Responses from Parag, Thompson and Donnelly

We thank all the discussants and contributors for a stimulating debate on the merits and demerits of different summary statistics such as the reproduction number (R) and epidemic growth rate (r). Many interesting and thought-provoking points have been raised, some of which we respond to below. Here R refers to the instantaneous, time-varying reproduction number (often called R_t or R_e). Similarly, r specifically denotes the instantaneous, time-varying epidemic growth rate (sometimes denoted as r_t).

To: Prof Peter Diggle

The use of Gaussian process-based growth rate processes (with incorporation of covariates) would be an important addition to existing methodology, especially as the literature on r estimation is sparse and underdeveloped. We fully support such developments and think these refinements could form useful additions to existing outbreak analysis toolkits. However, we also note that even such principled approaches would not completely circumvent (though it may ameliorate or make more explicit) the tensions between mechanistic and smoothing assumptions that we outlined in our contributed paper. Specifically, the benefit of trading mechanistic for covariate assumptions (e.g., mobility patterns) may depend on, as Prof Diggle points out, our level of knowledge of the epidemic.

However, a central thesis of our contribution was that while model-agnostic (or non-mechanistic) and model-based estimates of transmissibility might offer different levels of risk in terms of assumptions and biases, they are not mutually exclusive. Consequently, we share Prof Diggle's vision for bolstered early-warning methodologies such as his proposed approach (we started looking into this as well in [1]) and think these should be used as part of a wider framework that applies multiple methodologies to assess transmissibility and outbreak dynamics. Initiatives focussed on model averaging and consensus forecasting (e.g., [2,3]) and more formal outbreak analytics software [4] might be our best bet for mitigating pandemic uncertainties, if combined with improved surveillance.

To: Dr John Dagpunar

The added investigation of the R-r relationship and the influence of generation times is excellent, and we agree that further investigation of how R and r interact (and how their relationships may change) is a key direction for future study. As to whether the difference between Dr Dagpunar's derivation and the approximation often used has a significant effect in practice, all we can say is that the effect is limited for the simulated examples we considered in our contribution (which use generation times based on those estimated for Ebola virus or SARS-CoV-2). This follows because we found a close correspondence between a completely model-agnostic r estimate (which is independent of any relationship with R or an estimated generation time) and that derived from the approximation.

We agree with Dr Dagpunar's clear analysis of the sensitivity of estimates of transmissibility (e.g., of competing pathogen variants) to inferred serial interval and generation time distributions and in fact echo these sentiments in our contribution, where we have suggested that if we are not confident in the accuracy of these distributions then r would be the more reliable metric. Last, we point out that – together with improving methodology – there must be an accompanying enhancement of syndromic and other surveillance measures, as also outlined by other discussants.

To: Prof Sir John Kingman

True heterogeneity, as opposed to random fluctuations from one sub-population to another, is important, but it is not an argument in and of itself against reporting a mean. One R estimate may not provide all the important information needed to understand a varied transmission landscape, but in that case one r estimate may not either. There is no need to report only a single estimate for a large population. There are many examples in which R estimates were reported both overall and by region in government publications (e.g. [5]) as well as academic papers (e.g. [6] which has estimates for the whole of England in Table 2 and for English regions in Table S3).

Regarding the challenges in producing ensemble estimates, in their analysis of The RAPIDD Ebola forecasting challenge Viboud et al. [2] commented "While there has been considerable attention devoted to combining models and estimation procedures to improve accuracy in recent years, further work is needed to optimize the number of models and diversity of model structures to be included in successful ensemble predictions." This ongoing work needs to consider ensemble estimates of key parameters (including R and r) as well as incidence predictions.

To: Dr Lorenzo Pellis

We strongly agree with the points that the weaknesses of R and r are similar and that there has often perhaps been undue emphasis on R estimates. In fact, beyond our contribution and Dr Pellis' paper [7], there have been surprisingly few studies on computing time-varying r estimates. We further add that the quality of either metric in being able to describe salient epidemic dynamics may be more a function of how we use them than their inherent definitions. Specifically, as Dr Pellis mentions, the averaging behind each measure is central to its interpretation and description.

A country-wide R or r estimate may be too simplistic for tracking the state of the epidemic, with its shortcomings deriving from the choice of averaging over the many heterogeneous parts of a country (and its various subpopulations), rather than any mathematical property of the summary statistic itself. However, very detailed agent-based analyses may lose some of the interpretability that is often sought from simple statistics. Getting this balance right should be a key focus of future studies, in tandem with improving surveillance. Growing emphasis on testing for structural uncertainties [8], model averaging [3] and ongoing work into better model selection [9] all suggest that the field is in fact heading in this direction.

To: Prof Phillip O'Neill

As Prof O'Neill asserts, the model-dependence of R is often neglected, a point underscored in [8]. We completely agree that further nuanced definitions of R, together with assessments of whether model-based R values actually map to our intuition about the number of secondary cases resulting per primary case, are vital for advancing outbreak analyses. We think that along these lines, more work focussed on better quantifying the uncertainty in R estimates, their dependence on structural assumptions and what controls their statistical identifiability would be especially helpful. Some examples of this have already been given in [9,10] which have identified and illustrated how surveillance delays, noise and smoothing assumptions can strongly change the estimates of R obtained

from the same data. Moreover, from this statistical identifiability perspective, we think it unlikely (without making strong assumptions) that both generation times and R can be co-estimated, making improved surveillance combined with two-step approaches like [11] the more viable route.

An important related point is the need for better understanding of how to best leverage available data to obtain the most informed and robust R estimates. The different usage of case and instantaneous R numbers may be a good example. Case or cohort R estimates use future information when inferring transmissibility and benefit retrospective studies (e.g., the Wallinga-Teunis method [12]), while instantaneous R estimates (e.g., the Cori et al method [13]) consider past information and are better for real-time analyses. However, recent work [14] shows that both past and future incidence information can be fused to derive a meaningful R estimate that works both retrospectively and in real time. Last, we suggest that more exploration into the theoretical properties of R is vital, especially given debates as in [15] about whether in certain contact networks threshold quantities even exist!

To: Prof Sylvia Richardson

We fully support the design and execution of surveillance initiatives aimed at uncovering changes to and properties of the serial interval distribution (and that can also be used to infer generation time distributions)[16–18]. As we illustrate in our contribution, misspecification of the serial interval can severely reduce how accurate R estimates are, potentially causing misinterpretation of epidemic dynamics. While r would be less vulnerable to such issues, we would lose insight into the 'branching' nature of the epidemic if we only consider r. Further, better characterisation of serial intervals (and e.g., incubation periods) would enhance our ability to forecast epidemic trajectories [19].

Thus, preparedness should definitely include developing effective study designs to collect data on serial intervals before outbreaks start. In the absence of genetic tracking of an outbreak pathogen, these studies would likely need to focus on transmission events in settings where transmission from sources other than the studied primary cases is unlikely. That is one of the reasons why most of the data from which the serial interval is analysed arise early in outbreaks before transmission becomes widespread. Where genetic testing can strengthen confidence in the source of an infection, there will be more opportunities to study serial intervals.

To: Prof Steven Riley

As one of us is a co-investigator with Prof Riley in the REal-time Assessment of Community Transmission (REACT) study, it is not surprising that we agree that random surveys of populations are powerful tools for understanding trends in the prevalence of infections in communities. Such surveys are unaffected by test-seeking behaviour and test availability to the public.

To: Prof Justin Lessler and Prof Jessica Metcalf

We share Profs Lessler and Metcalf's confidence that R will remain a useful indicator of transmissibility during future outbreaks. They make an important point that it is crucial to consider the scale on which R is estimated (e.g., should estimates of transmissibility be inferred for individual towns, regions or countries – or separately at multiple scales?). There is also an important outstanding challenge in deciding how best to account for heterogeneity between hosts or different population groups when

providing simple summaries of pathogen transmission. As Profs Lessler and Metcalf assert, the structure of relevant contact networks, and changes to that structure, are challenging to infer.

Most importantly, however, we agree and emphasise that it is essential to consider estimates of R alongside other quantities, such as r and measured incidence/prevalence of infections, deaths and hospitalisations. Estimates of R provide a meaningful, but incomplete, picture of an ongoing outbreak. For example, the recent increase in R above 1 in the UK was perhaps inevitable as restrictions are being lifted, but the extent to which increasing case numbers will lead to substantial numbers of hospitalisations is the most important question and remains to be seen, given a background of high vaccination coverage and the potential for new variants of concern to emerge. In conclusion, a range of statistics – including R – that provide an easy-to-understand summary of an ongoing outbreak is useful for guiding policy and essential for communicating the current situation in real-time during outbreaks. As Profs Lessler and Metcalf state, R will remain a fundamental quantity of interest.

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