Note added for release: This draft paper relates to discussion within SPI-M-O that was shared with SAGE for information. It is not a final product, as further work was intended on the scope and content of this exercise.

SPI-M-O Collaborative Working Document on Sensitivity Analysis of Modelling

Date: 30th September 2020

Summary

1. SPI-M-O are considering what the key parameters and processes are that have the biggest impact on our modelling estimates and which we are most uncertain about, what assumptions are being made about these.
2. Three key overlapping areas have been used to categorise model parameters as impacting either:
    - Long term dynamics and projections for the epidemic
    - Impact of interventions aimed at suppressing viral transmission
    - Estimation of R
3. **Long term dynamics and projections** are most influenced by the temporal dynamics of immunity and heterogeneity in susceptibility. Longer-term trends in behaviour, and the impacts of future policy and behaviour changes at local and national level that might be implemented are unknowable but hugely influential.
4. **Impact of interventions aimed at suppressing transmission** are most influenced by the role of asymptomatic individuals in transmission, heterogeneities in behaviour and infectiousness (by age, for example), and adherence to interventions to manage transmission.
5. **R estimation** is most influenced by uncertainty in biological processes (infectiousness, test sensitivity), behaviour (adherence to isolation, contact rates), and interactions between the two (e.g. generation time distribution). COVID-security in different settings and environmental factors are important. Delays and inconsistency in data streams is a significant issue for estimation.
6. Of particular concern is the uncertainty about the adherence to behavioural and social interventions and, for example, test, trace, and isolate requests, including understanding how this may vary by age group. Characteristics of asymptomatic infection and transmission also concerns SPI-M-O.
7. This initial paper shows the sheer volume of aspects of modelling that are uncertain yet could be affect the modelling performed and decisions based on that analysis. SPI-M-O

have not yet had the opportunity to formally estimate the scale that changing these parameters significantly may have on the modelling detailed here. Further work is needed to understand the scope.

8. Nonetheless, the SPI-M-O mode of working, which encourages variation between models and takes consensus views after consideration of multiple results, overcomes formal sensitivity analyses to a large extent with respect to providing evidence for policy.

Appendix

Long-term dynamics

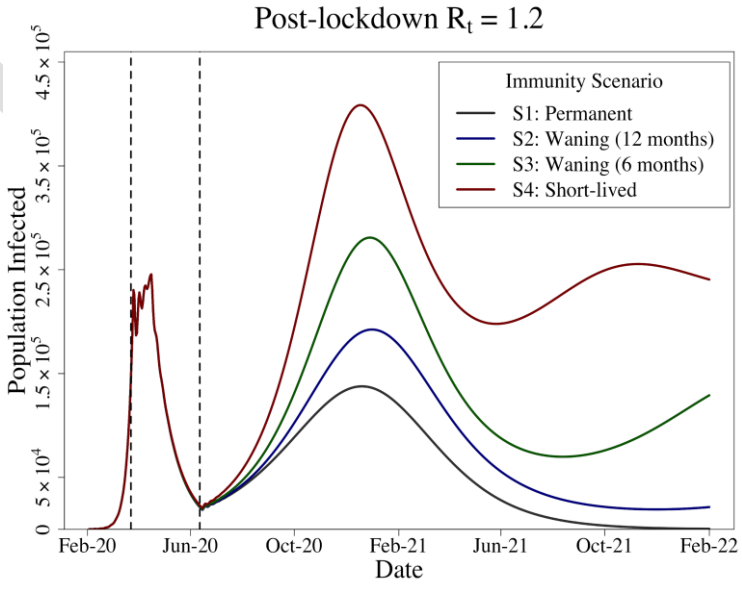
a) Policy changes

9. Rapid and regular changes in policy make long term predictions challenging. For example, current medium-term projections are based on the assumption that behaviour and the impact of restrictions has remained unchanged over the past 3 weeks.

b) Duration of immunity

10. Most COVID-19 models assume immunity following infection is 100% effective at blocking reinfection over the time horizon being modelled (typically 12-18 months). However, data on antibody waning following SARS-CoV-2 infection, a few reports of reinfection occuring and data from seasonal coronaviruses suggest that immunity may wane, likely over the 12-24 month timescale. The effect of waning is to limit the impact of herd immunity on future transmission, leading to more pessimistic "second wave" scenarios (Crellen et al. 2020).

Figure 1: Hypothetical UK second-wave scenarios assuming Rt=1.2 following relaxation of lockdown measures for a range of assumptions about the duration of naturally acquired immunity.



c) Behaviour and adherence

11. Behaviour has a major impact on epidemic projections. At a population-scale, changes in the average behaviour influence the reproduction number, growth rate and doubling time. At an individual-level, heterogeneity in behaviour and risk is likely to be correlated with infection status and immunity. In terms of immunity, demographic groups (e.g. young adults, healthcare workers) who were most likely to be infected early in the first wave would be expected to be the first to lose immunity, changing predictions about the contribution of those groups to transmission in the second wave.

12. Engagement with interventions is difficult to measure and important in model projections. For example, adherence to contact tracing, reporting rates of symptoms and self-isolation determine the effectiveness of modelled interventions. Mobility (i.e. movements between locations, e.g. LTLA) influence the distribution of transmission. This has changed hugely and will continue to do so. Monitoring movement in near real-time would go a long way to reduce this uncertainty.

13. Mixing patterns in response to increased control may also vary with time. In response to perceived lack of adherence to control measures, further restrictions may be introduced, but this may have a further effect upon adherence (either positive or negative). For example, a strategy that includes repeated precautionary breaks may exhibit diminishing returns with reduced adherence for later breaks. This will have significant influence upon our prediction of an “optimal” long term policy.

14. The source of infection of HCW/SCW is uncertain (community/infected by patient/ infected by HCW) but can be partially drawn out from longitudinal testing data on HCWs if the shape of the prevalence curve can be clearly identified. The interaction of CWs with the community (potential say for assortative mixing with other similar professionals in households or socially) is unknown. Contact rates within care homes and care settings are unknown between staff and residents (though studies are underway to quantify these rates). Types of contacts made by visitors and critically the usage of visiting professionals in social care (or bank staff in hospital).

15. There remain data gaps in measuring behaviour, including mixing patterns of children, individuals with comorbidities and quantifying the relationship between contact patterns and adherence to guidelines.

d) Individual heterogeneity

16. In addition to changing behaviour, **individual variation** in infectiousness and behaviour can impact overall dynamics and the impact of interventions. The majority of models assume that the probability of severe disease and developing symptoms are independent

of initial viral load and the characteristics of the infecting person. This might change due to, for example, increased within-household transmission, or if within household transmission scales with household size and composition.

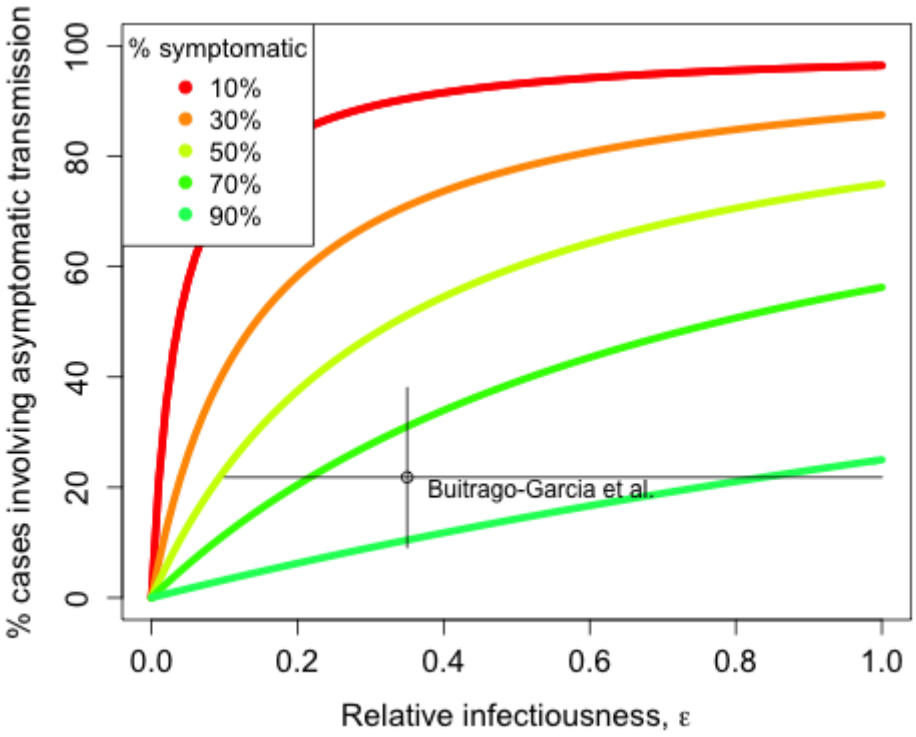
17. Some individual variation is explained by **setting-specific transmission risk**. We have access to substantial data upon contacts in different settings (work/school/home/social settings etc). But there is uncertainty in how that translates to transmission risk, particularly in different working sectors (and their "COVID-secure" modifications). This will have an influence on a model's ability to accurately establish the relative impact of specific sector closures upon disease spread. Resolution of these uncertainties is important if, for example, we wish to determine how we might safely ensure that schools can remain open through reactive closure of other sectors.

Impact of interventions

a) Fraction of asymptomatic infections and the infectiousness of asymptomatic cases

18. The effectiveness of interventions that are aimed at symptomatic cases only, such as case isolation, and the time it takes for those interventions to become effective, will be dependent on the fraction of asymptomatic cases and the infectiousness of those cases. A recent systematic review of asymptomatic transmission by Buitrago-Garcia et al. estimated that 20% (17%-25%) of infections remained asymptomatic and that the secondary attack rate in contacts of asymptomatic cases was 35% (10%-127%) that of symptomatic cases. The proportion of cases that involve asymptomatic transmission is more dependent on the fraction of asymptomatic cases than the infectiousness of those cases (figure 2). Taken in combination with Buitrago-Garcia et al.'s estimates, it suggested that between 10% and 40% of cases involve asymptomatic infections.

Figure 2: The percentage of cases involving asymptomatic transmission (such as asymptomatic-symptomatic) as a function of the proportion of asymptomatic cases and their relative infectiousness.



b) Interaction with other pathogens and cross-immunity

19. The herd immunity threshold predicted by epidemic models is principally determined by R0 but is also affected by any potential cross-immunity to other coronaviruses and heterogeneity in contact patterns (e.g. by age or setting). There has been speculation in the media and pre-print literature that the latter two factors might mean the herd immunity threshold for COVID might be reached with as little as 20% of the population being infected. However, there is very limited evidence to support the hypothesis that a large proportion of the population had pre-existing immunity which would prevent infection (and thus sero-converting), though cross-reactive T-cell mediated immunity might be one of the factors explaining the substantial fraction of asymptomatic infections seen. Likewise, very high levels of variation in exposure risk are needed to substantially reduce the herd immunity threshold, well beyond what has been estimated from large-scale contact studies (Klepac et al. 2020). Furthermore, there is increasing evidence - from both community serological studies and outbreaks in closed settings that epidemic sizes can exceed 60% of the population in the absence of effective controls.

Estimates of the reproduction number

20. SPI-M-O contributors generate multiple estimates of the reproduction number and the differences between estimates have been quantified and understood in terms of

assumptions about the generation time, data streams and model type. The generation time is impacted by control measures and mixing patterns, therefore is liable to change over time. **Generation interval distributions** under different policies and in different settings (household vs. school vs workplace etc) are largely unestimated.

21. When projecting the impact of interventions on the reproduction number (e.g. as part of the "ready reckoners"), we do not know the effectiveness of **COVID-security**, e.g. face coverings, visors and distancing, on transmission probability, therefore we have used a variety of scenarios.

Methods for quantifying importance of parameters

Value of Information

22. From a modelling perspective it is often useful to understand how our inferences/estimates/projections would change if we had some piece of additional information. A value of information study (see here) allows us to estimate the fraction of the uncertainty in a modelled outcome that could be resolved if we had perfect knowledge of a particular parameter or input. Therefore, if we can identify aspects of our models that we have difficulty in being able to estimate with any robustness, we can use these methods to identify quantities that may need to be researched or investigated further.

23. For example: preliminary results looking at the value of information of the parameters of PHE/Cambridge's transmission model show that the uncertainty in the IFR and sensitivity of serological testing is responsible for over 90% of the posterior variance in our estimates of the number of infections occurring on the 22nd March (see figure below). Their contribution decreases over time, contributing 15-17% of the posterior variance of the nowcast infection incidence (based on an analysis using data up to 7th Aug, and "nowcasting" on that date) but remain the parameters with the largest contribution to the uncertainty (formally: the parameters with the largest expected value of partial perfect information).

Figure 3: parameter values for each MCMC iteration plotted against the estimated number of infections on the 22nd March (pre-lockdown) within that iteration. Each point represents one posterior sample.