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Vaccine Effectiveness Against the SARS-CoV-2 B.1.1.529 Omicron Variant in Solid Organ and Islet Transplant Recipients in England: A National Retrospective Cohort Study

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Background. The effectiveness of vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.529 Omicron variant in immunosuppressed solid organ and islet transplant (SOT) recipients is unclear. **Methods.** National registries in England were linked to identify SARS-CoV-2 positive tests, noninjury hospitalization within 14 d, and deaths within 28 d between December 7, 2020, and March 31, 2022 in adult SOT recipients. Incidence rate ratios (IRRs) for infection, and hospitalization or death, were adjusted for recipient demographics and calendar month for the Omicron-dominant period (December 20, 2021, to March 31, 2022). Mortality risk following SARS-CoV-2 infection was adjusted for recipient demographics and dominant variant using a Cox proportional-hazards model for the entire time period. **Results.** During the Omicron-dominant period, infection IRRs (95% confidence intervals) were higher in those receiving 2, 3, and 4 vaccine doses than in unvaccinated patients (1.25 [1.08-1.45], 1.46 [1.28-1.67], and 1.79 [1.54-2.06], respectively). However, hospitalization or death IRRs during this period were lower in those receiving 3 or 4 vaccine doses than in unvaccinated patients (0.62 [0.45-0.86] and 0.39 [0.26-0.58], respectively). Risk-adjusted analyses for deaths after SARS-CoV-2 infection between December 7, 2020, and March 31, 2022, found hazard ratios (95% confidence intervals) of 0.67 (0.46-0.98), 0.46 (0.30-0.69), and 0.18 (0.09-0.35) for those with 2, 3, and 4 vaccine doses, respectively, when compared with the unvaccinated group. **Conclusions.** In immunosuppressed SOT recipients, vaccination is associated with incremental, dose-dependent protection against hospitalization or death after SARS-CoV-2 infection, including against the Omicron variant.

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INTRODUCTION

Vaccination has been shown to reduce the risk of severe outcomes after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the general population.[1-3] The clinical trials to establish vaccine efficacy, which subsequently enabled emergency-use authorization, were performed when the wild-type or Alpha variant were the dominant SARS-CoV-2 strains in circulation. In November 2021, the B.1.1.529 variant, first observed in cases from Botswana and South Africa, was designated as the Omicron variant and identified as a variant of concern by the World Health Organization.[4] The variant is

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characterized by numerous mutations, with a significant number located within the receptor binding domain; it was therefore predicted to be less susceptible to neutralizing antibodies elicited by previous SARS-CoV-2 infection or vaccination.[5] Subsequent publications have reported on reduced vaccine effectiveness (VE) and breakthrough infection with this variant in the general population following 2 or more vaccine doses.[6-9]

Solid organ and islet transplant (SOT) recipients were not included in vaccine efficacy trials despite having a significantly higher mortality risk following SARS-CoV-2 infection than the general population.[10] Because of the requirement for continual systemic immunosuppression to prevent allograft rejection, vaccine responses are generally impaired in SOT recipients,[11] and suboptimal responses to SARS-CoV-2 vaccination have been similarly reported in this population during the Alpha- and Delta-variant-dominant periods.[12,13] Thus, the emergence of the Omicron variant with predicted relative resistance to established SARS-CoV-2 vaccines is a particular concern for the vulnerable SOT patient population, a concern heightened by the coincidental reduction in most countries in mandated nonpharmacological interventions (NPIs) such as mask wearing and social distancing. However, although small-scale serological studies in transplant recipients have confirmed limited postvaccination neutralizing antibody responses to the Omicron variant,[14] how this relates to protection from hospitalization or death is not clear, and large-scale national analyses of SOT recipients during the Omicron wave have not been reported.

Here, we report on a risk-adjusted national registry study aiming to determine real-world VE in SOT recipients during the Omicron-dominant period in England. Three key outcomes were analyzed: incidence of testing positive for SARS-CoV-2, incidence of noninjury hospitalization within 14 d of testing positive for SARS-CoV-2, and risk of death within 28 d following a positive test for SARS-CoV-2.

MATERIALS AND METHODS

Study Cohort and Outcome Definitions

The at-risk cohort we examined were patients aged 16 y or more, residing in England, that were recipients of an organ or organs from a deceased or live donor with a functioning graft on December 7, 2020, and those transplanted between that date and March 31, 2022 (Figure 1).

We only included those patients who received 2 homologous doses of Pfizer-BioNTech BNT162b2 mRNA vaccine (BNT162b2), Oxford University-AstraZeneca ChAdOx1-S vaccine (ChAdOx1-S), or Moderna mRNA-1273 vaccine (mRNA-1273) as their first 2 doses (or "spine"). Recipients of any other vaccine type as a first or second dose or those who received a different vaccine type as a second dose (ie, a heterologous schedule) were excluded because of small numbers and the inability to attribute any protective effect to a particular vaccine spine.

SOT recipients who were unmatched in the National Immunisation Management Service register were excluded, as were those without a valid National Health Service (NHS) number, a unique identifier for all patients in England for care provided by the NHS. Patients who had >1 episode of SARS-CoV-2 positive infection during the study period had outcomes analyzed for their first infection only. Individuals with a SARS-CoV-2 positive infection before December 7, 2020, were excluded from the Cox proportional-hazards analysis. Patients who received >4 vaccine doses were censored at the time of their fifth dose.

Outcomes of interest were the date of testing positive for SARS-CoV-2, noninjury hospitalization via emergency care within 14 d of a positive test, and patient death within 28 d of a positive test. Cohorts were followed until March 31, 2022, for SARS-CoV-2 infections and until April 28, 2022, for hospitalization or death (to allow for 28 d exposure). This study period covered an era when there was unrestricted access to testing for SARS-CoV-2 in the United Kingdom.

Vaccination status was defined as "unvaccinated" if the recipient had not received a vaccine dose during the study period or was ≤14 d after a first vaccine dose; "1 dose" if >14 d after the first dose and ≤14 d after the second dose; "2 doses" if >14 d after the second dose and ≤14 d after a third dose; "3 doses" if >14 d after a third dose and ≤14 d after a fourth dose; and "4 doses" if >14 d after a fourth dose.

Vaccination Program

The vaccination program commenced in December 2020, with most SOT recipients completing their first 2 doses by July 2021. They were eligible to receive a third dose from September 2021 and a fourth dose from January 2022.[15] The vaccination program in the United Kingdom required the third does or subsequent doses to be either BNT162b2 or mRNA-1273 vaccine type in general. Other than prioritization for early receipt, SOT recipients were not assigned any particular vaccine. National policy mandated a 10- to 12-wk gap between first and second vaccine doses, irrespective of vaccine type, and a minimum of 3 mo between the second and third doses and the third and fourth doses.[16] Vaccine rollout for the general population in the United Kingdom, including SOT recipients, has been described previously.[12,17,18]

The UK Health Security Agency designated Omicron as the dominant SARS-CoV-2 variant in the United Kingdom from December 2021,[18] with Alpha- and Delta-dominant periods described as before.[12] SARS-CoV-2 variant information was not available for each individual patient testing positive.

Study Design, Data Sources, Statistical Analyses, and Ethical Approval

This was a national retrospective cohort study enabled by linkage of 5 national registries in England, as described previously.[12,19] Unlike previous analyses from this group, positive tests included both lateral flow (antigen-based) tests reported to the UK Government and laboratory-confirmed tests for SARS-CoV-2 RNA. Data on the number of positive SARS-CoV-2 tests in the general population of England were obtained from the UK Government (https://coronavirus.data.gov.uk). Data on patient symptoms were not available.

In line with publications related to this pandemic, noninjury hospitalization within 14 d or death within 28 d of SARS-CoV-2 positive infection was assumed to be because of, or related to, COVID-19. Causes of death were not definitively known.

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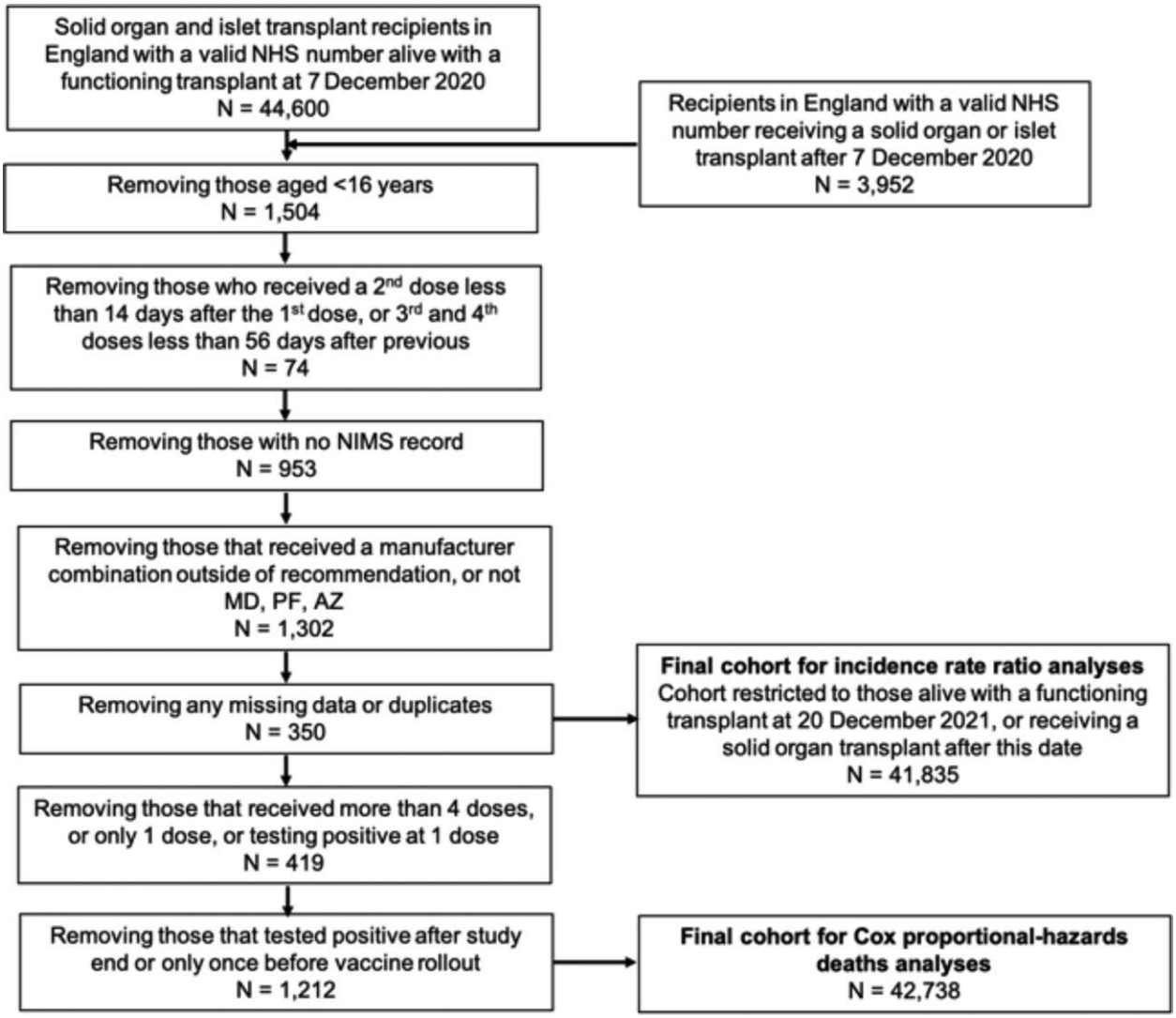

FIGURE 1. Study inclusion and exclusion criteria and patient flow. AZ, ChAdOx1-S vaccine; MD, mRNA-1273 vaccine; NHS, National Health Service; NIMS, National Immunisation Management Service; PF, BNT162b2 vaccine.

Demographic characteristics (type of organ received, time since transplant, sex, age, ethnicity, and NHS region) for SOT recipients were summarized and stratified by vaccination status. Differences in characteristics between groups of SOT recipients were tested univariately using the chi-square test. Three risk periods (<90 d, 90 d–1 y, and >1 y posttransplant) were arbitrarily selected a priori in an attempt to account for the changing burden of immunosuppression after transplantation.

In order to provide estimates of VE within the Omicron-dominant period, data from December 20, 2021, to March 31, 2022, were analyzed. To minimize temporal bias and to take into account variations in community prevalence of SARS-CoV-2 infections during that period, infection incidence rate was defined as the number of events divided by the person-time at risk, stratified by the 6 demographic characteristics above and calendar month and, in some analyses, vaccine type. A Poisson regression model was used to derive infection incidence rate ratios (IRRs) with 95% confidence intervals adjusted for the variables above, in which IRR is the risk-adjusted incidence rate in vaccinated recipients divided by the incidence rate for unvaccinated recipients. Hospitalization IRRs and hospitalization or death IRRs were adjusted for the same variables as infection IRRs.

To further investigate findings regarding risk of death, an additional analysis was conducted using Cox proportional-hazards modeling. The analysis period covered December 7, 2020, to March 31, 2022, rather than the Omicron-dominant period alone, with deaths observed to April 28, 2022. A Cox proportional-hazards model was used to estimate the hazard ratio of risk of death after SARS-CoV-2 positive infection, adjusting for type of organ received, time since transplant, sex, age, ethnicity, NHS region, vaccination status, and vaccine type. Unadjusted Kaplan-Meier estimates of patient survival from the day of SARS-CoV-2 positive infection were stratified by vaccination status and vaccine type and were compared using the log-rank test.

Analyses were undertaken using SAS, version 9.4 (SAS Institute Inc, Cary, NC), and STATA, version 14.2.

Ethical approval was as described previously.[12]

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RESULTS

By March 31, 2022, 2646 (6.2%) SOT recipients meeting study inclusion criteria were unvaccinated, 3822 (8.9%) had received 2 doses, 18 725 (43.8%) had received 3 doses, and 17 545 (41.1%) had received 4 doses (Table 1). Vaccination in SOT recipients began in December 2020, with the majority of patients having received 2 doses by June 2021; rollout of third doses began in September 2021 and fourth doses in January 2022 (Figure 2). The median (interquartile range) interval between first and second vaccine doses was 77 d (70–79 d), with intervals between the second and third doses, and third and fourth doses, of 191 d (182–205 d) and 105 d (95–123 d), respectively. There were no differences in intervals between vaccine types (data not shown). The overwhelming majority of SOT recipients received 1 or more vaccines after their transplant (Figure 1). The median (interquartile range) time between transplantation and first vaccine dose effective date was 6.5 y (2.6–12.5 y). Of the 3952 patients who were transplanted after the start of the study date, 3194 were vaccinated with 1 or more doses before their transplant.

Demographic characteristics of unvaccinated SOT recipients and those who had received 2, 3, or 4 vaccine doses by March 31, 2022, are shown in Table 1. Recipients who received 4 vaccine doses were more likely to be older, White, and female and to live outside London than those who did not. Of the 17 545 patients who received 4 vaccine doses, 9637 (54.9%) had been given 2 ChAdOx1-S doses followed by 2 mRNA vaccine doses (either BNT162b2 or mRNA-1273), whereas 7908 (45.1%) received 4 doses of mRNA vaccines (**Table S1, SDC**, http://links.lww.com/TP/C694).

TABLE 1.

Demographic characteristics of unvaccinated and vaccinated solid organ and islet transplant recipients on March 31, 2022

	Vaccination status								
	Unvaccinated		Two doses		Three doses		Four doses		
Variable	n	%	n	%	n	%	n	%	*P*
Total	2646	6.2	3822	8.9	18 725	43.8	17 545	41.1	
Transplant type									
Kidney[a]	1827	6	2748	9	13 234	43.5	12 583	41.4	<0.0001
SPK[b]	97	6	118	7.3	741	45.5	671	41.2	
Liver	532	7.1	620	8.3	3353	45	2950	39.6	
Heart	115	6.2	172	9.3	827	44.6	741	39.9	
Lung[c]	57	5	132	11.5	497	43.2	464	40.3	
Intestinal and multiorgan[d]	18	6.9	32	12.4	73	28.2	136	52.5	
Ethnicity									
White	1629	5.1	2341	7.3	13 470	41.8	14 761	45.8	<0.0001
Asian	359	7.4	807	16.7	2585	53.5	1080	22.4	
Black	438	18	425	17.5	1221	50.2	346	14.2	
Other	120	10.1	119	10	615	51.6	338	28.4	
Unknown	100	4.8	130	6.2	834	40	1020	48.9	
Age (y)									
16–49	1200	8.4	1777	12.4	6935	48.4	4428	30.9	<0.0001
50+	1446	5.1	2045	7.2	11 790	41.5	13 117	46.2	
Sex									
Male	1661	6.4	2327	8.9	11 577	44.5	10 469	40.2	<0.0001
Female	985	5.9	1495	8.9	7148	42.8	7076	42.4	
Time from transplant									
<90 d	111	12	68	7.3	619	66.8	129	13.9	<0.0001
90 d to 1 y	61	3	270	13.3	980	48.2	723	35.5	
>1 y	2474	6.2	3484	8.8	17 126	43.1	16 693	42	
NHS region									
East of England	267	5.1	369	7.1	2162	41.6	2403	46.2	<0.0001
London	776	10.3	904	12	3822	50.6	2049	27.1	
Midlands	429	5.6	752	9.7	3337	43.2	3199	41.5	
North East and Yorkshire	357	5.3	550	8.2	2721	40.6	3067	45.8	
North West	308	6.2	525	10.5	2379	47.7	1773	35.6	
South East	308	4.8	461	7.2	2690	41.9	2965	46.2	
South West	201	4.8	261	6.3	1614	38.8	2089	50.2	

[a]Includes single kidney, en bloc kidney, and double kidney transplants.
[b]Simultaneous pancreas-kidney transplants, including pancreas only, islet only, and simultaneous islet-kidney transplants.
[c]Includes single lung, double lung, partial lung, and heart-lung transplants.
[d]Includes if any other organ was transplanted with the intestine, as well as liver-kidney, heart-lung-liver, liver-pancreas, heart-kidney, heart-liver, and lung-liver transplants.
NHS, National Health Service; SPK, simultaneous pancreas-kidney transplant.

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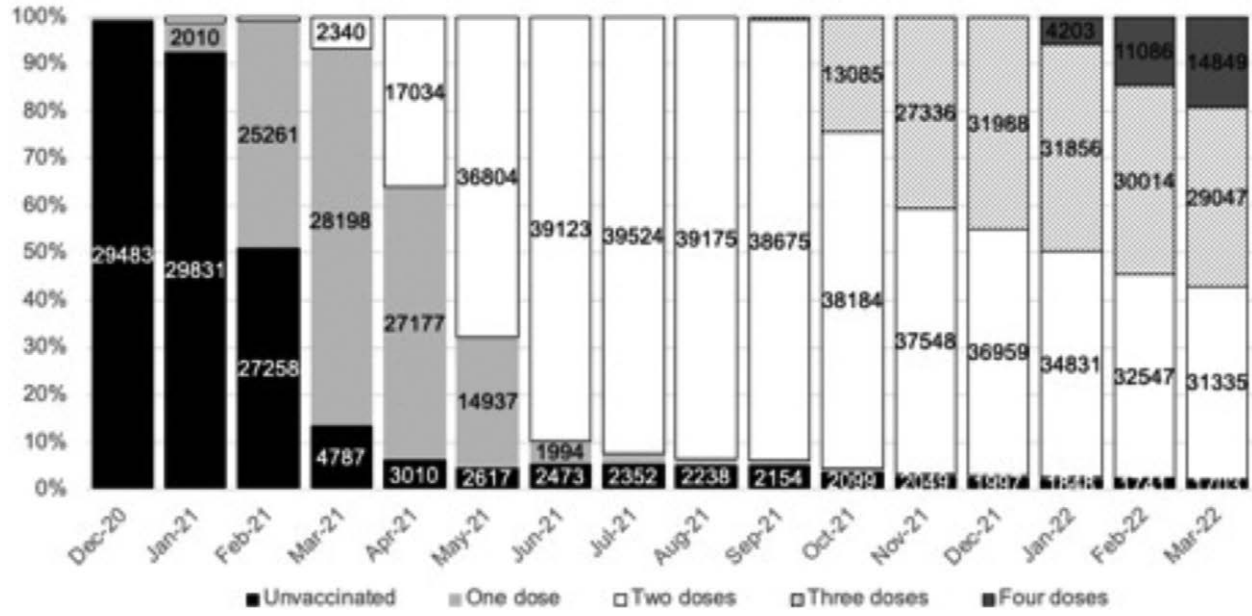

FIGURE 2. Percentage of unvaccinated and vaccinated solid organ and islet transplant recipients through the study period. Numbers >1000 are shown on the graph. Recipients can be counted more than once in each month as they receive a vaccine. Numbers in each month do not add up to the summary data by the end of the study date because of patient deaths, incident transplants, and censoring.

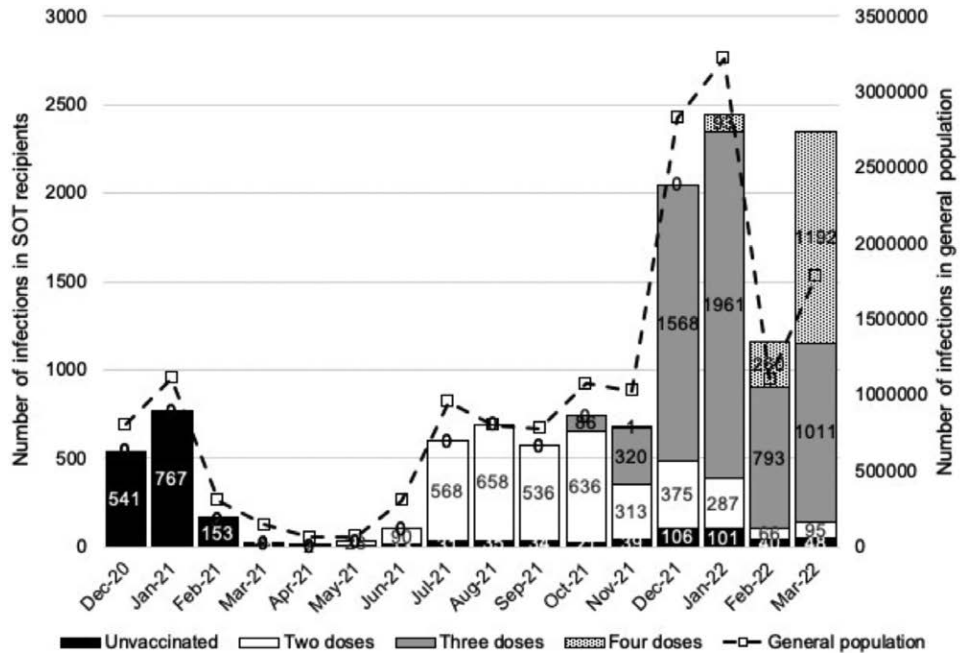

FIGURE 3. Number of SARS-CoV-2 positive infections per month in SOT recipients, by vaccination status compared with the general population in England, December 7, 2020, to March 31, 2022. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ and islet transplant.

SARS-CoV-2 Infections

Overall, there were 12 454 SOT recipients with at least 1 SARS-CoV-2 infection between December 7, 2020, and March 31, 2022. Cases peaked in December 2020 to January 2021, July 2021 to September 2021, and December 2021 to January 2022, corresponding to Alpha, Delta, and Omicron variant surges in the general UK population (Figure 3). The first peak occurred before vaccine rollout, whereas for later peaks, the majority of those testing positive had been vaccinated. Demographic characteristics of SOT recipients with SARS-CoV-2 infections at the time of the last positive test are shown in Table 2, stratified by vaccination status. Data by vaccine type are shown in **Table S2** (**SDC**, http://links.lww.com/TP/C694). The median (interquartile range) interval from latest vaccine-effective date before the last known positive

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TABLE 2.

Demographic characteristics of solid organ and islet transplant recipients with SARS-CoV-2 infection or death within 28 d of the latest positive test, by vaccination status, December 7, 2020, to March 31, 2022

	Unvaccinated			Two vaccine doses			Three vaccine doses			Four vaccine doses			
	Cases	Deaths		Cases	Deaths		Cases	Deaths		Cases	Deaths		
Variable	n	n	%	n	n	%	n	n	%	n	n	%	*P*
Total	1764	210	11.9	3465	265	7.6	5702	153	2.7	1523	14	0.9	
Transplant type													
Kidney[a]	1333	155	11.6	2533	191	7.5	4170	112	2.7	1133	10	0.9	0.90
SPK[b]	58	8	13.8	145	6	4.1	239	4	1.7	55	0	0	
Liver	279	27	9.7	493	29	5.9	809	19	2.3	199	2	1	
Heart	57	8	14	180	17	9.4	271	10	3.7	74	1	1.4	
Lung[c]	34	12	35.3	92	22	23.9	181	8	4.4	50	1	2	
Intestinal and multiorgan[d]	3	0	0	22	0	0	32	0	0	12	0	0	
Ethnicity													
White	1029	122	11.9	2514	193	7.7	4456	111	2.5	1330	14	1.1	0.002
Asian	357	45	12.6	518	41	7.9	564	18	3.2	84	0	0	
Black	224	28	12.5	227	19	8.4	269	8	3	16	0	0	
Other	79	6	7.6	82	2	2.4	156	6	3.8	25	0	0	
Unknown	75	9	12	124	10	8.1	257	10	3.9	68	0	0	
Age group (y)													
16–49	745	27	3.6	1570	37	2.4	2329	8	0.3	530	2	0.4	0.05
50+	1019	183	18	1895	228	12	3373	145	4.3	993	12	1.2	
Sex													
Male	1064	135	12.7	2074	179	8.6	3399	109	3.2	871	9	1	0.6
Female	700	75	10.7	1391	86	6.2	2303	44	1.9	652	5	0.8	
Time from transplant													
<90 d	47	7	14.9	61	1	1.6	77	0	0	10	0	0	0.05
90 d to 1 y	103	9	8.7	197	9	4.6	280	4	1.4	75	0	0	
>1 y	1614	194	12	3207	255	8	5345	149	2.8	1438	14	1	
NHS region													
East of England	177	33	18.6	353	24	6.8	712	12	1.7	225	1	0.4	0.002
London	537	47	8.8	563	35	6.2	1013	20	2	194	0	0	
Midlands	333	47	14.1	689	65	9.4	1035	38	3.7	257	3	1.2	
North East and Yorkshire	169	18	10.7	619	54	8.7	855	22	2.6	239	0	0	
North West	207	22	10.6	503	35	7	692	23	3.3	155	3	1.9	
South East	246	26	10.6	451	29	6.4	841	20	2.4	268	3	1.1	
South West	95	17	17.9	287	23	8	554	18	3.2	185	4	2.2	

[a]Includes single kidney, en bloc kidney, and double kidney transplants.
[b]Simultaneous pancreas-kidney transplants, including pancreas only, islet only, and simultaneous islet-kidney transplants.
[c]Includes single lung, double lung, partial lung, and heart-lung transplants.
[d]Includes if any other organ was transplanted with the intestine, as well as liver-kidney, heart-lung-liver, liver-pancreas, heart-kidney, heart-liver, and lung-liver transplants.
NHS, National Health Service; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SPK, simultanoues pancreas-kidney transplant.

SARS-CoV-2 infection result was 77 d (45–125 d) (**Figure S1, SDC**, http://links.lww.com/TP/C694). Of the 12 454 recipients who tested positive for SARS-CoV-2 at least once, just 608 (4.9%) had received 1 or more vaccines pretransplant.

VE in the Omicron-dominant Period

This cohort comprised 41 835 SOT recipients, of whom 1997 remained unvaccinated. Between December 20, 2021, and March 31, 2022, the incidence rate of SARS-CoV-2 infections was 146.0 per 100 000 person-days for unvaccinated recipients, 168.1 per 100 000 person-days for those who received 2 vaccine doses, 183.6 per 100 000 person-days for those who received 3 doses, and 238.6 per 100 000 for those recipients who received 4 doses (Table 3). Compared with the unvaccinated SOT cohort, the risk-adjusted infection IRR was 1.25 (1.08–1.45), 1.46 (1.28–1.67), and 1.79 (1.54–2.06) for those receiving 2, 3, and 4 doses, respectively, indicating that vaccination did not reduce the risk of testing positive for SARS-CoV-2. When vaccine type was analyzed, no regimen showed a protective effect from SARS-CoV-2 infection. Risk-adjusted IRRs by vaccine status, demographic variables, and month are shown in **Table S3** (**SDC**, http://links.lww.com/TP/C694).

Severe event (hospitalization or death) data were also analyzed using IRR methods. During the Omicron-dominant period, there were 515 noninjury hospitalizations within 14 d of a positive SARS-CoV-2 test (Table 4). Vaccination was associated with a reduction in the risk of hospitalization and hospitalization or death following a positive test but only in those who had received

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TABLE 3.

SARS-CoV-2 infection incidence rates and risk-adjusted incidence rate ratios in solid organ and islet transplant recipients in the Omicron-dominant period, December 20, 2021, to March 31, 2022

	Unvaccinated		Two doses		Three doses		Four doses			
Vaccination status	Cases	Incidence rate per 100 000 person-days	Cases	Incidence rate per 100 000 person-days	Cases	Incidence rate per 100 000 person-days	Cases	Incidence rate per 100 000 person-days	Risk-adjusted incidence rate ratio (95% CI)	*P*
Total	252	146.0	697	168.1					1.25 (1.08-1.45)	0.002
					4857	183.6			1.46 (1.28-1.67)	<0.001
							1522	238.6	1.79 (1.54-2.06)	<0.001
By vaccine type										
AZ spine only			432	171.0					1.29 (1.11-1.52)	0.001
mRNA spine only			265	163.6					1.20 (1.01-1.43)	0.04
AZ spine + mRNA booster					2740	180.8			1.45 (1.27-1.66)	<0.001
mRNA spine + mRNA booster					2117	187.3			1.49 (1.30-1.70)	<0.001
AZ spine + 2 mRNA boosters							779	230.3	1.73 (1.49-2.01)	<0.001
mRNA spine + 2 mRNA boosters							743	248.1	1.84 (1.58-2.13)	<0.001

AZ, ChAdOx1-S vaccine; CI, confidence interval; mRNA, BNT162b2 or mRNA-1273 vaccines; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 4.

Vaccine effectiveness against hospitalization and against hospitalization or death, by vaccine number and type, during the Omicron-dominant period December 20, 2021, to March 31, 2022

Vaccination status	Person-years	Hospitalizations within 14 d of SARS-CoV-2 positive infection	Deaths within 28 d of SARS-CoV-2 positive infection	Hospitalizations within 14 d or deaths within 28 d of SARS-CoV-2 positive infection	Risk-adjusted hospitalization incidence rate ratio (hospitalization within 14 d of SARS-CoV-2 positive infection)	*P*	Risk-adjusted hospitalization or death incidence rate ratio (hospitalization within 14 d or death within 28 d of SARS-CoV-2 positive infection)	*P*
Unvaccinated	497	38	10	43	–		–	
Two doses	870.5	82	13	92	1.27 (0.86-1.88)	0.2	1.27 (0.88-1.83)	0.2
Three doses	6793	341	106	389	0.66 (0.46-0.93)	0.02	0.62 (0.45-0.86)	0.004
Four doses	1983	54	14	63	0.43 (0.27-0.66)	<0.0001	0.39 (0.26-0.58)	<0.0001
By vaccine type								
Unvaccinated	497	38	10	43	–		–	
AZ spine only	520.5	52	8	57	1.36 (0.89-2.07)	0.2	1.32 (0.89-1.97)	0.2
mRNA spine only	350	30	5	35	1.15 (0.71-1.86)	0.6	1.19 (0.76-1.87)	0.4
AZ spine + mRNA booster	3944.4	194	65	220	0.66 (0.46-0.94)	0.02	0.62 (0.44-0.87)	0.01
mRNA spine + mRNA booster	2848.6	147	41	169	0.65 (0.45-0.94)	0.02	0.62 (0.44-0.88)	0.01
AZ spine + 2 mRNA boosters	1055.8	32	8	36	0.48 (0.29-0.79)	0.004	0.42 (0.27-0.67)	<0.0001
mRNA spine + 2 mRNA boosters	927.1	22	6	27	0.36 (0.21-0.63)	<0.0001	0.35 (0.21-0.57)	<0.0001

"–" represents 'Not relevant' in this context.
AZ, ChAdOx1-S vaccine; mRNA, BNT162b2 or mRNA-1273 vaccines; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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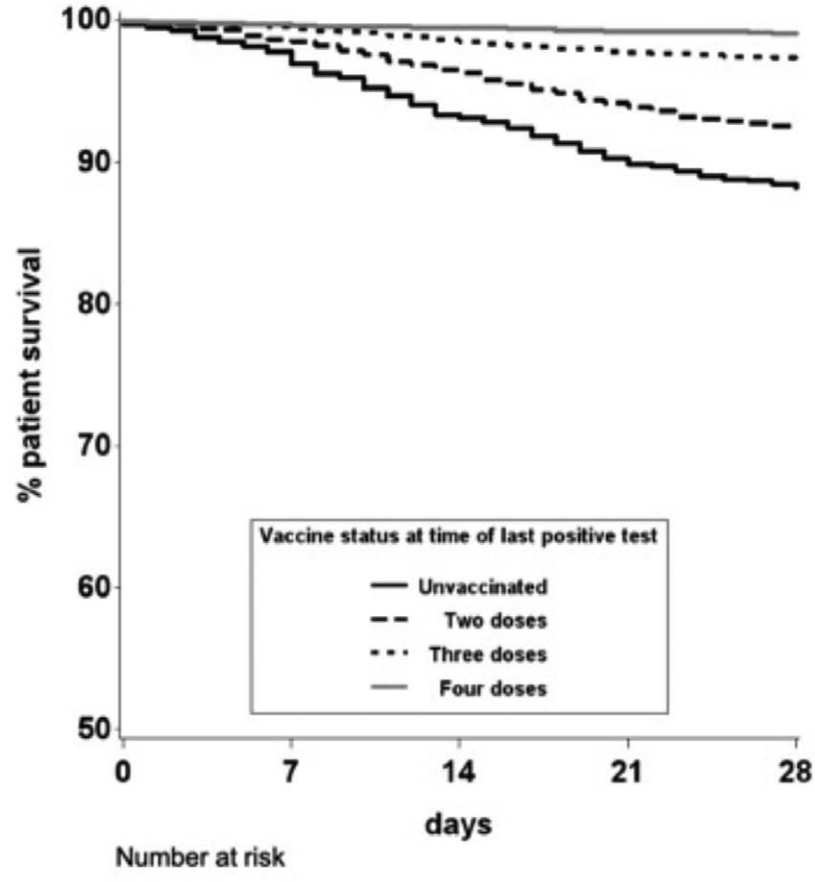

Number at risk

Unvaccinated	1761	1722	1644	1590	1558
Two doses	3463	3416	3342	3262	3206
Three doses	5701	5675	5624	5577	5551
Four doses	1523	1519	1515	1511	1509

FIGURE 4. Unadjusted patient survival within 28 d of infection with SARS-CoV-2 from date of testing positive, by vaccination status, December 7, 2020, to March 31, 2022. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

3 or more vaccine doses. The greatest protection from a severe event after SARS-CoV-2 infection occurred in those who had received 4 vaccines, particularly for those who received an mRNA vaccine spine and 2 mRNA boosters (Table 4).

Deaths Within 28 d of a Last Reported Positive SARS-CoV-2 Test

Insufficient mortality events were observed to enable a meaningful Cox proportional-hazards analysis of death data during the Omicron-dominant period. Therefore, to expand on the IRR severe events analysis, a broader time period was used. Between December 7, 2020, and March 31, 2022, 12 454 SOT recipients had at least 1 SARS-CoV-2 infection, and 642 (5.2%) died within 28 d. Demographic characteristics of recipients dying after SARS-CoV-2 infection are shown in Table 2. Overall, of those SOT recipients who were unvaccinated at the time of positive test, 11.9% (210/1764) died within 28 d of a SARS-CoV-2 infection, compared with 7.6% of those who had received 2 doses (265/3465), 2.7% receiving 3 doses (153/5702), and 0.9% of those receiving 4 doses (14/1523).

Patient survival from the day of last reported SARS-CoV-2 positive result was plotted using an unadjusted Kaplan-Meier analysis, stratified by vaccination status (Figure 4). SOT recipients who had received 2 doses, 3 doses, or 4 doses had a higher survival at 28 d than those who were unvaccinated (92.4%, 97.3%, and 99.1%, respectively, versus 88.2%, respectively; $P < 0.0001$).

After risk-adjustment, a statistically significant increased chance of death within 28 d of a SARS-CoV-2 infection was found in those who were aged ≥50 y, from Black or Asian ethnic groups, male, and a recipient of a heart or lung transplant; those living outside of London (except for the South East); and those testing positive during the Alpha- or Delta-dominant periods (Figure 5 and **Table S4, SDC**, http://links.lww.com/TP/C694). The risk-adjusted hazard ratio (95% confidence interval) for death within 28 d of SARS-CoV-2 infection was 0.67 (0.46-0.98) for those with 2 vaccine doses, 0.46 (0.30-0.69) for those with 3 vaccine doses, and 0.18 (0.09-0.35) for those who had received 4 vaccine doses, in comparison to the unvaccinated group. The risk-adjusted hazard ratio for death within 28 d of SARS-CoV-2 infection during the Omicron-dominant

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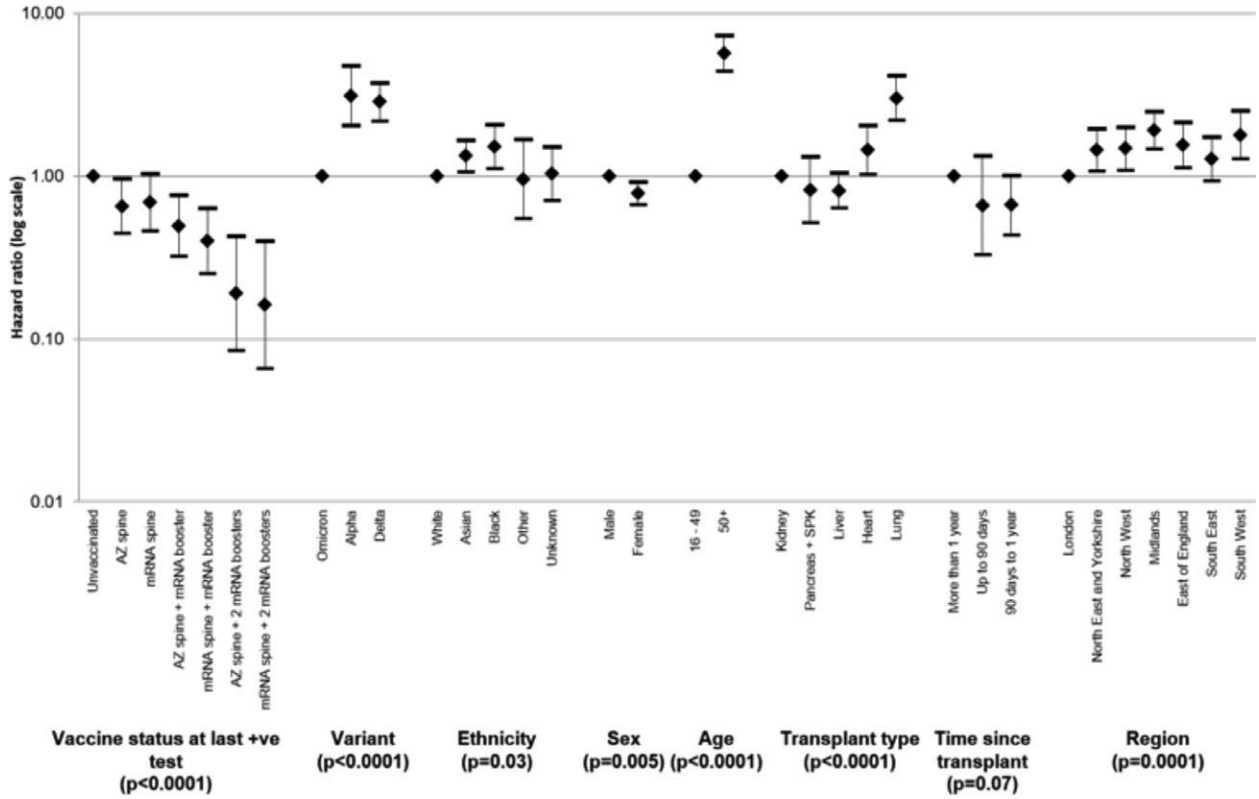

FIGURE 5. Hazard ratios (95% confidence intervals) of risk of death within 28 d of SARS-CoV-2 infection in solid organ and islet transplant recipients, by vaccination status, variant dominant period, and demographic characteristics, December 7, 2020, to March 31, 2022. AZ, ChAdOx1-S vaccine; mRNA, either BNT162b2 or mRNA-1273 vaccine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

period was significantly lower than that during the Alpha- and Delta-dominant periods (3.12 [2.04-4.78] and 2.86 [2.18-3.76], respectively).

Differences in effectiveness between vaccine types were investigated with unadjusted and risk-adjusted analyses. Kaplan-Meier survival curves suggested that rates of death within 28 d following SARS-CoV-2 infection were lowest after vaccination with an mRNA spine followed by 2 mRNA boosters (Figure 6). Inclusion of vaccine type as a variable in the Cox proportional-hazards model allowed investigation of protective effect of different vaccine types (Figure 7 and **Table S5, SDC**, http://links.lww.com/TP/C694). Those receiving an mRNA spine followed by 2 mRNA boosters had the largest reduction in risk of death after SARS-CoV-2 infection (84%) when compared with unvaccinated recipients.

DISCUSSION

This national registry linkage analysis shows that the majority of SOT recipients in England received 3 or 4 doses of SARS-CoV-2 vaccines. There was an incremental benefit against hospitalization or death during the Omicron-dominant period in England for recipients of 3 or 4 doses compared with recipients of 2 doses or fewer. However, there was no vaccine-associated protection against the risk of testing positive for SARS-CoV-2 infection. As reported previously,[12] demographic factors including age, ethnicity, and organ transplant type were associated with adverse outcomes.

The high number of mutations in the receptor binding domain of the Omicron variant raised concerns of reduced VE.[20] VE following third or fourth doses including effectiveness against the Omicron variant in the general population have been recently reported.[6,7,21-24] Grewal et al[21] showed that a fourth vaccine dose was associated with a strong protection against severe outcomes due to the Omicron variant in vaccinated care home residents compared with unvaccinated residents. Similar to the findings in our study, Grewal et al[21] also showed greater VE with each additional dose for all outcomes. Bar-on et al[22] demonstrated that recipients of a fourth dose of BNTb162b had lower rates of confirmed SARS-CoV-2 infection and severe COVID-19 compared with 3-dose recipients. Andrews et al[6] showed that, in the UK general population, immunization with 2 doses of ChAdOx1-S or BNT162b2 vaccine provided limited protection against symptomatic disease caused by the Omicron variant. A BNT162b2 or an mRNA-1273 booster after either the ChAdOx1-S or BNT162b2 primary course substantially increased protection. Although the above and other studies described outcomes in the general population following third and fourth doses of vaccine, large-scale studies describing outcomes in immunocompromised patients, including SOT recipients, are lacking. A number of studies report on immunogenicity, including both humoral and cell-mediated responses, in transplant recipients of 2 or more vaccine doses, but these reports do not include clinical outcome data. These studies have been reviewed by Napuri et al[25] and Lee et al.[26]

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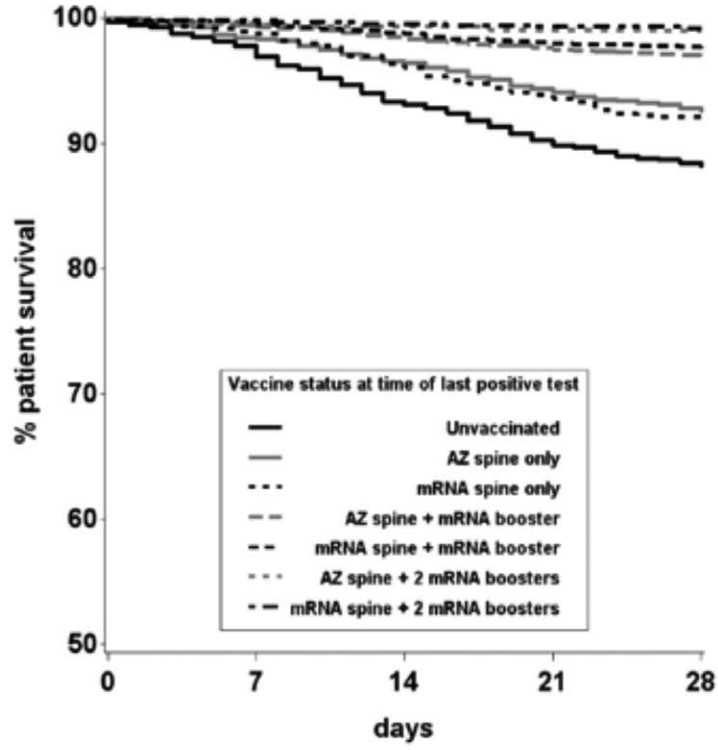

Unvaccinated	1761	1722	1644	1590	1558
AZ spine only	2156	2123	2082	2035	2002
mRNA spine only	1307	1293	1260	1227	1204
AZ spine + mRNA booster	3213	3194	3165	3137	3120
mRNA spine + mRNA booster	2488	2481	2459	2440	2431
AZ spine + 2 mRNA boosters	778	775	773	771	770
mRNA spine + 2 mRNA boosters	745	744	742	740	739

FIGURE 6. Unadjusted patient survival from date of testing positive for SARS-CoV-2, by vaccination status and vaccine type, December 7, 2020, to March 31, 2022. AZ, ChAdOx1-S vaccine; mRNA, either BNT162b2 or mRNA-1273 vaccine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Our study is one of the first to report outcomes during the Omicron era in SOT patients on a national scale.[27] Pinto-Alvarez et al[27] recently reported VE in a Colombian cohort of almost 7000 solid organ transplant recipients, showing that 3 vaccine doses appeared to provide almost 95% protection against death due to COVID-19 between March 2021 and May 2022. We were able to examine outcomes in a larger population, enabling us to specifically study VE during the Omicron-dominant period between December 2021 and March 2022. Our study suggests that 3 or 4 vaccine doses reduced severe events (hospitalization or death) after SARS-CoV-2 infection by between 40% and 60% during the Omicron era. Linkage of the 5 national registries that host data on immunization, infection, organ transplantation, hospitalizations, and survival allowed near real-time complete identification of new SARS-CoV-2 infections and severe events in this patient cohort. Inclusion and comprehensive follow-up of the entire at-risk population in England provided a more accurate effect estimate when comparing vaccinated versus unvaccinated SOT patients in the real world and is therefore likely to be translatable to similar patient populations in other countries.

Although the study findings of incremental protection with successive vaccine doses against severe outcomes following SARS-CoV 2 infections will be heartening, the finding of vaccination being associated with a higher risk of infection may seem counterintuitive. The absence of "sterilizing immunity" following vaccination in this patient population is not surprising because this is the same as the general population, with the benefit of vaccination predominantly being a reduced risk of hospitalization and death. Furthermore, it is possible that vaccinated SOT patients, with the confidence derived from vaccination, relaxed their NPIs more than unvaccinated patients and therefore were exposed to a higher risk of infection. The observational cohort study design does not allow us to accurately control for the confounding from relative uptake and adherence to NPIs and the associated risks of acquiring infection.

Because of the registry-based retrospective methodology, it is not possible to account for asymptomatic infections that were not confirmed with either a lateral flow or polymerase chain reaction test. Similar to published vaccine efficacy trials, it is not possible to disaggregate

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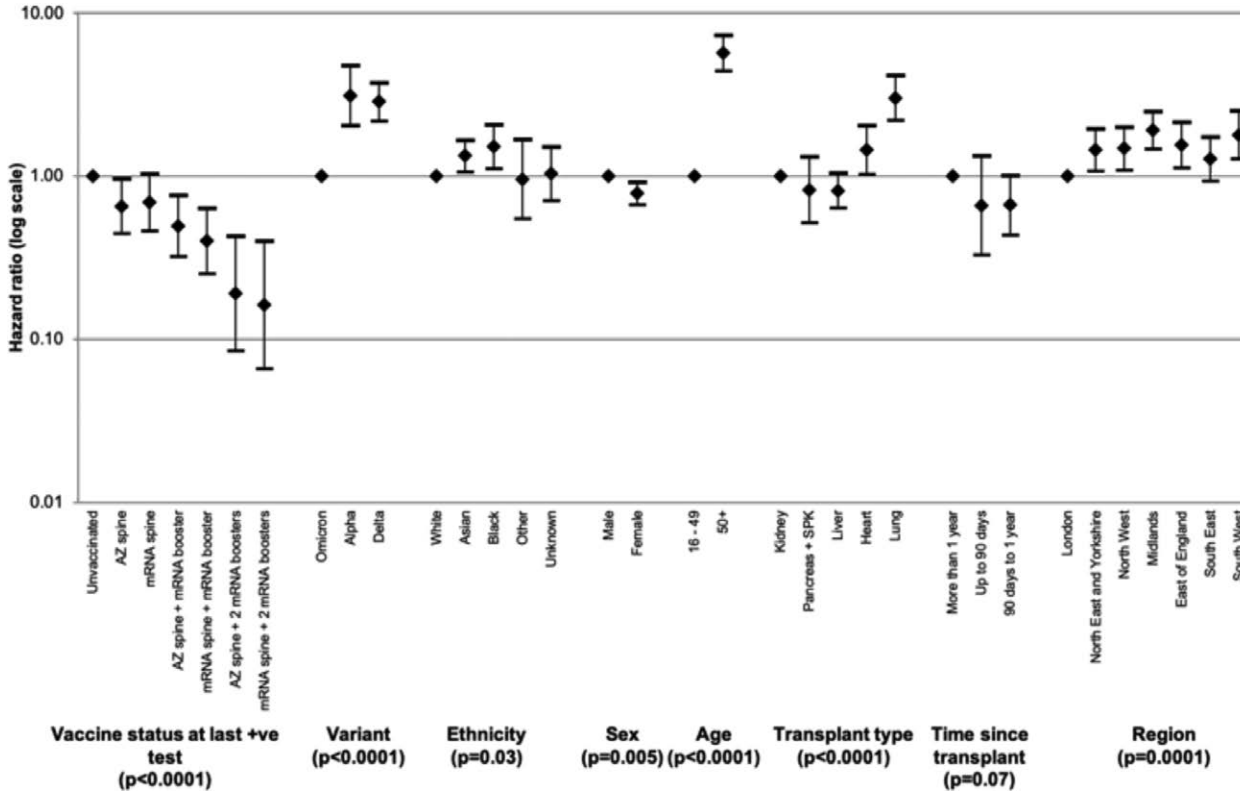

FIGURE 7. Hazard ratios with 95% confidence intervals of risk of death within 28 d of testing positive for SARS-CoV-2 in solid organ and islet transplant recipients, by vaccination status, vaccine type, and demographic characteristics, December 7, 2020, to March 31, 2022. AZ, ChAdOx1-S vaccine; mRNA, BNT162b2 or mRNA-1273 vaccines; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

the protective influence of NPIs from any vaccine-derived protection. Approved antiviral treatments, including remdesivir, molnupiravir, and sotrovimab, for at-risk populations, such as SOT recipients, were available for use in the United Kingdom during the study period. It was not possible to identify patients who had received such antiviral treatments, and although it is unlikely any of the cohorts described in our study were systematically biased for or against receiving antiviral therapy, the absence of this information is a weakness.[28] Furthermore, we were not able to analyze VE by immunosuppressant regimen because of incomplete data. Finally, it is not possible to rule out residual confounding due to factors that we were unable to control for or were unknown to the study team.

The SARS-CoV-2 pandemic has had significant on organ transplant services and patients across the globe.[29] Furthermore, COVID-19 outcomes in SOT recipients are significantly worse than the general population.[10,30] Our finding that there is incremental protection in vulnerable SOT recipients with each additional vaccine dose (at least up to the fourth vaccine dose), and that this extends to the Omicron variant, is heartening for patients and clinicians alike. Certainly, the mortality rate of <1% in those SOT recipient testing SARS-CoV-2 positive who had 4 vaccine doses is a very different perspective than the >10% mortality rates reported in this population at the onset of the pandemic.[10] This is especially relevant because mandated NPI and universal access to polymerase chain reaction testing of symptomatic citizens have been stood down in most countries and SOT recipients can no longer rely on such measures for protection.

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