Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland

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Summary

Background Since its emergence in November 2021 in southern Africa, the SARS-CoV-2 Omicron variant of concern (VOC) has rapidly spread across the world. There remain many unanswered questions about Omicron – in particular, in relation to its severity and the extent to which existing vaccines are effective in preventing COVID-19.

Methods Using the Scotland-wide Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) platform, which comprises of linked primary care, vaccination, reverse transcriptase polymerase chain reaction (RT-PCR), sequencing, hospitalisation and mortality data on 5.4 million (99% of the population), we undertook a cohort analysis with a nested test negative design incident case control study covering the period November 1 to December 19, 2021 to provide initial estimates of Omicron severity and vaccine effectiveness (VE) against symptomatic disease. We used S gene status as a surrogate for Delta and Omicron VOCs, with S gene positive status indicating Delta whereas S gene negative indicated Omicron. Cox proportional hazard models were used to estimate the risk of COVID-19 hospitalisation adjusted for age, sex, socioeconomic status, vaccination status and clinical risk factors. Generalised additive logistic regression modelling with spline terms for age and sex were used to estimate VE relative to ≥25 weeks post second vaccine dose.

Findings The first case of Omicron confirmed by viral sequencing was recorded in Scotland on November 23, 2021, By December 19, 2021, there were 23,840 S gene negative cases. These S gene negative cases were predominantly in the age group 20-39 (11,732; 49.2%). The proportion of S gene negative cases that were possible reinfections was more than 10 times that of S gene positive (7.6% versus 0.7%). There were 15 hospital admissions in those S gene negative giving an adjusted observed/expected ratio of 0.32 (95% CI 0.19, 0.52). The third/booster vaccine dose was associated with a 57% (95% CI 55, 60) reduction in the risk of symptomatic S gene negative symptomatic infection relative to ≥25 weeks post second dose.

Interpretation These early national data suggest that Omicron is associated with a two-thirds reduction in the risk of COVID-19 hospitalisation when compared to Delta. Whilst offering the greatest protection against Delta, the third/booster dose of vaccination offers substantial additional protection against the risk of symptomatic COVID-19 for Omicron when compared to ≥25 weeks post second vaccine dose.

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Research in context

Evidence before this study

There is currently only one preprint available assessing vaccine effectiveness (VE) against the Omicron variant of concern (VOC) at a population level. This found that two doses of BNT162b2 and ChAdOx1 were significantly less effective against Omicron than against Delta. Studies using sera from vaccinated individuals have also found that the antibodies produced are less effective at neutralising Omicron than Delta.

Added value of this study

This national investigation is one of the first to show that Omicron is less likely to result in COVID-19 hospitalisation than Delta. It finds the rate of possible reinfection for Omicron is 10 times that of Delta. It also finds that third/booster vaccine doses offer considerable additional protection against symptomatic disease when compared to ≥25 weeks post second vaccine dose with these benefits being seen with all available vaccines.

Implications for all the available evidence

The findings provide evidence for the acceleration and extension of the vaccine booster programme. Whilst these are early observations of a reduced severity of Omicron relative to Delta in risk of hospitalisation, they are encouraging. The combination of increased risk of transmission and immune evasion of Omicron mean that any advantage in reduced hospitalisation could potentially exceeded by increased rates of infection in the community. Incorporation of these data on risks of hospitalisation within modelling output will inform decisions by policymakers regarding the speed, range, nature and duration of societal measures that otherwise would be needed to control the risk of spread of infection and minimise the risk of overwhelming health system capacity.

Introduction

The Omicron (B.1.1.529) COVID-19 variant of concern (VOC) was first detected in South Africa from a sample taken on November 9, 2021.[1] This was reported to the World Health Organization (WHO) by South African authorities on November 24, 2021 following which the WHO's Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) was reconvened on November 26, 2021, which led to B.1.1.529 being denoted as a VOC.[2] As of December 18, 2021, WHO has reported Omicron in 89 countries.[3]

Omicron is characterised by a number of mutations of the spike protein, particularly in the region that recognises receptors on human cells.[4] The limited body of evidence thus far available suggests that these mutations result in increased transmissibility when compared to both the wild type and previous VOCs – including Delta – and reduced potency of neutralising antibodies.[4] There are however major unanswered questions relating to the severity of Omicron, the extent to which previous infection with SARS-CoV-2 is protective, and the effectiveness of available COVID-19 vaccines in preventing symptomatic infection and more serious COVID-19 outcomes.

Following the first reported case of Omicron in Scotland in late November 2021, there has been a rapid rise in case numbers such that we are now in a position to report on our first estimates of hospital admission associated with Omicron and vaccine effectiveness (VE) against symptomatic disease.

Methods

Study design and population

As our methods have been described in detail in a number of previous publications, we confine ourselves to a brief description here.[5-9] We used the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) Scotland-wide prospective cohort, which comprises of linked datasets on 5.4 million people in Scotland (~99% of the population), to construct a nested test negative design (TND) among individuals with incident symptomatic infections.

Primary care data derived from 940 general practices across Scotland were linked to laboratory data from the Electronic Communication of Surveillance in Scotland (ECOSS),[9] and hospital admission data available from the Rapid Preliminary Inpatient Data (RAPID).[10] Vaccination data were available from general practices and the Turas Vaccination Management Tool (TVMT),[11] which is a web-based tool to capture vaccinations in the community and create real-time vaccination records. Laboratory data from ECOSS included all reverse transcription polymerase chain reaction (RT-PCR) test results from NHS laboratories (Pillar 1) and the Lighthouse Government laboratory based in

Glasgow (Pillar 2).[12] Data were deterministically linked using the Community Health Index (CHI) number, which is a unique identifier used in all healthcare contacts across Scotland.[5]

Information on S gene status is routinely available from individuals tested in the community within the Glasgow Lighthouse laboratory. This information is not available from those who are tested in NHS laboratories. The majority of hospital admissions arise from those tested in the NHS laboratories and S gene information is not routinely available from those laboratories. There is a national sequencing surveillances system and a representative sample of positive cases are sequenced with around 2,000 samples sequenced each week, though a slightly greater proportion of cases from NHS laboratories are sequenced compared to community cases. There is a delay of about two weeks for the sequencing results.

The main analysis in this report is based upon all patients who tested positive in Scotland from November 1 to December 19, 2021, with follow up from the date of testing positive to the date of admission to hospital. The analysis of hospitalisations used the last date of admission to hospital - i.e., December 21, 2021, and follow up was censored at 15 days. In the test negative design, the first positive test result after the beginning of the study was used for individuals with at least one positive test. For individuals with only multiple negative tests during the period, one test was selected at random. Only individuals reporting symptoms at the time of test were included in this study and the date of symptom onset was used. A few individuals reported symptoms with no date of onset and this was imputed as five days before the test.

Exposure definitions

We studied the second doses of the BNT162b2 COVID-19 (also known as the Pfizer-BioNTech) vaccine,[13] ChAdOx1 nCoV-19 (AZD1222; also known as the Oxford-AstraZeneca) vaccine [14] and mRNA-1273 (also known as Moderna) [15] and third or booster doses of BNT162b2 and mRNA-1273. An individual was defined as exposed if they had received second or third doses of these vaccine between November 1 and December 19, 2021. Vaccination information was extracted from the GP records and the TVMT system and included individuals vaccinated in general practices, community vaccination hubs and other settings such as care homes.

Vaccination status was defined on the date the of the positive RT-PCR test. It was coded using the following categories: unvaccinated (uv), 27 days post first dose (v1_0:3), 28+ days post first dose (v1_4+), 0-13 days post second dose (v2_0:1), 14-41 days post second dose (v2_2:5), 42-69 days post second dose (v2_6:9), 10 or more weeks (70+ days) post second dose (v2_10+). For those with a dose 3 or booster dose, the categories were 0 or 1 week post third/booster dose (v3_0:1) or 2 or more weeks post third/booster dose (v3_2+).

Vaccinated groups were stratified by time intervals since second and third dose vaccines and whether infection was caused by Delta (S gene positive) or Omicron (S gene target failure or S gene negative). The S gene variable took one of five values: S positive (Delta VOC), weak S positive (usually also Delta VOC), S negative (Omicron VOC), Other and Unknown. Unknown corresponded to individuals who were tested in NHS laboratories (where S gene status was unavailable) or who were tested in the Glasgow Lighthouse lab, but the sample did not yield any cycle threshold (CT) values. Other corresponded to CT values that could not otherwise be classified.

Definition of outcomes

We assessed VE against symptomatic SARS-CoV-2 infection i.e., COVID-19 with infection being confirmed through a positive RT-PCR test for SARS-CoV-2.

A COVID-19 hospitalisation was defined as an emergency admission in an individual who had a positive COVID-19 test within 14 days prior to admission or who tested positive within two days of admission. Patients who were already in hospital and then tested positive more than two days post admission were excluded from the analysis. Hospital admission data come from the RAPID database and the reason for admission is unknown. Details of the admission and discharge codes are available from SMR01, but this has a two-month delay for validation. From historic data from June 2021 to October 2021, when Delta was dominant in Scotland, we have estimated that 75% of admissions within 14 days of a positive test were admitted for SARS-CoV-2. This percentage was constant over this five-month period.

Patient characteristics and confounders

At the baseline of our cohort (i.e., December 8, 2020), a number of population characteristics that could potentially confound the association between COVID-19 vaccination and the outcome of interest were determined. These included socio-economic status (SES) measured by quintiles of the Scottish Index of Multiple Deprivation (SIMD) (1 refers to most deprived and 5 refers to least deprived),[5] residential settlement measured by the urban/rural 6-fold classification (1 refers to large urban areas and 6 refers to small remote rural areas),[5] and the number and types of comorbidities commonly associated with COVID-19 illness.[16] Age and sex were recorded at the date of test and date of vaccination.

Statistical analysis

The expected numbers of COVID-19 hospitalisations were calculated by fitting a Cox proportional hazards regression model to the S positive cases only in the study period using predictors of age group, sex, deprivation status, previous positive history, number of co-morbid QCOVID clinical risk groups and vaccine status including vaccine type, dose and duration, as well as a calendar period effect in weeks. The expected number of cases was derived from the predictions of expected survival from the model. Hence the expected

number of hospitalisations in the S positive group matched the observed. Confidence intervals were derived from Byar's method.[17]

Analysis of the risk of symptomatic SARS-CoV-2 disease was by generalised additive logistic regression including spline terms for age and the temporal trend during the study period. All models included vaccine status. Further adjustment was made for health board, sex and deprivation, whether the individual had tested previously tested positive at any time before the specimen date, and number of QCOVID clinical risk groups (0, 1, 2, 3, 4, 5+), and whether the individual was recorded as being: (i) immunosuppressed; or (ii) in a shielding category. This analysis was carried out separately for those aged 16-49 and ≥50 to assess any differential reduction in risk in these age groups and because the majority of the unvaccinated were in the younger age group.

In the test negative design, the reduction in the odds ratio (OR) of testing positive for S negative or S positive following receipt of a booster or third dose of any vaccine was measured relative to individuals who had received two vaccine doses at least 25 weeks before the date of symptom onset. There were three reasons for this. First, there were very few unvaccinated individuals in Scotland, particularly among the older adult population, and so the precision of estimates of vaccine effect relative to unvaccinated would be low. Second, associated with this is potential bias in the unvaccinated group in a population where most are vaccinated and the two dose ≥25 weeks group represents those who were initially targeted for the booster dose. Third, studies have demonstrated significant vaccine waning by ≥25 weeks after the receipt of the second dose.[18] Omicron appears significantly different to previous strains. Comparing to a vaccinated group is similar to that which is undertaken for analysis of the VE for seasonal influenza in which the vaccine effect in each season is deduced from a population that have previously been naturally exposed to previous influenza or prior recipients of seasonal flu vaccine.

All analyses were done with R statistical software (version 3.6.1). Analyses were checked by two independent statisticians.

Sensitivity analyses

Three sensitivity analyses were carried out for the calculation of the expected number of hospitalisations. In the first, only individuals with at least seven days follow up post testing positive were included in the analysis as most admissions from the community to hospital will have occurred by that time among those with a S positive infection. The majority of individuals with a S negative infection were aged 20-59 and so we carried out a sub-analysis in this group only. Finally, a small percentage of those testing positive did not link into EAVE II and while we know their age, sex and vaccine and testing status, their QCOVID risk groups and deprivation status were unknown. The

number of risk groups was imputed as 0 risk groups, the modal value; deprivation status was imputed as level 3 - the middle group.

Ethics and permissions

Approvals were obtained from the National Research Ethics Service Committee, Southeast Scotland 02 (reference number: 12/SS/0201) and Public Benefit and Privacy Panel for Health and Social Care (reference number: 1920-0279).

Reporting

Our protocol and cohort profile are published.[5][6] We followed the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) checklist to guide transparent reporting of this study. Our analysis code is publicly available at https://github.com/EAVE-II/B.1.1.529-variant

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of this report.

Results

Vaccination status

At the time the first Omicron case was detected in Scotland, 80% of children were unvaccinated, while 50% of those aged ≥65 years had two doses plus a booster for at least two weeks. Among young adults aged 16-39, 24% were unvaccinated and 33% had 2 doses 10 or more weeks ago. Among adults aged 40-64 years, 53% had 2 doses ≥20 weeks ago (Figure S1).

Characteristics of those testing positive

There were 162,946 RT-PCR positive tests in Scotland over the study period. The characteristics of those testing positive by S gene status is summarised in Table 1. Of these, 152,496 (93.6%) were available in the EAVE II platform. The rate of S gene positive infection is greater among the unvaccinated, mainly children while almost half of individuals with a S gene negative infection were aged 20-39 (48.9%), (Table 1, Figure S2, S3)

Risk of possible re-infection

The rate of possible reinfection for S gene negative was approximately 10 times that of S gene positive, but there was still evidence of protection (7.6% versus 0.7%; see Table 1).

S gene status by sequencing variant

Of the S positive samples sequenced 99.9% (22,572/22,596) of were Delta (Table 2). Similarly, of those who were S negative and sequenced 97.8% (654/667) were Omicron (Table 2). Among the 672 sequenced as Omicron, 97.3% had a S gene negative infection.

Risk of COVID-19 hospitalisation associated with S gene negative

Trends in hospital admission among those testing positive from November 1 showed that the majority of admissions were associated with a S gene positive infection and very few were associated with S gene negative infection (Figure S4). Hospitalisation rates by age group are shown in Figure S5 demonstrating lower admission rates in adults 20-59 who had S gene negative infection compared to S gene positive. There were no admission to date among those aged over 60 years.

As shown in Table 3, there was a lower-than-expected number of hospital admissions for COVID-19 in those who were S gene negative. The adjusted observed/expected ratio was 0.32 (95% CI 0.19, 0.52). Using the entire cohort i.e., including the relatively few cases that could not be linked into EAVE II, yielded a comparable observed/expected ratio of 0.36 (95% CI 0.22, 0.56) (Table S4). These latter estimates needed to be interpreted with more caution because of our imputation of QCOVID clinical risk groups. The cumulative incidence curves are presented in Figure S6 and the hazard ratios from the Cox model in Table S7.

Third/booster vaccine effectiveness against S gene negative symptomatic disease

Relative to ≥25 weeks post second vaccine dose, the third/booster vaccine was associated with a 56% (95% CI 51, 60) reduction in the odds of developing symptomatic disease with S gene negative two or more weeks after booster, among those aged 16-49 years. For individuals aged ≥50 years the corresponding reduction was 57% (95% CI 52, 62). Over all ages the reduction was 57% (95% CI, 54, 60). These reductions in the odds of infection were lower than for symptomatic S positive infection where the booster was associated with an 83% (95% CI 81, 84) reduction in those aged 16-49 and 88% (95% CI 86, 89) in those aged ≥50 years.

Within this analysis, adjustment was made for the impact of a previous positive test. For symptomatic individuals tested for SARS-CoV-2 the odds ratio of a S gene positive infection having been positive more than 90 days before symptom onset was 0.08 (95% CI 0.07, 0.09); for testing positive between 28 and 90 days before symptom onset the odds ratio was 0.06 (95% CI 0.05, 0.08). The corresponding odds ratios for a S gene negative infection were 0.57 (95% CI 0.53, 0.61) and 0.25 (95% CI 0.20, 0.32), respectively.

Sensitivity analyses

The sensitivity analyses for the expected numbers of hospitalisations showed that using only those who had been followed up for at least seven days had a similar observed/ expected ratio as the principal analysis of 0.33 (95% CI 0.15, 0.65). When using only those aged 20-59 years, the ratio was slightly higher at 0.44 (95% CI 0.25, 0.70), but with overlapping 95% CIs.

Discussion

Omicron has spread very rapidly across a highly vaccinated population in Scotland, replacing Delta as the dominant VOC within less than a month. Though preliminary, our national data suggest that Omicron is substantially less likely to result in COVID-19 hospitalisation than Delta. We also show that, the third/booster dose is associated with substantial additional protection within two weeks of this additional dose, compared to two doses of vaccine received 25 or more weeks ago. This protection is greatest for Delta, but still substantial for Omicron.

To our knowledge, this is one of the first national investigations into Omicron severity and VE against symptomatic disease. Key strengths include our use of a national linked datasets which has created a platform that allowed rapid access to and analysis of data on clinical, testing and vaccination status.[5] This study is therefore less susceptible to recall or misclassification bias than studies of samples of the population.

Our study also had several limitations. First, we used the surrogate of S gene status as a marker of Delta and Omicron. Sequencing data were only available on a subset of the Scottish population and there is furthermore a lag in obtaining these data. That said, our data indicate that these are likely to be reliable markers with >99% of those S gene positive being sequenced as Delta and 98% of those with S gene negative being sequenced as Omicron (Table 2). It is therefore reasonable to assume that S gene positive equates with Delta and S gene negative status equates with Omicron. Another limitation is that S gene status can only be determined in those tested in Glasgow Lighthouse laboratory (Pillar 2) meaning that we are not in a position to comment on VE in those testing positive in hospital settings. This is because the Thermo Fisher Taq-Path COVID-19 Multiple Diagnostic assay is only available in the Glasgow Lighthouse laboratory. We had too few serious COVID-19 outcomes in those who were S gene negative to enable analysis of VE against COVID-19 deaths. Finally, because of the low number of hospital admissions we had considerable uncertainty in the estimation of the observed over expected ratio. Additionally, a striking observation thus far has been a paucity of hospitalised cases over the age of 65 years of age – whether this remains the case or whether waning following third dose occurs differentially across age groups will require follow-up over time.

The modelling analysis has a number of key assumptions. It is based upon the assumption that the pattern of time to admission to hospital from the community following a positive test is the same for S negative infections as has been observed for S gene positive infections. It will take time to asses if this is indeed the case. If S gene negative patients take longer to be admitted than S gene positive patients our expected values will be an over-estimate leading to an artificial claim of reduced severity with Omicron. Secondly, there is limited circulation of S gene negative infections among the elderly in Scotland in this early part of the epidemic. If hospitalisation rates with Omicron among the elderly are higher that with Delta then that will again lean to over optimistic conclusions from this early report. Another threat is that we have limited data on the time since the booster dose of the vaccine and if there is waning after the booster that will have an impact on hospitalisations, particularly in the elderly who received their booster doses in the early autumn of 2021. A final point is that the majority of hospital admissions come from individuals tested in NHS laboratories in Scotland and this analysis does not cover these admissions.

A number of reports have previously pointed to increased transmission associated with Omicron when compared to Delta, which has resulted in considerable concern amongst governments, public health officials and the public as there is a very real risk that health system surge capacity will be breached. These concerns have been added to by data showing reduced VE associated with two doses of vaccines and reduced neutralising antibodies suggesting increased potential for vaccine escape.[17-20] The available modelling, which has assumed comparable severity to Delta, suggest that in most scenarios there will be a very sharp increase in the number of hospital admissions and deaths as Omicron begins to replace Delta. A key gap in the evidence base has been the absence of data on severity of disease associated with Omicron, which has led to a number of governments beginning to re-impose social restrictions. The very limited data available from South Africa indicate that Omicron is associated with reduced risk of severe disease.[21] It is however difficult to make inferences to countries with different population age structures and lower levels of natural immunity (as is the case in the UK). Our data should now reduce the uncertainty in at least one key parameter used to model the impact of the growth of Omicron can be plugged. The reduced severity may also have implications for isolation rules that are in the UK also contributing to the closing down of society as ever-increasing numbers of people het infected and need to isolate threatening the viability of essential services such as the NHS and public transport. A further piece of information from the study is the proportion of cases identified as possible reinfections which need to be factored into modelling output.

The combination of increased risk of transmission and immune evasion of Omicron mean that any advantage in reduced hospitalisation could potentially be exceeded by increased rates of infection in the community. Incorporation of the risks of hospitalisation within modelling output will however allow balanced views by policymakers regarding the speed, range, nature and duration of societal measures

that otherwise would be needed to control the risk of spread of infection for the expected proportion of cases to be hospitalised.

Although preliminary, these national data should provide reassurance that Omicron is substantially less likely to result in severe outcomes than Delta and that third/booster vaccine doses are associated with considerable added protection against symptomatic disease when compared to second doses. We will continue to analyse the Scottish data, which should lead to greater precision in our estimates over the coming weeks. The policy implications of these findings are potentially substantial. There is a need for confirmatory findings from research groups in other countries.

Contributors: AS and CR conceived the idea for this study. Analysis was undertaken by CR and SK. All authors critically revised the manuscript and approved the final version for submission.

Data sharing: A data dictionary covering the datasets used in this study can be found at https://github.com/EAVE-II/EAVE-II-data-dictionary. All code used in this study is publicly available at https://github.com/EAVE-II/B.1.1.529-variant. The data used in this study are sensitive and will not be made publicly available.

Declaration of interests: AS, MW, CR and JMcM are members of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group and AS its Standing Committee on Pandemics. AS & JMcM are also members of the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG). JMcM is the Chair of the multidisciplinary Scottish COVID-19 National Incident Management Team. AS is a member of AstraZeneca's Thrombotic Thrombocytopenic Taskforce. All AS' roles are unremunerated. CR and MW are members of SPI-M.

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Table 1: Characteristics of those testing positive by S gene status

Characteristic	Levels	S Positive	S Negative	Weak S Positive	Other	Unknown
Total		126,511 (100.0%)	23,840 (100.0%)	2,385 (100.0%)	1,081 (100.0%)	9,129 (100.0%)
Sex	Female	65,128 (51.5%)	12,805 (53.7%)	1,355 (56.8%)	553 (51.2%)	4,659 (51.0%)
	Male	61,383 (48.5%)	11,035 (46.3%)	1,030 (43.2%)	528 (48.8%)	4,470 (49.0%)
Age group	0-11	29,329 (23.2%)	1,389 (5.8%)	500 (21.0%)	253 (23.4%)	1,238 (13.6%)
	10-19	14,665 (11.6%)	2,277 (9.6%)	253 (10.6%)	126 (11.7%)	549 (6.0%)
	20-39	32,628 (25.8%)	11,732 (49.2%)	879 (36.9%)	352 (32.6%)	2,037 (22.3%)
	40-59	39,528 (31.2%)	6,862 (28.8%)	609 (25.5%)	278 (25.7%)	2,535 (27.8%)
	60-74	9,101 (7.2%)	1,354 (5.7%)	126 (5.3%)	66 (6.1%)	1,401 (15.3%)
	75+	1,260 (1.0%)	226 (0.9%)	18 (0.8%)	6 (0.6%)	1,369 (15.0%)
Number of risk groups	0	86,753 (68.6%)	15,888 (66.6%)	1,634 (68.5%)	736 (68.1%)	4,553 (49.9%)
	1	25,341 (20.0%)	5,206 (21.8%)	457 (19.2%)	208 (19.2%)	1,911 (20.9%)
	2	5,410 (4.3%)	888 (3.7%)	91 (3.8%)	34 (3.1%)	863 (9.5%)
	3	1,206 (1.0%)	170 (0.7%)	12 (0.5%)	10 (0.9%)	456 (5.0%)
	4	352 (0.3%)	39 (0.2%)	5 (0.2%)	1 (0.1%)	256 (2.8%)
	5+	151 (0.1%)	23 (0.1%)	1 (0.0%)	1 (0.1%)	216 (2.4%)
	Unknown	7,298 (5.8%)	1,626 (6.8%)	185 (7.8%)	91 (8.4%)	874 (9.6%)

Vaccine status	uv	47,972 (37.9%)	3,548 (14.9%)	712 (29.9%)	408 (37.7%)	2,749 (30.1%)
	v1_0:3	965 (0.8%)	123 (0.5%)	18 (0.8%)	8 (0.7%)	54 (0.6%)
	v1_4+	9,323 (7.4%)	1,460 (6.1%)	145 (6.1%)	89 (8.2%)	528 (5.8%)
	v2_0:1	311 (0.2%)	88 (0.4%)	13 (0.5%)	5 (0.5%)	25 (0.3%)
	v2_2-5	219 (0.2%)	127 (0.5%)	15 (0.6%)	7 (0.6%)	23 (0.3%)
	v2_6-9	728 (0.6%)	258 (1.1%)	28 (1.2%)	6 (0.6%)	37 (0.4%)
	v2_10+	56,099 (44.3%)	12,612 (52.9%)	943 (39.5%)	435 (40.2%)	3,816 (41.8%)
	v3_0:1	6,351 (5.0%)	2,364 (9.9%)	188 (7.9%)	58 (5.4%)	664 (7.3%)
	v3_2+	4,543 (3.6%)	3,260 (13.7%)	323 (13.5%)	65 (6.0%)	1,233 (13.5%)
Previously tested positive	Never	125,064 (98.9%)	21,949 (92.1%)	2,123 (89.0%)	1,034 (95.7%)	8,285 (90.8%)
	1 to 28 days before	292 (0.2%)	NA	4 (0.2%)	4 (0.4%)	375 (4.1%)
	29 to 90 days before	207 (0.2%)	91 (0.4%)	39 (1.6%)	10 (0.9%)	249 (2.7%)
	> 90 days before	948 (0.7%)	1,800 (7.6%)	219 (9.2%)	33 (3.1%)	220 (2.4%)

The numbers in some cells are suppressed to avoid counts of less than 5, denoted *. Where only one cell for a characteristic has a count of less than 5 then the next largest number is also suppressed to avoid deduction of the suppressed number by subtraction.

The individuals whose comorbid status is unknown are those who did not link into the EAVE II study. This can occur if a person recently moved into Scotland or was not registered with a GP practice in December 2020,

The majority of individuals whose S gene status is unknown tested positive in an NHS laboratory and S Gene status is not routinely available. They are included for completeness but are not used in any of the modelling analysis.

Table 2: Number of samples with S gene status by sequencing variant

S gene status	Delta	Omicron	Other	Not sequenced
S gene positive	22,572	1	23	81,538
S gene negative	10	654	5	2,201
Weak S positive	<5	0	0	922
Other	11	0	0	749
Unknown	2,810	17	16	4,326

The information in this table is based upon sequencing information available up to December 9th. The majority of individuals whose S Gene status is unknown tested positive in an NHS laboratory and S Gene status is not routinely available. A greater proportion of NHS laboratory cases are sequenced compared to community cases.

Table 3: Observed vs expected analysis for risk of hospital admission by S gene status

	S Gene Status	N	Person Years	Hospital Admissions	Expected Admissions	Observed/ Expected	LCL	UCL
All cases linking into the EAVE II dataset	S Positive	119100	4375.1	856	856.9	1	0.93	1.07
	S Negative	22205	413.4	15	46.6	0.32	0.19	0.52
	Weak S Positive	2199	57.3	7	6.9	1.02	0.45	2
	Other	990	33.8	*	*	0.79	0.26	1.88
	Unknown	1647	58.2	14	14.8	0.94	0.54	1.54
All cases	S Positive	126464	4643.5	967	903.7	1.07	1	1.14
	S Negative	23830	443.1	18	50.1	0.36	0.22	0.56
	Weak S Positive	2384	62.1	9	7.5	1.2	0.59	2.19
	Other	1080	36.5	*	*	0.71	0.24	1.69
	Unknown	1813	63.3	17	16.1	1.05	0.64	1.65
All cases followed up for at least 7 days	S Positive	102765	4096.2	824	824.9	1	0.93	1.07
	S Negative	4111	140.2	7	21.2	0.33	0.15	0.65
	Weak S Positive	995	37.5	7	5.3	1.32	0.59	2.59
	Other	748	29.5	*	*	0.64	0.18	1.7
	Unknown	1336	52.8	10	14.1	0.71	0.36	1.25
All cases aged 20-59	S Positive	68035	2489.4	575	575.6	1	0.92	1.08
	S Negative	17302	322.9	15	34.4	0.44	0.25	0.7
	Weak S Positive	1373	34.7	6	5.1	1.18	0.49	2.44
	Other	567	19.1	*	*	0.58	0.11	1.85
	Unknown	1057	36.4	5	8.6	0.58	0.22	1.28

N – Number of individuals testing positive; Person Years is the total follow up time from testing positive. Hospital Admissions is the number of people admitted to hospital for at least 1 day within 14 days of a positive test; LCL/UCL are the lower and upper confidence intervals for the observed over expected ratio based upon a Poisson distribution for the admissions. As the model is fitted to the S Positive data the observed and expected will match exactly. This table gives the expected number of hospitalisations for the other S gene categories assuming that the observed pattern among the S Positive cases applies.

Some cells have small numbers of admissions and these have been suppressed (*) as well as the expected values.

Table 4: Vaccine effectiveness for symptomatic positive S Negative test associated with third/booster doses compared to individuals who had 2 doses of a vaccine more than 25 weeks before testing positive

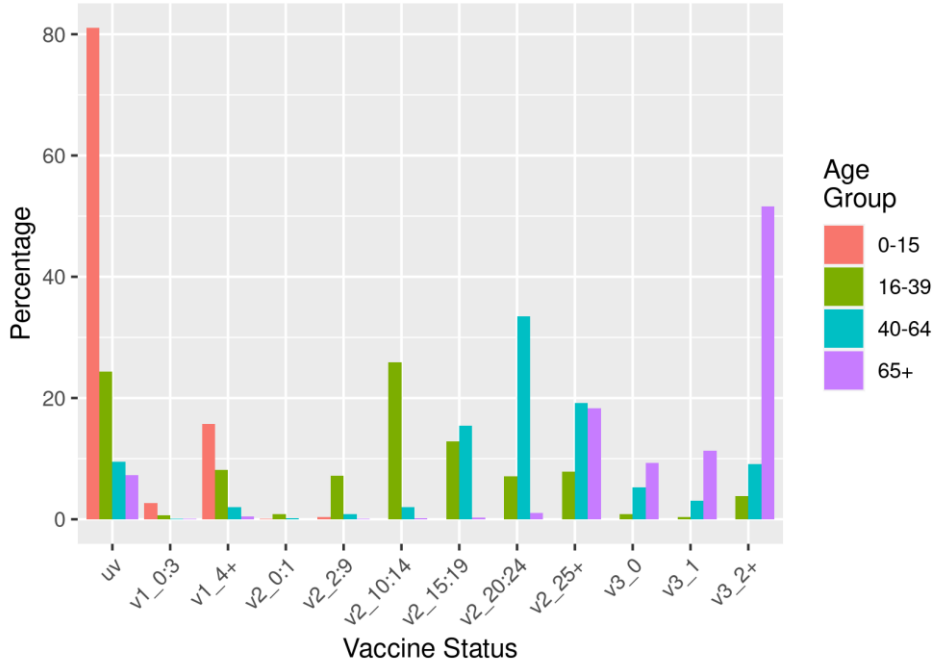
		S gene negative infections			S gene positive infections		
Age	**Vaccine Status**	**Tested**	**Positive**	**VE% (95% CI)**	**Tested**	**Positive**	**VE% (95% CI)**
16–49	uv	10,302	1,003	22 (14 – 29)	14,583	5,284	-98 (-109 – -87)
	v1_0:3	550	36	47 (24 – 63)	676	162	-24 (-50 – -3)
	v1_4+	6,570	581	30 (21 – 38)	8,339	2,350	-39 (-49 – -30)
	v2_0:1	732	46	58 (42 – 70)	805	119	31 (16 – 44)
	v2_2:9	4,248	256	53 (46 – 60)	4,258	266	73 (69 – 46)
	v2_10:14	1,2581	814	33 (26 – 50)	1,3559	1,792	50 (46 – 53)
	v2_15:19	2,9209	3503	15 (9 – 21)	3,1963	6,257	32 (29 – 36)_
	v2_20:24	1,4986	1,824	3 (-5 – 11)	1,7991	4,829	9 (4 – 13)
	v2_25+	1,3183	1,435	0	1,5462	3,714	0
	v3_0	3,773	515	26 (16 – 34)	4,003	745	33 (27 – 39)
	v3_1	2,185	143	62 (54 – 68)	2,155	113	84 (80 – 87)
	v3_2+	12,887	783	56 (51 – 60)	12,798	694	83 (81 – 84)

50+	uv	716	48	33 (7 – 52)	1158	490	-45 (-65 – -28)
	v1_0:3	27	4	0 (-230 – 70)	36	13	-16 (-134 – 42)
	v1_4+	256	13	48 (7 – 72)	343	100	10 (-15 – 30)
	v2_0:1	23	1	62 (-207 – 95)	23	1	90 (27 – 99)
	v2_2:9	120	9	5 (-98 – 54)	131	20	62 (38 – 77)
	v2_10:14	128	12	8 (-76– 52)	149	33	40 (10 – 60)
	v2_15:19	463	17	35 (-10 – 62)	634	188	20 (4 – 33)
	v2_20:24	5513	265	4 (-13 – 19)	8205	2957	4 (-3 – 10)
	v2_25+	8007	799	0	10856	3648	0
	v3_0	3522	420	0 (-15 – 13)	4352	1250	20 (13 – 26)
	v3_1	3006	180	54 (46 – 62)	3146	320	77 (74 – 80)
	v3_2+	17572	1045	57 (52 – 62)	17504	977	88 (86 – 89)

VE is vaccine effectiveness measured as 1-Odds Ratio. Tested are the number of symptomatic individuals who were tested in the analysis and the Positive is the number who tested positive. The number testing negative for SARS-CoV-2 infection is the difference between the Tested and Positive and this is the same in both the S negative and S positive analysis. The numbers in some cells have been suppressed where they are below 5 (*).

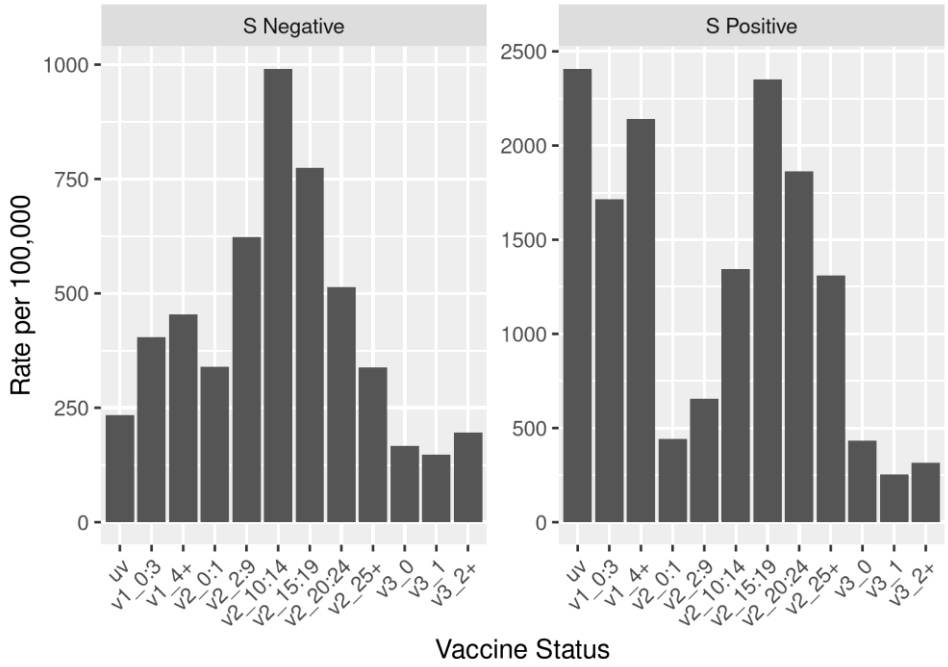
Supplementary materials

Figure S1: Vaccine uptake in Scotland by age group and vaccine status on 15th November 2021



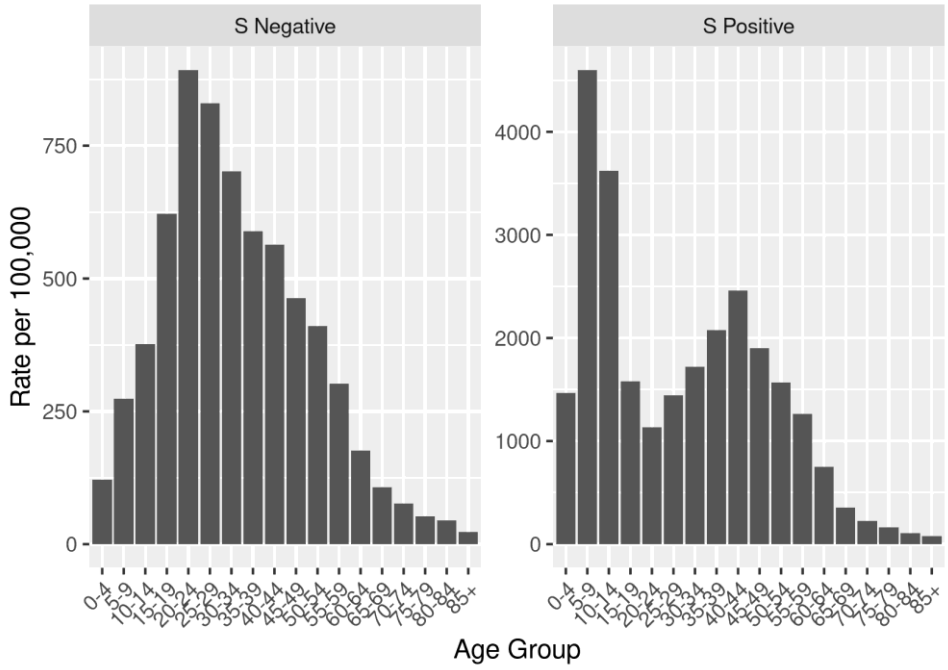
The above chart shows that 80% of children are unvaccinated, while 50% of those aged 65+ have had 2 doses plus a booster for at least 2 weeks. Among young adults aged 16-39, 24% are unvaccinated and 33% had 2 doses 10 or more weeks ago, while among adults aged 40-64 53% had 2 doses 20+ weeks ago.

Figure S2: Rate of S positive and S negative confirmed infections from community samples in Scotland from November 15, 2021 onwards by vaccine status



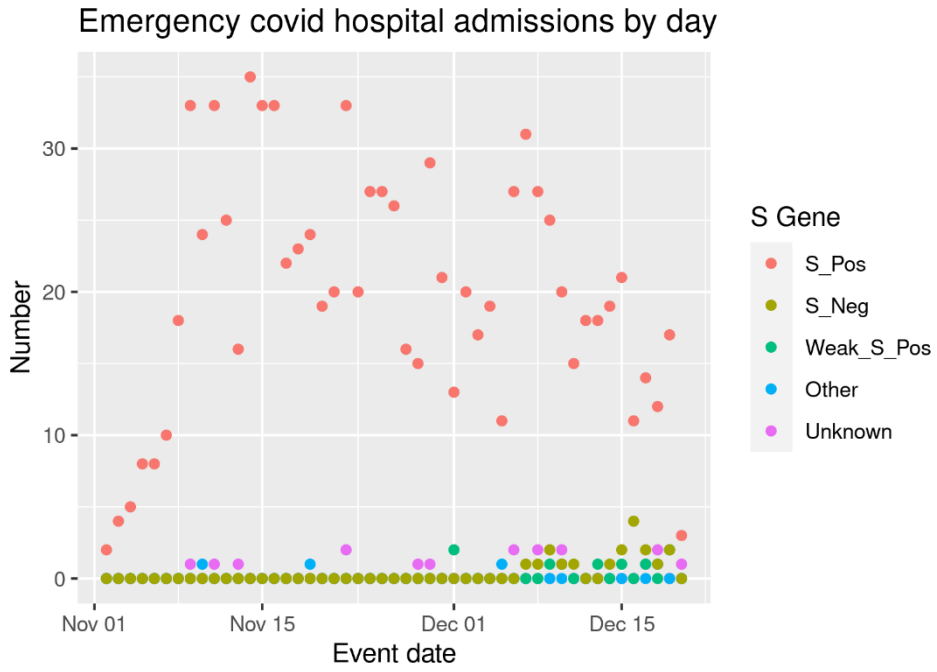
The above chart shows that the pattern of tested positive S negative infections is not the same as for S positive infections. In particular, for S positive the rate is high among the unvaccinated and low among those who have had their third/booster of who have recently received their second dose. S negative infections show high rates among those who received the second dose of the vaccine 10 to 20 weeks ago. This, in part, reflects the age distribution of those who are most commonly affected with S negative infections – those aged 20-39.

Figure S3: Rate of S gene positive and S gene negative confirmed infections from community samples in Scotland from November 15, 2021 onwards by age group



This chart shows that the age distributions of S Positive and S Negative infections in Scotland is quite different. The rate of S Positive infections is much higher in children whereas the highest rates of S Negative infections are in young adults

Figure S4: Hospital admissions within 14 days of a positive test among individuals who tested positive in the community in Scotland from November 1, 2021 by S gene status. These individuals were not in hospital at the time of test



In this graph the increase in admissions at the beginning of the time period for individuals with S Positive infections reflects the selection criterion of testing positive from November 1st and the time to hospital admission from testing positive. Individuals can be admitted any day following the positive test but most are admitted within 5-10 days following testing positive.

Figure S5: Rates of admission to hospital within 14 days of a positive community test by age group

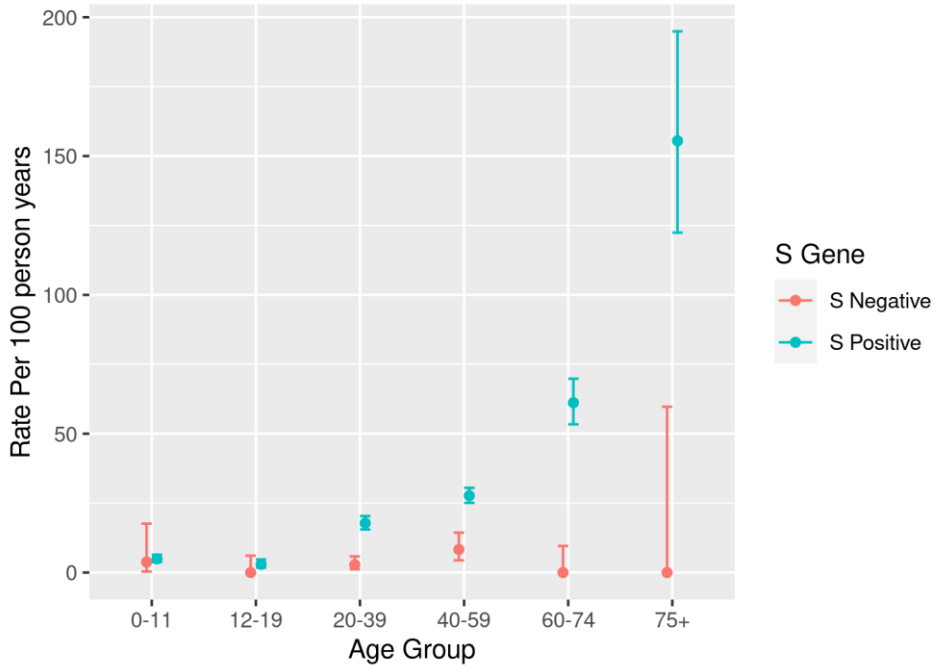


Figure S6: Cumulative incidence curves for an emergency COVID-19 admission to hospital within 14 days of a positive test by S gene status

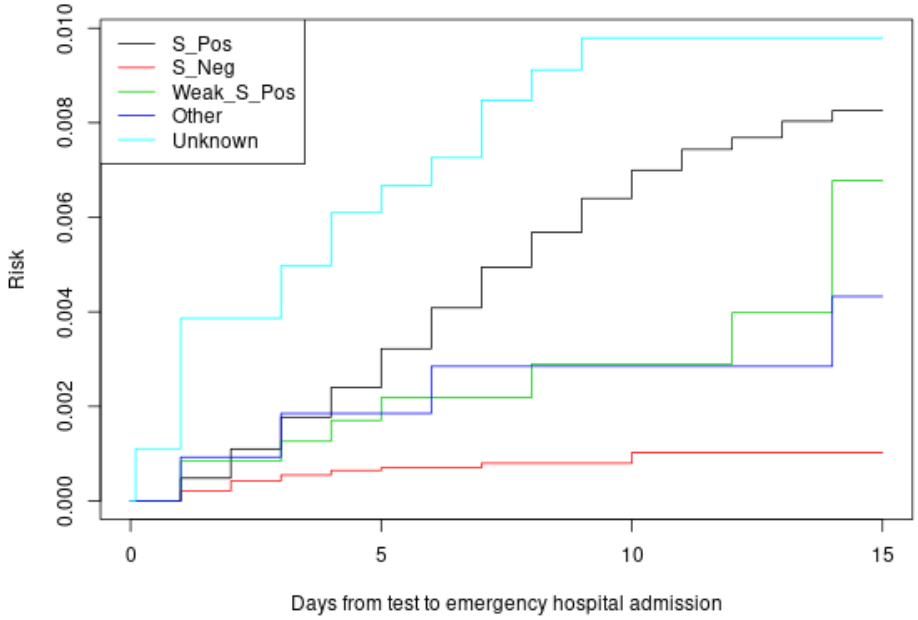


Table S7: Numbers, percentages and hazard ratios for each characteristic included in the Cox regression model

		S Positive					S Negative
Characteristic.	Levels	Total	Hosp	HR	LCL	UCL	Total
Week	week_1	17,030 (14.3%)	174 (20.3%)	1.00	-	-	10 (0.0%)
	week_2	18,902 (15.9%)	173 (20.2%)	0.98	0.79	1.21	5 (0.0%)
	week_3	18,056 (15.2%)	141 (16.5%)	0.86	0.68	1.07	8 (0.0%)
	week_4	15,587 (13.1%)	112 (13.1%)	0.83	0.65	1.05	73 (0.3%)
	week_5	17,055 (14.3%)	141 (16.5%)	0.99	0.79	1.24	436 (2.0%)
	week_6	18,181 (15.3%)	91 (10.6%)	0.67	0.52	0.87	4,450 (20.0%)
	week_7	14,289 (12.0%)	24 (2.8%)	0.43	0.28	0.67	17,223 (77.6%)
Age Group	0-11	27,282 (22.9%)	36 (4.2%)	1.00	-	-	1,244 (5.6%)
	12-19	13,906 (11.7%)	15 (1.8%)	1.14	0.62	2.11	2,140 (9.6%)
	20-39	30,410 (25.5%)	193 (22.5%)	9.12	6.32	13.18	10,801 (48.6%)
	40-59	37,625 (31.6%)	382 (44.6%)	16.72	11.53	24.25	6,501 (29.3%)
	60-74	8,695 (7.3%)	181 (21.1%)	28.67	19.22	42.75	1,302 (5.9%)
	75+	1,182 (1.0%)	49 (5.7%)	38.56	23.43	63.48	217 (1.0%)
Sex	Female	61,556 (51.7%)	429 (50.1%)	1.00	-	-	11,997 (54.0%)
	Male	57,544 (48.3%)	427 (49.9%)	1.07	0.93	1.22	10,208 (46.0%)
Deprivation	1 - High	21,995 (18.5%)	228 (26.6%)	1.00	-	-	3,811 (17.2%)
	2	23,188 (19.5%)	194 (22.7%)	0.87	0.72	1.05	3,993 (18.0%)

	3	22,537 (18.9%)	166 (19.4%)	0.80	0.65	0.98	3,862 (17.4%)
	4	24,687 (20.7%)	141 (16.5%)	0.67	0.54	0.83	4,654 (21.0%)
	5-Low	25,892 (21.7%)	124 (14.5%)	0.62	0.50	0.78	5,688 (25.6%)
	NA	801 (0.7%)	<5 (0.4%)	0.46	0.15	1.43	197 (0.9%)
Number	0	86,717 (72.8%)	364 (42.5%)	1.00	-	-	15,884 (71.5%)
Co-morbid	1	25,304 (21.2%)	272 (31.8%)	1.90	1.62	2.23	5,204 (23.4%)
Conditions	2	5,398 (4.5%)	130 (15.2%)	3.41	2.77	4.20	886 (4.0%)
	3	1,193 (1.0%)	56 (6.5%)	5.45	4.05	7.32	170 (0.8%)
	4	346 (0.3%)	22 (2.6%)	6.17	3.93	9.70	39 (0.2%)
	5+	142 (0.1%)	12 (1.4%)	7.12	3.91	12.98	22 (0.1%)
Vaccine	uv	44,091 (37.0%)	264 (30.8%)	1.00	-	-	2,944 (13.3%)
Status	v1_4+_AZ	798 (0.7%)	10 (1.2%)	0.36	0.19	0.68	80 (0.4%)
and	v2_6-9_AZ	122 (0.1%)	<5 (0.1%)	0.24	0.03	1.69	14 (0.1%)
Type for	v2_10+_AZ	32,703 (27.5%)	362 (42.3%)	0.32	0.27	0.39	3,668 (16.5%)
first 2	v3_0:1_AZ	4,596 (3.9%)	46 (5.4%)	0.21	0.15	0.30	1,584 (7.1%)
doses	v3_2+_AZ	1,717 (1.4%)	44 (5.1%)	0.39	0.27	0.56	1,460 (6.6%)
	v1_4+_Mo	352 (0.3%)	<NA>	0.00	0.00	Inf	105 (0.5%)
	v2_6-9_Mo	126 (0.1%)	<5 (0.1%)	0.43	0.06	3.08	44 (0.2%)
	v2_10+_Mo	1,649 (1.4%)	<5 (0.1%)	0.04	0.01	0.29	1,382 (6.2%)
	v1_0:3_PB	839 (0.7%)	<5 (0.4%)	0.53	0.17	1.65	84 (0.4%)
	v1_4+_PB	7,655 (6.4%)	14 (1.6%)	0.33	0.19	0.56	1,172 (5.3%)

	v2_0:1_PB	236 (0.2%)	0(0.0%)	0.00	0.00	Inf	72 (0.3%)
	v2_2-5_PB	119 (0.1%)	0(0.0%)	0.00	0.00	Inf	90 (0.4%)
	v2_6-9_PB	423 (0.4%)	0(0.0%)	0.00	0.00	Inf	176 (0.8%)
	v2_10+_PB	19,293 (16.2%)	76 (8.9%)	0.18	0.14	0.23	6,930 (31.2%)
	v3_0:1_PB	1,502 (1.3%)	7 (0.8%)	0.10	0.05	0.21	614 (2.8%)
	v3_2+_PB	2,645 (2.2%)	26 (3.0%)	0.26	0.17	0.40	1,663 (7.5%)
Previous	not_prev_pos	117,724 (98.8%)	852 (99.5%)	1.00	-	-	20,398 (91.9%)
Positive	pos_1:28	274 (0.2%)	<5 (0.2%)	0.51	0.13	2.06	0(0.0%)
Test	pos_29:90	195 (0.2%)	<5 (0.1%)	0.66	0.09	4.67	84 (0.4%)
	pos_91+	907 (0.8%)	<5 (0.1%)	0.14	0.02	1.02	1,723 (7.8%)

Total is the total number of individuals who tested positive with each type of infection (S positive or S negative) and Hospital are the numbers admitted to hospital from the community with a S positive infection. The percentages are column percentages and sum to 100 for each characteristic and so can be used to compare the distribution of the levels of the characteristic in the total positive cases and in the hospitalised cases. HR is the hazard ratio of admission to hospital and LCL/UCL and the lower and upper 95% confidence intervals. NA – corresponds to individuals who have missing information on deprivation. Hospital information is not shown for S Negative infections as the numbers are too small.