

COVID-19 epidemiological parameters summary document

IEMAG Epidemiology Modelling subgroup

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Abstract

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 (NPHE) in their decision-making during the pandemic. A subcommittee from IEMAG (the epidemiological parameters team) 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. These parameters include:

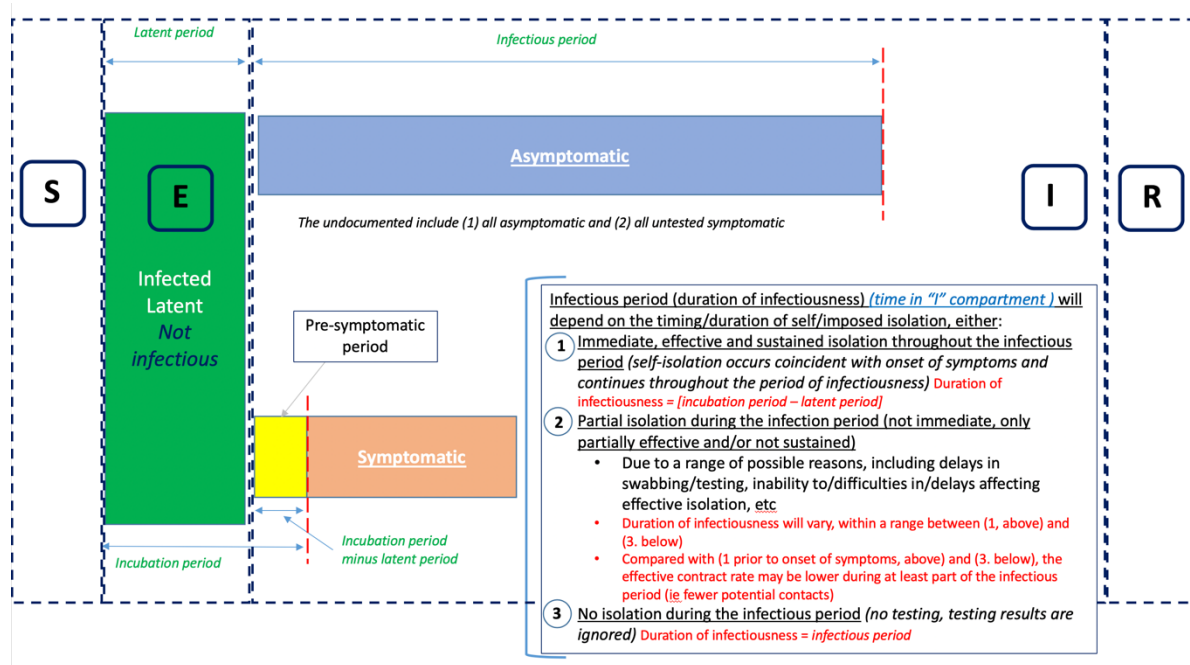
- R_0/R
- Latent period & relative importance of pre-symptomatic period
- Incubation period
- Generation time & serial interval
- Proportion of infected who are asymptomatic, by age
- Length of infectious period in asymptomatic people and in symptomatic people who do not isolate
- Time from onset of symptoms to diagnosis/test results and to hospitalisation
- Length of hospital stay and admission to ICUs
- Relative infectiousness of asymptomatic versus symptomatic infected people

The current document presents an up-to-date summary of these synthesis documents.

A further synthesis document on age-related susceptibility and age-related infectiousness is in preparation.

1. Conceptual diagram

This figure is a pictorial description of many of the parameters and pathways relevant to COVID-19 infection, based on current understanding.



SEIR model (S: susceptible; E: exposed; I: infected; R: recovered)

2. Synthesis documents

2.1 R₀/R

Manuscript in preparation

The basic reproduction number, R_0 , is the expected number of additional cases that are generated, on average, by a single but typical case, over the course of its infectious period, in an otherwise uninfected population. The effective reproduction number, R , is a dynamic estimate of the average number of secondary cases generated by a single but typical case, over the course of its infectious period, in a population where an outbreak is ongoing and there are changes in the frequency of susceptibles (i.e. through immunity or intervention).

R_0 is a function of three components:

- Average contact rate between susceptible and infectious individuals per unit time
- The probability that the contact leads to infection
- The average duration of the infectious period

The different components of R_0 can be targeted for intervention, for example:

- Social distancing, *reducing contact rate per unit time*

- Wearing protective equipment upon contact, *reducing probability that contact leads to infection*
- Early diagnosis, isolation and treatment, *reducing average duration of (effective) infectious period*

R_0 and R are both population- and context-specific, and caution is needed when interpreting these parameter estimates:

- R_0 is sensitive to the timing of the epidemic, and should be measured for the early epidemic phase.
- R is not sensitive to the timing of the epidemic. It is a dynamic parameter that chronicles the time-dependent variation in transmission across a population consisting of both susceptible and non-susceptible individuals. Therefore, R can be evaluated in a time-varying context, typically to monitor the progress of intervention.

Based on a review of available literature between 01 December 2019 and 11 April 2020, a mean R_0 (*ie prior to mitigation*) of 3.73 (median 3.1) was estimated.

From the European Centre for Disease Control and Prevention (ECDC, 2020):

- *A recent review of 12 modelling studies [from China] reports the mean R_0 at 3.28, with a median of 2.79. This is in accordance with recent estimations in Italy with R_0 estimates between 2 and 3 depending on the region considered (Riccardo et al., 2020).*
- *A scientific report ... on data from 11 European countries reported an initial reproduction number R_0 estimate of 3.87 [95% CI 3.01-4.66] (Flaxman et al., 2020).*

2.2 Latent period & relative importance of pre-symptomatic transmission

Pre-print manuscript: Casey, M., Griffin, J., McAloon, C.G., Byrne, A.W., Madden, J.M., McEvoy, D., Collins, Á.B., Hunt, K., Barber, A., Butler, F., Lane, E.A., O'Brien, K., Wall, P., Walsh, K.A., More, S.J. Estimating pre-symptomatic transmission of SARS-CoV-2 infection: a secondary analysis using published data. *MedRxiv*, <https://doi.org/10.1101/2020.05.08.20094870>

Latent period

The latent period is the period from the point of infection to the beginning of the state of infectiousness

The latent period cannot be directly observed. However, several methods are available to allow the duration of this period to be inferred:

- The latent period can be estimated by subtracting duration of pre-symptomatic infectiousness from the incubation period. The duration of infectiousness can be estimated based on evidence of transmission from contact tracing (so-called ‘time of

transmission relative to symptom onset) or from virological studies of viral shedding prior to symptoms. Estimates of incubation period are available (for example from the meta-analysis presented below (McAloon et al., pre-print).

- The latent period can be converged upon through statistical or mathematical modelling to fit large datasets of observed variables (e.g. confirmed cases or deaths in a COVID-19 outbreak) and validated with different datasets.

In addition, inferences about the upper limit of latent period can be made from generation time (time between infection of the infector and infection of the infectee found by contact tracing).

Based on ongoing work with pre-symptomatic transmission, our best estimates for the earliest time of transmission relative to symptom onset is from a mean of 2.95 days before to 1.72 days after symptom onset, with a simple unweighted pooling of estimates giving a most-likely mean of 0.67 days before symptom onset.

Therefore, the estimated earliest mean time of transmission is 2.85 days (mean incubation period of 5.8 days *minus* 2.95 days) through to 7.5 days (5.8 *plus* 1.72 days) after the time of infection. Based on the unweighted mean, above, the most likely is a mean of 5.13 days (5.8 minus 0.67 days). Latent period is likely towards the lower end of the range between 2.85 days (the earliest) and 5.13 days (the most likely). Larger numbers of simulations are being run to inform measures of uncertainty for these estimates.

Whilst transmission depends on contact rates, type of contact, infectiousness and susceptibility, latent period should not vary greatly between countries. It depends on the characteristics of the virus and the person it is infecting, and not on population density, movements or health service infrastructure.

From the European Centre for Disease Control and Prevention (ECDC, 2020):

- ... the virus has been identified in respiratory tract specimens 1-2 days before the onset of symptoms (Wölfel et al., 2020).

The relative importance of pre-symptomatic transmission

A pre-symptomatic person is somebody infected with SARS-CoV-2 who is in the incubation period and will go on to develop symptoms.

Understanding the extent of virus transmission that can occur before symptom onset is vital for targeting control measures against the global pandemic of COVID-19. Simulations were generated of incubation period and of serial interval or generation time. From these, transmission times relative to symptom onset were calculated and the proportion of pre-symptomatic transmission was estimated. A total of 23 estimates of serial interval and five estimates of generation time from 17 publications from a range of countries were included.

The proportion of pre-symptomatic transmission ranged from 33.7% in Wuhan to 72.7% in Hong Kong suggesting that there is the substantial potential for pre-symptomatic transmission of COVID-19 in a range of different contexts.

Virological studies (Hu et al., 2020; Kam et al., 2020; Kimball et al., 2020) support the occurrence of pre-symptomatic transmission suggested by quantitative approaches. Whilst samples testing positive by polymerase chain reaction (PCR) do not always fully correlate with infectiousness (Wölfel et al., 2020), relatively lower cycle threshold (CT) values suggest higher virus loads. Two studies (Kimball et al., 2020; Kam et al., 2020) that reported pre-symptomatic PCR CT values included some relatively low values. A report of pre-symptomatic PCR positive samples in ten nursing home residents reported a mean time of 3 days from sampling to onset of symptoms. In addition, the isolation of live virus from upper respiratory samples very soon after patient presentation with symptoms has been reported (Wölfel et al., 2020).

From the European Centre for Disease Control and Prevention (ECDC, 2020):

- *Pre-symptomatic transmission has been reported; exposure in these cases occurred 1–3 days before the source patient developed symptoms (Wei et al., 2020)*
- *It has been inferred through modelling that, in the presence of control measures, pre-symptomatic transmission contributed to 48% and 62% of transmissions in Singapore and China (Tianjin data), respectively (Ganyani et al., 2020)*
- *Based on the data from within and outside mainland China, 44% (95% confidence interval, 25–69%) of secondary cases were estimated to be infected during the index cases' pre-symptomatic stage (He et al., 2020)*
- *Although transmission from asymptomatic infected individuals has also been reported, the risk of transmission from pre-symptomatic or symptomatic patients is considered to be higher; viral RNA shedding is higher at the time of symptom onset and declines after days or weeks (Lavezzo et al., 2020)*

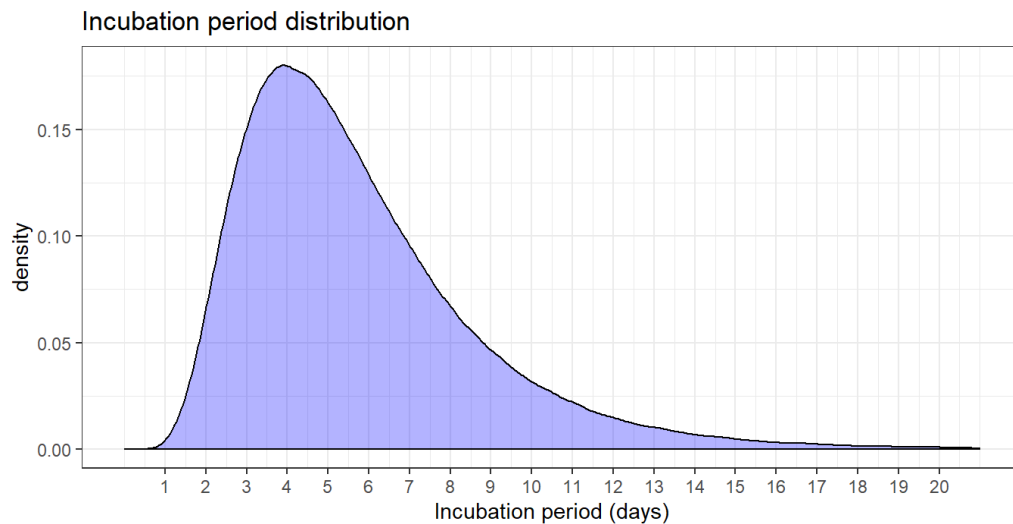
2.3 Incubation period

Pre-print manuscript: McAloon, C.G., Collins, Á.B., Hunt, K., Barber, A., Byrne, A.W., Butler, F., Casey, M., Griffin, J., Lane, E., McEvoy, D., Wall, P., Green, M.J., O'Grady, L., More, S.J. The incubation period of Covid-19 – A rapid systematic review and meta-analysis of observational research. *MedRxiv*, <https://doi.org/10.1101/2020.04.24.20073957>

Period from the point of infection to onset of symptoms

A systematic review and meta-analysis of studies estimating the incubation period was conducted. Studies were selected for meta-analysis if they reported either the parameters and confidence intervals of the distributions fit to the data, or sufficient information to facilitate calculation of those values. The majority of studies suitable for inclusion in the final analysis modelled incubation period as a lognormal distribution. We conducted a random effects meta-analysis of the parameters of this distribution.

The incubation period distribution may be modelled with a lognormal distribution with pooled mu and sigma parameters of 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55) respectively. The corresponding mean was 5.8 (5.01, 6.69 days). It should be noted that uncertainty increases towards the tail of the distribution: the pooled parameter estimates resulted in a median incubation period of 5.1 (4.5, 5.8) days, whereas the 95th percentile was 11.6 (9.5, 14.2) days.



Several points of caution:

- Studies to determine incubation period are likely most precise during the early phase of the outbreak, before the pathogen is widespread. This is because exposure windows can be determined with some confidence during this early phase.
- By definition, case data needs to include both exposure (window) and onset of symptoms. Precisely estimating these events can be difficult, although statistical methods are available to estimate incubation period distribution from coarse data (that is, exposure and/or symptom onset are not observed exactly but known to fall within an interval of time)
- Characterized cases may be biased towards more severe cases, which has the potential to bias the estimate downwards

The incubation period should be similar across different populations. Nonetheless, there may be factors that might impact on incubation period, such as infectious dose for example that might vary between populations (and possibly within populations over the course of the outbreak) meaning that the resulting distribution may vary for different populations, or potentially at different stages of the outbreak. Incubation periods may be different for people of different ages.

From the European Centre for Disease Control and Prevention (ECDC, 2020):

- *Current estimates suggest median incubation period from 5-6 days for COVID-19, with a range from between 1 and 14 days.*

- *One study reported that in 97.5% of people with SARS-CoV-2 infection, COVID-19 compatible symptoms will appear within 11.5 days (Lauer et al., 2020)*
- *A recent modelling study confirmed that it remains prudent to consider the incubation period of at least 14 days (Backer et al., 2020; Chinese Centre for Disease Control and Prevention, 2020)*

2.4 Generation time & serial interval

Pre-print manuscript: Griffin, J., Collins, Á.B., Hunt, K., Casey, M., McEvoy, D., Byrne, A.W., McAloon, C.G., Barber, A., Lane, E.A., More, S.J. A rapid review of available evidence on the serial interval and generation time of COVID-19. *MedRxiv*, <https://doi.org/10.1101/2020.05.08.20095075>

The serial interval and generation time are key parameters for assessing the dynamics of a disease. The generation time is the duration between the time of infection of a secondary case and that of its primary case. The serial interval is the duration between symptom onset of a secondary case and that of its primary case.

- *The serial interval and the generation time have the same mean value, provided the incubation times of the infectee and infector are independent and identically distributed.*
- *The serial interval can be negative. As reported by Ma et al., in 3.9% of 689 infector/infectee pairs, infectees' symptom onsets occurred before those of infectors.*
- *By definition, generation time is the upper limit of the latent period. That is, the latent period cannot be longer than the generation time, but could be substantially shorter (ie if effective contact were not to occur until the end of the infectious period)*
- *Generation time will vary in different circumstances (countries, stage of epidemic), given the contribution of the effective contact rate.*

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.

The following estimates were obtained:

- 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).
- The mean estimate of generation time ranged from 3.9 to 5.2 days, based on three estimates. One estimate of 5.0 days was provided for the median of the generation time.

Many authors concluded that the serial interval of COVID-19 was shorter than its median incubation period suggesting that that a substantial proportion of secondary transmission may occur prior to illness onset.

The estimation of generation time and serial interval is challenging and is open to a number of biases and methodological errors and these occurred to a greater or lesser degree in all of the studies under review. Du et al. (2020) outline possible sources of bias:

- If 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
- The identity of each infector and the timing of symptom onset is based on individual recollection of past events. 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)

Further, Ganyani et al. (2020) highlight the mathematical relationship between the serial interval and the generation time, which has important implications for the calculation of the R_0 .

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. (2020) 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 should be estimated from early cases and careful consideration should be given to the methodology that is used.

2.5 Proportion of infected who are asymptomatic, by age

Manuscript in preparation

An asymptomatic person is somebody infected with SARS-CoV-2 who never develops symptoms of COVID-19 disease

Three studies provide robust insights into the proportion of infected that are asymptomatic:

- 30.8%, Nishiura et al.
- 19.5%, Bi et al.
- 17.9%, Mizumoto et al.

Each is based on viral detection using PCR. In the study of Mizumoto et al. (2020), the study subjects (people onboard the *Diamond Princess* cruise ship) were 60 years and older, therefore the proportion asymptomatic may be underestimated if older individuals tend to experience more symptoms.

Location	Study	Time Period under surveillance	Population under surveillance	n under surveillance	n testing positive	n infected with no symptoms	% infected with no symptoms
Japanese evacuees from mainland China	(Nishiura et al.)	4 week monitoring period 6 th Feb – 6 th Mar	Evacuees, no information on age	565	13	4	30.8% (95% CI 7.7, 53.8).
Shenzhen China	(Bi et al.)	391 SARS-CoV-2 cases from January 14 to February 12, 2020 and 1286 close contacts.		1,286 monitored and tested close contacts of confirmed cases	98 of 1286 contacts infected; 87 of these had full data available	17	19.5% (17 out of 87)
<i>Diamond Princess</i> cruise ship	(Mizumoto et al.)	5-20 Feb	Most passengers over 60	3,711	634		17.9% (95% CI 15.5, 20.2)

Based on data from the *Diamond Princess*, and in contrast to the above-mentioned article by Mizumoto et al. (2020) (with an estimate of 17.9 % asymptomatic), Emery et al. (2020) suggest that 74% (95% posterior interval (PI) = 70-78%) of infections proceeded asymptotically. The authors suggest that due to heterogeneity in sampling coverage throughout the surveillance period, many of the asymptomatic infections (especially the earlier ones) were missed by diagnostic testing with PCR.

There are reports emerging, including Gudbjartsson et al. (2020) and Lavezzo et al. (2020) of mass sampling and PCR testing of potentially exposed populations. These give a useful snapshot of the proportion of people with detectable viral genome and without symptoms, but do not explicitly report whether the people who tested positive developed symptoms later or not. Therefore, the people who tested positive with no symptoms may be those a mixture of pre-symptomatic and asymptomatic infections.

The results from serological testing will shortly emerge, which will help to clarify the relative importance of asymptomatic infection.

From the European Centre for Disease Control and Prevention (ECDC, 2020):

- *Asymptomatic infection at time of laboratory confirmation has been reported from many settings, including Ki et al. (2020) and Mizumoto et al. (2020).*

- *Some of these cases developed some symptoms at a later stage of infection, however, the proportion of cases that will develop symptoms is not yet fully understood (Cereda et al., 2020; Lou et al., 2020)*
- *There are also reports of cases remaining asymptomatic throughout the whole duration of laboratory monitoring, which revealed viral RNA shedding in various sample types.*
- *A recent modelling study suggested that asymptomatic individuals might be major drivers for the growth of the COVID-19 pandemic (Aguilar et al., 2020)*

2.6 Length of infectious period in asymptomatic people, length of infectious period in symptomatic people that do not isolate

Pre-print manuscript: Byrne, A.W., McEvoy, D., Collins, Á.B., Hunt, K., Casey, M., Barber, A., Butler, F., Griffin, J., Lane, E., McAloon, C.G., O'Brien, K., Wall, P., Walsh, K., More, S.J. Inferred duration of infectious period of SARS-CoV2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases. *MedRxiv*, <https://doi.org/10.1101/2020.04.25.20079889>

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

A rapid scoping review was conducted. Literature review with fixed search terms, up to 1st April 2020. Central tendency and variation of the parameter estimates for infectious period in (a) asymptomatic (b) symptomatic cases from (i) virological studies (repeated testing), (ii) tracing studies (iii) modelling studies were gathered. A narrative review of viral dynamics was undertaken. Search strategies were developed and the following databases were searched: PubMed, Google Scholar, MedRxiv, BioRxiv. Additionally, the Health Information Quality Authority (Ireland) viral load synthesis was utilised, which screened literature from PubMed, Embase, ScienceDirect, NHS evidence, Cochrane, medRxiv and bioRxiv, HRB open databases.

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

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

From the European Centre for Disease Control and Prevention (ECDC, 2020):

- *Over the course of the infection, the virus has been identified in respiratory tract specimens 1-2 days before the onset of symptoms, and it can persist for up to eight days after the onset of symptoms in mild cases infection (Wölfel et al., 2020), and for longer periods in more severe cases, peaking in the second week after infection (Liu et al., 2020; Wölfel et al., 2020)*
- *In a retrospective study of 113 symptomatic patients, the median duration of SARS-CoV-2 RNA detection was 17 days (Interquartile Range [IQR], 13–22 days) as measured from illness onset. When comparing patients with early (<15 days) and late viral RNA clearance (≥ 15 days after illness onset), prolonged SARS-CoV-2 RNA shedding was associated with male sex ($p=0.009$), old age ($p=0.033$), concomitant with hypertension ($p=0.009$), delayed admission to hospital after illness onset ($p=0.001$), severe illness at admission ($p=0.049$), invasive mechanical ventilation ($p=0.006$), and corticosteroid treatment ($p=0.025$). Patients with longer SARS-CoV-2 RNA shedding duration had slower recovery of body temperature ($p<0.001$) and focal absorption on radiograph images ($p<0.001$) than patients with early SARS-CoV-2 RNA clearance (Xu et al., 2020a)*
- *Viral RNA has been detected in faeces (Cai et al., 2020), whole blood (Young et al., 2020), serum (Chang et al., 2020; Huang et al., 2020), saliva (Backer et al., 2020; Lavezzo et al., 2020), nasopharyngeal specimens (Zhou et al., 2020), urine (Peng et al., 2020) and ocular fluid (Colavita et al., 2020)*
- *It should be noted that viral RNA shedding does not equate with infectivity. [Nonetheless,] the viral load can be a potentially useful marker for assessing disease severity and prognosis*

2.7a Time from onset of symptoms to diagnosis/test results

Time (days) from onset of symptoms [self-reported] to diagnosis, as determined by RT-PCR testing

The literature

The most comprehensive published information is presented in Bi et al. (2020).

Mean time (days) from self-reported onset of illness to diagnostic test					
Study	Location	Time Period	Parameter	n	95% Confidence Interval
Bi et al. [contact based surv.]	Shenzhen, China	14 January - 12 February	3.18	183	2.65-3.76 [gamma dist]
Bi et al. [symptom based surv.]	Shenzhen, China	14 January - 12 February	5.46	183	4.99-5.92 [gamma dist]

Available international data

Data from the analysis of the dataset from Kraemer et al. (2020) should possibly be the best starting values, before Irish data are analysed and used.

- 947 people, multiple countries including China (outside Hubei Province)
- *Onset of symptoms to date of confirmation*: mean 6.55 days, median 5 days, 5th and 95th percentile: 1 and 15; max: 39 days.
- Fitting a gamma distribution to the data (replacing 0 day difference between symptoms and testing, with 0.1), suggested a distribution with an alpha of 1.78 and a beta of 3.68 (Stata/MP 14, GAMMAFIT). The estimated mean from this ($\alpha/(1/\beta)$) = 6.55 days.
- There was no evidence of sex differences for this parameter
- There was significant variation across reporting countries in this dataset, however some countries had few records to inform our inference
- There is evidence that this parameter is affected significantly by time since outbreak started. For example, regression estimated mean duration in China decline from 12.5 days to 1.8 days over the epidemic [recorded from Dec-19 – Mar-20]

Early data from Ireland

(March 2020)

- The early Irish data (29 February – 21 March 2020) for time from onset of symptoms to diagnosis/test results indicated a mean of 5.15 days (gamma distribution with shape = 2.317, rate = 0.449558) (C. Walsh, personal communications). These results do not reflect likely differences between hospital and non-hospital settings

In conclusion

- This parameter is highly country and context specific
- Timings of onset of symptoms will be imprecise, as they are patient self-reporting
- Time from symptoms to diagnosis/test results may not be generalisable, as this will depend on patient awareness, access to testing facilities, availability of diagnostic tests, and the stage of the epidemic when a patient falls ill
- Data from case-reports from Ireland should be used as they may be more informative to the local epidemic, if available. There is a need for comparison among cases in hospital and non-hospital settings
- If sensitivity analyses are to be performed, information from the publicly available database (Kraemer et al., 2020) may be most useful

2.7b Time from onset of symptoms to hospitalisation

Time (days) from onset of symptoms [self-reported] to hospitalisation

The literature

Time (days) from self-reported onset of illness to hospitalisation						
Study	Location	Time Period	Parameter	n	Mean/ Median	Range
Xu et al. (2020b) [overall]	Zhejiang province, China	10 January 2020 to 26 January 2020	2.0	62	Median	(1.0-4.3)
Xu et al. (2020b) [cohort 1 - <10 days onset to hosp.]	Zhejiang province, China	10 January 2020 to 26 January 2020	1.0	29	Median	1.0-2.0 days IQR
Xu et al. (2020b) [cohort 2 - >10 days onset to hosp.]	Zhejiang province, China	10 January 2020 to 26 January 2020	6.5	33	Median	5.0-9.0 days IQR
Zhang et al. (2020)	Wuhan, China	2 Jan – 10 Feb 2020	7.0	221	Median	4.0-10.0 IQR
Lauer et al. (2020)	China, other than Wuhan	Before 28 January	2.7	101	Median	0.2-26.2 range

Linton et al. (2020) – living cases	China (Wuhan and other places w/I China)	Up to 31 January	3.3	155	Mean	2.7, 4.0 [gamma distribution]
Linton et al. (2020) – deceased cases	China (Wuhan and other places w/I China)	Up to 31 January	6.5	34	Mean	5.2, 8.0 [gamma distribution]

Papers reporting this parameter have varied, with a mean duration of 3.3-6.5 days, and a median duration of 1-7 days.

Analysing case data presented by Kraemer et al. (2020), the mean duration for 645 observations was 4.05 days; median 3; SD: 4.33; IQR: 1-6; Range: 0-33 days. Analysis suggested that time from onset to hospitalisation was shorter for young and older cohorts, relative to middle aged cohorts (>40-60). There also appeared some variation across reporting countries, albeit with few records for a number of countries. There was no evidence of differences in this parameter between sexes.

Some key conclusions:

- This parameter is highly country and context specific. Nonetheless, ‘*time from onset of symptoms to hospitalisation*’ will be more generalisable than ‘*time from onset of symptoms to diagnosis/test results*’ as it primarily relates to disease progression.
- Timings of onset of symptoms will be imprecise, as they are patient self-reporting
- Time to hospitalisation may not correlate well with time to diagnosis, as during the peak of infection, symptomatic cases can be admitted straight to hospital without diagnostic confirmation
- The studies by Zhang et al. (2020) and Xu et al. (2020b) are informative and are not dissimilar to the parameter estimate used in the Imperial model
- Data from case-reports from Ireland should be used when available, as they may be more informative to the local epidemic
- Data from the analysis of the dataset from Kraemer et al. (2020) should possibly be the best starting values before Irish data are analysed and used

2.8 Length of hospital stay and admission to ICUs

Pre-print manuscript: Lane, E.A., Barrett, D.J., Casey, M., McAloon, C.G., Collins, Á.B., Hunt, K., Byrne, A.W., McEvoy, D., Barber, A., Griffin, J., Wall, P., More, S.J. Country differences in hospitalisation, length of stay and admission to Intensive Care Units due to SARS-CoV-2 infection: a rapid review of available literature. *MedRxiv*, <https://doi.org/10.1101/2020.05.12.20099473>

A detailed search of the scientific literature and government reports, using Google Scholar, PubMed, MedRxiv and BioRxiv, was conducted for the time period 1st December 2019 to 30th April 2020; using appropriate keywords: resultant articles were scrutinised in detail, and appraised for reported data pertaining to hospitalization and time spent hospitalised.

Hospitalisation rate. Disease presentation was described in China, with 81% mild, 14% moderate and 5% severe presentations (Wu and McGoogan, 2020). The experience, thus far, in Europe and the USA are suggestive of a higher degree of severity. Initial reports suggest high hospitalisation and rates of admission to intensive care units (ICUs). Advice from ECDC lowers this estimation of ICU cases (median 2%). The relative age of the population, the level of pre-existing conditions, and other health factors may be contributors to the observed differences.

Length of stay. The evidence regarding the length of stay in ICU is reported in eighteen studies, fifteen deemed relevant, including from China, Italy, Mexico, Switzerland, UK and USA. A number of studies report ICU stay length of 7 to 10 days. Many of these studies are likely skewed towards shorter stay due to study cut-off dates. Indications based on ICU length of stay reported for patients continuing care suggest median ICU stay will be longer.

2.9 Relative infectiousness of asymptomatic versus symptomatic infected people

Manuscript in preparation

Relative infectious is an estimate of the probability that an asymptomatic infected person will pass on infection to another, susceptible person compared to a symptomatic infected person.

A summary of values relevant to the relative infectiousness of asymptomatic individuals is included in the Table below:

Author	Location	n	Estimate (95% CI)
<i>Viral load studies</i>			
Cereda et al., 2020	Lombardy, Italy	Not clear	NS (p=0.51)
Zhou, 2020	Guandong, China	1 asymptomatic, 17 symptomatic	ND
Lavezzo et al., 2020	Vo, Italy	80 (35 asymp)	NS

<i>Modelling studies</i>			
Li et al., 2020	China	801	0.55 (0.46, 0.62)
Li et al., 2020	China	Not available	0.50 (0.37, 0.69)
Li et al., 2020	China	Not available	0.43 (0.31, 0.61)
Ferreti et al., 2020	Singapore and China		0.25 (0, 0.98) ¹
Zhang et al., 2020	China	Not available	0.50
<i>Contact tracing studies</i>			
Lavezzo et al., 2020	Vo', Italy	8	1.15 (0.33, 3.07) ¹

NS = not significantly different; ND = Reported as not different, not statistically tested;

¹*Constructed estimate based on data presented in that study*

Overall, few studies are available to provide a quantitative estimate of the relative infectiousness of asymptomatic cases. Three study types were identified that might help indicate the value for this parameter. However, there are issues with each of these approaches with respect to informing the parameter of interest.:

- Studies reporting viral loads have generally concluded that there is no significant difference from asymptomatic individuals compared with symptomatic. However, these studies generally involved few cases. Further, viral load is not directly relatable to infectiousness of the individual.
- Contact tracing of individuals potentially offers a method to determine the infectiousness of individuals. However, this approach is especially prone to bias introduced through the selection of cases.
- Estimates from modelling studies could provide perhaps the most reliable estimate of relative infectiousness. However, the posterior estimates from these studies are often very sensitive to the input parameters used.

Taking these estimates together we cautiously suggest that asymptomatic cases could be considered to have a degree of infectiousness which is about 0.25 – 0.50 that of symptomatic cases. However, it must be stressed that this suggestion comes from a very low evidence base.

It should be noted that one contact tracing study (Luo et al., 2020) was removed as there was insufficient data presented. However, this study presented much lower estimates of relative infectiousness (<10%).

3. References

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