# Inferring the reproduction number using the renewal equation in heterogeneous epidemics

**Abstract**

Real-time estimation of the reproduction number has become the focus of modelling groups around the world as the SARS-CoV-2 pandemic unfolds. One of the most widely adopted means of inference of the reproduction number is via the renewal equation, which uses the incidence of infection and the generation time distribution. In this paper, we derive a multi-type equivalent to the renewal equation to derive an adjusted reproduction number which accounts for heterogeneity in transmissibility including through asymptomatic transmission, symptomatic isolation, and vaccination. We demonstrate how use of the renewal equation that misses these heterogeneities can result in biased estimates of the reproduction number. While the bias is small with symptomatic isolation, it can be much larger with asymptomatic transmission or transmission from vaccinated individuals if these groups exhibit substantially different generation time distributions to unvaccinated symptomatic transmitters, whose generation time distribution is often well defined. The bias in estimate becomes larger with greater population size or transmissibility of the poorly characterised group, as well as if the population exhibits disassortative mixing. We apply our methodology to Ebola in West Africa in 2014 and the SARS-CoV-2 in the UK in 2020-21.

**Introduction**

The effective reproduction number, R, defined as the average number of secondary infections generated by each primary case, is of fundamental importance in infectious disease epidemiology. When R is above 1, infection prevalence will increase, whereas when R is below 1, it will decline. As such, interventions for epidemic control generally aim to reduce the R to below unity.

Estimation of R has taken on particular significance over the past year in light of the global COVID-19 pandemic, which is so far responsible for over 200 million cases, and 4.5 million deaths worldwide (1). Given the importance of R in elucidating the extent of control measures required to suppress the epidemic, real-time estimation of R has been the focus of disease modelling groups and government health departments worldwide (2).

The effective reproduction number principally depends on the underlying infectiousness of the pathogen in a totally susceptible population and the level of immunity in the population. The underlying infectiousness is often represented by the basic reproduction number, R0, defined as the average number of secondary infections arising from a primary case in a large totally susceptible population (one with no existing immunity). R may be further modified by changes in the number, frequency, and closeness of contacts in a population, hygiene practices, seasonal variation, population demographics and pathogen evolution. R is generally estimated from trends in infections, cases, hospitalizations or deaths over time (3–6).

There are two distinct reproduction numbers than can be derived from data on infection incidence. The instantaneous reproduction number, henceforth denoted *R(t)*, represents the average number of individuals someone infected at time *t* would infect if conditions remained unchanged. Conversely, the case reproduction number, *Rc(t)*, represents the average number of people an individual infected at time *t* actuallyinfects, which will depend on changes in policy or behaviour over the period of that cohort’s infection, and can thus only be estimated in retrospect (7,8). The work of this paper focusses on the former, which is better suited to track changes in transmissibility in real-time, and which will reduce immediately following the start of a successful intervention, unlike *Rc(t)* which will change gradually and is only possible to calculate with hindsight (7).

A simple and widely used approach to estimate the effective reproduction number is via the renewal equation, which uses as inputs the generation time distribution, *ω(τ)* (the distribution of times, *τ*, between infection in a case and infection of their infector) and the time-series of infection incidence (7). In this method, all infected individuals are assumed to have the same transmissibility profile in terms of both the timing of onward infection (the generation time distribution), and the extent of onward infection (the reproduction number).

However, variation in transmissibility may result from biological and behavioural differences between individuals. An example of a biological difference between individuals is symptomatic and asymptomatic infection. Similarly, a subset of symptomatic individuals may change their behaviour to limit their social contacts (self-isolation), as is currently mandated in UK law for both confirmed SARS-CoV-2 cases and their immediate household. Different transmissibility profiles may also arise due to deployment of novel pharmaceuticals (e.g. antiretroviral therapy) or through vaccination priming the immune response in a subset of individuals.

The generation time distribution is hard to estimate directly, given that it is often difficult to identify the exact timing of an infection event, let alone the timing of two sequential infection events required for inference of the generation time distribution. One of two approaches is typically used:

1. Fitting a generation time distribution to infector-infectee relationships where the time of infection of the index case and infection of the secondary case are unambiguously known
2. Estimating via the serial interval distribution (the time between symptom onset in a case and symptom onset of their infector), which is much easier to measure. It is worth noting that the observed distribution of serial intervals can be affected by both censorship (given long serial intervals cannot be observed) (9) and by the epidemic dynamics at the time of measurement (given in an exponentially growing outbreak, there will be many more recent infecteds) (10). The generation time distribution is then calculated from the serial interval distribution in one of two ways:
   1. Assuming the generation time distribution is equivalent to the serial interval distribution. While the distributions have the same mean, they will have a different variance given the dependence of symptom onset on the incubation period (10). Additionally, serial intervals can be negative, while generation times are always positive (10). Recent literature has suggested using forward-looking serial intervals (in which time is measured forwards from symptom onset in an infector) gives the same estimate of R as with the generation time distribution (11).
   2. By convolution with the incubation period distribution (the time from infection to onset of symptoms). The optimal approach will depend upon the joint relationship of the infectious distribution and the incubation period (12).

In a novel outbreak, initial estimates of the generation time distribution are typically based on an analysis of the “first few hundred cases” (FFHC) (13–17), with little emphasis on characterizing heterogeneities among infected individuals.

In this paper, we derive a multi-type equivalent of the renewal equation which accounts for heterogeneity in transmissibility profiles including variation in case isolation behaviour, symptomatic/asymptomatic infection, and heterogeneity introduced owing to vaccine roll-out. We refer to the R derived through the multi-type approach that accounts for these sources of heterogeneity as the *adjusted* R. We then explore how much the adjusted R differs from an *unadjusted* R derived from a single-type branching process based on the generation time distribution of the *reference* group (the group of unvaccinated, non-isolating, symptomatic individuals, from which the generation time distribution is calculated).

We consider two applications: to Ebola Virus Disease in Guinea in 2014-15, and to SARS-CoV-2 in the UK between March 2020 and January 2021, to illustrate the potential impact on R estimates of neglecting heterogeneities due to case isolation and asymptomatic transmission.

**Methods**

*Single-type renewal equation*

For a single-type epidemic, the renewal equation gives the relationship between the expected incidence, or number of new infected individuals on time *t*, , with the known historic number of cases a time τ ago, , the instantaneous reproduction number at time *t,* , and the generation time distribution, as function of time *τ* since infection, *:* (18). The renewal equation assumes deterministic growth of infection incidence, which will be locally exponential. This assumes that the generation time distribution remains constant in the period up from time *t - τmax* to time *t,* where τmax is the maximum time after infection at which a case can onwardly infect.

Assuming exponential growth/decay for the incidence gives the relationship between the reproduction number and the growth rate *r* when the growth rate is a constant (Equation 1) (19,20).

Equation 1

This enables us to generate the relationship between the reproduction number and growth rate for various generation time distributions in a homogeneous epidemic. In the work which follows in this paper we use the gamma distribution, both because it is frequently used in fitting generation time distributions, and for analytical tractability. For a pathogen where the generation time distribution is well described by a gamma distribution with shape and rate the analytic equation for the reproduction number in terms of the epidemic growth rate is given by Equation 2.

Equation 2

*Multitype renewal equation*

Moving to a paradigm where there are *n* groups with generation time distribution for a case in group *i* given by , we consider the next generation matrix, a *n* x *n* matrix where represents the average number of secondary cases in group *i* resulting from one index case in group *j*. The values of in turn will depend on the overall susceptibility and infectiousness of each group, and the extent of assortativity between groups.

In this case the renewal equation becomes multi-dimensional, and takes the form given in Equation 3. As above, this assumes that the generation time distribution for each group remains constant in the period up from time *t - τmax* to time *t*.

Equation 3

We can assume an exponential solution as for the single-type case, with a vectorized *k*, with elements *ki*corresponding to the steady-state proportion of infections occurring in group *i* (Equation 4).

Equation 4

Substituting Equation 4 into Equation 3 yields an eigenvalue equation (Equation 5).

Equation 5

To infer the overall reproduction number *R* we factorise the matrix into the product of the scalar reproduction number *R* and the normalized next generation matrix *M*, whose elements  give the relative risk posed to a member of group *i* by an infected member of group *j*. Rearranging shows that for a growth rate *r*, the corresponding *R* will be the reciprocal of the dominant eigenvalue of the elementwise product of the matrix *M* and the matrix of Laplace transforms of the generation time distributions (Equation 6).

Equation 6

We assume that the matrix *M* can be simply expressed using (i) the relative infectiousness of each group, *ηi*; (ii) the relative susceptibility of each group, *ξi*, and (iii) the assortativity between the groups, given by a matrix *A* whose elements *Aij* give the proportion of group *j*’s contacts which are made with individuals in group *i* (Equation 7). The relative infectiousness and susceptibility of each group are denoted relative to the most infectious and most susceptible group respectively. We can consider *η* to be determined by biological factors and fixed through the course of an outbreak.

Equation 7

The deterministic formulation above means we only consider the central estimates. In reality, there is stochastic variation that can be accounted for using a Poisson or negative binomial offspring distribution. In the applications we present in this paper we have used EpiEstim to capture this confidence interval, which uses a Poisson distributed offspring distribution (see below).

*Mathematical treatment of heterogeneity*

In what follows, we will sometimes refer to heterogeneity in the generation time distribution, and sometimes refer to heterogeneity in the transmissibility profile.

We use the same formalism as outlined by Fraser in (7). In this formalism, the transmissibility is denoted β(t, τ), and is a function of time since infection τ and calendar time t. The transmissibility gives the instantaneous rate of onward infections generated by a primary case over the course of an infection. As in (7), we assume β(t, τ) can be decomposed into two components: the instantaneous reproduction number which depends only on calendar time, R(t), and the generation time distribution which depends only on time since infection ω(τ). Transmissibility will include both the viral shedding rate and the extent of contacts an infected person has over the course of their infection.

We consider three scenarios relevant to many infectious diseases, but in particular to SARS-Cov-2: heterogeneity due to i) the isolation of symptomatic cases on symptom onset; ii) the presence of asymptomatic carriers; and iii) differential transmission potential of vaccinated individuals, which will be increasingly important as vaccination is rolled-out. In all cases, we consider epidemic growth rates of -0.3, -0.15, 0, 0.15, 0.3 day-1 which correspond to halving times of 2.3 days and 4.6 days, steady state and doubling times of 4.6 days and 2.3 days respectively. We consider reference group sizes corresponding to 20%, 50% and 80% of the total population. In (i) and (ii) we assume homogeneous mixing between groups, while in (iii) we allow for assortativity in mixing. In all scenarios, we assume the incidence of infection is known accurately, with no reporting delays in the days prior, which would enable calculation of the epidemic growth rate. We also assume the generation time distribution is well charachterised for the reference group.

For isolating vs non-isolating cases we assume isolation reduces and individual’s contact rate to zero such that isolation is modelled as truncation of the transmissibility profile of the non-isolating group. If the non-isolating population has a transmissibility distribution described by , and isolate after a proportion q of their onward infectiousness has passed (at time *s* into their infection) the transmissibility function of the non-isolating population is given by Equation 8.

Equation 8

For symptomatic vs asymptomatic transmission, we explore the impact of asymptomatic transmitters having half (Equation 9A) and double (Equation 9B) the generation time of the reference group. We also explore a continuum of relative infectiousness of asymptomatics from 0 (where only symptomatics are infectious) to ∞ (where only asymptomatics are infectious).

Equation 9

For vaccinated vs non-vaccinated cases, we explore simultaneous decreases in both the generation time and peak transmissibility to v% of the reference case, such that the transmissibility profile of a vaccinated person is given by Equation 10.

Equation 10

For vaccinated vs non vaccinated cases, we also explore the impact on estimated R of assortative mixing – varied from fully disassortative mixing in which all contacts of the smaller group are with individuals in the larger group, to fully assortative mixing, in which all contacts are between individuals in the same group. We assume vaccination reduces susceptibility to infection by 70%.

We parameterize the assortativity matrix A in a similar way to (21), which described HIV transmission by considering mixing within and between sexual activity groups via the contact rates of members from each group c1 and c2; the population size in each group, *p1* and *p2*, and an assortativity parameter *δ*. We do not explore the effect of heterogeneity in contact rate by individuals in each group; making the simplifying assumption that contact rates are uniform independent of group, resulting in the parameterization given in Equation 8. This parameterization requires *p1* to be the smaller group such that all matrix elements are less than or equal to 1.

Equation 11

For plotting, we vary *δ* in a two-part linear manner, from 0 (disassortative) to *p1* (homogeneous) from the left of the x-axis to the middle, and from *p1* to 1 (assortative) from the middle of the x-axis to the right-hand side. This standardizes homogeneous mixing at the centre of the x-axis - where the proportion of group i’s interaction with j is equal to the proportion of the population that is in group j.

*Equivalent single type formulation*

The single-type formalism of the reproduction number provides a more straightforward means of inferring the reproduction number. Additionally, existing software packages used for epidemic analysis will typically only work with single-type renewal processes, so there is a benefit to expressing the multi-type renewal processes as an equivalent single-type.

Equation 3 and Equation 4 can be re-written as Equation 9.

Equation 12

The total number of newly infected individuals is then:

Equation 13

Where is given by Equation 11, and C is chosen as a normalising constant such that .

Equation 14

Equation 13 shows that the multi-type renewal equation can be written as single-type renewal equation with a weighted mean generation time distribution. The weighting is given by the overall relative infectiousness of the group j, and the jth element of the eigenvector, which corresponds to the equilibrium proportion of infections that occur in group j. It is worth noting that in real-time epidemics the true equilibrium proportion of infections occurring in each group may not be known exactly owing to importation and stochasticity. This is not a problem in what follows as we derive the equilibrium proportion of infections directly from the eigenvector of the mixing matrix shown in Equation 12. (Equation 14). Given this *weighted single-type* approach derived in Equation 13 will return the same *adjusted* R as the *multi-type* approach derived in Equation 6.

*Use in EpiEstim for application to COVID-19 in the UK and Ebola Virus Disease in Guinea*

Equation 1 and Equation 6 describe the relationship between the instantaneous reproduction number, the growth rate, and the generation time distribution of different groups. In practice, the growth rate is not directly observed, but can be estimated from the incidence time-series. This leads to uncertainty in the growth rate estimates, and in turn the corresponding reproduction number estimates, which are not represented in the equations above.

The EpiEstim package for R software implements estimation of the instantaneous reproduction number, based on an incidence time series and a discrete generation time distribution. We used EpiEstim given its frequent use in real-time epidemic modelling, and it being the preferred means of R estimation in Gostic *et al* (8). EpiEstim uses a single-type renewal equation to estimate the posterior distribution of the instantaneous reproduction number, capturing uncertainty in the estimates. We therefore use EpiEstim to compare the unadjusted R estimated using an unadjusted single-type renewal equation, with the adjusted R based on appropriately weighted single-type generation time distribution (equivalent to the multi-type approach ). In all applications R values were estimated over sliding weekly windows.

We estimate the instantaneous reproduction number for Ebola Virus Disease (EVD) case data from Guinea between March 2014 and July 2016, with data taken from (22). The generation time distribution is assumed to be Gamma distributed with mean 15.3 days and standard deviation 9.3 days following (23). This is assumed to be reflective of a non-isolating cohort. We assume that isolation occurs at the point of hospitalization at 14.9 days after infection (56.5% of the way into a non-isolated transmissibility profile), based on the sum of the mean incubation period and the mean delay from symptoms to hospitalization given in (24). While the delay to hospitalisation is in reality a distribution, we use the mean as a single time-point delay to illustrate the impact of accounting for isolation in a simple way. We assume that 34% of infected individuals are hospitalized (Unwin *et al, unpublished*), and that individuals who seek hospitalization and individuals who do not seek hospitalization mix homogeneously.

We estimate the instantaneous reproduction number of SARS-CoV-2 using timeseries of COVID-19 deaths in the UK from March 2020 to January 2021. We use incidence of deaths rather than cases because ascertainment of deaths is significantly better than that of cases, especially during the early months of the epidemic when testing capacity was highly constrained. As such, we are assuming that deaths remained a constant fraction of cases over time. This increases our uncertainty in R compared to having accurate cases data. Additionally, due to a delay between infection and death, the resulting estimates of R will be lagged and smoothed – the average delay from infection to symptom onset is estimated to be around 5.5 days in the UK (25), while estimates of the delay from symptom onset to death range from around 13 days (26) to 18 days (27). Other papers have demonstrated inference of R accounting for lagged metrics, for example (28). Daily UK COVID-19 deaths were taken from the Government’s coronavirus data repository, at (29). We assumed a generation time distribution in the absence of isolation gamma distributed with mean 5.7 days and standard deviation 3.09 days as in (30). We consider two scenarios: an optimistic scenario in which 75% of symptomatic individuals (47% of all infected) isolate 30% of the way into their infection, and a pessimistic scenario in which 25% of symptomatic individuals (16% of all infected) isolate 70% of the way into their infection.

**Results**

*Symptomatic isolation and non-isolation*

Isolation of symptomatic cases on onset will necessarily reduce the transmissibility profile for those who isolate (for example, Figure 1A-C – corresponding to isolation 25%, 50% and 75% into the generation time distribution, compared to Figure 1D – corresponding to no isolation). In a growing epidemic, isolation will mean the adjusted R (using the multi-type approach) is lower than the unadjusted R (using the single-type approach) and vice-verse for shrinking epidemics (Figure 1E). This error is higher with higher growth/reduction rates, as well as with higher isolating populations (Figure 1E). The error is zero at the extremes: if isolation occurs immediately upon infection; or if isolation occurs following all infection (Figure 1E). This is because if isolation occurs immediately, isolators do not contribute to the infectious pool, so the weighting of the non-isolating group in Equation 11 is zero. Likewise, if isolation occurs following the infectivity period, it is equivalent to no isolation occurring.

Overall, the adjusted R with the reference generation time distribution explored is a maximum of 1.4x higher than the unadjusted R when the epidemic growth rate is -0.3 day-1, and isolation occurs among 80% of the population 39% of the way into the transmissibility profile. The adjusted R is 0.75x lower than the unadjusted R when the epidemic growth rate is 0.3 day-1, and isolation occurs among 80% of the population 23% of the way into the transmissibility profile (Figure 1E).

One can understand why the error remains relatively small across the range by considering the one-dimensional approach presented in Equation 11. When constructing the weighted generation time distribution, early isolation will lead to a low weighting of the isolating group in the overall generation time distribution; on the other hand, later isolation will result in little difference in the generation time distributions. This inherently constrains the impact isolation has on the derived R.

Figure 1: (A-C) Infectivity curves for individuals isolating 25%, 50%, 75% through their infection respectively. (D) Infectivity curve for non-isolating individuals. (E) The relative difference in R inferred by considering a multi-type branching process as compared to an unadjusted single-type branching process, accounting for isolation of a subset of cases by (i) the amount of infectivity that has passed at the time of isolation (x-axis), (ii) the size of the isolating population (linetype) and (iii) the growth rate of the epidemic (colour). All graphs correspond to a reference generation time distribution which is gamma distributed with a mean of 5.71 days and a standard deviation of 3.09 days.

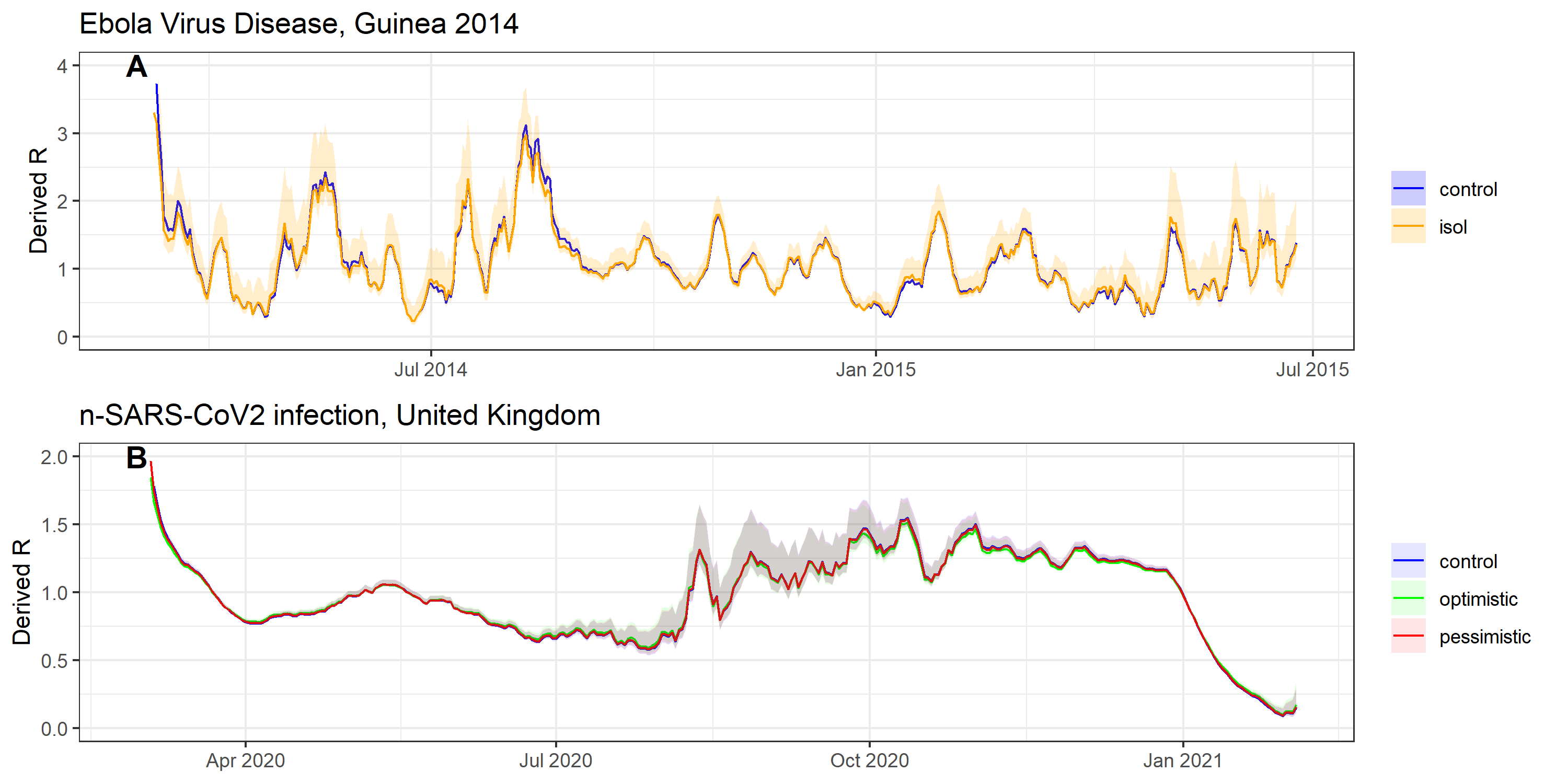
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Case isolation heterogeneity was considered in the context of the Ebola Virus Disease outbreak in Guinea between March 2014 and July 2015 in Figure 2A, and for SARS-CoV-2 between March 2020 and February 2021 in Figure 2B. Both applications confirm that case isolation has limited impact on the overall derived R.

The reason for the limited impact can be also be seen by considering the equivalent single-type renewal process airing from Equation 10 and Equation 11. The isolating group have a lower infectiousness than the non-isolating group which means their contribution to the weighted generation time distribution is often more muted. Additionally, the resulting weighted generation time distribution undergoes a Laplace transform (Equation 10) which reduces the relative contribution of late transmission in the inference of R – and it is only the late-stage transmission that case isolation has an impact on.

Figure 2: (A) Time varying R values for the Ebola Virus Disease outbreak from March 2014 to July 2015 in Guinea from EpiEstim, derived using an unadjusted generation time distribution (black), and a weighted generation time distribution (equivalent to a multi-type branching process) accounting for case isolation (orange). Credible intervals are shown for the weighted generation time distribution, demonstrating that consideration of case isolation makes little difference to the overall estimated R. The reference generation time distribution is assumed to be gamma distribution with a mean of 15.3 days and a standard deviation of 9.3 days. We assume 36% of cases isolate with isolation occurring 55% of the way into the infectious distribution. (B) Time varying R values for the SARS-CoV-2 outbreak from March 2020 to February 2021 in the United Kingdom, based on optimistic and pessimistic assumptions around isolation. In both cases we assume 63% of infections are symptomatic and the reference generation time distribution (corresponding to non-isolating symptomatic individuals) is gamma distributed with a mean of 5.71 days and a standard deviation of 3.10 days. Optimistic assumptions are that isolation occurs among 75% of symptomatic infection after 30% of infectivity has passed. Pessimistic assumptions are that isolation occurs in 25% of symptomatic infection after 70% of infectivity has passed. In both cases R estimates are based on sliding weekly windows.



*Symptomatic and asymptomatic transmission*

As discussed previously, for a pathogen with symptomatic and asymptomatic infection courses, the generation time distribution is generally only easily obtainable from symptomatic transmission. We therefore compare unadjusted R estimates from the single-type model (Equation 1) using the generation time distribution of the symptomatic individuals with the R estimates from the multi-type model assuming asymptomatics have a different generation time distribution (Equation 6). We explore this difference as we vary the relative infectiousness of symptomatic and asymptomatic individuals.

If the generation time distribution of asymptomatic carriers is longer than that of symptomatic carriers (Figure 3 - right), the adjusted R derived using a multitype approach will exceed the unadjusted R in a growing epidemic and will be lower than the unadjusted R in a declining epidemic. This trend is reversed for dynamics in which the generation time distribution of asymptomatic carriers is shorter than that of symptomatic carriers (Figure 3 -left). The error in inferred R becomes greater at higher absolute values of growth rate, with higher asymptomatic infection rates, and with higher relative infectiousness of asymptomatic individuals (Figure 3C and Figure 3D).

With the extent of variation explored the adjusted R exceeded the unadjusted R by up to 4x, when the generation time distribution of asymptomatics was twice as long as that of symptomatics, and asymptomatics were responsible for all onward infection (Figure 3D). While this represents a relatively extreme scenario, it may be relevant for pathogens with early onset of symptoms among symptomatic cases but late onset of infectiousness, by which point symptomatic individuals may have reduced their contacts substantially, meaning asymptomatic individuals would be more responsible for onward transmission.

Figure 3: (A-B) Explored generation time distributions for symptomatic and asymptomatic individuals. In (A) the generation time distribution of asymptomatics is half that of symptomatics, whereas in (B) the generation time distribution of symptomatics is half that of asymptomatics. In both cases the symptomatic (reference) generation time distribution has a mean of 5.71 days and a standard deviation of 3.09 days. (C-D) The relative difference in R obtained using a multi-type branching proves vs an unadjusted single-type branching process, accounting for asymptomatic transmission by (i) the relative infectiousness of asymptomatics (x-axis), (ii) the size of the asymptomatic population (linetype) and (iii) the growth rate of the epidemic (colour). (C) corresponds to the generation time distributions given in (A) while (D) corresponds to those given in (B).

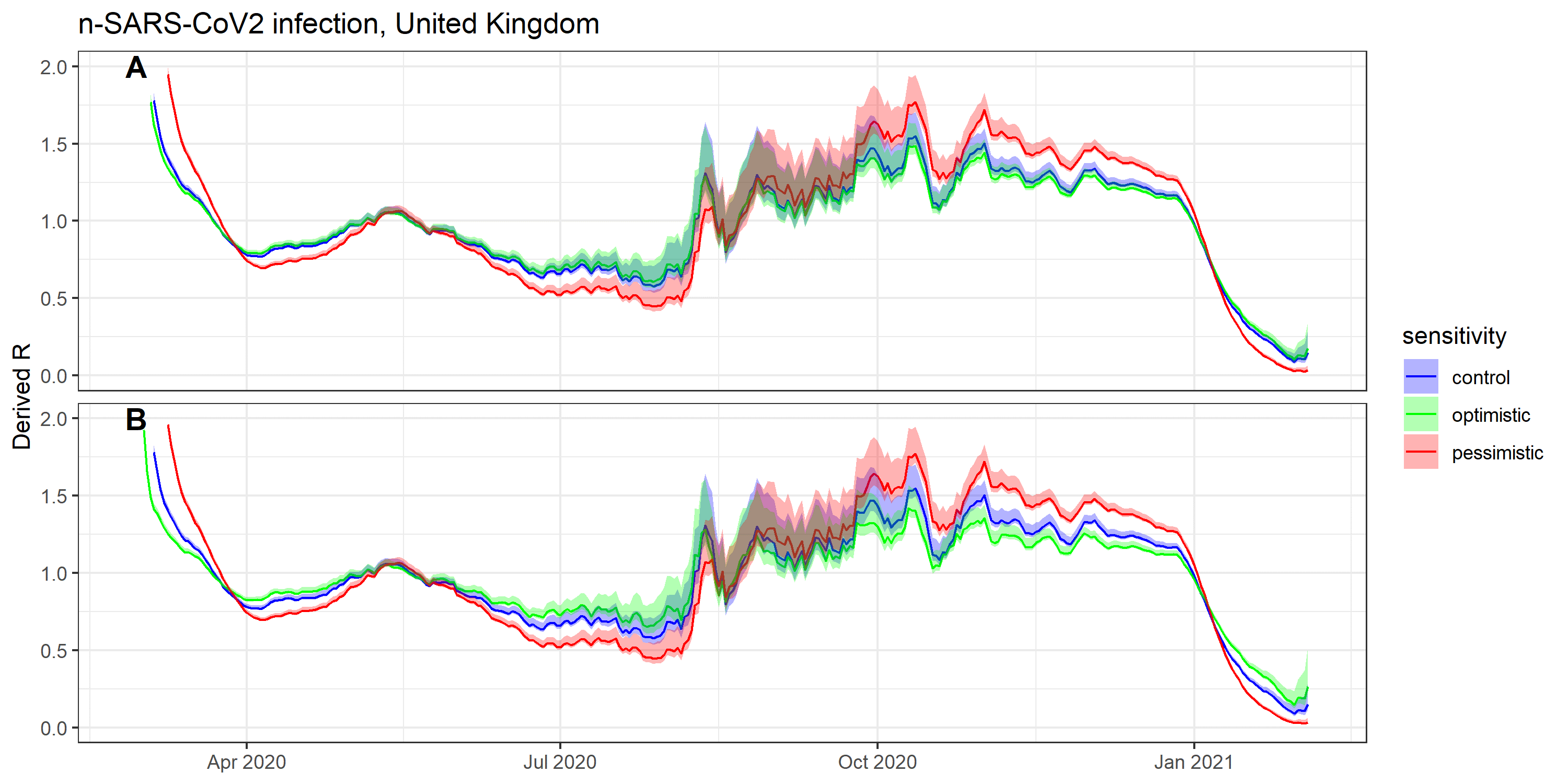
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Potential asymptomatic transmission of SARS-CoV-2 in the UK is considered in Figure 4A. A different asymptomatic generation time distribution can result in a substantial difference in the inferred R. We explore an optimistic case, in which asymptomatic transmitters are half as infectious and have half the generation time distribution as symptomatic counterparts, and a pessimistic case, in which asymptomatic transmitters have a prolonged generation time distribution and are twice as infectious as their symptomatic counterparts.

In Figure 4B we consider a three-type branching process consisting of asymptomatic carriers, symptomatic carriers who isolate and symptomatic carriers who do not isolate.

Figure 4: Derived value of R based on UK deaths using a multi-type and unadjusted branching process for (A) asymptomatic transmission, (B) asymptomatic transmission and symptomatic isolation together. We assume homogeneous mixing for both cases. Optimistic assumptions correspond to asymptomatics with half the generation time distribution of symptomatics and half the infectivity. Pessimistic assumptions correspond to asymptomatics having twice the generation time distribution of symptomatics and twice the infectivity. For case isolation which is included in (B) the optimistic and pessimistic assumptions given in Figure 2 apply. Optimistic assumptions are that isolation occurs among 75% of symptomatic infection after 30% of infectivity has passed. Pessimistic assumptions are that isolation occurs in 25% of symptomatic infection after 70% of infectivity has passed. We assume 63% of infections are symptomatic and the reference generation time distribution (corresponding to non-isolating symptomatic individuals) is gamma distributed with a mean of 5.71 days and a standard deviation of 3.10 days. In both cases R estimates are based on sliding weekly windows.



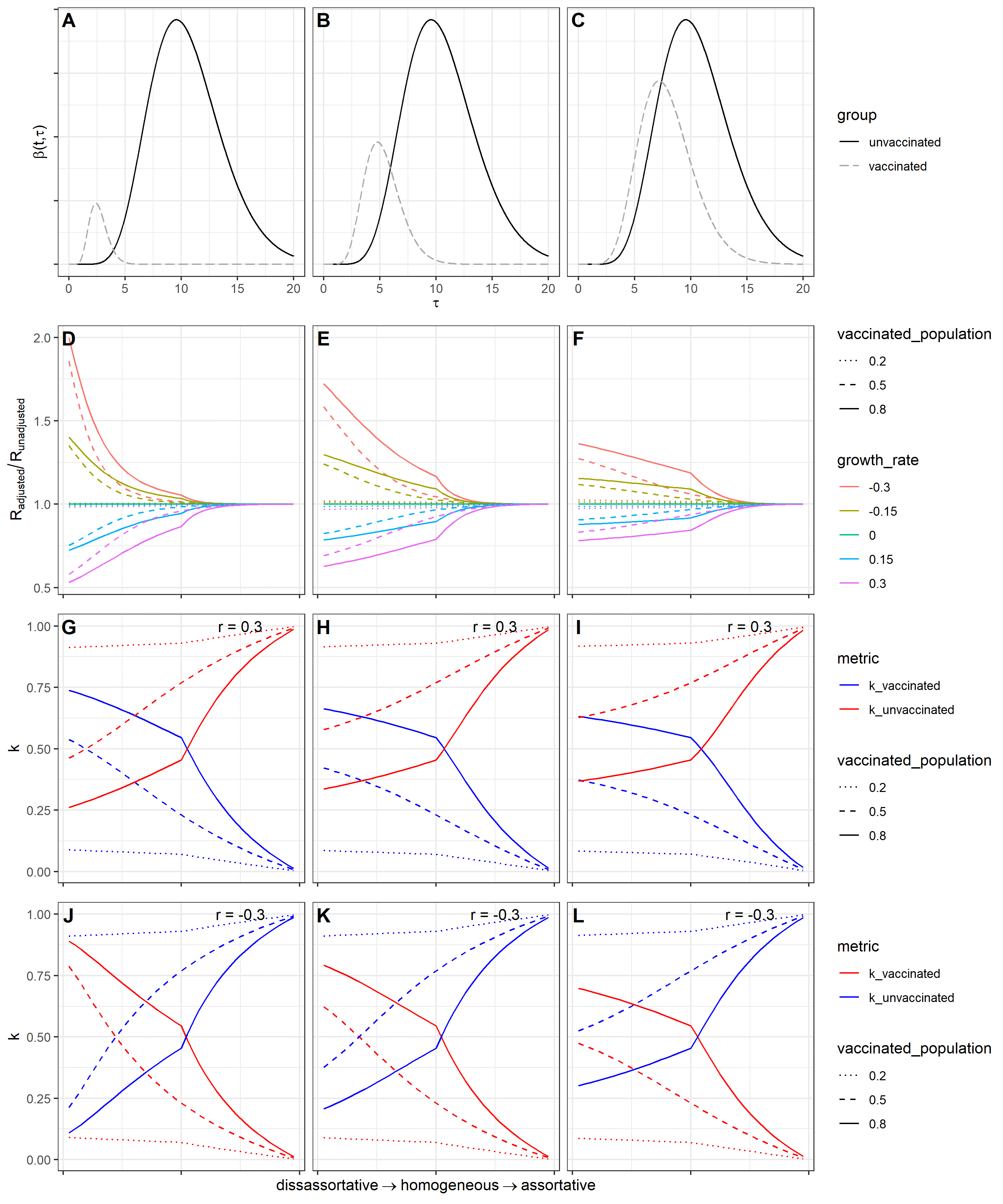
*Vaccinated and unvaccinated groups with assortative and disassortative mixing*

Early studies demonstrate vaccinated individuals infected with SARS-CoV-2 have a lower viral-load than unvaccinated individuals (31), with a noticeable difference from around 12 days post first dose of vaccine (32). Reduction in peak viral load and viral clearance times have also been demonstrated with oral and inactivated poliovirus vaccine (33,34). Additionally, data gathered from routine testing of healthcare workers has shown vaccination reduces individuals’ susceptibility to SARS-CoV-2 infection (35). As such, in what follows, we explore scenarios in which vaccination reduces susceptibility to infection, and results in a simultaneous and equal reduction in both the generation time distribution and the peak transmissibility among the subset of vaccinated individuals who still get infected.

In previous examples we have considered homogeneous mixing between groups. However, vaccination is a clear case in which we may also have to consider the assortativity of mixing. This could be because of vaccination policy such as targeting of age cohorts (36,37) or because of differential vaccine uptake (38,39).

We assume vaccination reduces individuals’ susceptibility to infection by 70%. We trial three different reduction factors in the y=x direction for the infectivity curves of vaccinated individuals: 0.25, 0.5, and 0.75, corresponding to transmission reductions of 93.75%, 75%, and 44% from the vaccinated group (Figure 5A-C). The difference in the unadjusted and adjusted R is highest for disassortative mixing, given with disassortative mixing a significant share of transmission passes through the vaccinated group, whose generation time distribution is not included in the unweighted single-type approach. The difference in inferred R reduces to zero in the limit of totally assortative mixing, as this represents two isolated outbreaks, for which the epidemic growth rate is totally driven by the unvaccinated group (Figure 5D-F). The difference in inferred R reduces especially quickly as the contribution of the unvaccinated group (for whom the generation time distribution is well characterized) increases. This can be seen by considering the relative sizes of the elements of the eigenvector in Equation 5 corresponding to the proportion of infections that are in the vaccinated and unvaccinated groups (shown in Figure 5G-I for a growing epidemic, and in Figure 5J-L for a shrinking epidemic). The greater the k value corresponding to the unvaccinated group, the closer the adjusted R is to the unadjusted R.

Figure 5: (A-C) Explored scenarios for vaccine impact on the infectivity distribution; (D-F) The relative difference in R obtained using a multi-type branching proves vs an unadjusted single-type branching process with unvaccinated reference group, accounting for vaccinated individuals by (i) the extent of assortativity (x-axis), (ii) the size of the asymptomatic group (linetype) and (iii) the growth rate of the epidemic (colour). We assume that vaccination reduces susceptibility by 70% in all explored scenarios; (G-I) elements of the eigenvector corresponding to the vaccinated and unvaccinated groups in a growing epidemic with r=0.3, normalised such that their sum is 1; (J-L) elements of the eigenvector corresponding to the vaccinated and unvaccinated groups in a declining epidemic with r=-0.3, normalised such that their sum is 1. For graphs D to L, the x-axis is a two-part discontinuous linear scale from disassortative to homogeneous and from homogeneous to assortative.



**Discussion**

In this paper we have shown how and when heterogeneity in the generation time distribution can distort estimates of the reproduction number. While the impact on the inferred reproduction number is limited in the case of symptomatic case isolation in the parameter range explored here, it can be considerable if asymptomatic or vaccinated individuals have particularly different generation time distributions from unvaccinated, symptomatic individuals (for whom the generation time distribution will be best characterized). The difference in inferred R will be smaller for lower growth rates; where the poorly characterized groups represent a small part of the population; or where there is highly assortative mixing between groups.

In using the renewal equation, we assumed transmissibility could be separated into a reproduction number, depending only on calendar time *t*, and a generation time distribution depending only on time since infection, *τ*. However, behaviour is likely to change as an epidemic progresses, for instance through a reduction in out-of-household contacts, which may cause the generation time distribution to change independently of case-isolation.

For the multi-group case, we assumed that relative infectiousness and susceptibility between groups remained constant through time. This too is a simplifying assumption: interventions such as the adoption of face coverings may alter the relative susceptibility and infectiousness between groups, especially if there is a correlation between the group and the adoption of certain behaviours. For example, isolation on symptom onset may well be correlated with compliance to mask-wearing and handwashing.

Multiple pathogens have been demonstrated to have both symptomatic and asymptomatic clinical courses, including important epidemic viruses SARS-CoV-2 (40), Influenza (41), Ebola Virus Disease (42) and Middle East Respiratory Syndrome (MERS) (43). Previous work has shown that a difference in the generation time distribution of asymptomatic vs symptomatic carriers of COVID can lead to biased estimates of the effective reproduction number (44).

The transmissibility profile of an individual depends principally on the extent and duration of viral shedding, and their effective contact rate. Symptom presentation may impact both variables.

Viral shedding will itself depend on individual viral load, and the efficiency and duration of viral expulsion. Viral load studies for influenza infection have shown that asymptomatic and paucisymptomatic cases had 1-2 log10 fewer copies of viral RNA than symptomatic cases, and shorter shedding times (45). Similarly, studies on MERS found the duration of PCR-positivity increased with disease severity (46). Symptoms themselves also increase viral expulsion: a cough can produce an estimated 3,000 droplets, and a sneeze an estimated 40,000 (47); both far more efficient shedding processes than breathing or talking (48).

There have been varying conclusions from studies on the difference in viral load between symptomatic and asymptomatic infections in SARS-CoV-2 infection. Where some studies have found viral load to be similar between symptomatic and asymptomatic SARS-CoV-2 patients (49,50), others have found statistically significant differences in viral load (51,52) and clearance time (53,54), or that shedding duration increases with disease severity (55). A further study in Catalonia has found severity to be positively correlated with viral load, and that higher viral loads led to a greater extent of onward transmission (56). A recent literature review including 79 studies on SARS-CoV-2 concluded that the sum of evidence suggests viral load is similar between symptomatic and asymptomatic individuals, most studies ‘demonstrate faster viral clearance among asymptomatic than those who are symptomatic’ (57). A further systematic review of the reproduction number and secondary attack rate suggested asymptomatic cases were around one seventh as infectious as symptomatic individuals (58).

Conversely, symptomatic SARS-CoV-2 infecteds are likely to reduce their contacts following onset: in the UK, isolation of 10 days is mandated for individuals developing symptoms (and subsequently receiving a positive test for) of COVID-19, and for their households (59).

Vaccination often has an important impact on viral load and/or infectiousness over time, for instance with oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV) (33,34). The importance of understanding the generation time distribution of multiple groups becomes increasingly important with disassortative mixing. This may be particularly important when estimating the reproduction number of sexually transmitted infections in heterosexual contact networks, for instance with HPV, for which vaccination uptake was previously limited to females.

As vaccines against SARS-CoV-2 are rolled out over the coming months, understanding the impact of the vaccine on the susceptibility and transmissibility profile will be increasingly important for accurate inference of R. Given the vaccine schedule is broadly age-prioritised, mixing by vaccination status will be more assortative.

Estimating the contemporaneous generation time distribution should be regarded as similarly important to estimation of the reproduction number itself, which currently occupies the work of academic modelling groups worldwide for SARS-CoV-2. Better capturing the heterogeneities of the generation time distribution will become increasingly important as vaccination is rolled out, as well as with the emergence of new strains which may exhibit different transmissibility profiles. Upcoming SARS-CoV-2 challenge trials in the UK should enable detailed analysis of viral load profiles and symptomatic rates, which can inform updated generation time distributions (59).

While estimation of the generation time distribution is necessarily a time-consuming endeavour, testing systems should integrate additional epidemiological information in tandem with their test and trace protocols. Updated estimates of the serial interval could be obtained by requiring test applicants to supply their symptom onset date, with linkage to traced contacts should they also enter the testing system. For a more direct means to estimate changes in the generation time distribution, or indeed the incubation period, individuals could be asked for dates of contact with known infected in the previous week, and this too linked with contacts who enter the test and trace system.

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