Dear Editor,

We are pleased to submit to you our research manuscript *Inferring the reproduction number using the renewal equation in heterogeneous epidemics*.

Real-time estimation of the reproduction number, R, has become of vital importance over the course of the last year in light of the global SARS-CoV-2 pandemic. The simplest and most widely adopted means of inferring the reproduction number is via the renewal equation, which relates the historic incidence of infection with the generation time distribution to infer the reproduction number. Given difficulty of measuring the generation time distribution, it is often only well characterised for transmission between symptomatic individuals early in an epidemic before widespread symptomatic isolation and vaccination occur. We sought to understand how these heterogeneities may affect inference of R through an outbreak.

In this paper, we derive a multi-type equivalent of the renewal equation which accounts for heterogeneity, including asymptomatic transmission, symptomatic isolation and transmission from vaccinated individuals. We demonstrate that while the impact of accounting for symptomatic isolation on the inferred R is small, it can be significant in the cases of asymptomatic transmission and transmission from vaccinated individuals if these groups have substantially different generation time distributions to symptomatic non-isolators. We mathematically derive the single-type equivalent renewal process to the multi-type approach, and apply this to Ebola in West Africa in 2014 and to SARS-CoV-2 in the UK in 2020-21 using the *EpiEstim* package.

We have chosen to submit our paper to the Royal Society Interface for three reasons:

1. The Royal Society Interface is a premier publication in the intersection of the physical and life sciences. This paper clearly falls at the intersection of mathematics and biology.
2. The manuscript has good alignment and strong intersection with prior publications in your journal, notably
   a. *Estimation in emerging epidemics: biases and remedies* (T. Britton, G. Scalia Tomba, 2019)
   b. *On the relationship between serial interval, infectiousness profile and generation time* (S. Lehtinen, P. Ashcroft, S. Bonhoeffer, 2021)
   c. *Inferring generation-interval distributions from contact-tracing data* (S. W. Park, D. Champredon, J. Dushoff, 2020)
3. The Royal Society has played a leading role in convening researchers and informing policy through the course of the COVID-19 pandemic

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with its submission to Royal Society Interface.

Best wishes,

William Green