Meta-analysis of the SARS-CoV-2 serial interval and the impact of parameter uncertainty on the COVID-19 reproduction number

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Abstract

The serial interval of an infectious disease, commonly interpreted as the time between onset of symptoms in sequentially infected individuals within a chain of transmission, is a key epidemiological quantity involved in estimating the reproduction number. The serial interval is closely related to other key quantities, including the incubation period, the generation interval (the time between sequential infections) and time delays between infection and the observations associated with monitoring an outbreak such as confirmed cases, hospital admissions and deaths. Estimates of these quantities are often based on small data sets from early contact tracing and are subject to considerable uncertainty, which is especially true for early COVID-19 data. In this paper we estimate these key quantities in the context of COVID-19 for the UK, including a meta-analysis of early estimates of the serial interval. We estimate distributions for the serial interval with a mean 5.9 (95% CI 5.2; 6.7) and SD 4.1 (95% CI 3.8; 4.7) days (empirical distribution), the generation interval with a mean 4.9 (95% CI 4.2; 5.5) and SD 2.0 (95% CI 0.5; 3.2) days (fitted gamma distribution), and the incubation period with a mean 5.2 (95% CI 4.9; 5.5) and SD 5.5 (95% CI 5.1; 5.9) days (fitted log normal distribution). We quantify the impact of the uncertainty surrounding the serial interval, generation interval, incubation period and time delays, on the subsequent estimation of the reproduction number, when pragmatic and more formal approaches are taken. These estimates place empirical bounds on the estimates of most relevant model parameters and are expected to contribute to modelling COVID-19 transmission.

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Introduction

The purpose of this paper is to determine the best estimates for the parameters we need to calculate the effective reproduction number (R_t) for the UK, and in particular the key quantities of the serial interval and generation interval. The calculation of R_t can be made pragmatically using simplifying assumptions, or in a more formal manner, for which other key parameters are also required, in particular the delay between infection and diagnosis. Given that these parameters are all associated with uncertainty we investigate how this uncertainty may affect our estimates of the reproduction number, and we qualitatively compare the pragmatic approach compared to the more formal approach.

Since the end of 2019, the novel strain of coronavirus, SARS-CoV-2 has caused a global pandemic of disease. The speed with which the virus spreads is dependent on biological determinants that enable viral replication within individuals and onward transmission to others. The minimal set of parameters required for understanding the dynamics of any novel infectious disease pathogen include the potential for transmission, the duration of infectiousness (often captured in models as a recovery rate) and the generational interval: the time between two subsequent cases in a chain of infection.

Estimating the generation interval is particularly challenging due to the fundamentally hidden nature of transmission events. In Figure 1 we summarise the timeline of key events for two adjacent infected individuals (infector and infectee) in a chain of transmission.

As described by Svensson et al.[1] the generation interval is defined as the time between the infection of an infector and infectee, and in practice is not easy to observe, as an infection goes through some latent period, during which it is undetectable[2], and a pre-symptomatic phase during which an individual may be infectious, but possibly detectable through screening, before the disease manifests with clinical symptoms. The latent period and pre-symptomatic phase are together usually referred to as the incubation period ($T_{incubation}$). From the onset of symptoms, the diagnosis will be confirmed by some canonical test after some time delay ($T_{onset \to test}$), later the patient may require admission to hospital ($T_{onset \to admission}$), or may die ($T_{onset \to death}$). These subsequent events clearly may not happen in that order, and even diagnosis may occur after death. The time between these key events (onset of symptoms, test confirmation of case, hospital admission, and death) for two sequentially infected people in a chain of transmission are described as serial intervals[1], although in general usage, and in the rest of this paper, the term "serial interval" is taken to mean the interval between onset of symptoms (SI_{onset}). In Figure 1 and the rest of this paper we use the terms "case interval" (SI_{case}), "admission interval" ($SI_{admission}$), and "death interval" (SI_{death}) to differentiate the other intervals. The generation interval is by definition a non-negative quantity, but all the other measures may be negative if the variation of the delay from the event of infection from person to person exceeds the period between infections. This is more likely for death interval than for serial interval, and for diseases with long pre-symptomatic periods, for example HIV[3]. The generation interval is defined for all transmission pairs, but the other intervals may or may not be, if for example one of the infector, or infectee is asymptomatic, or does not go to hospital, or does not die, in which case the related intervals are not defined for this pair.

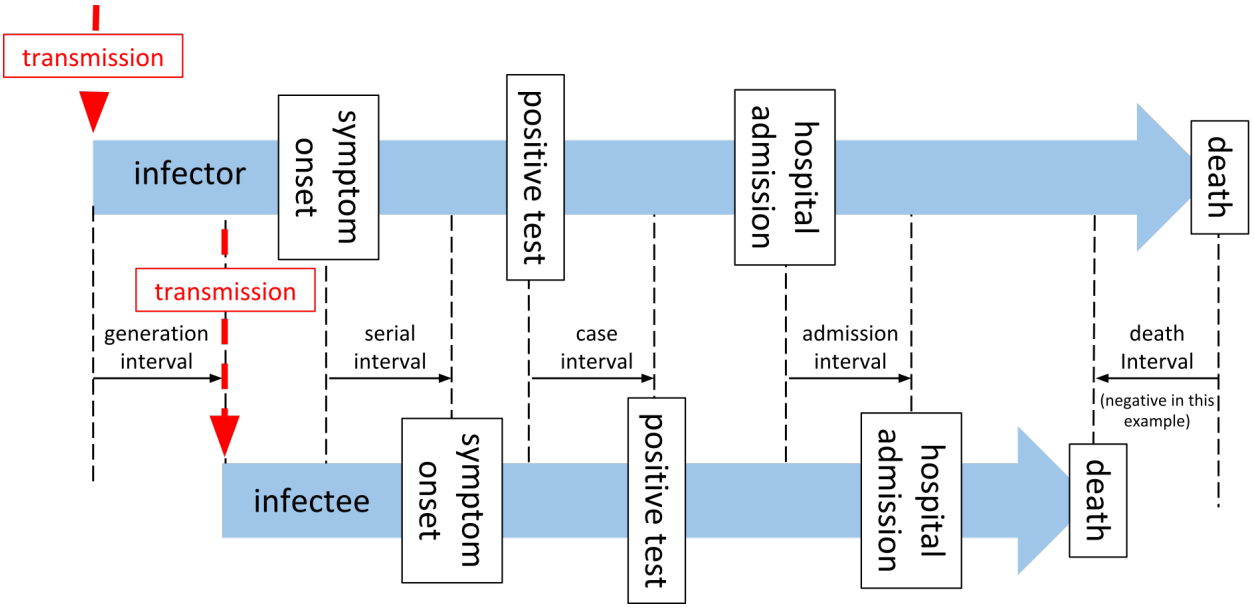

Figure 1: A timeline of events associated with a single infector-infectee pair in a transmission chain

The effective reproduction number (R_t) is a key measure of the state of the epidemic. In its simplest form, for a given population, the effective reproduction number is the number of secondary infections that are expected to arise from one primary infection, at any given instant, and depends on the biological properties of the virus, the immune status and the behaviour of that population. Estimation of the effective reproduction number can either be done forward in time, where we estimate the number of infections that arose from cases detected on a given day (case or cohort reproduction number[4]), or backwards in time where we estimate the number of cases that caused the infections observed on a given day (instantaneous reproduction number[5]).

Estimation of the instantaneous reproduction number is implemented in the "renewal equation" method for estimating R_t, and depends on a time series of infections, and on the "infectivity profile" - a measure of the probability that a secondary infection occurred on a specific day after the primary case, given that a secondary infection occurred.[6,7] A Bayesian framework is then used to update a prior probabilistic estimate of R_t on any given day with both information gained from the time series of infections and the infectivity profile to produce a posterior estimate of R_t. From this point we refer to R_t to specifically describe the instantaneous reproduction number estimated using the renewal equation method.

The infectivity profile in the renewal equation method is the probability a secondary infection occurred on a particular day after the primary infection, given a secondary infection occurred. This is the same as the probability density function of the generation interval distribution over all transmission pairs. However, in both the original[5] and revised[7] implementations of this method, the authors acknowledge the pragmatic use of the serial interval distribution, as a proxy measure for the infectivity profile, and the incidence of symptom onset or case identification as a proxy for the incidence of infection, with the caveat that these introduce a time lag into the estimates of R_t. It has been noted by various authors that use of the serial interval distribution as a proxy for infectivity profiles is a pragmatic choice[5,7] but can introduce a bias into estimates of R_t[9,10].

In the COVID-19 outbreak a limited number estimates of the serial interval distribution are available from studies of travelers from infected areas, and early contact tracing studies (detailed in Table 2). The infectivity profile is comprised of non-negative values by definition. The serial interval, on the other hand, can be measured as negative for several reasons. For example, if the incubation period of the infector is at the short end of the distribution and that of the infectee is at the tail, a negative serial interval would be observed. Negative values have been noted as a feature in at least one estimate of the serial interval of SARS-CoV-2 to date[11], but cannot be used in renewal equation based estimates of R_t.

Direct measurement of the serial interval distribution is further complicated by the fact that symptom onset

is often not observed due to the scale of the outbreak and that infection may be asymptomatic[12,13]. The data available during an epidemic are a time series of counts of observations, such as confirmed cases (test results confirming diagnosis), hospital admissions, and deaths. As depicted in Figure 1 these events occur after infection, following a period of time. Therefore the observed time series of observed cases is a result of the unobserved time series of infections governed by the serial interval, convolved by the distribution of the time delay from infection to case identification.

Since renewal equation based estimates of R_t are predicated on infections a "formal" approach to estimation is to infer the unobserved incidence of infection from the observations we have using back propagation or de-convolution[3,10], using the generation interval as the infectivity profile. However this requires knowledge of the temporal relationship between unobserved infections and observed cases, admissions or deaths.

A pragmatic alternative[10] is to simply calculate R_t using a serial interval as the infectivity profile, and un-adjusted case numbers with a simple correction for the time delay between infection and cases by shifting our R_t estimates backwards in time. As the renewal equation methods assumes that the time between 2 infections cannot be negative, the serial interval distribution must be truncated at zero in this pragmatic approach.

Both formal and pragmatic approaches need estimates of the generation interval or serial interval, and the time delays between infection and symptom onset (incubation period), infection and case identification (test), infection and admission, and between infection and death. The formal method also needs an understanding of the shape of the distribution of these delays. In the rest of this paper we estimate these key quantities and investigate the impact that uncertainty in these quantities has on estimation of R_t.

Table 1: Comparison of 2 approaches for estimating the reproduction number and parameters needed to support each approach

Pragmatic approach	Formal approach
No adjustment prior to estimation of Rt.	Deconvolution of observations (e.g. cases) to putative infection date. (requires distribution of time from infection to observation delay requires incubation period estimate and delay from symptoms to observation)
Serial interval as proxy for infectivity profile, truncated at zero if necessary. (requires estimate of serial interval distribution)	Generation interval as proxy for serial interval. (requires generation interval estimate which depends on serial interval estimate; and incubation period estimate)
Simple shift of Rt estimates to align to date of infection. (requires point estimate of time delay from infection to observation, based on point estimate of mean delay of observation)	No adjustment after estimation of Rt required.

Methods

Serial interval estimation

Firstly, we conducted a literature review for studies that describe serial interval estimates using PubMed and the search terms "(SARS-CoV-2 or COVID-19) and 'Serial interval' " and reviewed the abstracts of relevant original research papers. These were compared to papers reported on the MIDAS Online Portal for COVID-19 Modeling Research[14], and with existing meta-analyses[15]. From these papers, serial interval mean and standard deviation estimates were extracted, along with information about assumed statistical distributions, and the sample size of the study. A random effects meta-analysis was conducted[16] on the subset of papers that reported confidence intervals. The assumption of normal distribution underpinning the meta-analysis[17–19] is reasonable for the mean of the serial interval, given the central limit theorem, however we cannot extend this to the standard deviation of the serial interval distribution, and hence cannot assess the overall shape of the serial interval distribution. To address this and combine parameterised distribution

estimates from multiple studies into a single distribution we undertook a re-sampling exercise, as described below, the goal of which was to reconstruct a data set of serial intervals that accurately reflect the distributions reported in each of the studies above, so that they could be combined and analysed together.

Most studies reported a central estimate of a probability distribution for the serial interval, specified in terms of the mean and standard deviation of a given serial interval distribution. They also reported uncertainty on these mean and standard deviations as confidence or credible intervals. For these studies, we randomly selected one hundred probability distributions consistent with the central estimates and confidence intervals reported in each paper (further details are available in Supplemental table 1). From this family of probability distributions we drew random samples based on the original sample size[20,21]. This gives us a set of samples that are consistent with the shape and uncertainty of the distributions reported by the source studies and which represent their sample size in a comparable way. Other studies reported empirical distributions and for these we obtained original serial interval data where available and made 100 random bootstrap sub-samples with replacement, to a relative size determined by the original sample size of the study.

The 100 empirical and 100 probability distribution based serial interval samples were combined into 100 groups, with each group containing serial intervals representative of each source article with numbers proportional to the size of the original study. This allows us to calculate 100 empirical probability distribution estimates from which we can derive summary statistics with confidence intervals (from here on referred to as the "re-sampled serial interval estimate").

As much of the data is captured at the resolution of a single day, serial intervals appear as integer numbers of days in the data. The discrete nature of the data was estimated using continuous distributions by replacing integer values, x, with interval censored ranges spanning from the value $x - 0.5$ to $x + 0.5$ days. Normal, weibull and gamma probability distributions were then fitted to these 100 groups of interval censored data using maximum likelihood estimation, implemented in R[22,23], This additionally gives us 100 parametric probability distribution estimates for each distribution from which we can derive confidence intervals for the parameters and 100 empirical probability distributions estimates of the combination of all the source studies.

As a comparison we also used data collected under the "First Few Hundred" (FF100) case protocol by Public Health England[24,25] which provides a limited number of linked cases of proven transmission, mostly within households, and interval censored symptom onset dates. To this data we fitted normal, gamma and weibull distributions using the same methodology as above.

In both cases when fitting gamma and weibull distributions we truncated the interval censored data at zero, to prevent negative values, and for the gamma distributions we required that the shape parameter had a lower bound of 1, which enforces that the distribution density is zero at time zero. This however makes goodness of fit statistics not comparable between the normal distribution fit and the 2 other distributions.

Incubation period estimation

The incubation period has been previously estimated by Lauer et al. and Sanche et al.[26,27] for China in the early phase of the epidemic. The FF100 data contains interval censored exposure data coupled to symptom onset; using this we derived a UK specific estimate to assess if it was consistent. Furthermore, the Open COVID-19 Data Working Group[28,29] provides a large international data set which includes some travel history and symptom onset data.

Compared to data on which earlier estimates of the incubation period were made[26,27] where travel principally originated from Wuhan, the travel cases in the Open COVID-19 data set include travellers between a far wider set of destinations, and in a later stage of the epidemic, which we believe reduces selection bias[30]. As we are performing this analysis retrospectively we also benefit from fewer issues due to right censoring of the data.

For both data sets we use random samples with replacement and fit 100 of each of gamma, weibull and log normal probability distributions to the interval between putative exposure and symptom onset, accounting for censoring where present, to estimate the incubation period distribution and uncertainty associated with

its parameters. We remove from the data records where the time from exposure to symptom onset is negative or when it is longer than 21 days (on the basis of biological implausibility).

For subsequent phases of the analysis we retain the 100 parameterised distributions of the distribution with the best overall fit to the data from Open COVID-19 Data Working Group data set. From these we can generate a parameterised bootstrap sample representative of the Open COVID-19 Data Working Group data set but without censoring.

Generation interval estimation

The generation interval is the fundamental variable for modelling transmission. Under the assumption that the generation interval follows a gamma distribution we can infer its parameters using the bootstrap samples from the re-sampled serial interval data set, and the bootstrap samples from the incubation period data set from earlier stages, and the constraint that the generation interval is a non-negative quantity. We combined random samples from a parameterised gamma distribution for the generation interval with two of the bootstrap samples from the incubation period to satisfy the following relationship, thus simulating the serial interval:

$$SI_{onset,A\to B} = SI_{infection,A\to B} + T_{incubation,B} - T_{incubation,A}$$
$$E[SI_{onset}] = E[SI_{infection} + T_{incubation} - T_{incubation}]$$

The mean and standard deviation of the simulated serial interval distribution were then compared to the empirical re-sampled serial interval distributions we estimated in an earlier stage. The parameters for the generation interval distribution were then optimized by a recursive linear search on the standard deviation, with the constraints that the mean of the simulated and empirical distributions must be the same[9], and the standard deviation must be smaller than the mean (ensuring the gamma function scale parameter is larger than one and hence the density is zero at time zero). The minimization function we employed was the absolute difference in inter-quartile ranges of simulated and observed distributions. This process was repeated for 100 different simulated samples that were compared to the 100 different empirical re-sampled serial interval estimates from the previous stage of our analysis to get confidence intervals on our estimates of the generation interval distribution. This approach does not use the parameterised serial interval estimate, and only the samples direct from the combination of data and literature. For the incubation period we use parametric re-sampling of multiple fits to the original interval censored incubation period data to generate bootstrap samples. This approach minimises any assumptions we make about the distribution of these other quantities when estimating the generation interval.

Impact of using the serial interval on estimation of R_t

With various estimates of serial interval and generation interval we wished to understand the qualitative impact this variation might have on our estimates of R_t. To investigate this we used the forward equation approach implemented in the R library EpiEstim[5,6,31]. We estimate values of R_t for 4 time points in the first wave of the COVID-19 pandemic in England representative of the ascending phase, the peak, the early descending phase and the late descending phase. We used data retrieved from the Public Health England API[32,33] representing cases with positive test results, hospital admissions and deaths within 28 days of a positive test, in the first wave of the outbreak in England. For this analysis we assume the infectivity profile can be represented using a parameterised gamma distribution, and estimate R_t for a wide range of combinations of mean and standard deviation, using a fixed calculation window of 7 days, at each of our four time points. The resulting relationship between R_t, mean infectivity profile, and standard deviation of infectivity profile were compared visually to qualitatively examine how the serial interval estimates influence the estimates of R_t.

Time delays from infection to case identification, admission, and death

Estimation of the time interval between the onset of symptoms and the observations of positive test result, hospital admission, and death was performed ($T_{onset \to test}$, $T_{onset \to admission}$, and $T_{onset \to death}$) using the CHESS data set[34]. The CHESS data set is hospital based, and was initially limited to intensive care admissions, but a subset of hospitals have reported all admissions, and this is what we focused on (see Supplemental table 2). Within the CHESS data set there are a set of patients who have symptom onset dates recorded, dates that a specimen was taken that subsequently was tested positive, hospital admission date, and date of death, if the patient died. We restricted cases to those in which a positive test was found no more than 14 days before and 28 days after symptom onset on the grounds of biological implausibility. Because we conducted this analysis at the end of the first wave of COVID-19 in the UK when patient numbers in hospital had fallen to a low level there was minimal right censoring present in the data and this was not accounted for.

The time delay from infection to observation was obtained by combining our estimate of the incubation period distribution from the Open COVID-19 Data Working Group data set[28,29] with onset to observation delays from the CHESS data set[34] using the following relationship.

$$\begin{aligned} T_{infection \to observation} &= T_{infection \to onset} + T_{onset \to observation} \\ &= T_{incubation} + T_{onset \to observation} \end{aligned}$$

We combined the incubation period and onset to observation distributions using a random sampling approach, assuming independence of the two variables. These random samples were then estimated as parameterised statistical distributions in the same manner as above, with the constraint that all the time delays from infection to observation are non-negative quantities, and their probability is zero at time zero.

The resulting time delays from infection to the different observations of positive test result, hospital admission or death were calculated and fitted to probability distributions using the same maximum likelihood estimation methods implemented in R[23] as described above.

Impact of deconvolution

In the final piece of our analysis we sought to qualitatively compare estimates of R_t based on data for England from the Public Health England API[32,33], in each of the following two scenarios.

Firstly, following the "pragmatic" course outlined in the introduction, we based R_t estimates on observational data (cases, admissions, deaths) as a proxy for infection events, and used a truncated empirical serial interval distribution derived from our re-sampling procedure as a proxy for infectivity profile. In line with the pragmatic approach a simple to the dates of these R_t estimates was made to align the estimate to date of infection rather than date of observation.

Secondly, the more formal approach was employed: using the time delay distributions from the previous stage, we used de-convolution to infer a set of time series of infections from the same observational data and used our estimate of the generation interval as a proxy for the infectivity profile. This second approach has been recommended by Gostic et al[10]. To do this we applied a non parametric back projection algorithm from the surveillance R package[35], based on work by Becker et al.[3] and Yip et al.[36], to infer three putative infection time series from observed cases, admissions or deaths. The inferred time series were then used to estimate R_t through EpiEstim using the parametric gamma distributed estimate of the generation interval from above. In applying the de-convolution we discovered it requires a full time series beginning with zero cases for sensible results and this required we impute the early part of the hospital admission time series, which we did by assuming an early constant exponential growth phase.

In both cases we used a the renewal equation method with 14 day sliding window to estimate a continuous time series of R_t. The resulting R_t time series were compared qualitatively.

Results

Serial interval estimation

Our PubMed search retrieved 62 search hits of which 14 were original research articles containing estimates of serial intervals[11,37–50]. The mean and standard deviation of parameterised distributions were extracted and are presented in Table 2. The estimates of the mean range from 3.95 days to 7.5 days. The majority of studies provided their results as gamma distributions defined by mean and standard deviation. Some studies, particularly Xu et al.[11] noted that the serial interval was not infrequently negative.

Table 2: Sources of serial interval estimates from a literature search

Reference	Statistic	Mean (95% CrI) days	Std (95% CrI) days	N	Distribution	Population
Bi, Q. et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. The Lancet Infectious Diseases 20, 911–919 (2020).	serial interval	6.30 (5.20-7.60)	4.20 (3.10-5.30)	48	gamma	Shenzhen
Cereda, D. et al. The early phase of the COVID-19 outbreak in Lombardy, Italy. arXiv:2003.09320 [q-bio] (2020).	serial interval	6.60 (0.70-19.00)	4.88 (unk-unk)	90	gamma	Italy
Du, Z. et al. Serial Interval of COVID-19 among Publicly Reported Confirmed Cases. Emerg Infect Dis 26, 1341–1343 (2020).	serial interval	3.96 (3.53-4.39)	4.75 (4.46-5.07)	468	norm	China
Ganyani, T. et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. Eurosurveillance 25, 2000257 (2020).	serial interval	5.21 (-3.35-13.94)	4.32 (4.06-5.58)	54	empirical	Singapore
	serial interval	3.95 (-4.47-12.51)	4.24 (4.03-4.95)	45	empirical	Taijin
Kwok, K. O., Wong, V. W. Y., Wei, W. I., Wong, S. Y. S. & Tang, J. W.-T. Epidemiological characteristics of the first 53 laboratory-confirmed cases of COVID-19 epidemic in Hong Kong, 13 February 2020. Eurosurveillance 25, 2000155 (2020).	serial interval	4.58 (3.35-5.85)	3.28 (2.18-4.01)	26	lnorm	Hong Kong
Li, Q. et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. New England Journal of Medicine 382, 1199–1207 (2020).	serial interval	7.50 (5.30-19.00)	3.40 (unk-unk)	5	unknown	Wuhan
Nishiura, H., Linton, N. M. & Akhmetzhanov, A. R. Serial interval of novel coronavirus (COVID-19) infections. Int. J. Infect. Dis. 93, 284–286 (2020).	serial interval	4.70 (3.70-6.00)	2.90 (1.90-4.90)	28	lnorm	SE Asia
Son, H. et al. Epidemiological characteristics of and containment measures for COVID-19 in Busan, Korea. Epidemiol Health 42, (2020).	serial interval	5.54 (4.08-7.01)	3.90 (2.47-5.32)	28	gamma	Korea
Tindale, L. C. et al. Evidence for transmission of COVID-19 prior to symptom onset. eLife 9, e57149 (2020).	serial interval	4.17 (2.44-5.89)	1.06 (unk-unk)	93	unknown	Singapore
	serial interval	4.31 (2.91-5.72)	0.94 (unk-unk)	135	unknown	Taijin
Xia, W. et al. Transmission of corona virus disease 2019 during the incubation period may lead to a quarantine loophole. medRxiv 2020.03.06.20031955 (2020) doi:10.1101/2020.03.06.20031955.	serial interval	4.10 (unk-unk)	3.30 (unk-unk)	124	empirical	China outside Hubei
Xu, X.-K. et al. Reconstruction of Transmission Pairs for novel Coronavirus Disease 2019 (COVID-19) in mainland China: Estimation of Super-spreading Events, Serial Interval, and Hazard of Infection. Clin Infect Dis doi:10.1093/cid/ciaa790.	serial interval (household)	4.95 (unk-unk)	5.24 (unk-unk)	643	empirical	China outside Hubei
	serial interval (non-household)	5.19 (unk-unk)	5.28 (unk-unk)	643	empirical	China outside Hubei
You, C. et al. Estimation of the time-varying reproduction number of COVID-19 outbreak in China. International Journal of Hygiene and Environmental Health 228, 113555 (2020).	serial interval	4.27 (unk-unk)	3.95 (unk-unk)	71	empirical	China outside Hubei
Zhang, J. et al. Evolving epidemiology and transmission dynamics of coronavirus disease 2019 outside Hubei province, China: a descriptive and modelling study. The Lancet Infectious Diseases 20, 793–802 (2020).	serial interval	5.00 (0.80-13.00)	3.22 (unk-unk)	28	gamma	China outside Hubei
Zhao, S. et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. Int. J. Infect. Dis. 92, 214–217 (2020).	serial interval	4.40 (2.90-6.70)	3.00 (1.80-5.80)	21	gamma	Hong Kong

The random effects meta-analysis on the subset of studies which reported modelled distributions, resulted in an overall estimate of the mean of the serial interval of 4.83 (95% CI 3.93–5.70) (for more details see Supplemental figure 1). This estimate is limited in its value by the fact that it only covers the subset of the studies in the table above, and does not represent the distributional nature of the serial interval.

In Figure 2, panel A we present the results of the re-sampled serial interval estimate. The histogram shows the empirical distribution of the combination of all the studies, reinforcing the finding of a substantial proportion of the serial interval being negative. For the gamma and weibull distribution fit the data is truncated at zero, and the full data used for the normal distribution, resulting with mean values of 5.72 (gamma), 4.87 (norm), or 5.70 (weibull) days. Full detail of the parameterisation of this is available in Supplemental table 3.

In Figure 2 panel B we present the distribution of the 50 linked cases in the FF100 data set for which onset dates are available for both infector and infectee. As with the re-sampled data the parameterised versions of this are based on truncated data for weibull and gamma distributions, and hence shows a poorer fit against the whole distribution (full detail of the parameterisation of this is available in Supplemental table 4). Supporting the observations of Xu et al.[11], the FF100 data shows evidence of negative serial intervals. The mean of the serial interval from FF100 data was 3.50 (gamma) or 3.52 (weibull) when data truncated to exclude negative serial intervals, and 2.81 (norm) with no truncation. This is on the lower end of the values reported in the literature.

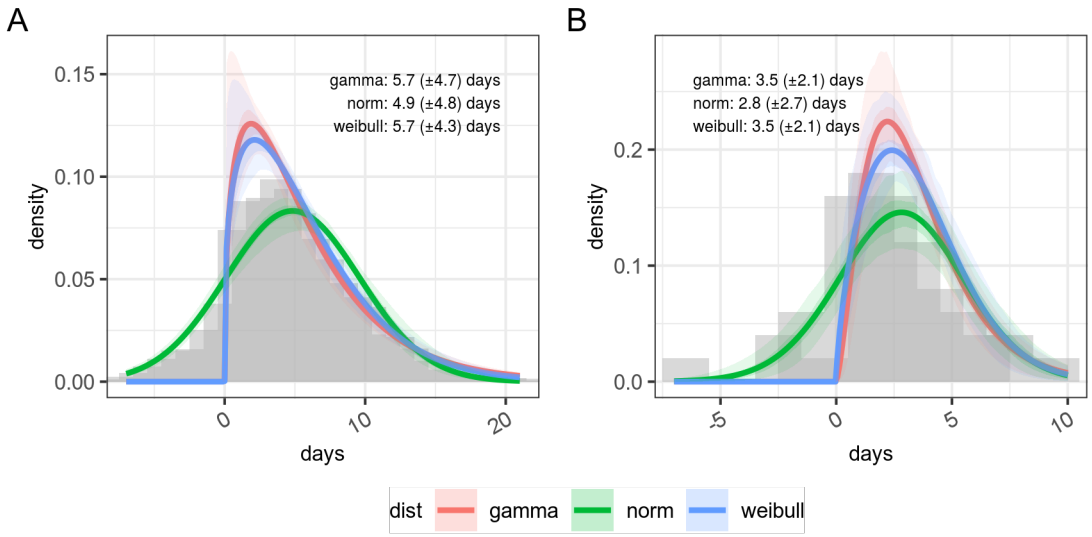

Figure 2: Panel A - Days between infected infectee disease onset based on a resampling of published estimates from the literature and Panel B - Estimates of serial interval from FF100 data. The histogram in panel A shows the combined density of all sets of samples within the original research.

As noted in the methods, the re-sampling process allows us to estimate the serial interval as an empirical distribution. Within EpiEstim, our chosen framework for estimating R_t however the use of negative serial intervals are not supported as a proxy for the infectivity profile. In the pragmatic approach to estimating R_t we truncate the empirical distribution at zero to support this. Once truncated the resulting estimate therefore has a mode of 3.86 days, shorter than the normal distribution parameterisation and is a truncated empirical distribution, with a mean plus 95% confidence interval of 5.88 days (5.22; 6.70), and a standard deviation of 4.12 days (3.79; 4.72), which is more in line with the gamma distribution parameterisation.

Incubation period estimation

Figure 3 and Table 3 show the results of estimating a parametric probability distribution to data from FF100 and data from the Open COVID-19 Data Working Group. Histograms of the data are not shown as it is

interval censored, which is not straightforward to represent graphically. There are only a small number of records from the FF100 data which suggest the mean of the incubation period is between 1.82 to 1.94 days. The data from the Open COVID-19 Data Working Group suggests the incubation period is longer with a mean of 5.19 days with best fitting distribution, and this agrees better with other estimates in the literature[15,26,27]. The best fit to the Open COVID-19 data is obtained with a log normal distribution as seen in Table 3, with the lowest Akaike information criterion, Bayesian Information Criterion (both representing least information lost) and the largest value for the log-likelihood. (Full details of the fitting parameters and graphical assessment of the quality of fit are in Supplemental table 5 and Supplemental figure 2).

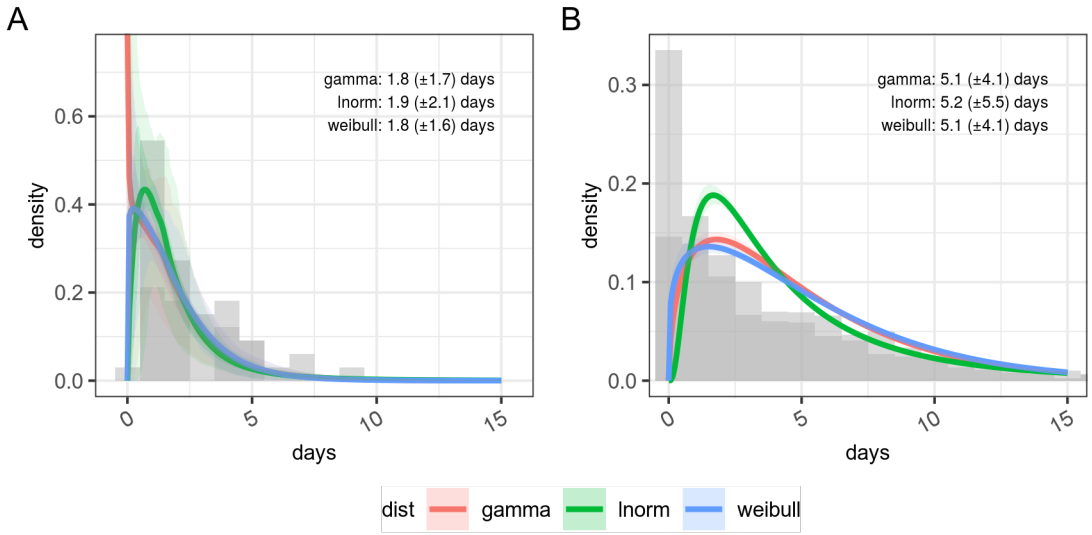

Figure 3: Incubation period distributions reconstructed from Open COVID-19 Data Working Group and from FF100 data. Histogram data is approximate due to interval censoring.

Table 3: Goodness of fit statistics for incubation period distributions reconstructed from Open COVID-19 Data Working Group and from FF100 data

Source	N	AIC	BIC	Log-likelihood	Distribution
FF100	33	62.1	65.1	-29.1	gamma
		62.1	65.1	-29.0	weibull
		63.5	66.5	-29.7	log-normal
Open COVID-19 Data Working Group	1062	5157.2	5167.1	-2576.6	log-normal
		5191.7	5201.6	-2593.8	gamma
		5216.6	5226.5	-2606.3	weibull

Generation interval estimation

The generation interval is then inferred from the incubation period and empirical serial interval distribution prior to truncation. Our best estimate for this is a gamma distribution, with a mean plus 95% confidence interval of 4.87 days (4.24; 5.51), and a standard deviation of 1.98 days (0.53; 3.19), as shown in Figure 4. The mean of 4.87 days is identical to that of the empirical serial interval distribution prior to truncation in panel B, Figure 2 as a result of the constraints imposed during fitting. The standard deviation of our generation interval estimate is 1.98. This is within the confidence limits of estimates from the literature from both China (0.74 - 2.97) and Singapore (0.91 - 3.93)[51]. The mean and standard deviation of these distributions are not independent, and this is explored further in Supplemental figure 3.

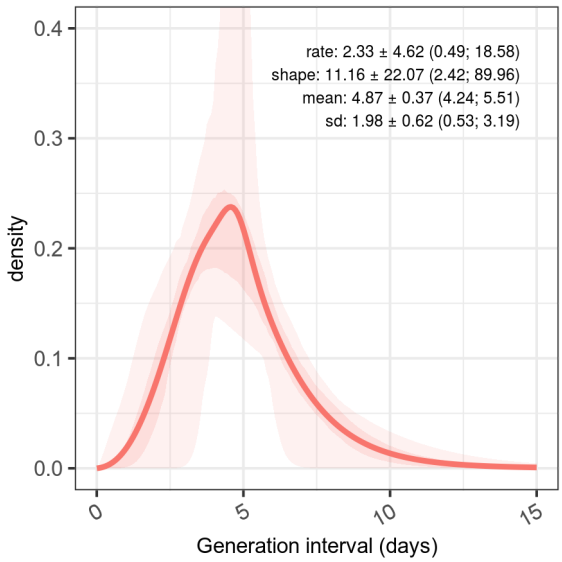

Figure 4: Estimated generation interval distributions, from resampled serial intervals as predictor, and estimated serial intervals from incubation period combined with samples from a generation interval assumed as a gamma distributed quantity.

Impact of using the serial interval on estimation of R_t

With our 3 estimates of the serial interval and 1 generation interval and observed COVID-19 case counts, we investigate the impact on the estimates of R_t, of using these estimates as a proxy for the infectivity profile. This uses data at 4 time points on an epidemic curve from the first wave of the COVID-19 outbreak in England, shown in Figure 5, which are 19th March, 12th April, 12th May and 23rd June, corresponding to the ascending, peak, early descending and late descending phases respectively.

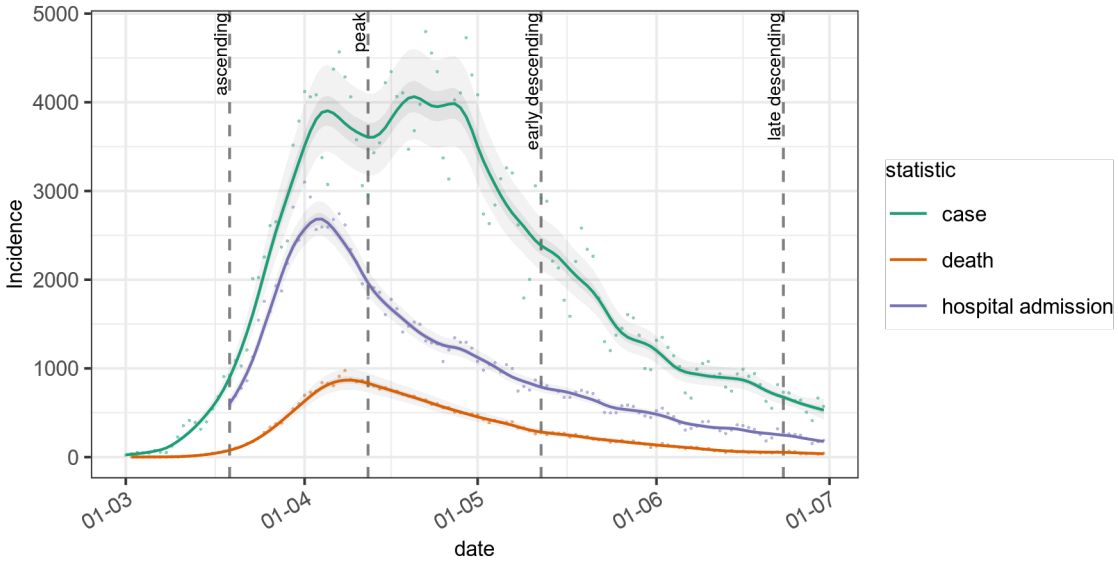

Figure 5: Epidemic curve for cases, deaths and hospital admissions are used for analysis in this paper. Dashed vertical lines show dates at which we conduct our analysis, chosen to represent the ascending, peak, early and late descending phases of cases during the first wave in the UK.

At each of these 4 time points Figure 6 shows the estimated R_t under the range of different assumptions about the mean and standard deviation of the infectivity profile, modeled as a gamma distribution. In the top left, bottom left and bottom right panels the effect of increasing the mean of the infectivity profile is to push the resulting estimate of R_t away from the critical value of 1 at which the epidemic is growing. In the top right panel, at the peak, the mean of the infectivity profile has a less clear-cut effect. The impact of changes to standard deviation is likewise varied. In the top left, bottom left and bottom right panels during ascending and descending phases there is relatively little impact of changing the standard deviation of the infectivity profile on the estimates of R_t, and any small changes that do occur depend on the shape of the preceding epidemic curve. At the peak however, in the top right panel, the wider the standard deviation the more historical information influences the estimation of R_t and this acts to delay the estimated transition from positive to negative growth. The overall result of this is that estimates of the infectivity profile with a high standard deviation will predict R_t crossing 1 later than estimates based on an infectivity profile with a low standard deviation, but the point of crossing 1 is relatively insensitive to the value of the mean of the infectivity profile.

When we consider using the various estimates of the serial interval or generation interval, as a proxy for the infectivity profile, on the resulting estimates of R_t we can see from the coloured crosses on Figure 6 representing the different estimates of serial or generation interval, that in the situations of dynamic change such as the ascending phase the variability may have quite a large impact on subsequent estimates of R_t but at other times the impact is much smaller [ascending - 28% variation (R_t: 1.66 to 2.20); peak - 3% variation (R_t: 0.97 to 1.00); early descending - 8% variation (R_t: 0.83 to 0.90); late descending - 6% variation (R_t: 0.83 to 0.88)].

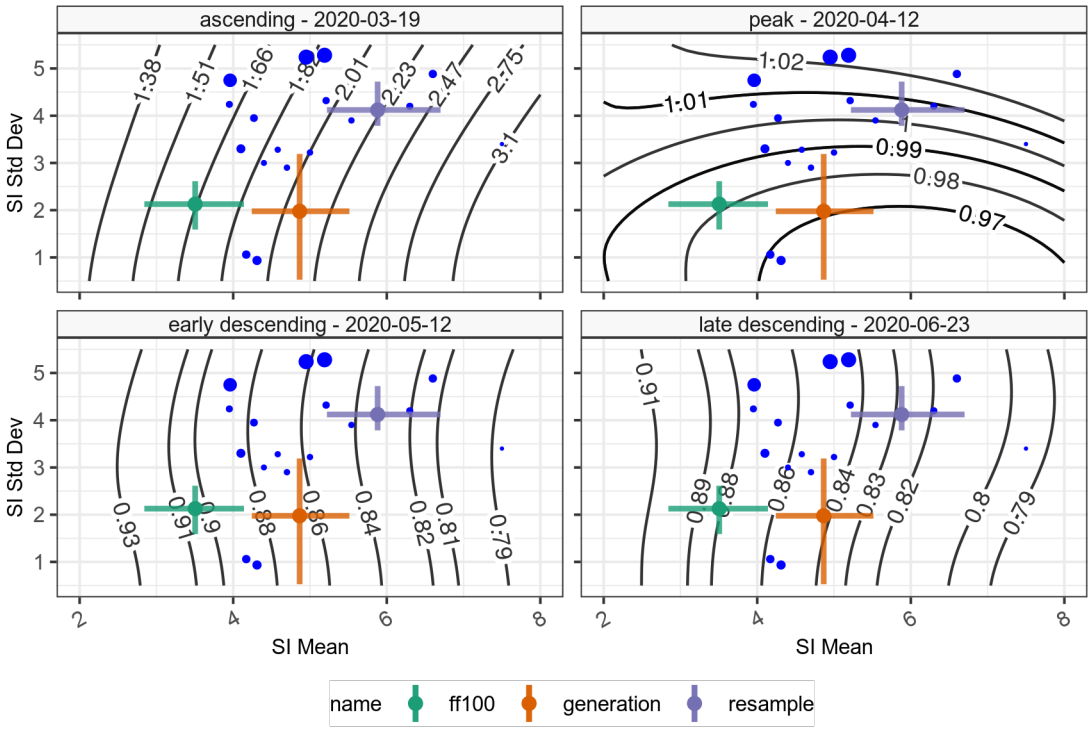

Figure 6: Time varying reproduction number given various assumptions on the serial interval mean and standard deviation. The blue points show the central estimate of serial intervals from the literature, whereas the coloured error bars show the mean and standard deviation of the 2 serial interval (green, violet) and 1 generation interval (orange) estimates presented in this paper. Contours show the R_t estimate for that combination of mean and standard deviation serial interval. The four panels represent the 4 different time points investigated.

Time delays from infection to case identification, admission, and death

There are 9902 patients in the subset of the CHESS database we examined of which 82.3% had a symptom onset date. In Figure 7 we show probability distributions fitted to data from the CHESS data set which define times from symptom onset (Panel A) to case identification ($T_{onset \to case}$), admission ($T_{onset \to admission}$), or death ($T_{onset \to death}$). Symptom onset to test (case identification) can be a negative quantity if a swab is taken during disease screening and the patient is pre-symptomatic. In this data the time point that defines the time of test is the date when the specimen is taken, which will subsequently be tested positive for SARS-CoV-2, so does not include sample processing delays. However in this hospital based data source of admitted patients the onset data was collected retrospectively. We also note peaks at 1 day, 1 week, 2 weeks, and so on which suggests approximation on data entry, and there may well be biases in the data collection.

It is more obvious from the clinical course of COVID-19 that admission should occur after disease onset. In the data, a large number of cases are reported to have symptom onset on day of admission. This is potentially a reporting artifact as in the absence of certain knowledge about onset, it is possible that the day of admission may have been captured instead, and we again see the peaks at 1 week, 2 weeks, and so on, suggesting approximations in data entry.

The time between onset of symptoms and death can also be assumed as a positive quantity given this is based on an in hospital cohort. This distribution shows a large tail, and some patients in that tail were noted to be admitted many months before the appearance of COVID-19. These patients likely represent hospital acquired cases in chronically unwell patients. The extreme outlying values (with delay from admission to death greater than 100 days, or with an admission before 1st Jan 2020) were removed as they prevented sensible estimation of the rest of the distribution.

By combining the incubation period distribution in panel B in Figure 3 with the time delay distributions in panel A of Figure 7, we can obtain probability distributions from infection to observation, and these are shown in panel B for the 3 observations of test (case identification), admission and death. These distributions provide us with a means of estimating a time series of infection from observed case counts, admissions and deaths. As above full details of their parameterisations are available in Supplemental table 6. The mean time from infection to the various time points described in the timeline in Figure 1 are presented in Table 4. The infection to onset is the incubation period, with a mean of 4.2 days. On average 6.4 days pass from infection to diagnosis, a subsequent 1.2 days until admission, and a further 8.3 days until death, however it also shows considerable variation in these delays, exemplified by the 95% quantiles for the time from infection to death estimated as ranging from 3.6 days to 42.9 days.

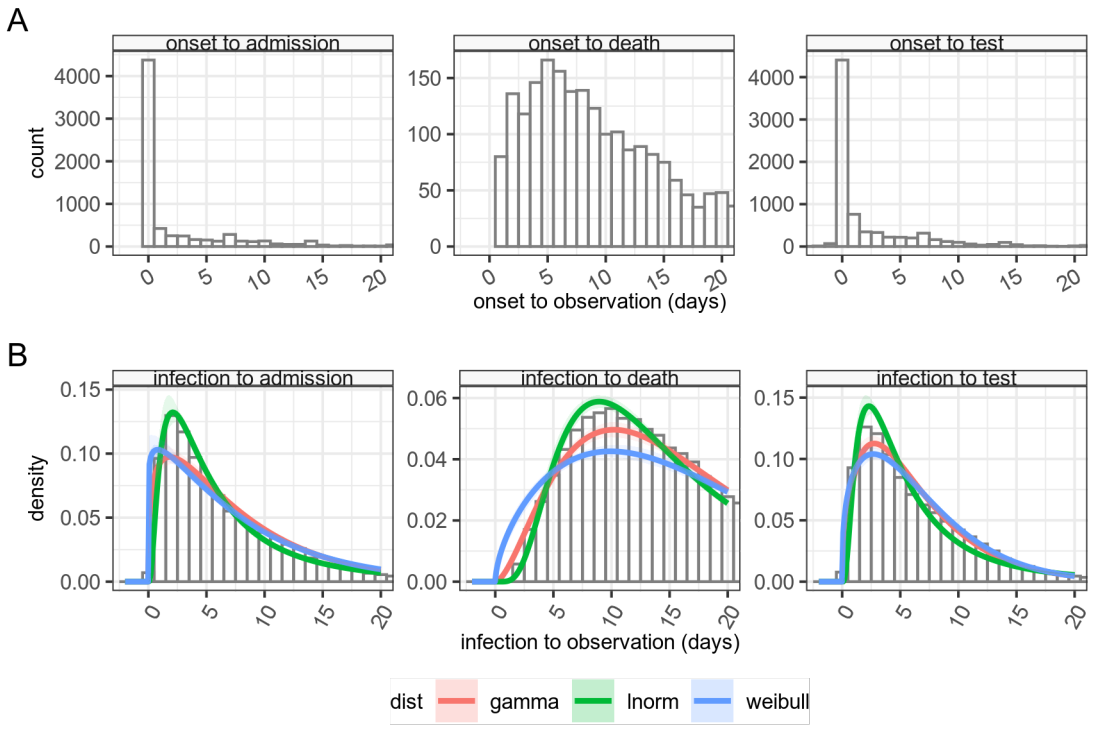

Figure 7: Panel A: Time delay distributions from symptom onset to test (diagnosis or case identification), admission or death, estimated from CHESS data set, plus in Panel B estimated delays from infection to observation, and can be negative in certain cases. based on incubation period and observation delay. These can be used for deconvolution.

Table 4: Estimated time delays between infection and various observations over the course of an infection, based on the combination of incubation period and symptom onset to observation delay

Observation	Mean delay (days)	SD (days)	95% quantiles (days)
onset	4.21	3.00	0.64; 11.99
test	6.43	4.97	0.78; 19.18
admission	7.64	8.73	0.78; 30.67
death	15.98	10.90	3.59; 42.87

Estimation of R_t

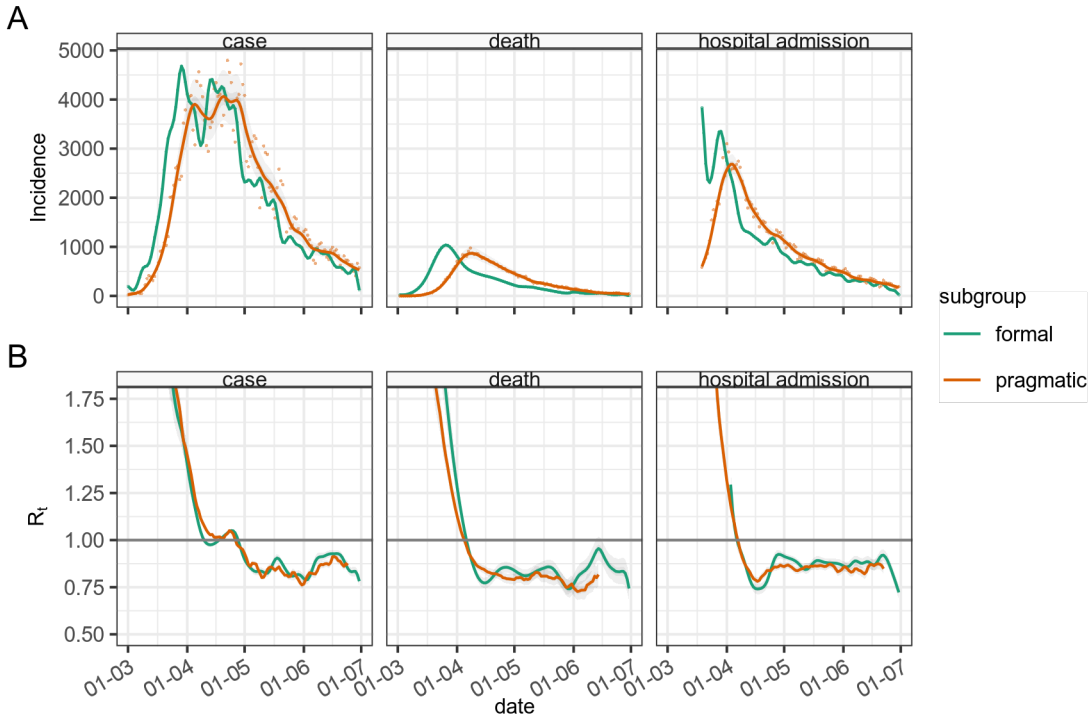

Figure 8: Panel A: The epidemic incidence curves in England for different observations (orange - formal) and inferred estimates of infection rates (green - pragmatic) based on a deconvolution of the time delay distributions. Panel B, the resulting R_t values calculated either using infection rate estimates and generation interval (formal subgroup) or unadjusted incidence of observation, and serial interval (pragmatic). The R_t estimated direct from observed incidence curves (pragmatic) have their dates adjusted by the mean delay estimate

With the estimates of delay from infection to observation we are able to use a non parametric back propagation as described in the methods to estimate a time series of infections as recommended by Gostic et al.[10] when using EpiEstim. The results of the back propagation is shown in Figure 8, panel A which depicts resulting point and smoothed infection curves associated with observation curves from England. The back projection results in a sharper and narrower epidemic curve than the observation it is derived from, and indicates additional structures (such as more pronounced fluctuations) which are not obvious from the underlying observations. Estimates of R_t are shown in panel B based on de-convolved time series plus generation interval, versus raw observation counts, re-sampled serial interval estimates, with time adjustment on the resulting R_t estimates to align R_t estimate date to putative date of infection. We have not calculated confidence intervals for the estimates of R_t. The estimates of R_t differ from their mean (using symmetric mean absolute percentage error, sMAPE) by between 3.33% to 6.51% [case: sMAPE 3.44% (IQR 1.86%; 5.17%); death: sMAPE 6.51% (IQR 2.62%; 12.24%); hospital admission: sMAPE 3.33% (IQR 1.46%; 5.60%)].

Discussion

Our estimate of the serial interval from the FF100 UK data was found to be short, compared to international estimates. The FF100 data was collected in the early stage of the epidemic and is based mainly on household contacts of international travelers which may impart bias. As the participants in the study were put into self-isolation upon discovery observations the contact period tends to be shortened, leading to shorter serial

interval estimates, and because of this we do not believe the estimate from the FF100 study to be specific to the UK but rather that the data set is not broadly representative of the UK population.

In contrast, our literature search allowed us to estimate the serial interval from a much larger pooled sample drawn from multiple studies. Random effects and a re-sampling meta-analyses produced comparable results (random effects: mean 4.83 (95% CI 3.93–5.70) days and re-sampling: mean 5.9 (95% CI 5.2; 6.7) and SD 4.1 (95% CI 3.8; 4.7) days), but our re-sampling study more clearly showed the potential for the serial interval to be negative, due to the relatively long and variable incubation period of SARS-CoV-2. This is seen in the unsatisfactory fits of parameterised probability distributions in figure 2, and we choose not to use these in our pragmatic estimation of R_t. instead of which we rely on the set of empirical distributions resulting from our sampling analysis. Even so, the negative values of the serial interval within these are theoretically problematic for their use as a proxy for the infectivity profile of SARS-CoV-2 in transmission modelling, which requires the infectee is infected after the infector. As a way around this, we truncate the re-sampled serial interval at zero, and use this as the infectivity profile, but as seen here this truncation increases the mean of the resulting serial interval distribution from 4.87 to 5.88 days.

An alternative to this is to use the generation interval as a proxy for the infectivity profile, but there are limited estimates of this quantity available in the literature[51]. Derivation of the generation interval from the serial interval is possible using knowledge of the incubation period. We again looked at the FF100 data for estimates of incubation period and again found that the UK data suggests a value which is shorter that international estimates, for the same reasons as mentioned above[26,47,52–54]. We cross referenced this with a second estimate derived from the Open COVID-19 Data Working Group data set[28,29], which is based on a large international data set of people who tested positive for SAR-CoV-2 after travelling from areas with outbreaks. The resulting estimates of the mean incubation period of 5.5 days (log normally distributed) is much closer to previous estimates, and we expect to be less influenced by right censoring. Again, we regard the short incubation period calculated from the FF100 data set to be a feature of the data set rather than a UK specific finding. In fact the estimate based on the Open COVID-19 Data may in itself be an under-estimate as the majority of travel histories only include the return date of the visit in question and not the start date.

With incubation period and serial interval estimates, we derived an estimate for generation interval, assuming a gamma distribution. This was comparable to previous estimates in that although it is based on a different serial interval, and hence has a different mean, the standard deviation of our estimate is in accordance with that estimated by Ganyani et al.[51] Although the confidence intervals for the mean and standard deviation of the generation interval are comparable, the variation in the shape and rate parameters of the underlying gamma distribution are quite large. Care should be taken when generating bootstrap samples from the generation interval when it is specified as an uncertain gamma distribution parameterised with mean and standard deviation, as it is possible that some combinations of parameters produce unrealistic distributions, particularly when the standard deviation is small and the mean is large, which could in theory result in posterior estimates for R_t being largely determined by the reciprocal of just a small number of observations.

Using estimates of the serial interval distribution and generation interval distribution as a proxy for infectivity profile, we investigated the resulting variation in the estimation of R_t using incident cases in England and the forward equation approach. We found the bias between the smallest and largest of our estimates to be as high as 20-25% of the central estimate of R_t when R_t was high, but somewhat smaller when R_t values were 1 or lower. Distributions with lower values of the mean tended to result in estimates of R_t that were closer to one. This suggests that biases introduced by the use of different serial interval distributions should not influence the answer to the key question, "is R_t greater or less than 1?" which defines whether the epidemic is expanding or contracting in size. It is also to be expected that the nature of change of R_t over time is not affected by this bias, so an increasing value of R_t will be increasing regardless of the infectivity profile that is used to estimate it.

Estimating R_t is based on knowledge of the incidence of infections. This is not a quantity that is readily observed in the SARS-CoV-2 epidemic, and pragmatically use of observations including symptom onset, case identification, admission and death are expected to be used as proxy measures for infection[5,31]. However, as pointed out elsewhere[10] the variable time between infection and such observations causes the signal to

be both delayed and blurred. By combining our estimates of incubation period with data from hospital admissions in the CHESS data set we were able to make estimates of the distribution of the delay from infection to observation for the UK. There are several caveats to this part of our analysis that must be kept in mind. The CHESS data set relies on a retrospective report of onset of symptoms, and this field is not recorded for all patients. We select only those patients who have reported an onset date and it may be the case that these patients represent a subgroup of patients whose symptom onset is significantly different from the average patient. The data collection around these dates was noted above to show patterns suggestive of rounding or approximation and this could also introduce some bias. The delay distributions are also unlikely to remain fixed during the outbreak, as we would hope to see the time from infection to case identification shorten during the epidemic, and the time from infection to death lengthen as treatment improves, and as the cohort of susceptible individuals changes. Our confidence in these distributions is therefore somewhat low, although we note acceptable agreement between our estimates produced using a mixture of international and UK data, and previously published estimates from different countries, most notably China[54–57] which cite an onset to admission of 2.7-5.9 days[46,54,58] and onset to death delay of 16.1-17.8 days[54,58]. Given our estimate of the incubation period is log normally distributed, it is unsurprising that the combination of incubation period and delay from onset to observation is also best described by log normal distributions (Figure 7, panel B), and with these we can apply non parametric back propagation to infer a time series of putative infections from the delayed observations we have available.

In Figure 8 we bring all the different parts of the analysis together and compare the two approaches of formal estimation of R_t using the generation interval and back propagation of case, admission or death counts to putative infection, versus an pragmatic estimation using the truncated re-sampled serial interval, and direct use of observation numbers, combined with the simple-but-incorrect adjustment to the resulting R_t time series, shifting the date backwards by the mean of the delay distribution[10].

In comparing formal versus pragmatic methods, given the number of moving parts in this comparison it is encouraging to see the level of agreement between the R_t estimates from the two methods (Figure 8 panel B) in the early phase of the epidemic, and also to see that there is some similar structure of the R_t time series in the later parts. This is particularly the case for estimates based on cases and admissions, but less so for deaths where the de-convolution time series shows additional features that are not obvious from the data. We have no gold standard in comparing the R_t estimates for England, so we are limited in what we can conclude, but we do observe that R_t estimates based on our attempt at de-convolution have more variability than ones from un-adjusted observations, and de-convolved estimates have additional features not present in the un-adjusted estimates. The de-convolved estimates of infection are also noted to run to the end of the time series, which is somewhat surprising as estimates of infection rates at the end of the time series should depend on data which has not yet been observed. This is a feature of the back propagation algorithm which needs to be used with caution as the resulting estimates of R_t based on de-convolution for the latter part of the time series appear inconsistent with each other.

Limitations

We did not fully quantify uncertainty in our analysis and estimation of R_t. The informal approach to estimating R_t has uncertainty arising from the serial interval distribution, and stochastic noise in the value of the observation in question. The formal approach involves uncertainty in the initial estimation of the serial interval, uncertainty in the incubation period, resulting in uncertainty in the generation interval, the back propagation itself is a source of uncertainty and involves uncertain time delay distributions which are in turn based on uncertain incubation period, and finally the stochastic noise in the observation under consideration. Accurately tracking the uncertainty of all these components into a final estimate remains a challenge. One of the key reasons we choose to make simplifying assumptions in our use of the pragmatic approach in estimating R_t is that it makes comparatively transparent assumptions that can be backed up by experimental data, and for which the resulting biases are best understood.

Our estimates are based on the best available information at the present stage of the epidemic. However the serial interval is not a fixed quantity and may be affected by behavioral changes such as case isolation, or

social distancing. The assumption it is constant is questionable although we have very little hard evidence about how it may vary over time. Similarly time distributions from infection to case identification, admission and death are expected to be highly variable over the course of an outbreak. This has implications for their use in de-convolution, as changing time distributions will have a significant effect on the shape of inferred infection incidence curves, and the complexity of the de-convolution.

There are implicit selection biases in all the data sources we use. A large proportion of SARS-CoV-2 cases are asymptomatic[13,59,60]. It is highly likely that these people participate in transmission chains, and they may do so with a very different infectivity profile to those that are symptomatic, however we have no information about these people in the data sets, and hence all the estimates presented here could be quite different, when asymptomatic cases are taken into consideration.

The data used to assess delays to death rely on hospital based data as this was the best UK specific data we had. However this means that delays to deaths are only assessed for the subset of patients that die in hospital, and we are forced to generalise this to the whole population.

Our approach in estimating key parameters has been to combine different data sets, which come from different international sources, and which have potentially different biases. In combining data sets we assume that time delays are independent of one another, and can be combined randomly, as we have no other evidence to the contrary. This assumption is questionable, as physiologically we can imagine that patients with a long incubation period, for example, may well have a longer period from symptom onset to admission, for example. This could have unpredictable effects on our estimates of time delays but the most likely is that our estimated variance is too small as a result.

Conclusions

We argue that our estimates for the statistical distributions of these key parameters or serial interval, incubation period, generation interval, for the UK, along with their uncertainty represent the best available estimates for the UK, at the time of writing (September 2020), given the current state of knowledge.

As there is a wide range of candidate values for these quantities, we have assessed the bias that the variation in choice of parameters introduces to R_t estimation, when using the forward equation method. Whilst these introduce significant variation in the worst case scenario, we find that even large differences in infectivity profile can have only small impacts on estimates of R_t when R_t is close to 1. Larger values for the mean of the infectivity profile appear to result in R_t estimates that are further away from 1. This is a relatively reassuring finding in that the answer to the key question "is the epidemic under control?" is insensitive to the mean of the infectivity profile.

Using more formal methods for estimating R_t by back propagation inference of infection rate and estimates of the generation interval, produces R_t estimates that are more variable when compared to the more pragmatic direct use of case counts as a proxy for infection. Both methods agree on when the epidemic crossed the R_t threshold of 1. However there is considerable uncertainty in the quantities needed to perform the back propagation, and we are not able to ensure that all this uncertainty could be faithfully quantified in our resulting R_t estimates. We did not set out to assess whether one method is better than another, and this would be a natural extension to this work, however we note that new methods for combining back propagation with estimation of R_t are under active development[61,62] and may very well address such further questions.

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