Severity of Omicron BA.5 variant and protective effect of vaccination: national cohort and matched analyses in Scotland

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To the Editor:

The BA.5 sub-lineage was first detected in South Africa in January 2022.[1] It was designated a variant of concern by the UK Health and Security Agency on May 18, 2022, and became dominant in the UK by June 24, 2022.[2] There are few longitudinal population-based studies on the risks of infection and serious COVID-19 outcomes of BA.5. A case control and cross-sectional study in Denmark found that BA.5 was associated with an increased risk of COVID-19 hospitalisation compared to BA.2.[3] A test negative case–control study in England found no evidence of reduced vaccine effectiveness (VE) against hospitalisation for BA.5 compared to BA.2.[4] In this study, we analysed severity of the BA.5 variant compared to BA.2, which was the most recent dominant Omicron sub-lineage in the UK prior to BA.5.[5]

The Scotland-wide Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) platform comprises of linked primary care, vaccination, reverse transcriptase polymerase chain reaction (RT-PCR), viral-sequencing, hospitalisation and mortality data on 5.4 million (99% of the population). We have previously used EAVE II to report on VE and the impact of new variants, including Delta and Omicron.[6–8]

COVID-19 hospitalisation was defined as hospital admission with an International Classification of Diseases (ICD)-10 codes for COVID-19 and with an RT-PCR positive test for SARS-CoV-2 within the 28 days prior to admission, or 2 days after admission. COVID-19 death was defined as death with ICD-10 codes for COVID-19 on the death certificate within a 56 day follow up from the test date.

We undertook cohort and matched analyses investigating risk of COVID-19 hospitalisation and death associated with BA.5 compared to BA.2 using EAVE II. The study start date was April 1, 2022, and the study end was September 30, 2022. In all analyses, for the event that was being studied as the dependent variable, we used the first event that occurred in the study period, and we restricted to the subset of individuals that were virologically-sequenced with the BA.2 or BA.5 variants and who were not in hospital at the time the specimen was collected. Any inferences to those already in hospital should therefore be undertaken with caution. Vaccination status was defined at the specimen date for the positive RT-PCR test.

We fitted Cox proportional hazards models with COVID-19 hospitalisation, and COVID-19 death separately as outcomes using only the BA.2 and BA.5 cases and used these to calculate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). The cohort analyses included the following as explanatory variables: variant, sex, socioeconomic status, number of QCOVID risk groups,[9] whether the test was in the community or in hospital, immunosuppression, presence at any time on the shielding list, vaccination status as a categorical variable with levels for time period elapsed since the last vaccine dose, previous positive test as a categorical variable with levels for time period elapsed since the last positive test, and penalised splines in both age and calendar days since start of the study. The only variable that had missing values was socioeconomic status. The 43,881 (0.8%) records that had missing values for this variable were excluded from our complete case analysis (Table S1). We carried out a sensitivity analysis for hospitalisations, taking the outcome to instead be hospitalisation with a positive RT-PCR test in the 14 days prior or 2 days after admission. In the matched analysis, we matched BA.5 and BA.2 cases by specimen date, test laboratory location (community or hospital), age group in 5-year bands. We fitted a conditional logistic regression with COVID-19 hospitalisation as the outcome, including the same explanatory variables as in the cohort analyses except for test location and splines in age and calendar time, as these were matched. The results were averaged over 100 random sets of matchings, and 95% CIs adjusted to appropriately take account of this sampling variation. The average number of matched pairs in the matched analysis was 2223.

Table S1 shows summary statistics for the entire cohort, those who had a positive RT-PCR test, and those who were virologically sequenced. The marginal distributions of characteristics among those sequenced were broadly similar to those who tested positive, with some

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exceptions. Compared to the whole population, those who were virologically sequenced tended to be older, more socioeconomically deprived, and to be tested in NHS laboratories as opposed to the community Lighthouse Laboratory.

Table S2 shows summary statistics for those who had a positive RT-PCR test for BA.2 and BA.5, with 48,524 people in total. Individuals virologically sequenced with BA.5 tended to be older than those with BA.2, with a higher number of risk groups, were more socioeconomically deprived, more likely to be tested in hospital as opposed to the community, and more likely to have received a higher number of doses at specimen date. Event rates per 100 person-years and HRs adjusted for age and time in days are shown in Supplementary Figs. S1–S6. Of note, was the high rate in children aged 0–11 (Fig. S1).

Table 1 shows unadjusted rates of COVID-19 hospitalisation and death per 100 person-years of follow up time, as well as aHRs/odds ratios by variant of concern. Unadjusted rates of COVID-19 hospitalisation and death were higher for BA.5 compared to BA.2, particularly in older age groups We found that BA.5 was associated with a higher adjusted risk of COVID-19 hospitalisation than BA.2, aHR = 1.21, 95% CI 1.03, 1.43 (Table 1).

There was evidence of a protective effect of vaccination, for both variants of concern, against hospitalisation, with third dose vaccination more than 26 weeks prior to positive test associated with aHR = 0.54, 95% CI 0.46, 0.64 (Table S3). We found similar results in our sensitivity analysis for hospitalisations (Table S4), and in the matched analysis (Table S7). We also found similar results in a repeat of the matched analysis, but with the study period restricted to 26 May–6 July in order to examine the effect of changes in selection of individuals who were sequenced (Supplementary material: Temporal changes in sequenced cases). There was also evidence for a protective effect of previous infection.

We found that the HR of COVID-19 death with BA.5 compared to BA.2 was also increased, but the 95% CIs were much wider (aHR = 1.55, 95% CI 0.78, 3.08), with comparable protective effects offered by vaccination (Table S5).

A possible weakness in our study is that mass testing ended in Scotland on the 18 April 2022. Therefore COVID-19 hospitalisation and death may have been under-recorded. Despite the fact that we adjusted for a number of covariates, there may have still been residual confounding. There may also have been differential selection bias in virological sequencing of positive tests by variant.

In summary, our national longitudinal analysis found that, compared to BA.2, BA.5 was associated with an approximately 20% increased risk of COVID-19 hospitalisation and a possible increased risk of mortality although our mortality estimates lacked precision, Vaccination offered protection against both BA.5 associated hospitalisation and death.

Variable	Number of events (event rate per 100 person years)	Estimate (95% CI)
COVID-19 hospitalisation		
BA.2	828 (33.7)	Ref
BA.5	1218 (112.6)	aHR = 1.21 (1.03, 1.43)
COVID-19 hospitalisation sensitivity analysis		
BA.2	344 (27.9)	Ref
BA.5	562 (121.8)	aHR = 1.20 (0.92, 1.57)
COVID-19 hospitalisation matched analysis		
BA.2	129[a] (5.8%[b])	Ref
BA.5	154[a] (6.9%[b])	aHR = 1.24 (0.91, 1.69)
COVID-19 death		
BA.2	64 (1.4)	Ref
BA.5	70 (3.9)	OR = 1.55 (0.78, 3.08)

aHR = adjusted Hazard ratio. OR = Odds ratio. [a]This was the average number of confirmed hospitalisations over all samples. [b]There were 2223 matched pairs, on average, and these are the % hospitalised.

Table 1: **Event hazard rates by variant.**

Contributors

AS and CR conceived of this study. SK wrote the initial draft of the manuscript. CR carried out the statistical analysis.

Data sharing statement

The data used to undertake this analysis are not publicly available because they are based on deidentified national clinical records. These data are available, subject to approval by the NHS Scotland Public Benefit and Privacy Panel, by application through the Scotland National Safe Haven. The R code used to perform this analysis is available from https://github.com/EAVE-II/BA.4-5-variant.

Declaration of interests

AS and CR are members of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group and AS is a member of its Standing Committee on Pandemics. AS is a member of AstraZeneca's Thrombotic Thrombocytopenic Taskforce. All AS' roles are unremunerated. CR are members of the Scientific Pandemic Influenza Group on Modelling. SK declares no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100638.

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