

RAPID RESEARCH IN COVID-19 PROGRAMME

Modelling the Evolution of SARS-CoV-2 Virulence Under Different Social Isolation Regimes

AIMS

Study how social distancing measures might cause evolution of more (or less) dangerous SARS-CoV-2 variants.

KEY FINDINGS

- Virulence describes how much damage the virus causes to infected people.
- Transmission is how the virus moves from person to person.
- We modelled how social distancing affects viral transmission, and how transmission rate affects evolution of SARS-CoV-2 virulence.
- Our analysis assumed that people are socially isolated in groups, e.g. households, and the virus is allowed to transmit among them.
- In a basic model, the virus evolves greater virulence when allowed to transmit more freely.
- If uninfected hosts rapidly replace infected hosts, then higher virulence evolves even faster.
- Initial findings suggest higher virulence may evolve within isolated but crowded groups (e.g. crowded family groups, care homes, schools). However, social distancing that cuts ties between groups likely favours lower virulence.
- Therefore, the overall direction of viral evolution may depend on the balance of within- versus between-group forces.
- We can extend the work to investigate effects of vaccination and exchange of variants between groups e.g. through travel.

WHAT DID THE STUDY INVOLVE?

The study involved writing mathematical expressions using variables that describe virus transmission, group size, virus effects on people, etc. Then we simulated how virulence changes when we alter realistic 'real-world' values for those variables. We began drafting an initial manuscript based on the findings above. However, we obtained follow-up funding to continue the project. We therefore decided to expand the study to include effects of vaccination. We are delaying publication to ensure that any findings are suitably reliable.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

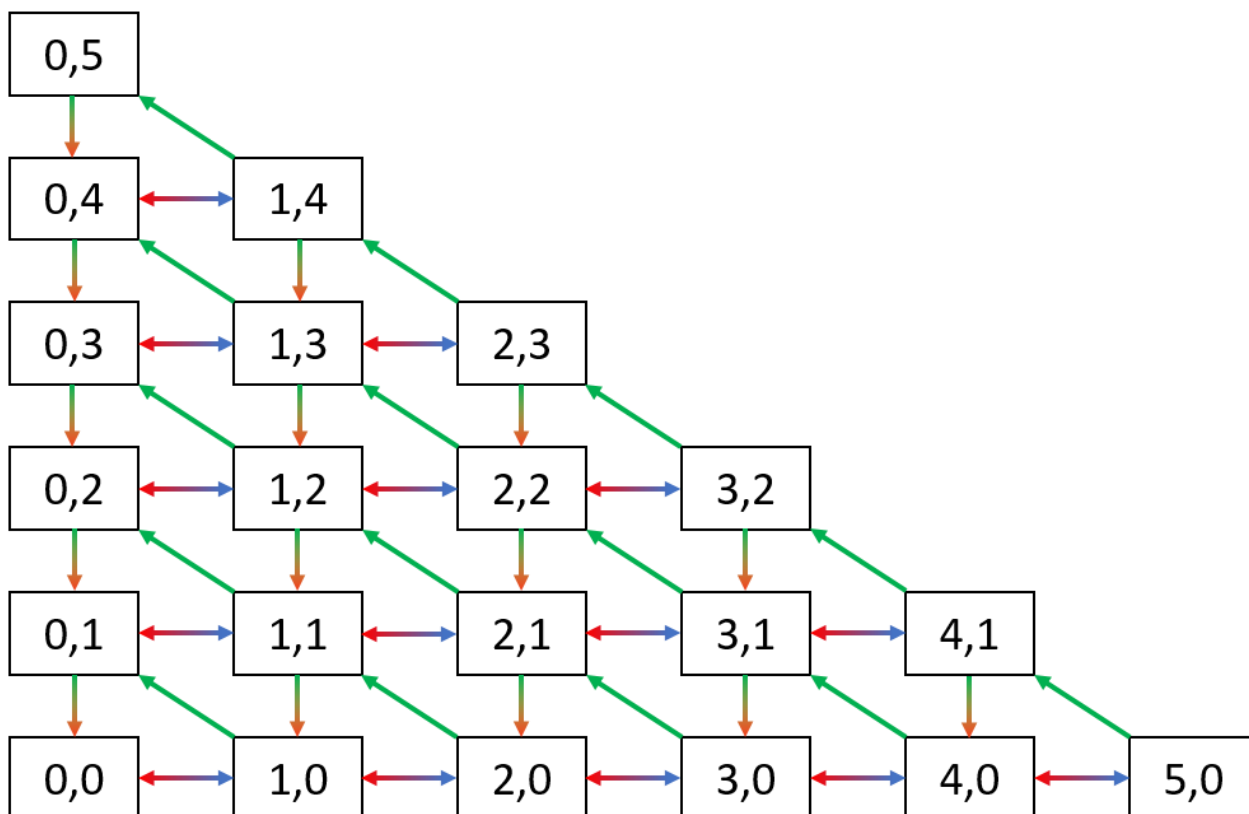


Figure 1: Illustration of the model. Each box is a group, e.g. a home. The number of uninfected and infected people (uninfected, infected) per group is inside each box. A groups can contain different numbers of uninfected and infected individuals, up to 5. Coloured arrows show how the composition of the groups changes due to virus transmission (green), death of an infected person (orange), death of an uninfected person (red), and the arrival of a new uninfected host (blue) For example, a group with 2 uninfected individuals and 1 infected individual (2,1) can change to become a group with 2 uninfected individuals and zero uninfected individuals (2,0) if the one infected individual dies, as represented by the green-to-orange arrow. If an uninfected person dies due to non-Covid causes, the group now contains one uninfected and one infected individual (red arrow from (2,1) to (1,1)). This model is used to test how changes in transmission rates, group size, and the mix of healthy and unhealthy individuals in groups affects the evolution of viral virulence.

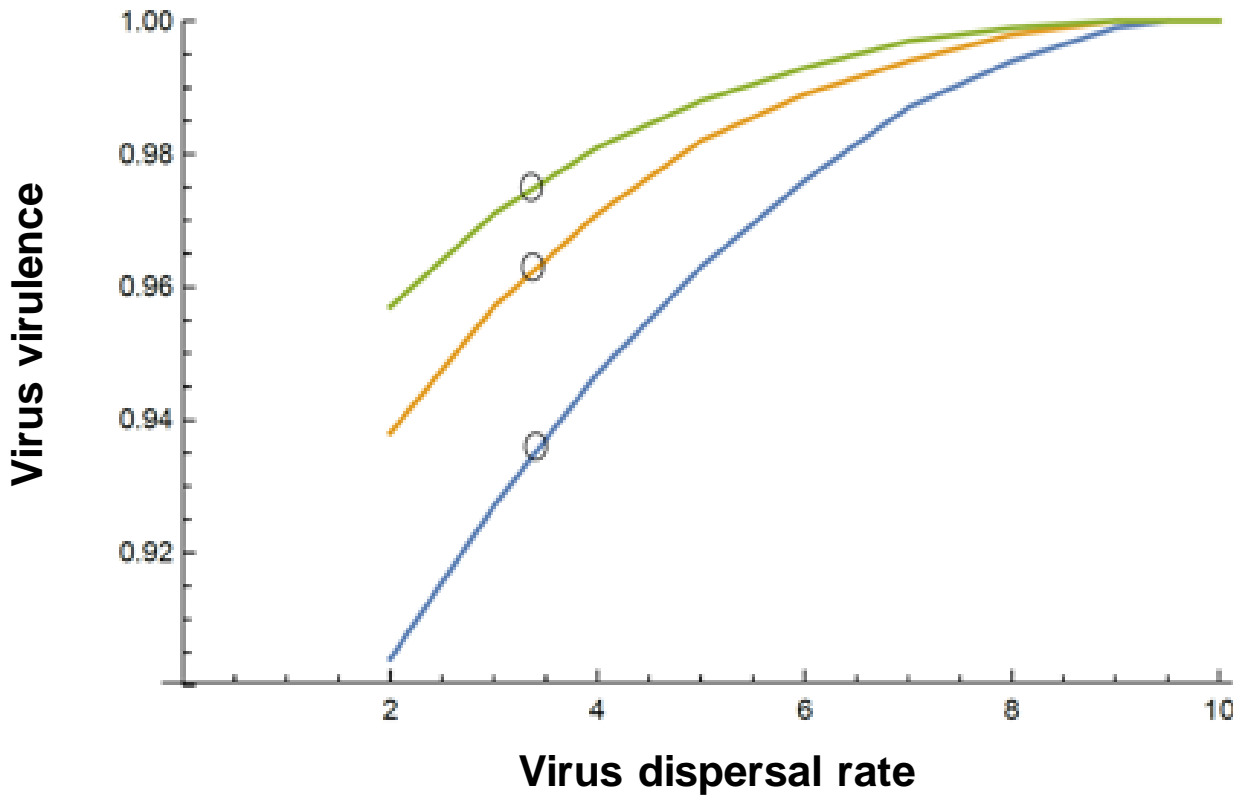


Figure 2: The relationship between the rate of virus transmission and its virulence. This simulation verifies the basic model that we adapted for our study (cf. Figure 2; Wild et al. 2009 *Nature* 459:983-986). The rate the virus transmits from group to group is shown on the x axis as its “dispersal rate”. For a given rate of dispersal, the most evolutionarily optimal virulence from the virus’s point of view is shown on the y-axis. That is, if a virus is permitted to move between people and groups at a given rate, the model predicts how it should evolve to balance the amount of damage it does to people so that it does not kill them before passing on copies of itself by infecting other individuals, but also does not get out-competed by a more virulent variant which transmits faster. In general, pathogen virulence increases with dispersal – highly virulent variants have an advantage when there is a lot of opportunity to spread to new people. However, the exact nature of this relationship depends on how quickly uninfected people are introduced into groups. The different coloured lines show different scenarios – for example, the green line shows what is expected when uninfected hosts replace others quickly. That case favours more virulent variants. The simulation is set up to find “evolutionarily stable” conditions, represented by the open circles. This is the set of conditions such as dispersal, replacement, group size, etc. where no further change in virulence along the coloured lines would be expected. These points are useful for testing what happens if we change some of these factors – does virulence increase or decrease?

WHAT IMPACT COULD THE FINDINGS HAVE?

- Help plan the pandemic response to reduce chances of more dangerous coronavirus variants arising.
- Help design less socially and economically damaging coronavirus control interventions.
- More generally help prevent highly virulent strains of other human or agricultural pathogens from evolving and spreading.

HOW WILL THE OUTCOMES BE DISSEMINATED?

When we have completed our analyses, we will post a manuscript describing the findings on a publicly-available website for sharing scientific research (bioRxiv). Then we will submit the manuscript to a peer-reviewed journal for publication. We will contact CSO before sharing findings according to the CSO's requirement that they review research findings prior to publication. At that point we will work with CSO to identify channels for advising public health policymakers if appropriate. In response to the funders' (CSO) requests, we have simplified the language, replaced complex terminology, and reformatted figures in this report.

CONCLUSION

We are still finalising the mathematical formulae underlying the model. After that, we will continue to test how different factors are expected to increase the virulence of SARS-CoV-2 or decrease it. This is done by simulating many different values of the variables described above. Therefore, formal public policy recommendations are not advised at this point. The relationship between the opportunity the virus has to spread and the most successful level of virulence from the virus's point of view shown in Figure 2 describes a classic prediction in evolutionary science. Our findings indicate that interrupting the transmission of SARS-CoV-2 through social distancing measures would be predicted to favour less virulent pathogen strains. However, it is unknown whether highly transmissible variants will simply overtake and replace less transmissible variants once they evolve and begin spreading. Over the life of this project, numerous new SARS-CoV-2 variants have been identified and are beginning to be linked to variation in transmissibility and patient outcome. The rapid development of this data will help us to adjust our theoretical model to answer future questions. A critical unanswered question is whether globally, SARS-CoV-2 has reached its maximum level of virulence, or whether more transmissible and virulent strains are likely to evolve. This is because more widespread, rapid, and global movement of human beings may be expected to favour virus variants that themselves can move more rapidly between hosts and cause worsened health outcomes. In contrast to this prediction, vaccination campaigns that disrupt the link between virus transmission and its virulence within infected individuals might be predicted to push virulence down, meaning that low-virulence forms of SARS-CoV-2 come to predominate as a larger fraction of a given population is vaccinated. Our study cannot currently comment on this, but the exact balance of these factors at local and global levels needs urgently to be modelled.

RESEARCH TEAM & CONTACT

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ADDITIONAL INFORMATION

This project encountered several significant delays that are worth noting. The first is that computing resources required for simulation runs using Mathematica were difficult to acquire during the early stages of the work due to licensing issues with the university's high performance computing cluster. Then, there were supply-chain disruptions when we pursued purchase of laptop computers to run simulations. That problem was ultimately solved, and we received additional funding to support the PDRA and finalise the modelling. However, the second UK lockdown this year further disrupted our ability to work. Both the PI and Co-PI have caring responsibilities for young children, but were not classed as key workers for the purposes of this covid-related research. Thus, we both went without childcare for several months, and as both have working spouses, this caused a challenging slowdown of our pace of work.