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COVID-19 vaccine effectiveness against hospitalisation and death of people in clinical risk groups during the Delta variant period: English primary care network cohort study

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SUMMARY

Background: COVID-19 vaccines have been shown to be highly effective against hospitalisation and death following COVID-19 infection. COVID-19 vaccine effectiveness estimates against severe endpoints among individuals with clinical conditions that place them at increased risk of critical disease are limited.

Methods: We used English primary care medical record data from the Oxford-Royal College of General Practitioners Research and Surveillance Centre sentinel network (N > 18 million). Data were linked to the National Immunisation Management Service database, Second Generation Surveillance System for virology test data, Hospital Episode Statistics, and death registry data. We estimated adjusted vaccine effectiveness (aVE) against COVID-19 infection followed by hospitalisation and death among individuals in specific clinical risk groups using a cohort design during the delta-dominant period. We also report mortality statistics and results from our antibody surveillance in this population.

Findings: aVE against severe endpoints was high, 14–69d following a third dose aVE was 96.4% (95.1%–97.4%) and 97.9% (97.2%–98.4%) for clinically vulnerable people given a Vaxzevria and Comirnaty primary course respectively. Lower aVE was observed in the immunosuppressed group: 88.6% (79.1%–93.8%) and 91.9% (85.9%–95.4%) for Vaxzevria and Comirnaty respectively. Antibody levels were significantly lower among the immunosuppressed group than those not in this risk group across all vaccination types and doses. The standardised case fatality rate within 28 days of a positive test was 3.9/1000 in people not in risk groups, compared to 12.8/1000 in clinical risk groups. Waning aVE with time since 2nd dose was also demonstrated, for example, Comirnaty aVE against hospitalisation reduced from 96.0% (95.1–96.7%) 14–69days post-dose 2–82.9% (81.4–84.2%) 182days+ post-dose 2.

Interpretation: In all clinical risk groups high levels of vaccine effectiveness against severe endpoints were seen. Reduced vaccine effectiveness was noted among the immunosuppressed group.

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Introduction

While the effectiveness of COVID-19 vaccines has been evaluated extensively, data on how clinical risk factors impact on vaccine effectiveness, in particular effectiveness against severe disease, is limited. Understanding differences in vaccine effectiveness between such groups is important for supporting decision makers to strategise around vaccine and antiviral prioritisation.

The Delta variant of SARS-CoV-2 (B.1.617.2) began to spread in the United Kingdom during April 2021.[1] At that time, the Alpha variant was dominant, but case numbers were relatively low. May 2021 was a period of relatively low SARS-CoV-2 incidence in the UK, but dominance shifted from the Alpha to the Delta variant, and over June and July case numbers rose. Relatively high incidence of Delta continued into the beginning of December 2021, until it was replaced by the Omicron variant, by the end of the month the number of Delta infections had decreased considerably.[2]

Roll out of COVID-19 vaccines was ongoing as Delta emerged in the UK. By 18 June 2021, all adults in England age 18+ had been invited to book their first vaccination dose, while most elderly and clinically vulnerable patients were fully vaccinated before Delta case numbers rose considerably.[3] COVID-19 vaccines were effective against Alpha-variant symptomatic infection, including among most clinical risk groups.[4,5] However, it soon became evident that vaccine effectiveness against symptomatic infection was lower against the Delta-variant and that there were indications of waning as time since vaccination progressed.[6–8] Third primary doses for immunosuppressed patients and booster doses for those age 50+ or clinically vulnerable and fully vaccinated were both introduced during September 2021.[9,10]

While vaccination was found to be less effective against symptomatic infection as the dominant variant changed from Alpha to Delta, vaccine effectiveness against severe outcomes, such as hospitalisation and death, remained high.[11] However, effectiveness and waning may differ by age and clinical risk status.[8] Advanced age is associated with immunosenescence and inflammaging that impair vaccine response.[12] Suppressed immunity resulting from health conditions or their therapies, such as active cancers, organ/stem cell transplants, primary immunodeficiencies and immune-mediated inflammatory disease, have been found to lead to reduced vaccine immune responses.[13] Kidney disease, liver disease and diabetes are associated with immune dysfunction.[14–16] Clinical risk groups are defined for those who are considered at greater risk of severe COVID-19 disease.[17–19] While vaccine response should not be impaired by many clinical conditions forming these risk groups, they may be associated with advanced age and poor health, in addition to living in congregate settings. These factors, together with differences in underlying risk of hospitalisation, may impact vaccine effectiveness in clinical risk groups.

In this study we use computerised medical record (CMR) data from a cohort of general practice patients linked to Hospital Episode Statistics (HES) and death registry data to estimate vaccine effectiveness against severe COVID-19 outcomes among patients belonging to specific clinical risk groups. We focus on the delta-variant dominant period, our study period covers 17th May to 6th December 2021.

Methods

We conducted cohort vaccine effectiveness (VE) analyses. Our population of interest were people in clinical risk groups, including chronic heart disease (CHD), diabetes, chronic kidney disease (CKD), learning disabilities, chronic neurological disease (including stroke), asplenia, morbid obesity, chronic liver disease, chronic respiratory disease and immunosuppression, following Green Book definitions,[18] as coded by PRIMIS[20] between Sept 2020 and 2021. Our outcomes were hospitalisation with a > = 2-night stay or death following COVID-19.

Data sources

We used pseudonymised CMR data collected by the Oxford-Royal College of General Practitioners Research and Surveillance Centre (RSC) to define a cohort comprising the registered patients from 1768 English general practices (N = 18,787,562), approximately one-third of the English population. These practices used the Systematised Nomenclature of Medicine Clinical Terms (SNOMED CT) to record key data. Data were held in Oxford-RCGP Clinical Informatics Digital Hub (ORCHID), a trusted research environment (TRE).[21]

National COVID-19 testing results through community testing, hospital laboratories and public health laboratories are posted electronically into the general practice CMR. For a subset of 317 *sentinel surveillance* practices, swabs were collected from individuals presenting with respiratory infection or flu- or COVID-like symptoms and sent to UKHSA for PCR testing for SARS-CoV-2, and other respiratory viruses. The cohort was linked to the Second Generation Surveillance System (SGSS) database as a secondary source of positive COVID-19 test results.

Vaccination is recorded in general practice CMRs, but the cohort was additionally linked to the National Immunisation Management Service (NIMS) database, a national individual-level COVID-19 vaccination registry, to maximise capture of COVID-19 vaccination events and details.[22]

Death is recorded in CMRs and additionally linked through ONS mortality data, while hospitalisation was identified through linkage to Hospital Episode Statistics (HES).

A subset of 271 practices collected sera from patients presenting at their GP for a routine blood test as part of SARS-CoV-2 serological surveillance. Samples were tested at UKHSA Porton using two assays from Roche diagnostics (Basel, Switzerland): the Elecsys Anti-SARS-CoV-2 spike (S) and nucleocapsid (N) assays.[23] The S assay is specific to the SARS-CoV-2 spike receptor binding domain (RBD). The S assay tests for antibodies following vaccination or infection and N assay for antibodies due to infection alone.

VE outcomes and exposures

Our outcomes were (i) hospital admission resulting in a stay of 2 nights or more, occurring up to 2 days before or up to 14 days after a new positive COVID-19 test and (ii) death within 0–28 days of a new positive COVID-19 test. Concurrent hospital admissions were aggregated. A new positive COVID-19 test was defined as the first reported positive test within any series of tests, which was at least 90 days after any prior new positive test. Tests may be PCR tests through sentinel surveillance or the national testing process, or via self-administered and self-reported lateral flow tests. Symptom onset dates were not available, so test dates were used as event dates.

The exposure of interest was full COVID-19 vaccination following a Comirnaty (Pfizer-BioNTech mRNA vaccine BNT162B2) or Vaxzevria (AstraZeneca ChAdOx1-S COVID-19 Vaccine AZD1222) primary course and including an mRNA, Comirnaty or half-dose Spikevax (Moderna mRNA-1273), third or booster dose. Our dataset included the date and dose of vaccine given, manufacturer and batch number. The specific vaccine was inferred from the batch number if manufacturer was unavailable. The focus periods were 14+ days after a second or third dose, split into 6-week periods: 14–69, 70–125, 126–181, 182+ days after the dose was given.

Table 1
Descriptive statistics and death rates. Descriptive statistics include median age, the percentage of individual aged 65 and over, percentage male, percentage ethnic minorities, the percentage unvaccinated and percentage who received dose 3 2 weeks before the study end. Three rates are given: an age standardized death rate in non-cases (those without a positive test during the study period), an age standardized case fatality rate within 28 days of a positive SARS-CoV-2 test and a crude case fatality rate within 28 days of a positive test.

	N individuals	median age	% age ≥ 65	% male	% ethnic minorities	% un-vaccinated[a]	% received dose 3[a]	age standardized death rate per 1000 persons per 28 days in non-cases	age-standardized case fatality rate per 1000 persons within 28 days of a new positive test	Crude case fatality rate per 1000 persons within 28 days of a new positive test
whole cohort	10,575,212	49	24	48	16	15	30	0.7	10.1	3.9
non-risk	7,198,880	43	13	48	17	19	18	0.2	3.9	0.4
all risk groups	3,376,332	64	49	48	13	6	55	1	12.8	14.5
chronic kidney	1,324,481	78	84	43	9	3	73	1.2	21.8	61.9
CHD	917,453	72	67	54	8	5	63	1.2	15.1	29.3
chronic respiratory	709,289	71	69	50	7	5	65	2	22.3	48.4
neurological	545,222	70	59	49	8	6	57	1.6	15.1	29.3
diabetes	396,902	66	53	55	21	5	56	1	16.6	22.5
immunosuppressed	421,962	63	47	42	13	5	65	1.4	21.5	24.4
chronic liver	310,232	58	33	54	16	9	45	1.3	14.8	11
severe asthma	255,131	58	37	36	10	7	50	1.1	17.8	14.4
asplenia	171,949	56	33	37	11	7	52	1	7	4.5
morbid obesity	68,407	52	21	31	11	8	38	0.9	17.2	6.9
learning disability	66,701	38	11	60	13	9	34	1.9	15.8	7.5

[a] by 21/11/2021, 14 days before the end of study.

Descriptive analyses and death rates

The median age, percentage age ≥ 65, male and ethnic minorities (excluding white minorities), both for the whole cohort and for each specific risk group were calculated. The percentages unvaccinated and received a 3rd or booster dose 14 days before the study end (21/11/2021) are given.

The death rate per 1000 population within 28 days of a new positive test within the study period (from 17th May 2021 up to 28 days after the study end on 6th December 2021) is given as an approximate case fatality rate, this was calculated regardless of vaccination status and both crude and age-standardized measures are given. A new positive test was defined as for the cohort study, at least 90 days apart. Age-standardized death rates per 1000 persons per 28 days among individuals with no positive test (i.e. non-COVID19 cases) are also given, to give a measure of frailty that is directly comparable with case fatality rates. Population by 5-year age group for standardisation was taken from 2021 census statistics for England. Patients who had a positive test in the 8 weeks before the start of the study period were excluded from death statistics.

VE statistical analyses

The cohort study start date was 17th May 2021 and the end date was 5th December 2021, corresponding with the Delta-variant dominant period in England. Person-time included was right censored at death, deregistration, a 4th vaccine dose or positive test date i.e. only the first positive test within the study period was included in this analysis.

Separate models were fitted for each specific risk group (but including the whole population, which ensured accurate estimation of temporal effects and covariates, the validity of this approach is explored in Supplementary material S3). Poisson regression was used, including vaccination status as a time-varying covariate, and its interaction with risk group. Estimates are reported for each risk group with unvaccinated risk group members as the reference category. Covariates adjusted for included a time and region interaction by fitting cubic splines over weeks for each NHS region, age group (in 5-year bands, then 90+), sex, ethnicity, index of multiple deprivation (IMD) quintile, GP record indicating prior COVID-19 (person time was left censored at 90 days after a past infection), large household (≥10 persons, divided into those with a median age < 70 and ≥70 years old), GP consultation rate quartile, Cambridge Multimorbidity Score (CMMS),[24] shielding recommendation, and latest smoking status. Overall VE was additionally adjusted for overall PRIMIS risk group status, while risk group VE was adjusted for membership of another risk group; note that risk groups are not mutually exclusive e.g. a kidney transplantation patient would be both a member of the chronic kidney disease and immunosuppressed groups. For the large household variable an unknown category was created, otherwise only complete cases were retained.

Antibody response to vaccination statistical analyses

Comirnaty and Vaxzevria post-vaccination spike (S) antibody responses were assessed in strongly nucleocapsid (N)-negative individuals (< 0.4au/ml) i.e. in those who had no evidence of antibodies from prior infection, and who had received 2 or 3 doses of COVID-19 vaccination at 14–182 days prior.

Geometric mean (GM) ratios of antibody levels were calculated using multivariable mixed effects interval regression, accounting for repeat samples from the same individual using random effects and allowing for 116 dose 2 antibody levels capped at 2500au/ml using interval regression methods. The relationship between antibody level and time since dose was investigated for each vaccine and dose

Table 2
adjusted vaccine effectiveness (aVE) against 2-night hospitalisation within 14 days of a positive SARS-CoV-2 test, post dose two and post mRNA booster, by risk group and primary vaccine course.

	Unvaccinated		Dose 2: 14-69 days			Dose 2: 70-125 days			Dose 2: 126-181 days			Dose 2: 182+ days			Dose 3: 14-69 days		
group	person years	pos	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE
Vaxzevria																	
all	1002811.1	4963	639778.9	424	92.5% (91.7% - 93.2%)	682760	1571	88.0% (87.2% - 88.7%)	600407.1	2322	81.5% (80.4% - 82.6%)	117425.9	1192	68.7% (66.3% - 71.0%)	81680.4	113	96.9% (96.2% - 97.4%)
non-risk	877317.5	2507	416194.2	98	95.4% (94.4% - 96.3%)	425666.1	258	91.8% (90.7% - 92.8%)	360837.6	363	88.0% (86.5% - 89.3%)	55787.3	117	78.8% (74.3% - 82.5%)	31434.6	7	98.3% (96.5% - 99.2%)
all risk groups	125493.5	2456	223584.8	326	90.3% (89.0% - 91.4%)	257094	1313	85.7% (84.7% - 86.7%)	239569.4	1959	78.3% (76.8% - 79.6%)	61638.6	1075	64.7% (61.8% - 67.5%)	50245.9	106	96.5% (95.7% - 97.1%)
CHD	33734.4	1014	80744.4	140	90.9% (89.1% - 92.4%)	97387.4	707	85.6% (84.1% - 87.0%)	91844.4	1078	77.9% (75.8% - 79.8%)	25106.8	650	63.4% (59.4% - 67.0%)	22630.7	60	96.7% (95.7% - 97.5%)
diabetes	28503.3	847	60174.4	124	89.8% (87.6% - 91.5%)	69564.1	540	84.1% (82.2% - 85.8%)	65367.2	764	76.7% (74.3% - 79.0%)	17772.6	469	59.7% (54.7% - 64.2%)	13643.7	36	96.5% (95.1% - 97.5%)
neurological	22666.7	444	44354.4	74	88.2% (84.8% - 90.8%)	53956.5	341	83.2% (80.6% - 85.5%)	50513.1	538	73.8% (70.2% - 77.0%)	15019	322	60.9% (54.7% - 66.3%)	11566.2	31	95.8% (94.0% - 97.1%)
chronic kidney	9164.8	319	27416.4	74	83.6% (78.8% - 87.3%)	36120.6	335	80.9% (77.7% - 83.7%)	34334.9	513	71.0% (66.6% - 74.9%)	10745.8	320	54.9% (47.1% - 61.5%)	10588.2	41	94.5% (92.3% - 96.0%)
morbid obesity	19454.5	439	30500.1	65	90.7% (87.9% - 92.8%)	32359.7	220	85.7% (83.1% - 87.8%)	29652	318	78.4% (74.9% - 81.3%)	6807.7	152	67.8% (61.1% - 73.4%)	3616.8	8	97.6% (95.1% - 98.8%)
chronic respiratory	10527.2	298	25539.3	61	86.2% (81.8% - 89.6%)	31684.5	333	79.0% (75.4% - 82.1%)	29954.9	483	68.9% (64.0% - 73.1%)	9115.2	301	49.8% (40.8% - 57.4%)	8025.9	27	95.6% (93.4% - 97.0%)
immunosuppressed	9267.6	194	20053.3	53	82.9% (76.8% - 87.4%)	23891.9	203	80.2% (75.9% - 83.8%)	21388.8	319	67.1% (60.6% - 72.5%)	5396.6	136	57.2% (46.5% - 65.7%)	7095.1	41	91.5% (88.0% - 93.9%)
chronic liver	12549.5	195	18713.5	28	89.3% (84.0% - 92.8%)	20492.9	108	82.7% (78.1% - 86.3%)	18874.6	182	69.3% (62.4% - 75.0%)	4444.3	79	57.6% (44.7% - 67.4%)	3146.8	5	97.0% (92.8% - 98.8%)
severe asthma	6823	145	11765.5	27	87.9% (81.7% - 92.0%)	13378.6	129	80.1% (74.8% - 84.4%)	12367.2	187	70.0% (62.6% - 75.9%)	3269.2	91	59.0% (46.5% - 68.5%)	2457.8	12	94.4% (89.8% - 96.9%)
asplenia	2832.6	39	4558.7	7	85.6% (67.7% - 93.5%)	5133.3	17	87.9% (78.5% - 93.1%)	4761.3	21	84.6% (73.8% - 90.9%)	1182.3	13	70.6% (44.8% - 84.3%)	997.1	<3	
learning disability	3697.8	31	5427.1	5	88.8% (71.1% - 95.6%)	6251.1	20	81.5% (67.4% - 89.4%)	5833.3	45	58.4% (34.1% - 73.7%)	1905.2	19	56.7% (23.2% - 75.6%)	862.4	<3	92.2% (67.3% - 98.1%)
Comirnaty																	
all	1002811.1	4963	410427.9	110	96.0% (95.1% - 96.7%)	468110.7	516	94.5% (93.9% - 95.0%)	344202.7	977	90.6% (89.8% - 91.2%)	135711.6	880	82.9% (81.4% - 84.2%)	131388	181	97.1% (96.6% - 97.6%)
non-risk	877317.5	2507	282932.2	37	96.4% (95.1% - 97.4%)	282666.3	63	96.3% (95.2% - 97.1%)	158642.6	61	95.3% (94.0% - 96.4%)	61148.3	55	89.9% (86.7% - 92.3%)	52793.7	7	98.9% (97.8% - 99.5%)
all risk groups	125493.5	2456	127495.7	73	95.4% (94.2% - 96.4%)	185444.4	453	93.4% (92.7% - 94.1%)	185560	916	88.8% (87.9% - 89.7%)	74563.3	825	80.3% (78.5% - 81.9%)	78594.3	174	96.7% (96.1% - 97.2%)
CHD	33734.4	1014	49042.1	33	95.8% (94.0% - 97.0%)	79676.5	285	93.0% (92.0% - 93.9%)	83162.1	566	88.9% (87.6% - 90.0%)	35969.5	569	79.7% (77.4% - 81.8%)	39633.9	109	96.9% (96.2% - 97.5%)
diabetes	28503.3	847	37496.8	28	95.5% (93.4% - 96.9%)	52994	168	93.5% (92.4% - 94.5%)	53373.4	336	88.9% (87.4% - 90.3%)	21209.4	330	79.1% (76.1% - 81.7%)	21104.4	43	97.7% (96.8% - 98.3%)
neurological	22666.7	444	24570.5	19	93.4% (89.5% - 95.8%)	39315.3	129	91.5% (89.7% - 93.1%)	40479	291	85.2% (82.8% - 87.2%)	18330.1	260	77.5% (73.7% - 80.8%)	18109.3	65	95.2% (93.7% - 96.3%)
chronic kidney	9164.8	319	19324.9	11	95.6% (92.0% - 97.6%)	36879.8	179	89.1% (86.9% - 91.0%)	40022.7	353	84.0% (81.4% - 86.3%)	19396.5	320	76.1% (72.0% - 79.6%)	21914.1	83	95.1% (93.7% - 96.1%)
morbid obesity	19454.5	439	15425.8	6	98.1% (95.7% - 99.1%)	18676.4	51	94.6% (92.7% - 96.0%)	17211	88	90.9% (88.5% - 92.8%)	6121.7	61	84.8% (80.1% - 88.4%)	4954.3	7	98.3% (96.3% - 99.2%)
chronic respiratory	10527.2	298	15443.5	15	93.5% (89.1% - 96.1%)	25030.8	131	89.9% (87.5% - 91.8%)	25995.7	251	84.2% (81.2% - 86.6%)	11168.9	222	74.6% (69.7% - 78.7%)	12238.4	55	95.0% (93.3% - 96.3%)
immunosuppressed	9267.6	194	11597.8	15	90.5% (83.9% - 94.4%)	17498.1	104	86.8% (83.2% - 89.6%)	17035.7	204	77.7% (72.8% - 81.8%)	6384.4	115	73.7% (66.8% - 79.2%)	8703.5	69	90.0% (86.7% - 92.4%)
chronic liver	12549.5	195	9758.3	6	94.9% (88.4% - 97.7%)	12502.6	40	90.2% (86.2% - 93.0%)	11967.9	52	88.0% (83.7% - 91.2%)	4217.8	42	78.0% (69.3% - 84.3%)	4051.4	7	96.9% (93.4% - 98.5%)
severe asthma	6823	145	6326.3	11		8858.4	47		8629.9	102		3421.1	68		3480.9	16	

(*continued on next page*)

Table 2 (*continued*)

group	Unvaccinated		Dose 2: 14-69 days			Dose 2: 70-125 days			Dose 2: 126-181 days			Dose 2: 182+ days			Dose 3: 14-69 days		
	person years	pos	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE
					89.5% (80.6% - 94.3%)			89.9% (86.0% - 92.8%)			80.9% (75.3% - 85.2%)			74.4% (65.8% - 80.9%)		95.3% (92.0% - 97.2%)
asplenia	2832.6	39	2812.6	<3		3771.1	8	92.3% (83.6% - 96.4%)	3646.2	15	87.3% (76.9% - 93.0%)	1314.4	13	75.7% (54.4% - 87.0%)	1392	4	94.6% (84.9% - 98.1%)
learning disability	3697.8	31	2128.1	<3		2313.9	3	92.2% (74.6% - 97.6%)	2091.1	4	89.4% (69.9% - 96.3%)	776.6	<3	88.3% (51.1% - 97.2%)	354.9	<3	

*adjusted for week-NHS region interaction, 5-yr age group, sex, ethnicity, IMD quintile, GP record of prior COVID-19, large household, GP consultation quartile, Cambridge Multimorbidity Score, shielding recommendation, overall PRIMIS risk group status (overall only) or membership of another risk group (risk groups only), latest smoking status

combination using polynomial transformations and splines; a square root transformation independently minimised Akaike information criterion for each combination. Included as explanatory variables were: vaccine x √days since dose interaction, vaccine x dosing schedule interaction, vaccine x age group interaction, sex and each specific risk group. Risk groups were the main variables of interest, and trajectories for each vaccine combination were also plotted.

All statistical analyses were carried out using STATA version 14.2.

Results

Exclusions for the vaccine effectiveness and case fatality analyses are given in Supplementary material S1. Descriptive characteristics, death rates and approximate case fatality rates by risk group are shown in Table 1. With the exception of the learning disability risk group, all risk groups are on average older than those not belonging to a risk group. The chronic kidney, CHD and chronic respiratory risk groups, in particular, contain a high proportion of elderly individuals.

The percentage of individuals completely unvaccinated before the study end is low among risk groups, 3–9%, compared with 19% among those not belonging to a risk group. Within the chronic kidney group, 73% had received a booster dose before the end of the study, followed by the CHD, chronic respiratory and immunosuppressed groups (63–65%). Further detail on the vaccination status of the cohort at the beginning, middle and end of the study is given in supplementary material S2.

After age-standardization, death rates and case fatality rates are higher among those within risk groups than non-risk. Particularly high crude case fatality rates among the chronic kidney and chronic respiratory risk groups are likely a result of a combination of the underlying health condition (e.g. SARS-CoV-2 infection may exacerbate an existing respiratory condition) and advanced age.

Vaccine effectiveness

Table 2 and Fig. 1 show estimates of adjusted vaccine effectiveness (aVE) against hospitalisation within 14 days of a positive test by risk group and primary vaccine course. The aVE 14–69 days post-dose 2 was high across all groups, but waned with time following the 2nd dose. aVE was typically higher for Comirnaty than for Vaxzevria, and this was particularly apparent in the periods 126–181 and 182+ days post-dose 2. Regardless of primary course or risk group, aVE was raised to very high within the window 14–69 days post mRNA 3rd or booster dose. For example, Vaxzevria aVE against hospitalisation for all risk groups combined was 90.3% (89.0–91.4%) 14–69d post-dose 2, 78.3% (76.8–79.6%) 182–181d post-dose 2% and 96.5% (95.7–97.1%) 14–69d following a 3rd dose, while Comirnaty aVE was 95.4% (94.2–96.4%) 14–69d post-dose 2, 88.8% (87.9–89.7%) 182–181d post-dose 2% and 96.7% (96.1–97.2%) 14–69d post-dose 3.

Table 3 and Fig. 2 similarly show estimates of aVE against death within 28 days of a positive test by risk group and primary vaccine course. Patterns of waning and boosting mirror those of the hospitalisations analysis, albeit confidence intervals are wider given the relatively small number of death events.

When considering all risk groups, aVE was typically lower than for those not belonging to a risk group, for example aVE against hospitalisation 126–181d post-dose 2 for all risk groups combined was 78.3% (76.8–79.6%) for Vaxzevria and 88.8% (87.9–89.7%) for Comirnaty, and for non-risk group members was 88.0% (86.5–89.3%) for Vaxzevria and 95.3% (94.0–96.4%) for Comirnaty. However, aVE was not equal across risk groups. aVE for the morbidly obese was only a little lower than those not within a risk group, and aVE was a little lower still for the three largest risk groups: CHD, diabetes and neurological. However, the lowest aVE was among the immunosuppressed, followed by the chronic respiratory, chronic liver, severe asthma and, to a lesser extent, the chronic kidney groups. For

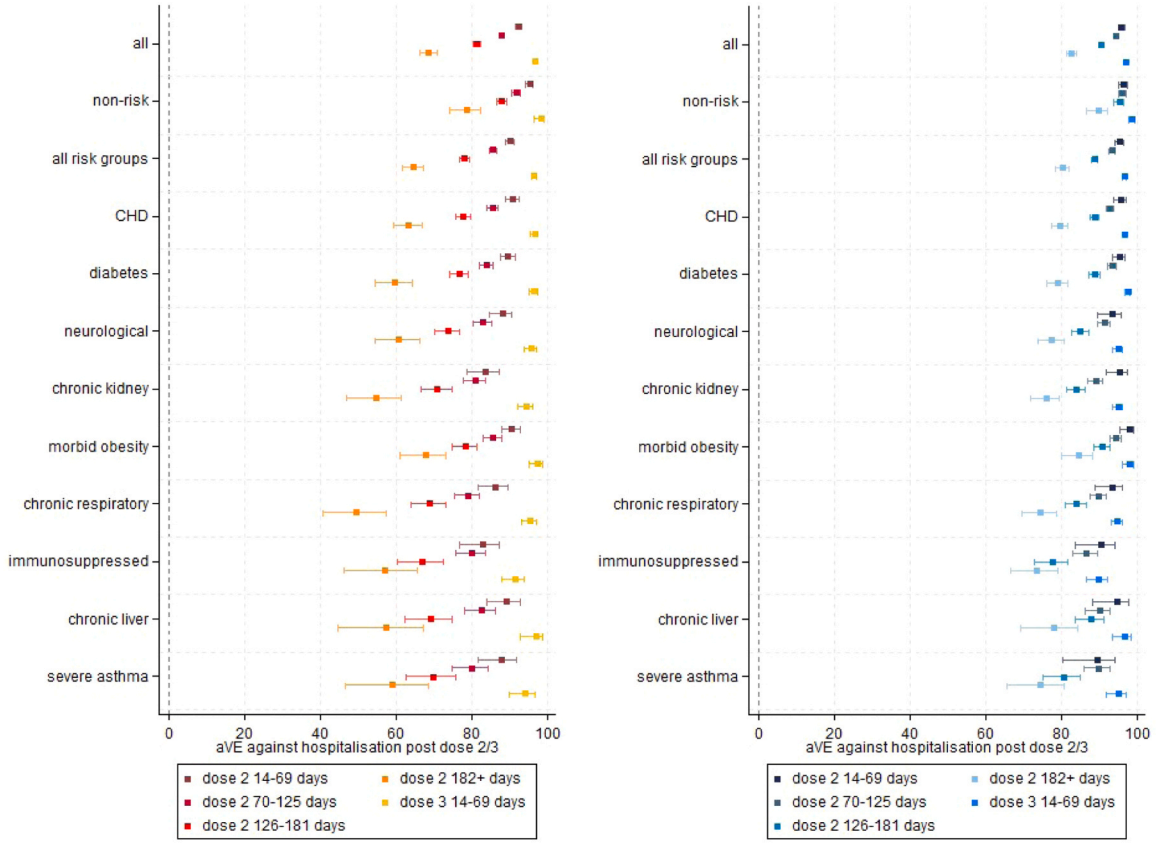

Fig. 1. Cohort adjusted vaccine effectiveness (aVE) against 2-night hospitalisation within 14 days of a positive SARS-CoV-2 test. Left panel: Vaxzevria primary course, right panel: Comirnaty primary course.

example, Vaxzevria aVE against hospitalisation 126–181d post-dose 2 was 67.1% (60.6–72.5%) among the immunosuppressed, 68.9% (64.0–73.1%) chronic respiratory, 69.3% (62.4–75.0%) chronic liver, 70.0% (62.6–75.9%) severe asthma and 71.0% (66.6–74.9%) CKD; while the same Comirnaty aVE was 77.7% (72.8–81.8%) immunosuppressed, 84.2% (81.2–86.6%) chronic respiratory, 88.0% (83.7–91.2%) chronic liver and 80.9% (75.3–85.2%) severe asthma and 84.0% (81.4–86.3%) CKD. The asplenia and learning disability risk groups were small and aVE estimates were based on fewer events and person-time, findings were not always consistent and confidence intervals were wide. aVE was greatly raised after a 3rd dose was given, and point estimates were ≥ 88% for every risk group regardless of primary course.

Vaccine-induced spike antibodies

Spike (S) serology outcomes were available for 11,844 strongly N negative (levels < 0.4au/ml) samples in 11,298 adults who had received dose 2 or 3 vaccination 14–182 days prior. We assume most will not have been previously infected. Fig. 3 demonstrates the boost and wane in mean spike antibody levels post-vaccination predicted from a multivariable regression model of S antibody levels in individuals with low N antibody levels (< 0.4). There is a clear difference in Vaxzevria and Comirnaty dose 2 responses, but after a booster dose mean antibody levels are similar regardless of primary course or booster vaccination brand.

Table 4 gives estimates for risk groups from the same model. The immunosuppressed group, especially, stands out as having lower antibody levels versus those not immunosuppressed, for all vaccine and dose combinations (Vaxzevria dose 2 adj GM ratio 0.64 [95% CI 0.56 – 0.73], Comirnaty dose 2 adj GM ratio 0.26 [95% CI 0.22 – 0.29], Vaxzevria dose 3 adj GM ratio 0.61 [95% CI 0.54–0.69], Comirnaty dose 3 0.53 [95% CI 0.46–0.61]). The immunosuppressed group's geometric mean ratio appeared lower after Comirnaty dose 2 than after other vaccine/dose combinations. Significantly lower antibody levels were also found among the diabetes, chronic kidney and chronic respiratory risk groups post both Vaxzevria and Comirnaty dose 2, while results for dose 3 were inconsistent. Antibody levels were also lower among the CHD group post-dose 2 Vaxzevria, but not following any mRNA vaccine.

Post-vaccination antibody levels for the immunosuppressed group are highlighted in Fig. 4. Most antibody levels for immunosuppressed individuals sit within the main cloud of data suggesting that vaccine-induced antibody response is normal, but for some antibody levels do appear lower. For example, low dose 2 antibody levels < 10au/ml were seen among 6.5% (36/550) of those immunosuppressed, compared with 0.7% (36/5017) individuals not members of the immunosuppressed risk group; similarly low dose 3 antibody levels < 100au/ml were seen among 3.4% (17/497) of those immunosuppressed, compared with 0.04% (2/5234) individuals non-immunosuppressed risk group members. 37 patients had made no antibody response to vaccination (levels below the reactive cut-off at 0.8au/ml), 24 of whom were members of the immunosuppressed risk group. There are fewer individuals with antibody levels sitting below the main cloud of data (antibody levels < 500au/ml) after the 3rd dose than after the 2nd dose.

Discussion

Principal findings

This study demonstrates vaccine effectiveness against severe outcomes as well as demonstrating antibody response post-vaccination. We present results by clinical risk group and most notably

Table 3
adjusted vaccine effectiveness (aVE) against death within 28 days of a positive SARS-CoV-2 test, post dose two and post mRNA booster, by risk group and primary vaccine course.

	Unvaccinated		Dose 2: 14-69 days			Dose 2: 70-125 days			Dose 2: 126-181 days			Dose 2: 182+ days			Dose 3: 14-69 days		
group	person years	pos	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE
Vaxzevria																	
all	1002811.1	527	639778.9	52	89.9% (86.1% - 92.6%)	682760	265	86.8% (84.4% - 88.9%)	600407.1	443	82.7% (80.1% - 84.9%)	117425.9	333	72.3% (67.6% - 76.4%)	81680.4	44	96.4% (95.1% - 97.4%)
non-risk	877317.5	122	416194.2	4	96.5% (90.5% - 98.7%)	425666.1	17	93.9% (89.8% - 96.4%)	360837.6	25	93.0% (89.1% - 95.5%)	55787.3	16	83.5% (71.9% - 90.4%)	31434.6	<3	98.2% (92.5% - 99.6%)
all risk groups	125493.5	405	223584.8	48	87.7% (82.8% - 91.1%)	257094	248	85.1% (82.2% - 87.5%)	239569.4	418	80.4% (77.3% - 83.1%)	61638.6	317	70.1% (64.8% - 74.6%)	50245.9	42	96.1% (94.6% - 97.2%)
CHD	33734.4	204	80744.4	28	86.6% (79.6% - 91.2%)	97387.4	156	83.8% (79.8% - 87.1%)	91844.4	286	77.1% (72.3% - 81.0%)	25106.8	214	67.5% (60.2% - 73.5%)	22630.7	28	95.7% (93.6% - 97.2%)
diabetes	28503.3	149	60174.4	20	85.9% (77.1% - 91.3%)	69564.1	97	83.2% (78.0% - 87.2%)	65367.2	152	79.2% (73.7% - 83.6%)	17772.6	135	63.7% (53.6% - 71.6%)	13643.7	11	96.8% (94.0% - 98.3%)
neurological	22666.7	120	44354.4	12	89.7% (81.1% - 94.4%)	53956.5	84	85.1% (80.1% - 88.9%)	50513.1	156	79.3% (73.5% - 83.8%)	15019	134	68.8% (59.7% - 75.9%)	11566.2	16	96.0% (93.3% - 97.7%)
chronic kidney	9164.8	111	27416.4	13	87.5% (77.3% - 93.1%)	36120.6	102	80.4% (74.0% - 85.2%)	34334.9	191	72.0% (64.3% - 78.0%)	10745.8	136	64.4% (53.8% - 72.5%)	10588.2	16	95.7% (92.7% - 97.5%)
morbid obesity	19454.5	46	30500.1	8	86.3% (70.6% - 93.6%)	32359.7	29	85.2% (76.3% - 90.8%)	29652	44	82.0% (72.7% - 88.1%)	6807.7	24	78.8% (65.1% - 87.2%)	3616.8	4	95.5% (87.3% - 98.4%)
chronic respiratory	10527.2	76	25539.3	18	77.7% (61.8% - 86.9%)	31684.5	97	73.7% (64.2% - 80.7%)	29954.9	140	69.9% (59.9% - 77.4%)	9115.2	97	60.4% (46.1% - 70.9%)	8025.9	17	92.8% (87.7% - 95.8%)
immunosuppressed	9267.6	31	20053.3	8	79.5% (54.6% - 90.7%)	23891.9	48	73.0% (57.3% - 83.0%)	21388.8	63	71.4% (55.8% - 81.5%)	5396.6	48	52.5% (25.0% - 70.0%)	7095.1	16	88.6% (79.1% - 93.8%)
chronic liver	12549.5	24	18713.5	7	72.6% (35.8% - 88.3%)	20492.9	19	79.0% (61.5% - 88.5%)	18874.6	30	73.2% (54.1% - 84.4%)	4444.3	18	64.2% (33.8% - 80.7%)	3146.8	3	93.9% (79.7% - 98.2%)
severe asthma	6823	20	11765.5	5	79.7% (45.5% - 92.5%)	13378.6	20	81.1% (64.6% - 89.9%)	12367.2	32	75.6% (57.2% - 86.1%)	3269.2	19	71.3% (46.0% - 84.7%)	2457.8	5	92.2% (79.1% - 97.1%)
asplenia	2832.6	4	4558.7	<3		5133.3	<3		4761.3	3	87.8% (45.3% - 97.3%)	1182.3	3	73.1% (-20.4% - 94.0%)	985.4	<3	
learning disability	3697.8	7	5427.1	<3		6251.1	<3	94.3% (72.7% - 98.8%)	5833.3	5	89.4% (66.4% - 96.6%)	1905.2	5	80.4% (38.1% - 93.8%)	851.5	<3	
Comirnaty																	
all	1002811.1	527	410427.9	12	95.5% (91.8% - 97.5%)	468110.7	128	92.2% (90.3% - 93.7%)	344202.7	281	89.3% (87.4% - 90.9%)	135711.6	332	81.7% (78.7% - 84.3%)	131388	55	97.9% (97.2% - 98.4%)
non-risk	877317.5	122	282932.2	<3		282666.3	6	96.0% (90.8% - 98.2%)	158642.6	9	95.6% (91.2% - 97.8%)	61148.3	13	87.7% (77.9% - 93.1%)	52793.7	<3	98.9% (95.5% - 99.7%)
all risk groups	125493.5	405	127495.7	12	94.3% (89.7% - 96.9%)	185444.4	122	91.3% (89.1% - 93.0%)	185560	272	88.1% (85.9% - 89.9%)	74563.3	319	80.2% (76.8% - 83.1%)	78594.3	53	97.7% (96.9% - 98.3%)
CHD	33734.4	204	49042.1	7	94.2% (87.3% - 97.3%)	79676.5	85	90.2% (87.1% - 92.5%)	83162.1	193	86.7% (83.6% - 89.2%)	35969.5	244	77.5% (72.7% - 81.5%)	39633.9	37	97.6% (96.6% - 98.4%)
diabetes	28503.3	149	37496.8	3	96.1% (87.7% - 98.8%)	52994	51	89.3% (85.1% - 92.3%)	53373.4	91	88.1% (84.4% - 90.9%)	21209.4	125	77.5% (71.2% - 82.4%)	21104.4	19	97.5% (95.9% - 98.4%)
neurological	22666.7	120	24570.5	<3	96.6% (86.0% - 99.2%)	39315.3	44	90.1% (85.8% - 93.1%)	40479	95	87.7% (83.8% - 90.7%)	18330.1	116	81.0% (75.3% - 85.3%)	18109.3	23	97.2% (95.5% - 98.2%)
chronic kidney	9164.8	111	19324.9	4	93.7% (82.5% - 97.7%)	36879.8	60	88.0% (83.3% - 91.3%)	40022.7	126	85.6% (81.3% - 89.0%)	19396.5	151	78.2% (71.9% - 83.0%)	21914.1	32	96.8% (95.1% - 97.8%)
morbid obesity	19454.5	46	15425.8	<3		18676.4	6	95.2% (88.7% - 97.9%)	17211	10	94.2% (88.6% - 97.1%)	6121.7	11	88.8% (78.4% - 94.2%)	4954.3	<3	98.3% (93.2% - 99.6%)
chronic respiratory	10527.2	76	15443.5	<3	95.6% (82.1% - 98.9%)	25030.8	36	88.8% (83.1% - 92.5%)	25995.7	82	84.1% (78.2% - 88.5%)	11168.9	106	72.0% (62.2% - 79.3%)	12238.4	18	96.7% (94.4% - 98.0%)
immunosuppressed	9267.6	31	11597.8	3	86.5% (55.3% - 95.9%)	17498.1	26	83.1% (71.3% - 90.0%)	17035.7	63	74.1% (60.0% - 83.2%)	6384.4	51	67.8% (49.5% - 79.5%)	8703.5	22	91.9% (85.9% - 95.4%)
chronic liver	12549.5	24	9758.3	<3	84.2% (32.5% - 96.3%)	12502.6	7	89.1% (74.6% - 95.3%)	11967.9	13	86.1% (72.7% - 93.0%)	4217.8	14	76.0% (53.4% - 87.6%)	4051.4	3	96.3% (87.7% - 98.9%)

(*continued on next page*)

Table 3 (*continued*)

group	Unvaccinated		Dose 2: 14-69 days			Dose 2: 70-125 days			Dose 2: 126-181 days			Dose 2: 182+ days			Dose 3: 14-69 days		
	person years	pos	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE	person years	pos	aVE
severe asthma	6823	20	6326.3	<3		8858.4	11	87.2% (73.0% - 93.9%)	8629.9	21	84.1% (70.5% - 91.4%)	3421.1	24	73.2% (51.3% - 85.3%)	3480.9	5	96.2% (89.9% - 98.6%)
asplenia	2832.6	4	2812.6	<3		3771.1	<3		3646.2	<3	91.9% (55.5% - 98.5%)	1314.4	4	74.4% (-2.6% - 93.6%)	1392	<3	
learning disability	3697.8	7	2128.1	<3		2313.9	<3		2091.1	<3	87.5% (39.6% - 97.4%)	776.6	<3		354.9	<3	

*adjusted for week-NHS region interaction, 5-yr age group, sex, ethnicity, IMD quintile, GP record of prior COVID-19, large household, GP consultation quartile, Cambridge Multimorbidity Score, shielding recommendation, overall PRIMIS risk group status (overall only) or membership of another risk group (risk groups only), latest smoking status

see reduce aVE and antibody levels among the broad immunosuppressed risk group.

Individuals belonging to clinical risk groups are at greater risk from severe outcomes following infection with SARS-CoV-2.[17,19,25] Prevention of infection and/or reducing the risk of severe outcomes is therefore especially important to protect individuals risk groups and to reduce pressure on health services. This study provides evidence of high levels of vaccine effectiveness against severe COVID-19-related outcomes across all clinical risk groups following recent receipt of a new vaccine dose. Vaccine effectiveness wanes with time since dose, and vaccine effectiveness is attenuated 6 months or more after the 2nd dose: this is especially true for individuals belonging to risk groups who see a greater absolute drop in aVE as compared with those not in risk groups. This supports maximising coverage of both the primary course and subsequent booster doses for all.

Clinical risk often corresponded with advanced age, which led to very high crude case fatality rates among some groups, particularly the chronic kidney and chronic respiratory groups. Hippisley-Cox et al. have looked at more specific predictors of severe SARS-CoV-2 infection, and found that a long list of conditions are associated with severe infection, most notably chronic kidney disease, chemotherapy, recent radiotherapy, Downs syndrome, solid organ transplant, diabetes, liver cirrhosis, rare neurological conditions and HIV/AIDS; while neither asthma nor morbid obesity feature in their list of predictors of severe infection.[17,19] Although vaccine effectiveness against severe outcomes in almost all risk groups is lower than that for those not belonging to a risk group, differences in aVE between different clinical risk groups were modest. However, aVE, particularly after the 3rd dose, was a little lower for the broad immunosuppressed / immunocompromised group. Also, aVE against hospitalisation 6+ months after the 2nd dose was a little lower for the elderly chronic kidney and chronic respiratory disease groups, and a little higher for the younger morbid obesity risk group.

Vaccine-induced spike antibody responses of individuals in clinical risk groups were frequently in-line with those not in that clinical risk group. Antibody response was slightly lower, on average, for the diabetes, chronic kidney and chronic respiratory disease groups. However, the immunosuppressed risk group showed a considerably lower vaccine-induced antibody response, on average. However, there is clear heterogeneity within the immunosuppressed group, most immunosuppressed individuals appear to make a normal antibody response, and only some immunosuppressed individuals make no antibody response, or a low antibody response. This implies that vaccine effectiveness may differ by immunosuppression severity or subgroups, and further research to explore heterogeneity in both antibody response and aVE between immunosuppressed groups is needed. Of the 37 individuals with no antibody response in our data, we noted that 24 were members of the immunosuppressed risk group and, where known, 15 of these individuals had bone marrow compromising conditions (haematological malignancies and bone marrow/stem cell transplant recipients). 19 of these 37 individuals were members of the chronic kidney risk group; there was an overlap of 12 individuals who were both chronic kidney and immunosuppressed risk group members. Martin et al. found that concomitant immunosuppressant use was a risk factor for non-response in end stage kidney disease patients.[16] We note that the relationship between antibody response and vaccine effectiveness is not clearly established, but higher antibody levels are associated with protection against infection[26–28] and individuals with no antibody response are unlikely to be protected by the vaccine. The dose 2 differences in antibody levels between vaccines, and the dose 3 boost, together with waning antibodies do tie in with general observed patterns of vaccine effectiveness. An absence of antibody response was seldom seen after 3 doses.

Our principal findings show that 2-dose aVE is higher for Comirnaty than for Vaxzevria, this suggests that it is worth

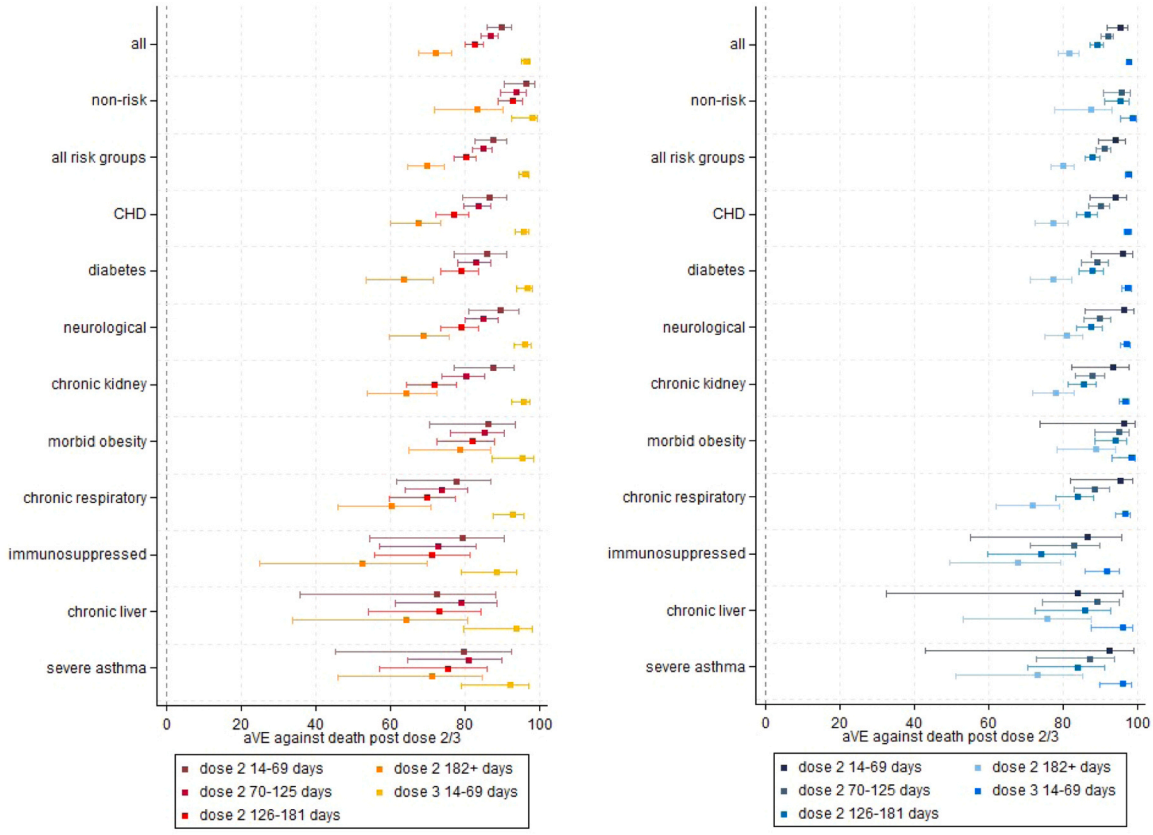

Fig. 2. Cohort adjusted vaccine effectiveness (aVE) against death within 28-days of a positive SARS-CoV-2 test. Left panel: Vaxzevria primary course, right panel: Comirnaty primary course.

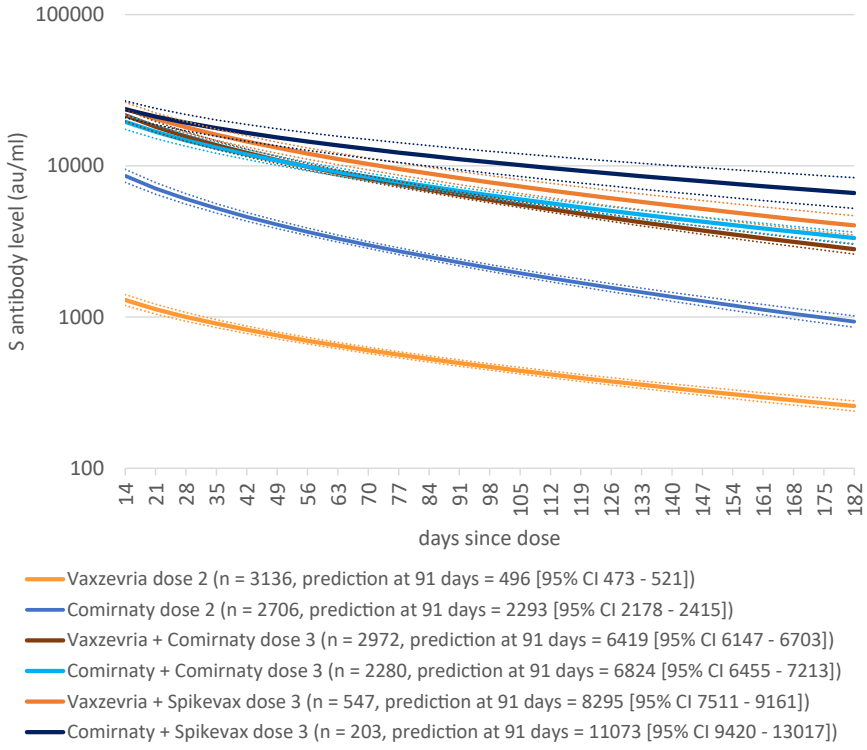

Fig. 3. Predicted mean S antibody levels by time since dose for six vaccination combinations: Vaxzevria dose 2, Comirnaty dose 2, Vaxzevria primary course followed by Comirnaty dose 3, Comirnaty primary course followed by Comirnaty dose 3, Vaxzevria primary course followed by Spikevax dose 3, Comirnaty primary course followed by Spikevax dose 3. The figure legend gives the number of samples and the prediction at 91-days post-vaccination.

Table 4
Spike (S) antibody levels 14+ days after dose 2 or 3 of COVID-19 vaccination in N-negative individuals by risk group status: N samples, geometric mean (GM) ratio of responses and predicted mean antibody level at 91-days post-dose.

risk group	n samples	adjusted GM ratio (95% CI)	p-value	predicted antibody level at 91-days post-dose (95% CI)	n samples	adjusted GM ratio (95% CI)	p-value	predicted antibody level at 91-days post-dose (95% CI)
	Vaxzevria dose 2				Comirnaty dose 2			
immunosuppressed	345	0.64 (0.56–0.73)	< 0.001	331 (291–375)	338	0.26 (0.22–0.29)	< 0.001	672 (589–767)
chronic respiratory	290	0.86 (0.74–0.99)	0.041	433 (376–498)	308	0.75 (0.64–0.87)	< 0.001	1757 (1519–2031)
chronic kidney	416	0.86 (0.76–0.97)	0.018	437 (389–491)	653	0.84 (0.75–0.94)	0.003	1978 (1774–2205)
diabetes	654	0.86 (0.78–0.96)	0.004	442 (403–486)	721	0.85 (0.77–0.94)	0.002	2020 (1842–2217)
CHD	895	0.81 (0.74–0.89)	< 0.001	430 (396–466)	1143	0.98 (0.89–1.08)	0.636	2256 (2076–2452)
neurological	347	0.91 (0.80–1.04)	0.157	457 (404–518)	473	0.92 (0.81–1.04)	0.195	2133 (1891–2406)
learning disability	18	0.92 (0.55–1.53)	0.74	455 (274–758)	10	0.68 (0.33–1.39)	0.288	1559 (765–3179)
morbid obesity	188	1.12 (0.94–1.33)	0.207	551 (465–653)	139	0.88 (0.71–1.08)	0.205	2022 (1652–2475)
severe asthma	124	1.06 (0.86–1.31)	0.594	525 (426–647)	85	1.00 (0.75–1.32)	0.976	2284 (1732–3012)
asplenia	33	1.06 (0.72–1.57)	0.761	527 (357–777)	43	0.96 (0.66–1.38)	0.812	2194 (1520–3167)
chronic liver	210	0.97 (0.83–1.14)	0.74	484 (413–567)	191	1.09 (0.91–1.30)	0.345	2483 (2092–2947)
non-risk	1429	(ref)		595 (560–633)	774	(ref)		2925 (2718–3147)
	Vaxzevria primary course + Comirnaty/Spikevax dose 3				Comirnaty primary course + Comirnaty/Spikevax dose 3			
immunosuppressed	341	0.61 (0.54–0.69)	< 0.001	4120 (3636–4668)	244	0.53 (0.46–0.61)	< 0.001	3829 (3324–4412)
chronic respiratory	326	0.90 (0.79–1.03)	0.119	5834 (5135–6627)	267	0.91 (0.78–1.05)	0.195	6244 (5396–7224)
chronic kidney	451	0.98 (0.88–1.10)	0.767	6325 (5677–7048)	477	0.86 (0.76–0.96)	0.009	5980 (5341–6695)
diabetes	699	0.90 (0.82–0.99)	0.037	5921 (5417–6472)	626	1.04 (0.94–1.16)	0.409	7062 (6425–7762)
CHD	1048	0.97 (0.89–1.06)	0.498	6289 (5834–6779)	949	1.07 (0.97–1.18)	0.158	7155 (6571–7792)
neurological	405	0.90 (0.80–1.02)	0.095	5876 (5250–6577)	349	1.03 (0.90–1.17)	0.673	6991 (6159–7935)
learning disability	16	0.91 (0.54–1.53)	0.711	5816 (3450–9806)	5	0.56 (0.23–1.38)	0.208	3841 (1566–9422)
morbid obesity	220	1.04 (0.88–1.21)	0.67	6632 (5677–7748)	159	1.07 (0.89–1.29)	0.449	7303 (6090–8758)
severe asthma	94	0.89 (0.70–1.12)	0.317	5718 (4536–7208)	83	0.84 (0.65–1.07)	0.161	5736 (4469–7361)
asplenia	47	1.00 (0.72–1.39)	0.996	6414 (4629–8888)	29	1.22 (0.80–1.86)	0.354	8310 (5458–12,652)
chronic liver	201	0.97 (0.83–1.14)	0.724	6246 (5333–7316)	134	0.95 (0.78–1.16)	0.63	6520 (5360–7930)
non-risk	1484	(ref)		7148 (6758–7560)	749	(ref)		7287 (6764–7850)

[1]adjusted for vaccine X age interaction, sex, vaccine X √days since dose interaction and vaccine X dosing schedule interaction and each specific risk group.

prioritising mRNA vaccines as a primary course. However, aVE is raised after an mRNA booster dose to similar levels regardless of primary course. A 3rd dose is particularly important among those in clinical risk groups given greater reductions in aVE 6 months after dose 2.

Comparison with the literature

Our overall aVE for hospitalisation in England during the Delta variant period is a little lower than that reported in Andrews et al.,[8] which used a test-negative design and included only hospitalisations through emergency care. Findings of waning effectiveness with time since vaccination and lower VE among clinically vulnerable groups is similar. Our aVE for hospitalisation is higher than that reported for Scotland during the Delta variant period,[29] but this included hospitalisations of any length following a positive test while we restricted to hospital stays of 2 nights or more. Our overall aVE for death within 28 days of a positive test shortly after a 2nd dose was similar to that reported for Scotland.[11] Findings of lower vaccine effectiveness among immunosuppressed individuals have been reported in multiple studies with a variety of endpoints including hospitalisation, Di Fusco et al. provide a comprehensive review.[13] For example, Embi et al. contrasted a 2nd dose mRNA VE of 77% among the immunosuppressed with a VE of 90% among non-immunosuppressed individuals in the USA using a test negative design,[30] which aligns with our estimates. In this study VE differed across groups of immunosuppressed individuals and was lowest in a group of organ and stem cell transplant patients.

Several studies have reported on immunological responses following vaccination in specific immunosuppressed cohorts. For example, Kearns et al. looked at responses in a broad range of immunosuppressive conditions, and noted lower seroconversion rates after two vaccine doses among individuals with ANCA-associated vasculitis, hepatic disease and end-stage kidney disease requiring dialysis.[31] However, most immunosuppressed patients in this study made a response, corresponding with our results, and additionally patients in the study typically made a T-cell response regardless of seroconversion status. Lim et al. saw no antibody response in 52% of recruited Lymphoma patients undergoing active cancer treatment.[32] We note that in practice, timing of immunosuppression as defined for our study and timing of vaccination may not overlap; indeed it is advised to avoid coinciding vaccination with immunosuppressive therapies where possible.[18] Thomson et al. observed 24% of recruited kidney transplant patients remained seronegative after a 3rd vaccination dose.[33] Non-response after 3 doses was seldom seen in our study. Note that for the purposes of our study, The Green Book assigns patients with advanced kidney disease and kidney transplant to the chronic kidney disease risk group,[18] but this groups includes patients with stage 3 and above kidney disease, so patients with milder disease dominate the group.

Strengths and limitations

This study has a number of strengths: the study population is large, and there is a wide array of data on medical history and demographics from clinical records that we are able to adjust for in analyses, including variables related to morbidity and health care seeking (GP consultations). Furthermore, we have both immunogenicity data and vaccine effectiveness data. However, we lack some important variables, for example groups at higher risk of infection such as care home residents and health care workers were not identifiable.

In antibody analyses we assume that S positive outcomes in N negative individuals will primarily indicate vaccine-induced antibodies, though we acknowledge that not everyone makes an N response following infection and that N antibodies may have waned to levels < 0.4.

The specific reason for hospitalisation or death was not taken into account and we rely on temporal proximity with a positive SARS-CoV-2 test. SARS-CoV-2 testing upon hospitalisation was universal during the period of study, hence hospitalisations will include some co-incidental hospitalisations and false positives in addition to those with respiratory and cardiovascular events causally linked to COVID-19. Inclusion of only hospitalisations resulting in at least a 2-

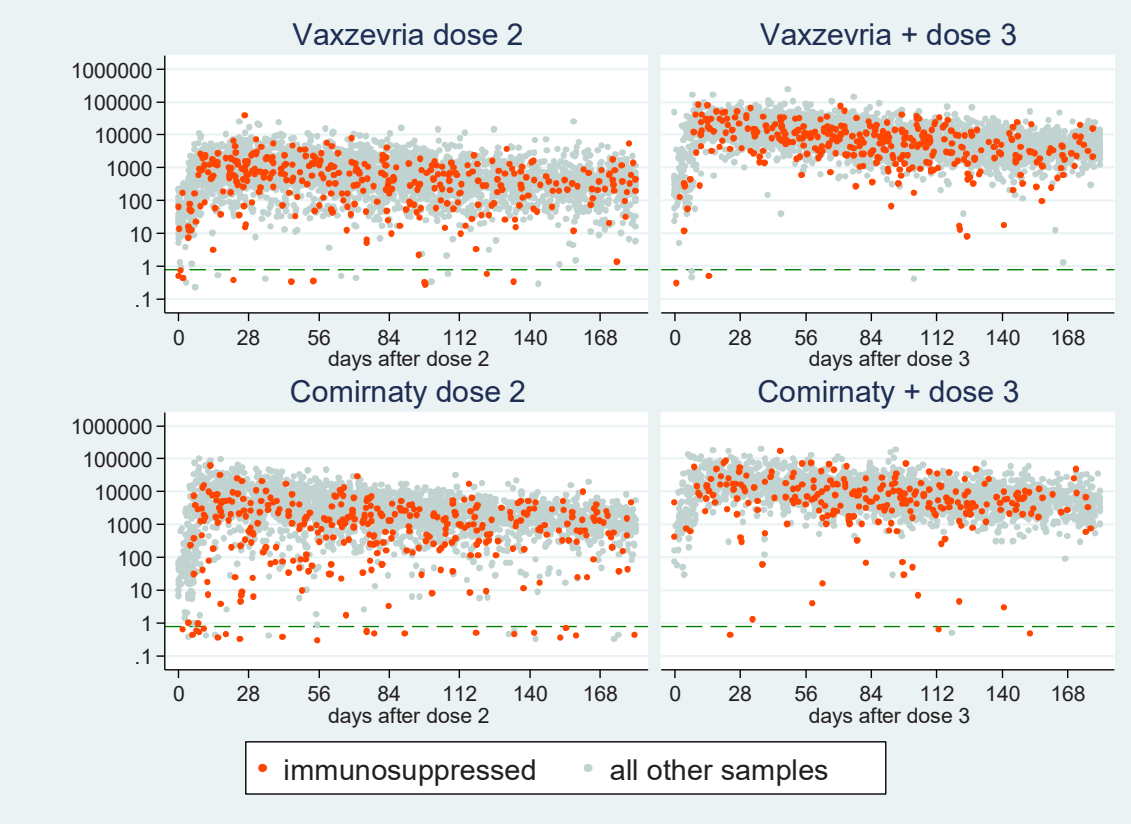

Fig. 4. Spike (S) antibody levels (au/ml) after dose 2 or 3 of COVID-19 vaccination in N-negative individuals, by primary course manufacturer and last dose received, coloured red for members of the immunosuppressed risk group (or coloured grey for non-members). The green dashed line is the assay positive/negative cut-off at 0.8au/ml. Antibody levels are on a logarithmic scale.

night stay should help ensure outcomes are sufficiently severe to minimise unmeasured confounding by health care seeking behaviour.

The clinical risk groups are based on 'Green Book' definitions and groups are broad. We have already noted that further research is warranted into heterogeneity of outcomes for immunosuppressed subgroups, but this also applies to other groups. For example, the chronic kidney disease group includes those with chronic kidney disease at stage 3 and above, kidney failure and kidney transplant, and exploration of heterogeneity in outcomes by stage or in transplant patients is also of interest.

Our analysis spanned the Delta-dominant period. We acknowledge that current vaccine effectiveness will differ considerably to that presented here because this variant is no longer in circulation and also because population immunity has since grown with newly acquired infections and additional vaccine doses.

We note that the vaccination schedule differed for the immunosuppressed group in that third primary vaccinations was available to this group only. Occasionally this meant that a third Vaxzevria dose was given, but this group was too small to give dose 3 Vaxzevria VE estimates. Spikevax would also have been given as a third primary dose to some of these individuals, which may have meant different dosing to those receiving half-dose boosters; however we did not extract this information for our study.

Conclusion

In all clinical risk groups and healthy individuals, high levels of VE against severe outcomes were seen within the first few months since full 2-dose vaccination with both Comirnaty and Vaxzervria. Vaccine effectiveness waned with time since vaccination, and for individuals belonging to most clinical risk groups, effectiveness was moderate 6 months or more post-vaccination. However, a 3rd or booster mRNA vaccine showed higher initial effectiveness than the 2nd Comirnaty vaccine dose. Our findings support maximising vaccine coverage of all individuals and demonstrate the added value of booster doses.

In the Delta period of the COVID-19 pandemic there was a higher mortality among risk groups notably those with chronic kidney disease and chronic respiratory disease and people who are immunosuppressed. Vaccine effectiveness was generally good for six months after the second dose of COVID-19 vaccine, but waned more quickly in some risk groups, notably the immunosuppressed. These findings were triangulated by our serological analysis which again found a reduced response to vaccination in people with chronic kidney and respiratory diseases, in the immunosuppressed and diabetes risk groups. These findings reinforce the need for booster vaccinations, especially in these risk groups. Further research is needed to better understand vaccine effectiveness against severe disease among immunosuppressed subgroups.

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Ethical approval

Surveillance and COVID-19 VE studies were approved by the UKHSA Caldicott Guardian as Health Protection and permitted under

Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002.

CRediT authorship contribution statement

HW, RT, JLB, SdeL, NA drafted the manuscript, with direction from MR. HW, NA, MS, SdeL, JLB designed the vaccine effectiveness study. HW carried out all statistical analyses. NA, JLB, SdeL, SA provided oversight of vaccine effectiveness. MZ, JE were responsible for overseeing testing of sentinel surveillance swabs. PSP, RB, JS for data management and linkage of swab data. JW, HC, EL, JH, JS, WE for data management and linkage of serology data. EB, WV, GH, ML for data quality and sampling from contributing GPs. AO oversaw testing of serology samples, with SDA and CR. GA, KB provided oversight of serology. All authors read and approved the manuscript.

Declaration of Competing Interest

Simon de Lusignan is the Director of the Oxford-RCGP RSC and has received funding through his University for studies from Astra-Zeneca, Eli Lilly, Sanofi, GSK, MSD. Seqirus and Takeda; and been member of advisory boards for Astra-Zeneca, Seqirus and Sanofi.

Ezra Linley reports that the UKHSA Vaccine Evaluation Unit performs contract research on behalf of GSK, Sanofi and Pfizer which is outside the submitted work.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.08.005.

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