

[Home](#)[Author](#)[Review](#)

Submission

- ✓ Step 1: Type, Title, & Abstract >
- ✓ Step 2: File Upload >
- ✓ Step 3: Attributes >
- ✓ Step 4: Authors & Institutions >
- ✓ Step 5: Referees >
- ✓ Step 6: Details & Comments >
- Step 7: Review & Submit** >

You're almost done!

[Submit >](#)

Step 7: Review & Submit

Review the information below for correctness and make changes as needed. **After reviewing the manuscript proofs at the foot of this page, you MUST CLICK 'SUBMIT' to complete your submission.**

* = Required Fields

* Verify Step Information

✓ Step 1: Type, Title, & Abstract

[Edit](#)

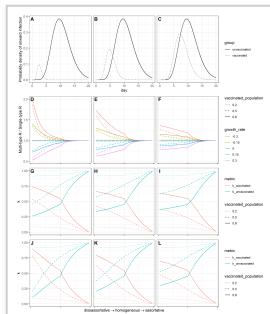
FIELD	RESPONSE
Article Type	Research
Title	Inferring the reproduction number using the renewal equation in heterogeneous epidemics

FIELD	RESPONSE
Abstract	<p>Real-time estimation of the reproduction number has become the focus of modelling groups around the world as the SARS-CoV-2 pandemic unfolds. One of the most widely adopted means of inference of the reproduction number is via the renewal equation, which uses the incidence of infection and the generation time distribution. In this paper, we derive a multi-type equivalent to the renewal equation which accounts for heterogeneity including asymptomatic transmission, symptomatic isolation, and vaccination. We demonstrate how use of the renewal equation that misses these heterogeneities can result in biased estimates of the reproduction number. While the bias is small with symptomatic isolation, it can be much larger with asymptomatic transmission or transmission from vaccinated individuals if these groups exhibit substantially different generation time distribution to unvaccinated symptomatic transmitters, whose generation time distribution is often well defined. The bias in estimate becomes larger with greater population size or infectiousness of the poorly characterised group, as well as if the population exhibits disassortative mixing. We apply our methodology to Ebola in West Africa in 2014 and the SARS-CoV-2 in the UK in 2020-21.</p> <p>Less text</p>

✓ Step 2: File Upload

[Edit](#)

FIELD	RESPONSE
File 1	<p>Inferring the reproduction number using the renewal equation in heterogeneous epidemics nCR.pdf</p>
File 2	<p>error_R_isol_no_isol6.png</p>
File 3	<p>R_isolation_UK_Guinea6.png</p>
File 4	<p>error_R_symp_asymp6.png</p>

FIELD	RESPONSE
File 5	R_UK_symp_plot6.png 
File 6	error_R_vacc_no_vacc_zoom7.png 

✓ Step 3: Attributes

 Edit

FIELD	RESPONSE
Categories	<ul style="list-style-type: none"> • Life Sciences - Mathematics interface
Subject	<ul style="list-style-type: none"> • Computational biology < CROSS-DISCIPLINARY SCIENCES
Keywords	<ul style="list-style-type: none"> • heterogeneous • epidemics • renewal equation • generation time • asymptomatic transmission

✓ Step 4: Authors & Institutions

 Edit

FIELD	RESPONSE
-------	----------

FIELD	RESPONSE
Author 1	<p>Green, William Daniel</p> <p>w.green18@imperial.ac.uk</p> <p> 0000-0001-8556-0389 ✓</p> <p>Imperial College London, Infectious Disease Epidemiology, London, W2 1PG, UK</p>
Author 2	<p>Ferguson, Neil</p> <p>neil.ferguson@imperial.ac.uk</p> <p> Imperial College London, MRC Centre for Global Infectious Disease Analysis, London, UK +44 207 594 3296</p> <p>Imperial College London, Abdul Latif Jameel Institute for Disease and Emergency Analytics, London, London, UK +44 207 594 3296</p>
Author 3	<p>Cori, Anne</p> <p>a.cori@imperial.ac.uk</p> <p> 0000-0002-8443-9162 ✓</p> <p> Imperial College, MRC Centre for Global Infectious Disease Analysis, London, UK</p>

✓ Step 5: Referees



FIELD	RESPONSE
Reviewer	<p>Jacco Wallinga (Recommended)</p> <p>Reason: Past publication on the relationship between generation time distribution, epidemic growth rate and R</p> <p>j.wallinga@lumc.nl</p> <p>Leiden University Medical Center Biomedical Data Science +31 71 526 9111</p>

FIELD	RESPONSE
Reviewer	<p>Sebastian Funk (Recommended)</p> <p>Reason: Past publications in inference of R of SARS-CoV-2 from national and subnational case data sebastian.funk@lshtm.ac.uk</p> <p>London School of Hygiene & Tropical Medicine Department of Infectious Disease Epidemi +44 (0)20 7927 2209</p>

✓ Step 6: Details & Comments Edit

FIELD	RESPONSE
Cover Letter	<p>Dear Editor,</p> <p>We are pleased to submit to you our research manuscript "Inferring the reproduction number using the renewal equation in heterogeneous epidemics".</p> <p>Real-time estimation of the reproduction number, R, has become of vital importance over 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.</p> <p>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.</p> <p>We have chosen to submit our paper to the Royal Society Interface for three reasons:</p> <ol style="list-style-type: none"> 1. The Royal Society Interface is a premier publication in the intersection of the physical and life sciences. This paper clearly falls at the

FIELD	RESPONSE
	intersection of mathematics and biology. 2. The manuscript has good alignment and strong intersection with prior publications in your journal, notably (i) Estimation in emerging epidemics: biases and remedies (T. Britton, G. Scalia Tomba, 2019); (ii) On the relationship between serial interval, infectiousness profile and generation time (S. Lehtinen, P. Ashcroft, S. Bonhoeffer, 2021); (iii) 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
	Less text
Funding	<p>MRC Centre for Global Infectious Disease Analysis MR/R015600/1 National Institute for Health Research (NIHR) Health Protection Research Unit in Modelling and Health Economics NIHR200908 Wellcome Trust 102169/Z/13/Z</p>

Manuscript Information

* Number of Figures: 5

* Number of Tables: 0

* Number of Words 7997
 (including references):

* Has a previous version of this manuscript been submitted to this or any other Royal Society journal (using a different manuscript ID)?

Yes

No

If yes, what is the manuscript ID of the previous submission?

Licence to publish

- * Confirm you accept the terms and conditions of the Royal Society's [Licence to Publish](#). Note that you are agreeing to the standard licence at initial submission, but may switch to the open access licence at revision. Please contact the Editorial Office if you have any special requirements, for example as a US government employee.

Ethics

- * I/we confirm that we have read and comply with the [Royal Society publishing ethics policy](#).
- * Does your article include research that required ethical approval or permits?

This article does not present research with ethical considerations

If yes, please provide text to be included in an 'ethics statement' in the published article. This must include information about ethical approval, licence or permit numbers associated with the study (including fieldwork permits) and specific guidelines followed. You may also include other details not included in your methods, such as specimen numbers. Please see the [instructions to authors](#) for details.

Competing interests

- * Please declare any competing interests held by any of the authors on this paper. We consider a competing interest to be anything which influences the objective presentation of your manuscript. Competing interests may be financial or non-financial; for more information please see our [publishing policies](#).

I/We declare a competing interest

If yes, please provide text to be included in a 'competing interests statement' in the published article. Please see the [instructions to authors](#) for details.

William Green has received payment from the Joint Biosecurity Centre for services in relation to the UK's response to the COVID-19 pandemic.

Anne Cori has received payment from Pfizer for teaching of mathematical modelling of infectious disease transmission and vaccination

Data

It is a [condition of publication](#) that data, code and materials supporting your paper are made publicly available on publication. **They must also be available for reviewers and Editors to assess during review**. Please provide below the following details when relevant:

- 1. For initial submission:** tell us how the editors and reviewers can access your data or code. This can be via temporary (private) links or as supplementary material.
- 2. On revision:** update the below with final details in the form of a data accessibility statement that will be published in the article. This must include information about how this data can be accessed, such as a link to a repository or previously published article, or if it is provided as supplementary material. At this stage,

please ensure that all datasets are also included in your reference list and that the citations are included here (example: "Climate data and MaxEnt input files: Dryad doi:10.5555/dryad.12345 [REF# or (Smith et al (2021))].

Please see the [instructions to authors](#) for details. If you cannot make your data available please contact the Editorial Office before submitting your manuscript.

* Does your paper present new data, or use data/models published elsewhere?

Yes

If yes, please provide a 'data accessibility statement'.

Data on Ebola cases and taken from: Heterogeneities in the case fatality ratio in the West African Ebola outbreak 2013–2016 (T. Garske, A. Cori et al, 2017)

Data on SARS-CoV-2 deaths in the UK taken from the Government dashboard:
<https://coronavirus.data.gov.uk/>

Both data and code are available in the github repository:

https://github.com/willgreen236/Heterogeneity_transmission.git

Author contributions

* Please provide text to be used in an authors' contributions section in your paper. Please see the [instructions to authors](#) for more information about what is required.

This paper has multiple authors and our individual contributions were as below

All authors were responsible for developing the project methodology. William Green developed the software, conducted the formal analysis and was responsible for output visualization and original draft preparation. Anne Cori and Neil Ferguson were jointly responsible for project conceptualization, project supervision and reviewing and editing the manuscript.

* Does your paper have electronic supplementary material (ESM)?

No

If yes, do any of the ESM files contain data, code or materials relevant to the reproducibility of the study?

No

Please provide a descriptive title (not the file name) and a short description for each separate file. These will be used online and must provide enough information for a reader to know what the supplement is before opening the file. If you have more than 5 files, please upload these titles and captions as a document along with your manuscript files.

ESM file 1

Title:

Legend/Caption:

ESM file 2

Title:

Legend/Caption:

ESM file 3

Title:

Legend/Caption:

ESM file 4

Title:

Legend/Caption:

ESM file 5

Title:

Legend/Caption:

*** What prompted you to consider this journal for this submission?**

Colleague recommendation

If other

*** View Proof**

You must view the PDF proof before you can submit

[View HTML Proof](#)

 [View PDF Proof](#)

[View MedLine Proof](#)

[Previous Step](#)

[Submit ➤](#)

Journal of the Royal Society Interface is published by the Royal Society

Royal Society Privacy Policy | Ethics and Policies | Royal Society Journals

© Clarivate Analytics | © ScholarOne, Inc., 2021. All Rights Reserved.

ScholarOne Manuscripts and ScholarOne are registered trademarks of ScholarOne, Inc.

ScholarOne Manuscripts Patents #7,257,767 and #7,263,655.

 @ScholarOneNews |  System Requirements |  Privacy Statement |  Terms of Use