

# An update of serial interval estimates for COVID-19: a meta-analysis

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**Abstract** – *Background:* Serial interval (SI) is one of the most important parameter for COVID-19 modelling purposes as it is related to the reproduction rate of the infection. The first meta-analysis of serial interval were performed with a range of uncertainty in the estimate. This meta-analysis aimed to reduce the uncertainty estimates by assessing publications over a longer period. *Methods:* A literature search was performed for articles published between 1st December 2019 and 15th February 2022. It retrieved 117 eligible studies containing some 80 for 90 serial interval estimates. A random effects model was used. Heterogeneity was checked. To detect a publication bias, a funnel plot was performed using an Egger's test. *Results:* For alpha variant, the serial interval was estimated at 5.17 days (95% CI = 4.87 – 5.47) with a significant heterogeneity ( $I^2 = 97.1\%$ ). The meta-analysis did not exhibit evident publication bias (Egger's test =  $-0.55$ ,  $p = 0.58$ ). The meta-analysis allowed for reducing uncertainty in estimating the serial interval, although subgroup analysis did not reduce it sufficiently and showed that studies using a gamma distribution of serial intervals exhibited the highest estimate of 5.6 days. Compared to the other variants of concern, alpha serial interval estimate was bigger than delta, 4.07 days, and omicron, 3.06 days. *Conclusion:* The meta-analysis was carried out as a real-time monitoring of this parameter to make a choice and a rapid assessment of the control measures implemented, and the effectiveness of the vaccination campaign. The meta-analysis was unable to provide a suitable estimate of serial intervals for COVID-19 modelling purposes although its uncertainty was reduced. Furthermore, serial intervals estimate for alpha variant was close to earlier reports and lower than previous publications, respectively. Another limitation is, that meta-analysis of COVID pandemic studies in principle contains and produces itself a significant source of heterogeneity.

**Keywords:** Coronavirus, COVID-19, Meta-analysis, Modelling, Contact tracing, Pandemic, Reproduction rate, SARS-CoV-2, Statistics, Virus

## Introduction

One of the threats of the Coronavirus disease 2019 (COVID-19) pandemic is the occurrence of multiple variants since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019. Among these variants, three are of public health concern, alpha, delta, and omicron, and these have contributed to huge pandemics [1, 2]. For this reason, the effectiveness of vaccines remains a relevant question and non-pharmaceuticals interventions should be ongoing. Furthermore, control of the pandemic remains a major public health challenge three years after the emergence of SARS-CoV-2.

Modelling helps to manage pandemics by understanding how an infectious disease spreads in the population, the choice and the assessment of adequate control strategies, mainly non-pharmaceutical interventions as is the case with the COVID-19 [3, 4]. At the onset of the COVID-19 pandemic, one of the priorities was to estimate essential

parameters which allowed models to reliably describe the epidemic as it progressed. Among them, three were of great concern: the basic reproduction rate  $R_0$ , the case fatality rate of the disease and the average duration of infection [5, 6]. The basic reproduction rate is defined as the average number of secondary cases infected by a primary case during its infectious period in a population of fully susceptible subjects. Its value indicates whether the epidemic is able to continue ( $R_0 > 1$ ) or not in the population ( $R_0 < 1$  means the temporary decline or not of the epidemic). The level of uncertainty in the choice of a combination of control strategies is related to that in estimating model parameters, especially  $R_0$ . This last is also a parameter of concern as it is used to estimate vaccine coverage to stop the transmission and/or its required effectiveness  $E$  through the formula  $(1 - 1/R_0)/E$ . As  $R_0$  is measured at the beginning of the epidemic, the effective reproduction number  $R_t$  describes its evolution.

$R_0$  was initially estimated with a median value of 2.8 based on a review by Liu *et al.* [7]. The average duration of infection is another significant parameter to be

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considered. It is approximated by the serial interval (SI) or the generation time (GT). SI is defined as the difference between the date of onset of symptoms of a secondary case and an index case, while the GT corresponds to the difference between the dates of the onset of the infectious periods. As the onset of infectiousness is almost impossible to determine, SI is preferred to GT. The SI has been used in several analyses to model the spatiotemporal spread of the COVID-19 epidemic or to compare the effectiveness of control measures [3, 8–11]. Usually, reproduction rate values correlate positively with SI values. Nevertheless, negative SI can be observed if transmission to the secondary case occurs during the pre-symptomatic period of the primary case and the incubation time in the secondary case is shorter than that of the primary case. A SI distribution with a high variance taking into account negative values can skew this relationship. Higher variance of SI could explain an underestimation of reproduction rates [12, 13]. Moreover, distribution of the SI could bias the central estimation of the  $R_t$  by as much as 20–25% [14].

For COVID-19, meta-analyses of SI have been published in the first semester of 2020. They estimated the SI to be more than 5 days with varying confidence interval limits between 4.2 and 6.7 days [15–17]. The aim of this study is to provide an estimate of SI using a meta-analysis to produce more reliable reproduction rate for use in modelling.

## Material and methods

### Literature search

The search was performed for COVID-19 related articles published between 1st December 2019 and 15 February 2022. It was done from PubMed using the following keywords and combination: (serial AND interval) AND (SARS-CoV-2 OR COVID-19). The references of the publications found, in particular those of the meta-analyses or reviews, were also reviewed and potentially included. One serial interval (SI) estimate was kept if two publications or more from the same authors reported the same SI, standard deviation and number of infector/infected pairs.

### Eligibility and exclusion criteria

All types of studies were searched, original articles as well as letters, brief communications, preprint, abstracts. Recorded were the type of publication, country, source population of cases, type of variant, starting date of the study, estimates of SI with negative values or not, SI statistical distribution, if SI estimates came from published data or could be re-estimated from raw data.

The following publications were excluded:

- When one of the three parameters, mean, standard-deviation, number of infector/infected pairs, was/were not found in the publication and raw data was not available.
- When the language used was not in English.
- When the SI was estimated in the context of nosocomial transmission.

## Statistical analysis

As the studies differed in their temporality and location, i.e. SI could vary over time depending on the control measures implemented or the adaptive behaviour of populations as the epidemic spread. Therefore, heterogeneity in the mean of SI was expected. Moreover, studies investigated case-to-case intervals between primary and secondary cases with different designs or various methodological approaches. For these reasons, a random effects model with restricted maximum-likelihood (REML) estimator method was used. Heterogeneity with Cochran's  $Q$  and the  $I^2$  tests was checked. In order to detect a publication bias, a funnel plot was performed with an Egger's test. The meta-analysis was performed using R 3.6.1. software with the package metafor [18].

## Sub-groups analysis

A sensitivity analysis based on the following subgroups was performed:

- Statistical distribution of the SI as it could bias the reproductive number [14].
- SI estimate of published versus re-estimated from raw data when SI statistics were lacking, especially for statistical distribution.
- Country by supposing they could differ in organisation of their public health systems.
- SI estimated with or without negative values could bias both the mean and the standard deviation.
- Measures of control implemented or not during the study could have influenced behaviour of populations and transmission of the virus.

The meta-analysis was carried out on the basis of studies which reported the mean of the SI with its standard deviation (SD) calculated from the number of infector/infected pairs. In case the mean and/or SD and/or distribution of SI was not directly reported in the publication, raw data was used. Therefore, 15 SI from 14 studies were re-estimated as following: if the statistical distribution reported in the publication was gamma, the mean of SI was  $\alpha\beta$  and its standard-deviation  $\sqrt{\alpha\beta^2}$  with  $\alpha$  the shape and  $\beta$  the scale as the parameters of the distribution. If the reported distribution was a Weibull one, the mean and the SD were estimated from the `mixdist` package and the `weibullparinv` command of R. When the distribution was not known, the SI data was fitted according to four distributions, normal, lognormal, Weibull and gamma, and the best fit was chosen using AIC. Table 1 depicts the values re-estimated [19–32].

## Results

The query retrieved 244 studies from PubMed. The 98 publications excluded concerned mainly clinical studies (51), epidemiological studies like seroprevalence (24) or meta-analysis/review (17). Among the 146 publications screened, 29 were excluded as their data were not sufficient for 22, and seven concerned the generation time only.

**Table 1.** Statistics of SI re-estimated (in bold) from raw data of publications that do not or partly provide mean and/or SD and/or statistical distribution.

Author	Values used from raw data of the publication			
	$\bar{SI}$	SD	<i>N.</i> pairs	Distr.
Bohmer <i>et al.</i> [19]	<b>3.94</b>	<b>1.75</b>	15	<b>W</b>
Cereda <i>et al.</i> [20]	6.64	<b>4.67</b>	90	$\gamma$
He <i>et al.</i> [21]	5.80 → <b>5.95<sup>a</sup></b>	<b>3.78</b>	77	$\gamma$
Huang <i>et al.</i> [22]	<b>2.36<sup>b</sup></b>	<b>1.60</b>	<b>5</b>	<b>Log-N</b>
Ki <i>et al.</i> [23]	6.60 → <b>4.94<sup>c</sup></b>	<b>3.46</b>	<b>9</b>	<b>Log-N</b>
Liao <i>et al.</i> [24]	6.50 → <b>8.22<sup>d</sup></b>	<b>2.22</b>	<b>9</b>	<b>N</b>
Lu <i>et al.</i> [25]	<b>5.96</b>	<b>3.58</b>	265	<b>W</b>
Mettler <i>et al.</i> [26]	3.43	<b>4.17</b>	102	<b>N</b>
Tindale <i>et al.</i> [27]	4.17 → <b>5.96<sup>a</sup></b>	<b>2.96</b>	56	$\gamma$
Tindale <i>et al.</i> [27]	4.31 → <b>5.96<sup>a</sup></b>	<b>3.18</b>	72	$\gamma$
Wang <i>et al.</i> [28]	7.60 → <b>7.85<sup>a</sup></b>	<b>5.43</b>	76	$\gamma$
Zhang <i>et al.</i> [29]	5.10 → <b>5.15<sup>a</sup></b>	<b>2.70</b>	35	$\gamma$
De Laval <i>et al.</i> [30]	<b>5.34</b>	<b>5.07</b>	23	<b>Log-N</b>
Pung <i>et al.</i> [31]	<b>4.97</b>	<b>4.23</b>	63	<b>N</b>
Zhu <i>et al.</i> [32]	6.60	<b>5.11</b>	74	$\gamma$

$\bar{SI}$ : mean of SI, SD: standard deviation, *N.* pairs: number of infector/infected pairs, Distr.: statistical distribution, NA: not available parameter estimated from raw data,  $\gamma$ : gamma distribution, *W*: Weibull, *N*: Normal, Log-N: log-normal.

<sup>a</sup> After removing negative and null values and fitting a gamma distribution.

<sup>b</sup> After removing null values and fitting a log-normal distribution.

<sup>c</sup> After removing three pairs with date of symptom onset was uncertain and fitting a log-normal distribution.

<sup>d</sup> After removing null values and fitting a normal distribution.

Identification	244 articles identified through Pubmed query
	98 removed out of scope
Screening	146 records title and abstracts screened
	29 excluded
Eligibility	117 studies assessed
	47 excluded for their SI already published previously
	3 in double excluded
Included	67 studies from the Pubmed query
	13 additional studies from references of 17 reviews or meta-analysis

**Figure 1.** Cascade selection of publications reporting mean and standard-deviation for serial interval. SI: Serial interval.

The remaining 117 studies were assessed and 47 were excluded as they used previously published estimates of SI, mainly for modelling purpose. Finally, 67 studies and 76 estimates of SI were retained (Fig. 1). From the references of the eligible publications or meta-analysis/reviews, 13 additional studies with 14 SI estimates were found and included in the meta-analysis. A total of 90 SI estimates from 80 studies were obtained. Seventy five were retrieved directly from 66 publications and 15 were recalculated using raw data as described [10, 33–97].

**Table 2.** Characteristics description of the 90 SI estimates.

	<i>N</i> = 90	%
Countries		
China	32	35.6
South Korea	12	13.3
Other Asian countries	21	23.3
European countries	15	16.7
Other countries	10	11.1
Variants		
Alpha	75	83.3
Delta	8	8.9
Omicron	7	7.8
SI with negative values		
Yes	42	46.7
No	30	33.3
NA	18	20.0
Statistical distribution		
Gamma	33	36.7
Normal	30	33.3
Weibull	8	8.9
Log-N	11	12.2
NA	8	8.9
SI estimated from		
Direct published data	75	83.3
Raw data	15	16.7

SI: Serial interval; Gamma: Gamma distribution; Normal: Normal distribution; Weibull: Weibull distribution; Log-N: Log-normal distribution; NA: Not available.

The SI estimates provided were mainly from studies conducted in Asian countries, 72.2%, mainly China and South Korea, 35.6 and 13.3% respectively. The SI estimates were retrieved mainly for alpha variant, 83.3%. A gamma

**Table 3.** Meta-analysis for SI of three variants of concern and their summary statistics.

Variant	Number of SI estimates	Mean	95% CI	$I^2$	Cochran's $Q$	Egger
Alpha	75	5.17	4.87 – 5.47	97.10	2026*	0.58
Delta	8	4.07	3.03 – 5.10	99.10	700*	< 0.0001
Omicron	7	3.06	2.76 – 3.37	83.04	30.88*	0.22

\* $P$ -value < 0.0001. SI: Serial interval; 95% CI: 95% confidence interval;  $I^2$ :  $I$ -square or index of heterogeneity statistic; Cochran's  $Q$ : Cochran's  $Q$  heterogeneity statistic; Egger: Egger's test for publication bias.

**Table 4.** Meta-analysis according to subgroups for alpha variant.

Subgroup	SI				Heterogeneity		Egger's test
	$N$	Mean	95% CI		$I^2$	Cochran's $Q$	$p$ -value
All estimates	75	5.17	4.87	5.47	97.10	2026*	0.58
SI re-estimated:							
No	61	5.11	4.80	5.43	97.27	1910*	0.46
Yes	14	5.41	4.57	6.25	91.24	110*	0.93
Country:							
China	30	5.59	5.16	6.02	91.24	250.5*	0.07
Others	45	4.88	4.49	5.27	97.77	1765*	0.21
Distribution <sup>§</sup> :							
Gamma	32	5.60	5.20	6.00	94.74	345*	0.51
Normal	17	5.24	4.60	5.88	95.13	245*	0.87
Lognormal	11	4.46	3.69	5.24	91.43	150*	0.14
Weibull	8	5.45	4.74	6.15	87.84	65.76*	0.05
SI estimated with negative values:							
Yes	30	4.93	4.53	5.32	96.69	552*	0.15
No	28	5.61	5.01	6.21	94.36	363*	0.14
NA	17	4.98	4.41	5.55	94.86	344*	0.0015
Measures of control implemented:							
Yes	42	5.26	4.87	5.65	97.43	875*	0.56
No	6	4.67	3.75	5.58	73.20	16.85 <sup>†</sup>	0.63
NA	26	5.00	4.49	5.52	94.97	687*	0.0112

\* $P$ -value < 0.001, <sup>†</sup> $p$ -value < 0.005, <sup>§</sup> Statistical distribution was not available or not clear for seven studies. SI: Serial interval;  $N$ : Number; 95% CI: 95% confidence interval;  $I^2$ :  $I$ -square or index of heterogeneity statistic; Cochran's  $Q$ : Cochran's  $Q$  heterogeneity statistic; Egger: Egger's test for publication bias; NA: Not available.

distribution or a normal distribution were each used one out of three times to fit the SI (Tab. 2).

The overall estimate of SI was highest for the alpha variant, then the delta and omicron variants, respectively 5.17, 4.07, and 3.06 days (Tab. 3, Figs. 2, 4, and 5). The omicron SI estimate was lower than that of the alpha (Figs. 2 and 5). For all the variants, there was a heterogeneity according to the  $I^2$  and the Cochran tests. No publication bias were shown for alpha and omicron SI estimates contrary to delta (Figs. 3, 4, and 5).

From the sub-group analysis only performed for alpha variant, the highest SI were found for studies conducted in China, for those the SI values fitted with a gamma distribution, and for SI estimate with no negative value. In all subgroups, heterogeneity remained significant. For the majority of estimates, there was no publication bias (Tab. 4).

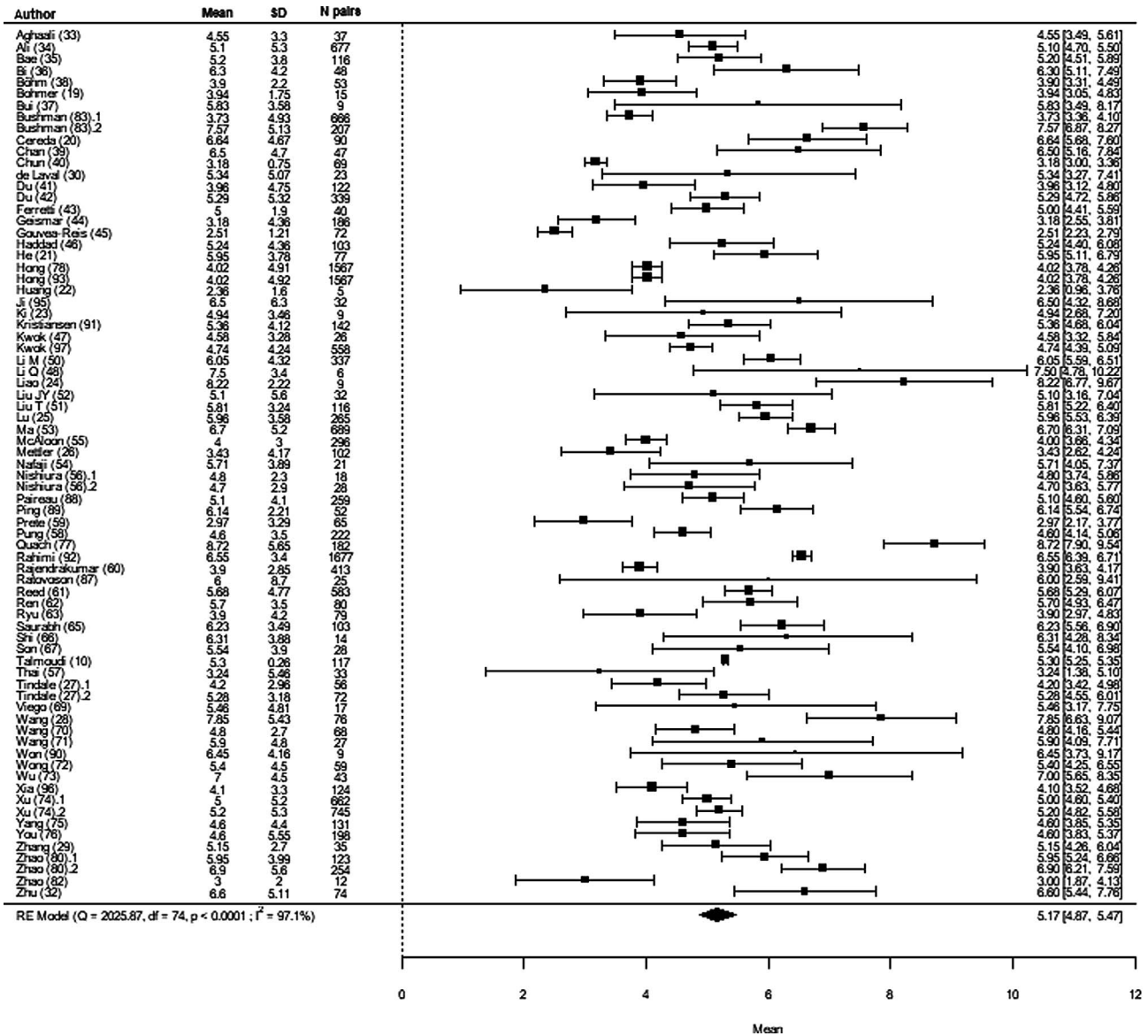
## Discussion

The meta-analysis was unable to provide a suitable estimate of SI for COVID-19 modelling purposes although its

uncertainty was reduced. The SI estimate for alpha variant was close to that found in Rai's meta-analysis, 5.19 days (95% CI = 4.37 – 6.02), and lower than those found by Zhang *et al.* and Hussein *et al.*, 5.35 (95% CI = 4.63 – 6.07) and 5.45 days (95% CI = 4.23 – 6.66), respectively [15–17]. However, like the previously published meta-analyses, our estimate was hampered by strong heterogeneity between the studies. Indeed, their SI estimates varied between 2.4 and 8.7 days. The heterogeneity of the present meta-analysis was also high,  $I^2 = 97.1\%$  as the included studies differed in their design, geographic locations, their populations, and the stage of the epidemic.

A part of this heterogeneity could be also explained by potentially large proportions of asymptomatic or presymptomatic infected individuals as reported by some studies, between 5 and 89% [98, 99]. These last proportions are more often discussed as limitations of the study rather than clearly quantified in the studies.

Individual behaviours are also greatly modified during an epidemic, people protect themselves from infection and follow the control measures advised by governments. These are factors explaining why the SI changed during the

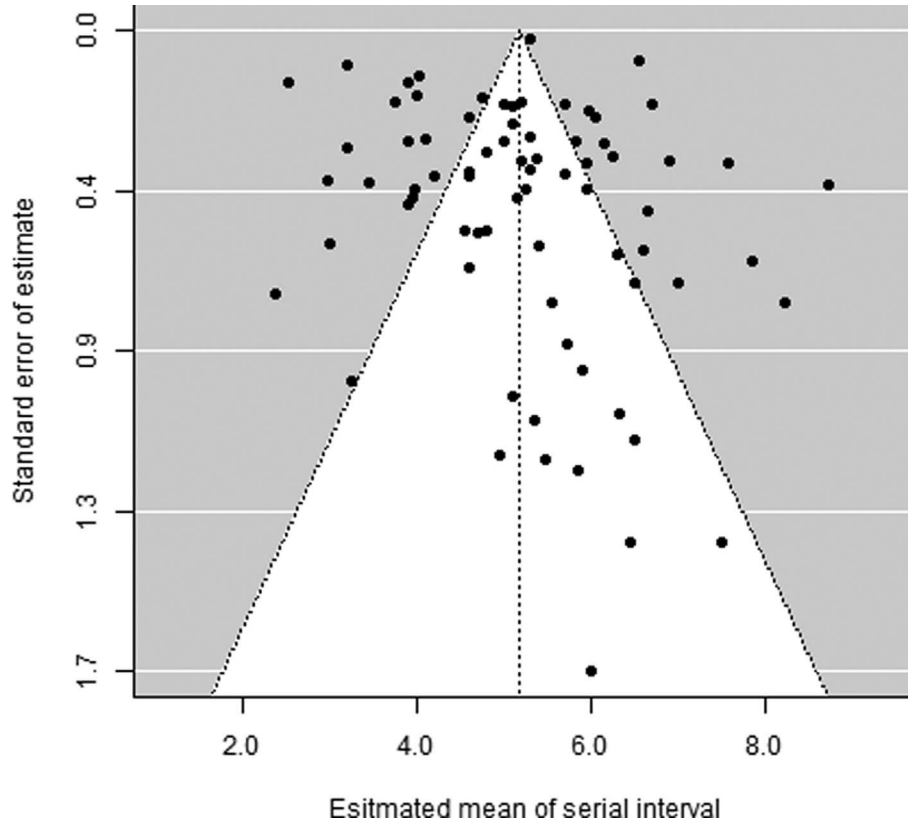


**Figure 2.** Forest plot of the 75 estimates of alpha variant’s SI included in the meta-analysis. SI: serial interval; SD: standard deviation; *N* pairs: number of pairs; RE model: random effect model; *I*<sup>2</sup>: I-square or index of heterogeneity statistic; *Q*: Cochran’s *Q* heterogeneity statistic.

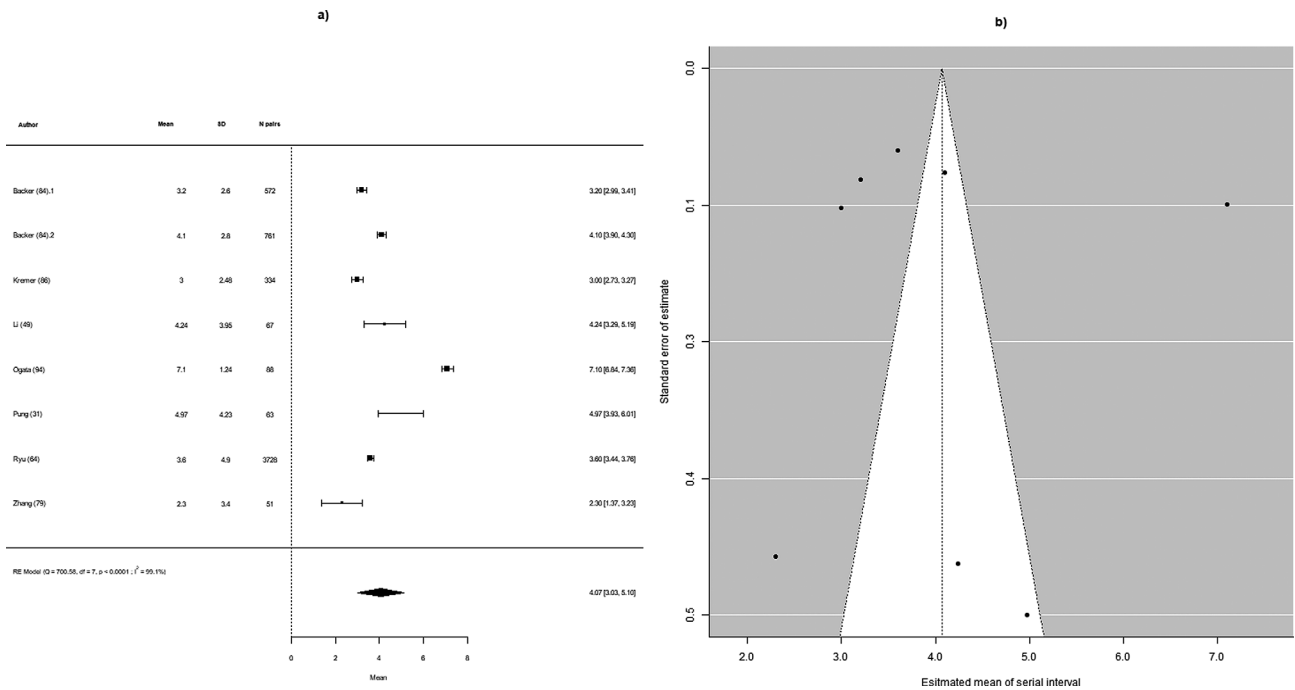
pandemic as shown by Ali *et al.* [100]. This work shows the SI decreased from 7.8 to 2.6 days during one month of the pandemic with implementation of control measures such as the delay in prophylactic isolation. This also emphasizes the importance of prophylactic isolation. Indeed, as shown by a meta-analysis, the SI correlated positively with the delay of isolation which drastically decreased after the peak of epidemic [101]. The studies included in the present meta-analysis also measured the SI at different stages of the epidemic and in various populations like households, clusters, work place. These stages were generally not clearly described probably explaining why the SI was not significantly different between studies reporting the implementation of control measures and those that did not. It was not possible to perform a sensitivity analysis using this

information. SI were also estimated according to different health information systems, which could also lead to a significant source of heterogeneity. Meta-analysis of studies with common and standardised methodology will be needed to obtain more reliable SI, for example, by sharing methodologic guidelines.

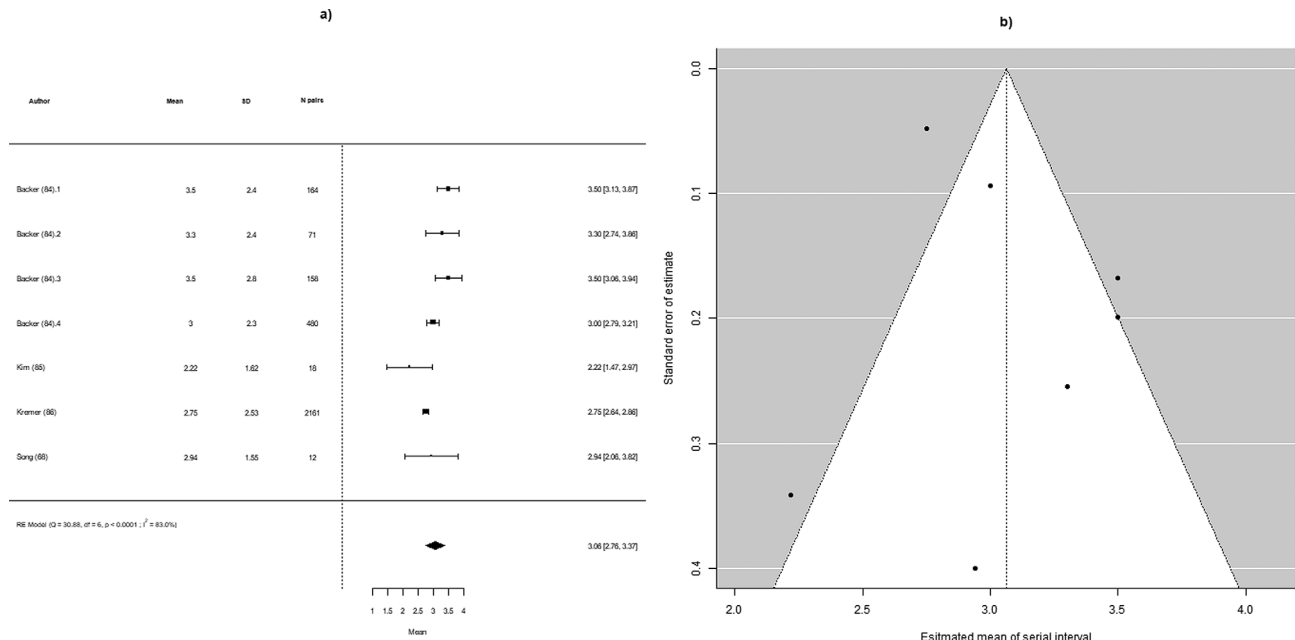
Given the differences between studies described above, a subgroup analysis was performed for the alpha variant. It was not possible to appreciably reduce the heterogeneity, especially taking into account the statistical distribution. However, it is noteworthy that SI following gamma and Weibull distributions were higher than that of the normal distribution. Therefore, the choice of the statistical distribution to fit the SI values of a given study should be taken into account. Indeed, the SI differs significantly, 4.5 days for the



**Figure 3.** Funnel plot of the 75 estimates of serial interval included in the meta-analysis for alpha variant. SI: serial interval.



**Figure 4.** Forest (a) and funnel (b) plot of the eight estimates of delta variant’s SI included in the meta-analysis. SI: serial interval; SD: standard deviation;  $N$  pairs: number of pairs; RE model: random effect model;  $I^2$ :  $I$ -square or index of heterogeneity statistic;  $Q$ : Cochran’s  $Q$  heterogeneity statistic.



**Figure 5.** Forest (a) and funnel (b) plot of the eight estimates of omicron variant’s SI included in the meta-analysis. SI: serial interval; SD: standard deviation; *N* pairs: number of pairs; RE model: random effect model; *I*<sup>2</sup>: *I*-square or index of heterogeneity statistic; *Q*: Cochran’s *Q* heterogeneity statistic.

lognormal distribution, 5.2 days for the normal one and more than 5.4 days for the Weibull and gamma distributions.

This meta-analysis gave SI estimates for variants of concern, alpha, delta and omicron. The omicron variant was significantly shorter than that of alpha, delta SI had an intermediate value. These results are surprising as the delta variant *R*<sub>0</sub> is 1.8 times that of the alpha variant and the omicron variant infectivity is 2.8 times that of delta variant, even if SI among unvaccinated delta variant was not found to be significant from that of unvaccinated non delta variant in one study [2, 7, 94]. These discrepancies can likely be explained by unvaccinated or “remaining to vaccinate” population either more exposed or more susceptible to new variants, a weaker vaccine effectiveness for delta and omicron variants, and epidemiological surveillance and contact tracing more efficient in their organisation and availability of screening tests throughout the epidemic.

Although the Egger’s test was non-significant except for SI estimate of delta variant, a selection bias of the studies cannot be excluded. It was impossible to use the SI from other publications either because of the language or the unavailability of sufficient information about SI.

Despite subgroup analysis, heterogeneity remained considerable. In a modelling context, this meta-analysis enables the use of SI values from 4.5 to 5.6 days according to the statistical distribution. After three years of the pandemic, surveillance and COVID tracing systems are working in routine and could provide SI from the field in real-time allowing a better estimate of the basic and efficient reproduction numbers. The advantage of this real-time monitoring of the SI would make it possible to follow

the evolution of the reproduction rate of the infection, the choice and rapid assessment of the control measures implemented, and the effectiveness of the vaccination campaign.

### Nomenclature of abbreviations

COVID-19	Coronavirus disease 2019
<i>df</i>	Degree of freedom
Distr.	Statistical distribution
GT	Generation time
<i>I</i> <sup>2</sup>	<i>I</i> -square or index of heterogeneity statistic
Log-N	Log-normal
MA	Meta-analysis
<i>N</i>	Number
NA	Not available
<i>Q</i>	<i>Q</i> heterogeneity statistic
RE	Random effect model
REML	Restricted Maximum-Likelihood Estimator
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard deviation
SI	Serial interval
W	Weibull distribution
$\gamma$	Gamma distribution

### Conflict of interest

Jean-François Jusot certifies that he has no financial conflict of interest in connection with this article. The author reports the following conflict of interest: Jean-François Jusot is Editorial Board member in Life Sciences-Medicine of

*4open* by EDP Sciences. This manuscript contains original material that has not previously been published.

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