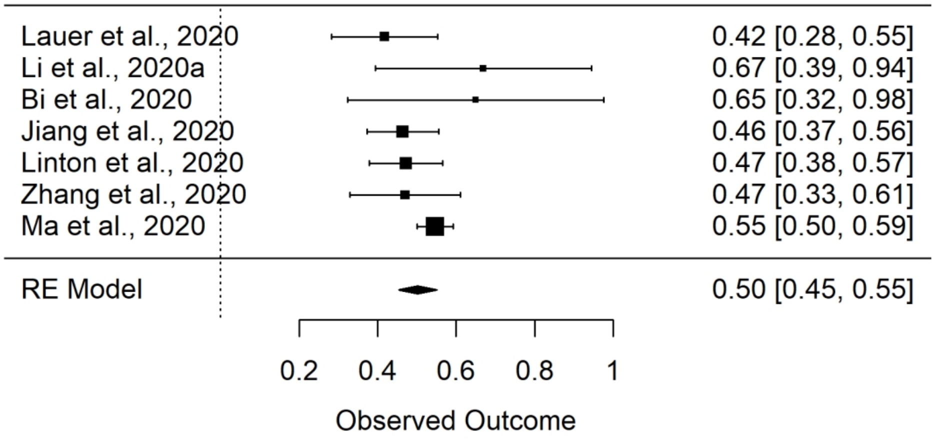

Figure 2. Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal distribution

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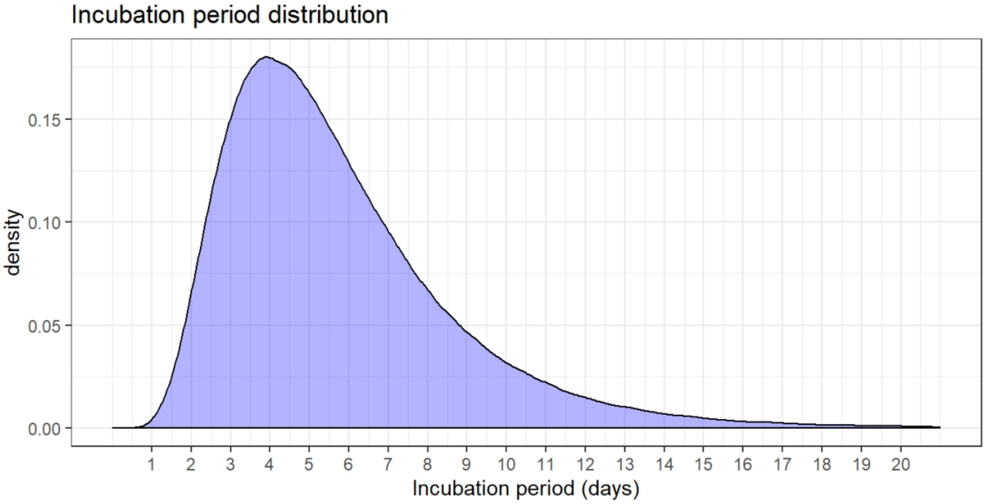

Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period with mu = 1.63 and sigma = 0.50

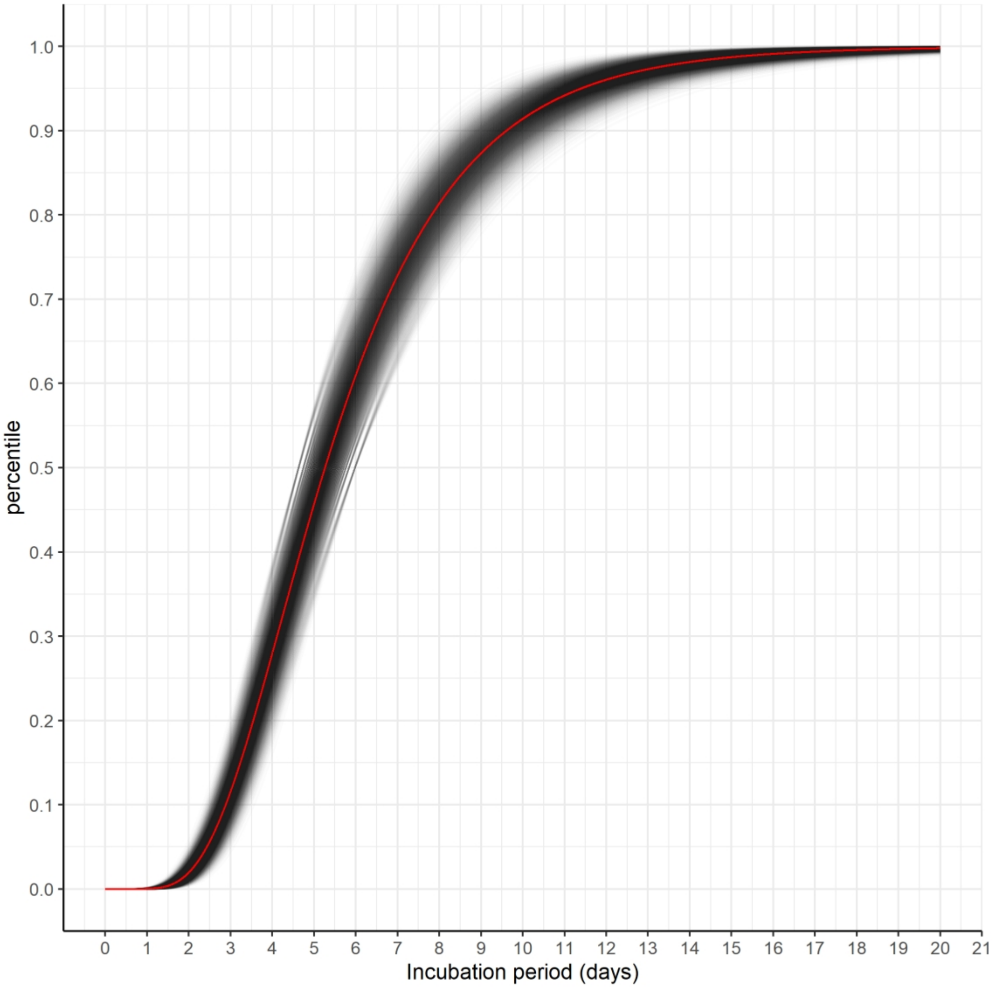

Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.

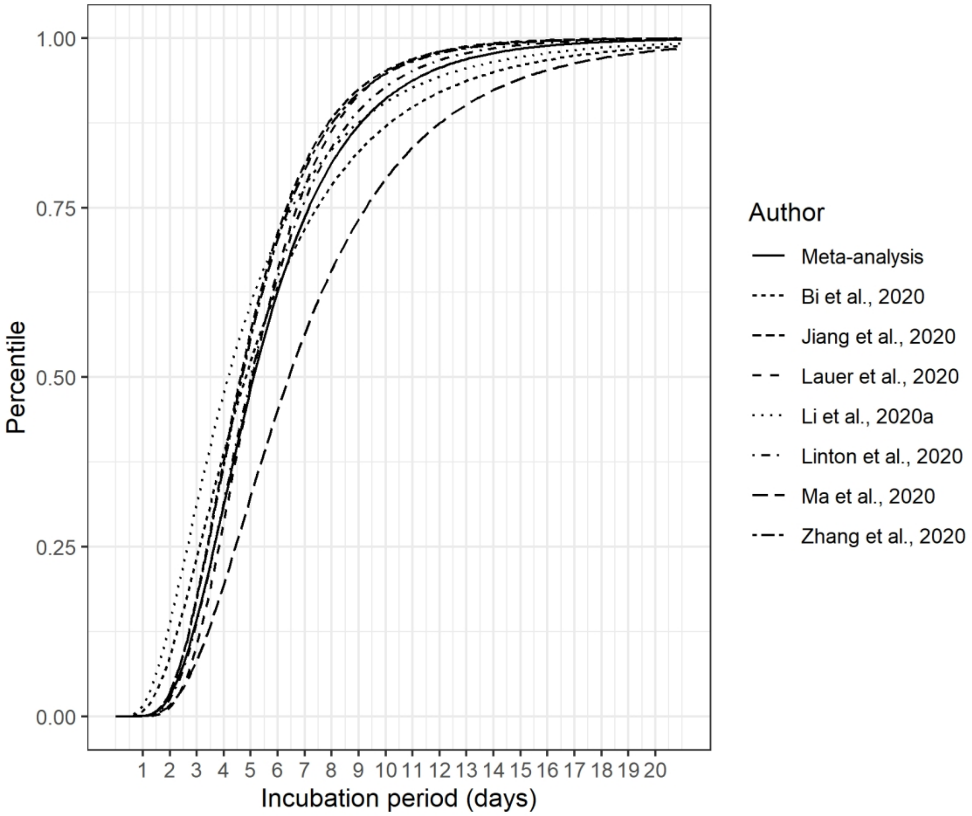

Figure 5. Cumulative distribution function of pooled lognormal distribution for incubation period and original input studies.

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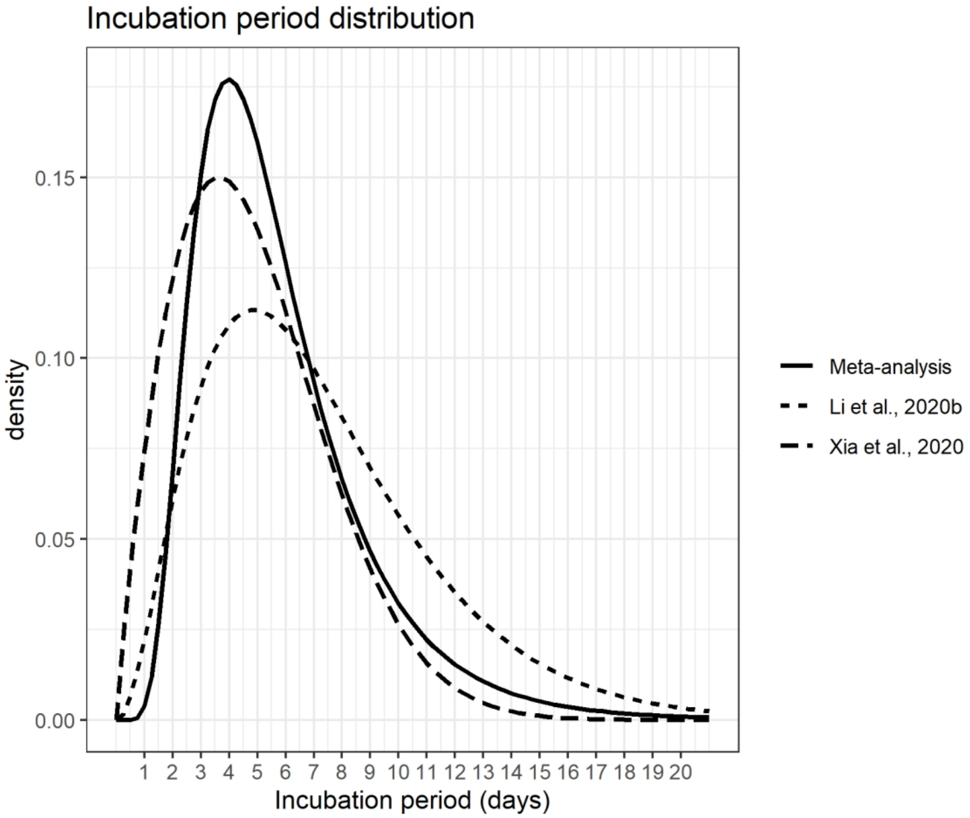


Figure 6. Probability density function of pooled lognormal distribution for incubation period and studies (n=2) not included in the meta-analysis because of the distribution used.

152x127mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Figure S1 – Funnel plot of estimates of mu parameter of the lognormal distribution

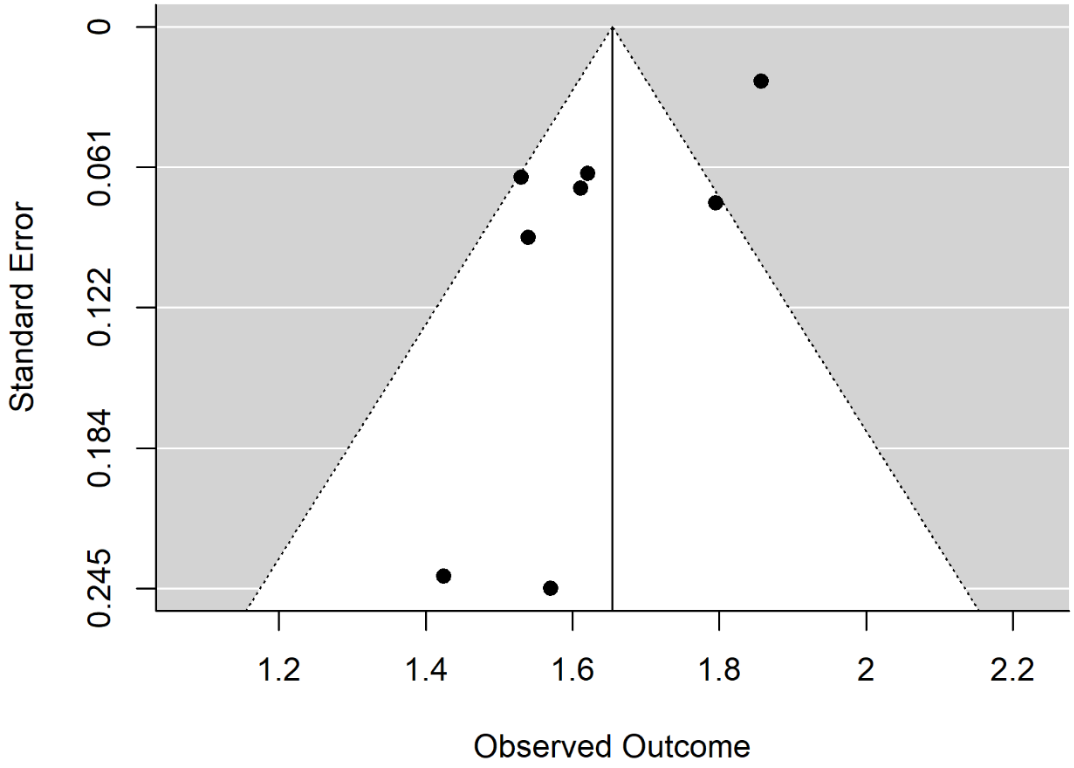


Figure S2 – Funnel plot of the sigma parameter of the lognormal distribution

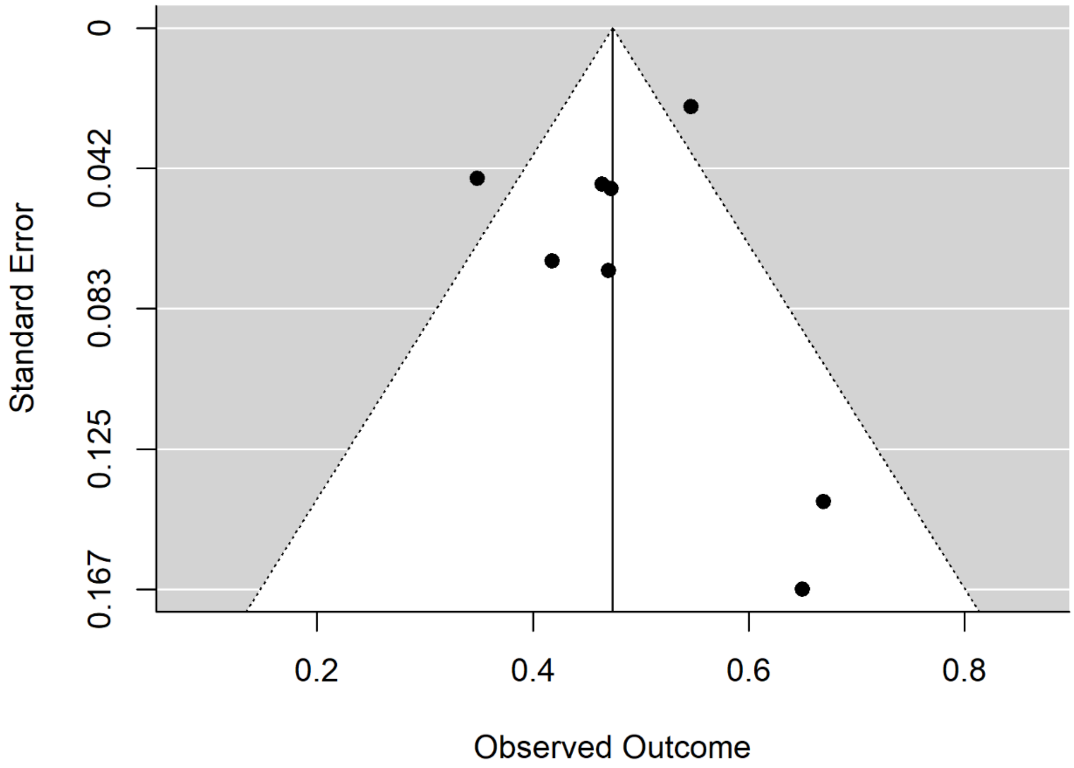
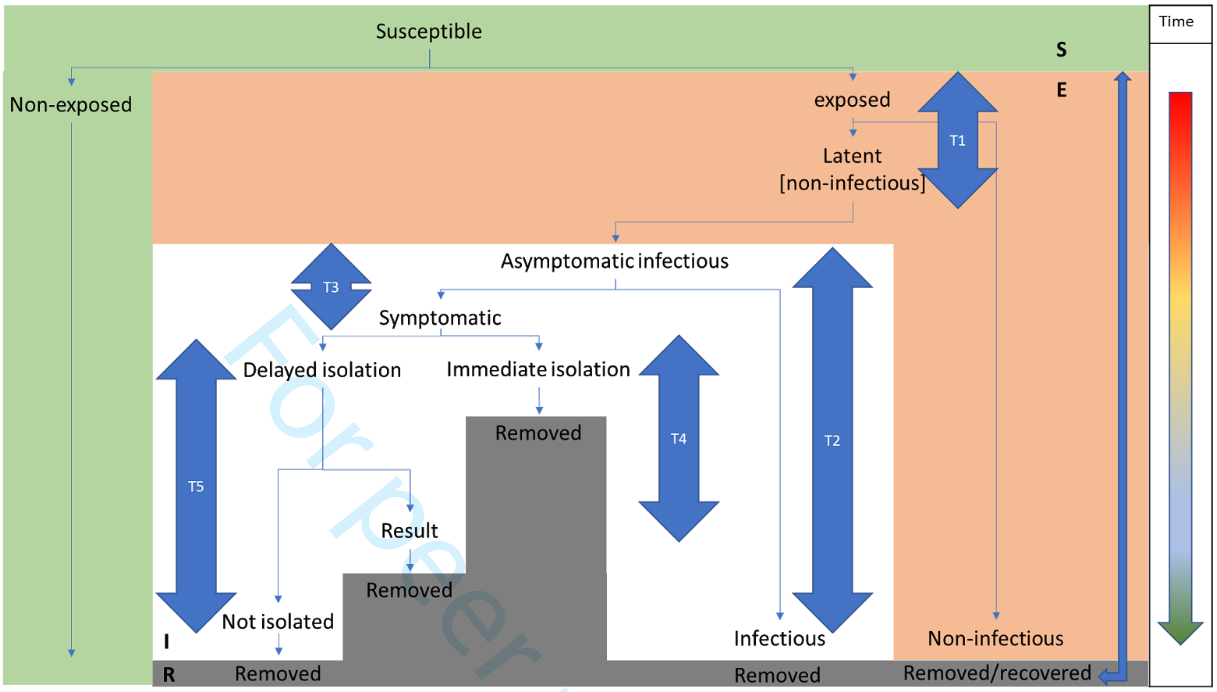


Figure S3 – Incubation period (T1 + T3) in the context of other key parameters important for the transmission of COVID-19.



Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the MOOSEreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title			
	#1	Identify the study as a meta-analysis of observational research	1
Abstract			

	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number (From PRISMA checklist)	2-3
Background			
	#3a	Problem definition	3-4
	#3b	Hypothesis statement	4
	#3c	Description of study outcomes	4-5
	#3d	Type of exposure or intervention used	4-5
	#3e	Type of study designs used	5
	#3f	Study population	5
Methods			
Search strategy	#4a	Qualifications of searchers (eg, librarians and investigators)	5
Search strategy	#4b	Search strategy, including time period included in the synthesis and keywords	5
Search strategy	#4c	Effort to include all available studies, including contact with authors	5
Search strategy	#4d	Databases and registries searched	5

Search strategy	#4e	Search software used, name and version, including special features used (eg, explosion)	5
Search strategy	#4f	Use of hand searching (eg, reference lists of obtained articles)	5
Search strategy	#4g	List of citations located and those excluded, including justification	9
Search strategy	#4h	Method of addressing articles published in languages other than English	5
Search strategy	#4i	Method of handling abstracts and unpublished studies	5
Search strategy	#4j	Description of any contact with authors	5
	#5a	Description of relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	5
	#5b	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
	#5c	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	6
	#5d	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9
	#5e	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	9

	#5f	Assessment of heterogeneity	8
	#5g	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7
	#5h	Provision of appropriate tables and graphics	8
Results			
	#6a	Graphic summarizing individual study estimates and overall estimate	Fig 1-2
	#6b	Table giving descriptive information for each study included	Table 1
	#6c	Results of sensitivity testing (eg, subgroup analysis)	10-11
	#6d	Indication of statistical uncertainty of findings	10
Discussion			
	#7a	Quantitative assessment of bias (eg. publication bias)	10
	#7b	Justification for exclusion (eg, exclusion of non–English-language citations)	13
	#7c	Assessment of quality of included studies	13
Conclusion			
	#8a	Consideration of alternative explanations for observed results	14

#8b	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15
#8c	Guidelines for future research	15
#8d	Disclosure of funding source	15

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BMJ Open

The incubation period of COVID-19 – A rapid systematic review and meta-analysis of observational research

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039652.R1
Article Type:	Original research
Date Submitted by the Author:	06-Jul-2020
Complete List of Authors:	McAloon, Conor; UCD School of Agriculture Food Science and Veterinary Medicine, School of Veterinary Medicine Collins, Aine; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Hunt, Kevin; University College Dublin, Centre for Food Safety Barber, Ann; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Byrne, Andrew; Government of Ireland Department of Agriculture Food and the Marine, One Health Scientific Support Unit Butler, Francis; University College Dublin, Centre for Food Safety Casey, Miriam; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Griffin, John Lane, Elizabeth; Government of Ireland Department of Agriculture Food and the Marine McEvoy, David; University College Dublin, School of Public Health, Physiotherapy and Sports Science Wall, Patrick; University College Dublin, Public health Green, Martin; University of Nottingham, School of Veterinary Medicine and Science O'Grady, Luke; University of Nottingham, School of Veterinary Medicine and Science; University College Dublin, School of Veterinary Medicine More, SImon; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Epidemiology < INFECTIOUS DISEASES, EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES

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TITLE PAGE

Title: The incubation period of COVID-19 – A rapid systematic review and meta-analysis of observational research

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Word Count: 4344

Key words: "COVID-19"; "Incubation period"; "Meta-analysis"

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ABSTRACT

Objectives: The aim of this study was to conduct a rapid systematic review and meta-analysis of estimates of the incubation period of COVID-19.

Design: Rapid systematic review and meta-analysis of observational research

Setting: International studies on incubation period of COVID-19

Participants: Searches were carried out in PubMed, Google Scholar, Embase, Cochrane library as well as the pre-print servers MedRxiv and BioRxiv. Studies were selected for meta-analysis if they reported either the parameters and confidence intervals of the distributions fit to the data, or sufficient information to facilitate calculation of those values. After initial eligibility screening, 24 studies selected for initial review, 9 of these were shortlisted for meta-analysis. Final estimates are from meta-analysis of 8 studies.

Primary outcome measures: Parameters of a lognormal distribution of incubation periods.

Results: The incubation period distribution may be modelled with a lognormal distribution with pooled mu and sigma parameters (95% confidence intervals) of 1.63 (1.51, 1.75) and 0.50 (0.46, 0.55) respectively. The corresponding mean (95% confidence intervals) was 5.8 (5.0, 6.7) days. It should be noted that uncertainty increases towards the tail of the distribution: the pooled parameter estimates (95% confidence intervals) resulted in a median incubation period of 5.1 (4.5, 5.8) days, whereas the 95th percentile was 11.7 (9.7, 14.2) days.

Conclusions: The choice of which parameter values are adopted will depend on how the information is used, the associated risks and the perceived consequences of decisions to be taken. These recommendations will need to be revisited once further relevant information becomes available. Accordingly, we present an RShiny app that facilitates updating these estimates as new data become available.

Key words: "COVID-19"; "Incubation period"; "Meta-analysis"

ARTICLE SUMMARY

Strengths and limitations of this study

- This study provides a pooled estimate of the distribution of incubation periods which may be used in subsequent modelling studies or to inform decision-making
- Several studies used data that was publicly available, therefore there is potential that some the data may be used for more than one study.
- This estimate will need to be revisited as subsequent data become available. Accordingly, we present an RShiny app to allow the meta-analysis to be updated with new estimates

INTRODUCTION

Reliable estimates of the incubation period are important for decision making around the control of infectious diseases in human populations. Knowledge of the incubation period can be used directly to inform decision-making around infectious disease control. For example, the maximum incubation period can be used to inform the duration of quarantine, or active monitoring periods of people who have been at high risk of exposure. Estimates of the duration of the incubation period, coupled with estimates of the latent period, serial interval or generation times, may help infer the duration of the pre-symptomatic infectious period, which is important in understanding both the transmission of infection and opportunities for control.[1] Finally, decision making in the midst of a pandemic often relies on predicted events, such as daily number of new infections, from mathematical models. Such models depend on key input parameters relevant to the transmission of the specific infectious disease. It is important that input parameters into such models are as robust as possible. Given that some models fit data to many parameters, only some of which are specifically of interest but all of which are interdependent, output estimates may be compared to the robust estimates as part of the validation of the model.

Earlier work has shown that for models of respiratory infections, statements regarding incubation periods are often poorly referenced, inconsistent, or based on limited data.[2] To date, many COVID-19 models have used input values from a single study. The decision on which study to use may vary from model to model. Recently, a systematic review of the epidemiological characteristics of COVID-19 reported that estimates of the central tendency of the incubation period ranged from 4-6 days. [3] However to the authors' knowledge no studies have yet sought to estimate the incubation period through a meta-analysis of data available to date. Furthermore, it is important to note that incubation periods are expected to vary across individuals within the population. For this reason, it is critically important to understand the variation in incubation periods (i.e. the distribution) within the population. However, a single measure of central tendency (i.e. mean or median) cannot adequately represent this variation. [4] To address this, studies often fit mathematical distributions to incubation period data.

We hypothesized that a pooled estimate of the distribution of incubation periods could be obtained through a meta-analysis of data published to date. Therefore, the aim of this study was to conduct a rapid systematic review and meta-analysis of estimates of the incubation periods of COVID-19, defined as the period of time (in days) from virus exposure to the onset of symptoms. Specifically, we aimed to find a pooled estimate for the parameters of an appropriate distribution that could be subsequently used as an input in modelling studies and that might help quantify uncertainty around the key percentiles of the distribution as an aid to decision making.

MATERIALS AND METHODS

For the purpose of this study we followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[5] The outcome was defined as the time in days from the point of exposure, (in this case, infection) to the onset of clinical signs; all observational studies were included in the analysis. Finally, the population was confirmed infected individuals, where an exposure time could be ascertained with some degree of certainty and precision.

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Search methodology, initial screening and categorisation

A survey of the literature between 1 December 2019 and 8th April 2020 for all countries was implemented using the following search strategy. Publications on the electronic databases PubMed, Google Scholar, Embase, Cochrane library as well as the pre-print servers MedRxiv and BioRxiv were searched with the following keywords: "Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19" AND "incubation period" OR "incubation" (Table S1, Supplementary Material). The dynamic curated PubMed database "LitCovid" was also monitored, in addition to national and international government reports. No restrictions on language or publication status were imposed so long as an English abstract was available. Articles were evaluated for data relating to the aim of this review, and all relevant publications were considered for possible inclusion. Bibliographies within these publications were also searched for additional resources. The initial searches were carried out by three of the investigators (ÁC, KH, FB). Authors of studies were contacted only to clarify reporting queries.

Initial study appraisal and selection for meta-analysis

Results of searches were screened in two stages. Firstly, titles and abstracts were screened, and only relevant articles retained. Studies were removed if they dealt with specific cohorts of cases that did not reflect the overall population. Next, articles were read in detail, studies were selected for meta-analysis if they reported either the parameters and confidence intervals of the distributions fit to the data, or sufficient information to facilitate calculation of those values. Specifically, this included studies that reported: the point estimate and confidence intervals or standard errors of each parameter; the mean and standard deviation on the original (non-transformed) scale with confidence intervals; the mean and one or more percentiles of the distribution (with confidence intervals); or two or more percentiles of the distribution (with confidence intervals). Studies were excluded if they described the distribution (e.g. with mean, median, percentile) but did not report any uncertainty around that figure. The selection of studies to include in the meta-analysis was conducted by the primary author (CMA).

Quality assessment of shortlisted studies

Once studies were shortlisted, two authors (CMA, SJM) independently conducted appraisals of study quality. To the authors' knowledge, no quality assessment tools are available to appraise studies reporting the incubation period of infectious disease. We used The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses [6] as a basis and modified it according to important quality and reporting indicators for studies investigating incubation period. In particular, fields were added which assessed the accuracy and precision with which the exposure windows were defined. Fields relevant to non-exposed cohorts were removed. Finally, we replaced the 'star' system with a lettered categorical system for each item on the scale. The modified scale is provided as supplementary material. (Supplementary Material). After both authors had appraised the studies, the results were compared and differences in scores resolved through discussion until a consensus was reached.

Data extraction

On initial appraisal, it was apparent that the majority of studies fitted a lognormal distribution to the data. Earlier work has shown that this distribution is appropriate for many acute infectious diseases.[2, 7] Therefore, the study proceeded as the meta-analysis (pooled estimate) of the parameters of this distribution.

A variable (X) has a lognormal distribution when the log-transformed values follow a normal distribution with mean, mu, and variance, sigma^2, i.e.:

ln(X) ~ N(mu, sigma^2)

Methods exist for the meta-analysis of studies that combine a mix of log transformed and non-transformed data.[8] In this case we opted to transform data, where possible to the log-transformed scale, and obtain a pooled estimate of both mu and sigma.

Calculation of distribution parameters from each study

Where the values for each parameter (mu and sigma) were available from the studies, along with corresponding confidence intervals/standard errors, these were extracted as reported. In the remaining studies, the values were calculated where possible from the information presented.

Calculation of mu and sigma from studies reporting the mean and standard deviation of the lognormal distribution on the original scale.

The mu and sigma parameters of the original lognormal distribution were calculated as:

$$mu = \ln{(m)} - \frac{sigma^2}{2}$$

$$sigma = \sqrt{\ln\left(\frac{v}{m^2}+1\right)}$$

Where v = variance (= sd^2), and m = the mean of the distribution on the original (i.e. non-log transformed) scale.

Similarly upper and lower confidence intervals of mu and sigma were found by substituting the upper and lower bounds of the mean or standard deviation (from the original scale) into the equation above, one at a time, whilst holding the value for the other parameter constant (as the point estimate for that parameter).

Calculation of mu and sigma from studies reporting mean and percentiles on the original scale

Where studies reported the results as the mean and 95th percentile on the original scale, the "lognorm" package in R was used to calculate the original values of mu and sigma and corresponding standard errors or confidence intervals.[9]

Calculation of variance of mu and sigma

For studies reporting confidence intervals, the standard error was calculated as (upper bound – lower bound)/(2 x 1.96). Finally, for studies reporting the parameters relative to a referent value, the standard error was calculated as:

$$\sqrt{SE1^2 + SE2^2}$$

Where SE1 and SE2 are the standard errors of the estimate of the referent category and coefficient respectively.

Meta-analysis

A random effects meta-analysis was conducted in R-studio Version 1.2.5033,[10] using the "metafor" package,[11] of the mu and sigma parameters of the lognormal distribution, specifying the point estimate and the standard error using "yi" (i.e. the point estimate) and "sei" (i.e. the standard error) arguments. Forest plots were produced using the same package. Quantitative estimates of bias were obtained using the Egger's test and funnel plots. Heterogeneity was quantified using the I^2 statistic and investigated by conducting subgroup analyses of the dataset.

Calculation of the se of the mean and sd on the original scale from pooled estimates of mu and sigma

The mean and standard deviation of the pooled estimate were converted to the original (i.e. non-log transformed) scale as:

$$\text{Mean} = e^{\left(mu + \frac{sigma^2}{2}\right)}$$

$$\text{SD} = \sqrt{e^{(2 \times mu + sigma^2)} \times e^{(sigma^2 - 1)}}$$

The upper and lower confidence intervals were found by substituting, one at a time, the upper and lower bounds for mu and sigma and recalculating the subsequent figures for mean and SD.

The resulting distribution was plotted using the "ggplot2" package in R.[12] In addition, the distributions for studies that did not fit a lognormal distribution, but that reported the parameters of an alternative distribution fitted were also plotted alongside the pooled lognormal distribution.

Finally, an R Shiny app was created which allows the meta-analysis estimates to be updated as new data become available.

RESULTS

After initial search and selection of relevant papers and removing duplicates, 24 studies were available for appraisal.

- Two papers were removed as they dealt with specific cohorts of cases – young adults [13] and children.[14]
- One study was removed since only the abstract was in English and there was not enough detail to extract the relevant results.[15]
- Several papers were removed since they contained insufficient data or methods description to facilitate their inclusion:
    - One study was removed since there was not enough detail in the paper to determine whether new parameters were being estimated or whether the parameters quoted were input values for their model.[16]
    - Seven papers were removed since the data were largely descriptive, with no confidence intervals reported.[17-23]
    - One study was removed because the error terms associated with the mean, median and percentiles were not reported and there was not enough information presented to recover the parameters of the lognormal distribution.[24]
    - One study was removed [25] since a novel statistical approach was employed that likely resulted in a significantly higher incubation period estimate to other studies.

Of the shortlisted studies (n=11), six reported lognormal distributions as best fitting the data. [26-31] Of the remaining 4, one reported that several distributions were trialled but it was not clear which distribution was used for the final estimates.[32] However, these authors provided raw data which we used to fit the parameters of the lognormal distribution using the "rriskDistributions" package.[33] The remaining 4 studies reported that either Weibull or gamma distributions fitted the data better. Of these, 2 study also presented the results of a log normal distribution fit to the data [34, 35], facilitating their inclusion in the subsequent analysis. One of these studies [35] reported the incubation period for two distinct cohorts: travellers and non-travellers to Hubei. The estimates for the cohorts were significantly different. The author suggested that this difference was possibly explained by multiple exposures in the traveller cohort. Therefore, we chose to only use the estimates reported for the non-traveller cohort in our analysis.

The final two studies reporting a Weibull [36] and a gamma distribution [37] were removed from further analysis at this stage, however, those distributions were plotted over the final distribution to evaluate the impact of removing those estimates. The characteristics of the final studies as well as the final mu and sigma values used for meta-analysis are shown in Table 1.

237 **Table 1.** Study size and extracted data for the lognormal mu and sigma parameters from the 9 studies that were used for meta-analysis.

Author	**n**	**Publication status 1st July 2020**	**Location**	**Observation period**	**Mean (*Median) (days)**	**97.5th (*95th) percentile (days)**	**Lognormal parameters used in meta-analysis**			
							mu	**se**	**sigma**	**se**
Backer et al., 2020	88	PR	Chinese and international - travellers from Wuhan	20th Jan – 28th Jan	6.4	11.1	1.796	0.077	0.349	0.045
Lauer et al., 2020	181	PR	Chinese and international - travellers from known affected areas	4th Jan – 24th Feb	5.5	11.5	1.621	0.064	0.418	0.069
Li et al., 2020	10	PR	Early cases in Wuhan	1st Dec - 31st Jan	5.2	12.5*	1.425	0.240	0.669	0.141
Bi et al., 2020	183	PR	Shenzhen - travellers from Wuhan	14th Jan - 12th Feb	4.8*	14.0	1.570	0.245	0.650	0.167
Jiang et al., 2020	40	PP	Location unclear	14th Dec - 8th Feb	4.9	9.7*	1.530	0.066	0.464	0.046
Linton et al., 2020	158	PR	Cases external to Wuhan	Start of epidemic until 31st Jan	5.6	10.8*	1.611	0.070	0.472	0.048
Zhang et al., 2020	49	PR	China - provinces other than Hubei	Start of epidemic until 27th Feb	5.2	10.5*	1.540	0.092	0.470	0.072
Ma et al., 2020	587	PP	Multiple countries including China	Not specified	7.4	17	1.857	0.024	0.547	0.023
Leung, 2020	[1]61	PR	China – provinces other than Hubei	10th Jan - 12th Feb	7.2	14.6	1.780	0.353	0.680	0.248

238 [1]Inferred from data reported

239 PR = Published, peer-reviewed; PP = Pre-print, not peer-reviewed

Quality assessment (Table S2, Supplementary Material) indicated that few studies precisely outlined the exposure windows and symptom onset windows that were used in their studies. Several studies reported that they conducted analysis on a small cohort of well characterized cases. Likely this only includes individuals with short (1-day) exposure and symptom onset windows. However, this was not clearly reported in several studies.

The initial pooled estimate of mu from this dataset (i.e. dataset 1, n=8 studies) was 1.66 (1.55, 1.76) and the pooled estimate of sigma was 0.48 (0.42, 0.54). The I^2 values were 75% and 56% for mu and sigma respectively. Egger's tests for mu and sigma were not statistically significant; p=0.31 and p=0.20 for mu and sigma respectively. However, evaluation of the funnel plots (Figures S1 and S2 Supplementary Material) suggests the potential for bias associated with one of the studies included in the analysis.[30] Evaluation of the meta-analyses results for mu demonstrated that two studies were responsible for much of the heterogeneity in the analysis of this value. In particular, the values reported by Ma et al. [30] and Backer et al. [34] were higher than the estimates from other studies. Both studies were further evaluated to determine whether these differences may have been due to methodological differences. The Backer et al. [34] study was subsequently excluded since it appeared that the exposure window was somewhat imprecisely defined which would have biased this estimate upwards. Conversely, the study reported by Ma et al. [30] used only patients where the exposure window was 3 days or less, with the majority of those of a 1-day duration. The meta-analysis was repeated with the Backer et al. [34] study removed (i.e. dataset 2, n=7 studies). The resulting pooled estimates were 1.63 (1.51, 1.75) and 0.50 (0.46, 0.55), whilst the I^2 values were 75% and 24% for mu and sigma respectively. Figures 1 and 2 show the resulting forest plots for the meta-analyses of mu and sigma respectively from dataset 2 (n=8), that is the 9 studies from which the parameters were extracted, minus the Backer et al. [34] estimate.

<Figure 1 here>

<Figure 2 here>

264 Figure 3 shows the resulting density plot of the pooled distribution. Figure 4 shows the cumulative density function plot of the same (pooled distribution). In this instance, all possible combinations of distributions across the 95% confidence intervals of the estimates of each of the mu and sigma values are plotted on the same graph. Table 2 shows the percentiles and corresponding confidence intervals of the pooled lognormal distribution.

269 <Figure 3 here>

270 <Figure 4 here>

271

272 **Table 2.** Percentiles of the pooled log normal distribution after simulating all possible combinations of mu and sigma within the 95% confidence intervals of the pooled estimates of both parameters. The median days for each percentile are shown along with the minimum and maximum values for that percentile.

Percentile	**Median (days)**	**min**	**max**	**Difference (max – min)**
2.5th	1.92	1.54	2.38	0.84
5th	2.24	1.83	2.75	0.92
10th	2.69	2.24	3.23	0.99
25th	3.64	3.12	4.25	1.13
50th	5.10	4.53	5.75	1.22
75th	7.15	6.13	8.34	2.21
90th	9.69	8.06	11.60	3.54
95th	11.60	9.49	14.20	4.71

97.5th	13.60	10.9	16.90	6.00

Figure 5 shows the cumulative density function plots of the pooled lognormal distribution along with the estimates from the original studies. Finally, Figure 6 shows the probability density function of the pooled lognormal distribution, plotted alongside the two studies that could not be included in the final meta-analysis due to the fact that they fit alternative distributions to the data.

<Figure 5 here>

<Figure 6 here>

DISCUSSION

For the purpose of this study we defined incubation period as the time in days from the point of COVID-19 exposure to the onset of symptoms. Figure S3 (Supplementary Material) shows a schematic of this time period with respect to other key parameters influencing COVID-19 transmission. Studies to determine incubation period are likely most precise during the early phase of the outbreak, before the pathogen is widespread.[26] During this early phase, exposure windows can be determined with some confidence. Most studies achieved this by conducting the analysis based on travellers from an epicentre of infection (Wuhan) to another country/region that was free from infection at that time point or in the very early stages of the outbreak.

Issues with ascertaining incubation period in primary studies

By definition, the required case data for the determination of individual incubation periods needs to include both exposure (window) and onset of symptoms. Precisely estimating these events can be difficult. Symptom onset is based on case recall, whereas exposure is determined either from: movement history, thereby providing a window prior to movement of potential exposure, or a known window of exposure (from earliest to latest) to a confirmed case (close contact). However, exposure and/or symptom onset are rarely observed exactly. The methods used to deal with this include restricting the analysis to data from patients where the exposure window could be narrowed to a short window (e.g. <3 days); taking a median point from the exposure window to determine the exposure timepoint. Alternatively, Linton et al.[29] included left exposure dates as parameters to be fitted in the model. However, several studies did not report the duration of the exposure and symptom onset windows for cases used in their analyses. In many cases, these were described as “well characterized” cohorts of cases and likely only included 1-day windows, however, we recommend that future studies explicitly report if this is the case.

Investigating heterogeneity

After the initial meta-analysis we decided to remove the Backer et al.[34] study from the pooled estimate. The estimates from that study were found to be shifted considerably to the right compared to other estimates. Examination of that study identified that many of the patients had long exposure windows which would be expected to bias the estimate upwards. Interestingly, that study conducted an additional subset analysis of patients whose exposure windows were well defined and for these data, the mean incubation period dropped from 6.4 to 4.5 days. However, it is interesting to note that Ma et al.[30] restricted their analysis to patients with a 3-day exposure window and still found a mean incubation period of 7.4 days. Since this study had the largest sample size (n = 587), it has a significant impact on the estimation of the lognormal parameters. Repeating the meta-analysis with both the Backer et al.[34] and Ma et al.[30] studies removed results in values of 1.58 (1.51, 1.64) and 0.47 (0.42, 0.53) respectively. With both of these studies removed the I^2 values drop to 0% for both parameters. The corresponding mean and median are 5.48 days and 4.85 days respectively. Interestingly, removing this study also increases the precision of the estimate of the value for mu.

Weaknesses and limitations

One of the weaknesses of our approach is that we extracted and analysed the parameters of the lognormal distribution independently. However, in reality the parameters and the initial distribution that they are fitted to are linked. We were unable to include two studies that did not fit lognormal distributions to the data. However, Figure 6 demonstrates that the impact of removing these studies is likely to be small since they are similar to the pooled estimate, with one falling to the left of the pooled estimate, and the other falling to the right. Ideally, we would have fit distributions to the raw data available from each of the studies, in a way that facilitated the distributions to vary across studies. Such an approach was taken by Lessler et al.[2] in reviewing acute respiratory viral infections. However, the raw data were not available in all cases for the studies that we examined. Another limitation is that many of the papers included in this study used publicly available data to estimate incubation period. Therefore, there is a reasonable chance that several of the analyses have re-used at least some of the same data. In these cases, the studies would not be independent of each other. Finally, since this study was conducted as a rapid review, we did not seek raw data from studies that were excluded, nor did we seek to translate studies that were not published in English. However, we provide a R ShinyApp (https://mcaloon-ucd.shinyapps.io/shiny2/) which facilitates testing the sensitivity of our pooled estimate to the inclusion of a single new study. This analysis demonstrates that our pooled estimate is largely unaffected by new estimates. Trialing the inclusion of a new study that reports considerably different estimates of the incubation period has very little impact on the overall pooled estimate.

Comparison with values used in epidemiological modelling studies

It is worth noting that the parameter values from our meta-analysis are somewhat higher than previously used in modelling studies. For example, Ferguson et al.[38] used a mean of 5.1 days for incubation period, citing two previous studies.[29, 37] Mean incubation period from our meta analysis was 5.8. Tuite et al.[39] on the other hand, used an incubation period of 5.0 days citing the study by Lauer et al.[27] . This figure, (5.0 days) was the median incubation period reported from that study,[27] which is much closer to the median estimate of 5.1 days from our meta analysis.

External validity

It is reasonable to assume that the incubation period estimated here should be relatively generalizable across different populations: unlike parameters such as serial interval for example, incubation period depends only on the interaction between the virus and the host, which is expected to be similar across populations, and not on behavioural factors such as frequency of contacts which might be expected to vary across different countries. However, there is potential for a number of biases in these data which may impact on their external validity: In order to accurately estimate incubation period, it is possible that well characterized cases which may be preferentially chosen to reduce the impact of prolonged exposure windows. It is possible that such cases could be biased towards more severe cases. In that case, the estimate for incubation period could be biased downwards, since it is possible that the incubation period could be shorter in more severely affected individuals. Furthermore, these well characterised cases (i.e. those cases where exposure windows and dates of symptom onset are determined with a high degree of certainty) may not have been representative of all cases (often male, often younger,[34]), highlighting the need for information on incubation period from older people, people with comorbidities, from women and those with mild symptoms. These findings are mostly based on studies from Chinese patients. Whilst the incubation period for a given set of circumstances should be similar across different populations, there may be factors that might impact on incubation period, such as infectious dose for example that might vary between populations (and possibly within populations over the course of the outbreak) meaning that the resulting distribution may vary for different populations, or potentially at different stages of the outbreak. Incubation periods may also be different for people of different ages.[13] Finally, a recent study has also suggested that patients undergoing surgery during the incubation period may have an accelerated progression to clinical signs, suggesting that those experiencing severe stresses during the incubation period may have a shorter time to the onset of clinical signs. [40]

Conclusion

Based on available evidence, we find that the incubation period distribution may be modelled with a lognormal distribution with pooled mu and sigma parameters of 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55) respectively. It should be noted that uncertainty increases towards the tail of the distribution (Figure 4 and Table 2). The choice of which parameter values are adopted will depend on how the information is used, the associated risks and the perceived consequences of decisions to be taken. The corresponding mean was 5.8 days and the median was 5.1 days. These recommendations will need to be revisited once further relevant information becomes available. Accordingly, we present an R Shiny app which facilitates users to update these estimates as new data become available https://mcaloon-ucd.shinyapps.io/shiny2/.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Author contributions: CM conducted the eligibility screening of shortlisted studies, extracted the data and conducted the analysis with input from all authors; ÁC, KH and FB conducted the initial literature searches; CM and SM completed the initial drafts of the manuscript; MG and LOG reviewed the statistical methods; All authors (CM, ÁC, KH, AB, AWB, FB, MC, JG, EL, DM, PW, MG, LOG, SM) read and approved the final manuscript.

Data statement: The data for the meta-analyses are presented as part of the manuscript (Table 2).

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Patient and public involvement statement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

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Figure 1. Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal distribution of incubation period.

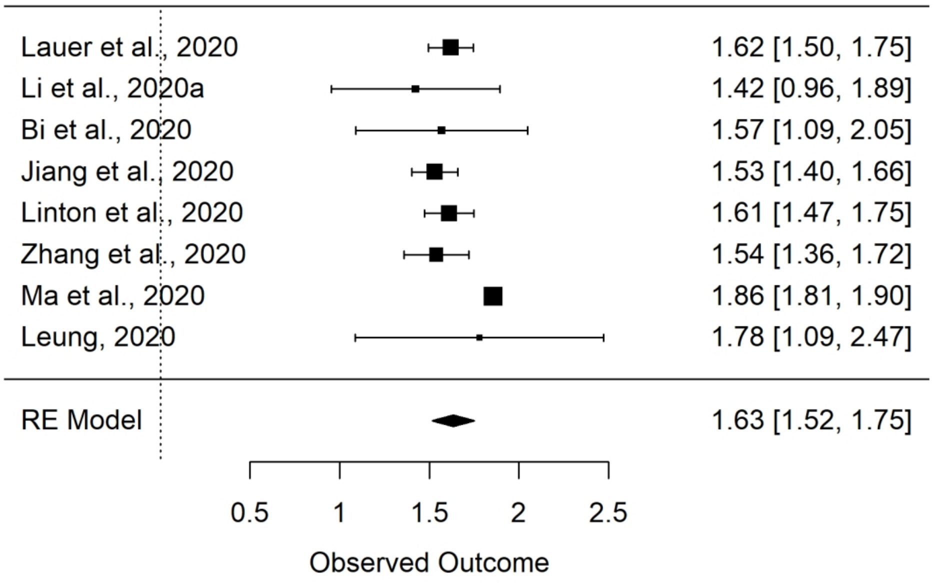
Figure 2. Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal distribution

Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period with mu = 1.63 and sigma = 0.50

Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.

Figure 5. Cumulative distribution function of pooled lognormal distribution for incubation period and original input studies.

Figure 6. Probability density function of pooled lognormal distribution for incubation period and studies (n=2) not included in the meta-analysis because of the distribution used.



Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal distribution of incubation period.

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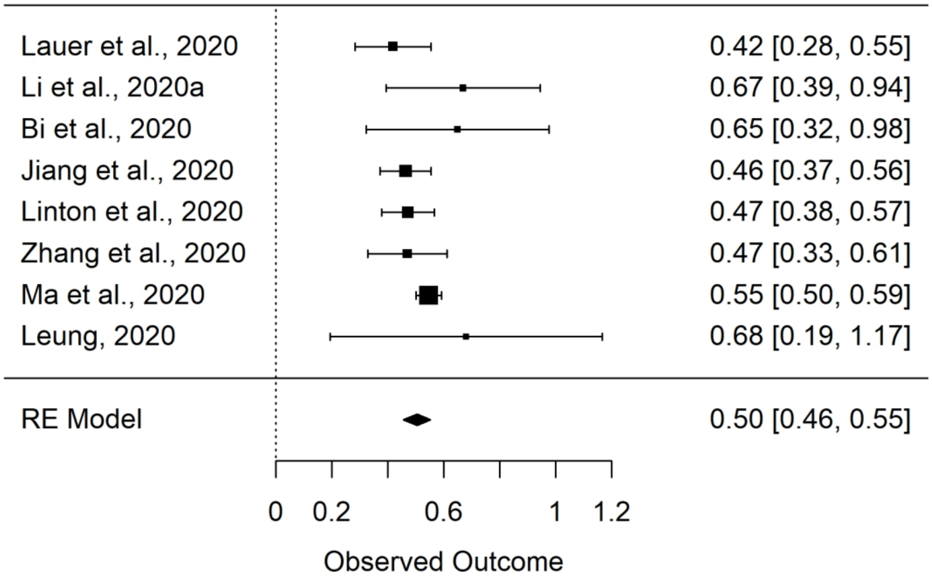

Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal distribution of incubation period.

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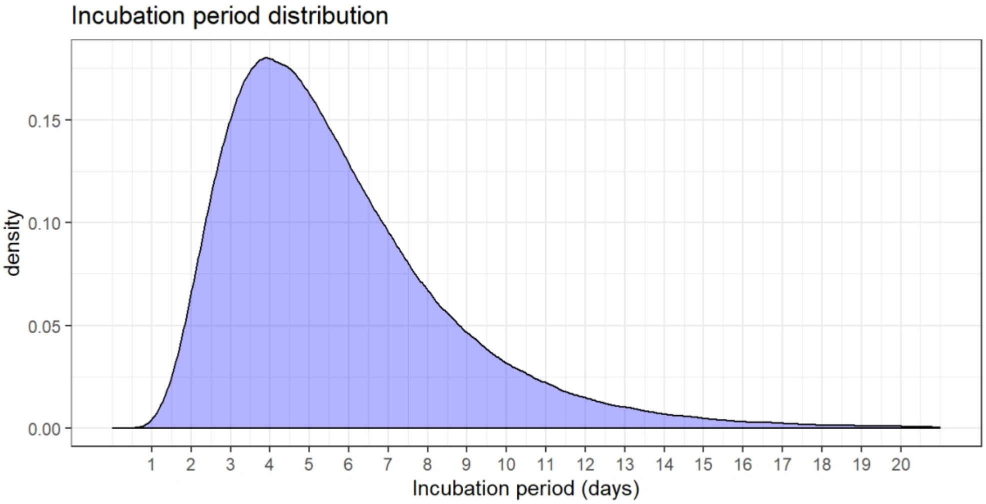


Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period with mu = 1.63 and sigma = 0.50

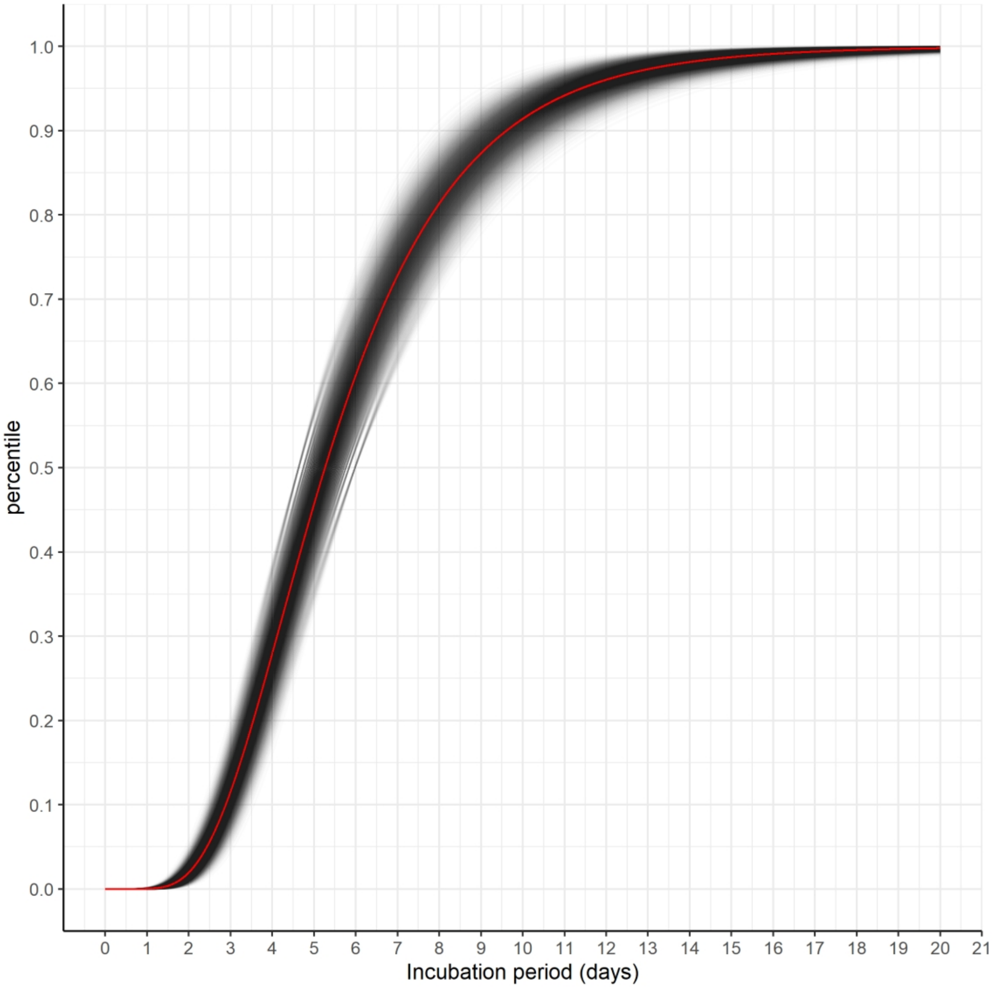
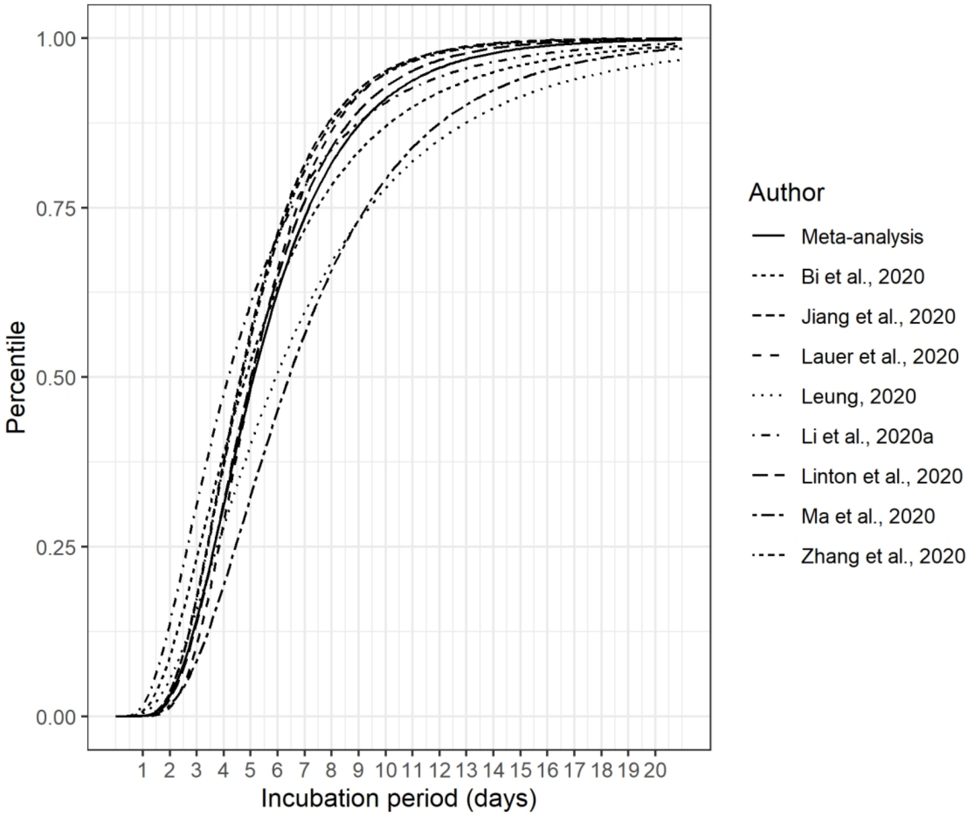


Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.



Cumulative distribution function of pooled lognormal distribution for incubation period and original input studies.

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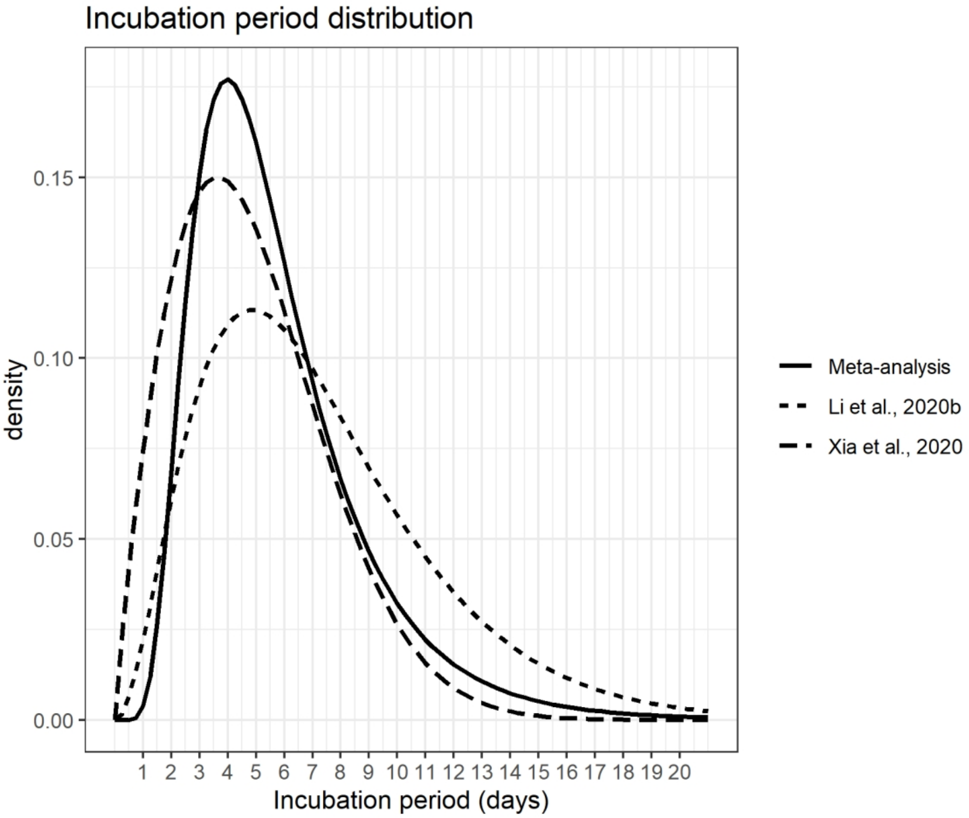

Figure 6. Probability density function of pooled lognormal distribution for incubation period and studies (n=2) not included in the meta-analysis because of the distribution used.

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SUPPLEMENTARY MATERIAL

Table S1. Search strategies for meta-analysis of observational studies reporting the Incubation period of COVID-19.

Database	**Search strategy (publications accessible 1st Dec 2019-8th April 2020)**
Pubmed	(“Novel coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR “COVID-19”) AND (“incubation period” OR “incubation”)
Cochrane	(“Novel coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR “COVID-19”) AND (“incubation period” OR “incubation”)
Google Scholar	(“Novel coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR “COVID-19”) AND (“incubation period” OR “incubation”)
Embase	(“Novel coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR “COVID-19”) AND (“incubation period” OR “incubation”)
Preprint servers (i.e. preliminary reports of work that have not been peer-reviewed)	
medRxiv and bioRxiv	Pre populated search: https://connect.medrxiv.org/relate/content/181

Quality assessment scale – adapted from Newcastle-Ottawa quality assessment scale for cohort studies.

External validity

1) <u>Representativeness of the study cohort</u>

a) No selection of cases based on age, sex or general health status, supported by descriptive statistics demonstrating comparability with overall population✹

b) No selection of cases based on age, sex or general health status, not supported by descriptive statistics✹

c) Cases are likely to be biased towards those with more severe COVID-19 symptoms due to selection process – e.g. records from hospitalised patients

d) Cases are selected (e.g. based on age or sex) to represent a particular cohort of individuals

e) No description of the derivation of the cohort

Internal validity

Exposure window

2) <u>Ascertainment of exposure</u>

- a) original data collected through interview ✹
- b) travel period only ✹
- c) secondary data (using publicly available reports)

<u>3) Precision of the exposure window for cases used in final analysis</u>

- a) only includes cases with a 1-day exposure window ✹
- b) only includes cases with less than or equal to 3-day exposure window
- c) includes cases with a range of exposure windows but statistical methods are used to account for this
- d) includes cases with a range of exposure windows
- e) no description/not clear

Outcome

4) <u>Assessment of outcome</u> (onset of symptoms)

- a) original data collected through interview ✹
- b) no description/not clear

<u>5) Precision of estimate of outcome</u>

- a) Precise date ✹
- b) Window
- c) no description/not clear

Table S2 Quality assessment of final studies used in the meta-analysis of incubation period

Study	**Quality assessment item category**				
	1	**2**	**3**	**4**	**5**
Backer et al., 2020	a	b	c	a	a
Lauer et al., 2020	a	b	c	a	b
Li et al., 2020	a	a	e	a	a
Bi et al., 2020	a	a	c	a	a
Jiang et al., 2020	b	c	e	b	c
Linton et al., 2020	b	b	c	b	a
Zhang et al., 2020	b	a	e	a	a
Ma et al., 2020	b	c	b	b	a
Leung, 2020	b	c	c	b	a

Figure S1 – Funnel plot of estimates of mu parameter of the lognormal distribution

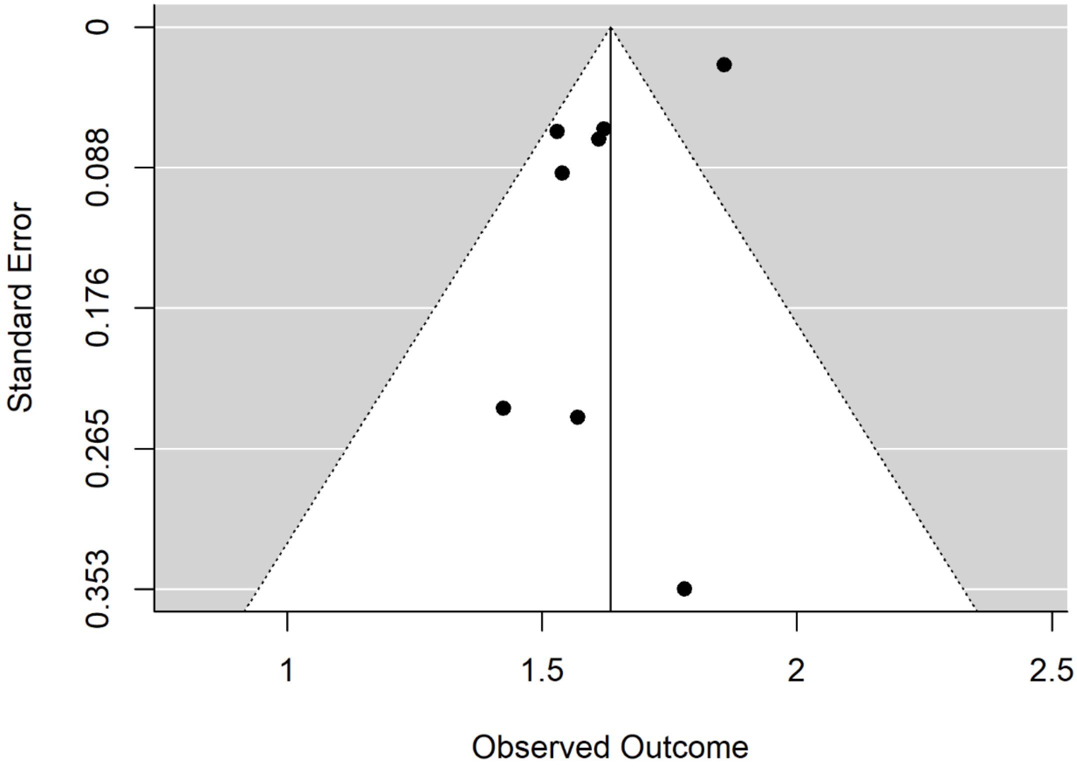


Figure S2 – Funnel plot of the sigma parameter of the lognormal distribution

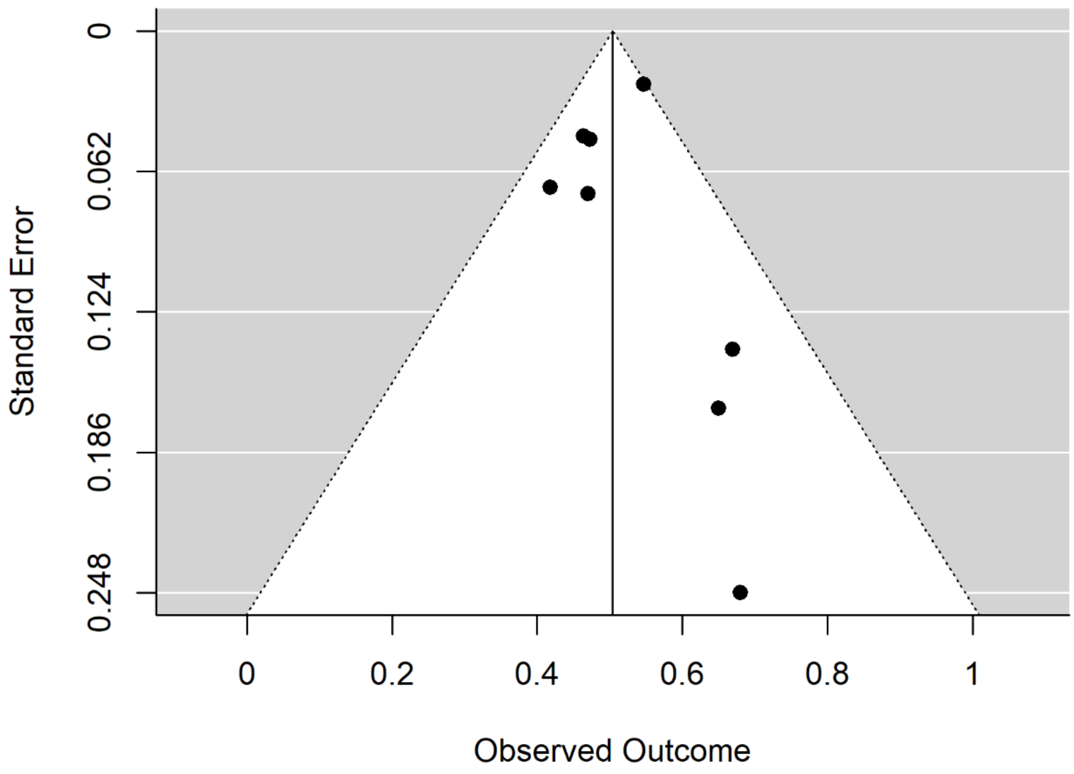
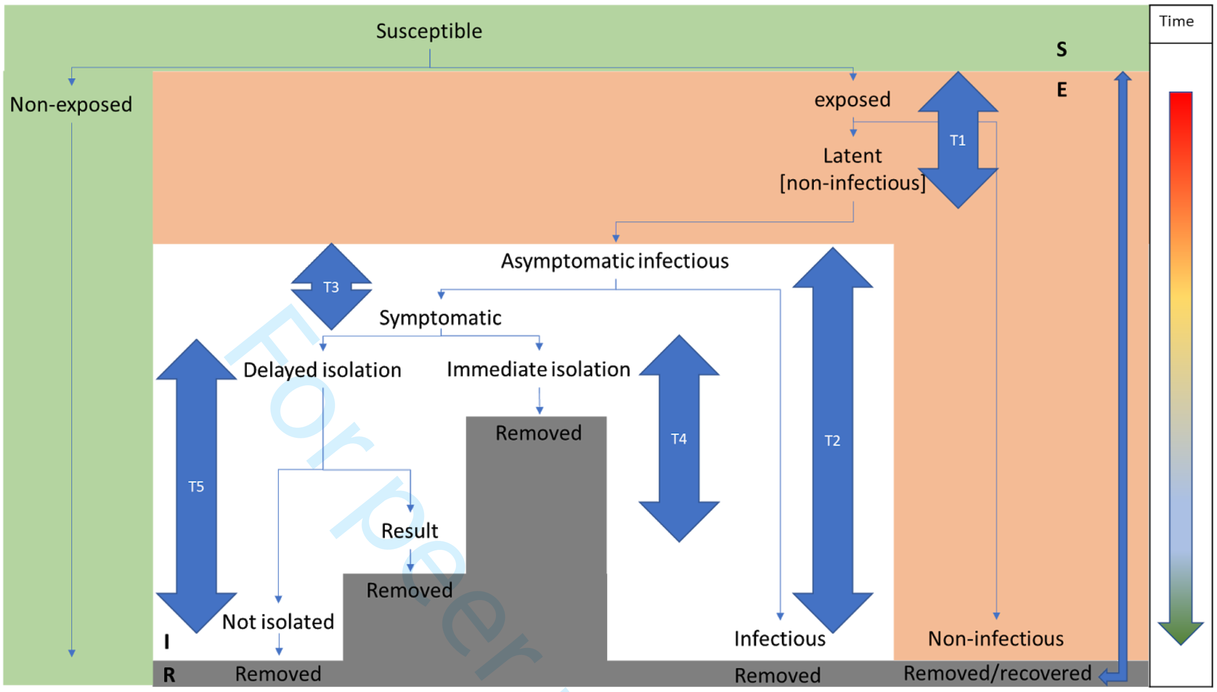


Figure S3 – Incubation period (T1 + T3) in the context of other key parameters important for the transmission of COVID-19.



Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the MOOSEreporting guidelines, and cite them as:

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-2012.

		Reporting Item	Page Number
Title			
	#1	Identify the study as a meta-analysis of observational research	1
Abstract			

	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number (From PRISMA checklist)	2-3
Background			
	#3a	Problem definition	3-4
	#3b	Hypothesis statement	4
	#3c	Description of study outcomes	4-5
	#3d	Type of exposure or intervention used	4-5
	#3e	Type of study designs used	5
	#3f	Study population	5
Methods			
Search strategy	#4a	Qualifications of searchers (eg, librarians and investigators)	5
Search strategy	#4b	Search strategy, including time period included in the synthesis and keywords	5
Search strategy	#4c	Effort to include all available studies, including contact with authors	5
Search strategy	#4d	Databases and registries searched	5

Search strategy	#4e	Search software used, name and version, including special features used (eg, explosion)	5
Search strategy	#4f	Use of hand searching (eg, reference lists of obtained articles)	5
Search strategy	#4g	List of citations located and those excluded, including justification	9
Search strategy	#4h	Method of addressing articles published in languages other than English	5
Search strategy	#4i	Method of handling abstracts and unpublished studies	5
Search strategy	#4j	Description of any contact with authors	5
	#5a	Description of relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	5
	#5b	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
	#5c	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	6
	#5d	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9
	#5e	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	9

	#5f	Assessment of heterogeneity	8
	#5g	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7
	#5h	Provision of appropriate tables and graphics	8
Results			
	#6a	Graphic summarizing individual study estimates and overall estimate	Fig 1-2
	#6b	Table giving descriptive information for each study included	Table 1
	#6c	Results of sensitivity testing (eg, subgroup analysis)	10-11
	#6d	Indication of statistical uncertainty of findings	10
Discussion			
	#7a	Quantitative assessment of bias (eg. publication bias)	10
	#7b	Justification for exclusion (eg, exclusion of non–English-language citations)	13
	#7c	Assessment of quality of included studies	13
Conclusion			
	#8a	Consideration of alternative explanations for observed results	14

#8b	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15
#8c	Guidelines for future research	15
#8d	Disclosure of funding source	15

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