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A rapid review of available evidence on the serial interval and generation time of COVID-19

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A rapid review of available evidence on the serial interval and generation time of COVID-19

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Abstract:

The serial interval is the time between symptom onsets in an infector-infectee pair. The generation time, also known as the generation interval, is the time between infection events in an infector-infectee pair. The serial interval and the generation time are key parameters for assessing the dynamics of a disease. A number of scientific papers reported information pertaining to the serial interval and/or generation time for COVID-19.

Objectives: Conduct a rapid review of available evidence to advise on appropriate parameter values for serial interval and generation time in national COVID-19 transmission models for Ireland and on methodological issues relating to those parameters.

Methods: A review of scientific literature was conducted covering the period between December 1, 2019 and April 27, 2020. Nineteen scientific papers were evaluated in detail from 27 papers that contained information on the serial interval and/or generation time for COVID-19.

Results: The mean of the serial interval ranged from 3.1 to 7.5 days, based on 22 estimates, and the median from 1.9 to 6.0 days (based on 7 estimates). Only three estimates were provided

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for the mean of the generation time. These ranged from 3.9 to 5.2 days. One estimate of 5.0 days was provided for the median of the generation time.

Discussion: The values of the estimates for serial interval and generation time are heavily influenced by the contact rates between infectious and susceptible individuals. Mitigation measures that are introduced in a country or region are of paramount importance in this regard. The serial interval estimate of 6.6 days (95% confidence interval: 0.7 – 19.0) from the paper by Cereda et al.[10] is likely to be the most relevant to European countries. National estimates should be obtained as soon as possible.

Strengths and limitations of this study

- The study provides timely information on serial interval and generation time for those involved in the development of models and in the implementation of control measures against COVID-19.
- This is a rapid review of available evidence in the scientific literature between December 1, 2019 and April 27, 2020 on the serial interval and/or the generation time and it contains the usual limitations associated with such a review.
- Eleven of the 19 papers reviewed in detail were pre-print articles.
- The statistical methods used in the different papers were not analysed in detail.

Introduction

In response to the coronavirus (COVID-19) outbreak, the Irish Epidemiological Modelling Advisory Group (IEMAG) for COVID-19 was established to assist the Irish National Public Health Emergency Team (NPHET) in their decision-making during the pandemic. A subcommittee from IEMAG was tasked with researching the various parameters, leading to the development of a series of synthesis documents relevant to the parameterisation of a COVID-19 transmission model for Ireland.

The serial interval is the time between symptom onsets in an infector-infectee pair, i.e. the interval between the onset of symptoms in an infectee and its presumed infector. This can be a negative number if the onset of symptoms in the infectee occurs prior to the onset of symptoms in the infector. The generation time, also known as the generation interval, is the time between infection events in an infector-infectee pair. The serial interval and the generation time are key parameters for assessing the dynamics of a disease. The generation time or its proxy, the serial interval, is an essential quantity for determining the reproduction number.

A number of scientific papers reported information pertaining to the serial interval and/or generation time for COVID-19. In the context of national control efforts in Ireland, our objective was to conduct a rapid review of available evidence to advise the IEMAG on the appropriate parameter values for serial interval or generation time in national COVID-19 transmission models and on methodological issues relating to those parameters. This information may also be of use to developers of models and those involved in the implementation of control programmes in other countries.

Material and methods

The guidelines in the protocol "Rapid reviews to strengthen health policy and systems: A practical guide" produced by the World Health Organization were used for carrying out this review. This can be accessed at https://apps.who.int/iris/bitstream/handle/10665/258698/9789241512763-eng.pdf;jsessionid=E033D9A6E3118CE0701D03815D63F648?sequence=1. The PRISMA-

ScR checklist (https://www.equator-network.org/wp-content/uploads/2018/09/PRISMA-ScR-Fillable-Checklist-1.pdf) for scoping reviews was also used.

We conducted a review of the literature between December 1, 2019 and April 27, 2020 for all countries. Publications on the electronic databases PubMed, Google Scholar, MedRxiv and BioRxiv were searched with the following keywords: "Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19" AND "serial interval" OR "generation time" OR "generation interval". In view of the fact that very limited information was likely to be available on serial interval and generation time for COVID-19, all relevant publications, including pre-print papers, were considered for possible inclusion. Bibliographies within these publications were also searched for additional resources and a manual search was also carried out. Summaries, citations and extracted parameters from these publications were added to a specifically designed database. The review was confined to papers that were published in the English language.

Papers that did not contain original parameter estimates of serial interval or generation time parameters were discarded. Some of the papers contained parameter estimates derived only from original data without the fitting of statistical distributions. As these papers were considered to be less useful for model development than papers containing distribution-derived estimates, they were also omitted from further consideration. Finally, those papers that did not provide a clear methodology on how the parameter estimate were obtained were also omitted.

Parameter estimates for the serial interval and the generation time, including means, medians and 95% confidence intervals, were extracted from the remaining papers. A critical appraisal was carried out on the retained papers with a view to identifying the most relevant findings, the strengths and weaknesses of each study and particularly the potential for bias.

Based on the parameters reported in the papers, we made simulations (n=10,000 samples) from serial interval or generation time distributions, we generated simulations (n=10,000 samples) based on the reported distributions and generated box-plots with the aim of allowing easy comparison between the estimated distributions from different studies. The box-plots were generated using the "ggplot2" package in the R statistical environment.

Results

Twenty seven scientific papers provided parameter estimates for the serial interval and/or the generation time. Seven of these papers[1-7] were removed as they only contained estimates derived from the original data or the methods for estimating the parameters were not clear. The paper by Zhang[8] was removed because that study used the same data as had previously been used by Du et al.[9] in estimating the serial interval.

Following the removal of these papers, 19 papers were further evaluated. The estimates for the serial interval and or generation time can be found in Table 1.

Most of the studies relate to Asian countries, particularly China. Some of the studies also used data from Germany, Italy and the USA. However, apart from the studies by Cereda et al.[10] and Lavezzo et al.[11] which deals solely with the COVID-19 outbreak in Italy, the number of datapoints from the non-Asian countries is very small.

Eleven of the papers had a pre-print status. The published studies consisted of research articles[12-14, 19], letters[15-16,9] and a brief communication[17].

All except two studies provided estimates for the population as a whole. The study by Liao et al.[18] provided estimates for adolescents and young adults. In the study by Zhao *et al*.[15], an

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estimate was provided for males as well as for the population as a whole. Some of the studies provided more than one estimate.

A total of 22 estimates were provided for the mean of the serial interval. These ranged from 3.1 to 7.5 days. A total of 7 estimates were provided for the median of the serial interval. These ranged from 1.9 to 6.0 days.

Three estimates were provided for the mean of the generation time. These ranged from 3.9 to 5.2 days. One estimate of 5.0 days was provided for the median of the generation time.

A variety of statistical distributions were fitted to the data in order to get the parameter estimates. These included, normal, lognormal, gamma and Weibull distributions. Figure 1 shows boxplots of the samples simulated from these distributions (n = 24 estimates from 18 publications). Estimates were plotted from all but the study by Liao et al.[18] included in Table 1. Pending clarification from the authors, we could not replicate the distribution described by Liao er al.[18].

Table 1. Estimates of serial interval and generation times for COVID-19 from 19 scientific papers by country. The parameter estimates relate to the serial interval unless otherwise stated

Author	Location	Mean (95% CI) (days)	Median (95% CI) (days)	Number of infector-infectee pairs
China				
Bi et al. [19]	Shenzhen, China	6.3 (5.2 – 7.6)	5.4	48
Du et al. [9]	China (outside Hubei Province)	3.96 (3.53 - 4.39)	Not provided	468
Li et al. [12]	Wuhan, China	7.50 (5.30 - 19.0)	Not provided	6
Liao et al. [18]	Chongqing University, China	6.5 (2.5 – 17.4)	1.9 (0.4 – 6.2)	12
Wang & Teunis [20]	Tianjin, China	4.8	Not provided	112 cases (Network analysis approach used)
Zhao et al. [21]	Hong Kong	4.4 (2.9 − 6.7)	Not provided	21
Zhao et al. [21]	Hong Kong	3.1 (2.0 - 5.4)	Not provided	12 infectees that matched with only one infector
Zhao et al. [15]	Hong Kong and Shenzhen	5.2	Not provided	48 pairs
Zhang et al. [14]	China (excluding Hubei Province)	5.1 (1.3 - 11.6).	Not provided	35
Du et al. [22]	China (86 cities)	5.29 (4.72 - 5.86)	Not provided	339
Taiwan				
Cheng et al. [23]	Taiwan,	7.0 (3.7 – 13.2)	Not provided	12
Italy				

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Cereda et al. [10]	Italy	6.6 (0.7 – 19.0)	5.5	90
Lavezzo et al. [11]	Italy	6.9 (2.6 - 13.4)	Not provided	120
Combination of countries				
Ferretti et al. [13]	China, Taiwan, South Korea, Vietnam, Singapore Germany, Italy	**Generation time** 5.0	**Generation time** 5.0	40
Ganyani et al. [24]	Singapore	**Generation time** 5.20 (3.78 – 6.78) Serial interval 5.21 (-3.35 – 13.94)	Not provided	91
Ganyani et al. [24]	Tianjin, China	**Generation time** 3.95 (3.01 – 4.91) Serial interval 3.95 (-4.47 – 12.51)	Not provided	135
He et al. [17]	China, Taiwan, Japan, Vietnam Malaysia, Singapore, USA	5.8 (4.8 - 6.8)	5.2 (4.1 - 6.4)	77
Ma et al. [25]	China (including Hong Kong, Macau, Taiwan), Japan, Singapore, South Korea, Malaysia, Vietnam, Germany	6.7 (6.31 - 7.10)	6.0	689
Nishiura et al. [26]	China, Taiwan, South Korea, Vietnam, Singapore Germany	4.7 (3.7 – 6.6)	4.0 (3.1 - 4.9)	28
Nishiura et al. [26]	China, Taiwan, South Korea, Vietnam, Singapore Germany	4.8 (3.8 - 6.1)	4.6 (3.5 - 5.9).	Estimate based only on 18 pairs where the infector infectee relationship was considered to be most reliable.
Tindale et al. [27]	Singapore,	4.56 (2.69 - 6.42)	Not provided	93
	Tianjin, China	4.22 (3.43 - 5.01)	Not provided	125
Wu et al. [16]	China, Taiwan, Singapore, Vietnam, Malaysia, USA	7.0 (5.8 – 8.1)	Not provided	43

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Discussion

Our scientific understanding of novel emerging pathogens is dynamic and constantly evolving as new information emerges. Early estimates of key parameters are vital in assessing the natural history of a novel emerging infectious disease such as COVID-19 and the likely impact of control measures. Pre-print papers are a valuable source of information in this regard with the proviso that the quality of these will be unclear given the lack of peer review. All the studies reviewed here were also compromised by constraints that are present at the beginning of a new disease, including the lack of specific surveillance systems, information gathering systems and precise case definitions.

Range of estimates obtained

The papers reviewed provide initial parameter estimates for the serial interval and/or the generation time for COVID-19. Most of the estimates were for the serial interval rather than the generation time because in real life infection times are rarely available, so generation times cannot be estimated. Instead, typically, the onset of symptoms is observed. The estimates for the mean of the serial interval ranged from 3.1 to 7.5 days. There are a number of reasons why the estimates are wide ranging. The interval between symptoms in an infector-infectee pair will be strongly influenced by the level of social contact. This will vary widely between different countries and indeed within countries. The impact of mitigation measures is also likely to be a key factor. The implementation of control measures will reduce the opportunity for an infected individual to transmit the disease to a susceptible individual. Consequently, the serial interval is likely to decrease during the course of an epidemic. Zhao *et al.*[15] showed that the serial interval decreased by 6.2% per day (95% CI, 0.4−11.6%) from January 10 to February 2 in Hong Kong and Shenzhen. They attributed this to the strengthening of the public health control measures over time. Stratified results produced by Bi et al.[19] showed that if the infector was isolated less than 3 days after symptom onset, the average serial interval was 3.6 days, increasing to 8.1 days if the infector was isolated on the third day after symptom onset or later. Du et al.[9] pointed out that the time between successive cases contracts around the epidemic peak and that this may have influenced their estimates. On the other hand, in a study of the Po' municipality of Italy, Lavezzo et al.[11] estimated that the serial interval increased from 6.90 days before the implementation of comprehensive control measures to 10.12 days after the implementation of these measures. Possible reasons for this increase are not discussed in the paper.

The value of estimating the serial interval, generation time and other key parameters at the start of an epidemic was emphasized by a number of authors. As highlighted by Bi et al.[19], the study of an emerging pathogen at the time of its introduction provides a unique opportunity to characterize its transmission and natural history. In particular, it is possible to make assumptions about when and where cases were likely infected that are more difficult when the pathogen is widespread. Furthermore, during these early phases, uninfected and asymptomatic contacts are often closely tracked, providing critical information on transmission and natural history.

Methods used for estimating the serial interval and the generation time

The estimation of the serial interval and the generation time parameters for COVID-19 presented a number of other challenges and the potential for obtaining biased estimates, as was acknowledged by a number of authors. We identified a number of specific issues in the papers that we reviewed, including the following:

- In clustered outbreaks, which is crucial to estimating the serial interval, the order of transmission (i.e., who is infector and who is infectee) can easily be mistaken. Also, given the possibility of pre-symptomatic and asymptomatic transmission particularly as the epidemic progresses, it can be difficult to determine the source of infection with certainty. In view of this, it is important that there is a well-defined methodology for determining the serial interval/generation time. Some of the studies did not describe how the order of

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transmission issue was handled. In other studies, efforts were made to deal with the difficulties related to the order of transmission and the true source of infection. Nishiura et al.[26] provided separate estimates of the serial interval parameter distribution for "18 most certain pairs". Zhao et al.[21] provided separate estimates of the serial interval parameter distribution for "infectees with only one infector". Tindale et al.[27] used a mixture model approach for serial intervals to avoid assuming that the presumed infector is always the true infector. Ganyani et al.[24] used a Markov chain Monte Carlo (MCMC) approach for the same purpose. Ma et al.[25] made an effort to overcome this issue by setting out a clear methodology for ensuring that the order of transmission was correct.

- Generally, publicly available datasets were used in the studies. Zhao et al.[21] mention the fact that the lack of information in publicly available datasets makes it difficult to fully interpret the data. Also as mentioned by Du et al.[9], if the data are restricted to online reports of confirmed cases, they might be biased toward more severe cases in areas with a high-functioning healthcare and public health infrastructure. The rapid isolation of such case-patients might prevent longer serial intervals, potentially shifting the estimates downward compared with serial intervals that might be observed in an uncontrolled epidemic. In general, it is likely that less severe and asymptomatic cases are underrepresented in the datasets examined.

- In some of the studies, infector-infectee pairs from a variety of countries were used to estimate the serial interval. The number of pairs from some countries were very small. For example, in the paper by He et al.[17], of the 77 pairs used, one was from the USA, one was from Singapore, two were from Malaysia, two were from Vietnam, four were from Taiwan, 12 were from Japan and the rest were from various parts of China. These cannot be considered representative of the countries from which they were drawn. The same conclusion applies to the studies by Ma et al.[25], Ferretti et al.[13], Nishiura et al.[26] and Wu et al.[16]. In other studies, pairs were drawn from particular countries or regions during particular time periods. These may have been more representative of the population from which they were drawn. However, in some cases, e.g. Li et al.[12], the number of pairs selected was very small compared to the total number of cases included in the study, again calling into question the representativeness of the pairs used to estimate the serial interval or generation time.

- The case data, including the identity of each infector and the timing of symptom onset, was based on individual recollection of past events. Du et al.[9] highlight the fact that if recall accuracy is impeded by time or trauma, case-patients might be more likely to attribute infection to recent encounters (short serial intervals) over past encounters (longer serial intervals). Therefore, it is likely that recall bias is present in all of the studies and it is not possible to distinguish the level of bias present in the different studies.

- The number of pairs used to estimate the serial interval varied considerably. Only six pairs were used in the study by Li et al.[12]. In contrast, a total of 468 pairs were used in the study by Du et al.[9] and 689 pairs were studied by Ma et al.[25]. However, the value of increased sample size must be evaluated against the difficulty of ensuring accuracy of the infector infectee relationship as the sample size increases. Lavezzo et al.[11] indicate that 120 pairs were used in their study but there is a lack of clarity on how this number was obtained.

- Cheng et al.[23] state that 12 pairs were used in their estimation of the serial interval. Figure 1 of their paper indicates that these included three cases with asymptomatic infection. It is not clear how these cases were handled in estimating the series interval. Moreover, pairs in which the exposure date of the infectee was earlier than the date of symptom onset of the infector were excluded from the study.

- In the study by Zhang et al.[14] and in other studies, the serial interval was estimated from cases in household clusters. The authors make the point that estimations based on household clusters may be 20% shorter than the true value of the serial interval.

- Zhao et al.[21] highlighted the possibility of right truncated selection bias, i.e. the possibility of infector-infectee pairs with longer SI being under-represented in the sample

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due to short investigation period. To minimise this possibility, the set that last date of onset symptoms for infectees as 16 days before the end of the study investigation point.

It should be borne in mind that some of the studies may have been using the same case data in estimating the serial interval or the generation time. For example, the studies by Tindale et al.[27] and Ganyani et al.[24] were carried out in Singapore and Tianjin over the same time period. Consequently, the estimates cannot be considered to be fully independent of each other. Likewise, it is possible that there was an overlap in the case data used by Du et al.[9] and Du et al.[22] as these studies were carried out by the same group of authors.

Statistical distributions used in estimating serial interval and generation time

In most of the studies, a gamma or Weibull distribution was fitted to the data to estimate the serial interval distribution. A problem with these distributions is that negative values of the serial interval (that is, when symptoms manifest in the infectee before the infector) cannot be included. In the study by Du et al.[9], 59 of the 468 reports indicate that the infectee had symptoms earlier than the infector. Du et al.[9] and Du et al.[22] cautioned against using distributions that excluded the non-positive data and making assessments and projections based on the truncated data. In their view, the normal distribution provides the best fit for the full dataset (shifted or not) and they recommended this distribution for future epidemiologic assessments. This approach was also used by Ma et al.[25] and Tindale et al.[27]. In Ma et al.[25] study, shifted lognormal, Weibull and gamma distributions were also fitted to the data for the serial interval.

Relationship between the serial interval, generation time and the reproduction number

The generation time is used to estimate the reproduction number. Because of the difficulty in estimating the generation time, the serial interval is often used as a surrogate for the generation time. The serial interval and the generation time will have the same mean value provided that the incubation times of the infectee and infector are independent and identically distributed but their variances are expected to be different. Britton and Scalia-Tomba[28] highlighted the fact that the difference in variance between the serial and generation time can lead to biased estimates of the reproduction number. More specifically, when the serial interval distribution has a larger variance than the generation time distribution, using the serial interval as a proxy for the generation time will lead to an underestimation of the basic reproduction number. Ganyani et al.[24] provided estimates for both parameters based on data from Singapore and China and described a method for obtaining an unbiased estimate of the generation time.

Conclusion

Overall, the availability of parameter estimates and information on the serial interval and generation time of the COVID-19 virus is very valuable at such an early stage of the pandemic. However, the estimations are very dependent on the specific factors that applied at the time that the data was collected, including the level of social contact. Consequently, the estimates may not be entirely relevant to other environments. The serial interval estimate of 6.6 days (CI 0.7 – 19.0) from the paper by Cereda et al.[10] is likely to be the most relevant to European countries. National estimates should be obtained as soon as possible. In light of the biases that could occur, the serial interval and or the generation time should be estimated from early cases and careful consideration should be given to the methodology that is used.

Competing interests: All authors have completed the ICMJE 508 uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in

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the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Authors contributions: Studies were selected and screened initially by AC, KH and FB using search terms outlined the methodology section, with parameters identified and recorded. This was reviewed and supplemented by a manual search by JG, again with parameters identified and recorded. JG conducted the eligibility screening of shortlisted studies, extracted the data and conducted the review with input from all authors. MC generated Figure 1. SJM, MC, ABC, AB, AWB, EAL and CGM undertook interim reviews. All authors read and approved the final manuscript.

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

Data sharing statement: All data relevant to the study are included in the article. All data are publicly available. Statistical code and datasets are available from the corresponding author at johnmgriffin@live.com.

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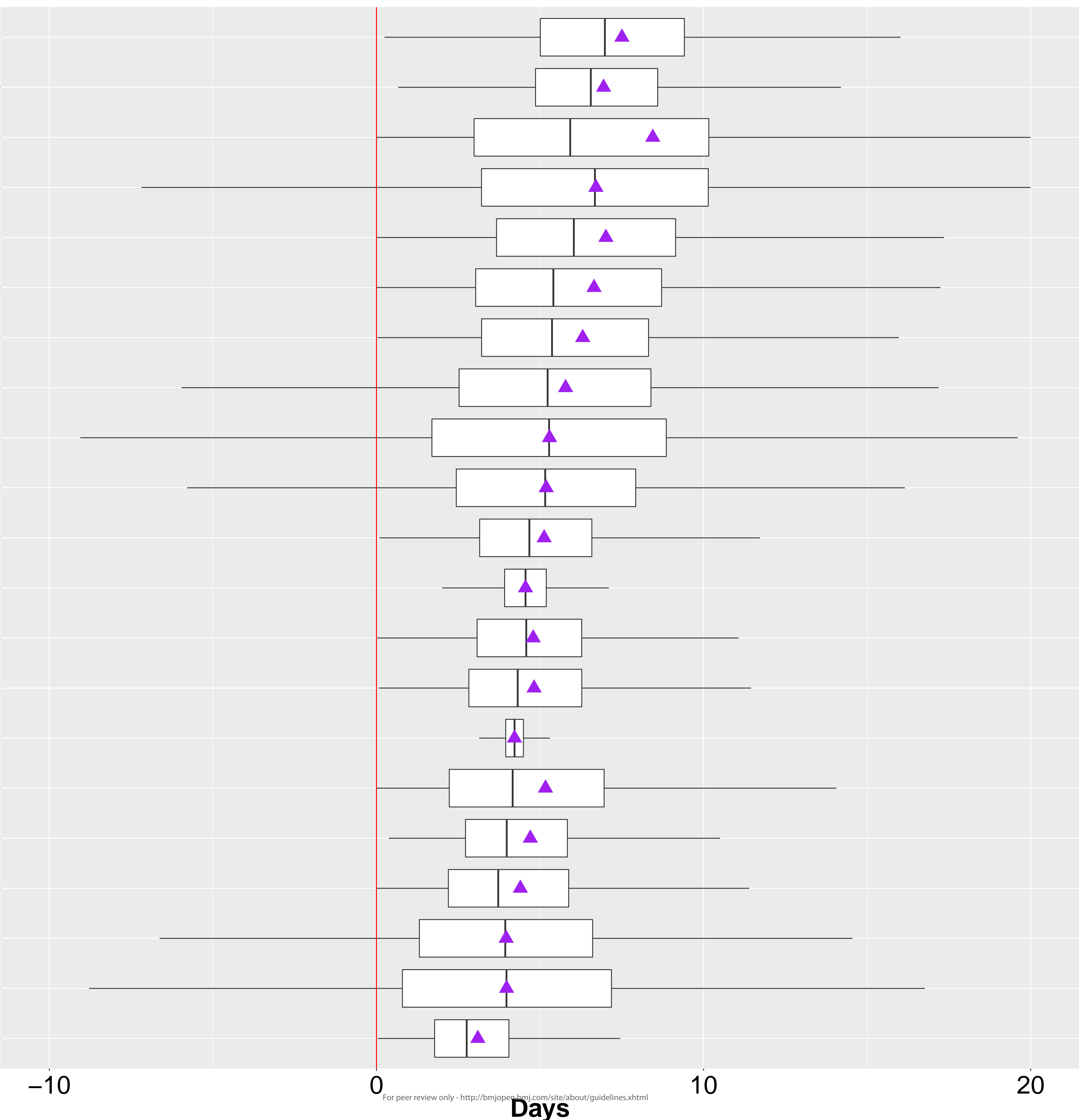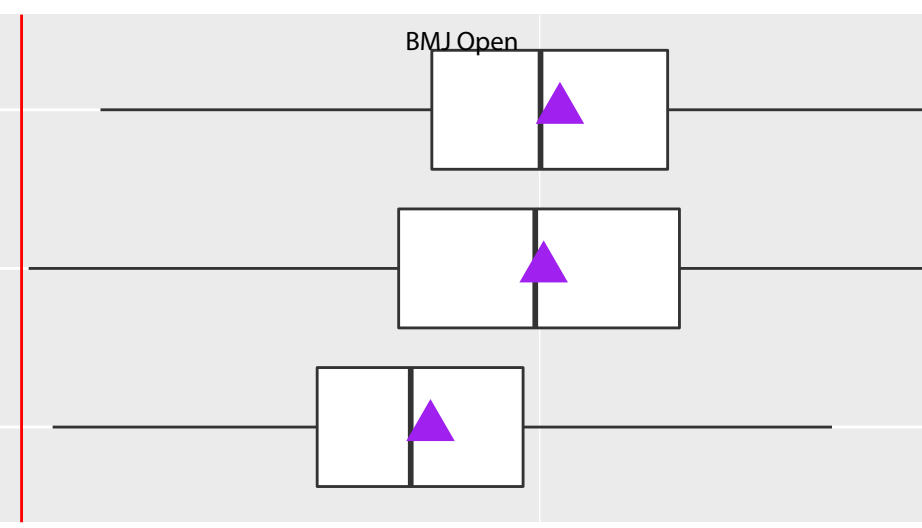9   Du Z, Xu X, Wu Y, et al. Serial Interval of COVID-19 among publicly reported confirmed cases. *Emerg Infect Dis*. 2020 June. https://doi.org/10.3201/eid2606.200357.

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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.	
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.	
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.	
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.	
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.	
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.	
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.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
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.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
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).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

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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.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
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.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
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.	
Limitations	20	Discuss the limitations of the scoping review process.	
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.	
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.	

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).

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A rapid review of available evidence on the serial interval and generation time of COVID-19

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A rapid review of available evidence on the serial interval and generation time of COVID-19

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Abstract:

The serial interval is the time between symptom onsets in an infector-infectee pair. The generation time, also known as the generation interval, is the time between infection events in an infector-infectee pair. The serial interval and the generation time are key parameters for assessing the dynamics of a disease. A number of scientific papers reported information pertaining to the serial interval and/or generation time for COVID-19.

Objective: Conduct a review of available evidence to advise on appropriate parameter values for serial interval and generation time in national COVID-19 transmission models for Ireland and on methodological issues relating to those parameters.

Methods: We conducted a rapid review of the literature covering the period January 1, 2020 and August 21, 2020, following pre-defined eligibility criteria. Forty scientific papers met our inclusion criteria and were included in the review.

Results: The mean of the serial interval ranged from 3.03 to 7.6 days, based on 38 estimates, and the median from 1.0 to 6.0 days (based on 15 estimates). Only three estimates were provided for the mean of the generation time. These ranged from 3.95 to 5.20 days. One estimate of 5.0 days was provided for the median of the generation time.

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Discussion: Estimates of the serial interval and the generation time are very dependent on the specific factors that apply at the time that the data are collected, including the level of social contact. Consequently, the estimates may not be entirely relevant to other environments. Therefore, national estimates should be obtained as soon as possible. Careful consideration should be given to the methodology that is used. Real-time estimations of the serial interval/generation time, allowing for variations over time, may provide more accurate estimates of reproduction numbers than using conventionally fixed serial interval/generation time distributions.

Strengths and limitations of this study

- The study provides timely information on serial interval and generation time for those involved in the development of models and in the implementation of control measures against COVID-19.
- This is a rapid review of available evidence in the scientific literature between January 1, 2020 and August 21, 2020 on the serial interval and the generation time and it contains the usual limitations associated with such a review.
- The statistical methods used in the different papers were not analysed in detail.

Introduction

In response to the coronavirus (COVID-19) outbreak, the Irish Epidemiological Modelling Advisory Group (IEMAG) for COVID-19 was established to assist the Irish National Public Health Emergency Team (NPHET) in their decision-making during the pandemic. A subcommittee from IEMAG was tasked with researching the various parameters, leading to the development of a series of synthesis documents relevant to the parameterisation of a COVID-19 transmission model for Ireland.

The serial interval is the time between symptom onsets in an infector-infectee pair, i.e. the interval between the onset of symptoms in an infectee and its presumed infector. This can be a negative number if the onset of symptoms in the infectee occurs prior to the onset of symptoms in the infector. The generation time, also known as the generation interval, is the time between infection events in an infector-infectee pair. The serial interval and the generation time are key parameters for assessing the dynamics of an infectious disease, and the generation time, or its proxy the serial interval, is an essential quantity for estimating the reproduction number.

A number of scientific papers reported information pertaining to the serial interval and/or generation time for COVID-19. In the context of national control efforts in Ireland, our objective was to conduct a rapid review of available evidence to advise the IEMAG on appropriate parameter values for serial interval and generation time in national COVID-19 transmission models and on methodological issues relating to those parameters. This information may also be of use to developers of models and those involved in the implementation of control programmes in other countries.

Material and methods

The guidelines in the protocol "Rapid reviews to strengthen health policy and systems: A practical guide" produced by the World Health Organization were used for carrying out this review. This can be accessed at https://apps.who.int/iris/bitstream/handle/10665/258698/9789241512763-eng.pdf;jsessionid=E033D9A6E3118CE0701D03815D63F648?sequence=1. The PRISMA-ScR checklist (https://www.equator-network.org/wp-content/uploads/2018/09/PRISMA-ScR-Fillable-Checklist-1.pdf) for scoping reviews was also used.

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We conducted a review of the literature between January 1, 2020 and August 21, 2020 for all countries. Publications in the electronic databases Medline, Embase and PubMed, were searched with the following keywords: "Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19" AND "serial interval" OR "generation time" OR "generation interval". Bibliographies within these publications were searched for additional papers, and a manual search was also carried out. Summaries, citations and extracted parameters from these publications were added to a specifically designed database. The review was confined to papers, including pre-proofs and accepted manuscripts, that were published in recognised journals in the English language. Data were managed during the review using Covidence (Melbourne, Australia).

Papers that did not contain original parameter estimates of serial interval or generation time parameters were discarded.

Parameter estimates for the serial interval and the generation time, including means, medians and 95% confidence intervals, were extracted from the remaining papers. A critical appraisal was carried out on the retained papers with a view to identifying the most relevant findings, the strengths and weaknesses of each study and particularly the potential for bias.

Each paper was reviewed by two authors (JG and MC) to extract the parameters required to recreate the statistical distributions described. If a statistical distribution was not fitted, or could not be recreated, the underlying serial interval data upon which the estimates reported in paper were based was extracted if available. The extracted serial interval and generation time data were summarised by box- and ridge- plots. All analyses were performed in the R statistical environment. (R version 3.6.1, https://www.r-project.org/). Extracted data and R code to generate the plots are available at https://github.com/miriamcasey/covid-19_presymptomatic_project.

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

Results

Seventy four papers were identified by the literature search. Of these, 34 papers met the eligibility criteria, and a further 6 papers were identified by searching the bibliographies of these papers or through manual searches, resulting in 40 papers being included in the review. The detailed selection process is illustrated in Figure 1.

 Insert Figure 1 here

Of the shortlisted studies, most relate to Asian countries, particularly China. Apart from the study by Lavezzo et al. [1] which deals solely with the COVID-19 outbreak in Italy, the study by Prete et al. [2] from Brazil, and the study by Böhmer et al. [3] from Germany, the number of datapoints from the non-Asian countries was very small.

The published studies consisted of twenty-eight research articles [1, 3-29], four letters [2, 30-32], two reports [33, 34], a brief communication [35], three accepted manuscripts [36, 37, 38] and two pre-proofs [39, 40].

All except two studies provided estimates for people of all age groups. Liao et al. [34] provided estimates for adolescents and young adults. However these estimates, particularly the estimate of the median, do not seem to be consistent with the individual serial interval values that can be extracted from Figure 2 of the paper. The study by Huang et al. [27] provided estimates on

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people aged 16-23. In the study by Zhao et al. [32], an estimate was provided for males as well as for the population as a whole. Some studies provided more than one estimate.

Different methods were used to describe the serial interval and the generation time data. Thirty studies [1-2, 4-8, 10-11, 13-25, 30-31, 33-37, 39] assumed that the observed sample of serial interval and/or generation time came from an overall distribution in the population that could be modelled using one of a number of probability distributions. Normal, lognormal, gamma and Weibull distributions were used. Statistical distributions were not fitted to the data in the other ten studies. In six of these [3, 26-29, 38], varying degrees of summary statistics such as the mean, median, quantiles are provided. In two studies [9,40], summary statistics are provided and confidence intervals were generated using boot-strapping. Zhao et al. [32] reported a mean value for the serial interval using a regression model. In the study by Qin et al. [12] summary statistics and confidence intervals are provided but the method used for obtaining the confidence intervals are unclear.

The estimates for the serial interval and/or generation time can be found in Table 1. A total of 38 estimates were provided for the mean of the serial interval. These ranged from 3.03 [2] to 7.6 [9] days. A total of 15 estimates were provided for the median of the serial interval. These ranged from 1.0 [27] to 6.0 [9] days.

Three estimates were provided for the mean of the generation time. These ranged from 3.95 [23] to 5.20 [23] days. One estimate of 5.0 days [22] was provided for the median of the generation time.

Supplementary Table 1 summarises the parameters and data that it was possible to extract from the 40 papers included in the review. For 33 estimates from 27 papers, we were able to recreate the distributions described for serial interval or generation time , draw samples (n=10000) from them, and, from the samples, generate with summary statistics consistent with what was reported in the papers. These simulated distributions are shown in the boxplot in Figure 2.

Two further papers [34,39] provided sufficient parameters to recreate serial interval distributions but we could not replicate summary statistics reported by the authors. From these papers, we also extracted underlying serial interval data from the transmission pairs used, but we could not replicate their summary statistics.

One further paper [16] reported fitting a gamma distribution to their serial interval data but did not provide sufficient information to simulate this distribution. We extracted underlying serial interval data from a figure in their paper for a portion of the transmission pairs used.

A further ten papers [3,9,12,26,27,28,29,32,38,40] reported serial intervals but did not report fitting statistical distributions to them. It was possible to extract underlying serial interval data from seven of these papers [3,9.26,27,28,32,40]. We could replicate summary statistics for all except Ki [26] .

For three papers from which we were unable to extract either sufficient parameters to simulate distributions, or underlying serial interval data [12,29,38], two [29,38] supplied histograms representing their distributions in their papers.

Supplementary Figure 1 is a ridge plot describing the 33 simulated distributions from the 27 papers where this was possible, alongside the underlying data from six further papers [3,9,27,28,32,40] where we could replicate the summary statistics by summarising extracted underlying data.

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Supplementary Figure 2 is a ridge plot describing the 33 simulated distributions alongside all available underlying data from ten further papers, including the four [16,26,34,39] for which we could not replicate reported summary statistics.

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Table 1. Estimates of serial interval and generation times for COVID-19 from 40 scientific papers, by country. All estimates relate to serial interval unless otherwise indicated

Country and author	Location	Mean (95% CI) (days)	Median (95% CI) (days)	Number of infector-infectee pairs
China				
Li et al. [4]	Wuhan	7.50 (5.30 - 19.0)	Not provided	6
Wang et al. [5]	Wuhan	5.2 (3.8 - 6.8)	Not provided	9
Yang et al. [6]	Hubei Province	Not provided	4.6 (3.7 – 5.5)	131
Du et al. [31]	Outside Hubei Province	3.96 (3.53 - 4.39)	Not provided	468
Ren et al. [7]	Outside Hubei Province	5.7 (4.7 – 6.8)	Not provided	80
Zhang et al. [8]	Outside Hubei Province	5.1 (1.3 - 11.6)	Not provided	35
Ali et al. [33]	Outside Hubei Province	5.1 (4.7 – 5.5)	Not provided	677
Xu et al. [37]	Outside Hubei Province	5.1 (4.7 -5.5)	Not provided	1407
You et al. [29]	Outside Hubei province	4.6	4.0	198
Huang et al. [27]	Outside Wuhan		1.0	7
Wang et al. [9]	Beijing	7.6 (6.4 – 8.9)	6.0	76
Bi et al. [10]	Shenzhen	6.3 (5.2 – 7.6)	5.4	48
Wang et al. [11]	Shenzhen	5.9 (3.9 – 9.6)	Not provided	27
Qin et al. [12]	Lu'an	6.5 (4.8 – 8.2)	Not provided	32
Liao et al. [34]	Chongqing University	6.5 (2.5 – 17.4)	1.9 (0.4 – 6.2)	12
Wang & Teunis [13]	Tianjin	4.8	Not provided	Not clear
Wu et al. [14]	Zhuhai	6.3	5.1 (4.3 – 6.2)	48
Zhao et al. [32]	Hong Kong and Shenzhen	5.2	Not provided	48 pairs
Kwok et al. [15]	Hong Kong	4.77 (3.47 – 6.90)	Not provided	26
Kwok et al. [15]	Hong Kong	6.23 (4.71 – 8.63)	Not provided	Estimate based only on 17 pairs where the infector infectee relationship was considered to be most reliable.
Bao et al. [16]	Not clear	4.4 (3.3 - -5.4)	Not provided	54
Taiwan				
Liu [38]	All	5.1	4	31
Singapore				

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Pung et al. [28]	All	Not provided	Not provided	3 (range 3-8 days)
South Korea				
Chun et al. [39]	All	Not provided	3.56 (2.72 – 4.44)	69
Bae et al. [17]	All	5.2 (SD ± 3.8)	Not provided	Not clear
Mettler et al. [40]	All	3.43 (2.62 - 4.24)	Not provided	102
Son et al. [18]	Busan	5.54 (4.08- 7.01)	Not provided	28
Ki [26]	South Korea	6.6,	4.0	12
Vietnam				
Pham et al. [36]	All	3.24 (1.38 – 5.10)	Not provided	33
Brunei				
Wong et al. [19]	All	5.4 (4.3 – 6.5)	Not provided	59
Iran				
Aghaali et al. [20]	Qom	4.55	Not provided	37
Najafi et al. [21]	Western Iran	5.71	Not provided	21
Brazil				
Prete et al. [2]	All	3.03 (2.26 – 3.73)	3.00	65
Italy				
Lavezzo et al. [1]	Municipality of Vo'	7.2 (5.9 – 9.6)	Not provided	Not clear
Germany				
Bohmer et al. [3]	Germany	Not provided	4.0	11
Combination of countries				
Ferretti et al. [22]	China, Taiwan, South Korea, Vietnam, Singapore Germany, Italy	Generation time: 5.0	Generation time: 5.0	40
Ganyani et al. [23]	Singapore	5.21 (-3.35 – 13.94) Generation time: 5.20 (3.78 – 6.78)	Not provided	91
Ganyani et al. [23]	Tianjin, China	3.95 (-4.47 – 12.51) Generation time: 3.95 (3.01 – 4.91)	Not provided	135
He et al. [35]	China, Taiwan, Japan, Vietnam Malaysia, Singapore, USA	5.8 (4.8 - 6.8)	5.2 (4.1 - 6.4)	77
Nishiura et al. [24]	China, Taiwan, South Korea, Vietnam, Singapore Germany	4.7 (3.7 – 6.6)	4.0 (3.1 - 4.9)	28
Nishiura et al. [24]	China, Taiwan, South Korea, Vietnam, Singapore Germany	4.8 (3.8 - 6.1)	4.6 (3.5 - 5.9).	Estimate based only on 18 pairs where the infector infectee relationship was

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				considered to be most reliable.
Tindale et al. [25]	Singapore,	4.17 (2.44 - 589)	Not provided	56
	Tianjin, China	4.31 (2.91 - 5.72)	Not provided	72
Wu et al. [30]	China, Taiwan, Singapore, Vietnam, Malaysia, USA	7.0 (5.8 – 8.1)	Not provided	43

Insert Figure 2 here

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Discussion

Our scientific understanding of novel emerging pathogens is dynamic and constantly evolving as new information emerges. Early estimates of key parameters are vital in assessing the natural history of a novel emerging infectious disease such as COVID-19 and the likely impact of control measures. All the studies reviewed here were compromised by constraints that are present at the beginning of a new disease, including the lack of specific surveillance systems, information gathering systems and precise case definitions.

Range of estimates obtained

The papers in this review provide initial parameter estimates for serial interval and/or generation time for COVID-19. Most of the estimates were for serial interval rather than generation time because infection times are difficult to measure and are generally not available. Consequently, data on generation times are rarely available. Instead, typically, the onset of symptoms is observed. The estimates for the mean of the serial interval ranged from 3.03 [2] to 7.6 [9] days. There are a number of reasons why the estimates are wide ranging. The interval between symptoms in an infector-infectee pair will be strongly influenced by the level of social contact. This will vary widely between different countries and indeed within countries. The impact of mitigation measures is also likely to be a key factor. The implementation of control measures will reduce the opportunity for an infected individual to transmit infection to a susceptible individual. Consequently, the serial interval is likely to decrease during the course of an epidemic. Zhao et al. [32] showed that the serial interval decreased by 6.2% per day (95% CI, 0.4−11.6%) from January 10 to February 2 in Hong Kong and Shenzhen, which they attributed to the strengthening of public health control measures over time. They also showed that male infectors were associated with shorter serial intervals than female infectors.

Ali et al. [33] showed that the serial interval shortened considerably from 7.8 days to 2.6 days over a period of one month. They attributed this to enhanced non-pharmaceutical interventions, in particular case isolation. In a study of the Po' municipality of Italy, Lavezzo et al. [1] estimated that the serial interval reduced from 7.6 days before the implementation of comprehensive control measures to 6.2 days after the implementation of these measures. The mean serial interval over the entire study period was 7.2 days.

Stratified results produced by Bi et al. [10] showed that if the infector was isolated less than 3 days after symptom onset, the average serial interval was 3.6 days, increasing to 8.1 days if the infector was isolated on the third day after symptom onset or later. Du et al. [31] pointed out that the time between successive cases contracts around the epidemic peak and that this may have influenced their estimates.

The value of estimating the serial interval, generation time and other key parameters at the start of an epidemic was emphasised by a number of authors. As highlighted by Bi et al. [10], the study of an emerging pathogen at the time of its introduction provides a unique opportunity to characterise its transmission and natural history. Following initial introduction, it is possible to make robust assumptions about when and where cases were likely infected. This is often more difficult when the pathogen is widespread. Furthermore, during these early phases, uninfected and asymptomatic contacts are often closely tracked, providing critical information on transmission and natural history.

Ali et al. [33] showed that the use of real-time estimations of the serial interval, which allows for variations over time, provides more accurate estimates of reproduction numbers than using conventionally fixed serial interval distributions.

Methods used for estimating the serial interval and the generation time

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The estimation of the serial interval and the generation time parameters for COVID-19 presented a number of other challenges and the potential for obtaining biased estimates, as was acknowledged by a number of authors. We identified a number of specific issues in the papers that we reviewed, including the following:

- In clustered outbreaks, which is crucial to estimating the serial interval, the order of transmission (i.e., who is infector and who is infectee) can easily be mistaken. Also, given the possibility of pre-symptomatic and asymptomatic transmission, particularly as the epidemic progresses, it can be difficult to determine the source of infection with certainty. In view of this, it is important that there is a well-defined methodology for estimating the serial interval/generation time. Some of the studies did not describe how the order of transmission issue was handled. In other studies, efforts were made to deal with the difficulties related to the order of transmission and the true source of infection. Nishiura et al. [24] provided separate estimates of the serial interval parameter distribution for "18 most certain pairs". A similar approach was taken by Kwok et al. [15]. Tindale et al. [25] used a mixture model approach for serial intervals to avoid assuming that the presumed infector is always the true infector. Ganyani et al. [23] used a Markov chain Monte Carlo (MCMC) approach for the same purpose. Wang et al. [11] allowed for the possibility of multiple infectors of a single infectee by using an interval censored likelihood function.

- Generally, publicly available datasets were used in the studies under review. Du et al. [31] mention the fact that if the data are restricted to online reports of confirmed cases, they might be biased toward more severe cases in areas with a high-functioning healthcare and public health infrastructure. The rapid isolation of such case-patients might prevent longer serial intervals, potentially shifting the estimates downward compared with serial intervals that might be observed in an uncontrolled epidemic. In general, it is likely that less severe cases are underrepresented in the datasets examined.

- In some of the studies, infector-infectee pairs from a variety of countries were used to estimate the serial interval. The number of pairs from some countries were very small. For example, in the paper by He et al. [35], of the 77 pairs used, one was from the USA, one was from Singapore, two were from Malaysia, two were from Vietnam, four were from Taiwan, 12 were from Japan and the rest were from various parts of China. These cannot be considered representative of the countries from which they were drawn. The same conclusion applies to the studies by Ferretti et al. [22], Nishiura et al. [24] and Wu et al. [30]. In other studies, pairs were drawn from particular countries or regions during particular time periods. These may have been more representative of the population from which they were drawn. However, in some cases, e.g. Li et al. [4], the number of pairs selected was very small compared to the total number of cases included in the study, again calling into question the representativeness of the pairs used to estimate the serial interval or generation time.

- The case data, including the identity of each infector and the timing of symptom onset, were based on individual recollection of past events. Du et al. [31] note that recall accuracy is impeded by time or trauma, and case-patients might be more likely to attribute infection to recent encounters (short serial intervals) over past encounters (longer serial intervals). Therefore, it is likely that recall bias is present in all studies. It is not possible to distinguish the level of bias present in the different studies.

- Tindale et al. [25] highlight the fact that different criteria for determining what qualifies as illness onset could result in differences in estimates of the serial interval in different reporting jurisdictions.

- The number of pairs used to estimate the serial interval varied considerably. Only three and six pairs were used in the study by Pung et al. [28] and Li et al.,[4] respectively.]. In contrast, a total of 677 pairs were used in the study by Ali et al. [33] and 1407 pairs were studied by Xu et al. [37]. However, the value of increased sample size must be evaluated against the difficulty of ensuring accuracy of the infector-infectee relationship as the sample size increases. There is a lack of clarity on the precise number of infector-infectee pairs that were used to estimate the serial interval in the study by Lavezzo et al. [1].

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However, there was a total number of 81 individuals who tested positive in the study and the infector-infectee pairs were drawn from this population.

- In the study by Zhang et al. [8] and in other studies, the serial interval was estimated from cases in household clusters. The authors make the point that estimations based on household clusters may be 20% shorter than the true value of the serial interval.
- A number of authors, including Mettler et al. [40], Kwok et al. [15] and Aghaali et al. [20] highlighted the possibility of right truncated selection bias, i.e. the possibility of infector-infectee pairs with longer serial intervals being under-represented in the sample due to short investigation period. Measures were taken in a number of studies to minimise this possibility.
- Some aspects of the methodology used by Ganyani et al. [23] were subsequently questioned by Bacallado et al. [41]. These related to the independence of the serial interval values used in the study, the independence of the generation time and the incubation period and the particular Metropolis-Hastings sampler that was used in the study. Kremer et al. [42] accepted that simplifying assumptions had been made in the Ganyani et al. study but stated that the study had certain advantages. Kremer et al. also accepted that the Metropolis-Hastings sampler that they used should be amended in light of the comments made by Bacallado et al. but they stated that the overall conclusions in their article would not change as a result of this modification.

It should be borne in mind that some of the studies may have used the same case data in estimating the serial interval or the generation time. Consequently, the estimates may not be fully independent of each other. For example, the studies by Tindale et al. [25] and Ganyani et al. [23] were carried out in Singapore and Tianjin over the same time period. Similarly, the same set of data seems to have been used in the studies by Xu et al. [37] and Ali et al. [33]. It is not clear why 1407 transmission pairs were available in the former study compared to 677 pairs in the latter study.

Mettler et al. [40] proposed that the diagnostic serial interval (the time between the diagnosis dates of the infector and infectee) be used as a new indicator for the effectiveness of a country's contact tracing as part of the epidemic surveillance.

Statistical distributions used in estimating serial interval and generation time
In most of the studies, a gamma, lognormal or Weibull distribution was fitted to the data to estimate the serial interval distribution. A problem with these distributions is that negative values of the serial interval (that is, when symptoms manifest in the infectee before the infector) cannot be included. In the study by Du et al. [31], 59 of the 468 reports indicate that the infectee had symptoms earlier than the infector. Du et al. cautioned against using distributions that excluded the non-positive data and making assessments and projections based on the truncated data. In their view, the normal distribution provides the best fit for the full dataset (shifted or not) and they recommended this distribution for future epidemiologic assessments. This approach was also used by other authors, including Ali et al. [33] and Xu et al. [37]. Prete et al. [2] used a modelling approach and also fitted a normal distribution to the data.

Relationship between the serial interval, generation time and the reproduction number
The generation time is used to estimate the reproduction number. Because of the difficulty in estimating the generation time, the serial interval is often used as a surrogate for the generation time. The serial interval and the generation time will have the same mean value if the incubation times of the infectee and infector are independent and identically distributed, however, their variances are expected to be different. Britton and Scalia-Tomba [43] note that the difference in variance between the serial and generation time can lead to biased estimates of the reproduction number. More specifically, when the serial interval distribution has a larger variance than the generation time distribution, using the serial interval as a proxy for the generation time will lead to an underestimation of the basic reproduction number. Ganyani et

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al. [23] provided estimates for both parameters based on data from Singapore and China and described a method for obtaining an unbiased estimate of the generation time.

Conclusion

The availability of parameter estimates and information on the serial interval and generation time of the COVID-19 virus are vital for measuring the dynamics of the disease and for estimating the reproduction number. These estimates are very dependent on the specific factors that apply at the time that the data are collected, including the level of social contact. Consequently, the estimates may not be entirely relevant to other environments. Therefore, national estimates should be obtained as soon as possible. Careful consideration should be given to the methodology that is used. Real-time estimations of the serial interval/generation time, allowing for variations over time, may provide more accurate estimates of reproduction numbers than using conventionally fixed serial interval/generation time distributions

Competing interests: All authors have completed the ICMJE 508 uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Data availability statement: All data relevant to the study are included in the article. The data were taken from previously published studies.

Authors contributions: Studies were selected and screened initially by ÁBC and KH using search terms outlined the methodology section, with parameters identified and recorded. This was reviewed and supplemented by a manual search by JG, again with parameters identified and recorded. JG conducted the eligibility screening of shortlisted studies, extracted the data and conducted the review with input from all authors. MC generated Figure 2 and read the full text of the papers. SJM, MC, ÁBC, AB, AWB, EAL, DM and CGM undertook interim reviews. All authors read and approved the final manuscript.

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Figure 1. PRISMA-ScR flow diagram

Figure 2: A boxplot summarising 33 estimates for serial interval or generation time from 27 papers. The purple triangles represent the means of the distributions. GT = Generation time. SI=Serial interval.

Supplementary Figure 1: A ridge plot summarising 33 estimates for serial interval or generation time from 27 papers from which it was possible to simulate distributions (white fill) and six further papers from which the underlying serial interval data could be extracted and summary statistics replicated (grey fill). GT = Generation time. SI=Serial interval.

Supplementary Figure 2: A ridge plot summarising 33 estimates for serial interval or generation time from 27 papers from which it was possible to simulate distributions (white fill) and ten further papers from which the underlying serial could be extracted (grey fill). Summary statistics could not be replicated for four of these papers. GT = Generation time. SI=Serial interval.

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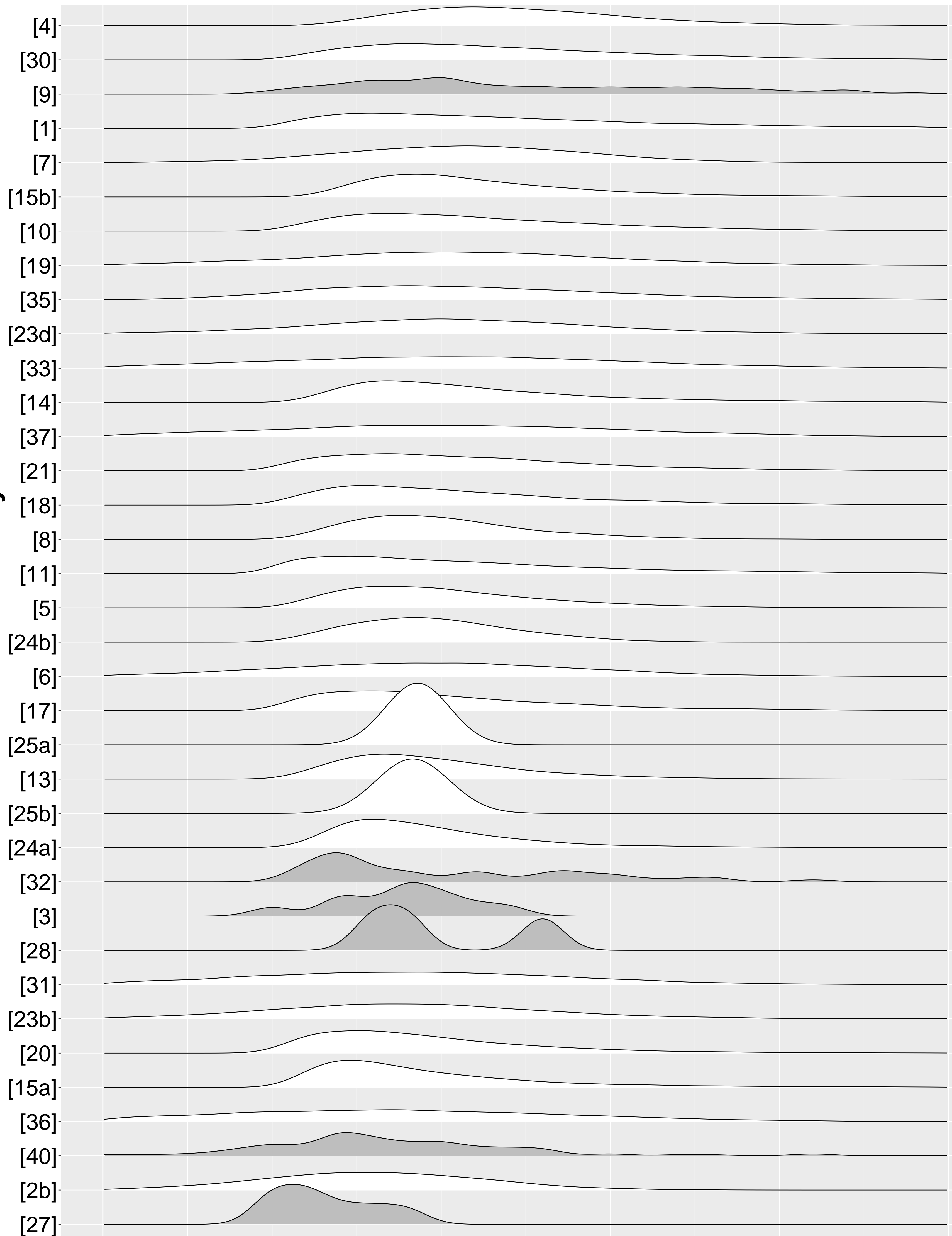|	
Identification	Records identified through database searching: Medline (n = 34), Embase (n = 60), Pubmed (n = 72). 74 records remaining after duplicates removed.
Screening	74 records titles and abstracts screened. 16 removed because they did not contain parameter estimates 5 removed because they were pre-printed papers rather than published papers.
Eligibility	53 full-text studies assessed for eligibility. 2 papers were excluded because they did not contain parameter estimates 17 papers were excluded because the parameter estimates were not original.
Included	34 papers eligible based on screen process. 6 paper identified from bibliographies or from manual searches. Total number of papers included in the review = 40.
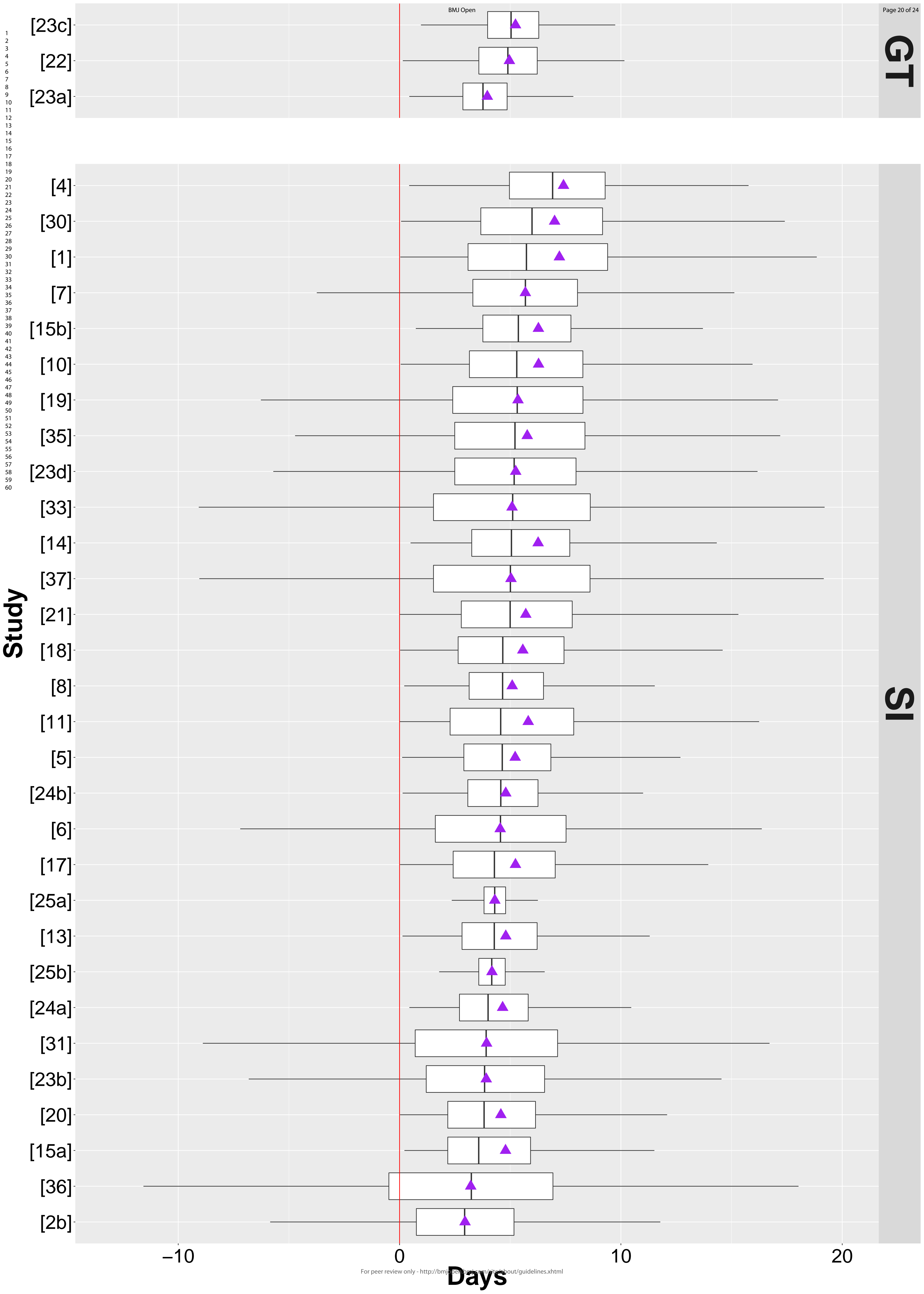
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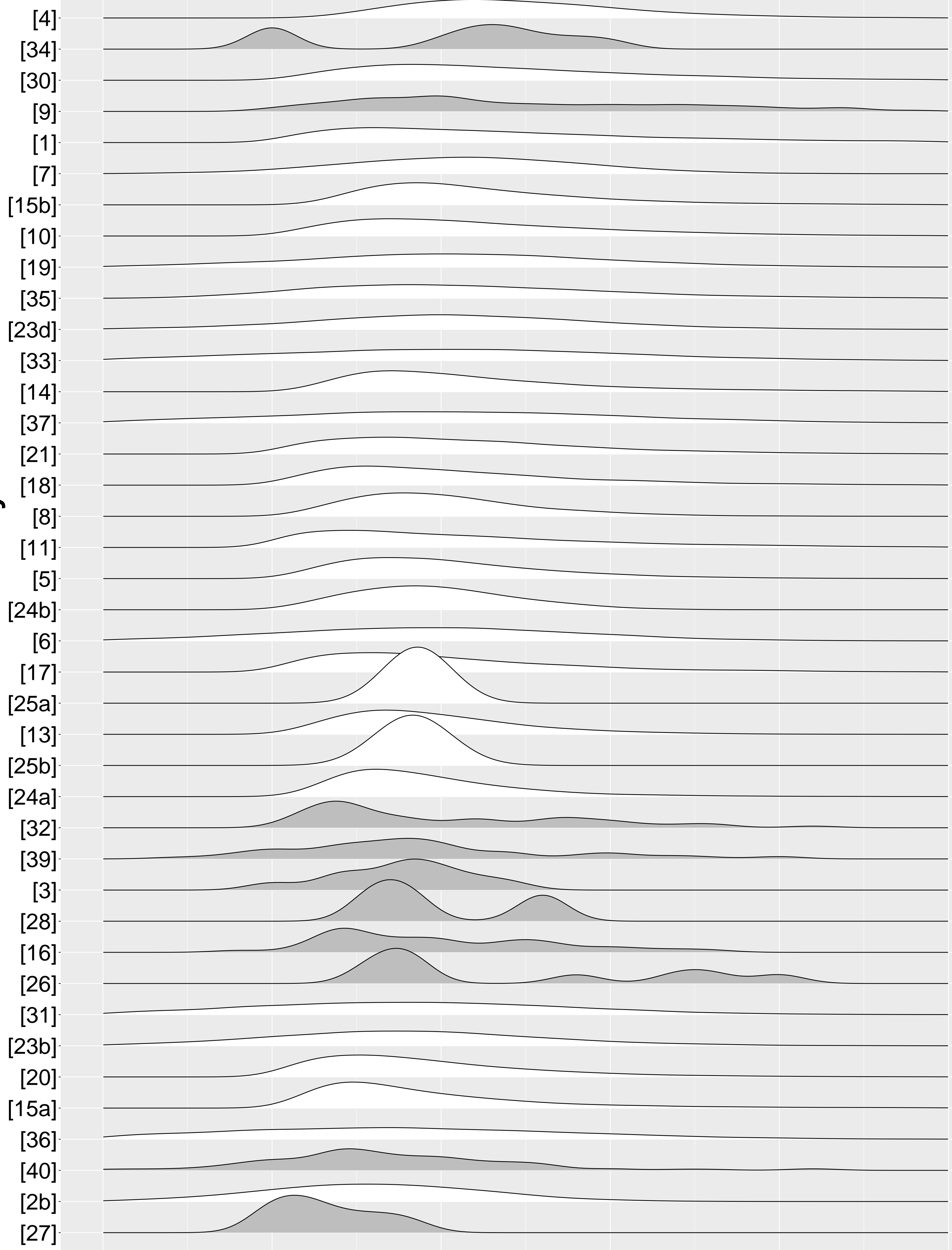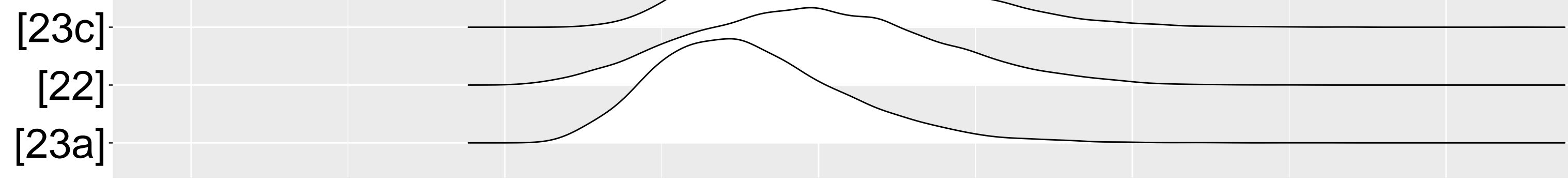**Supplementary table 1: A summary of the data available from the 40 papers included in the rapid systematic review.**

Data available	N papers	References	Comment
Able to simulate SI or GT distribution	27	1-2,4-8,10-11,13-15,17-25,30-31,33,35-37	33 estimates from 27 papers. Plotted in Figure 2
Information available to simulate distribution but could not replicate summary statistics in the paper	2	34,39	Extracted underlying data but could not replicate summary statistics from either
Reported fitting a distribution but not enough information available to simulate it.	1	16	Partial underlying data extracted
Distribution not fitted but underlying data available	7	3,9,26,27,28,32,40	Could not replicate summary statistics for Ki [26]
Distribution not fitted and unable to extract underlying data but plot of distribution available in paper.	2	29,38	
Distribution not fitted, unable to extract underlying data and no plot of distribution available in paper.	1	12	
TOTAL	40		

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SI

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BMJ Open

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.	
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.	
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.	
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.	
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.	
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.	
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.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
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.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
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).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

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.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
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.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
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.	
Limitations	20	Discuss the limitations of the scoping review process.	
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.	
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.	

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).