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Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases

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4 **1 Inferred duration of infectious period of SARS-CoV-2: rapid scoping review**
5 **2 and analysis of available evidence for asymptomatic and symptomatic**
6 **3 COVID-19 cases**

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18 Abstract

19 **Objectives:** Our objective was to review the literature on the inferred duration of the infectious
20 period of COVID-19, caused by SARS-COV-2 virus, and provide an overview of the variation
21 depending on the methodological approach.

22 **Design:** Rapid scoping review. Literature review with fixed search terms, up to 1st April 2020. Central
23 tendency and variation of the parameter estimates for infectious period in (a) asymptomatic (b)
24 symptomatic cases from (i) virological studies (repeated testing), (ii) tracing studies (iii) modelling
25 studies were gathered. Narrative review of viral dynamics.

26 **Information sources:** Search strategies developed and the following searched: PubMed, Google
27 Scholar, MedRxiv, BioRxiv. Additionally, the Health Information Quality Authority (Ireland) viral load
28 synthesis was utilised, which screened literature from PubMed, Embase, ScienceDirect, NHS
29 evidence, Cochrane, medRxiv and bioRxiv, HRB open databases.

30 **Results:** There was substantial variation in the estimates, and how infectious period was inferred.
31 One study provided approximate median infectious period for asymptomatic cases of 6.5-9.5 days.
32 Median pre-symptomatic infectious period across studies varied over <1-4 days. Estimated mean
33 time from symptom onset to two negative RT-PCR tests was 13.4 days (95%CI: 10.9-15.8), but was
34 shorter when studies included children or less severe cases. Estimated mean duration from
35 symptom onset to hospital discharge or death (potential maximal infectious period) was 18.1 days
36 (95%CI: 15.1–21.0); time to discharge was on average 4 days shorter than time-to-death. Viral
37 dynamic data and model infectious parameters were often shorter than repeated diagnostic data.

38 **Conclusions:** There are limitations of inferring infectiousness from repeated diagnosis, viral loads,
39 and viral replication data alone, and also potential patient recall bias relevant to estimating exposure
40 and symptom onset times. Despite this, available data provides a preliminary evidence base to
41 inform models of central tendency for key parameters, and variation for exploring parameter space
42 and sensitivity analysis. Some current models may be underestimating infectious period.

44 Strengths and limitations of this study

- 45 • A comprehensive overview of the literature pertaining to inferred infectious duration of
46 COVID-19, including indirect measures from virological, contact tracing, and modelling
47 studies to 1st April 2020.
- 48 • Both narrative review and quantitative analysis presented

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3 49 • Small number of comparable parameter estimates for meta-analysis is a limitation
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5 50 • Much of the current research material on COVID-19 is from preprint papers, and therefore
6
7 51 have not gone through formal peer review
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For peer review only

52 Introduction

53 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new coronavirus, emerged in
54 China in late 2019.[1,2] The virus causes COVID-19, a disease characterized by variable, mainly
55 respiratory, symptoms across cohorts, from asymptomatic cases through to mild (for example, dry
56 cough, fever) and severe cases (for example, pneumonia).[3,4] The severity of symptoms, and their
57 clinical outcome, have been reported to vary by age-class and whether patients have underlying
58 comorbidities. The case-fatality rate increases with age, and are highest for those above 70
59 years.[5,6] There are several cases of asymptomatic test-positive patients reported in the emerging
60 literature (e.g. [4,7,8]). Furthermore, asymptomatic (and pre-symptomatic) cases have been shown
61 to be infectious, and secondary cases have been reported.[9,10] However, the duration of this
62 infectious period is difficult to measure accurately, and the time course of the natural history of
63 infection generally must be inferred indirectly, via contact tracing of cases, serial repeated diagnostic
64 virological studies, and/or through modelling approaches. Symptomatic cases can experience an
65 infectious pre-symptomatic period before the onset of symptoms, therefore understanding the
66 whole infectious period for this cohort requires estimating the duration of both periods. It is
67 essential to rapidly gain insight into this key variable impacting our understanding of COVID-19
68 epidemiology. Anderson et al. [11] point out one of the “key unknowns” is the infectious period for
69 COVID-19, which they suggest may be 10 days but subject to great uncertainty.

70 Here we gathered data from published research from peer-reviewed and preprints from 1st
71 December to 1st April 2020, to characterize the variation in the infectious duration inferred from the
72 three lines of evidence. We also provide a narrative review of the viral dynamic literature. Our focus
73 was on duration, relative infectiousness has been dealt with elsewhere [12,13]

74 The aim of this review was to provide an overview and critical appraisal of published and preprint
75 articles and reports that assess or quantify the inferred duration of the infectious period in order to
76 best parameterise COVID-19 epidemiological transmission models.

77 **Materials and Methods**

78 ***Conceptual model of population infection dynamics***

79 Infectious period was contextualised in relation to a working conceptual model of COVID-19 disease
80 dynamics (Figure S1, supplementary material 1). From this conceptual model, three parameters
81 were identified as important in context of this study:

82 T2, defined as: Duration of the total infectious period for asymptomatic cases, post-latent to
83 recovery ['recover' in this context relates to clearing of infection]

84 T3, defined as: Duration of pre-symptomatic infectious period for those infected individuals
85 who subsequently develop symptoms (that is, post-latent to onset of symptoms)

86 T5, defined as: Duration from onset of symptoms to recovery* or death.

87 * recovery was inferred as either the first of two clear RT-PCR tests, or hospital discharge after
88 admission from COVID-19 related symptoms.

89 "Asymptomatic" case definition was interpreted pragmatically following Davies et al. [14,15], and
90 may include very mild symptoms that may occur but are unnoticed.

91 T2, T3, T5 represent readily measurable parameters, but may be upper limits of infectious period, as
92 patients may be non-infectious for a period before recovery or death. We also review evidence
93 where infectiousness is inferred from viral shedding and contact tracing [transmission], see below.

94 ***Literature search***

95 A survey of the literature between 1st December 2019 and 1st April 2020 for all countries was
96 implemented using the following search strategy. Publications on the electronic databases PubMed,
97 Google Scholar, MedRxiv and BioRxiv were searched with the following keywords: "Novel
98 coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19" AND "infectious". Additionally,
99 national and international government reports were monitored. No restrictions on language or
100 publication status were imposed so long as an English abstract was available. Articles were evaluated
101 for data relating to the aim of this review; all relevant publications were considered for possible
102 inclusion. Bibliographies within these publications were also searched for additional resources.

103 Manual searches of the literature was undertaken using daily updated COVID19 collections
104 from the National Centre for Biotechnology Information (NCBI) and MedRxiv servers
105 (<https://connect.medrxiv.org/relate/content/181>), respectively, searching specifically for
106 papers relating to "infectious period" or "infectious duration" from both empirical and
107 modelling studies.

108 Finally, we utilised the complementary work undertaken by the Health Information and Quality
109 Authority (HIQA) of Ireland, specifically the evidence summaries relating to asymptomatic
110 transmission and viral load [16,17]. The protocol for the evidence synthesis is published on the HIQA
111 website [18]. Briefly, the evidence synthesis process included searching databases from 30th

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3 112 December 2019 to 27th March 2020 (PubMed, Embase, ScienceDirect, NHS evidence, Cochrane,
4 113 medRxiv and bioRxiv, HRB open), screening, data extraction, critical appraisal and summarizing the
5 114 evidence.

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9 115 Our aim was to have as great a breadth for an evidential base as possible, to clarify what evidence
10 116 was available to inform on the infectious period of COVID19, and to identify key characteristics of
11 117 the data sources and their interpretation. Therefore, our approach is a scoping review (following
12 118 [19]). However, due to the emergent nature of COVID-19, this work is considered a rapid review.[20]
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14 119 This paper follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—
15 120 Extension for Scoping Reviews (PRISMA-ScR) checklist.

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22 122 Inclusion criteria were for papers that provided data to inform duration of infectious period based
23 123 on: time from symptoms to recovery; time from symptoms to death; time from symptoms to
24 124 diagnostic test clearance [\geq two clear tests, defined as at least two consecutive negative reverse
25 125 transcriptase polymerase chain reaction (RT-PCR) tests conducted 24 hours apart]; pre-symptomatic
26 126 infectious period; time from first diagnostic test to diagnostic test clearance [\geq two clear tests] for
27 127 pre-symptomatic/asymptomatic cases. Inclusion criteria for viral dynamics, were papers which
28 128 reported viral load via cycle threshold (Ct) values from RT-PCR testing over repeated sampling of
29 129 infected patients, and studies that additional reported viral isolation.

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34 130 For quality control, studies were (i) selected and screened initially by three members of the team
35 131 from search terms outlined above (*ABC, KH, FB*), with parameters identified and recorded. (ii) This
36 132 was reviewed and supplemented by manual search by a different two team members (*AWB, DM*),
37 133 again with parameters identified and recorded. (iii) Finally, the review was then internally reviewed
38 134 by an additional two members of the team (*CMc, MC*), and cross-referenced with other parameter
39 135 synthesis documents being worked on by the group (*all authors*).

40 41 42 43 44 45 46 136 ***Parameter comparison***

47 48 49 137 ***Parameters of interest***

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51 138 1. *A-priori* it was decided to harvest parameter estimates for (i) asymptomatic, and (ii)
52 139 symptomatic cases. As the period of infectiousness can only be estimated indirectly,
53 140 parameter estimates from the literature was gathered from three different methodological
54 141 approaches: Virological studies tracking patients overtime undertaking serial testing, where
55 142 infectious period was inferred from diagnostic testing history and/or by virus isolation.

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3 143 2. Contact tracing studies where infectiousness is inferred by infector-infectee histories and/or
4 144 clusters of infection.
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6 145 3. Model parameters entered into mathematical models [priors] representing explicitly
7 146 infectious periods, or model parameters estimated from mathematical models [posterior
8 147 estimates] estimating explicitly infectious periods
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15 149 Visual and quantitative comparisons

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17 150 To compare parameters visually, simulated distributions were estimated from the central tendencies
18 151 and variation metrics described in the primary literature. To simulate data, 10,000 random variates
19 152 were drawn from random number functions in Stata (ME, version 15.1; StataCorp. 2017. Stata
20 153 Statistical Software: Release 15. College Station, TX: StataCorp LLC) [rnormal, rgamma]. Where
21 154 possible, the distribution reported within the primary literature was used to represent the
22 155 distribution (e.g. Gaussian, Gamma). Where distributional data could not be inferred, point
23 156 estimates were presented.

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29 157 There were adequate comparable data gathered on the duration of T5 (duration from onset of
30 158 symptoms to death or recovery) from virological studies to employ a meta-analytic model. Many of
31 159 the studies report different central tendency estimates, including mean and median. Methods of
32 160 reporting variation across this central tendency included standard deviation, range, inter-quartile
33 161 range. To facilitate meta-analysis, reported estimates from all studies were converted to the mean
34 162 and standard deviations based on the formulae given in Wan et al. [21].

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40 163 To obtain the standard deviations from 95%CI, the method outlined in the Cochrane handbook [22]
41 164 was used:

$$42 \quad \text{SD: } \sqrt{n}(\text{Upper limit of CI} - \text{Lower limit of CI})/3.92$$

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48 167 Standard Error (SE) was calculated from Standard Deviation (SD) and sample size (n), using:

$$49 \quad \text{SE} = \text{SD}/\text{SQRT}(n)$$

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53 169 Comparisons were made using the METAAN package in Stata 15, using the random-effects
54 170 (DerSimonian-Laird) model.[23] This model assumes heterogeneity between the studies; that is, it
55 171 assumes that the true effect can be different for each study. The model assumes that the individual-
56 172 study true effects are distributed with a variance τ^2 around an overall true effect, but the model
57 173 makes no assumptions about the form of the distribution of either the within-study or the between-

174 studies effects. Weightings were derived from the standard error [precision] around the estimate.
175 Comparisons were presented as forest plots. Heterogeneity between studies was tested using
176 Cochran's Q; the magnitude of the heterogeneity was categorised using I^2 as high (>75%), moderate
177 (50-75%), or low (<50%).[24]

178 Variation in duration across T5 virological studies was compared using a random effects meta-
179 regression model, using the METAREG command in Stata 15.1. The hypothesis that heterogeneity
180 may be related to the inclusion of children or depending on symptom severity within the sample,
181 was tested in separate univariate models. Severity was dichotomised (0/1) into studies that included
182 patients described as having 'mild' or 'mild-moderate' symptoms, versus studies that included
183 patients with 'moderate-severe' or 'severe' symptoms. Similarly, studies were categorised into
184 having some samples from "children" (as reported in the paper), or wholly adult samples. These
185 variables were then fitted as a dichotomous dummy predictor [independent]. The parameter
186 estimates from the regression model was solved using restricted maximum likelihood (REML);
187 additionally, p-values were estimated using a Monte Carlo model with 1000 permutation test.[25]

188 Raw patient-level data were available from three studies in relation to time from onset to hospital
189 discharge or death (potentially inferring maximal T5 duration). To estimate the predicted mean and
190 95%CI duration across these studies, data were analysed using a Gaussian random effects model
191 (using XTREG command, Stata 15), with study categories fitted as the RE. A linear regression model
192 with 'study' fitted as a categorical dummy variable was used to estimate the difference between
193 duration across study datasets. Code and data are provided in Supplementary Material 2 & 3.

194 ***Viral dynamics***

195 A narrative comparison of reported viral dynamics from studies that undertook serial viral load
196 estimates from patients over their period of observation was undertaken. Trends in the literature,
197 strength and weaknesses were identified, and a conceptual model illustrated.

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2
3 198 **Results**

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5 199 ***Parameter comparison***

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8 200 Overall, 65 parameter estimates were harvested from 48 papers (Tables 1, 2, 3).

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10 201 *Infectious period for asymptomatic cases (T2)*

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12 202 The overall distributions and point estimates from studies for T2 are presented in Figure 1 and Table
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16 204 Two virological studies reported on infectious period based on serial diagnostic testing, for
17 205 asymptomatic cases, were found to have informative data. One of these studies reported on only
18 206 one asymptomatic case, with exposure to negative tests being 11 days (Zhou et al, 2020). This
19
20 206 one asymptomatic case, with exposure to negative tests being 11 days (Zhou et al, 2020). This
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22 207 duration should be considered an over-estimate, given that a latent period is not taken into
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24 208 consideration. Hu et al. [7] tracked infections of close contacts to infected persons and considered
25 209 patients asymptomatic at time of diagnosis. Infectious period was defined as time from diagnosis to
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27 210 the first of two clear tests, providing a median duration of 9.5 days (n=24) range: 1 – 21; 3.5-13.0
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29 211 IQR.

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31 212 Importantly, Hu et al. [7] found that the infectious period was different between those who
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33 213 subsequently exhibited symptoms (i.e. pre-symptomatic) and those who did not: The median
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35 214 duration for asymptomatic infectious was 6.0 days (IQR: 2.0 - 12.0; N=19). This was reduced to 4.0
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37 215 days (2.0 - 15.0) for cases that were asymptomatic without abnormal computed tomography (CT)
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39 216 scans (n=7).

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41 217 Two tracing studies provide informative data (Table 1; [7,8]). Infectious period was inferred
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43 218 indirectly from data provided in Ma et al. [8], whereby infectious period was estimated as the
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45 219 difference between the upper latent period estimate minus the serial interval. Ma et al. [8] reports
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47 220 on 49 asymptomatic cases and inferred serial interval from infector-infectee pairs. Serial interval was
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49 221 calculated by assuming “onset” was at first diagnosis. Hu et al. [7] reported on a case-study cluster
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51 222 of infection within a house where the primary case was asymptomatic. Secondary infections
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53 223 occurred 4-9 days after index case exposure, the index patient tested positive until day 29 post
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55 224 exposure.

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57 225 Modelling studies that have attempted to fit differing parameters depending on the severity of
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59 226 symptoms have used differing nomenclature, for example asymptomatic, “mild” or subclinical cases
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227 (Table 1).[14,15,26,27] Two papers by Davies and colleagues [14,15] model this parameter as a

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3 228 gamma distribution with a mean periods of 5-7 days (Fig. 2); importantly, these papers assume
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5 229 infectious period is the same for asymptomatic and symptomatic cases.

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7 230 Pre-symptomatic, infectious period (T3)
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10 231 Pan et al. [3] and Hoehl et al. [28] describe the cases of two individuals tracked and serially tested by
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12 232 real-time reverse transcriptase polymerase chain reaction (RT-PCR) after being exposed to a patient
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14 233 with confirmed infection. In the latter study, the virus was isolated from samples, indicating
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16 234 transmission potential.

17 235 Four studies from China, Germany and Singapore provide informative data through tracing infections
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19 236 from cluster of infections, and through infector-infectee pairs (Table 2).[4,9,29,30] These papers
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21 237 included the study by Rothe et al. [9], which clarified that an asymptomatic patient visiting Germany
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23 238 from China may have actually experienced very mild symptoms around the time of transmission
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25 239 occurred (see discussion).

26 240 Five modelling papers incorporated pre-symptomatic infectious period reported as prior
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28 241 distributions or estimated as a model output. Two papers describe the prior distribution using a
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30 242 gamma distribution.[14,15] Tindale et al. [31] provide mean point estimates under four different
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32 243 scenarios (two populations, early and late epidemic period). Peak et al. [32] derives estimates of the
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34 244 pre-symptomatic infectious duration from a model of serial interval, and report scenarios where
35
36 245 there are pre-symptomatic infectious periods.

37 246 The approximated distributions are simulated in Figure 2, which demonstrates the between-study
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39 247 heterogeneity in this parameter. The point estimates primarily cluster around the central tendencies
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41 248 of the distributions, except for Tindale et al. [31], for a model reporting for late occurring cases in
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43 249 Tianjin, China (8.2 days).

44 250 Post-symptom onset, infectious period (T5)
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46 251 The T5 parameter was informed from three lines of evidence from empirically driven studies:

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49 252 • time from symptoms onset to the first of two clear RT-PCR tests
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51 253 • time from symptoms to hospital discharge
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53 254 • time from symptoms to death

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55 255 Figure 3 presents the forest plot for the mean time from symptom onset to clearance, based on
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57 256 serial testing meta-analysis (n=15). The mean estimated duration was 13.4 days (95%CI: 10.9-15.8).
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59 257 There was high heterogeneity across studies (Cochrane's Q; p<0.001; I²>75%). A random effects (RE)
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258 meta-regression model suggested significant variation depending on whether studies included

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3 259 children as part of the sample (n=15 studies; Proportion of between-study variance explained
4 Adj. $R^2 = 43.8\%$). Overall, the model estimated studies including children had on average 5.8 days
5 260 shorter duration than adult only studies (95%CI: 1.7-10.0; $p=0.040$; $SE(p)=0.003$). A second univariate
6 261 RE meta-regression model suggested that there was non-significant increased mean duration of 4.0
7 262 days (95%CI: -0.6-8.6; $p=0.111$; $SE(p)=0.005$; Adj. $R^2 = 22.0\%$; $n=14$) for studies that included
8 263 moderate-severe or severe cases, relative to mild or mild-moderate severity cases.
9 264

10 265 High transmissibility during the first 5 days post symptom onset was described by Cheng et al. [33],
11 266 based on secondary attack rates for 12 infector-infectee pairs. No contacts (n=1043) with primary
12 267 cases were infected after five days of the index case onset of symptoms, inferred by the authors to
13 268 suggest transmission occurring at symptom onset (but conceivably also suggest pre-symptomatic
14 269 infection). Based on a cumulative density function, the authors suggest that infectiousness declines
15 270 rapidly from onset of infection (distribution was truncated at 30 days); estimated cumulative
16 271 infectiousness was 66.9% (95%CI: 28.7-94.8) by day 1, and reached 86.9% (95%CI: 64.3-99.5) by day
17 272 5 post-symptom onset (Figure S2).

18 273 For tracking studies relating to time to hospital discharge or death, raw case level data were
19 274 available (studies n=3).[31,34–36] Histograms of the raw data are presented in Figure 4, along with
20 275 the aggregated distribution. A random effect model suggested a mean duration of 18.1 days (95%ci:
21 276 15.1 – 21.0). However, there was significant variation across studies, with time to discharge being
22 277 4.96 days shorter (95%CI: 2.15- 7.76; [35]), or 3.79 days shorter (95%CI: 0.8-6.7; [31]), than time-to-
23 278 death [34].

24 279 Two modelling papers use priors (mean: 3.2-3.5 days) to represent clinical infectious period.[14,15]
25 280 However, the distribution for this parameter is right censored when patients are hospitalised or
26 281 isolated and therefore not an estimate of the full infectious period *per se*.

27 282 Infectious period for symptomatic cases (T3+T5)

28 283 Two tracing studies supplied parameter estimates for the full infectious period for patients who
29 284 develop symptoms. [8,29] He et al. [29] inferred from a publicly available dataset of 77 infector-
30 285 infectee pairs that infectiousness began 2.3 days (95% CI, 0.8–3.0 days) prior to symptom onset,
31 286 peaking at 0.7 days (95% CI, -0.2–2.0 days), and continued up to 7 days from onset. The authors
32 287 suggest that the transmission risk diminishes 7 days post symptom onset. This suggests that the
33 288 average infectious period, assuming a symptomatic infectious period of 7 days was approximately
34 289 9.3 days (7.8-10 days 95%CI, where CI is only reported for the pre-symptomatic period). He et al.
35 290 [29] estimated that the proportion of all transmission that was pre-symptomatic was 44% (95% CI,

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3 291 25–69%). Ma et al. [8] analysed data from a number of countries (China, Germany, Japan, Malaysia,
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5 292 Singapore, Vietnam), collating 1155 cases from public data. They estimate several parameters,
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7 293 including “maximum latent period” and the serial interval. The authors estimated the infectious
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9 294 period as maximum latent period minus the serial interval. Given their parameter estimates and
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11 295 methodological approach, infectious period would have been 5 days (range 0-24; IQR: 2-9;
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13 296 calculated from data presented within the paper).

14 297 Seven modelling papers reported duration of infectious period (T_3+T_5 ; Table 4), with the reported
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16 298 central tendency for the distribution varying from 3-20 days. The form of the distribution offered to
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18 299 models for this parameter varied considerably, including point estimates (deterministic models), flat
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20 300 (uniform), Gaussian, Weibull and gamma distributions. Li et al. [27] estimated the shortest median
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22 301 duration of 3.45 days, with a flat (uninformative) prior distribution corralled between 3-5 days. In
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24 302 contrast, Zhu et al. [37] used a mean prior of 10 days, with the model estimated mean duration
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26 303 being 12.5 days (variance 10; Weibull distribution). Piccolomini and Zama [38] used a fixed estimate
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28 304 of 20 days infectious period, to model the Italian epidemic. Two papers from the same group [14,15]
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30 305 suggested that infectious period for asymptomatic cases approximated for symptomatic cases where
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32 306 there was no right censoring (that is, transmission being halted through isolation or hospitalisation;
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34 307 gamma distributions of mean 5 or 7 days). Tuite et al. [26,39] also assumed the same duration for
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36 308 “mild” and “severe” symptomatic cases (6-6.5 days).

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310 ***Viral load dynamics***

311 Viral load was reported from 21 papers using real-time reverse transcriptase polymerase chain
312 reaction (rRT-PCR) testing, generally post-symptomatic monitoring.[3,29,40–59] Qualitatively, the
313 viral dynamics described early increase in viral load, peaking around onset or within 2-4 days of
314 symptom onset (Figure 5 for a theoretical model), before decreasing gradually over the next one to
315 three weeks post symptom onset. Maximum duration of detection ranged from approximately 20-49
316 days, with the longest duration associated with faecal samples (see below for discussion). The
317 duration where ribonucleic acid (RNA) was recoverable by RT-PCR may have been truncated due to
318 insufficient follow-up in some cases. Studies that have investigated blood samples have provided
319 some evidence for an association with severity of infection [16,60], though it is not clear whether
320 this is a consistent feature of SARS-CoV-2 infection [40].

321 It should be noted the lack of data on pre-symptomatic or asymptomatic cases with regards viral
322 load. An exception was Kam et al. [61] who describe a pre-symptomatic case in an infant. In another
323 study, Zou et al. [53] undertook serial RT-PCR testing from nasal and throat swab samples from 14
324 imported cases, and 4 secondary cases, in Guangdong, China. The dynamics of the infection in terms
325 of cycle threshold (Ct) values and RNA copy number were described; Ct values of 30.76, 27.67,
326 24.56, and 21.48 corresponding to 1.5×10^4 , 1.5×10^5 , 1.5×10^6 , and 1.5×10^7 copies per milliliter.
327 Hence, lower Ct values infer higher viral loads. The authors report on a patient without symptoms,
328 but with positive nasal swabs (Ct values, 22 to 28) and throat swabs (Ct values, 30 to 32) testing
329 positive on days 7, 10, and 11 after contact. Importantly, the authors suggest “the viral load that was
330 detected in the asymptomatic patient was similar to that in the symptomatic patients.”
331 Furthermore, Kimbell et al. [62] report that Ct values between asymptomatic (21.9 to 31.0), pre-
332 symptomatic (15.3 to 37.9), and symptomatic cases (18.6 to 29.2) within a nursing home
333 environment did not differ significantly. To et al. [59] present data on temporal profile of viral load
334 from saliva samples, and found that median initial and peak viral loads in severe cases were non-
335 significantly higher ($p > 0.5$) by approximately 1 log₁₀ higher than those in mild cases. Liu et al. [58]
336 present data showing viral load being 60 times greater for severe cases relative to mild cases.

337 This lack of pre-symptomatic data may result in left truncation of the risk distribution associated
338 with viral load and shedding. Therefore, the typical timing of peak viral shedding (whether prior to,
339 at, or after onset), and its impact on transmission, is still uncertain. He et al. [29] reported highest
340 viral load at symptom onset from patients sampled in a hospital in China. Furthermore, the author’s
341 estimate using a separate infector-infectee dataset (n=77) that 44% (95% CI: 25–69%) of infectee
342 cases were infected during the pre-symptomatic stage of the infector. Separately, a modelling paper

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3 343 by Ferretti et al. [63] also appears to support this, estimating that 47% (0.9/2) of total transmission
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5 344 contributing R_0 , an overall measure of transmission during an infection, was pre-symptomatic (also
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7 345 see [33]).

8
9 346 Wölfel et al. [50] provides important data on a cohort of nine 'mild' cases which were serially tested
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11 347 using sputum, swabs (throat and nasopharyngeal), urine and faecal samples over time. Importantly,
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13 348 the virus was isolated, and inferences on viral replication could be made. Viral Isolation, and insights
14
15 349 into viral replication, improve inference around viral dynamics and transmission risk. The study
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17 350 suggested high viral loads shortly after symptom onset, which declined thereafter over time. Positive
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19 351 cultures were found from day 3-8 post-symptom onset (Figure S3), and the minimum 5% isolation
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21 352 success was achieved up to 9.8 (95% CI: 8.5-21.8) days post onset from throat and lung samples but
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353 not faeces, blood or urine.

354 Discussion

355 Inferring infectiousness was challenging given the heterogeneity of evidence available. Virological
356 diagnostic studies provide robust time series of infection, however, is limited by inferring the
357 relationship between PCR diagnostics and infectiousness. These data can also be affected by
358 sampling procedure and sample sites (e.g. upper respiratory, lower respiratory, faeces, urine, blood).
359 We have excluded RT-PCR durations based on faecal sampling due to the uncertainty whether these
360 data pertain to transmission potential ([50]; see below). Virological studies where culturing has
361 taken place, and where viral replication can be inferred would also be considered superior data to
362 infer infectious period, relative to estimates of viral load alone.[50] Where this has taken place, the
363 data would suggest average infectious periods of up to 9.8 days post-symptoms. Recent modelling
364 work suggest that the duration of viral detectability could overestimate the infectious period
365 somewhere between 2-6 days.[64]

366 Viral load studies suggest peak viral load occurs close to symptom onset (potentially, -1 to 7 days of
367 onset), however there is uncertainty whether this typically occurs prior to, on, or after onset (Figure
368 5 for conceptual model). High viral loads, measured as Ct values, have been recorded for one week
369 to 20 days post symptom onset, with a general decreasing trend with time. For example, To et al.
370 [59] estimates a declining slope per day for log₁₀ RNA copies per ml of -0.15 (95% CI -0.19 to -0.11;
371 $R^2=0.71$). There are some studies reporting associations between viral load and symptom severity,
372 with higher metrics of viral load in severe cases.[3,58,59] However, Zou et al. [53], and more recent
373 data from Italy,[64,65] suggest similar viral loads in symptomatic and asymptomatic cases.

374 We tested the hypothesis that severity of symptoms had an effect on symptomatic infectious
375 duration using a meta-regression approach. There was a trend towards studies that included severe
376 cases tended to have longer duration (estimated to be 4.0 days longer), but the effect was not
377 significant. Some studies have reported an association between duration of infectiousness and
378 severity (e.g. [58]). But uncertainty of whether this is robust remains.

379 Virological studies that included children (either mixed adult children, or children only cohorts)
380 appeared to have shorter T5 durations (estimate: 5.8 days shorter). Liao et al. [66] present data
381 which suggests that children and 'young adults' (<35 years old) infected cases exhibited long
382 incubation time (exposure to symptom on-set; mean 7.2 days), and short serial interval (mean 6.5
383 days; median 1.9 days; time from onset in primary to onset in secondary case).

384 Contact tracing studies provided robust evidence of transmission events, and therefore
385 infectiousness, but can be limited by the inferred timing of events, and symptoms experienced, due

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3 386 to the self-reported nature of data collection (recall bias). The subjective nature of self-reporting
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5 387 indeed can have an impact on case definitions of 'asymptomatic', which has led to some doubt on
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7 388 asymptomatic transmission in one case.[9] Rothe et al. [9] describe a case of apparent asymptomatic
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9 389 transmission from a Chinese visitor to business associates in Germany, which was cast into doubt
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11 390 when health officials reported that the patient had indeed experienced some, albeit minor,
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13 391 symptoms.[67] Rothe et al. [9] subsequently updated the clarification of the patients self-reported
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15 392 symptoms during the presumed asymptomatic infectious period, which included "feeling warm" and
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17 393 "feeling cold". However, the patient only "recognized getting sick" after she returned to China on
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19 394 day four after the presumed exposure event.

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21 395 Modelling parameters provide information on how COVID-19 data are being used and interpreted in
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23 396 the research community, given the limited data available. Posterior estimates also provide
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25 397 information on the parameter space at which infectious period central tendency reside, given other
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27 398 parameters and assumptions in the model. Models used highly varied approaches to modelling
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29 399 infectious period, which in turn resulted in highly variable parameter estimates used to inform the
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31 400 studies.

401 *Overall duration findings*

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33 402 There are few data for the precise definition of the asymptomatic infectious period (T2) parameter.
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35 403 Some reported asymptomatic cases can actually be pre-symptomatic, when cases are subject to
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37 404 follow-up (e.g.[66]; see discussion above). However, Hu et al. [7] do provide the data for
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39 405 asymptomatic cases [that remain asymptomatic] across their presumed infectious period. Therefore,
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41 406 in the first instance a parameter mimicking their data is probably the best available data. Note, there
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43 407 is a large variation in this data parameter, and a gamma distribution of a shape alpha 3, beta 2, mean
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45 408 6, may be appropriate for the initial model runs. Despite these being the primary informative data,
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47 409 caution is required, given the uncertainty around the relationship between RT-PCR results and
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49 410 infectiousness. Overall, an informed central tendency of ~6 days, with very low probability draws for
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51 411 durations >20 days for the T2 parameter may be considered given the current state of knowledge.

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53 412 The pre-symptomatic period is sometimes referred to as 'preclinical infectious' period (parameter
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55 413 T3). This has been estimated from several papers, and the central tendency of these estimates vary
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57 414 from <1 - 4 days, cautiously approximating to 2 days, on average. The maximal reported period for
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59 415 T3 from any population, was reported by Tindale et al. [31] at 8.2 days. Current models have used
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416 central tendency estimates of 0.5 to 2.4 days.[14,15,26,39] It should be noted, that this period could
417 also be measured as the difference between incubation and latent period, or the difference between
418 serial interval and incubation period.[12] The relative consistency around the duration of this period

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3 419 allows for some confidence of its distribution. Current understanding of viral dynamics of infection
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5 420 suggest that viral load and shedding increases during post-latent phase, peaking around onset [for
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7 421 symptomatic cases], before declining.[29,50,53] This aspect of the natural history of infection may
8
9 422 be important when attempting to model transmission dynamics.

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11 423 Length of infectious period in symptomatic cases that do not isolate (T5 parameter) has also been
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13 424 rarely directly measured in the literature, as serial monitoring of patients in terms of symptoms or
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15 425 viral load (rt-PCR) generally occurs after diagnosis and/or after admission to hospital [from a
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17 426 modelling perspective, this means cases are censored as they are assumed to no longer contribute
18
19 427 to transmission]. If natural progression of infection after diagnosis or hospital admission mimics the
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21 428 course of infection for those who do not isolate, the review of the literature describing time to two
22
23 429 clear tests is informative. Symptom onset to serial testing clearance [assessed the time to first of two
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25 430 RT-PCR clear tests] averaged 13.4 days (95%CI: 10.9-15.8) from our meta-analysis. In the maximal
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27 431 case, where patients succumb or fully recover from infection, time from symptoms to death or
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29 432 discharge may be informative. Studies that collated such information suggest mean durations of
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31 433 18.07 days (95%ci: 15.14 - 20.99), but with time to discharge being 4.96 days shorter (95%CI: 2.15-
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33 434 7.76) on average than time to death. These values may represent an over estimation of the
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35 435 infectious period; one study suggested that there was on average 2.5 days between end of
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37 436 infectiousness and 'removal' (recovery or death).[37]

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39 437 Cheng et al. [33] provided evidence of transmissibility, based on attack rate from primary to
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41 438 secondary cases, at around symptom onset. The authors estimate cumulative infectiousness from
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43 439 onset, which suggests that 67% of total infectiousness potential occurs by the first day post-onset.
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45 440 Most of the total infectiousness occurs within 5 days (86.9%) post onset, with the remaining
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47 441 infectiousness potential (13.1%) being distributed up to day 30 (this truncation is an assumption by
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49 442 the authors). It is possible that pre-symptomatic transmission occurred during this study, but the
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51 443 authors do not estimate what proportion of transmissions occurred during a pre-symptomatic
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53 444 infectious period, or its potential duration.

54
55 445 A model by He et al. [29] is informative for overall symptomatic duration (T3+T5), using 77 infector-
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57 446 infectee pairs where COVID-19 transmission occurred in China. The study reported that
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59 447 infectiousness was apparent on average 2.5 days prior to symptoms, reached a peak in risk at 0.6
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448 days before symptoms, and decline up until 7 days after onset (9.5 days total infectious period). The
449 proportion of transmission before symptom onset (area under the curve) was estimated as 44%
450 (95% CI, 25–69%), based on inferences on incubation period. The authors suggest their data
451 supported the view that transmission risk decline substantially after 7 days post-symptoms onset.

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3 452 Model estimates used for infectious period parameter appears to be shorter than virological studies
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5 453 tracking RNA viral load over time. For example, Liu et al.[27] fitted a flat prior distribution for mean
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7 454 duration (D) fixed to vary between: $2 \leq D \leq 5$ days, and Lavezzo et al. [64] fixed infectious period to 2
8
9 455 days in their epidemic model; whereas viral repeat testing studies provide evidence to suggest high
10
11 456 viral loads can be detected to up 20 days [e.g. pharyngeal swabs], and potentially longer from faecal
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13 457 samples (up to 3-4 weeks post symptoms onset). Oral-faecal transmission risk is currently unknown,
14
15 458 but some doubt has been raised about studies that have reported positive RTPCR test results (see
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17 459 [68]; but there may be some evidence of the risk amongst children; [69]). Wölfel et al. [50] has
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19 460 produced an important study that provides some data on viral replication, and the site and duration
20
21 461 over which this may be taking place. Their data suggests that viral replication, with high viral loads,
22
23 462 occur in the upper respiratory tract, over the first week of symptoms peaking in day 4. Virus could
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25 463 not be isolated from faecal samples, despite high RNA concentration. Furthermore, virus was not
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27 464 isolated from blood or urine in that study.[50]

465 **Study limitations**

27 466 Overall, the studies included were of good quality, though due to the rapid need for information
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29 467 from the global research community many papers are pre-prints that have yet to be reviewed (at
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31 468 time of writing). Many papers were limited in terms of sample sizes, with several papers being case
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33 469 studies of one patient or single cluster outbreaks. There was a diversity of methods employed to
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35 470 infer dynamics of infectiousness across studies, and therefore the evidential base was variable. Some
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37 471 issues around nomenclature were noted, including definitions of asymptomatic, infectious period,
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39 472 latent, and incubation period. It is possible the same data may have been used across different
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41 473 studies, especially where publicly available data were used.

41 474 There was significant heterogeneity across study findings, and this was related to diversity of clinical
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43 475 findings and methods employed. The meta-analysis employed for one parameter (T_5) using
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45 476 virological studies, where cross study comparisons could be made, suggested that the heterogeneity
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47 477 was high. Fu et al.[70] cautions against combining studies to give an overall estimate without
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49 478 exploring subgroup or meta-regression analysis, which we have done here. The meta-regression was
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51 479 based on a small number of studies ($n=12-13$). Cochrane's handbook suggests 10 studies for each
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53 480 level of a meta-regression, however in practice much lower numbers have been used to test
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55 481 hypotheses [22], as is the case here. Fu et al. [70] recommend a minimum of 4 studies per category,
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57 482 and therefore we dichotomised our predictor variables to ensure we met this minimum. Aggregating
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59 483 our categories resulted in crude findings.

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3 484 Another limitation is that a systematic review was not undertaken to inform this research, hence
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5 485 there is a possibility that some relevant studies were overlooked. However, comprehensive search
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7 486 strategies were conducted by two independent research groups to inform this research, hence
8
9 487 limiting the potential for missing key studies.

10 488 **Conclusion**

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13 489 There are few data to inform asymptomatic infectious period (T2 parameter). One study provide
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15 490 data that suggest a median period of 4-9.5 days, however, given the viral dynamics, this distribution
16
17 491 could have an extended tail with low probability long infectious periods of up to 20 days. The pre-
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19 492 symptomatic infectious phase (T3) is quite narrowly defined to a mean of approximately 2 days
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21 493 (range: <1-4) within the literature. However, there is great uncertainty around the infectious period
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23 494 from onset to recovery or death (T5 parameter). The symptom onset until clearance (based on two
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25 495 negative RT-PCR tests) parameter estimate of 13.4 days (95%CI: 10.9-15.8) is informative for T5
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27 496 parameter, only if one assumes that RT-PCR positive results equate to having infectious potential.
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29 497 Many current models corral the infectious period to shorter time periods than what virological
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31 498 studies have suggested, with one recent study suggesting that duration of viral detectability over-
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33 499 estimates the infectious period on average by 2-6 days. While viral RNA can be detected for long
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35 500 periods of time, especially from faecal samples, the ability to isolate the virus ifrom nfecteds cases
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37 501 quickly declines after one-week post-symptoms. Some modelling papers have assumed that
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39 502 infectious period is invariant to whether cases are asymptomatic or symptomatic, however, the data
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41 503 available are not yet rich enough to inform whether this is a good assumption. Similarly, it is not yet
42
43 504 established whether viral loads are similar between asymptomatic and mild, moderate, or severe
44
45 505 symptomatic cases, with conflicting reports in the literature.

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48
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56
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58
59 512 literature searches; DM, KOB, KW conducted searches and screened shortlisted studies; AWB
60
61 513 completed the initial draft of the manuscript; CM reviewed the statistical methods; CM and MC
62
63 514 undertook quality control interim review; All authors read and approved the final manuscript.

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2
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5 517 www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted
6
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8
9 519 work in the previous three years; no other relationships or activities that could appear to have
10
11 520 influenced the submitted work

12 521 **Patient and public involvement statement:** It was not appropriate or possible to involve patients or
13
14 522 the public in the design, or conduct, or reporting, or dissemination plans of our research
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738 Tables and figures

739

740 **Figure 1:** Simulation of the parameter distribution inferred for duration infectious period for
741 asymptomatic cases (T2) inferred infectious period for Davies et al. (2020a), grey/blue curve, Davies
742 et al. (2020b) pink curve [model priors]. Green curve: Ma et al. (2020). Histogram is the distribution
743 of asymptomatic cases to two clear tests reported by Hu et al. (2020). Reference lines are point
744 estimates reported from Zhou et al. (2020), Li et al. (2020), and Tuite et al. (2020a &
745 b).[7,8,14,15,26,27,39,71]

746 **Figure 2:** Simulation of the parameter distribution used for T3 (the duration of the pre-symptomatic
747 infectious period for those infected individuals who subsequently develop symptoms). Curves
748 represent simulated approximations of distributions, given information provided from primary
749 literature. Vertical lines represent point estimates where distributions could not be inferred (see
750 table 2). 1. Peak et al. [posterior]; 2. Davies et al. 2020b [prior]; 3. Rothe et al. 2020; 4. He et al.
751 2020; 5. Davies et al. 2020a [prior]; 6. Wei et al. 2020. [9,14,15,29,30,32]

752 **Figure 3:** Forest plot of the mean duration from onset of symptoms to death or recovery (T5) based
753 on virological studies

754 **Figure 4:** Frequency distribution of T5, time from onset of symptoms to recovery (here hospital
755 discharge or death), using patient level raw data from Kraemer et al. ([35,36]; pink bars), Linton et al.
756 ([34]; purple bars) and Tindale et al. ([31]; green bars). Blue solid line is the kernel density of the
757 aggregated dataset Dashed lines represent the mean and 95%CI from a random effects regression
758 model.

759 **Figure 5:** Composite inferred model for cycle threshold (CT) value changes from serial RT-PCR testing
760 for SARS-COV2; currently uncertain whether peak viral load typically occurs prior to, on, or post-
761 symptom onset (primary literature informing this model includes [29,50,53,59]).

762

763 **Table 1:** Reported infectious period (IP) for asymptomatic cases (T5 parameter) from virological
 764 studies where serial diagnostic tests were undertaken to infer IP; tracking studies where IP is
 765 inferred from contact tracing; modelling studies where IP is reported as a prior (assumed parameter
 766 value) or an posterior estimate.

No.	Study	Countries	Parameter (days)	n	Central tendency reported	Variation (days; inclus.)	Comment
<i>Virological studies</i>							
[71]	Zhou et al. (2020)	China	11 days	1	Max		This study serially swabbed and tested symptomatic (17) and asymptomatic (1) cases via RTPCR. The single asymptomatic case tested positive up to 11 days post contact with an infected patient (presumed point of exposure).
[7]	Hu et al. (2020)	China	9.5 days	24	Median	1-21 range	Serial testing. Period between “onset” (where onset relates to first positive test) and clearance, adjudged via two negative RTPCR tests, deemed by the authors to be the ‘communicable period’. IQR: 3.5-13
<i>Tracking studies</i>							
[8]	Ma et al. (2020)	China, Germany, Japan, Singapore, South Korea, Malaysia, Vietnam	7.25 days*	49	Mean	5.91-8.69 (95%CI)	*Ma et al. (2020) does not report infectious period for asymptomatic cases explicitly within their paper. The authors estimated the infectious period as the upper estimated latent period minus the serial interval, using a dataset of 1155 cases from several countries (latent period was estimated with 11 infector-infectee pairs; serial interval was estimated from 689 infector-infectee pairs). Ma et al. (2020) reported a mean upper limit of latent period of 2.52 days; the mean serial interval for asymptomatic cases (using date of diagnosis for onset) was estimated to be 9.77 (94%CI: 8.43, 11.21).
[7]	Hu et al.	China		3		4-9	Cluster of infection within a

	(2020)					range	family, where the primary case was asymptomatic. The transmissions to secondary cases occurred over a period 4-9 days post the presumed point of exposure for the primary case.	
Modelling studies								
[27]	Li et al. (2020)	China	3.5* [posterior from a model estimating duration for undocumented cases]			Median	3.19-3.78 95%CI	Li et al. (2020) do not explicitly attempt to model asymptomatic cases, or their infectious duration. Instead the population infected is divided into 'documented' and 'undocumented'. Documented were all cases where patients had symptoms severe enough to be confirmed infected; all other cases were considered undocumented. Therefore, this estimate represents asymptomatic and 'mild' cases. The 95%CI around the median infectious period estimate was 3.19-3.78
[26,39]	Tuite et al. (2020a &b)	Canada	6-6.5 [Prior]			[Fixed parameter within a deterministic model]		Mathematical model [deterministic], with a fixed parameter estimate of 6 or 6.5 days. Important to note that duration for 'mild' was equal to severe cases.
[14]	Davies et al. (2020) (a)	UK	7 days [Prior]			Mean		Model with asymptomatic infection compartment. Modelled with a gamma distribution, beta 1.4; alpha 5. Despite, the subclinical aspect of this parameter, it could be considered analogous to total infectious period without intervention.
[15]	Davies et al. (2020) (b)	UK	5 days [Prior]			Mean		Model with asymptomatic infection compartment. Modelled with a gamma distribution, k=4. Authors: "Assumed to be the same duration as total infectious period for clinical cases, including preclinical transmission"

767

768 **Table 2:** Reported infectious period (IP) for pre-symptomatic cases (T3 parameter) from virological
 769 studies where serial diagnostic tests were undertaken to infer IP; tracking studies where IP is
 770 inferred from contact tracing; modelling studies where IP is reported as a prior (assumed parameter
 771 value) or an posterior estimate.

	Study	Location	Parameter (days)	Central tendency reported	Variation (days; inclus.)	Comment
	<i>Virological studies</i>					
[3]	Pan et al. (2020)	Beijing, China	1	Median		Case study of two individuals tracked due to exposure to an infected patient was serially tested prior to onset of symptoms.
[28]	Hoehl et al. (2020)	Flight from Wuhan to Germany	1	Median		Case study of serially tested at risk cohort flying from Wuhan to Germany. Two patients were asymptomatic test positive; additionally virus isolation was achieved, indicating potential infectiousness.
	<i>Tracking studies</i>					
[4]	Huang et al. (2020)	Nanjing, China	4	Median	3-5 range	Follow-up tracing case study cluster of infection within a family demonstrating pre-symptomatic infection (n=10)
[9]	Rothe et al. (2020)	Germany	2	Median	1-3 range	Tracing case study of a cluster of infections whereby pre-symptomatic transmission occurred (n=3).
[29]	He et al. (2020)	Vietnam, Malaysia, Japan, China, Taiwan, USA, Singapore	2.3	Mean	95% CI, 0.8–3.0	Tracing paper infector-infectee pairs. Estimated from serial interval and incubation periods. N=77
[30]	Wei et al. (2020)	Singapore	2.5	Median	2-3 (IQR)	Tracing study investigating pre-symptomatic infections from primary cases to secondary cases in 7 clusters. N=8 primary cases. T3 estimated as the min. days between transmission period (TP) and primary case

						symptom onset, when TP straddled >1 day. Range: 2-6 days.
	Modelling studies					
[32]	Peak et al. (2020)	Massachusetts	0.8 [estimate]	Mean	-0.29-1.98 95% CI*	Modelling paper estimated under two scenarios – a serial interval of 4.8 days or 7.5 days. Under scenario one, the model estimated a period of pre-symptomatic transmission (median: 0.71). * the lower range was fixed at zero as the model allowed for no pre-symptomatic infectious case.
[37]	Zhu et al. (2020)	Wuhan, China	1.0 [estimate]	Mean		Modelling paper. Model estimated point value – This is a model derived value
[14]	Davies et al. (2020) (a)	UK	2.4 [prior]	Mean		Modelling paper. Gamma distribution; k=5.
[15]	Davies et al. (2020) (b)	UK	1.5 [prior]	Mean		Modelling paper. Gamma distribution: k=4
[26,39]	Tuite et al. (2020a & b)	Canada	0.5, 1 [prior]	Fixed		Modelling paper. Fixed parameter within a deterministic model.
[72]	Ferguson et al. (2020)	UK	0.5 [prior]	Fixed		Modelling paper. Fixed parameter within a this model, whereby infectiousness was assumed to begin 12 hours before symptoms.
[31]	Tindale et al. (2020)	Tianjin, China, and Singapore	2.9-2.6 [estimate]	Mean	1.2-8.2 mean range, depending on early or late cases, or whether in Tianjin, Singapore	Statistical modelling study estimating period pre-symptomatic transmission inferred from estimates of serial interval and incubation periods for populations in Tianjin and Singapore (n=228).

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773

774 **Table 3:** Reported infectious period (IP) for post-symptomatic cases (T5 parameter) from virological
 775 studies where serial diagnostic tests were undertaken to infer IP [onset to ≥ 2 tests]; tracking studies
 776 where IP is inferred from patient histories from onset to recovery or death; modelling studies where
 777 IP is reported as a prior (assumed parameter value) or an posterior estimate.

No.	Study	Location	Parameter (days)	Central tendency reported	Variation (days; inclus.)	Comment
<i>Virological studies</i>						
[73]	Cai et al. 2020 (a)	China	12	Median	6-22 range	Serial testing study of n=10 mild cases RT-PCR confirmed in children. IQR: 8-15 days
[74]	Cai et al. 2020 (b)	China	14	Median	9-19 (IQR)	Serial testing study with n=298 confirmed (RT-PCR) cases treated within hospital setting
[75]	Chen et al.(2020)	China	12	Max.		Single case study for a patient admitted to hospital where RT-PCR serial testing was undertaken. Patient had an additional positive test at day 17, but subsequently tested negative
[76]	Cheng et al. (2020)	China	21	Max.		Case study of single patient serially tested by RT-PCR
[7]	Hu et al. (2020)	China	12	Median	12-14 (IQR)	Serial testing study of patients who were first tested (qRT-PCR) when asymptomatic; this subset subsequently developed symptoms (n=5).
[42]	Kim et al. (2020)	Korea	15.5	Median	14-17 (range)	Serial testing of two confirmed cases via RT-PCR. Viral load highest during early phase of infection (day 3-5).
[43]	Kujawski et al. (2020)	USA	26	Max.		Serial testing of two confirmed cases via RT-PCR. Mild to moderate symptoms.
[77]	Lee et al. (2020)	Taiwan	20	Max.		Serial testing (RT-PCR) of a single patient hospitalised presenting with pneumonia
[44]	Lim et al. (2020)	South Korea	16	Max.		Serial testing (RT-PCR) of a single patient hospitalised presenting with pneumonia. Two clear tests day 11, virus

						detectable again up to day 16.
[78]	Ling et al. (2020)	China	9.5	Median	2-22 (range)	Serial testing of two confirmed cases via RT-PCR. n=66. IQR: 6-11 days, oropharyngeal sampling. Mix of adult and children.
[79]	Liu et al. (2020)	China	11	Median	7-18 range	Serial testing of two confirmed cases via RT-PCR. n=10. 10-13 (IQR); adults, mild, moderate, and severe cases.
[45]	Marchand-Senéca et al. (2020)	Canada	23	Max		Serial testing (RT-PCR) of a single patient hospitalised presenting with pneumonia.
[3]	Pan et al. (2020)	China	10	Median	8-12 range	Serial testing (RT-PCR) of two patients hospitalised. Viral loads peaked days 5-6 post-onset.
[80]	Qu et al. (2020)	China	22	Max		Serial testing (RT-PCR) of a single patient hospitalised
[46]	Tan et al. (2020)	Vietnam	16	Max		Serial testing (RT-PCR) of a single patient hospitalised; throat sample.
[47]	Thevarajan et al. (2020)	Australia	7	Max		Serial testing (RT-PCR) of a single patient hospitalised; throat sample. Highest viral load on first test at day 4 in nasopharyngeal; day 6 for sputum.
[69]	Xing et al. (2020)	China	14	Median		Serial testing (RT-PCR) of a three (children) patients hospitalised. Mild-moderate infecting. Positive viral samples from faeces up to 4 weeks post-symptoms.
[52]	Young et al. (2020)	Singapore	12.5	Median		Serial testing (RT-PCR) of 18 patients hospitalised. Adults. Viral load peaked over testing series at day 4 since onset.
[81]	Yuan et al. (2020)	China	6	Median	4-10 (IQR)	Serial testing (RT-PCR) of 25 patients hospitalised. Children and adults. "Non-severe" cases.
[71]	Zhou et al. (2020)	China	20	Median	16-23 IQR	Serial testing (RT-PCR) of 191 patients hospitalised in two hospitals. Adults. 54 died. Survivors (n=137); Median (IQR) 20.0 days (17.0–24.0); Non-survivors

						(n=54); Median (IQR) 18.5 days (15.0–22.0); Shedding continued until death. Inferred shedding period; 8-37 days.
[82]	Chen J. et al. (2020)	China	11	Median	10-12 (95%CI)	Serial testing (RT-PCR) of 242 patients hospitalised. Adults. 90% mild/asymptomatic; 10% severe/critical.
[60]	Fang et al. (2020)	China	15.7	Mean	6.7 (sd)	Serial testing (RT-PCR) of 24 non-ICU patients hospitalised. Adults. Nasal samples.
[60]	Fang et al. (2020)	China	22.3	Mean	3.6 (sd)	Serial testing (RT-PCR) of 8 ICU patients hospitalised. Adults. Nasal samples.
[57]	Hill et al. (2020)	Scotland	9	Max.		Serial testing (RT-PCR) of a single patient (adult) hospitalised; nasal sample [throat sample: 6 days]. Mild.
[83]	Le et al. (2020)	Vietnam	12	Max.		Serial testing (RT-PCR) of a single patient (infant) hospitalised. Mild.
[58]	Liu et al. (2020)	China	10	Max.		Serial testing (RT-PCR) of a patients hospitalised. Adults. Mixed Mild/severe cases. N=76. 90% “early viral clearance” within 10days
[84]	Qiu et al. (2020)	China	10	Mean	7-22 range	Serial testing (RT-PCR) of a patients hospitalised. Children. N=36. Mild and moderate cases.
[59]	To et al. (2020)	Hong Kong	25	Max.		Serial testing (RT-PCR) of a patients hospitalised. N=7. Seven patients reported viral detection >20 days; viral load peaked during first week post-onset of symptoms.
[85]	Wu et al.	China	16.1	Mean	6.7 (sd)	Serial testing (RT-PCR) of patients hospitalised. Adults. N=74. Severe and non-severe cases.
Tracking studies						
[31]	Tindale et al. (2020)	Singapore	18	Median	9-33 range	Time from onset to discharge; range 9-33; n=53
[35,36]	Kraemer et al. (2020a);	Various	19	Median	3-37 range	Time from onset to discharge; Range: 3-37;

	[later published as: Xu et al. 2020]					n=70
[34]	Linton et al. (2020)	Wuhan, China	13	Median	6-41 range	Time from onset to death; range 6-41
[35,36]	Kraemer et al. (2020b)	Japan and China	19.25	Mean	12-24 range	Time from onset to death; n=4
[49,50]	Wölfel et al. (2020)	Germany	3-8 days	absolute	3-8 range	Tracked infection in mild cases in Germany, undertaking viral isolation studies to assess active replication across a number of samples sites (upper respiratory tract, blood, urine, faeces) over the duration of infection. 5% isolation success was achieved up to 9.78 (95% CI: 8.45-21.78) days post onset; n=9

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Table 4: Reported infectious period (IP) for symptomatic cases (T3+T5 parameter) from virological studies where serial diagnostic tests were undertaken to infer IP [exposure to ≥ 2 tests]; tracking studies where IP is inferred from patient histories from onset to recovery or death; modelling studies where IP is reported as a prior (assumed parameter value) or an posterior estimate.

No.	Study	Location	Parameter (days)	Central tendency reported	Variation (days; inclus.)	Comment
Tracking studies						
[29]	He et al. (2020)	Vietnam, Malaysia, Japan, China, Taiwan, USA, Singapore	9.3 days	Mean	7.8-10 (95%CI*)	The paper reported on 77 infector-infectee pairs which were sequential/serially tested, using publicly available data. Viral dynamics (Guangzhou, China; N=94) interpreted by the authors suggested an infectious period starting 2.3 (95% CI, 0.8–3.0 days) days prior to symptoms, peaking 0.7 days (95% CI, -0.2–2.0 days), continuing up to 7 days from onset. * CI from pre-symptom infectious period only.
[8]	Ma et al. (2020)	Various	~5 days	Median	Range 0-24	The authors estimated the infectious period as latent minus the serial interval, using a dataset of 1155 cases. Range 0-24; IQR: 2-9; calculated from data presented within the paper.
Modelling studies						
[27]	Li et al. (2020)	China	3.45 days [posterior estimated from model for documented cases]	median	95%CI for the mean: 3.19, 3.72	Mathematical model. Priors for <u>mean</u> documented infectious period was a flat [uniform] distribution 2-5. 'Documented' cases were defined as those severe enough to be confirmed. This corraling of the infectious period relative to other

						studies should take into account that the distribution is used for the central tendency, not the whole distribution.
[26,39]	Tuite et al. (a, b) (2020)	Canada	6-6.5 days [prior; fixed parameter within a deterministic model]	Fixed parameter		Mathematical model [deterministic], with a fixed parameter estimate of 6.5 days (a) and 6 days (b), respectively. Important to note that duration for 'mild' was equal to severe cases.
[86]	Lourenco et al. (2020)	UK	~3-5 days [posterior; approximate depending on scenario tested]	mean	95%ci of 3-6 days	Mathematical model. The prior used was given a Gaussian distribution (normal curve); mean 4.5; SD 1; approximate 95%ci of 3-6 days. The reported posterior of this parameter was presented graphically and depended on R0 and proportion at risk. Depending on the scenarios tested, mean duration of infectiousness appeared to vary from 3-5 days.
[37]	Zhu et al. (2020)	Wuhan, China	12.5 days [posterior estimated from model]	Mean	11.4 variance	Mathematical model. The parameter was estimated using a Weibull distribution. The prior for this parameter was 10 days. The posterior variance around the mean was 11.4, and therefore the distribution had a long tail. This study was a modelling [SEIR extended model].
[15]	Davies et al. (b) (2020)	UK	7 days [Prior]	Mean		Model with asymptomatic infection compartment. Modelled with a

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						gamma distribution, beta 1.4; alpha 5. Despite, the subclinical aspect of this parameter, it could be considered analogous to total infectious period without intervention.
[14]	Davies et al. (b) (2020)	UK	5 days [Prior]	Mean		Model with asymptomatic infection compartment. Modelled with a gamma distribution, k=4. Authors: "Assumed to be the same duration as total infectious period for clinical cases, including preclinical transmission"
[38]	Piccolomini and Zama (2020)	Italy	20 days [Prior]	Fixed		Parameter estimate assumed for the infectious period within an SEIRD model, fitted to data from the epidemic in Italy.

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Review only

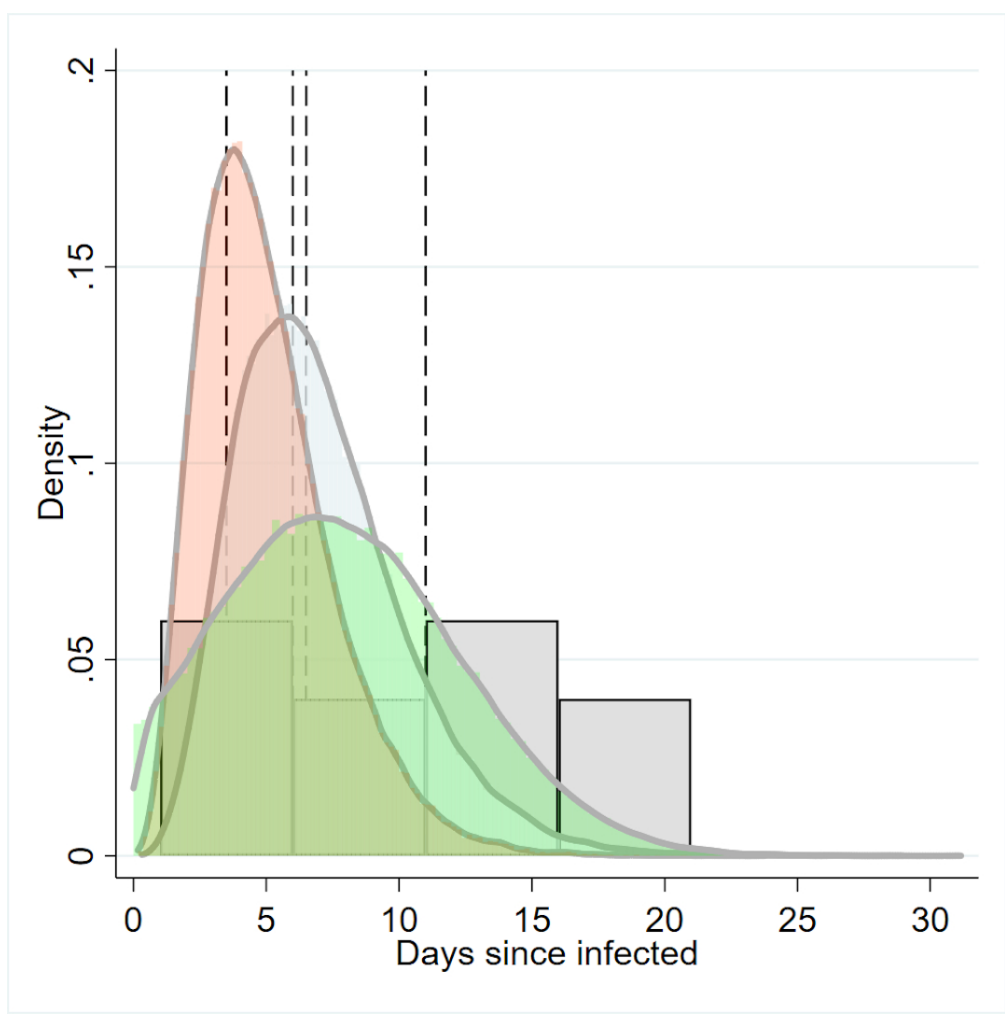


Figure 1: Simulation of the parameter distribution inferred for duration infectious period for asymptomatic cases (T2) inferred infectious period

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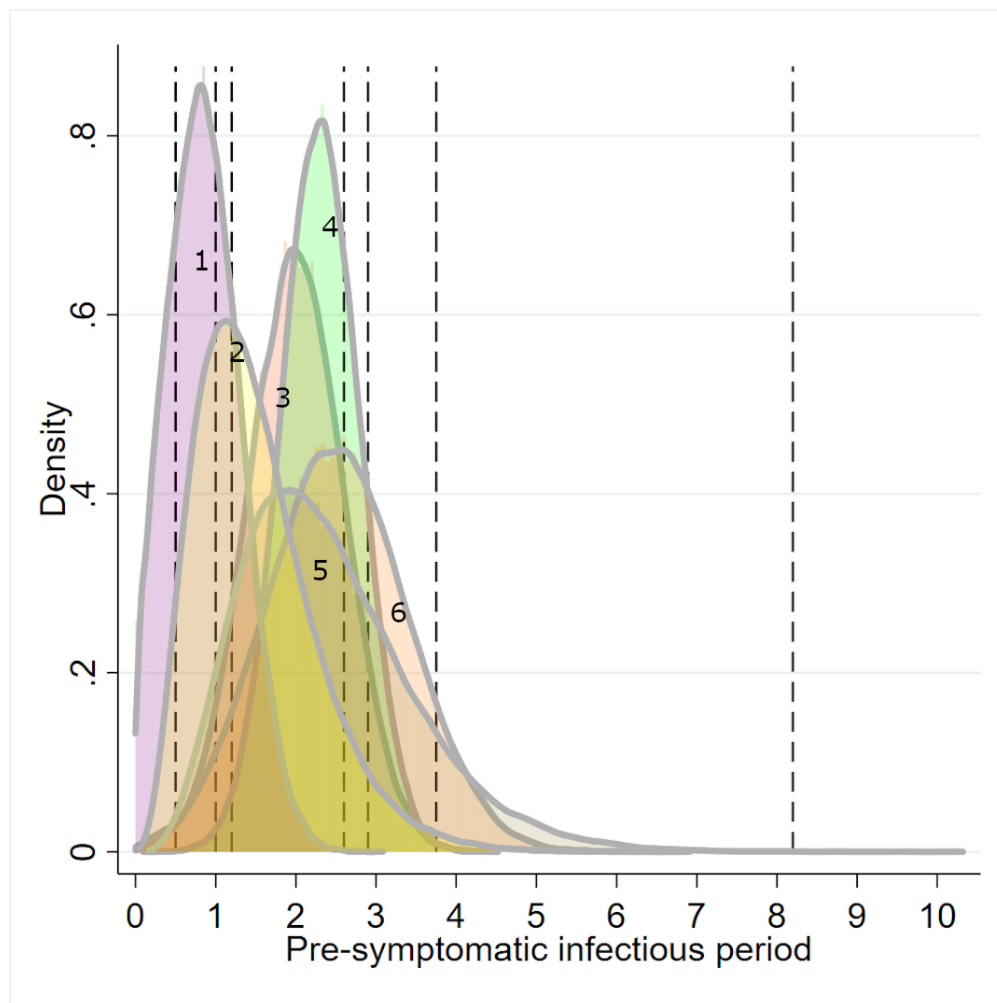


Figure 2: Simulation of the parameter distribution used for T3 (the duration of the pre-symptomatic infectious period for those infected individuals who subsequently develop symptoms). Curves represent simulated approximations of distributions, given information provided from primary literature.

90x90mm (300 x 300 DPI)

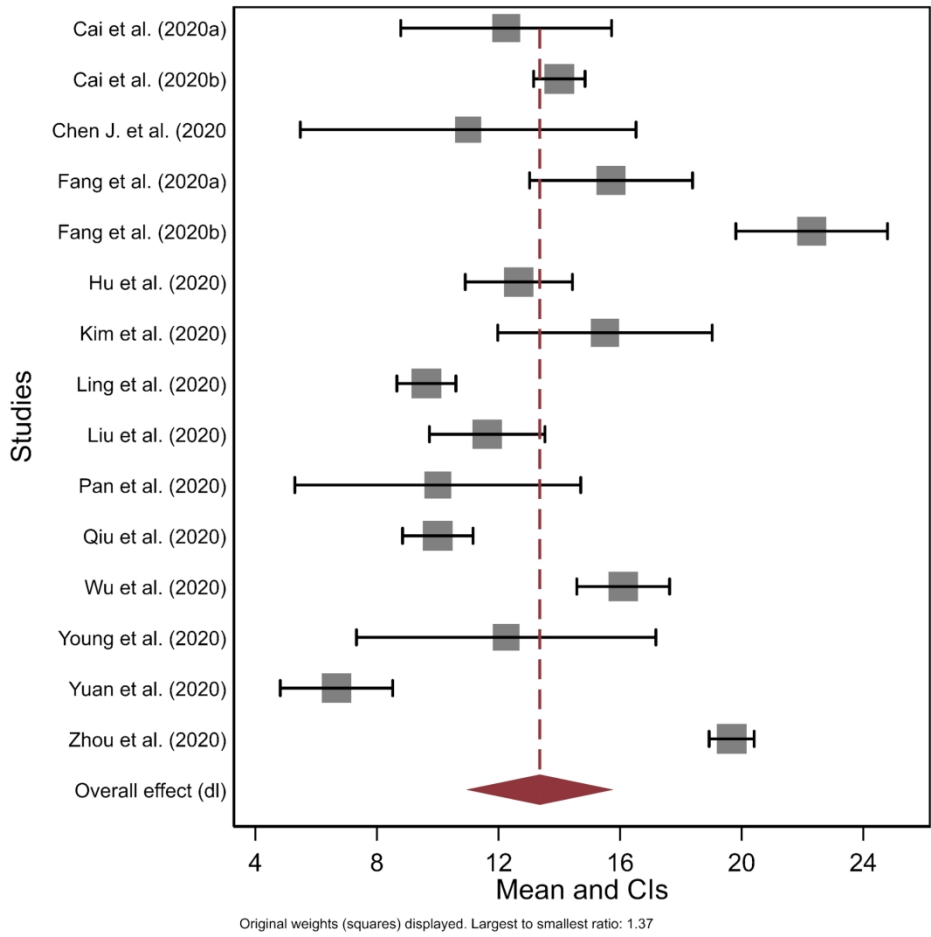


Figure 3: Forest plot of the mean duration from onset of symptoms to death or recovery (T5) based on virological studies

180x180mm (300 x 300 DPI)

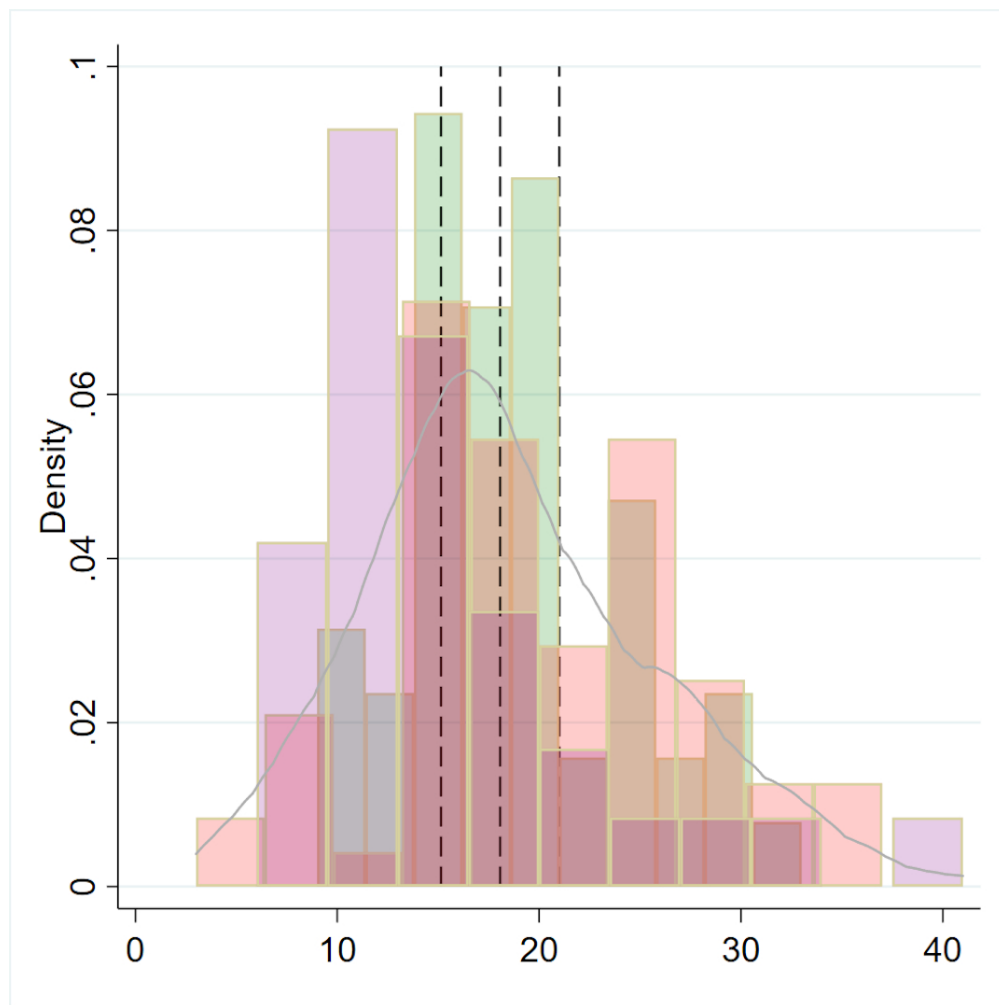


Figure 4: Frequency distribution of T5, time from onset of symptoms to recovery (here hospital discharge or death), using patient level raw data

90x90mm (300 x 300 DPI)

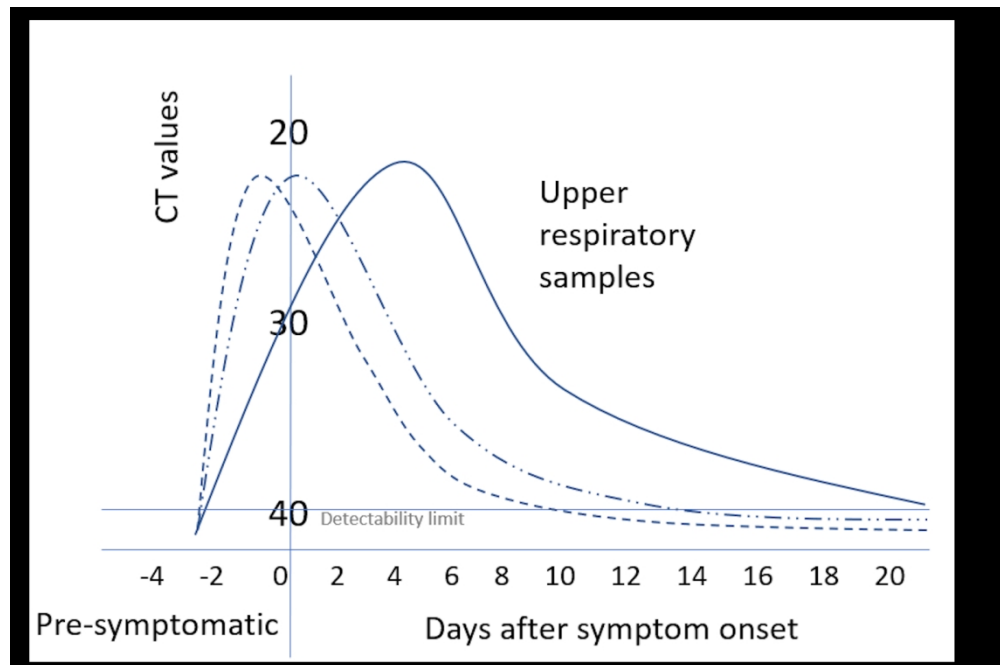
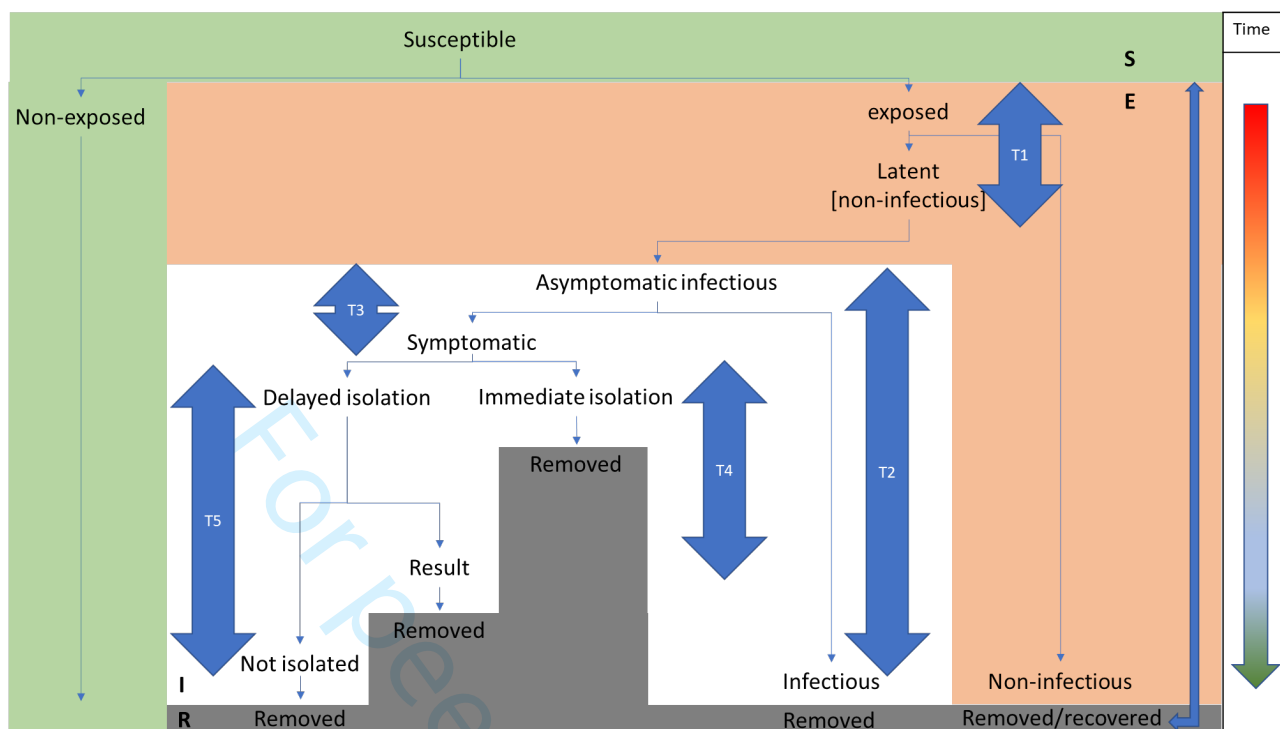


Figure 5: Composite inferred model for cycle threshold (CT) value changes from serial RT-PCR testing for SARS-COV2; currently uncertain whether peak viral load typically occurs prior to, on, or post-symptom onset

135x90mm (300 x 300 DPI)

1 **Supplementary material 1**



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3 **Figure S1:** Conceptual model of the key temporal parameters impacting COVID-19 infection
4 progression over time. T1: Latent period; T2: Asymptomatic infectious period; T3: Pre-
5 symptomatic infectious period; T4: Symptom onset to diagnosis [self-isolation] or
6 hospitalisation; T5: Symptom onset to removed [death or recovery]

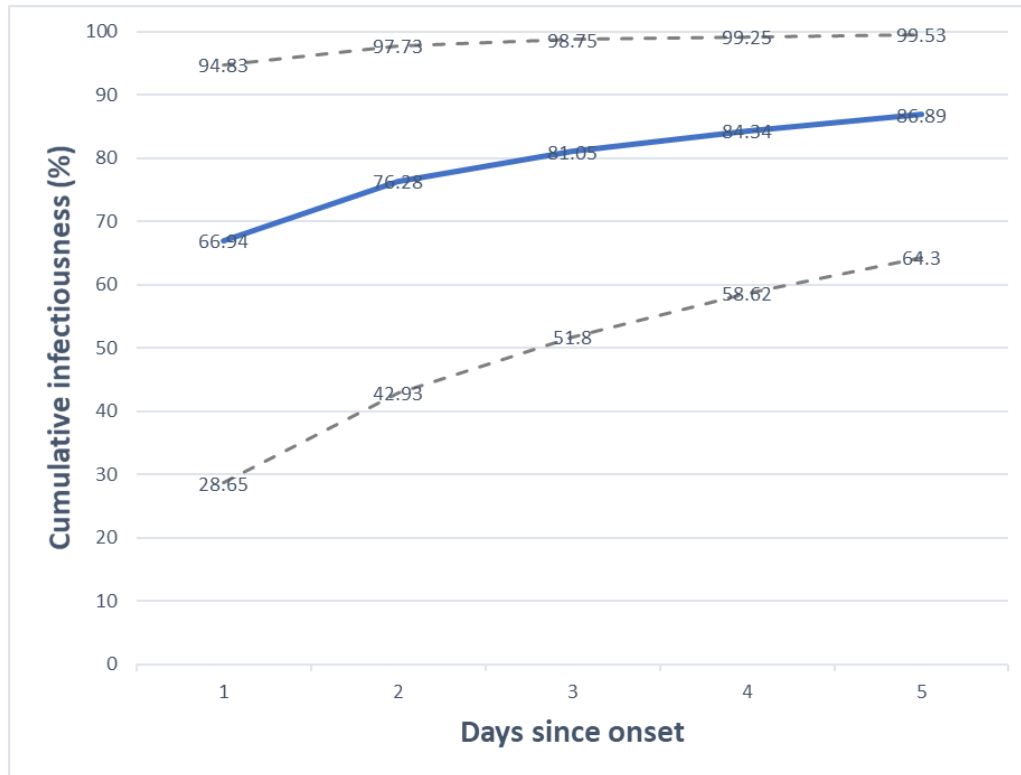


Figure S2: Cumulative infectiousness (% of total infectiousness) based on infector-infectee pair data in the paper by Cheng et al. 2020. The accumulation curve is based on a gamma density function, coupled with a probability function to capture the maximal probability if exposed to a primary case.

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Positive culture



Negative culture



0 2 4 6 8 10 12 14
Days after symptom onset

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17 **Figure S3:** Timeline for positive culture results of SARS-COV2 from throat, sputum and stool
18 samples; Yellow line = Throat swabs; Orange line = Sputum samples; Blue line = Stool samples;
19 Adapted from Wölfel et al.[50].

20

21 **Reference:**

22 Cheng, H.Y., Jian, S.W., Liu, D.P., Ng, T.C., Huang, W.T. and Lin, H.H., 2020. High transmissibility of
23 COVID-19 near symptom onset. *medRxiv*.

24 Wölfel R, Corman VM, Guggemos W, *et al*. Virological assessment of hospitalized
25 patients with COVID-2019. *Nature* 2020;:1–10.

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26 Supplementary material 2:Data for meta-analysis

paper	country	ct	ct_type	range	median	iqr	min	max	first_qt	third_qt	n	mean	sd	se	severity	sev_bin	kid_cat	
Cai et al. (2020a)	China	12	Median	6-22 range	12		6	22	8	15	10			6	2	mild	0	1
Cai et al. (2020b)	China	14	Median		14	9-19 (IQR)			9	19	298			7	0	mild- severe	1	2
Chen et al (2020)	China	12	Max.								1			0	0			2
Chen J. et al. (2020)	China	11	Median	10-12 (95%CI)	11						242			8	3	mild- severe	1	2
Cheng et al. (2020)	China	21	Max.								1			0	0	severe	1	2
Fang et al. (2020a)	China	16	Mean	6.7 (sd)							24			7	1	mild- moderate	0	2
Fang et al. (2020b)	China	22	Mean	3.6 (sd)							8			4	1	severe	1	2
Hill et al. (2020)	Scotland	9	Max.								1			0	0	mild	0	2
Hu et al. (2020)	China	12	Median		12	12-14 (IQR)			12	14	5			2	1	mild	0	2
Kim et al. (2020)	Korea	16	Median	14-17 (range)	16		14	17			2			3	2	mild- moderate	0	2
Kujawski et al. (2020)	USA	26	Max.								1			0	0	mild- moderate	0	2
Le et al. (2020)	Vietnam	12	Max.								1			0	0	mild	0	1
Lee et al. (2020)	Taiwan South	20	Max.								1			0	0	severe	1	2
Lim et al. (2020)	Korea	16	Max.								1			0	0			2
Ling et al. (2020)	China	10	Median	2-22 (range)	10		2	22	6	11	66			4	0			1
Liu et al. (2020)	China	11	Median	7-18 range	11		7	18	10	13	10			3	1	mild- severe	1	2
Liu et al. (2020)	China	10	Max.								76					mild- severe	1	2
Marchand-Senžca et al.	Canada	23	Max								1			0	0			

(2020)

Pan et al. (2020)	China	10	Median	8-12 range	10	8	12	2	3	2				
Qiu et al. (2020)	China	10	Mean	7-22 range		7	22	36	4	1	mild- moderate	0	1	
Qu et al. (2020)	China	22	Max					1	0	0				
Tan et al. (2020)	Vietnam	16	Max					1	0	0	severe	1		
Thevarajan et al. (2020)	Australia	7	Max					1	0	0	mild- moderate	0		
To et al. (2020)	Hong Kong	25	Max.					7	0	0	mild- severe	1	2	
Wu et al. (2020)	China	16	Mean	6.7 (sd)				74	7	1	mild- severe	1	2	
Xing et al (2020)	China	14	Median		14			3			mild- moderate	0	1	
Young et al. (2020)	Singapore	12	Median		12	1	24	18	6	3	mild- moderate	0	2	
Yuan et al. (2020)	China	6	Median		6	4-10 (IQR)	4	10	25	5	1	mild- moderate	0	1
Zhou et al. (2020)	China	20	Median		20	16-23 IQR	16	23	191	5	0	severe	1	2

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29 Supplementary material 3: Data for time to recovery or death

study	overall_time_disc_death	death	discharge	xb_t5	upp95	low95
kraemer	20	0	1	18.06537	15.13663	20.99411
kraemer	16	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	25	0	1	18.06537	15.13663	20.99411
kraemer	22	0	1	18.06537	15.13663	20.99411
kraemer	28	0	1	18.06537	15.13663	20.99411
kraemer	16	0	1	18.06537	15.13663	20.99411
kraemer	25	0	1	18.06537	15.13663	20.99411
kraemer	37	0	1	18.06537	15.13663	20.99411
kraemer	15	0	1	18.06537	15.13663	20.99411
kraemer	14	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	17	0	1	18.06537	15.13663	20.99411
kraemer	20	0	1	18.06537	15.13663	20.99411
kraemer	14	0	1	18.06537	15.13663	20.99411
kraemer	19	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	28	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	8	0	1	18.06537	15.13663	20.99411
kraemer	12	0	1	18.06537	15.13663	20.99411
kraemer	8	0	1	18.06537	15.13663	20.99411
kraemer	18	0	1	18.06537	15.13663	20.99411
kraemer	23	0	1	18.06537	15.13663	20.99411
kraemer	19	0	1	18.06537	15.13663	20.99411

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4	kraemer	3	0	1	18.06537	15.13663	20.99411
5	kraemer	17	0	1	18.06537	15.13663	20.99411
6	kraemer	26	0	1	18.06537	15.13663	20.99411
7	kraemer	19	0	1	18.06537	15.13663	20.99411
8	kraemer	16	0	1	18.06537	15.13663	20.99411
9	kraemer	35	0	1	18.06537	15.13663	20.99411
10	kraemer	14	0	1	18.06537	15.13663	20.99411
11	kraemer	14	0	1	18.06537	15.13663	20.99411
12	kraemer	15	0	1	18.06537	15.13663	20.99411
13	kraemer	29	0	1	18.06537	15.13663	20.99411
14	kraemer	30	0	1	18.06537	15.13663	20.99411
15	kraemer	30	0	1	18.06537	15.13663	20.99411
16	kraemer	24	0	1	18.06537	15.13663	20.99411
17	kraemer	32	0	1	18.06537	15.13663	20.99411
18	kraemer	15	0	1	18.06537	15.13663	20.99411
19	kraemer	24	0	1	18.06537	15.13663	20.99411
20	kraemer	24	0	1	18.06537	15.13663	20.99411
21	kraemer	9	0	1	18.06537	15.13663	20.99411
22	kraemer	18	0	1	18.06537	15.13663	20.99411
23	kraemer	16	0	1	18.06537	15.13663	20.99411
24	kraemer	16	0	1	18.06537	15.13663	20.99411
25	kraemer	33	0	1	18.06537	15.13663	20.99411
26	kraemer	18	0	1	18.06537	15.13663	20.99411
27	kraemer	21	0	1	18.06537	15.13663	20.99411
28	kraemer	19	0	1	18.06537	15.13663	20.99411
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30	kraemer	7	0	1	18.06537	15.13663	20.99411
31	kraemer	18	0	1	18.06537	15.13663	20.99411
32	kraemer	30	0	1	18.06537	15.13663	20.99411
33	kraemer	27	0	1	18.06537	15.13663	20.99411
34	kraemer	27	0	1	18.06537	15.13663	20.99411
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36	kraemer	33	0	1	18.06537	15.13663	20.99411
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38	kraemer	5	0	1	18.06537	15.13663	20.99411
39	kraemer	5	0	1	18.06537	15.13663	20.99411
40	kraemer	16	0	1	18.06537	15.13663	20.99411
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kraemer	14	0	1	18.06537	15.13663	20.99411
kraemer	8	0	1	18.06537	15.13663	20.99411
kraemer	34	0	1	18.06537	15.13663	20.99411
linton	10	1	0	18.06537	15.13663	20.99411
linton	21	1	0	18.06537	15.13663	20.99411
linton	8	1	0	18.06537	15.13663	20.99411
linton	11	1	0	18.06537	15.13663	20.99411
linton	11	1	0	18.06537	15.13663	20.99411
linton	30	1	0	18.06537	15.13663	20.99411
linton	32	1	0	18.06537	15.13663	20.99411
linton	10	1	0	18.06537	15.13663	20.99411
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linton	8	1	0	18.06537	15.13663	20.99411
linton	12	1	0	18.06537	15.13663	20.99411
linton	12	1	0	18.06537	15.13663	20.99411
linton	20	1	0	18.06537	15.13663	20.99411
linton	12	1	0	18.06537	15.13663	20.99411
linton	7	1	0	18.06537	15.13663	20.99411

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linton	11	1	0	18.06537	15.13663	20.99411
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linton	6	1	0	18.06537	15.13663	20.99411
linton	6	1	0	18.06537	15.13663	20.99411
linton	17	1	0	18.06537	15.13663	20.99411
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linton	11	1	0	18.06537	15.13663	20.99411
linton	13	1	0	18.06537	15.13663	20.99411
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linton	16	1	0	18.06537	15.13663	20.99411
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tindale	19	0	1	18.06537	15.13663	20.99411
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tindale	17	0	1	18.06537	15.13663	20.99411
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tindale	18	0	1	18.06537	15.13663	20.99411

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4	tindale	16	0	1	18.06537	15.13663	20.99411
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30	tindale	17	0	1	18.06537	15.13663	20.99411
31	tindale	17	0	1	18.06537	15.13663	20.99411
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33	tindale	16	0	1	18.06537	15.13663	20.99411
34	tindale	30	0	1	18.06537	15.13663	20.99411
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tindale	33	0	1	18.06537	15.13663	20.99411
tindale	19	0	1	18.06537	15.13663	20.99411
tindale	29	0	1	18.06537	15.13663	20.99411
tindale	22	0	1	18.06537	15.13663	20.99411
tindale	10	0	1	18.06537	15.13663	20.99411
tindale	20	0	1	18.06537	15.13663	20.99411
tindale	11	0	1	18.06537	15.13663	20.99411
tindale	15	0	1	18.06537	15.13663	20.99411
tindale	18	0	1	18.06537	15.13663	20.99411
tindale	11	0	1	18.06537	15.13663	20.99411

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6/bmjopen-2020-039856 on 5 August 2020. Downloaded from <http://bmjopen.bmj.com/> on April 7, 2024 by guest. Protected by copyright.

```
1
2
3 30 Supplementary material 4: Stata code
4
5 31 // 1st April 2020
6 32
7 33 /* Code for:
8 34
9 35 Byrne, AW, McEvoy, D, et al. 2020
10 36
11 37 Inferred duration of infectious period of SARS-CoV-2: rapid review and analysis of
12 38 available evidence for asymptomatic and symptomatic COVID-19 cases
13 39
14 40
15 41 */
16 42
17 43 * Figure 2
18 44
19 45 gen davies1_gamma = rgamma(5, 1.4)
20 46
21 47 gen davies2_gamma = rgamma(4, 1.25)
22 48
23 49 gen ma_normal = rnormal(7.2, 4.96)
24 50
25 51
26 52 input hu_data
27 53
28 54 12
29 55
30 56 1
31 57
32 58 1
33 59
34 60 11
35 61
36 62 3
37 63
38 64 16
39 65
40 66 6
41 67
42 68 4
43 69
44 70 6
45 71
46 72 18
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48 74 8
49 75
50 76 8
51 77
52 78 11
53 79
54 80 14
55 81
56 82 14
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58 84 12
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60 86 13
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62 88 1
63 89
64 90 17
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66 92 3
67 93
68 94 11
69 95
70 96 5
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1
2
3 97
4 98 6
5 99
6 100 21
7 101
8 102 end
9 103
10 104
11 105
12 106 // Fig 2 visualise
13 107
14 108 twoway (histogram hu_data, fcolor(gs14) lcolor(black)) (histogram davies1_gamma,
15 109 bin(180) fcolor(ltblueishgray%86) lcolor(none) lwidth(none)) (kdensity
16 110 davies1_gamma, lcolor(gs11) lwidth(thick)) (kdensity davies2_gamma, lcolor(gs11)
17 111 lwidth(thick)) (histogram davies2_gamma, bin(120) fcolor(orange_red%20)
18 112 lcolor(none) lwidth(none)) (histogram ma_normal, bin(100) fcolor(lime%20)
19 113 lwidth(none)) (kdensity ma_normal, lcolor(gs11) lwidth(thick)) if ma_n>=0,
20 114 yscale(line) xtitle(Days since infected) xline(6 6.5 11 3.5, lpattern(dash)
21 115 lcolor(black) noextend) xlabel(0(5)30) legend(off) scheme(s2color) xsize(20)
22 116 ysize(16) graphregion(fcolor(white)) plotregion(fcolor(white))
23 117
24 118
25 119
26 120 * Figure 3
27 121
28 122 gen rothet3_normal = rnormal(2, 0.6)
29 123
30 124 gen huangt3_normal = rnormal(3.75, 0.332)
31 125
32 126 gen het3_normal = rnormal(2.3, 0.49)
33 127
34 128 gen weit3_normal = rnormal(2.5, 0.89)
35 129
36 130 gen peakt3_normal = rnormal(0.8, 0.5)
37 131
38 132 gen daviesAt3_normal = rgamma(5, 0.48)
39 133
40 134 gen daviesBt3_normal = rgamma(4, 0.375)
41 135
42 136 twoway (histogram rothe, bin(120) fcolor(orange_red%20) lcolor(none) lwidth(none))
43 137 (kdensity rothe, lcolor(gs11) lwidth(thick)) (histogram he, bin(100)
44 138 fcolor(lime%20) lwidth(none)) (kdensity he, lcolor(gs11) lwidth(thick)) (histogram
45 139 wei, bin(100) fcolor(orange%20) lwidth(none)) (kdensity wei, lcolor(gs11)
46 140 lwidth(thick)) (histogram peak, bin(100) fcolor(purple%20) lwidth(none)) (kdensity
47 141 peak, lcolor(gs11) lwidth(thick)) (histogram daviesA, bin(100) fcolor(brown%20)
48 142 lwidth(none)) (kdensity daviesA, lcolor(gs11) lwidth(thick)) (histogram daviesB,
49 143 bin(100) fcolor(yellow%20) lwidth(none)) (kdensity daviesB, lcolor(gs11)
50 144 lwidth(thick)) if peak>=0 & wei>=0 & rothe>=0, yscale(line) xtitle(Pre-symptomatic
51 145 infectious period) xline(0.5 1 1.2 2.6 2.9 3.75 8.2, lpattern(dash) lcolor(black)
52 146 noextend) xlabel(0(1)10) legend(off) scheme(s2color) xsize(20) ysize(16)
53 147 graphregion(fcolor(white)) plotregion(fcolor(white)) ytitle(Density)
54 148
55 149 * Figure 4
56 150
57 151 // meta analysis & meta regression
58 152
59 153 clear
60 154
61 155
62 156
63 157 // open data =
64 158
65 159 * meta_analysis_dataset.xls
66 160
67 161
68 162
69 163 // Fit random effects meta-analytical model, and specify forest plot
70 164

```

```
1
2
3 165 metaan mean se, dl forest label(paper)
4 166
5 167 // forest plot is figure 4.
6 168
7 169 // meta regression
8 170
9 171 // binary child (y/n) variable
10 172
11 173 gen kid_cat = 1 if child==1
12 174
13 175 replace kid = 2 if adult==1 & child!=1
14 176
15 177 tab kid_cat
16 178
17 179 * binary children inclusion in sample [REML]
18 180
19 181 xi: metareg mean i.kid if se>0, wsse(se)
20 182
21 183 // monte carlo model of P-value
22 184
23 185 xi: metareg mean i.kid if se>0, wsse(se) permute(1000, joint(i.kid))
24 186
25 187
26 188
27 189 // binary severe (y/n) variable
28 190
29 191 encode sever, gen(sev_num) // 4 way categorical
30 192
31 193 gen sev_bin = 0 if sev_n<3
32 194
33 195 replace sev_bin = 1 if sev_n==3 | sev_n==4
34 196
35 197
36 198
37 199 xi: metareg mean i.sev_bin if se>0, wsse(se)
38 200
39 201 // monte carlo model of P-value
40 202
41 203 xi: metareg mean i.sev_bin if se>0, wsse(se) permute(1000, joint(i.sev_bin))
42 204
43 205
44 206
45 207 * Figure 5
46 208
47 209
48 210
49 211 // Import, open time_to_discharge_death.csv
50 212
51 213
52 214 // numeric indicator for study category
53 215
54 216 encode study, gen(study_)
55 217
56 218
57 219
58 220 // random effects model for time from onset to removal (discharge or death)
59 221
60 222 // 3 levels of study as RE
61 223
62 224 xi: xtreg overall_time, i(study_)
63 225
64 226 // summarise post-estimation
65 227
66 228 estat summarize
67 229
68 230 // Breusch and Pagan Lagrangian multiplier test for random effects
69 231
70 232 xttest0
```



```
1
2
3 233
4 234 // Figure 5: histogram plot with kernel density
5 235
6 236 twoway(hist overall_time if study_== 3 , bin(10) fcolor(green%20))( hist
7 237 overall_time if study_== 1, bin(10) fcolor(red%20))( hist overall_time if study_==
8 238 2, bin(10) fcolor(purple%20))(kdensity overall_time disc_death , lcolor(gs11)
9 239 lwidth(mthick)), scheme(s2gcolor) legend(off) xsize(20) ysize(16)
10 240 graphregion(fcolor(white)) plotregion(fcolor(white)) xline(15.13663 18.06537
11 241 20.99411, lpattern(dash) lcolor(black) noextend)
12 242
13 243
14 244
15 245 // GLM reporting the variation in mean duration across studies
16 246
17 247 xi: reg overall_time i.study_
18 248
19 249 // GOF test
20 250
21 251 estat hettest
22 252
23 253 // residuals plot
24 254
25 255 rvfplot
26 256
27 257 // prediction
28 258
29 259 predict pred_study
30 260
31 261 // visualise
32 262
33 263 twoway(scatter pred_study study_)
34 264
35 265
36 266
37 267 // GLM reporting the variation in mean duration across removal type [death or
38 268 discharge]
39 269
40 270 xi: reg overall_time i.discharge
41 271
42 272 // GOF test
43 273
44 274 estat hettest
45 275
46 276 // residuals plot
47 277
48 278 rvfplot
49 279
50 280 // prediction
51 281
52 282 predict pred_study
53 283
54 284 // visualise
55 285
56 286 twoway(scatter pred_study study_)
57
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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4-5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4-5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4-5
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	4-5
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	5-7
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	5-7
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5-7



SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	8, Tables 1-3
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Tables 1-3
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Tables 1-3
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	8-13
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	8-13; figures 1-5
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	14-17
Limitations	20	Discuss the limitations of the scoping review process.	17-18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	18
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	18

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med.* 2018;169:467–473. doi: 10.7326/M18-0850.



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BMJ Open

Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039856.R1
Article Type:	Original research
Date Submitted by the Author:	05-Jun-2020
Complete List of Authors:	Byrne, Andrew; Government of Ireland Department of Agriculture Food and the Marine, One-Health Scientific Support Unit McEvoy, David; University College Dublin, School of Public Health, Physiotherapy and Sports Science Collins, Aine; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis; Government of Ireland Department of Agriculture Food and the Marine Hunt, Kevin; University College Dublin, Centre for Food Safety Casey, Miriam; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Barber, Ann; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Butler, Francis; University College Dublin, Centre for Food Safety Griffin, John; Government of Ireland Department of Agriculture Food and the Marine Lane, Elizabeth; Government of Ireland Department of Agriculture Food and the Marine; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis McAloon, Conor; UCD School of Agriculture Food Science and Veterinary Medicine, School of Veterinary Medicine O'Brien, Kirsty; Health Information and Quality Authority Wall, Patrick; University College Dublin, Public health Walsh, Kieran; Health Information and Quality Authority More, SImon; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, VIROLOGY, INFECTIOUS DISEASES, PUBLIC HEALTH



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3 **1 Inferred duration of infectious period of SARS-CoV-2: rapid scoping review**
4 **and analysis of available evidence for asymptomatic and symptomatic**
5 **COVID-19 cases**
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9

10 **4 Andrew W. Byrne^{1^}, David McEvoy², Áine B. Collins^{3,6}, Kevin Hunt⁴, Miriam Casey³, Ann Barber³,**
11 **5 Francis Butler⁴, John Griffin⁶, Elizabeth A. Lane^{3,6}, Conor McAloon⁵, Kirsty O'Brien⁷, Patrick Wall²,**
12 **6 Kieran A. Walsh⁷, Simon J. More³**

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19 Abstract

20 **Objectives:** Our objective was to review the literature on the inferred duration of the infectious
21 period of COVID-19, caused by SARS-COV-2 virus, and provide an overview of the variation
22 depending on the methodological approach.

23 **Design:** Rapid scoping review. Literature review with fixed search terms, up to 1st April 2020. Central
24 tendency and variation of the parameter estimates for infectious period in (a) asymptomatic (b)
25 symptomatic cases from (i) virological studies (repeated testing), (ii) tracing studies (iii) modelling
26 studies were gathered. Narrative review of viral dynamics.

27 **Information sources:** Search strategies developed and the following searched: PubMed, Google
28 Scholar, MedRxiv, BioRxiv. Additionally, the Health Information Quality Authority (Ireland) viral load
29 synthesis was utilised, which screened literature from PubMed, Embase, ScienceDirect, NHS
30 evidence, Cochrane, medRxiv and bioRxiv, HRB open databases.

31 **Results:** There was substantial variation in the estimates, and how infectious period was inferred.
32 One study provided approximate median infectious period for asymptomatic cases of 6.5-9.5 days.
33 Median pre-symptomatic infectious period across studies varied over <1-4 days. Estimated mean
34 time from symptom onset to two negative RT-PCR tests was 13.4 days (95%CI: 10.9-15.8), but was
35 shorter when studies included children or less severe cases. Estimated mean duration from
36 symptom onset to hospital discharge or death (potential maximal infectious period) was 18.1 days
37 (95%CI: 15.1–21.0); time to discharge was on average 4 days shorter than time-to-death. Viral
38 dynamic data and model infectious parameters were often shorter than repeated diagnostic data.

39 **Conclusions:** There are limitations of inferring infectiousness from repeated diagnosis, viral loads,
40 and viral replication data alone, and also potential patient recall bias relevant to estimating exposure
41 and symptom onset times. Despite this, available data provides a preliminary evidence base to
42 inform models of central tendency for key parameters, and variation for exploring parameter space
43 and sensitivity analysis.

45 Strengths and limitations of this study

- 46 • A comprehensive overview of the literature pertaining to inferred infectious duration of
47 COVID-19, including indirect measures from virological, contact tracing, and modelling
48 studies to 1st April 2020.
- 49 • Both narrative review and quantitative analysis presented

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- 50 • Small number of comparable parameter estimates for meta-analysis is a limitation
- 51 • Much of the current research material on COVID-19 is from preprint papers, and therefore
- 52 have not gone through formal peer review

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53 Introduction

54 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new coronavirus, emerged in
55 China in late 2019.[1,2] The virus causes COVID-19, a disease characterized by variable, mainly
56 respiratory, symptoms across cohorts, from asymptomatic cases through to mild (for example, dry
57 cough, fever) and severe cases (for example, pneumonia).[3,4] The severity of symptoms, and their
58 clinical outcome, have been reported to vary by age-class and whether patients have underlying
59 comorbidities. The case-fatality rate increases with age, and are highest for those above 70
60 years.[5,6] There are several cases of asymptomatic test-positive patients reported in the emerging
61 literature (e.g. [4,7,8]). Furthermore, asymptomatic (and pre-symptomatic) cases have been shown
62 to be infectious, and secondary cases have been reported.[9,10] However, the duration of this
63 infectious period is difficult to measure accurately, and the time course of the natural history of
64 infection generally must be inferred indirectly, via contact tracing of cases, serial repeated diagnostic
65 virological studies, and/or through modelling approaches. Symptomatic cases can experience an
66 infectious pre-symptomatic period before the onset of symptoms, therefore understanding the
67 whole infectious period for this cohort requires estimating the duration of both periods. It is
68 essential to rapidly gain insight into this key variable impacting our understanding of COVID-19
69 epidemiology. Anderson et al. [11] point out one of the “key unknowns” is the infectious period for
70 COVID-19, which they suggest may be 10 days but subject to great uncertainty.

71 Here we gathered data from published research from peer-reviewed and preprints from 1st
72 December to 1st April 2020, to characterize the variation in the infectious duration inferred from the
73 three lines of evidence. We also provide a narrative review of the viral dynamic literature. Our focus
74 was on duration, relative infectiousness has been dealt with elsewhere [12,13]

75 The aim of this review was to provide an overview and critical appraisal of published and preprint
76 articles and reports that assess or quantify the inferred duration of the infectious period in order to
77 best parameterise COVID-19 epidemiological transmission models.

78 **Materials and Methods**

79 ***Conceptual model of population infection dynamics***

80 Infectious period was contextualised in relation to a working conceptual model of COVID-19 disease
81 dynamics (Figure S1, supplementary material 1). From this conceptual model, three parameters
82 were identified as important in context of this study:

83 T2, defined as: Duration of the total infectious period for asymptomatic cases, post-latent to
84 recovery [‘recover’ in this context relates to clearing of infection]

85 T3, defined as: Duration of pre-symptomatic infectious period for those infected individuals
86 who subsequently develop symptoms (that is, post-latent to onset of symptoms)

87 T5, defined as: Duration from onset of symptoms to recovery* or death.

88 * recovery was inferred as either the first of two clear RT-PCR tests, or hospital discharge after
89 admission from COVID-19 related symptoms.

90 “Asymptomatic” case definition was interpreted pragmatically following Davies et al. [14,15], and
91 may include very mild symptoms that may occur but are unnoticed.

92 T2, T3, T5 represent readily measurable parameters, but may be upper limits of infectious period, as
93 patients may be non-infectious for a period before recovery or death. We also review evidence
94 where infectiousness is inferred from viral shedding and contact tracing [transmission], see below.

95 ***Literature search***

96 A survey of the literature between 1st December 2019 and 1st April 2020 for all countries was
97 implemented using the following search strategy. Publications on the electronic databases PubMed,
98 Google Scholar, MedRxiv and BioRxiv were searched with the following keywords: “Novel
99 coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR “COVID-19” AND “infectious”. Additionally,
100 national and international government reports were monitored. No restrictions on language or
101 publication status were imposed so long as an English abstract was available. Articles were evaluated
102 for data relating to the aim of this review; all relevant publications were considered for possible
103 inclusion. Bibliographies within these publications were also searched for additional resources.

104 Manual searches of the literature was undertaken using daily updated COVID19 collections
105 from the National Centre for Biotechnology Information (NCBI) and MedRxiv servers
106 (<https://connect.medrxiv.org/relate/content/181>), respectively, searching specifically for
107 papers relating to “infectious period” or “infectious duration” from both empirical and
108 modelling studies.

109 Finally, we utilised the complementary work undertaken by the Health Information and Quality
110 Authority (HIQA) of Ireland, specifically the evidence summaries relating to asymptomatic
111 transmission and viral load [16,17]. The protocol for the evidence synthesis is published on the HIQA
112 website [18]. Briefly, the evidence synthesis process included searching databases from 30th

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3 113 December 2019 to 27th March 2020 (PubMed, Embase, ScienceDirect, NHS evidence, Cochrane,
4 114 medRxiv and bioRxiv, HRB open), screening, data extraction, critical appraisal and summarizing the
5 115 evidence.
6
7

8
9 116 Our aim was to have as great a breadth for an evidential base as possible, to clarify what evidence
10 117 was available to inform on the infectious period of COVID19, and to identify key characteristics of
11 118 the data sources and their interpretation. Therefore, our approach is a scoping review (following
12 119 [19]). However, due to the emergent nature of COVID-19, this work is considered a rapid review.[20]
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14 120 This paper follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—
15 121 Extension for Scoping Reviews (PRISMA-ScR) checklist.
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22 123 Inclusion criteria were for papers that provided data to inform duration of infectious period based
23 124 on: time from symptoms to recovery; time from symptoms to death; time from symptoms to
24 125 diagnostic test clearance [\geq two clear tests, defined as at least two consecutive negative reverse
25 126 transcriptase polymerase chain reaction (RT-PCR) tests conducted 24 hours apart]; pre-symptomatic
26 127 infectious period; time from first diagnostic test to diagnostic test clearance [\geq two clear tests] for
27 128 pre-symptomatic/asymptomatic cases. Inclusion criteria for viral dynamics, were papers which
28 129 reported viral load via cycle threshold (Ct) values from RT-PCR testing over repeated sampling of
29 130 infected patients, and studies that additional reported viral isolation.
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36 131 For quality control, studies were (i) selected and screened initially by three members of the team
37 132 from search terms outlined above (ÁBC, KH, FB), with parameters identified and recorded. (ii) This
38 133 was reviewed and supplemented by manual search by a different two team members (AWB, DM),
39 134 again with parameters identified and recorded. (iii) Finally, the review was then internally reviewed
40 135 by an additional two members of the team (CMc, MC), and cross-referenced with other parameter
41 136 synthesis documents being worked on by the group (*all authors*).
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47 137 ***Parameter comparison***

48 49 138 *Parameters of interest*

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51 139 1. *A-priori* it was decided to harvest parameter estimates for (i) asymptomatic, and (ii)
52 140 symptomatic cases. As the period of infectiousness can only be estimated indirectly,
53 141 parameter estimates from the literature was gathered from three different methodological
54 142 approaches: Virological studies tracking patients overtime undertaking serial testing, where
55 143 infectious period was inferred from diagnostic testing history and/or by virus isolation.
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3 144 2. Contact tracing studies where infectiousness is inferred by infector-infectee histories and/or
4 clusters of infection.
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6 146 3. Model parameters entered into mathematical models [priors] representing explicitly
7 infectious periods, or model parameters estimated from mathematical models [posterior
8 147 estimates] estimating explicitly infectious periods
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15 150 Visual and quantitative comparisons

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17 151 To compare parameters visually, simulated distributions were estimated from the central tendencies
18 and variation metrics described in the primary literature. To simulate data, 10,000 random variates
19 152 were drawn from random number functions in Stata (ME, version 15.1; StataCorp. 2017. Stata
20 153 Statistical Software: Release 15. College Station, TX: StataCorp LLC) [rnormal, rgamma]. Where
21 154 possible, the distribution reported within the primary literature was used to represent the
22 155 distribution (e.g. Gaussian, Gamma). Where distributional data could not be inferred, point
23 156 estimates were presented.
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29 158 There were adequate comparable data gathered on the duration of T5 (duration from onset of
30 159 symptoms to death or recovery) from virological studies to employ a meta-analytic model. Many of
31 160 the studies report different central tendency estimates, including mean and median. Methods of
32 161 reporting variation across this central tendency included standard deviation, range, inter-quartile
33 162 range. To facilitate meta-analysis, reported estimates from all studies were converted to the mean
34 163 and standard deviations based on the formulae given in Wan et al. [21].

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40 164 To obtain the standard deviations from 95%CI, the method outlined in the Cochrane handbook [22]
41 165 was used:

$$SD: \sqrt{n}(\text{Upper limit of CI} - \text{Lower limit of CI})/3.92$$

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48 168 Standard Error (SE) was calculated from Standard Deviation (SD) and sample size (n), using:

$$SE = SD/\text{SQRT}(n)$$

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53 170 Comparisons were made using the METAAN package in Stata 15, using the random-effects
54 171 (DerSimonian-Laird) model.[23] This model assumes heterogeneity between the studies; that is, it
55 172 assumes that the true effect can be different for each study. The model assumes that the individual-
56 173 study true effects are distributed with a variance τ^2 around an overall true effect, but the model
57 174 makes no assumptions about the form of the distribution of either the within-study or the between-

175 studies effects. Weightings were derived from the standard error [precision] around the estimate.
176 Comparisons were presented as forest plots. Heterogeneity between studies was tested using
177 Cochran's Q; the magnitude of the heterogeneity was categorised using I^2 as high (>75%), moderate
178 (50-75%), or low (<50%).[24]

179 Variation in duration across T5 virological studies was compared using a random effects meta-
180 regression model, using the METAREG command in Stata 15.1. The hypothesis that heterogeneity
181 may be related to the inclusion of children or depending on symptom severity within the sample,
182 was tested in separate univariate models. Severity was dichotomised (0/1) into studies that included
183 patients described as having 'mild' or 'mild-moderate' symptoms, versus studies that included
184 patients with 'moderate-severe' or 'severe' symptoms. Similarly, studies were categorised into
185 having some samples from "children" (as reported in the paper), or wholly adult samples. These
186 variables were then fitted as a dichotomous dummy predictor [independent]. The parameter
187 estimates from the regression model was solved using restricted maximum likelihood (REML);
188 additionally, p-values were estimated using a Monte Carlo model with 1000 permutation test.[25]

189 Raw patient-level data were available from three studies in relation to time from onset to hospital
190 discharge or death (potentially inferring maximal T5 duration). To estimate the predicted mean and
191 95%CI duration across these studies, data were analysed using a Gaussian random effects model
192 (using XTREG command, Stata 15), with study categories fitted as the RE. A linear regression model
193 with 'study' fitted as a categorical dummy variable was used to estimate the difference between
194 duration across study datasets. Code and data are provided in Supplementary Material 2 & 3.

195 ***Viral dynamics***

196 A narrative comparison of reported viral dynamics from studies that undertook serial viral load
197 estimates from patients over their period of observation was undertaken. Trends in the literature,
198 strength and weaknesses were identified, and a conceptual model illustrated.

199 **Results**

200 ***Parameter comparison***

201 Overall, 65 parameter estimates were harvested from 48 papers (Tables 1, 2, 3).

202 *Infectious period for asymptomatic cases (T2)*

203 The overall distributions and point estimates from studies for T2 are presented in Figure 1 and Table
204 1.

205 Two virological studies reported on infectious period based on serial diagnostic testing, for
206 asymptomatic cases, were found to have informative data. One of these studies reported on only
207 one asymptomatic case, with exposure to negative tests being 11 days (Table 1). This duration
208 should be considered an over-estimate, given that a latent period is not taken into consideration. Hu
209 et al. [7] tracked infections of close contacts to infected persons and considered patients
210 asymptomatic at time of diagnosis. Infectious period was defined as time from diagnosis to the first
211 of two clear tests, providing a median duration of 9.5 days (n=24) range: 1 – 21; 3.5-13.0 IQR.

212 Importantly, Hu et al. [7] found that the infectious period was different between those who
213 subsequently exhibited symptoms (i.e. pre-symptomatic) and those who did not: The median
214 duration for asymptomatic infectious was 6.0 days (IQR: 2.0 - 12.0; N=19). This was reduced to 4.0
215 days (2.0 - 15.0) for cases that were asymptomatic without abnormal computed tomography (CT)
216 scans (n=7).

217 Two tracing studies provide informative data (Table 1; [7,8]). Infectious period was inferred
218 indirectly from data provided in Ma et al. [8], whereby infectious period was estimated as the
219 difference between the upper (maximal) latent period estimate minus the serial interval. Ma et al.
220 [8] reports on 49 asymptomatic cases and inferred serial interval from infector-infectee pairs. Serial
221 interval was calculated by assuming “onset” was at first diagnosis. Hu et al. [7] reported on a case-
222 study cluster of infection within a house where the primary case was asymptomatic. Secondary
223 infections occurred 4-9 days after index case exposure, the index patient tested positive until day 29
224 post exposure.

225 Modelling studies that have attempted to fit differing parameters depending on the severity of
226 symptoms have used differing nomenclature, for example asymptomatic, “mild” or subclinical cases
227 (Table 1).[14,15,26,27] Two papers by Davies and colleagues [14,15] model this parameter as a
228 gamma distribution with a mean periods of 5-7 days (Fig. 2); importantly, these papers assume
229 infectious period is the same for asymptomatic and symptomatic cases.

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3 230 Pre-symptomatic, infectious period (T3)
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5 231 Pan et al. [3] and Hoehl et al. [28] describe the cases of two individuals tracked and serially tested by
6 232 real-time reverse transcriptase polymerase chain reaction (RT-PCR) after being exposed to a patient
7 233 with confirmed infection. In the latter study, the virus was isolated from samples, indicating
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9 234 transmission potential.

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13 235 Four studies from China, Germany and Singapore provide informative data through tracing infections
14 236 from cluster of infections, and through infector-infectee pairs (Table 2).[4,9,29,30] These papers
15 237 included the study by Rothe et al. [9], which clarified that an asymptomatic patient visiting Germany
16 238 from China may have actually experienced very mild symptoms around the time of transmission
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18 239 occurred (see discussion).

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22 240 Five modelling papers incorporated pre-symptomatic infectious period reported as prior
23 241 distributions or estimated as a model output. Two papers describe the prior distribution using a
24 242 gamma distribution.[14,15] Tindale et al. [31] provide mean point estimates under four different
25 243 scenarios (two populations, early and late epidemic period). Peak et al. [32] derives estimates of the
26 244 pre-symptomatic infectious duration from a model of serial interval, and report scenarios where
27 245 there are pre-symptomatic infectious periods.

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29 246 The approximated distributions are simulated in Figure 2, which demonstrates the between-study
30 247 heterogeneity in this parameter. The point estimates primarily cluster around the central tendencies
31 248 of the distributions, except for Tindale et al. [31], for a model reporting for late occurring cases in
32 249 Tianjin, China (8.2 days).

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36 250 Post-symptom onset, infectious period (T5)
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40 251 The T5 parameter was informed from three lines of evidence from empirically driven studies:

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45 252 • time from symptoms onset to the first of two clear RT-PCR tests
46 253 • time from symptoms to hospital discharge
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48 254 • time from symptoms to death
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50 255 Figure 3 presents the forest plot for the mean time from symptom onset to clearance, based on
51 256 serial testing meta-analysis (n=15). The mean estimated duration was 13.4 days (95%CI: 10.9-15.8).
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53 257 There was high heterogeneity across studies (Cochrane's Q; p<0.001; I²>75%). A random effects (RE)
54 258 meta-regression model suggested significant variation depending on whether studies included
55 259 children as part of the sample (n=15 studies; Proportion of between-study variance explained
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57 260 Adj. R² = 43.8%). Overall, the model estimated studies including children had on average 5.8 days
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261 shorter duration than adult only studies (95%CI: 1.7-10.0; $p=0.040$; $SE(p)=0.003$). A second univariate
262 RE meta-regression model suggested that there was non-significant increased mean duration of 4.0
263 days (95%CI: -0.6-8.6; $p=0.111$; $SE(p)=0.005$; Adj. $R^2 = 22.0\%$; $n=14$) for studies that included
264 moderate-severe or severe cases, relative to mild or mild-moderate severity cases.

265 High transmissibility during the first 5 days post symptom onset was described by Cheng et al. [33],
266 based on secondary attack rates for 12 infector-infectee pairs. No contacts ($n=1043$) with primary
267 cases were infected after five days of the index case onset of symptoms, inferred by the authors to
268 suggest transmission occurring at symptom onset (but conceivably also suggest pre-symptomatic
269 infection). Based on a cumulative density function, the authors suggest that infectiousness declines
270 rapidly from onset of infection (distribution was truncated at 30 days); estimated cumulative
271 infectiousness was 66.9% (95%CI: 28.7-94.8) by day 1, and reached 86.9% (95%CI: 64.3-99.5) by day
272 5 post-symptom onset (Figure S2).

273 For tracking studies relating to time to hospital discharge or death, raw case level data were
274 available (studies $n=3$).[31,34–36] Histograms of the raw data are presented in Figure 4, along with
275 the aggregated distribution. A random effect model suggested a mean duration of 18.1 days (95%ci:
276 15.1 – 21.0). However, there was significant variation across studies, with time to discharge being
277 4.96 days shorter (95%CI: 2.15- 7.76; [35]), or 3.79 days shorter (95%CI: 0.8-6.7; [31]), than time-to-
278 death [34].

279 Two modelling papers use priors (mean: 3.2-3.5 days) to represent clinical infectious period.[14,15]
280 However, the distribution for this parameter is right censored when patients are hospitalised or
281 isolated and therefore not an estimate of the full infectious period *per se*.

282 Infectious period for symptomatic cases (T3+T5)

283 Two tracing studies supplied parameter estimates for the full infectious period for patients who
284 develop symptoms. [8,29] He et al. [29] inferred from a publicly available dataset of 77 infector-
285 infectee pairs that infectiousness began 2.3 days (95% CI, 0.8–3.0 days) prior to symptom onset,
286 peaking at 0.7 days (95% CI, -0.2–2.0 days), and continued up to 7 days from onset. The authors
287 suggest that the transmission risk diminishes 7 days post symptom onset. This suggests that the
288 average infectious period, assuming a symptomatic infectious period of 7 days was approximately
289 9.3 days (7.8-10 days 95%CI, where CI is only reported for the pre-symptomatic period). He et al.
290 [29] estimated that the proportion of all transmission that was pre-symptomatic was 44% (95% CI,
291 25–69%). Ma et al. [8] analysed data from a number of countries (China, Germany, Japan, Malaysia,
292 Singapore, Vietnam), collating 1155 cases from public data. They estimate several parameters,

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3 293 including “maximum latent period” and the serial interval. The authors estimated the infectious
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5 294 period as maximum latent period minus the serial interval. Given their parameter estimates and
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7 295 methodological approach, infectious period would have been 5 days (range 0-24; IQR: 2-9;
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9 296 calculated from data presented within the paper).

10 297 Seven modelling papers reported duration of infectious period (T_3+T_5 ; Table 4), with the reported
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12 298 central tendency for the distribution varying from 3-20 days. The form of the distribution offered to
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14 299 models for this parameter varied considerably, including point estimates (deterministic models), flat
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16 300 (uniform), Gaussian, Weibull and gamma distributions. Li et al. [27] estimated the shortest median
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18 301 duration of 3.45 days, with a flat (uninformative) prior distribution corralled between 3-5 days. In
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20 302 contrast, Zhu et al. [37] used a mean prior of 10 days, with the model estimated mean duration
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22 303 being 12.5 days (variance 10; Weibull distribution). Piccolomini and Zama [38] used a fixed estimate
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24 304 of 20 days infectious period, to model the Italian epidemic. Two papers from the same group [14,15]
25
26 305 suggested that infectious period for asymptomatic cases approximated for symptomatic cases where
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28 306 there was no right censoring (that is, transmission being halted through isolation or hospitalisation;
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30 307 gamma distributions of mean 5 or 7 days). Tuite et al. [26,39] also assumed the same duration for
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32 308 “mild” and “severe” symptomatic cases (6-6.5 days).

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310 ***Viral load dynamics***

311 Viral load was reported from 21 papers using real-time reverse transcriptase polymerase chain
312 reaction (rRT-PCR) testing, generally post-symptomatic monitoring.[3,29,40–59] Qualitatively, the
313 viral dynamics described early increase in viral load, peaking around onset or within 2-4 days of
314 symptom onset (Figure 5 for a theoretical model), before decreasing gradually over the next one to
315 three weeks post symptom onset. Maximum duration of detection ranged from approximately 20-49
316 days, with the longest duration associated with faecal samples (see below for discussion). The
317 duration where ribonucleic acid (RNA) was recoverable by RT-PCR may have been truncated due to
318 insufficient follow-up in some cases. Studies that have investigated blood samples have provided
319 some evidence for an association with severity of infection [16,60], though it is not clear whether
320 this is a consistent feature of SARS-CoV-2 infection [40].

321 It should be noted the lack of data on pre-symptomatic or asymptomatic cases with regards viral
322 load. An exception was Kam et al. [61] who describe a pre-symptomatic case in an infant. In another
323 study, Zou et al. [53] undertook serial RT-PCR testing from nasal and throat swab samples from 14
324 imported cases, and 4 secondary cases, in Guangdong, China. The dynamics of the infection in terms
325 of cycle threshold (Ct) values and RNA copy number were described; Ct values of 30.76, 27.67,
326 24.56, and 21.48 corresponding to 1.5×10^4 , 1.5×10^5 , 1.5×10^6 , and 1.5×10^7 copies per milliliter.
327 Hence, lower Ct values infer higher viral loads. The authors report on a patient without symptoms,
328 but with positive nasal swabs (Ct values, 22 to 28) and throat swabs (Ct values, 30 to 32) testing
329 positive on days 7, 10, and 11 after contact. Importantly, the authors suggest “the viral load that was
330 detected in the asymptomatic patient was similar to that in the symptomatic patients.”
331 Furthermore, Kimbell et al. [62] report that Ct values between asymptomatic (21.9 to 31.0), pre-
332 symptomatic (15.3 to 37.9), and symptomatic cases (18.6 to 29.2) within a nursing home
333 environment did not differ significantly. To et al. [59] present data on temporal profile of viral load
334 from saliva samples, and found that median initial and peak viral loads in severe cases were non-
335 significantly higher ($p > 0.5$) by approximately 1 log₁₀ higher than those in mild cases. Liu et al. [58]
336 present data showing viral load being 60 times greater for severe cases relative to mild cases.

337 This lack of pre-symptomatic data may result in left truncation of the risk distribution associated
338 with viral load and shedding. Therefore, the typical timing of peak viral shedding (whether prior to,
339 at, or after onset), and its impact on transmission, is still uncertain. He et al. [29] reported highest
340 viral load at symptom onset from patients sampled in a hospital in China. Furthermore, the author’s
341 estimate using a separate infector-infectee dataset (n=77) that 44% (95% CI: 25–69%) of infectee
342 cases were infected during the pre-symptomatic stage of the infector. Separately, a modelling paper

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3 343 by Ferretti et al. [63] also appears to support this, estimating that 47% (0.9/2) of total transmission
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5 344 contributing R_0 , an overall measure of transmission during an infection, was pre-symptomatic (also
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7 345 see [33]).

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9 346 Wölfel et al. [50] provides important data on a cohort of nine 'mild' cases which were serially tested
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11 347 using sputum, swabs (throat and nasopharyngeal), urine and faecal samples over time. Importantly,
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13 348 the virus was isolated, and inferences on viral replication could be made. Viral Isolation, and insights
14
15 349 into viral replication, improve inference around viral dynamics and transmission risk. The study
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17 350 suggested high viral loads shortly after symptom onset, which declined thereafter over time. Positive
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19 351 cultures were found from day 3-8 post-symptom onset (Figure S3), and the minimum 5% isolation
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21 352 success was achieved up to 9.8 (95% CI: 8.5-21.8) days post onset from throat and lung samples but
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353 not faeces, blood or urine.

354 Discussion

355 Inferring infectiousness was challenging given the heterogeneity of evidence available. Virological
356 diagnostic studies provide robust time series of infection, however, is limited by inferring the
357 relationship between PCR diagnostics and infectiousness. These data can also be affected by
358 sampling procedure and sample sites (e.g. upper respiratory, lower respiratory, faeces, urine, blood).
359 We have excluded RT-PCR durations based on faecal sampling due to the current uncertainty
360 whether these data pertain to transmission potential ([50]; see below). Virological studies where
361 culturing has taken place, and where viral replication can be inferred would also be considered
362 superior data to infer infectious period, relative to estimates of viral load alone.[50] Where this has
363 taken place, the data would suggest average infectious periods of up to 9.8 days post-symptoms.
364 Recent modelling work suggest that the duration of viral detectability could overestimate the
365 infectious period somewhere between 2-6 days.[64]

366 Viral load studies suggest peak viral load occurs close to symptom onset (potentially, -1 to 7 days of
367 onset), however there is uncertainty whether this typically occurs prior to, on, or after onset (Figure
368 5 for conceptual model). High viral loads, measured as Ct values, have been recorded for one week
369 to 20 days post symptom onset, with a general decreasing trend with time. For example, To et al.
370 [59] estimates a declining slope per day for log₁₀ RNA copies per ml of -0.15 (95% CI -0.19 to -0.11;
371 $R^2=0.71$). There are some studies reporting associations between viral load and symptom severity,
372 with higher metrics of viral load in severe cases.[3,58,59] However, Zou et al. [53], and more recent
373 data from Italy,[64,65] suggest similar viral loads in symptomatic and asymptomatic cases.

374 We tested the hypothesis that severity of symptoms had an effect on symptomatic infectious
375 duration using a meta-regression approach. There was a trend towards studies that included severe
376 cases tended to have longer duration (estimated to be 4.0 days longer), but the effect was not
377 significant. Some studies have reported an association between duration of infectiousness and
378 severity (e.g. [58]). But uncertainty of whether this is robust remains. Caution is required when
379 comparing severity of symptoms, as objective or standardised metrics are not always reported.

380 Virological studies that included children (either mixed adult children, or children only cohorts)
381 appeared to have shorter T5 durations (estimate: 5.8 days shorter). Liao et al. [66] present data
382 which suggests that children and 'young adults' (<35 years old) infected cases exhibited long
383 incubation time (exposure to symptom on-set; mean 7.2 days), and short serial interval (mean 6.5
384 days; median 1.9 days; time from onset in primary to onset in secondary case).

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3 385 Contact tracing studies provided robust evidence of transmission events, and therefore
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5 386 infectiousness, but can be limited by the inferred timing of events, and symptoms experienced, due
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7 387 to the self-reported nature of data collection (recall bias). The subjective nature of self-reporting
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9 388 indeed can have an impact on case definitions of ‘asymptomatic’, which has led to some doubt on
10 389 asymptomatic transmission in one case.[9] Rothe et al. [9] describe a case of apparent asymptomatic
11 390 transmission from a Chinese visitor to business associates in Germany, which was cast into doubt
12 391 when health officials reported that the patient had indeed experienced some, albeit minor,
13 392 symptoms.[67] Rothe et al. [9] subsequently updated the clarification of the patients self-reported
14 393 symptoms during the presumed asymptomatic infectious period, which included “feeling warm” and
15 394 “feeling cold”. However, the patient only “recognized getting sick” after she returned to China on
16 395 day four after the presumed exposure event.

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22 396 Modelling parameters provide information on how COVID-19 data are being used and interpreted in
23 397 the research community, given the limited data available. Posterior estimates also provide
24 398 information on the parameter space at which infectious period central tendency reside, given other
25 399 parameters and assumptions in the model. Models used highly varied approaches to modelling
26 400 infectious period, which in turn resulted in highly variable parameter estimates used to inform the
27 401 studies. An important factor to consider when comparing parameter estimates between empirical
28 402 and modelling studies is the interpretation of the parameter by different disciplines, and even
29 403 between researchers from the same discipline. The infectious period can be considered significantly
30 404 context specific and dynamic, and the ability to transmit infection can be modulated by
31 405 interventions (e.g. through isolation or hospitalisation). Modelling papers, depending on the model
32 406 structure, can report truncated infectious period accounting for such interventions. Such estimates
33 407 are not comparable with our definition of the parameters reviewed, and we have attempted to
34 408 avoid such disparities where we found them.

409 *Overall duration findings*

410 There are few data for the precise definition of the asymptomatic infectious period (T2) parameter.
411 Some reported asymptomatic cases can actually be pre-symptomatic, when cases are subject to
412 follow-up (e.g.[66]; see discussion above). However, Hu et al. [7] do provide the data for
413 asymptomatic cases [that remain asymptomatic] across their presumed infectious period. Therefore,
414 in the first instance a parameter mimicking their data is probably the best available data over the
415 period of the present study. Note, there is a large variation in this data parameter, and a gamma
416 distribution of a shape alpha 3, beta 2, mean 6, may be appropriate for the initial model runs.
417 Despite these being the primary informative data, caution is required, given the uncertainty around

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3 418 the relationship between RT-PCR results and infectiousness. Overall, an informed central tendency
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5 419 of ~6 days, with very low probability draws for durations >20 days for the T2 parameter may be
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7 420 considered given the current state of knowledge.

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9 421 The pre-symptomatic period is sometimes referred to as 'preclinical infectious' period (parameter
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11 422 T3). This has been estimated from several papers, and the central tendency of these estimates vary
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13 423 from <1 - 4 days, cautiously approximating to 2 days, on average. Current models have used central
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15 424 tendency estimates of 0.5 to 2.4 days.[14,15,26,39] The relative consistency around the duration of
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17 425 this period allows for some confidence of its distribution. Current understanding of viral dynamics of
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19 426 infection suggest that viral load and shedding increases during post-latent phase, peaking around
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21 427 onset [for symptomatic cases], before declining.[29,50,53] This aspect of the natural history of
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23 428 infection may be important when attempting to model transmission dynamics.

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25 429 Length of infectious period in symptomatic cases that do not isolate (T5 parameter) has also been
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27 430 rarely directly measured in the literature, as serial monitoring of patients in terms of symptoms or
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29 431 viral load (rt-PCR) generally occurs after diagnosis and/or after admission to hospital [from a
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31 432 modelling perspective, this means cases are censored as they are assumed to no longer contribute
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33 433 to transmission]. If natural progression of infection after diagnosis or hospital admission mimics the
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35 434 course of infection for those who do not isolate, the review of the literature describing time to two
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37 435 clear tests is informative. Symptom onset to serial testing clearance [assessed the time to first of two
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39 436 RT-PCR clear tests] averaged 13.4 days from our meta-analysis. In the maximal case, where patients
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41 437 succumb or fully recover from infection, time from symptoms to death or discharge may be
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43 438 informative. Studies that collated such information suggest mean durations of 18.07 days, but with
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45 439 time to discharge being 4.96 days shorter on average than time to death. These values may
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47 440 represent an over estimation of the infectious period; one study suggested that there was on
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49 441 average 2.5 days between end of infectiousness and 'removal' (recovery or death).[37]

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51 442 Cheng et al. [33] provided evidence of transmissibility, based on attack rate from primary to
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53 443 secondary cases, at around symptom onset. The authors estimate cumulative infectiousness from
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55 444 onset, which suggests that 67% of total infectiousness potential occurs by the first day post-onset.
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57 445 Most of the total infectiousness occurs within 5 days (86.9%) post onset, with the remaining
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59 446 infectiousness potential (13.1%) being distributed up to day 30 (this truncation is an assumption by
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61 447 the authors). It is possible that pre-symptomatic transmission occurred during this study, but the
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63 448 authors do not estimate what proportion of transmissions occurred during a pre-symptomatic
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65 449 infectious period, or its potential duration.

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3 450 A model by He et al. [29] is informative for overall symptomatic duration (T3+T5), using 77 infector-
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5 451 infectee pairs where COVID-19 transmission occurred in China. The study reported that
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7 452 infectiousness was apparent on average 2.5 days prior to symptoms, reached a peak in risk at 0.6
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9 453 days before symptoms, and decline up until 7 days after onset (9.5 days total infectious period). The
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11 454 proportion of transmission before symptom onset (area under the curve) was estimated as 44%
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13 455 (95% CI, 25–69%), based on inferences on incubation period. The authors suggest their data
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15 456 supported the view that transmission risk decline substantially after 7 days post-symptoms onset.

16 457 Model estimates used for infectious period parameter appears to be shorter than virological studies
17
18 458 tracking RNA viral load over time. For example, Liu et al.[27] fitted a flat prior distribution for mean
19
20 459 duration (D) fixed to vary between: $2 \leq D \leq 5$ days, and Lavezzo et al. [64] fixed infectious period to 2
21
22 460 days in their epidemic model; whereas viral repeat testing studies provide evidence to suggest high
23
24 461 viral loads can be detected to up 20 days (e.g. pharyngeal swabs), and potentially longer from faecal
25
26 462 samples (up to 3-4 weeks post symptoms onset)). Oral-faecal transmission risk is currently unknown,
27
28 463 but some doubt has been raised about studies that have reported positive RTPCR test results (see
29
30 464 [68]; but there may be some evidence of the risk amongst children; [69]). Wölfel et al. [50] has
31
32 465 produced an important study that provides some data on viral replication, and the site and duration
33
34 466 over which this may be taking place. Their data suggests that viral replication, with high viral loads,
35
36 467 occur in the upper respiratory tract, over the first week of symptoms peaking in day 4. Virus could
37
38 468 not be isolated from faecal samples, despite high RNA concentration. Furthermore, virus was not
39
40 469 isolated from blood or urine in that study.[50]

41
42 470 It should be noted that some of the virological and tracing studies reviewed had small sample sizes
43
44 471 (see Study Limitations) and potentially biased towards more severe cases or clusters of infection. It is
45
46 472 unknown as to whether these cases are representative of infectious duration generally across
47
48 473 populations. However, if symptom severity is linked to infectious duration, one could speculate that
49
50 474 this bias could help to explain the some of the difference between model and empirical duration
51
52 475 estimates.

476 **Study limitations**

53
54 477 Overall, the studies included were of good quality, though due to the rapid need for information
55
56 478 from the global research community many papers are pre-prints that have yet to be reviewed (at
57
58 479 time of writing). Many papers were limited in terms of sample sizes, with several papers being case
59
60 480 studies of one patient or single cluster outbreaks. There was a diversity of methods employed to
481
482 481 infer dynamics of infectiousness across studies, and therefore the evidential base was variable. Some
482
483 482 issues around nomenclature were noted, including definitions of asymptomatic, infectious period,

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2
3 483 latent, and incubation period. It is possible the same data may have been used across different
4
5 484 studies, especially where publicly available data were used.
6

7 485 There was significant heterogeneity across study findings, and this was related to diversity of clinical
8
9 486 findings and methods employed. The meta-analysis employed for one parameter (T5) using
10
11 487 virological studies, where cross study comparisons could be made, suggested that the heterogeneity
12
13 488 was high. Fu et al.[70] cautions against combining studies to give an overall estimate without
14
15 489 exploring subgroup or meta-regression analysis, which we have done here. The meta-regression was
16
17 490 based on a small number of studies (n=12-13). Cochrane's handbook suggests 10 studies for each
18
19 491 level of a meta-regression, however in practice much lower numbers have been used to test
20
21 492 hypotheses [22], as is the case here. Fu et al. [70] recommend a minimum of 4 studies per category,
22
23 493 and therefore we dichotomised our predictor variables to ensure we met this minimum. Aggregating
24
25 494 our categories resulted in crude findings.

26 495 Another limitation is that a systematic review was not undertaken to inform this research, hence
27
28 496 there is a possibility that some relevant studies were overlooked. However, two independent
29
30 497 research groups conducted comprehensive search strategies as part of a broader epidemiological
31
32 498 parameters project for COVID-19 [12,13,71,72,73] to inform this research, hence limiting the
33
34 499 potential for missing key studies.

500 **Conclusion**

501 There are few data to inform asymptomatic infectious period (T2 parameter). One study provide
502
503 data that suggest a median period of 4-9.5 days, however, given the viral dynamics, this distribution
504
505 could have an extended tail with low probability long infectious periods of up to 20 days. The pre-
506
507 symptomatic infectious phase (T3) is quite narrowly defined to a mean of approximately 2 days
508
509 (range: <1-4) within the literature. However, there is great uncertainty around the infectious period
510
511 from onset to recovery or death (T5 parameter). The symptom onset until clearance (based on two
512
513 negative RT-PCR tests) parameter estimate of 13.4 days (95%CI: 10.9-15.8) is informative for T5
514
515 parameter, only if one assumes that RT-PCR positive results equate to having infectious potential.
516
517 Many current models corral the infectious period to shorter time periods than what virological
518
519 studies have suggested, with one recent study suggesting that duration of viral detectability over-
520
521 estimates the infectious period on average by 2-6 days. While viral RNA can be detected for long
522
523 periods of time, especially from faecal samples, the ability to isolate the virus from Infected cases
524
525 quickly declines after one-week post-symptoms. Some modelling papers have assumed that
526
527 infectious period is invariant to whether cases are asymptomatic or symptomatic, however, the data
528
529 available are not yet rich enough to inform whether this is a good assumption. Similarly, it is not yet
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1
2
3 516 established whether viral loads are similar between asymptomatic and mild, moderate, or severe
4
5 517 symptomatic cases, with conflicting reports in the literature.
6

7 518 **Word count:** 5829
8

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10
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12
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14
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38
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40
41 536 the public in the design, or conduct, or reporting, or dissemination plans of our research
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786 Tables and figures

787

788 **Figure 1:** Simulation of the parameter distribution inferred for duration infectious period for
789 asymptomatic cases (T2) inferred infectious period for Davies et al. (2020a), grey/blue curve, Davies
790 et al. (2020b) pink curve [model priors]. Green curve: Ma et al. (2020). Histogram is the distribution
791 of asymptomatic cases to two clear tests reported by Hu et al. (2020). Reference lines are point
792 estimates reported from Zhou et al. (2020), Li et al. (2020), and Tuite et al. (2020a &
793 b).[7,8,14,15,26,27,39,71]

794 **Figure 2:** Simulation of the parameter distribution used for T3 (the duration of the pre-symptomatic
795 infectious period for those infected individuals who subsequently develop symptoms). Curves
796 represent simulated approximations of distributions, given information provided from primary
797 literature. Vertical lines represent point estimates where distributions could not be inferred (see
798 table 2). 1. Peak et al. [posterior]; 2. Davies et al. 2020b [prior]; 3. Rothe et al. 2020; 4. He et al.
799 2020; 5. Davies et al. 2020a [prior]; 6. Wei et al. 2020. [9,14,15,29,30,32]

800 **Figure 3:** Forest plot of the mean duration from onset of symptoms to death or recovery (T5) based
801 on virological studies

802 **Figure 4:** Frequency distribution of T5, time from onset of symptoms to recovery (here hospital
803 discharge or death), using patient level raw data from Kraemer et al. ([35,36]; pink bars), Linton et al.
804 ([34]; purple bars) and Tindale et al. ([31]; green bars). Blue solid line is the kernel density of the
805 aggregated dataset Dashed lines represent the mean and 95%CI from a random effects regression
806 model.

807 **Figure 5:** Composite inferred model for cycle threshold (CT) value changes from serial RT-PCR testing
808 for SARS-COV2; currently uncertain whether peak viral load typically occurs prior to, on, or post-
809 symptom onset (primary literature informing this model includes [29,50,53,59]).

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811 **Table 1:** Reported infectious period (IP) for asymptomatic cases (T5 parameter) from virological
 812 studies where serial diagnostic tests were undertaken to infer IP; tracking studies where IP is
 813 inferred from contact tracing; modelling studies where IP is reported as a prior (assumed parameter
 814 value) or an posterior estimate.

No.	Study	Countries	Parameter (days)	n	Central tendency reported	Variation (days; inclus.)	Comment
Virological studies							
[74]	Zhou et al. (2020)	China	11 days	1	Max		This study serially swabbed and tested symptomatic (17) and asymptomatic (1) cases via RTPCR. The single asymptomatic case tested positive up to 11 days post contact with an infected patient (presumed point of exposure).
[7]	Hu et al. (2020)	China	9.5 days	24	Median	1-21 range	Serial testing. Period between "onset" (where onset relates to first positive test) and clearance, adjudged via two negative RTPCR tests, deemed by the authors to be the 'communicable period'. IQR: 3.5-13
Tracking studies							
[8]	Ma et al. (2020)	China, Germany, Japan, Singapore, South Korea, Malaysia, Vietnam	7.25 days*	49	Mean	5.91-8.69 (95%CI)	*Ma et al. (2020) does not report infectious period for asymptomatic cases explicitly within their paper. The authors estimated the infectious period as the upper estimated latent period minus the serial interval, using a dataset of 1155 cases from several countries (latent period was estimated with 11 infector-infectee pairs; serial interval was estimated from 689 infector-infectee pairs). Ma et al. (2020) reported a mean upper limit of latent period of 2.52 days; the mean serial interval for asymptomatic cases (using date of diagnosis for onset) was estimated to be 9.77 (94%CI: 8.43, 11.21).

[7]	Hu et al. (2020)	China		3		4-9 range	Cluster of infection within a family, where the primary case was asymptomatic. The transmissions to secondary cases occurred over a period 4-9 days post the presumed point of exposure for the primary case.
Modelling studies							
[27]	Li et al. (2020)	China	3.5* [posterior from a model estimating duration for undocumented cases]		Median	3.19-3.78 95%CI	Li et al. (2020) do not explicitly attempt to model asymptomatic cases, or their infectious duration. Instead the population infected is divided into 'documented' and 'undocumented'. Documented were all cases where patients had symptoms severe enough to be confirmed infected; all other cases were considered undocumented. Therefore, this estimate represents asymptomatic and 'mild' cases. The 95%CI around the median infectious period estimate was 3.19-3.78
[26,39]	Tuite et al. (2020a &b)	Canada	6-6.5 [Prior]		[Fixed parameter within a deterministic model]		Mathematical model [deterministic], with a fixed parameter estimate of 6 or 6.5 days. Important to note that duration for 'mild' was equal to severe cases.
[14]	Davies et al. (2020) (a)	UK	7 days [Prior]		Mean		Model with asymptomatic infection compartment. Modelled with a gamma distribution, beta 1.4; alpha 5. Despite, the subclinical aspect of this parameter, it could be considered analogous to total infectious period without intervention.
[15]	Davies et al. (2020) (b)	UK	5 days [Prior]		Mean		Model with asymptomatic infection compartment. Modelled with a gamma distribution, k=4. Authors: "Assumed to be the same duration as total infectious period for clinical cases, including preclinical transmission"

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816 **Table 2:** Reported infectious period (IP) for pre-symptomatic cases (T3 parameter) from virological
 817 studies where serial diagnostic tests were undertaken to infer IP; tracking studies where IP is
 818 inferred from contact tracing; modelling studies where IP is reported as a prior (assumed parameter
 819 value) or an posterior estimate.

	Study	Location	Parameter (days)	Central tendency reported	Variation (days; inclus.)	Comment
	<i>Virological studies</i>					
[3]	Pan et al. (2020)	Beijing, China	1	Median		Case study of two individuals tracked due to exposure to an infected patient was serially tested prior to onset of symptoms.
[28]	Hoehl et al. (2020)	Flight from Wuhan to Germany	1	Median		Case study of serially tested at risk cohort flying from Wuhan to Germany. Two patients were asymptomatic test positive; additionally virus isolation was achieved, indicating potential infectiousness.
	<i>Tracking studies</i>					
[4]	Huang et al. (2020)	Nanjing, China	4	Median	3-5 range	Follow-up tracing case study cluster of infection within a family demonstrating pre-symptomatic infection (n=10)
[9]	Rothe et al. (2020)	Germany	2	Median	1-3 range	Tracing case study of a cluster of infections whereby pre-symptomatic transmission occurred (n=3).
[29]	He et al. (2020)	Vietnam, Malaysia, Japan, China, Taiwan, USA, Singapore	2.3	Mean	95% CI, 0.8–3.0	Tracing paper infector-infectee pairs. Estimated from serial interval and incubation periods. N=77
[30]	Wei et al. (2020)	Singapore	2.5	Median	2-3 (IQR)	Tracing study investigating pre-symptomatic infections from primary cases to secondary cases in 7 clusters. N=8 primary cases. T3 estimated as the min. days between transmission period (TP) and primary case

						symptom onset, when TP straddled >1 day. Range: 2-6 days.
	Modelling studies					
[32]	Peak et al. (2020)	Massachusetts	0.8 [estimate]	Mean	-0.29-1.98 95% CI*	Modelling paper estimated under two scenarios – a serial interval of 4.8 days or 7.5 days. Under scenario one, the model estimated a period of pre-symptomatic transmission (median: 0.71). * the lower range was fixed at zero as the model allowed for no pre-symptomatic infectious case.
[37]	Zhu et al. (2020)	Wuhan, China	1.0 [estimate]	Mean		Modelling paper. Model estimated point value – This is a model derived value
[14]	Davies et al. (2020) (a)	UK	2.4 [prior]	Mean		Modelling paper. Gamma distribution; k=5.
[15]	Davies et al. (2020) (b)	UK	1.5 [prior]	Mean		Modelling paper. Gamma distribution: k=4
[26,39]	Tuite et al. (2020a & b)	Canada	0.5, 1 [prior]	Fixed		Modelling paper. Fixed parameter within a deterministic model.
[75]	Ferguson et al. (2020)	UK	0.5 [prior]	Fixed		Modelling paper. Fixed parameter within this model, whereby infectiousness was assumed to begin 12 hours symptom onset.
[31]	Tindale et al. (2020)	Tianjin, China, and Singapore	2.9-2.6 [estimate]	Mean	1.2-8.2 mean range, depending on early or late cases, or whether in Tianjin, Singapore	Statistical modelling study estimating period pre-symptomatic transmission inferred from estimates of serial interval and incubation periods for populations in Tianjin and Singapore (n=228).

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822 **Table 3:** Reported infectious period (IP) for post-symptomatic cases (T5 parameter) from virological
 823 studies where serial diagnostic tests were undertaken to infer IP [onset to ≥ 2 tests]; tracking studies
 824 where IP is inferred from patient histories from onset to recovery or death; modelling studies where
 825 IP is reported as a prior (assumed parameter value) or an posterior estimate.

No.	Study	Location	Parameter (days)	Central tendency reported	Variation (days; inclus.)	Comment
<i>Virological studies</i>						
[76]	Cai et al. 2020 (a)	China	12	Median	6-22 range	Serial testing study of n=10 mild cases RT-PCR confirmed in children. IQR: 8-15 days
[77]	Cai et al. 2020 (b)	China	14	Median	9-19 (IQR)	Serial testing study with n=298 confirmed (RT-PCR) cases treated within hospital setting
[78]	Chen et al.(2020)	China	12	Max.		Single case study for a patient admitted to hospital where RT-PCR serial testing was undertaken. Patient had an additional positive test at day 17, but subsequently tested negative
[79]	Cheng et al. (2020)	China	21	Max.		Case study of single patient serially tested by RT-PCR
[7]	Hu et al. (2020)	China	12	Median	12-14 (IQR)	Serial testing study of patients who were first tested (qRT-PCR) when asymptomatic; this subset subsequently developed symptoms (n=5).
[42]	Kim et al. (2020)	Korea	15.5	Median	14-17 (range)	Serial testing of two confirmed cases via RT-PCR. Viral load highest during early phase of infection (day 3-5).
[43]	Kujawski et al. (2020)	USA	26	Max.		Serial testing of two confirmed cases via RT-PCR. Mild to moderate symptoms.
[80]	Lee et al. (2020)	Taiwan	20	Max.		Serial testing (RT-PCR) of a single patient hospitalised presenting with pneumonia
[44]	Lim et al. (2020)	South Korea	16	Max.		Serial testing (RT-PCR) of a single patient hospitalised presenting with pneumonia. Two clear tests day 11, virus

						detectable again up to day 16.
[81]	Ling et al. (2020)	China	9.5	Median	2-22 (range)	Serial testing of two confirmed cases via RT-PCR. n=66. IQR: 6-11 days, oropharyngeal sampling. Mix of adult and children.
[82]	Liu et al. (2020)	China	11	Median	7-18 range	Serial testing of two confirmed cases via RT-PCR. n=10. 10-13 (IQR); adults, mild, moderate, and severe cases.
[45]	Marchand-Senéca et al. (2020)	Canada	23	Max		Serial testing (RT-PCR) of a single patient hospitalised presenting with pneumonia.
[3]	Pan et al. (2020)	China	10	Median	8-12 range	Serial testing (RT-PCR) of two patients hospitalised. Viral loads peaked days 5-6 post-onset.
[83]	Qu et al. (2020)	China	22	Max		Serial testing (RT-PCR) of a single patient hospitalised
[46]	Tan et al. (2020)	Vietnam	16	Max		Serial testing (RT-PCR) of a single patient hospitalised; throat sample.
[47]	Thevarajan et al. (2020)	Australia	7	Max		Serial testing (RT-PCR) of a single patient hospitalised; throat sample. Highest viral load on first test at day 4 in nasopharyngeal; day 6 for sputum.
[69]	Xing et al. (2020)	China	14	Median		Serial testing (RT-PCR) of a three (children) patients hospitalised. Mild-moderate infecting. Positive viral samples from faeces up to 4 weeks post-symptoms.
[52]	Young et al. (2020)	Singapore	12.5	Median		Serial testing (RT-PCR) of 18 patients hospitalised. Adults. Viral load peaked over testing series at day 4 since onset.
[84]	Yuan et al. (2020)	China	6	Median	4-10 (IQR)	Serial testing (RT-PCR) of 25 patients hospitalised. Children and adults. "Non-severe" cases.
[74]	Zhou et al. (2020)	China	20	Median	16-23 IQR	Serial testing (RT-PCR) of 191 patients hospitalised in two hospitals. Adults. 54 died. Survivors (n=137); Median (IQR) 20.0 days (17.0–24.0); Non-survivors

						(n=54); Median (IQR) 18.5 days (15.0–22.0); Shedding continued until death. Inferred shedding period; 8-37 days.
[85]	Chen J. et al. (2020)	China	11	Median	10-12 (95%CI)	Serial testing (RT-PCR) of 242 patients hospitalised. Adults. 90% mild/asymptomatic; 10% severe/critical.
[60]	Fang et al. (2020)	China	15.7	Mean	6.7 (sd)	Serial testing (RT-PCR) of 24 non-ICU patients hospitalised. Adults. Nasal samples.
[60]	Fang et al. (2020)	China	22.3	Mean	3.6 (sd)	Serial testing (RT-PCR) of 8 ICU patients hospitalised. Adults. Nasal samples.
[57]	Hill et al. (2020)	Scotland	9	Max.		Serial testing (RT-PCR) of a single patient (adult) hospitalised; nasal sample [throat sample: 6 days]. Mild.
[86]	Le et al. (2020)	Vietnam	12	Max.		Serial testing (RT-PCR) of a single patient (infant) hospitalised. Mild.
[58]	Liu et al. (2020)	China	10	Max.		Serial testing (RT-PCR) of patients hospitalised. Adults. Mixed Mild/severe cases. N=76. 90% “early viral clearance” within 10days
[87]	Qiu et al. (2020)	China	10	Mean	7-22 range	Serial testing (RT-PCR) of patients hospitalised. Children. N=36. Mild and moderate cases.
[59]	To et al. (2020)	Hong Kong	25	Max.		Serial testing (RT-PCR) of patients hospitalised. N=7. Seven patients reported viral detection >20 days; viral load peaked during first week post-onset of symptoms.
[88]	Wu et al.	China	16.1	Mean	6.7 (sd)	Serial testing (RT-PCR) of patients hospitalised. Adults. N=74. Severe and non-severe cases.
Tracking studies						
[31]	Tindale et al. (2020)	Singapore	18	Median	9-33 range	Time from onset to discharge; range 9-33; n=53

[35,36]	Kraemer et al. (2020a); [later published as: Xu et al. 2020]	Various	19	Median	3-37 range	Time from onset to discharge; Range: 3-37; n=70
[34]	Linton et al. (2020)	Wuhan, China	13	Median	6-41 range	Time from onset to death; range 6-41
[35,36]	Kraemer et al. (2020b)	Japan and China	19.25	Mean	12-24 range	Time from onset to death; n=4
[49,50]	Wölfel et al. (2020)	Germany	3-8 days	absolute	3-8 range	Tracked infection in mild cases in Germany, undertaking viral isolation studies to assess active replication across a number of samples sites (upper respiratory tract, blood, urine, faeces) over the duration of infection. 5% isolation success was achieved up to 9.78 (95% CI: 8.45-21.78) days post onset; n=9

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828 **Table 4:** Reported infectious period (IP) for symptomatic cases (T3+T5 parameter) from virological
 829 studies where serial diagnostic tests were undertaken to infer IP [exposure to ≥ 2 neg. tests]; tracking
 830 studies where IP is inferred from patient histories from onset to recovery or death; modelling studies
 831 where IP is reported as a prior (assumed parameter value) or an posterior estimate.

No.	Study	Location	Parameter (days)	Central tendency reported	Variation (days; inclus.)	Comment
Tracking studies						
[29]	He et al. (2020)	Vietnam, Malaysia, Japan, China, Taiwan, USA, Singapore	9.3 days	Mean	7.8-10 (95%CI*)	The paper reported on 77 infector-infectee pairs which were sequential/serially tested, using publicly available data. Viral dynamics (Guangzhou, China; N=94) interpreted by the authors suggested an infectious period starting 2.3 (95% CI, 0.8–3.0 days) days prior to symptoms, peaking 0.7 days (95% CI, -0.2–2.0 days), continuing up to 7 days from onset. * CI from pre-symptom infectious period only.
[8]	Ma et al. (2020)	Various	~5 days	Median	Range 0-24	The authors estimated the infectious period as latent minus the serial interval, using a dataset of 1155 cases. Range 0-24; IQR: 2-9; calculated from data presented within the paper.
Modelling studies						
[27]	Li et al. (2020)	China	3.45 days [posterior estimated from model for documented cases]	median	95%CI for the mean: 3.19, 3.72	Mathematical model. Priors for <u>mean</u> documented infectious period was a flat [uniform] distribution 2-5. 'Documented' cases were defined as those severe enough to be confirmed. This corraling of the infectious period relative to other

						studies should take into account that the distribution is used for the central tendency, not the whole distribution.
[26,39]	Tuite et al. (a, b) (2020)	Canada	6-6.5 days [prior; fixed parameter within a deterministic model]	Fixed parameter		Mathematical model [deterministic], with a fixed parameter estimate of 6.5 days (a) and 6 days (b), respectively. Important to note that duration for 'mild' was equal to severe cases.
[89]	Lourenco et al. (2020)	UK	~3-5 days [posterior; approximate depending on scenario tested]	mean	95%ci of 3-6 days	Mathematical model. The prior used was given a Gaussian distribution (normal curve); mean 4.5; SD 1; approximate 95%ci of 3-6 days. The reported posterior of this parameter was presented graphically and depended on R0 and proportion at risk. Depending on the scenarios tested, mean duration of infectiousness appeared to vary from 3-5 days.
[37]	Zhu et al. (2020)	Wuhan, China	12.5 days [posterior estimated from model]	Mean	11.4 variance	Mathematical model. The parameter was estimated using a Weibull distribution. The prior for this parameter was 10 days. The posterior variance around the mean was 11.4, and therefore the distribution had a long tail. This study was a modelling [SEIR extended model].
[15]	Davies et al. (b) (2020)	UK	7 days [Prior]	Mean		Model with asymptomatic infection compartment. Modelled with a

						gamma distribution, beta 1.4; alpha 5. Despite, the subclinical aspect of this parameter, it could be considered analogous to total infectious period without intervention.
[14]	Davies et al. (b) (2020)	UK	5 days [Prior]	Mean		Model with asymptomatic infection compartment. Modelled with a gamma distribution, k=4. Authors: "Assumed to be the same duration as total infectious period for clinical cases, including preclinical transmission"
[38]	Piccolomini and Zama (2020)	Italy	20 days [Prior]	Fixed		Parameter estimate assumed for the infectious period within an SEIRD model, fitted to data from the epidemic in Italy.

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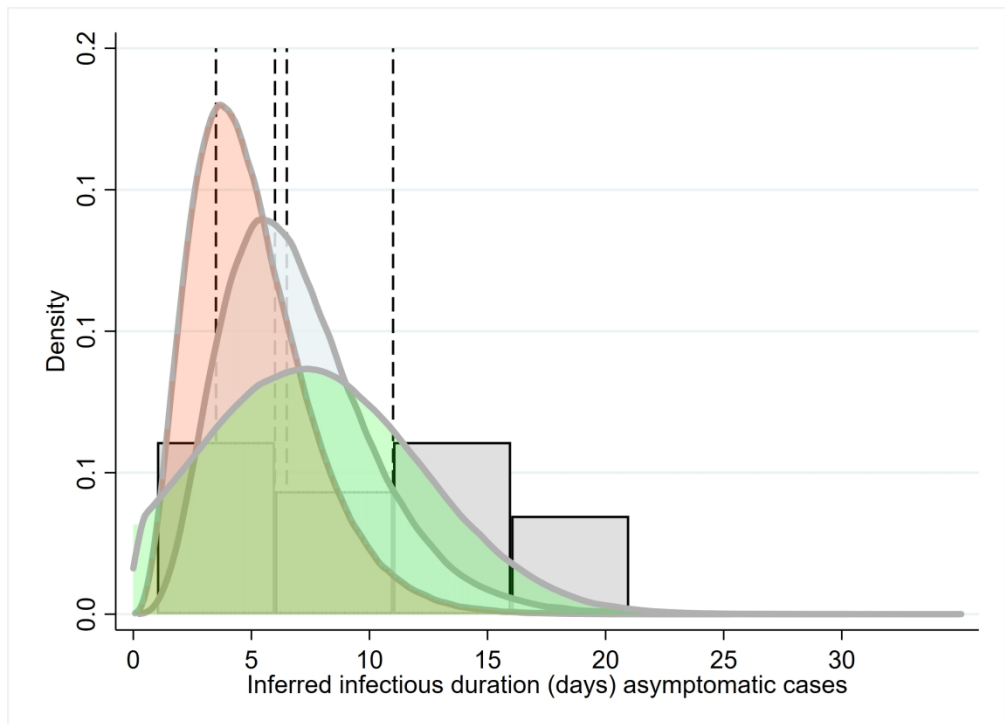


Figure 1: Simulation of the parameter distribution inferred for duration infectious period for asymptomatic cases

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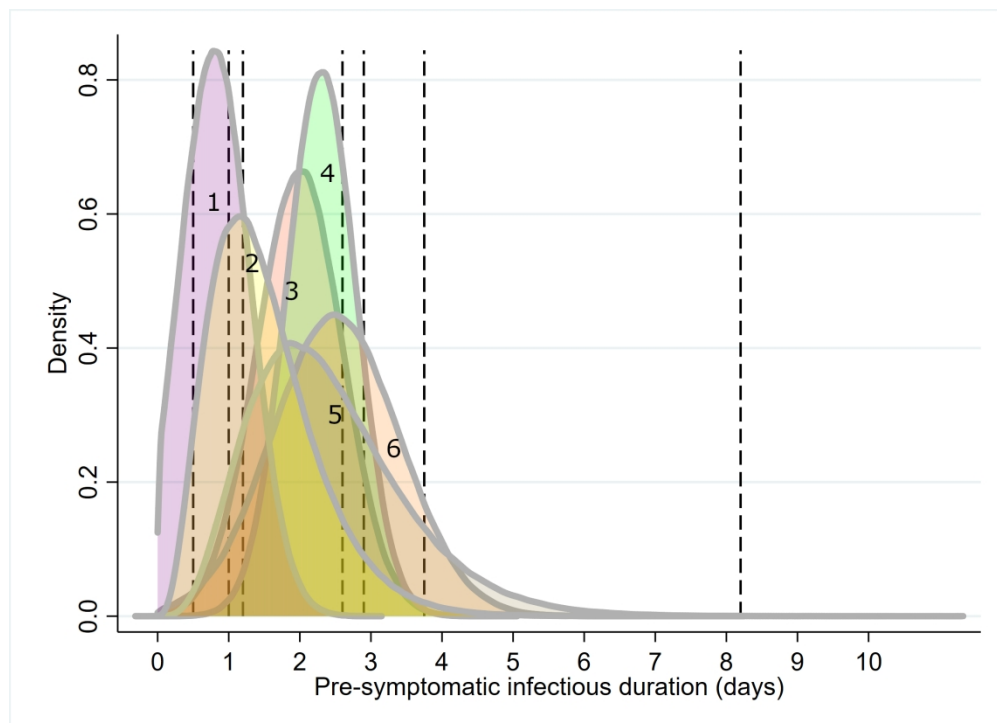


Figure 2: Simulation of the parameter distribution used for T3 (the duration of the pre-symptomatic infectious period for those infected individuals who subsequently develop symptoms).

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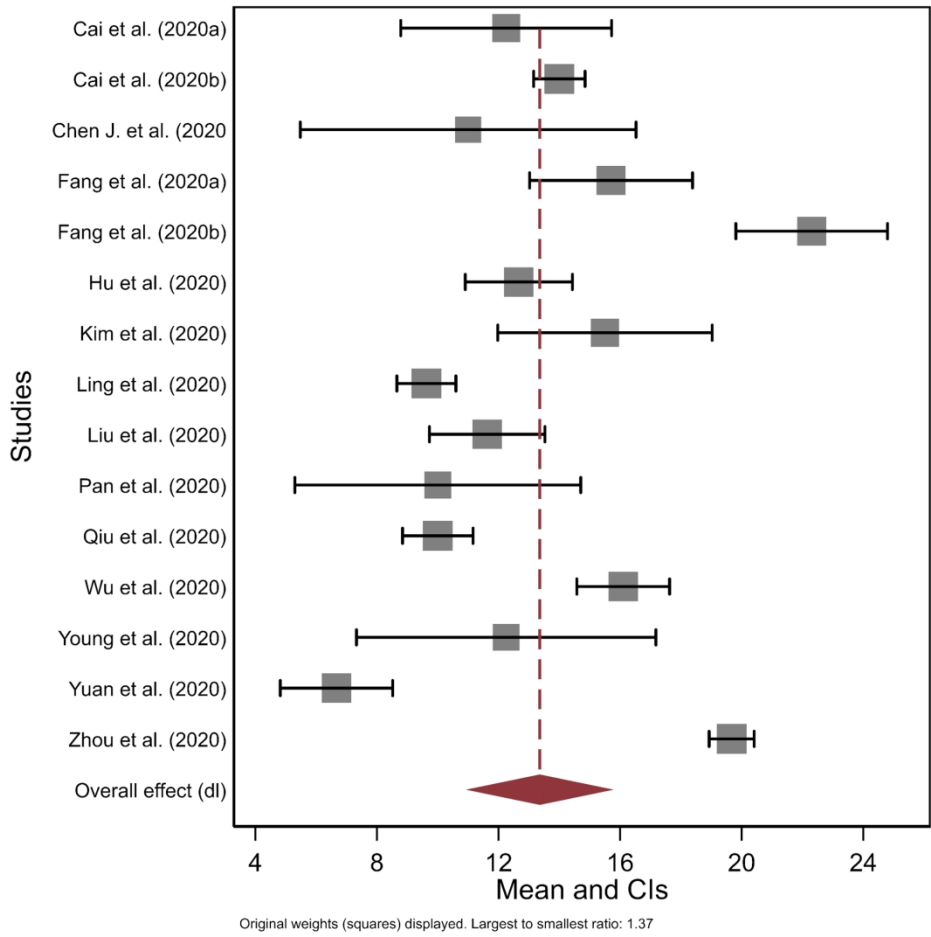


Figure 3: Forest plot of the mean duration from onset of symptoms to death or recovery (T5) based on virological studies

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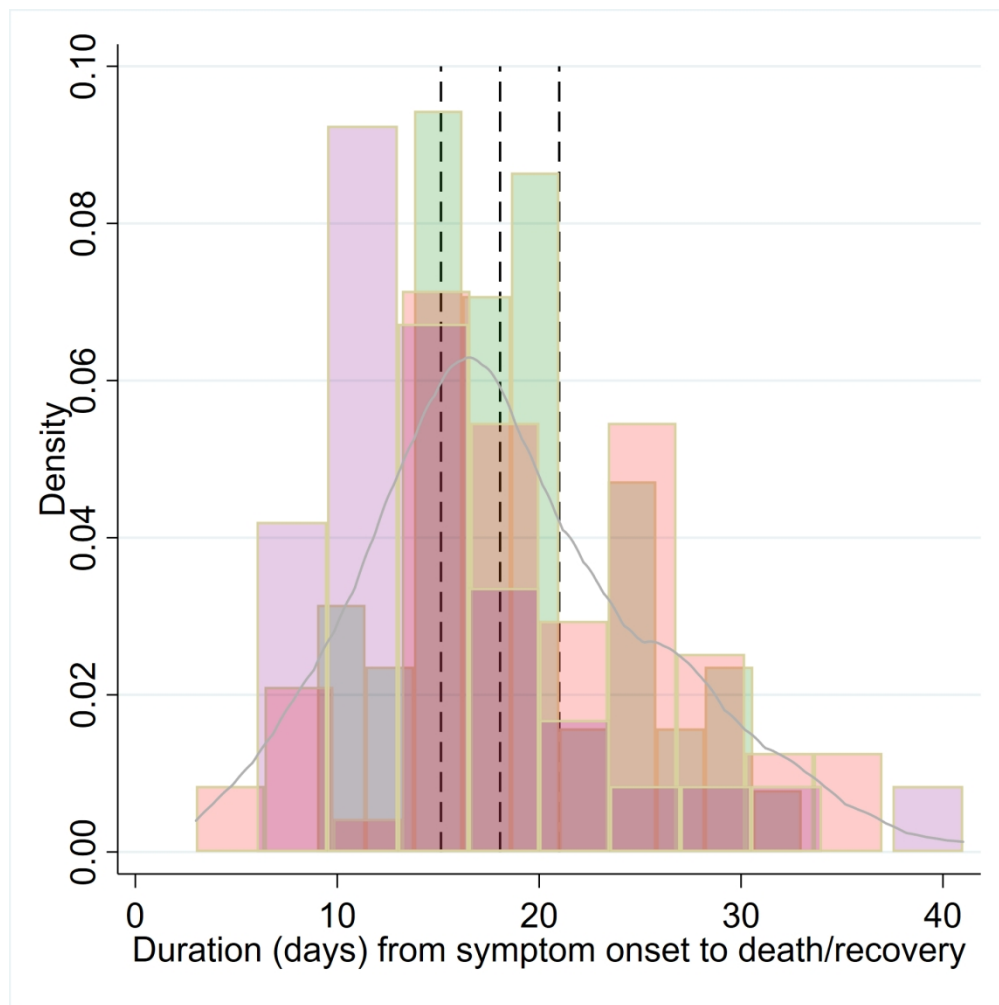


Figure 4: Frequency distribution of T5, time from onset of symptoms to recovery (here hospital discharge or death), using patient level raw data

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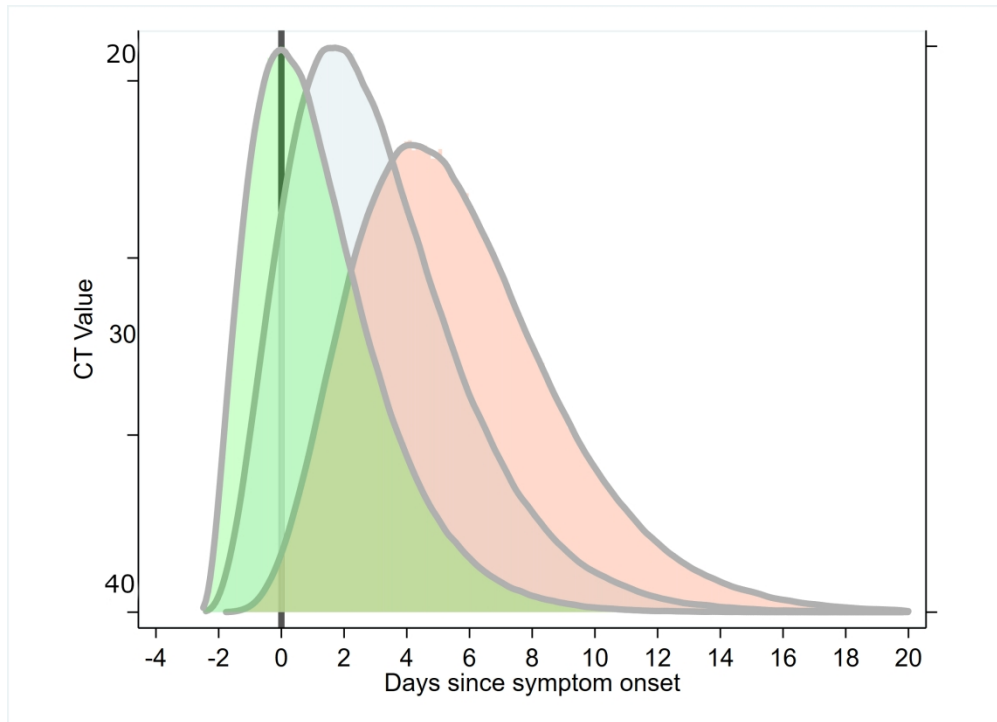
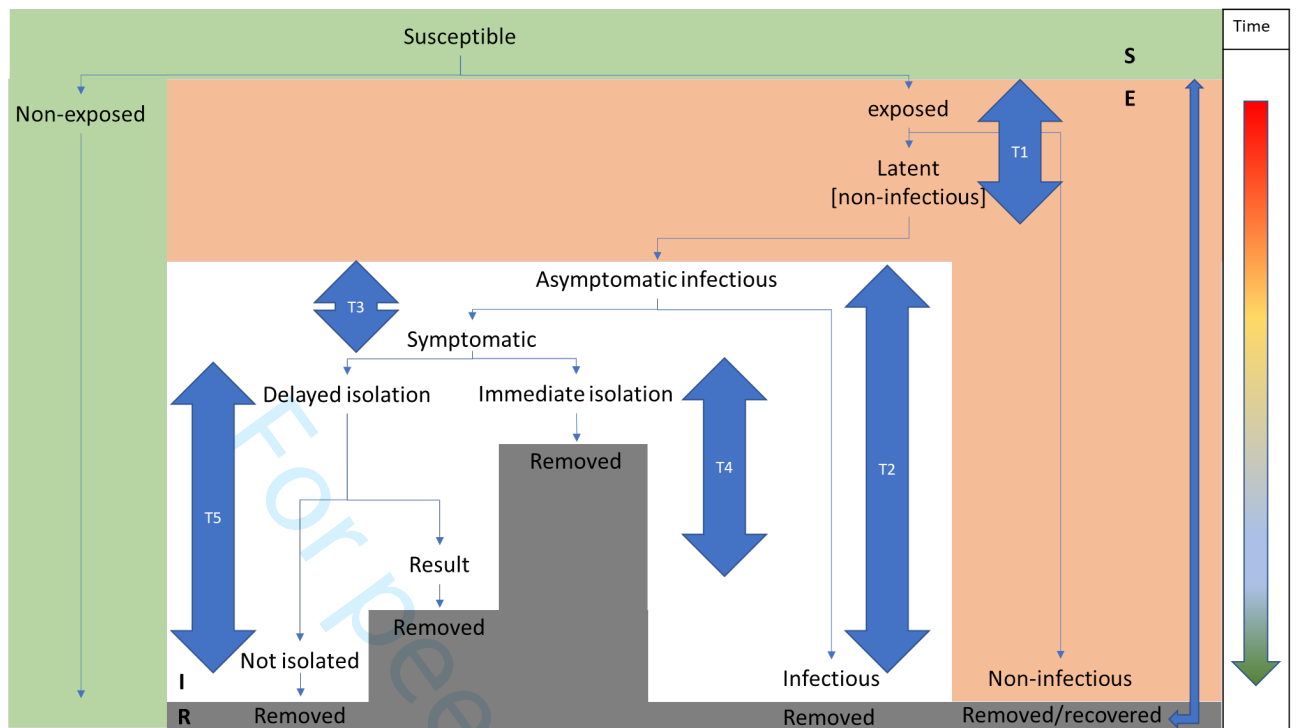


Figure 5: Composite inferred model for cycle threshold (CT) value changes from serial RT-PCR testing for SARS-COV2

211x152mm (300 x 300 DPI)

1 **Supplementary material 1**

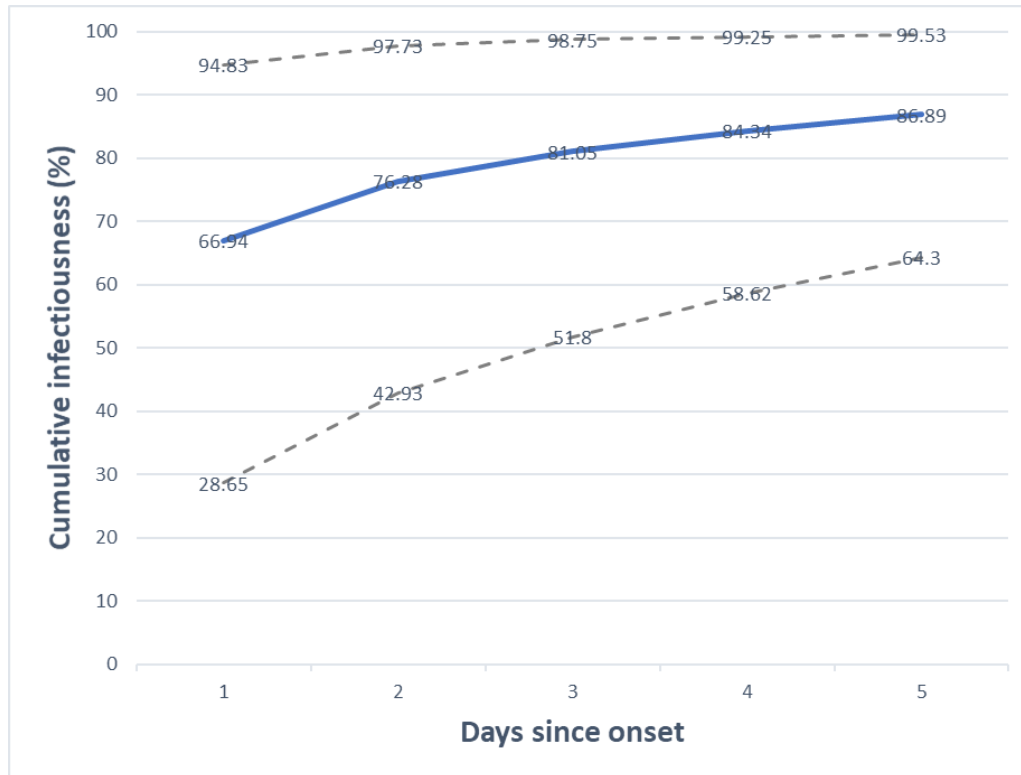


2

3 **Figure S1:** Conceptual model of the key temporal parameters impacting COVID-19 infection
 4 progression over time. T1: Latent period; T2: Asymptomatic infectious period; T3: Pre-
 5 symptomatic infectious period; T4: Symptom onset to diagnosis [self-isolation] or
 6 hospitalisation; T5: Symptom onset to removed [death or recovery]

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9

10 **Figure S2:** Cumulative infectiousness (% of total infectiousness) based on infector-infectee pair
11 data in the paper by Cheng et al. 2020. The accumulation curve is based on a gamma density
12 function, coupled with a probability function to capture the maximal probability if exposed to a
13 primary case.

14

15

Positive culture



Negative culture



0 2 4 6 8 10 12 14
Days after symptom onset

16

17 **Figure S3:** Timeline for positive culture results of SARS-COV2 from throat, sputum and stool
18 samples; Yellow line = Throat swabs; Orange line = Sputum samples; Blue line = Stool samples;
19 Adapted from Wölfel et al.[50].

20

21 **Reference:**

22 Cheng, H.Y., Jian, S.W., Liu, D.P., Ng, T.C., Huang, W.T. and Lin, H.H., 2020. High transmissibility of
23 COVID-19 near symptom onset. *medRxiv*.

24 Wölfel R, Corman VM, Guggemos W, *et al*. Virological assessment of hospitalized
25 patients with COVID-2019. *Nature* 2020;:1–10.

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26 Supplementary material 2:Data for meta-analysis

paper	country	ct	ct_type	range	median	iqr	min	max	first_qt	third_qt	n	mean	sd	se	severity	sev_bin	kid_cat	
Cai et al. (2020a)	China	12	Median	6-22 range	12		6	22	8	15	10			6	2	mild	0	1
Cai et al. (2020b)	China	14	Median		14	9-19 (IQR)			9	19	298			7	0	mild- severe	1	2
Chen et al (2020)	China	12	Max.								1			0	0			2
Chen J. et al. (2020)	China	11	Median	10-12 (95%CI)	11						242			8	3	mild- severe	1	2
Cheng et al. (2020)	China	21	Max.								1			0	0	severe	1	2
Fang et al. (2020a)	China	16	Mean	6.7 (sd)							24			7	1	mild- moderate	0	2
Fang et al. (2020b)	China	22	Mean	3.6 (sd)							8			4	1	severe	1	2
Hill et al. (2020)	Scotland	9	Max.								1			0	0	mild	0	2
Hu et al. (2020)	China	12	Median		12	12-14 (IQR)			12	14	5			2	1	mild	0	2
Kim et al. (2020)	Korea	16	Median	14-17 (range)	16		14	17			2			3	2	mild- moderate	0	2
Kujawski et al. (2020)	USA	26	Max.								1			0	0	mild- moderate	0	2
Le et al. (2020)	Vietnam	12	Max.								1			0	0	mild	0	1
Lee et al. (2020)	Taiwan South	20	Max.								1			0	0	severe	1	2
Lim et al. (2020)	Korea	16	Max.								1			0	0			2
Ling et al. (2020)	China	10	Median	2-22 (range)	10		2	22	6	11	66			4	0			1
Liu et al. (2020)	China	11	Median	7-18 range	11		7	18	10	13	10			3	1	mild- severe	1	2
Liu et al. (2020)	China	10	Max.								76					mild- severe	1	2
Marchand-Senžca et al.	Canada	23	Max								1			0	0			

(2020)

Pan et al. (2020)	China	10	Median	8-12 range	10	8	12	2	3	2				
Qiu et al. (2020)	China	10	Mean	7-22 range		7	22	36	4	1	mild- moderate	0	1	
Qu et al. (2020)	China	22	Max					1	0	0				
Tan et al. (2020)	Vietnam	16	Max					1	0	0	severe	1		
Thevarajan et al. (2020)	Australia	7	Max					1	0	0	mild- moderate	0		
To et al. (2020)	Hong Kong	25	Max.					7	0	0	mild- severe	1	2	
Wu et al. (2020)	China	16	Mean	6.7 (sd)				74	7	1	mild- severe	1	2	
Xing et al (2020)	China	14	Median		14			3			mild- moderate	0	1	
Young et al. (2020)	Singapore	12	Median		12	1	24	18	6	3	mild- moderate	0	2	
Yuan et al. (2020)	China	6	Median		6	4-10 (IQR)	4	10	25	5	1	mild- moderate	0	1
Zhou et al. (2020)	China	20	Median		20	16-23 IQR	16	23	191	5	0	severe	1	2

27

28

29 Supplementary material 3: Data for time to recovery or death

study	overall_time_disc_death	death	discharge	xb_t5	upp95	low95
kraemer	20	0	1	18.06537	15.13663	20.99411
kraemer	16	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	25	0	1	18.06537	15.13663	20.99411
kraemer	22	0	1	18.06537	15.13663	20.99411
kraemer	28	0	1	18.06537	15.13663	20.99411
kraemer	16	0	1	18.06537	15.13663	20.99411
kraemer	25	0	1	18.06537	15.13663	20.99411
kraemer	37	0	1	18.06537	15.13663	20.99411
kraemer	15	0	1	18.06537	15.13663	20.99411
kraemer	14	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	17	0	1	18.06537	15.13663	20.99411
kraemer	20	0	1	18.06537	15.13663	20.99411
kraemer	14	0	1	18.06537	15.13663	20.99411
kraemer	19	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	28	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	8	0	1	18.06537	15.13663	20.99411
kraemer	12	0	1	18.06537	15.13663	20.99411
kraemer	8	0	1	18.06537	15.13663	20.99411
kraemer	18	0	1	18.06537	15.13663	20.99411
kraemer	23	0	1	18.06537	15.13663	20.99411
kraemer	19	0	1	18.06537	15.13663	20.99411

1							
2							
3							
4	kraemer	3	0	1	18.06537	15.13663	20.99411
5	kraemer	17	0	1	18.06537	15.13663	20.99411
6	kraemer	26	0	1	18.06537	15.13663	20.99411
7	kraemer	19	0	1	18.06537	15.13663	20.99411
8	kraemer	16	0	1	18.06537	15.13663	20.99411
9	kraemer	35	0	1	18.06537	15.13663	20.99411
10	kraemer	14	0	1	18.06537	15.13663	20.99411
11	kraemer	14	0	1	18.06537	15.13663	20.99411
12	kraemer	15	0	1	18.06537	15.13663	20.99411
13	kraemer	29	0	1	18.06537	15.13663	20.99411
14	kraemer	30	0	1	18.06537	15.13663	20.99411
15	kraemer	30	0	1	18.06537	15.13663	20.99411
16	kraemer	24	0	1	18.06537	15.13663	20.99411
17	kraemer	32	0	1	18.06537	15.13663	20.99411
18	kraemer	15	0	1	18.06537	15.13663	20.99411
19	kraemer	24	0	1	18.06537	15.13663	20.99411
20	kraemer	24	0	1	18.06537	15.13663	20.99411
21	kraemer	9	0	1	18.06537	15.13663	20.99411
22	kraemer	18	0	1	18.06537	15.13663	20.99411
23	kraemer	16	0	1	18.06537	15.13663	20.99411
24	kraemer	16	0	1	18.06537	15.13663	20.99411
25	kraemer	33	0	1	18.06537	15.13663	20.99411
26	kraemer	18	0	1	18.06537	15.13663	20.99411
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28	kraemer	19	0	1	18.06537	15.13663	20.99411
29	kraemer	19	0	1	18.06537	15.13663	20.99411
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31	kraemer	18	0	1	18.06537	15.13663	20.99411
32	kraemer	18	0	1	18.06537	15.13663	20.99411
33	kraemer	30	0	1	18.06537	15.13663	20.99411
34	kraemer	27	0	1	18.06537	15.13663	20.99411
35	kraemer	20	0	1	18.06537	15.13663	20.99411
36	kraemer	33	0	1	18.06537	15.13663	20.99411
37	kraemer	15	0	1	18.06537	15.13663	20.99411
38	kraemer	5	0	1	18.06537	15.13663	20.99411
39	kraemer	5	0	1	18.06537	15.13663	20.99411
40	kraemer	16	0	1	18.06537	15.13663	20.99411
41							
42							
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44							
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4	kraemer	14	0	1	18.06537	15.13663	20.99411
5	kraemer	21	0	1	18.06537	15.13663	20.99411
6	kraemer	15	0	1	18.06537	15.13663	20.99411
7	kraemer	26	0	1	18.06537	15.13663	20.99411
8	kraemer	17	0	1	18.06537	15.13663	20.99411
9							
10	kraemer	17	0	1	18.06537	15.13663	20.99411
11	kraemer	16	0	1	18.06537	15.13663	20.99411
12	kraemer	16	0	1	18.06537	15.13663	20.99411
13	kraemer	26	0	1	18.06537	15.13663	20.99411
14	kraemer	19	0	1	18.06537	15.13663	20.99411
15	kraemer	19	0	1	18.06537	15.13663	20.99411
16	kraemer	14	0	1	18.06537	15.13663	20.99411
17	kraemer	8	0	1	18.06537	15.13663	20.99411
18	kraemer	34	0	1	18.06537	15.13663	20.99411
19							
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21	linton	21	1	0	18.06537	15.13663	20.99411
22	linton	8	1	0	18.06537	15.13663	20.99411
23	linton	11	1	0	18.06537	15.13663	20.99411
24	linton	11	1	0	18.06537	15.13663	20.99411
25	linton	11	1	0	18.06537	15.13663	20.99411
26	linton	30	1	0	18.06537	15.13663	20.99411
27	linton	32	1	0	18.06537	15.13663	20.99411
28	linton	10	1	0	18.06537	15.13663	20.99411
29	linton	19	1	0	18.06537	15.13663	20.99411
30	linton	19	1	0	18.06537	15.13663	20.99411
31	linton	19	1	0	18.06537	15.13663	20.99411
32	linton	14	1	0	18.06537	15.13663	20.99411
33	linton	8	1	0	18.06537	15.13663	20.99411
34	linton	12	1	0	18.06537	15.13663	20.99411
35	linton	12	1	0	18.06537	15.13663	20.99411
36	linton	12	1	0	18.06537	15.13663	20.99411
37	linton	20	1	0	18.06537	15.13663	20.99411
38	linton	12	1	0	18.06537	15.13663	20.99411
39							
40	linton	7	1	0	18.06537	15.13663	20.99411
41							
42							
43							
44							
45							
46							

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3							
4	linton	11	1	0	18.06537	15.13663	20.99411
5	linton	16	1	0	18.06537	15.13663	20.99411
6	linton	6	1	0	18.06537	15.13663	20.99411
7	linton	6	1	0	18.06537	15.13663	20.99411
8	linton	17	1	0	18.06537	15.13663	20.99411
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11	linton	41	1	0	18.06537	15.13663	20.99411
12	linton	10	1	0	18.06537	15.13663	20.99411
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14	linton	13	1	0	18.06537	15.13663	20.99411
15	linton	13	1	0	18.06537	15.13663	20.99411
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17	linton	16	1	0	18.06537	15.13663	20.99411
18	linton	13	1	0	18.06537	15.13663	20.99411
19	linton	13	1	0	18.06537	15.13663	20.99411
20	linton	14	1	0	18.06537	15.13663	20.99411
21	linton	18	1	0	18.06537	15.13663	20.99411
22	linton	12	1	0	18.06537	15.13663	20.99411
23	linton	19	0	1	18.06537	15.13663	20.99411
24	tindale	25	0	1	18.06537	15.13663	20.99411
25	tindale	25	0	1	18.06537	15.13663	20.99411
26	tindale	20	0	1	18.06537	15.13663	20.99411
27	tindale	20	0	1	18.06537	15.13663	20.99411
28	tindale	13	0	1	18.06537	15.13663	20.99411
29	tindale	28	0	1	18.06537	15.13663	20.99411
30	tindale	25	0	1	18.06537	15.13663	20.99411
31	tindale	24	0	1	18.06537	15.13663	20.99411
32	tindale	14	0	1	18.06537	15.13663	20.99411
33	tindale	17	0	1	18.06537	15.13663	20.99411
34	tindale	15	0	1	18.06537	15.13663	20.99411
35	tindale	18	0	1	18.06537	15.13663	20.99411
36	tindale						
37	tindale						
38	tindale						
39	tindale						
40	tindale						
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1							
2							
3	tindale	15	0	1	18.06537	15.13663	20.99411
4	tindale	16	0	1	18.06537	15.13663	20.99411
5	tindale	16	0	1	18.06537	15.13663	20.99411
6	tindale	16	0	1	18.06537	15.13663	20.99411
7	tindale	20	0	1	18.06537	15.13663	20.99411
8	tindale	17	0	1	18.06537	15.13663	20.99411
9	tindale	12	0	1	18.06537	15.13663	20.99411
10	tindale	24	0	1	18.06537	15.13663	20.99411
11	tindale	24	0	1	18.06537	15.13663	20.99411
12	tindale	26	0	1	18.06537	15.13663	20.99411
13	tindale	16	0	1	18.06537	15.13663	20.99411
14	tindale	16	0	1	18.06537	15.13663	20.99411
15	tindale	20	0	1	18.06537	15.13663	20.99411
16	tindale	9	0	1	18.06537	15.13663	20.99411
17	tindale	15	0	1	18.06537	15.13663	20.99411
18	tindale	14	0	1	18.06537	15.13663	20.99411
19	tindale	18	0	1	18.06537	15.13663	20.99411
20	tindale	30	0	1	18.06537	15.13663	20.99411
21	tindale	19	0	1	18.06537	15.13663	20.99411
22	tindale	17	0	1	18.06537	15.13663	20.99411
23	tindale	16	0	1	18.06537	15.13663	20.99411
24	tindale	17	0	1	18.06537	15.13663	20.99411
25	tindale	20	0	1	18.06537	15.13663	20.99411
26	tindale	23	0	1	18.06537	15.13663	20.99411
27	tindale	19	0	1	18.06537	15.13663	20.99411
28	tindale	12	0	1	18.06537	15.13663	20.99411
29	tindale	19	0	1	18.06537	15.13663	20.99411
30	tindale	17	0	1	18.06537	15.13663	20.99411
31	tindale	17	0	1	18.06537	15.13663	20.99411
32	tindale	14	0	1	18.06537	15.13663	20.99411
33	tindale	16	0	1	18.06537	15.13663	20.99411
34	tindale	16	0	1	18.06537	15.13663	20.99411
35	tindale	17	0	1	18.06537	15.13663	20.99411
36	tindale	17	0	1	18.06537	15.13663	20.99411
37	tindale	14	0	1	18.06537	15.13663	20.99411
38	tindale	16	0	1	18.06537	15.13663	20.99411
39	tindale	30	0	1	18.06537	15.13663	20.99411
40	tindale	30	0	1	18.06537	15.13663	20.99411
41							
42							
43							
44							
45							
46							

1							
2							
3	tindale	33	0	1	18.06537	15.13663	20.99411
4	tindale	19	0	1	18.06537	15.13663	20.99411
5	tindale	29	0	1	18.06537	15.13663	20.99411
6	tindale	22	0	1	18.06537	15.13663	20.99411
7	tindale	10	0	1	18.06537	15.13663	20.99411
8	tindale	20	0	1	18.06537	15.13663	20.99411
9	tindale	11	0	1	18.06537	15.13663	20.99411
10	tindale	15	0	1	18.06537	15.13663	20.99411
11	tindale	18	0	1	18.06537	15.13663	20.99411
12	tindale	18	0	1	18.06537	15.13663	20.99411
13	tindale	11	0	1	18.06537	15.13663	20.99411
14	tindale						
15	tindale						
16							
17							
18							
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30 Supplementary material 4: Stata code

```
31 // 1st April 2020
32
33 /* Code for:
34
35 Byrne, AW, McEvoy, D, et al. 2020
36
37 Inferred duration of infectious period of SARS-CoV-2: rapid review and analysis of
38 available evidence for asymptomatic and symptomatic COVID-19 cases
39
40
41 */
42
43 * Figure 2
44
45 gen davies1_gamma = rgamma(5, 1.4)
46 gen davies2_gamma = rgamma(4, 1.25)
47 gen ma_normal = rnormal(7.2, 4.96)
48
49
50
51
52 input hu_data
53
54 12
55
56 1
57
58 1
59
60 11
61
62 3
63
64 16
65
66 6
67
68 4
69
70 6
71
72 18
73
74 8
75
76 8
77
78 11
79
80 14
81
82 14
83
84 12
85
86 13
87
88 1
89
90 17
91
92 3
93
94 11
95
96 5
```



```

1
2
3 97
4 98 6
5 99
6 100 21
7 101
8 102 end
9 103
10 104
11 105
12 106 // Fig 2 visualise
13 107
14 108 twoway (histogram hu_data, fcolor(gs14) lcolor(black)) (histogram davies1_gamma,
15 109 bin(180) fcolor(ltblueishgray%86) lcolor(none) lwidth(none)) (kdensity
16 110 davies1_gamma, lcolor(gs11) lwidth(thick)) (kdensity davies2_gamma, lcolor(gs11)
17 111 lwidth(thick)) (histogram davies2_gamma, bin(120) fcolor(orange_red%20)
18 112 lcolor(none) lwidth(none)) (histogram ma_normal, bin(100) fcolor(lime%20)
19 113 lwidth(none)) (kdensity ma_normal, lcolor(gs11) lwidth(thick)) if ma_n>=0,
20 114 yscale(line) xtitle(Days since infected) xline(6 6.5 11 3.5, lpattern(dash)
21 115 lcolor(black) noextend) xlabel(0(5)30) legend(off) scheme(s2color) xsize(20)
22 116 ysize(16) graphregion(fcolor(white)) plotregion(fcolor(white))
23 117
24 118
25 119
26 120 * Figure 3
27 121
28 122 gen rothet3_normal = rnormal(2, 0.6)
29 123
30 124 gen huangt3_normal = rnormal(3.75, 0.332)
31 125
32 126 gen het3_normal = rnormal(2.3, 0.49)
33 127
34 128 gen weit3_normal = rnormal(2.5, 0.89)
35 129
36 130 gen peakt3_normal = rnormal(0.8, 0.5)
37 131
38 132 gen daviesAt3_normal = rgamma(5, 0.48)
39 133
40 134 gen daviesBt3_normal = rgamma(4, 0.375)
41 135
42 136 twoway (histogram rothe, bin(120) fcolor(orange_red%20) lcolor(none) lwidth(none))
43 137 (kdensity rothe, lcolor(gs11) lwidth(thick)) (histogram he, bin(100)
44 138 fcolor(lime%20) lwidth(none)) (kdensity he, lcolor(gs11) lwidth(thick)) (histogram
45 139 wei, bin(100) fcolor(orange%20) lwidth(none)) (kdensity wei, lcolor(gs11)
46 140 lwidth(thick)) (histogram peak, bin(100) fcolor(purple%20) lwidth(none)) (kdensity
47 141 peak, lcolor(gs11) lwidth(thick)) (histogram daviesA, bin(100) fcolor(brown%20)
48 142 lwidth(none)) (kdensity daviesA, lcolor(gs11) lwidth(thick)) (histogram daviesB,
49 143 bin(100) fcolor(yellow%20) lwidth(none)) (kdensity daviesB, lcolor(gs11)
50 144 lwidth(thick)) if peak>=0 & wei>=0 & rothe>=0, yscale(line) xtitle(Pre-symptomatic
51 145 infectious period) xline(0.5 1 1.2 2.6 2.9 3.75 8.2, lpattern(dash) lcolor(black)
52 146 noextend) xlabel(0(1)10) legend(off) scheme(s2color) xsize(20) ysize(16)
53 147 graphregion(fcolor(white)) plotregion(fcolor(white)) ytitle(Density)
54 148
55 149 * Figure 4
56 150
57 151 // meta analysis & meta regression
58 152
59 153 clear
60 154
61 155
62 156
63 157 // open data =
64 158
65 159 * meta_analysis_dataset.xls
66 160
67 161
68 162
69 163 // Fit random effects meta-analytical model, and specify forest plot
70 164

```

```

1
2
3 165 metaan mean se, dl forest label(paper)
4 166
5 167 // forest plot is figure 4.
6 168
7 169 // meta regression
8 170
9 171 // binary child (y/n) variable
10 172
11 173 gen kid_cat = 1 if child==1
12 174
13 175 replace kid = 2 if adult==1 & child!=1
14 176
15 177 tab kid_cat
16 178
17 179 * binary children inclusion in sample [REML]
18 180
19 181 xi: metareg mean i.kid if se>0, wsse(se)
20 182
21 183 // monte carlo model of P-value
22 184
23 185 xi: metareg mean i.kid if se>0, wsse(se) permute(1000, joint(i.kid))
24 186
25 187
26 188
27 189 // binary severe (y/n) variable
28 190
29 191 encode sever, gen(sev_num) // 4 way categorical
30 192
31 193 gen sev_bin = 0 if sev_n<3
32 194
33 195 replace sev_bin = 1 if sev_n==3 | sev_n==4
34 196
35 197
36 198
37 199 xi: metareg mean i.sev_bin if se>0, wsse(se)
38 200
39 201 // monte carlo model of P-value
40 202
41 203 xi: metareg mean i.sev_bin if se>0, wsse(se) permute(1000, joint(i.sev_bin))
42 204
43 205
44 206
45 207 * Figure 5
46 208
47 209
48 210
49 211 // Import, open time_to_discharge_death.csv
50 212
51 213
52 214 // numeric indicator for study category
53 215
54 216 encode study, gen(study_)
55 217
56 218
57 219
58 220 // random effects model for time from onset to removal (discharge or death)
59 221
60 222 // 3 levels of study as RE
61 223
62 224 xi: xtreg overall_time, i(study_)
63 225
64 226 // summarise post-estimation
65 227
66 228 estat summarize
67 229
68 230 // Breusch and Pagan Lagrangian multiplier test for random effects
69 231
70 232 xttest0

```

```
1
2
3 233
4 234 // Figure 5: histogram plot with kernel density
5 235
6 236 twoway(hist overall_time if study_== 3 , bin(10) fcolor(green%20))( hist
7 237 overall_time if study_== 1, bin(10) fcolor(red%20))( hist overall_time if study_==
8 238 2, bin(10) fcolor(purple%20))(kdensity overall_time disc_death , lcolor(gs11)
9 239 lwidth(mthick)), scheme(s2gcolor) legend(off) xsize(20) ysize(16)
10 240 graphregion(fcolor(white)) plotregion(fcolor(white)) xline(15.13663 18.06537
11 241 20.99411, lpattern(dash) lcolor(black) noextend)
12 242
13 243
14 244
15 245 // GLM reporting the variation in mean duration across studies
16 246
17 247 xi: reg overall_time i.study_
18 248
19 249 // GOF test
20 250
21 251 estat hettest
22 252
23 253 // residuals plot
24 254
25 255 rvfplot
26 256
27 257 // prediction
28 258
29 259 predict pred_study
30 260
31 261 // visualise
32 262
33 263 twoway(scatter pred_study study_)
34 264
35 265
36 266
37 267 // GLM reporting the variation in mean duration across removal type [death or
38 268 discharge]
39 269
40 270 xi: reg overall_time i.discharge
41 271
42 272 // GOF test
43 273
44 274 estat hettest
45 275
46 276 // residuals plot
47 277
48 278 rvfplot
49 279
50 280 // prediction
51 281
52 282 predict pred_study
53 283
54 284 // visualise
55 285
56 286 twoway(scatter pred_study study_)
57
58
59
60
```

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4-5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4-5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4-5
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	4-5
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	5-7
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	5-7
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5-7



SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	8, Tables 1-3
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Tables 1-3
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Tables 1-3
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	8-13
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	8-13; figures 1-5
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	14-17
Limitations	20	Discuss the limitations of the scoping review process.	17-18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	18
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	18

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med.* 2018;169:467–473. doi: 10.7326/M18-0850.



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BMJ Open

Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039856.R2
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	Epidemiology < INFECTIOUS DISEASES, VIROLOGY, INFECTIOUS DISEASES, PUBLIC HEALTH



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3 **1 Inferred duration of infectious period of SARS-CoV-2: rapid scoping review**
4 **and analysis of available evidence for asymptomatic and symptomatic**
5 **COVID-19 cases**
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9

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11 **5 Francis Butler⁴, John Griffin⁶, Elizabeth A. Lane^{3,6}, Conor McAloon⁵, Kirsty O'Brien⁷, Patrick Wall²,**
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19 Abstract

20 **Objectives:** Our objective was to review the literature on the inferred duration of the infectious
21 period of COVID-19, caused by SARS-COV-2 virus, and provide an overview of the variation
22 depending on the methodological approach.

23 **Design:** Rapid scoping review. Literature review with fixed search terms, up to 1st April 2020. Central
24 tendency and variation of the parameter estimates for infectious period in (a) asymptomatic (b)
25 symptomatic cases from (i) virological studies (repeated testing), (ii) tracing studies (iii) modelling
26 studies were gathered. Narrative review of viral dynamics.

27 **Information sources:** Search strategies developed and the following searched: PubMed, Google
28 Scholar, MedRxiv, BioRxiv. Additionally, the Health Information Quality Authority (Ireland) viral load
29 synthesis was utilised, which screened literature from PubMed, Embase, ScienceDirect, NHS
30 evidence, Cochrane, medRxiv and bioRxiv, HRB open databases.

31 **Results:** There was substantial variation in the estimates, and how infectious period was inferred.
32 One study provided approximate median infectious period for asymptomatic cases of 6.5-9.5 days.
33 Median pre-symptomatic infectious period across studies varied over <1-4 days. Estimated mean
34 time from symptom onset to two negative RT-PCR tests was 13.4 days (95%CI: 10.9-15.8), but was
35 shorter when studies included children or less severe cases. Estimated mean duration from
36 symptom onset to hospital discharge or death (potential maximal infectious period) was 18.1 days
37 (95%CI: 15.1–21.0); time to discharge was on average 4 days shorter than time-to-death. Viral
38 dynamic data and model infectious parameters were often shorter than repeated diagnostic data.

39 **Conclusions:** There are limitations of inferring infectiousness from repeated diagnosis, viral loads,
40 and viral replication data alone, and also potential patient recall bias relevant to estimating exposure
41 and symptom onset times. Despite this, available data provides a preliminary evidence base to
42 inform models of central tendency for key parameters, and variation for exploring parameter space
43 and sensitivity analysis.

45 Strengths and limitations of this study

- 46 • A comprehensive overview of the literature pertaining to inferred infectious duration of
47 COVID-19, including indirect measures from virological, contact tracing, and modelling
48 studies to 1st April 2020.
- 49 • Both narrative review and quantitative analysis presented

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- 50 • Small number of comparable parameter estimates for meta-analysis is a limitation
- 51 • Much of the current research material on COVID-19 is from preprint papers, and therefore
- 52 have not gone through formal peer review

For peer review only

53 Introduction

54 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new coronavirus, emerged in
55 China in late 2019.[1,2] The virus causes COVID-19, a disease characterized by variable, mainly
56 respiratory, symptoms across cohorts, from asymptomatic cases through to mild (for example, dry
57 cough, fever) and severe cases (for example, pneumonia).[3,4] The severity of symptoms, and their
58 clinical outcome, have been reported to vary by age-class and whether patients have underlying
59 comorbidities. The case-fatality rate increases with age, and are highest for those above 70
60 years.[5,6] There are several cases of asymptomatic test-positive patients reported in the emerging
61 literature (e.g. [4,7,8]). Furthermore, asymptomatic (and pre-symptomatic) cases have been shown
62 to be infectious, and secondary cases have been reported.[9,10] However, the duration of this
63 infectious period is difficult to measure accurately, and the time course of the natural history of
64 infection generally must be inferred indirectly, via contact tracing of cases, serial repeated diagnostic
65 virological studies, and/or through modelling approaches. Symptomatic cases can experience an
66 infectious pre-symptomatic period before the onset of symptoms, therefore understanding the
67 whole infectious period for this cohort requires estimating the duration of both periods. It is
68 essential to rapidly gain insight into this key variable impacting our understanding of COVID-19
69 epidemiology. Anderson et al. [11] point out one of the “key unknowns” is the infectious period for
70 COVID-19, which they suggest may be 10 days but subject to great uncertainty.

71 Here we gathered data from published research from peer-reviewed and preprints from 1st
72 December to 1st April 2020, to characterize the variation in the infectious duration inferred from the
73 three lines of evidence. We also provide a narrative review of the viral dynamic literature. Our focus
74 was on duration, relative infectiousness has been dealt with elsewhere [12,13]

75 The aim of this review was to provide an overview and critical appraisal of published and preprint
76 articles and reports that assess or quantify the inferred duration of the infectious period in order to
77 best parameterise COVID-19 epidemiological transmission models.

78 **Materials and Methods**

79 ***Conceptual model of population infection dynamics***

80 Infectious period was contextualised in relation to a working conceptual model of COVID-19 disease
81 dynamics (Figure S1, supplementary material 1). From this conceptual model, three parameters
82 were identified as important in context of this study:

83 T2, defined as: Duration of the total infectious period for asymptomatic cases, post-latent to
84 recovery [‘recover’ in this context relates to clearing of infection]

85 T3, defined as: Duration of pre-symptomatic infectious period for those infected individuals
86 who subsequently develop symptoms (that is, post-latent to onset of symptoms)

87 T5, defined as: Duration from onset of symptoms to recovery* or death.

88 * recovery was inferred as either the first of two clear RT-PCR tests, or hospital discharge after
89 admission from COVID-19 related symptoms.

90 “Asymptomatic” case definition was interpreted pragmatically following Davies et al. [14,15], and
91 may include very mild symptoms that may occur but are unnoticed.

92 T2, T3, T5 represent readily measurable parameters, but may be upper limits of infectious period, as
93 patients may be non-infectious for a period before recovery or death. We also review evidence
94 where infectiousness is inferred from viral shedding and contact tracing [transmission], see below.

95 ***Literature search***

96 A survey of the literature between 1st December 2019 and 1st April 2020 for all countries was
97 implemented using the following search strategy. Publications on the electronic databases PubMed,
98 Google Scholar, MedRxiv and BioRxiv were searched with the following keywords: “Novel
99 coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR “COVID-19” AND “infectious”. Additionally,
100 national and international government reports were monitored. No restrictions on language or
101 publication status were imposed so long as an English abstract was available. Articles were evaluated
102 for data relating to the aim of this review; all relevant publications were considered for possible
103 inclusion. Bibliographies within these publications were also searched for additional resources.

104 Manual searches of the literature was undertaken using daily updated COVID19 collections
105 from the National Centre for Biotechnology Information (NCBI) and MedRxiv servers
106 (<https://connect.medrxiv.org/relate/content/181>), respectively, searching specifically for
107 papers relating to “infectious period” or “infectious duration” from both empirical and
108 modelling studies.

109 Finally, we utilised the complementary work undertaken by the Health Information and Quality
110 Authority (HIQA) of Ireland, specifically the evidence summaries relating to asymptomatic
111 transmission and viral load [16,17]. The protocol for the evidence synthesis is published on the HIQA
112 website [18]. Briefly, the evidence synthesis process included searching databases from 30th

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3 113 December 2019 to 27th March 2020 (PubMed, Embase, ScienceDirect, NHS evidence, Cochrane,
4 114 medRxiv and bioRxiv, HRB open), screening, data extraction, critical appraisal and summarizing the
5 115 evidence.
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9 116 Our aim was to have as great a breadth for an evidential base as possible, to clarify what evidence
10 117 was available to inform on the infectious period of COVID19, and to identify key characteristics of
11 118 the data sources and their interpretation. Therefore, our approach is a scoping review (following
12 119 [19]). However, due to the emergent nature of COVID-19, this work is considered a rapid review.[20]
13
14 120 This paper follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—
15 121 Extension for Scoping Reviews (PRISMA-ScR) checklist. In accordance with the PRISMA-ScR checklist,
16 122 the electronic search strategy can be found in the supplementary material (Supplementary material
17 123 2).
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23 124 Inclusion criteria were for papers that provided data to inform duration of infectious period based
24 125 on: time from symptoms to recovery; time from symptoms to death; time from symptoms to
25 126 diagnostic test clearance [\geq two clear tests, defined as at least two consecutive negative reverse
26 127 transcriptase polymerase chain reaction (RT-PCR) tests conducted 24 hours apart]; pre-symptomatic
27 128 infectious period; time from first diagnostic test to diagnostic test clearance [\geq two clear tests] for
28 129 pre-symptomatic/asymptomatic cases. Inclusion criteria for viral dynamics, were papers which
29 130 reported viral load via cycle threshold (Ct) values from RT-PCR testing over repeated sampling of
30 131 infected patients, and studies that additionally reported viral isolation.
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37 132 For quality control, studies were (i) selected and screened initially by three members of the team
38 133 from search terms outlined above (ÁBC, KH, FB), with parameters identified and recorded. (ii) This
39 134 was reviewed and supplemented by manual search by a different two team members (AWB, DM),
40 135 again with parameters identified and recorded. (iii) Finally, the review was then internally reviewed
41 136 by an additional two members of the team (CMc, MC), and cross-referenced with other parameter
42 137 synthesis documents being worked on by the group (*all authors*).
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48 138 ***Parameter comparison***

49 139 *Parameters of interest*

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52 140 1. *A-priori* it was decided to harvest parameter estimates for (i) asymptomatic, and (ii)
53 141 symptomatic cases. As the period of infectiousness can only be estimated indirectly,
54 142 parameter estimates from the literature was gathered from three different methodological
55 143 approaches: Virological studies tracking patients overtime undertaking serial testing, where
56 144 infectious period was inferred from diagnostic testing history and/or by virus isolation.
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3 145 2. Contact tracing studies where infectiousness is inferred by infector-infectee histories and/or
4 146 clusters of infection.
5
6 147 3. Model parameters entered into mathematical models [priors] representing explicitly
7 148 infectious periods, or model parameters estimated from mathematical models [posterior
8 149 estimates] estimating explicitly infectious periods
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15 151 Visual and quantitative comparisons

16
17 152 To compare parameters visually, simulated distributions were estimated from the central tendencies
18 153 and variation metrics described in the primary literature. To simulate data, 10,000 random variates
19 154 were drawn from random number functions in Stata (ME, version 15.1; StataCorp. 2017. Stata
20 155 Statistical Software: Release 15. College Station, TX: StataCorp LLC) [rnormal, rgamma]. Where
21 156 possible, the distribution reported within the primary literature was used to represent the
22 157 distribution (e.g. Gaussian, Gamma). Where distributional data could not be inferred, point
23 158 estimates were presented.

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29 159 There were adequate comparable data gathered on the duration of T5 (duration from onset of
30 160 symptoms to death or recovery) from virological studies to employ a meta-analytic model. Many of
31 161 the studies report different central tendency estimates, including mean and median. Methods of
32 162 reporting variation across this central tendency included standard deviation, range, inter-quartile
33 163 range. To facilitate meta-analysis, reported estimates from all studies were converted to the mean
34 164 and standard deviations based on the formulae given in Wan et al. [21].

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39
40 165 To obtain the standard deviations from 95%CI, the method outlined in the Cochrane handbook [22]
41 166 was used:

$$SD: \sqrt{n}(\text{Upper limit of CI} - \text{Lower limit of CI})/3.92$$

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48 169 Standard Error (SE) was calculated from Standard Deviation (SD) and sample size (n), using:

$$SE = SD/\text{SQRT}(n)$$

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53 171 Comparisons were made using the METAAN package in Stata 15, using the random-effects
54 172 (DerSimonian-Laird) model.[23] This model assumes heterogeneity between the studies; that is, it
55 173 assumes that the true effect can be different for each study. The model assumes that the individual-
56 174 study true effects are distributed with a variance τ^2 around an overall true effect, but the model
57 175 makes no assumptions about the form of the distribution of either the within-study or the between-

176 studies effects. Weightings were derived from the standard error [precision] around the estimate.
177 Comparisons were presented as forest plots. Heterogeneity between studies was tested using
178 Cochran's Q; the magnitude of the heterogeneity was categorised using I^2 as high (>75%), moderate
179 (50-75%), or low (<50%).[24]

180 Variation in duration across T5 virological studies was compared using a random effects meta-
181 regression model, using the METAREG command in Stata 15.1. The hypothesis that heterogeneity
182 may be related to the inclusion of children or depending on symptom severity within the sample,
183 was tested in separate univariate models. Severity was dichotomised (0/1) into studies that included
184 patients described as having 'mild' or 'mild-moderate' symptoms, versus studies that included
185 patients with 'moderate-severe' or 'severe' symptoms. Similarly, studies were categorised into
186 having some samples from "children" (as reported in the paper), or wholly adult samples. These
187 variables were then fitted as a dichotomous dummy predictor [independent]. The parameter
188 estimates from the regression model was solved using restricted maximum likelihood (REML);
189 additionally, p-values were estimated using a Monte Carlo model with 1000 permutation test.[25]

190 Raw patient-level data were available from three studies in relation to time from onset to hospital
191 discharge or death (potentially inferring maximal T5 duration). To estimate the predicted mean and
192 95%CI duration across these studies, data were analysed using a Gaussian random effects model
193 (using XTREG command, Stata 15), with study categories fitted as the RE. A linear regression model
194 with 'study' fitted as a categorical dummy variable was used to estimate the difference between
195 duration across study datasets. Code and data are provided in Supplementary Material 3 & 4.

196 ***Viral dynamics***

197 A narrative comparison of reported viral dynamics from studies that undertook serial viral load
198 estimates from patients over their period of observation was undertaken. Trends in the literature,
199 strength and weaknesses were identified, and a conceptual model illustrated.

200 **Results**

201 ***Parameter comparison***

202 Overall, 65 parameter estimates were harvested from 48 papers (Tables 1, 2, 3).

203 *Infectious period for asymptomatic cases (T2)*

204 The overall distributions and point estimates from studies for T2 are presented in Figure 1 and Table
205 1.

206 Two virological studies reported on infectious period based on serial diagnostic testing, for
207 asymptomatic cases, were found to have informative data. One of these studies reported on only
208 one asymptomatic case, with exposure to negative tests being 11 days (Table 1). This duration
209 should be considered an over-estimate, given that a latent period is not taken into consideration. Hu
210 et al. [7] tracked infections of close contacts to infected persons and considered patients
211 asymptomatic at time of diagnosis. Infectious period was defined as time from diagnosis to the first
212 of two clear tests, providing a median duration of 9.5 days (n=24) range: 1 – 21; 3.5-13.0 IQR.

213 Importantly, Hu et al. [7] found that the infectious period was different between those who
214 subsequently exhibited symptoms (i.e. pre-symptomatic) and those who did not: The median
215 duration for asymptomatic infectious was 6.0 days (IQR: 2.0 - 12.0; N=19). This was reduced to 4.0
216 days (2.0 - 15.0) for cases that were asymptomatic without abnormal computed tomography (CT)
217 scans (n=7).

218 Two tracing studies provide informative data (Table 1; [7,8]). Infectious period was inferred
219 indirectly from data provided in Ma et al. [8], whereby infectious period was estimated as the
220 difference between the upper (maximal) latent period estimate minus the serial interval. Ma et al.
221 [8] reports on 49 asymptomatic cases and inferred serial interval from infector-infectee pairs. Serial
222 interval was calculated by assuming “onset” was at first diagnosis. Hu et al. [7] reported on a case-
223 study cluster of infection within a house where the primary case was asymptomatic. Secondary
224 infections occurred 4-9 days after index case exposure, the index patient tested positive until day 29
225 post exposure.

226 Modelling studies that have attempted to fit differing parameters depending on the severity of
227 symptoms have used differing nomenclature, for example asymptomatic, “mild” or subclinical cases
228 (Table 1).[14,15,26,27] Two papers by Davies and colleagues [14,15] model this parameter as a
229 gamma distribution with a mean periods of 5-7 days (Fig. 2); importantly, these papers assume
230 infectious period is the same for asymptomatic and symptomatic cases.

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3 231 Pre-symptomatic, infectious period (T3)
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5 232 Pan et al. [3] and Hoehl et al. [28] describe the cases of two individuals tracked and serially tested by
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7 233 real-time reverse transcriptase polymerase chain reaction (RT-PCR) after being exposed to a patient
8
9 234 with confirmed infection. In the latter study, the virus was isolated from samples, indicating
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11 235 transmission potential.

12
13 236 Four studies from China, Germany and Singapore provide informative data through tracing infections
14
15 237 from cluster of infections, and through infector-infectee pairs (Table 2).[4,9,29,30] These papers
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17 238 included the study by Rothe et al. [9], which clarified that an asymptomatic patient visiting Germany
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19 239 from China may have actually experienced very mild symptoms around the time of transmission
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21 240 occurred (see discussion).

22 241 Five modelling papers incorporated pre-symptomatic infectious period reported as prior
23
24 242 distributions or estimated as a model output. Two papers describe the prior distribution using a
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26 243 gamma distribution.[14,15] Tindale et al. [31] provide mean point estimates under four different
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28 244 scenarios (two populations, early and late epidemic period). Peak et al. [32] derives estimates of the
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30 245 pre-symptomatic infectious duration from a model of serial interval, and report scenarios where
31
32 246 there are pre-symptomatic infectious periods.

33 247 The approximated distributions are simulated in Figure 2, which demonstrates the between-study
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35 248 heterogeneity in this parameter. The point estimates primarily cluster around the central tendencies
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37 249 of the distributions, except for Tindale et al. [31], for a model reporting for late occurring cases in
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39 250 Tianjin, China (8.2 days).

40 251 Post-symptom onset, infectious period (T5)
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42 252 The T5 parameter was informed from three lines of evidence from empirically driven studies:
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- 45 253 • time from symptoms onset to the first of two clear RT-PCR tests
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47 254 • time from symptoms to hospital discharge
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49 255 • time from symptoms to death

50 256 Figure 3 presents the forest plot for the mean time from symptom onset to clearance, based on
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52 257 serial testing meta-analysis (n=15). The mean estimated duration was 13.4 days (95%CI: 10.9-15.8).
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54 258 There was high heterogeneity across studies (Cochrane's Q; p<0.001; I²>75%). A random effects (RE)
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56 259 meta-regression model suggested significant variation depending on whether studies included
57
58 260 children as part of the sample (n=15 studies; Proportion of between-study variance explained
59
60 261 Adj. R² = 43.8%). Overall, the model estimated studies including children had on average 5.8 days

262 shorter duration than adult only studies (95%CI: 1.7-10.0; $p=0.040$; $SE(p)=0.003$). A second univariate
263 RE meta-regression model suggested that there was non-significant increased mean duration of 4.0
264 days (95%CI: -0.6-8.6; $p=0.111$; $SE(p)=0.005$; Adj. $R^2 = 22.0\%$; $n=14$) for studies that included
265 moderate-severe or severe cases, relative to mild or mild-moderate severity cases.

266 High transmissibility during the first 5 days post symptom onset was described by Cheng et al. [33],
267 based on secondary attack rates for 12 infector-infectee pairs. No contacts ($n=1043$) with primary
268 cases were infected after five days of the index case onset of symptoms, inferred by the authors to
269 suggest transmission occurring at symptom onset (but conceivably also suggest pre-symptomatic
270 infection). Based on a cumulative density function, the authors suggest that infectiousness declines
271 rapidly from onset of infection (distribution was truncated at 30 days); estimated cumulative
272 infectiousness was 66.9% (95%CI: 28.7-94.8) by day 1, and reached 86.9% (95%CI: 64.3-99.5) by day
273 5 post-symptom onset (Figure S2).

274 For tracking studies relating to time to hospital discharge or death, raw case level data were
275 available (studies $n=3$).[31,34–36] Histograms of the raw data are presented in Figure 4, along with
276 the aggregated distribution. A random effect model suggested a mean duration of 18.1 days (95%ci:
277 15.1 – 21.0). However, there was significant variation across studies, with time to discharge being
278 4.96 days shorter (95%CI: 2.15- 7.76; [35]), or 3.79 days shorter (95%CI: 0.8-6.7; [31]), than time-to-
279 death [34].

280 Two modelling papers use priors (mean: 3.2-3.5 days) to represent clinical infectious period.[14,15]
281 However, the distribution for this parameter is right censored when patients are hospitalised or
282 isolated and therefore not an estimate of the full infectious period *per se*.

283 Infectious period for symptomatic cases (T3+T5)

284 Two tracing studies supplied parameter estimates for the full infectious period for patients who
285 develop symptoms. [8,29] He et al. [29] inferred from a publicly available dataset of 77 infector-
286 infectee pairs that infectiousness began 2.3 days (95% CI, 0.8–3.0 days) prior to symptom onset,
287 peaking at 0.7 days (95% CI, -0.2–2.0 days), and continued up to 7 days from onset. The authors
288 suggest that the transmission risk diminishes 7 days post symptom onset. This suggests that the
289 average infectious period, assuming a symptomatic infectious period of 7 days was approximately
290 9.3 days (7.8-10 days 95%CI, where CI is only reported for the pre-symptomatic period). He et al.
291 [29] estimated that the proportion of all transmission that was pre-symptomatic was 44% (95% CI,
292 25–69%). Ma et al. [8] analysed data from a number of countries (China, Germany, Japan, Malaysia,
293 Singapore, Vietnam), collating 1155 cases from public data. They estimate several parameters,

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3 294 including “maximum latent period” and the serial interval. The authors estimated the infectious
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5 295 period as maximum latent period minus the serial interval. Given their parameter estimates and
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7 296 methodological approach, infectious period would have been 5 days (range 0-24; IQR: 2-9;
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9 297 calculated from data presented within the paper).

10
11 298 Seven modelling papers reported duration of infectious period (T_3+T_5 ; Table 4), with the reported
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13 299 central tendency for the distribution varying from 3-20 days. The form of the distribution offered to
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15 300 models for this parameter varied considerably, including point estimates (deterministic models), flat
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17 301 (uniform), Gaussian, Weibull and gamma distributions. Li et al. [27] estimated the shortest median
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19 302 duration of 3.45 days, with a flat (uninformative) prior distribution corralled between 3-5 days. In
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21 303 contrast, Zhu et al. [37] used a mean prior of 10 days, with the model estimated mean duration
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23 304 being 12.5 days (variance 10; Weibull distribution). Piccolomini and Zama [38] used a fixed estimate
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25 305 of 20 days infectious period, to model the Italian epidemic. Two papers from the same group [14,15]
26
27 306 suggested that infectious period for asymptomatic cases approximated for symptomatic cases where
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29 307 there was no right censoring (that is, transmission being halted through isolation or hospitalisation;
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31 308 gamma distributions of mean 5 or 7 days). Tuite et al. [26,39] also assumed the same duration for
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33 309 “mild” and “severe” symptomatic cases (6-6.5 days).

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311 ***Viral load dynamics***

312 Viral load was reported from 21 papers using real-time reverse transcriptase polymerase chain
313 reaction (rRT-PCR) testing, generally post-symptomatic monitoring.[3,29,40–59] Qualitatively, the
314 viral dynamics described early increase in viral load, peaking around onset or within 2-4 days of
315 symptom onset (Figure 5 for a theoretical model), before decreasing gradually over the next one to
316 three weeks post symptom onset. Maximum duration of detection ranged from approximately 20-49
317 days, with the longest duration associated with faecal samples (see below for discussion). The
318 duration where ribonucleic acid (RNA) was recoverable by RT-PCR may have been truncated due to
319 insufficient follow-up in some cases. Studies that have investigated blood samples have provided
320 some evidence for an association with severity of infection [16,60], though it is not clear whether
321 this is a consistent feature of SARS-CoV-2 infection [40].

322 It should be noted the lack of data on pre-symptomatic or asymptomatic cases with regards viral
323 load. An exception was Kam et al. [61] who describe a pre-symptomatic case in an infant. In another
324 study, Zou et al. [53] undertook serial RT-PCR testing from nasal and throat swab samples from 14
325 imported cases, and 4 secondary cases, in Guangdong, China. The dynamics of the infection in terms
326 of cycle threshold (Ct) values and RNA copy number were described; Ct values of 30.76, 27.67,
327 24.56, and 21.48 corresponding to 1.5×10^4 , 1.5×10^5 , 1.5×10^6 , and 1.5×10^7 copies per milliliter.
328 Hence, lower Ct values infer higher viral loads. The authors report on a patient without symptoms,
329 but with positive nasal swabs (Ct values, 22 to 28) and throat swabs (Ct values, 30 to 32) testing
330 positive on days 7, 10, and 11 after contact. Importantly, the authors suggest “the viral load that was
331 detected in the asymptomatic patient was similar to that in the symptomatic patients.”
332 Furthermore, Kimbell et al. [62] report that Ct values between asymptomatic (21.9 to 31.0), pre-
333 symptomatic (15.3 to 37.9), and symptomatic cases (18.6 to 29.2) within a nursing home
334 environment did not differ significantly. To et al. [59] present data on temporal profile of viral load
335 from saliva samples, and found that median initial and peak viral loads in severe cases were non-
336 significantly higher ($p > 0.5$) by approximately 1 log₁₀ higher than those in mild cases. Liu et al. [58]
337 present data showing viral load being 60 times greater for severe cases relative to mild cases.

338 This lack of pre-symptomatic data may result in left truncation of the risk distribution associated
339 with viral load and shedding. Therefore, the typical timing of peak viral shedding (whether prior to,
340 at, or after onset), and its impact on transmission, is still uncertain. He et al. [29] reported highest
341 viral load at symptom onset from patients sampled in a hospital in China. Furthermore, the author’s
342 estimate using a separate infector-infectee dataset (n=77) that 44% (95% CI: 25–69%) of infectee
343 cases were infected during the pre-symptomatic stage of the infector. Separately, a modelling paper

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3 344 by Ferretti et al. [63] also appears to support this, estimating that 47% (0.9/2) of total transmission
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5 345 contributing R_0 , an overall measure of transmission during an infection, was pre-symptomatic (also
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7 346 see [33]).

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9 347 Wölfel et al. [50] provides important data on a cohort of nine 'mild' cases which were serially tested
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11 348 using sputum, swabs (throat and nasopharyngeal), urine and faecal samples over time. Importantly,
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13 349 the virus was isolated, and inferences on viral replication could be made. Viral Isolation, and insights
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15 350 into viral replication, improve inference around viral dynamics and transmission risk. The study
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17 351 suggested high viral loads shortly after symptom onset, which declined thereafter over time. Positive
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19 352 cultures were found from day 3-8 post-symptom onset (Figure S3), and the minimum 5% isolation
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21 353 success was achieved up to 9.8 (95% CI: 8.5-21.8) days post onset from throat and lung samples but
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354 not faeces, blood or urine.

355 Discussion

356 Inferring infectiousness was challenging given the heterogeneity of evidence available. Virological
357 diagnostic studies provide robust time series of infection, however, is limited by inferring the
358 relationship between PCR diagnostics and infectiousness. These data can also be affected by
359 sampling procedure and sample sites (e.g. upper respiratory, lower respiratory, faeces, urine, blood).
360 We have excluded RT-PCR durations based on faecal sampling due to the current uncertainty
361 whether these data pertain to transmission potential ([50]; see below). Virological studies where
362 culturing has taken place, and where viral replication can be inferred would also be considered
363 superior data to infer infectious period, relative to estimates of viral load alone.[50] Where this has
364 taken place, the data would suggest average infectious periods of up to 9.8 days post-symptoms.
365 Recent modelling work suggest that the duration of viral detectability could overestimate the
366 infectious period somewhere between 2-6 days.[64]

367 Viral load studies suggest peak viral load occurs close to symptom onset (potentially, -1 to 7 days of
368 onset), however there is uncertainty whether this typically occurs prior to, on, or after onset (Figure
369 5 for conceptual model). High viral loads, measured as Ct values, have been recorded for one week
370 to 20 days post symptom onset, with a general decreasing trend with time. For example, To et al.
371 [59] estimates a declining slope per day for log₁₀ RNA copies per ml of -0.15 (95% CI -0.19 to -0.11;
372 $R^2=0.71$). There are some studies reporting associations between viral load and symptom severity,
373 with higher metrics of viral load in severe cases.[3,58,59] However, Zou et al. [53], and more recent
374 data from Italy,[64,65] suggest similar viral loads in symptomatic and asymptomatic cases.

375 We tested the hypothesis that severity of symptoms had an effect on symptomatic infectious
376 duration using a meta-regression approach. There was a trend towards studies that included severe
377 cases tended to have longer duration (estimated to be 4.0 days longer), but the effect was not
378 significant. Some studies have reported an association between duration of infectiousness and
379 severity (e.g. [58]). But uncertainty of whether this is robust remains. Caution is required when
380 comparing severity of symptoms, as objective or standardised metrics are not always reported.

381 Virological studies that included children (either mixed adult children, or children only cohorts)
382 appeared to have shorter T5 durations (estimate: 5.8 days shorter). Liao et al. [66] present data
383 which suggests that children and 'young adults' (<35 years old) infected cases exhibited long
384 incubation time (exposure to symptom on-set; mean 7.2 days), and short serial interval (mean 6.5
385 days; median 1.9 days; time from onset in primary to onset in secondary case).

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3 386 Contact tracing studies provided robust evidence of transmission events, and therefore
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5 387 infectiousness, but can be limited by the inferred timing of events, and symptoms experienced, due
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7 388 to the self-reported nature of data collection (recall bias). The subjective nature of self-reporting
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9 389 indeed can have an impact on case definitions of ‘asymptomatic’, which has led to some doubt on
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11 390 asymptomatic transmission in one case.[9] Rothe et al. [9] describe a case of apparent asymptomatic
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13 391 transmission from a Chinese visitor to business associates in Germany, which was cast into doubt
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15 392 when health officials reported that the patient had indeed experienced some, albeit minor,
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17 393 symptoms.[67] Rothe et al. [9] subsequently updated the clarification of the patients self-reported
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19 394 symptoms during the presumed asymptomatic infectious period, which included “feeling warm” and
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21 395 “feeling cold”. However, the patient only “recognized getting sick” after she returned to China on
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23 396 day four after the presumed exposure event.

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25 397 Modelling parameters provide information on how COVID-19 data are being used and interpreted in
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27 398 the research community, given the limited data available. Posterior estimates also provide
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29 399 information on the parameter space at which infectious period central tendency reside, given other
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31 400 parameters and assumptions in the model. Models used highly varied approaches to modelling
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33 401 infectious period, which in turn resulted in highly variable parameter estimates used to inform the
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35 402 studies. An important factor to consider when comparing parameter estimates between empirical
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37 403 and modelling studies is the interpretation of the parameter by different disciplines, and even
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39 404 between researchers from the same discipline. The infectious period can be considered significantly
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41 405 context specific and dynamic, and the ability to transmit infection can be modulated by
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43 406 interventions (e.g. through isolation or hospitalisation). Modelling papers, depending on the model
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45 407 structure, can report truncated infectious period accounting for such interventions. Such estimates
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47 408 are not comparable with our definition of the parameters reviewed, and we have attempted to
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49 409 avoid such disparities where we found them.

410 *Overall duration findings*

411 There are few data for the precise definition of the asymptomatic infectious period (T2) parameter.
412 Some reported asymptomatic cases can actually be pre-symptomatic, when cases are subject to
413 follow-up (e.g.[66]; see discussion above). However, Hu et al. [7] do provide the data for
414 asymptomatic cases [that remain asymptomatic] across their presumed infectious period. Therefore,
415 in the first instance a parameter mimicking their data is probably the best available data over the
416 period of the present study. Note, there is a large variation in this data parameter, and a gamma
417 distribution of a shape alpha 3, beta 2, mean 6, may be appropriate for the initial model runs.
418 Despite these being the primary informative data, caution is required, given the uncertainty around

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3 419 the relationship between RT-PCR results and infectiousness. Overall, an informed central tendency
4 420 of ~6 days, with very low probability draws for durations >20 days for the T2 parameter may be
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6 421 considered given the current state of knowledge.
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9 422 The pre-symptomatic period is sometimes referred to as 'preclinical infectious' period (parameter
10 423 T3). This has been estimated from several papers, and the central tendency of these estimates vary
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12 424 from <1 - 4 days, cautiously approximating to 2 days, on average. Current models have used central
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14 425 tendency estimates of 0.5 to 2.4 days.[14,15,26,39] The relative consistency around the duration of
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16 426 this period allows for some confidence of its distribution. Current understanding of viral dynamics of
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18 427 infection suggest that viral load and shedding increases during post-latent phase, peaking around
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20 428 onset [for symptomatic cases], before declining.[29,50,53] This aspect of the natural history of
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22 429 infection may be important when attempting to model transmission dynamics.

23 430 Length of infectious period in symptomatic cases that do not isolate (T5 parameter) has also been
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25 431 rarely directly measured in the literature, as serial monitoring of patients in terms of symptoms or
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27 432 viral load (rt-PCR) generally occurs after diagnosis and/or after admission to hospital [from a
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29 433 modelling perspective, this means cases are censored as they are assumed to no longer contribute
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31 434 to transmission]. If natural progression of infection after diagnosis or hospital admission mimics the
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33 435 course of infection for those who do not isolate, the review of the literature describing time to two
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35 436 clear tests is informative. Symptom onset to serial testing clearance [assessed the time to first of two
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37 437 RT-PCR clear tests] averaged 13.4 days from our meta-analysis. In the maximal case, where patients
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39 438 succumb or fully recover from infection, time from symptoms to death or discharge may be
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41 439 informative. Studies that collated such information suggest mean durations of 18.07 days, but with
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43 440 time to discharge being 4.96 days shorter on average than time to death. These values may
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45 441 represent an over estimation of the infectious period; one study suggested that there was on
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47 442 average 2.5 days between end of infectiousness and 'removal' (recovery or death).[37]

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49 443 Cheng et al. [33] provided evidence of transmissibility, based on attack rate from primary to
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51 444 secondary cases, at around symptom onset. The authors estimate cumulative infectiousness from
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53 445 onset, which suggests that 67% of total infectiousness potential occurs by the first day post-onset.
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55 446 Most of the total infectiousness occurs within 5 days (86.9%) post onset, with the remaining
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57 447 infectiousness potential (13.1%) being distributed up to day 30 (this truncation is an assumption by
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59 448 the authors). It is possible that pre-symptomatic transmission occurred during this study, but the
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449 authors do not estimate what proportion of transmissions occurred during a pre-symptomatic
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infectious period, or its potential duration.

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3 451 A model by He et al. [29] is informative for overall symptomatic duration (T3+T5), using 77 infector-
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5 452 infectee pairs where COVID-19 transmission occurred in China. The study reported that
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7 453 infectiousness was apparent on average 2.5 days prior to symptoms, reached a peak in risk at 0.6
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9 454 days before symptoms, and decline up until 7 days after onset (9.5 days total infectious period). The
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11 455 proportion of transmission before symptom onset (area under the curve) was estimated as 44%
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13 456 (95% CI, 25–69%), based on inferences on incubation period. The authors suggest their data
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15 457 supported the view that transmission risk decline substantially after 7 days post-symptoms onset.

16 458 Model estimates used for infectious period parameter appears to be shorter than virological studies
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18 459 tracking RNA viral load over time. For example, Liu et al.[27] fitted a flat prior distribution for mean
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20 460 duration (D) fixed to vary between: $2 \leq D \leq 5$ days, and Lavezzo et al. [64] fixed infectious period to 2
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22 461 days in their epidemic model; whereas viral repeat testing studies provide evidence to suggest high
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24 462 viral loads can be detected to up 20 days (e.g. pharyngeal swabs), and potentially longer from faecal
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26 463 samples (up to 3-4 weeks post symptoms onset)). Oral-faecal transmission risk is currently unknown,
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28 464 but some doubt has been raised about studies that have reported positive RTPCR test results (see
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30 465 [68]; but there may be some evidence of the risk amongst children; [69]). Wölfel et al. [50] has
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32 466 produced an important study that provides some data on viral replication, and the site and duration
33
34 467 over which this may be taking place. Their data suggests that viral replication, with high viral loads,
35
36 468 occur in the upper respiratory tract, over the first week of symptoms peaking in day 4. Virus could
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38 469 not be isolated from faecal samples, despite high RNA concentration. Furthermore, virus was not
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40 470 isolated from blood or urine in that study.[50]

41
42 471 It should be noted that some of the virological and tracing studies reviewed had small sample sizes
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44 472 (see Study Limitations) and potentially biased towards more severe cases or clusters of infection. It is
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46 473 unknown as to whether these cases are representative of infectious duration generally across
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48 474 populations. However, if symptom severity is linked to infectious duration, one could speculate that
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50 475 this bias could help to explain the some of the difference between model and empirical duration
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52 476 estimates.

477 **Study limitations**

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54 478 Overall, the studies included were of good quality, though due to the rapid need for information
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56 479 from the global research community many papers are pre-prints that have yet to be reviewed (at
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58 480 time of writing). Many papers were limited in terms of sample sizes, with several papers being case
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60 481 studies of one patient or single cluster outbreaks. There was a diversity of methods employed to
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483 infer dynamics of infectiousness across studies, and therefore the evidential base was variable. Some
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485 issues around nomenclature were noted, including definitions of asymptomatic, infectious period,

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3 484 latent, and incubation period. It is possible the same data may have been used across different
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5 485 studies, especially where publicly available data were used.
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7 486 There was significant heterogeneity across study findings, and this was related to diversity of clinical
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9 487 findings and methods employed. The meta-analysis employed for one parameter (T5) using
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11 488 virological studies, where cross study comparisons could be made, suggested that the heterogeneity
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13 489 was high. Fu et al.[70] cautions against combining studies to give an overall estimate without
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15 490 exploring subgroup or meta-regression analysis, which we have done here. The meta-regression was
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17 491 based on a small number of studies (n=12-13). Cochrane's handbook suggests 10 studies for each
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19 492 level of a meta-regression, however in practice much lower numbers have been used to test
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21 493 hypotheses [22], as is the case here. Fu et al. [70] recommend a minimum of 4 studies per category,
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23 494 and therefore we dichotomised our predictor variables to ensure we met this minimum. Aggregating
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25 495 our categories resulted in crude findings.

26 496 Another limitation is that a systematic review was not undertaken to inform this research, hence
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28 497 there is a possibility that some relevant studies were overlooked. However, two independent
29
30 498 research groups conducted comprehensive search strategies as part of a broader epidemiological
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32 499 parameters project for COVID-19 [12,13,71,72,73] to inform this research, hence limiting the
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34 500 potential for missing key studies.

501 **Conclusion**

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36 502 There are few data to inform asymptomatic infectious period (T2 parameter). One study provide
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38 503 data that suggest a median period of 4-9.5 days, however, given the viral dynamics, this distribution
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40 504 could have an extended tail with low probability long infectious periods of up to 20 days. The pre-
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42 505 symptomatic infectious phase (T3) is quite narrowly defined to a mean of approximately 2 days
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44 506 (range: <1-4) within the literature. However, there is great uncertainty around the infectious period
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46 507 from onset to recovery or death (T5 parameter). The symptom onset until clearance (based on two
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48 508 negative RT-PCR tests) parameter estimate of 13.4 days (95%CI: 10.9-15.8) is informative for T5
49
50 509 parameter, only if one assumes that RT-PCR positive results equate to having infectious potential.
51
52 510 Many current models corral the infectious period to shorter time periods than what virological
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54 511 studies have suggested, with one recent study suggesting that duration of viral detectability over-
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56 512 estimates the infectious period on average by 2-6 days. While viral RNA can be detected for long
57
58 513 periods of time, especially from faecal samples, the ability to isolate the virus from Infected cases
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60 514 quickly declines after one-week post-symptoms. Some modelling papers have assumed that
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516 515 infectious period is invariant to whether cases are asymptomatic or symptomatic, however, the data
available are not yet rich enough to inform whether this is a good assumption. Similarly, it is not yet

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3 517 established whether viral loads are similar between asymptomatic and mild, moderate, or severe
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5 518 symptomatic cases, with conflicting reports in the literature.

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14
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785 Tables and figures

786

787 **Figure 1:** Simulation of the parameter distribution inferred for duration infectious period for
788 asymptomatic cases (T2) inferred infectious period for Davies et al. (2020a), grey/blue curve, Davies
789 et al. (2020b) pink curve [model priors]. Green curve: Ma et al. (2020). Histogram is the distribution
790 of asymptomatic cases to two clear tests reported by Hu et al. (2020). Reference lines are point
791 estimates reported from Zhou et al. (2020), Li et al. (2020), and Tuite et al. (2020a &
792 b).[7,8,14,15,26,27,39,71]

793 **Figure 2:** Simulation of the parameter distribution used for T3 (the duration of the pre-symptomatic
794 infectious period for those infected individuals who subsequently develop symptoms). Curves
795 represent simulated approximations of distributions, given information provided from primary
796 literature. Vertical lines represent point estimates where distributions could not be inferred (see
797 table 2). 1. Peak et al. [posterior]; 2. Davies et al. 2020b [prior]; 3. Rothe et al. 2020; 4. He et al.
798 2020; 5. Davies et al. 2020a [prior]; 6. Wei et al. 2020. [9,14,15,29,30,32]

799 **Figure 3:** Forest plot of the mean duration from onset of symptoms to death or recovery (T5) based
800 on virological studies

801 **Figure 4:** Frequency distribution of T5, time from onset of symptoms to recovery (here hospital
802 discharge or death), using patient level raw data from Kraemer et al. ([35,36]; pink bars), Linton et al.
803 ([34]; purple bars) and Tindale et al. ([31]; green bars). Blue solid line is the kernel density of the
804 aggregated dataset Dashed lines represent the mean and 95%CI from a random effects regression
805 model.

806 **Figure 5:** Composite inferred model for cycle threshold (CT) value changes from serial RT-PCR testing
807 for SARS-COV2; currently uncertain whether peak viral load typically occurs prior to, on, or post-
808 symptom onset (primary literature informing this model includes [29,50,53,59]).

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810 **Table 1:** Reported infectious period (IP) for asymptomatic cases (T5 parameter) from virological
 811 studies where serial diagnostic tests were undertaken to infer IP; tracking studies where IP is
 812 inferred from contact tracing; modelling studies where IP is reported as a prior (assumed parameter
 813 value) or an posterior estimate.

No.	Study	Countries	Parameter (days)	n	Central tendency reported	Variation (days; inclus.)	Comment
Virological studies							
[74]	Zhou et al. (2020)	China	11 days	1	Max		This study serially swabbed and tested symptomatic (17) and asymptomatic (1) cases via RTPCR. The single asymptomatic case tested positive up to 11 days post contact with an infected patient (presumed point of exposure).
[7]	Hu et al. (2020)	China	9.5 days	24	Median	1-21 range	Serial testing. Period between "onset" (where onset relates to first positive test) and clearance, adjudged via two negative RTPCR tests, deemed by the authors to be the 'communicable period'. IQR: 3.5-13
Tracking studies							
[8]	Ma et al. (2020)	China, Germany, Japan, Singapore, South Korea, Malaysia, Vietnam	7.25 days*	49	Mean	5.91-8.69 (95%CI)	*Ma et al. (2020) does not report infectious period for asymptomatic cases explicitly within their paper. The authors estimated the infectious period as the upper estimated latent period minus the serial interval, using a dataset of 1155 cases from several countries (latent period was estimated with 11 infector-infectee pairs; serial interval was estimated from 689 infector-infectee pairs). Ma et al. (2020) reported a mean upper limit of latent period of 2.52 days; the mean serial interval for asymptomatic cases (using date of diagnosis for onset) was estimated to be 9.77 (94%CI: 8.43, 11.21).

[7]	Hu et al. (2020)	China		3		4-9 range	Cluster of infection within a family, where the primary case was asymptomatic. The transmissions to secondary cases occurred over a period 4-9 days post the presumed point of exposure for the primary case.
Modelling studies							
[27]	Li et al. (2020)	China	3.5* [posterior from a model estimating duration for undocumented cases]		Median	3.19-3.78 95%CI	Li et al. (2020) do not explicitly attempt to model asymptomatic cases, or their infectious duration. Instead the population infected is divided into 'documented' and 'undocumented'. Documented were all cases where patients had symptoms severe enough to be confirmed infected; all other cases were considered undocumented. Therefore, this estimate represents asymptomatic and 'mild' cases. The 95%CI around the median infectious period estimate was 3.19-3.78
[26,39]	Tuite et al. (2020a &b)	Canada	6-6.5 [Prior]		[Fixed parameter within a deterministic model]		Mathematical model [deterministic], with a fixed parameter estimate of 6 or 6.5 days. Important to note that duration for 'mild' was equal to severe cases.
[14]	Davies et al. (2020) (a)	UK	7 days [Prior]		Mean		Model with asymptomatic infection compartment. Modelled with a gamma distribution, beta 1.4; alpha 5. Despite, the subclinical aspect of this parameter, it could be considered analogous to total infectious period without intervention.
[15]	Davies et al. (2020) (b)	UK	5 days [Prior]		Mean		Model with asymptomatic infection compartment. Modelled with a gamma distribution, k=4. Authors: "Assumed to be the same duration as total infectious period for clinical cases, including preclinical transmission"

814

815 **Table 2:** Reported infectious period (IP) for pre-symptomatic cases (T3 parameter) from virological
 816 studies where serial diagnostic tests were undertaken to infer IP; tracking studies where IP is
 817 inferred from contact tracing; modelling studies where IP is reported as a prior (assumed parameter
 818 value) or an posterior estimate.

	Study	Location	Parameter (days)	Central tendency reported	Variation (days; inclus.)	Comment
	<i>Virological studies</i>					
[3]	Pan et al. (2020)	Beijing, China	1	Median		Case study of two individuals tracked due to exposure to an infected patient was serially tested prior to onset of symptoms.
[28]	Hoehl et al. (2020)	Flight from Wuhan to Germany	1	Median		Case study of serially tested at risk cohort flying from Wuhan to Germany. Two patients were asymptomatic test positive; additionally virus isolation was achieved, indicating potential infectiousness.
	<i>Tracking studies</i>					
[4]	Huang et al. (2020)	Nanjing, China	4	Median	3-5 range	Follow-up tracing case study cluster of infection within a family demonstrating pre-symptomatic infection (n=10)
[9]	Rothe et al. (2020)	Germany	2	Median	1-3 range	Tracing case study of a cluster of infections whereby pre-symptomatic transmission occurred (n=3).
[29]	He et al. (2020)	Vietnam, Malaysia, Japan, China, Taiwan, USA, Singapore	2.3	Mean	95% CI, 0.8–3.0	Tracing paper infector-infectee pairs. Estimated from serial interval and incubation periods. N=77
[30]	Wei et al. (2020)	Singapore	2.5	Median	2-3 (IQR)	Tracing study investigating pre-symptomatic infections from primary cases to secondary cases in 7 clusters. N=8 primary cases. T3 estimated as the min. days between transmission period (TP) and primary case

						symptom onset, when TP straddled >1 day. Range: 2-6 days.
	Modelling studies					
[32]	Peak et al. (2020)	Massachusetts	0.8 [estimate]	Mean	-0.29-1.98 95% CI*	Modelling paper estimated under two scenarios – a serial interval of 4.8 days or 7.5 days. Under scenario one, the model estimated a period of pre-symptomatic transmission (median: 0.71). * the lower range was fixed at zero as the model allowed for no pre-symptomatic infectious case.
[37]	Zhu et al. (2020)	Wuhan, China	1.0 [estimate]	Mean		Modelling paper. Model estimated point value – This is a model derived value
[14]	Davies et al. (2020) (a)	UK	2.4 [prior]	Mean		Modelling paper. Gamma distribution; k=5.
[15]	Davies et al. (2020) (b)	UK	1.5 [prior]	Mean		Modelling paper. Gamma distribution: k=4
[26,39]	Tuite et al. (2020a & b)	Canada	0.5, 1 [prior]	Fixed		Modelling paper. Fixed parameter within a deterministic model.
[75]	Ferguson et al. (2020)	UK	0.5 [prior]	Fixed		Modelling paper. Fixed parameter within this model, whereby infectiousness was assumed to begin 12 hours symptom onset.
[31]	Tindale et al. (2020)	Tianjin, China, and Singapore	2.9-2.6 [estimate]	Mean	1.2-8.2 mean range, depending on early or late cases, or whether in Tianjin, Singapore	Statistical modelling study estimating period pre-symptomatic transmission inferred from estimates of serial interval and incubation periods for populations in Tianjin and Singapore (n=228).

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821 **Table 3:** Reported infectious period (IP) for post-symptomatic cases (T5 parameter) from virological
 822 studies where serial diagnostic tests were undertaken to infer IP [onset to ≥ 2 tests]; tracking studies
 823 where IP is inferred from patient histories from onset to recovery or death; modelling studies where
 824 IP is reported as a prior (assumed parameter value) or an posterior estimate.

No.	Study	Location	Parameter (days)	Central tendency reported	Variation (days; inclus.)	Comment
<i>Virological studies</i>						
[76]	Cai et al. 2020 (a)	China	12	Median	6-22 range	Serial testing study of n=10 mild cases RT-PCR confirmed in children. IQR: 8-15 days
[77]	Cai et al. 2020 (b)	China	14	Median	9-19 (IQR)	Serial testing study with n=298 confirmed (RT-PCR) cases treated within hospital setting
[78]	Chen et al.(2020)	China	12	Max.		Single case study for a patient admitted to hospital where RT-PCR serial testing was undertaken. Patient had an additional positive test at day 17, but subsequently tested negative
[79]	Cheng et al. (2020)	China	21	Max.		Case study of single patient serially tested by RT-PCR
[7]	Hu et al. (2020)	China	12	Median	12-14 (IQR)	Serial testing study of patients who were first tested (qRT-PCR) when asymptomatic; this subset subsequently developed symptoms (n=5).
[42]	Kim et al. (2020)	Korea	15.5	Median	14-17 (range)	Serial testing of two confirmed cases via RT-PCR. Viral load highest during early phase of infection (day 3-5).
[43]	Kujawski et al. (2020)	USA	26	Max.		Serial testing of two confirmed cases via RT-PCR. Mild to moderate symptoms.
[80]	Lee et al. (2020)	Taiwan	20	Max.		Serial testing (RT-PCR) of a single patient hospitalised presenting with pneumonia
[44]	Lim et al. (2020)	South Korea	16	Max.		Serial testing (RT-PCR) of a single patient hospitalised presenting with pneumonia. Two clear tests day 11, virus

						detectible again up to day 16.
[81]	Ling et al. (2020)	China	9.5	Median	2-22 (range)	Serial testing of two confirmed cases via RT-PCR. n=66. IQR: 6-11 days, oropharyngeal sampling. Mix of adult and children.
[82]	Liu et al. (2020)	China	11	Median	7-18 range	Serial testing of two confirmed cases via RT-PCR. n=10. 10-13 (IQR); adults, mild, moderate, and severe cases.
[45]	Marchand-Senéca et al. (2020)	Canada	23	Max		Serial testing (RT-PCR) of a single patient hospitalised presenting with pneumonia.
[3]	Pan et al. (2020)	China	10	Median	8-12 range	Serial testing (RT-PCR) of two patients hospitalised. Viral loads peaked days 5-6 post-onset.
[83]	Qu et al. (2020)	China	22	Max		Serial testing (RT-PCR) of a single patient hospitalised
[46]	Tan et al. (2020)	Vietnam	16	Max		Serial testing (RT-PCR) of a single patient hospitalised; throat sample.
[47]	Thevarajan et al. (2020)	Australia	7	Max		Serial testing (RT-PCR) of a single patient hospitalised; throat sample. Highest viral load on first test at day 4 in nasopharyngeal; day 6 for sputum.
[69]	Xing et al. (2020)	China	14	Median		Serial testing (RT-PCR) of a three (children) patients hospitalised. Mild-moderate infecting. Positive viral samples from faeces up to 4 weeks post-symptoms.
[52]	Young et al. (2020)	Singapore	12.5	Median		Serial testing (RT-PCR) of 18 patients hospitalised. Adults. Viral load peaked over testing series at day 4 since onset.
[84]	Yuan et al. (2020)	China	6	Median	4-10 (IQR)	Serial testing (RT-PCR) of 25 patients hospitalised. Children and adults. "Non-severe" cases.
[74]	Zhou et al. (2020)	China	20	Median	16-23 IQR	Serial testing (RT-PCR) of 191 patients hospitalised in two hospitals. Adults. 54 died. Survivors (n=137); Median (IQR) 20.0 days (17.0–24.0); Non-survivors

						(n=54); Median (IQR) 18.5 days (15.0–22.0); Shedding continued until death. Inferred shedding period; 8-37 days.
[85]	Chen J. et al. (2020)	China	11	Median	10-12 (95%CI)	Serial testing (RT-PCR) of 242 patients hospitalised. Adults. 90% mild/asymptomatic; 10% severe/critical.
[60]	Fang et al. (2020)	China	15.7	Mean	6.7 (sd)	Serial testing (RT-PCR) of 24 non-ICU patients hospitalised. Adults. Nasal samples.
[60]	Fang et al. (2020)	China	22.3	Mean	3.6 (sd)	Serial testing (RT-PCR) of 8 ICU patients hospitalised. Adults. Nasal samples.
[57]	Hill et al. (2020)	Scotland	9	Max.		Serial testing (RT-PCR) of a single patient (adult) hospitalised; nasal sample [throat sample: 6 days]. Mild.
[86]	Le et al. (2020)	Vietnam	12	Max.		Serial testing (RT-PCR) of a single patient (infant) hospitalised. Mild.
[58]	Liu et al. (2020)	China	10	Max.		Serial testing (RT-PCR) of patients hospitalised. Adults. Mixed Mild/severe cases. N=76. 90% “early viral clearance” within 10days
[87]	Qiu et al. (2020)	China	10	Mean	7-22 range	Serial testing (RT-PCR) of patients hospitalised. Children. N=36. Mild and moderate cases.
[59]	To et al. (2020)	Hong Kong	25	Max.		Serial testing (RT-PCR) of patients hospitalised. N=7. Seven patients reported viral detection >20 days; viral load peaked during first week post-onset of symptoms.
[88]	Wu et al.	China	16.1	Mean	6.7 (sd)	Serial testing (RT-PCR) of patients hospitalised. Adults. N=74. Severe and non-severe cases.
Tracking studies						
[31]	Tindale et al. (2020)	Singapore	18	Median	9-33 range	Time from onset to discharge; range 9-33; n=53

[35,36]	Kraemer et al. (2020a); [later published as: Xu et al. 2020]	Various	19	Median	3-37 range	Time from onset to discharge; Range: 3-37; n=70
[34]	Linton et al. (2020)	Wuhan, China	13	Median	6-41 range	Time from onset to death; range 6-41
[35,36]	Kraemer et al. (2020b)	Japan and China	19.25	Mean	12-24 range	Time from onset to death; n=4
[49,50]	Wölfel et al. (2020)	Germany	3-8 days	absolute	3-8 range	Tracked infection in mild cases in Germany, undertaking viral isolation studies to assess active replication across a number of samples sites (upper respiratory tract, blood, urine, faeces) over the duration of infection. 5% isolation success was achieved up to 9.78 (95% CI: 8.45-21.78) days post onset; n=9

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827 **Table 4:** Reported infectious period (IP) for symptomatic cases (T3+T5 parameter) from virological
 828 studies where serial diagnostic tests were undertaken to infer IP [exposure to ≥ 2 neg. tests]; tracking
 829 studies where IP is inferred from patient histories from onset to recovery or death; modelling studies
 830 where IP is reported as a prior (assumed parameter value) or an posterior estimate.

No.	Study	Location	Parameter (days)	Central tendency reported	Variation (days; inclus.)	Comment
Tracking studies						
[29]	He et al. (2020)	Vietnam, Malaysia, Japan, China, Taiwan, USA, Singapore	9.3 days	Mean	7.8-10 (95%CI*)	The paper reported on 77 infector-infectee pairs which were sequential/serially tested, using publicly available data. Viral dynamics (Guangzhou, China; N=94) interpreted by the authors suggested an infectious period starting 2.3 (95% CI, 0.8–3.0 days) days prior to symptoms, peaking 0.7 days (95% CI, -0.2–2.0 days), continuing up to 7 days from onset. * CI from pre-symptom infectious period only.
[8]	Ma et al. (2020)	Various	~5 days	Median	Range 0-24	The authors estimated the infectious period as latent minus the serial interval, using a dataset of 1155 cases. Range 0-24; IQR: 2-9; calculated from data presented within the paper.
Modelling studies						
[27]	Li et al. (2020)	China	3.45 days [posterior estimated from model for documented cases]	median	95%CI for the mean: 3.19, 3.72	Mathematical model. Priors for <u>mean</u> documented infectious period was a flat [uniform] distribution 2-5. 'Documented' cases were defined as those severe enough to be confirmed. This corraling of the infectious period relative to other

						studies should take into account that the distribution is used for the central tendency, not the whole distribution.
[26,39]	Tuite et al. (a, b) (2020)	Canada	6-6.5 days [prior; fixed parameter within a deterministic model]	Fixed parameter		Mathematical model [deterministic], with a fixed parameter estimate of 6.5 days (a) and 6 days (b), respectively. Important to note that duration for 'mild' was equal to severe cases.
[89]	Lourenco et al. (2020)	UK	~3-5 days [posterior; approximate depending on scenario tested]	mean	95%ci of 3-6 days	Mathematical model. The prior used was given a Gaussian distribution (normal curve); mean 4.5; SD 1; approximate 95%ci of 3-6 days. The reported posterior of this parameter was presented graphically and depended on R0 and proportion at risk. Depending on the scenarios tested, mean duration of infectiousness appeared to vary from 3-5 days.
[37]	Zhu et al. (2020)	Wuhan, China	12.5 days [posterior estimated from model]	Mean	11.4 variance	Mathematical model. The parameter was estimated using a Weibull distribution. The prior for this parameter was 10 days. The posterior variance around the mean was 11.4, and therefore the distribution had a long tail. This study was a modelling [SEIR extended model].
[15]	Davies et al. (b) (2020)	UK	7 days [Prior]	Mean		Model with asymptomatic infection compartment. Modelled with a

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						gamma distribution, beta 1.4; alpha 5. Despite, the subclinical aspect of this parameter, it could be considered analogous to total infectious period without intervention.
[14]	Davies et al. (b) (2020)	UK	5 days [Prior]	Mean		Model with asymptomatic infection compartment. Modelled with a gamma distribution, k=4. Authors: "Assumed to be the same duration as total infectious period for clinical cases, including preclinical transmission"
[38]	Piccolomini and Zama (2020)	Italy	20 days [Prior]	Fixed		Parameter estimate assumed for the infectious period within an SEIRD model, fitted to data from the epidemic in Italy.

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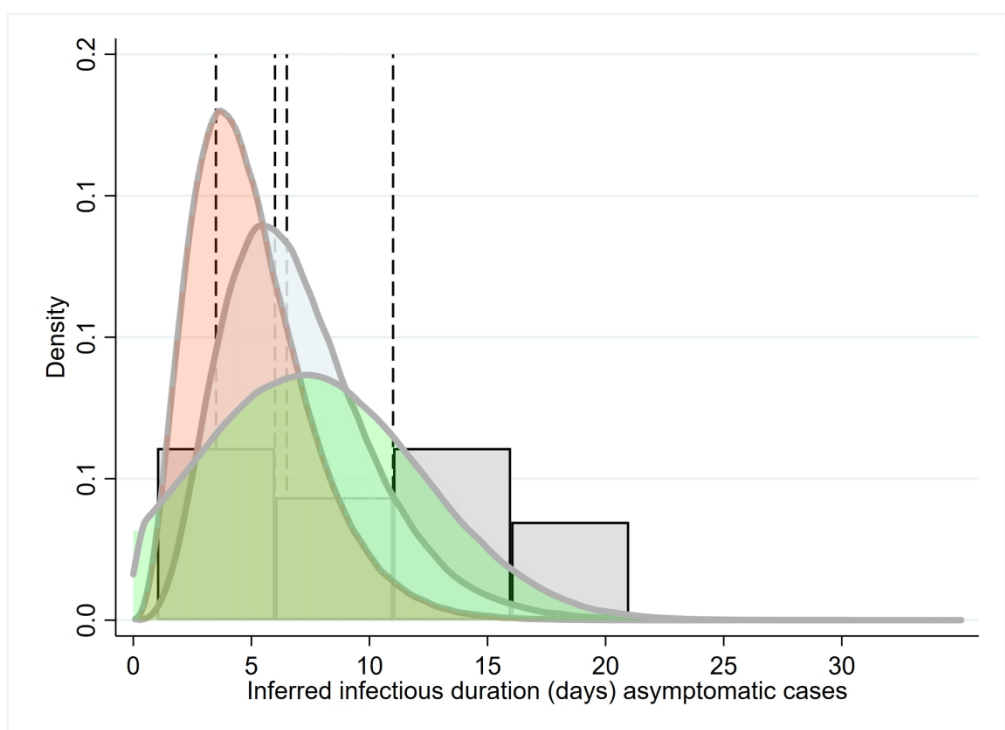


Figure 1: Simulation of the parameter distribution inferred for duration infectious period for asymptomatic cases

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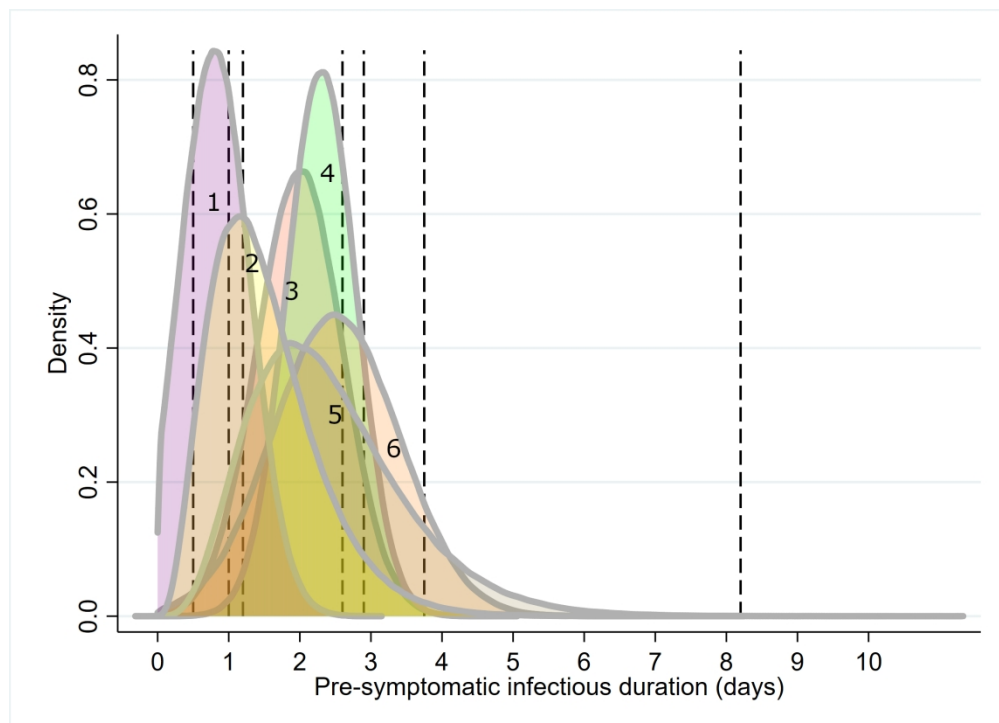


Figure 2: Simulation of the parameter distribution used for T3 (the duration of the pre-symptomatic infectious period for those infected individuals who subsequently develop symptoms).

881x635mm (72 x 72 DPI)

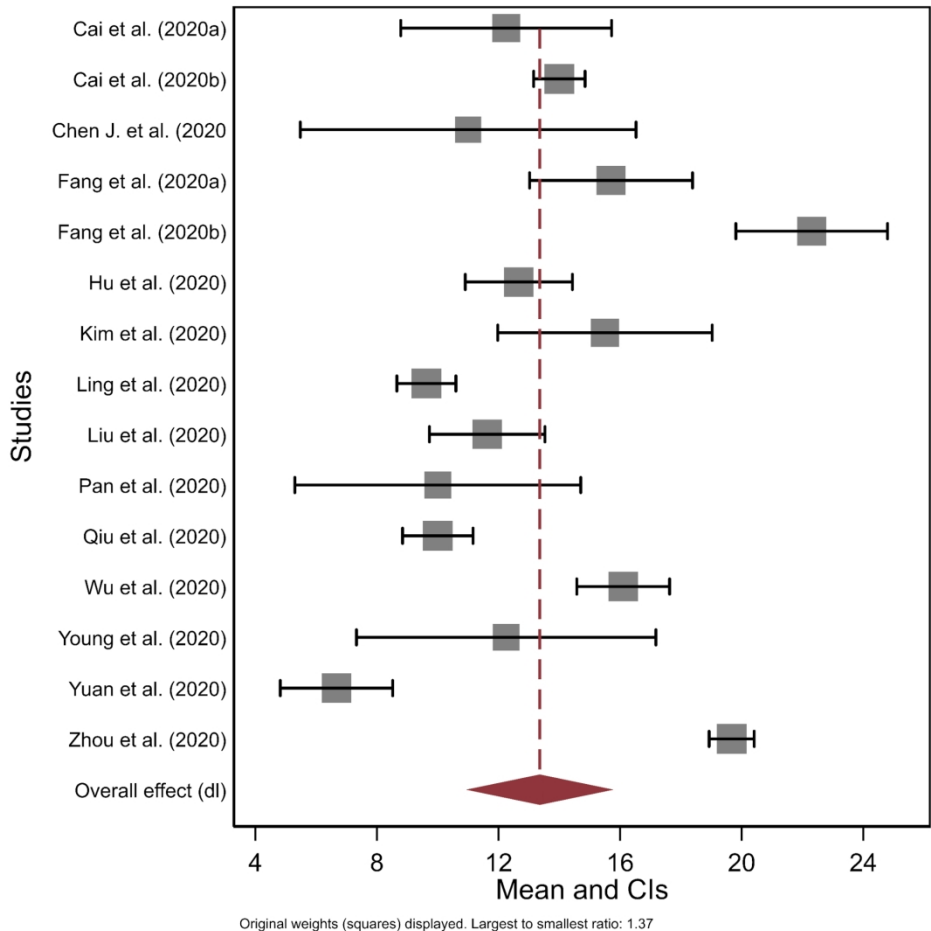


Figure 3: Forest plot of the mean duration from onset of symptoms to death or recovery (T5) based on virological studies

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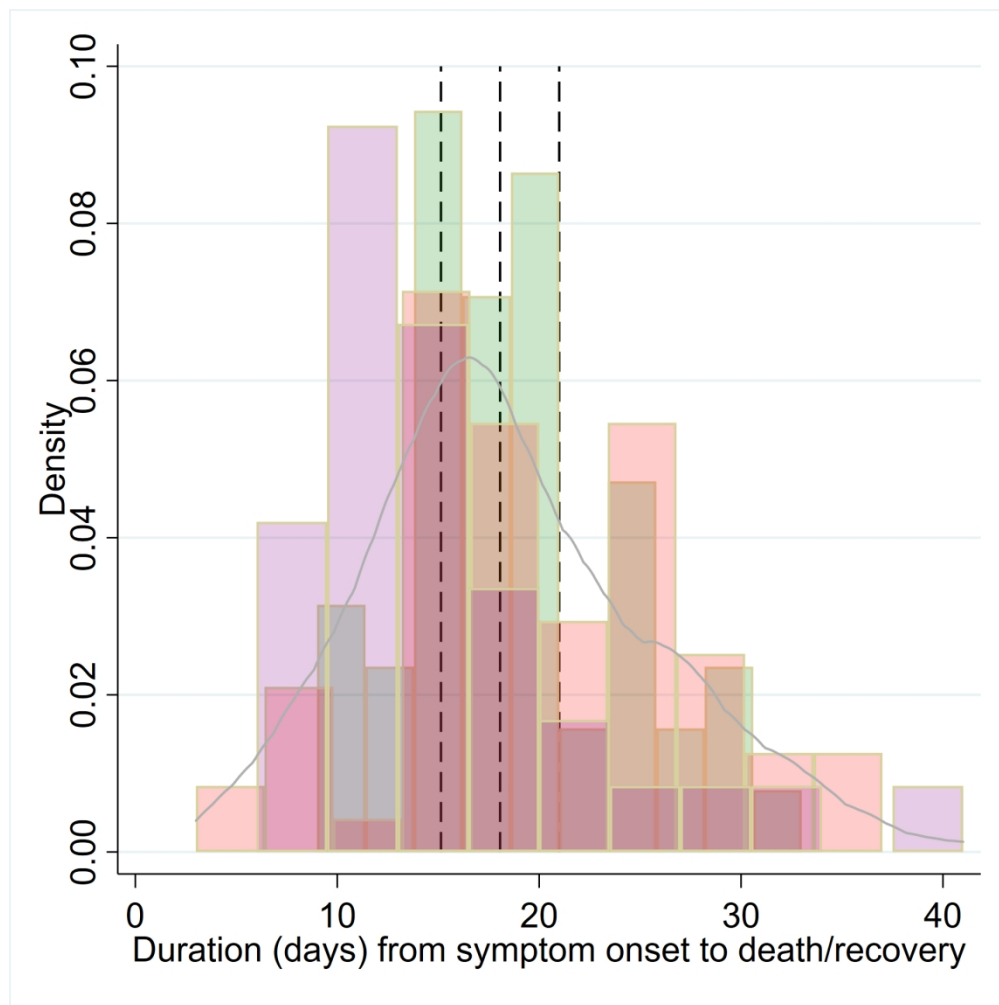


Figure 4: Frequency distribution of T5, time from onset of symptoms to recovery (here hospital discharge or death), using patient level raw data

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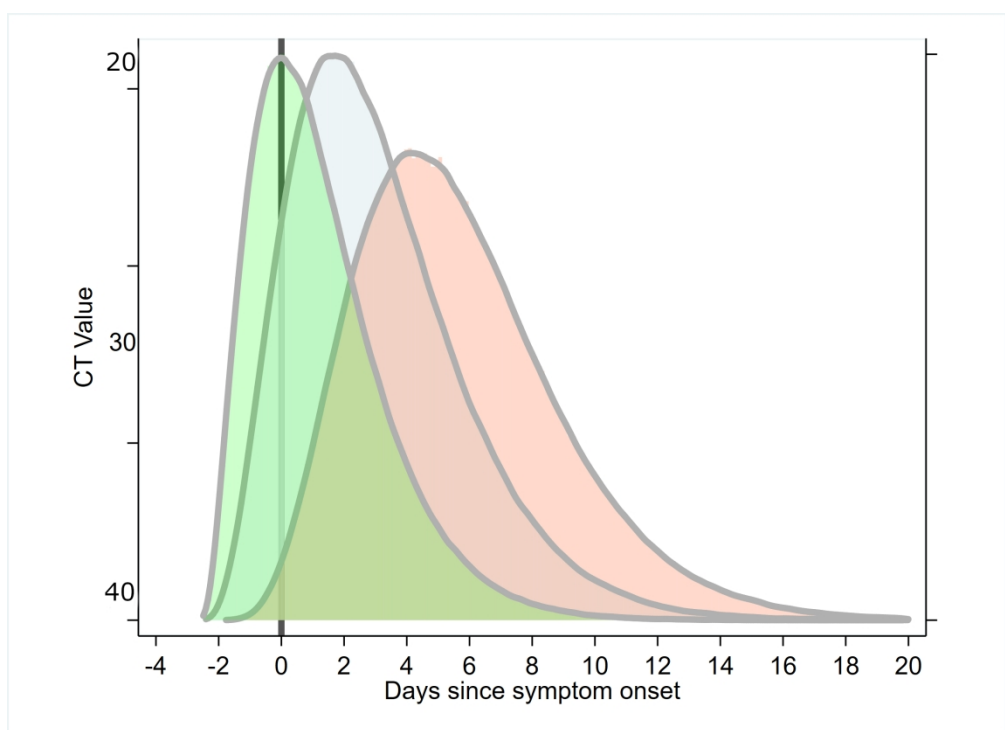
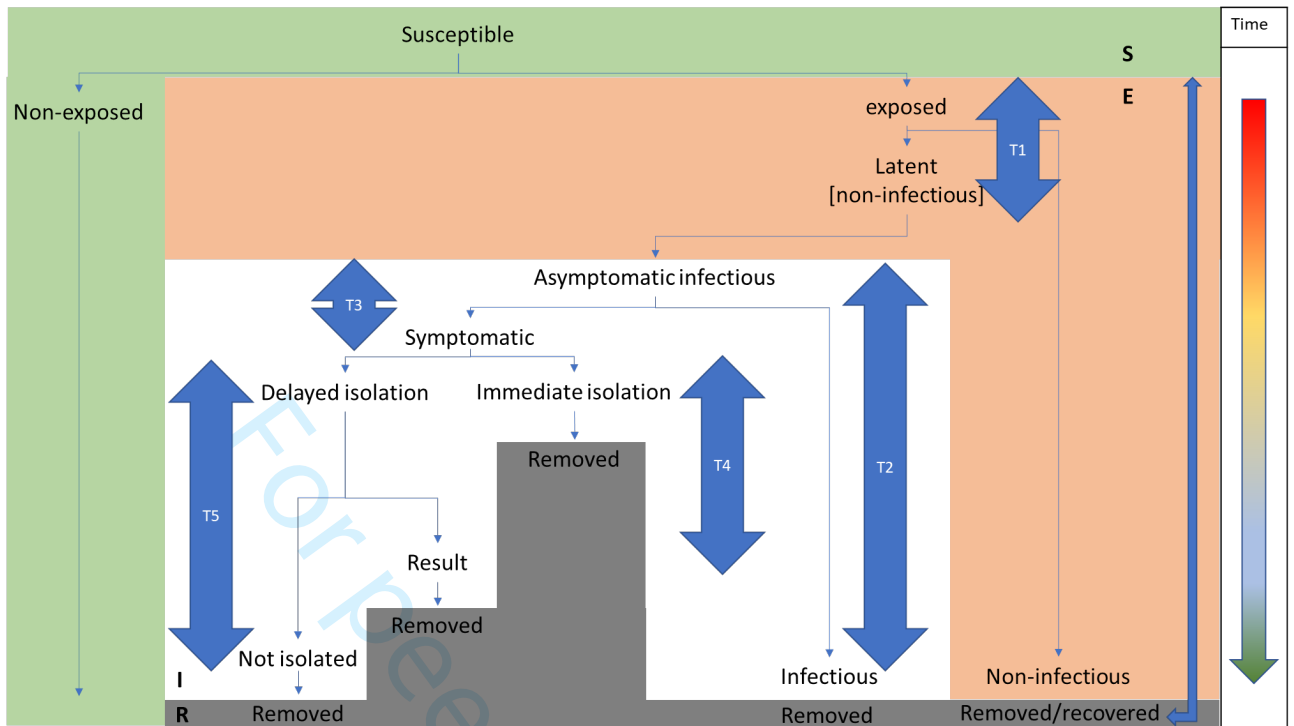


Figure 5: Composite inferred model for cycle threshold (CT) value changes from serial RT-PCR testing for SARS-COV2

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1 **Supplementary material 1**

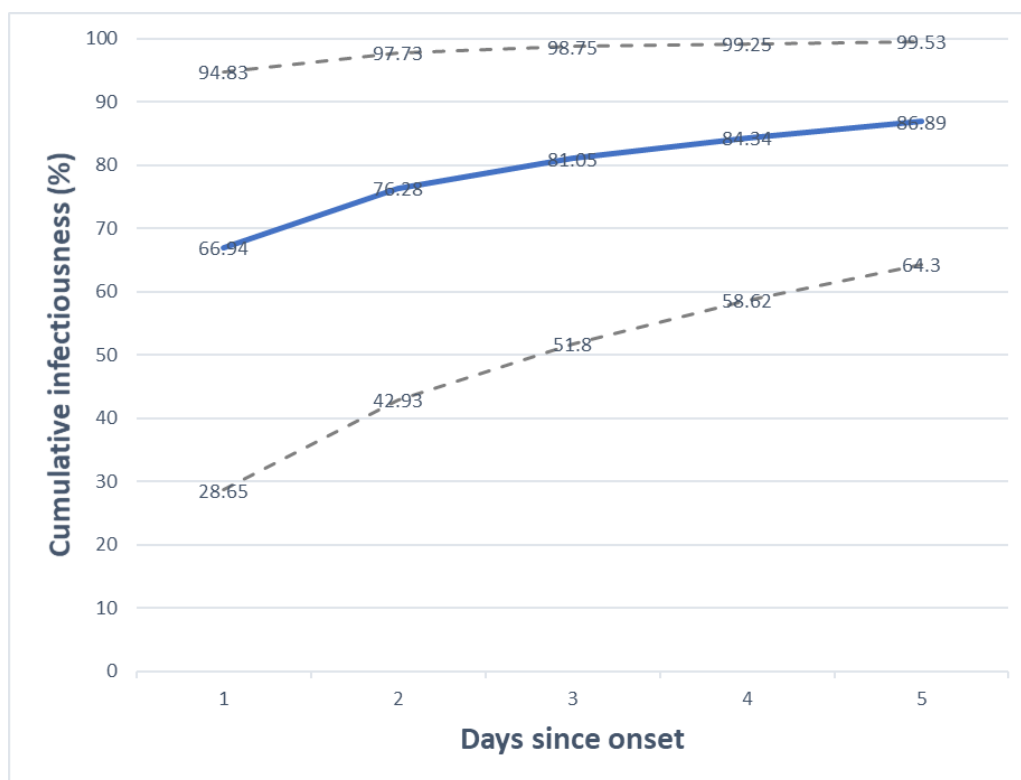


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3 **Figure S1:** Conceptual model of the key temporal parameters impacting COVID-19 infection
 4 progression over time. T1: Latent period; T2: Asymptomatic infectious period; T3: Pre-
 5 symptomatic infectious period; T4: Symptom onset to diagnosis [self-isolation] or
 6 hospitalisation; T5: Symptom onset to removed [death or recovery]

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10 **Figure S2:** Cumulative infectiousness (% of total infectiousness) based on infector-infectee pair
11 pair data in the paper by Cheng et al. 2020. The accumulation curve is based on a gamma density
12 function, coupled with a probability function to capture the maximal probability if exposed to a
13 primary case.

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Positive culture



Negative culture



0 2 4 6 8 10 12 14
Days after symptom onset

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17 **Figure S3:** Timeline for positive culture results of SARS-COV2 from throat, sputum and stool
18 samples; Yellow line = Throat swabs; Orange line = Sputum samples; Blue line = Stool samples;
19 Adapted from Wölfel et al.[50].

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21 **Reference:**

22 Cheng, H.Y., Jian, S.W., Liu, D.P., Ng, T.C., Huang, W.T. and Lin, H.H., 2020. High transmissibility of
23 COVID-19 near symptom onset. *medRxiv*.

24 Wölfel R, Corman VM, Guggemos W, *et al*. Virological assessment of hospitalized
25 patients with COVID-2019. *Nature* 2020;:1–10.

Database	Search strategy (publications accessible 1 st Dec 2019-1 st April 2020)
Pubmed	"coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "COVID-19" Filter: humans Filter: 30 December 2019
Embase.com	('coronavirinae'/exp OR 'coronavirinae' OR 'coronaviridae infection'/exp OR 'coronaviridae infection' OR 'coronavirus disease 2019'/exp OR 'coronavirus'/exp OR coronavirus OR 'coronavirus infection'/de) NOT [medline]/lim AND 'human'/de Filter: 30 December 2019
Science direct	"COVID-19" OR "2019 novel coronavirus infection" OR "2019-nCoV"
Cochrane	"coronavirus" OR "COVID-19"
Infectious diseases society of America search of infectious disease journals	coronavirus OR corona virus OR covid-19 https://academic.oup.com/idsa/search-results?allJournals=1&fl_SiteID=5567&page=1&qb=%7b%22ArticleTitle1%22%3a%22coronavirus+OR+corona+virus+OR+covid-19%22%7d&sort=Date+%E2%80%93+Newest+First
NHS Evidence	"COVID-19" OR "2019 novel coronavirus infection" OR "2019-nCoV" Filter: 30 December 2019
Google Scholar	"Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19" AND "infectious"
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
HRB Open	"coronavirus" OR "COVID-19"

26 Supplementary material 2:Data for meta-analysis

paper	country	ct	ct_type	range	median	iqr	min	max	first_qt	third_qt	n	mean	sd	se	severity	sev_bin	kid_cat	
Cai et al. (2020a)	China	12	Median	6-22 range	12		6	22	8	15	10			6	2	mild	0	1
Cai et al. (2020b)	China	14	Median		14	9-19 (IQR)			9	19	298			7	0	mild- severe	1	2
Chen et al (2020)	China	12	Max.								1			0	0			2
Chen J. et al. (2020)	China	11	Median	10-12 (95%CI)	11						242			8	3	mild- severe	1	2
Cheng et al. (2020)	China	21	Max.								1			0	0	severe	1	2
Fang et al. (2020a)	China	16	Mean	6.7 (sd)							24			7	1	mild- moderate	0	2
Fang et al. (2020b)	China	22	Mean	3.6 (sd)							8			4	1	severe	1	2
Hill et al. (2020)	Scotland	9	Max.								1			0	0	mild	0	2
Hu et al. (2020)	China	12	Median		12	12-14 (IQR)			12	14	5			2	1	mild	0	2
Kim et al. (2020)	Korea	16	Median	14-17 (range)	16		14	17			2			3	2	mild- moderate	0	2
Kujawski et al. (2020)	USA	26	Max.								1			0	0	mild- moderate	0	2
Le et al. (2020)	Vietnam	12	Max.								1			0	0	mild	0	1
Lee et al. (2020)	Taiwan South	20	Max.								1			0	0	severe	1	2
Lim et al. (2020)	Korea	16	Max.								1			0	0			2
Ling et al. (2020)	China	10	Median	2-22 (range)	10		2	22	6	11	66			4	0			1
Liu et al. (2020)	China	11	Median	7-18 range	11		7	18	10	13	10			3	1	mild- severe	1	2
Liu et al. (2020)	China	10	Max.								76					mild- severe	1	2
Marchand-Senžca et al.	Canada	23	Max								1			0	0			

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(2020)

Pan et al. (2020)	China	10	Median	8-12 range	10	8	12	2	3	2				
Qiu et al. (2020)	China	10	Mean	7-22 range		7	22	36	4	1	mild- moderate	0	1	
Qu et al. (2020)	China	22	Max					1	0	0				
Tan et al. (2020)	Vietnam	16	Max					1	0	0	severe	1		
Thevarajan et al. (2020)	Australia	7	Max					1	0	0	mild- moderate	0		
To et al. (2020)	Hong Kong	25	Max.					7	0	0	mild- severe	1	2	
Wu et al. (2020)	China	16	Mean	6.7 (sd)				74	7	1	mild- severe	1	2	
Xing et al (2020)	China	14	Median		14			3			mild- moderate	0	1	
Young et al. (2020)	Singapore	12	Median		12	1	24	18	6	3	mild- moderate	0	2	
Yuan et al. (2020)	China	6	Median		6	4-10 (IQR)	4	10	25	5	mild- moderate	0	1	
Zhou et al. (2020)	China	20	Median		20	16-23 IQR	16	23	191	5	0	severe	1	2

29 Supplementary material 3: Data for time to recovery or death

study	overall_time_disc_death	death	discharge	xb_t5	upp95	low95
kraemer	20	0	1	18.06537	15.13663	20.99411
kraemer	16	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	25	0	1	18.06537	15.13663	20.99411
kraemer	22	0	1	18.06537	15.13663	20.99411
kraemer	28	0	1	18.06537	15.13663	20.99411
kraemer	16	0	1	18.06537	15.13663	20.99411
kraemer	25	0	1	18.06537	15.13663	20.99411
kraemer	37	0	1	18.06537	15.13663	20.99411
kraemer	15	0	1	18.06537	15.13663	20.99411
kraemer	14	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	17	0	1	18.06537	15.13663	20.99411
kraemer	20	0	1	18.06537	15.13663	20.99411
kraemer	14	0	1	18.06537	15.13663	20.99411
kraemer	19	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	28	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	8	0	1	18.06537	15.13663	20.99411
kraemer	12	0	1	18.06537	15.13663	20.99411
kraemer	8	0	1	18.06537	15.13663	20.99411
kraemer	18	0	1	18.06537	15.13663	20.99411
kraemer	23	0	1	18.06537	15.13663	20.99411
kraemer	19	0	1	18.06537	15.13663	20.99411

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kraemer	3	0	1	18.06537	15.13663	20.99411
kraemer	17	0	1	18.06537	15.13663	20.99411
kraemer	26	0	1	18.06537	15.13663	20.99411
kraemer	19	0	1	18.06537	15.13663	20.99411
kraemer	16	0	1	18.06537	15.13663	20.99411
kraemer	35	0	1	18.06537	15.13663	20.99411
kraemer	14	0	1	18.06537	15.13663	20.99411
kraemer	15	0	1	18.06537	15.13663	20.99411
kraemer	29	0	1	18.06537	15.13663	20.99411
kraemer	30	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	32	0	1	18.06537	15.13663	20.99411
kraemer	15	0	1	18.06537	15.13663	20.99411
kraemer	24	0	1	18.06537	15.13663	20.99411
kraemer	9	0	1	18.06537	15.13663	20.99411
kraemer	18	0	1	18.06537	15.13663	20.99411
kraemer	16	0	1	18.06537	15.13663	20.99411
kraemer	33	0	1	18.06537	15.13663	20.99411
kraemer	18	0	1	18.06537	15.13663	20.99411
kraemer	21	0	1	18.06537	15.13663	20.99411
kraemer	19	0	1	18.06537	15.13663	20.99411
kraemer	7	0	1	18.06537	15.13663	20.99411
kraemer	18	0	1	18.06537	15.13663	20.99411
kraemer	30	0	1	18.06537	15.13663	20.99411
kraemer	27	0	1	18.06537	15.13663	20.99411
kraemer	20	0	1	18.06537	15.13663	20.99411
kraemer	33	0	1	18.06537	15.13663	20.99411
kraemer	15	0	1	18.06537	15.13663	20.99411
kraemer	5	0	1	18.06537	15.13663	20.99411
kraemer	16	0	1	18.06537	15.13663	20.99411

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4	kraemer	14	0	1	18.06537	15.13663	20.99411
5	kraemer	21	0	1	18.06537	15.13663	20.99411
6	kraemer	15	0	1	18.06537	15.13663	20.99411
7	kraemer	26	0	1	18.06537	15.13663	20.99411
8	kraemer	17	0	1	18.06537	15.13663	20.99411
9	kraemer	17	0	1	18.06537	15.13663	20.99411
10	kraemer	17	0	1	18.06537	15.13663	20.99411
11	kraemer	16	0	1	18.06537	15.13663	20.99411
12	kraemer	16	0	1	18.06537	15.13663	20.99411
13	kraemer	26	0	1	18.06537	15.13663	20.99411
14	kraemer	19	0	1	18.06537	15.13663	20.99411
15	kraemer	19	0	1	18.06537	15.13663	20.99411
16	kraemer	14	0	1	18.06537	15.13663	20.99411
17	kraemer	8	0	1	18.06537	15.13663	20.99411
18	kraemer	34	0	1	18.06537	15.13663	20.99411
19	linton	10	1	0	18.06537	15.13663	20.99411
20	linton	21	1	0	18.06537	15.13663	20.99411
21	linton	21	1	0	18.06537	15.13663	20.99411
22	linton	8	1	0	18.06537	15.13663	20.99411
23	linton	11	1	0	18.06537	15.13663	20.99411
24	linton	11	1	0	18.06537	15.13663	20.99411
25	linton	11	1	0	18.06537	15.13663	20.99411
26	linton	30	1	0	18.06537	15.13663	20.99411
27	linton	32	1	0	18.06537	15.13663	20.99411
28	linton	10	1	0	18.06537	15.13663	20.99411
29	linton	19	1	0	18.06537	15.13663	20.99411
30	linton	19	1	0	18.06537	15.13663	20.99411
31	linton	19	1	0	18.06537	15.13663	20.99411
32	linton	14	1	0	18.06537	15.13663	20.99411
33	linton	8	1	0	18.06537	15.13663	20.99411
34	linton	8	1	0	18.06537	15.13663	20.99411
35	linton	12	1	0	18.06537	15.13663	20.99411
36	linton	12	1	0	18.06537	15.13663	20.99411
37	linton	20	1	0	18.06537	15.13663	20.99411
38	linton	12	1	0	18.06537	15.13663	20.99411
39	linton	12	1	0	18.06537	15.13663	20.99411
40	linton	7	1	0	18.06537	15.13663	20.99411
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3	linton	11	1	0	18.06537	15.13663	20.99411
4	linton	16	1	0	18.06537	15.13663	20.99411
5	linton	6	1	0	18.06537	15.13663	20.99411
6	linton	6	1	0	18.06537	15.13663	20.99411
7	linton	17	1	0	18.06537	15.13663	20.99411
8	linton	15	1	0	18.06537	15.13663	20.99411
9	linton	24	1	0	18.06537	15.13663	20.99411
10	linton	41	1	0	18.06537	15.13663	20.99411
11	linton	10	1	0	18.06537	15.13663	20.99411
12	linton	11	1	0	18.06537	15.13663	20.99411
13	linton	13	1	0	18.06537	15.13663	20.99411
14	linton	13	1	0	18.06537	15.13663	20.99411
15	linton	16	1	0	18.06537	15.13663	20.99411
16	linton	13	1	0	18.06537	15.13663	20.99411
17	linton	14	1	0	18.06537	15.13663	20.99411
18	linton	18	1	0	18.06537	15.13663	20.99411
19	linton	12	1	0	18.06537	15.13663	20.99411
20	tindale	19	0	1	18.06537	15.13663	20.99411
21	tindale	25	0	1	18.06537	15.13663	20.99411
22	tindale	25	0	1	18.06537	15.13663	20.99411
23	tindale	20	0	1	18.06537	15.13663	20.99411
24	tindale	20	0	1	18.06537	15.13663	20.99411
25	tindale	13	0	1	18.06537	15.13663	20.99411
26	tindale	28	0	1	18.06537	15.13663	20.99411
27	tindale	25	0	1	18.06537	15.13663	20.99411
28	tindale	24	0	1	18.06537	15.13663	20.99411
29	tindale	14	0	1	18.06537	15.13663	20.99411
30	tindale	17	0	1	18.06537	15.13663	20.99411
31	tindale	15	0	1	18.06537	15.13663	20.99411
32	tindale	18	0	1	18.06537	15.13663	20.99411
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3	tindale	15	0	1	18.06537	15.13663	20.99411
4	tindale	16	0	1	18.06537	15.13663	20.99411
5	tindale	16	0	1	18.06537	15.13663	20.99411
6	tindale	16	0	1	18.06537	15.13663	20.99411
7	tindale	20	0	1	18.06537	15.13663	20.99411
8	tindale	17	0	1	18.06537	15.13663	20.99411
9	tindale	12	0	1	18.06537	15.13663	20.99411
10	tindale	24	0	1	18.06537	15.13663	20.99411
11	tindale	24	0	1	18.06537	15.13663	20.99411
12	tindale	24	0	1	18.06537	15.13663	20.99411
13	tindale	26	0	1	18.06537	15.13663	20.99411
14	tindale	16	0	1	18.06537	15.13663	20.99411
15	tindale	16	0	1	18.06537	15.13663	20.99411
16	tindale	20	0	1	18.06537	15.13663	20.99411
17	tindale	9	0	1	18.06537	15.13663	20.99411
18	tindale	15	0	1	18.06537	15.13663	20.99411
19	tindale	14	0	1	18.06537	15.13663	20.99411
20	tindale	14	0	1	18.06537	15.13663	20.99411
21	tindale	18	0	1	18.06537	15.13663	20.99411
22	tindale	30	0	1	18.06537	15.13663	20.99411
23	tindale	19	0	1	18.06537	15.13663	20.99411
24	tindale	17	0	1	18.06537	15.13663	20.99411
25	tindale	17	0	1	18.06537	15.13663	20.99411
26	tindale	16	0	1	18.06537	15.13663	20.99411
27	tindale	17	0	1	18.06537	15.13663	20.99411
28	tindale	20	0	1	18.06537	15.13663	20.99411
29	tindale	23	0	1	18.06537	15.13663	20.99411
30	tindale	23	0	1	18.06537	15.13663	20.99411
31	tindale	19	0	1	18.06537	15.13663	20.99411
32	tindale	12	0	1	18.06537	15.13663	20.99411
33	tindale	19	0	1	18.06537	15.13663	20.99411
34	tindale	19	0	1	18.06537	15.13663	20.99411
35	tindale	17	0	1	18.06537	15.13663	20.99411
36	tindale	17	0	1	18.06537	15.13663	20.99411
37	tindale	14	0	1	18.06537	15.13663	20.99411
38	tindale	16	0	1	18.06537	15.13663	20.99411
39	tindale	16	0	1	18.06537	15.13663	20.99411
40	tindale	30	0	1	18.06537	15.13663	20.99411
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tindale	33	0	1	18.06537	15.13663	20.99411
tindale	19	0	1	18.06537	15.13663	20.99411
tindale	29	0	1	18.06537	15.13663	20.99411
tindale	22	0	1	18.06537	15.13663	20.99411
tindale	10	0	1	18.06537	15.13663	20.99411
tindale	20	0	1	18.06537	15.13663	20.99411
tindale	11	0	1	18.06537	15.13663	20.99411
tindale	15	0	1	18.06537	15.13663	20.99411
tindale	18	0	1	18.06537	15.13663	20.99411
tindale	11	0	1	18.06537	15.13663	20.99411

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30 **Supplementary material 4: Stata code**

```
31 // 1st April 2020
32
33 /* Code for:
34
35 Byrne, AW, McEvoy, D, et al. 2020
36
37 Inferred duration of infectious period of SARS-CoV-2: rapid review and analysis of
38 available evidence for asymptomatic and symptomatic COVID-19 cases
39
40
41 */
42
43 * Figure 2
44
45 gen davies1_gamma = rgamma(5, 1.4)
46
47 gen davies2_gamma = rgamma(4, 1.25)
48
49 gen ma_normal = rnormal(7.2, 4.96)
50
51
52 input hu_data
53
54 12
55
56 1
57
58 1
59
60 11
61
62 3
63
64 16
65
66 6
67
68 4
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70 6
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72 18
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74 8
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76 8
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78 11
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80 14
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82 14
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84 12
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86 13
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88 1
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90 17
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92 3
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94 11
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96 5
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3 97
4 98 6
5 99
6 100 21
7 101
8 102 end
9 103
10 104
11 105
12 106 // Fig 2 visualise
13 107
14 108 twoway (histogram hu_data, fcolor(gs14) lcolor(black)) (histogram davies1_gamma,
15 109 bin(180) fcolor(ltblueishgray%86) lcolor(none) lwidth(none)) (kdensity
16 110 davies1_gamma, lcolor(gs11) lwidth(thick)) (kdensity davies2_gamma, lcolor(gs11)
17 111 lwidth(thick)) (histogram davies2_gamma, bin(120) fcolor(orange_red%20)
18 112 lcolor(none) lwidth(none)) (histogram ma_normal, bin(100) fcolor(lime%20)
19 113 lwidth(none)) (kdensity ma_normal, lcolor(gs11) lwidth(thick)) if ma_n>=0,
20 114 yscale(line) xtitle(Days since infected) xline(6 6.5 11 3.5, lpattern(dash)
21 115 lcolor(black) noextend) xlabel(0(5)30) legend(off) scheme(s2color) xsize(20)
22 116 ysize(16) graphregion(fcolor(white)) plotregion(fcolor(white))
23 117
24 118
25 119
26 120 * Figure 3
27 121
28 122 gen rothet3_normal = rnormal(2, 0.6)
29 123
30 124 gen huangt3_normal = rnormal(3.75, 0.332)
31 125
32 126 gen het3_normal = rnormal(2.3, 0.49)
33 127
34 128 gen weit3_normal = rnormal(2.5, 0.89)
35 129
36 130 gen peakt3_normal = rnormal(0.8, 0.5)
37 131
38 132 gen daviesAt3_normal = rgamma(5, 0.48)
39 133
40 134 gen daviesBt3_normal = rgamma(4, 0.375)
41 135
42 136 twoway (histogram rothe, bin(120) fcolor(orange_red%20) lcolor(none) lwidth(none))
43 137 (kdensity rothe, lcolor(gs11) lwidth(thick)) (histogram he, bin(100)
44 138 fcolor(lime%20) lwidth(none)) (kdensity he, lcolor(gs11) lwidth(thick)) (histogram
45 139 wei, bin(100) fcolor(orange%20) lwidth(none)) (kdensity wei, lcolor(gs11)
46 140 lwidth(thick)) (histogram peak, bin(100) fcolor(purple%20) lwidth(none)) (kdensity
47 141 peak, lcolor(gs11) lwidth(thick)) (histogram daviesA, bin(100) fcolor(brown%20)
48 142 lwidth(none)) (kdensity daviesA, lcolor(gs11) lwidth(thick)) (histogram daviesB,
49 143 bin(100) fcolor(yellow%20) lwidth(none)) (kdensity daviesB, lcolor(gs11)
50 144 lwidth(thick)) if peak>=0 & wei>=0 & rothe>=0, yscale(line) xtitle(Pre-symptomatic
51 145 infectious period) xline(0.5 1 1.2 2.6 2.9 3.75 8.2, lpattern(dash) lcolor(black)
52 146 noextend) xlabel(0(1)10) legend(off) scheme(s2color) xsize(20) ysize(16)
53 147 graphregion(fcolor(white)) plotregion(fcolor(white)) ytitle(Density)
54 148
55 149 * Figure 4
56 150
57 151 // meta analysis & meta regression
58 152
59 153 clear
60 154
61 155
62 156
63 157 // open data =
64 158
65 159 * meta_analysis_dataset.xls
66 160
67 161
68 162
69 163 // Fit random effects meta-analytical model, and specify forest plot
70 164

```

```
1
2
3 165 metaan mean se, dl forest label(paper)
4 166
5 167 // forest plot is figure 4.
6 168
7 169 // meta regression
8 170
9 171 // binary child (y/n) variable
10 172
11 173 gen kid_cat = 1 if child==1
12 174
13 175 replace kid = 2 if adult==1 & child!=1
14 176
15 177 tab kid_cat
16 178
17 179 * binary children inclusion in sample [REML]
18 180
19 181 xi: metareg mean i.kid if se>0, wsse(se)
20 182
21 183 // monte carlo model of P-value
22 184
23 185 xi: metareg mean i.kid if se>0, wsse(se) permute(1000, joint(i.kid))
24 186
25 187
26 188
27 189 // binary severe (y/n) variable
28 190
29 191 encode sever, gen(sev_num) // 4 way categorical
30 192
31 193 gen sev_bin = 0 if sev_n<3
32 194
33 195 replace sev_bin = 1 if sev_n==3 | sev_n==4
34 196
35 197
36 198
37 199 xi: metareg mean i.sev_bin if se>0, wsse(se)
38 200
39 201 // monte carlo model of P-value
40 202
41 203 xi: metareg mean i.sev_bin if se>0, wsse(se) permute(1000, joint(i.sev_bin))
42 204
43 205
44 206
45 207 * Figure 5
46 208
47 209
48 210
49 211 // Import, open time_to_discharge_death.csv
50 212
51 213
52 214 // numeric indicator for study category
53 215
54 216 encode study, gen(study_)
55 217
56 218
57 219
58 220 // random effects model for time from onset to removal (discharge or death)
59 221
60 222 // 3 levels of study as RE
61 223
62 224 xi: xtreg overall_time, i(study_)
63 225
64 226 // summarise post-estimation
65 227
66 228 estat summarize
67 229
68 230 // Breusch and Pagan Lagrangian multiplier test for random effects
69 231
70 232 xttest0
```

```
1
2
3 233
4 234 // Figure 5: histogram plot with kernel density
5 235
6 236 twoway(hist overall_time if study_== 3 , bin(10) fcolor(green%20))( hist
7 237 overall_time if study_== 1, bin(10) fcolor(red%20))( hist overall_time if study_==
8 238 2, bin(10) fcolor(purple%20))(kdensity overall_time disc_death , lcolor(gs11)
9 239 lwidth(mthick)), scheme(s2gcolor) legend(off) xsize(20) ysize(16)
10 240 graphregion(fcolor(white)) plotregion(fcolor(white)) xline(15.13663 18.06537
11 241 20.99411, lpattern(dash) lcolor(black) noextend)
12 242
13 243
14 244
15 245 // GLM reporting the variation in mean duration across studies
16 246
17 247 xi: reg overall_time i.study_
18 248
19 249 // GOF test
20 250
21 251 estat hettest
22 252
23 253 // residuals plot
24 254
25 255 rvfplot
26 256
27 257 // prediction
28 258
29 259 predict pred_study
30 260
31 261 // visualise
32 262
33 263 twoway(scatter pred_study study_)
34 264
35 265
36 266
37 267 // GLM reporting the variation in mean duration across removal type [death or
38 268 discharge]
39 269
40 270 xi: reg overall_time i.discharge
41 271
42 272 // GOF test
43 273
44 274 estat hettest
45 275
46 276 // residuals plot
47 277
48 278 rvfplot
49 279
50 280 // prediction
51 281
52 282 predict pred_study
53 283
54 284 // visualise
55 285
56 286 twoway(scatter pred_study study_)
57
58
59
60
```

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4-5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4-5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4-5
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	4-5
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	5-7
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	5-7
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5-7



SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	8, Tables 1-3
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Tables 1-3
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Tables 1-3
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	8-13
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	8-13; figures 1-5
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	14-17
Limitations	20	Discuss the limitations of the scoping review process.	17-18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	18
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	18

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med.* 2018;169:467–473. doi: 10.7326/M18-0850.



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