It is a pleasure to thank the speakers and authors for three interesting papers. My comments cover three areas.

Reproduction numbers Time-dependent reproduction numbers such as R_t have been especially prevalent in UK media reports and government publications during the COVID-19 pandemic, as well as appearing in numerous scientific publications. Estimates of R_t provide some indication of the state of the epidemic in a particular location at a particular time, although as pointed out in the papers under discussion there are many dangers in relying on R_t alone. Additionally, R_t has also been used to some extent as a way of evaluating control measures introduced in response to the pandemic. As an aside: the vast majority of epidemic models contain no feedback mechanism in which the dynamics change in response to the outbreak, although some work has been done on behaviour-change models for HIV/AIDS. It may be fruitful to explore ways of incorporating such feedback to provide a more holistic view of future outbreaks.

Although R_t is easy to define informally, is there scope for more nuanced definitions? Fraser (2007) draws the distinction between the case reproduction number and the instantaneous reproduction number. The basic reproduction number R_0 can be defined in several different sensible ways for non-homogeneously-mixing models such as models with households, and some of these approaches could be translated to R_t.

The papers under discussion also remind us that reproduction numbers are implicitly model-dependent, although this fact is apparently not always fully appreciated in the applied literature. Simply taking estimates from one study and using them in another for a different time or place can lead to misleading results.

Estimation and models There are two prevalent views as to how to estimate R_t or any other reproduction number. The first view is to define a mechanistic transmission model in which R_t appears as a parameter or function of parameters, and upon fitting the model to data we can obtain the desired estimate. Although this approach works well for smaller outbreaks, it is far more challenging for national-scale modelling because of the many extra assumptions that need to be incorporated. As Coffeng and de Vlas illustrate, the fact that a complex model fits the observed data to date is no guarantee that such assumptions are reasonable. In addition, the estimation procedure itself can be challenging, and current approaches typically rely on approximations of some kind. Nevertheless, this area merits further research. The second view, as illustrated in Parag *et al*, building on the approach developed by Fraser (2007) and Cori (2013), dispenses with a transmission model *per se* and instead uses an auto-regressive time series model to explain the observed incidence curve. This approach has the merit of simplicity, but the lack of more detailed assumptions can be a drawback. Parag *et al* demonstrate the dependence of R_t estimation on the assumed generation time interval. Can anything theoretically be said here? For instance, can conditions be found under which R_t is invariably underestimated or overestimated? Also, is there any merit in attempting to estimate the generation time distribution with R_t simultaneously, as opposed to the kind of two-step procedure in Thompson *et al.* (2019)?

Hetereogeneity Coffeng and de Vlas provide a timely reminder of the importance of heterogeneity, particularly in regard to the ability of models to make long-term predictions. However, short-term predictions are typically more robust to model misspecification. Heterogeneity, in the sense of how members of a population mix with each other, is well-known to be crucial to many aspects of epidemic outbreaks, and also to the choice and efficacy of associated control measures. Temporal heterogeneity is far less commonly accounted for in transmission models, such as the very real differences in population mixing between weekdays and weekends, or different times of day and night. Understanding and utilising information about how real-life populations mix remains an important challenge for the epidemic modelling community. Finally, pathogen heterogeneity is also of vital importance. Being able to account for different variants, with different potential for transmission, is crucial for both estimation and modelling.

References

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