Severity of BA.2 variant and vaccine effectiveness against symptomatic disease in Scotland

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The Lancet Regional Health - Europe 2022;23: 100533

Published Online xxx https://doi.org/10.1016/j.lanepe.2022.100533

The first confirmed case of SARS-CoV-2 omicron BA.2 was identified in Scotland on December 23, 2021.[1] BA.2 was the dominant variant in Scotland, replacing omicron BA.1.1.529 (BA.1) and accounting for >90% of new cases as of March 23, 2022 (Fig. S1, Supplementary Appendix).[1] Initial research suggested that BA.2 was associated with an increase in the odds ratio of infection for both unvaccinated and fully vaccinated individuals compared to BA.1.[2] Since then, other studies from Qatar have shown that vaccination can provide protection against symptomatic BA.1 and BA.2 infection,[3] but vaccination effectiveness is stronger after a third 'booster' dose. We undertook a test-negative design (TND) study of all individuals over the age of 18 in Scotland who had a RT-PCR test for SARS-CoV-2 from the community, were symptomatic at time of test, had their sample virally sequenced between November 1, 2021 and March 20, 2022, and did not have a record of a previous positive test using the Early Pandemic Evaluation and Enhanced Surveillance (EAVE II) platform.

EAVE II is a longitudinal COVID-19 surveillance platform that links primary care, secondary care, mortality, vaccination, virological-sequencing, and SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test data for 5.4 million people in Scotland. We have previously used EAVE II and similar methods to report on vaccine effectiveness (VE) and the impact of new variants.[4–6] For the TND analysis, where an individual had multiple eligible tests we used the very first positive test, or otherwise a random negative test. A generalised additive logistic model was fitted including adjustments for sex, socioeconomic status and number of QCOVID risk groups.[7] Separate penalised splines in age and calendar days were also included. Adjusted odds ratios and 95% confidence intervals were calculated and reported in Table S2. Full details of the cohort are available in Table S1 with more detail provided in the published protocol[8] and cohort profile.[4]

We also undertook an analysis of severity of BA.2 infection compared to BA.1 and SARS-CoV-2 B.1.617.2 (delta) using a Cox proportional hazards model amongst all those who tested positive and were virally-sequenced. COVID-19 hospitalisation was defined as an emergency hospitalisation with a community positive RT-PCR test in the 14 days prior to admission, or within two days following admission. COVID-19 death was defined as death with COVID-19 listed as a cause of death on the death certificate or death within 28 days of a positive RT-PCR test. Hospital admission was derived from the Rapid Preliminary Inpatient Data (RAPID) database.[9] Individual vaccination status was classified at the time of RT-PCR test. We included the same adjustments as in the TND analysis. Time to hospitalisation/death was measured starting from the specimen date. The Cox model was used to estimate the hazard ratio of COVID-19 hospitalisation or COVID-19 death, where BA.1 was the reference variant and the reference vaccination status was unvaccinated. Both adjusted hazard ratios and 95% confidence intervals were calculated and reported in Table 1.

53,454 (53.6%) RT-PCR sequenced samples were positive for BA.1 and 25,891 (26.0%) were positive for BA.2, with the remaining positive for other variants (20,354, 20.4%, see Table S1 for demographic and vaccination status breakdowns and comparisons of subcohorts). TND analysis showed a protective effect of three vaccination doses ≥14 days after administration against symptomatic infection for both BA.2 and BA.1; vaccine effects were slightly greater with BA.1, but the confidence intervals overlapped (Table S2). Having a second dose of vaccine more than 14 days prior to test was associated with a higher risk of symptomatic disease than being unvaccinated. This could be due to behavioural confounding due to greater social mixing in the vaccinated. Our Cox regression model showed that the adjusted hazard ratio (aHR) for COVID-19 hospitalisation or death was similar for BA.2 relative to BA.1 (aHR: 0.84, 95% CI 0.60–1.18, Table 1), with three doses of any vaccine associated with a 48% reduction in the risk of COVID-19 associated hospitalisation or death

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Population characteristic		Total sequenced cases	Number of events[a]	Adjusted hazard ratio	95% confidence interval	Person-years of exposure
Sex	Female	50,749	263	Reference	NA	3205.0
	Male	40,315	226	1.02	0.85–1.22	2566.0
COVID-19 variant	BA.1 variant	48,322	183	Reference	NA	3147.8
	BA.2 variant	23,325	67	0.84	0.60–1.18	1298.3
	Delta variant	13,896	168	2.33	1.39–3.90	931.7
	Other variants	5521	71	2.47	1.46–4.18	393.6
Vaccination Status[b]	No vaccination	12,188	102	Reference	NA	772.5
	One vaccine dose 0-27 days before test	210	1	0.57	0.08–4.08	14.1
	One vaccine dose >28 days before test	2751	17	0.85	0.51–1.42	174.2
	Two vaccine doses 0-27 days before test	219	1	0.69	0.10–4.94	14.0
	Two vaccine doses >28 days before test	27,977	167	0.47	0.36–0.61	1923.1
	Three vaccine doses 0-27 days before test	6401	25	0.25	0.16–0.39	446.6
	Three vaccine doses >28 days before test	41,318	176	0.52	0.39–0.70	2426.6
Number of pre-existing conditions[c]	No pre-existing Condition	NA	NA	Reference	NA	NA
	One condition	55,672	182	1.86	1.50–2.32	3713.0
	Two conditions	24,101	153	2.90	2.19–3.84	1540.0
	Three conditions	7230	74	5.89	4.17–8.33	392.0
	Four conditions	2397	47	6.68	4.05–11.04	90.0
	Five or more conditions	993	19	10.02	5.58–18.00	26.0
Scottish Index of Multiple Deprivation (SIMD) Quintile (2020)	1 (lowest)	671	14	Reference	NA	11.0
	2	18,927	106	0.82	0.63–1.04	1185.0
	3	16,843	83	0.71	0.54–0.93	1062.0
	4	17,819	80	0.67	0.51–0.89	1136.0
	5 (highest)	17,316	82	0.71	0.53–0.94	1136.0

Population characteristics shown in table comprise all covariates used in the Cox regression model. Effects are presented as adjusted hazard ratios and 95% confidence intervals compared to the reference baseline of symptomatic infection with BA.1. [a]COVID-19 associated hospitalization or death was defined as either (i) a hospital admission from the community flagged as an emergency with a positive RT-PCR test in the 14 days prior to admission, or within 2 days following admission, or (ii) death with COVID-19 listed as a cause of death on the death certificate or death within 28 days of a positive community RT-PCR test. [b]Vaccination status includes Oxford/AstraZeneca (ChAdOx1-S) vaccine, Moderna (mRNA-1273) vaccine, and Pfizer-BioNTech (BNT162b2) vaccines. See Table S1 for comparison of vaccine status. [c]Number of existing conditions was determined using the QCOVID algorithm risk groups.

Table 1: **Effect of variant and vaccination on emergency COVID-19 associated hospitalization or COVID-19 death for individuals sequenced in the community**

among those who tested positive (aHR: 0.52, 95% CI 0.39–0.70, Table 1). We also tested for an interaction between vaccination status and infection with BA.1 or BA.2 and found no overall difference between vaccination status and HR (Likelihood ratio p = 0.34).

In summary, our analysis shows that BA.2 is associated with comparable risk of serious COVID-19 outcomes to BA.1, and that three vaccination doses (including a booster dose) provide reasonable protection against symptomatic BA.2 infection and COVID-19 hospitalisation or death.

Contributors
A.S. and C.R. conceived of this study. S.H. wrote the initial draft of the manuscript. S.K. and C.R. carried out the statistical analysis. C.S. and Z.G. provided critical input on the manuscript.

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.2-variant.

Declaration of interests
A.S. and C.R. are members of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group and A.S. is a member of its Standing Committee on Pandemics. A.S. is a member of AstraZeneca's Thrombotic Thrombocytopenic Taskforce. All A.S.' roles are unremunerated. C.R. are members of the Scientific Pandemic Influenza Group on Modelling. S.K., Z.G. and C.S. declares no competing interests. S.H. was previously in receipt of PhD funding from the Natural Environment Research Council. S.H. was employed by AstraZeneca commencing on 5 September 2022, but did not carry out any work on this paper while in this role.

Acknowledgements

This study is part of the EAVE II project. EAVE II is funded by the MRC (MC_PC_19075) with the support of BREATHE—The Health Data Research Hub for Respiratory Health (MC_PC_19004), which is funded through the UK Research and Innovation Industrial Strategy Challenge Fund and delivered through Health Data Research UK. This research 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 (MC_PC_20058). Additional support has been provided through Public Health Scotland, the Scottish Government Director General Health and Social Care, and the University of Edinburgh. The original EAVE project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (11/46/23). The views expressed are those of the authors and not necessarily those of the NIHR, the Department of Health and Social Care, or the UK Government. We thank Dave Kelly from Albasoft (Inverness, UK) for his support with making primary care data available, and Wendy Inglis-Humphrey, Vicky Hammersley, and Laura Brook (University of Edinburgh, Edinburgh, UK) for their support with project management and administration.

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