Risk of COVID-19 related deaths for SARS-CoV-2 Omicron (B.1.1.529) compared with Delta (B.1.617.2)

Isobel L. Ward, senior statistician [1], Charlotte Bermingham, senior statistician [1], Daniel Ayoubkhani, principal statistician [1], Owen J. Gethings, principal statistician [1], Koen B. Pouwels, senior researcher [2] Tomas Yates, professor of physical activity, sedentary behaviour and health[3,4], Kamlesh Khunti professor of primary care diabetes and vascular medicine [3,4], Julia Hippisley-Cox, professor of clinical epidemiology and general practice [5], Amitava Banerjee, professor of clinical data science and honorary consultant cardiologist [6,7], Ann Sarah Walker professor of medical statistics and epidemiology [8], Vahé Nafilyan, ORCID ID: 0000-0003-0160-217X, lead statistician [1 *]

1. Office for National Statistics, Newport, NP10 8XG

2. Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford

3. Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, LE5 4PW, UK

4. National Institute for Health Research (NIHR) Leicester Biomedical Research Centre (BRC), Leicester General Hospital, Leicester, LE5 4PW, UK

5. Nuffield Department of Primary Care Health Sciences, University of Oxford.

6. Institute of Health Informatics, University College London, London NW1 2DA.

7. Department of Cardiology, Barts Health NHS Trust, London E1 1BB.

8. Nuffield Department of Medicine, University of Oxford, Oxford, UK

* Corresponding author: vahe.nafilyan@ons.gov.uk

Abstract

Objective To assess the risk of COVID-19 death following infection from Omicron BA.1 relative to Delta (B.1.617.2).

Design Retrospective cohort study.

Setting England, UK, 1 December 2021 to 30st December 2021.

Participants1,035,149 people aged 18-100 years who tested positive for SARS-CoV-2 in the national surveillance programme, and had an infection identified as either Omicron BA.1- or Delta compatible.

Main outcome measures COVID-19 death as identified from death certification records. The exposure of interest was the SARS-CoV-2 variant identified from NHS Test and Trace PCR positive tests taken in the community (pillar 2) and analysed by Lighthouse laboratories. Cause-specific Cox proportional hazard regression models (censoring non-COVID-19 deaths) were adjusted for sex, age, vaccination status, previous infection, calendar time, ethnicity, Index of Multiple Deprivation rank, household deprivation, university degree, keyworker status, country of birth, main language, region, disability, and comorbidities. Additionally, we tested for interactions between variant and sex, age, vaccination status and comorbidities.

Results The risk of COVID-19 death was 66% lower (95% CI: 54% to 75%) for Omicron BA.1 compared to Delta. The reduction in the risk of death involving COVID-19 for Omicron compared to Delta was more pronounced in 18-59-year-olds (HR=0.14, 95%CI: 0.07 to 0.27) compared to individuals over 70 years of age (HR=0.44, 95%CI: 0.32 to 0.61) ($p < 0.0001$). We find no evidence of a difference in risk between variant and number of comorbidities (0, 1-2, 3+).

Conclusions Our results support early work showing the relative reduction in severity of Omicron BA.1 compared to Delta in terms of hospitalisation and extends this research to assess COVID-19 mortality.

Summary box

What is already known on this topic

The Omicron variant, which refers to the whole lineage (including BA.1, BA.2, BA.3, BA.4 and BA.5) had already been shown to be more transmissible than the Delta variant, but emerging evidence suggests that the risk of hospitalisation and risk of death within 28 days after a SARS-COV-2 positive test is lower. However, with a highly transmissible infection and high levels of population testing, definition of death within 28 days of a positive test is more likely to be susceptible to misclassification bias due to asymptomatic or co-incidental infection. There is no study so far comparing the risk of COVID-19 death as identified from death certification records, with the cause of death assessed by the physician who attended the patient in the last illness.

What this study adds

Using data from a large cohort of COVID-19 infections that occurred in December 2021, we examined the risk of COVID-19 death, as identified from death certification records, between the Delta and Omicron BA.1 variant. Our study shows that risk of COVID-19 death was reduced by 66% following infection with the Omicron BA.1 variant relative to the Delta variant after adjusting for a wide range of potential confounders, including vaccination status and comorbidities.

Introduction

On 27 November 2021 the UK Health Security Agency (UKHSA) identified the first UK cases of coronavirus disease 19 (COVID-19) variant B.1.1.529/BA.1, a variant of concern named, together with its sub-variants including BA.2 and BA.3, as Omicron (Department of Health and Social Care, 2021). As the Omicron variant, which refers to the whole lineage (including BA.1, BA.2, BA.3) had already been shown to be more transmissible, identifying whether the severity of disease, risk of hospitalisation, death or long-term complications is increased relative to Delta, is critical to enable pandemic and policy planning.

Omicron lineage BA.1 has a large number of mutations, 37 of which are in the Spike (S) protein (Ford, 2021), which leads to S-gene target failure (SGTF) in some molecular diagnostic assay (WHO, 2021). This can be identified from non-detectable S gene and a Cycle threshold (Ct) value of 30 or lower for the N and ORF1ab targets in positive polymerase chain reaction (PCR) tests using National testing data for England (based on the NHS Test and Trace programme), supplemented with data from the National Pathology Exchange (NPEx). Several studies have used a similar approach to compare the severity of Alpha (B.1.1.7) and Delta (B.1.617.2) with other variants [1]–[3].

Emerging data also indicate that risk of hospitalisation is lower following Omicron than Delta infection [4], [5], as is the risk of death within 28 days after a SARS-COV-2 test [5]. Taken together, Nyberg and colleagues report that the risk of severe outcomes following positive SARS-COV-2 tests was substantially lower for Omicron than for Delta. However, this analysis used death within 28 days of a positive test as a measure of COVID-19 death, rather than COVID-19 death identified using information from the death certificate, which include deaths at any time period and a cause of death classified by the physician who attended the patient in the last illness. Also, with a highly transmissible infection and high levels of population testing, definition of death within 28 days is more likely to be susceptible to misclassification bias due to asymptomatic co-incidental infection, than when infection rates are lower, ultimately resulting in severity estimates between variants being susceptible to bias.

In this study, we compared the risk of COVID-19 death using death registration data in a large population-based cohort of people infected in England in December 2021, a period where both Delta and Omicron BA.1 variants were circulating, but Omicron BA.2 remained rare. In addition, we adjusted for a range of potential confounders, including pre-existing health conditions which previous work has not assessed.

Methods

Study data

We used data from the ONS Public Health Data Asset (PHDA), a linked dataset combining the 2011 Census, mortality records, the General Practice Extraction Service (GPES) data for pandemic planning and research, Hospital Episode Statistics (HES), NHS Test and Trace data (Pillar 2: swab testing for the virus in the wider population) and national vaccination data from the National Immunisation Management Service (NIMS). NIMS includes all vaccinations administered for all persons residing in England since the vaccination program started on 8th Dec 2020.

To obtain NHS numbers, the 2011 Census was linked to the 2011-2013 NHS Participant Registers. Of the 53,483,502 Census records, 50,019,451 were linked deterministically. 555,291 additional matches were obtained using probabilistic matching (overall linkage rate: 94.6%). All subsequent linkages were conducted using NHS number. The ONS Public Health Data Asset include data on 35 million adults, an estimated 79% of the population of England in 2020.

Study Population

The study population included all individuals between 18-100 years old who had a positive PCR test for COVID-19 between 1st December 2021 and 30st December 2021, reported as part of pillar 2 of NHS Test and Trace and analysed by Lighthouse Laboratories, who were enumerated at the 2011 Census and were living in England and were registered with a general practitioner on 1 November 2019. We specifically selected people who tested positive in December 2021 for our study population because both Delta and Omicron BA.1 variants were circulating during this period, but Omicron BA.2 remained rare. In January 2022, nearly all cases were due to the Omicron BA.1 or BA.2 variants, limiting the possibility to compare outcomes with Delta over the same period. Our sample contained 1,035,163 people who tested positive in the NHS Test and Trace pillar 2 with an Omicron BA.1- or Delta-compatible infection between 1st and 31st December 2021 and could be linked to the PHDA [Supplementary Table S1]. This covers approximately 44% of all positive tests in adults in England in December 2021. The denominator was calculated using positive cases per day in England for all age groups except 18-19-year-olds, where the proportion was calculated as 40% of the daily cases in the 20-24 age group due to the unavailability of the relevant data[6].

Individuals entered the cohort on the index date which is the date of the first positive PCR test recorded between 1st to 30st December 2021. Individuals left the cohort on the earliest of: end of study date (28th February 2022) (censored), COVID-19 death (event), or death from other cause (censored).

Outcome

The primary outcome was time from positive PCR test to COVID-19 related death, defined as confirmed COVID-19 death identified by International Classification of Disease 10th Revision code (IDC-10) U07.1 mentioned anywhere on the death certificate. The U07.1 code usage is for when COVID-19 has been confirmed by laboratory testing irrespective of severity of clinical signs or symptoms, but should only be stated on a death certificate if the primary or a contributory cause of death.

Exposure

The exposure of interest was the COVID-19 variant in PCR positive tests taken in the community (pillar 2) and analysed by Lighthouse laboratories. Namely, defined by S-gene target failure (SGTF) as Omicron BA.1-compatible if S-negative, N-positive, ORF1ab-positive (with mean Ct <30 for N and ORF1ab) or Delta-compatible if S-positive/N-positive/ORF1ab-positive or ORF1ab-positive/S-positive or N-positive/S-positive, and mean Ct <30. Of all Omicron BA.1- and Delta-compatible infections, a small proportion (2.9%) of total

positive tests had mean Ct values greater than 30, indicative of a low viral load and were excluded because Delta cases with high Ct values could be mistakenly classified as S-negative [see Supplementary Table S3]

Covariates

Our main objective was to compare the risk of COVID-19 death between Delta and Omicron BA.1. We adjusted for a wide range of potential confounders of the relationship between variant type and the risk of COVID-19 death once infected, either in relation to vulnerability or testing behaviours, to account for any bias in our sample of individuals presenting as positive in the national surveillance programme.

Socio-demographic characteristics included age at time of infection (as a natural spline with boundary knots at the 10^{th} and 90^{th} percentile and three interior knots), sex, ethnicity (White/Black/South Asian/Other), region (North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East of England, London, South East, South West), disability, key worker status, Index of Multiple Deprivation rank (as a natural spline with boundary knots at the 5^{th} and 95^{th} percentile and three interior knots), country of birth (UK/Non-UK), university degree, household deprivation and English language ability. We also adjusted for baseline vaccination status (unvaccinated, one dose, two doses AstraZeneca ≤180 days previously, two doses mRNA vaccine (Pfizer or Moderna) ≤180 days previously, two doses AstraZeneca >180 days previously, two doses mRNA >180 days previously, any booster or third dose, which re refer to as boosters), previous infection (defined by a positive test at least 90 days before the date of the current positive test), for calendar date of infection using a natural spline (with boundary knots at the 10^{th} and 90^{th} percentile and three interior knots), and for clinical risk factors by counting the number of conditions identified as being associated with an elevated risk of COVID-19 deaths in the QCovid 3 risk model (0 – 8). QCovid risk factors were identified using 5 years of General Practice Extraction Service (GPES) Data for Pandemic Planning and Research (GDPPR) primary care data up till 31st March 2022, and the absence of a code for a condition during this period was treated as the individual not having the condition. Further details of the comorbidities are in Supplementary Table S2. For any other missing data, a missing category was included in the models, as shown in Table 1.

Characteristics of the study population were summarised overall, and stratified by variant type, using means for continuous variables and proportions for categorical variables.

We used cause-specific Cox proportional hazard regression model to estimate the hazard ratio of COVID-19 related death for individuals infected with Omicron BA.1 versus Delta variants. Follow-up time was calculated from positive PCR test to the earliest of COVID-19 death or end of study. For non-COVID-19 deaths, individuals were censored at the date of death if this occurred before the end of study date. We estimated four models, sequentially adjusted for age, sex, vaccination status and previous infection (Model 1); plus, calendar time (Model 2); plus, socio-economic factors (Model 3); and finally, plus pre-existing health conditions (Model 4).

To test whether the relative risk of mortality of Omicron BA.1 varied by age and sex, we included interactions between variant type and age, and variant type and sex. To test whether the relative risk of

mortality of Omicron BA.1 varied by vaccination status (unvaccinated, one dose, two doses and booster) and the number comorbidities (0, 1-2, 3+), we compared a model adjusted for interactions between variant type and age, and age and vaccination status (or comorbidities) to a model that included a three-way interaction between variant type, age and vaccination status (or comorbidities). The rationale for this approach was that vaccination status and the number of comorbidities are very closely related to age, and in the absence of an interaction between variant type and age, the interaction between vaccination status (or comorbidities) could capture the interaction between variant type and age.

We assessed the proportional hazard assumption by testing for the independence between the scaled Schoenfeld residuals and time-at-risk. We used Schoenfeld residuals from the fitted Cox models, smoothed using generalized additive models, to assess whether relative differences in the hazard of COVID-19 death between variant was constant over time following the positive test.

Patient and public involvement

We did not directly involve patients and the public in the design and conception of the study, primarily because of the pace at which this study was conducted to inform the UK Government's response to the Covid-19 pandemic. However, the manuscript was read by several members of the public.

Dissemination to participants and related patient and public communities

The use of deidentified data precludes direct dissemination to participants. For the purpose of open access, the authors have applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising. Results will also be disseminated by all co-authors through their home institutions.

Results

Characteristics of study population

There were 1,035,149 people in our study population. Of these, 814, 003 (78.6%) individuals had Omicron-compatible and 221,146 (21.4%) Delta-compatible infections, with the number of Omicron infections increasing per day across the study period [Supplementary Figure S1]. This covers approximately 44% of all positive tests in adults in England in December 202136.7% of all positive tests in England in December 2021 [6] . In our study population, 54% of infections were in females [Table 1, Supplementary Table S3]. The mean age at infection was two years younger in those infected with Omicron BA.1 (39.9 years, SD=15.2) than Delta (42.2 years, SD=13.1). There were 160 COVID-19 deaths and 196 non-COVID-19 deaths in those infected with Omicron BA.1, and 204 and 76, respectively, in those infected with Delta [Table 2]. The mean time from positive result to COVID-19 death was 18 days (SD=12.0) for Omicron BA.1 and 18 days (SD=12.2) for Delta.

Table 1. Baseline characteristics of patients infected with either Omicron or Delta variants

Variable	**Group**	**% of Delta total** (n = 221,146)	**% of Omicron total** (n = 814, 003)	**Total**
Country of birth	Non-UK	11.3%	11.4%	117764
	UK	88.7%	88.6%	917385
Degree	No	71.5%	77.5%	788964
	Yes	28.5%	22.5%	246185
Disability	None/Day-to-day activities not limited or limited a little	98.0%	98.2%	1015941
	Day-to-day activities limited a lot	2.0%	1.8%	19208
Ethnicity	Black	2.1%	4.3%	39305
	Other	4.7%	6.6%	63944
	South Asian	4.2%	4.5%	46034
	White	89.0%	84.6%	885866
Household deprivation	1	59.1%	58.6%	607754
	2	26.6%	27.2%	280530
	3	10.2%	9.9%	103552
	4	3.0%	2.7%	28721
	5	0.3%	0.2%	2558
	Missing	0.8%	1.3%	12034
Key worker †	No	27.2%	23.7%	253009
	Yes	72.8%	76.3%	782140
Main Language	English	6.9%	6.4%	66908

	Other	93.1%	93.6%	968241
Previous COVID-19 infection	No	99.0%	93.4%	979297
	Yes	1.0%	6.6%	55852
Region	North East	4.0%	4.6%	46624
	North West	16.6%	19.1%	192220
	Yorkshire and the Humber	12.7%	11.4%	120800
	East Midlands	9.2%	7.7%	83248
	West Midlands	11.5%	8.1%	91289
	East of England	13.3%	10.9%	118094
	London	12.0%	19.9%	188942
	South East	15.3%	14.9%	155299
	South West	5.3%	3.3%	38633
Sex	Male	45.9%	46.3%	478268
	Female	54.1%	53.7%	556881
Count of comorbidities ‡	0	88.5%	87.6%	908641
	1-2	11.1%	12.0%	122585
	3	0.4%	0.4%	3923
Vaccination status	Booster	9.3%	26.1%	233172
	One dose	3.8%	3.0%	32574
	Two doses AZ > 180 days	7.7%	6.6%	70295
	Two doses AZ < 180 days	5.1%	2.3%	30178
	Two doses mRNA > 180 days	25.2%	16.2%	187980
	Two doses mRNA < 180 days	33.6%	36.1%	368390
	Unvaccinated	15.4%	9.7%	112560

† Information on Census 2011 variables that were used to define key worker status. ‡ Count of comorbidities grouped for disclosure control reasons, added as linear continuous predictor to fully adjusted model (Model 4).

Table 2. Counts of cases, deaths involving COVID-19 and not involving COVID-19

	Total	**Delta**	**Omicron**
Positive COVID-19 cases	1035149	221146	814003
COVID-19 deaths	364	204	160
Age 18-59 years	57	46	11
Age 60-69 years	59	45	14
Age 70+ years	248	113	135
Deaths not-involving COVID-19	272	76	196

Relative risk of COVID-19 death by variant

The risk of COVID-19 death was 66% lower (HR=0.34, 95%CI: 0.25 to 0.46) [Table S4] for Omicron BA.1 compared to Delta infections in our fully adjusted model (Model 4), accounting for sex, age, vaccination status, previous infection, calendar time, ethnicity, Index of Multiple Deprivation rank, household deprivation, university degree, keyworker status, country of birth, main language, region, disability, and health risk factors defined in the QCovid 3 model [Figure 1]. In our minimally adjusted model (Model 1) accounting only for sex, vaccination status, age and previous infection, the risk of death was 78% lower (HR=0.22, 95%CI: 0.18 to 0.28) for Omicron BA.1 versus Delta. Adjusting for the date of infection (Model 2) reduced the difference (HR=0.3, 95%CI: 0.24 to 0.43). Further adjusting for socio-demographic characteristics (Model 3) and pre-existing health conditions (Model 4) had little impact on the relative difference between Omicron BA.1 and Delta related mortality (HR=0.33 and 0.34 respectively). Sensitivity analyses using all-cause death as the outcome, and several different COVID-19 death definitions, also showed substantial risk reductions. As expected, given dilution bias from misclassification, for all-cause death the reduction in risk for Omicron BA.1 versus Delta was slightly smaller, at 52% lower (HR=0.48, 95%CI: 0.39 to 0.61) [Table S5].

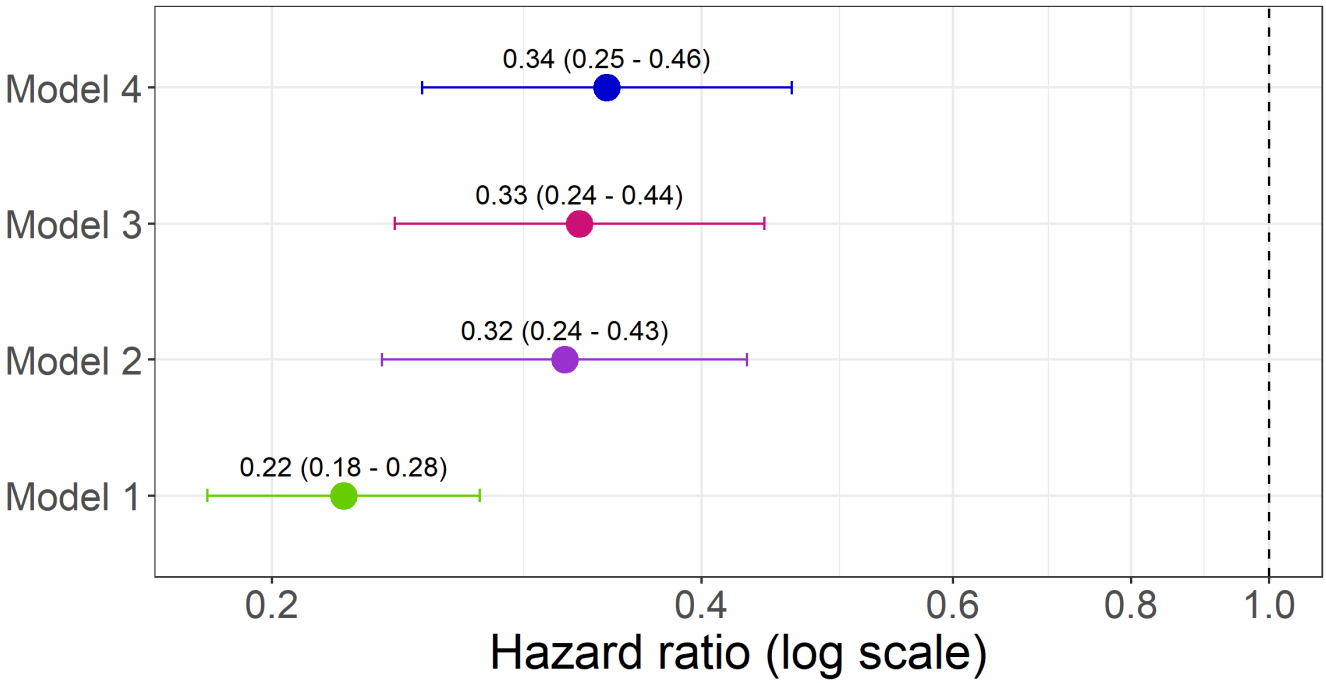

Figure 1. Hazard ratio for COVID-19 death for Omicron BA.1 vs Delta infections for fully adjusted (Model 4) and alternative models. The risk is shown for Omicron BA.1 relative to Delta, with the dashed line showing the null (no different to delta).

Footnote: **Model 1** adjusted for sex, age (natural spline), vaccination status and previous infection. **Model 2** adjusted for sex, age (natural spline), vaccination status, previous infection, and calendar time (natural spline). **Model 3** adjusted for sex, age (natural spline), vaccination status, previous infection, calendar time, ethnicity, Index of Multiple Deprivation rank (natural spline), household deprivation, university degree, keyworker status, country of birth, main language, region and disability. **Model 4** adjusted for sex, age (natural spline), vaccination status, previous infection, calendar time, ethnicity, Index of Multiple Deprivation rank (natural spline), household deprivation, university degree, keyworker status, country of birth, main language, region, disability, and comorbidities.

Relative risk of COVID-19 death by variant and age, sex vaccination status and comorbidities

Estimates of the difference in the relative risk of COVID-19 death between Omicron BA.1 and Delta by sex and age are presented in Figure 2, from a fully adjusted model. The difference in mortality risk varied strongly by age with greater reduction in COVID-19 mortality with Omicron BA.1 compared to Delta for people aged 18-59 (HR=0.14, 95%CI: 0.07 to 0.27) compared to those over 70 years of age ($p < 0.0001$) (HR=0.44, 95%CI: 0.32 to 0.61). The risk for Omicron relative to Delta was also reduced in aged60-69 year olds (HR=0.21, 95%CI: 0.11 to 0.38), however this did not differ significantly compared to the 18-59 year old group ($p = 0.33$) For the interaction between sex and variant the reduction in COVID-19 mortality risk was more pronounced in males (HR=0.9, 95%CI: 0.2 to 0.41) than in females (HR=0.42, 95%CI: 0.29 to 0.61), however this difference did not reach the threshold for significance ($p = 0.07$).

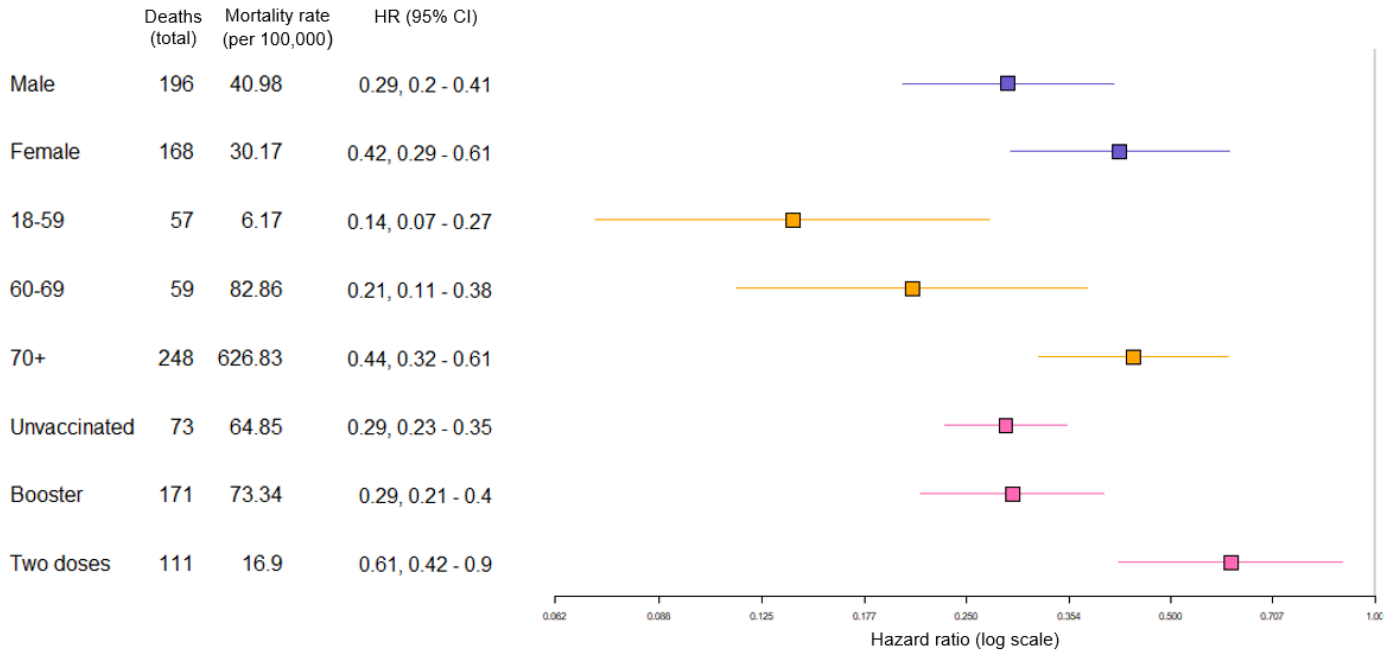

Figure 2. Hazard ratio for COVID-19 death for Omicron BA.1 vs Delta infections by sex, age vaccination status and comorbidities. The risk is shown for Omicron relative to Delta, with the dashed line showing the null (no different to delta). To investigate the interaction between variant type and sex, the model was fully adjusted (Model 4) with an interaction term for variant and sex. For the variant type and age, the fully adjusted model also included a variable for age group 18-59, 60-69 or 70+ which was interacted with variant. For the interaction between variant and vaccination status additional interaction terms were included between variant and re-grouped vaccination categories and adjusted for an interaction between variant and age. For the interaction between variant and comorbidities, additional interactions term was included between variant and re-grouped comorbidity counts which was also adjusted for a variant and age interaction.

We found a significant interaction between variant and vaccination status ($X^2(25) = 48.19$, $p = 0.004$), compared to a model which only included interaction terms for variant and age, age and vaccination status. Due to low counts of events in the 'One dose' group, the HR for this group is not reported, but the level is included in the model. We found the relative risk was reduced for all vaccination statuses for Omicron relative to Delta (Two doses: HR = 0.61, 0.43 to 0.90, Booster: HR = 0.29, 0.21to 0.40) and unvaccinated individuals (HR = 0.28, 0.23 to 0.35) [Figure 2]. We find a significant difference between individuals who had received two doses compared to those that were unvaccinated ($p < 0.001$). There was no difference between individuals who had received a booster dose compared to the unvaccinated group ($p = 0.84$). We found no significant interaction between number of comorbidities and variant ($X^2(5) = 2.57$, $p = 0.77$), compared to a model which only included interaction terms for variant and age, age and number of comorbidities.

We tested the proportional hazard assumption by testing for the independence between the scaled Schoenfeld residuals and time-at-risk (p=0.03). The test failed to reject the independence for the key exposure (variant: p = 0.43), suggesting that the proportional hazard assumption was unlikely to be violated.

Discussion

Main Findings

Using data from a large cohort of COVID-19 infections that occurred in December 2021, we examined the relative difference in COVID-19 mortality between the Delta and Omicron BA.1 variant. Our study shows that risk of COVID-19 death was reduced by 66% following infection with the Omicron BA.1 variant relative to the Delta variant after adjusting for a wide range of potential confounders, including vaccination status and comorbidities. Importantly, we found that the relative risk of COVID-19 death following Omicron versus Delta infection varied by age, with lower relative risk in younger individuals. It also varied by vaccination status, with the difference in COVID-19 mortality between the Delta and Omicron BA.1 being lower for all vaccination statuses but less pronounced for people who had received two vaccinations.

Comparison with other studies

Early work exploring the clinical severity of COVID-19 Omicron variant in a South African cohort found significantly reduced odds of hospitalisation following SGTF versus non-SGTF infection across the same period [4]. A subsequent study in California on positive PCR tests between 30 November 2021 and 1 January 2022 also showed risk reductions for hospital admission, ICU admission and mortality following Omicron relative to Delta infections [7]. In Canada, in a matched sample, the risk of hospitalisation or death was found to be 65% lower among Omicron than Delta cases [8]. Emerging evidence has found that Omicron replicates more readily in the upper airways than the lungs, potentially indicating a biological mechanism for the reduction in risk of COVID-19 death following infection with Omicron relative to Delta [9].

Our results extend these initial analyses quantifying intrinsic risk of Omicron severity in terms of hospital admissions, to COVID-19 mortality. Nyberg et al. 2022 report a reduction in death following Omicron infection (HR=0.31) relative to Delta, which is similar to our findings. Importantly, our results account for more sociodemographic factors and comorbidities, and highlight that the reduction in risk remains consistent even after adjusting for these additional variables. Furthermore, our study specifically quantifies the risk of cause-specific COVID-19 mortality, utilising death registration data, unlike previous work which has defined COVID-19 death as death within 28 days of a positive SARS-CoV-2 test.

Given the emergence of the Omicron variant resulted in an increased rate of transmission, the number of Omicron cases in our sample of infected individuals increased significantly across the study period. To account for the difference in infection rate across the period, a cubic spline for calendar time was included in Models 2 – 4. The BA.2 sub-variant of Omicron does not have the spike gene deletion that causes SGTF. The UK noted an increase in the number of sub-variant BA.2 cases in the week commencing 3rd January 2022 [10]. Our data include Omicron-compatible and Delta-compatible infections identified between 1st and 30st December 2021, therefore in a period where BA.1 was prominent, and Omicron could be identified from SGTF.

These results provide clear evidence that the risk of COVID-19 mortality following infection with Omicron is significantly less than Delta in the UK.

Strengths and limitations

First, we use a large sample of positive cases from the national testing programme, allowing us to precisely estimate the relative risk of COVID-19 death following infection with Omicron BA.1 and Delta. Second, by linking these infection data to information on vaccination status, comprehensive socio-demographic characteristics from the Census and information on pre-existing conditions based on primary care and hospital data, we were able to estimate the relative difference in mortality between the Omicron BA.1 and Delta variants, adjusting for a wide range of potential confounders, including vaccination status with manufacturer type, and key worker status. We also tested whether the relative mortality risk of Omicron BA.1 vs Delta depended on vaccination status and the number of comorbidities, by including interactions between variant type and vaccination status (or comorbidities). This is an important result to discuss as we show that regardless of vaccination status Omicron was milder than Delta. However, there was no difference by number of comorbidities. To control for the prioritisation of the vaccination roll out, we adjusted for the interaction between vaccination status and age. Third, we use death certificate data to confirm COVID-19 mortality, preventing our sample being conflated with non-COVID-19 related deaths of individuals that die of other causes following a positive COVID-19 test. Additionally, it is important to note that the number of COVID-19 deaths were small in individuals under the age of 70 years, with 68.1% of events occurring in the 70+ population. Nevertheless, we still had sufficient power to demonstrate significant risk reductions in younger age groups, adjusting for a very wide range of potential confounders. We also compared the outcomes during the same time periods overcoming any differences due to changes in management of infected patients over the time period of the pandemic.

One study limitation is an ascertainment bias since the data do not cover all SARS-CoV-2 infections, but only a subset of people who tested positive as part of the national testing programme in the community and analysed by Lighthouse laboratories. Tests conducted in the community but processed by other laboratories and tests conducted in hospitals could not be used because they do not use the S-gene molecular diagnostic assay, which we used to identify the variant type. A limitation of our work is not having access to data to derive COVID-19 variants from tests in hospital (NHS Pillar 1), and explains why our total sample is smaller than other research [5]. Differences in testing behaviours between groups may bias the estimates of risk of COVID-19 death among people who tested positive. If some people only get tested if they experience severe symptoms, the estimated risk of death would be higher in this group than in people who get tested more routinely, even if the population has the same underlying risk. To mitigate this issue, we also adjusted the models for factors that may affect the propensity to get tested and may also be related to the severity of a SARS-CoV-2 infection, including ethnicity, region, calendar date of infection, and key worker status. However, adjusting for these factors in models 3 and 4 had little effect on our overall estimates, suggesting that any selection effects according to these characteristics were having smaller impacts than might be hypothesised. One explanation for this could be due to restriction of our analysis to a short time period where both variants were circulating. Socio-demographic information was used from Census 2011 as was the most up to date at time of publishing, however future validation work should be

conducted once Census 2021 data has been released and potentially using more granular breakdowns of variables, such as region.

Because of death registration delays, not all deaths that occurred in the period may yet have been registered. Deaths that occurred amongst people who tested positive in late December are less likely to have been registered than those which occurred in people who tested positive at the beginning of the month. As the proportion of cases which are from the Omicron BA.1 variant increased during December, the delay in death registration, if unaccounted for, could lead to underestimation of the severity of the Omicron BA.1 variant. However, we accounted for the effect of registration delay in December by adjusting for calendar time of infection in our models, reducing the difference between Omicron BA.1 compared to Delta as expected. To assess fully the impact of COVID-19, additional outcome measures such as hospitalisation need to be considered. Furthermore, if data permits, symptom profiles could be used to predict outcomes in order to facilitate better management of healthcare requirements.

Conclusions

Given the emergence of the more transmissible Omicron BA.1 variant, there was an urgent healthcare requirement to quantify the risk of COVID-19 death relative to other variants to support pandemic planning responses. Our results support early work showing the relative reduction in severity of Omicron BA.1 compared to Delta in terms of hospitalisation and extends this research to assess COVID-19 mortality, being the first to our knowledge to assess cause-specific COVID-19 death using death certification to accurately capture COVID-19 deaths. Our work also highlights the importance of the vaccination booster campaign, since the reduction in risk of COVID-19 death was most pronounced in individuals who had received a booster/third vaccination. However, mortality is only one metric that should be considered when assessing of the impact of COVID-19 and subsequent work should investigate long-term outcomes of infection, such as the prevalence of long COVID following Omicron BA.1 infection relative to Delta.

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Contributors: IW, ASW and VN conceptualised and designed the study. IW and CB prepared the study data. IW performed the statistical analysis, which were quality checked by CB, DA and VN. All authors contributed to interpretation of the findings. IW and VN wrote the original draft. All authors contributed to review and editing of the manuscript and approved the final manuscript. VN is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: None

Ethical approval: Ethical approval was obtained from the National Statistician's Data Ethics Advisory Committee (NSDEC(20)12).

Transparency: The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient communities: The use of deidentified data precludes direct dissemination to participants. For the purpose of open access, the authors have applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising. Results will also be disseminated by all co-authors through their home institutions.

Acknowledgements: TY received funding from a grant from the UKRI (MRC)-DHSC (NIHR) COVID-19 Rapid Response Rolling Call (MR/V020536/1) and is part of the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by

UK Research and Innovation (HDRUK2020.138). ASW is an NIHR Senior Investigator and is supported by the Oxford Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, UKSHA or the Department of Health and Social Care. KBP is supported by the Huo Family Foundation.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; KK chair of the Ethnicity Subgroup of the UK Scientific Advisory Group for Emergencies (SAGE) and is a member of SAGE. JH-C is chair of the NERVTAG risk stratification subgroup and is a member of SAGE.

Data sharing: In accordance with NHS Digital's Information Governance requirements, the study data cannot be shared.

Provenance and peer review: Not commissioned; externally peer reviewed.

Supplementary Tables

Table S1: Sample flow

Processing Stage	Count
Total number of records in Test and Trace	382458741
Sample that links to Census/PHDA	299084765
Sample with non-logical dates removed	297701958
Sample with positive infection	10647556
Sample with PCR test	9140824
Sample with Pillar 2 PCR	7634416
Sample tested in Lighthouse Laboratory	5245792
De-duplication of records	5238805
Sample with one infection per person per 90-day spell	5092528
Sample with infection date >= 01-12-2021	1339606
Removal of erroneous vaccination dates	1339311
Individuals aged 18-100 on infection date	1200166
Removal of erroneous date of death	1200150
Sample with Omicron- or Delta-compatible infection	1067003
Exclusion of non-England region from Census records	1066572
Exclude Omicron/Delta compatible infections with Ct average > 30	1035149

Table S2: Variables grouping

Variable	Group
Key worker †	Health professionals
	Health associate professionals
	Support staff
	Social care
	Education
	Food retail and distribution
	Taxi and cab drivers and chauffeur
	Bus and coach drivers
	Van drivers
	Other transport workers
	Police and protective services
	Sanitary Workers
Comorbidity	Asthma
	Atrial fibrillation
	Blood or bone marrow cancer
	Chronic kidney disease
	Congenital heart problems
	COPD
	Coronary heart disease
	Cystic fibrosis
	Dementia
	Diabetes
	Epilepsy
	Heart failure
	Learning disability or Downs Syndrome
	Liver cirrhosis
	Lung or oral cancer
	Motor neurone disease
	Multiple sclerosis
	Myasthenia

	Huntington's disease
	Chorea
	Parkinson's disease
	Peripheral vascular disease
	Prior fracture of hip, wrist, spine, humorous
	Pulmonary hypertension or fibrosis
	Rheumatoid arthritis
	Systemic lupus erythematosus
	Severe combined immunodeficiency
	Sickle cell
	Stroke
	Transient ischaemic attack
	Thrombosis
	Pulmonary embolism
	Schizophrenia

	HR (95%CI lower to upper)
Model 1	0.22 (0.17 to 0.28)
Model 2	0.31 (0.23 to 0.43)
Model 3	0.32 (0.23 to 0.44)
Model 4	0.33 (0.24 to 0.45)

† Key workers status is defined based on the occupation and industry information collected at 2011 Census and includes people working in education & childcare, food & necessity goods, health & social care, public services, national & local government, public safety & national security, transport, utilities & communication

Table S3: Continuous variables in model average/SD

Variable	**Average (SD)**
Age	40.39 (14.82)
IMD rank	17098.29 (9394.9)
Calendar time	19.92 (7.38)

Table S4: Risk of mortality from COVID-19 cases with Omicron compared to Delta for each model.

Model 1 *adjusted for sex, age (natural spline), vaccination status and previous infection.* ***Model 2*** *adjusted for sex, age (natural spline), vaccination status, previous infection, and calendar time (natural spline).* ***Model 3*** *adjusted for sex, age (natural spline), vaccination status, previous infection, calendar time, ethnicity, Index of Multiple Deprivation rank (natural spline), household deprivation, university degree, keyworker status, country of birth, main language, region and disability.* ***Model 4*** *adjusted for sex, age*

(natural spline), vaccination status, previous infection, calendar time, ethnicity, Index of Multiple Deprivation rank (natural spline), household deprivation, university degree, keyworker status, country of birth, main language, region, disability, and comorbidities.

Table S5: Hazard Ratio (HR) for risk of death (for each definition) following Omicron relative to Delta from fully adjusted model (Model 4)

Death definition	HR (95%CI lower to upper)
All cause death	0.48 (0.39 to 0.61)
COVID-19 death	**0.34 (0.25 to 0.46)**
Death due to COVID-19	0.29 (0.21 to 0.40)
All cause death within 28 days of a positive PCR	0.48 (0.36 to 0.64)
All cause death over 28 days to 60 days of a positive PCR	0.44 (0.29 to 0.66)
All cause death over 60 days of a positive PCR	0.75 (0.32 to 1.76)

'COVID-19 death' in bold is the definition of a COVID-19 death used in the main analysis of this report, and means that COVID-19 was mentioned anywhere on the death certificate, possibly along with other health conditions. When we say that a death was 'due to' COVID-19, we mean that COVID-19 was the underlying cause of death, because it was either the only health condition mentioned on the death certificate, or it was the one that started the train of events leading to death. The additional death definitions were derived as sensitivity analyses.

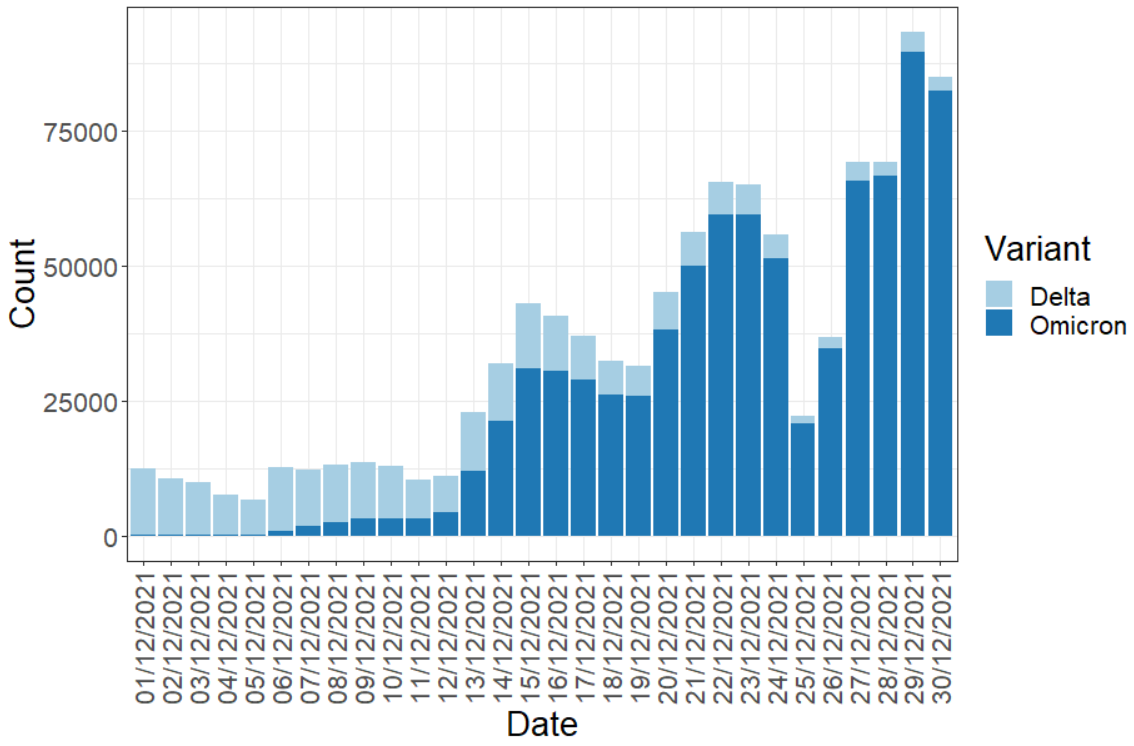

Figure S1. Number of infections by variant

The stacked bar plot shows the number of infections by variant per day between 1st December 2021 and 31st December 2021. The date is the date of specimen from NHS Test and Trace. Omicron infections are shown in dark blue, and delta in light blue.