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Reproduction number (R) and growth rate (r) of the COVID-19 epidemic in the UK: methods of estimation, data sources, causes of heterogeneity, and use as a guide in policy formulation

This rapid review of the science of the reproduction number and growth rate of COVID-19 from the Royal Society is provided to assist in the understanding of COVID-19.

This paper is a pre-print and has been subject to formal peer-review.

1. Executive summary

Purpose of the report

This paper examines how estimates of the reproduction number R and the epidemic growth rate r are made, what data are used in their estimation, the models on which the estimation methods are based, what other data sources and epidemiological parameters could be employed to assess the effectiveness of social distancing measures ('lockdown') and to evaluate the impact of the relaxation of these measures.

Throughout this report we refer to the reproduction number as R . This number reflects the infectious potential of a disease. R_0 represents the basic reproduction number, which is the number of secondary infections generated from an initial case at the beginning of an epidemic, in an entirely susceptible population. In contrast, R_t is the reproduction number at time t since the start of the epidemic. As more individuals are infected or immunised, R_t captures the number of secondary infections generated from a population consisting of both naïve/susceptible and exposed/immune individuals and therefore it both changes in value over time and will always be less than R_0 .

Overall conclusions

High quality data underpins the ongoing assessment of key epidemiological parameters, such as the reproduction number, R , which defines the average number of secondary cases generated by one primary case, and the growth rate of the epidemic, r . The pristine value of R at the start of the epidemic, R_0 , gives wide insights into the epidemiology of the virus, such as determining the level of herd immunity

required in the UK (as a proportion of the population), that must be effectively immunised to halt transmission and protect the population when a vaccine becomes available.

There remains much uncertainty in estimates of key epidemiological parameters defining the growth and decay of the epidemic and, concomitantly, the impact of the relaxation or strengthening of control measures. This is largely due to data availability and quality. This uncertainty must be factored into policy formulation.

The responsibilities of SAGE with respect to COVID-19 will eventually be taken over by the new Joint Biosecurity Centre (JBC) which is to be part of a new body called the National Institute for Health Protection (NIHP) to replace Public Health England (PHE). This new body will also include existing Test and Trace activities. This JBC must seek independent scientific advice on epidemiology, and mathematical plus statistical analyses of infectious disease transmission and control. The UK university sector has world renowned expertise in infectious disease epidemiology and JBC, like SAGE before it, should make full use of this independent resource.

As the Government response to the COVID-19 pandemic reaches the end of its first phase, there are opportunities to be taken and some important challenges to be met. Specific opportunities include greatly improving data collection and management – and putting in place as quickly as possible an effective 'Test and trace' system for the UK. Both are of immediate and high priority. The challenges include the

creation of a high level of research expertise within the new body (JBC) in the many fields that are required to tackle a novel epidemic. The new body should be an informed customer that distils knowledge for policy formulation, rather than a creator of that knowledge.

Uneven data quality and slow access to information on COVID-19 spread and impact collected by different government organisations such as Public Health England, Office for National Statistics (ONS) and NHS Trusts have been a major impediment to good epidemiological analysis of the state of the epidemic and predictions of future trends. Timely access through one portal, and ensuring that data definition, accuracy and consistency over time are of the highest standards possible are essential. An authoritative body should both acquire timely and relevant data at scale across government bodies and distributing it openly through a carefully curated portal. Careful thought should be given to how a national data base is effectively fed by local public health bodies, and how in return this national information portal feeds back to facilitate local action. The National Statistician has a key role here, as do societies such as the Royal Society, the Academy of Medical Sciences, and the Royal Statistical Society.

The most informative data on epidemic trends arise from longitudinal (over time) cohort based (following the same individuals) studies of seroprevalence of past infection and the incidence of new infections, stratified by the appropriate variables such as home and work locations, age, gender and ethnicity. The UK needs to greatly expand collection of these data and to continue to review the sensitivity and specificity of the currently available diagnostic tests (both antibody to detect past infection and the polymerase chain reaction (PCR) to detect current infection).

Effective contact tracing at scale which relies on testing for active viral infection is an essential part of the ability to control and limit chains of transmission, especially so-called 'super-spreading' events where a single individual is responsible for transmitting infection to many other people. A high degree of competence in this area, notably before a summer or autumn resurgence in incidence is essential. This information is needed for the day to day management of the epidemic, it also feeds into making forward projections through models of trends that give advanced warning of resurgence.

Given the importance of testing for active viral infection in any expanded contact tracing system to improve control measures, the provision of adequate testing facilities with a fast turn round time is an important requirement.

Science and research orientated conclusions

A wide variety of models of COVID-19 transmission, data sources and methods of parameter estimation have been employed to advise SAGE through SPI-M on transmission and control within the UK. This is a strength.

More comparative studies of model outcomes need to be conducted in the near future to examine the sensitivity of epidemiological predictions to model structure, the data source used and parameter uncertainty with the aim of improving analyses supporting policy formulation.

With regards to reproduction numbers and rates, the two parameters, R and r , measure different facets of epidemic pattern. Negative values for the growth rate in infections, r , clearly reveals a contracting epidemic, while if the reproduction number of the virus, R , is less than unity in value, onward transmission is insufficient to sustain the infection in the population in the longer term and is therefore the desired outcome of control measures.

The growth rate, r , is more easily measured than the reproduction number R . The latter however, provides more information about the impact of control measures given the very non-linear epidemic curve for COVID-19 which will have a long right-hand tail, possibly with further peaks due to resurgence, which complicates the interpretation of r . The magnitude of R at the start of the unmitigated epidemic (R_0) also provides information on what level of herd immunity must be created by those recovered from infection and vaccination to halt transmission.

Lock down measures and modifications in behaviour may not totally eliminate the occurrence of local outbreaks of infection that are patchy in nature across time and space. These do not necessarily mark the beginning of the second wave, provided the average R value across the country (or a defined region) is less than unity in value. Targeted measures and good contact tracing are required to bring local outbreaks rapidly under control.

If patterns of human behaviour (eg mixing and movement) return to the pre-epidemic state, the pristine value of the basic reproduction number, R_0 , in the UK will be reduced somewhat by any herd immunity created by people who have recovered from infection. This level is low at present hence each new case of infection is likely on average to generate two to three further cases and the epidemic will rapidly increase again with a doubling time of 3 – 5 days.

COVID-19 research priorities must include reducing uncertainties about and heterogeneities in key epidemiological parameters, such as the level and duration of infectiousness in infected people who never show clear symptoms of infection, and the average duration of infectiousness prior to the appearance of symptoms in those who do show clear symptoms of COVID-19 infection. The average values of these parameters have a very big impact on the epidemic pattern and the severity of control measures required for effective control.

Specific longitudinal (over time) studies on the duration of seropositivity to COVID-19 in both symptomatic and asymptomatic infected people are an urgent priority, as is understanding how seropositivity correlates with protective immunity and its duration.

The rate of change of the epidemic growth rate r (the second derivative of the incidence) is informative since it can be an early indicator of the effects of a slow release in lock down measures but due note must be taken of the non-linear character of epidemic growth and decay phases.

Uncertainty

The estimates of the epidemic growth rate r and reproduction number R are affected by many sources of variability and these have not been clearly explained model by model.

Uncertainty intervals so far reported on estimates of the reproduction number R are too narrow – much more uncertainty exists in the estimates depending on many factors, including substantial variability between infected people on how many individuals they transmit the infection on to.

If these estimates of R and r are based on deaths, then they reflect transmission weeks before. If based on confirmed cases, then the temporal trends in the data may be affected by changes in testing strategies and capacity for data capture and reporting.

Uncertainty bounds should be placed on the estimated R and r values model by model, with methods and underlying assumptions described, ideally stratified by region as well as the time window over which the estimates refer to.

Uncertainty intervals on the epidemic growth rate, r , in a defined region are narrower relative to an average value than those on R and, as such, r is a useful measure of the state of the epidemic.

Ideally estimates of r and R should be reported together region by region in the UK. However, it is important to note that for many of the published methodologies, determining the value of R requires calculations and information in addition to estimating r , which introduces greater uncertainty for this measure.

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2. Objectives of this paper

A committee of the Royal Society, Science in Emergencies Tasking – COVID (SET-C), was set up to respond to questions on COVID-19, from the Chief Scientist and Her Majesty's Government (HMG), and to provide a timely view of the science that could contribute to assessing and improving the impact of implemented or planned control policies. The membership is listed in Appendix 4.

The committee set up a small subgroup (membership also listed in the Appendix 4) to examine how estimates of the reproduction number R and the epidemic growth rate r are made, what data are used in their estimation, the models on which the estimation methods are based, what other data sources and epidemiological parameters could be employed to assess the effectiveness of social distancing measures ('lock down') and to evaluate the impact of the relaxation of these measures.

Details on the definition of R , r and other key epidemiological parameters are presented, as are methods of estimation and the construction of some sort of uncertainty interval around an estimate. In brief, the reproduction number of an infectious disease R_t at time t is the average number of secondary cases of infection generated by one primary case over a defined past time interval¹. This epidemiological parameter changes as an epidemic progresses due to both herd immunity (the fraction of a population who have had the infection and recovered to develop immunity – for COVID-19, for an unknown period of time), and as a consequence of control measures such as social distancing ('lock down' is an extreme form of social distancing) and vaccination.

This report focuses on data sources, the methods and models employed in the estimation of key epidemiological parameters, the assumptions made within models employed to make predictions, and on sources of heterogeneity in R and r . The latter aspect is geared to provide insights into the uncertainty surrounding given estimates and what relevance this has for the advice given to policy makers. Parameters other than R and r which give insight into the course of the epidemic and the impact of implemented mitigation measures are also discussed. Particular attention is given to data collection, management and access.

3. How advice is given to government on the epidemiology and control of the COVID-19 epidemic

The advice given to government through the Chief Scientific Advisor on the COVID-19 epidemic is guided at present by the Scientific Advisory Group for Emergencies (SAGE) subgroup Scientific Pandemic Influenza Group on Modelling (SPI-M), which is focused on the epidemiology and mathematical modelling of the course of the epidemic and the impact of various interventions. The responsibilities of SAGE (and hence SPI-M) will be progressively transferred over the coming months to a new body entitled the Joint Biosecurity Centre (JBC). This Centre, along with Public Health England and Test and Trace activities, are to be merged into a new body entitled the National Institute for Health Protection (NIHP). It has been the tradition on government committees convened to advise on the control of novel epidemics to invite a number of modelling groups based in universities and Public Health England (PHE) to generate predictions of the course of the epidemic and the impact of various control strategies. For COVID-19, given its importance as a source of serious morbidity and high mortality (a case fatality ratio currently estimated as between 0.5 to 1.0%²), ten groups were invited to make predictions for consideration by SPI-M. These groups use a variety of different models, different assumptions about the biology and epidemiology of the virus and different sources of data on which to base estimates of key parameters. One of these is the effective reproduction number of the virus at time t in a defined population, R_t , which is discussed in detail in the following section.

SPI-M has the difficult task of coalescing the results from the different models into one coherent narrative for SAGE, on, for example, how the parameter R_t is changing under lock down or its gradual lifting, in defined regions of the country. The approach adopted is to seek a consensus from the different groups, independent from views about the sophistication of the models employed or quality of data used.

In the case of the reproduction number, R , a range of model frameworks and estimation procedures have been employed given a range of different data sources. Some models estimate R , some r , and some both. Estimates of R and r depend on the data sources employed and models used. Methods of estimation vary between the groups and as such the different estimates are compared and the members of the sub-group collectively agree a range which R and r are likely to lie within. The estimates presented to SAGE are typically stratified by region of the UK and city in some cases.

This is a sensible and pragmatic approach when decisions are required rapidly to inform policy and when many uncertainties exist about what is the most appropriate model framework, the typical course of infection (and how this varies between people), what are the best data sources and how best to estimate R .

4. Definitions of key epidemiological parameters

4.1 The reproduction number, R

Throughout this report we refer to the reproduction number as R . This number reflects the infectious potential of a disease. R_0 represents the basic reproduction number, which is the number of secondary infections generated from an initial case at the beginning of an epidemic, in an entirely susceptible population. In contrast, R is the reproduction number at any time during an epidemic, which changes over time. As more individuals are infected or immunised, R captures the number of secondary infections generated from a population consisting of both naïve/susceptible and exposed/immune individuals and therefore will always be less than R_0 . R can sometimes be expressed as R_t , reflecting the fact that it changes over time t . Alternatively, it can also be referred to as R_e . In summary, reference to the basic reproduction number refers to transmission potential at the beginning of the pandemic, and the effective reproduction number to the potential during the pandemic at a specified timepoint. All these measures will vary greatly between regions due to different levels of density, demographics, and immunity in a community.

The epidemic growth rate, r , represents the number of new infections at an increasing or decreasing exponential rate. It is dependent on the reproduction number and timescale between infections. From herein, as we define these concepts further we will refer to these parameters solely by their symbols for simplicity.

R_0 , and R_t , are related quantities in epidemiology. Many of the key insights and much of the intuition around these concepts are based on an understanding of R_0 , and so we focus on this initially.

R_0 is the average number of secondary cases generated by an average infected person throughout their infectious period in a wholly susceptible population (no herd immunity) in which no mitigation strategies are in place (whether these be social distancing, immunisation or prophylactic and/or infected person treatment that suppresses the typical duration and/or the intensity of infectiousness). It is an important epidemiological parameter for all infectious diseases³. It is essentially a concept that is analogous to the ‘net reproductive value’ in human demography first described in 1930 which defines whether a population will expand or decay⁴. The concept is central to any discussion of the population biology of an organism. Infectious disease epidemiology combines the population biology of the infectious agent within the human host and within a defined population.

For an infectious agent of humans, $R_0 > 1$ if an infectious agent is to be capable of invading and establishing itself within a human population. The objective of many outbreak control programmes is to lower the number of onward infections per infectious individual to less than unity by whatever measures are available such that the infection cannot persist in a defined population. When $R_0 < 1$ the infection cannot be established in the population and dies out. On the appearance of COVID-19 late in 2019, no treatments or vaccines were available (nor are vaccines available today, some therapeutics have been tested and a few show benefit in terms of reducing mortality for seriously ill patients), such that social distancing was (and is) the only measure available to mitigate the spread of the virus and reduce its impact on net morbidity and mortality until vaccines and therapeutic agents (drugs or biologicals) are developed.

R_0 is a composite measure of various features of the infectious agent that include the typical course of infection within a person (clinical epidemiology) and variation between people, and how this pattern impacts the likelihood of transmission between people. Net transmission within a population is therefore influenced by both the typical course of infection in a person, and social plus behavioural features of the human host population. The precise details of how R_0 is constituted depend critically on many biological and behavioural factors, and what is either known, or assumed, is central to model formulation of infectious agent spread and control, and often the estimation of R_0 , from defined data sources. A later section will focus on the data sources and various factors that create heterogeneity in the estimation of R_0 .

4.2 The components of the basic reproduction number, R_0

Before moving on to COVID-19 specifically, a simple illustration is provided to outline key relationships between the biology of an infection and the reproduction number. We consider an infectious disease that infects people at a per capita rate β per unit time. At the population level, there is then a net rate of infection proportional to the fraction of the population infected multiplied by the number of susceptible people, a non-infectious and asymptomatic but infected period of $1/g$, and an infectious and symptomatic period of $1/a$ days. Once an individual has recovered from infection, life-long immunity to reinfection that results in infectiousness to others is assumed. This is the classical SEIR model, and various adaptations to this model type form the template for most of the mathematical models of COVID-19 spread (but with much more complexity included and often within an individual-based stochastic framework where events are modelled person by person and/or regions by region).

In Appendix 1, Figure A1 gives an idea of the diagrammatic framework that results from these assumptions and the algebraic definition of R_0 given the biological and epidemiological assumptions made.

An idea of how different biological assumptions determine R_0 and illustration for the simplest susceptible, incubation, infectious and recovered (SEIR) model is provided in Figure 1 with how R_0 is specified in terms of the key rates of movement between the classes and infection rates.

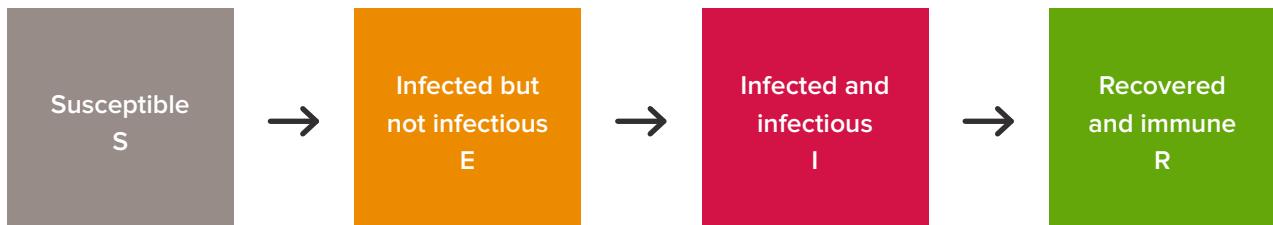
The known biology and epidemiology of COVID-19 is more complex than this, with some important modifications including asymptomatic individuals, who may or may not be infectious to others⁵ a pre-symptomatic infectious period and the impact of partial or full ('lock down') isolation to prevent onward transmission. A 'known unknown' is the duration of immunity post recovery. Limited data from other coronavirus infections suggest full immunity to reinfection is a matter of months rather than years for SARS and MERS^{6,7,8} but it is not clear if those reinfected are again infectious to others or exhibit symptoms of infection that result in measurable morbidity^{9,10}. There may of course be 'unknown unknowns' (meaning unmeasured parameters and unknown pathways of infection, transmission and disease) – time will tell.

Figure 2 (and Figure A1 in Appendix 1) gives a diagrammatic representation of these assumptions including one of full immunity for a year or more. It is important to note how changing the assumptions about the course of infection in an individual, how the human population behaves and the classification of the population into two groups of people, one who experience symptoms the other who do not, greatly complicates the definition of R_t (see next section – it is R_0 modified by the partial or full isolation) and its constituent parameters.

Those not versed in research on infectious disease epidemiology might ask why the estimation of R_0 or R_t is such an important measure of the progression of an epidemic or why it might be of use in policy formulation. Clearly, cumulative case numbers, cases newly diagnosed, deaths attributable to the infection, and instantaneous rates (or discrete time finite rates) of growth or decay in cases (the term r_t at time t), the number of deaths or seropositives (possessing antibodies to COVID-19 viral antigens which indicate past infection) all provide valuable information on the progression of the epidemic (eg growing or declining) and the impact of mitigation measures. Observers can tell by eye if cases/deaths are going up or down.

FIGURE 1

The flow chart for a simple SEIR model. Here $R_0 = \beta N / \sigma$ where β is the transmission parameter which encapsulates many epidemiological, environmental and social factors, and $1/\sigma$ is the average duration of infectiousness and it is assumed that the net rate of transmission is directly proportional to population size N (who are all susceptible at the beginning of the epidemic).



The value of R matters – not just whether it is greater or less than 1 – but because the value of R when greater than unity tells you what proportion of new infections you need to prevent in order to go from increasing incidence to stable or decreasing incidence. In addition, the magnitude of R_0 also provides information on what level of herd immunity will drive the value of R to less than unity such that the infection cannot persist. This gives the target for vaccination programmes of what fraction of the community to immunise. As a rough approximation, the expression $p=1-1/R_0$ gives the critical proportion (or percentage) p that must be immune if transmission is to be halted. For a value of 2.5 as recorded in Wuhan in the early stages of the epidemic, this critical proportion is 0.6 or 60%.

For policy makers, it would seem sensible to make use of a variety of epidemiological indicators, including cases diagnosed, deaths recorded and estimates of R , taking due note of data reliability and the accuracy of the methods employed in estimation. This is especially the case if case numbers are low in a small spatial location since chance (= stochastic) effects will affect the accuracy of measurement.

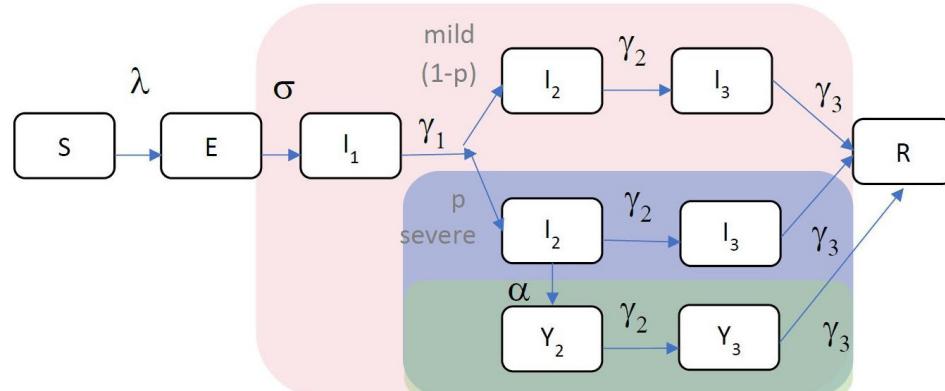
4.3 The effective reproduction number, R_t , at time t

R_t is the average number of secondary cases generated by one infected person during the epidemic. Even in an unconstrained epidemic, this changes through the course of an epidemic. For example, the reason that an epidemic of an immunising infection reaches a peak and starts to come down is that the population is saturated, there are fewer people to infect, and R falls. Mitigation strategies aim to reduce transmission from its baseline value of R_0 . For control strategies to be judged as adequate, R must fall below unity in value for cases numbers to decline.

There are some important nuances in defining R_t during an epidemic. There are two main definitions, sometimes called the instantaneous, or backward looking $R^{12,13}$ or the case, or forward-looking R^{14} . Consider an epidemic where there was an effective intervention and cases began to fall. What was R for cases infected at the time when the intervention was put in place? For the backward-looking R , it is calculated under the assumption that the future is not known, and so it is the R_t for cases infected at that time, assuming nothing changes in the future. For the forward-looking case R , it is calculated using the data after these cases were infected, estimating the actual number of infections caused by those people infected at that point in time, which is lower as a consequence of the interventions.

FIGURE 2

One possible flow chart of a simple epidemic model for COVID-19 of individual states and pathways representing rates of transfer between states. The top pathway is for asymptomatics with mild or no symptoms who stay in the community and eventually recover – but contribute to transmission. The bottom pathway is for those with clear symptoms who either self-isolate or get admitted to hospital. No social distancing or lock down is represented in the diagram. Below the flow chart is the R_t equation that arises from this flow chart. It is an effective reproduction number because self or mandatory isolation takes place. In this equation $1/\alpha$ is the average number of days it takes from symptom onset to isolation (a measure of control). The term p is the fraction of people with clear symptoms and the β terms are the infection rates from each infectious state, while the γ terms define rates of leaving a given state ($1/\gamma$ is the average duration of stay)¹¹.



$$R = \frac{\beta_1}{\gamma_1} + (1-p)\frac{\beta_2}{\gamma_2} + (1-p)\frac{\beta_3}{\gamma_3} + \frac{pb}{\gamma_2 + \alpha} \left(\beta_2 + \frac{\gamma_2 \beta_3}{\gamma_3} \right) + \frac{par}{\gamma_2 + \alpha} \left(\frac{\beta_2}{\gamma_2} + \frac{\beta_3}{\gamma_3} \right)$$

When the dynamics of an epidemic are changing on a timescale which is similar to the timescale of one infection to the next (see below), this nuance can be important. For the most recent data, we cannot see the future and so only the backward-looking, instantaneous R can be estimated, and care must be taken with censoring (we may not yet have seen all the infections generated by people infected recently), and so this distinction is not so important. However, when looking back to see which interventions have been effective when, the two methods may give different timing of a decrease in R , leading to different policy implications¹⁵.

4.4 Time between one infection to the next

R is informative about the dynamics of an infectious disease and the effort required to control it. However, it does not, on its own, characterise the timescale over which the epidemic will grow. This is dependent on the time between one infection and the next. There are two key quantities which are used to describe the time between infections: the generation time and the serial interval. There are important differences between these quantities, and they must be carefully used when relating r and R .

4.5 The generation time, T

The generation time, T , for an infectious disease is the time between infection events in an infector-infected pair of individuals. In conjunction with estimates of R , the generation time can provide insights into the speed of COVID-19 spread; driven by the profile of infectiousness over time (see above) and arises from the model assumptions. It is challenging to measure directly as it is hard to ascertain time of infection due to the fact it is usually unobserved. There are far more estimates of serial interval because it is far easier to measure (see Table 1), which are then often used as a proxy of the former. However, ignoring the difference between the serial interval and generation time can lead to biased estimates of R ¹⁷.

After the chance events at the beginning of the epidemic (when case numbers are small and reporting unreliable) are over, the cases of infection (or a measure of this statistic) grow exponentially until herd immunity or control measures move R to less than unity in value. At this early stage the instantaneous r of the exponentially growing epidemic curve, is approximately given by $r = (R_0 - 1)/T$

The equation gives a link between the value of R_0 and the speed with which infection spread from one person to the next in chains of transmission^{18,19,20}. Both R_0 and T determine r , but R_0 dominates the area under the unmitigated epidemic curve and hence the total number of cases, and T greatly influences the time scale of the epidemic's growth and decay. Note that as a statistic, the control of transmission by mitigation measures requires the value of $r < 0$.

As highlighted in this simple equation, the generation time is a crucial determinant of r . Early in the COVID-19 epidemic, it was noted that although the incubation period (the time from infection to symptoms) was on average about 5 days, the r was so fast that it was likely there was pre-symptomatic infectiousness. A further complication is the likelihood that the epidemic started in the UK well before January 2020. For different model assumptions on the underlying natural history of infection and how this is distributed across the population, the relationship is more complex and can give very different estimates for similar input parameters^{21,22}.

4.6 Serial interval, s

Serial intervals describe the average time between symptoms of infection in the transmitter to when the person he or she infects develops symptoms. It is easier to measure than the generation time as symptom onset is easier to identify than time of infection acquisition. This value is often used interchangeably with the generation time since it is easier to measure via contact tracing studies. However, in the case of COVID-19 it has less relevance given that many infections especially in the young do not seem to generate marked and easily identifiable symptoms. Some studies suggest that between 5% to 80% of infected people do not show clear symptoms of infection (Table 1). This very wide range depends on many confounding variables such as age, gender, location and the existence of other predisposing medical conditions. Some of the more precise studies have been connected with epidemics on ships such as the Diamond Princess cruise ship, where in a sample of 640 people tested, 18% reported no symptoms (on average an older population than other examples perhaps connected to lower proportion asymptomatic). In an Italian village (Vo'Eugano), between 50% to 75% reported no symptoms^{25,26}.

4.7 Dynamic relationships

It is important to remember that both the generation time and the serial interval are dynamically changing through the course of an epidemic. For example, as interventions are put in place there are different transmission patterns, and therefore different time between infections, often biasing towards shorter generation times early in the epidemic, and longer ones as the epidemic is declining. This will then change the relationship between R and r , and it is important to consider what data on these intervals is informing these estimates^{27,28}. In addition, for a highly variable incubation period there may be negative serial intervals, which may be misinterpreted as the wrong direction of transmission. Considering this possibility is important in order to trace the complete transmission chain. If the wrong direction of transmission is assumed, contact tracing efforts may stop prematurely and miss new infections that then may lead to further uncontrolled transmission events.

4.8 Epidemic growth rate, r

The parameter r is a measure of the rate at which new cases are arising. It can be a positive number (the number of new infections is increasing) or a negative number (the number of new infections is decreasing). As highlighted above, it is driven by a combination of R – the higher the number of cases caused by each infectious individual, the faster the epidemic will grow – and the timescale over which infections occur. A useful comparison for understanding the effects of R and the generation time of new infections is provided by HIV, which has an R_0 of around 2 in some populations, and influenza, which has an R_0 around 1.3²⁹, the most important being the reproduction number R , but the timescale from one infection to the next is days for influenza but months or years for HIV.

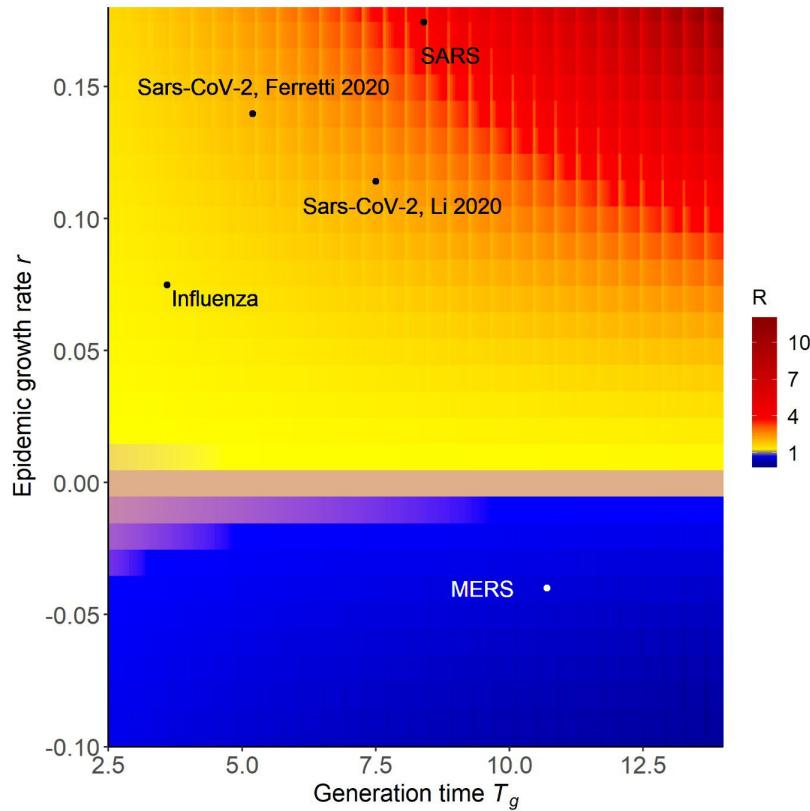
4.9 The doubling time of the epidemic, d_t

r is sometimes explained in a more accessible way through use of the closely related doubling time of the epidemic (the number of days or time units which leads to a doubling in cases). The doubling time d_t in the early stages is therefore: $d_t = \ln(2)/r$

To give a simple example, the doubling times of cases in the UK in the rapid growth phase of the epidemic in March 2020 before 'lock down', was of the order of 3 to 4 days³⁰. Taking a value of 3.5, this gives an r estimate of 0.2 per day. It is important to note that there was some debate on this value early in the epidemic, with some groups reporting longer doubling times due to uncertainty in the natural history of infection.

FIGURE 3

R values depending on the generation time T_g and the epidemic growth rate r with indications where individual viral diseases fall within this parameter space. The longer the generation time and the higher the epidemic growth rate, the higher the value of R . The goal of any intervention is to move the epidemic system as far to the bottom left of the parameter space as possible. Data from Wallinga & Teunis 2004 (SARS)³¹, Cowling *et al* 2011 (influenza)³², Cauchemez *et al* 2014 (MERS)³³, Li *et al* 2020³⁴ (Sars-CoV-2), Ferretti *et al* 2020³⁵ (Sars-CoV-2).



The doubling time is an intuitive number – the time taken for cases to double – and so it facilitates understanding during the early stages of this epidemic, but it has limited usefulness during the current phase where the number of new infections is stable or declining slowly. As the value of r potentially switches from positive to negative (and possibly back again during a resurgence), it passes through zero, at which point the doubling time briefly tends to infinity. For a stable decline in infections, r informs us about the halving time, the time required for the number of cases to halve and hence how rapidly or slowly the remaining cases will decline to eradication.

For parameter estimation, the problem with determining R is that two epidemiological quantities determine its value, r and the generation time, and to get estimates of both, either some other epidemiological information is required, or model fitting procedures must be employed. Figure 3 illustrates the relationship between r , the generation time and R and where different respiratory pathogens fall within this parameter space. It is important to note that the parameter r itself can only be directly measured providing case reporting, hospital admissions, recorded deaths due to COVID-19 or serological data are good (the topic of data quality will be examined in a later section). There is a close relationship between r for infections and cases given information on the incubation period and the fraction who go on to have symptoms, but when the main source of data is deaths other information is required such as the probability distribution of times from infection to death and the fraction who die from infection. Interestingly, the Warwick model employed in the SPI-M range of models, has a higher uncertainty bound around r when their model is fitted to deaths compared with hospital admissions. When fitting a transmission model to case data, both r and R are estimated concurrently because they are linked through the assumptions in the model and are therefore influenced by the inputs to and structure of the model (see later sections).

4.10 The probability distribution of R in a defined population

All of the quantities described in the preceding sections are distributed variables with, in some cases, great variability around any average value. Of greatest importance to the central topic of this paper is the ability to place some sort of uncertainty interval around estimates of R_t . This and the following sections describe different sources of variability that all contribute to the question of how best to accurately express this uncertainty. In this section we focus on R itself and data on other infections plus what is available for COVID-19. One of the best descriptions of the overall pattern of variability in R within small defined populations is by Lloyd-Smith *et al* (2005)³⁶ drawing on data from a variety of infectious diseases including SARS. In all the cases examined by the authors, contact tracing played a key role in describing the variation in R within a defined group of individuals.

In general, for virtually all infectious diseases where good contact tracing data are available, most transmission is generated by a small fraction of the infected group of people. The term ‘super spreading events’ is often used. Some have coined the phrase the ‘20/80 rule’ to define that in many cases 80% of the transmission results from 20% of the infected in any one generation of infection spread³⁷.

More precisely, the distribution of the quantity R where contact tracing has been available is best described by the negative binomial probability model where the variance is typically much greater than the mean. It can take many shapes from a J shaped pattern with most zeros, to a humped unimodal distribution with a big mean and a longer right-hand tail when compared with the left-hand tail. The discrete probability distribution has two parameters, the mean and a parameter k which measures inversely the degree of aggregation of the transmission events within the population. As k gets large (>5), the distribution converges on the Poisson distribution. In some of the COVID-19 modelling a parameter η is used so that its value is positively related to the degree of aggregation where $\eta = R_m/k$ (MRC Cambridge model) where R_m is an average value.

The variance of the distribution, V is given by: $V = R_m + R_m^2/k$ from which it can be seen that the variance is always bigger than the mean.

For all studies with good data, k tends to be small (<1) which reveals that most transmission events are created by a few infected people. The 20/80 rule is too precise – much variability exists between different settings in both the mean value and k .

The relationship between the mean R , R_m , and k is given by: $P = [1 - (1 + R_m/k)^k]$. Here P is the fraction who do transmit infection and $1-P$ is the fraction who do not. Note that P is zero in value when $R_m < 1$.

The plot below in Figure 4 shows how the inverse aggregation measurement parameter k influences how P varies as a function of R_m for low (large k) and high (small k) aggregation which reflects the importance of super spreaders. Once the value of k is below 0.1, for any mean R value, the majority of transmission events arise from a few people.

Distribution data R for infections other than COVID-19 is well summarised in Lloyd-Smith *et al* (2005)³⁸ and an example of the distribution of R for SARS in Singapore is illustrated in Figure 5.

FIGURE 4

The relationship between the fraction of primary cases who generate secondary cases for three different levels of clumping of case generation amongst a few individuals as predicted by the negative binomial probability model. The parameter k is an inverse measure of the degree of aggregation of the generation of secondary cases, where the variance in cases generation is much bigger than the mean value of R in a sample of primary cases.

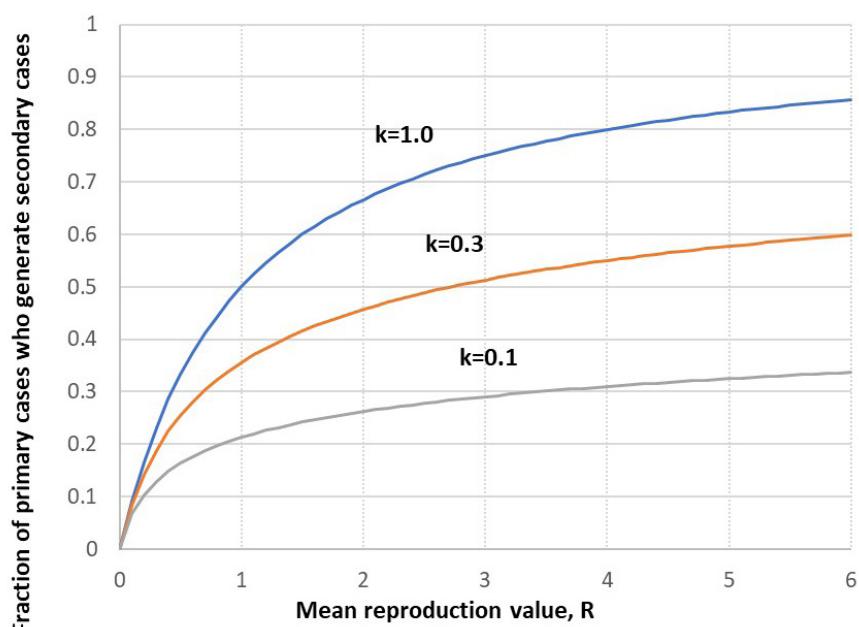
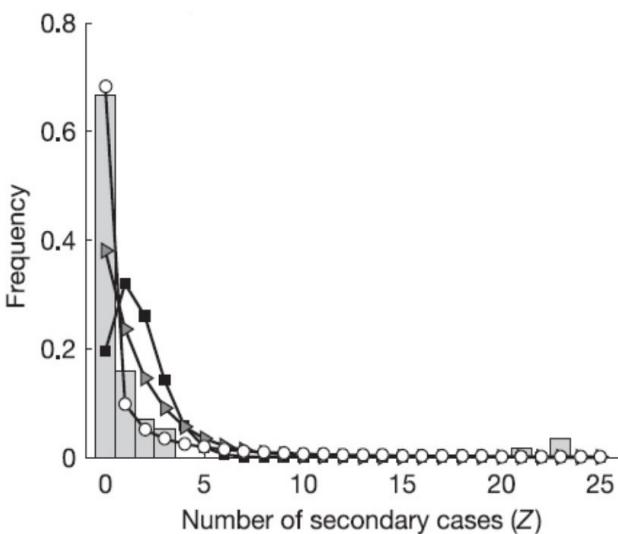
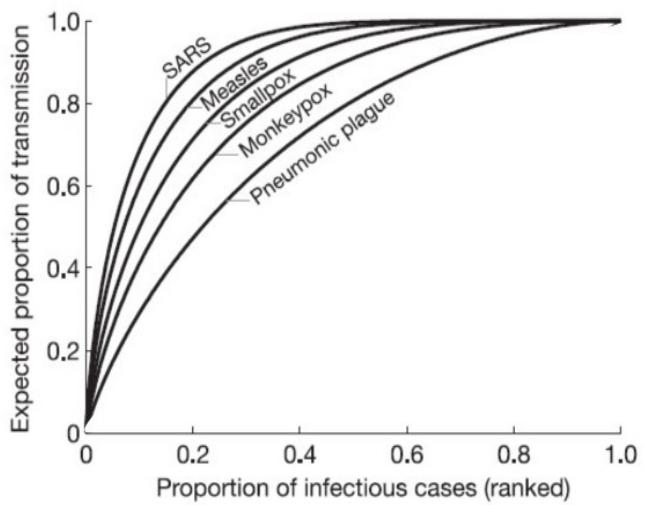


FIGURE 5

SARS in Singapore in 2003 (Leo *et al* 2003)³⁹. The white circles are the fit of the negative binomial probability distribution. Note the superspreading events in the right-hand tail of the distribution. The negative binomial k value is around 0.01 describing extreme heterogeneity in the R value across a small sample of people, with a mean close to 3. Taken from Lloyd-Smith *et al* 2005⁴⁰.

**FIGURE 6**

Predicted fraction of secondary cases generated by different fractions of the primary cases from contact tracing studies for a variety of infections including SARS based on negative binomial fits to the observed data. Taken from Lloyd-Smith *et al* 2005⁴¹.

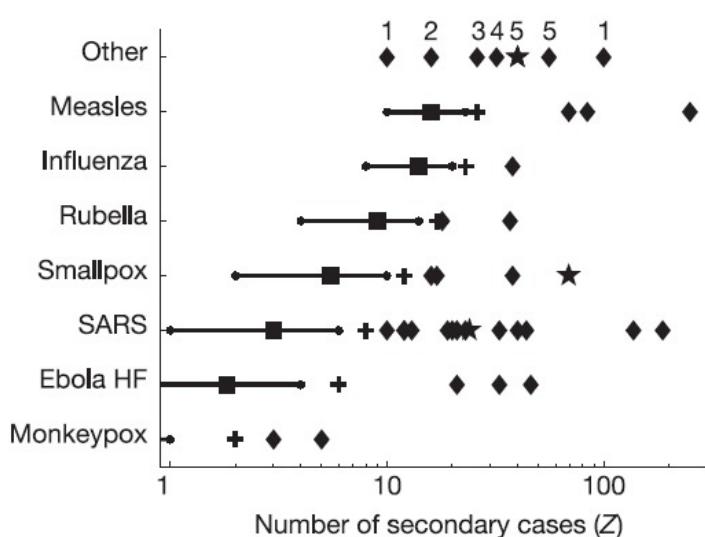


Other graphs from the Lloyd-Smith paper are also illuminating. Figure 6 shows the expected (negative binomial fit – a reasonable mirror of observed pattern but tending to fail to capture extreme super spreaders) proportion of cases generated by a measured fraction of the infectious cases for a range of infectious agents. Amongst these, SARS seems to be an extreme case which may be closest to COVID-19. The aggregation goes from small to moderate as you move from SARS to plague reflecting high aggregation at the low values of k .

Of equal interest are the fraction of super spreaders. To identify such a group, a case generation number must be defined, but this is obvious from contact tracing data since these individuals lie in the extreme righthand side of the negative binomial distribution. This is illustrated in Figure 7.

FIGURE 7

The super spreading events (SSEs) as defined in the original publications are marked by the diamonds. Taken from Lloyd-Smith *et al* 2005⁴².

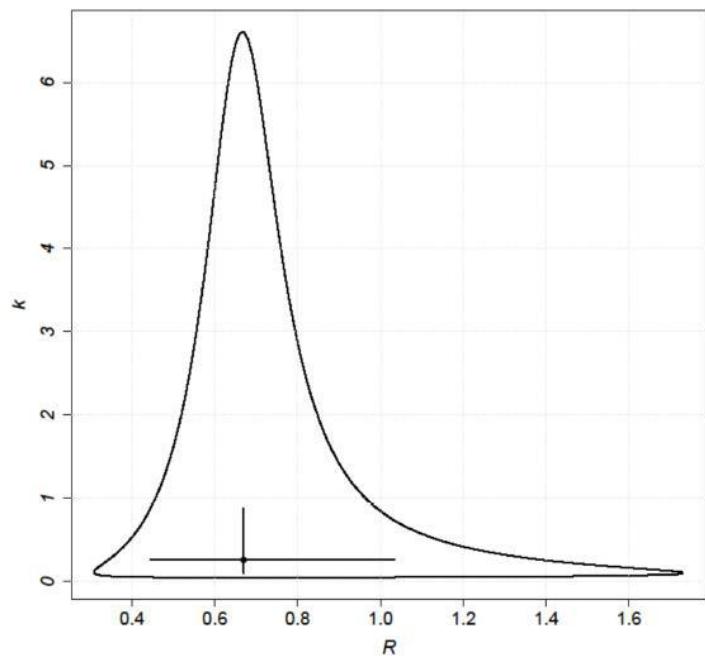


The data for COVID-19 at present is very limited although a wide variety of papers and reports use the term “super spreading events” and many such explosive events (called SSEs) have occurred in mass gatherings in enclosed settings⁴³. One recent report focuses on the distribution of R in a study of 135 cases in Tianjin, China during January and February 2020. Contact tracing enabled chains of transmission to be deduced⁴⁴. They included what was described as one super spreading event of 6 cases. The negative binomial model was employed to describe the distribution of cases and to deduce confidence bounds around the estimates of the mean R . This approach produces understandably wide confidence bounds (R values with 95% confidence regime of roughly 0.14 to 1.06), as would be expected from a distribution with a variance bigger than the mean value.

This study is illustrated in Figure 8 which records the R bounds and the range of k estimates (varies inversely with the degree of aggregation of case generation in a few transmitters). It is important to note that this study straddled a period in which mitigation measures were introduced such that the mean R was less than unity in value.

FIGURE 8

The circle cross-hairs represent the estimated 95% confidence intervals for R and k from a contact tracing study of COVID-19 transmission in China. Note the wide bounds on R with a mean of 0.67. The average k value was 0.25 showing much aggregation in case transmission amongst a few primary cases. Figure taken from Zhang *et al*, 2020⁴⁵.



The authors of this study also looked at how mitigation measures introduced in Tianjin starting on 28 January influenced R and k . The mean R decreased from 0.74 to 0.53 and k increased (less aggregation) from 0.14 to 0.77. This is a small study, but it does clearly illustrate the variance around any estimate of R , even in a defined population in one city over a short interval of time.

Leclerc *et al* (2020)⁴⁶ are compiling a live database of clusters of cases, showing high variability and associations with particular venues, such as shared accommodation (including prisons, and elderly care), but the authors caution that this may be a very biased view of the transmission dynamics of the disease.

Effective contact tracing should offer an opportunity to capture these distributions in close to real time, and for specific settings in the UK.

4.11 Inferring R from deaths or diagnosed cases

One of the challenges of estimating R for COVID-19 has been the incomplete and lagged data on deaths caused by the infection (the average time from infection to death is estimated as 18.8 days)⁴⁷. In the early stages of the epidemic, R could not be estimated accurately from either cases or deaths since under reporting was a function of time – getting better as those responsible for diagnosing and reporting became more familiar with the infection and the morbidity and mortality it caused.

It is important to note that there are real challenges inferring the underlying dynamics from the data streams that were available by examining reports of either cases or deaths over time, rather than fitting a model to the shape of the epidemic, because it is necessary to back calculate when these cases were likely to have been infected/symptomatic and then try and say who infected who.

5. Sources of variability in model predictions and the estimation of R values

Section 4.10 discussed the variability in the value of R for a sample of people and defined this distribution as well described by the negative binomial model. Section 9 and Appendix 2 outline the diversity of models employed by the groups making predictions for SPI-M. There are clearly many sources of variability influencing the estimation of transmission between people, in the data itself, in the structure of the models, and over time and spatial location. All will influence the confidence and uncertainty in estimated R values. The following sections look at the key issues.

5.1 Structural variability arising from different model assumptions

In terms of model predictions, do structural differences matter and do they also influence how R is estimated?

The reply to the former is yes – quantitative detail and even qualitative patterns will depend on model structure. As illustrated in the Table in Appendix 2 much structural heterogeneity exists in each of the models making predictions for SPI-M (Scientific Pandemic Influenza Group on Modelling advising the UK government). As yet, it is not clear if model outputs have been compared in a systematic manner given a defined prediction problem and a defined set of parameters. Such sensitivity analyses are time consuming but necessary. Given that the immediate emergency of trying to assess what mitigation strategies could be put in place and how might each work to reduce R , now is the time to try and conduct such sensitivity analyses across the models with defined data and parameter sets and make the results accessible to all. The distinction between qualitative and quantitative predictions is important. If all give the same qualitative conclusion that mitigation strategy A works best – then the advice to policy makers is clear even when large quantitative differences arise between each model outputs. However, if qualitative differences arise in important areas that affect policy such as the requirement for hospital beds over time or the number of predicted deaths, then it is necessary to identify which assumption, or set of assumptions, create the differences.

Ideally, a comparative study of the behaviour of the models should be conducted in the shorter term, before a possible ‘second wave’ of infection arises in the autumn or earlier, to create more confidence in model predictions.

The answer to the second question is yes and no. It is no, if the structural components of R are ignored and the epidemiological parameter is simply estimated from the rate of change in case numbers or another epidemiological variable such as those seropositive at a series of time points, perhaps stratified by confounding variables such as spatial location, age and gender. If case numbers are used, due note must be taken of the average interval between infection and diagnosis, and if at all possible, its distribution. This is done in certain of the modelling efforts (see Table A1 in Appendix 2).

It is yes if separate estimates of the components that make up R , such as average infectious periods and their distribution, are used in estimating the overall value of R . This again points to the need to do robust model output comparisons.

Perhaps one of the most important structural issues concerns acquired immunity. In the longer term, which may encompass next year (2021), a key question is clearly the duration of protective immunity. All models to date make the assumption that, if an individual recovers they are immune for the duration of the epidemic. However, infection spread may last, with peaks and troughs, for some time until effective vaccines are in wide scale use. Epidemiological data on other coronaviruses does suggest reinfection within one year is possible, but it is uncertain if those infected a second or third time are infectious or show symptoms of infection^{48,49}. For short term predictions (the rest of this year) this issue is not important, because the proportion of individuals with immunity will remain small. In the longer term it is very important, as is the duration of protection created by vaccines that hopefully will become available. The duration of immunity will also influence the proportion of the population that will need to be vaccinated to ensure that the level of herd immunity is always above the value required to halt the epidemic. A further important structural issue concerns whether or not asymptomatic infection is associated with infectiousness to others.

5.2 Parameter assignments informing COVID-19 models

Many parameters influence the predictions generated by models, including the obvious components that make up R and various social, behavioural and demographic factors which all can change over time and space (eg different regions of the country and different types of locations such as city or small village). In many cases parameter uncertainty and parameter distributional properties have been addressed by the different modelling groups but perhaps not always in a clear manner and not in a systematic way across the modelling groups. Again, given that the urgency issue that pertained in the early stages of the epidemic may have slightly abated, it should be a priority to examine this aspect given that data are constantly emerging that may necessitate changing parameter assignments of model structures.

A good example is the fraction of asymptomatic individuals. Initially, many assumed this was moderate to low⁵⁰. Although estimates in different studies vary widely, the surprising feature is the high overall values emerging especially in certain demographic groups such as the young^{51,52,53}. A crucial question is how infectious are asymptomatic people? Clinical studies of virus dynamics in patients tentatively suggest no great difference in viral titres to those recorded in people with symptoms^{54,55}. However, data are limited at present. How this influences prediction is not clear from the work that has been published in the peer reviewed literature (or as a prepublication print) or provided in reports.

Sensitivity analyses, parameter by parameter, starting with the most uncertain such as the generation time and its distribution, should be conducted and released as soon as possible. Some idea of the degree of uncertainty in key parameters is provided in Table 1.

Recommendations relating to use of the most appropriate estimates of epidemiological parameters to inform mathematical models of COVID-19:

- Further studies to estimate generation time empirically rather than derived from estimates of the serial interval. This is always a difficult parameter to estimate and even more so with an infection that can be asymptomatic in a high fraction of people. Contact tracing is the most valuable source of data, but such data may be biased to the interval in symptomatic people.

- To improve our understanding of the importance of asymptomatic cases in driving transmission, further studies are required to:
 - provide more robust estimates of the proportion of asymptomatic COVID-19 infections, including in sub-populations such as children;
 - to quantify the relative infectiousness of asymptomatic and symptomatic and pre-symptomatic individuals.
- Further estimates of other COVID-19 natural history parameters described in this document (incubation time, generation time/serial interval), stratified by age, particularly for children and young people.
- Ongoing data collection and reporting for those inputs that are particularly context specific eg, duration from symptom onset to hospitalisation, which varies between and within countries and over the course of the epidemic.
- Model input estimates vary in quality, methodological approach in derivation, peer-review status of where data are reported and relevance to the epidemiological landscape of the UK. We recommend repeated review going beyond the analysis presented here, with rigorous evaluation of the quality and relevance of each included study, to develop consensus around the best estimates to use for inputs. As evidence rapidly accumulates and evolves, this must be an ongoing process.
- Improved clarity is recommended for authors publishing model input estimates, both as preprints and peer-reviewed publications: clear identification of version numbers, dates of submission and publication, listing previous versions with explanation of any changes in results between version.
- Encourage authors reporting model input estimates to make individual-level data publicly available so that modelling groups may fit to the data according to their own model needs and assumptions and/or to allow for more nuanced statistical analysis (eg accounting for truncated observations and exponential growth in the number of infected cases).
- Encourage PHE to make all data available to them more widely available to modelling groups.

5.3 Spatial and social heterogeneity

The epidemic has clear spatial and social structure, and in most countries including the UK. Typically, initial spread has been greatest in large cities often with airports associated with frequent international travel. There are some exceptions to this trend such as South Korea where religious groups triggered early super-spreading events.

Some models employed by SPI-M do include spatial structure and are therefore able to mimic transmission from seeding events to all areas of the UK. Initial conditions are obviously important but social movement patterns soon dominate with large urban settings playing a key role in seeding remoter regions. The consequences of the including within models spatial, demographic (age, gender and ethnicity) and social heterogeneity, which is very apparent in the case notification and death data stratified by region, age, gender and ethnicity should in principle lead to a better understanding of the current pattern of the epidemic and better predictions of future trends. Such models can also generate finer scale estimates for R and r such that some targeting of messages can be put in place on, for example, social distancing and the relaxation of other mitigation measures. Reporting in the UK by PHE is clumped into regions encompassing multiple NHS trusts and this reveals different patterns of temporal change in R and r . One downside of these more complex models is the considerable increase in the parameters than have to be estimated from data. As such, the predictions may be less precise if data sources other than the case numbers, deaths or seropositives are not employed to population this much larger data requirement.

5.3.1 Stochasticity – chance effects

In chains of infection transmission, chance effects typically play a major role in determining pattern and concomitantly, the magnitude of R in a defined population. These effects are very marked at the beginning of an epidemic in a given location, and more generally in small populations. Many of the models employed within SPI-M are individual based stochastic models (with random number generation employed to determine which event occurs at any given time point and the time between events) and hence repeated runs employing different seeding numbers generate uncertainty bounds in the absence of other sources of heterogeneity as outlined in the preceding sub-sections.

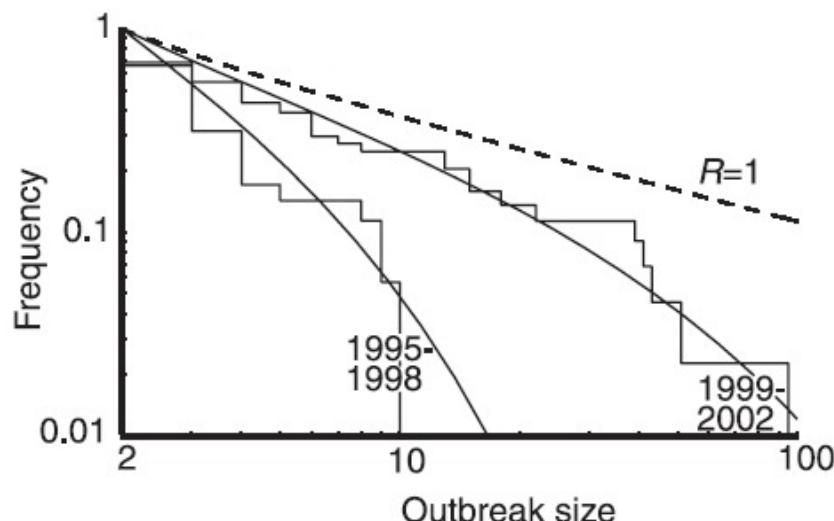
5.3.2 Dynamics of R close to 1 – outbreaks of increasing size

It is important to note that infectious disease transmission is a stochastic process, that transmission is a chance event governed by probabilities. Therefore, even when R is below 1, there can be localised outbreaks by chance. If these outbreaks can be well characterised, which is challenging for COVID-19, then the distribution of the size of these outbreaks can be very informative for estimating R .

One good example of this was outbreaks of measles in the UK following falling vaccine coverage in the wake of the Wakefield scandal⁵⁶. As vaccine coverage dropped and R increased, there were outbreaks of increasing sizes (Figure 9).

FIGURE 9

The frequency distribution of outbreaks of measles of a certain size in England and Wales in two different time periods and the theoretical predictions of a stochastic model (solid line) for $R < 1$. Taken from Jansen *et al.* (2003)⁵⁷.



There are some challenges in measuring outbreak size for COVID-19 due mainly to asymptomatic cases and possible transmission onwards from them. Nonetheless, an effective contact tracing scheme offers the opportunity to measure the size and drivers of outbreaks and will be crucial in informing the estimates of R and understanding the transmission dynamics. Recent modelling of contact tracing suggests that the outbreak size at the point where contact tracing is instigated can be informative in this regard⁵⁸. More will be said about contact tracing in a later section.

5.3.3 Maintenance of a low R in the community? – the impact of hospitals and care homes

An area of active debate in COVID-19 epidemiology is whether R will be kept close to, or even below, one through population-level changes in behaviour alone, rather than mandated social distancing. Evidence from Sweden would suggest that this may have been the case in that particular population in the early stages, but subsequent events demonstrated extensive spread. In New Zealand, estimates for R were as low as 0.36⁵⁹, suggesting that changes in behaviour and mandated lockdown all but eliminated transmission.

In the UK, there is also evidence of altered behaviour over the current course of the epidemic, such that mobility data and transmission rates may be less correlated as proximity may not be as closely tied to transmission due to mask wearing and hand washing⁶⁰.

A particular challenge for evaluating the epidemic in the UK up to this point, has been the presence of outbreaks and seeding of infection in the community from social care and health centres, which then led to higher case numbers overall, and an increased national-level R . Stratification of case data by likely site of acquisition through effective outbreak investigation could allow estimates of R in particular locations (such as care homes) and in the community or region more generally. This would then allow restrictions to be lifted more quickly if community transmission was limited or imposed if an outbreak arises in a defined locality.

Interpreting R numbers by site is challenging as they cannot simply be added or multiplied. However, these types of stratified estimates could be highly informative.

6. Model parameter estimates

There are a growing number of estimates for the key model inputs relating to the epidemiology of COVID-19 (see Table 1). Measures such as the proportion of infections that are asymptomatic are relatively straightforward to measure (but require sufficient follow-up duration to distinguish pre-symptomatic from asymptomatic individuals). In contrast, model inputs relating to durations are more problematic to measure and may be biased by factors such as the stage of the epidemic at the time of measurement and truncation of data, when there is incomplete follow-up. Studies reporting estimates of these durations vary in the level of statistical analysis undertaken attempting to adjust for these biases.

6.1 Incubation period (time from infection to symptom onset)

Incubation estimates used to parameterise the mathematical models include Lauer *et al*⁶¹, Linton *et al*⁶² and Li *et al*⁶³. The latter has a very small sample size but was published very early in the pandemic (January 2020) and so was among the earliest sources available. Many more incubation estimates are now available (Table 1), several of which test various distributions to fit to the data and report estimates using the best fit (most commonly log-normal and Weibull distributions). Care must be taken to select high quality sources where only cases for whom authors could identify the earliest and latest possible time of exposure and who had a date of symptom onset are included in analysis. There may be potential bias in using publicly reported cases, such as Lauer, because they may overrepresent severe cases, the incubation period for which may differ from that of mild cases. More recently, Pellis *et al*⁶⁴ re-analysed published data informing a previous incubation estimate⁶⁵ in order to adjust for biases, and we would encourage further publication of individual case data to allow researchers to nuance estimates for their particular modelling requirements.

Despite variations in analysing these data, estimates of the COVID-19 incubation are generally very similar, with the majority of estimates included in Table 1 reporting a mean or median estimate of between 4 and 6 days. However, there is increasing evidence that there may be a longer incubation period in children: Hua *et al* reported an estimate of 9.1 days⁶⁶, while Men *et al*⁶⁷ found that the incubation period was statistically significantly shorter for those aged 40 years and older.

6.2 Generation time and serial interval

The serial interval is the time period between the onset of symptoms in an index (infector) case and the onset of symptoms in a secondary (infectee) case. The generation interval is the time between infection events in an infector–infectee pair of individuals. A recent rapid review identified 22 estimates of the serial interval and only three estimates of the generation time (mean serial interval: 3.1 to 7.5 days ($n=22$), median 1.9 to 6.0 days ($n=7$); mean generation time 3.9 to 5.2 days ($n=3$), median 5.0 days ($n=1$)⁶⁸). The two generation time estimates reported by Ganyani⁶⁹ are for Singapore and Tianjin, China, actually use data measuring the serial interval, together with estimates of the incubation period, to infer the generation time. Authors used symptom onset data while acknowledging uncertainty about the incubation period distribution and the underlying transmission network. The remaining generation time estimate was calculated using 40 well-characterised infector–infectee pairs from multiple countries to estimate the generation time (Ferretti *et al*)⁷⁰. This represents the only available direct estimate of the generation time. However, the rarity of identifying reliable dates of infection for infector–infectee pairs means those included by Ferretti *et al* are from multiple countries, with only a few transmission pairs from each. Despite the methodological difficulties, it is important to supplement this estimate with further data from carefully designed contact tracing studies.

Nevertheless, serial interval data can be used to inform generation time estimates, and methods have been developed to address the potential biases that can arise from not accounting for changes in serial intervals across cohorts⁷¹. A variety of statistical distributions were used by authors to generate serial interval estimates, including normal, log-normal, gamma and Weibull distributions. Best fitting distributions varied between studies, and even within one study when estimates used different eligibility criteria for infector–infectee pairs⁷². The most robust estimates are those that assessed fit using a range of distributions and attempted to adjust for right truncation of the data (eg, Ganyani *et al*⁷³, Nishiura *et al*⁷⁴).

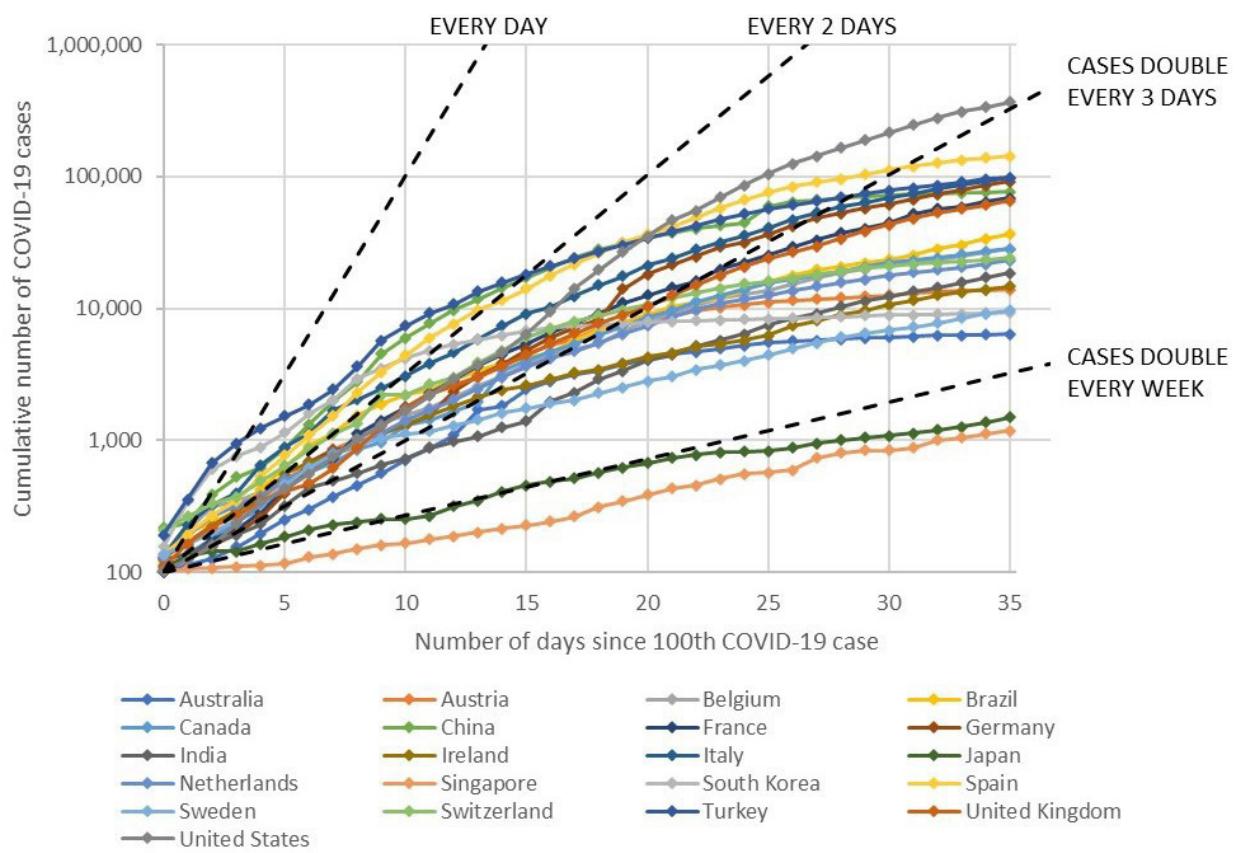
Mathematical models of COVID-19 have generally used serial interval data, either directly or with adjusting, to serve as the generation time estimate. Models have sometimes stated central values for the interval without providing an uncertainty range or source, but from these values it appears that Bi *et al*⁷⁵, Ganyani *et al*⁷⁶, Li *et al*⁷⁷, Cereda *et al*⁷⁸, Nishiura *et al*⁷⁹, Tindale *et al*⁸⁰ and Du *et al*⁸¹ have all been used. Particular care must be given to using the most up-to-date estimate from Du *et al*, as estimates have changed markedly between versions: original preprint and recent publication⁸² (estimate 3.96 days, $n=468$) is substantially different from second preprint⁸³ (estimate 5.29 days, $n=339$). This demonstrates the pace at which knowledge is evolving, and given the large number of serial interval estimates, the risks of reporting biased estimates with inappropriate analyses, and the overlap between published estimates as different research groups re-analyse the same or overlapping datasets, there is a need for ongoing, repeated re-evaluation of the most appropriate estimates to use.

6.3 Exponential growth rate r of the epidemic

The exponential r can be estimated using the doubling time of the epidemic. If an epidemic is growing exponentially with a constant r , the doubling time remains constant and equals $(\ln 2)/r$. An increase in the doubling time indicates a slowdown in transmission if the underlying reporting rate remains unchanged. The real-time growth rate, r_t , can be more informative than precise estimates of R_0 for initiating and lifting interventions⁸⁴. However, while numerous estimates of R_0 and R for COVID-19 exist (see Table 3), there are far fewer reports of r_t and, where published, these have been criticised⁸⁵ for lacking robustness or are restricted to single country analyses on a single dataset^{86,87}. As of 18 June 2020, SPI-M has been producing estimates of both R and r for SAGE and these are now reported openly. An intuitive way of visualising r or the doubling time is plotting the cumulative case numbers since the 100th confirmed case over time as illustrated in Figure 10 [Grattan Institute blog⁸⁸, FT Figure from 28 March, *Our World In Data* page⁸⁹]. The slope of the resulting curve gives an indication of the doubling time which can be converted to r using the formula given above.

FIGURE 10

Cumulative number of confirmed COVID-19 for selected countries, by number of days since 100th case reported.
Data taken from <https://ourworldindata.org/identify-covid-exemplars>, accessed on 18 August 2020. Dashed black lines indicate doubling times.



The majority of commonly cited doubling time estimates are from China^{90,91,92,93,94,95,96} but a recent study by Pellis *et al* (2020)⁹⁷ has calculated estimates for 18 European countries using a consistent methodology, primarily based on WHO data on confirmed cases augmented with hospital and intensive care unit bed occupancy and death Figures from Italy⁹⁸. Pellis et al found European doubling times to be relatively consistent, at around 3 days, before control measures were implemented, and confirmed the robustness of their estimates by calculating using two different methods. These European values are significantly shorter than the majority of estimates from China (5 – 7 days^{99,100,101,102} and Hubei¹⁰³ estimates, Table 1) with some exceptions (2 – 4 days^{104,105} and outside Hubei¹⁰⁶).

6.4 Onset of symptoms to death

Models rely on fitting to observed death data and so assumptions regarding the time between onset of symptoms to death are very influential. This input is likely more context-specific than some other COVID-19 natural history parameters and will evolve over time. Experience gained with treating COVID-19 patients, leading to better treatment modalities, in particular the use of dexamethasone going forward, will reduce the case fatality ratio but may also change the distribution of duration of symptom onset to death. Over the course of an epidemic, there may be points at which health systems are overwhelmed beyond surge capacity which may shorten the duration between symptom onset and death¹⁰⁷.

The majority of estimates of duration from onset of symptoms to death use data from early in the epidemic in Hubei province, China or specifically from its capital Wuhan and so there is likely data overlap between these, and the estimates are similar (see Table 1^{108,109,110}). Verity *et al* ¹¹¹ and Wu *et al* ¹¹² both fitted using a gamma distribution. Verity *et al*¹¹³ a range of case fatality ratio estimates for coronavirus disease 2019 (COVID-19) additionally described imputing missing onset dates on the basis of dates of report, where available, and adjusting the gamma model to account for exponential growth, meaning a higher proportion of cases will have been infected recently. In contrast to these estimates from Hubei, a much shorter estimate of duration was reported from the UK (median 9 days¹¹⁴ compared to mean 17 – 20 days^{115,116}, and median 18.5 days¹¹⁷ from Hubei). The UK retrospective audit study included only patients who had not been considered for escalation of care to critical care because of a combination of frailty and comorbidities and so this represents a different patient population from the Hubei studies. It is not a representative of duration of symptom onset to death for patients in the UK.

6.5 Duration of onset of symptoms to hospital admission

Time from onset of symptoms to hospitalisation will change markedly over time¹¹⁸, decreasing as the processes of symptom recognition and hospitalisation become more efficient. It will also be context-specific, as these processes will vary between settings. Pellis *et al* highlighted this heterogeneity, with longer duration to hospitalisation for the UK (mean 5.14 days) than for Singapore (2.62 days) and Hong Kong (mean 4.41 days). Linton *et al*¹¹⁹ reported shorter duration for cases who died than for survivors. Reasons for this were not clear, but authors stated that some infected patients were hospitalised for the purposes of isolation rather than treatment of severe disease. Furthermore, deceased cases for whom information was available had onset dates closer to the beginning of the outbreak compared to the living cases. Given the heterogeneity of this measure and the relative ease in its measurement, model input should be as setting-specific as possible, more studies estimating this and other measures of duration from symptom onset (to death, to case confirmation) should be undertaken, with more extensive data gathering and availability (eg from PHE).

6.6 Proportion of infections that are asymptomatic and their contribution to transmission

There is a large range of estimates of the proportion of COVID-19 infections which are asymptomatic. This uncertainty is problematic, because this model input greatly influences model predictions. Studies must have sufficiently long follow-up to identify pre-symptomatic cases. Wu *et al* (2020)¹²⁰ examined how sensitive model predictions were to the assumptions made on the proportion of asymptomatic cases (in their terminology *P_{sym}*) who could still transmit infection (but perhaps at a lower rate than symptomatic people). They concluded that estimates of R_0 , the mean generation time, T , and intervention effectiveness would all be altered by different assumptions on this proportion, while other parameter estimates were relatively insensitive to this assumption.

Individual variation plays a large part in outbreak dynamics. Analysis of contact tracing from other infections such as SARS has indicated that the contribution of individuals to infection transmission is highly skewed: a small proportion transmit lots of infection, while the majority transmit relatively little¹²¹. These findings have indicated that “superspreading events”, in which certain individuals infect large numbers of secondary cases, are not unusual but are a normal feature of infection spread. Importantly, it is not high pathogen load or shedding that is generally responsible for this, but unrecognised or misdiagnosed illness which has been identified as the most common cause of these superspreading events. Individuals carry on their day-to-day activities unchecked for their full infectious period, infecting others as they go. It is therefore crucial to use a reliable estimate of numbers of asymptomatically-infected COVID-19 individuals and their capacity to transmit to others, for models to provide reliable predictions¹²².

A systematic review including only studies assessed as low risk-of-bias and only PCR-confirmed cases, reported estimates from 4% to 41% from nine studies (see Table 1¹²³). Combining data from these studies produced a pooled estimate of 14.0% (95%CI 4.9 – 24.0%) (15.0% (95%CI 4.5 – 25.8%) for non-aged care; 12.0% (95%CI 0.0 – 31.1%) for aged care). Several high profile studies reporting higher estimates were excluded, for

reasons including short follow-up duration (limits our ability to distinguish asymptomatic from pre-symptomatic individuals, who may have gone on to develop symptoms after follow-up) and selection bias (eg, repatriation studies, following up individuals flying to their home countries: symptomatic people may have been prevented from boarding a plane). The review also excluded analysis of the Diamond Princess cruise ship outbreak involving 3711 passengers leading to 712 infections, because many infected patients were transferred to medical facilities in Japan and lost to follow-up. Fifty-eight percent of infections on the cruise ship were asymptomatic at the time of testing, but it became apparent from following part of this cohort, that many of these individuals were pre-symptomatic rather than asymptomatic¹²⁴. However, an analysis has attempted to adjust for this right censoring and estimated that 17.9% (95%CI 15.5% – 20.2%) of positive cases were asymptomatic¹²⁵ and has been included in Table 1.

Studies included in the review had high rates of testing: all contacts regardless of symptoms^{126, 127, 128, 129, 130, 131} >97% of nursing home residents^{132, 133} and 85.9% testing of an entire town¹³⁴. Length of follow-up for monitored individuals in the skilled nursing facility (SNF) studies was 7 days^{135, 136}, 14 days for the Bruneian¹³⁷, Taiwanese¹³⁸, South Korean¹³ and Chinese close contacts¹⁴⁰; 7 – 14 days in the Italian community¹⁴¹; 12 days for 95% of all contacts in the Shenzhen community surveillance¹⁴², and 16±6 days in Liaocheng, China¹⁴³.

Most individuals in studies included in the review were adults (mean age >79 years in the two SNF studies, >31 years in the non-aged care studies). The proportions of children and young people (0 – 20 years) ranged from 6% to 23.5%. Only one study reported age-specific proportions of asymptomatic infection, finding similar proportions across age groups¹⁴⁴. In addition to studies included in the review, 23.3% of children in China were estimated to be asymptomatic in Hua *et al*¹⁴⁵ and a systematic review of paediatric COVID-19 reported a pooled estimate of 14.9% (range of study estimates: 0 – 53.3%), although care must be taken to assess the follow-up duration of each of these studies. This evidence suggests that proportion of infections that are asymptomatic are similar for children and adults, but more studies are required to confirm this.

Large-scale studies published since Byambasuren *et al*'s review include Lavezzo *et al*¹⁴⁶, where 42.5% (95%CI 31.5 – 54.6%) of COVID-19 cases were asymptomatic, taken from the small town of Vo', Italy, where the population were tested at two time points (85.9% and 71.5% coverage). Pollan *et al* reported the proportion of COVID-19 infections that are asymptomatic using a national, population-based study from Spain¹⁴⁷. Researchers used both a point-of-care test and an immunoassay. The proportion of individuals with a positive test who were asymptomatic was 32.7% (95%CI 30.2 – 35.4) and 28.5% (95%CI 25.6 – 31.5) respectively, with a specificity-sensitivity range of 21.9% (19.1 – 24.9, both tests positive) to 35.8% (33.1 – 38.5, either test positive). Higher still, the German Medical Association²¹ reported 85% of confirmed cases never developed symptoms in Ischgl, Germany (no uncertainty range stated)¹⁴⁸.

6.6.1 Infectiousness of asymptomatic individuals

Case reports have demonstrated transmission from asymptomatic carriers¹⁴⁹ and four studies have been identified which attempt to quantify this forward transmission risk, suggesting considerably lower rates of transmission than for symptomatic cases (see Table 1^{150, 151, 152, 153}). There is evidence that viral load is similar for symptomatic and asymptomatic individuals^{154, 155}. However, measurable virus shedding does not necessarily equate with infectivity. Further research is required to determine the relationship between RT-PCR Ct values and infectiousness¹⁵⁶.

While it was first suggested that children may play a minor part in transmission, evidence of their infection accumulates, including viral shedding, with high concentration of viral RNA detectable in nasopharyngeal swabs of asymptomatic children reported, but with lower viral concentrations for asymptomatic compared to symptomatic children, and a very small sample size (three asymptomatics)¹⁵⁷. There is also evidence that children may shed SARS-CoV-2 virus in the stool for a prolonged period (up to 30 days)^{158, 159}.

6.6.2 Duration of infectiousness of asymptomatic individuals

The duration of SARS-CoV-2 RNA shedding has not yet been well characterised. Long *et al*¹⁶⁰ reported median duration of viral shedding of 37 asymptomatic cases in China as 19 days (IQR 15 – 26 day). This was significantly longer than shedding from patients with mild symptoms (median 14 days, IQR 9 – 22 days, p=0.028). Duration of shedding was calculated as the number of days from the first PCR-positive nasopharyngeal sample to the last positive sample; however this likely underestimates duration of shedding, which may have started before the first test. Counter to this, nasopharyngeal swabs may continue to test PCR-positive long after the disappearance of infectious virus¹⁶¹, which would overestimate duration of infectiousness. Long *et al*'s estimates of infectiousness duration for symptomatic individuals are shorter than other reports (median 20 days¹⁶² and up to at least 24 days¹⁶³) but indicate that this measure is likely to be longer for asymptomatic individuals. As mentioned above, there is evidence that faecal shedding may persist beyond nasopharyngeal shedding in children¹⁶⁴.

To improve our understanding of the importance of asymptomatic cases in driving transmission (understandably given the limited time span this infection has been spreading worldwide) further studies are required to. A short summary of some of the most urgent needs are listed below.

- provide more robust estimates of the proportion of asymptomatic COVID-19 infections, including in sub-populations such as children;
- quantify the relative infectiousness of asymptomatic and symptomatic and pre-symptomatic individuals;
- quantify the duration of infectiousness of asymptomatic individuals.

TABLE 1

Summary of data sources for key COVID-19 model inputs.

Study	Setting	Estimate and distribution	Sample size
Incubation period			
Li et al ¹⁶⁵	Wuhan, China	Mean 5.2 days (95%CI 4.1 – 7.0), 95th percentile 12.5 days, log-normal distribution	10 cases
Bi et al ¹⁶⁶	Shenzhen, China	Median 4.8 days (95%CI 4.2 – 5.4), 5% percentile 1.6 days (95%CI 1.3 – 2.0), 95% percentile 14.0 days (95%CI 12.2 – 15.9), log-normal distribution	183 cases
Backer et al ¹⁶⁷	Travel data from Wuhan	Mean 6.4 days (95%CrI 5.6 – 7.7), 2.5th to 97.5th percentile 2.1 – 11.1 days, SD 2.3	88 cases
Linton et al ¹⁶⁸	Global, excluding Wuhan	Mean 5.6 days (95%CrI 4.4 – 7.4), median 4.6 days (95%CrI 3.7 – 5.7), SD 3.9 (95%CrI 2.4 – 6.9), 5th percentile 1.7, 95th percentile 12.3, log-normal distribution	52 cases
Liu et al ¹⁶⁹	China	Mean 4.8 days (95%CI 2.2 – 7.4), range: 2 – 11	16 cases
Guan et al ¹⁷⁰	China	4.0 days (IQR 2.0 – 7.0)	291 cases
Lauer et al ¹⁷¹	Global, excluding Hubei, China	Median 5.1 days (95%CrI 4.5 – 5.8), 2.5th percentile 2.2 (1.8 – 2.9), 25th percentile 3.8 (3.3 – 4.4), 75th percentile 6.7 (5.7 – 7.9), 97.5th percentile 11.5 (8.2 – 15.6), log-normal distribution	181 cases
Pellis et al ¹⁷² reanalysing data from Sun et al ¹⁷³ and line-list data from PHE ⁽¹⁰⁾	Global	Mean 4.84, SD 2.79	162 cases
Kraemer et al ¹⁷⁴	Mobility data from Wuhan	Mean 5.1 days, SD 3.0	38 cases
Hua et al ¹⁷⁵	Zhejiang, China	Mean 9.1 days ⁽¹⁾ (range 4 – 21), SD 3.7 days Three patients (9.4%, 3/32) had incubation period >14 days	32 paediatric cases (mean age of total cohort 8.2 years, n=43)
Ki et al ¹⁷⁶	South Korea	3.6 days (range 1.0 – 9.0)	22 cases
Jiang et al ¹⁷⁷	Global	4.9 days (95%CI 4.4 – 5.5)	50 cases
Wu et al ¹⁷⁸	Zhuhai, China	Mean 5.8 days; median 4.3 days (95%CI 3.4 – 5.3), 5% percentile 1.2 days (95%CI 0.76 – 1.8), 95% percentile 15.3 days (95%CI 10.4 – 21.1). Estimated dispersion parameter: 2.2 (95%CI 1.8 – 2.5), assumed log-normal distribution	48 cases
You et al ¹⁷⁹	China	Mean 8.00 days (SD 4.75 days, range 0.00 – 23.50, IQR 4.50 – 10.00, median 7.00)	169 cases

Study	Setting	Estimate and distribution	Sample size
Men <i>et al</i> ¹⁸⁰	China	Mean 5.84, median 5.0 days Incubation period did not follow general incubation distributions such as log-normal, Weibull and gamma distributions. Authors estimated incubation via bootstrap and proposed Monte Carlo simulations.	59 cases
Qiu <i>et al</i> ¹⁸¹	Hunan, China	Median 6 days (range 1 – 32 days), 8 patients ranged 18 – 32 days	71 cases
Generation time			
Ferretti <i>et al</i> ¹⁸²	China, Taiwan, South Korea, Vietnam, Singapore, Germany, Italy	Mean 5.0 days; median 5.0 days (SD 1.9 days) Best fit: Weibull distribution	40 infector–infectee pairs
Ganyani <i>et al</i> ¹⁸³	Singapore	Mean 5.20 days (95%CrI 3.78 – 6.78)	Unclear
Ganyani <i>et al</i> ¹⁸⁴	Tianjin, China	Mean 3.95 days (95%CrI 3.01 – 4.91)	Unclear
Serial interval			
Ganyani <i>et al</i> ¹⁸⁵	Singapore	Mean 5.21 (95%CrI -3.35 – 13.94), SD 4.32 days (95%CrI 4.06 – 5.58)	54 infector–infectee pairs
Ganyani <i>et al</i> ¹⁸⁶	Tianjin, China	Mean 3.95 (95%CrI -4.47 – 12.51), SD 4.24 days (95%CrI 4.03 – 4.95)	45 infector–infectee pairs
Nishiura <i>et al</i> ¹⁸⁷	Vietnam, Germany, China, South Korea, Taiwan and Singapore	Mean 4.8 days (95%CI 3.8 – 6.1), SD 2.3 days (95%CrI 1.6 – 3.5), median 4.6 days (95%CrI: 3.5 – 5.9), Weibull distribution (Mean 4.7 days (95%CrI 3.7 – 6.0), SD 2.9 days (95%CrI 1.9 – 4.9); median 4.0 days (95%CrI 3.1 – 4.9), log-normal distribution)	18 certain infector–infectee pairs (Additionally including 10 probable infector–infectee pairs)
Wu <i>et al</i> ¹⁸⁸	Data taken from Li <i>et al</i> ¹⁸⁹ plus data from early cases in Shenzheng and Hong Kong, China, and the US, Taiwan, Singapore, Vietnam, Malaysia	Mean 7.0 days (95%CI 5.8 – 8.1), SD 4.5 days (95%CI 3.5 – 5.5), assumed pdf of serial interval is gamma	43 infector–infectee pairs
Bi <i>et al</i> ¹⁹⁰	Shenzhen, China	Mean 6.3 days (95%CI 5.2 – 7.6), SD 4.2 days (95%CI 3.1 – 5.3), median 5.4 days (95%CI 4.4 – 6.5) 5% percentile 1.3 days (95%CI 0.9 – 1.9), 95% percentile 14.3 days (95%CI 11.1 – 17.6), gamma distribution	48 infector–infectee pairs
Cereda <i>et al</i> ¹⁹¹	Italy	Mean 6.6 days (95%CrI 0.7 – 19.0)	90 infector–infectee pairs
Chan <i>et al</i> ¹⁹²	Hong Kong, China	Mean 6.5 days (SD 4.7 days), gamma distribution	47 infector–infectee pairs
Li <i>et al</i> ¹⁹³	Wuhan, China	Mean 7.5 days (95%CI 5.3 – 19.0), SD 3.4 days, gamma distribution	6 infector–infectee pairs
Tindale <i>et al</i> ¹⁹⁴	Singapore	Mean 4.56 days (95%CI 2.69 – 6.42), SD 0.95 days	93 infector–infectee pairs
Tindale <i>et al</i> ¹⁹⁵	Tianjin, China	Mean 4.22 days (95%CI 3.43 – 5.01), SD 0.4 days	135 infector–infectee pairs
Du <i>et al</i> ^{(2), 196}	Mainland China, excluding Hubei	Mean 5.29 days (95%CI 4.72 – 5.86), SD 5.32 days (95%CI 4.95 – 5.75), normal distribution	339 infector–infectee pairs

Study	Setting	Estimate and distribution	Sample size
Zhang <i>et al</i> ¹⁹⁷	China, excluding Hubei	5.1 days (95%CI 1.3 – 11.6)	35 infector–infectee pairs
Zhao <i>et al</i> ¹⁹⁸	Hong Kong, China	Mean 4.4 days (95%CI 2.9 – 6.7), SD 3.0 days (95%CI 1.8 – 5.8)	21 infector–infectee pairs
Wang <i>et al</i> ¹⁹⁹	Shenzhen, China	Mean 5.9 days (95%CI 3.9 – 9.6), SD 4.8 days (95%CI 3.1 – 10.1) Weibull distribution	27 infector–infectee pairs
Wu <i>et al</i> ²⁰⁰	Zhuhai, China	Mean 6.3 days; median 5.1 days (95%CI 4.3 – 6.2), 5% percentile 1.8 days (95%CI 1.4 – 2.4), 95% percentile 14.8 days (95%CI 11.0 – 19.2). Estimated dispersion parameter: 1.9 (95%CI 1.65 – 2.2), assumed log-normal distribution	48 within household infector–infectee pairs
Aghaali <i>et al</i> ²⁰¹	Iran	Mean 4.55 days (SD 3.30 days), gamma distribution	37 infector–infectee pairs
Lavezzo <i>et al</i> ²⁰²	Italy	7.2 days (95% CI 5.9 – 9.6)	
Exponential growth rate			
Remuzzi and Remuzzi ²⁰³	Italy	0.225	Fitted to infected patient data up to 8 March 2020
Dehning <i>et al</i> ^{204, (11)}	Germany	0.43 (95% CI 0.35 – 0.51)	Data up to 7 March
Epidemic doubling time			
Pellis <i>et al</i> ²⁰⁵	Multiple European countries	“consistently found doubling times of about 3 days” 2.9 days (95%CI 2.4 – 3.6) Austria 3.1 days (95%CI 2.4 – 4.4) Belgium 2.5 days (95%CI 2.3 – 2.7) Czechia 2.6 days (95%CI 2.1 – 3.6) Denmark 3.7 days (95%CI 3.0 – 5.0) France 2.6 days (95%CI 2. – 3.2) Germany 2.3 days (95%CI 2.1 – 2.4) Republic of Ireland 3.0 days (95%CI 2.7 – 3.5) Italy 3.4 days (95%CI 3.0 – 3.9) Portugal 3.4 days (95%CI 3.0 – 4.0) Netherlands 2.3 days (95%CI 2.0 – 2.7) Norway 4.3 days (95%CI 3.2 – 6.5) Poland 2.5 days (95%CI 2.2 – 2.9) Portugal 3.7 days (95%CI 3.1 – 4.5) Romania 3.5 days (95%CI 2.9 – 4.5) Spain 2.5 days (95%CI 2.3 – 2.8) Sweden 2.2 days (95%CI 1.9 – 2.5) Switzerland 2.3 days (95%CI 2.1 – 2.5) United Kingdom	WHO confirmed cases up to 31 March 2020 plus selected surveillance data (including deaths and hospital and ICU daily counts) from Italy
Kraemer <i>et al</i> ²⁰⁶	Mobility data from Wuhan	4.0 days outside Hubei (range 3.6 – 5.0 across provinces) 7.2 days within Hubei	
Li <i>et al</i> ²⁰⁷	Wuhan, China	7.4 days (95%CI 4.2 – 14.0)	First 425 confirmed cases

Study	Setting	Estimate and distribution	Sample size
Wu <i>et al</i> ²⁰⁸	Wuhan, China	6.4 days (95%CrI 5.8 – 7.1)	Confirmed cases up to 28 March 2020
Du <i>et al</i> ²⁰⁹	Mobility data from Wuhan	7.31 days (95%CrI 6.26 – 9.66)	First 19 cases outside China
Wu <i>et al</i> ²¹⁰	Wuhan, China	5.2 days (95%CI 4.6 – 6.1)	
Lau <i>et al</i> ²¹¹	China	2.0 days (95%CI 1.9 – 2.6) – pre-lockdown 4.0 days (3.5 – 4.3) – since lockdown	
Liu <i>et al</i> ²¹²	China	2.4 days (no uncertainty range reported)	
Chinazzi <i>et al</i> ²¹³	Number of confirmed cases outside China and travel data	4.6 days	
Zhao <i>et al</i> ²¹⁴	Number of confirmed cases outside China and travel data	2.9 days	
Aghaali <i>et al</i> ²¹⁵	Qom, Iran	3.47 days (95%CI 3.16 – 3.84)	
Aghaali <i>et al</i> ²¹⁶	Iran	1.82 days (95%CI 1.64 – 2.05)	
Aghaali <i>et al</i> ²¹⁷	Italy – WHO data	3.37 days (95%CI 3.03 – 3.81)	
Aghaali <i>et al</i> ²¹⁸	South Korea – WHO data	1.78 days (95%CI 1.36 – 2.58)	
Aghaali <i>et al</i> ²¹⁹	China – WHO data	2.55 days (95%CI 2.25 – 2.96)	
Duration onset of symptoms of death			
Verity <i>et al</i> ²²⁰	Hubei, China	Mean 17.8 days (95%CrI: 16.9 – 19.2), gamma distribution	24 deaths
Linton <i>et al</i> ²²¹	Global	Mean 20.2 days (95%CrI 15.1 – 29.5), median 17.1 days (95%CrI 13.5 – 24.1), SD 11.6 (95%CrI 6.6 – 21.8), 5th percentile 7.4, 95th percentile 39.9, log-normal distribution	34 deaths
Wu <i>et al</i> ²²²	Wuhan, China	Mean 20 days (95%CI 17 – 24), SD 10 days (95%CI 7 – 14) (3), gamma distribution	41 deaths
Zhou <i>et al</i> ²²³	Wuhan, China	Median 18.5 days (IQR 15.0 – 22.0)	54 deaths
Turner <i>et al</i> ²²⁴	United Kingdom	Median 9 days (range 2 – 30) (4)	30 deaths
Duration hospitalisation to death			
Linton <i>et al</i> ²²⁵	Global	Mean 13.0 days (95%CrI 8.7 – 20.9), median 9.1 days (95%CrI 6.7 – 13.7), SD 12.7, 5th percentile 2.5, 95th percentile 33.1, log-normal distribution	39 deaths
Duration onset of symptoms to hospital admission			
Linton <i>et al</i> ²²⁶	Global	Mean 9.7 days (95%CrI 5.4 – 17.0), median 2.6 days (95%CrI 1.9 – 3.8), 5th percentile 0.2, 95th percentile 35.1, log-normal distribution	155 survivors
Linton <i>et al</i> ²²⁷	Global	Mean 6.6 days (95%CrI 5.2 – 8.8), median 5.3 days (95%CrI 4.2 – 6.8), 5th percentile 1.9, 95th percentile 15.0, log-normal distribution	34 deaths

Study	Setting	Estimate and distribution	Sample size
Thompson <i>et al</i> ²²⁸	Global (predominantly China)	Mean 6.5 days – 2 – 14 January Mean ~2 days – 22 January	212 cases (China n=190, other countries n=22) from ²²⁹
Pellis <i>et al</i> ²³⁰	UK (PHE data)	Mean 5.14 days, SD 4.20	90 cases
Pellis <i>et al</i> ²³¹ reanalysing data from Sun <i>et al</i> ²³²	Singapore	Mean 2.62, SD 2.38	92 cases
Pellis <i>et al</i> ²³³ reanalysing data from Sun <i>et al</i> ²³⁴	Hong Kong	Mean 4.41, SD 4.63	52 cases
Bi <i>et al</i> ²³⁵	Shenzhen, China.	Median 3.4 days (95%CI 3.1 – 3.8), 95th percentile 12.4 days (95%CI 10.9 – 13.8) – symptom-based surveillance Median 2.1 days (95%CI 1.7 – 2.6), 95th percentile 6.0 days (95%CI 4.5 – 7.5) – contact-based surveillance	183 cases
Huang <i>et al</i> ^{236, (5)}	Wuhan, China	Median 7.0 days (IQR 4.0 – 8.0)	41 cases
Duration onset of symptoms to case confirmation			
Bi <i>et al</i> ²³⁷	Shenzhen, China	Median 4.6 days (95%CI 4.2 – 5.0), 95th percentile 12.7 days (95%CI 11.5 – 13.8) – symptom-based surveillance Median 2.9 days (95%CI 2.4 – 3.4), 95th percentile 6.6 days (95%CI 5.3 – 8.0) – contact-based surveillance	183 cases
Kraemer <i>et al</i> ²³⁸	Mobility data from Wuhan	Mean 4.8 days, SD 3.03 days	38 cases
Proportion Asymptomatic			
Estimates included in Byasaburam <i>et al</i> systematic review ²³⁹			
Roxby <i>et al</i> ²⁴⁰	USA	40% (95%CI 5 – 85%)	2/5 infected cases
Arons <i>et al</i> ²⁴¹	USA	5% (95%CI 1 – 15%)	3/57 infected cases
Tian <i>et al</i> ²⁴²	China	29% (95%CI 13 – 51%)	7/24 infected cases
Cheng <i>et al</i> ²⁴³	Taiwan	19% (95%CI 4 – 46%)	3/16 infected cases
Lavezzo <i>et al</i> ²⁴⁴	Italy	41% (95%CI 29 – 53%)	30/73 infected cases
Bi <i>et al</i> ²⁴⁵	China	20% (95%CI 12 – 29%)	17/87 infected cases
Chaw <i>et al</i> ²⁴⁶	Brunei	13% (95%CI 6 – 23%)	9/71 infected cases
Luo <i>et al</i> ²⁴⁷	China	6% (95%CI 3 – 12%)	8/129 infected cases
Park <i>et al</i> ²⁴⁸	South Korea	4% (95%CI 1 – 10%)	4/97 infected cases
Estimates excluded by Byasaburam <i>et al</i> ²⁴⁹			
Mizumoto <i>et al</i> ²⁵⁰	Diamond Princess cruise ship	17.9% (95%CI 15.5 – 20.2%)	328 of 634 confirmed cases ⁽⁶⁾

Study	Setting	Estimate and distribution	Sample size
Estimates published after Byasaburam <i>et al</i> ²⁵¹			
Patel <i>et al</i> ²⁵²	USA	37% (NS)	13/35 infected cases
Payne <i>et al</i> ²⁵³	USS Theodore Roosevelt	18.5% (NS)	44/238 infected cases
Hua <i>et al</i> ^{254, (7)}	Zhejiang, China	23.3% (NS)	10/32 paediatric infected cases (mean age 8.2 years)
Patel <i>et al</i> ^{255, (8)}	Systematic review, multiple countries	Pooled estimate: 14.9% (range between studies: 0 – 53.3%)	51/342 paediatric infected cases
German Medical Association ²⁵⁶	Ischgl, Germany	85% (NS)	NS
Lavezzo <i>et al</i> ²⁵⁷	Italy	42.5% (95%CI 31.5 – 54.6%)	81 cases
Pollan <i>et al</i> ²⁵⁸	Spain	28.5% (95%CI 25.6 – 31.5%) – immunoassay 32.7% (95%CI 30.2 – 35.4%) – point-of-care test	~2800 cases ~3050 cases
Relative infectiousness of asymptomatics			
Chaw <i>et al</i> ²⁵⁹	15/691 (2.2%)	28/1010 (2.8%)	0.79
Cheng <i>et al</i> ²⁶⁰	0/91 (0%)	22/2644 (0.8%)	0.0
Luo <i>et al</i> ²⁶¹	1/305 (0.3%)	117/2305 (5.1%)	0.06
Park <i>et al</i> ²⁶²	0/4 (0%)	34/221 (15.4%)	0.0
Study	Setting	Estimate and distribution	Sample size
Duration of infectiousness of asymptomatics			
Long <i>et al</i> ²⁶³	Wanzhou, China	Median 19 days (IQR 15 – 26) viral shedding, range 6 – 45 days ⁽⁹⁾	37 asymptomatic cases

NB 95%CI – 95% confidence interval; 95%CrI – 95% credible interval; ICU – intensive care unit; IQR – interquartile range; NS – not stated; pdf – probability density function; PHE – Public Health England; SD – standard deviation.

Serial interval estimates excluded from a recent rapid review²⁶⁴ due to unclear presentation of methods or other methodological issues^{265, 266, 267, 268, 269, 270, 271}.

- (1) Unclear if 9.1 days represents the mean, median or both.
- (2) Pre-print values widely cited (Du *et al*)²⁷²: 468 infector–infectee pairs, 3.96 days (95%CI 3.53 – 4.39). Zhang *et al*²⁷³ uses the same data as Du *et al* and so is excluded. You *et al* is also excluded as it likely uses the same or overlapping data.
- (3) Du *et al*²⁷⁴ reported data on 109 patients in Wuhan over the same time period: (mean duration 22.3 days, SD 9.2 days), likely covering the patients used by Wu *et al*²⁷⁵. All 109 patients required ICU admission but only 51 (47%) received ICU care because of limited availability. The period of hospitalisation to death in the ICU and non-ICU groups were 15.9 days (SD, 8.8 days) and 12.5 days (8.6 days, P =0.044), respectively. The mean period for COVID-19 pneumonia patients waiting for a hospital bed was 9.7 days (SD, 5.3 days).
- (4) Researchers highlighted the heterogeneity in this duration, grouping patients as having: 1) fulminant COVID-19 (mean illness duration 5.17 days, n=11); 2) longer illness and slower deaths (duration 11.15 days, n=14); and 3) long illness, stability, and rapid death (16.6 days, n=5).
- (5) Data from cases at start of epidemic: data up to 2 January 2020. Time from symptom onset to hospital admission may be longer because COVID-19 was not yet recognised.
- (6) Analysis adjusts for right censoring of data.
- (7) Duration of follow-up unclear. Hospital stay ranged from 3 to 32 days with a mean of 20.2 (SD: 7.9) days.
- (8) Definition of asymptomatic was “without any clinical symptoms and signs or imaging findings or disease, whereas the 2019-nCoV/SARS-CoV-2 testing result was positive”. Therefore, the duration of follow-up to exclude pre-symptomatic cases is unclear.
- (9) Asymptomatic cases were PCR-confirmed but without clinical symptoms in the preceding 13 days and during hospitalisation. PCR cases claiming no symptoms in the previous 14 days were quarantined; those defined as having mild or atypical symptoms assessed by clinicians were excluded. Individuals developing symptoms 4 – 17 days after admission were also excluded.
- (10) Data reanalysed to account for both truncated observations and exponential growth in the number of infected cases.
- (11) Initial growth rate before a decrease observed using the full dataset up to 21 April 2020, corresponding with the implementation of interventions in the country.

7. Data sources in the UK

Estimation of key epidemiological parameters starts with data and no amount of sophisticated modelling can make up for inadequate measurement. The epidemiological data informing the science and policy formulation have been of poor quality in the early phases of the epidemic in the UK. For the future, an authoritative body must think carefully about acquiring timely and relevant data, at scale, and distributing it openly through a carefully curated portal. The National Statistician has a key role here, as would the Royal Society, the Academy of Medical Sciences, the British Academy and the Royal Statistical Society in ensuring good collection, analysis and presentation procedures.

In late June 2020, the government released a Beta version of a new website that provides a summary of the data available in a downloadable form. This is a very constructive change in data reporting since the site helps coalesce disparate sources of information for professionals and the public at large. What follows is a brief description of the main data sources²⁷⁶.

PHE provides a weekly Coronavirus Disease 2019 (COVID-19) surveillance report. The Week 22 report provides a summary of the information available from surveillance systems used to monitor viral spread and the impact of mitigation measures. Other sources of data come from Department of Health (DoH) funded and other funding agency studies on serology and contact tracing. Mortality data especially on excess mortality for any given week by comparison with previous years is provided by the Office for National Statistics (ONS). PHE labels a series of Pillars to describe the type COVID-19 testing and methods employed²⁷⁷.

The definitions of Pillars in testing is as follows. Pillar 1: swab testing in Public Health England (PHE) labs and NHS hospitals for those with a clinical need, and health and care workers. Pillar 2: swab testing for the wider population, as set out in government guidance. Pillar 3: serology testing to show if people have antibodies from having had COVID-19. Pillar 4: serology and swab testing for national surveillance supported by PHE, ONS, Biobank, universities and other partners to learn more about the prevalence and spread of the virus and for other testing research purposes, for example on the accuracy and ease of use of home testing²⁷⁸.

Current sources of data for the UK are listed in Table 2.

TABLE 2

UK data sources for the epidemiological study of trends in the COVID-19 epidemic.

Data Source	Body	Info
Daily tests and deaths ²⁷⁹	GOV.UK	Lab-confirmed cases (daily) UK deaths with +ve test result (total and daily) Deaths by nation Estimated excess deaths
Daily transport in UK ²⁸⁰	GOV.UK	Transport data for GB – cars, light commercial vehicles, HGV, all motor vehicles, national rail, TFL (tube and bus), bus excluding London, and cycling Daily % increase from previous day, from 1 March 2020
Weekly Surveillance Reports and Summaries ²⁸¹	PHE	Confirmed cases (in hospital and community testing) stratified by age, gender, UK region, ethnicity. Acute respiratory outbreaks, '111' calls, online search activity, GP activity, RCGP swabbing scheme, hospital surveillance, deaths, excess mortality, seroprevalence, global outlook
Weekly deaths, social impact, finance reports, labour markets ²⁸²	ONS	Weekly deaths by gender and region in England and Wales. Defined as death by cause – underlying cause was respiratory disease or COVID-19 mentioned on death certificate
Serology Test Evaluation ²⁸³	GOV.UK	DiSorin LIAISON SARS-CoV-2 S1/S2 IgG serology assay specificity 97.7% (95.8 – 99.0), sensitivity 64.0% (53.8 – 73.4) Euroimmun anti-SARS-CoV-2 ELISA (IgG) serology assay specificity of 99.0% (97.5 – 99.7), sensitivity of 72.0% (61.8 – 80.9) Abbott SARS-CoV-2 IgG kit specificity 100.00% (99.1 – 100.0), sensitivity 92.7% (85.6 – 97.0) Roche Elecsys Anti-SARS-CoV-2 serology assay, specificity 100% (99.1 – 100), sensitivity 83.9% (74.8 – 90.7) Ortho Clinical Diagnostics VITROS Immunodiagnostic Products anti-SARS-CoV-2 IgG serology assay, specificity 99.7% (98.6 – 100), sensitivity 77.4% (67.6 – 85.4)
London Cases, Hospital cases, 111/999 triages ²⁸⁴	London Datastore	Uses PHE daily data
Coalesced COVID-19 data ²⁸⁵	GOV.UK	Records up to date data on cases, deaths, infected patients in health care settings
International daily cases, deaths, recovered ²⁸⁶	Worldometer	Active cases defined as mild, serious or critical, closed cases as recovered/discharged or deaths. Cases and tests per 1M of the population.

NB Available data sources reporting COVID cases and deaths, or related information such as mobility or test accuracy for England or the UK. Cases and deaths are provided predominantly on a daily basis.

Each source of data for parameter estimation for the models (of either R or r , or both), has particular biases. To date these have not been explored and documented in a systematic manner.

Table 3 records the published (or preprint plus report located) data on R_0 and R_t estimates for the UK.

Government reports arising from SAGE on a regular basis have been reporting on estimates of R by region.

TABLE 3

Reproduction number estimates in the UK pre (R_0) and post (R_t) lockdown.

Authors	Date	R_0 estimate
Ferguson N, Laydon D, Nedjati-Gilani G, et al ²⁸⁷	16/03/2020	2.4 (2.0 – 2.6)
Lourenço J, Paton R, Ghafari M ²⁸⁸	Pre-print	2.25 or 2.75
Chen X, Dong Y, Xiaoyue Y ²⁸⁹	05/04/2020	4.8 (4.7 – 4.9)
Jarvis C, Zandvoort I, Gimma K ²⁹⁰	07/05/2020	2.6 (SD 0.54) pre-lockdown 0.62 (0.37 – 0.89) post-lockdown
Lonergan M, Chalmers J ²⁹¹	01/06/2020	2.1 (1.8 – 2.3) pre-lockdown, 0.99 (0.96 – 1.02) post-lockdown (based on confirmed cases) 2.6 (2.4 – 2.9) pre-lockdown, 0.85 (0.80 – 0.90) post-lockdown (based on confirmed deaths)
Tang J, Young S, May S ²⁹²	19/05/2020	1.13 hospitalised patients 1.38 community patients 1.21 hospital staff
Brett T, Rohani P ²⁹³	Pre-print	2.3
Jit M et al ²⁹⁴	07/05/2020	2.0 (1.9 – 2.1)
Goscé L, Phillips A, Gupta P ²⁹⁵	24/05/2020	2.56 (post-lockdown, no interventions) 2.07, 1.94, 1.87 (less stringent social distancing with weekly universal testing x1, x2, x3 a week) 3.07 (shielding 60+ year olds) 1.92 (weekly universal testing, and face covering use) 0.5, 0.44, 0.27 (during lockdown with weekly universal testing, face coverings, face covering and contact tracing) 2.23, 1.59, 1.53, 0.64 (post-lockdown with 30% facemask and face coverings, 50% facemasks and coverings, 80% facemasks and 50% face coverings, 80% facemasks and face coverings)
Althouse B, Wenger E, Miller J ²⁹⁶	Pre-print	2.6
European Centre for Disease Prevention and Control ²⁹⁷	23/04/2020	3.28

NB All available estimates of R_t and R_0 Figures in the UK. Estimates provided at both a high level across the UK, or for specific demographics such as hospital staff members.

7.1 Case numbers

Laboratory confirmed cases of COVID-19 up to 24 June employing PCR testing for viral presence are shown in Figure 11 and reveal the significant impact of lock down measures up to this time but perhaps with a slight hint of a slowing in the rate of decline in case reports in recent weeks.

As noted in the Pillar definitions provided by government, these reports have many biases as a representation of the state of the epidemic. In particular, two are of special significance. The Pillar one tests are for those with clinical need who are often the very ill who have been moved to hospitals post calls to the NHS 111 line. As such, they are not an accurate measure of current transmission in the wider community and would have to be adjusted for both time delays (average time from infection to seeking care post onset of symptoms) and the fraction who develop serious disease requiring hospital admission taking due account of confounding variables such as age and gender to accurately reflect ongoing transmission.

Pillar 2 test are a better reflection of the current transmission situation since they are swab test based for presence of virus in the wider community. However, they are not cohort based so they do not provide a precise measure of infection incidence for a given time period and they must be adjusted for the duration of time an individual from a given risk/population group is virus positive.

Pillars 3 and 4 potentially provide the best measures of current transmission for the estimation of R and r and more is said about this later under the serology subsection. However, it is important to note that the type of data reported in Figure 11 does provide a good source of information on when r turns negative and its rate of decline week by week. As the prevalence of infection decays to lower levels, the measures of r , are probably more reliable as a reflection of mitigation measure impact. Confidence bounds should be placed around r , reflecting different data sources, what is to be expected in national data where heterogeneity exists between regions of England, and aspects of prevalence measure sensitivity form a defined underlying distribution. The heterogeneity by region is shown clearly in Figure 12a and b which record incidence cumulatively and per week 24 per 100,000 head of population based on Pillar 1 and 2 testing by a large-scale region (amalgamation of NHS trusts).

FIGURE 11

The laboratory confirmed UK COVID-19 cases reported on a daily basis. The solid line is the 7-day average. The data are up to 23 August 2020 and records the very significant impact of 'lock down' measures. Number of individuals who have had at least one lab-confirmed positive COVID-19 test result, by date reported. On 2 July, case data from pillars 1 and 2 of the testing programme were combined and de-duplicated, resulting in a step decrease in the cumulative number of cases reported.

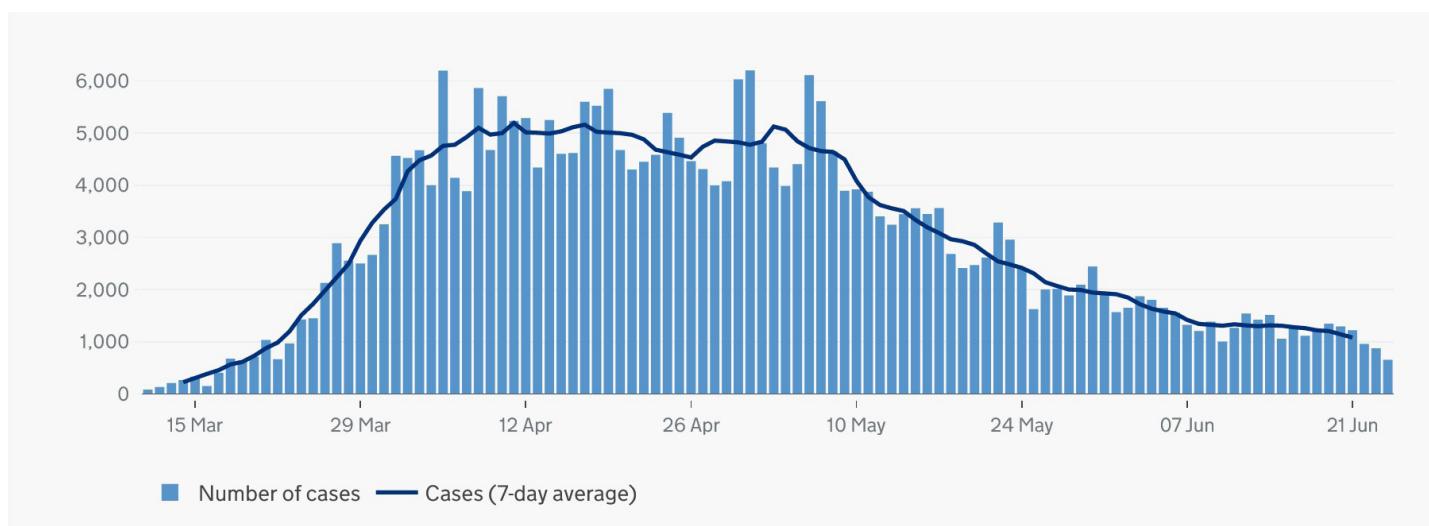
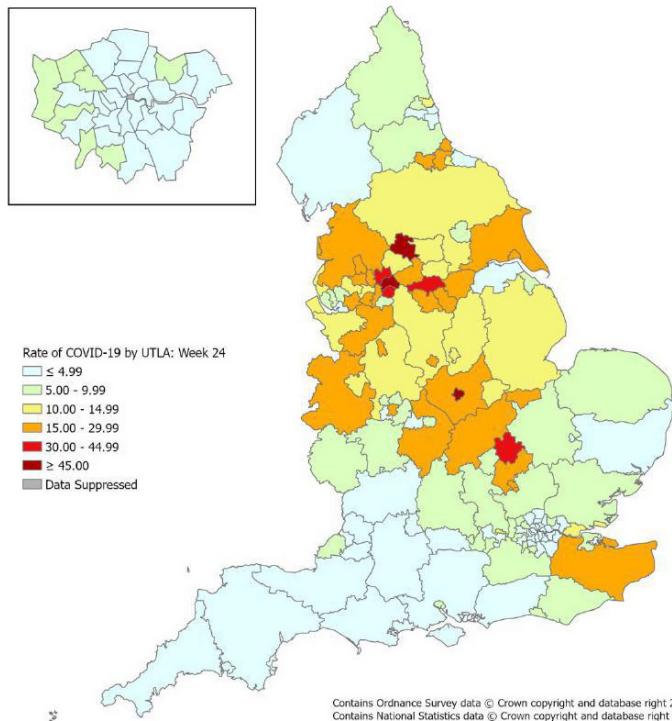


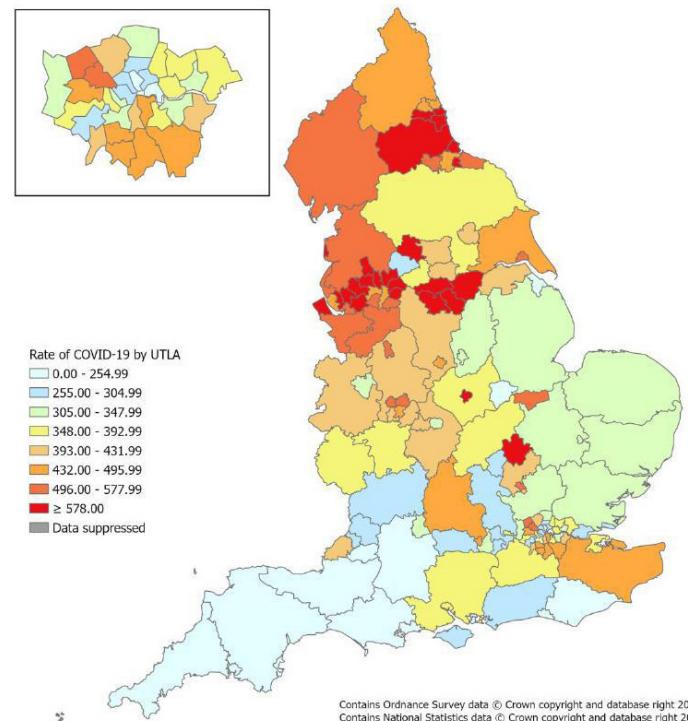
FIGURE 12

(a) Weekly rate of COVID-19 cases per 100,000 population tested under Pillar 1 and 2, by upper-tier local authority, England (box shows enlarged maps of London area, (b) Cumulative rate of COVID-19 cases per 100,000 population tested under Pillar 1 and 2, by upper-tier local authority, England (box shows enlarged maps of London area) (source PHE).

(a)



(b)

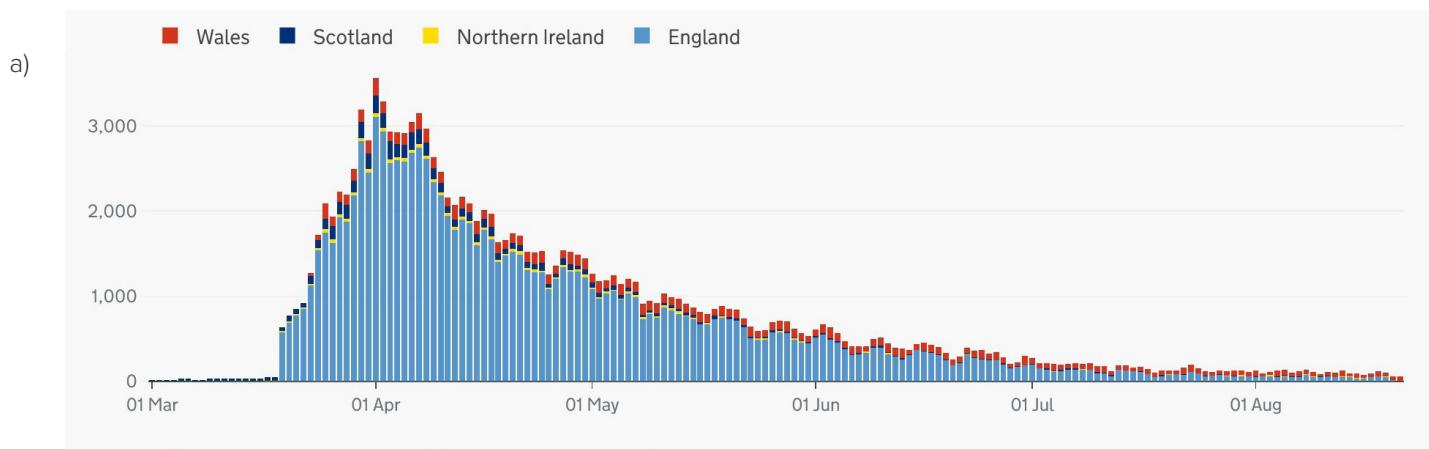


Other sources of acute case numbers, such as those admitted to intensive care units (ICUs) are also available to assess overall trends in the severity of the epidemic over time. One example is children admitted to ICUS and recorded by the PICA Net (Paediatric Intensive Care Audit

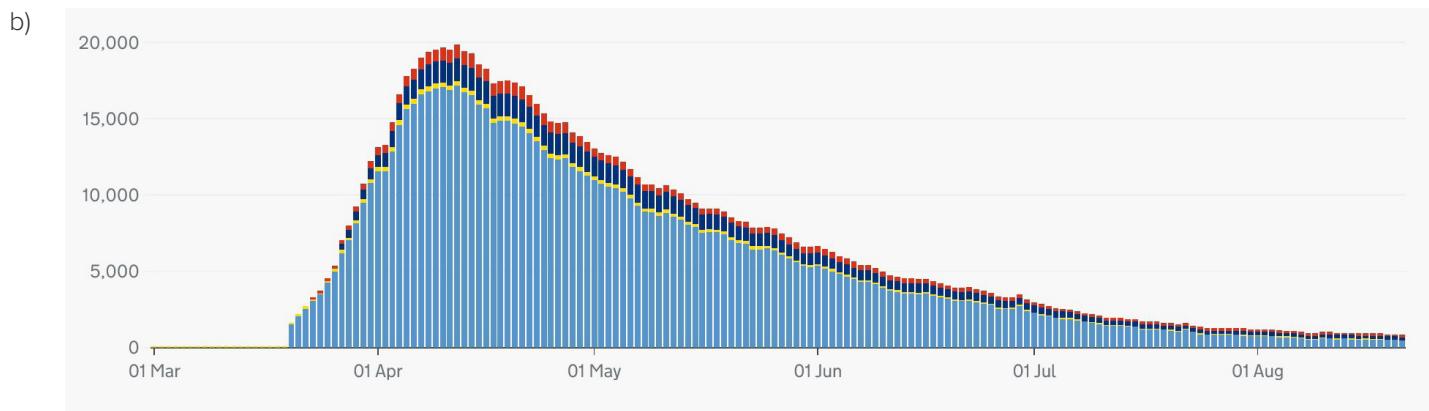
Network) based at the University of Leicester. These can be useful checks on the patterns recorded in overall case numbers. Some examples of additional data of interests in tracking the course of the epidemic are shown in Figure 13 which records patients in hospital and on ventilation.

FIGURE 13

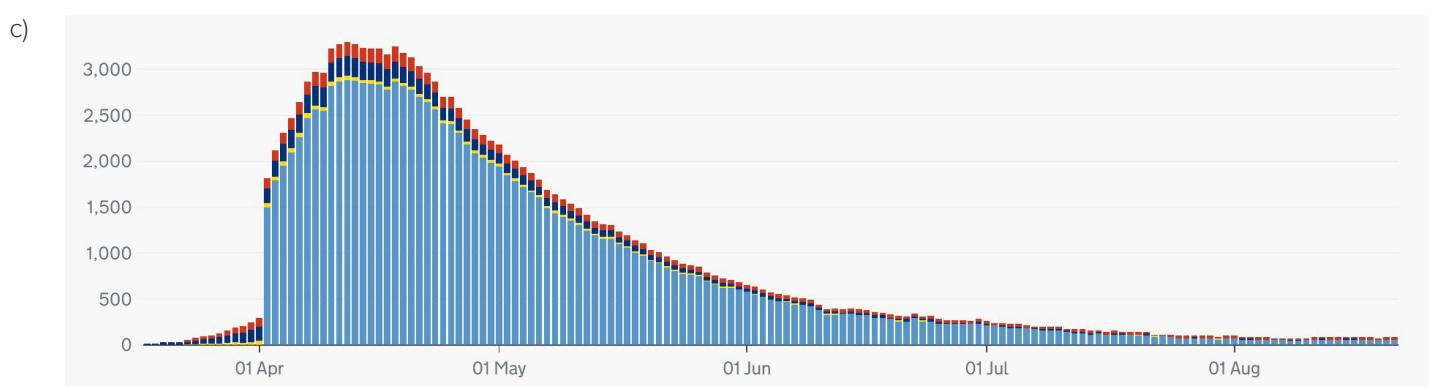
Patient numbers a) admitted to hospital, b) in hospital and c) on mechanical ventilation²⁹⁸.



N.B. Daily and cumulative numbers of COVID-19 patients admitted to hospital. Data are not updated every day by all four nations and the figures are not comparable as Wales include suspected COVID-19 patients while the other nations only include confirmed cases



N.B. Daily count of confirmed COVID-19 patients in hospital at midnight the preceding night. Data from the four nations may not be directly comparable as data about COVID-19 patients in hospitals are collected differently. Data are not reported by each nation every day. The UK figure is the sum of the four nations' figures and can only be calculated when all nations' data are available.



N.B. Confirmed COVID-19 patients in mechanical ventilation beds. Data from the four nations may not be directly comparable as data about COVID-19 patients in hospitals are collected differently. Data are not reported by each nation every day and England data are not available before 2 April. The UK figure is the sum of the four nations' figures and can only be calculated when all nations' data are available

Linked to case number reports, is the volume of testing taking place and who precisely is being tested (eg Health care staff or more broadly). Data on testing is of course time sensitive due to both testing capability and who is targeted so as a source of parameter estimation it is unreliable.

Data on testing is now released by government and an example is presented in Figure 14.

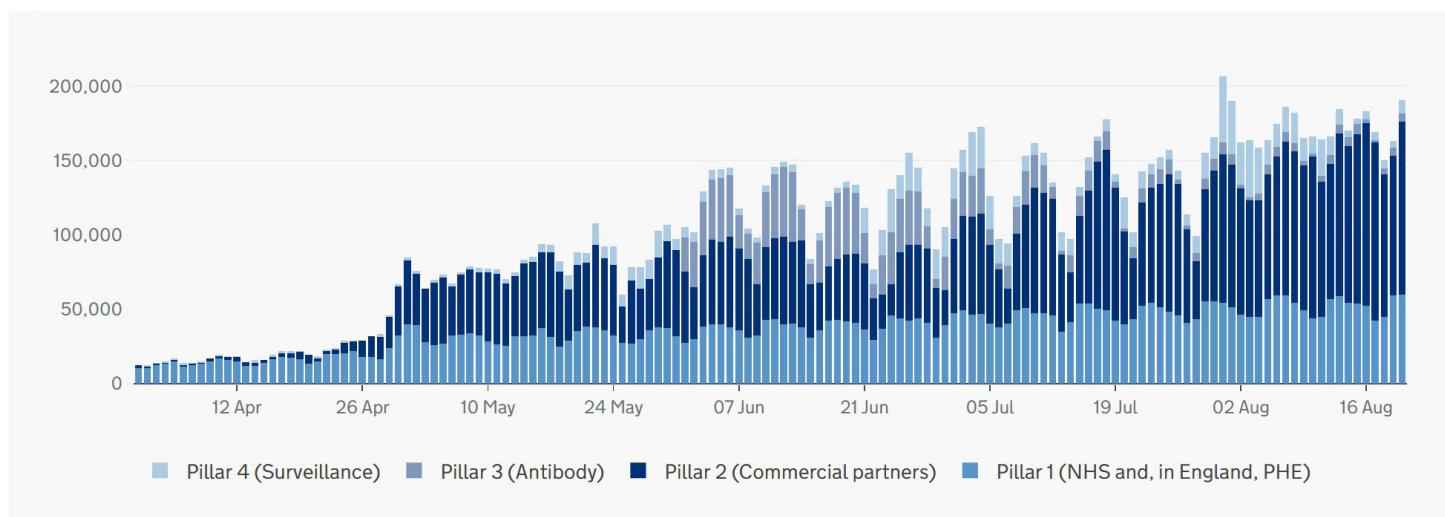
PCR based testing for active viral infection gives a snapshot of the proportion of people currently infected. This proportion is typically very small in the total population, given the relative duration of detectable viraemia in those infected, versus the typical duration of seropositivity to past infection. The efficacy of testing for the purpose of infection control crucially depends on the time interval between when a test is taken and when the results are made available. If it takes more than three or four days to get results, the numbers tested become less significant as a source of information about the efficacy of control. Therefore, the time from testing to notification of test results should be reported alongside the volume of testing carried out. The timing of testing relative to the time of infection is also important because the accuracy of tests varies with changes in viral shedding in the week post infection²⁹⁹. Serology, although hampered by a time delay of a few weeks from active infection to when antibodies are reliably detected,

represents all past infection and not just a snapshot of the relatively small proportion with active infection at any one point in time. The duration of detectable antibody levels remains uncertain at present but recent work suggests this may be short. This does not necessarily imply lack of protection from infection or disease since cell mediated responses may persist for some time. This is an urgent area for future research³⁰⁰.

The Office for National Statistics also runs a Coronavirus (COVID-19) infection survey Pilot that reports frequently on cases detected by PCR. The reports refer to the number of cases of infection within a community population which refers to private residential households, and it excludes those in hospitals, care homes or other institutional settings. This is a statistically designed sampling scheme for the population of England but still on a relatively small scale at present. Once expanded this is likely to be the most important resource for examining trends in the epidemic. It should be noted, however, that the period over which infection can be detected by PCR is a matter of days to weeks while an accurate serological test reflects is thought to reflect all past infection by the virus. It is too early to say as yet if antibodies for COVID-19 will remain detectable for many years (even lifelong), but that is the case for many viral infections. The value of PCR and serology testing to determine trends in the epidemic of course depends on test sensitivity and specificity.

FIGURE 14

Number of tests done according to government data which reflects testing capacity and who is being offered and taking up test use. Note that antibody testing started late in the course of the epidemic and surveillance testing is limited in numbers at present.



N.B. Number of lab-confirmed positive or negative COVID-19 test results, by pillar (type of testing), by date reported. This is a count of test results and may include multiple tests for an individual person. Data for antibody and surveillance testing (pillars 3 and 4) are only available for the UK as a whole.

Sample size is key to the accuracy of this programme of testing for active infection and as of latest release of survey data on the 25 June 2020, 27,494 individuals out of 17139 households enrolled have agreed to continue to be tested. This is a small start but a promising one.

7.2 Mortality data

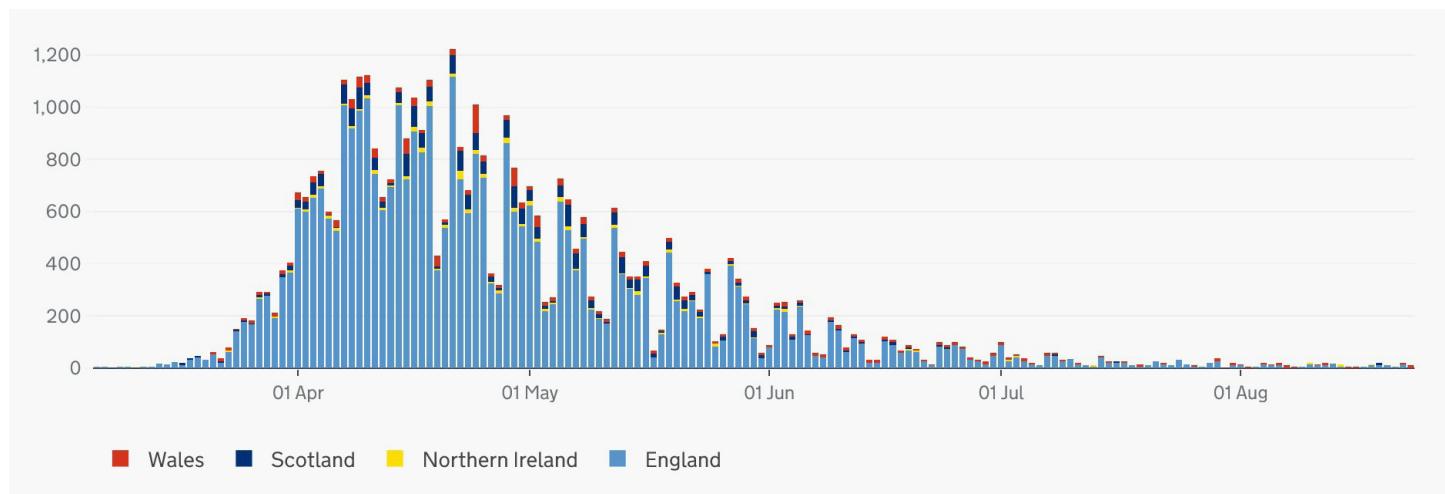
There is often some confusion about different death statistics reported in England and more broadly in the UK. The Department of Health and Social Care (DHSC) releases daily Figures on the total number of deaths reported from patients testing positive for COVID-19, regardless of place of death. These Figures include all deaths up to 5pm the day before from England, Wales, Scotland and Northern Ireland.

The Office of National Statistics (ONS) releases data on all deaths registered according to death certification either in or out of hospital for England and Wales. From these data Figures, excess deaths can be derived by comparing current deaths in a given week with the data from previous years. During the epidemic to date in the UK there has been a marked rise in deaths as a total Figure over what is normally experienced in any given week. Although increase may not necessarily be due to COVID-19 directly, it may arise from an inability amongst the elderly and others to get professional medical help or hospital admission for non-COVID-19 conditions.

The recorded daily deaths ascribed to COVID-19 in England and Wales are released by government³⁰¹ and by the Office of National Statistics (ONS)³⁰² on a regular basis. Figure 15 shows these death records. Temporal trends in mortality data, once adjusted for reporting delays and the average time from infection to death (stratified by the range of confounding variables such as age, gender, ethnic and religious groups), can provide estimates of both R and r .

FIGURE 15

Death statistics on COVID-19 released by ONS up to 23 August 2020 showing the considerable fall since mid-April 2020 after lockdown measures were installed on 23 March 2020³⁰³.



N.B. Number of deaths of people who had had a positive test result for COVID-19 and died within 28 days of the first positive test. The actual cause of death may not be COVID-19 in all cases. People who died from COVID-19 but had not tested positive are not included and people who died from COVID-19 more than 28 days after their first positive test are not included. Data from the four nations are not directly comparable as methodologies and inclusion criteria vary.

7.3 Serology and cohort studies

Key to the collection of good serological data is the sampling scheme adopted, a longitudinal component (follow individuals over time), and a sensitive and specific test. A recent Cochrane review³⁰⁴ of studies looking at the accuracy of COVID-19 antibody tests, shows that antibody tests could have a major role in detecting if someone has had COVID-19, but that timing is important. The tests were better at detecting COVID-19 in people two or more weeks after their symptoms started, but it is not known at present how well they work more than five weeks after symptoms started. It is not known if this is true for people who have milder disease or no symptoms, because the studies in the review were mainly done in people who were in hospital. It is also important to note that the review did not cover the Roche and Abbott tests which are in wide use in the UK since it only covered published information before a certain date. These two important tests will be covered in subsequent revisions of the review. Time will be required to learn whether having previously had COVID-19 provides individuals with immunity to future infection.

A review of the relevance of seroprevalence studies, based on blood or saliva test for antibodies to COVID-19 to detect past infection, to understanding COVID-19 epidemiology is provided by Clapham *et al* (2020)³⁰⁵. Such data, given a sensitive antibody test, when cross sectional (eg by age, gender and spatial location) at one point in time, or longitudinal either via random sampling of a population stratified by a variety of confounding variables as for cross sectional surveys, or cohort (same individual sampled repeatedly over time) based is potentially the most precise data framework for estimating rates of infection (= seroconversion) and hence the key epidemiological parameters, R_t and r_t . The most informative data does come from cross sectional cohort-based studies like the REACT-2 UK study based on home-based testing kits and other studies on blood donor samples. In a rapidly developing or declining epidemic, cohort studies should ideally involve sampling the same individuals every week.

In the first part of the programme, dubbed REACT-1, 100,000 randomly selected individuals across England have been invited to provide nose and throat swabs which will be tested for the virus. The second part of the programme, REACT-2, is assessing a range of antibody tests, including testing their accuracy and ease of use at home. Antibody tests will provide authorities with a clearer picture of how far the infection has spread, what proportion of the population has been infected and will also be able to identify individuals who may have some immunity to the virus³⁰⁶.

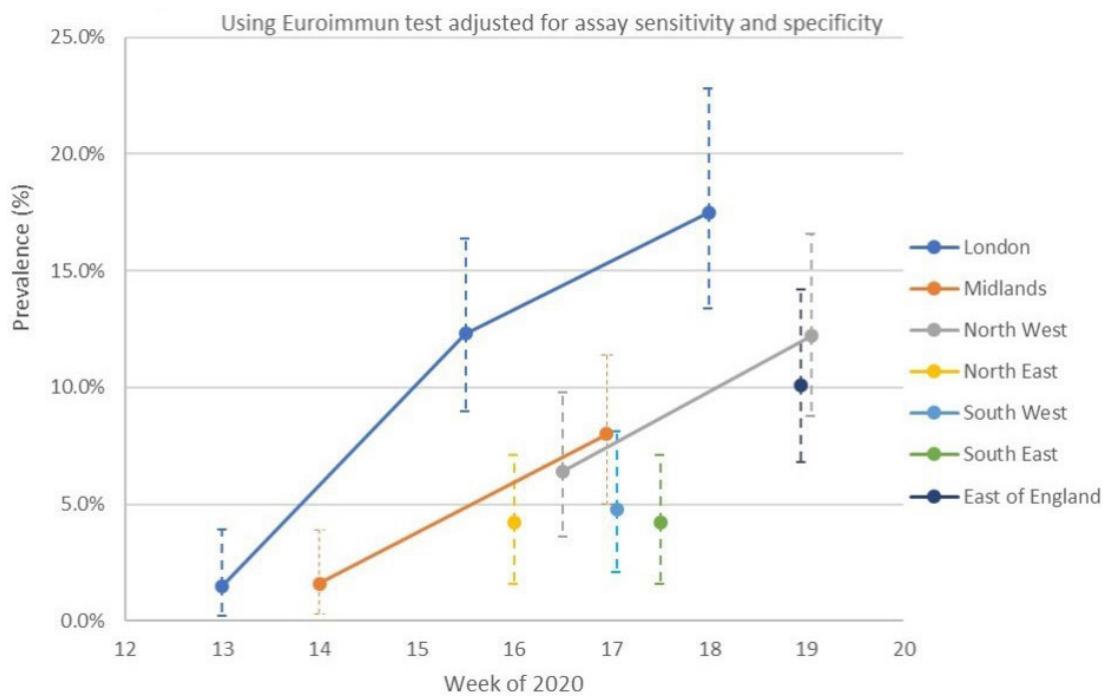
A number of serological sample collections have been established by PHE to provide an age-stratified geographically representative sample across England over time. These include samples from healthy adult blood donors, supplied by the NHS Blood and Transplant (NHS BT). Donor samples from different geographic regions (approximately 1000 samples per region) in England are tested each week. An example of the results from these PHE collections is presented in Figure 16 stratified by region and for the early phase of the epidemic.

Outside of the UK, some of the most interesting serological studies have emerged from outbreaks on ships such as the Diamond Princess and the USS Theodore Roosevelt aircraft carrier. In the latter case as recently reported by Payne *et al* (2020)³⁰⁷, over 1000 service personnel out of a total of 1417 were determined to be infected with COVID-19. Among 382 participants who volunteered to join a serological survey (median age 30 years), 60% had reactive antibodies, and 59% of those also had neutralizing antibodies at the time of specimen collection. One fifth of infected participants reported no symptoms. Preventive measures, such as using face coverings and observing social distancing, reduced the risk for infection.

Emery *et al* (2020)³⁰⁸ recently reported on the Diamond Princess cruise ship outbreak in January 2020 in a preprint. Of the 3700 passengers 17% tested positive for active viral infection. From subsequent case studies, on the Diamond Princess 74% (70 – 78%) of infections proceeded asymptotically, ie a 1:3.8 case-to-infection ratio. Despite the intense testing, 53% (51 – 56%) of infections remained undetected, most of them asymptomatic. Asymptomatic individuals were the source for 69% (20 – 85%) of all infections. While the data did not allow identification of the infectiousness of asymptomatic infections, assuming no or low infectiousness resulted in posterior estimates for the net reproduction number R of an individual progressing through pre-symptomatic and symptomatic stages in excess of 15. A full serological survey of the passengers has not been completed to date, but this would seem highly desirable to see if the asymptomatic fraction increased further. Other cruise ship outbreaks with serology have been reported by Hung *et al* (2020)³⁰⁹, who concluded that patients with COVID-19 can develop asymptomatic lung infection with viral shedding and those with evidence of pneumonia on imaging tend to have an increased antibody response. Positive IgG or IgM confirmed infection of COVID-19 in both symptomatic and asymptomatic patients.

FIGURE 16

COVID-19 serology tests on Blood Donors in England using the Euroimmun test adjusted for the accuracy of the assay (PHE, 19 June 2020). The last reported week in this graph, week 19, is 4 – 10 May 2020 (weekdays only). The confidence limits reflect test specificity and sensitivity.



7.4 Contact tracing

Contact tracing is an important technique in community-based infection control and in epidemiological study for many reasons. Two of the most important are as follows. First, it can generate information on key epidemiological parameters such as R , the generation time, T , the serial interval, s , and the incubation period. It also provides information on the distributional properties of these quantities. Second, in the context of public health and infection control, it is the key measure to find and isolate contacts with an infectious person to try and limit onward spread and hence the generation of secondary cases. It has been employed very effectively in the control of sexually transmitted infections for many decades throughout the world.

In an international context, contact tracing has been employed with success in a number of countries/regions, including South Korea, Taiwan, Singapore, China, Japan and Hong Kong. This has given rise to some of the best estimates of key epidemiological parameters and their distributions such as the incubation period and R . More importantly, in some of these countries the effective implementation of contact tracing has played the key role in mitigation measures to stop spread. Early action on contact tracing by Hong Kong, Singapore and Japan has enabled the estimation of R_0 and k estimations very early in the epidemic and many chains of transmission plus super spreading events were effectively controlled^{310, 311}.

One example is that of Kwok *et al* (2020)³¹² of transmission clusters in Hong Kong, Japan and Singapore which focusses on the distribution of R . Others include Hellewell *et al* (2020)³¹³ who simulated the efficiency of contact tracing for controlling outbreaks alongside isolation. Outbreaks simulated with an initial 5 cases and an R_0 of 1.5 and 0% transmission before symptom onset could be controlled with low contact tracing probability, but this decreased with an R_0 of 2.5 or 3.5 with transmission before symptom onset, which is the more realistic scenarios. The level of contact tracing required for effective control as R_0 increased in value requiring 50%, 70% and 90% of contacts successfully traced for R_0 values of 1.5, 2.5 and 3.5 respectively. The probability of control further decreases as the time between symptom onset and isolation occurs.

An investigation by Korea Centre for Disease Control and Prevention³¹⁴ in South Korea of the first 30 cases reported, and the first 2,370 individuals who came into contact with them, concluding different secondary attack rates based on age and modes of transmission. Twelve individuals contracted COVID-19 from the initial 30, resulting in an overall secondary attack rate of 0.55% (0.31–0.96); higher for males than females (0.75, 0.38–1.47) versus (0.38, 0.16–0.89). Household contact attack rate was highest for secondary case mode of contact, with attack rate 7.56% (3.73–14.26). The chains of transmission arising from one infected individual ranged from 15 to 649, over a period of 5.7 to 31.3 days.

Some of the most detailed studies have arisen from outbreaks on large ships including the Diamond Princess cruise ship. Rocklöv *et al* (2020)³¹⁵, for example, employed the outbreak data to record R values and how they changed over time due to isolation measures.

Progress in the UK on contact tracing and the development of associated technologies such as individual proximity tracking by mobile phone apps has been very disappointing to date. The current stage of decline in the epidemic in the UK due to ‘lock down’ measures has been encouraging, but as the measures in place are slowly released over the months of June, July and August, contact tracing becomes of high importance to rapidly eliminating small outbreaks before they expand.

The Department of Health stated recently that the next phase of the development of effective contact tracing will bring together the work done so far on the NHS COVID-19 app and the new Google/Apple framework. Following field testing and a trial on the Isle of Wight, challenges have been identified with both the NHS app and the Google/Apple app framework. The department says it will now be taking forward a solution that brings together the work on its app and the Google/Apple solution. They argue it is an important step, allowing them to develop an app that will

bring together the functionality required to carry out contact tracing, but also making it easy to order tests, and access proactive advice and guidance to aid self-isolation.

In England, people are contacted by the NHS Test and Trace service if an individual tests positive for coronavirus (COVID-19) following submitting a test sample (often through a health care setting or testing station). They will be asked where they have been recently and who they have been in close contact with. They will also be asked to self-isolate for 14 days. This helps the NHS contact anyone who may have caught the virus from a test positive person.

The NHS Test and Trace system is designed as a crude form of contact tracing to facilitate stopping the spread of coronavirus. The NHS argues that tens of thousands more people who may have otherwise unwittingly spread the virus are now remaining safely at home because of this system. The evidence on its effectiveness is unclear at present.

What is urgently required at present is a much greater focus on using our experience in, for example contact tracing for STDs and TB, to put in place as soon as possible a system to follow up all cases and contacts of diagnosed COVID-19 infection. Part of such an effort is greatly expanding the countries capability to offer tests to detect active COVID-19 infection to all who ask for them and all contacts of a known infected individuals. The large percentage of asymptomatic infections highlights the need to contact trace and test rapidly if a high proportion of onward chains of transmission are to be eliminated. This issue must be effectively managed by government before a resurgence of COVID-19 cases arises as ‘lock down’ is relaxed and autumn approaches.

Recently, SAGE has recently released a report on case identification, contact tracing and case isolation (CCI). They conclude that PHE capacity is insufficient to carry out this task effectively and recommends a 10-fold increase in capacity. Even this would be probably too little in a rapidly expanding phase of the epidemic as noted in a recent publication³¹⁶ using simulation methods to look at what number of contacts would be required to be traced in a growing epidemic to effectively mitigate infection spread. They also recommend ceasing CCI if the tracing activity required exceeds 8000 events per day as a rough guide. This conclusion may have unintended consequences in the sense that it could discourage the building of capacity in the UK to do this task effectively. The need is to convince government to put adequate resources into this activity to reduce the burden of morbidity and mortality especially over a low phase of case number generation at present before a surge in cases in the autumn (or before). This need will continue for some time – since vaccine manufacturing and distribution on scale is not likely (even if all goes well) until mid to late next year.

8. Data management, collection and access to information

The availability of accurate data in as close to real time as possible, is key to the management of any epidemic whether it be Ebola or COVID-19. The new website of GOV.UK that coalesces various data sources is an important recent improvement³¹⁷.

What do we need to do better, or more of, to ensure data are available to inform policy in a timely manner? Three key areas are apparent. They are serological surveys, contact tracing and better data management and access. The late aspect includes reporting of case numbers and deaths in amalgamated data bases available to all modelling and epidemiology/public health analysis groups.

8.1 Serological surveys

In any study of a new infection, spread is usually best measured by reported cases of infection and associated morbidity and mortality, where reporting is the responsibility of a government run agency such as PHE under the guidance of the Department of Health. Reporting delays must be accounted for in the assessment of such data. However, this approach is much less effective if many cases of infection are asymptomatic but infectious, as appears to be the case for COVID-19, especially in the younger age groups. In this case, serology is by far the best option for reporting based on blood (serum) or saliva samples since it can accurately determine the proportion of people in a sample who have been infected sometime in the past. If studies are then longitudinal in nature, where samples are collected from the same individuals repeatedly over time, seroconversion gives a direct measure of the incidence of infection and hence the growth or decay rate of the epidemic, r . With additional knowledge of the generation time or serial interval this in turn provides estimates of R . It obviously requires a sensitive and specific serological test.

The development of such tests was a little slow in the case of COVID-19, given their importance. However, today they are available and should be used on a much wider scale in monitoring the UK epidemic and the impacts of mitigation measures and their relaxation. Designing the sampling scheme is key to accurately represent the many heterogeneities that influence the likelihood of infection (eg spatial location, social and behavioural factors), but it needs to be carefully thought through and if possible home testing devised with an electronic data capture system associate with testing.

8.2 Trace and treat

Contact tracing has been discussed in the section above, but it does require further emphasizing in relation to the UK government's trace and treat programme. Accurate estimation of key epidemiological parameters in the UK setting is important, but even more important is its role in shortening chains of transmission as part of effective mitigation measures. Public Health England (PHE) has contact tracing expertise in its health protection teams. The workload involved is high during the mid-phase of an epidemic, given the large number of cases and contacts. It is much easier at the beginning phase of growth and in a decay period. A recent publication by Keeling *et al* (2020)³¹⁸ highlights this point. However, this should not detract from the urgent need to build capacity in this area in the UK and use modern technology to make the task easier and more automated.

Weekly NHS Test and Trace bulletins report on the performance of this tracing programme. For example, in the 11 – 17 July Bulletin, since 28 May 2020 21,105 people tested positive for coronavirus (COVID-19) under pillars 1 and 2. Of these, 20,968 (99.4%) people had their case transferred to the contact tracing system, of whom 15,225 people (72.6%) were reached and asked to provide details of their recent close contacts. 113,925 (88.6%) people were identified as recent close contacts and reached through the contact tracing system out of 128,566 people reported. This sounds like a good response, but the failure in the system is the capture of cases in the pillars 1 to 4 of the UK system. As illustrated by the few serological studies that have been completed to date, the cases identified in the pillars are a small fraction of the total number infected per unit of time.

8.3 Data management and access

At present, the SPI-M modelling groups work with a range of data sets often released by different government organisations. There are very good reasons for this, given different responsible departments or organisation for collecting different types of data such as deaths and cases of infection. For an epidemic of this seriousness in terms of morbidity and mortality, and importance to the economy, it would seem sensible to try and create one portal for all the data amalgamated as far as is possible with accurate information on reporting delays such that confusions do not arise as to what are the deaths due to COVID-19, and what are the case numbers diagnosed from all sources, on any given day. Progress has very recently been made in this direction but much more remains to be achieved to provide one portal for all epidemiological data collected by government bodies.

Furthermore, some continuous assessment needs to be made of the frailties in data collection and reporting, as systems, requirements and practices change over time since the start of the epidemic. Estimating key parameters requires a good understanding of any changes in reporting practices, otherwise calculated changes in for example, R and r , may reflect these changes rather than true changes in the pattern of the epidemic.

For forward projections and forecasting the effect of different mitigation measures the modelling groups, in particular, should have rapid access to all data including the serological studies as data accumulates. Accurate predictions are founded on timely access to good quality data.

9. Diversity of models used by SPI-M to inform SAGE

The diversity of models employed by SPI-M to produce predictions is a strength not a weakness, especially with a novel infectious disease where there are many unknowns. Multiple models are frequently used in infectious disease research to provide independent assessments of the potential policy options.

When this approach is adopted it is important to assess both strengths and weaknesses plus sources of data used for parameterisation. This has not always been done in a systematic manner at present for very understandable reason given the urgency of the need to generate predictions to guide policy in what is still the early stages of viral spread worldwide.

Table A1 in Appendix 2 gives details on the key models employed and information on data sources and parameter values. Here, we simply provide Figure 17 which illustrates model diversity by reference to flow charts capturing individual flow between the various infection states to recovery or death (analogous to Figure 1 and the Figure A1 in Appendix 1).

FIGURE 17

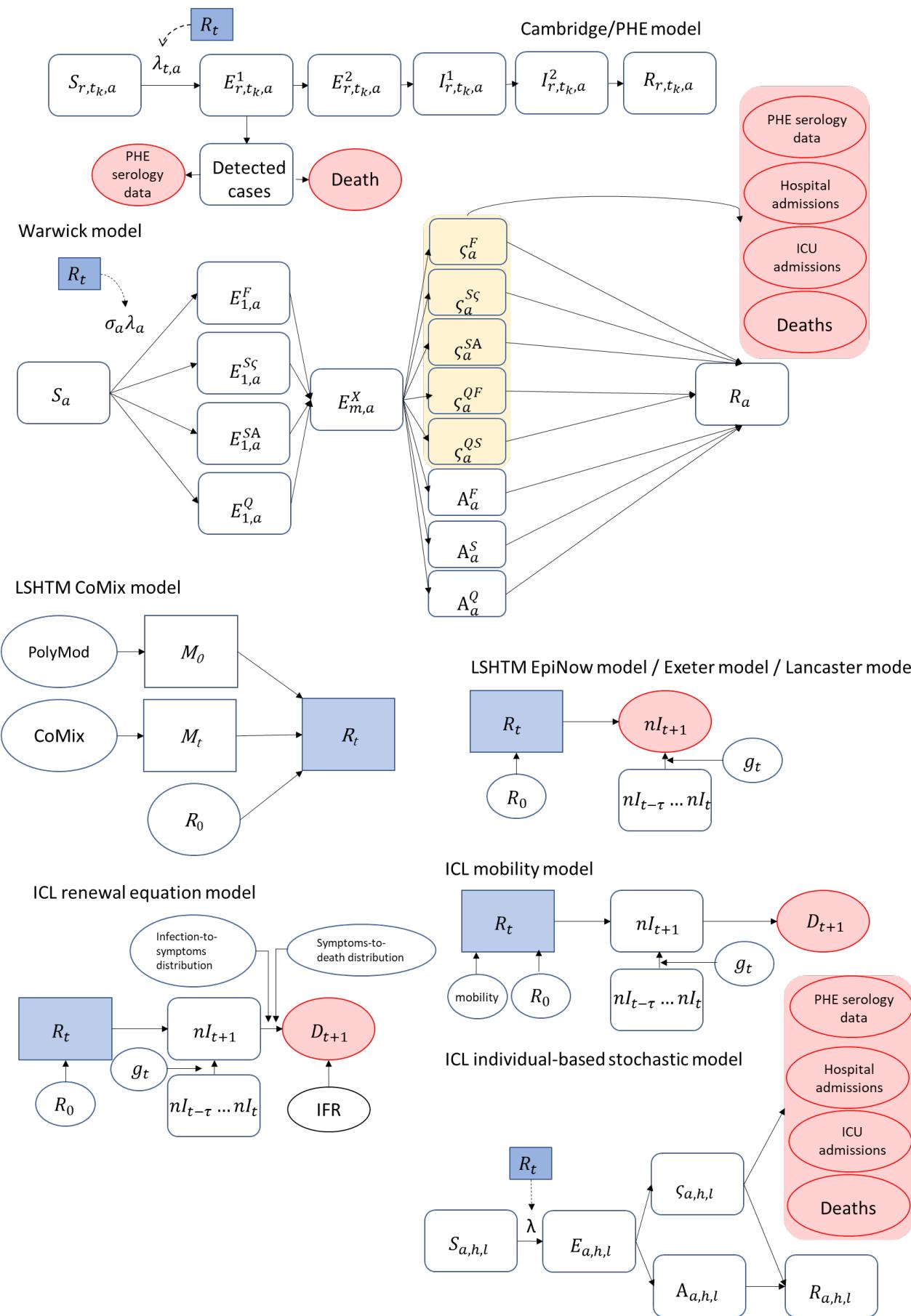
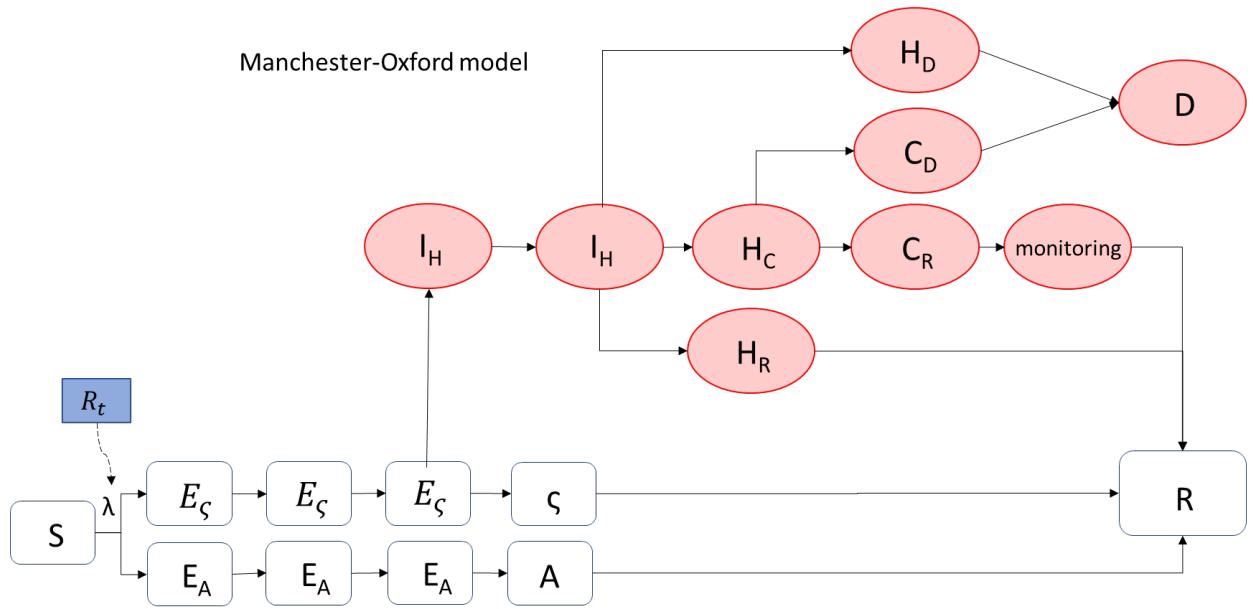


FIGURE 17 CONTINUED



ICL stochastic difference equation model and individual-based stochastic model

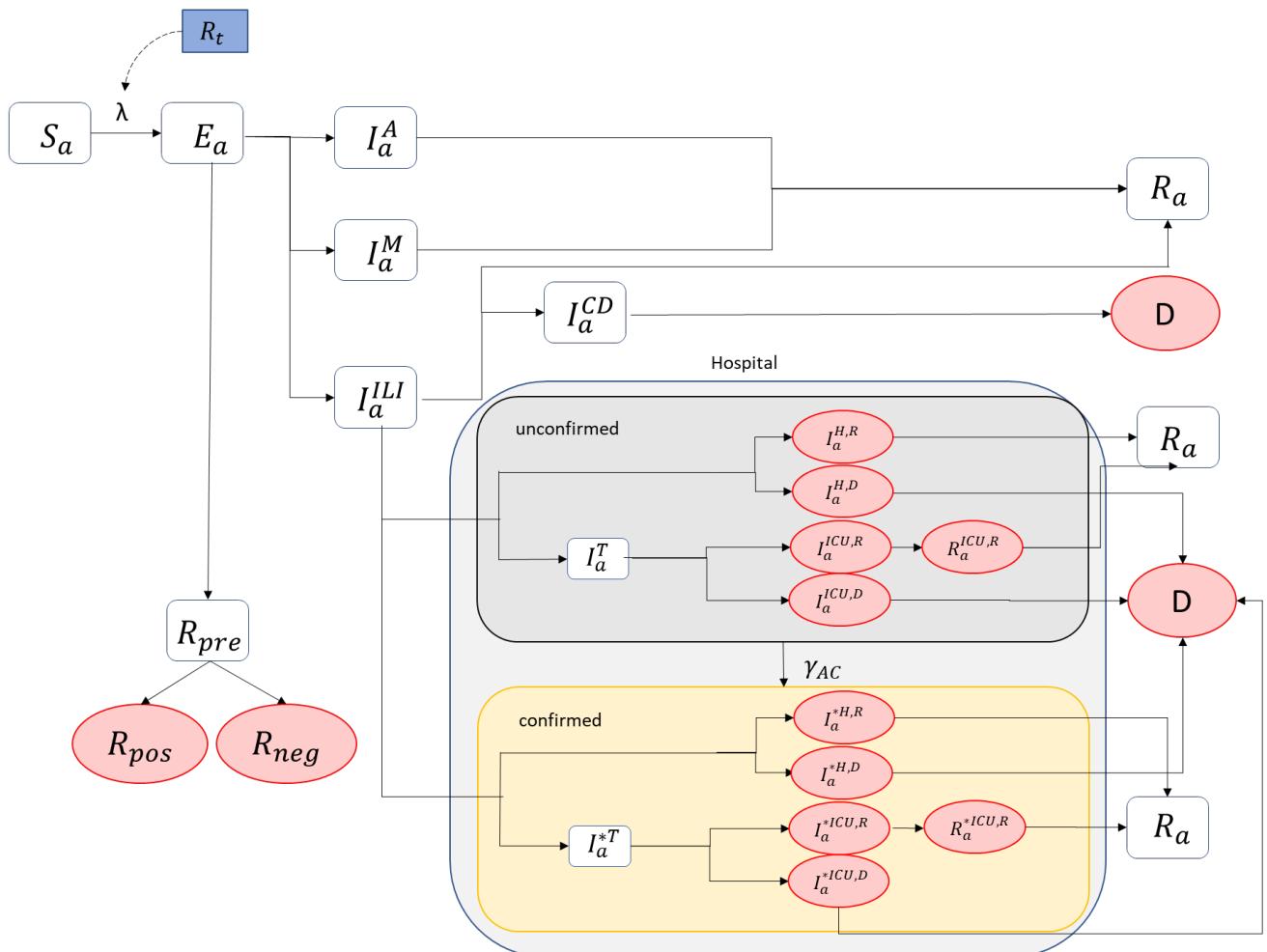


FIGURE 17 NOTES

Schematic diagrams of the models used to estimate R_t . Ovals represent data sources that were used to inform model parameters and variables. Red ovals represent data that was used to fit the models. Square boxes indicate model parameters that were fitted. Blue square boxes represent R_t . Rounded boxes indicate model variables (eg disease states). Solid arrows indicate the direction in which information flows in the model. Dashed arrows indicate indirect relationships.

Symbols explained

S – susceptible individuals, E – exposed individuals, I – infected individuals, n/t – new infections at time t , ς – symptomatic infected individuals, A – asymptomatic infected individuals, R – recovered individuals (note that this class is not explicitly represented in the models, but individuals that exit the infected state either die or recover), D – death, R_0 – basic reproduction number, R_t – effective reproduction number, M – contact matrix, λ – force of infection, gt – generation time distribution

Subscripts

a – age class, t – time, r – region (within the UK)

Model-specific notation

Cambridge/PHE model

t_k – timestep k in a discrete-time model, $\lambda_{t,a}$ – force of infection at time t acting on age class a , superscript 1, 2: the exposed and infected states have been divided into two separate compartments each to achieve an Erlang distribution of the time delay of passing from the exposed to the infected and from the infected to the recovered state (with a single compartment the distribution of the delay times would be exponential which does not necessarily correspond to reality)

Warwick model

λ_a – force of infection acting on age class a , σ_a – susceptibility to infection of age class a , F – the first individual within a household that gets infected, S – individual within a household that gets infected subsequently following a first infection within this same household, C – individual that gets infected by exposure to a symptomatic individual, A – individual that gets infected by exposure to an asymptomatic individual, Q – individual in quarantine, X any of the superscripts above depending on preceding compartment, $1, m$ – the model assumes m compartments of the exposed state to achieve an Erlang distribution of the delay time of passing from the exposed to the infected state (with a single compartment the distribution of the delay times would be exponential which does not necessarily correspond to reality)

LSHTM CoMix model

M_0 – contact matrix before social distancing measures were implemented, M_t – contact matrix after social distancing measures were implemented

Oxford/Manchester/Lancaster model

E_ς – exposed individuals that will progress to the symptomatic infected class, E_A – exposed individuals that will progress to the asymptomatic infected class, I_H – hospitalised individuals, H_C – individuals admitted to ICU, H_R – individuals in normal hospital wards that will recover, H_D – individuals in normal hospital wards that will die, C_R – individuals in ICU that will recover, C_D – individuals in ICU that will die

Imperial College stochastic difference equation model and stochastic individual-based model (IBM)

The two models have the same transmission structure, but in the IBM individuals are tagged by their place (school, university, workplace or other) and location. In addition, the stochastic difference equation model assumes an Erlang distributed delay time to pass from the exposed to infected stage, while the IBM can use arbitrary delay times.

I_a^A – infected individuals in age class a that are asymptomatic, I_a^M – infected individuals in age class a that have mild symptoms, I_a^{IL} – infected individuals in age class a that have influenza-like illness (ie severe symptoms), I_a^{CD} – infected individuals in age class a that suffer from severe symptoms and will die outside of hospital (eg care homes), R_{pre} – recovered individuals that will receive an antibody test for COVID-19, R_{pos} – recovered individuals that test positive for COVID-19 antibodies, R_{neg} – recovered individuals that test negative for COVID-19 antibodies

In hospital settings asterisks indicate confirmed COVID-19 cases, states without asterisks are hospitalised patients in whom COVID-19 has not yet been confirmed, upon confirmation of diagnostic test results they transfer to the confirmed compartment that corresponds to their current unconfirmed compartment, this happens at rate γ_{AC}

I_a^T – infected individuals in age class a that will be admitted to ICU but whether they will recover or die has not yet been decided, $I_a^{H,R}$ – individuals in age class a that are in a normal hospital ward and will recover, $I_a^{H,D}$ – infected individuals in age class a that are in a normal hospital ward and will die, $I_a^{ICU,R}$ – infected individuals in age class a that are in ICU and will recover, $I_a^{ICU,D}$ – individuals in age class a that are in ICU and will die, $I_a^{ICU,R}$ – individuals in age class a that are in ICU and on their way to recovery.

These flow diagrams highlight the diversity of model assumptions which are plausible given the available data and demonstrate the importance of working with multiple models.

The variability in model structure illustrated in Figure 17 (structural uncertainty) does not characterise all the variability between models (see section 10). There are different assumptions on key parameters (parameter uncertainty), informed by the use of different datasets (heterogeneity in the data employed in either parameter estimation or model fitting). In a formal model comparison these could be standardised to allow investigation of the impact of different structural assumptions. However, as the evidence is evolving every week at present, it is crucial that the expert modelling groups on SPI-M are able to evaluate the empirical sources independently.

10. Methods of estimation of R and r and the representation of uncertainty

Given that no systematic reconciliation of the strengths and weaknesses of each model has been made to date (for very understandable reasons outlined elsewhere), the approach adopted by SPI-M has been a very pragmatic one where the range of central values produced by the different models for both R_t and r_t (some models generate both, some only one of these parameters) are discussed and some consensus reached on how to represent the uncertainty and stratification by region of the UK. In short, the ranges presented to SAGE represent the diversity of the model predictions of central values rather than some defined uncertainty interval based on sensitivity analyses of model structures and/or parameter uncertainty plus derived credible intervals.

At this stage of the epidemic before a resurgence (a ‘second wave’) appears in the autumn (or before), it would seem sensible to focus more effort on the uncertainties such that ‘clouds’ of possible outcomes of R plus r estimates, are presented to SAGE. Communicating uncertainty to policy makers always presents difficulties, but a sensible approach would seem to be very open and honest about these when quantitative projections are being made on the likelihood of effective control ($R < 1$) or bounce back ($R > 1$). The value of using r in addition to R is that it provides information on the time it will take before doubling, or halving of infected cases might be detected. R alone does not provide this. Values of R a little below 1 may give a false sense of security that all will soon be well, although r may indicate that the decline in infected cases is very slow and even a slight relaxation in control measures may lead to a new increase in case numbers. In this sense, r is similar to the rate of return on investment in economics and accountancy.

A summary of the methods employed in the models to represent uncertainty is in part given in Table A1 in Appendix 2. However, a short summary is given here.

The models that estimate R_t use a number of different data sources or a combination of these sources. The main data sources are PHE line list data of recorded cases and deaths, NHS hospital admission records (by nation and/or region within the UK), ICU admissions and hospital deaths. Some models use death data submitted to ECDC, and one model uses serology data from a PHE survey of NHS blood donors. Data sources to estimate the contact rates include the POLYMOD survey³¹⁹, the ONS time use survey³²⁰, the CoMix survey³²¹ and mobility data from Apple³²² and Google³²³. These data sources are of varying quality, and a significant part of the uncertainty in the R_t estimates is attributable to uncertainty in the reported data.

The models that have been used to estimate the value of R_t in the UK are summarised in Table A1 in Appendix 2 and Figure 17. There is a lot of overlap between the data sources and model structures used but important sources of difference.

Out of the 10 models reviewed, two are compartmental individual-based stochastic simulations, one is a deterministic compartmental model, five models are based on renewal equations describing the time series of infected individuals or deaths and one model evaluates the value of R_t by comparing the relative reduction in contact rates derived from two different contact matrices. One model draws on general non-linear mixed effects regression to estimate the epidemic growth/decline rate (r) (Daren Austen’s) and uses this value to calculate R_t . Other models generally do not estimate r as a free parameter, but r can usually be calculated from these models.

The models differ in their structural complexity. Two models (Warwick³²⁴, ICL³²⁵ and ICL IBM) incorporate household structure and distinguish between symptomatic and asymptomatic infections^{326, 327}.

The models also differ by the degree of spatial structure that they assume. Only two models explicitly assume a spatially structured population (ICL – Neil Ferguson IBM, Lancaster³²⁸). Only one of these (ICL – Neil Ferguson IBM) accounts for human movement. The model developed by Pierre Nouvellet *et al*³²⁹ does not incorporate spatial structure but uses mobility data from Apple and Google to estimate R_t relative to mobility prior to the introduction of social distancing and lockdown³³⁰. The remaining models may fit their model to regional data, but assume that human movement is negligible for the estimation of infection rates and R_t .

This assumption may have to be revised when the infection incidence reaches very low levels to rely more on estimates of r_t . The critical point is when this rate is negative. The 18 June 2020 report from SAGE documented both R and r .

The number of free parameters varies by model (0 – 11). Among the reviewed models, those with freer parameters, that were estimated by various fitting procedures (eg Monte Carlo Markov Chain (MCMC) to data on cases, deaths or seropositives, reported narrower credible intervals for R_t . This may be explained by overfitting to the available data (trying to estimate too many parameters, many of which enter into the numerator and denominator of R) but is confounded by the data sources chosen for model fitting. For example, death and serological data are assumed to be more reliable than incidence data of case numbers because the latter is more strongly affected by the level of testing and case definitions. Serological data from cohort studies are certainly the best source from which to estimate both R and r given careful choice in sampling and definition of which groups are being sampled with defined confounding variables such as age and gender.

A very useful recent summary of the strengths and weaknesses of the methods employed to estimate R is given by Gostic *et al* (2020)³³¹. Epidemiologists and scientists have used R for some time in both addressing how best to intervene in an epidemic, in the design of vaccination programmes and, for example, in designing control programmes for the neglected tropical disease (NTDs)³³². However, this is the first time in a novel epidemic that policymakers and public health officials are using R_t to assess the effectiveness of interventions and to inform policy. As such, accuracy in estimation is of high importance given the significance of the boundary $R=1$. This point is stressed in the preprint of the Gostic *et al* (2020)³³³ review. They recommend the approach of Cori *et al* (2013)³³⁴ currently implemented in the open software R package EpiEstim which uses data before time t and empirical estimates of the time between infections (the generation time and its distribution). This approach estimates R , not r , and the method makes minimal assumptions about the underlying epidemic processes (model structure). However, it is sensitive to the assumptions made about the generation time interval. Independent estimates are required of this very important epidemiological parameter. Some useful extensions of this approach are embedded in R package EpiNow that embeds some methods for recording uncertainty.

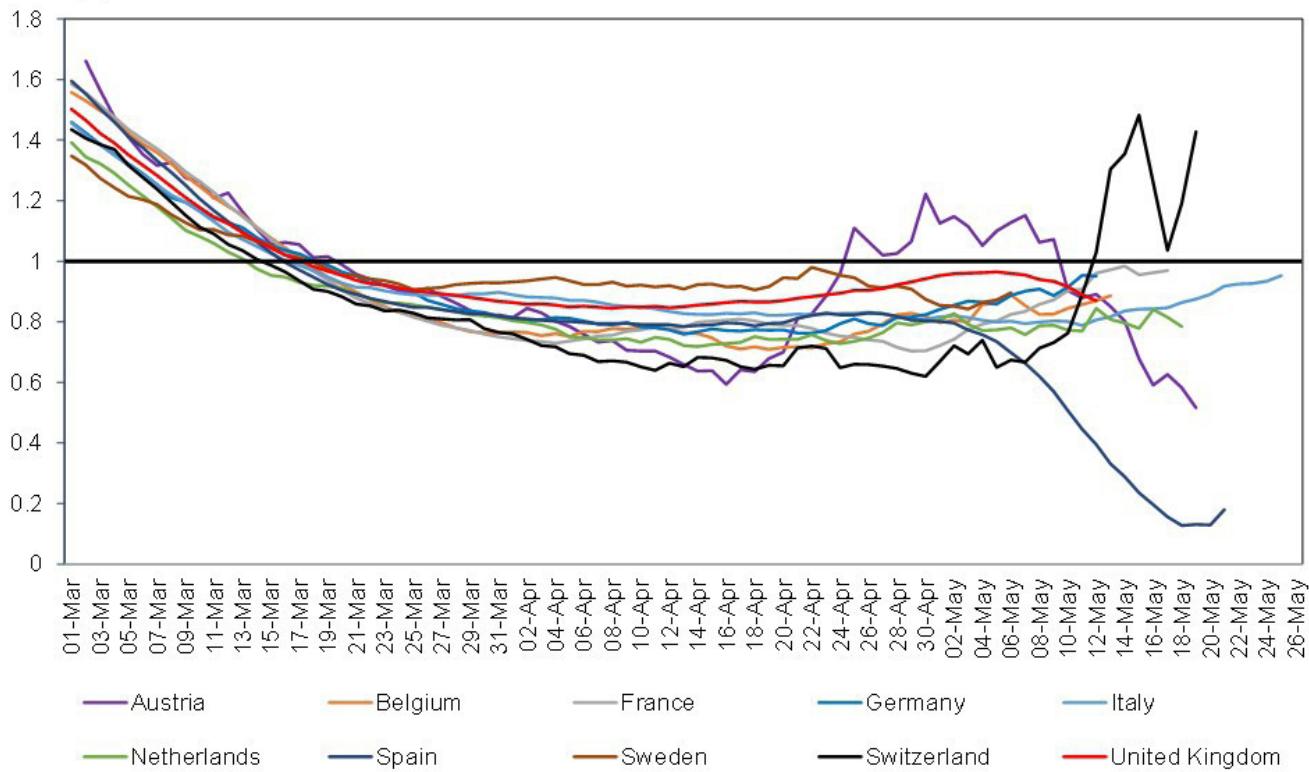
Other approaches described by Wallinga and Teunis (2004)³³⁵ and Bettencourt and Ribiero (2008)³³⁶ that focus on R_t are advised against, due either to poor accuracy for near time estimation or dependence on precise model structure.

Much information on the different approaches is given on a website run by ETH Zurich³³⁷. A comparative study by Stadler *et al* (2020)³³⁸ posted on this website gives estimates of R_t using the Cori *et al* (2013)³³⁹ methods as shown in Figure 18.

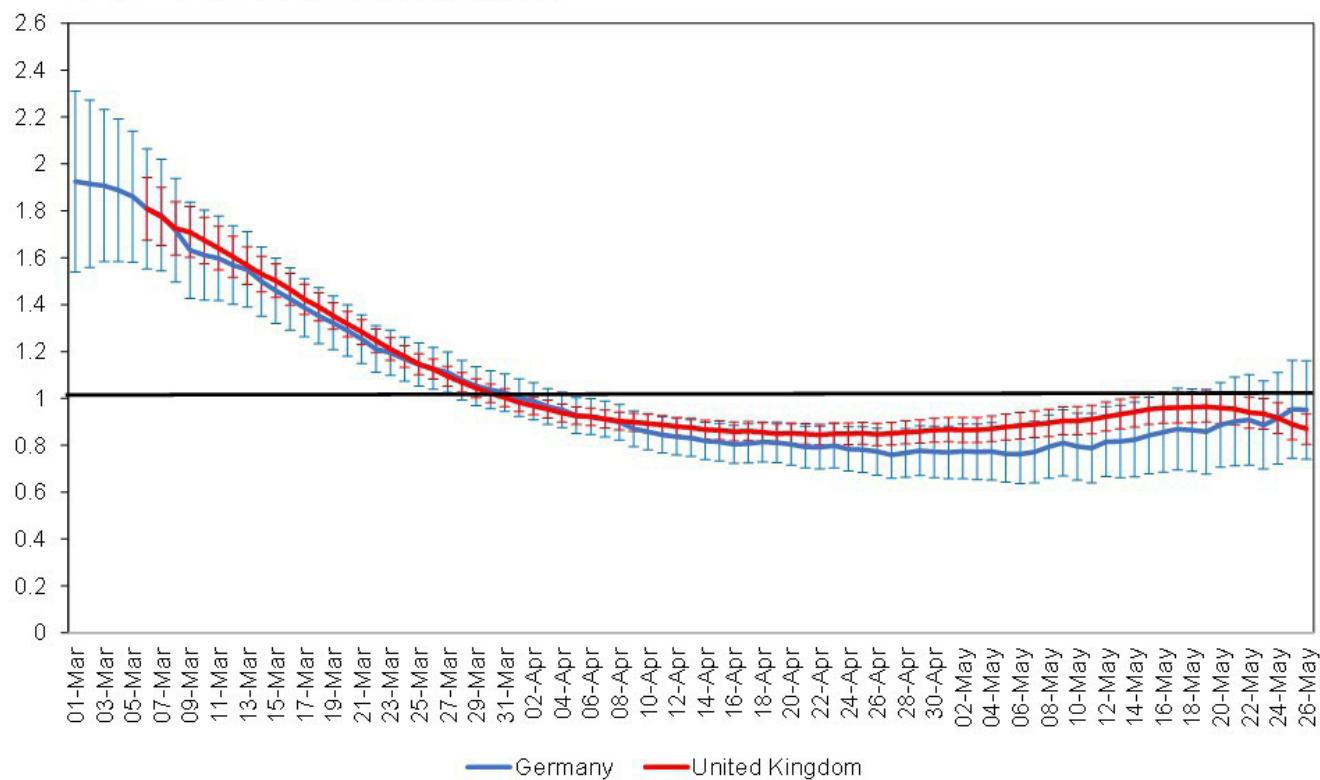
FIGURE 18

Estimates of R as a function of time (labelled as $R_e(R_t)$) from the ETH Zurich website showing post lock down effects in all countries in Europe from which data was analysed. The confidence bounds depicted are as defined in Cori *et al* (2013)³⁴⁰. These are too narrow to adequately represent all the known degrees of uncertainty, but the general trends and impact of lock down measures are clear for policy makers. The early values for R_e (which is in essence close to the value of R_0) also look a little low given the list of estimates given in Table 3.

(a) Estimated R_e - continuous



(b) R_e - Germany and United Kingdom



The review concludes with comments on the major research needs. One obvious but important conclusion is that all methods, however sophisticated, will fail to estimate R_t accurately if changes in sampling over time are not known and accounted for. They note that if testing shifts from more to less infected subpopulations, or if test availability shifts over time, the resulting changes in case numbers will be ascribed to changes in R_t . Quality surveillance therefore lies at the foundation of accurate R_t estimation. Case counts in most countries derive from clinical testing within hospital or other care settings such as for the elderly. These approaches are often outside of any formal surveillance structure. The most powerful inferential methods will fail to estimate R_t accurately if changes in sampling are not known and accounted for.

Counts of deaths caused by COVID-19, are more reliably sampled, but are typically lagged in reporting in the UK by 2 – 3 weeks. Also note that excess deaths typically exceed those ascribed to COVID-19 for most countries. As such excess deaths may be the better measure. Any R_t estimates must take account of the time to death delay if near time estimates are required, and that might require extra assumptions on trends over time in the reporting delay period.

The establishment of large sentinel populations or cohorts for intensive study, and concomitantly for R_t estimation, is the ideal approach since it would more easily help to accurately identify the effectiveness of different interventions and recent trends in transmission. Ideally these cohorts should be for serological testing for past infection as well as virus positivity plus mortality.

One other aspect to note is the use of Bayesian methods to fit complex models to data on trends in case numbers, mortality figures and seropositives over time. It is possible to have different models which adequately fit the data which produce differing posterior estimates. Results produced by each model should be regarded as the best estimates given the available data, but only relative to that particular model. The strength of having multiple model estimates is that the degree of uncertainty attributable to model misspecification can be judged. If estimates of R and its uncertainty are robust to different model structures (structural uncertainty), this confers confidence that the estimates are reliable. A consideration of how well each model fits the available data, in and out of sample, can be used to judge how much weight should be placed on each estimate. Where models are fit to the same data, a suite of quantitative methods for model comparison is available, however many of the groups have employed different datasets and so quantitative comparisons are difficult. It is possible to have different models which adequately fit the data which produce differing posterior estimates. Results produced by each model should be regarded as the best estimates given the available data, but only relative to that particular model. The strength of having multiple model estimates is that the degree of uncertainty attributable to model misspecification can be judged. If estimates of R and its uncertainty are robust to different model structures (epistemic uncertainty), this confers confidence that the estimates are reliable. A consideration of how well each model fits the available data, in and out of sample, can be used to judge how much weight should be placed on each estimate.

Within a single model structure, it is important to assess the sensitivity of the posterior estimates to both the assumptions about the prior distributions, and the statistical properties of the observed variables. Where possible, prior distributions should be obtained from data. If estimates of R are highly sensitive to the choice of priors, then further effort to reduce uncertainty in this parameter would be beneficial through targeted data collection. One such parameter is the generation time, T . Sensitivity can be assessed quantitatively using the Sobol or Morris methods³⁴¹. Models which describe the transmission process in greater detail, using more parameters, will generate more insight in such sensitivity analyses. The statistical model that informs the likelihood should also be assessed. For example, if the distribution of daily case counts is over-dispersed, a model that assumes Poisson counts may bias the estimate and underestimate the uncertainty of the posterior distributions (see Imperial Report 26³⁴²).

Currently SPI-M is carrying out a review of the various estimates of R (nationally and regionally) based on a mixed effects meta-analysis. The process is still under scrutiny of how best to perform the analysis based on the correct assumptions (eg the estimates are treated as independent in mixed effect meta-analyses, which they are not given that in many cases the same data are employed to obtain any single estimate). As such discussions are continuing about the best method to employ in any such meta-analysis.

11. What is the best epidemiological measure of the current pattern of the epidemic and what is the best data to use to get estimates?

For policy makers and public health officials the search for simple statistics that provide information on a number of key questions is understandable. Four examples of such questions are as follows. Is the epidemic contained by lock down measures? Is it likely to move to a state where transmission is eliminated? Will the imposed relaxation of certain mitigation measures result in resurgence? What provides early warning of this?

However, just one statistic is not enough, and ideally a variety of data summary statistics should be employed as well as the key epidemiological parameters R and r . In addition, much uncertainty will surround some measures, whether deriving from models of transmission or the reported data. The relative simplicity of the very direct measurement, r , which avoids many of the inferential difficulties associated with R , suggests that r should receive greater emphasis in future reporting on the epidemic. Communicating uncertainty to policy makers is always difficult since understandably they seek clear and unambiguous advice³⁴³. Much uncertainty is related to data quality and this fact should be influential in deciding what actions improve decision making.

In considering the value of different epidemiological measures it is important to note that the words and phrases ‘estimate’ and ‘uncertainty interval’ need careful interpretation. The models employed to obtain estimates vary widely from simple linear regression methods, to the use of modern Bayesian computational methods to fit complex models to data on case, death and serology reports over time as described in the previous but one section. In the case of complex model fits to time trends in, for example, reported case numbers, the estimates of R_t are closer to model projections or predictions than to estimates in the usual sense which would require detailed contact tracing data to derive average R numbers and variance therein.

In this sense ‘estimates’ are best viewed as predictions from data-calibrated models which represent a careful quantitative synthesis of published data that gives prior and independent information on some parameters. This is important to emphasise, because of the heterogeneity in the models employed models to inform dynamic estimation of R_t , and the further fact that some data sources (case data for example) are highly problematic as the basis for inference about R_t given, for example, time variation in collection methods and the low fraction of the total number infected represented by case reports. Indeed, arguably almost none of the available data sources can reasonably be viewed as reliable for real time R_t estimation and variation therein. However, the cases, deaths and serology data, even if poorly collected, are what is available, and use must be made of them. Given the necessity for decision makers to form reasonable judgements of how to weight the R_t predictions, it is important that they do judge them on some understanding of the limitations of the data from which they are estimated.

The effectiveness of social distancing measures represented in many countries by lockdown to minimise people to people contact, has been answered in many different countries over the past few months by simply examining case report and death statistics. China provided the first example of their effectiveness. Isolation of individuals and their contacts has worked to bring R to below unity in value following effective messaging from government and wide acceptance of the measures by the population. No country has eliminated transmission, except perhaps New Zealand, but with a high proportion of asymptomatic infection transmission elimination is always difficult to ascertain in the shorter term. Even in New Zealand, new cases of infection have been introduced recently. Figures 11 to 15 show this clearly for the UK. If fully sustained for many more months they might have eradicated chains of transmission. However, it is impossible to both minimise COVID-19-related mortality, and the economic impact of social distancing measures³⁴⁴. Most governments have been keen to slowly (or quickly in some cases, such as certain states in the US and in Iran) lift these mitigation measures to reduce the very severe effect of full lock down on the economic wellbeing of a country. The consequences of rapid lifting of mitigation measures is all too apparent in Iran and some states in the US.

Most European countries have adopted a slow, more measured response in lifting measures, and the central question in these cases, as for the UK, is what measure best gives advanced warning of a rapid rise in cases? Both R (despite the wide uncertainty bounds on this measure) and r , are of use – and the rate of change of r (the second derivative of the rate of growth or decay) is also informative.

However, in all epidemic decay processes, the decay itself is non-linear even if $R < 1$. Thus, care must be taken on reacting to small changes in the rate of change of r . A rather arbitrary rule might be that alarm bells should be ringing if the decay rate (as opposed to r on the upward phase of the epidemic) shows a sudden decrease. A constant rate of decay is fine but when it is small in value, case numbers will decay very slowly. Arguably, it is difficult to be more precise than that.

It is important to distinguish between estimating r and R from confirmed cases versus deaths. If based on deaths, then this reflects transmission rates weeks before. If based on confirmed cases, then the temporal trends in the data may be affected by changes in testing strategies and capacity. Any change of policy will take at least two weeks to produce a discernible change in the trajectory of any metric used to evaluate the epidemic. The King's College COVID Symptoms Study App could help to reduce this delay by enabling early detection of infected individuals³⁴⁵.

Aside from epidemiological parameter estimates, careful examination of the pattern of fall in case numbers and deaths by simple visual inspection is of great value provided due note is taken of any changes in testing or reporting strategies. This highlights the value of the new government website that brings together COVID-19 data from multiple sources discussed in the section 8. However, two issues should be noted about this approach, First, time delays in reporting especially for death data, and second, initial rises in either quantities are likely to be slow as transmission chains develop. These time-delayed effects mean that it is virtually impossible to detect the precise moment in time where transmission accelerates in a defined population. When it is detected, this implies that very speedy action is required by policy makers to strengthen mitigation measures.

Another approach of value in detecting surges in infection is that used by a team at King's College London using information from an app, the COVID Symptom Study app³⁴⁶. The app is used by roughly 4m people in the UK who record any symptoms of COVID-19 infection on a frequent basis. According to the latest Figures from the app, there are currently an estimated 1,445 daily new cases of COVID in the UK on average over the two weeks, 14 – 27 June 2020. The number of cases has continued to fall nationally, and this week the number fell by 34 % since last week. The highest rates of new cases are still found in The Midlands.

Very recent use of the data collected by the app suggests it is of value in picking up hotspots of infection based on three criteria. For a local authority area to be identified as a hotspot it must: (1) have significantly higher prevalence than its neighbouring authorities; (2) be in the top 10th percentile of prevalence for the UK; and (3) have higher prevalence today than 10 days ago. The research shows a number of areas as potential new hotspots of infection that have attracted local restrictions. As well as Leicester, which is already back in lockdown as of the end of June 2020, the data have highlighted a number of regions in the North of England, Luton and Northampton with local outbreaks that have led to the imposition of local restrictions

A further data resource to record slow changes in transmission leading to a renewed growth in the epidemic would be large-scale serological sampling taking account of confounding variables such as age, gender, socio-economic status, ethnicity and spatial location (region) of home and work, with a strong longitudinal component where identified individuals are followed over time to record the incidence of new infections. Some studies are underway in this area involving, for example, blood donors, but serological surveillance needs to be introduced on a much bigger scale to be of use in detecting changes in incidence and hence in r and R .

12. Discussion

Policy formulation founded on careful scientific analysis lies at the core of the effective management and eventual control of the COVID-19 epidemic³⁴⁶. With no treatments and vaccines immediately available, government has had to rely on social distancing measures to limit transmission and the morbidity and mortality associated with COVID-19 infection. Scientific analysis is obviously not the only important factor, since the way in which government provides information to the public and how they respond in the case where behaviour change is the only option to reduce transmission, are of great significance.

In such analyses data quality is also key. More needs to be done to both improve management and dissemination of data, document any changes in collection methods over time and promote understanding of limitations in how collected and how presented. If these estimates of R and r are based on deaths, then this reflects transmission rates weeks before. If based on confirmed cases, then the temporal trends in the data may be affected by changes in testing strategies and capacity. In future advisory bodies and organisations, such as the new Joint Biosecurity Centre (JBC), statistical expertise in data collection and analysis must be adequately represented.

What degree of change in behaviour is required by isolation (= lock down) activity to halt transmission is difficult to define, but hints are provided by certain epidemiological measures such as R , and r . The former provides an overall measure of how much change is required in the behaviours that result in transmission, such as close contact, aerosol expulsion via coughing and sneezing and contact with contaminated surfaces. If the pristine R_0 , when the epidemic starts is 2.5, to get below unity in value, transmission must be reduced by a proportion of 0.6 or 60%. Similarly, if a vaccine of, say, perfect efficacy becomes available and life-long duration of protection, a fraction $1-1/R_0$ of the population would have to be immunised to stop transmission. This is > 60% for an R_0 value of 2.5. If the duration of protection is short, as is the case for other coronaviruses, immunisation may have to be repeated annually. It is important to note however, that even if the duration of protection to infection is short, this may not be equivalent to a short duration of protection to serious disease arising from infection.

The range in R values reported by SPI-M to SAGE only deal with the variation in the different values produced by the various modelling groups. The real uncertainty is much greater than that reported due to all the issues described in Section 5. For this reason, it may be seen as an unreliable parameter when the epidemic is in retreat. However, its estimation is still important, even when case numbers are low, if heterogeneity between regions is high, and if guidance is needed on what mitigation measures done enough to cause the eventual elimination of transmission. Ideally, estimates of both parameters, region by region should be reported, as started by the government in recent communications. However difficult, uncertainty bounds should be placed on the estimated R and r values, with methods and assumptions made described, ideally stratified by region as well as the time window over which the estimates refer to.

For all estimation activities, however sophisticated the model of transmission and the estimation procedures adopted, data quality over time is key. As noted in the previous section, more attention needs to be given to quality of collection procedures, how these have changed over time and data management practices.

Diversity in the models of COVID-19 transmission employed by SPI-M to inform SAGE is a strength not a weakness. There is no one correct model, especially given the many uncertainties that still surround the biology and epidemiology of COVID-19. Is greater complexity in model structure always desirable? This depends on data availability and knowledge of the key determinants of transmission.

A large number of unquantified parameters, estimated by model fitting, is not necessarily a better predictive tool than that provided by simple models with few parameters where good estimates are available. The urgency of producing predictions and trying to assess the potential impact of different mitigation measures have understandably resulted in some delays in making available to a wide audience the precise assumptions made, the data employed and methods of estimation for key parameters of the different models employed by SPI-M. This now needs to happen via the peer reviewed literature and/or via detailed reports made widely accessible. Furthermore, much more detailed sensitivity analyses need to be performed across models and over ranges of values for the most uncertain parameters, such as the proportion of asymptomatics and their infectiousness stratified by age. It is, in part, via such sensitivity analyses that uncertainty bounds can be constructed for model outputs including estimates of R and r . However, many more sources of uncertainty need to be acknowledged as outlined in Section 5.

The relative simplicity of the very direct measurement, r , and its second derivative (the rate of change in the rate of change), which avoids many of the inferential difficulties associated with R employing complex models of transmission and social distancing impact in estimation, suggests that r should receive greater emphasis in future advice to policy makers. However, weighed against the attractiveness of this measure, is in its estimation no account is taken of the non-linear stochastic dynamics of the epidemic when R is near to or below unity in value. Ideally, both statistics should be reported.

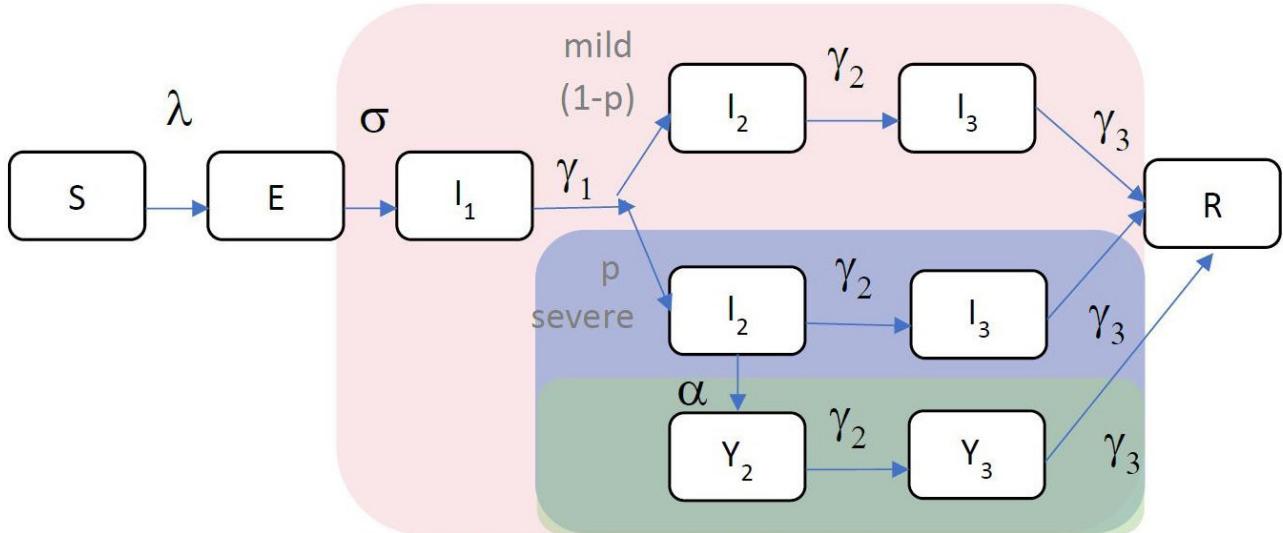
Given the suggested wide bounds of uncertainty that surround estimates of R in particular, and to a lesser extent, r , are they still of value in policy formulation? The answer is definitely, yes – since even with uncertainty, guidance can still be given on a central estimate – and this is certainly a much better place to be in than just making a guess through verbal argument as opposed to detailed analysis where the assumptions are clearly laid out for all to see. The need at present is for greater clarity on the assumptions made and improving the quality of the data employed in producing estimates of key epidemiological parameters and forward projections.

Appendix 1

FIGURE A1

A) A flow chart of a simple epidemic model for COVID-19 of individual states and pathways representing rates of transfer between states. The top pathway is for asymptomatics with mild or no symptoms who stay in the community and eventually recover – but contribute to transmission. B) The bottom pathways are for those with clear symptoms who either self-isolate or get admitted to hospital. No social distancing or lock down is represented in the diagram.

A)



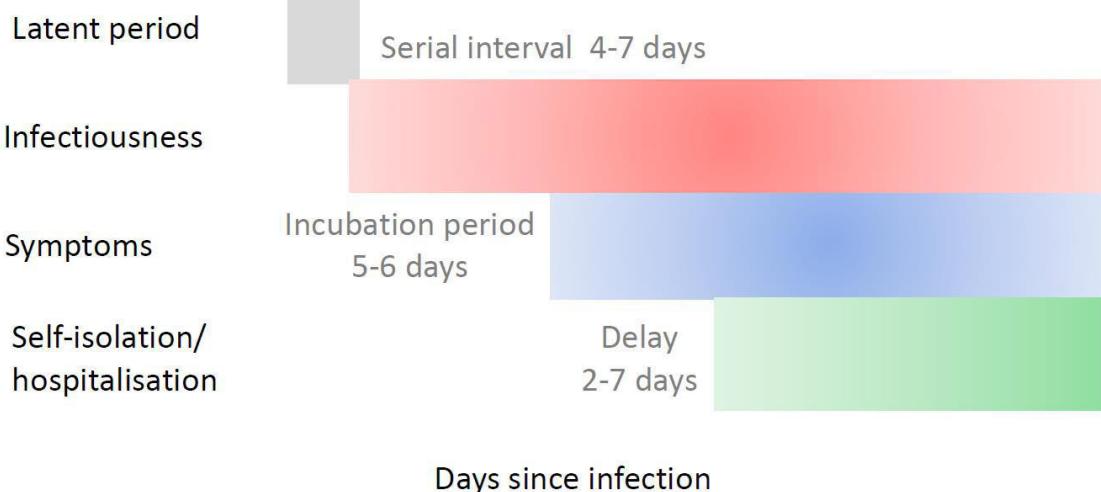
B)

$$R = \frac{\beta_1}{\gamma_1} + (1 - p) \frac{\beta_2}{\gamma_2} + (1 - p) \frac{\beta_3}{\gamma_3} + \frac{pb}{\gamma_2 + \alpha} \left(\beta_2 + \frac{\gamma_2 \beta_3}{\gamma_3} \right) + \frac{par}{\gamma_2 + \alpha} \left(\frac{\beta_2}{\gamma_2} + \frac{\beta_3}{\gamma_3} \right)$$

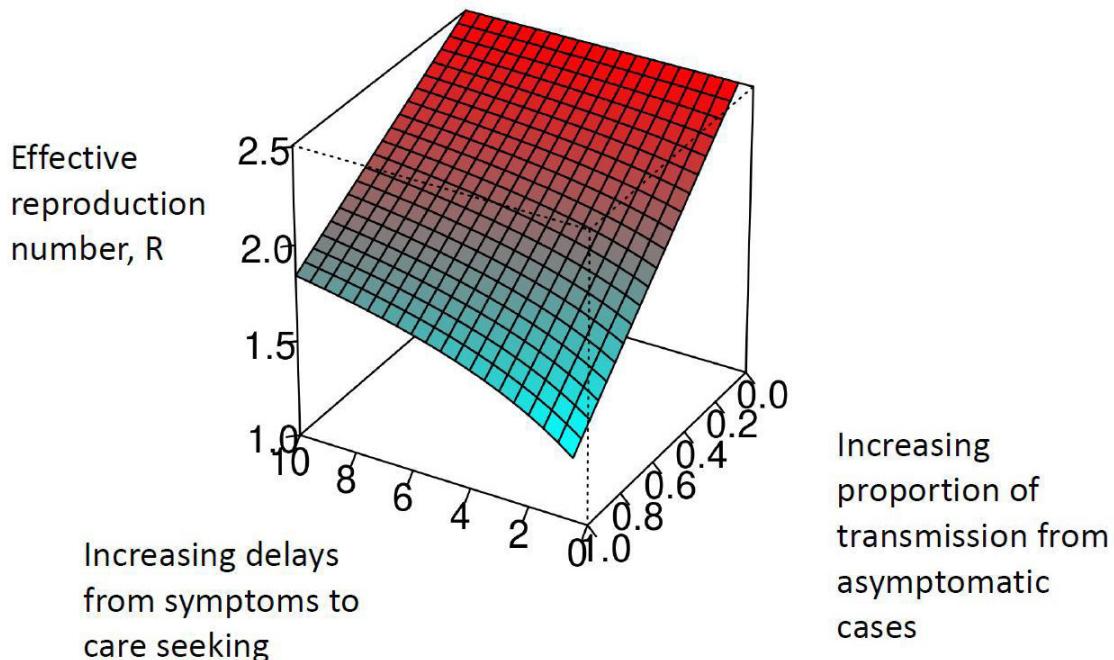
FIGURE A1 CONTINUED

C) Below the flow chart is the Effective Reproduction number equation that arises from this flow chart. It is an effective reproduction number because self or mandatory isolation takes place. In this equation $1/\alpha$ is the average number of days it takes from symptom onset to isolation (a measure of control). The term ρ is the fraction of people with clear symptoms and the β terms are the infection rates from each infectious state, while the γ terms define rates of leaving a given state ($1/\gamma$ is the average duration of stay). D) The graph below this equation records how $1/\alpha$ influences R and for the parameters chosen (an R_0 of 2.5), isolation fails to take R below unity. It requires general measures of social distancing in the entire population (= lock down) to achieve that goal.

C)



D)



Appendix 2

TABLE A1

UK models of COVID-19 transmission and mitigation measure impact – used by SPI-M.

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
LSHTM, EpiNow ³⁴⁹ uses EpiEstim ³⁵⁰ Contact: Sam Abbott, sam.abbott@lshtm.ac.uk	<p>Model structure: Renewal equation model Given $\mathbf{R}_{t,\tau}$, \mathbf{I}_0, \mathbf{I}_{t-1}, \mathbf{w}_s the probability of I_t new cases at time t is Poisson distributed:</p> $P(I I_0, I_t, w, R_{t,\tau}) = \prod_{s=t-\tau+1}^t \frac{(\mathbf{R}_{t,\tau} \Lambda_s)^{I_s} e^{-R_{t,\tau} I_s}}{I_s!}$ <p>Where $\Lambda_s = \sum_{s=t-\tau+1}^t I_{t-s} w_s$</p> <p>Data: Estimates are based on different data streams provided by DSTL: <ul style="list-style-type: none"> – hospital admissions (relatively little delay and no (hopefully) testing bias), – deaths (long delay but no testing bias), and – laboratory-reported cases (testing bias but the least delay). All based on data provided by DSTL. Our estimate for the report delay is fitted to confidential DSTL supplied line-list data for both admissions and deaths. Data for subnational-level analysis on website: https://epiforecasts.io/covid/</p>	<p>Instantaneous reproduction number (assumed to be piece-wise constant):</p> $R_t = \frac{I_t}{\sum_{s=1}^t I_{t-s} w_s}$ <p>I_t: number of new infections generated at time t</p> <p>w_s: infectivity profile represented as probability distribution dependent on time since infection s, estimated from generation time/serial interval that is assumed to be Gamma distributed</p> <p>LSHTM model assumes generation time with mean 3.6 days (SD: 0.7 days), and SD 3 days (SD: 0.8 days)</p> <p>R_t assumed to be constant over time period $[t-\tau+1; t]$</p> <p>➔ $R_{t,\tau}$ posterior Gamma-distributed with mean:</p> $\frac{a + \sum_{s=t-\tau+1}^t I_s}{b + \sum_{s=t-\tau+1}^t \Lambda_s}$ <p>And CV</p> $\frac{1}{\sqrt{a + \sum_{s=t-\tau+1}^t I_s}}$	<p>Uncertainty of generation time: <ul style="list-style-type: none"> – Use 1000 samples from assumed log-normal distribution (using log mean and log sd) </p> <p>Uncertainty of R estimation procedure: <ul style="list-style-type: none"> – Use 1000 samples for each time point using the optimal window τ for each to construct credible interval – Window τ is optimised using one-day head case prediction and RPS scoring </p> <p>Other sources of uncertainty: <ul style="list-style-type: none"> – reporting delay: fit exponential and gamma distributions to 100 subsamples of linelist data (each with 250 samples drawn with replacement), then 10 samples of distribution parameters are drawn from best-fit distribution → 1000 date-of-onset samples for each confirmed case – alternatively use mean shift to over-smooth the underlying infection curve – The impact of bias introduced from estimating the reporting delay will likely be to reduce R_t estimates when $R_t > 1$ and increase them when $R_t < 1$. This source of bias is expected to be marginal (except for the over-smoothing) when compared to other sources of bias due to not adjusting for delay in reported cases. – right-truncation of notification dates: number of onsets on day $t-j$ assumed to follow a negative binomial distribution – R_0 values reflect the number of reported cases, unclear on whether it also applies to dynamics of asymptomatic cases (true for all models using this type of data) </p>

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
		<p>a, b: parameters of prior Gamma distribution of $R_{t,\tau}$</p> <p>LSHTM model assumes Gamma prior of $R_{t,\tau}$ with mean 2.6 and SD 2 (based on early estimates from Wuhan)</p> <p>Optimal τ balances rapid detection of changes in transmission vs. precision of estimates; precision depends on number of incident cases in τ</p> <p>LSHTM model evaluates τ from 1 – 7 days</p>	<ul style="list-style-type: none"> – R_0 value is a reflection on the relative change in case numbers across a period of time, so the absolute error in when the cases occur is secondary (unless that uncertainty is really big) - but uncertainty in the onset-to-reporting time will obviously contribute to the uncertainty in R_0
LSHTM, CoMix ³⁵¹ Contact: Christopher Jarvis, Christopher.Jarvis@lshtm.ac.uk	<p>Model structure:</p> <p>Uses next-generation matrix (NGM) to estimate R_0 from contact rate data</p> <p>The NGM is constructed from a transmission matrix (rates of infection) between types of individuals and a transition matrix (rates of conversion between types or death/removal)</p> <p>Transmission rates are assumed to be proportional to surveyed contact rates.</p> <p>Transition matrix as implicitly assumed to be a constant → implies one infectious state, and that duration of infection is independent of age</p> <p>Data:</p> <p>Contact matrix prior to NPEs assumed to follow POLYMOD data</p> <p>Change in contact matrix after NPEs inferred from CoMix study[132]many countries have adopted unprecedented physical distancing policies, including the UK. We evaluate whether these measures might be sufficient to control the epidemic by estimating their impact on the reproduction number (R_0)</p> <p>This study does not use any case or death data.</p>	<p>R_0 is dominant eigenvalue of the NGM → assumed to be proportional to the dominant eigenvalue of the contact matrix</p> <p>The relative reduction in R equals the reduction in the dominant eigenvalues of the contact matrices before and after lockdown/interventions.</p> <p>This involves scaling the previous value of R_0 by the ratio of the dominant eigenvalues of the CoMix over the POLYMOD matrix.</p> <p>The duration of infection cancels out in the construction of the NGM as it is the same in both cases.</p> <p>Prior to interventions R_0 assumed to follow normal distribution with mean=2.6 and sd=0.54 obtained from meta-analysis of published values</p>	<p>Uncertainties in original R_0 prior to interventions:</p> <ul style="list-style-type: none"> – Uncertainty in published values, central estimate range 0.3 – 7.05, confidence interval range 0.17 – 8.46 – each included estimate (average and uncertainty) was fitted to a PERT distribution – each parameterised distribution was sampled 10,000 times to produce the final consensus distribution <p>→ uncertainty in R value is dominated by uncertainty in baseline R_0 estimate</p> <p>Uncertainty in the construction of contact matrices:</p> <ul style="list-style-type: none"> – age-specific daily contacts determined using negative binomial regression controlling for sex and household size – uncertainty about contact of <18 year-olds because they were not included in CoMix survey → imputed from POLYMOD contact matrix – uncertainty of imputation assessed with 10,000 bootstrapped samples, comment – alternative assessment assumes that contacts of 5 – 18 year-olds reduce by 50%

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
			<ul style="list-style-type: none"> – model does not take into account reduction of contacts because of symptoms or quarantine <p>The effective duration of infectiousness is likely to change after lockdown, since isolation, hospitalization, quarantine, etc, will shorten the period of contact. This assumes that infectiousness duration will cancel out when estimating current R compared to R_0 a potential problem.</p>
MRC Biostatistics Unit at the University of Cambridge and Public Health England ³⁵³ https://www.mrc-bsu.cam.ac.uk/now-casting/ Contact: Daniela De Angelis, daniela.deangelis@mrc-bsu.cam.ac.uk Paul Birrell, paul.birrell@mrc-bsu.cam.ac.uk	<p>Model structure:</p> <p>Deterministic age-structured compartmental model</p> <p>Difference equations (modified SEIR = SEEIR, Reed-Frost formulation)</p> <p>Population subdivided by age and geographic area; age classes used: <1, 1 – 4, 5 – 14, 15 – 25,..., 65 – 74, 75+</p> <p>$t_n = n\delta t, n = 1 \dots T, \delta t = 0.5 \text{ days}$</p> <p>Age class and area define a population stratum j</p> <p>Separate system of forward simulation equations for each UK region</p> <p>Model does not consider the proportion symptomatic or discern between symptomatic and asymptomatic infection because a) estimates an age-specific infection-fatality ratio (IFR); and b) does not assume any different contribution to transmission between the two</p> <p>Likelihood:</p> <p>The observed number of deaths $X_{r,t_k,l}$ in the interval t_k, region r and age group i are assumed to be a realisation of a negative binomial:</p> <p>$X_{r,t_k,i} \sim NegBin(\mu_{r,t_k,i}, \eta)$</p>	<p>Region-specific reproduction number in spatial version of the model:</p> $R_{0,r} = \psi_r d_I \frac{\left(\frac{\psi_r d_L}{2} + 1 \right)^2}{1 - \frac{1}{\left(\frac{\psi_r d_L}{2} + 1 \right)^2}}$ <p>ψ_r: initial growth rate of epidemic in region r</p> <p>d_L: duration of latent infection stage</p> <p>R_0 is related to the infection rate matrix $M(t)$ via</p> $\beta(t) = M(t) \frac{R_0}{R_0^*}$ <p>$\beta(t)$: matrix of infection rates of susceptible individuals in stratum j due to individuals in stratum i</p> <ul style="list-style-type: none"> • There is a lockdown effect parameter m which described the reduction in the likelihood of transmission after the initiation of the lockdown. 	<p>Sources of uncertainty:</p> <ul style="list-style-type: none"> – Assumptions that symptomatic and asymptomatic cases contribute equally to transmission -incubation period: 4 days (95% confidence interval [CI], 4.1 to 7.0); the 95th percentile of the distribution was 12.5 days (95% CI, 9.2 to 18) based on data shared by Neil Ferguson – probability distribution of times from onset of symptoms to death 15 days (SD: 12.1 days) based on intermediate analysis carried out at MRC-BSU led by Anne Presanis of onset-to-death in the PHE line-listing of deaths (manuscript in preparation) <p>Uncertainty in model fitting procedure:</p> <p>Typically multiple runs of a MCMC chain of 900,000 iterations, with burn-in of 90,000 iterations, and thinning interval of 125 iterations (ie 1 in 125 iterations are retained for the posterior sample).</p>

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
	<p>with mean $\mu_{r,t_k,i}$ and dispersion parameter η. Here</p> $\mu_{r,t_k,i} = p_i \sum_{l=0}^k f_l \Delta_{r,t_l,i}^{\text{infec}}$ <p>where</p> <p>f_l: probability that infection will occur l days after infection</p> <p>$\Delta_{r,t_k,i}^{\text{infec}}$: new infections in time step δt</p> <p>p_i: infection fatality rate in age group i</p> <p>The observed positive serological tests $Y_{r,t_k,i}$ is assumed to be a realisation from a binomial distributed:</p> $Y_{r,t_k,i} \sim \text{Bin}(n_{r,t_k,i}, k_{\text{sens}} \left(1 - \frac{S_{r,t_k,i}}{N_{r,i}}\right) + (1 - k_{\text{spec}}) \frac{S_{r,t_k,i}}{N_{r,i}})$ <p>where k_{sens}: sensitivity of test</p> <p>k_{spec}: specificity of test</p> <p>$n_{r,t_k,i}$: number of blood samples taken on day t_k in region r from individuals of age group i</p> <p>$S_{r,t_k,i}$: number of susceptible individuals on day t_k in region r from age group i</p> <p>$N_{r,i}$: number of individuals in region r in age group i</p> <p>Data:</p> <ul style="list-style-type: none"> - death data from PHE (include all COVID-19 confirmed deaths occurring in hospital and outside hospital) - NHS England and serology from blood donors from PHE survey of NHS Blood Transfusion donors, <p>Data are stratified by age group and region</p> <p>POLYMOD data – contact matrix</p> <p>ONS time use survey</p> <p>Google community mobility survey</p>	<ul style="list-style-type: none"> • Age dependent susceptibility, $b_a(t)$, is assumed. There is a separate $b(t)$ for the over-75s to one for the under-75s. They both vary weekly according to a random walk process and are estimated. • m and $b(t)$ are both absorbed into the time-varying contact matrix $M(t)$. • $M(t)$ is also constructed on the basis of POLYMOD, google mobility, time-use survey and DfE school attendance data. <p>$M(t)$: contact matrix between any two individuals in different strata, derived from POLYMOD data for UK</p> <p>R_0^*: dominant eigenvalue of the next generation matrix M^* where</p> $M_{j,i}^* = N_j M_{j,i}(\mathbf{0}) d_I$ <p>N_j: size of population in stratum j</p> <p>d_I: duration of infectious stage</p>	

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
Warwick ³⁵⁵ Contact: Matt Keeling, m.j.keeling@warwick.ac.uk	<p>Model structure:</p> <p>Deterministic age-structured SEIR model where the infected compartment is subdivided into detectable/symptomatic cases and undetectable/asymptomatic cases</p> <p>Compartments stratified into 5-year age-bands</p> <p>Age-dependent contact rates based on UK contact patterns (contact matrices taken from Prem et al³⁵⁶, POLYMOD data³⁵⁷ could also be used)</p> <p>Model considers infection within and outside of households and quarantine of households, hence forces of infection act on individuals depend on age class and location (household, school, workplace, other)</p> <p>Quarantine</p> <p>Fraction quarantined parameterised by H. H is proportional to the relative strength of lockdown ϕ_R within a region: $H^R = 0.8\phi_R$</p> <p>The impact on quarantine on the susceptible population is ignored because only few individuals are expected to be quarantined at any one time.</p> <p>Susceptibility and symptoms</p> <p>Both susceptibility and probability to display symptoms assumed to be dependent on age (not separable by model), scaling factor between age-specific susceptibility σ_a and age-specific "detectability" d_a $Q_a = \sigma_a d_a$</p> <p>If $d_a = \kappa Q_a^{(1-\alpha)}$ and $\sigma_a = k Q_a^\alpha$</p> <p>→ $Q_a = \kappa k d_a \sigma_a$ and κ and k are chosen such that the oldest age group has a 90% probability of displaying symptoms $d_{>90} = 0.9$ and such that $R_0 = 2.7$ (symptomatic and asymptomatic cases are assumed to contribute differently to infection dynamics)</p> <p>Regional parameters capture heterogeneity in epidemic evolution in different geographic regions within the UK</p>	<p>Estimation of R</p> <p>Two different methods are used to estimate R which are in good numerical agreement</p> <p>1) R is calculated from the next-generation matrix $\frac{\beta_{ba}}{\gamma}$ using current distribution of infection across age classes and states; subscripts a, b indicate age groups a and b</p> <p>2) use the relationship between R and r (epidemic growth rate) for SEIR-type model with multiple latent classes</p> $R = \left(1 + \frac{r}{\varepsilon M}\right)^M \left(1 + \frac{r}{\gamma}\right)$ <p>The epidemic growth rate r is estimated by fitting the full deterministic ODE to multiple data streams and using the daily estimated incidence to calculate the growth rate</p>	<p>Sources of uncertainty:</p> <p>Uncertainty in fixed parameters:</p> <ul style="list-style-type: none"> – Proportion of asymptomatic infected individuals and relative infectiousness of asymptomatic infected individuals – assumption is that all household members are infected by index case within household → this would underestimate R_0 within households → contact rate in households scaled by 1.3 (derived from testing the simulation model and comparing against a baseline model in which saturation effects are ignored) <p>Uncertainty in data used for fitting:</p> <p>Data biased by testing protocol, and case definition of COVID-19 patient in hospital</p> <ul style="list-style-type: none"> – hospitalisation rates: <ul style="list-style-type: none"> i) proportion of clinical cases in each age group that require hospital admission – obtained from comparing age distribution of hospital admissions with that of early detected cases ii) age-independent distribution of symptom onset to hospitalisation both estimates informed by CHES data – Bed occupancy: estimated from distributions of length of stay in ICU and of length of stay in hospital – risk of death: determined from PHE death records – inherent uncertainty in some of the timeseries data used for fitting (eg ICU bed occupancy) – ICU admission data not yet available → complete likelihood cannot be used yet <p>Uncertainty in model fitting procedure:</p> <ul style="list-style-type: none"> – New data becomes available on a daily basis → posterior of previous fitting can be used as prior for subsequent fitting – Fitting only to death produces the greatest uncertainty in estimates of the growth rate r, because deaths are a small fraction of the total outbreak

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
	<p>Regional parameters include:</p> <ul style="list-style-type: none"> - initial level of infection, rescaled from early age-distribution of cases with regional scaling factor - age-dependent susceptibility differs between regions to account for regional differences in social mixing and hence early R0 - relative strength of lockdown <p>Regional scaling factors derived from MCMC fitting of model</p> <p>Social distancing measures</p> <ul style="list-style-type: none"> - modelled by scaling down the different contact rates in school, work and other places, and scaling up contact matrices in households, scaling of contact patterns is assumed to be age-dependent - contact reduction of service sector workers assumed to scale as a function of their contact reduction and the reduction of contact by others - proportion of working population in services assumed to be 0.3 <p>Public health measurable quantities</p> <ul style="list-style-type: none"> - Admissions to hospital of age a on day d: $P_a^{C \rightarrow H} \sum_q D_q^{C \rightarrow H} n D_{d-q}$ <p>$P_a^{C \rightarrow H}$: fraction of symptomatic cases that will be admitted to hospital</p> <p>$D_q^{C \rightarrow H}$: distribution of delay of time q from onset of symptoms to hospitalisation</p> <ul style="list-style-type: none"> - Admissions to ICU, modelled in the same way as admissions to hospital with different fraction of symptomatic individuals that will be admitted to ICU $P_a^{C \rightarrow I}$ and different time delay - Number of hospital beds occupied: modelled by two distributions quantifying if someone admitted to hospital is still in hospital q days later and if someone admitted to ICU occupies a normal ward bed q days later - Number of ICU beds occupied: <p>Modelled by a distribution representing if someone admitted to ICU is still in ICU q days later</p>		<ul style="list-style-type: none"> - Fitting to all available data streams results in the least uncertainty of the estimate of r, but fitting to hospital admissions alone or hospital admissions plus deaths does not reduce the uncertainty <p>Sensitivity analysis:</p> <ul style="list-style-type: none"> - Different compliance levels assumed in sensitivity analysis - Different ratios for susceptibility and detectability assumed - The model can be fitted to data divided into different temporal phases, the mean and the variance of the estimate for r are sensitive to the number of phases assumed - removing patients that have previously tested positive for COVID-19 and have later been (re-)admitted to hospital produces a lower estimate of r

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
	<p>- Number of deaths:</p> <p>Mortality ratio $P_a^{H \rightarrow Death}$ determines probability that an individual of age a that is hospitalised dies, time from hospitalisation to death defined by delay distribution $D_q^{H \rightarrow Death}$</p> <p>- Proportion testing seropositive:</p> <p>Seropositivity modelled by sigmoidal function for which sigmoid is independently fitted to PHE data, and asymptote representing sensitivity of test is estimated by fitting the whole ODE using MCMC</p> <p>Model fitting:</p> <p>Likelihood:</p> <p>All public health measurable quantities are assumed to be Poisson distributed (L_p), apart from seropositivity which is assumed to be binomial distributed (L_B)</p> $LL^R(\theta) = \sum_d L_p(\sum_a H_{obs,d} \sum_a H_{pred,d}) + \\ \sum_d L_p(\sum_a ICU_{obs,d} \sum_a ICU_{pred,d}) + \\ \sum_d L_p(\sum_a B_{obs,d} \sum_a B_{pred,d}) + \\ \sum_d L_p(\sum_a B_{obs,d}^{ICU} \sum_a B_{pred,d}^{ICU}) + \\ \sum_d L_p(\sum_a D_{obs,d} \sum_a D_{pred,d}) + \\ \sum_d \sum_a L_B(SP_{obs,d} n, p_{pos})$ <p>$H_{obs,d}$: observed hospitalisations on day d $H_{pred,d}$: predicted hospitalisations on day d $ICU_{obs,d}$: observed ICU admissions on day d $ICU_{pred,d}$: predicted ICU admissions on day d $B_{obs,d}, B_{obs,d}^{ICU}$: observed occupancy of normal hospital beds and ICU beds on day d $B_{pred,d}, B_{pred,d}^{ICU}$: predicted occupancy of normal hospital beds and ICU beds on day d $D_{obs,d}$: observed deaths on day d $D_{pred,d}$: predicted deaths on day d</p>		

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
	<p>$\mathbf{SP}_{obs,d}$: observed positive serology tests on day d</p> <p>$\mathbf{SP}_{pred,d}$: predicted positive serology tests on day d</p> <p>Subscript a – age class, subscript d - day</p> <p>Data:</p> <p>The model has been fitted to individual patient data in CHESS and CO-CIN databases; fitted distributions represent national-level average → to obtain regional-level distributions scaling parameters are defined for the probabilities $\mathbf{P}_a^{\zeta \rightarrow H}$, $\mathbf{P}_a^{\zeta \rightarrow I}$, $\mathbf{P}_a^{H \rightarrow Death}$ and two shape parameters that define the distributions of times spent in hospital and ICU</p>		
University of Exeter ³⁶¹ Contact: Rob Challen rc538@exeter.ac.uk Leon Danon (Computer Science) L.Danon@exeter.ac.uk	<p>Model structure:</p> <p>Uses EpiEstim³⁶² package to estimate R_t, details as described above for LSHTM estimations</p> <p>Assumption: negligible mixing of populations between regions (probably not valid in early outbreak)</p> <p>Data:</p> <p>Incidence statistics released on PHE website:</p> <ul style="list-style-type: none"> – Cases by authority and NHS region in England³⁶³ – Country-level summary of cases for England, Scotland, Wales, Northern Ireland³⁶⁴ – regional data from PHE Wales and PHE Scotland^{365, 366} – data for Northern Ireland³⁶⁷ <p>Data sources are not combined for different models, UK estimate is either the sum of cases for the 4 nations or from the headline Figure on the PHE website</p> <p>7-day rolling average used for death data because of weekend reporting delay</p> <p>Additional analysis:</p> <p>Regional time series of R_t compared to national time series using two-sided t-tests</p> <p>Future plans: use weighted sum of incidences of different data sources as input</p>	<p>\mathbf{R}_t assumed to be constant over time period $[t-\tau+1; t]$</p> <p>→ $\mathbf{R}_{t,\tau}$ posterior Gamma-distributed with mean:</p> $\frac{\mathbf{a} + \sum_{s=t-\tau+1}^t \mathbf{I}_s}{\mathbf{b} + \sum_{s=t-\tau+1}^t \Lambda_s}$ <p>And CV</p> $\frac{1}{\sqrt{\mathbf{a} + \sum_{s=t-\tau+1}^t \mathbf{I}_s}}$ <p>a, b: parameters of prior Gamma distribution of $\mathbf{R}_{t,\tau}$</p> <p>Optimal τ balances rapid detection of changes in transmission vs. precision of estimates; precision depends on number of incident cases in \mathbf{T}</p> <p>Exeter model assumes 7 days sliding time window</p>	<p>Issues with data (all models would have to have dealt with these issues):</p> <ul style="list-style-type: none"> – local breakdowns don't add up to total → some cases cannot be attributed to a location – negative incidence on some days due to reassignment of some cases to another region – fragmented nature of reporting → complete time series at regional levels (especially Wales and Northern Ireland) – regional differences in processing time for diagnostic test may introduce bias into data – Missing data is imputed from a linear interpolation of the logarithm of cumulative Figures – changes in reporting cases and deaths <p>Uncertainty in serial interval:</p> <p>Weighted mean of means and sds of serial interval of 7 published studies (in total 977 individuals)</p> <p>Assumed to be gamma-distributed with mean 4.98 days (Crl: 2.16; 8.44) and standard deviation 3.61 days (Crl: 2.70; 5.42)</p> <p>Sensitivity analysis:</p> <p>Direct calculation of serial interval based on early contact tracing in the UK</p> <p>Resampling process of data that informs serial intervals.</p> <p>Currently methods for estimating serial interval are under review.</p>

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
<p>Imperial College London Transmission Dynamics Model³⁶⁸</p> <p>Contacts: Neil Ferguson, neil.ferguson@imperial. ac.uk</p> <p>Weblink</p>	<p>Model: stochastic, spatially structured individual-based SEIR model with 3 levels of mixing (households, places and random) in total the model has $2 + N_{place}$ transmission parameters, where N_{place} is the number of types of places the model can represent different interventions in a mechanistic manner the model can also represent severity and health care demand estimated from individual level hospital data Latency: latent period distribution assumed gamma for COVID-19, symptoms start with a fixed time delay after latency ends in individuals that become symptomatic, alternatively the model can handle arbitrary delay time distributions Infectiousness: proportion of symptomatic infected individuals is user-defined, time varying infectiousness profile (follows gamma function form), infectiousness can be assumed to be over-dispersed (negative binomial distributed) by drawing a scaling factor for individual's infectiousness from a gamma distribution with mean 1 and shape k Age-dependent parameters: susceptibility, infectiousness, proportion symptomatic can be specified in an age-dependent way if data are available for parameterisation Spatial, place and household structure: Additional complexity beyond a standard household-workplace-community model is the explicit representation of space in the construction of the bipartite graph of individuals, households and places and the spatially localised random contacts. Types of places in model: primary schools, secondary schools, universities, workplaces, care homes</p>	<p>No simple analytical expressions exist for this type of complex model (with age and spatial structure) Instead estimate R_{rand} defined as the average number of secondary infections generated by a randomly selected individual in the population when the rest of the population is susceptible Evaluating previous flu model: $R_0 \approx R_{rand} + 0.2$</p> <p>Because of higher work/school transmission than household transmission</p>	<p>Sensitivity analyses (underway performed by two RAMP groups): – Parameter values, most sensitive ones: transmission rate, age-dependent transmission, contribution of asymptomatic individuals to transmission – Data streams used for fitting – model fitted to data from different countries</p>

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
	<p>Option: group structure can be modelled within places, ie small groups of individuals within a place who mix more intensely than everyone in a place does, eg school classes</p> <p>population described by empirical distribution</p> $\text{Poisson}(\int_{\omega} \rho(r) dr)$ <p>Where</p> <p>$\rho(r)$: the empirical population density function</p> <p>r: coordinate vector</p> <p>ω: subset of the total geographic area Ω</p> <p>individual i is defined by age a_i, household h_i and place l^j</p> <p>in any time-step of $\Delta T=0.25$ days, a susceptible individual i has probability $1-\exp(-\lambda_i \Delta T)$ of being infected</p> <p>where</p> $\begin{aligned} \lambda_i = & \sum_{k h_k=h_i} \frac{I_k \beta_h \kappa(t - \tau_k) \rho_k [1 + C_k (\omega - 1)]}{n_i^\alpha} \\ & + \sum_{j,k l_k^j=l_i^j} \frac{I_k \beta_p^j \kappa(t - \tau_k) \rho_k [1 + C_k (\omega \psi_p^j(t - \tau_k) - 1)]}{m_i^j} \\ & + \frac{\sum_k I_k \zeta(a_i) \beta_c \kappa(t - \tau_k) \rho_k f(d_{i,k}) [1 + C_k (\omega - 1)]}{\sum_k f(d_{i,k})} \end{aligned}$ <p>k indexes individuals, j indexes places</p> <p>$l_i = 1$ if individual i is infective, $l_i=0$ if individual i is not infective</p> <p>$C_i=1$ if individual i has severe infection, $C_i=0$ if not</p> <p>τ_i: time individual i became infectious</p> <p>$\beta_h, \beta_p^j, \beta_c$: transmission coefficients for household, place (as in workplace or other defined place) and community transmission</p> <p>ω: infectiousness of symptomatic relative to asymptomatic cases</p>		

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
	<p>$\alpha=0.8$: coefficient scaling the intensity of household transmission with household size</p> <p>$\psi_p(x)$: reduction in within-place contact rates by workplace/school absenteeism caused by symptomatic infection, x: time of symptoms onset</p> <p>$\varsigma(ai)$: travel-related contact rate of an individual of age a</p> <p>probability that individual i infects individual j follows a gravity model with kernel $f(d_{ik})$ where d_{ik} is the distance between i and k</p> <p>assumption: 75% of an individual's contacts were within-group, and 25% with individuals picked randomly from the entire population of the school or workplace</p> <p>Data:</p> <ul style="list-style-type: none"> -Rasterised instantaneous population density data from https://www.worldpop.org/ - census data to generate age and household size distribution (ONS census projections for 2020) - Contact rates prior to social distancing were estimated from POLYMOD data³⁶⁹ - ONS data was used to estimate number of individuals in places (schools, universities, workplaces) - ONS census data on commuting was used (1991), resolution biases short-distance data; age of data does not lead to bias, because spatial range of commutes has not changed - Individual level hospital data to model severity of infection and healthcare demand CO-CIN³⁷⁰, CHESS³⁷¹ → severity of disease progression was estimated using separate model and these data streams 		

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
Imperial College London Difference Equation Model Contact: Marc Baguelin m.baguelin@imperial.ac.uk	<p>Model structure:</p> <p>Compartmental model described by stochastic discrete difference equations</p> <p>The model assumes an Erlang distributed delay time from passing from the exposed to the infectious stage</p> <p>Model stratified into 17 age groups (5-year bands until age 80, and 80+)</p> <p>Model fitting:</p> <p>The model is fitted using particle MCMC with MH algorithm</p> <p>The model has 17 free parameters that are fitted, all of these are informed by priors</p> <p>Data:</p> <ul style="list-style-type: none"> – PHE line list data for deaths – new hospital admissions with COVID – newly tested case in general beds – general bed prevalence – ICU prevalence – PHE serology data – POLYMOD³⁷² and CoMix³⁷³ surveys to inform contact structure before and after social distancing measures are implemented – contact matrices from both surveys are used as priors in a Bayesian framework. 	<p>Estimation of R:</p> <p>R is defined as the maximum Eigenvalue of the next generation matrix at the time considered</p> <p>Transmission parameters are fitted to assess the transmission pre-lockdown, after the lockdown, and in the more recent three weeks</p> <p>Parameter estimates obtained from fitting to the most recent data are used to estimate the current value of R</p>	<p>Estimate of R depends heavily on the quality of data used to estimate the most recent transmission parameters (data over the last three weeks)</p> <p>Uncertainty in the construction of contact matrices</p>

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
Imperial College London Renewal Equation Model ³⁷⁴ Contacts: Seth Flaxman, s.flaxman@imperial.ac.uk Samir Bhatt, s.bhatt@imperial.ac.uk Weblink	<p>Model structure:</p> <p>Bayesian mechanistic model of infection inferring the total populations infected (attack rates) and the reproduction number over time (R_t). Uses renewal equation.</p> <p>Daily deaths in country m on day t assumed to be negative-binomial distributed:</p> $D_{t,m} \sim NB(d_{t,m}, d_{t,m} + \frac{d_{t,m}^2}{\psi})$ <p>$d_{t,m}$: mean</p> $d_{t,m} + \frac{d_{t,m}^2}{\psi}$: variance $\psi \sim N^+(0, 5)$ <p>Number of infections in country m on day t:</p> $c_{t,m} = (1 - \frac{\sum_{i=1}^{t-1} c_{i,m}}{N_m}) R_{t,m} \sum_{\tau=0}^{t-1} c_{\tau,m} g_{t-\tau}$ <p>N_m: population size of country m</p> <p>Attack rate age-specific using country-specific contact matrices</p> <p>Data:</p> <p>Fitted to death data pooled from 11 European countries (pooling decreases uncertainty due to idiosyncrasies in data from individual countries)</p>	<p>Piece-wise constant R:</p> $R_{t,m} = R_{0,m} \exp \left(- \sum_{k=1}^6 \alpha_k I_{k,t,m} - \beta_m I_{t,m} \right)$ <p>$I_{k,t,m}$: intervention indicator of intervention k in place in country m at time t</p> <p>$I_{t,m}^*$: indicator for last intervention implemented in a country up to now</p> <p>α_k: impact of intervention k</p> <p>β_m: country-specific random effect</p> <p>Prior of $R_{0,m} \sim N^+(3.28 \kappa)$, $\kappa \sim N(0, 0.5)$ 3.28 based on previous meta-analysis</p> <p>Prior of $\alpha_k \sim Gamma(\frac{1}{6}, 1) - \frac{\log(1.05)}{6}$</p> <p>Prior of $\beta_m \sim N(0, \gamma)$, $\gamma \sim N^+(0, 0.2)$</p>	<p>Uncertainty in model fitting:</p> <p>Parameters estimated using HMC, 4000 samples used to infer credible intervals</p> <p>Sources of uncertainty:</p> <ul style="list-style-type: none"> – negative binomial distribution of daily deaths – Infection-to-death distribution (first term representing infection to onset of symptoms, second term representing onset of symptoms to death): <p>$\pi \sim Gamma(5.1, 0.86) + Gamma(17.8, 0.45)$</p> <ul style="list-style-type: none"> – Generation time distribution assumed to be gamma distributed with Gamma(6.5, 0.62) – Generation time mean can influence R_t substantially, but posterior credible intervals of all estimates varying the generation time mean are largely overlapping – Initial R_0: <ul style="list-style-type: none"> i) initially epidemic fuelled by introduction rather than local transmission, ii) ascertainment bias in number of deaths before testing was widespread – underreporting in sensitivity analysis assumed to be constant over time: only R changes predicted number of cases, not R_0

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
Imperial College London Mobility Data Model ³⁷⁶ Contacts: p.nouvellet@imperial.ac.uk pierre.nouvellet@sussex.ac.uk	<p>Model structure:</p> <p>Uses a regression model to link R_t with mobility data</p> <p>R_t is linked to death data via renewal equation:</p> $D_{t,i} \sim NB(R_{t,i}^D \sum_{s=0}^t D_{s,i} w_{t-s}, \delta)$ <p>$D_{t,i}$: reported deaths on day t in country i</p> <p>w: serial interval (here: time between death of infector and infectee) assumed to be gamma distributed with mean of 6.48 days and standard deviation 3.83 days³⁷⁷</p> <p>alternative social distancing measures assumed to decouple mobility from transmission → new relationship needs to be fitted once new data becomes available; threshold when this becomes necessary assumed to be reached when observed R obtained from EpiEstim is less than 2.5th percentile of $R_{t,i}$ estimate</p> <p>Data:</p> <ul style="list-style-type: none"> - Death data from ECDC - Apple and Google mobility data <ul style="list-style-type: none"> - data streams were combined - weekly average calculated - assigned weekly average to Thursday - interpolated mobility on other days relative to Thursdays - mobility rescaled to interval 0 – 1 relative to maximum observed on Monday-Thursday 	$\log(R_{t,i}) = \log(R_{0,i}) - \beta_i(1 - m_i)$ <p>$R_{0,i}$: basic reproduction number in country i</p> <p>$R_{t,i}$: instantaneous reproduction number on day t in country i</p> <p>$m_{t,i}$: mobility on day t in country i</p> <p>β_i: if positive leads to reduction in R_0 when mobility is reduced</p> $R_{t,i}^D = \sum_{s=0}^t R_{s,i} h(t-s)$ <p>$R_{t,i}^D$: instantaneous reproduction number experienced by those dying on day t in country i</p> <p>$h(t-s)$: gamma distribution describing the infection to death interval, assumed mean 18.8 days and sd 8.46 days</p>	<p>Uncertainty in model fitting procedure:</p> <p>$R_{0,i}$ and β_i fitted with MCMC with MH algorithm</p> <p>Prior for R_0: uniform[2, 5]</p> <p>Prior for β_i: uniform[-100, 100]</p> <p>Death data assumed to be negative binomial distributed with overdispersion parameter δ</p> <p>Prior for δ: exponential with mean 1</p> <p>NB distribution commonly used in two different parameterisations:</p> <p>NB1:</p> $NB1: var(X) = \mu_x + \frac{\mu_x}{\delta_1} = \omega_1 \mu_x \quad \text{where } \omega_1 = 1 + \frac{1}{\delta_1}$ <p>NB2:</p> $NB2: var(X) = \mu_x + \frac{\mu_x^2}{\delta_2} = \omega_2 \mu_x \quad \text{where } \omega_2 = 1 + \frac{\mu_x}{\delta_2}$ <p>NB1 overestimates variance when incidence is low</p> <p>NB2 overestimates variance when incidence is high</p> <p>Proposed alternative parameterisation NBsqrt:</p> $NBsqrt: var(X) = \mu_x + \frac{\mu_x^2}{\delta_{sqrt} \sqrt{\mu_x}} = \omega_{sqrt} \mu_x \quad \text{where } \omega_{sqrt} = 1 + \frac{\sqrt{\mu_x}}{\delta_{sqrt}}$ <p>Fits data best according to DIC</p> <p>Possible explanation: uncertainty in data derives from both heterogeneity in transmissibility and heterogeneity in reporting, the aggregation parameter k varies with incidence</p> <p>The equation that links transmissibility with deaths is only exact if the overall infectivity is constant, when the epidemic is growing/ declining the approximation underestimates/ overestimates recent changes in mobility</p>

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
			<p>Given uncertainty about other data types inaccuracy would only bias predictions if rapid fluctuations of infectivity occur</p> <p>Uncertainty associated with data sources:</p> <ul style="list-style-type: none"> – variance of death data results from heterogeneity in transmissibility and heterogeneity in reporting – mobile phone mobility data is only a proxy for mobility – accuracy depends on how many people have mobile phones and how they use them – high levels of noise in mobility data that was dealt with using statistical methods <p>Sensitivity analysis:</p> <ul style="list-style-type: none"> - Assume deaths are Poisson distributed - use alternative serial interval distribution with mean=4.8 days and sd=2.7 days - null model where $\beta_i=0 \rightarrow$ transmissibility not linked to mobility - comparison of fits with results obtained from EpiEstim - discard very early epidemic data as part of sensitivity analysis of epidemiological parameters
University of Manchester Contacts: Lorenzo Pellis, lorenzo.pellis@manchester.ac.uk	<p>Model structure:</p> <p>Deterministic compartmental ODE model</p> <p>SEIR structure with exposed state subdivided into three compartments</p> <p>No age structure</p> <p>Piece-wise constant infection rate β with two change points in basic version of model (one at time of lockdown, and another four weeks later to reflect clear trends in the data in most regions)</p> <p>Further change points can be added but are not supported by visual inspection of the data</p>	<p>R is estimated from most recent β value and associated CI</p> $R_t = \beta_t k \frac{S(t)}{N}$ <p>With</p> $k = (1 - p_A) \left[\frac{f}{r_E} + \frac{p_H}{r_{IH}} + \frac{(1 - p_H)}{r_{IR}} \right] + p_A f \left[\frac{1}{r_E} + \frac{1}{r_A} \right]$ <p>where</p> <p>p_A: probability of being infected and asymptomatic</p>	<p>Uncertainty in predictions:</p> <p>A 90% CI around the last infection rate β generates uncertainty in forward predictions of the model</p> <p>Uncertainty in data:</p> <ul style="list-style-type: none"> – Negative binomial noise in data – Fitting to fewer data streams leads to wider confidence intervals – To estimate R_t accurately, changes in $S(t)$ need to be documented \rightarrow depends on good serology data <p>Uncertainty in time window assumed for data fitting:</p>

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
	<p>Because rates of disease progression and recovery differ between individuals that have no or mild symptoms, individuals that are admitted to hospital and those admitted to ICU, the model splits the infected class into nine partly parallel and partly sequential compartments depending on the course of disease</p> <p>Example: newly hospitalised individuals take on average 8 days to recover, but only 2 days to pass to ICU</p> <p>The model does not consider nosocomial transmission or deaths outside of hospital, mainly because data on these events initially was lacking</p> <p>Model parameters:</p> <ul style="list-style-type: none"> – The probability of being symptomatic is informed by literature values – The probability of being hospitalised was initially fixed, but can be estimated from serology data – The probability of death in ICU is estimated from the CO-CIN dataset (same value as Lancaster group) – The probability of ICU admission and the probability of death in hospital but outside of ICU are estimated from the input data streams - Rates of disease progression within hospital are estimated directly from CHESS data, but given the lack of good data on recovery the rate of recovery of patients in hospital and of infected individuals outside of hospital are estimated by fitting the model to data - Assumption: pre-symptomatic and asymptomatic individuals are 75% less infectious than symptomatic individuals <p>Model fitting:</p> <ul style="list-style-type: none"> - model fitted separately for each region in the UK using MLE and MCMC (numerically estimates and credible intervals are comparable between the two fitting methods, MCMC better characterises uncertainty in data if anomalies are present) <p>The likelihood is negative binomial distributed</p>	<p>f: infectiousness of asymptomatic individuals relative to symptomatic individuals</p> <p>pH: probability of being hospitalised</p> <p>rE: rate of progression from one exposed compartment to the next or to the infected state</p> <p>rR: recovery rate of infected symptomatic individuals outside of hospital</p> <p>rA: recovery rate of infected asymptomatic individuals</p> <p>To estimate R, β is fitted to data, all other parameters are assumed to be constant over time</p> <p>Because nosocomial transmission is not considered, only infection parameters outside of hospital are required to estimate R</p>	<ul style="list-style-type: none"> – Longer time window leads to tighter CI (because little uncertainty in overall data stream) – Shorter time window leads to broader CI (because much uncertainty in few datapoints most recently reported) → model can also display unexpected behaviour depending on flukes in data, eg can predict $R > 1$ although all data streams are going down <p>In the model, the generation time distribution is assumed to be constant → reduces uncertainty of estimates</p>

Group	Model description and data used	R estimation	Confidence intervals and uncertainty
	<p>Because the model is fitted to hospital data, infection parameters for individuals outside of hospital are not unambiguously identifiable, this can be ameliorated by incorporating serology data</p> <p>Data:</p> <p>4 data streams, each separate from 4 UK regions:</p> <ul style="list-style-type: none"> - Hospital incidence - hospital prevalence (normal wards beds occupied) - ICU incidence - Deaths 		
Lancaster Contact: Jonathan Read Jonathan.read@lancaster.ac.uk	<p>Model structure:</p> <p>Estimates time-varying instantaneous R_t from incidence time series using EpiEstim³⁷⁹</p> <p>Data:</p> <p>Swab-positive tests (England, Scotland)</p> <p>Hospital admissions (Wales, Northern Ireland)</p> <p>Time from symptoms onset to hospital admission/day of test assumed to be negative binomial distributed fitted to data from CO-CIN study³⁸⁰</p> <p>Fitted parameters: size=0.79708040; mu=5.86257026, giving a median 4 days, mean 5.7 days, and IQR of 1 to 8 days</p> <p>400 realisations of onset dates constructed for R_t analysis, constructed counts for recent dates inflated according to negative binomial probability to account for delays in presentation, last 5 days excluded from analysis to account for reporting delays</p>	R_t assumed to be constant over time period $[t-\tau+1; t]$ $\Rightarrow R_{t,\tau}$ posterior Gamma-distributed with mean: $\frac{a + \sum_{s=t-\tau+1}^t I_s}{b + \sum_{s=t-\tau+1}^t \Lambda_s}$ <p>And CV</p> $\frac{1}{\sqrt{a + \sum_{s=t-\tau+1}^t I_s}}$ <p>a, b: parameters of prior Gamma distribution of $R_{t,\tau}$</p> <p>Optimal τ balances rapid detection of changes in transmission vs. precision of estimates; precision depends on number of incident cases in T</p> <p>Lancaster model assumes 7 days sliding time window</p> <p>Estimates of R_t medians and 95% CIs were pooled and 2.5%, 5%, 25%, 50%, 75%, 95% and 97.5% quantiles re-estimated</p>	<p>Uncertainty:</p> <p>R_t estimates at very large and very small geographical areas are likely unreliable,</p> <p>reason: model assumes random mixing, no movement between locations, and all locations independent of others</p> <p>– Estimates for England and Scotland are based on the analysis of swab positive cases → increased testing can bias estimates upwards</p> <p>– assumes that delays in data are due to disease process (onset to presentation/admission), not systematic reporting delays</p> <p>serial interval with mean 4.7 days and standard deviation 2.9 days³⁸¹</p>

Appendix 3

Literature search

A literature search was conducted using SCOPUS, PubMed and reference searches to generate a library of both peer-reviewed and preprint (medRxiv and bioRxiv) articles, reporting estimations for primarily Ro , R_t and other epidemiological parameters contained within models. The phrasing used was: (((sars-cov-2 OR covid-19 OR 2019-ncov) AND (reproduct* AND number OR basic AND reproduct*) OR reproduct* AND rate OR generation AND time OR mathematical AND modelling OR transmission AND *) AND (uk OR united AND kingdom OR great AND britain))).

As of 23/06/20 a systematic literature search using terms above generated a total of 480 papers as broken down in A). Papers were evaluated based upon their abstract content, keeping those which mentioned the use of modelling or explicitly detailed R or R_0 Figures. This focused the search down to 182 papers focused on predictive modelling of the pandemic, of which 30 predicted

epidemiological parameters for the UK as shown in B). The discarded 298 papers were classed as irrelevant to this search and mainly focused on clinical, phylogenetic, social or health institution aspects of COVID. Of the 30 relevant UK papers, those predicting R ranged from 4.8 to 0.44, and averaged 1.86 as illustrated in C). The left-hand graph is calculated R values for current data and the right-hand graph is projected values of R . There is a difference in estimated R values between peer-reviewed and pre-print papers, generating an average of 1.82 and 2.47 respectively. Papers estimating R in the UK were divided into those predicting the current R , and those projecting R estimations based on different scenarios. Pre-print papers are distinguished from peer-reviewed papers by triangular points. 95% confidence intervals are shown in grey and orange, where provided in the literature. Working from left to right the symbols represent hospital patients, community patients, hospital staff, pre-lockdown, post-lockdown, weekly testing, shielding of 60< years, mask wearing (known infection status), mask wearing (preventative), active lockdown, contact tracing.

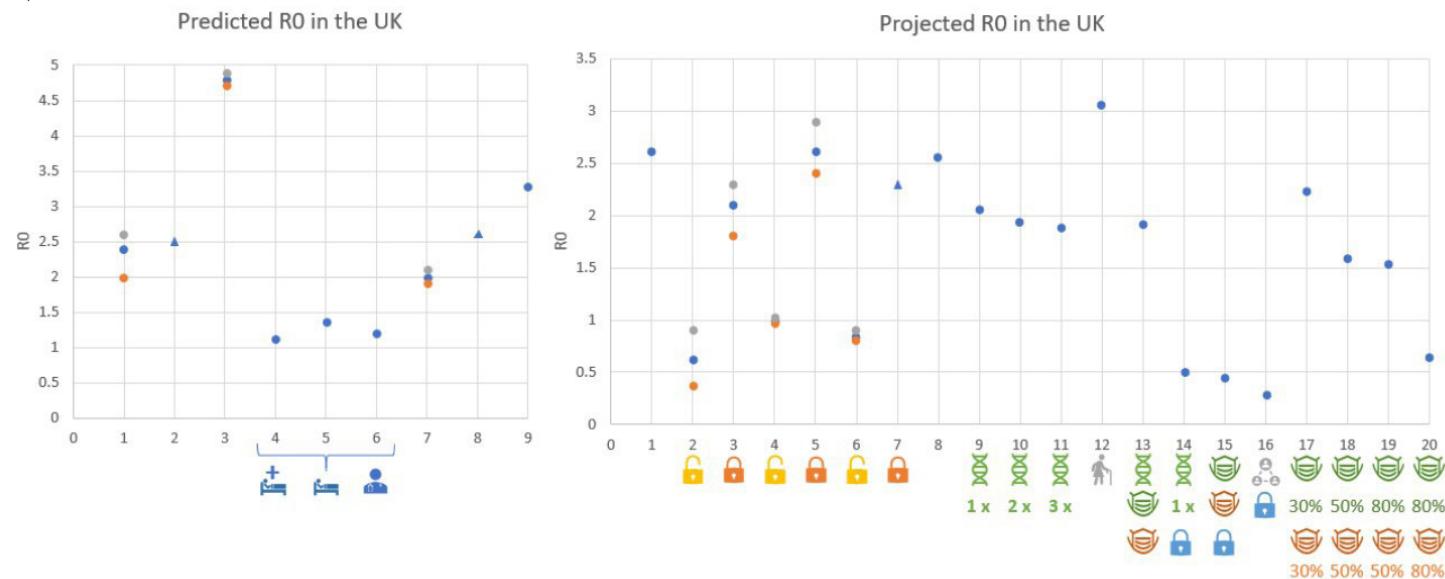
A)

Search provider	Papers generated
SCORPUS	60
PubMed	341
Reference Search	79
Total	480

B)

Continent	Papers
Africa	5
Asia	108
North/South America	11
Europe	25
UK	30
Oceania	3
Total	182

C)



Appendix 4

Members of the Royal Society SET-C and members of the SET-C sub-group.

Members of SET-C Steering Committee

Professor Peter Bruce FRS (Chair), The Royal Society

Professor Sir Roy Anderson FMedSci FRS,
Imperial College London

Professor Charles Bangham FMedSci FRS,
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Professor Richard Catlow FRS, The Royal Society

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DISCLAIMER

This paper has drawn on the most recent evidence up to 24 August 2020 and has been subject to formal peer-review. Further evidence on this topic is constantly published and the Royal Society may return to this topic in the future. This independent overview of the science has been provided in good faith by subject experts and the Royal Society and paper authors accept no legal liability for decisions made based on this evidence.

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