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## **BMJ Open**

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

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15 16 17 18	27	ABSTRACT
19 20	28	Objectives: The aim of this study was to conduct a rapid systematic review and meta-analysis of
21 22 23	29	estimates of the incubation period of COVID-19.
23 24 25	30	Design: Rapid systematic review and meta-analysis of observational research
26 27 28	31	Setting: International studies on incubation period of COVID-19
29 30	32	Participants: Studies were selected for meta-analysis if they reported either the parameters and
31 32 33	33	confidence intervals of the distributions fit to the data, or sufficient information to facilitate calculation of
34 35	34	those values. Twenty studies selected for initial review, 8 of these were shortlisted for meta-analysis.
36 37	35	Final estimates conducted on meta-analysis of 7 studies.
38 39 40	36	Primary outcome measures: Parameters of a lognormal distribution of incubation periods.
41 42	37	Results: The incubation period distribution may be modelled with a lognormal distribution with pooled
43 44 45	38	mu and sigma parameters (95% confidence intervals) of 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55)
46 47	39	respectively. The corresponding mean (95% confidence intervals) was 5.8 (5.01, 6.69) days. It should be
48 49	40	noted that uncertainty increases towards the tail of the distribution: the pooled parameter estimates (95%
50 51	41	confidence intervals) resulted in a median incubation period of 5.1 (4.5, 5.8) days, whereas the $95^{\text{th}}$
52 53 54 55 56 57 58	42	percentile was 11.6 (9.5, 14.2) days.

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43	Conclusions: The choice of which parameter values are adopted will depend on how the information is
44	used, the associated risks and the perceived consequences of decisions to be taken. These
45	recommendations will need to be revisited once further relevant information becomes available. Finally,
46	we present an RShiny app that facilitates updating these estimates as new data become available.
47	Key words: "COVID-19"; "Incubation period"; "Meta-analysis"
48	
49	ARTICLE SUMMARY
50	Strengths and limitations of this study
51	• This study provides a pooled estimate of the distribution of incubation periods which may be used
52	in subsequent modelling studies or to inform decision-making
53	• Several studies used data that was publicly available, therefore there is potential that some the
54	data may be used for more than one study.
55	• This estimate will need to be revisited as subsequent data become available.
56	• We present an RShiny app to allow the meta-analysis to be updated with new estimates
57	
58	INTRODUCTION
59	Reliable estimates of the incubation period are important for decision making around the control of
60	infectious diseases in human populations. However, incubation periods are expected to vary across
61	individuals within the population. A single measure of central tendency (i.e. mean or median) does not
62	adequately represent this variation accurately.[1] Therefore, it is critically important to understand the
63	variation in incubation periods (i.e. the distribution) within the population.
64	Knowledge of the incubation period distribution can be used directly to inform decision-making around
65	infectious disease control. For example, the maximum incubation period can be used to inform the

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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.

#### 87 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

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3 4	90	case, infection) to the onset of clinical signs; all observational studies were included in the analysis.
5 6	91	Finally, the population was confirmed infected individuals, where an exposure time could be ascertained
7 8 9	92	with some degree of certainty and precision.
10 11	93	Patient and public involvement
12 13 14	94	It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting,
15 16	95	or dissemination plans of our research.
17 18 19	96	Search methodology, initial screening and categorisation
20 21	97	A survey of the literature between 1 December 2019 and 8th April 2020 for all countries was
22 23	98	implemented using the following search strategy. Publications on the electronic databases PubMed,
24 25	99	Google Scholar, MedRxiv and BioRxiv were searched with the following keywords: "Novel coronavirus"
26 27 28	100	OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19" AND "incubation period" OR "incubation". The
29 30	101	dynamic curated PubMed database "LitCovid" was also monitored, in addition to national and
31 32	102	international government reports. No restrictions on language or publication status were imposed so long
33 34	103	as an English abstract was available. Articles were evaluated for data relating to the aim of this review,
35 36	104	and all relevant publications were considered for possible inclusion. Bibliographies within these
37 38	105	publications were also searched for additional resources. The initial searches were carried out by three of
39 40 41	106	the investigators (ÁC, KH, FB). Authors of studies were contacted only to clarify reporting queries.
42 43 44	107	
45 46	108	Study appraisal and selection of meta-analysis
47 48 49	109	Studies were selected for meta-analysis if they reported either the parameters and confidence intervals of
49 50 51	110	the distributions fit to the data, or sufficient information to facilitate calculation of those values.
52 53	111	Specifically, this included studies that reported: the point estimate and confidence intervals or standard
54 55 56 57 58	112	errors of each parameter; the mean and standard deviation on the original (non-transformed) scale with
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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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<sup>2</sup>, i.e.:  $ln(X) \sim N(mu, sigma^2)$ 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. 

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

 $mu = \ln\left(m\right) - \frac{sigma^2}{2}$  $sigma = \sqrt{\ln\left(\frac{v}{m^2} + 1\right)}$ Where  $v = \text{variance} (= \text{sd}^2)$ , 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 95<sup>th</sup> 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)/ $(2 \times 1.96)$ 

**Meta-analysis** 

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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:

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

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.

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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.

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2							
3 4 5	177	RESULTS					
5 6 7	178	After initial search and selection of relevant papers and removing duplicates, 20 studies were available for					
8 9	179	appraisal.					
10 11 12	180	• Two papers were removed as they dealt with specific cohorts of cases – young adults [11] and					
12 13 14	181	children.[12]					
15 16	182	• One study was removed since only the abstract was in English and there was not enough detail to					
17 18	183	extract the relevant results.[13]					
19 20	184	• Several papers were removed since they contained insufficient data or methods description to					
21 22 22	185	facilitate their inclusion:					
23 24 25	186	• One study was removed since there was not enough detail in the paper to determine					
25 26 27	187	whether new parameters were being estimated or whether the parameters quoted were					
28 29	188	input values for their model.[14]					
30 31	189	• Five papers were removed since the data were largely descriptive, with no confidence					
32 33	190	intervals reported.[15-19]					
34 35	191	• One study was removed because the error terms associated with the mean, median and					
36 37	192	percentiles were not reported and there was not enough information presented to recover					
38 39 40	193	the parameters of the lognormal distribution.[20]					
41 42	194						
43 44 45	195	Of the shortlisted studies (n=10), six reported lognormal distributions as best fitting the data. [21-26] Of					
46 47	196	the remaining 4, one reported that several distributions were trialled but it was not clear which					
48 49	197	distribution was used for the final estimates.[27] However, these authors provided raw data which we					
50 51	198	used to fit the parameters of the lognormal distribution using the "rriskDistributions" package.[28] The					
52 53	199	remaining 3 studies reported that either Weibull or gamma distributions fitted the data better. Of these, 1					
54 55 56 57 58 59	200	study also presented the results of a log normal distribution fit to the data,[29] facilitating its inclusion in					

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201 the subsequent analysis. The final two studies reporting a Weibull [30] and a gamma distribution [31] 202 were removed from further analysis at this stage, however, those distributions were plotted over the final 203 distribution to evaluate the impact of removing those studies. The values extracted from each study are 204 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 88 Backer et al., 2020 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 0.141 0.240 0.669 Bi et al., 2020 183 1.570 0.245 0.650 0.167 Jiang et al., 2020 40 1.530 0.066 0.046 0.464 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 0.023 208

209 The initial pooled estimate of mu from this dataset (i.e. dataset 1, n=8 studies) was 1.65 (1.55, 1.76) and 210 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 211 212 and sigma respectively. However, evaluation of the funnel plots (Figures S1 and S2 Supplementary 213 Material) suggests the potential for bias associated with one of the studies included in the analysis.[25] 214 Evaluation of the meta-analyses results for mu demonstrated that two studies were responsible for much 215 of the heterogeneity in the analysis of this value. In particular, the values reported by Ma et al. [25] and

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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

239 percentile.

Percentile	Median	min	max	Difference
	(days)			(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

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 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.

49 246 <Figure 5 here>

247 <Figure 6 here>

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#### **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

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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*<sup>2</sup> 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.

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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.

320 the associated risks and the perceived consequences of decisions to be taken. The corresponding mean

321 was 5.8 days and the median was 5.1 days. These recommendations will need to be revisited once further

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322	relevant information becomes available. Finally, we present an R Shiny app which facilitates users to
323	update these estimates as new data become available <u>https://mcaloon-ucd.shinyapps.io/shiny2/</u> .
324	Funding: All investigators are full-time employees (or retired former employees) of University College
325	Dublin, the Irish Department of Food and the Marine or University of Nottingham. No additional funding
326	was obtained for this research.
327	Author contributions: CMA conducted the eligibility screening of shortlisted studies, extracted the data
328	and conducted the analysis with input from all authors; AC, KH and FB conducted the initial literature
329	searches; CMA and SM completed the initial drafts of the manuscript; MG and LOG reviewed the
330	statistical methods; All authors read and approved the final manuscript.
331	Data statement: The data for the meta-analyses are presented as part of the manuscript (Table 2).
332	Competing interests: All authors have completed the ICMJE uniform disclosure form at
333	www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work;
334	no financial relationships with any organisations that might have an interest in the submitted work in the
335	previous three years; no other relationships or activities that could appear to have influenced the
336	submitted work."
337	Patient and public involvement statement: It was not appropriate or possible to involve patients or the
338	public in the design, or conduct, or reporting, or dissemination plans of our research
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17 18	394	analysis of publicly reported individual data of 1155 cases from seven countries. medRxiv					
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	411	interventions (NPIs) to reduce COVID19 mortality and healthcare demand. 2020.						
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3 4	417	Figure 1. Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal
5 6 7	418	distribution of incubation period.
, 8 9	419	
10	420	Figure 2. Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal
11 12	421	distribution
13 14	422	
15 16	423	Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period
17 18	424	with $mu = 1.63$ and $sigma = 0.50$
19 20	425	
21 22	426	Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination
23 24	427	of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.
25 26 27	428	
28 29 30 31 32 33 34 35 36 37 38 39 40 41 42	429	Figure 5. Cumulative distribution function of pooled lognormal distribution for incubation period and
	430	original input studies.
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	432	Figure 6. Probability density function of pooled lognormal distribution for incubation period and studies
	433	(n=2) not included in the meta-analysis because of the distribution used.
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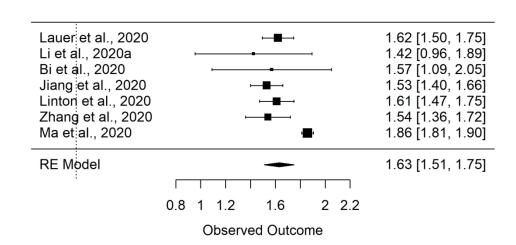


Figure 1. Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal distribution of incubation period.

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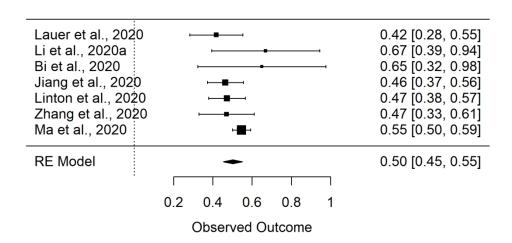


Figure 2. Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal distribution

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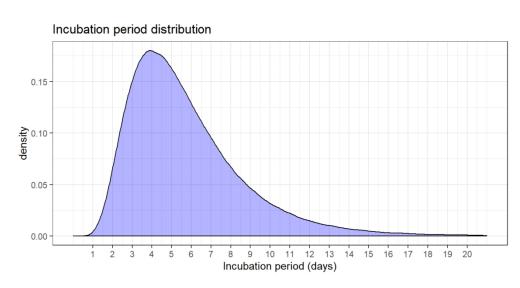


Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period with mu = 1.63 and sigma = 0.50

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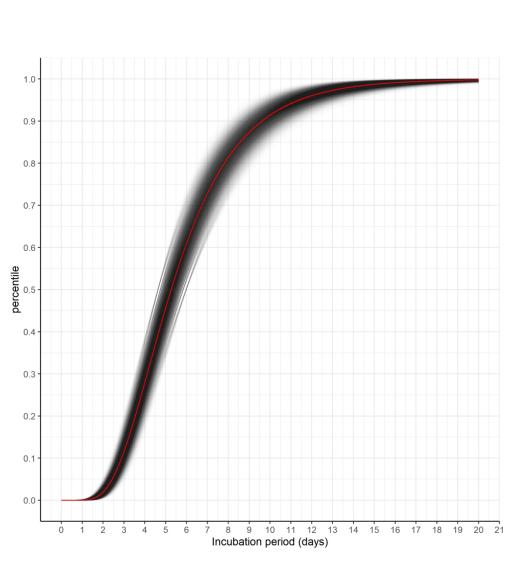
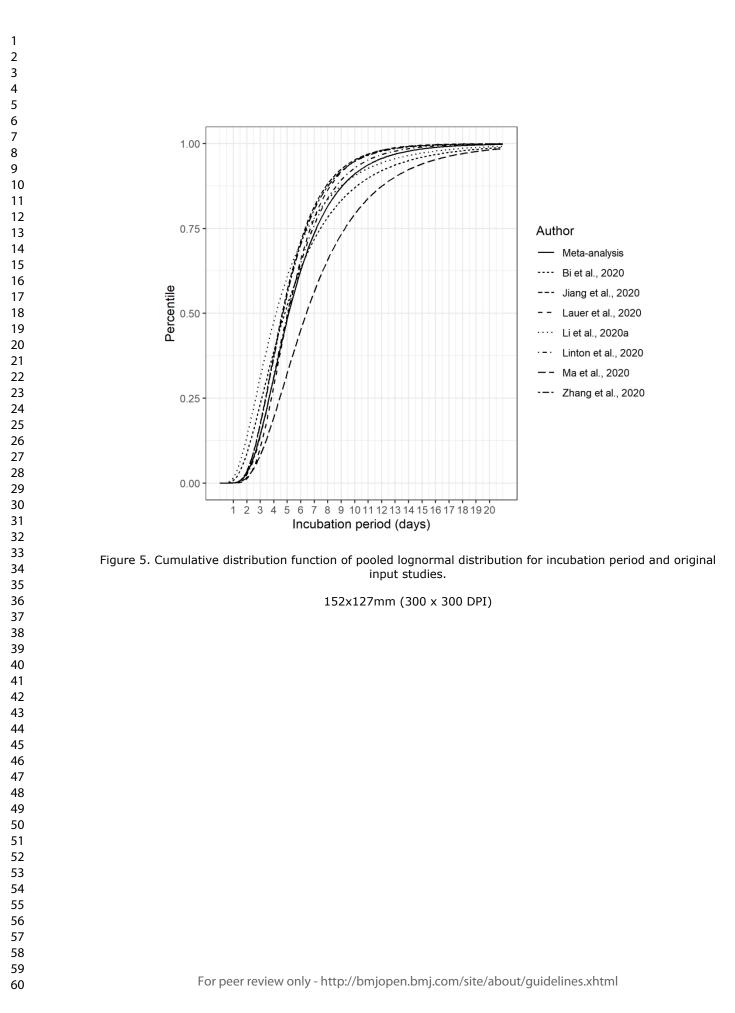
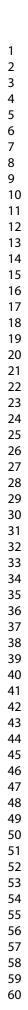


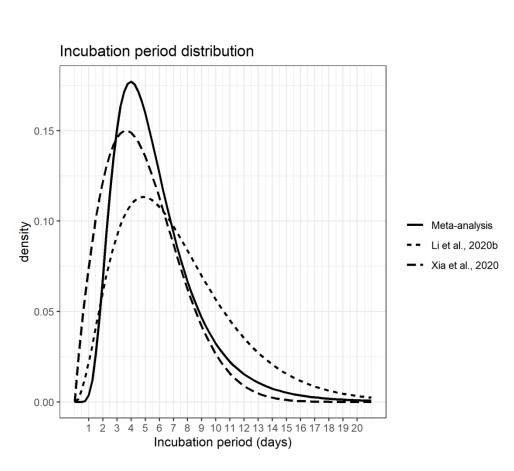
Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.

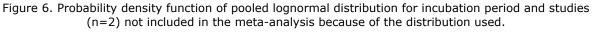


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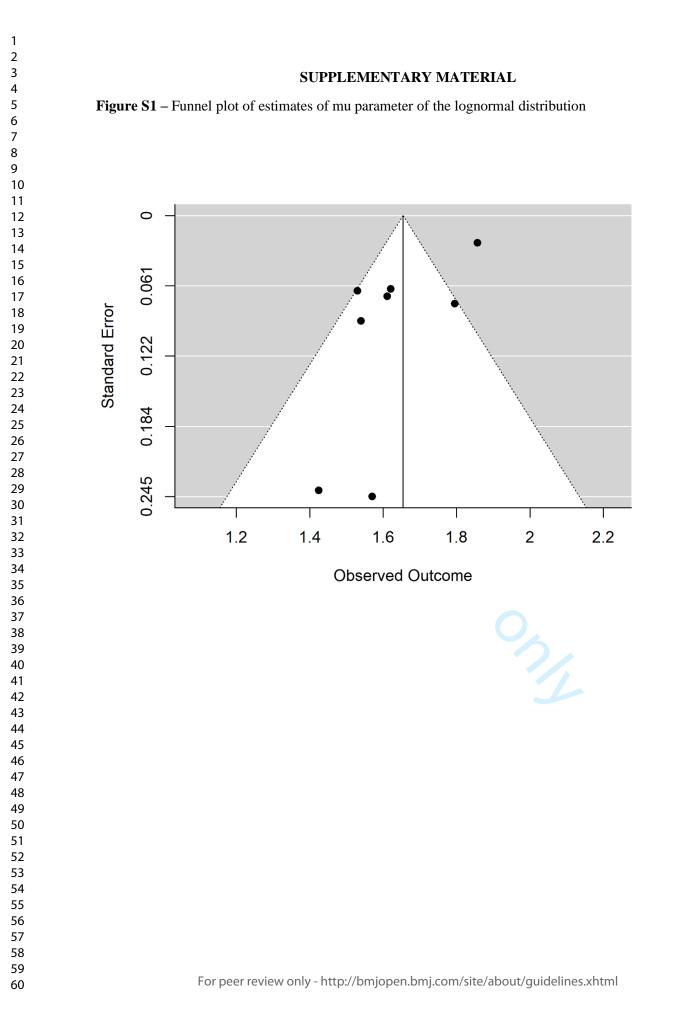
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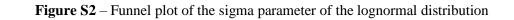


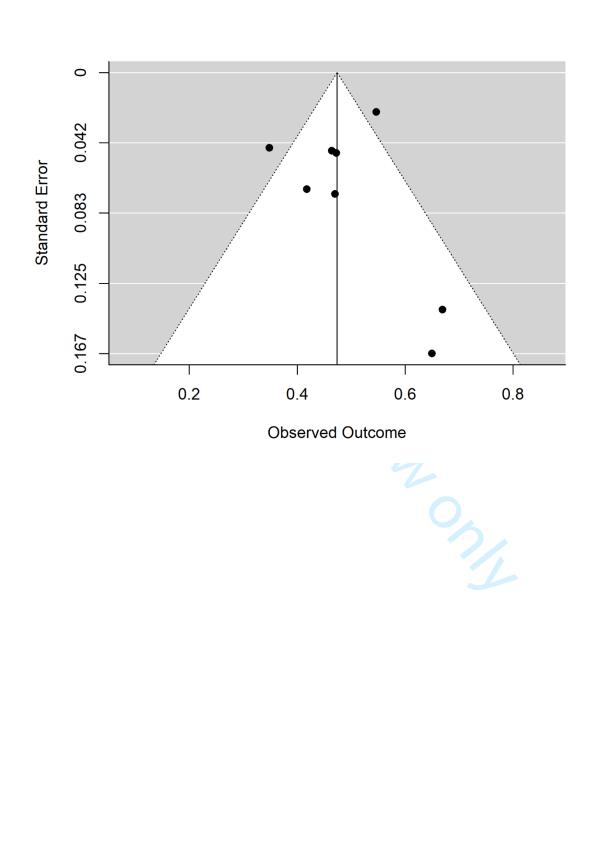




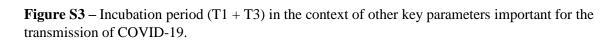
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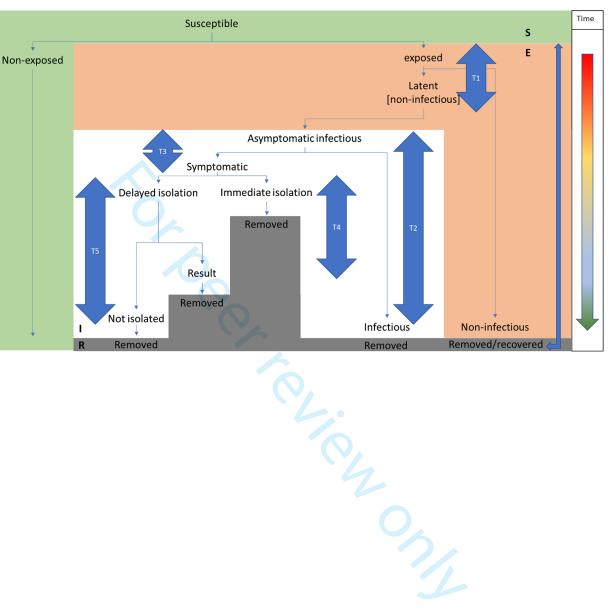












# Reporting checklist for meta-analysis of observational studies.

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. Metaanalysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-

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Reporting Item



#1

Identify the study as a meta-analysis of observational research

#### Abstract

Title

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1 2		<u>#2</u>	Provide a structured summary including, as applicable: background;	2-3
3 4			objectives; data sources; study eligibility criteria, participants, and	
5 6			interventions; study appraisal and synthesis methods; results;	
7 8 9			limitations; conclusions and implications of key findings; systematic	
9 10 11			review registration number (From PRISMA checklist)	
12 13				
14 15	Background			
16 17		<u>#3a</u>	Problem definition	3-4
18 19				
20 21		<u>#3b</u>	Hypothesis statement	4
22 23		<u>#3c</u>	Description of study outcomes	4-5
24 25 26		#2.4	Turne of our option used	4 E
26 27 28		<u>#3d</u>	Type of exposure or intervention used	4-5
29 30		<u>#3e</u>	Type of study designs used	5
31 32		#3f	Study population	5
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37 38	Search	#4a	Qualifications of searchers (eg, librarians and investigators)	5
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43 44 45	Search	<u>#4b</u>	Search strategy, including time period included in the synthesis and	5
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	Search	<u>#4d</u>	Databases and registries searched	5
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1 2	Search	<u>#4e</u>	Search software used, name and version, including special features	5
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11 12 13	Search	<u>#4g</u>	List of citations located and those excluded, including justification	9
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17 18	Search	<u>#4h</u>	Method of addressing articles published in languages other than	5
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25 26	strategy			
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30 31 32	strategy			
33 34		<u>#5a</u>	Description of relevance or appropriateness of studies gathered for	5
35 36 37			assessing the hypothesis to be tested	
38 39		<u>#5b</u>	Rationale for the selection and coding of data (eg, sound clinical	5
40 41 42			principles or convenience)	
43 44 45		<u>#5c</u>	Documentation of how data were classified and coded (eg, multiple	6
46 47			raters, blinding, and interrater reliability)	
48 49 50		<u>#5d</u>	Assessment of confounding (eg, comparability of cases and	9
51 52			controls in studies where appropriate)	
53 54 55		#5e	Assessment of study quality, including blinding of quality assessors;	9
56 57 58			stratification or regression on possible predictors of study results	-
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1 2 3		<u>#5f</u>	Assessment of heterogeneity	8
4 5		<u>#5g</u>	Description of statistical methods (eg, complete description of fixed	7
6 7			or random effects models, justification of whether the chosen	
8 9 10			models account for predictors of study results, dose-response	
11 12			models, or cumulative meta-analysis) in sufficient detail to be	
13 14			replicated	
15 16 17 18 19		<u>#5h</u>	Provision of appropriate tables and graphics	8
20 21	Results			
22 23 24 25 26		<u>#6a</u>	Graphic summarizing individual study estimates and overall estimate	Fig 1-2
27 28 29 30		<u>#6b</u>	Table giving descriptive information for each study included	Table 1
31 32		<u>#6c</u>	Results of sensitivity testing (eg, subgroup analysis)	10-11
33 34 35 36		<u>#6d</u>	Indication of statistical uncertainty of findings	10
37 38 39	Discussion			
40 41 42		<u>#7a</u>	Quantitative assessment of bias (eg. publication bias)	10
43 44 45 46		<u>#7b</u>	Justification for exclusion (eg, exclusion of non–English-language citations)	13
47 48 49 50 51		<u>#7c</u>	Assessment of quality of included studies	13
52 53 54 55 56 57 58 59	Conclusion	<u>#8a</u>	Consideration of alternative explanations for observed results	14
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1	#8	Generalization	of the conclusions (ie, appropriate for the data	15
2 3			within the domain of the literature review)	
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6 7	#8	Guidelines for	future research	15
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10 11	<u>#8</u>	Disclosure of f	unding source	15
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# **BMJ Open**

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

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2 3 4	1	TITLE PAGE							
5 6 7	2	Title: The incubation period of COVID-19 – A rapid systematic review and meta-analysis of							
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10 11 12	25	University College Dublin, Dublin, Ireland, 01 716 6083
13 14 15	26	
16 17 18	27	ABSTRACT
19 20	28	Objectives: The aim of this study was to conduct a rapid systematic review and meta-analysis of
21 22 22	29	estimates of the incubation period of COVID-19.
23 24 25	30	Design: Rapid systematic review and meta-analysis of observational research
26 27 28	31	Setting: International studies on incubation period of COVID-19
29 30	32	Participants: Searches were carried out in PubMed, Google Scholar, Embase, Cochrane library as well
31 32 33	33	as the pre-print servers MedRxiv and BioRxiv. Studies were selected for meta-analysis if they reported
34 35	34	either the parameters and confidence intervals of the distributions fit to the data, or sufficient information
36 37	35	to facilitate calculation of those values. After initial eligibility screening, 24 studies selected for initial
38 39 40	36	review, 9 of these were shortlisted for meta-analysis. Final estimates are from meta-analysis of 8 studies.
41 42	37	Primary outcome measures: Parameters of a lognormal distribution of incubation periods.
43 44 45	38	Results: The incubation period distribution may be modelled with a lognormal distribution with pooled
46 47	39	mu and sigma parameters (95% confidence intervals) of 1.63 (1.51, 1.75) and 0.50 (0.46, 0.55)
48 49	40	respectively. The corresponding mean (95% confidence intervals) was 5.8 (5.0, 6.7) days. It should be
50 51	41	noted that uncertainty increases towards the tail of the distribution: the pooled parameter estimates (95%
52 53	42	confidence intervals) resulted in a median incubation period of 5.1 (4.5, 5.8) days, whereas the 95 <sup>th</sup>
54 55 56 57 58	43	percentile was 11.7 (9.7, 14.2) days.

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**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 

#### 60 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 Page 5 of 42

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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.

1		
2 3	92	
4 5		
6 7	93	MATERIALS AND METHODS
8 9	94	For the purpose of this study we followed the Meta-analysis of Observational Studies in Epidemiology
10 11	95	(MOOSE) guidelines.[5] The outcome was defined as the time in days from the point of exposure, (in this
12 13 14	96	case, infection) to the onset of clinical signs; all observational studies were included in the analysis.
15 16	97	Finally, the population was confirmed infected individuals, where an exposure time could be ascertained
17 18 19	98	with some degree of certainty and precision.
20 21	99	Patient and Public Involvement
22 23 24	100	It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting,
25 26	101	or dissemination plans of our research.
27 28 29	102	Search methodology, initial screening and categorisation
30 31	103	A survey of the literature between 1 December 2019 and 8th April 2020 for all countries was
32 33	104	implemented using the following search strategy. Publications on the electronic databases PubMed,
34 35 36	105	Google Scholar, Embase, Cochrane library as well as the pre-print servers MedRxiv and BioRxiv were
37 38	106	searched with the following keywords: "Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR
39 40	107	"COVID-19" AND "incubation period" OR "incubation" (Table S1, Supplementary Material). The
41 42	108	dynamic curated PubMed database "LitCovid" was also monitored, in addition to national and
43 44 45	109	international government reports. No restrictions on language or publication status were imposed so long
45 46 47	110	as an English abstract was available. Articles were evaluated for data relating to the aim of this review,
48 49	111	and all relevant publications were considered for possible inclusion. Bibliographies within these
50 51	112 113	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.
52 53	112	the investigators (AC, KH, FD). Authors of studies were contacted only to clarify reporting queries.
54 55 56 57 58 59	114	

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115	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). 

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#### 128 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. 

Page 8 of 42

2 3 4	139									
5 6 7	140	Data extraction								
8 9 10 11	141	On initial appraisal, it was apparent that the majority of studies fitted a lognormal distribution to the data.								
	142	Earlier work has shown that this distribution is appropriate for many acute infectious diseases.[2, 7]								
12 13 14	143	Therefore, the study proceeded as the meta-analysis (pooled estimate) of the parameters of this								
15 16	144	distribution.								
17 18 19	145	A variable (X) has a lognormal distribution when the log-transformed values follow a normal distribution								
20 21	146	with mean, mu, and variance, sigma <sup>2</sup> , i.e.:								
22 23 24	147	$ln(X) \sim N(mu, sigma^2)$								
25 26	148	Methods exist for the meta-analysis of studies that combine a mix of log transformed and non-								
27 28 29 30	149	transformed data.[8] In this case we opted to transform data, where possible to the log-transformed scale,								
	150	and obtain a pooled estimate of both mu and sigma.								
31 32 33 34	151									
35 36	152	Calculation of distribution parameters from each study								
37 38 20	153	Where the values for each parameter (mu and sigma) were available from the studies, along with								
39 40 41	154	corresponding confidence intervals/standard errors, these were extracted as reported. In the remaining								
42 43	155	studies, the values were calculated where possible from the information presented.								
44 45 46	156	Calculation of mu and sigma from studies reporting the mean and standard deviation of the lognormal								
47 48	157	distribution on the original scale.								
49 50 51	158	The mu and sigma parameters of the original lognormal distribution were calculated as:								
52 53 54 55 56 57 58 59	159	$mu = \ln(m) - \frac{sigma^2}{2}$								

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3 4 5	160	$sigma = \sqrt{\ln\left(\frac{v}{m^2} + 1\right)}$
6 7	161	Where $v =$ variance (= sd <sup>2</sup> ), and $m =$ the mean of the distribution on the original (i.e. non-log transformed)
8 9 10	162	scale.
11 12	163	Similarly upper and lower confidence intervals of mu and sigma were found by substituting the upper and
13 14	164	lower bounds of the mean or standard deviation (from the original scale) into the equation above, one at a
15 16 17	165	time, whilst holding the value for the other parameter constant (as the point estimate for that parameter).
18 19 20	166	
21 22 23	167	Calculation of mu and sigma from studies reporting mean and percentiles on the original scale
24 25	168	Where studies reported the results as the mean and 95th percentile on the original scale, the "lognorm"
26 27	169	package in R was used to calculate the original values of mu and sigma and corresponding standard errors
28 29 30	170	or confidence intervals.[9]
31 32	171	
33 34 35	172	Calculation of variance of mu and sigma
36 37	173	For studies reporting confidence intervals, the standard error was calculated as (upper bound – lower
38 39	174	bound)/ $(2 \times 1.96)$ . Finally, for studies reporting the parameters relative to a referent value, the standard
40 41 42	175	error was calculated as:
43 44 45	176	$\sqrt{SE1^2 + SE2^2}$
46 47	177	Where SE1 and SE2 are the standard errors of the estimate of the referent category and coefficient
48 49 50	178	respectively.
51 52	179	
53 54 55 56 57 58 59	180	Meta-analysis

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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 "vi" (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  $l^2$  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:  $Mean = e^{(mu + \frac{sigma^2}{2})}$  $SD = \sqrt{e^{(2 \times mu + sigma^2)} \times e^{(sigma^2 - 1)}}$ 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

1												
2 3 4	203	After initial search and selection of relevant papers and removing duplicates, 24 studies were available for										
5 6 7	204	appraisal.										
7 8 9	205	• Two papers were removed as they dealt with specific cohorts of cases – young adults [13] and										
10 11	206	children.[14]										
12 13	207	• One study was removed since only the abstract was in English and there was not enough detail to										
14 15	208	extract the relevant results.[15]										
16 17 18	209	• Several papers were removed since they contained insufficient data or methods description to										
19	210	facilitate their inclusion:										
20 21 22	211	• One study was removed since there was not enough detail in the paper to determine										
23	212	whether new parameters were being estimated or whether the parameters quoted were										
24 25 26	213	input values for their model.[16]										
27 28	214	• Seven papers were removed since the data were largely descriptive, with no confidence										
29 30	215	intervals reported.[17-23]										
31 32	216	• One study was removed because the error terms associated with the mean, median and										
33 34	217	percentiles were not reported and there was not enough information presented to recover										
35 36 37	218	the parameters of the lognormal distribution.[24]										
38 39	219	• One study was removed [25] since a novel statistical approach was employed that likely										
40 41	220	resulted in a significantly higher incubation period estimate to other studies.										
42 43 44	221											
45 46	222	Of the shortlisted studies (n=11), six reported lognormal distributions as best fitting the data. [26-31] Of										
47 48 49	223	the remaining 4, one reported that several distributions were trialled but it was not clear which										
50 51	224	distribution was used for the final estimates.[32] However, these authors provided raw data which we										
52 53	225	used to fit the parameters of the lognormal distribution using the "rriskDistributions" package.[33] The										
54 55	226	remaining 4 studies reported that either Weibull or gamma distributions fitted the data better. Of these, 2										
56 57 58												
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml										

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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.

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Page 13 of 42	2 BMJ Open Table 1. Study size and extracted data for the lognormal mu and sigma parameters from the 9 studies that were used for meta-analy										
1 2 3 237 4 5	Table 1. Study	y size a	es that were	by open-2 e used foometa-analysis.							
6 7 8 9 10 11 12	Author	n	Publi catio n statu s 1 <sup>st</sup> July 2020	Location	Observation period	Mean (*Median) (days)	97.5th (*95 <sup>th</sup> ) percentile (days)	965222222222222222222222222222222222222	rmal par nalysis	ameters	used in
13								dingu s	se	sigma	se
14 15	Backer et al., 2020	88	PR	Chinese and international - travellers from Wuhan	20th Jan – 28th Jan	6.4	11.1	Down h@ges e <u>x</u> t ar	0.077	0.349	0.045
16 17 18 19	Lauer et al., 2020	181	PR	Chinese and international - travellers from known affected areas	4th Jan – 24th Feb	5.5	11.5	1. Downloaded from http://bmjepen.bmj.com/ on May 14, 3 shegeschool . 42 77 text and data mining, Altraining, and similar technologic	0.064	0.418	0.069
20 21	Li et al., 2020	10	PR	Early cases in Wuhan	1st Dec - 31st Jan	5.2	12.5*		0.240	0.669	0.141
22 23	Bi et al., 2020	183	PR	Shenzhen - travellers from Wuhan	14th Jan - 12th Feb	4.8*	14.0	A1578 bn	0.245	0.650	0.167
24 25	Jiang et al., 2020	40	PP	Location unclear	14th Dec - 8th Feb	4.9	9.7*		0.066	0.464	0.046
26 27	Linton et al., 2020	158	PR	Cases external to Wuhan	Start of epidemic until 31st Jan	5.6	10.8*	1261 mj.	0.070	0.472	0.048
28 29 30	Zhang et al., 2020	49	PR	China - provinces other than Hubei	Start of epidemic until 27th Feb	5.2	10.5*		0.092	0.470	0.072
30 31 32	Ma et al., 2020	587	PP	Multiple countries including China	Not specified	7.4	17	n-May <u>C</u> nno	0.024	0.547	0.023
33 34	Leung, 2020	<sup>1</sup> 61	PR	China – provinces other than Hubei	10th Jan - 12th Feb	7.2	14.6	<b>1</b> <u>0</u> 78 <b>, 2025</b>	0.353	0.680	0.248
35 238	<sup>1</sup> Inferred from	data r	eported								
36 37 38 39 40 41	PR = Publishe	ed, pee	r-review	ed; PP = Pre-print, not peer-review	wed			at Department GEZ-LTA			
42 43 44								Z-LTA			

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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.

262 <Figure 1 here>

263 <Figure 2 here>

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264	Figure 3 shows the resulting density plot of the pooled distribution. Figure 4 shows the cumulative										
265	density function plot of the same (pooled distribution). In this instance, all possible combinations of										
266	distributions across the 95% confidence intervals of the estimates of each of the mu and sigma values are										
267	plotted on the same graph. Table 2 shows the percentiles and corresponding confidence intervals of the										
268	pooled lognormal distribution.										
269	<figure 3="" here=""></figure>										
270	<figure 4="" here=""></figure>										
271											
272	<b>Table 2.</b> Percentiles of the pooled log normal distribution after simulating all possible combinations of										
273	mu and sigm	a within th	e 95% co	nfidence in	tervals of the p	ooled estimates of both parameters. The					
274	median days	for each p	ercentile a	are shown a	llong with the r	ninimum and maximum values for that					
275	percentile.										
	Percentile	Median	min	max	Difference						
		(days)			(max –	- 4					
	min)										
	2.5th 1.92 1.54 2.38 0.84										
	25 <sup>th</sup>	3.64	3.12	4.25	1.13						
	50th         5.10         4.53         5.75         1.22										

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97.5th	13.60	10.9	16.90	6.00

278 Figure 5 shows the cumulative density function plots of the pooled lognormal distribution along with the 279 estimates from the original studies. Finally, Figure 6 shows the probability density function of the pooled 280 lognormal distribution, plotted alongside the two studies that could not be included in the final meta-281 analysis due to the fact that they fit alternative distributions to the data.

282 <Figure 5 here>

283 <Figure 6 here>

284

#### 285 DISCUSSION

'n For the purpose of this study we defined incubation period as the time in days from the point of COVID-286 287 19 exposure to the onset of symptoms. Figure S3 (Supplementary Material) shows a schematic of this 288 time period with respect to other key parameters influencing COVID-19 transmission. Studies to 289 determine incubation period are likely most precise during the early phase of the outbreak, before the 290 pathogen is widespread. [26] During this early phase, exposure windows can be determined with some 291 confidence. Most studies achieved this by conducting the analysis based on travellers from an epicentre of 292 infection (Wuhan) to another country/region that was free from infection at that time point or in the very 293 early stages of the outbreak.

294 Issues with ascertaining incubation period in primary studies

By definition, the required case data for the determination of individual incubation periods needs to 295 296 include both exposure (window) and onset of symptoms. Precisely estimating these events can be 297 difficult. Symptom onset is based on case recall, whereas exposure is determined either from: movement Page 17 of 42

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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.

307 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  $l^2$  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.

321 Weaknesses and limitations

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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.

340 Comparison with values used in epidemiological modelling studies

341 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].
- 345 This figure, (5.0 days) was the median incubation period reported from that study,[27] which is much
- 346 closer to the median estimate of 5.1 days from our meta analysis.
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347	External val	iditv

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 

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371	Based on available evidence, we find that the incubation period distribution may be modelled with a
372	lognormal distribution with pooled mu and sigma parameters of 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55)
373	respectively. It should be noted that uncertainty increases towards the tail of the distribution (Figure 4 and
374	Table 2). The choice of which parameter values are adopted will depend on how the information is used,
375	the associated risks and the perceived consequences of decisions to be taken. The corresponding mean
376	was 5.8 days and the median was 5.1 days. These recommendations will need to be revisited once further
377	relevant information becomes available. Accordingly, we present an R Shiny app which facilitates users
378	to update these estimates as new data become available <u>https://mcaloon-ucd.shinyapps.io/shiny2/</u> .
379	Funding: This research received no specific grant from any funding agency in the public, commercial or
380	not-for-profit sectors
381	Author contributions: CM conducted the eligibility screening of shortlisted studies, extracted the data
382	and conducted the analysis with input from all authors; ÁC, KH and FB conducted the initial literature
383	searches; CM and SM completed the initial drafts of the manuscript; MG and LOG reviewed the
384	statistical methods; All authors (CM, ÁC, KH, AB, AWB, FB, MC, JG, EL, DM, PW, MG, LOG, SM)
385	read and approved the final manuscript.
386	<b>Data statement:</b> The data for the meta-analyses are presented as part of the manuscript (Table 2).
387	Competing interests: All authors have completed the ICMJE uniform disclosure form at
388	www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work;
389	no financial relationships with any organisations that might have an interest in the submitted work in the
390	previous three years; no other relationships or activities that could appear to have influenced the
391	submitted work."
392	Patient and public involvement statement: It was not appropriate or possible to involve patients or the
393	public in the design, or conduct, or reporting, or dissemination plans of our research
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3 4	489	Figure 1. Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal
5 6 7	490	distribution of incubation period.
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9 10 11 12	492 493	<b>Figure 2.</b> Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal distribution
13	494	
14 15 16	495	Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period
17 18	496	with $mu = 1.63$ and $sigma = 0.50$
19 20	497	
21 22	498	Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination
23 24 25	499	of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.
26 27 28	500	
29 30	501	Figure 5. Cumulative distribution function of pooled lognormal distribution for incubation period and
31 32	502	original input studies.
33 34	503	
35 36	504	Figure 6. Probability density function of pooled lognormal distribution for incubation period and studies
37 38 39	505	(n=2) not included in the meta-analysis because of the distribution used.
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Lauer et al., 2020	<b>⊢</b>	-		1.62 [1.50, 1.75]
Li et al., 2020a	<b>—</b>			1.42 [0.96, 1.89]
Bi et al., 2020	<b></b>			1.57 [1.09, 2.05]
Jiang et al. 2020	⊢∎⊣			1.53 [1.40, 1.66]
Linton et al., 2020	⊢∎-	-		1.61 [1.47, 1.75]
Zhang et al., 2020	⊢-∎	ł	1.54 [1.36, 1.72]	
Ma et al., 2020				1.86 [1.81, 1.90]
Leung, 2020	<b></b>	•	1	1.78 [1.09, 2.47]
RE Model	-	•		1.63 [1.52, 1.75]
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Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal distribution of incubation period.

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Lauer et al., 2020	<b>⊢</b> ∎1	0.42 [0.28, 0.55]
Li et al., 2020a	F	0.67 [0.39, 0.94]
Bi et al., 2020	F4	0.65 [0.32, 0.98]
Jiang et al., 2020	<b>⊢</b> ∎-1	0.46 [0.37, 0.56]
Linton et al., 2020	<b>⊢</b> ∎→1	0.47 [0.38, 0.57]
Zhang et al., 2020	<b>⊢_</b> ∎1	0.47 [0.33, 0.61]
Ma et al., 2020	H <b>an</b> t	0.55 [0.50, 0.59]
Leung, 2020	<b></b>	0.68 [0.19, 1.17]
RE Model	•	0.50 [0.46, 0.55]
	0 0.2 0.6 1 1.2	
	Observed Outcome	

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

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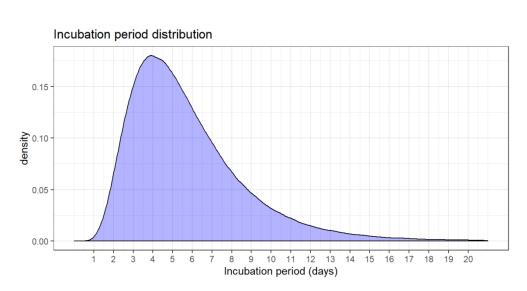


Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period with mu = 1.63 and sigma = 0.50

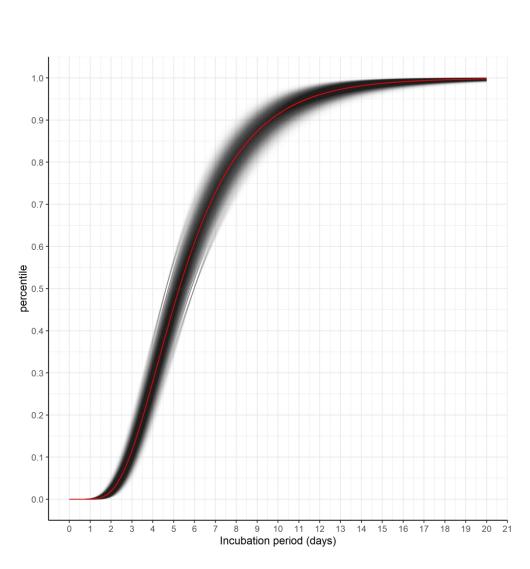
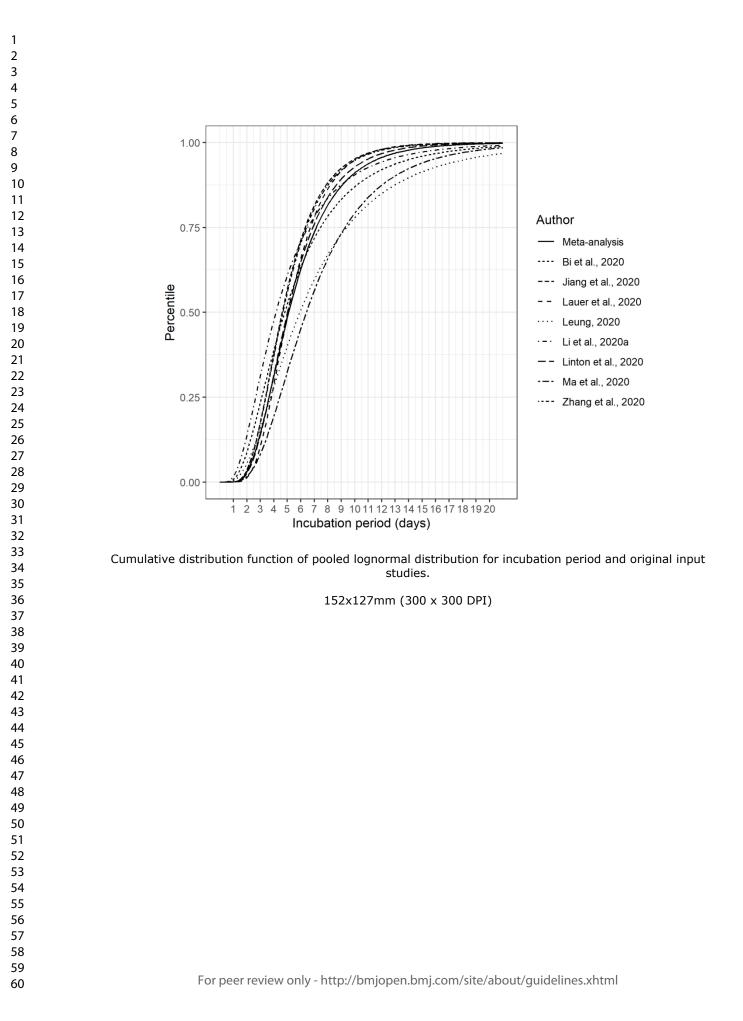
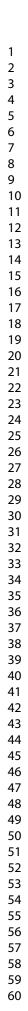


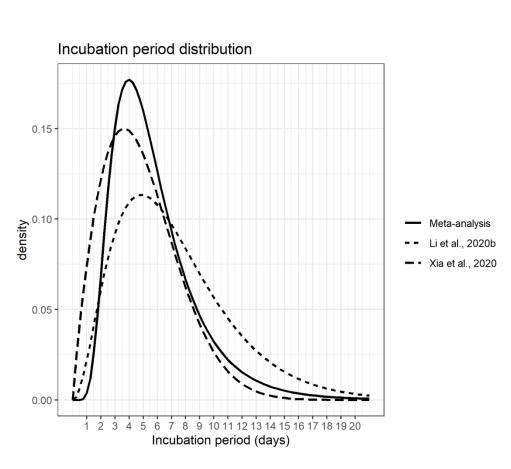
Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.

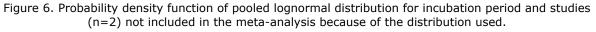


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**Table S1.** Search strategies for meta-analysis of observational studies reporting the Incubation period of COVID-19.

Database	Search strategy (publications accessible 1 <sup>st</sup> Dec 2019-8th		
Luunun	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) Representativeness of the study cohort

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) Ascertainment of exposure
  - a) original data collected through interview \*
  - b) travel period only \*
  - c) secondary data (using publicly available reports)
- 3) Precision of the exposure window for cases used in final analysis
  - 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

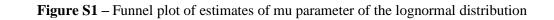
#### Outcome

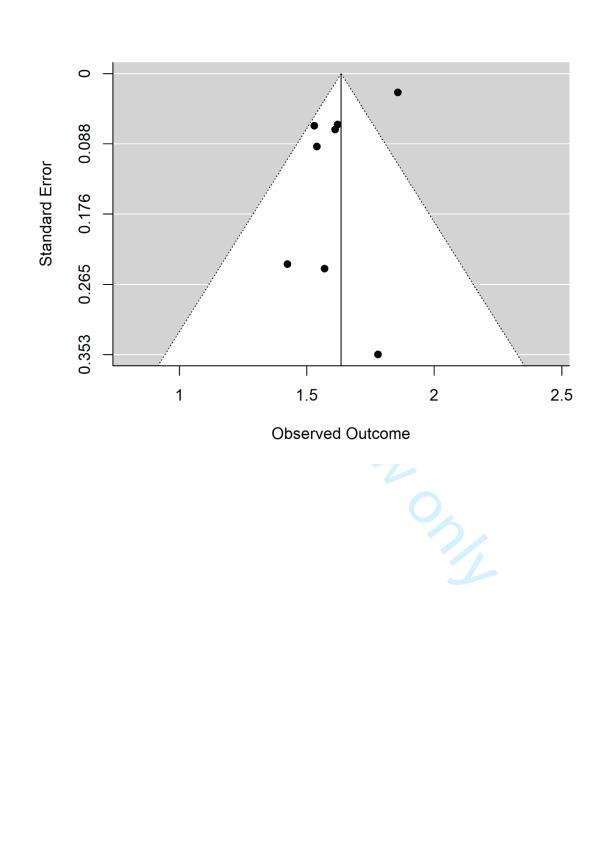
- 4) Assessment of outcome (onset of symptoms)
  - a) original data collected through interview \*
    - b) no description/not clear
- 5) Precision of estimate of outcome
  - a) Precise date 🟶
  - b) Window
  - c) no description/not clear

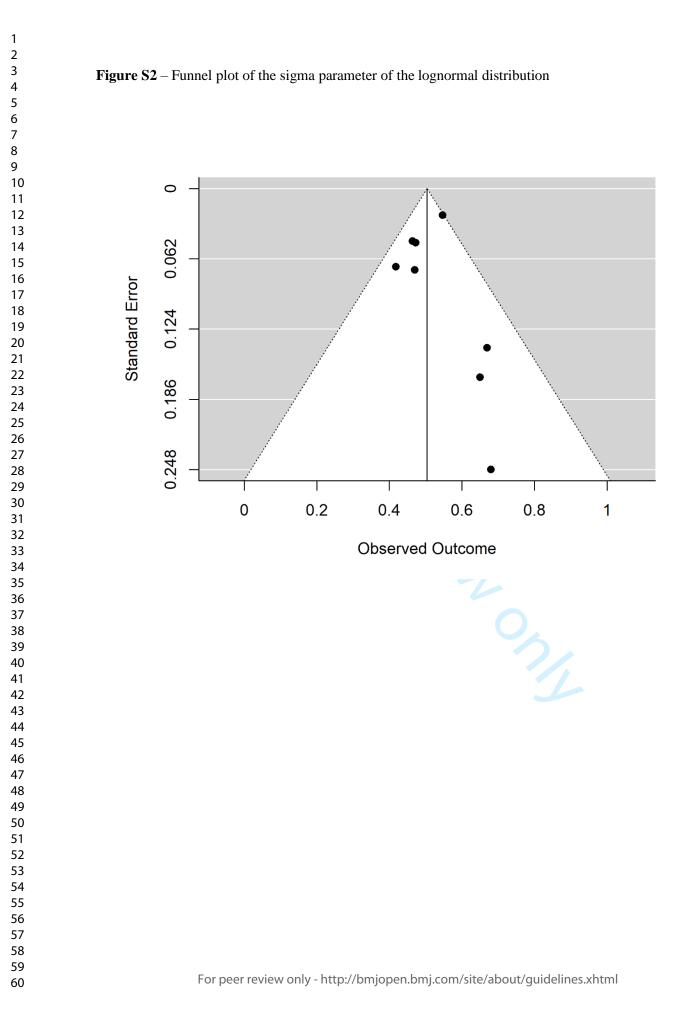
#### Table S2 Quality assessment of final studies used in the meta-analysis of incubation period

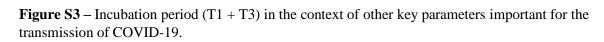
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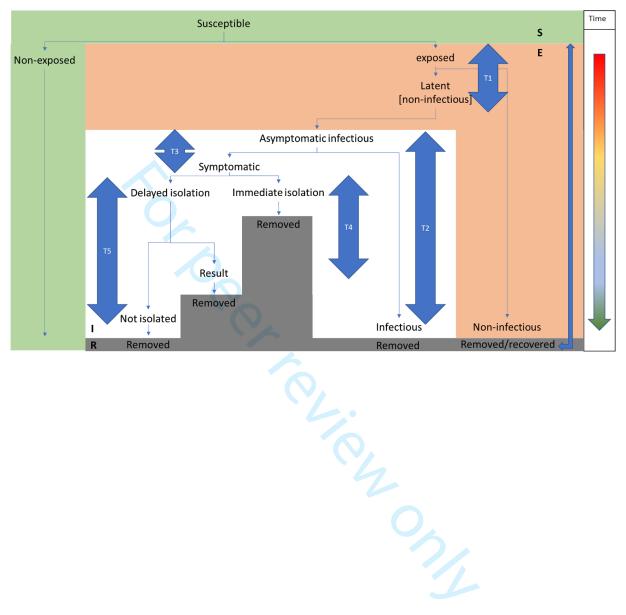
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## Reporting checklist for meta-analysis of observational studies.

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. Metaanalysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-

2012.

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Reporting Item

#1

Identify the study as a meta-analysis of observational research

Abstract

Title

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1 2		<u>#2</u>	Provide a structured summary including, as applicable: background;	2-3
3 4			objectives; data sources; study eligibility criteria, participants, and	
5 6 7			interventions; study appraisal and synthesis methods; results;	
, 8 9			limitations; conclusions and implications of key findings; systematic	
10 11			review registration number (From PRISMA checklist)	
12 13	Background			
14 15	Baonground			
16 17 18		<u>#3a</u>	Problem definition	3-4
19 20		#3b	Hypothesis statement	4
21 22				
23 24		<u>#3c</u>	Description of study outcomes	4-5
25 26		<u>#3d</u>	Type of exposure or intervention used	4-5
27 28 29		#2.5	Turne of etudu decigne used	F
30 31		<u>#3e</u>	Type of study designs used	5
32 33		<u>#3f</u>	Study population	5
34 35	Methods			
36 37				
38 39 40	Search	<u>#4a</u>	Qualifications of searchers (eg, librarians and investigators)	5
40 41 42	strategy			
43 44	Search	<u>#4b</u>	Search strategy, including time period included in the synthesis and	5
45 46	strategy		keywords	
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49 50	Search	<u>#4c</u>	Effort to include all available studies, including contact with authors	5
51 52 53	strategy			
54 55	Search	<u>#4d</u>	Databases and registries searched	5
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58 59			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	
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1 2	Search	<u>#4e</u>	Search software used, name and version, including special features	5
3 4 5	strategy		used (eg, explosion)	
6 7 8	Search	<u>#4f</u>	Use of hand searching (eg, reference lists of obtained articles)	5
9 10	strategy			
11 12 13	Search	<u>#4g</u>	List of citations located and those excluded, including justification	9
14 15 16	strategy			
17 18	Search	<u>#4h</u>	Method of addressing articles published in languages other than	5
19 20 21	strategy		English	
22 23 24	Search	<u>#4i</u>	Method of handling abstracts and unpublished studies	5
25 26 27	strategy			
28 29	Search	<u>#4j</u>	Description of any contact with authors	5
30 31 32	strategy			
33 34 35		<u>#5a</u>	Description of relevance or appropriateness of studies gathered for	5
36 37			assessing the hypothesis to be tested	
38 39 40		<u>#5b</u>	Rationale for the selection and coding of data (eg, sound clinical	5
41 42 43			principles or convenience)	
44 45 46		<u>#5c</u>	Documentation of how data were classified and coded (eg, multiple	6
47 48			raters, blinding, and interrater reliability)	
49 50 51		<u>#5d</u>	Assessment of confounding (eg, comparability of cases and	9
52 53 54			controls in studies where appropriate)	
55 56		<u>#5e</u>	Assessment of study quality, including blinding of quality assessors;	9
57 58 59			stratification or regression on possible predictors of study results	
60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2 3		<u>#5f</u>	Assessment of heterogeneity	8
4 5		<u>#5g</u>	Description of statistical methods (eg, complete description of fixed	7
6 7			or random effects models, justification of whether the chosen	
8 9 10			models account for predictors of study results, dose-response	
10 11 12			models, or cumulative meta-analysis) in sufficient detail to be	
13 14			replicated	
15 16 17 18		<u>#5h</u>	Provision of appropriate tables and graphics	8
19 20 21	Results			
22 23 24 25		<u>#6a</u>	Graphic summarizing individual study estimates and overall estimate	Fig 1-2
26 27			estimate	
28 29		<u>#6b</u>	Table giving descriptive information for each study included	Table 1
30 31 32 33		<u>#6c</u>	Results of sensitivity testing (eg, subgroup analysis)	10-11
34 35 36		<u>#6d</u>	Indication of statistical uncertainty of findings	10
37 38 39	Discussion			
40 41 42		<u>#7a</u>	Quantitative assessment of bias (eg. publication bias)	10
43 44 45		<u>#7b</u>	Justification for exclusion (eg, exclusion of non–English-language	13
46 47			citations)	
48 49 50 51		<u>#7c</u>	Assessment of quality of included studies	13
52 53	Conclusion			
54 55 56 57		<u>#8a</u>	Consideration of alternative explanations for observed results	14
58 59 60			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2	<u>#8b</u>	Generalization of the conclusions (ie, appropriate for the data	15
2 3 4		presented and within the domain of the literature review)	
5 6			
7 8	<u>#8c</u>	Guidelines for future research	15
9 10 11	<u>#8d</u>	Disclosure of funding source	15
12 13 14	None Reproduced w	vith permission from JAMA. 2000. 283(15):2008-2012. Copyright $\mbox{@}$ 200	0
15 16	American Medical A	ssociation. All rights reserved. This checklist can be completed online u	ising
17 18	https://www.goodrep	ports.org/, a tool made by the <u>EQUATOR Network</u> in collaboration with	
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