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Short communication

Differences in the case fatality risks associated with SARS-CoV-2 Delta and non-Delta variants in relation to vaccine coverage: An early ecological study in the United Kingdom

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ABSTRACT

The circulation of SARS-CoV-2 Delta (i.e., B.1.617.2) variants challenges the pandemic control. Our analysis showed that in the United Kingdom (UK), the reported case fatality ratio (CFR) decreased from May to July 2021 for non-Delta variant, whereas the decreasing trends of the CFR of Delta variant appeared weak and insignificant. The association between vaccine coverage and CFR might be stratified by different circulating variants. Due to the limitation of ecological study design, the interpretation of our results should be treated with caution.

1. Introduction

Assessment of mutation influence on clinical severity of infectious diseases provides important information for characterizing disease burden at population scale. The Delta variant (B.1.617.2) of SARS-CoV-2 is spreading rapidly around the world, which was first detected in India by the end of 2020. In the United Kingdom (UK), it first appeared in February 2021 and quickly reached fixation in July 2021 (Fig. 1B).

Although the Delta variant is considered with higher transmissibility that leads to the growth in COVID-19 epidemic curve (Fig. 1A) (Ito et al., 2021), the fatality risk of Delta variants remains largely unassessed.

2. Methods

The national-wide COVID-19 surveillance data of cases and deaths (Fig. 1A) and SARS-CoV-2 genetic sequences (Fig. 1B), which were grouped into Delta and non-Delta variants, in the UK were collected from April to July 2021 (Supplementary Information S1). We reconstructed variant-specific delay-adjusted case fatality ratio (CFR) on a real-time basis by the statistical framework in (Zhao et al., 2021), see Supplementary Information S2. The relative risk (ζ) between the fatality risks of Delta against non-Delta variants is quantified as a time-varying relative ratio (RR) between variant-specific CFRs. The percentage of vaccine recipients of two doses in the UK, namely vaccine coverage, was collected on a daily basis (Fig. 1D). We examined and compared the relationships between vaccine coverage and CFRs of Delta or non-Delta variants using generalized linear regression models.

3. Results and discussion

The estimated CFR of non-Delta gradually decreased from 0.57% to 0.20% with interquartile range (IQR) of (0.39% – 0.23%) = 0.16%, whereas the CFR of Delta appears relatively stable at 0.19% with IQR of (0.21% – 0.16%) = 0.05% from May to July 2021 (Fig. 1C). We found that ζ is slightly but not significantly lower than 1 (Fig. 1D) implying no statistically significant difference between the CFRs of Delta and non-Delta variants.

The vaccine coverage increased steadily since the end of 2020 and reached 52.4% as of July 15, 2021 (Fig. 1D). The CFR of non-Delta was negatively associated with lagged vaccine coverage with p-value <0.01 (Fig. 1E), and we also testify that the estimated linear relationship in Fig. 1E is consistent with the CFR of Alpha variants (i.e., B.1.1.7) and vaccine coverage around early 2021. However, the negative association for CFR of Delta appeared weak and not statistically evident (Fig. 1F). As
such, the statistical relation between vaccine coverage and CFR is stratified by Delta or non-Delta variants. For sensitivity analysis, see Supplementary Information S3, we report that the statistical relations between vaccine coverage and CFRs are consistent with alternative settings (data not shown).

Evidence suggests that neutralizing antibody activities from prior infection or vaccination scaled down against Delta variants (Yadav et al., 2021; Planas et al., 2021). As Delta variant showed transmission advantage and became dominant in many places globally (Ito et al., 2021), we highlight that the fatality risk of Delta might result in a short-term growing volume of COVID-19 patients with critical status, which alters an increasing burden to healthcare system. Despite the stratified effect on fatality, the vaccine-stimulated herd immunity maintains crucial to provide protection against infection, mitigate outbreak size, and improve public health conditions on the whole.

Importantly, although the effect of vaccine coverage on reducing the CFR of Delta appears minor in our study, we remark that as an ecological study, heterogeneities in fatality risks and vaccination distribution for different groups of population, e.g., age groups, or groups with different healthcare-seeking behaviors, cannot be adjusted without individual-based datasets. Even the fatality risk estimates of Alpha variants appeared higher than those of Delta variants (Fig. 1C), it is possible that most of the vulnerable individuals were dead before April 2021, when Alpha variants were circulating, but individuals ‘survived from Alpha variants’ with relatively healthy conditions were more likely to recovery from infection by Delta variants. Without accounting for different levels of vulnerability of the population exposed to Alpha or Delta variants, the seemingly high mortality rate might be produced from an unadjusted calculation. Similar ecological fallacy might also occur without considering the heterogeneity in the distribution of vaccines. Therefore, the

Fig. 1. The COVID-19 cases and deaths, Delta variants, case fatality ratios, and vaccine coverage in the UK.
The daily number of COVID-19 cases and deaths (A), proportion of the SARS-CoV-2 Delta variants (B), the reconstructed instantaneous (or time-varying) case fatality ratios (CFR) (D), and vaccine coverage (D) in the United Kingdom (UK). In panel (B), the sample size of SARS-CoV-2 strains collected on each day (denoted by n) is reflected by the size of each dot. Panel (C) shows that the estimated CFRs of non-Delta (blue), and Delta (red) variants. In panel (D), the green curve is the vaccine coverage, and the orange bars and area are the estimated relative ratios (RR) of CFR of Delta against that of non-Delta variants. In panels (C) and (D), the horizontal bars are the maximal likelihood estimates (MLE), and the shading areas indicate the 95% confidence intervals (95%CI). Panels (E) and (F) show that the statistical relation between vaccine coverage and CFR of non-Delta (triangular) and Delta (diamond) variants, respectively. In panel (E), the circled dots at the top-right corner are the CFR of Alpha variants. In panels (E) and (F), the dashed lines are the estimated linear associations between vaccine coverage (lagged for +21 days accounting for the delay in the effects of immune responses) and CFR, where the statistical significances are presented in the panel legends. The dots and bars are the MLEs and 95%CIs, respectively.

Note: The contents in panels (E) and (F) are directly extracted from the CFR estimates and vaccine coverage observations in panels (C) and (D) by matching the calendar dates. The scales of axes in panels (E) and (F) are the same. From April 1 to July 15, 2021, more than 99.9% out of a total of over 150 thousand SARS-CoV-2 strain samples in the UK are either Delta or Alpha (i.e., B.1.1.7) variants, and thus non-Delta variants are (almost) equivalent to the Alpha variants in the situation of this study. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
interpretation of our results should be treated with caution, and merely limited to a general populational scale at current stage, e.g., before a sufficiently high vaccine coverage is reached. Strengths and other limitations of the data and analysis are discussed in Supplementary Information S4, some of which are pointed out in (Ong et al., 2021).

4. Conclusions

The association between vaccine coverage and CFR may be stratified by different circulating variants. Due to the limitation of ecological study design, the interpretation of this finding should be treated with caution.

Ethics approval and consent to participate

The COVID-19 number of cases and SARS-CoV-2 sequence data are collected via public domains, and thus neither ethical approval nor individual consent is applicable.

Consent for publication

Not applicable.

Access to data and data analysis

All data used in this work are publicly available. SZ and MHW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of funder/sponsor statement

The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Non-author contributions

None.

Declaration of Competing Interest

MHW is a shareholder of Beth Bioinformatics Co., Ltd. BCYZ is a shareholder of Beth Bioinformatics Co., Ltd. and Health View Bioanalytics Ltd. Other authors declared no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.meegid.2021.105162.

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