Report 50: Hospitalisation risk for Omicron cases in England

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Summary

To assess differences in the risk of hospitalisation between the Omicron variant of concern (1) and the Delta variant, we analysed data from all PCR-confirmed SARS-CoV-2 cases in England with last test specimen dates between 1st and 14th December inclusive. Variant was defined using a combination of S-gene Target Failure (SGTF) and genetic data. Case data were linked by National Health service (NHS) number to the National Immunisation Management System (NIMS) database, the NHS Emergency Care (ECDS) and Secondary Use Services (SUS) hospital episode datasets. Hospital attendance was defined as any record of attendance at a hospital by a case in the 14 days following their last positive PCR test, up to and including the day of attendance. A secondary analysis examined the subset of attendances with a length of stay of one or more days. We used stratified conditional Poisson regression to predict hospitalisation status, with demographic strata defined by age, sex, ethnicity, region, specimen date, index of multiple deprivation and in some analyses, vaccination status. Predictor variables were variant (Omicron or Delta), reinfection status and vaccination status.

Overall, we find evidence of a reduction in the risk of hospitalisation for Omicron relative to Delta infections, averaging over all cases in the study period. The extent of reduction is sensitive to the inclusion criteria used for cases and hospitalisation, being in the range 20-25% when using any attendance at hospital as the endpoint, and 40-45% when using hospitalisation lasting 1 day or longer or hospitalisations with the ECDS discharge field recorded as "admitted" as the endpoint (Table 1). These reductions must be balanced against the larger risk of infection with Omicron, due to the reduction in protection provided by both vaccination and natural infection. A previous infection reduces the risk of any hospitalisation by approximately 50% (Table 2) and the risk of a hospital stay of 1+ days by 61% (95%CI:55-65%) (before adjustments for under ascertainment of reinfections).

High historical infection attack rates and observed reinfection rates with Omicron mean it is necessary to correct hazard ratio estimates to accurately quantify intrinsic differences in severity between Omicron and Delta and to assess the protection afforded by past infection. The resulting adjustments are moderate (typically less than an increase of 0.2 in the hazard ratio for Omicron vs Delta and a reduction of approximately 0.1 in the hazard ratio for reinfections vs primary infections) but significant for evaluating severity overall. Using a hospital stay of 1+ days as the endpoint, the adjusted estimate of the relative risk of reinfections versus primary cases is 0.31, a 69% reduction in hospitalisation risk (Table 2).

Stratifying hospitalisation risk by vaccination state reveals a more complex overall picture, albeit consistent with the unstratified analysis. This showed an apparent difference between those who received AstraZenca (AZ) vaccine versus Pfizer or Moderna (PF/MD) for their primary series (doses 1 and 2). Hazard ratios for hospital attendance with Omicron for PF/MD are similar to those seen for Delta in those vaccination categories, while Omicron hazard ratios are generally lower than for Delta for the AZ vaccination categories. Given the limited samples sizes to date, we caution about over-interpreting these trends, but they are compatible with previous findings that while protection afforded against mild infection from AZ was substantially reduced with the emergency of Delta, protection against more severe outcomes was sustained (2,3). We emphasise that these are estimates which condition upon infection; net vaccine effectiveness against hospital attendance may not vary between the vaccines, given that PF/MD maintain higher effectiveness against symptomatic infection with Omicron than AZ (4).

Our estimates will assist in refining mathematical models of potential healthcare demand associated with the unfolding European Omicron wave. The hazard ratios provided in Table 3 can be translated into estimates of vaccine effectiveness (VE) against hospitalisation, given estimates of VE against infection (4). In broad terms, our estimates suggest that individuals who have received at least 2 vaccine doses remain substantially protected against hospitalisation, even if protection against infection has been largely lost against the Omicron variant (4,5).

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1. Methods

1. 1 Data

We analysed UK Health Security Agency (UKHSA) and National Health Service (NHS) data from all PCR-confirmed SARS-CoV-2 cases in England where the variant causing the infection could be identified. We combined genetic and S-gene target failure (SGTF) data to distinguish Delta and Omicron infections, given the 69-70 Spike deletion is present in Omicron but not in Delta. SGTF was only scored for PCR tests with Ct values under 30 for other targets, to minimise the risk of false negatives.

The UKHSA England COVID-19 line-list was linked by NHS number to the National Immunisation Management System (NIMS) database, the SGTF results database, the NHS Emergency Care (ECDS) and Secondary Use Services (SUS) hospital episode datasets and a separate list of known reinfections. We excluded cases which were not able to be linked to NIMS (due to an invalid NHS number), and where age, region, or variant type were not available. Cases associated with documented recent overseas travel were also excluded. Specimen date was taken to be the *last* reported specimen date for each unique NHS number across all linked datasets. Reinfections were identified as two positive test results for the same individual 90 or more days apart. This analysis made use of datasets available on 21st December 2021 and included cases having a last PCR test date between 1st and 14th December 2021 inclusive. Later specimen dates were not considered to allow sufficient follow-up time. There were a very low number of recorded hospitalisations for later cases at the time of analysis, a result of lags in routine hospital data flows.

For our primary analysis, we considered only cases with a positive test recorded through "Pillar 2" of the England COVID-19 surveillance system, which handles routine community testing. We also conduct two sub-analyses making use of (a) only symptomatic pillar 2 test, and (b) all positive tests in both Pillar 1 (hospital-based testing) and Pillar 2.

Hospitalisation was defined as a recorded attendance at hospital (including Accident and Emergency departments) occurring up to 14 days after a positive COVID-19 PCR test. Cases tested after the day of admission were not included, to prevent possible confounding effects from nosocomial transmission or hospitalisations being included where COVID status was unrelated to the reason for hospitalisation. For our main analysis, we include all hospitalisations thus defined, but in secondary analyses we consider hospitalisations where the length of stay in hospital was at least 1 day, and hospitalisations where the ECDS discharge field was recorded as "Admitted" (more closely matching UKHSA analyses).

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

1.2 Statistical analysis

Hospitalisation risk for COVID-19 increases sharply with age, and varies by sex, ethnicity and other socioeconomic factors. The demographic distributions of Omicron and Delta cases across the English population differed markedly across the study period, and Omicron cases were growing rapidly over time (giving less follow-up time for Omicron cases on average), while Delta case incidence was relatively flat. Hence simple division of numbers hospitalised by total cases for each variant gives a misleading impression of relative severity. We used conditional Poisson regression (6) to predict hospitalisation status. This shares many of the same benefits and assumptions of proportional hazards regression, in implicitly adjusting for different periods of follow-up (if specimen date is used in the stratification) but in also assuming that the rate of progression from testing to hospital attendance does not vary by variant.

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We present two analyses, one examining overall risk of hospitalisation and one stratifying by vaccination status. The first estimates the hazard ratios for hospitalisation associated with variant type and reinfection status, with strata defined by the interaction of vaccination status, 10-year age-band, sex, ethnicity, NHS region and specimen date. Here the estimates represent the overall risk of hospitalisation associated with an Omicron case compared with a Delta case, averaged over all strata.

In the second analysis, we estimate the hazard ratio for hospitalisation for Omicron vs Delta cases separately for each category of vaccination status examined, with strata defined by the interaction of 10-year age-band, sex, ethnicity, NHS region and specimen date. Here the estimates give, for each vaccination category and variant, the risk of hospitalisation with Omicron relative to that estimated for unvaccinated Delta cases.

Since reinfection status proved to be a major predictor of hospitalisation risk, we also considered methods for correcting hazard ratio estimates in unvaccinated individuals for under ascertainment of past infection status. If θ_i is the proportion of variant i cases which are observed to be reinfections, ρ is the proportion of reinfections detected, ϕ is the true hazard ratio of a previously uninfected Omicron case being hospitalised compared with a Delta case and γ is the true relative risk of a reinfection being hospitalised compared with a primary infections, then the naive estimate of the hazard ratio of an Omicron case (excluding known reinfections, but including unknown reinfections) being hospitalised relative to a Delta cases is

$$HR_{Omicron:Delta} = \frac{\phi(1-(1-\gamma)(1-\rho)\theta_{Omicron}/\rho)}{(1-(1-\gamma)(1-\rho)\theta_{Delta}/\rho)} \approx \phi(1-(1-\gamma)(1-\rho)\theta_{Omicron}/\rho)$$

where the approximation is appropriate when the proportion of Delta cases which are reinfections is small.

Similarly, the naive estimate of the hazard ratio of a detected Omicron reinfection being hospitalised compared with an Omicron case not known to be a reinfection being hospitalised is

$$HR_{reinfection} = \frac{\gamma\phi}{\phi(1-(1-\gamma)(1-\rho)\theta_{Omicron}/\rho)}$$

Thus

$$\gamma\phi \approx HR_{reinfection}HR_{Omicron:Delta}$$

And substituting, it can be shown that

$$\phi \approx HR_{Omicron:Delta}\frac{\left[1-HR_{reinfection}(1-\rho)\theta_{Omicron}/\rho\right]}{1-(1-\rho)\theta_{Omicron}/\rho}$$

and then

$$\gamma \approx \frac{HR_{reinfection}HR_{Omicron:Delta}}{\phi}$$

We apply this assuming $\rho = 0.33$ to give an indication of the scale of potential biases involved, on the basis that pillar 2 has captured approximately 1/3 or less of historical infections (7,8), meaning that 2/3 of past infections will be undetected in new cases. We can then estimate the true proportion of reinfections among hospitalised cases by scaling the observed proportion by $\gamma/(\rho\ HR_{reinfection})$.

All analyses were conducted in R version 4.1.0 using the package gnm.

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1.3 Ethical approval

Surveillance of COVID-19 testing and vaccination is undertaken under Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002 to collect confidential patient information (https://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made) under Sections 3(i) (a) to (c), 3(i)(d) (i) and (ii) and 3(3). Data were shared with the investigators as part of the UK's emergency response to the COVID-19 pandemic, via the SPI-M subcommittee of the UK Scientific Advisory Group for Emergencies (SAGE). Ethics permission was sought for analyses of these data via Imperial College London's standard ethical review processes and the study was approved by the College's Research Governance and Integrity Team (ICREC reference: 21IC6945).

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2. Results

2.1 Data trends

Table 1 shows Delta and Omicron cases and hospitalisations for cases with specimen dates in the period 1-14 December 2021. We note that total of 8 of 200 and 87 of 3091 Omicron and Delta hospital attendance records, respectively, were missing a completed hospital departure date.

Table 1. Delta and Omicron cases and hospitalisations for cases with specimen dates in the period 1-14 December 2021. Results are shown for all cases, Pillar 2 cases only and Pillar 2 symptomatic cases only. For all Pillar 2 cases, we also show hospitalisations involving at least 1 night's stay. Numbers between 1 and 5 shown as ≤5.

	All cases (pillars 1 and 2)				Pillar 2 cases						Pillar 2 symptomatic cases			
Last PCR test specimen date (December 2021)	Delta cases	Omicron Cases	Delta hospital-isations	Omicron hospital-isations	Delta cases	Omicron Cases	Delta hospital-isations	Omicron hospital-isations	Delta hospital-isations (>0 days)	Omicron hospital-isations (>0 days)	Delta cases	Omicron Cases	Delta hospital-isations	Omicron hospital-isations
1	25098	164	586	≤5	24615	156	465	≤5	122	0	10548	76	174	≤5
2	23212	226	493	≤5	22783	208	368	≤5	109	0	9831	110	125	≤5
3	21111	252	449	7	20704	241	313	≤5	78	0	8635	122	99	≤5
4	17235	303	372	≤5	16924	291	256	0	73	0	7258	144	86	0
5	16164	434	337	20	15868	418	214	12	52	≤5	6650	205	65	≤5
6	20745	977	397	14	20288	927	291	≤5	64	≤5	8769	453	89	≤5
7	21058	1916	395	24	20609	1869	265	16	66	≤5	8588	848	79	8
8	20551	2956	353	25	20133	2886	223	18	65	≤5	8398	1243	66	8
9	21639	4047	316	29	21302	3991	205	15	43	≤5	9075	1725	64	6
10	21869	5214	255	33	21567	5153	156	19	43	≤5	8921	2294	51	9
11	15581	4807	177	30	15392	4767	114	21	28	≤5	6463	2116	32	7
12	13746	6550	123	40	13639	6519	81	26	20	≤5	5667	3003	23	13
13	17489	11933	109	26	17391	11908	88	25	22	7	7573	5801	28	14
14	13819	15804	52	36	13805	15802	52	36	12	6	6240	7579	22	7

Note that differences in the distribution of Omicron by age and other demographic variables mean that simple ratios of hospitalisations to cases gives a misleading impression of hospitalisation risk. The mean ages of Omicron and Delta cases attending hospital were 30.8 (95%CI:28.6-33.0) years and 38.3 (95%CI:37.5-39.1) years, respectively. Mean lengths of hospital stay (averaging over days measured as integers) for Delta and Omicron cases in our primary analysis were 0.32 (95%Ci: 0.29-0.34) and 0.22 (95%CI: 0.15-0.28) days, respectively – though Omicron cases (given rapidly rising incidence over the study period) on average had less follow-up time.

2.1 Hospitalisation hazard ratios for Omicron vs Delta across all cases

Table 2 shows the hazard ratio (HR) for hospitalisation for Omicron vs Delta cases and for reinfections vs primary infections computed over all vaccination categories, for five data subsets. Estimates, uncorrected for under ascertainment of reinfection status, show that Omicron cases have a 15-20% reduced risk of any hospitalisation and a 41% (95% CI: 37%-45%) reduced risk of a hospitalisation resulting in a stay of 1 or more nights. Reinfection is associated with approximately a 50-60% reduction in hospitalisation risk compared with primary infections. However, assuming only 33% of true reinfections are identified as such, corrected estimates suggest lower reduction in Omicron hospitalisation compared with Delta (ranging from approximately 0-30% depending on the data subset), and a higher reduction in the risk of hospitalisation associated with reinfection (of approximately 55-70%).

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Table 2. Estimates of the hazard ratio (HR) for hospitalisation for Omicron vs Delta cases and for reinfections vs primary infections. The percentage of Delta and Omicron cases and hospitalisations that were reinfections is also shown. Uncorrected estimates are generated via conditional Poisson regression. Corrected estimates (only the mean estimate is shown) adjust for under ascertainment of reinfection, assuming 1/3 of all infections are detected through community surveillance. Results for five data subsets are shown. 95% confidence intervals are shown in parentheses for the uncorrected estimates.

Data subset	Corrected or uncorrected for ascertainment of reinfection	% Reinfection (Delta cases)	% Reinfection (Omicron cases)	% Reinfection (Delta hosp)	% Reinfection (Omicron hosp)	Omicron: Delta HR	Reinfection HR
All Pillar 2 cases	Uncorrected	2.5%	13.1%	1.2%	7.5%	0.75 (0.7-0.81)	0.5 (0.45-0.56)
	Corrected	7.7%	39.7%	3.2%	19.3%	0.89	0.43
All Pillar 2 cases, >0 night hospital stay	Uncorrected	2.5%	13.1%	1.1%	5.0%	0.59 (0.55-0.63)	0.39 (0.35-0.45)
	Corrected	7.7%	39.7%	2.8%	12.4%	0.72	0.32
All symptomatic Pillar 2 cases	Uncorrected	1.8%	11.8%	1.6%	9.6%	0.77 (0.7-0.83)	0.52 (0.45-0.61)
	Corrected	5.4%	35.8%	3.0%	18.5%	0.88	0.45
All Pillar 1 and Pillar 2 cases	Uncorrected	2.5%	13.0%	0.9%	5.4%	0.8 (0.75-0.86)	0.39 (0.35-0.44)
	Corrected	7.7%	39.5%	2.2%	13.5%	0.98	0.32
All Pillar 1 and Pillar 2 cases, ECDS "Admitted"	Uncorrected	2.5%	13.0%	0.6%	7.3%	0.55 (0.51-0.59)	0.49 (0.44-0.54)
	Corrected	7.7%	39.5%	1.5%	18.6%	0.65	0.41

2.2 Hospitalisation hazard ratios stratified by vaccination status

The estimates above give an indication of the overall changes in the risk of hospitalisation associated with Omicron compared with Delta averaged across all COVID-19 cases in England in the study period. However, different strata of the English population have widely varying prior immunity from both vaccination and natural infection. We therefore also provide estimates stratified by vaccination status, for our main analysis data subset of all Pillar 2 cases and any hospitalisation (Table 3). Such stratification is less appropriate when analysing Pillar 1 and 2 combined, as Pillar 1 is biased towards hospitalised cases, complicating the interpretation of the resulting vaccination status-specific hazard ratio estimates. Restricting the analysis to only hospitalisations of one or more night also leads to very small numbers in several vaccination strata but will be possible as more data accumulate.

It is important to interpret the estimates in Table 3 appropriately. The hazard ratios for each vaccination category represent the relative risk that a primary infection in that category will be hospitalised, relative to the reference group, namely primary Delta infections in unvaccinated individuals. The hazard ratio for reinfection is the relative risk that a reinfected person will be hospitalised, relative to a primary infection, and applies to both variants and all vaccination categories. With more data it may be possible to estimate the reinfection risk separately for each variant and all vaccination categories.

The estimates in Table 3 suggest unvaccinated cases have somewhat lower risk of hospitalisation with Omicron versus Delta, though the magnitude of this reduction drops when under ascertainment of reinfections is accounted for. Cases vaccinated with Pfizer or Moderna for doses 1 and 2 have a similar or higher risk of hospitalisation with Omicron compared with Delta, while cases vaccinated with AstraZeneca for their primary series tend to have a lower risk of hospitalisation relative to Delta.

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Table 3. Estimates of the hazard ratio (HR) for hospital attendance for Omicron vs Delta cases and for reinfections vs primary infections, stratified by vaccination status. The percentage of cases and hospitalisations that were reinfections is also shown. Uncorrected estimates are generated via conditional Poisson regression. Corrected estimates (only the mean estimates for Omicron are shown) adjust for under ascertainment of reinfection, assuming 1/3 of all infections are detected through community surveillance. 95% confidence intervals are shown in parentheses for the uncorrected estimates. D1, D2 and D3 categories are post-dose 1, 2 and 3, respectively. D3 categories all received a mRNA booster and are distinguished by the dose 1/2 vaccine used. Numbers in category names (14, 21) refer to days since last dose.

	Variant	Vaccination or reinfection category	Cases	Hospital-isations	% Reinfections (cases)	% Reinfections (hosp)	HR relative to primary Delta infection in unvaccinated	p-value
Uncorrected	All	Not reinfection	306194	3238	-	-	-	
	All	Reinfection	13962	53	4.6%	1.6%	0.53 (0.47-0.61)	<1e-6
	Delta	Unvaccinated	109331	1466	1.9%	0.8%	1 (1-1)	<1e-6
	Delta	AZ:D1:<21	6	0	0.0%	-	-	-
	Delta	AZ:D1:21+	1676	38	3.9%	5.3%	0.69 (0.58-0.81)	<1e-5
	Delta	AZ:D2:<14	144	≤5	4.2%	100.0%	0.29 (0.12-0.66)	0.003
	Delta	AZ:D2:14+	67717	857	2.2%	1.3%	0.38 (0.36-0.4)	<1e-6
	Delta	AZ:D3:<14	13259	110	1.7%	0.9%	0.24 (0.22-0.27)	<1e-6
	Delta	AZ:D3:14+	4231	70	4.1%	1.4%	0.36 (0.31-0.41)	<1e-6
	Delta	PF/MD:D1:<21	2602	24	2.6%	0.0%	0.76 (0.63-0.92)	0.005
	Delta	PF/MD:D1:21+	15558	109	2.4%	0.0%	0.54 (0.49-0.59)	<1e-6
	Delta	PF/MD:D2:<14	1060	≤5	5.6%	0.0%	0.1 (0.05-0.18)	<1e-6
	Delta	PF/MD:D2:14+	41477	293	4.6%	2.7%	0.25 (0.23-0.27)	<1e-6
	Delta	PF/MD:D3:<14	2268	25	2.9%	0.0%	0.32 (0.27-0.39)	<1e-6
	Delta	PF/MD:D3:14+	5691	96	3.8%	2.1%	0.3 (0.26-0.34)	<1e-6
	Omicron	Unvaccinated	9585	56	18.6%	8.9%	0.59 (0.5-0.69)	<1e-6
	Omicron	AZ:D1:<21	0	0	-	-	-	-
	Omicron	AZ:D1:21+	257	≤5	23.3%	0.0%	0.29 (0.11-0.77)	0.012
	Omicron	AZ:D2:<14	29	0	3.4%	-	-	0.905
	Omicron	AZ:D2:14+	11440	46	14.0%	4.3%	0.31 (0.27-0.36)	<1e-6
	Omicron	AZ:D3:<14	2877	≤5	9.0%	0.0%	0.07 (0.04-0.12)	<1e-6
	Omicron	AZ:D3:14+	2384	8	7.0%	0.0%	0.2 (0.14-0.28)	<1e-6
	Omicron	PF/MD:D1:<21	293	0	14.3%	-	-	0.693
	Omicron	PF/MD:D1:21+	2526	10	12.9%	20.0%	0.57 (0.42-0.78)	<1e-3
	Omicron	PF/MD:D2:<14	249	≤5	20.5%	0.0%	0.44 (0.19-1.02)	0.057
	Omicron	PF/MD:D2:14+	22249	60	11.9%	6.7%	0.22 (0.19-0.26)	<1e-6
	Omicron	PF/MD:D3:<14	780	≤5	9.7%	25.0%	0.55 (0.36-0.85)	0.007
	Omicron	PF/MD:D3:14+	2467	11	8.0%	9.1%	0.34 (0.25-0.45)	<1e-6
Corrected	All	Not reinfection	277847	3164	-	-	-	-
	All	Reinfection	42309	127	15.2%	3.9%	0.42	-
	Omicron	Unvaccinated	9585	56	56.4%	21.1%	0.76	-
	Omicron	AZ:D1:<21	0	0	-	-	-	-
	Omicron	AZ:D1:21+	257	≤5	70.7%	0.0%	0.42	-
	Omicron	AZ:D2:<14	29	0	10.4%	-	-	-
	Omicron	AZ:D2:14+	11440	46	42.5%	11.1%	0.37	-
	Omicron	AZ:D3:<14	2877	≤5	27.3%	0.0%	0.07	-
	Omicron	AZ:D3:14+	2384	8	21.1%	0.0%	0.21	-
	Omicron	PF/MD:D1:<21	293	0	43.4%	-	-	-
	Omicron	PF/MD:D1:21+	2526	10	39.1%	52.0%	0.66	-
	Omicron	PF/MD:D2:<14	249	≤5	62.1%	0.0%	0.59	-
	Omicron	PF/MD:D2:14+	22249	60	36.1%	17.6%	0.26	-
	Omicron	PF/MD:D3:<14	780	≤5	29.5%	67.9%	0.61	-
	Omicron	PF/MD:D3:14+	2467	11	24.3%	25.3%	0.37	-

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3. Discussion

From an individual perspective, the estimates presented in this paper quantify the risk of hospitalisation for someone testing positive for Omicron relative to someone testing positive for Delta. The overall hazard ratios presented in Table 2 apply specifically to England, given they average over all vaccination states. The stratified estimates in Table 3 are more generalisable, notwithstanding country-to-country variation in community surveillance, but should be interpreted cautiously at the current time given the small numbers of hospitalisation in many categories.

Overall, we find evidence of a reduction in the risk of hospitalisation for Omicron infections relative to Delta infections when averaging over all cases. The extent of reduction is sensitive to the inclusion criteria used for cases and hospitalisation, being in the range 20-25% when using any attendance at hospital as the endpoint, and 40-45% when using hospitalisation lasting 1 day or longer or hospitalisations with the ECDS discharge field recorded as "admitted" as the endpoint (Table 2). However, these reductions should be balanced against the much larger risk of infection with Omicron, due to reduction in protection acquired from both vaccination and natural infection.

This analysis is an initial step towards assessing the clinical severity and risk posed by the Omicron variant. Given the limited period of follow-up, the primary outcome used in our study was attendance at a hospital, the lowest level of severity associated with tertiary care. Secondary analyses examining both Pillar 1 and 2 cases or just symptomatic Pillar 2 cases gave similar results to our primary analysis (Table 1). Our secondary analysis of hospital attendance associated with 1+ days spent in hospital suggests a larger reduction (28% versus 11%, using estimates corrected for reinfection under ascertainment) in the severity of Omicron compared with Delta than our primary analysis, as does the additional secondary analysis only analysing hospitalisations where the ECDS discharge flag was recorded as "admitted". Moderately reduced severity is also supported by the observation that the mean lengths of hospital stay (averaging over days measured as integer) for Delta and Omicron cases in our primary analysis were 0.32 (95%Ci: 0.29-0.34) and 0.22 (95%CI: 0.15-0.28) days, respectively – though it should be noted that Omicron cases (given rapidly rising incidence over the study period) on average had less follow-up time.

As more data accumulate, with longer periods of follow-up, assessment of more severe outcomes will become feasible. Currently, vaccination-status stratified hazard ratio estimates for the two more stringent endpoints listed in Table 2 remain very sensitive to small numbers of hospitalisation, particularly in the unvaccinated Omicron group. It is quite possible that larger reductions in hospitalisation risk for Omicron vs Delta may be estimated for the endpoints of ICU admission and death, given that remaining immune protection against more severe outcomes of infection are expected to be much higher than those against milder endpoints.

Stratifying hospitalisation risk by vaccination state reveals a more complex overall picture, albeit consistent with the unstratified analysis. Most intriguing is an apparent difference between those who received AstraZenca (AZ) vaccine versus Pfizer or Moderna (PF/MD) for their primary series (doses 1 and 2). Hazard ratios for hospital attendance with Omicron for those who received PF/MD as their primary vaccination schedule are similar to those seen for Delta in those vaccination categories, while Omicron hazard ratios are generally lower than for Delta for those who received AZ as their primary vaccination. Given the limited samples sizes to date, we caution about over-interpreting these trends, but they are compatible with previous findings that while protection afforded against mild infection from AZ was substantially reduced with the emergence of Delta, protection against more severe outcomes was sustained (2,3). We would also emphasise that these are estimates which condition upon infection; overall vaccine effectiveness against hospital attendance may not vary between the vaccines, given that PF/MD maintain higher effectiveness against symptomatic infection with Omicron than AZ (4).

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It is essential to place the severity of Omicron in the context of reinfection risk in countries, like England and South Africa, where a large proportion of the population may have already been infected. A total of 9.8 million people had tested positive for SARS-CoV-2 in England by 21st December 2021, equating to 17.3% of the population. Across the whole epidemic, it is likely that fewer than a third of infected individuals were tested through the country's "Pillar 2" community surveillance system (7,8). Hence overall cumulative infection attack rates may exceed half the population at this stage in the epidemic, with approximately half those infections occurring in the last 6 months. The proportion of unvaccinated individuals infected is likely to be substantially higher. In that context, our finding that a previous infection reduces the risk of any hospitalisation by approximately 50% (Table 1) and the risk of a hospital stay of 1+ days by 61% (95%CI:55-65%) (before adjustments for under ascertainment of reinfections) is significant. One caveat to this is that the highest infection attack rates have been in young people during the Delta wave, at a time where infection rates in the elderly – those at most risk of severe outcomes from SARS-CoV-2 infection – had been substantially reduced by vaccination.

High historical attack rates (and observed reinfection rates with Omicron) means it is necessary to correct hazard ratio to accurately quantify intrinsic differences in severity between Omicron and Delta, and to assess the protection afforded by past infection. We developed a method for making such corrections and hence derive adjusted estimates which account for reinfection under ascertainment. The resulting adjustments are moderate (typically less than an increase of 0.2 in the HR for Omicron vs Delta and a reduction of approximately 0.1 in the HR for reinfections vs primary infections) but significant for evaluating severity overall. Using a hospital stay of 1+ days as the endpoint, the adjusted estimate of the relative risk of reinfections versus primary cases is 0.31, a 69% reduction in hospitalisation risk (Table 2).

In the post-vaccination era, SARS-CoV-2 case numbers can be high while hospitalisations are low compared to the pre-vaccine era, and a substantial proportion of hospitalisations attributed to COVID-19 may be incidental; all persons admitted to UK hospitals are currently routinely tested for SARS-Cov-2 infection and testing positive may be unrelated to the clinical reason for admission. We mitigated this potential issue by restricting our analysis to individuals with last specimen dates on or before the day of hospital attendance, and for our primary analysis to cases who had a positive test via the UK "Pillar 2" community surveillance programme, which is distinct from the "Pillar 1" hospital testing system. Furthermore, our finding that variables associated with protection from both SARS-CoV-2 infection and severe disease (such as vaccination and reinfection status) are highly predictive of hospitalisation risk suggests that most of the hospitalisation events recorded were in some way infection-related; no association with vaccination or reinfection status would otherwise be expected, particularly given we stratified by demographic variables predictive of COVID-19 hospitalisation risk.

A recent paper analysing the South African Omicron epidemic has estimated an odds-ratio for hospitalisation for Omicron vs Delta infection of approximately 0.2 (9). However, that study compared consecutive waves of the epidemic, spaced 5 months apart, rather than contemporaneous cases of Delta and Omicron infection, as in our analysis. It also did not control for vaccination status or seroprevalence. Given approximately 70% of the unvaccinated Gauteng population were seropositive prior to the Omicron wave (rising to over 90% of the vaccinated population, with vaccine coverage and seropositivity being highest in the elderly at most risk of hospitalisation) (10) , an odds-ratio of 0.2 is not incompatible with the hazard ratios for protection from prior infection and vaccination in Tables 2 and 3 (notably those adjusting for reinfection under ascertainment), especially given the predominant use of the AZ and Johnson & Johnson vaccine in that country.

The estimates provided in this paper will assist in refining mathematical models of potential healthcare demand associated with the unfolding European Omicron wave. The hazard ratios provided in Table 3 can be translated into estimates of vaccine effectiveness (VE) against hospitalisation, given estimates of VE

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against infection (4). In broad terms, our estimates suggest that individuals who have received at least 2 doses of either AZ or PF/MD vaccine remain substantially protected against hospitalisation, even if protection against infection has been largely lost against the Omicron variant (4,5).

There are several limitations of our analysis. The conditional Poisson regression models we have used implicitly assume that the timescale of progression to more severe infection outcomes does not vary by variant. We are analysing data in real-time, with shorter follow-up periods than is usual for studies of hospitalisation outcomes of disease; while our analysis controls for right-censoring, our estimates may be biased by any differences in rapidity of reporting or in admission practices between the largely inner-city hospitals responding to Omicron cases in the study period and the more varied range of hospitals responding to Delta cases. We did not have access to or make use of data on reported reasons for hospital attendance, so some proportion of the hospital events recorded may be unrelated to SARS-CoV-2 infection (though see earlier comments above). Over the study period, the demographic distribution of Omicron and Delta cases still differed substantially in England, with Omicron more commonly affecting younger adults of non-White ethnicities living in major cities than Delta. While the stratified regression (akin to a case control study) we adopted aims to control for such differences, residual bias may be inevitable. Last, there was limited power to examine more severe outcomes than hospital attendance; this analysis will be updated to include a wider range of outcomes as data accumulate.

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