Reconstructing the secondary case distribution of SARS-CoV-2 from heterogeneity in viral load trajectories and social contacts

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Summary

- We used an individual-based model of wild-type SARS-CoV-2 viral load trajectories over the course of infection combined with social contact data to estimate the expected number of secondary cases generated by each infected person (the reproduction number, *R),* and variation in *R*, *k*, for varying levels of contact restriction over the course of the pandemic in the UK.
- We also investigated the effect of varying levels of self-isolation upon symptom onset, as well as the effect of regular lateral-flow testing.
- Using this method we estimate that in the absence of testing, symptomatic self-isolation, or any contact restrictions (i.e., contact rates as observed prior to the pandemic), R_0 would be 2.76 (95% CI 2.10 - 3.68) for wild-type SARS-CoV-2, with k_0 = 0.57 (0.42 - 0.81) (lower values of *k* indicating greater variation in numbers of secondary cases).
- When contact rates were reduced as a result of national control measures during the third national lockdown (January/February 2021), we estimated R_c (*R* in the presence of contact reducing interventions) was 0.58 (0.42 - 1.18) and k_c was 0.55 (0.17 - 1.11), assuming 75% of individuals fully self-isolated upon developing symptoms. During a period of relaxed restrictions (August/September 2020) R_c was 1.10 (0.72 - 1.94) and k_c was 0.37 (0.18 - 0.58).
- Restrictions aimed at reducing the number of contacts effectively reduce the number of secondary cases. Encouraging and facilitating a high proportion of cases to self-isolate upon symptom onset may offset increases in contact rates. Regular lateral-flow testing may reduce R_c by identifying highly infectious individuals who may go on to cause superspreading events, increasing k_c in the process (Figure 2). The marginal effect of regular testing was largest in scenarios where contact rates were higher and/or symptomatic self-isolation was lower.
- This model does not investigate the impact of other *R*-reducing interventions such as vaccination or contact tracing, nor the increased transmissibility of variants of concern.

Main

Transmission of SARS-CoV-2 occurs primarily through superspreading, with around 20% of cases generating 80% of secondary infections[1,2]. A review and meta-regression by Chen et al.[3] indicates that substantial variation in the respiratory viral load of individuals infected with SARS-CoV-2 is a primary driver of overdispersion in secondary case generation. However, a high number of contacts coinciding with the period of high viral load is a necessary prerequisite in generating a large number of secondary infections[4].

We reconstruct the secondary case distribution of SARS-CoV-2 using a model of intra- and inter-host heterogeneity in infectiousness derived from viral load trajectories and infectivity combined with data on reported numbers of daily contacts. The distribution of the number of secondary cases generated by each infectious individual can be characterised in terms of the mean number of secondary cases R_c and an overdispersion parameter k_c that represents the variation in the number of secondary cases (with smaller values of k_c representing greater variation). Even if the mean number of secondary cases R_c is below 1, there may still be a considerable probability of 1 or more secondary cases if k_c is small. We estimate the likely impact of self-isolation upon symptom onset, as well as the utility of regular rapid lateral-flow antigen tests (LFTs) on reducing R_c and the potential for superspreading events (by decreasing variation in numbers of secondary cases, i.e. increasing k_c).

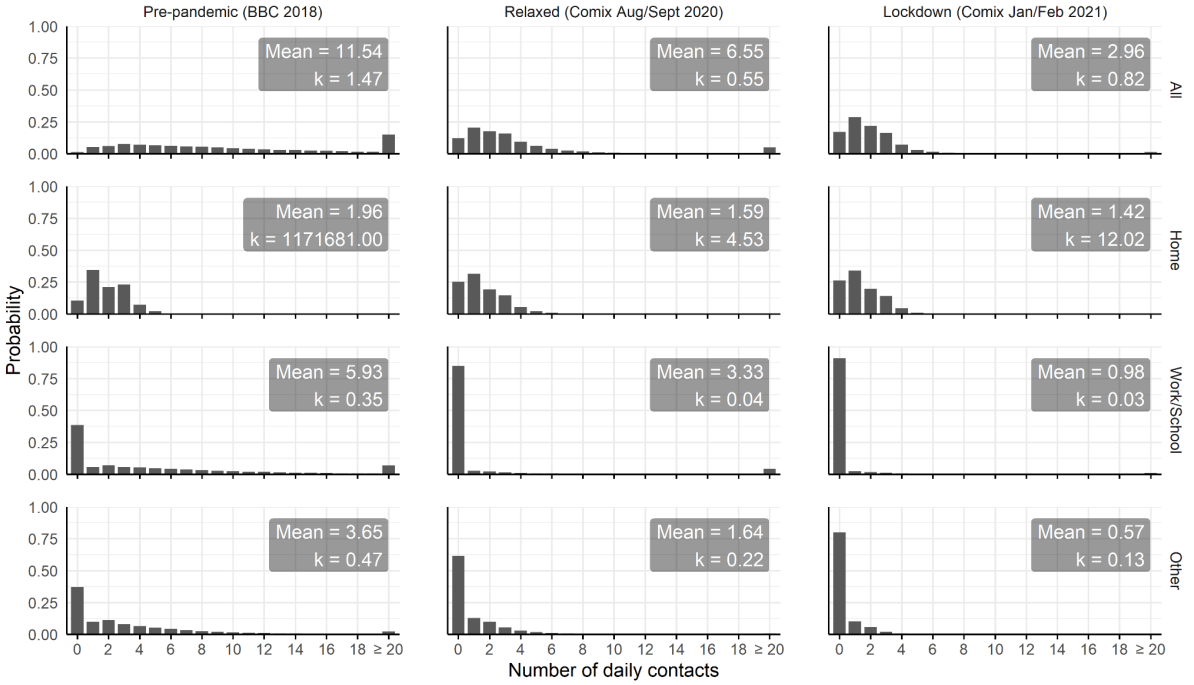

Figure 1: Number of daily contacts before (pre-pandemic, BBC 2018) and during the pandemic in the UK (relaxed restrictions (Comix, Aug/Sept 2020) and during the third national lockdown (Comix, Jan/Feb 2021)).

We find that under pre-pandemic levels of contact (mean 11.5 contacts per day, (Figure 1)), even 100% self-isolation by symptomatic individuals following symptom onset and testing with LFTs every 3 days is insufficient to bring R_c below 1 (R_c = 1.36, 95% CI 1.10-1.72) (Figure 2). Under relaxed restrictions similar to those in August-September 2020 (mean 6.6 contacts per day) a high percentage (>75%) of self-isolation of symptomatic cases is required to bring R_c below 1 when there is no testing with LFTs (Figure 2). However, testing with LFTs every 3 days was sufficient to reduce R_c below 1 without any self-isolation of symptomatic cases (R_c = 0.90, 0.59-1.49) (Figure 2). For levels of contact similar to those during the third lockdown (mean 2.96 contacts per day), R_c was estimated to be below 1 even without any isolation of symptomatic cases or LFT testing. Despite these trends in R_c with different levels of self-isolation and testing, the secondary case distributions show substantial levels of variation (Figure 2), with >40% probability of 1 or more secondary cases for all levels of contact, self-isolation and testing considered apart from those during the third lockdown.

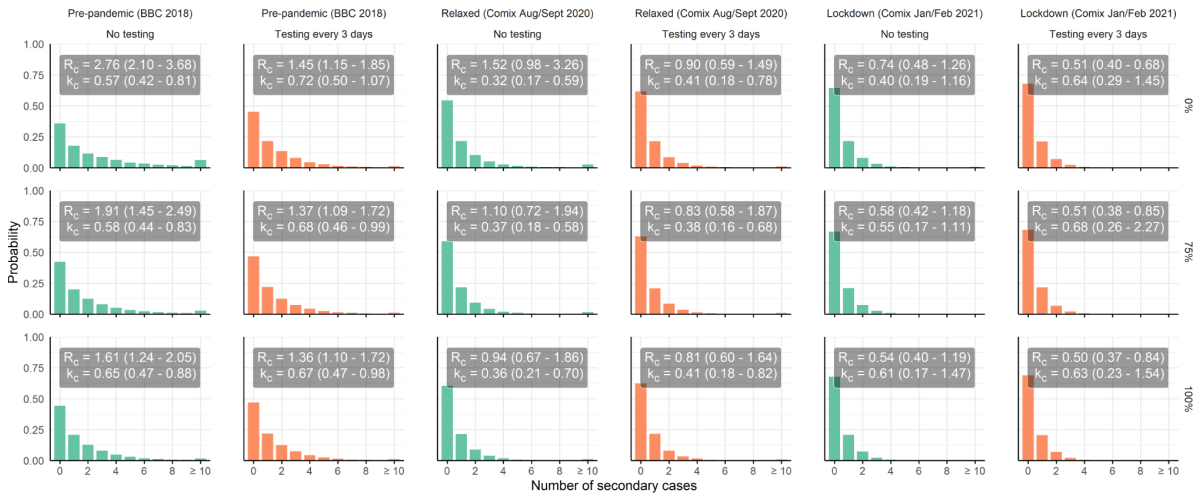

Figure 2: Secondary case distributions and corresponding *R* and *k* given changes in the number of contacts before (pre-pandemic, BBC 2018) and during the pandemic in the UK (relaxed restrictions (Comix, Aug/Sept 2020) and during the third national lockdown (Comix, Jan/Feb 2021), the effect of regular testing with lateral-flow tests every 3 days, and the impact of self-isolation at home after symptom onset (proportion self-isolating: 0% (top row), 75% (middle row) or 100% (bottom row)). Figure S1 also includes the impact of 25% and 50% of symptomatic cases self-isolating after symptom onset.

We find that regular lateral-flow testing may reduce R_c and increase k_c (reduce the mean and variation of numbers of secondary cases) through the detection and rapid isolation of individuals with high viral loads who are most likely to infect a high proportion of their contacts in potential superspreading events. For example, for pre-pandemic contact levels with 0% symptomatic self-isolation, lateral-flow testing every three days reduced the proportion of cases infecting ≥10 of their contacts from 6% to 1% (Figure 2). This indicates lateral-flow tests taken regularly, or prior to entering high contact settings such as entertainment and sporting events, may reduce the potential for large outbreaks.

In this work we do not consider other interventions which may have an impact on R_c or k_c such as vaccination and contact tracing. We also do not consider the impact of variants with increased transmissibility. We assume that the probability of shedding infectious virus is equal to the probability of culturing virus, which in turn is dependent on intra-host viral load kinetics over the course of infection. We assume that self-isolating individuals (either after the onset of symptoms or after a positive lateral-flow test) are unable to self-isolate from their household members as reported by the majority of those surveyed by the ONS in England in April[5]. Further decreases in R_c may be possible if self-isolating individuals isolate themselves from household members. We also have not investigated the degree of engagement or continued adherence with regular lateral-flow testing upon which maximal impact would be contingent.

Methods

- We simulate individual viral load trajectories of index cases over the course of infection as described in previous work[6], then estimate the probability of infectiousness for a given viral load (in Ct) on a given day since exposure by fitting a logistic regression model to the probability of culturing virus at that viral load[7].
- We then calculate the number of secondary cases as the product of the probability of infectiousness and the number of contacts from the BBC Pandemic contact survey[4] and Comix contact surveys[8] in the UK with each index case having:
    - N_1 repeated contacts (home, work and school contacts) with a probability of infection equal to the normalised area under the infectiousness curve (i.e, who may be infected at any time over the course of infection, P_1);
    - and N_2 daily casual contacts (other contacts) with a probability of infection equal to the normalised probability of infectiousness on the day the contact took place P_2.

- We then estimate the corresponding *R* (mean number of secondary cases) and *k* (overdispersion in the number of secondary cases) by fitting a negative binomial distribution to the number of secondary cases, with 95% confidence intervals estimated by bootstrapping 1000 times for each scenario.
- We compare the number of secondary cases expected given contact distributions at three timepoints:
    - pre-pandemic (BBC, 2018);
    - during relaxed restrictions (Comix, Aug/Sept 2020);
    - and during the third national lockdown (Comix, Jan/Feb 2021).
- We also estimate the effect of full symptomatic self-isolation on *R* and *k* by setting the number of work, school and casual contacts to zero after symptom onset, while leaving home contacts unchanged.
- We also estimate the impact of regular testing every 3 days with LFTs (with detection calculated by fitting a logistic regression model to the probability of detection with LFTs given viral load[7], with individuals self-isolating at-home upon their first positive test (i.e, reduce the number of work, school and casual contacts to zero after the date of the positive test while leaving home contacts unchanged).

Supplementary figures

Figure S1: Secondary case distributions and corresponding R_c and k_c given changes in the number of contacts before (pre-pandemic, BBC 2018) and during the pandemic in the UK (relaxed restrictions (Comix, Aug/Sept 2020) and during the third national lockdown (Comix, Feb/Mar 2021)), and the impact of different proportions of individuals self-isolating at home after symptom onset (rows).

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