Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study

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Summary

Background The SARS-CoV-2 delta (B.1.617.2) variant was first detected in England in March, 2021. It has since rapidly become the predominant lineage, owing to high transmissibility. It is suspected that the delta variant is associated with more severe disease than the previously dominant alpha (B.1.1.7) variant. We aimed to characterise the severity of the delta variant compared with the alpha variant by determining the relative risk of hospital attendance outcomes.

Methods This cohort study was done among all patients with COVID-19 in England between March 29 and May 23, 2021, who were identified as being infected with either the alpha or delta SARS-CoV-2 variant through whole-genome sequencing. Individual-level data on these patients were linked to routine health-care datasets on vaccination, emergency care attendance, hospital admission, and mortality (data from Public Health England’s Second Generation Surveillance System and COVID-19-associated deaths dataset; the National Immunisation Management System; and NHS Digital Secondary Uses Services and Emergency Care Data Set). The risk for hospital admission and emergency care attendance were compared between patients with sequencing-confirmed delta and alpha variants for the whole cohort and by vaccination status subgroups. Stratified Cox regression was used to adjust for age, sex, ethnicity, deprivation, recent international travel, area of residence, calendar week, and vaccination status.

Findings Individual-level data on 4338 COVID-19-positive patients (8682 with the delta variant, 34 656 with the alpha variant; median age 31 years [IQR 17–43]) were included in our analysis. 196 (2.3%) patients with the delta variant versus 764 (2.2%) patients with the alpha variant were admitted to hospital within 14 days after the specimen was taken (adjusted hazard ratio [HR] 2.26 [95% CI 1.32–3.89]). 498 (5.7%) patients with the delta variant versus 1448 (4.2%) patients with the alpha variant were admitted to hospital or attended emergency care within 14 days (adjusted HR 1.45 [1.08–1.95]). Most patients were unvaccinated (32078 [74.0%] across both groups). The HRs for vaccinated patients with the delta variant versus the alpha variant (adjusted HR for hospital admission 1.94 [95% CI 0.47–8.05] and for hospital admission or emergency care attendance 1.58 [0.69–3.61]) were similar to the HRs for unvaccinated patients (2.32 [1.29–4.16] and 1.43 [1.04–1.97]; p=0.82 for both) but the precision for the vaccinated subgroup was low.

Interpretation This large national study found a higher hospital admission or emergency care attendance risk for patients with COVID-19 infected with the delta variant compared with the alpha variant. Results suggest that outbreaks of the delta variant in unvaccinated populations might lead to a greater burden on health-care services than the alpha variant.

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Introduction

As SARS-CoV-2 evolves and new variants emerge worldwide, sustained monitoring and rapid assessment of genetic changes are required to inform the public health response and health-care management of COVID-19. WHO has outlined three key criteria to designate variants of concern (VOCs) in relation to global public health: increased transmissibility, increase in virulence or change in clinical disease presentation, and decrease in effectiveness of public health and social measures or available diagnostics, vaccines, and therapeutics.1 One of the first VOCs, alpha (B.1.1.7), was initially detected in England in November, 2020. Alpha had increased transmissibility compared with the previous wildtype lineage,2,3 and became the predominant lineage accounting for 95% of cases in England by early February, 2021.4 This variant has been identified in...
Research in context

Evidence before this study
We did a literature review to identify all publications on the severity of the SARS-CoV-2 delta variant (B.1.617.2). We searched PubMed on June 18, 2021, using the query: “((SARS-CoV-2) OR (COVID-19) OR (coronavirus disease 2019)) AND ((B.1.617.2) OR (Delta) OR (VOC-21APR-02)) AND ((severity) OR (hospitalisation) OR (hospital) OR (emergency care) OR (mortality) OR (lethality) OR (death))”. The search was restricted to articles published from Dec 1, 2020, with no language restrictions. Only one relevant publication was found. Based on record linkage of data on 7,723 delta and 11,820 alpha variant COVID-19 cases between April 1 and June 6, 2021, with routine health-care data, the EAVE II study in Scotland reported a higher risk of hospital admission within 14 days for patients with the delta variant compared with the alpha variant (hazard ratio [HR] 1.85 [95% CI 1.39–2.47]). The patients had been tested through PCR tests and variant status was determined based on S-gene positivity, a proxy test for SARS-CoV-2 variant.

Added value of this study
This study included data on 8,682 patients with the delta variant and 34,656 patients with the alpha variant, confirmed by whole-genome-sequencing. Hence, to our knowledge, it is the largest study to date to report on hospitalisation risk for the delta variant compared with the alpha variant, and the first to do so based on sequencing-confirmed variants. The HR of hospital admission within 14 days was 2.26 (95% CI 1.32–3.89) after stratification and regression adjustment for confounders. We also believe this study is the first to estimate a risk for emergency care attendance or hospital admission within 14 days; the adjusted HR was 1.45 (1.08–1.95).

Implications of all the available evidence
The evidence from these two studies in Scotland and England consistently suggest that patients with COVID-19 who are infected with the delta variant have approximately two times the risk of hospital admission compared with patients with the alpha variant. These findings should be considered for resource and policy planning in secondary care, particularly in areas where the delta variant is increasing and is likely to become the dominant circulating SARS-CoV-2 variant.

154 countries and was until recently the most prevalent lineage in Europe and North America. The B.1.617 lineage was first reported in India in December, 2020. Following previous waves of COVID-19, the number of confirmed cases and test positivity in India rapidly increased, with the latter reaching 30% by the end of April, 2021. In Delhi, this coincided with the B.1.617 lineages overtaking the alpha lineage, accounting for 60% of all sequenced samples. During this increase, the sub-lineage delta (B.1.617.2) also increased to approximately 80% of B.1.617 cases.

The delta variant was first detected in England in March, 2021, and was designated as a VOC on May 6, 2021. The proportion of COVID-19 cases in England caused by the delta variant has rapidly increased, reaching more than 50% of sequenced isolates by May 25, 2021. Studies in India have estimated that the delta variant could be up to 50% more transmissible than the alpha variant. In England, the secondary attack rate for the delta variant was found to be nearly 3%, compared with less than 2% for the alpha variant. In addition, there is evidence of modest reduction in vaccine effectiveness against infection with the delta variant. However, among patients infected with the delta variant, previous vaccination has been reported to reduce the risk of hospital admission.

To inform the public health response to the delta variant, we did two analyses. First, we characterised the severity of the delta variant compared with the alpha variant by determining the relative risk of hospital attendance or admission following infection using a stratified analysis. Second, we assessed whether associations with hospital attendance outcomes were modified by vaccination.

Methods

Data sources and definitions
This cohort study was done in England among individuals with laboratory-confirmed COVID-19. COVID-19 is a notifiable disease and Public Health England collects data on all positive cases in England held within the Second Generation Surveillance System (SGSS). Individual-level data on patients with laboratory-confirmed COVID-19 with first positive specimen dates between March 29 and May 23, 2021, were linked with sequencing data uploaded to the Cloud Infrastructure for Big Data Microbial Bioinformatics database. Sampling for whole-genome sequencing mainly includes geographic-weighted population-level sampling of community cases, but can be supplemented by targeted selection such as recent international travellers, care homes, or National Health Service (NHS) diagnostic laboratories. Variant classification was assigned on the basis of lineage definitions from Public Health England. Patients with whole-genome-sequencing-confirmed alpha and delta variants were deterministically linked with data on vaccination, hospital care, and mortality using NHS number. A full description of the data sources is in the appendix (p 1).

Potential cases of re-infection were removed to avoid misallocation of variants to different episodes of care by excluding observations for which the sequenced
specimen collection date was more than 14 days after the specimen collection date of the individual’s first recorded positive test. Observations without an NHS number could not be linked to health-care datasets and were excluded.

The surveillance activities within which this study was conducted are part of Public Health England’s responsibility to monitor COVID-19 during the current pandemic. Public Health England has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002 to process confidential patient information under Sections 3(i)–c, 3(ii)–d(i) and (ii), and 3(iii) as part of its outbreak response activities. This study falls within the research activities approved by the Public Health England Research Ethics and Governance of Public Health Practice Group.

Hospital attendance categorisation

Hospital care data from the Emergency Care Data Set (ECDS) and Secondary Uses Service (SUS) were linked to data for patients with confirmed COVID-19 on June 7, 2021, thereby including data submitted by NHS Trusts up to June 5, 2021. Two outcomes of hospital attendance were defined: (1) hospital admission only, and (2) attendance to emergency care or hospital admission.

Due to a lag between an individual’s hospital admission and submission of corresponding SUS data (up to 8 weeks), the definition of hospital admission was determined using a combination of ECDS and SUS variables, some of which exist in only one data source. Where ECDS data were available, hospital admissions were classified as COVID-19 related if a patient presented to emergency care between 1 and 14 days after the patient’s first SARS-CoV-2-positive specimen date, there was no International Classification of Disease version 10 (ICD10) code indicating that the attendance was injury-related, and discharge details did not indicate transfer or admission.

Where SUS data were available, hospital admissions were defined using two sets of criteria. The first set of criteria defined if the hospital visit was related to COVID-19 infection and the second evaluated whether the hospital visit qualified as an admission. All hospital visits for which the attendance date was between 1 and 14 days after the first positive specimen date were considered COVID-19 related. If the admission date was the same as the specimen date, the visit was considered COVID-19 related if (1) the patient’s symptom onset date recorded in the laboratory system at the time of test was reported between 1–7 days before the specimen was taken, or (2) if hospital records included ICD10 codes relevant to COVID-19 and the patient died in hospital. These criteria add the flexibility of including records with evidence of onset preceding hospital attendance and severe COVID-19 related outcomes, without including coincidental hospitalisations among infected individuals. Admissions were defined as those where the interval between admission and discharge was more than 0 days; or if the interval between admission and discharge was 0 days and either the hospital record included ICD10 codes relevant to COVID-19 symptoms, or the patient died in hospital, or both.

Attendances to emergency care were included in the second hospital attendance outcome category. A patient was defined as having a COVID-19-related emergency care attendance if ECDS data indicated presentation to emergency care between 1 and 14 days after the patient’s first SARS-CoV-2-positive specimen date, there was no ICD10 code indicating that the attendance was injury-related, and discharge details did not indicate transfer or admission.

Unless meeting the criteria described in this section, individuals who first tested positive on the same date as their hospital admission or attendance date were excluded to reduce bias of routine testing at admission for non-COVID-19 related attendances.

Covariates and confounders

Age, sex, and area of residence were extracted from SGSS for patients with COVID-19. National-level Index of Multiple Deprivation (IMD) quintile groups were matched to the patient’s lower super output area of residence. IMD is an area-level measure of relative socioeconomic deprivation. Ethnicity was determined from linkage to NHS England’s Hospital Episodes Statistics data and through self-reported ethnicity at the COVID-19 test request.

Recent travel was defined as a record of travel outside of the UK within 14 days before the patient’s positive COVID-19 test. This indicator was derived from five data sources: public health passenger locator forms, contact tracing of patients done by Public Health England and NHS Test and Trace, travel reported in the COVID-19 test request form, records from the International Arrival COVID-19 testing programme, and additional questionnaires completed through telephone interview for patients for whom no other travel information was available.

Confounder sets were chosen for either stratification or regression adjustment on the basis of the expected strength of the association with exposure or outcomes. The initial outbreaks of the delta variant were localised to northern England and observed in south Asian ethnic groups, and increasing prevalence of the delta variant coincided with the expansion of the COVID-19 vaccination programme to younger age groups. Therefore, the set of most likely confounders included age (10-year age bands), ethnicity (White; Asian; Black; and mixed, other, or unknown), calendar week of specimen, area of residence (lower tier local authority [LTLA]: 314 areas), and vaccination status.

Additional potential confounders included sex and socioeconomic deprivation (IMD quintiles) due to association with hospitalisation risk, and international travel within 14 days of positive test, which was more
common for patients with the delta variant when its incidence first began to increase in England. There was no a-priori expectation that these variables would strongly confound the associations between variant and outcomes so they were considered for regression adjustment rather than stratification.

Statistical analysis
Patients were followed up for a maximum of 14 days from their earliest COVID-19-positive specimen until the hospital admission or emergency care attendance date. Patients were censored at the date of death if this occurred without a previous hospital attendance event within the 14-day period.

In the primary analysis, stratified Cox regression was used to estimate hazard ratios (HRs) of the hospitalisation outcomes (hospital admission or emergency care attendance) for patients with the delta variant compared with patients with the alpha variant. Strata were created by intersecting the likely confounders. Additional potential confounders were included using main effects. Linear main effects terms for age and calendar date were used to adjust for residual confounding after stratification.

In the secondary analysis, the HRs of the hospitalisation outcomes by variant were estimated by vaccination status. The base models were refitted with an interaction term between variant and vaccination. Due to low numbers of patients with COVID-19 who had been vaccinated, and consequently low numbers within some vaccination categories, vaccination status was grouped into two categories: unvaccinated or less than 21 days since the first vaccination dose; and 21 days or more since the first vaccination dose, with or without the second dose.

In additional analyses, the proportional hazards assumption of the Cox regression model was graphically assessed using Schoenfeld residual plots and formally tested using the Schoenfeld test. Post-evaluations of the relative magnitudes of the confounders’ contribution to the adjusted HRs were done by sequentially adding the adjustment variables in the order of the percentage change in the adjusted HRs for patients with the delta variant versus the alpha variant. To assess the impact of stratification versus regression modelling on the HRs and 95% CIs, the primary model was refitted with each stratification variable instead included as a regression variable.

HRs were assessed for sensitivity to stratification by alternative region or calendar period covariates, confounding due to recent international travel or symptomatic status subgroups, or to the precise outcome definitions. Details are shown in the appendix (p 8).

Data were prepared using Stata version 15.1. Statistical analyses were done in R version 4.1.0.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication.

Results
Of the 49,930 sequencing-confirmed cases of alpha and delta variants in England from March 29 to May 23, 2021, 43,338 were included in our analysis (appendix p 2). 5634 records were excluded due to missing NHS numbers (4240 [10·7%] of 39,677 patients with the alpha variant and 1394 [13·6%] of 10,253 patients with the delta variant). Missing NHS number occurred more frequently among Black and Asian individuals than White individuals (1512 [15·0%] of 10,075 Asian, 291 [19·3%] of 1508 Black, and 2574 [7·7%] of 33,306 White individuals), and among international travellers (871 [29·5%] of 2952 international travellers vs 4762 [10·1%] of 46,977 non-travellers).

34,656 patients were infected with the alpha variant and 8682 patients had the delta variant; the proportion of weekly cases by variant changed across the study period with alpha decreasing from 7593 (99·8%) of 7606 cases in the week of March 29, 2021, to 2117 (34·8%) of 6090 cases in the week of May 17, 2021. Patients with the delta variant were younger (median age 29 years [IQR 15–41]) than patients with the alpha variant (median age 31 years [17–43]). Compared with patients with the alpha variant, a greater proportion of patients with the delta variant were from an Asian background, or lived in the north west of England or London (table 1).

The results of the analysis of hospital attendance outcomes among patients with the alpha variant versus the delta variant are shown in table 2. The estimated risk for hospital admission within 14 days after the specimen was taken was higher among patients with the delta variant than the alpha variant. The estimated risk for hospital admission or emergency care within 14 days was also higher among patients with the delta variant than the alpha variant.

Table 3 shows the HRs of the hospital attendance outcomes for patients with the delta variant versus the alpha variant by vaccination status. Among patients who were unvaccinated or had less than 21 days since the first vaccination dose, patients with the delta variant had a higher estimated risk of hospital admission and a higher risk of either hospital admission or emergency care attendance than patients with the alpha variant. In the subgroup of vaccinated patients (≥21 days after first vaccination dose, with and without a second dose), no significant difference was detected in the estimated risk for either hospital attendance outcome between patients with the delta variant and patients with the alpha variant. The risk estimates for the delta versus the alpha variant among vaccinated patients were limited by low precision and wide CIs. There were no significant interactions when comparing the HRs in the vaccinated versus unvaccinated subgroups (table 3).

The Schoenfeld residuals and test showed no significant deviation from the proportional hazards...
Discussion

New SARS-CoV-2 infections in England are increasingly caused by the delta variant. Although the proportion of cases caused by the delta variant was 20% overall during the study period, this increased to 74% of new sequenced cases in the week starting May 31, 2021. To our knowledge, this study provides the largest whole-genome-sequencing dataset for SARS-CoV-2 in a high-income country to date, enabling the assessment of hospitalisation risk for the delta variant compared with the alpha variant using linked administrative data. The results suggest that patients with the delta variant had more than two times the risk of hospital admission compared with patients with the alpha variant. Emergency care attendance combined with hospital admission was also higher for patients with the delta variant, showing increased use of emergency care services as well as inpatient hospitalisation. Similar results were observed for the subgroup of unvaccinated patients when comparing risks of both hospital care outcomes between the two variants.

In the subgroup of patients who had received at least one vaccine dose (≥21 days since their first dose), the precision of both hospital care outcomes was higher for patients with the delta variant than for patients with the alpha variant (appendix p 7). The sensitivity analyses in which the impact on the results was assessed after adjustment for alternative region or calendar period variables, symptomatic status, analyses of subgroups, or after varying the outcome definitions are shown in the appendix (pp 8–9). The estimated risk for both categories of hospital attendance outcomes was consistently higher for patients with the delta variant than for patients with the alpha variant in all sensitivity analyses. The differences were consistently statistically significant, except the subgroup analysis by symptom status, in which the CIs were wider, and in some instances included 1.

### Table 1

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Overall (n=43338)</th>
<th>Alpha variant (B.1.1.7; n=34656)</th>
<th>Delta variant (B.1.617.2; n=8682)</th>
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<td>&lt;10</td>
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<td>22 152 (6.9%)</td>
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<td>Male</td>
<td>21 176 (6.9%)</td>
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<td>25 940 (7.8%)</td>
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<td>2</td>
<td>9474 (21.9%)</td>
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<td>1957 (22.5%)</td>
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<td>3</td>
<td>7326 (16.9%)</td>
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<td>1329 (15.9%)</td>
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<td>6737 (15.5%)</td>
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<td>5</td>
<td>5321 (12.3%)</td>
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<td>5568 (16.1%)</td>
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<td>443 (12.0%)</td>
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<td>Unvaccinated</td>
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<td>&lt;21 days after first vaccination dose</td>
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<td>≥21 days after first vaccination dose</td>
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<td>6172 (17.8%)</td>
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<td>≥14 days after second vaccination dose</td>
<td>794 (1.8%)</td>
<td>455 (1.3%)</td>
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<thead>
<tr>
<th>Recent international travel within 14 days before specimen</th>
<th>Overall (n=43338)</th>
<th>Male (n=21767)</th>
<th>Female (n=21571)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>41 435 (95.6%)</td>
<td>33 218 (95.9%)</td>
<td>8217 (94.6%)</td>
</tr>
<tr>
<td>Yes</td>
<td>1903 (4.4%)</td>
<td>1438 (4.1%)</td>
<td>465 (5.4%)</td>
</tr>
</tbody>
</table>

(continued on next page)
Articles

This analysis is strengthened by using national, timely datasets on COVID-19 cases, hospital care episodes, and vaccinations. The individual-level data included all laboratory-confirmed COVID-19 cases, up to 98% of hospital activity, and all vaccinated individuals registered with a general practitioner in England, \cite{10.1016/S1473-3099(21)00475-8} with these data updated daily. Whole-genome sequencing coverage in England increased throughout the study period: for new positive tests between April 23 and May 24, 2021, more than 60% were successfully sequenced.\textsuperscript{1}

Compared with a matched study design, the stratified Cox regression method offers the advantage of using all potential matches rather than a fixed number of patients with the alpha variant per patient with the delta variant. Confounders such as changing demographic profiles of patients by variant or local interventions over time are accounted for. However, this method results in a loss of informative observations when stratifying by many covariates, reducing precision compared with estimates based on adjustment through regression modelling.

Administrative data have several limitations in this context. First, hospital admission data received via SUS can have a reporting delay due to monthly submission periods, which could lead to confounding. This delay and potential confounding was mitigated by both using more rapid ECDS data to identify hospital admissions via presentation to emergency care and stratification by calendar time. The confounder post-evaluation found that the HRs were most changed by adjustment for calendar week, indicating that the unadjusted estimates were indeed confounded by registration delays or other calendar-period-specific factors. Also, given regression adjustment on specific calendar date, residual confounding due to registration delays seems unlikely and is expected to affect the more recent delta cases primarily, causing a slight underestimation of the HRs. Second, there was suboptimal information on the reason for a hospital visit, preventing conclusive attribution of attendance or admission to COVID-19. However, some data flags such as injury-related attendance and ICD10 codes were used as proxies to define outcomes in the primary analysis. Nevertheless, non-COVID-19-related visits might have been included, resulting in a slight underestimate of the HRs because this misclassification is not expected to differ by variant. A strength of considering alternative outcomes is that different categories of hospital use, which could indicate levels of disease severity, have been assessed; these sensitivity analyses showed some variation in HRs but estimated risks were consistently higher for patients with the delta variant than with the alpha variant. Finally, there were no available data on comorbidities, which are known to contribute to hospitalisation risk.\textsuperscript{2} This study instead indirectly accounted for comorbidities using related covariates, including age, sex, ethnicity, and deprivation.\textsuperscript{2}

Linkage was not possible for all sequenced cases due to missing NHS numbers. 5634 (11.3%) of 930 sequenced cases during the study period were excluded for this reason. International travellers and minority ethnic groups were overrepresented among patients with missing NHS numbers. These groups were also overrepresented in the delta variant group compared

### Table 1: Observed number and proportion of cases by variant and patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Alpha variant</th>
<th>Delta variant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=43 338)</td>
<td>(B.1.1.7; n=34 656)</td>
<td>(B.1.617.2; n=8682)</td>
</tr>
<tr>
<td>(Continued from previous page)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptom status at the time of specimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>18 593 (42.9%)</td>
<td>14 934 (43.1%)</td>
<td>3659 (42.1%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>22 091 (51.0%)</td>
<td>17 757 (51.2%)</td>
<td>4334 (49.9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2654 (6.1%)</td>
<td>1965 (5.7%)</td>
<td>689 (7.9%)</td>
</tr>
</tbody>
</table>

Data are n (%). *Quintiles are ranked from most deprived (quintile 1) to least deprived (quintile 5).

### Table 2: Hospitalisation outcomes for patients with the delta variant compared with patients with the alpha variant

<table>
<thead>
<tr>
<th></th>
<th>Alpha variant*</th>
<th>Delta variant*</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated or &lt;21 days after first vaccination dose</td>
<td>536/28 029 (1.9%)</td>
<td>149/6681 (2.2%)</td>
<td>0.002 (0.00-0.46)</td>
</tr>
<tr>
<td>≥21 days after first vaccination dose with or without second vaccination dose</td>
<td>228/6627 (3.4%)</td>
<td>47/2001 (2.3%)</td>
<td>0.19 (0.07-0.89)</td>
</tr>
<tr>
<td>Hospital admission or emergency care attendance</td>
<td>1095/28 029 (3.9%)</td>
<td>369/6681 (5.5%)</td>
<td>0.43 (1.04-1.97)</td>
</tr>
</tbody>
</table>

Data are n/N (%) except where otherwise stated. HR=hazard ratio. *Unadjusted and adjusted* adjustment on specific calendar date, residual confounding due to registration delays or other calendar-period-specific factors. Also, given regression adjustment on specific calendar date, residual confounding due to registration delays seems unlikely and is expected to affect the more recent delta cases primarily, causing a slight underestimation of the HRs. Second, there was suboptimal information on the reason for a hospital visit, preventing conclusive attribution of attendance or admission to COVID-19. However, some data flags such as injury-related attendance and ICD10 codes were used as proxies to define outcomes in the primary analysis. Nevertheless, non-COVID-19-related visits might have been included, resulting in a slight underestimate of the HRs because this misclassification is not expected to differ by variant. A strength of considering alternative outcomes is that different categories of hospital use, which could indicate levels of disease severity, have been assessed; these sensitivity analyses showed some variation in HRs but estimated risks were consistently higher for patients with the delta variant than with the alpha variant. Finally, there were no available data on comorbidities, which are known to contribute to hospitalisation risk. This study instead indirectly accounted for comorbidities using related covariates, including age, sex, ethnicity, and deprivation. Linkage was not possible for all sequenced cases due to missing NHS numbers. 5634 (11.3%) of 930 sequenced cases during the study period were excluded for this reason. International travellers and minority ethnic groups were overrepresented among patients with missing NHS numbers. These groups were also overrepresented in the delta variant group compared

### Table 3: Hospitalisation outcomes for patients with the delta variant compared with patients with the alpha variant, by vaccination status

This analysis is strengthened by using national, timely datasets on COVID-19 cases, hospital care episodes, and vaccinations. The individual-level data included all laboratory-confirmed COVID-19 cases, up to 98% of hospital activity, and all vaccinated individuals registered with a general practitioner in England, \cite{10.1016/S1473-3099(21)00475-8} with these data updated daily. Whole-genome sequencing coverage in England increased throughout the study period: for new positive tests between April 23 and May 24, 2021, more than 60% were successfully sequenced.\textsuperscript{1}

Compared with a matched study design, the stratified Cox regression method offers the advantage of using all potential matches rather than a fixed number of patients with the alpha variant per patient with the delta variant. Confounders such as changing demographic profiles of patients by variant or local interventions over time are accounted for. However, this method results in a loss of informative observations when stratifying by many covariates, reducing precision compared with estimates based on adjustment through regression modelling.

Administrative data have several limitations in this context. First, hospital admission data received via SUS can have a reporting delay due to monthly submission periods, which could lead to confounding. This delay and potential confounding was mitigated by both using more rapid ECDS data to identify hospital admissions via presentation to emergency care and stratification by calendar time. The confounder post-evaluation found that the HRs were most changed by adjustment for calendar week, indicating that the unadjusted estimates were indeed confounded by registration delays or other calendar-period-specific factors. Also, given regression adjustment on specific calendar date, residual confounding due to registration delays seems unlikely and is expected to affect the more recent delta cases primarily, causing a slight underestimation of the HRs. Second, there was suboptimal information on the reason for a hospital visit, preventing conclusive attribution of attendance or admission to COVID-19. However, some data flags such as injury-related attendance and ICD10 codes were used as proxies to define outcomes in the primary analysis. Nevertheless, non-COVID-19-related visits might have been included, resulting in a slight underestimate of the HRs because this misclassification is not expected to differ by variant. A strength of considering alternative outcomes is that different categories of hospital use, which could indicate levels of disease severity, have been assessed; these sensitivity analyses showed some variation in HRs but estimated risks were consistently higher for patients with the delta variant than with the alpha variant. Finally, there were no available data on comorbidities, which are known to contribute to hospitalisation risk. This study instead indirectly accounted for comorbidities using related covariates, including age, sex, ethnicity, and deprivation. Linkage was not possible for all sequenced cases due to missing NHS numbers. 5634 (11.3%) of 930 sequenced cases during the study period were excluded for this reason. International travellers and minority ethnic groups were overrepresented among patients with missing NHS numbers. These groups were also overrepresented in the delta variant group compared
with the alpha variant group. Although there are no data
to suggest that the hospital attendance or admission risk
would systematically differ for the excluded individuals
compared with their included peers, this cannot be
ruled out.

Hospital use and admission risk might be influenced
by heterogeneous health-care-seeking behaviour and
transmission across the variants, ethnic groups, and
particularly over time and area. Changes over time in
hospital admission policy might have occurred—eg, due
to local hospital burden or increased use of at-home
pulse oximeter monitoring. Such changes might have
resulted in reduced length of stay, with shorter stays less
affected by reporting delays in more recent weeks.
However, stratification for calendar week and area of
residence should account for such differences.

The conditions for whole-genome-sequencing selection
and successful sequencing might restrict the
generalisability of the study findings. Samples that test
positive by PCR are most likely to be successfully
sequenced if they have a low enough cycle threshold
value (<30), which might be more likely in patients with
a high viral load. In addition, when comparing sequenced
and non-sequenced samples in the study period, there
was an overrepresentation in sequenced samples from
patients in younger age groups and from areas in
northern England. This is likely to be due to geographic
area-based increases in sequencing to understand the
initial outbreaks of the delta variant. There was also a
higher proportion of pillar 2 (ie, community-based)
samples that were sequenced compared with samples
taken through pillar 1 (public health and hospital testing
and routine screening). Despite the potential that a
higher proportion of delta variant samples might have
been sequenced due to increased regional coverage,
slightly higher ascertainment is not likely to have
significantly reduced detection of the alpha variant
because alpha was the most prevalent variant throughout
March and April, 2021. The same sequence-quality
metrics were also applied across all samples and the area-
level sampling would have included a mixture of
individuals with the alpha variant and individuals
with the delta variant. There was no expected sample
prioritisation by variant based on clinical status,
particularly as most sequenced samples were from
community testing.

During the study period, the incidence of the delta
variant in England was increasing, and so individuals
with shorter times from infection to positive test (ie, more
recent infections) might be overrepresented among
those who tested positive. By contrast, the incidence of
the alpha variant was decreasing during the study period,
and so individuals with longer times to positive test
(ie, less recent infections) are likely to be overrepresented.
Time from infection to testing positive among the
patients in this study might be dependent on symptoms
that prompt someone to be tested, because most the
study population had community (pillar 2) testing, rather
than routine testing in hospital or for screening (pillar 1).
People who test quickly might be more likely to have
earlier or more symptoms than people who test less
quickly, suggesting that their disease progression might
have been both faster and more severe. This differential
selection of patients with potentially more severe
symptoms from the delta variant and patients with less
severe symptoms from the alpha variant might result in
an overestimation of the HRs. However, this bias might
be mitigated by the overall preferential selection of
patients with low cycle threshold values (higher viral
load), that might affect the alpha and delta variant groups
similarly. Furthermore, the estimated HRs were similar
for patients who were asymptomatic at the time the
specimen was taken, for whom the time from infection
to test is unlikely to reflect differences in test-seeking
behaviour. To address this bias, incidence would need to
be modelled jointly with severity.

The impact of the delta variant within India has been
substantial. Alongside high infection incidence, major
cities also experienced overwhelming hospital burden
leading to shortages of supplies and life-saving
equipment. However, there has been little research done
to quantify the hospitalisation risk for patients with this
variant. The EAVE II study is a recent, large-scale study
reporting on the hospital admission risk for patients with
the delta variant in Scotland. Based on record-linkage
of routine health-care data, it used S-gene target detection
through diagnostic tests as a proxy for delta compared
with the alpha profile that includes S-gene target failure.
Their results showed an adjusted HR of hospital
admission of 1·85 (95% CI 1·39–2·47), which is
consistent with the HR of 2·26 (1·32–3·89) estimated in
this study.

Supplementary sensitivity analyses provide assurance
regarding the robustness of outcomes; however, future
work should include metrics based on richer but less
timely data on severe COVID-19 outcomes, such as
length of hospital stay, admission to intensive care, or
indicators of critical illness. Further work is also needed
to measure the risk of mortality due to the delta variant,
as a large proportion of the cohort included in this study
was still within the 28-day follow-up period when analysis
was done.

To our knowledge, this study is the largest assessment
of hospitalisation risk for the delta variant using cases
confirmed by whole-genome sequencing, providing
important foundational evidence of increased risk
compared with the alpha variant. Before the emergence
of the delta variant, the evidence base largely focused on
the alpha variant and its higher transmissibility
and severity when compared with previous wildtype
strains. Further research is needed to clarify if the
hospitalisation risks differ in vaccinated individuals
infected with the delta variant compared with the alpha
variant; however, a previous study has estimated low

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hospitalisation risks for vaccinated individuals after infection with either variant. Together, these two studies suggest that outbreaks of the delta variant in unvaccinated populations might lead to a higher health-care burden, particularly compared with the previous prevalent SARS-CoV-2 strains. The findings are key for resource planning and policy decisions to mitigate the impact of the delta variant in the UK, where the delta variant now dominates, and in other high-income countries where the rapid spread of the delta variant might occur.

Contributors
KAT, TN, AZ, ST, MAS, SA, RJH, AC, DDA, AMP, and GD designed the study. RJH, JL-B, and EG contributed to data collection and creation of data resources. KAT and AZ checked and verified the dataset and prepared it for analysis. TN did the statistical analysis, with support from SRS, KAT, ST, RJH, DDA, and AMP. AMP, AC, and DDA acquired funding. KAT, TN, AZ, ST, MAS, SA, AMP, and GD wrote the manuscript. SRS, RJH, RL-B, EG, AC, and DDA reviewed and edited the manuscript. AMP and GD supervised the work. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
GD’s employer, Public Health England, has received funding from GlaxoSmithKline for a research project related to seasonal influenza and antiviral treatment; this project preceded and had no relation to COVID-19, and GD had no role in and received no funding from the project. All other authors declare no competing interests.

Data sharing
This analysis was based on routine health-care data, which cannot be made available to others by the study authors. Requests to access this non-publicly available data are handled by the Public Health England Office for Data Release.

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