# Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 Omicron (B.1.1.529) and Delta (B.1.617.2) variants in England: a cohort study

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**Abstract**

*Background*

The Omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine escape and high transmissibility, with early studies indicating lower severity of infection compared with Delta (B.1.617.2). We sought to better characterise Omicron severity relative to Delta by assessing the relative risk of hospital attendance, hospital admission or death in a large national cohort.

*Methods*

Individual-level data on laboratory-confirmed COVID-19 cases resident in England between 22 November 2021 and 9 January 2022 were linked to routine datasets on vaccination status, hospitalisation and mortality. The relative risk of attendance at hospital within 14 days, or death within 28 days following confirmed infection, was estimated using proportional hazards regression. Analyses were stratified by test date, 10-year age band, ethnicity, region and vaccination status and further adjusted for sex, index of multiple deprivation decile, evidence of a prior infection and year of age within each age band. A secondary analysis estimated variant- and vaccine-specific vaccine effectiveness and the intrinsic relative severity of Omicron infection compared with Delta; i.e. the relative risk in unvaccinated cases.

*Findings*

We found that the adjusted hazard ratio (HR) of hospital attendance (not necessarily resulting in admission) with Omicron compared with Delta was 0.56 (95%CI: 0.54-0.58); for hospital admission and death the estimates were 0.41 (95%CI: 0.39-0.43) and 0.31 (95%CI: 0.26-0.37), respectively. Omicron vs Delta HR estimates varied with age for all endpoints examined: the adjusted HR for hospital admission was 1.10 (95%CI: 0.85-1.42) in <10 year-olds, falling to 0.25 (95%CI: 0.21-0.30) in 60-69 year-olds, and rising to 0.47 (95%CI: 0.40-0.56) in ≥80 year-olds. For both variants, past infection gave some protection against death both in vaccinated (HR: 0.47 [95%CI: 0.32-0.68]) and unvaccinated (0.18 [95%CI: 0.06-0.57]) cases. In vaccinated cases, past infection offered no additional protection against hospital admission beyond that provided by vaccination (HR: 0.96 [95%CI: 0.88-1.04]), whilst for unvaccinated cases moderate protection remained (HR: 0.55 [95%CI: 0.48-0.63]). The Omicron vs Delta HR estimates were lower for hospital admission (0.30 [95%CI: 0.28-0.32]) in unvaccinated cases than the corresponding HR estimated for all cases in the primary analysis. Booster vaccination with an mRNA vaccine was highly protective against hospitalisation and death in Omicron cases (HR for hospital admission 8-11 weeks post booster, compared with unvaccinated: 0.22 [95%CI: 0.20-0.24]), with the protection afforded after a booster not being significantly affected by the vaccine used for doses 1 and 2.

*Interpretation*

The risk of severe outcomes following SARS-CoV-2 infection is substantially lower for Omicron compared with Delta cases, with higher reductions for more severe endpoints and significant variation with age. The risk of hospital admission in children <10 years of age did not differ significantly by variant, while 60-69 year-olds had an approximately 75% reduced risk of hospital admission with Omicron compared with Delta. Underlying the observed HRs is a larger reduction in intrinsic severity (in unvaccinated individuals) counterbalanced by a reduction in vaccine effectiveness. A documented previous SARS-CoV-2 infection offered some protection against hospitalisation and high protection against death in unvaccinated individuals, but only offered additional protection in vaccinated individuals for the death endpoint. Booster vaccination with mRNA vaccines maintains over 70% protection against hospitalisation and death in breakthrough confirmed Omicron infections.

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## Research in context

### Evidence before this study

We aimed to identify all available evidence on the relative severity of Omicron compared to other SARS-CoV-2 variants. On 29 January, we searched PubMed with the query (("B.1.1.529" OR "Omicron" OR "VOC-21NOV-01") AND ("SARS-CoV-2" OR "COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus disease 2019")) AND ("severity" OR "hospitalisation" OR "hospitalization" OR "hospital" OR "emergency care" OR "mortality" OR "lethality" OR "death"). We further searched preprint databases using combinations of the above search terms and included additional relevant literature from the reference lists of identified publications. This search identified three peer-reviewed publications and eight preprints. Comparing Omicron with Delta cases across all ages, published estimates of the reduction in the risk of hospitalisation or emergency department attendance lay in the range 35% to 80%, with higher reductions in risk generally being reported for more severe outcomes such as intensive care unit admission and death. A Norwegian cohort study reported age-stratified relative risk estimates and saw no significant differences with age for people aged under 75, but that study did not have the power to disaggregate the <30 year-old age group. Conversely, a Danish cohort study reported a relative risk of hospitalisation of 0.64 overall, but 1.59 in 0-19 year-olds, but again had insufficient power to disaggregate further. A US cohort study of <5 year-olds reported relative risks of emergency department attendance and intensive care unit admission of 0.71 and 0.32, respectively.

### Added value of this study

To date, this is the largest national study quantifying the risk of hospitalisation or death following infection with Omicron compared with Delta, based on individual-level data on 1,516,702 COVID-19 cases of whom 1,067,859 were infected with the Omicron variant. We provide age-specific estimates of the risk of hospitalisation and death for Omicron relative to Delta, and the disaggregation of the reduction in the risk of hospitalisation into estimates of the intrinsic severity reduction in unvaccinated cases and changes in vaccine-induced protection against hospitalisation in breakthrough cases. Furthermore, we estimate the additional protection provided by prior infection for both unvaccinated and vaccinated individuals.

### Implications of all the available evidence

The risk of severe outcomes for Omicron infection is substantially lower than that for Delta overall. However, this reduction in risk is age-specific and our results indicate that the risk of hospitalisation among children under 10 years of age does not significantly differ between Omicron and Delta. The reduction in the risk of hospitalisation observed at the population level is composed of a larger reduction in intrinsic severity coupled with a moderate reduction in the protection afforded by vaccination against hospitalisation.

## Introduction

During the COVID-19 pandemic of 2020-2022, multiple variants of SARS-CoV-2 have emerged that have been found to vary in transmissibility and severity. The Omicron (B.1.1.529) variant was first detected in a sample collected in Botswana on 11 November 2021 and first reported by South Africa on 24 November 2021.[1,2] Omicron was designated a variant of concern (VOC) by WHO on 26 November 2021.[1] This variant has been identified in 133 countries and is now the most prevalent lineage globally, representing 85% of variant cases reported in late January 2022.[3]

Delta (B.1.617.2) was the dominant variant in England from May to December 2021. The first Omicron case was reported in England on 27 November 2021, at a time when daily case numbers by specimen date had been approximately 30,000-50,000 per day since July 2021 and incidence of infection was estimated to vary over the same months between 40,000 and 80,000 per day.[4] Since then, the number of confirmed Omicron cases has rapidly increased in England, and by the week commencing 10 January 2022 Omicron cases represented >99% of all sequenced cases.[5]

A number of studies have indicated that the clinical severity of infection is lower for Omicron than Delta.[6-17] Vaccine effectiveness estimates show reduced protection against Omicron symptomatic infection compared to Delta symptomatic infection, with little protection after the primary course but moderate protection against infection and high protection against hospitalisation following a booster dose.[18] In England, such estimates have been obtained in a context of high vaccination coverage. By 9 January 2022, >95% of people in England over 70 years of age had received one vaccine dose, >93% had received two vaccine doses, and >90% had received three vaccine doses.[19] Coverage, notably of boosters, was lower in younger age groups, with 81%, 52% and 43% having received three doses in the 55-59, 40-44 and 30-34 year-old age groups, respectively.[19]

However, a detailed understanding of how reductions in both severity and immunity have shaped observed patterns of hospitalisations and deaths in the Omicron wave is lacking, and there has been limited characterisation of age variation in the severity of Omicron infection to date. To inform the public health response, we sought to assess the relative risks of hospitalisation and death by age for cases with Omicron compared to those with Delta. In addition, we provide estimates of how immunity from both vaccination and past infection modifies disease severity in breakthrough cases.

## Methods

*Data Sources*

COVID-19 is a notifiable disease and data for all positive cases in England are reported to UKHSA, which maintains a definitive line list of all individuals who have had confirmed SARS-CoV-2 infection.[20] UKHSA also maintains separate line lists of COVID-19 associated deaths, reinfection episodes, S-gene target failure (SGTF) data and sequencing and genotyping test results. The UK sequencing and genotyping strategy has been previously described,[21,22] but briefly, includes geographic-weighted population-level sampling of community cases, supplemented by targeted selection of recent international travellers, hospitalised cases and hospital staff. Over the study period, between 6 and 20% of cases were sequenced, and between 16 and 35% of cases were either sequenced or genotyped. S-gene information was available from the three largest ("Lighthouse") PCR-testing laboratories using TaqPath assays, covering 47% of cases identified from community testing during the inclusion period.[23] SARS-CoV-2 vaccinations are recorded in the National Immunisation Management Service (NIMS).[24] Hospital attendance data are recorded in the Emergency Care Data Set (ECDS)[25] and Secondary Uses Service (SUS)[26] datasets. We linked these datasets by National Health Service (NHS) number, a unique individual identifier.

*Study design and study population*

We undertook a retrospective cohort study of individuals resident in England with laboratory-confirmed SARS-CoV-2 infection with a specimen date in the 6 weeks between 29 November 2021 and 9 January 2022. Cases

were retrospectively followed up until 24 January 2022, the date of data extraction. Cases were included (see appendix p. 2) if their specimen was: whole-genome-sequencing-confirmed Omicron or Delta; genotyping-confirmed Omicron or Delta; or, if no known sequencing or genotyping-confirmed variant information was available, S-gene negative (Omicron) or positive (Delta). S-gene data were only used for test dates up to and including 30 December 2021, since increasing incidence of the S-gene positive BA.2 lineage of Omicron reduced the positive predictive value of S-gene positivity for Delta after that date (appendix, p. 4). Reinfections were defined as two positive tests in the same individual taken more than 90 days apart. If there were multiple positive tests within 90 days of each other for the same individual, these were attributed to the same infection episode and the earliest test date in that episode was used.

Cases were excluded if: the NHS number recorded was missing or invalid (since such cases could not be linked to hospitalisation or vaccination records); information was missing for any adjustment variables; there were more than 14 days between the date of the first positive test and the date of the test which led to the variant being identified (via sequencing, genotyping or S-gene positivity); or the specimen date was after an individual had died. In addition, we excluded a small number of cases in individuals: (i) who had received a vaccine other than AstraZeneca, Pfizer or Moderna or had received more than 3 doses of vaccine; (ii) who had received a third dose of vaccine which was not Pfizer or Moderna; or (iii) where the third dose of vaccine was administered less than 80 days after the second dose.

Three hospitalisation outcomes, of differing severity level, were examined: (a) hospital admissions; (b) hospital attendances, including admissions; and (c) hospital attendances, including both admissions and diagnoses during hospital stay. Specifically, outcome (a) was defined as hospital admissions occurring between 0 and 14 days after first positive specimen date of the most recent infection episode, where either (i) length of stay in hospital was 1 or more days; or (ii) the ECDS discharge field recorded a patient as admitted or transferred; or (iii) the patient died in hospital on the same day as hospital attendance. Outcome (b) was defined as any hospital attendance, including admissions and attendances at Accident and Emergency departments, between 0 and 14 days after the first specimen date of the most recent infection episode. Outcome (c) was defined the same as outcome (b), but additionally included cases with a first specimen date occurring during their hospital stay ("hospital-onset cases"[27]), to approximately match the definition used in NHS COVID-19 hospitalisation statistics.[28] The mortality outcome was defined as death occurring between 0 and 28 days after the first positive specimen date of the most recent infection episode, again matching the definition used in routine UK government reporting.

*Statistical analysis*

Stratified Cox proportional hazards regression was used to estimate hazard ratios (HRs) for the hospitalisation and mortality outcomes. For the hospitalisation outcomes, the cases were followed from specimen date until hospitalisation, or censored at the earliest of death, date of data extraction, and 14 days after their specimen date. For the death outcome, cases were followed up for 28 days. If an outcome occurred on or before the specimen date, the follow-up time was taken to be 0.5 days. The model used for the primary analysis was stratified by date of specimen, NHS region of residence of the case, 10-year age band, ethnicity group and vaccination status (defined as vaccine of the primary series – AstraZeneca or Pfizer/Moderna – and the number of doses received); and further included regression adjustments for sex, index of multiple deprivation (a measure of socioeconomic deprivation for the local area), year of age within each age band and an interaction term between prior infection status and any history of vaccination (to allow the effect of prior infection to vary by vaccination status). The secondary analysis differed from the primary analysis in removing vaccination status from the stratification and instead simultaneously estimating Omicron:Delta HRs for unvaccinated individuals, variant-specific HRs for different vaccination strata compared with unvaccinated cases, and vaccination status-specific HRs for cases with prior infection compared to those without prior infection. In sensitivity analyses, we examined the impact of: finer age stratification (appendix p. 10); restriction to the subgroup of unvaccinated cases (appendix p. 11); interaction of past infection status with variant (appendix p. 12); alternative variant classifications (appendix p. 13); alternative adjustment and/or stratification strategies (appendix p. 14-15); alternative definitions of hospitalisation endpoints (appendix p. 16); epidemic phase bias[29] (appendix p. 17); and adjusting for under-ascertainment of past infection status

(appendix p. 18-21). Data were prepared and statistical analyses were carried out using R version 4.1.12 (R Foundation for Statistical Computing, Vienna, Austria).

*Role of the funding source*

The funders had no role in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

## Results

Between 22 November 2021 and 9 January 2022, 4,135,347 COVID-19 cases were detected in England, of which 1,516,702 (37%) had available variant classification data and met the criteria to be included in the analysis (Figure 1; appendix p. 2). These comprised 448,843 Delta and 1,067,859 Omicron cases (appendix, p. 6), with 1.3% (5,983) of Delta cases and 9.6% (102,957) of Omicron cases (appendix, p. 6) being reinfections of people with documented earlier infection 90 or more days prior to their latest confirmed infection. The appendix (p. 6) shows the distribution of Omicron and Delta cases by age, sex, ethnicity, region, index of multiple deprivation, week of specimen date, vaccination category and prior infection status. The proportion of cases which were Omicron increased steadily each week during December 2021. Omicron cases were more likely than Delta cases to be from a Black ethnic group, or to live in London or the North-West of England. The patterns of number of cases detected and hospitalisations were similar between the included cases and all cases during the inclusion period (Figure 1 and appendix, p.4). Compared to cases included in the analysis, cases who did not fulfil the inclusion criteria had similar characteristics but were slightly more likely to reside in London or East of England and to be from non-White ethnic groups. As expected, a high proportion of cases were not included after 30th December, corresponding to the time when sequencing coverage decreased and S gene target failure information was not used due to the increase in BA.2 cases (appendix,p.6).

Figure 2 presents estimates of the adjusted HRs for hospitalisation and mortality endpoints comparing Omicron with Delta, across all ages and stratifying by 10-year age group, from both the primary and the secondary analyses (appendix, pp.7-9). Unadjusted HRs (appendix, p.7) give a biased picture of relative severity due to differences in the distribution of Omicron and Delta cases over time, by age (even within age bands), by ethnicity and by region. The adjustment for single year of age within age band is particularly important for the <10 years age band, where differences in the detailed age distribution of Omicron and Delta cases (appendix, p. 4) can bias estimates otherwise. For the least severe and least COVID-19 specific endpoint examined, hospital attendances including admissions and diagnoses during hospital stay, the adjusted HR estimate (0.59, 95%CI: 0.57-0.61) indicates a lower risk of hospitalisation with Omicron versus Delta, averaging over all age groups and vaccination strata. A greater reduction is estimated for the most severe and specific hospital endpoint, hospital admission up to 14 days after a positive test (adjusted HR 0.41, 95%CI: 0.39-0.43), with the greatest reduction estimated in the risk of death within 28 days of a positive test (adjusted HR 0.31, 95% CI: 0.26-0.37).

We found considerable variation in the severity of Omicron relative to Delta with age for all endpoints examined (Figure 2). There were no significant differences in the hazard ratio for hospitalisation between the two variants in <10 year-olds, only small (and sometimes non-significant) reductions in the risk of hospitalisation in 10-19 year-olds, but increasingly large reductions with age in 20-69 year-olds. HR estimates increased again with age in 70+ year olds compared with the 60-69 age group, though remained substantially below 1. Similar trends were seen for the mortality endpoint in adults over 30, but we had insufficient power to examine this endpoint in the <30 age groups. In a secondary analysis (appendix p.10), we disaggregated the <10 age group into <1, 1-4 and 5-9 age bands. The results are suggestive of a higher relative risk in <1s than 1-4 or 5-9 year-olds, but these differences were not statistically significant.

There was a high level of immunity in the English population by the time Omicron emerged, both from vaccination and prior infection. It is therefore informative to disaggregate the HRs for hospitalisation and death into estimates of changes in intrinsic viral severity applying to unvaccinated cases (Figure 2, secondary analysis), and changes in the protection vaccines afford against severe outcomes in breakthrough infections.

Figure 3 presents estimates of variant-specific HRs of each hospitalisation endpoint for different vaccination strata compared with unvaccinated cases (see also appendix pp. 8-9). We estimated a larger reduction (comparing Omicron with Delta) in the risk of hospitalisation and death in unvaccinated cases than for all cases (Figure 3 and appendix pp.8-9). Furthermore, the relative risk of hospitalisation or death in vaccinated cases compared with unvaccinated cases was lower for Delta cases than for Omicron cases (Figure 3 and appendix pp. 8-9). These estimates indicate that the overall observed reductions in hospitalisation and mortality risk understate the intrinsic reduction in the risk of severe infection outcomes associated with the Delta to Omicron transition, due to those reductions being partially counteracted by reductions in vaccine effectiveness. The largest reductions in vaccine effectiveness against hospitalisation in breakthrough cases were seen for people who had not received a booster dose, particularly for those who had received the AstraZeneca vaccine for their primary vaccination series (Figure 3). However, relative protection (versus unvaccinated) against hospital admission with Omicron in breakthrough cases remained above 70% (HR<0.3) for all vaccination categories including a booster dose (appendix pp.8-9).

Documented past infection was found to protect unvaccinated cases against hospitalisation (appendix pp.8-9), with HR estimates of 0.55 (95%CI: 0.48-0.63) and 0.18 (95%CI: 0.06-0.57) for hospital admission and death, respectively. These estimates imply a similar level of protection against Omicron as that provided by two doses of the AstraZeneca vaccine or one dose of the Pfizer or Moderna vaccines (appendix pp. 8-9). In vaccinated cases, past infection did not provide additional protection against hospitalisation (HR for admission 0.96, 95%CI: 0.88-1.04) beyond that afforded by vaccination but did provide additional protection against death (HR 0.47, 95%CI: 0.32-0.68). We found no evidence that the protection against hospitalisation or death afforded by documented past infection differed significantly between Omicron and Delta cases (appendix, p.12).

While the HR estimates for unvaccinated cases in Figure 2 were derived from a model fitted to all cases, adjusted HR estimates were similar for a model fitted to the subgroup of unvaccinated cases only (appendix, p.11). A sensitivity analysis using imputation to account for under-ascertainment of past infection (appendix pp. 18-21) gave, as expected,[8] slightly higher estimates of Omicron:Delta HRs than our secondary analysis (appendix pp.8-9) but slightly lower estimates of the HRs for vaccinated cases versus unvaccinated for Omicron, and lower estimates of the HRs for reinfections versus first infections. Other sensitivity analyses (appendix, p.13) indicated that HR estimates did not vary significantly if only Pillar 2 (community testing) cases were included in the analysis but were slightly closer to 1 than in the primary analysis if only sequencing data were used to determine variant status, and slightly further from 1 than the primary analysis if sequencing and genotyping (but not SGTF data) were used. Estimates were relatively robust to alternative choices of adjustment/stratification (appendix pp.14-15) and to precise inclusion criteria for hospital endpoints (appendix p.16). As expected, exploratory analysis of the potential impacts of epidemic phase bias[29] indicated that the primary analysis might overestimate the Omicron vs Delta HR if the delay from infection to test is substantially shorter in hospitalised cases than in cases who are not hospitalised (appendix p.17).

**Figure 1. (A) Number of cases identified with Delta or Omicron variant during the inclusion period 29 November 2021-9 January 2022; (B) number of hospital admissions; (C) number of hospital attendances (including admissions); and (D) number of hospital attendances (including admissions and diagnoses during hospital stay), by variant and date of positive test. The study included cases whose positive specimen had been classified as Delta or Omicron based on whole genome sequencing or genotyping, or, for positive tests until 30 December, cases whose positive specimen was assessed for S gene target failure; for illustration purposes, the figure shows the number of cases with S gene information (in grey) from 31 December 2021 but these cases were not included in the analysis.**

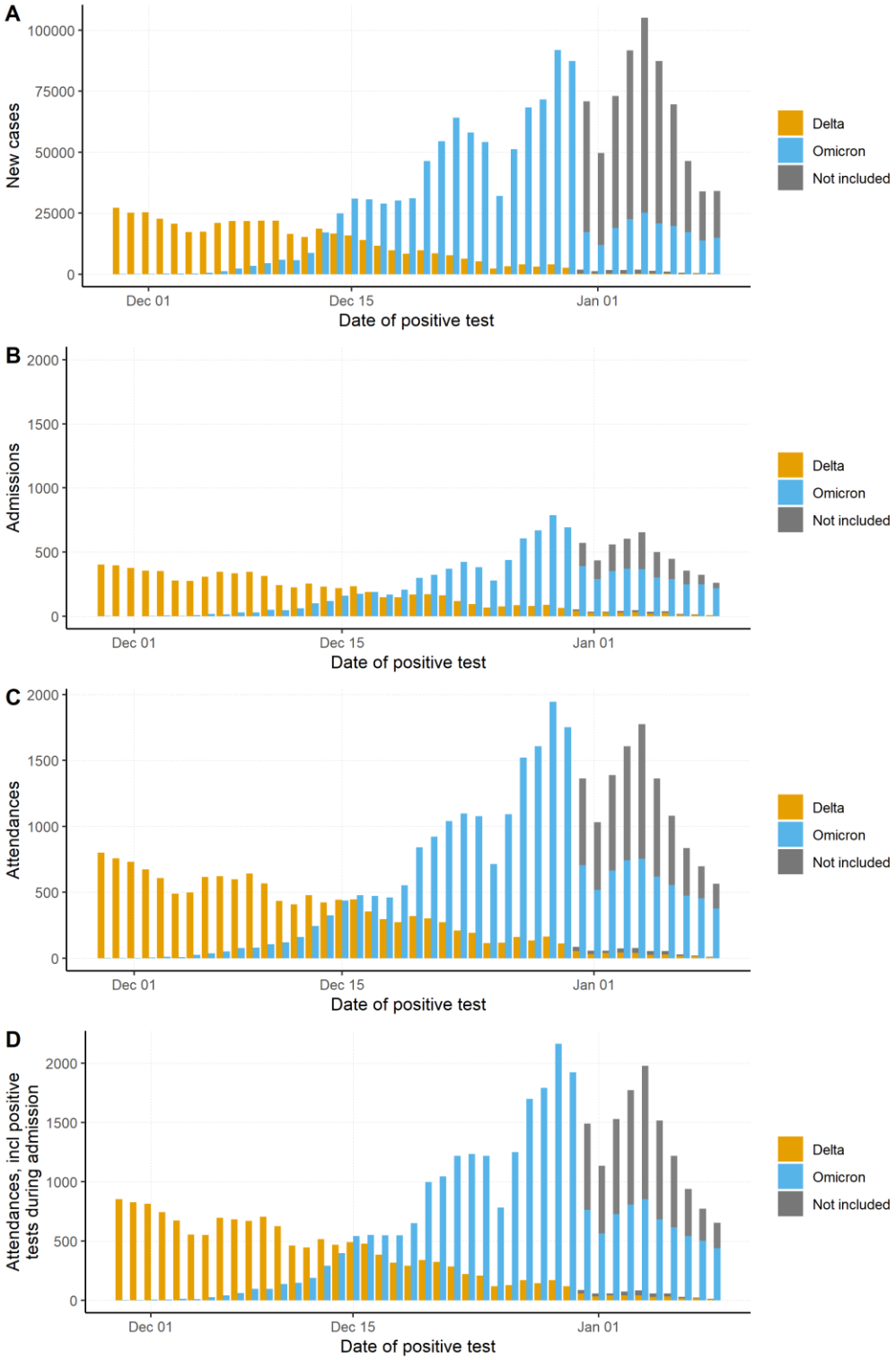


**Figure 2: Risk of hospitalisation and mortality for COVID-19 cases with Omicron compared with Delta, overall and by age group: (A) hospital admission; (B) hospital attendance (including admission); (C) hospital attendance (including admissions and diagnoses during hospital stay); (D) Death. The plots show adjusted hazard ratio estimates and 95% confidence intervals: * derived from the primary analysis, which stratifies by vaccination category, but does not estimate vaccine effectiveness; and † adjusted estimates of intrinsic severity (for the unvaccinated population) from the secondary analysis, which estimated variant-specific hazard ratios for hospitalisation or death in vaccinated groups versus unvaccinated (see Figure 3) in addition to the Omicron vs Delta hazard ratios. Hazard ratios of death were not estimated for cases aged <30 years due to small numbers. See appendix p.7 for counts and both unadjusted and adjusted HR estimates.**

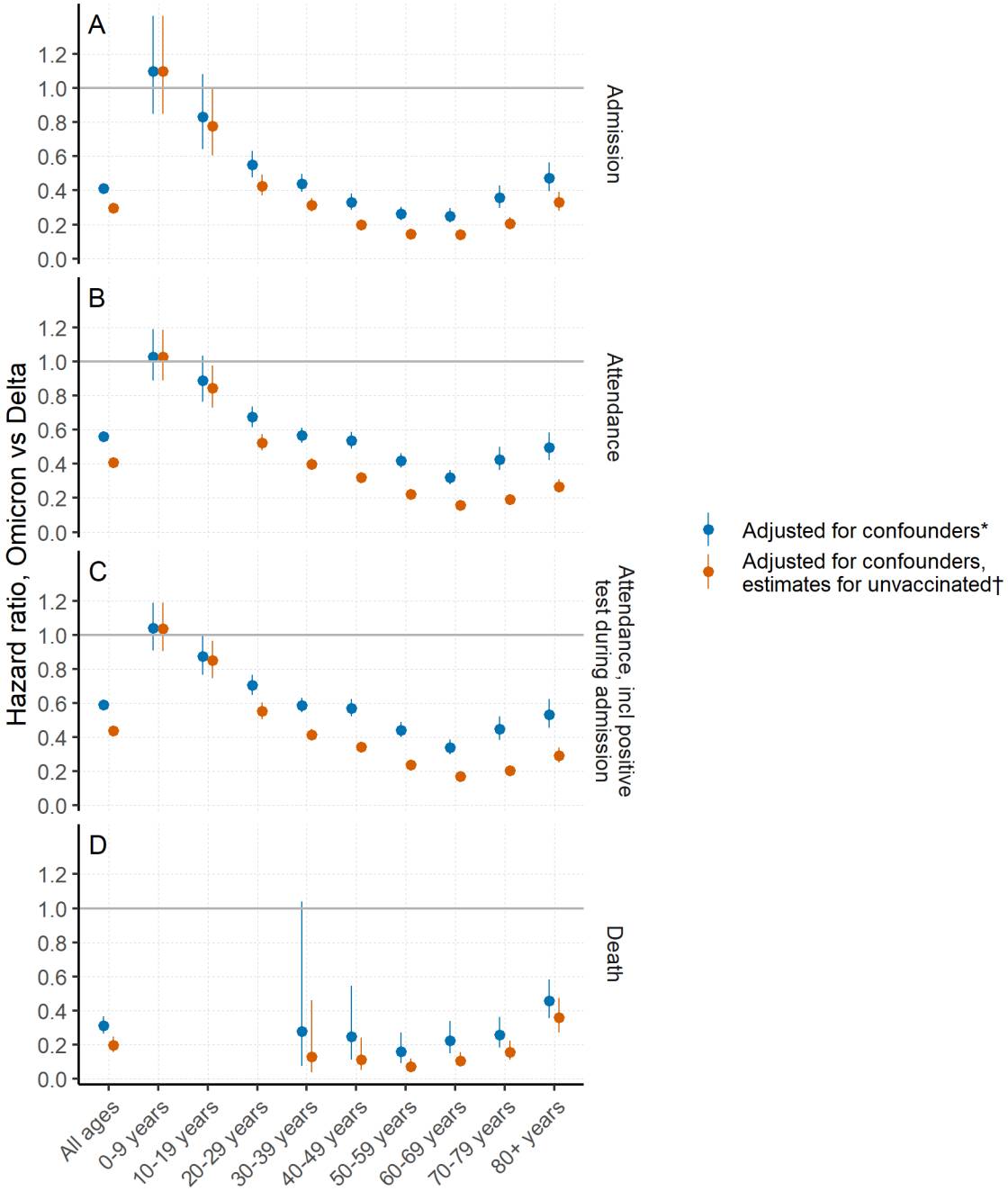
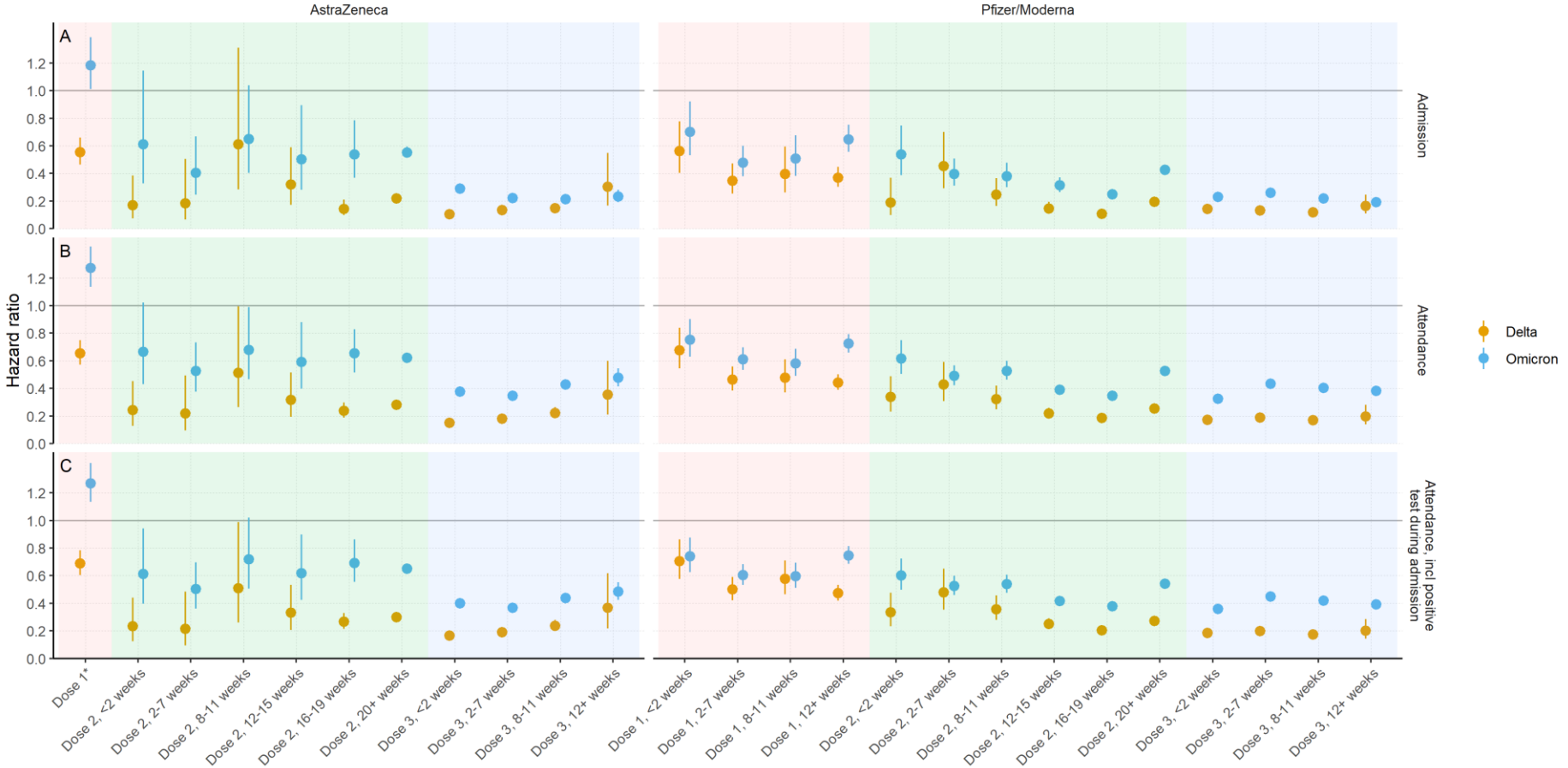


**Figure 3. Estimated HRs for vaccination categories from secondary analysis. Variant-specific hazard ratios of (A) hospital admission; (B) any hospital attendance (including admission); or (C) any hospital attendance (including admission, or positive test during hospital stay), by type of vaccine used for doses 1 and 2, number of vaccine doses and time since last dose, relative to unvaccinated cases. These HRs can be interpreted as 1 – vaccine effectiveness at preventing hospitalisation conditional upon diagnosed infection. Booster doses were Pfizer or Moderna (not disaggregated). * Due to small numbers, all cases who had received a single dose of the AstraZeneca vaccine were grouped together and not separated by time since vaccine dose.**



## Discussion

Since mid-December 2021, most new SARS-CoV-2 cases in England have been caused by the Omicron variant. Our results suggest that confirmed Omicron cases had a 59% lower risk of hospital admission, a 44% lower risk of any hospital attendance and a 69% lower risk of death compared with confirmed Delta cases. We find strong evidence of age-dependence in the magnitude of this risk reduction. In those over 20 years of age we estimate a statistically significant reduction in the risk of hospitalisation for Omicron compared with Delta. In cases aged 50 years and above, the estimated reduction in the risk of hospitalisation is in the range 50-75% depending on the endpoint examined. The magnitude of severity reduction is lower for those aged 80+, but still over 50% for most endpoints. In 0–9-year-old confirmed cases, for whom the risk of disease sufficiently severe to result in death is very low, we estimate that the risk of hospitalisation from Omicron infection is not significantly different from Delta infection. Dividing the 0-9 age group into <1, 1-4 and 5-9 bands indicated no statistically significant differences in the Omicron:Delta hazard ratio with age in that age group, though statistical power was more limited for this finer disaggregation of age. A lack of difference in the risk of hospitalisation for young children between Omicron and Delta may be explained by a different clinical presentation of Omicron infection in children. Laboratory studies have shown that Omicron replicates more in upper airway cells and less in the lungs.[30,31] Children with Omicron infection may therefore be more likely than those with Delta infection to present with fever and upper respiratory symptoms which would trigger clinical pathways for admission, for example to rule out sepsis.[32,33] The lack of severity attenuation in children may therefore reflect a lower clinical threshold for hospital admission for young children due to symptoms common to Omicron infection, rather than more severe disease.[6,33] However, further analyses are required to investigate COVID-19 illness in children and reasons for admission.

We find that pre-existing immunity, both from vaccination and past infection, substantially reduces the risk of hospitalisation. In a secondary analysis, we estimated both variant-specific vaccine effectiveness and age-specific risks of hospitalisation in unvaccinated cases. We estimated lower severity for Omicron versus Delta compared to the primary analysis where vaccination status was included in the stratification. This finding is explained by the lower estimates of protection afforded by vaccination against hospitalisation in breakthrough cases for the Omicron variant compared to the Delta variant. Hence, underlying the observed risks for hospitalisation and death in our primary analysis is a larger reduction in intrinsic severity (i.e. for unvaccinated cases) counterbalanced by a reduction in vaccine effectiveness against Omicron compared to Delta. However, mRNA booster vaccination was still found to be highly protective against hospitalisation and death in Omicron breakthrough cases, in line with studies solely examining vaccine effectiveness.[18] In unvaccinated cases, documented past infection provides moderate protection against hospitalisation and higher protection against death. In vaccinated cases, past infection offered no additional protection against hospitalisation over vaccination alone, but did offer moderate additional protection over the more severe endpoint of death.[18] An imputation-based sensitivity analysis to examine the effect of under-ascertainment of past infections gave estimates indicating a larger protective effect of past infection, together with slightly higher estimates of the severity of Omicron relative to Delta.[8]

To our knowledge, this is the largest study to date to report on the relative hospitalisation and mortality risks for cases with the Omicron variant compared with Delta. Strengths of the study include the use of a nation-wide cohort, covering 37% of all COVID-19 cases in England during the inclusion period. Our results support those of a number of other studies which have reported that Omicron has substantially reduced overall severity compared with Delta.[6-17] However, relatively few studies have examined how the reduction in severity might vary with age. A US study [12] compared 3-day follow-up outcomes in <5 year-old cases in the prior Delta wave with those in the ongoing Omicron epidemic and found a relative risk of ED attendance of 0.71 (95% CI: 0.66-0.75) and a relative risk of admission of 0.33 (95%CI: 0.26-0.43). A second study involved a contemporaneous comparison of Omicron and Delta (distinguished via SGTF) cases in Southern California [10] and estimated unadjusted odds ratios for hospitalisation in 0-17 year-olds of 0.7 (95%CI: 0.43-1.18) and 0.94 (0.26-3.42) using denominators of only outpatient tests and both inpatient and outpatient tests, respectively. A Danish study [11] estimated a relative risk of hospitalisation of 1.59 (95% CI:1.09-2.32) in 0-19 year-olds, though this estimate was based on only 31 hospitalisations in that age group. Last, a Norwegian cohort study [13] found no significant differences by age in the relative risk of hospitalisation for people aged under 75, with a

point estimate for <30-year-olds of 0.24 [95%CI: 0.09-0.60], but did not have the power to stratify that age group further.

There are several limitations to our analysis. Stratified analyses have the benefit of controlling for confounding by interactions between variables such as ethnicity, age and time, but the disadvantage of discarding data from strata where cases from one of the two groups being compared are absent. However, we found estimates showed little sensitivity to the level of stratification used. If rates of progression from infection to symptom onset or test date differ by variant, the hazard ratios presented may be biased. Data on hospital activity, deaths and vaccination status are subject to reporting delays, and while we mitigated potential biases arising from these delays by using survival analysis stratified by test date, age and region, residual bias may remain. NHS numbers are required to link case data to hospital attendance information and vaccination status, therefore 89,184 people (5.4% of cases) without NHS numbers were excluded from our primary analysis. However, we have no reason to expect a strong association between lack of NHS number and SARS-CoV-2 variant. During the study period, the Omicron variant experienced a rapidly increasing incidence, while the Delta variant was experiencing a decreasing/less rapidly increasing incidence. These trends may result in epidemic phase bias if infection severity is correlated with time from infection to test.[29] Exploratory analysis suggested that such bias would lead to similar or lower HRs between Omicron and Delta cases compared with those estimated in our primary analysis. It is also unclear whether virologically confirmed cases represent a comparable fraction of underlying infections for the two variants we compare. If the proportion of Omicron infections confirmed via PCR testing is lower/higher than for contemporaneous Delta infections, our hospitalisation hazard ratio estimates will be over/under-estimates of the true severity of Omicron relative to Delta. Finally, cases of the BA.2 lineage of Omicron were not considered in this analysis, as incidence of that lineage only reached substantial levels after the start of 2022, meaning insufficient data have accumulated to allow reliable severity estimates to be generated.

It is not inevitable that viral evolution leads to lower severity. The risk of hospitalisation appeared to increase comparing Delta with Alpha infections,[21,34-36] and also comparing Alpha with previously circulating lineages.[36-38] However, our analysis indicates that Omicron is associated with a substantially lower risk of severe outcomes in adults than the previously dominant Delta variant. Lower severity also needs to be counterbalanced against the ability of a variant to evade pre-existing immunity and thus transmit more readily within highly immune populations: we find evidence of moderate reductions in the protection vaccines provide against hospitalisation in breakthrough Omicron cases compared with Delta, and previous studies indicate substantial reductions in vaccine effectiveness against symptomatic infection.[18] However, we find that receiving a mRNA vaccine booster dose gives over 70% protection against hospitalisation or mortality outcomes in breakthrough Omicron cases; absolute vaccine effectiveness will be substantially higher once protection against infection is accounted for.[19]

We were not able to evaluate more detailed measures of relative clinical severity in hospitalised patients (such as intensive care unit admittance), but our finding that estimated severity reductions comparing Omicron with Delta are larger for more severe endpoints (death and hospital admission versus hospital attendance) agrees with observations that the proportion of hospitalised COVID-19 patients requiring intensive care and/or mechanical ventilation has been substantially lower during the Omicron wave in England than the preceding Delta wave.[39] The 5-fold overall reduction in the intrinsic risk of death that we estimate for Omicron infection compared with Delta will make the goal of “living with COVID” in the absence of socially and economically disruptive public health interventions substantially easier to achieve at the current time. However, it is not guaranteed that future variants will have a similarly reduced severity. It is therefore critical that sufficiently detailed and systematic surveillance is maintained to allow timely detection and characterisation of new viral lineages.

## Ethics

The surveillance activities within which this study was conducted are part of UKHSA's responsibility to monitor COVID-19 during the current pandemic. UKHSA 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) a–c, 3(i) d(i and ii), and 3(iii) as part of its outbreak response activities. This study falls within the research activities approved by the UKHSA's Research Ethics and Governance of Public Health Practice Group. Data were shared with the investigators as part of the UK's emergency response to the COVID-19 pandemic, via the SPI-M subcommittee of the UK Scientific Advisory Group for Emergencies (SAGE). Ethics permission was sought for analyses of these data via Imperial College London's standard ethical review processes and the study was approved by the College's Research Governance and Integrity Team (ICREC reference: 21IC6945).

## Data sharing

While all data used in this analysis were anonymised, the individual-level nature of the data used risks individuals being identified, or being able to self-identify, if it is released publicly. Requests for access to the underlying source data should be directed to UKHSA.

## Code availability

The code used to analyse the data is included in Supplementary Materials.

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**Author Contributions**

Conceptualisation: TN, NMF, SF, MC, DDA, AP, ST. Data curation: SN, HHW, WH, MK, PB, AZ, JLB, NA, MK, MC, NAA, KH, RH, AC, GD, ST. Formal analysis: TN, NMF, SFlaxman, SFunk, SA, SB, ST. Funding acquisition: NMF, SB, SFunk, ACG, DDA, AP. Methodology: TN, NMF,SB, EV, SRS, DDA, AP. Project administration: NMF, MC, GD, DDA, AP, ST. Software: TN, NMF, WH, SA. Supervision: NMF, MC, GD, DDA, AP, ST. Validation: TN, NMF. Visualisation: TN, NMF. Writing – original draft: TN, NMF, SN, DDA, AP, ST. Writing – review & editing: all authors.

**Declaration of interests**

GD declares that his employer UK Health Security Agency (previously operating as Public Health England) received funding from GlaxoSmithKline for a research project related to influenza antiviral treatment. This preceded and had no relation to COVID-19, and GD had no role in and received no funding from the project. The other authors declare no conflicts of interest.

# Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 Omicron (B.1.1.529) and Delta (B.1.617.2) variants in England

## Appendix

### Table of Contents

**Figure S1. Data selection flow chart**

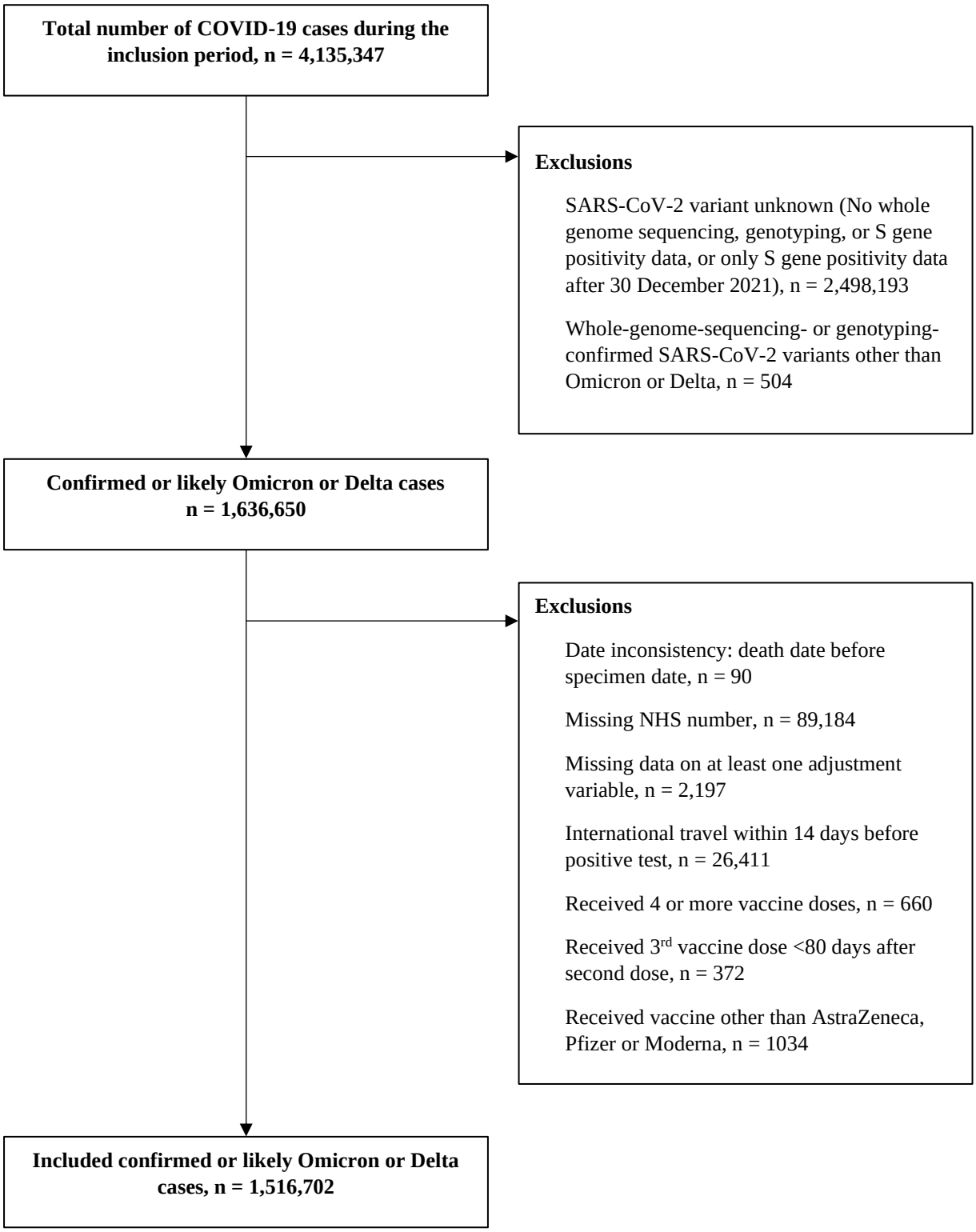

**Figure S2. Positive and negative predictive values for the use of S-gene target failure (SGTF)** to classify Omicron or Delta, by date of positive test, calculated by comparison of SGTF data with results from genotyping or sequencing for cases where both data types were available. PPV was defined as the probability that cases whose specimen was associated with SGTF were confirmed to be infected with Omicron, and NPV was defined as the probability that case with S gene positive specimens were confirmed to be infected with Delta. The PPV to classify Omicron cases was estimated to be 78% at the start of the inclusion period and rose to >99% consistently after 8 December. The NPV was >99% at the start of the inclusion period but declined (due to the BA.2 S-gene positive Omicron variant) to 87% by 30 December and to 20% at the end of the inclusion period.

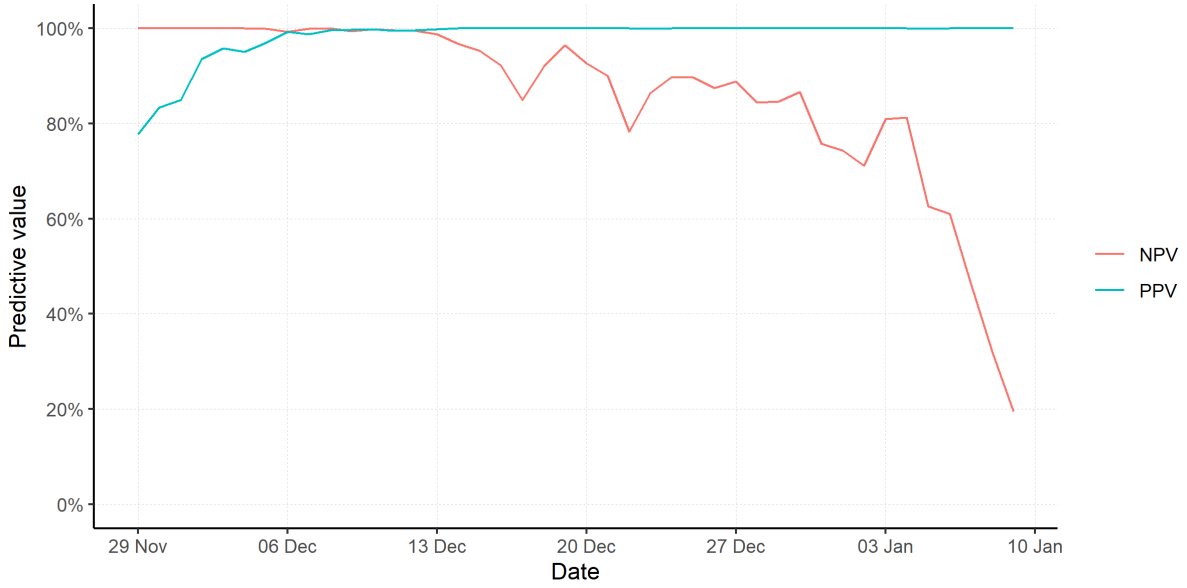

**Figure S3. Descriptive frequencies for all cases identified between 29 November 2021 and 9 January 2022, including cases not fulfilling the inclusion criteria for the study**: (A) Number of COVID-19 cases in total; and the corresponding (B) number of hospital admissions; and (C) number of hospital attendances (including admissions); and (D) number of hospital attendances (including admissions and diagnoses during ongoing hospital admissions), within 14 days, by variant and date of positive test.

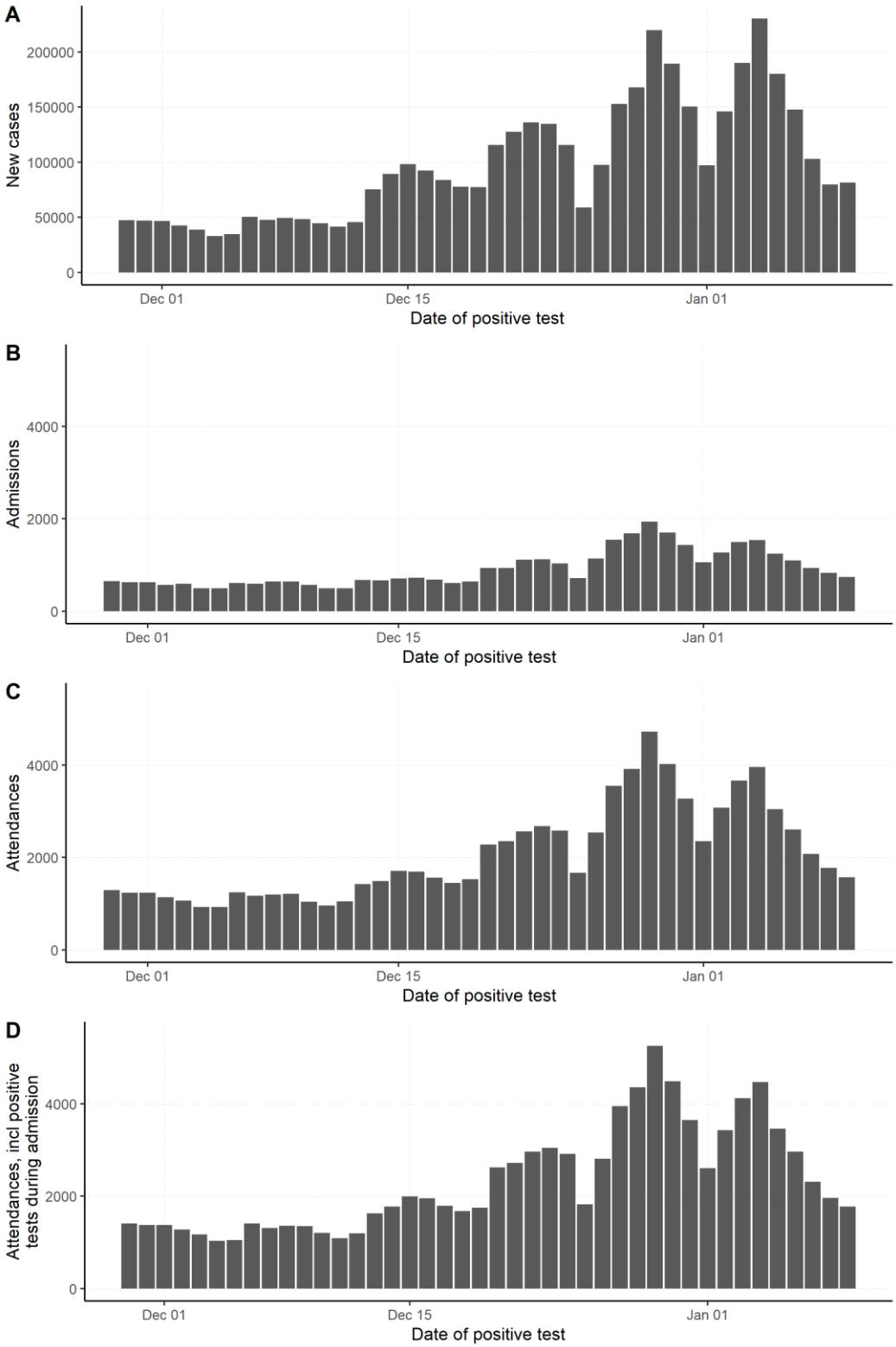

**Figure S4. COVID-19 cases and hospitalisations in 0-9 year age band, by SARS-CoV-2 variant**: (A) Proportion of cases by year of age within age band, (B) proportion of 0-9 year-old cases with different hospitalisation outcomes for Delta and Omicron, (C) proportion of 0-9 year-old cases with different hospitalisation outcomes for Delta and Omicron by individual year of age.

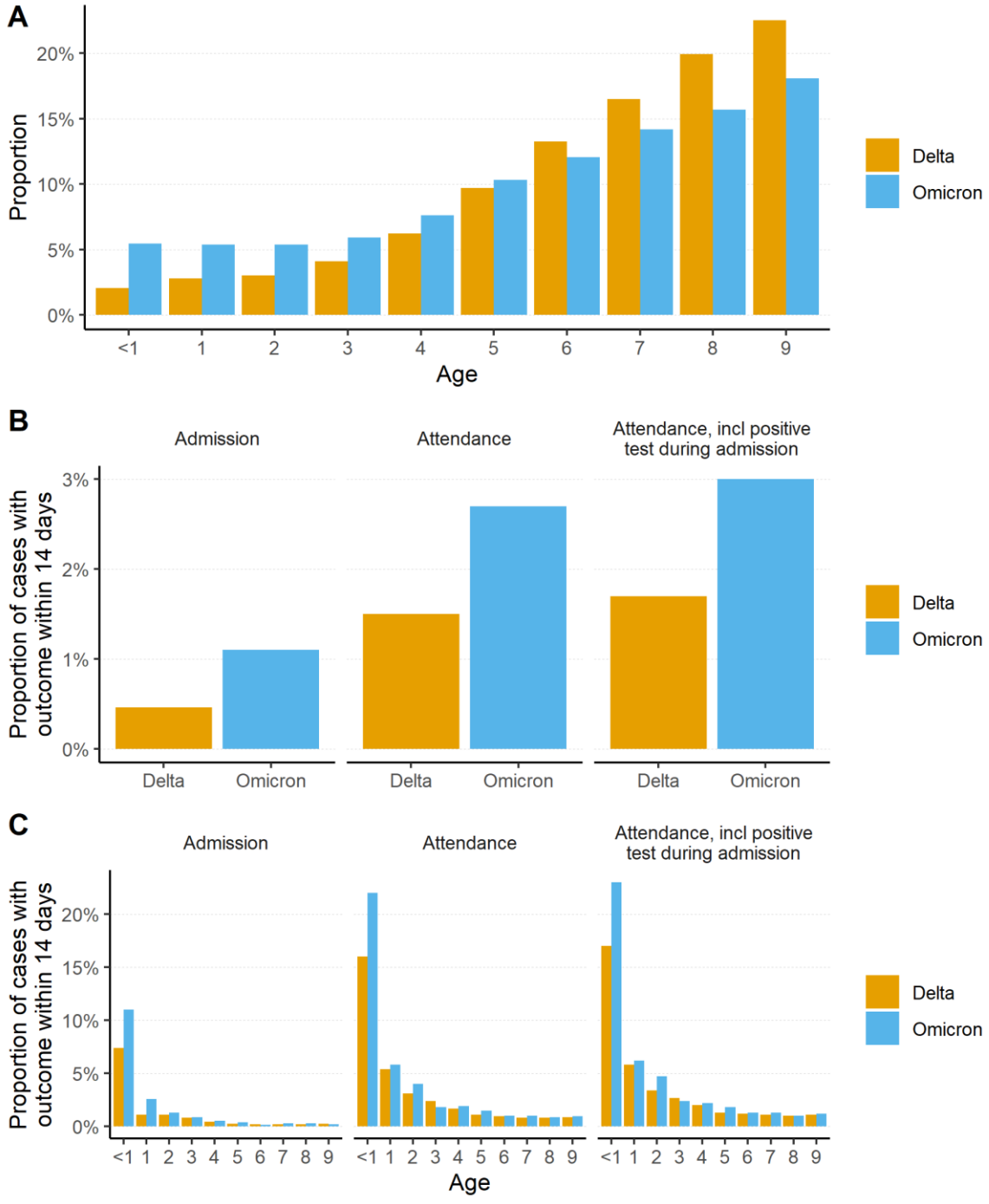

**Table S1. Characteristics of COVID-19 cases included and not included in the analysis** (see appendix, p. 2 for inclusion criteria).

| Characteristic | Overall n (%) | Omicron n (%) | Delta n (%) | Not included n (%) |
|---|---|---|---|---|
| Total | 1516702 | 1067859 | 448843 | 2618645 |
| Age | | | | |
| <10 | 117631 (7.8%) | 43147 (4.0%) | 74484 (16.6%) | 198431 (7.6%) |
| 10-19 | 207545 (13.7%) | 119261 (11.2%) | 88284 (19.7%) | 353151 (13.5%) |
| 20-29 | 313377 (20.7%) | 265199 (24.8%) | 48178 (10.7%) | 562890 (21.5%) |
| 30-39 | 308316 (20.3%) | 228915 (21.4%) | 79401 (17.7%) | 515098 (19.7%) |
| 40-49 | 248805 (16.4%) | 167045 (15.6%) | 81760 (18.2%) | 396404 (15.1%) |
| 50-59 | 183484 (12.1%) | 134186 (12.6%) | 49298 (11.0%) | 315746 (12.1%) |
| 60-69 | 83205 (5.5%) | 64875 (6.1%) | 18330 (4.1%) | 157609 (6.0%) |
| 70-79 | 37009 (2.4%) | 31066 (2.9%) | 5943 (1.3%) | 75679 (2.9%) |
| 80+ | 17330 (1.1%) | 14165 (1.3%) | 3165 (0.7%) | 41588 (1.6%) |
| Unknown | 0 | 0 | 0 | 2049 (0.1%) |
| Sex | | | | |
| Female | 807595 (53.2%) | 573387 (53.7%) | 234208 (52.2%) | 1395832 (53.3%) |
| Male | 709107 (46.8%) | 494472 (46.3%) | 214635 (47.8%) | 1208051 (46.1%) |
| Unknown | 0 | 0 | 0 | 14762 (0.6%) |
| Ethnicity | | | | |
| White | 1263101 (83.3%) | 875219 (82.0%) | 387882 (86.4%) | 2007015 (76.6%) |
| Black | 80921 (5.3%) | 65891 (6.2%) | 15030 (3.3%) | 167671 (6.4%) |
| Indian | 43720 (2.9%) | 33072 (3.1%) | 10648 (2.4%) | 82076 (3.1%) |
| Pakistani or Bangladeshi | 31317 (2.1%) | 21864 (2.0%) | 9453 (2.1%) | 71296 (2.7%) |
| Other | 77761 (5.1%) | 56926 (5.3%) | 20835 (4.6%) | 149784 (5.7%) |
| Unknown | 19882 (1.3%) | 14887 (1.4%) | 4995 (1.1%) | 140803 (5.4%) |
| Region of residence | | | | |
| East of England | 141840 (9.4%) | 92486 (8.7%) | 49354 (11.0%) | 334940 (12.8%) |
| London | 252343 (16.6%) | 204397 (19.1%) | 47946 (10.7%) | 548400 (20.9%) |
| Midlands | 247866 (16.3%) | 164390 (15.4%) | 83476 (18.6%) | 470581 (18.0%) |
| North East and Yorkshire | 270200 (17.8%) | 185596 (17.4%) | 84604 (18.8%) | 326718 (12.5%) |
| North West | 255793 (16.9%) | 191748 (18.0%) | 64045 (14.3%) | 335558 (12.8%) |
| South East | 224973 (14.8%) | 152095 (14.2%) | 72878 (16.2%) | 384155 (14.7%) |
| South West | 123687 (8.2%) | 77147 (7.2%) | 46540 (10.4%) | 188521 (7.2%) |
| Unknown | 0 | 0 | 0 | 29772 (1.1%) |
| Index of multiple deprivation | | | | |
| 1st decile (most deprived) | 141357 (9.3%) | 97415 (9.1%) | 43942 (9.8%) | 244369 (9.3%) |
| 2nd decile | 148090 (9.8%) | 107484 (10.1%) | 40606 (9.0%) | 274341 (10.5%) |
| 3rd decile | 155276 (10.2%) | 113873 (10.7%) | 41403 (9.2%) | 283659 (10.8%) |
| 4th decile | 152424 (10.0%) | 109294 (10.2%) | 43130 (9.6%) | 272240 (10.4%) |
| 5th decile | 150133 (9.9%) | 106650 (10.0%) | 43483 (9.7%) | 263609 (10.1%) |
| 6th decile | 151767 (10.0%) | 106112 (9.9%) | 45655 (10.2%) | 261359 (10.0%) |
| 7th decile | 151693 (10.0%) | 105859 (9.9%) | 45834 (10.2%) | 249140 (9.5%) |
| 8th decile | 155589 (10.3%) | 108428 (10.2%) | 47161 (10.5%) | 252031 (9.6%) |
| 9th decile | 155708 (10.3%) | 107643 (10.1%) | 48065 (10.7%) | 247841 (9.5%) |
| 10th decile (least deprived) | 154665 (10.2%) | 105101 (9.8%) | 49564 (11.0%) | 240284 (9.2%) |
| Unknown | 0 | 0 | 0 | 29772 (1.1%) |
| Calendar week of specimen | | | | |
| 29 November - 5 December 2021 | 157414 (10.4%) | 1516 (0.1%) | 155898 (34.7%) | 133084 (5.1%) |
| 6 December - 12 December 2021 | 171374 (11.3%) | 31382 (2.9%) | 139992 (31.2%) | 156067 (6.0%) |
| 13 December - 19 December 2021 | 288549 (19.0%) | 193630 (18.1%) | 94919 (21.1%) | 306153 (11.7%) |
| 20 December - 26 December 2021 | 402599 (26.5%) | 359492 (33.7%) | 43107 (9.6%) | 384067 (14.7%) |
| 27 December 2021 - 2 January 2022 | 361392 (23.8%) | 347683 (32.6%) | 13709 (3.1%) | 762132 (29.1%) |
| 3 January - 9 January 2022 | 135374 (8.9%) | 134156 (12.6%) | 1218 (0.3%) | 877142 (33.5%) |
| Vaccination status at date of specimen | | | | |
| Unvaccinated | 380712 (25.1%) | 192426 (18.0%) | 188286 (41.9%) | 573805 (21.9%) |
| AstraZeneca, 1 dose | 8757 (0.6%) | 5640 (0.5%) | 3117 (0.7%) | 12952 (0.5%) |
| AstraZeneca, 2 doses | 237755 (15.7%) | 134262 (12.6%) | 103493 (23.1%) | 282063 (10.8%) |
| AstraZeneca, 3 doses | 251224 (16.6%) | 215603 (20.2%) | 35621 (7.9%) | 440129 (16.8%) |
| Pfizer/Moderna, 1 dose | 89141 (5.9%) | 58776 (5.5%) | 30365 (6.8%) | 137778 (5.3%) |
| Pfizer/Moderna, 2 doses | 337023 (22.2%) | 268430 (25.1%) | 68593 (15.3%) | 488328 (18.6%) |
| Pfizer/Moderna, 3 doses | 212090 (14.0%) | 192722 (18.0%) | 19368 (4.3%) | 399325 (15.2%) |
| Unknown | 0 | 0 | 0 | 284265 (10.9%) |
| Reinfection status | | | | |
| First infection | 1407762 (92.8%) | 964902 (90.4%) | 442860 (98.7%) | 2393834 (91.4%) |
| Reinfection | 108940 (7.2%) | 102957 (9.6%) | 5983 (1.3%) | 224811 (8.6%) |

**Table S2: Risk of hospitalisation and mortality for COVID-19 cases with Omicron compared with Delta, overall and by age group.** From left to right, columns show: observed counts and proportions for three hospitalisation endpoints and death within 28 days of a positive test; unadjusted hazard ratio (HR) estimates by each age stratum; adjusted estimates derived from the primary analysis, which stratifies by vaccination category, but does not estimate vaccine effectiveness; and adjusted estimates for the unvaccinated population, from the secondary analysis, which estimated variant-specific HRs for hospitalisation or death in vaccinated groups versus unvaccinated, additionally to the Omicron vs Delta HRs.

| Outcome | Age group | Omicron, n/N (%)* | Delta, n/N (%)* | HR (95% CI), Omicron vs Delta | | |
|---|---|---|---|---|---|---|
| | | | | Unadjusted | Adjusted for confounders† | Adjusted for confounders, estimates for unvaccinated‡ |
| Hospital admission up to 14 days after positive test | All ages | 9624/1067859 (0.90%) | 7358/448843 (1.64%) | 0.55 (0.53-0.56) | 0.41 (0.39-0.43) | 0.30 (0.28-0.32) |
| | <10 years | 475/43147 (1.10%) | 345/74484 (0.46%) | 2.39 (2.08-2.74) | 1.10 (0.85-1.42) | 1.10 (0.85-1.42) |
| | 10-19 years | 456/119261 (0.38%) | 288/88284 (0.33%) | 1.17 (1.01-1.36) | 0.83 (0.64-1.08) | 0.78 (0.60-1.00) |
| | 20-29 years | 1593/265199 (0.60%) | 642/48178 (1.33%) | 0.45 (0.41-0.49) | 0.55 (0.48-0.63) | 0.43 (0.37-0.49) |
| | 30-39 years | 1500/228915 (0.66%) | 1192/79401 (1.50%) | 0.43 (0.40-0.47) | 0.44 (0.39-0.50) | 0.31 (0.28-0.35) |
| | 40-49 years | 987/167045 (0.59%) | 1147/81760 (1.40%) | 0.42 (0.39-0.46) | 0.33 (0.29-0.38) | 0.20 (0.17-0.23) |
| | 50-59 years | 1031/134186 (0.77%) | 1175/49298 (2.38%) | 0.32 (0.29-0.35) | 0.26 (0.23-0.30) | 0.14 (0.12-0.17) |
| | 60-69 years | 900/64875 (1.39%) | 970/18330 (5.29%) | 0.26 (0.23-0.28) | 0.25 (0.21-0.30) | 0.14 (0.12-0.16) |
| | 70-79 years | 1108/31066 (3.57%) | 795/5943 (13.4%) | 0.25 (0.23-0.28) | 0.36 (0.30-0.43) | 0.20 (0.17-0.24) |
| | ≥80 years | 1574/14165 (11.1%) | 804/3165 (25.4%) | 0.40 (0.37-0.44) | 0.47 (0.40-0.56) | 0.33 (0.28-0.39) |
| Any hospital attendance (including admission) up to 14 days after positive test | All ages | 22798/1067859 (2.13%) | 13519/448843 (3.01%) | 0.71 (0.69-0.72) | 0.56 (0.54-0.58) | 0.41 (0.39-0.43) |
| | <10 years | 1158/43147 (2.68%) | 1111/74484 (1.49%) | 1.81 (1.67-1.97) | 1.03 (0.89-1.19) | 1.03 (0.89-1.19) |
| | 10-19 years | 1390/119261 (1.17%) | 933/88284 (1.06%) | 1.10 (1.02-1.20) | 0.89 (0.76-1.03) | 0.84 (0.73-0.98) |
| | 20-29 years | 4758/265199 (1.79%) | 1448/48178 (3.01%) | 0.59 (0.56-0.63) | 0.67 (0.62-0.74) | 0.52 (0.48-0.57) |
| | 30-39 years | 4406/228915 (1.92%) | 2596/79401 (3.27%) | 0.58 (0.56-0.61) | 0.57 (0.52-0.61) | 0.40 (0.37-0.43) |
| | 40-49 years | 2949/167045 (1.77%) | 2230/81760 (2.73%) | 0.64 (0.61-0.68) | 0.54 (0.49-0.59) | 0.32 (0.29-0.35) |
| | 50-59 years | 2632/134186 (1.96%) | 1938/49298 (3.93%) | 0.49 (0.47-0.52) | 0.42 (0.38-0.46) | 0.22 (0.20-0.25) |
| | 60-69 years | 1801/64875 (2.78%) | 1377/18330 (7.51%) | 0.36 (0.34-0.39) | 0.32 (0.28-0.37) | 0.16 (0.14-0.18) |
| | 70-79 years | 1681/31066 (5.41%) | 963/5943 (16.2%) | 0.31 (0.29-0.34) | 0.42 (0.36-0.50) | 0.19 (0.16-0.22) |
| | ≥80 years | 2023/14165 (14.3%) | 923/3165 (29.2%) | 0.45 (0.41-0.48) | 0.49 (0.42-0.58) | 0.27 (0.23-0.31) |
| Any hospital attendance (including admission) up to 14 days after positive test, or positive test during hospital stay | All ages | 25815/1067859 (2.42%) | 14739/448843 (3.28%) | 0.73 (0.72-0.75) | 0.59 (0.57-0.61) | 0.44 (0.42-0.46) |
| | <10 years | 1304/43147 (3.02%) | 1300/74484 (1.75%) | 1.75 (1.62-1.89) | 1.04 (0.91-1.19) | 1.04 (0.91-1.19) |
| | 10-19 years | 1749/119261 (1.47%) | 1203/88284 (1.36%) | 1.08 (1.00-1.16) | 0.88 (0.77-1.00) | 0.85 (0.75-0.97) |
| | 20-29 years | 5593/265199 (2.11%) | 1577/48178 (3.27%) | 0.64 (0.61-0.68) | 0.70 (0.65-0.77) | 0.55 (0.51-0.60) |
| | 30-39 years | 5000/228915 (2.18%) | 2788/79401 (3.51%) | 0.62 (0.59-0.65) | 0.59 (0.55-0.63) | 0.41 (0.38-0.45) |
| | 40-49 years | 3315/167045 (1.98%) | 2375/81760 (2.90%) | 0.68 (0.65-0.72) | 0.57 (0.52-0.62) | 0.34 (0.31-0.37) |
| | 50-59 years | 2920/134186 (2.18%) | 2044/49298 (4.15%) | 0.52 (0.49-0.55) | 0.44 (0.40-0.49) | 0.24 (0.22-0.26) |
| | 60-69 years | 1976/64875 (3.05%) | 1447/18330 (7.89%) | 0.38 (0.35-0.40) | 0.34 (0.30-0.39) | 0.17 (0.15-0.19) |
| | 70-79 years | 1802/31066 (5.80%) | 1007/5943 (16.9%) | 0.32 (0.30-0.35) | 0.45 (0.38-0.52) | 0.20 (0.18-0.24) |
| | ≥80 years | 2156/14165 (15.2%) | 998/3165 (31.5%) | 0.43 (0.40-0.47) | 0.53 (0.45-0.62) | 0.29 (0.25-0.34) |
| Death within 28 days after positive test | All ages | 1225/1067859 (0.11%) | 1205/448843 (0.27%) | 0.44 (0.41-0.48) | 0.31 (0.26-0.37) | 0.20 (0.16-0.25) |
| | <10 years | 2/43147 (0.005%) | 1/74484 (0.001%) | --§ | --§ | --§ |
| | 10-19 years | 1/119261 (0.001%) | 1/88284 (0.001%) | --§ | --§ | --§ |
| | 20-29 years | 5/265199 (0.002%) | 2/48178 (0.004%) | --§ | --§ | --§ |
| | 30-39 years | 11/228915 (0.005%) | 28/79401 (0.04%) | 0.14 (0.07-0.28) | 0.28 (0.07-1.04) | 0.13 (0.04-0.46) |
| | 40-49 years | 25/167045 (0.01%) | 43/81760 (0.05%) | 0.29 (0.18-0.48) | 0.25 (0.11-0.55) | 0.11 (0.05-0.24) |
| | 50-59 years | 71/134186 (0.05%) | 128/49298 (0.26%) | 0.21 (0.16-0.28) | 0.16 (0.09-0.27) | 0.07 (0.04-0.12) |
| | 60-69 years | 128/64875 (0.20%) | 206/18330 (1.12%) | 0.19 (0.15-0.23) | 0.22 (0.15-0.34) | 0.11 (0.07-0.16) |
| | 70-79 years | 257/31066 (0.83%) | 294/5943 (4.95%) | 0.17 (0.14-0.20) | 0.26 (0.18-0.36) | 0.16 (0.11-0.22) |
| | ≥80 years | 725/14165 (5.12%) | 502/3165 (15.9%) | 0.32 (0.29-0.36) | 0.46 (0.36-0.58) | 0.36 (0.27-0.48) |

* These crude descriptive frequencies are unadjusted for age and other confounders, and so are not directly comparable between groups.
† Based on models stratified for calendar date, region, age group, ethnicity and vaccination status, and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and vaccine-status-specific past infection status.
‡ Adjusted HR estimates for unvaccinated cases. Based on models stratified for calendar date, region, age group and ethnicity, and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and explicit modelling of the effects of past infection and vaccination history. Variant-specific HRs for vaccinated compared with unvaccinated cases are shown in Figure 2 and appendix p. 6-7.
§ Not estimated due to small numbers.

**Table S3. HR estimates for vaccination and prior infection categories** for the secondary analysis model used to estimate age-specific hazard ratios (HRs) for Omicron versus Delta and variant-specific vaccine effectiveness. Corresponding age-specific hazard ratios for Omicron vs Delta cases in unvaccinated individuals are shown in the rightmost column of Table 1. HRs for vaccination categories are versus unvaccinated cases, those for past infection categories are versus cases with no documented past infection. Vaccination categories are stratified by vaccine given for doses 1 and 2, number of doses received (dose 3 was always Pfizer or Moderna booster), and weeks elapsed from last dose to positive SARS-CoV-2 specimen date.

| Variable | HR (95% CI) | | | |
|---|---|---|---|---|
| | Hospital admission up to 14 days after positive test | Any hospital attendance (including admission) up to 14 days after positive test | Any hospital attendance (including admission) up to 14 days after positive test, or positive test during hospital stay | Death within 28 days after positive test |
| Delta: AstraZeneca, dose 1, any time* | 0.55 (0.46-0.66) | 0.65 (0.57-0.75) | 0.69 (0.60-0.78) | 0.57 (0.37-0.88) |
| Delta: AstraZeneca, dose 2, <2 weeks | 0.17 (0.08-0.38) | 0.24 (0.13-0.45) | 0.23 (0.13-0.44) | -- |
| Delta: AstraZeneca, dose 2, 2-7 weeks | 0.18 (0.07-0.50) | 0.22 (0.10-0.49) | 0.21 (0.09-0.48) | 0.31 (0.04-2.47) |
| Delta: AstraZeneca, dose 2, 8-11 weeks | 0.61 (0.28-1.31) | 0.51 (0.26-0.99) | 0.51 (0.26-0.99) | 0.37 (0.05-2.87) |
| Delta: AstraZeneca, dose 2, 12-15 weeks | 0.32 (0.17-0.59) | 0.32 (0.19-0.51) | 0.33 (0.21-0.53) | -- |
| Delta: AstraZeneca, dose 2, 16-19 weeks | 0.14 (0.10-0.21) | 0.24 (0.19-0.30) | 0.27 (0.21-0.33) | 0.23 (0.07-0.78) |
| Delta: AstraZeneca, dose 2, 20+ weeks | 0.22 (0.20-0.23) | 0.28 (0.27-0.29) | 0.30 (0.29-0.32) | 0.27 (0.23-0.33) |
| Delta: AstraZeneca, dose 3, <2 weeks | 0.11 (0.09-0.12) | 0.15 (0.14-0.17) | 0.16 (0.15-0.18) | 0.11 (0.08-0.16) |
| Delta: AstraZeneca, dose 3, 2-7 weeks | 0.13 (0.12-0.16) | 0.18 (0.16-0.20) | 0.19 (0.17-0.21) | 0.13 (0.10-0.17) |
| Delta: AstraZeneca, dose 3, 8-11 weeks | 0.15 (0.12-0.19) | 0.22 (0.18-0.26) | 0.24 (0.20-0.28) | 0.16 (0.11-0.23) |
| Delta: AstraZeneca, dose 3, 12+ weeks | 0.30 (0.17-0.55) | 0.35 (0.21-0.60) | 0.37 (0.22-0.62) | 0.06 (0.01-0.48) |
| Delta: Pfizer/Moderna, dose 1, <2 weeks | 0.56 (0.41-0.78) | 0.68 (0.55-0.84) | 0.70 (0.58-0.86) | 0.42 (0.13-1.43) |
| Delta: Pfizer/Moderna, dose 1, 2-7 weeks | 0.35 (0.25-0.47) | 0.46 (0.38-0.56) | 0.50 (0.42-0.59) | 0.79 (0.29-2.14) |
| Delta: Pfizer/Moderna, dose 1, 8-11 weeks | 0.39 (0.26-0.59) | 0.48 (0.37-0.61) | 0.58 (0.47-0.71) | 0.21 (0.03-1.57) |
| Delta: Pfizer/Moderna, dose 1, 12+ weeks | 0.37 (0.30-0.45) | 0.44 (0.39-0.50) | 0.47 (0.42-0.53) | 0.39 (0.20-0.76) |
| Delta: Pfizer/Moderna, dose 2, <2 weeks | 0.19 (0.10-0.37) | 0.34 (0.23-0.49) | 0.33 (0.23-0.48) | -- |
| Delta: Pfizer/Moderna, dose 2, 2-7 weeks | 0.45 (0.29-0.70) | 0.43 (0.31-0.59) | 0.48 (0.35-0.65) | 0.11 (0.01-0.96) |
| Delta: Pfizer/Moderna, dose 2, 8-11 weeks | 0.24 (0.16-0.37) | 0.32 (0.25-0.42) | 0.36 (0.28-0.46) | 0.19 (0.05-0.80) |
| Delta: Pfizer/Moderna, dose 2, 12-15 weeks | 0.14 (0.11-0.19) | 0.22 (0.18-0.26) | 0.25 (0.21-0.29) | -- |
| Delta: Pfizer/Moderna, dose 2, 16-19 weeks | 0.11 (0.09-0.13) | 0.18 (0.16-0.21) | 0.20 (0.18-0.23) | 0.08 (0.02-0.34) |
| Delta: Pfizer/Moderna, dose 2, 20+ weeks | 0.19 (0.17-0.22) | 0.25 (0.23-0.28) | 0.27 (0.25-0.29) | 0.30 (0.24-0.38) |
| Delta: Pfizer/Moderna, dose 3, <2 weeks | 0.14 (0.11-0.18) | 0.17 (0.15-0.21) | 0.18 (0.16-0.22) | 0.16 (0.10-0.25) |
| Delta: Pfizer/Moderna, dose 3, 2-7 weeks | 0.13 (0.11-0.15) | 0.19 (0.17-0.21) | 0.20 (0.18-0.22) | 0.14 (0.11-0.19) |
| Delta: Pfizer/Moderna, dose 3, 8-11 weeks | 0.12 (0.10-0.14) | 0.17 (0.15-0.19) | 0.17 (0.15-0.20) | 0.12 (0.09-0.15) |
| Delta: Pfizer/Moderna, dose 3, 12+ weeks | 0.17 (0.11-0.25) | 0.20 (0.14-0.28) | 0.20 (0.14-0.29) | 0.13 (0.07-0.26) |
| Omicron: AstraZeneca, dose 1, any time* | 1.18 (1.01-1.39) | 1.27 (1.14-1.43) | 1.27 (1.14-1.42) | 1.06 (0.69-1.64) |
| Omicron: AstraZeneca, dose 2, <2 weeks | 0.61 (0.33-1.14) | 0.66 (0.43-1.02) | 0.61 (0.40-0.94) | -- |
| Omicron: AstraZeneca, dose 2, 2-7 weeks | 0.40 (0.24-0.67) | 0.53 (0.38-0.73) | 0.50 (0.36-0.70) | 0.16 (0.02-1.15) |
| Omicron: AstraZeneca, dose 2, 8-11 weeks | 0.65 (0.41-1.04) | 0.68 (0.47-0.99) | 0.72 (0.51-1.02) | 0.79 (0.34-1.83) |
| Omicron: AstraZeneca, dose 2, 12-15 weeks | 0.50 (0.28-0.89) | 0.59 (0.40-0.88) | 0.62 (0.42-0.90) | 0.59 (0.18-1.98) |
| Omicron: AstraZeneca, dose 2, 16-19 weeks | 0.54 (0.37-0.79) | 0.65 (0.52-0.83) | 0.69 (0.55-0.86) | 1.08 (0.38-3.14) |
| Omicron: AstraZeneca, dose 2, 20+ weeks | 0.55 (0.51-0.59) | 0.62 (0.59-0.65) | 0.65 (0.62-0.68) | 0.83 (0.66-1.03) |
| Omicron: AstraZeneca, dose 3, <2 weeks | 0.29 (0.26-0.33) | 0.38 (0.35-0.40) | 0.40 (0.37-0.43) | 0.26 (0.17-0.40) |
| Omicron: AstraZeneca, dose 3, 2-7 weeks | 0.22 (0.20-0.24) | 0.35 (0.33-0.37) | 0.37 (0.35-0.39) | 0.18 (0.14-0.23) |
| Omicron: AstraZeneca, dose 3, 8-11 weeks | 0.21 (0.19-0.24) | 0.43 (0.40-0.46) | 0.44 (0.41-0.47) | 0.16 (0.12-0.20) |
| Omicron: AstraZeneca, dose 3, 12+ weeks | 0.23 (0.19-0.28) | 0.48 (0.42-0.54) | 0.48 (0.42-0.55) | 0.23 (0.16-0.33) |
| Omicron: Pfizer/Moderna, dose 1, <2 weeks | 0.70 (0.53-0.92) | 0.75 (0.63-0.90) | 0.74 (0.62-0.88) | 0.60 (0.21-1.70) |
| Omicron: Pfizer/Moderna, dose 1, 2-7 weeks | 0.48 (0.38-0.60) | 0.61 (0.53-0.70) | 0.60 (0.53-0.68) | 0.13 (0.02-0.93) |
| Omicron: Pfizer/Moderna, dose 1, 8-11 weeks | 0.51 (0.38-0.68) | 0.58 (0.49-0.69) | 0.60 (0.51-0.69) | 0.68 (0.27-1.72) |
| Omicron: Pfizer/Moderna, dose 1, 12+ weeks | 0.65 (0.56-0.75) | 0.72 (0.66-0.79) | 0.75 (0.68-0.81) | 0.58 (0.28-1.23) |
| Omicron: Pfizer/Moderna, dose 2, <2 weeks | 0.54 (0.39-0.75) | 0.62 (0.51-0.75) | 0.60 (0.50-0.72) | 1.37 (0.30-6.30) |
| Omicron: Pfizer/Moderna, dose 2, 2-7 weeks | 0.40 (0.31-0.51) | 0.49 (0.42-0.57) | 0.52 (0.46-0.60) | 0.97 (0.44-2.14) |
| Omicron: Pfizer/Moderna, dose 2, 8-11 weeks | 0.38 (0.30-0.48) | 0.53 (0.46-0.60) | 0.54 (0.48-0.61) | 0.05 (0.01-0.43) |
| Omicron: Pfizer/Moderna, dose 2, 12-15 weeks | 0.31 (0.27-0.37) | 0.39 (0.35-0.43) | 0.42 (0.38-0.45) | 0.19 (0.05-0.77) |
| Omicron: Pfizer/Moderna, dose 2, 16-19 weeks | 0.25 (0.22-0.28) | 0.35 (0.32-0.37) | 0.38 (0.35-0.40) | 0.09 (0.01-0.69) |
| Omicron: Pfizer/Moderna, dose 2, 20+ weeks | 0.43 (0.39-0.46) | 0.53 (0.50-0.56) | 0.54 (0.51-0.57) | 0.81 (0.62-1.04) |

| | | | | |
|---|---|---|---|---|
| Omicron: Pfizer/Moderna, dose 3, <2 weeks | 0.23 (0.20-0.26) | 0.32 (0.30-0.35) | 0.36 (0.33-0.39) | 0.28 (0.16-0.51) |
| Omicron: Pfizer/Moderna, dose 3, 2-7 weeks | 0.26 (0.23-0.29) | 0.43 (0.40-0.47) | 0.45 (0.42-0.48) | 0.22 (0.16-0.30) |
| Omicron: Pfizer/Moderna, dose 3, 8-11 weeks | 0.22 (0.20-0.24) | 0.40 (0.38-0.43) | 0.42 (0.39-0.45) | 0.15 (0.12-0.20) |
| Omicron: Pfizer/Moderna, dose 3, 12+ weeks | 0.19 (0.17-0.22) | 0.38 (0.35-0.42) | 0.39 (0.36-0.43) | 0.13 (0.10-0.17) |
| Past infection, unvaccinated | 0.55 (0.48-0.63) | 0.68 (0.62-0.74) | 0.72 (0.67-0.78) | 0.18 (0.06-0.57) |
| Past infection, vaccinated | 0.96 (0.88-1.04) | 1.03 (0.98-1.09) | 1.04 (0.99-1.09) | 0.47 (0.32-0.68) |

* Due to small numbers, all cases who had received a single dose of the AstraZeneca vaccine are grouped together.

**Table S4: As Table S2, but showing HRs for Omicron versus Delta cases, by the age bands <1 year, 1-4 years, 5-9 years, and 10-year bands subsequently**.

| Outcome | Age group | Omicron, n/N (%)* | Delta, n/N (%)* | HR (95% CI), Omicron vs Delta | | |
|---|---|---|---|---|---|---|
| | | | | Unadjusted | Adjusted for confounders† | Adjusted for confounders, estimates for unvaccinated‡ |
| Hospital admission up to 14 days after positive test | <1 year | 260/2346 (11.1%) | 112/1517 (7.38%) | 1.54 (1.23-1.92) | 1.36 (0.87-2.12) | 1.35 (0.87-2.11) |
| | 1-4 years | 131/10475 (1.25%) | 93/11981 (0.78%) | 1.62 (1.24-2.11) | 0.76 (0.47-1.23) | 0.76 (0.47-1.23) |
| | 5-9 years | 84/30326 (0.28%) | 140/60986 (0.23%) | 1.21 (0.92-1.58) | 1.04 (0.63-1.70) | 1.04 (0.63-1.70) |
| | 10-19 years | 456/119261 (0.38%) | 288/88284 (0.33%) | 1.17 (1.01-1.36) | 0.83 (0.64-1.08) | 0.78 (0.60-1.00) |
| | 20-29 years | 1593/265199 (0.60%) | 642/48178 (1.33%) | 0.45 (0.41-0.49) | 0.55 (0.48-0.63) | 0.43 (0.37-0.49) |
| | 30-39 years | 1500/228915 (0.66%) | 1192/79401 (1.50%) | 0.43 (0.40-0.47) | 0.44 (0.39-0.50) | 0.31 (0.28-0.35) |
| | 40-49 years | 987/167045 (0.59%) | 1147/81760 (1.40%) | 0.42 (0.39-0.46) | 0.33 (0.29-0.38) | 0.20 (0.17-0.23) |
| | 50-59 years | 1031/134186 (0.77%) | 1175/49298 (2.38%) | 0.32 (0.29-0.35) | 0.26 (0.23-0.30) | 0.14 (0.12-0.17) |
| | 60-69 years | 900/64875 (1.39%) | 970/18330 (5.29%) | 0.26 (0.23-0.28) | 0.25 (0.21-0.30) | 0.14 (0.12-0.16) |
| | 70-79 years | 1108/31066 (3.57%) | 795/5943 (13.4%) | 0.25 (0.23-0.28) | 0.36 (0.30-0.43) | 0.20 (0.17-0.24) |
| | ≥80 years | 1574/14165 (11.1%) | 804/3165 (25.4%) | 0.40 (0.37-0.44) | 0.47 (0.40-0.56) | 0.33 (0.28-0.39) |
| Any hospital attendance (including admission) up to 14 days after positive test | <1 year | 511/2346 (21.78%) | 242/1517 (15.95%) | 1.43 (1.23-1.67) | 1.30 (0.96-1.76) | 1.29 (0.96-1.75) |
| | 1-4 years | 333/10475 (3.18%) | 335/11981 (2.80%) | 1.14 (0.98-1.33) | 0.93 (0.71-1.20) | 0.93 (0.71-1.20) |
| | 5-9 years | 314/30326 (1.04%) | 534/60986 (0.88%) | 1.18 (1.03-1.36) | 0.99 (0.78-1.25) | 0.99 (0.78-1.25) |
| | 10-19 years | 1390/119261 (1.17%) | 933/88284 (1.06%) | 1.10 (1.02-1.20) | 0.89 (0.76-1.03) | 0.84 (0.73-0.98) |
| | 20-29 years | 4758/265199 (1.79%) | 1448/48178 (3.01%) | 0.59 (0.56-0.63) | 0.67 (0.62-0.74) | 0.52 (0.48-0.57) |
| | 30-39 years | 4406/228915 (1.92%) | 2596/79401 (3.27%) | 0.58 (0.56-0.61) | 0.57 (0.52-0.61) | 0.40 (0.37-0.43) |
| | 40-49 years | 2949/167045 (1.77%) | 2230/81760 (2.73%) | 0.64 (0.61-0.68) | 0.54 (0.49-0.59) | 0.32 (0.29-0.35) |
| | 50-59 years | 2632/134186 (1.96%) | 1938/49298 (3.93%) | 0.49 (0.47-0.52) | 0.42 (0.38-0.46) | 0.22 (0.20-0.25) |
| | 60-69 years | 1801/64875 (2.78%) | 1377/18330 (7.51%) | 0.36 (0.34-0.39) | 0.32 (0.28-0.37) | 0.16 (0.14-0.18) |
| | 70-79 years | 1681/31066 (5.41%) | 963/5943 (16.2%) | 0.31 (0.29-0.34) | 0.42 (0.36-0.50) | 0.19 (0.16-0.22) |
| | ≥80 years | 2023/14165 (14.3%) | 923/3165 (29.2%) | 0.45 (0.41-0.48) | 0.49 (0.42-0.58) | 0.27 (0.23-0.31) |
| Any hospital attendance (including admission) up to 14 days after positive test, or positive test during hospital stay | <1 year | 528/2346 (22.51%) | 251/1517 (16.55%) | 1.43 (1.23-1.66) | 1.34 (1.00-1.81) | 1.33 (0.99-1.80) |
| | 1-4 years | 387/10475 (3.69%) | 373/11981 (3.11%) | 1.19 (1.04-1.38) | 1.00 (0.78-1.28) | 1.00 (0.78-1.28) |
| | 5-9 years | 389/30326 (1.28%) | 676/60986 (1.11%) | 1.16 (1.02-1.31) | 0.96 (0.78-1.19) | 0.96 (0.78-1.19) |
| | 10-19 years | 1749/119261 (1.47%) | 1203/88284 (1.36%) | 1.08 (1.00-1.16) | 0.88 (0.77-1.00) | 0.85 (0.75-0.97) |
| | 20-29 years | 5593/265199 (2.11%) | 1577/48178 (3.27%) | 0.64 (0.61-0.68) | 0.70 (0.65-0.77) | 0.55 (0.51-0.60) |
| | 30-39 years | 5000/228915 (2.18%) | 2788/79401 (3.51%) | 0.62 (0.59-0.65) | 0.59 (0.55-0.63) | 0.41 (0.38-0.45) |
| | 40-49 years | 3315/167045 (1.98%) | 2375/81760 (2.90%) | 0.68 (0.65-0.72) | 0.57 (0.52-0.62) | 0.34 (0.31-0.37) |
| | 50-59 years | 2920/134186 (2.18%) | 2044/49298 (4.15%) | 0.52 (0.49-0.55) | 0.44 (0.40-0.49) | 0.24 (0.22-0.26) |
| | 60-69 years | 1976/64875 (3.05%) | 1447/18330 (7.89%) | 0.38 (0.35-0.40) | 0.34 (0.30-0.39) | 0.17 (0.15-0.19) |
| | 70-79 years | 1802/31066 (5.80%) | 1007/5943 (16.9%) | 0.32 (0.30-0.35) | 0.45 (0.38-0.52) | 0.20 (0.18-0.24) |
| | ≥80 years | 2156/14165 (15.2%) | 998/3165 (31.5%) | 0.43 (0.40-0.47) | 0.53 (0.45-0.62) | 0.29 (0.25-0.34) |
| Death within 28 days after positive test | <1 year | 2/2346 (0.09%) | 0/1517 (0.00%) | --§ | --§ | --§ |
| | 1-4 years | 0/10475 (0%) | 1/11981 (0.01%) | --§ | --§ | --§ |
| | 5-9 years | 0/30326 (0%) | 0/60986 (0%) | --§ | --§ | --§ |
| | 10-19 years | 1/119261 (0.001%) | 1/88284 (0.001%) | --§ | --§ | --§ |
| | 20-29 years | 5/265199 (0.002%) | 2/48178 (0.004%) | --§ | --§ | --§ |
| | 30-39 years | 11/228915 (0.005%) | 28/79401 (0.04%) | 0.14 (0.07-0.28) | 0.28 (0.07-1.04) | 0.13 (0.04-0.46) |
| | 40-49 years | 25/167045 (0.01%) | 43/81760 (0.05%) | 0.29 (0.18-0.48) | 0.25 (0.11-0.55) | 0.11 (0.05-0.24) |
| | 50-59 years | 71/134186 (0.05%) | 128/49298 (0.26%) | 0.21 (0.16-0.28) | 0.16 (0.09-0.27) | 0.07 (0.04-0.12) |
| | 60-69 years | 128/64875 (0.20%) | 206/18330 (1.12%) | 0.19 (0.15-0.23) | 0.22 (0.15-0.34) | 0.11 (0.07-0.16) |
| | 70-79 years | 257/31066 (0.83%) | 294/5943 (4.95%) | 0.17 (0.15-0.20) | 0.26 (0.18-0.36) | 0.16 (0.11-0.22) |
| | ≥80 years | 725/14165 (5.12%) | 502/3165 (15.9%) | 0.32 (0.29-0.36) | 0.46 (0.36-0.58) | 0.36 (0.27-0.48) |

* These crude descriptive frequencies are unadjusted for age and other confounders, and so are not directly comparable between groups.
† Based on models stratified for calendar date, region, age group, ethnicity and vaccination status, and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and vaccine-status-specific past infection status.
‡ Adjusted HR estimates for unvaccinated cases. Based on models stratified for calendar date, region, age group and ethnicity, and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and explicit modelling of the effects of past infection and vaccination history.
§ Not estimated due to small numbers.

**Table S5. Sensitivity analyses: adjusted HR estimates for Omicron vs Delta, restricted to the subgroup of unvaccinated cases.**

| Outcome | Age group | HR (95% CI), unvaccinated Omicron vs Delta Adjusted for confounders* |
|---|---|---|
| Hospital admission within 14 days after positive test | Overall | 0.33 (0.31-0.36) |
| | <10 years | 1.09 (0.84-1.41) |
| | 10-19 years | 0.68 (0.50-0.92) |
| | 20-29 years | 0.51 (0.42-0.62) |
| | 30-39 years | 0.31 (0.26-0.37) |
| | 40-49 years | 0.18 (0.14-0.22) |
| | 50-59 years | 0.13 (0.10-0.16) |
| | 60-69 years | 0.18 (0.14-0.25) |
| | 70-79 years | 0.28 (0.19-0.42) |
| | ≥80 years | 0.30 (0.20-0.46) |
| Any hospital attendance (including admission) within 14 days after positive test | Overall | 0.47 (0.44-0.49) |
| | <10 years | 1.02 (0.89-1.18) |
| | 10-19 years | 0.85 (0.71-1.03) |
| | 20-29 years | 0.62 (0.54-0.70) |
| | 30-39 years | 0.38 (0.34-0.43) |
| | 40-49 years | 0.28 (0.24-0.33) |
| | 50-59 years | 0.19 (0.16-0.24) |
| | 60-69 years | 0.20 (0.16-0.26) |
| | 70-79 years | 0.34 (0.23-0.48) |
| | ≥80 years | 0.35 (0.24-0.52) |
| Any hospital attendance (including admission) within 14 days after positive test, or positive test during hospital admission | Overall | 0.50 (0.47-0.53) |
| | <10 years | 1.04 (0.90-1.18) |
| | 10-19 years | 0.87 (0.73-1.02) |
| | 20-29 years | 0.64 (0.57-0.73) |
| | 30-39 years | 0.40 (0.36-0.45) |
| | 40-49 years | 0.31 (0.26-0.36) |
| | 50-59 years | 0.21 (0.17-0.25) |
| | 60-69 years | 0.22 (0.17-0.28) |
| | 70-79 years | 0.34 (0.24-0.49) |
| | ≥80 years | 0.45 (0.30-0.65) |
| Death within 28 days after positive test | Overall | 0.21 (0.15-0.29) |
| | <10 years | --† |
| | 10-19 years | --† |
| | 20-29 years | --† |
| | 30-39 years | 0.09 (0.01-0.64) |
| | 40-49 years | 0.24 (0.08-0.74) |
| | 50-59 years | 0.19 (0.09-0.40) |
| | 60-69 years | 0.22 (0.11-0.46) |
| | 70-79 years | 0.18 (0.09-0.37) |
| | ≥80 years | 0.27 (0.14-0.52) |

* Restricted to unvaccinated subgroup. Based on models stratified for calendar date, region, age group and ethnicity; and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and reinfection status.
† Not estimated due to small numbers.

**Table S6. Sensitivity analyses: effect of allowing past infection to vary by variant.** HR estimates for cases with at least one known past infection compared with cases with no known past infection shown, by SARS-CoV-2 variant.

| Outcome | HR (95% CI)*, past infection versus no past infection | |
|---|---|---|
| | Omicron | Delta |
| Hospital admission up to 14 days after positive test | 0.82 (0.76-0.89) | 0.69 (0.55-0.88) |
| Any hospital attendance (including admission) up to 14 days after positive test | 0.93 (0.88-0.97) | 0.84 (0.72-0.99) |
| Any hospital attendance (including admission) up to 14 days after positive test, or positive test during hospital stay | 0.94 (0.90-0.99) | 0.86 (0.74-1.01) |
| Death within 28 days after positive test | 0.34 (0.22-0.54) | 0.48 (0.21-1.09) |

* Based on model stratified for calendar date, region, age group, ethnicity and vaccination status; and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and reinfection status.

**Table S7. Sensitivity analyses: effect of variant classification method and pillar**. Age-specific adjusted hazard ratio (HR) estimates for hospitalisation and mortality outcomes for cases with the Omicron compared to the Delta variant, in three subgroups of cases: variant identified via whole genome sequencing; variant identified via sequencing or provisional genotyping; cases identified via Pillar 2 community testing alone. Pillar 2 only results were comparable to the primary analysis, while HR estimates were higher for the sequence-only analysis than the primary analysis, and lower for the genotyping-only analysis than the primary analysis.

| Outcome | Age group | HR (95% CI)* | | | |
|---|---|---|---|---|---|
| | | Primary analysis | Subgroup | | |
| | | | Variant classification by whole-genome sequencing | Variant classification by whole-genome sequencing or genotyping | Identified through the Pillar 2 community testing programme |
| Hospital admission up to 14 days after positive test | <10 years | 1.10 (0.85-1.42) | 1.33 (0.82-2.18) | 0.81 (0.59-1.11) | 0.97 (0.64-1.46) |
| | 10-19 years | 0.83 (0.64-1.08) | 0.76 (0.46-1.25) | 0.56 (0.39-0.81) | 0.89 (0.63-1.25) |
| | 20-29 years | 0.55 (0.48-0.63) | 0.70 (0.53-0.92) | 0.40 (0.33-0.49) | 0.48 (0.40-0.57) |
| | 30-39 years | 0.44 (0.39-0.50) | 0.53 (0.41-0.67) | 0.28 (0.24-0.34) | 0.47 (0.40-0.55) |
| | 40-49 years | 0.33 (0.29-0.38) | 0.42 (0.32-0.57) | 0.20 (0.17-0.25) | 0.38 (0.32-0.46) |
| | 50-59 years | 0.26 (0.23-0.30) | 0.43 (0.32-0.57) | 0.17 (0.14-0.21) | 0.32 (0.26-0.40) |
| | 60-69 years | 0.25 (0.21-0.30) | 0.33 (0.23-0.47) | 0.22 (0.17-0.27) | 0.27 (0.20-0.36) |
| | 70-79 years | 0.36 (0.30-0.43) | 0.40 (0.27-0.59) | 0.33 (0.26-0.41) | 0.38 (0.27-0.53) |
| | ≥80 years | 0.47 (0.40-0.56) | 0.57 (0.42-0.79) | 0.45 (0.37-0.55) | 0.43 (0.30-0.61) |
| Any hospital attendance (including admission) up to 14 days after positive test | <10 years | 1.03 (0.89-1.19) | 1.16 (0.85-1.59) | 0.77 (0.62-0.94) | 1.11 (0.93-1.33) |
| | 10-19 years | 0.89 (0.76-1.03) | 0.87 (0.63-1.22) | 0.66 (0.52-0.84) | 0.93 (0.78-1.11) |
| | 20-29 years | 0.67 (0.62-0.74) | 0.83 (0.69-1.00) | 0.56 (0.49-0.64) | 0.66 (0.59-0.74) |
| | 30-39 years | 0.57 (0.52-0.61) | 0.62 (0.53-0.74) | 0.39 (0.34-0.43) | 0.60 (0.55-0.66) |
| | 40-49 years | 0.54 (0.49-0.59) | 0.58 (0.47-0.70) | 0.34 (0.30-0.39) | 0.61 (0.55-0.69) |
| | 50-59 years | 0.42 (0.38-0.46) | 0.51 (0.42-0.64) | 0.25 (0.22-0.29) | 0.53 (0.46-0.61) |
| | 60-69 years | 0.32 (0.28-0.37) | 0.36 (0.27-0.48) | 0.22 (0.18-0.27) | 0.39 (0.32-0.48) |
| | 70-79 years | 0.42 (0.36-0.50) | 0.48 (0.34-0.66) | 0.36 (0.30-0.44) | 0.55 (0.42-0.72) |
| | ≥80 years | 0.49 (0.42-0.58) | 0.58 (0.43-0.77) | 0.46 (0.39-0.56) | 0.44 (0.32-0.61) |
| Any hospital attendance (including admission) up to 14 days after positive test, or positive test during hospital stay | <10 years | 1.04 (0.91-1.19) | 1.19 (0.89-1.61) | 0.79 (0.65-0.97) | 1.10 (0.93-1.29) |
| | 10-19 years | 0.88 (0.77-1.00) | 0.91 (0.68-1.21) | 0.72 (0.58-0.88) | 0.90 (0.77-1.04) |
| | 20-29 years | 0.70 (0.65-0.77) | 0.81 (0.68-0.96) | 0.56 (0.49-0.64) | 0.71 (0.64-0.78) |
| | 30-39 years | 0.59 (0.55-0.63) | 0.64 (0.55-0.75) | 0.41 (0.37-0.46) | 0.62 (0.57-0.68) |
| | 40-49 years | 0.57 (0.52-0.62) | 0.64 (0.53-0.77) | 0.39 (0.34-0.45) | 0.64 (0.58-0.72) |
| | 50-59 years | 0.44 (0.40-0.49) | 0.54 (0.44-0.67) | 0.28 (0.24-0.32) | 0.56 (0.49-0.64) |
| | 60-69 years | 0.34 (0.30-0.39) | 0.40 (0.31-0.53) | 0.24 (0.20-0.28) | 0.43 (0.36-0.52) |
| | 70-79 years | 0.45 (0.38-0.52) | 0.53 (0.38-0.73) | 0.39 (0.32-0.47) | 0.55 (0.42-0.72) |
| | ≥80 years | 0.53 (0.45-0.62) | 0.67 (0.51-0.90) | 0.49 (0.41-0.59) | 0.44 (0.32-0.61) |
| Death within 28 days after positive test | <10 years | --† | --† | --† | --† |
| | 10-19 years | --† | --† | --† | --† |
| | 20-29 years | --† | --† | --† | --† |
| | 30-39 years | 0.28 (0.07-1.04) | --† | 0.20 (0.04-1.05) | 0.21 (0.03-1.45) |
| | 40-49 years | 0.25 (0.11-0.55) | 0.30 (0.07-1.24) | 0.17 (0.07-0.44) | 0.24 (0.06-1.02) |
| | 50-59 years | 0.16 (0.09-0.27) | 0.57 (0.24-1.35) | 0.11 (0.06-0.20) | 0.17 (0.06-0.48) |
| | 60-69 years | 0.22 (0.15-0.34) | 0.43 (0.20-0.92) | 0.17 (0.10-0.27) | 0.37 (0.15-0.91) |
| | 70-79 years | 0.26 (0.18-0.36) | 0.30 (0.14-0.61) | 0.23 (0.15-0.35) | 0.34 (0.15-0.78) |
| | ≥80 years | 0.46 (0.36-0.58) | 0.59 (0.37-0.93) | 0.46 (0.34-0.60) | 0.44 (0.26-0.75) |

* Based on models stratified for calendar date, region, age group, ethnicity and vaccination status; and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and vaccine-status-specific reinfection status.
† Not estimated due to small numbers.

**Table S8: Sensitivity analyses: effect of stratification versus regression adjustments** for alternative or additional variables. Confounder adjustment by stratification is based on fewer model assumptions than adjustments using regression models. Stratification may however result in lower precision estimates due to a lower effective sample size, resulting from the omission of uninformative strata. The primary analysis used models stratified for calendar date, region, age group, ethnicity and vaccination status, and used regression to further adjust for within-age-group age differences, sex, index of multiple deprivation and vaccine status-specific reinfection status. To assess the sensitivity of the results to the set of variables used for stratification or regression adjustment, we (1) stratified for the narrower level upper tier local authority (UTLA) instead of region, (2) stratified for calendar date only and used regression adjustment for all other variables, (3) excluded one variable from the stratification set at a time and instead included it in the regression adjustment, and (4) additionally included one more variable in the stratification set at a time. All estimated HRs were consistent with those from the primary analysis, with the greatest variation being seen in the <10 age band. Stratification for UTLA instead of region or for additional covariates resulted in estimates with marginally wider CIs, and stratification for fewer covariates yielded estimates with marginally narrower CIs.

| Outcome | Age group | HR (95% CI)* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Primary analysis | Alternative stratification | | | | | | | |
| | | | UTLA instead of region | Specimen date only | Not stratified for age group | Not stratified for region | Not stratified for ethnicity | Not stratified for vaccination status | Additional stratification for sex | Additional stratification for IMD |
| Hospital admission up to 14 days after positive test | <10 years | 1.10 (0.85-1.42) | 1.32 (0.94-1.87) | 1.03 (0.89-1.20) | 1.26 (1.08-1.47) | 1.01 (0.80-1.28) | 1.04 (0.82-1.33) | 1.10 (0.85-1.43) | 1.12 (0.85-1.46) | 1.25 (0.92-1.70) |
| | 10-19 years | 0.83 (0.64-1.08) | 0.81 (0.60-1.10) | 0.81 (0.69-0.95) | 0.96 (0.81-1.13) | 0.78 (0.61-1.00) | 0.79 (0.61-1.02) | 0.91 (0.71-1.16) | 0.84 (0.64-1.10) | 0.89 (0.67-1.19) |
| | 20-29 years | 0.55 (0.48-0.63) | 0.60 (0.50-0.71) | 0.53 (0.48-0.58) | 0.55 (0.49-0.60) | 0.52 (0.45-0.59) | 0.54 (0.47-0.62) | 0.58 (0.51-0.67) | 0.55 (0.48-0.64) | 0.59 (0.51-0.70) |
| | 30-39 years | 0.44 (0.39-0.50) | 0.43 (0.38-0.50) | 0.44 (0.41-0.48) | 0.45 (0.41-0.49) | 0.44 (0.39-0.49) | 0.44 (0.39-0.49) | 0.46 (0.41-0.51) | 0.44 (0.39-0.50) | 0.44 (0.38-0.51) |
| | 40-49 years | 0.33 (0.29-0.38) | 0.38 (0.31-0.45) | 0.39 (0.36-0.43) | 0.36 (0.33-0.40) | 0.33 (0.29-0.37) | 0.33 (0.28-0.37) | 0.34 (0.30-0.39) | 0.34 (0.29-0.39) | 0.35 (0.30-0.41) |
| | 50-59 years | 0.26 (0.23-0.30) | 0.31 (0.26-0.38) | 0.32 (0.29-0.35) | 0.28 (0.26-0.31) | 0.26 (0.22-0.29) | 0.25 (0.21-0.28) | 0.25 (0.22-0.28) | 0.26 (0.22-0.30) | 0.28 (0.24-0.33) |
| | 60-69 years | 0.25 (0.21-0.30) | 0.32 (0.24-0.42) | 0.27 (0.24-0.30) | 0.25 (0.22-0.27) | 0.26 (0.22-0.30) | 0.25 (0.22-0.29) | 0.23 (0.19-0.26) | 0.26 (0.22-0.32) | 0.26 (0.21-0.33) |
| | 70-79 years | 0.36 (0.30-0.43) | 0.31 (0.23-0.43) | 0.27 (0.25-0.30) | 0.27 (0.24-0.30) | 0.37 (0.31-0.43) | 0.37 (0.31-0.44) | 0.32 (0.27-0.37) | 0.37 (0.30-0.45) | 0.33 (0.25-0.43) |
| | ≥80 years | 0.47 (0.40-0.56) | 0.56 (0.40-0.77) | 0.39 (0.35-0.43) | 0.36 (0.33-0.40) | 0.48 (0.42-0.56) | 0.49 (0.42-0.58) | 0.52 (0.45-0.60) | 0.48 (0.40-0.59) | 0.51 (0.39-0.67) |
| Any hospital attendance (including admission) up to 14 days after positive test | <10 years | 1.03 (0.89-1.19) | 1.10 (0.92-1.31) | 0.92 (0.84-1.00) | 1.14 (1.03-1.25) | 1.00 (0.87-1.14) | 1.00 (0.87-1.15) | 1.03 (0.89-1.19) | 1.05 (0.91-1.22) | 1.04 (0.89-1.23) |
| | 10-19 years | 0.89 (0.76-1.03) | 0.89 (0.75-1.06) | 0.79 (0.72-0.87) | 0.95 (0.86-1.05) | 0.84 (0.73-0.98) | 0.86 (0.75-1.00) | 0.97 (0.84-1.12) | 0.90 (0.77-1.04) | 0.99 (0.84-1.16) |
| | 20-29 years | 0.67 (0.62-0.74) | 0.70 (0.63-0.78) | 0.65 (0.61-0.69) | 0.67 (0.63-0.72) | 0.65 (0.59-0.70) | 0.67 (0.61-0.73) | 0.71 (0.65-0.77) | 0.68 (0.62-0.75) | 0.69 (0.62-0.76) |
| | 30-39 years | 0.57 (0.52-0.61) | 0.59 (0.54-0.64) | 0.57 (0.54-0.60) | 0.58 (0.54-0.61) | 0.56 (0.52-0.60) | 0.56 (0.52-0.61) | 0.58 (0.54-0.63) | 0.57 (0.52-0.61) | 0.57 (0.52-0.62) |
| | 40-49 years | 0.54 (0.49-0.59) | 0.59 (0.53-0.66) | 0.58 (0.55-0.62) | 0.54 (0.51-0.58) | 0.53 (0.49-0.58) | 0.53 (0.49-0.58) | 0.55 (0.50-0.60) | 0.54 (0.50-0.60) | 0.56 (0.51-0.62) |
| | 50-59 years | 0.42 (0.38-0.46) | 0.48 (0.42-0.55) | 0.46 (0.43-0.49) | 0.41 (0.38-0.44) | 0.41 (0.37-0.45) | 0.39 (0.35-0.43) | 0.39 (0.35-0.43) | 0.41 (0.37-0.46) | 0.44 (0.39-0.50) |
| | 60-69 years | 0.32 (0.28-0.37) | 0.41 (0.33-0.49) | 0.34 (0.32-0.37) | 0.32 (0.29-0.34) | 0.32 (0.28-0.36) | 0.32 (0.28-0.36) | 0.27 (0.24-0.30) | 0.34 (0.30-0.39) | 0.35 (0.30-0.42) |
| | 70-79 years | 0.42 (0.36-0.50) | 0.39 (0.30-0.50) | 0.30 (0.28-0.33) | 0.30 (0.27-0.32) | 0.43 (0.38-0.50) | 0.44 (0.38-0.50) | 0.35 (0.30-0.40) | 0.43 (0.36-0.51) | 0.41 (0.33-0.51) |
| | ≥80 years | 0.49 (0.42-0.58) | 0.60 (0.45-0.80) | 0.40 (0.36-0.43) | 0.38 (0.35-0.41) | 0.50 (0.44-0.58) | 0.53 (0.45-0.61) | 0.49 (0.43-0.56) | 0.50 (0.42-0.60) | 0.52 (0.40-0.66) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Any hospital attendance (including admission) up to 14 days after positive test, or positive test during hospital stay | <10 years | 1.04 (0.91-1.19) | 1.07 (0.91-1.26) | 0.93 (0.85-1.01) | 1.14 (1.05-1.25) | 1.03 (0.90-1.17) | 1.02 (0.89-1.16) | 1.04 (0.91-1.19) | 1.05 (0.91-1.21) | 1.04 (0.90-1.21) |
| | 10-19 years | 0.88 (0.77-1.00) | 0.86 (0.74-1.00) | 0.82 (0.75-0.89) | 0.97 (0.89-1.06) | 0.88 (0.77-1.00) | 0.85 (0.75-0.97) | 0.95 (0.84-1.08) | 0.87 (0.76-1.00) | 0.93 (0.81-1.08) |
| | 20-29 years | 0.70 (0.65-0.77) | 0.73 (0.66-0.81) | 0.69 (0.65-0.73) | 0.71 (0.67-0.76) | 0.68 (0.63-0.74) | 0.70 (0.64-0.76) | 0.74 (0.69-0.81) | 0.72 (0.66-0.78) | 0.72 (0.65-0.78) |
| | 30-39 years | 0.59 (0.55-0.63) | 0.61 (0.56-0.66) | 0.60 (0.57-0.63) | 0.60 (0.57-0.64) | 0.58 (0.54-0.62) | 0.59 (0.55-0.63) | 0.60 (0.56-0.65) | 0.59 (0.55-0.63) | 0.59 (0.55-0.64) |
| | 40-49 years | 0.57 (0.52-0.62) | 0.64 (0.57-0.71) | 0.63 (0.59-0.66) | 0.58 (0.54-0.61) | 0.57 (0.52-0.62) | 0.57 (0.52-0.62) | 0.58 (0.53-0.63) | 0.58 (0.53-0.63) | 0.60 (0.55-0.66) |
| | 50-59 years | 0.44 (0.40-0.49) | 0.52 (0.46-0.59) | 0.49 (0.46-0.52) | 0.43 (0.41-0.46) | 0.43 (0.39-0.47) | 0.41 (0.38-0.45) | 0.41 (0.38-0.45) | 0.44 (0.40-0.49) | 0.46 (0.41-0.52) |
| | 60-69 years | 0.34 (0.30-0.39) | 0.44 (0.37-0.53) | 0.36 (0.34-0.39) | 0.33 (0.31-0.36) | 0.34 (0.30-0.38) | 0.34 (0.30-0.38) | 0.29 (0.26-0.32) | 0.36 (0.31-0.41) | 0.38 (0.32-0.45) |
| | 70-79 years | 0.45 (0.38-0.52) | 0.43 (0.33-0.55) | 0.31 (0.29-0.34) | 0.30 (0.28-0.33) | 0.45 (0.39-0.52) | 0.46 (0.40-0.52) | 0.37 (0.32-0.42) | 0.45 (0.38-0.54) | 0.44 (0.35-0.54) |
| | ≥80 years | 0.53 (0.45-0.62) | 0.60 (0.45-0.81) | 0.39 (0.36-0.42) | 0.37 (0.34-0.40) | 0.53 (0.47-0.61) | 0.56 (0.49-0.65) | 0.53 (0.46-0.60) | 0.54 (0.45-0.64) | 0.55 (0.43-0.70) |
| Death within 28 days after positive test | <10 years | --† | --† | --† | --† | --† | --† | --† | --† | --† |
| | 10-19 years | --† | --† | --† | --† | --† | --† | --† | --† | --† |
| | 20-29 years | --† | --† | --† | --† | --† | --† | --† | --† | --† |
| | 30-39 years | 0.28 (0.07-1.04) | 0.26 (0.05-1.19) | 0.18 (0.09-0.37) | 0.18 (0.09-0.37) | 0.30 (0.09-1.00) | 0.29 (0.08-1.03) | 0.21 (0.06-0.74) | 0.30 (0.08-1.16) | 0.51 (0.11-2.25) |
| | 40-49 years | 0.25 (0.11-0.55) | 0.27 (0.10-0.75) | 0.37 (0.22-0.61) | 0.32 (0.19-0.54) | 0.25 (0.12-0.52) | 0.27 (0.13-0.57) | 0.21 (0.10-0.45) | 0.27 (0.12-0.61) | 0.22 (0.07-0.67) |
| | 50-59 years | 0.16 (0.09-0.27) | 0.18 (0.09-0.37) | 0.30 (0.22-0.40) | 0.26 (0.18-0.35) | 0.17 (0.11-0.28) | 0.15 (0.09-0.24) | 0.13 (0.08-0.21) | 0.17 (0.10-0.29) | 0.17 (0.09-0.32) |
| | 60-69 years | 0.22 (0.15-0.34) | 0.20 (0.10-0.40) | 0.27 (0.21-0.34) | 0.26 (0.20-0.34) | 0.23 (0.16-0.33) | 0.21 (0.14-0.30) | 0.17 (0.12-0.25) | 0.22 (0.14-0.34) | 0.16 (0.09-0.30) |
| | 70-79 years | 0.26 (0.18-0.36) | 0.26 (0.14-0.47) | 0.26 (0.21-0.31) | 0.25 (0.20-0.31) | 0.29 (0.22-0.39) | 0.26 (0.19-0.36) | 0.24 (0.18-0.32) | 0.30 (0.20-0.43) | 0.29 (0.17-0.50) |
| | ≥80 years | 0.46 (0.36-0.58) | 0.50 (0.31-0.81) | 0.42 (0.36-0.49) | 0.41 (0.34-0.49) | 0.50 (0.41-0.61) | 0.50 (0.40-0.63) | 0.56 (0.46-0.69) | 0.46 (0.35-0.60) | 0.46 (0.30-0.70) |

* Based on models stratified for calendar date, region, age group, ethnicity and vaccination status, and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and vaccine-status-specific past infection status.
† Not estimated due to small numbers.

**Table S9: Sensitivity analyses: effect of hospitalisation outcome definition**. Primary analysis (which examined hospitalisation 0-14 days after positive test) compared with analysis where only hospitalisations 1-14 days after a positive test are included, or where the follow-up time is varied to instead include hospitalisations within 7, 28 or 60 days after a positive test.

| Outcome | Age group | HR (95% CI)* | | | | |
|---|---|---|---|---|---|---|
| | | Primary analysis | Restricted to events 1 to 14 days after positive test | Events within 0 to 7 days after positive test | Events within 0 to 28 days after positive test | Events within 0 to 60 days after positive test |
| Hospital admission | <10 years | 1.10 (0.85-1.42) | 0.74 (0.50-1.09) | 1.19 (0.90-1.58) | 1.13 (0.90-1.41) | 1.11 (0.90-1.38) |
| | 10-19 years | 0.83 (0.64-1.08) | 0.83 (0.59-1.16) | 0.76 (0.56-1.03) | 0.91 (0.74-1.12) | 0.91 (0.75-1.10) |
| | 20-29 years | 0.55 (0.48-0.63) | 0.46 (0.39-0.55) | 0.53 (0.45-0.62) | 0.56 (0.50-0.63) | 0.58 (0.51-0.65) |
| | 30-39 years | 0.44 (0.39-0.50) | 0.41 (0.35-0.47) | 0.40 (0.35-0.46) | 0.49 (0.44-0.55) | 0.50 (0.45-0.56) |
| | 40-49 years | 0.33 (0.29-0.38) | 0.33 (0.28-0.39) | 0.30 (0.25-0.35) | 0.41 (0.36-0.46) | 0.42 (0.37-0.47) |
| | 50-59 years | 0.26 (0.23-0.30) | 0.35 (0.29-0.42) | 0.23 (0.19-0.27) | 0.30 (0.26-0.34) | 0.32 (0.28-0.36) |
| | 60-69 years | 0.25 (0.21-0.30) | 0.33 (0.26-0.42) | 0.23 (0.19-0.28) | 0.30 (0.26-0.35) | 0.31 (0.26-0.36) |
| | 70-79 years | 0.36 (0.30-0.43) | 0.50 (0.39-0.65) | 0.32 (0.26-0.39) | 0.39 (0.32-0.46) | 0.39 (0.33-0.47) |
| | ≥80 years | 0.47 (0.40-0.56) | 0.56 (0.43-0.74) | 0.47 (0.39-0.56) | 0.49 (0.41-0.58) | 0.51 (0.43-0.60) |
| Any hospital attendance (including admission) | <10 years | 1.03 (0.89-1.19) | 0.96 (0.80-1.15) | 1.06 (0.90-1.25) | 1.03 (0.91-1.16) | 1.01 (0.90-1.13) |
| | 10-19 years | 0.89 (0.76-1.03) | 0.86 (0.72-1.03) | 0.81 (0.67-0.98) | 0.98 (0.88-1.09) | 0.98 (0.89-1.08) |
| | 20-29 years | 0.67 (0.62-0.74) | 0.65 (0.58-0.72) | 0.63 (0.57-0.70) | 0.75 (0.69-0.80) | 0.78 (0.72-0.83) |
| | 30-39 years | 0.57 (0.52-0.61) | 0.55 (0.51-0.60) | 0.51 (0.47-0.56) | 0.64 (0.60-0.68) | 0.66 (0.62-0.70) |
| | 40-49 years | 0.54 (0.49-0.59) | 0.55 (0.50-0.61) | 0.46 (0.42-0.52) | 0.64 (0.59-0.69) | 0.66 (0.61-0.71) |
| | 50-59 years | 0.42 (0.38-0.46) | 0.53 (0.46-0.60) | 0.35 (0.31-0.40) | 0.53 (0.48-0.58) | 0.56 (0.51-0.61) |
| | 60-69 years | 0.32 (0.28-0.37) | 0.41 (0.35-0.49) | 0.29 (0.25-0.34) | 0.41 (0.36-0.46) | 0.43 (0.38-0.48) |
| | 70-79 years | 0.42 (0.36-0.50) | 0.59 (0.48-0.73) | 0.39 (0.33-0.46) | 0.46 (0.40-0.53) | 0.46 (0.40-0.53) |
| | ≥80 years | 0.49 (0.42-0.58) | 0.55 (0.44-0.70) | 0.49 (0.41-0.59) | 0.55 (0.47-0.64) | 0.57 (0.49-0.66) |

* Based on models stratified for calendar date, region, age group, ethnicity and vaccination status; and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and vaccine-status-specific reinfection status.

**Table S10: Sensitivity analyses: effect of epidemic phase bias**. When two virus variants are in different phases of incidence growth or decline, controlling for the date of positive test may bias relative severity estimates if the mean time from infection to positive test is shorter for cases with more severe disease. Under this scenario, the apparent severity of the variant that is in a phase of growth may be overestimated and the severity of the variant with declining incidence may be underestimated. To examine the potential magnitude of this bias, a sensitivity analysis was recently proposed that applies a correction to the date of positive test for cases with the outcome of interest that corresponds to the assumed difference in mean time from infection to positive test between those without and with that outcome of interest.[1] We examined the effect of a difference of up to 2 days in the mean time from infection to positive test between cases who did not experience and cases who did experience each outcome, and refitted the primary analysis model stratified for the resulting proxy date. As expected, applying the correction resulted in somewhat lower adjusted HRs than in the primary analysis between cases with Omicron compared to Delta in all age groups.

| **Outcome** | **Age group** | **HR (95% CI)*** | | |
|---|---|---|---|---|
| | | **Assumed difference in mean time from infection to positive test between cases without outcome and cases with outcome** | | |
| | | **0 days (primary analysis)** | **1 day** | **2 days** |
| Hospital admission up to 14 days after positive test | <10 years | 1.10 (0.85-1.42) | 0.81 (0.62-1.04) | 0.69 (0.53-0.89) |
| | 10-19 years | 0.83 (0.64-1.08) | 0.60 (0.46-0.78) | 0.46 (0.35-0.59) |
| | 20-29 years | 0.55 (0.48-0.63) | 0.43 (0.38-0.50) | 0.36 (0.31-0.41) |
| | 30-39 years | 0.44 (0.39-0.50) | 0.35 (0.31-0.39) | 0.27 (0.24-0.31) |
| | 40-49 years | 0.33 (0.29-0.38) | 0.26 (0.23-0.30) | 0.21 (0.18-0.24) |
| | 50-59 years | 0.26 (0.23-0.30) | 0.21 (0.18-0.24) | 0.17 (0.14-0.19) |
| | 60-69 years | 0.25 (0.21-0.30) | 0.21 (0.18-0.25) | 0.19 (0.16-0.22) |
| | 70-79 years | 0.36 (0.30-0.43) | 0.30 (0.25-0.36) | 0.26 (0.22-0.32) |
| | ≥80 years | 0.47 (0.40-0.56) | 0.36 (0.30-0.43) | 0.34 (0.29-0.41) |
| Any hospital attendance (including admission) up to 14 days after positive test | <10 years | 1.03 (0.89-1.19) | 0.78 (0.67-0.90) | 0.63 (0.54-0.72) |
| | 10-19 years | 0.89 (0.76-1.03) | 0.68 (0.58-0.79) | 0.51 (0.44-0.59) |
| | 20-29 years | 0.67 (0.62-0.74) | 0.53 (0.49-0.58) | 0.44 (0.40-0.48) |
| | 30-39 years | 0.57 (0.52-0.61) | 0.45 (0.42-0.48) | 0.36 (0.33-0.38) |
| | 40-49 years | 0.54 (0.49-0.59) | 0.43 (0.39-0.47) | 0.34 (0.31-0.37) |
| | 50-59 years | 0.42 (0.38-0.46) | 0.32 (0.29-0.36) | 0.26 (0.23-0.29) |
| | 60-69 years | 0.32 (0.28-0.37) | 0.25 (0.22-0.29) | 0.22 (0.19-0.25) |
| | 70-79 years | 0.42 (0.36-0.50) | 0.35 (0.30-0.41) | 0.30 (0.26-0.35) |
| | ≥80 years | 0.49 (0.42-0.58) | 0.39 (0.33-0.45) | 0.36 (0.30-0.42) |
| Any hospital attendance (including admission) up to 14 days after positive test, or positive test during hospital stay | <10 years | 1.04 (0.91-1.19) | 0.79 (0.69-0.90) | 0.63 (0.55-0.72) |
| | 10-19 years | 0.88 (0.77-1.00) | 0.67 (0.59-0.77) | 0.50 (0.44-0.57) |
| | 20-29 years | 0.70 (0.65-0.77) | 0.55 (0.51-0.60) | 0.46 (0.42-0.50) |
| | 30-39 years | 0.59 (0.55-0.63) | 0.47 (0.43-0.50) | 0.37 (0.35-0.40) |
| | 40-49 years | 0.57 (0.52-0.62) | 0.45 (0.41-0.49) | 0.36 (0.33-0.39) |
| | 50-59 years | 0.44 (0.40-0.49) | 0.34 (0.31-0.38) | 0.27 (0.25-0.30) |
| | 60-69 years | 0.34 (0.30-0.39) | 0.27 (0.24-0.31) | 0.24 (0.21-0.27) |
| | 70-79 years | 0.45 (0.38-0.52) | 0.37 (0.32-0.43) | 0.31 (0.27-0.36) |
| | ≥80 years | 0.53 (0.45-0.62) | 0.41 (0.35-0.48) | 0.38 (0.32-0.44) |
| Death within 28 days after positive test | <10 years | --† | --† | --† |
| | 10-19 years | --† | --† | --† |
| | 20-29 years | --† | --† | --† |
| | 30-39 years | 0.28 (0.07-1.04) | 0.19 (0.05-0.77) | 0.17 (0.04-0.70) |
| | 40-49 years | 0.25 (0.11-0.55) | 0.20 (0.09-0.44) | 0.16 (0.07-0.36) |
| | 50-59 years | 0.16 (0.09-0.27) | 0.14 (0.08-0.24) | 0.10 (0.06-0.18) |
| | 60-69 years | 0.22 (0.15-0.34) | 0.17 (0.11-0.25) | 0.14 (0.09-0.21) |
| | 70-79 years | 0.26 (0.18-0.36) | 0.21 (0.15-0.31) | 0.19 (0.13-0.26) |
| | ≥80 years | 0.46 (0.36-0.58) | 0.37 (0.29-0.48) | 0.31 (0.24-0.40) |

* Based on models stratified for calendar date, region, age group, ethnicity and vaccination status; and using regression adjustment for within-age-group linear age, sex, index of multiple deprivation and vaccine-status-specific reinfection status.
† Not estimated due to small numbers.

**Table S11. Sensitivity analysis: adjustment for under-ascertainment of past infections.** Adjusted estimates for the unvaccinated population, from the secondary analysis, which estimated variant-specific HRs for hospitalisation or death in vaccinated groups versus unvaccinated, additionally to the Omicron vs Delta HRs, after imputation of undetected past infections. Undetected past infections in cases with no known past infections were imputed using the methods described in the appendix, p. xx. The HRs and 95% CIs were estimated using non-parametric bootstrapping (200 repetitions).

| Outcome | Age group | HR (95% CI)* | |
|---|---|---|---|
| | | Main analysis of intrinsic severity | Using imputation of under-ascertained past infections |
| Hospital admission within 14 days after positive test | <10 years | 1.10 (0.85-1.42) | 1.12 (0.86-1.44) |
| | 10-19 years | 0.78 (0.60-1.00) | 0.87 (0.66-1.15) |
| | 20-29 years | 0.43 (0.37-0.49) | 0.48 (0.42-0.55) |
| | 30-39 years | 0.31 (0.28-0.35) | 0.35 (0.31-0.40) |
| | 40-49 years | 0.20 (0.17-0.23) | 0.22 (0.19-0.25) |
| | 50-59 years | 0.14 (0.12-0.17) | 0.16 (0.13-0.18) |
| | 60-69 years | 0.14 (0.12-0.16) | 0.15 (0.13-0.18) |
| | 70-79 years | 0.20 (0.17-0.24) | 0.21 (0.17-0.26) |
| | ≥80 years | 0.33 (0.28-0.39) | 0.35 (0.28-0.41) |
| Any hospital attendance (including admission) within 14 days after positive test | <10 years | 1.03 (0.89-1.19) | 1.08 (0.94-1.24) |
| | 10-19 years | 0.84 (0.73-0.98) | 0.92 (0.80-1.05) |
| | 20-29 years | 0.52 (0.48-0.57) | 0.57 (0.51-0.63) |
| | 30-39 years | 0.40 (0.37-0.43) | 0.43 (0.39-0.46) |
| | 40-49 years | 0.32 (0.29-0.35) | 0.34 (0.31-0.38) |
| | 50-59 years | 0.22 (0.20-0.25) | 0.24 (0.21-0.26) |
| | 60-69 years | 0.16 (0.14-0.18) | 0.16 (0.14-0.19) |
| | 70-79 years | 0.19 (0.16-0.22) | 0.20 (0.17-0.23) |
| | ≥80 years | 0.27 (0.23-0.31) | 0.28 (0.23-0.32) |
| Any hospital attendance (including admission) within 14 days after positive test, or positive test during hospital admission | <10 years | 1.04 (0.91-1.19) | 1.08 (0.95-1.23) |
| | 10-19 years | 0.85 (0.75-0.97) | 0.91 (0.81-1.02) |
| | 20-29 years | 0.55 (0.51-0.60) | 0.59 (0.54-0.66) |
| | 30-39 years | 0.41 (0.38-0.45) | 0.44 (0.40-0.48) |
| | 40-49 years | 0.34 (0.31-0.37) | 0.36 (0.33-0.40) |
| | 50-59 years | 0.24 (0.22-0.26) | 0.25 (0.23-0.28) |
| | 60-69 years | 0.17 (0.15-0.19) | 0.18 (0.16-0.20) |
| | 70-79 years | 0.20 (0.18-0.24) | 0.21 (0.18-0.25) |
| | ≥80 years | 0.29 (0.25-0.34) | 0.30 (0.26-0.34) |
| Death within 28 days after positive test | <10 years | --§ | --§ |
| | 10-19 years | --§ | --§ |
| | 20-29 years | --§ | --§ |
| | 30-39 years | 0.13 (0.04-0.46) | 0.16 (0.04-0.63) |
| | 40-49 years | 0.11 (0.05-0.24) | 0.13 (0.06-0.26) |
| | 50-59 years | 0.07 (0.04-0.12) | 0.08 (0.05-0.14) |
| | 60-69 years | 0.11 (0.07-0.16) | 0.11 (0.07-0.18) |
| | 70-79 years | 0.16 (0.11-0.22) | 0.16 (0.11-0.23) |
| | ≥80 years | 0.36 (0.27-0.48) | 0.37 (0.27-0.51) |

**Table S12. Sensitivity analysis: adjustment for under-ascertainment of past infections. HR estimates for vaccination and prior infection categories** for the model used to estimate age-specific hazard ratios (HRs) for Omicron versus Delta and variant-specific vaccine effectiveness. Corresponding age-specific hazard ratios for Omicron vs Delta cases in unvaccinated individuals are shown in the rightmost column of Table 1. HRs for vaccination categories are versus unvaccinated cases, those for past infection categories are versus cases with no documented past infection. Vaccination categories are stratified by vaccine given for doses 1 and 2, number of doses received (dose 3 was always Pfizer or Moderna booster), and weeks elapsed from last dose to positive SARS-CoV-2 specimen date.

| Variable | HR (95% CI) | | | |
|---|---|---|---|---|
| | Hospital admission up to 14 days after positive test | Any hospital attendance (including admission) up to 14 days after positive test | Any hospital attendance (including admission) up to 14 days after positive test, or positive test during hospital stay | Death within 28 days after positive test |
| Delta: AstraZeneca, dose 1, any time* | 0.55 (0.45-0.65) | 0.65 (0.57-0.75) | 0.69 (0.60-0.78) | 0.53 (0.33-0.90) |
| Delta: AstraZeneca, dose 2, <2 weeks | 0.16 (0.06-0.33) | 0.23 (0.11-0.42) | 0.23 (0.11-0.41) | – |
| Delta: AstraZeneca, dose 2, 2-7 weeks | 0.19 (0.00-0.53) | 0.22 (0.06-0.46) | 0.22 (0.06-0.45) | – |
| Delta: AstraZeneca, dose 2, 8-11 weeks | 0.59 (0.17-1.39) | 0.50 (0.20-0.96) | 0.49 (0.20-0.95) | – |
| Delta: AstraZeneca, dose 2, 12-15 weeks | 0.32 (0.14-0.54) | 0.31 (0.17-0.48) | 0.32 (0.19-0.49) | – |
| Delta: AstraZeneca, dose 2, 16-19 weeks | 0.14 (0.09-0.19) | 0.23 (0.18-0.29) | 0.26 (0.21-0.31) | – |
| Delta: AstraZeneca, dose 2, 20+ weeks | 0.21 (0.19-0.23) | 0.27 (0.26-0.29) | 0.29 (0.28-0.31) | 0.26 (0.21-0.31) |
| Delta: AstraZeneca, dose 3, <2 weeks | 0.10 (0.09-0.11) | 0.15 (0.13-0.16) | 0.16 (0.15-0.18) | 0.10 (0.07-0.15) |
| Delta: AstraZeneca, dose 3, 2-7 weeks | 0.13 (0.11-0.15) | 0.17 (0.15-0.19) | 0.18 (0.16-0.21) | 0.12 (0.08-0.16) |
| Delta: AstraZeneca, dose 3, 8-11 weeks | 0.14 (0.11-0.18) | 0.21 (0.18-0.26) | 0.23 (0.19-0.27) | 0.14 (0.10-0.20) |
| Delta: AstraZeneca, dose 3, 12+ weeks | 0.28 (0.14-0.45) | 0.32 (0.18-0.57) | 0.34 (0.18-0.58) | – |
| Delta: Pfizer/Moderna, dose 1, <2 weeks | 0.56 (0.37-0.76) | 0.68 (0.54-0.83) | 0.71 (0.57-0.84) | – |
| Delta: Pfizer/Moderna, dose 1, 2-7 weeks | 0.33 (0.23-0.44) | 0.45 (0.37-0.54) | 0.49 (0.40-0.57) | 0.64 (0.17-1.54) |
| Delta: Pfizer/Moderna, dose 1, 8-11 weeks | 0.39 (0.22-0.54) | 0.46 (0.36-0.57) | 0.56 (0.46-0.69) | – |
| Delta: Pfizer/Moderna, dose 1, 12+ weeks | 0.36 (0.30-0.42) | 0.43 (0.38-0.48) | 0.47 (0.41-0.52) | 0.36 (0.17-0.66) |
| Delta: Pfizer/Moderna, dose 2, <2 weeks | 0.18 (0.06-0.36) | 0.33 (0.21-0.46) | 0.32 (0.21-0.45) | – |
| Delta: Pfizer/Moderna, dose 2, 2-7 weeks | 0.43 (0.25-0.65) | 0.40 (0.29-0.56) | 0.46 (0.34-0.63) | – |
| Delta: Pfizer/Moderna, dose 2, 8-11 weeks | 0.24 (0.14-0.34) | 0.31 (0.23-0.38) | 0.34 (0.26-0.43) | – |
| Delta: Pfizer/Moderna, dose 2, 12-15 weeks | 0.14 (0.10-0.19) | 0.21 (0.18-0.25) | 0.24 (0.21-0.28) | – |
| Delta: Pfizer/Moderna, dose 2, 16-19 weeks | 0.10 (0.08-0.13) | 0.18 (0.16-0.20) | 0.20 (0.18-0.22) | – |
| Delta: Pfizer/Moderna, dose 2, 20+ weeks | 0.18 (0.17-0.21) | 0.25 (0.23-0.27) | 0.27 (0.25-0.29) | 0.28 (0.22-0.36) |
| Delta: Pfizer/Moderna, dose 3, <2 weeks | 0.13 (0.10-0.17) | 0.17 (0.14-0.20) | 0.18 (0.15-0.21) | 0.14 (0.09-0.21) |
| Delta: Pfizer/Moderna, dose 3, 2-7 weeks | 0.12 (0.10-0.14) | 0.18 (0.16-0.21) | 0.19 (0.17-0.22) | 0.13 (0.09-0.18) |
| Delta: Pfizer/Moderna, dose 3, 8-11 weeks | 0.11 (0.09-0.13) | 0.16 (0.14-0.18) | 0.17 (0.15-0.19) | 0.10 (0.07-0.13) |
| Delta: Pfizer/Moderna, dose 3, 12+ weeks | 0.15 (0.10-0.22) | 0.19 (0.13-0.25) | 0.19 (0.13-0.26) | 0.11 (0.04-0.21) |
| Omicron: AstraZeneca, dose 1, any time* | 1.09 (0.91-1.27) | 1.17 (1.03-1.30) | 1.17 (1.03-1.30) | 0.96 (0.62-1.64) |
| Omicron: AstraZeneca, dose 2, <2 weeks | 0.56 (0.28-0.96) | 0.61 (0.38-0.86) | 0.57 (0.35-0.81) | – |
| Omicron: AstraZeneca, dose 2, 2-7 weeks | 0.34 (0.18-0.55) | 0.48 (0.32-0.62) | 0.46 (0.32-0.61) | – |
| Omicron: AstraZeneca, dose 2, 8-11 weeks | 0.59 (0.32-0.92) | 0.63 (0.40-0.90) | 0.67 (0.40-0.89) | 0.69 (0.26-1.77) |
| Omicron: AstraZeneca, dose 2, 12-15 weeks | 0.44 (0.24-0.76) | 0.54 (0.35-0.76) | 0.57 (0.39-0.80) | – |
| Omicron: AstraZeneca, dose 2, 16-19 weeks | 0.48 (0.33-0.67) | 0.59 (0.46-0.74) | 0.63 (0.48-0.78) | – |
| Omicron: AstraZeneca, dose 2, 20+ weeks | 0.50 (0.46-0.54) | 0.56 (0.53-0.60) | 0.60 (0.56-0.63) | 0.79 (0.62-1.06) |
| Omicron: AstraZeneca, dose 3, <2 weeks | 0.26 (0.22-0.29) | 0.34 (0.31-0.37) | 0.37 (0.34-0.39) | 0.25 (0.15-0.41) |
| Omicron: AstraZeneca, dose 3, 2-7 weeks | 0.20 (0.18-0.22) | 0.31 (0.30-0.34) | 0.34 (0.32-0.36) | 0.16 (0.12-0.23) |
| Omicron: AstraZeneca, dose 3, 8-11 weeks | 0.19 (0.17-0.21) | 0.39 (0.36-0.42) | 0.40 (0.37-0.44) | 0.14 (0.11-0.20) |
| Omicron: AstraZeneca, dose 3, 12+ weeks | 0.21 (0.17-0.25) | 0.44 (0.38-0.50) | 0.45 (0.39-0.51) | 0.21 (0.14-0.31) |
| Omicron: Pfizer/Moderna, dose 1, <2 weeks | 0.61 (0.44-0.82) | 0.68 (0.56-0.80) | 0.67 (0.58-0.80) | – |
| Omicron: Pfizer/Moderna, dose 1, 2-7 weeks | 0.42 (0.33-0.51) | 0.55 (0.48-0.61) | 0.55 (0.48-0.61) | – |
| Omicron: Pfizer/Moderna, dose 1, 8-11 weeks | 0.45 (0.33-0.61) | 0.53 (0.44-0.62) | 0.55 (0.47-0.63) | 0.55 (0.10-1.77) |
| Omicron: Pfizer/Moderna, dose 1, 12+ weeks | 0.58 (0.48-0.66) | 0.66 (0.58-0.73) | 0.69 (0.62-0.75) | 0.51 (0.20-0.99) |
| Omicron: Pfizer/Moderna, dose 2, <2 weeks | 0.48 (0.34-0.62) | 0.55 (0.44-0.65) | 0.54 (0.45-0.63) | – |
| Omicron: Pfizer/Moderna, dose 2, 2-7 weeks | 0.35 (0.27-0.45) | 0.44 (0.37-0.51) | 0.48 (0.41-0.55) | 0.94 (0.26-2.53) |
| Omicron: Pfizer/Moderna, dose 2, 8-11 weeks | 0.34 (0.26-0.41) | 0.48 (0.42-0.55) | 0.50 (0.45-0.56) | – |
| Omicron: Pfizer/Moderna, dose 2, 12-15 weeks | 0.28 (0.24-0.33) | 0.35 (0.32-0.38) | 0.38 (0.35-0.41) | – |
| Omicron: Pfizer/Moderna, dose 2, 16-19 weeks | 0.22 (0.19-0.25) | 0.31 (0.29-0.34) | 0.35 (0.32-0.37) | – |

| | | | | |
|---|---|---|---|---|
| Omicron: Pfizer/Moderna, dose 2, 20+ weeks | 0.38 (0.34-0.42) | 0.48 (0.45-0.51) | 0.50 (0.47-0.53) | 0.73 (0.53-0.98) |
| Omicron: Pfizer/Moderna, dose 3, <2 weeks | 0.20 (0.18-0.23) | 0.29 (0.27-0.32) | 0.33 (0.30-0.35) | 0.24 (0.11-0.41) |
| Omicron: Pfizer/Moderna, dose 3, 2-7 weeks | 0.23 (0.20-0.26) | 0.39 (0.36-0.42) | 0.41 (0.38-0.45) | 0.19 (0.13-0.27) |
| Omicron: Pfizer/Moderna, dose 3, 8-11 weeks | 0.19 (0.18-0.22) | 0.37 (0.35-0.40) | 0.39 (0.36-0.42) | 0.13 (0.10-0.18) |
| Omicron: Pfizer/Moderna, dose 3, 12+ weeks | 0.17 (0.15-0.19) | 0.35 (0.32-0.38) | 0.36 (0.33-0.40) | 0.11 (0.08-0.16) |
| Past infection, unvaccinated | 0.46 (0.38-0.53) | 0.63 (0.56-0.71) | 0.68 (0.60-0.75) | 0.10 (0.00-0.22) |
| Past infection, vaccinated | 0.85 (0.75-0.96) | 1.02 (0.96-1.09) | 1.02 (0.97-1.09) | 0.31 (0.19-0.44) |

* Due to small numbers, all cases who had received a single dose of the AstraZeneca vaccine are grouped together.

**Supplementary methods. Sensitivity analysis adjusting for under-ascertainment of past infections**

The secondary analysis estimated intrinsic severity in unvaccinated cases based on a model that included vaccination-status-specific effects of known past infections. To account for the possibility that a fraction of those with no known past infections have had an untested past infection, we imputed past infections in a sensitivity analysis. The imputations for cases with no observed past infections were based on the model

$$\Pr(r' = 1|X,\ r = 0) = \frac{\Pr(r = 1|X)/\Pr(r = 0|X)}{\Pr(r = 1|X,\ r' = 1)/\Pr(r = 0|X,\ r' = 1)}$$

where $r$ and $r'$ are indicator variables for whether a case has an observed and a true past infection, respectively, and $X$ are other individual-level covariates. This equality follows from Bayes' theorem, noting that $\Pr(r = 1|X)\ = \Pr(r = 1|X,\ r' = 1)\ \Pr(r' = 1|X)$ under the assumption that $\Pr(r = 1|X,\ r' = 0) = 0$. No imputation was done for the past infection status of cases with observed past infections. We estimated the numerator based on the observed frequencies of cases with observed past infection or no past infection in strata defined by age group, date of positive test, vaccination status, variant, and outcome.

For the denominator, we used estimates of the mean cumulative population infection incidence up to 28 November 2021, based on an independent model of age-stratified population infection prevalence (https://github.com/epiforecasts/inc2prev/) that used data from the ONS infection survey[2] and from UKHSA serological surveys[3].

We assumed that the number of infections per person in age group $a$ up to 28 November 2021, $I_a$, follow a Poisson distribution parametrised by the estimated mean cumulative per-capita infection incidence, $m_a$. We then estimated, for cases after 28 November 2021, the probability that a previous infection would have been observed as $\Pr(r = 1|a,\ r' = 1) \approx (n_a/N_a)/\ \Pr(I_a \geq 1)$. Here $n_a$ is the number of unique individuals in age group $a$ who had tested positive for SARS-CoV-2 up to 28 November 2021 (from the national line list maintained by UKHSA[4]), $N_a$ is the population size of age group $a$ (mid-2020 estimates; https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland), and $\Pr(I_a \geq 1) = 1 - \exp(-m_a)$ is the Poisson probability that individuals in age group $a$ had been infected at least once up to 28 November 2021. The table below summarises the resulting estimates.

| Age band | A. Estimated mean cumulative infections per person up to 28/11/2021 | B. Standard deviation of posterior of cumulative infection incidence per person | C. Proportion of people with 1 or more past infections = 1-exp(column A) | D..Number of people with one or more infections detected up to 28/11/2021 | E. Population size (ONS) | F. Proportion of population who have had one or more infections detected = column D /column E | G. Proportion of all past first infections reported =column F /column C |
|---|---|---|---|---|---|---|---|
| 2-10 | 0.92 | 0.033 | 0.60 | 582781 | 6254603 | 0.09 | 0.16 |
| 11-15 | 1.21 | 0.046 | 0.70 | 853211 | 3370248 | 0.25 | 0.36 |
| 16-24 | 0.87 | 0.029 | 0.58 | 1344870 | 5950637 | 0.23 | 0.39 |
| 25-34 | 0.56 | 0.020 | 0.43 | 1463940 | 7596145 | 0.19 | 0.45 |
| 35-49 | 0.57 | 0.023 | 0.44 | 1977072 | 10853151 | 0.18 | 0.42 |
| 50-69 | 0.42 | 0.015 | 0.34 | 1741162 | 13618246 | 0.13 | 0.37 |
| 70+ | 0.27 | 0.010 | 0.24 | 619572 | 7679719 | 0.08 | 0.34 |

We used linear interpolation (using the mid-point of age bands) to estimate $\Pr(r = 1|a,\ r' = 1)$ and its posterior standard deviation for <1, 1-4, 5-9 and then 10 year age bands from the estimates with the age stratification given in the above table, making the assumption that the values for <1s and 1-4 year-olds were the same as those estimated for 2-10 year-olds above.

To account for the added uncertainty, used a non-parametric bootstrap (200 repetitions) of all cases in the study period. For each repetition, we first sampled $\Pr(r = 1|a,\ r' = 1)$ from the posterior distribution for each age band, and then used the above imputation model to sample "true" reinfection status for every case with no known past infection. We then refitted the secondary analysis model (that estimates intrinsic severity and the effect of vaccine status and past infection) to the resulting imputed dataset. We estimated HRs from the bootstrap medians and 95% CIs based on the bootstrap quantiles.

## References

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