PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Growth, reproduction numbers, and factors affecting the spread of SARS-CoV-2 novel variants of concern in the United Kingdom from October 2020 to July 2021: a modelling analysis
AUTHORS	Ward, Thomas; Glaser, Alex; Johnsen, Alexander; Xu, Feng; Hall, Ian; Pellis, Lorenzo

VERSION 1 – REVIEW

REVIEWER	Hasnain, Seyed E. IIT Delhi
REVIEW RETURNED	29-Jul-2021

GENERAL COMMENTS	The manuscript by Ward et al presents interesting analyses on temporal evolution of delta variants within the UK. With a non-evolutionary biologist background, I have some fundamental minor concerns about this manuscript. 1. The study plainly indicates exponential growth and decay of delta and alpha variants on the basis of location, age and ethnicity. While much of this macro information is already present in public domains, I failed to comprehend the overall impact of this data. The discussion section too repeats the interpretation of results without actually discussing previously published literature. This section needs to be expanded thoroughly. 2. The reader is left to understand on own to understand all the figures. Figure legends can be more explanatory. 3. The reduction of NPIs can significantly provide transmission advantage to a variant which has been shown in many previous studies. The following figure indicates temporal variation of stringency measures across the UK. The exponential growth of alpha (B.1.1.7) was witnessed in the high stringency index (>80) conditions in the UK, which can describe its high transmission and infectivity rate. The exponential increase in delta variant coincides with a rapid decrease in stringency measures to an index below 50 (https://ourworldindata.org/grapher/covid-stringency-index?tab=chart&country=~GBR) . The authors should statistically verify their data that the transmission advantage is

	independent of stringency measures. Otherwise, it is mere comparison of temporal variant distribution. 4. Likewise, there are other ways which can potentially introduce bias particularly for delta variants, not limited to populations with locally elevated transmission, targeting sequencing as a result of a recent declaration of VOC. Authors should present/discuss how their results are not affected by these confounding factors. • Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references. Answer: Yes, although some of the information is already present in public domain on transmission advantage of variants globally and in specific nations through https://cov-spectrum.ethz.ch/. • Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it? Answer: Yes. The figure legends could be explained in detail to appeal wide readership. • Scientific reliability • Research Question - clearly defined and appropriately answered? Answer: Yes • Overall design of study - adequate ? Answer: This can be improved by statistically comparing emergence of delta variants with relaxation in stringency measures. • Participants studied - adequately described and their conditions defined? Answer: Yes • Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ? Answer: Yes • Results - answer the research question? Credible? Well presented? Answer: Yes • Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear? Answer: The interpretations could be supported with thorough discussion on previously published literature. This section is weak and needs more expansion to communicate clear conclusions. • References - up to date and relevant? Any glaring omissions? Answer: Yes • Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says? Answer: Yes

REVIEWER	Hira, Subhash K.
REVIEW RETURNED	31-Jul-2021

GENERAL COMMENTS	Review BMJ-2021-067675 BMJ : "The Growth and Implications for the Imports of Novel Variants of Concern in the United Kingdom" Reviewer: Subhash Hira, MD, MPH

	General comment: Occurrence of COVID cases sequenced for identification of variants were analysed in the study using Weibull distribution. It is a well-designed study started in January 2021. The case occurrence and Rt is calculated for several non-essential relaxations in restrictions in various geographic locations of the UK, and classified in four categories. However, the sample size of number of cases with each variant is not stated. Analysis of the database is fairly innovative, reliable, and adds a fresh perspective for the general readership and scientists to understand this methodology of monitoring the COVID waves. Title: Authors can consider simplifying the title. The word 'import' is not justified since it doesn't appear in methods and results. My suggestion is for the title to read as "The growth and its factors affecting the spread of novel Variants of Concern (VOC) in the United Kingdom". Introduction: Authors should list virologic name all VOC with their WHO given-names in Greek alphabets. It is suggested to follow that nomenclature through-out in the manuscript. Methods: The Weibull distribution applied to time data is well chosen, but it does not mention the size of the sample. Authors should mention a clear listing of variables such as the UK regions, age groups, hospitalization, sequencers used for testing, NHS laboratories etc to complete this section. This is required to make it easier for the readership to connect with patient profiles, institutions, and regions. Results: Fairly complete section with graphs. The doubling time ranged between 2.9 and 7.5 days. The results appear credible and well presented. Discussion: Authors should add a few sentences related to B.1.351 (Beta variant) that is emerging of late in some areas of the UK. A reference is made to Beta variant in conclusions; hence, for the sake of continuity, a proper link needs to be established by authors. Conclusions: Fairly clear conclusions that are based on results and data analysis. Authors should consider adding few sentences on the concept that if new variants do not emerge, is it likely that Alpha or Beta variants may or may not gain traction as was seen to occur in April 2021? References: References are adequate and appropriate. However, few references such as Wood, WHO etc are left incomplete. Authors are requested to re-check and complete the references. Figures: Captions of Figures 28-30 have typo errors. These need to be checked and corrected by the authors. Tables: These are bit busy tables. I am not sure if these tables add much value for general readership. Instead, these can be shifted to the appendix section. Abstract: Authors should consider re-writing the abstract after the manuscript has incorporated reviewers' suggestions.

REVIEWER	Reviewer 3: Wallau, Gabriel Fundação Oswaldo Cruz
REVIEW RETURNED	02-Aug-2021

GENERAL COMMENTS	Ward and collaborators have investigated the growth rate of different SARS-CoV-2 variants of concern circulating in the United Kingdom. They described several important epidemiological results and impact of these

	variants in age groups, geographic regions and dynamics through time considering the easing of non-pharmacological interventions. These results are timely and highly relevant to understanding the dynamics of VOCs and reproduction number differences mainly concerning the current replacement of B.1.1.7 by B.1.617.2 lineage. Accordingly they estimated that B.1.617.2 has a transmission advantage to B.1.1.7 that partially explains its successful introduction and spread in the United Kingdom. However, I suggest that the authors should better contextualize the results based on vaccination rate in the United Kingdom and vaccine efficacy against B.1.617.2 reported in the literature. Therefore I recommend publication after major review. Raised points: Introduction Page 2 - line 5 - change "artificial immunity" to "vaccine induced immunity" Page 2 - line 5 - "The rate of mutation for coronaviruses is poorly understood;". This is not correct when considering SARS-CoV-2, the deluge of genomic data available allowed many researchers to independently estimate the low mutation rate of this virus. See references below. https://www.nature.com/articles/s41564-020-0771-4 https://www.sciencedirect.com/science/article/abs/pii/S1567134820301829 https://academic.oup.com/ve/article/6/2/veaa061/5894560?login=true Moreover, the comparison with influenza virus can not be done directly. These two viruses belong to different viral families having very different genomic structure and mutation rate. See references below. Page 2 line 29 - “There is also now increasing evidence that B.1.617.2 also has mutated to facilitate increased transmissibility “ please change to “There is also growing evidence that B.1.617.2 acquired mutations that increased the viral fitness improving the transmissibility of this lineage“ Page 2 line 35 - what the authors mean with “triple positive variant” or “novel triple positive VOCs”?. As far as I understood, those comprise VOCs that are positive for the three markers used for qRT-PCR test, correct? Please describe it in more detail the first time it is quoted in the text and consistently reference it afterwards. Discussion: Although the authors mentioned that vaccination in underway in England it would be very important to contextualize vaccination regarding vaccines being applied, their efficacy against each VOC currently circulating in England, the proportion of single and double dose vaccinated patients by age groups and more importantly add a vaccination proxy in some key figures such as 34 and 35. General comments:

	A map of the United Kingdom would particularly benefit the readers. As a suggestion, the authors can generate a figure highlighting the main subdivision discussed in the manuscript and a second map summarizing the main conclusions showing key transitions (Rt positive/negative growth) in space and time for each of the lineages studied.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Recommendation:

Comments:

The manuscript by Ward et al presents interesting analyses on temporal evolution of delta variants within the UK. With a non-evolutionary biologist background, I have some fundamental minor concerns about this manuscript.

1. The study plainly indicates exponential growth and decay of delta and alpha variants on the basis of location, age and ethnicity. While much of this macro information is already present in public domains, I failed to comprehend the overall impact of this data. The discussion section too repeats the interpretation of results without actually discussing previously published literature. This section needs to be expanded thoroughly.

Response

Growth in hospitalisations by variant and the fully sequenced data is not presently available publicly. We have included further citations and literature in the discussion.

2. The reader is left to understand on own to understand all the figures. Figure legends can be more explanatory.

Response

The plots already have a lot of information in them and legends are explained thoroughly in the methods section.

3. The reduction of NPIs can significantly provide transmission advantage to a variant which has been shown in many previous studies. The following figure indicates temporal variation of stringency measures across the UK.

The exponential growth of alpha (B.1.1.7) was witnessed in the high stringency index (>80) conditions in the UK, which can describe its high transmission and infectivity rate. The exponential increase in delta variant coincides with a rapid decrease in stringency measures to an index below 50 (https://ourworldindata.org/grapher/covid-stringency-index?tab=chart&country=~GBR) . The authors should statistically verify their data that the transmission advantage is independent of stringency measures. Otherwise, it is mere comparison of temporal variant distribution.

Response

NPIs are included in the descriptive analysis and we discuss their potential impacts on transmission by variant. Including NPI impact analysis would naturally impact both variants and can be rather speculative. NPIs clearly substantially impact the transmission potential of the SARS-CoV-2 virus however, for this analysis to be included in a meaningful way by variant we would require far more detail than currently exists on the geographical and temporal prevalence of each variant.

4. Likewise, there are other ways which can potentially introduce bias particularly for delta variants, not limited to populations with locally elevated transmission, targeting sequencing as a result of a recent declaration of VOC. Authors should present/discuss how their results are not affected by these confounding factors.

Response

We discuss geographic bias in the sequencing and we have included further information on surge testing around VOCs in the discussion.

• Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references.

Answer: Yes, although some of the information is already present in public domain on transmission advantage of variants globally and in specific nations through https://cov-spectrum.ethz.ch/.

• Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it?

Answer: Yes. The figure legends could be explained in detail to appeal wide readership.

• Scientific reliability

• Research Question - clearly defined and appropriately answered?

Answer: Yes

• Overall design of study - adequate ?

Answer: This can be improved by statistically comparing emergence of delta variants with relaxation in stringency measures.

• Participants studied - adequately described and their conditions defined?

Answer: Yes

• Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ?

Answer: Yes

• Results - answer the research question? Credible? Well presented?

Answer: Yes

• Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear?

Answer: The interpretations could be supported with thorough discussion on previously published literature. This section is weak and needs more expansion to communicate clear conclusions.

• References - up to date and relevant? Any glaring omissions?

Answer: Yes

• Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says?

Answer: Yes

Response

Addressed in the above

Reviewer: 2

Recommendation:

Comments:
Review BMJ-2021-067675 BMJ : "The Growth and Implications for the Imports of Novel Variants of Concern in the United Kingdom"
Reviewer: Subhash Hira, MD, MPH
General comment: Occurrence of COVID cases sequenced for identification of variants were analysed in the study using Weibull distribution. It is a well-designed study started in January 2021. The case occurrence and Rt is calculated for several non-essential relaxations in restrictions in various geographic locations of the UK, and classified in four categories. However, the sample size of number of cases with each variant is not stated. Analysis of the database is fairly innovative, reliable, and adds a fresh perspective for the general readership and scientists to understand this methodology of monitoring the COVID waves.

Response

Sample size is indicative by the uncertainty in the confidence intervals of the GAM model, which is explained in the results section. We have provided sample sizes for the doubly interval censored Weibull model in Appendix H
Title: Authors can consider simplifying the title. The word ‘import’ is not justified since it doesn’t appear in methods and results. My suggestion is for the title to read as “The growth and its factors affecting the spread of novel Variants of Concern (VOC) in the United Kingdom”.

Response

The title has been changed as suggested by the Editor and reviewer

Introduction: Authors should list virologic name all VOC with their WHO given-names in Greek alphabets. It is suggested to follow that nomenclature through-out in the manuscript.

Response

Included in the introduction

Methods: The Weibull distribution applied to time data is well chosen, but it does not mention the size of the sample. Authors should mention a clear listing of variables such as the UK regions, age groups,

hospitalization, sequencers used for testing, NHS laboratories etc to complete this section. This is required to make it easier for the readership to connect with patient profiles, institutions, and regions.

Response

We do not have ethical approval to provide this level of disclosive data but it can be provided upon application to Public Health England

Results: Fairly complete section with graphs. The doubling time ranged between 2.9 and 7.5 days. The results appear credible and well presented.
Discussion: Authors should add a few sentences related to B.1.351 (Beta variant) that is emerging of late in some areas of the UK. A reference is made to Beta variant in conclusions; hence, for the sake of continuity, a proper link needs to be established by authors.

Response

Further information has been included on B.1.351 in the discussion

Conclusions: Fairly clear conclusions that are based on results and data analysis. Authors should consider adding few sentences on the concept that if new variants do not emerge, is it likely that Alpha or Beta variants may or may not gain traction as was seen to occur in April 2021?
References: References are adequate and appropriate. However, few references such as Wood, WHO etc are left incomplete. Authors are requested to re-check and complete the references.
Figures: Captions of Figures 28-30 have typo errors. These need to be checked and corrected by the authors.
Tables: These are bit busy tables. I am not sure if these tables add much value for general readership. Instead, these can be shifted to the appendix section.
Abstract: Authors should consider re-writing the abstract after the manuscript has incorporated reviewers' suggestions.

Response

Further information included in the conclusion. Reference issue has been resolved. The table on Doubly Interval Censored Model has been moved to the appendix H. Abstract has been restructured in line with BMJ Open policy

Reviewer: 3

Recommendation:
Comments:
Ward and collaborators have investigated the growth rate of different SARS-CoV-2 variants of concern circulating in the United Kingdom. They described several important epidemiological results and impact of these variants in age groups, geographic regions and dynamics through time considering the easing of non-pharmacological interventions. These results are timely and highly relevant to understanding the dynamics of VOCs and reproduction number differences mainly concerning the current replacement of B.1.1.7 by B.1.617.2 lineage. Accordingly they estimated that B.1.617.2 has a transmission advantage to B.1.1.7 that partially explains its successful introduction and spread in the United Kingdom. However, I suggest that the authors should better contextualize the results based on vaccination rate in the United Kingdom and vaccine efficacy against B.1.617.2 reported in the literature. Therefore I recommend publication after major review.

Response

The comment for review related to literature of vaccine efficacy against B.1.617.2. We have included further context related to vaccination and literature related to efficacy.

Raised points:

Introduction

Page 2 - line 5 - change "artificial immunity" to "vaccine induced immunity"

Response

Changed

Page 2 - line 5 - "The rate of mutation for coronaviruses is poorly understood;". This is not correct when considering SARS-CoV-2, the deluge of genomic data available allowed many researchers to independently estimate the low mutation rate of this virus. See references below.

https://www.nature.com/articles/s41564-020-0771-4

https://www.sciencedirect.com/science/article/abs/pii/S1567134820301829

https://academic.oup.com/ve/article/6/2/veaa061/5894560?login=true

Moreover, the comparison with influenza virus can not be done directly. These two viruses belong to different viral families having very different genomic structure and mutation rate. See references below.

Response

This comment was in comparison to influenza that has been more thoroughly studied over the years and much literature has been published that draws a comparison between the influenza and the COVID-19 rate of mutation as cited in the article. We have included further information and amended some of the text but the provided references were assessed for this paper and are not conclusive evidence of a low rate of mutation, as much literature disputes, also given the context of a high number of infections.

Page 2 line 29 - “There is also now increasing evidence that B.1.617.2 also has mutated to facilitate increased transmissibility “ please change to “There is also growing evidence that B.1.617.2 acquired mutations that increased the viral fitness improving the transmissibility of this lineage“

Response

This has been amended

Page 2 line 35 - what the authors mean with “triple positive variant” or “novel triple positive VOCs”?. As far as I understood, those comprise VOCs that are positive for the three markers used for qRT-PCR test, correct? Please describe it in more detail the first time it is quoted in the text and consistently reference it afterwards.

Discussion:

Although the authors mentioned that vaccination in underway in England it would be very important to contextualize vaccination regarding vaccines being applied, their efficacy against each VOC currently

circulating in England, the proportion of single and double dose vaccinated patients by age groups and more importantly add a vaccination proxy in some key figures such as 34 and 35.

Response

Added as context in the introduction and tables has been included on the vaccination rate by ages in the results section

General comments:

A map of the United Kingdom would particularly benefit the readers. As a suggestion, the authors can generate a figure highlighting the main subdivision discussed in the manuscript and a second map summarizing the main conclusions showing key transitions (Rt positive/negative growth) in space and time for each of the lineages studied.

Response

A map would not lend itself to temporal changes in the growth rate. Moreover, the appendix is very thorough and there are a lot of graphs in the paper so I am reluctant to include further images as a reduction of images has been requested by the editor.

VERSION 2 – REVIEW

REVIEWER	Hira, Subhash University of Washington, Global Health
REVIEW RETURNED	13-Sep-2021

GENERAL COMMENTS	If authors have obtained the NHS permission to include the table of sample size of each variant, it will considerably improve quality of the manuscript.

REVIEWER	Wallau, Gabriel
REVIEW RETURNED	13-Sep-2021

GENERAL COMMENTS	Ward and collaborators have investigated the growth rate of different SARS-CoV-2 variants of concern circulating in the United Kingdom. They described several important epidemiological results and impact of these variants in age groups, geographic regions and dynamics through time considering the relaxation of non-pharmacological interventions. These results are timely and highly relevant to understanding the dynamics of VOCs and reproduction number differences mainly concerning the current replacement of B.1.1.7 by B.1.617.2 lineage. Accordingly, they estimated that B.1.617.2 has a transmission advantage to B.1.1.7 that partially explains its successful introduction and spread in the United Kingdom. I have reviewed an early version of this manuscript to another journal and the authors followed my suggestions satisfactorily.

	Minor points Introduction Page 2 line8 - “Periods of high global prevalence of the virus has driven novel mutations through” change to “Periods of high global prevalence of the virus has allowed the emergence of novel mutations through” Page 2 line 18 “finding that individuals that had recently travelled had a higher relative reproductive number.” What did the authors mean with that sentence? If I understood well they meant “SARS-CoV-2 lineages derived from individuals that had recently travelled had a higher relative reproductive number”. If yes, please correct it. Page 3 line 17-18 - Spell out “LTLA” the first time it is quoted in the text. Gabriel Luz Wallau

REVIEWER	Hasnain, Seyed H Institute of Molecular Medicine
REVIEW RETURNED	17-Sep-2021

GENERAL COMMENTS	The manuscript by Ward et al presents interesting analyses on temporal evolution of delta variants within UK. The manuscript is well written and can be accepted for publication after addressing the following concerns. 1. The authors discuss role of various factors which affect spread of new variants. The data however correspond to temporal variation of triple positive cases among various groups. I could not ascertain exact role of factors in the entire manuscript. This should be addressed or authors may change title as it is misleading. 2. Figure legends should be more explanatory. 3. Discussion could be more extensive rather being repetitive of the manuscript text.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. Subhash Hira, University of Washington, Public Health Foundation of India Comments to the Author:
If authors have obtained the NHS permission to include the table of sample size of each variant, it will considerably improve quality of the manuscript.
The sample size has now been included for every figure in the main text.

Reviewer: 2
Dr. Gabriel Wallau
Comments to the Author:

Ward and collaborators have investigated the growth rate of different SARS-CoV-2 variants of concern circulating in the United Kingdom. They described several important epidemiological results and impact of these variants in age groups, geographic regions and dynamics through time considering the relaxation of non-pharmacological interventions. These results are timely and highly relevant to understanding the dynamics of VOCs and reproduction number differences mainly concerning the current replacement of B.1.1.7 by B.1.617.2 lineage. Accordingly, they estimated that B.1.617.2 has a transmission advantage to B.1.1.7 that partially explains its successful introduction and spread in the United Kingdom. I have reviewed an early version of this manuscript to another journal and the authors followed my suggestions satisfactorily.

Minor points

Introduction

Page 2 line8 - “Periods of high global prevalence of the virus has driven novel mutations through” change to “Periods of high global prevalence of the virus has allowed the emergence of novel mutations through”
Changed as suggested
Page 2 line 18 “finding that individuals that had recently travelled had a higher relative reproductive number.” What did the authors mean with that sentence? If I understood well they meant “SARS-CoV-2 lineages derived from individuals that had recently travelled had a higher relative reproductive number”. If yes, please correct it.
Changed as suggested

Page 3 line 17-18 - Spell out “LTLA” the first time it is quoted in the text.
I have included this on line 17-18.

Reviewer: 3
Dr. Seyed Hasnain, JH Institute of Molecular Medicine Comments to the Author:
The manuscript by Ward et al presents interesting analyses on temporal evolution of delta variants within UK. The manuscript is well written and can be accepted for publication after addressing the following concerns.

1. The authors discuss role of various factors which affect spread of new variants. The data however correspond to temporal variation of triple positive cases among various groups. I could not ascertain exact role of factors in the entire manuscript. This should be addressed or authors may change title as it is misleading.

   It is made clear in the limitations and discussion that the factors which impact transmission and are analysed descriptively.

2. Figure legends should be more explanatory.

   The plots are very detailed, and the legends are explained in depth in the methodology section.

3. Discussion could be more extensive rather being repetitive of the manuscript text.

   It is not clear which part of the text the reviewer is referring to here. Some repetition with the results section is necessary for this paper to contextualise and explain the trends observed.