

Comparative effectiveness of two- and three-dose COVID-19 vaccination schedules involving AZD1222 and BNT162b2 in people with kidney disease: a linked OpenSAFELY and UK Renal Registry cohort study



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Summary

Background Kidney disease is a key risk factor for COVID-19-related mortality and suboptimal vaccine response. Optimising vaccination strategies is essential to reduce the disease burden in this vulnerable population. We therefore compared the effectiveness of two- and three-dose schedules involving AZD1222 (AZ; ChAdOx1-S) and BNT162b2 (BNT) among people with kidney disease in England.

Methods With the approval of NHS England, we performed a retrospective cohort study among people with moderate-to-severe kidney disease. Using linked primary care and UK Renal Registry records in the OpenSAFELY-TPP platform, we identified adults with stage 3–5 chronic kidney disease, dialysis recipients, and kidney transplant recipients. We used Cox proportional hazards models to compare COVID-19-related outcomes and non-COVID-19 death after two-dose (AZ–AZ vs BNT–BNT) and three-dose (AZ–AZ–BNT vs BNT–BNT–BNT) schedules.

Findings After two doses, incidence during the Delta wave was higher in AZ–AZ ($n = 257,580$) than BNT–BNT recipients ($n = 169,205$; adjusted hazard ratios [95% CIs] 1.43 [1.37–1.50], 1.59 [1.43–1.77], 1.44 [1.12–1.85], and 1.09 [1.02–1.17] for SARS-CoV-2 infection, COVID-19-related hospitalisation, COVID-19-related death, and non-COVID-19 death, respectively). Findings were consistent across disease subgroups, including dialysis and transplant recipients. After three doses, there was little evidence of differences between AZ–AZ–BNT ($n = 220,330$) and BNT–BNT–BNT recipients ($n = 157,065$) for any outcome during a period of Omicron dominance.

Interpretation Among individuals with moderate-to-severe kidney disease, two doses of BNT conferred stronger protection than AZ against SARS-CoV-2 infection and severe disease. A subsequent BNT dose levelled the playing field, emphasising the value of heterologous RNA doses in vulnerable populations.

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Research in context

Evidence before this study

We searched Medline for studies published between 1st December 2020 and 7th September 2022 using the following term: “(coronavir* or covid* or sars*) and (vaccin* or immuniz* or immuniz*) and (kidney or dialysis or haemodialysis or transplant or renal) and (efficacy or effectiveness)”. We identified studies reporting on the effectiveness of various COVID-19 vaccines in individuals with chronic kidney disease (CKD) or end-stage renal disease. Several studies have reported no clear differences in effectiveness against outcomes of varying severity after two doses of BNT162b2 or AZD1222 compared to unvaccinated controls, which is contrary to the significantly higher antibody levels observed after BNT162b2 in immunogenicity studies. One study also showed that a third dose of RNA vaccine restored some protection against the Omicron variant among BNT162b2- and AZD1222-primed individuals, with no clear differences between these groups. This finding is consistent with immunogenicity data suggesting that a third dose of BNT162b2 may reduce the gap in antibody levels observed after two of AZD1222 versus BNT162b2. Notably, we found few studies directly comparing effectiveness in BNT162b2 versus AZD1222 recipients, which reduces biases associated with comparison to a small and potentially unrepresentative group of unvaccinated controls. We also found no studies exploring COVID-19 vaccine effectiveness in kidney disease groups of varying severity (CKD, dialysis, and kidney transplant).

Added value of this study

This is the largest study to compare the effectiveness of two- and three-dose regimens involving AZD1222 and BNT162b2 among people with moderate-to-severe kidney disease. We compared effectiveness after two and three doses in 426,780 and 377,395 individuals, respectively, and harnessed unique data linkages between primary care records and UK Renal Registry data to identify people with CKD and end-stage renal disease (including dialysis and kidney transplant recipients) with high accuracy. During the Delta wave of infection, we observed a higher risk of COVID-19-related outcomes of varying severity after two doses of AZD1222 versus BNT162b2, with consistent findings in CKD, dialysis, and transplant subgroups. After a third dose of BNT162b2, AZD1222- and BNT162b2-primed individuals had similar rates of COVID-19-related outcomes during a period of Omicron dominance.

Implications of all the available evidence

A growing body of immunogenicity and effectiveness data – including the present study – suggest that two doses of BNT162b2 confers stronger protection than AZD1222 among people with moderate-to-severe kidney disease. However, a third dose of BNT162b2 appears to compensate for this immunity deficit, providing equivalent protection in BNT162b2- and AZD1222-primed individuals. Achieving high coverage with additional RNA vaccine doses (whether homologous or heterologous) has the capacity to reduce the burden of disease in this vulnerable population.

Introduction

During the SARS-CoV-2 pandemic, the burden of morbidity and mortality has not been shared equally across society. Social and demographic factors have underpinned stark inequities in SARS-CoV-2 exposure, while clinical factors have shaped the ensuing risk of harm among those infected. Although COVID-19 vaccines have the potential to mitigate these inequities, people with compromised immune systems may fail to mount a protective response to primary or booster doses,^{1,2} leaving them at increased risk of subsequent infection and disease compared with healthy adults.^{3,4}

Kidney disease is a key risk factor for both COVID-19-related mortality and suboptimal COVID-19 vaccine response.^{4,5} Observational studies of vaccine immunogenicity have highlighted possible ways to optimise immunisation strategies in this population. In people receiving haemodialysis, antibody levels are significantly lower following two doses of the vectored vaccine AZD1222 (AZ; ChAdOx1-S) compared with the RNA vaccine BNT162b2 (BNT).^{6,7} However, a heterologous BNT third dose among AZ-primed individuals (AZ–AZ–BNT) appears to reduce the immunogenicity gap, inducing antibody levels equivalent⁷ or closer^{8,9} to those observed after a homologous three-dose series (BNT–BNT–BNT).

The extent to which these immunogenicity data translate to protection against infection and severe COVID-19 remains uncertain. To address this, we harnessed unique data linkages within the OpenSAFELY-TPP database to estimate the comparative effectiveness of two-dose (AZ–AZ vs BNT–BNT) and three-dose (AZ–AZ–BNT vs BNT–BNT–BNT) schedules among people with kidney disease in England.

Methods

Data sources

All data were linked, stored, and analysed securely within the OpenSAFELY platform <https://opensafely.org/>. OpenSAFELY is a data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions. The dataset analysed within OpenSAFELY-TPP is based on 24 million people currently registered with GP surgeries using TPP SystemOne software. Data include pseudonymised data such as coded diagnoses, medications, and physiological parameters. No free text data are included. All code is shared openly for review and re-use under MIT open license (<https://github.com/opensafely/ckd-coverage-ve>). Detailed pseudonymised patient data is potentially re-

identifiable and therefore not shared. Primary care data are linked through OpenSAFELY with other pseudonymised datasets, including COVID-19 testing records via the Second Generation Surveillance System (SGSS), A&E attendance and hospital records via NHS Digital's Hospital Episode Statistics (HES), national death registry records from the Office for National Statistics (ONS), and renal replacement therapy (RRT) status via the UK Renal Registry (UKRR). Vaccination status is directly available within GP records via the National Immunisation Management System.

Study population

We defined separate cohorts for the two- and three-dose analyses. Baseline characteristics were defined as of dose 1 (two-dose cohort) or dose 3 (three-dose cohort), except for age, which was calculated as of 31st March 2021 as per UK Health Security Agency recommendations.¹⁰ We assessed potential eligibility among individuals who were at least 16 years of age and had been registered in OpenSAFELY-TPP for at least 3 months before their first COVID-19 vaccine dose.

Each cohort comprised: (i) individuals receiving RRT (dialysis or transplant), as listed within the UKRR as of 31st December 2020; and (ii) individuals with evidence of stage 3–5 chronic kidney disease (CKD) in the absence of RRT. Individuals with CKD were identified based on their most recent serum creatinine measurement in the 2 years preceding baseline. Creatinine levels were converted into estimated glomerular filtration rate (eGFR) using the CKD epidemiology collaboration equation without specification of ethnicity,¹¹ and an eGFR of <60 ml/min/1.73 m² used as a threshold for inclusion. To assess CKD severity, we distinguished between stage 3a (eGFR of 45–59 ml/min/1.73 m²), stage 3b (eGFR of 30–44 ml/min/1.73 m²), and stage 4–5 CKD (eGFR <30 ml/min/1.73 m²). Individuals with primary care codes suggesting prior dialysis or kidney transplant but absent from the UKRR were excluded given their ambiguous kidney disease status at the point of recruitment.

Individuals were included in the two-dose cohort if they: (i) had complete data on sex, ethnicity, NHS region, and index of multiple deprivation (IMD), given that missing data for these key variables are likely to indicate poor data quality; (ii) received AZ–AZ or BNT–BNT; (iii) received their first vaccine dose on or after 4th January 2021 (when both AZ and BNT were in concurrent use); (iv) had a dose 1–2 interval of 8–14 weeks; (v) were not health or social care workers, residents in care or nursing homes, medically housebound, or receiving end-of-life care (given atypical testing and exposure patterns in these groups); (vi) were not aged ≥80 years (given significant vaccination in this age group before AZ was available); (vii) received their second dose on or before 17th October 2021 (ensuring 30 days of potential follow-up); and (viii) had no

documented SARS-CoV-2 infection in the 90 days preceding dose 1 or between doses 1 and 2.

Individuals were included in the three-dose cohort if they fulfilled criteria (i) to (vi) above and received BNT as a third dose between 1st September 2021 (the date on which third primary doses were recommended for immunosuppressed individuals¹²) and 1st March 2022. Additionally, individuals were excluded if they had a dose 2–3 interval of <12 weeks or were infected with SARS-CoV-2 between doses 1 and 3 (to mitigate the influence of hybrid immunity). We did not distinguish between third primary and booster doses.

Outcomes

We assessed the following post-vaccination outcomes: SARS-CoV-2 infection; COVID-19-related hospitalisation; COVID-19-related death; and non-COVID-19 death. SARS-CoV-2 infections were defined based on positive PCR or lateral flow tests (irrespective of symptom status). COVID-19-related hospitalisations were defined based on completed hospital episodes with a COVID-19-related diagnostic code. COVID-19-related and non-COVID-19 deaths were defined based on death certificates with versus without a COVID-19-related code anywhere on the death certificate (i.e. as a contributing or underlying cause). This inclusive definition of COVID-19-related deaths allows for clinical judgement alongside recent testing information. Further coding details are provided in [Supplementary Table S1](#).

For the two-dose cohort, follow-up started on the date of dose 2 and extended until 16th November 2021 (2 months after all individuals became eligible for a third dose¹³). For the three-dose cohort, follow-up started on the date of dose 3 and extended until 31st March 2022 for SARS-CoV-2 infection (the date when free testing for the public came to an end) or 21st May 2022 for other outcomes (2 months after the launch of the spring booster campaign^{14,15}).

Potential confounding variables

We defined the following potential confounders in each cohort: age; sex; ethnicity; social deprivation based on IMD quintile; setting (urban, urban conurbation, or rural); kidney disease subgroup (CKD3a, CKD3b, CKD4–5, dialysis, or transplant); clinical comorbidities that influenced vaccine prioritisation ([Supplementary Table S1](#)); prior SARS-CoV-2 infection; and number of SARS-CoV-2 tests (0, 1, 2, or 3+) in the 90 days preceding 4th January 2021 (two-dose cohort) or 1st September 2021 (three-dose cohort) as an indicator of testing behaviour. After excluding individuals data with missing data on sex, ethnicity, NHS region, or IMD (as defined in the inclusion criteria above), there were no missing values as remaining variables were defined by the presence or absence of codes or events.

Statistical analysis

Follow-up started on the day of vaccination (dose 2 or 3) and was censored at the earliest of death, deregistration, the administration of a subsequent COVID-19 vaccine dose, 182 days, the end of the study period (as defined above), or the outcome of interest. We used the Kaplan–Meier (KM) method to estimate cumulative incidence and associated 95% confidence intervals (CIs). We used Cox proportional hazards models to compare effectiveness of AZ–AZ versus BNT–BNT (two-dose cohort) and AZ–AZ–BNT versus BNT–BNT–BNT (three-dose cohort) for each outcome. Hazard ratios (HRs) and 95% CIs were estimated for the whole study period and during the following time periods: days 1–14, 15–70, 71–126, and 127–182. HRs should be interpreted as a weighted average of the time-varying HRs in each follow-up period.¹⁶

For each outcome, we fitted: (i) unadjusted models; (ii) models stratified by NHS region and adjusting for calendar-time effects by including a natural cubic spline for the date of vaccination with two knots at the first and second tertiles; and (iii) fully adjusted models additionally adjusting for the demographic and clinical confounders described above (with age as a quadratic polynomial). Fully adjusted models for the overall study period were explored in the following subgroups: CKD3, CKD4–5, kidney transplant, dialysis, and any RRT (combining transplant and dialysis). To avoid issues with model convergence, we excluded binary covariates if cross-tabulating the variable with vaccine group yielded any cell with fewer than three outcome events. For categorical variables with more than two levels, we merged categories until all levels fulfilled these cross-tabulation criteria or one level remained, in which case the variable was excluded. Final model structures are summarised in [Supplementary Tables S2 and S3](#).

As an alternative to confounder adjustment via regression, we conducted a sensitivity analysis in which vaccination groups were matched 1:1 based on: age (within 3 years); date of vaccination (within 3 days); date of preceding dose (within 7 and 14 days for the two- and three-dose cohorts, respectively); sex; IMD quintile; NHS region; kidney disease subgroup; classification as clinically extremely vulnerable; prior SARS-CoV-2 infection; and the presence of any indicator of immunosuppression (recent immunosuppressive therapy, permanent immunosuppression, asplenia, haematologic malignancy, or transplant).

In compliance with re-identification minimisation requirements for OpenSAFELY, we rounded any reported counts to the nearest 5, redacted non-zero counts of ≤ 10 , and delayed KM steps until ≥ 5 events had occurred.

Patient and public involvement

People living with kidney disease were among the team that planned this work and reviewed the manuscript.

The work will be shared through involvement of the team with kidney charities and other organisations.

Role of the funding source

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

Results

Study population

426,785 individuals with kidney disease were eligible for the two-dose cohort ([Supplementary Table S4](#)), of whom 257,580 (60%) received AZ–AZ and 169,205 (40%) received BNT–BNT. Baseline clinical and demographic characteristics were similar across the vaccine groups ([Table 1](#)). The most common kidney disease subgroup was CKD3a (76% vs 75% among AZ–AZ vs BNT–BNT recipients, respectively), followed by CKD3b (17% vs 18%), CKD4–5 (4% vs 4%), transplant (2% vs 2%), and dialysis (1% vs 1%).

377,395 individuals were eligible for the three-dose cohort, of whom 222,330 (58%) received AZ–AZ–BNT and 157,065 (42%) received BNT–BNT–BNT. Again, baseline clinical and demographic characteristics were similar across vaccine groups ([Supplementary Table S5](#)).

When stratified by kidney disease subgroup, baseline characteristics remained similar across vaccine groups ([Supplementary Tables S6 and S7](#)). RRT recipients were notably younger than people with CKD and had a higher prevalence of immunosuppression, minority ethnicity, and prior SARS-CoV-2 infection.

Comparative effectiveness after two doses

Eligible individuals began to receive their second doses in March 2021, with follow-up spanning the Delta wave of SARS-CoV-2 up to the analysis cut-off of 16th November 2021 ([Supplementary Fig. S1A](#)). There were a total of 10,405 SARS-CoV-2 infections, 1660 COVID-19-related hospitalisations, 305 COVID-19-related deaths, and 4050 non-COVID-19 deaths across a median follow-up time of 182 (interquartile range [IQR] 182–182) days for each outcome ([Fig. 1](#)).

Incidence rates and HRs are summarised in [Figs. 1–3](#) and [Supplementary Table S8](#). Across the overall follow-up period, SARS-CoV-2 infections occurred at a rate of 58.7 per 1000 person-years in AZ–AZ recipients and 37.1 per 1000 person-years in BNT–BNT recipients (fully adjusted HR [95% CI] of 1.43 [1.37–1.50]). HRs were similar across modelling strategies, including in the matched sub-cohort ([Supplementary Table S8](#)). When stratified by time period, discrepancies between AZ–AZ and BNT–BNT recipients were absent from days 1–14 (when few cases occurred), but consistent across all subsequent time periods ([Fig. 3](#)).

Characteristic	Unmatched		Matched	
	AZ-AZ N = 257,580	BNT-BNT N = 169,205	AZ-AZ N = 130,765	BNT-BNT N = 130,765
Age				
16-64	54,330 (21.1%)	29,485 (17.4%)	15,040 (11.5%)	18,015 (13.8%)
65-69	41,890 (16.3%)	21,740 (12.8%)	19,120 (14.6%)	19,030 (14.6%)
70-74	80,215 (31.1%)	45,125 (26.7%)	43,710 (33.4%)	39,420 (30.1%)
75-79	81,150 (31.5%)	72,855 (43.1%)	52,895 (40.5%)	54,300 (41.5%)
Sex				
Female	136,300 (52.9%)	89,095 (52.7%)	69,475 (53.1%)	69,475 (53.1%)
Male	121,280 (47.1%)	80,110 (47.3%)	61,295 (46.9%)	61,295 (46.9%)
Ethnicity				
White	240,905 (93.5%)	159,055 (94.0%)	124,655 (95.3%)	124,810 (95.4%)
Black	4675 (1.8%)	2535 (1.5%)	1330 (1.0%)	1370 (1.0%)
South Asian	8825 (3.4%)	5685 (3.4%)	3555 (2.7%)	3360 (2.6%)
Mixed	1370 (0.5%)	835 (0.5%)	475 (0.4%)	530 (0.4%)
Other	1805 (0.7%)	1095 (0.6%)	750 (0.6%)	695 (0.5%)
Index of multiple deprivation quintile				
1 most deprived	43,860 (17.0%)	27,650 (16.3%)	20,270 (15.5%)	20,270 (15.5%)
2	49,590 (19.3%)	32,590 (19.3%)	24,695 (18.9%)	24,695 (18.9%)
3	58,295 (22.6%)	38,860 (23.0%)	30,420 (23.3%)	30,420 (23.3%)
4	55,655 (21.6%)	36,980 (21.9%)	29,130 (22.3%)	29,130 (22.3%)
5 least deprived	50,175 (19.5%)	33,120 (19.6%)	26,250 (20.1%)	26,250 (20.1%)
Setting				
Urban city or town	138,500 (53.8%)	90,055 (53.2%)	71,810 (54.9%)	70,565 (54.0%)
Urban conurbation	50,345 (19.5%)	33,035 (19.5%)	23,815 (18.2%)	23,345 (17.9%)
Rural	68,735 (26.7%)	46,115 (27.3%)	35,145 (26.9%)	36,855 (28.2%)
Kidney disease				
CKD3a	195,125 (75.8%)	126,335 (74.7%)	102,350 (78.3%)	102,350 (78.3%)
CKD3b	44,255 (17.2%)	30,630 (18.1%)	22,365 (17.1%)	22,365 (17.1%)
CKD4-5	10,325 (4.0%)	6985 (4.1%)	3825 (2.9%)	3825 (2.9%)
RRT (dialysis)	2335 (0.9%)	1870 (1.1%)	505 (0.4%)	505 (0.4%)
RRT (transplant)	5540 (2.2%)	3385 (2.0%)	1720 (1.3%)	1720 (1.3%)
Primary care coding of kidney disease				
CKD3-5	137,395 (53.3%)	96,025 (56.8%)	72,400 (55.4%)	73,350 (56.1%)
Dialysis code	5470 (2.1%)	3655 (2.2%)	1520 (1.2%)	1525 (1.2%)
Kidney transplant code	5800 (2.3%)	3585 (2.1%)	1740 (1.3%)	1725 (1.3%)
Morbidities				
Immunosuppression	16,155 (6.3%)	10,885 (6.4%)	6345 (4.9%)	6360 (4.9%)
Severe obesity	15,815 (6.1%)	10,165 (6.0%)	7665 (5.9%)	7760 (5.9%)
Diabetes	70,690 (27.4%)	47,975 (28.4%)	37,580 (28.7%)	36,390 (27.8%)
Chronic respiratory disease (inc. asthma)	27,565 (10.7%)	18,585 (11.0%)	14,485 (11.1%)	14,010 (10.7%)
Chronic heart disease	88,375 (34.3%)	61,725 (36.5%)	48,160 (36.8%)	47,685 (36.5%)
Chronic liver disease	11,165 (4.3%)	7165 (4.2%)	5595 (4.3%)	5350 (4.1%)
Asplenia	2490 (1.0%)	1580 (0.9%)	985 (0.8%)	930 (0.7%)
Haematologic cancer	4675 (1.8%)	3355 (2.0%)	1985 (1.5%)	1970 (1.5%)
Organ transplant (non-kidney)	960 (0.4%)	525 (0.3%)	290 (0.2%)	260 (0.2%)
Chronic neurological disease	26,335 (10.2%)	17,920 (10.6%)	14,390 (11.0%)	13,775 (10.5%)
Learning disability	1140 (0.4%)	605 (0.4%)	375 (0.3%)	400 (0.3%)
Severe mental illness	3785 (1.5%)	2135 (1.3%)	1650 (1.3%)	1605 (1.2%)
Clinically extremely vulnerable	48,735 (18.9%)	32,475 (19.2%)	20,485 (15.7%)	20,485 (15.7%)
Prior SARS-CoV-2 infection	3880 (1.5%)	2235 (1.3%)	565 (0.4%)	565 (0.4%)
No. of SARS-CoV-2 tests in 90-day pre-vaccination window				
0	221,940 (86.2%)	145,815 (86.2%)	114,135 (87.3%)	114,665 (87.7%)
1	22,910 (8.9%)	15,020 (8.9%)	11,010 (8.4%)	10,985 (8.4%)

(Table 1 continues on next page)

Characteristic	Unmatched		Matched	
	AZ-AZ N = 257,580	BNT-BNT N = 169,205	AZ-AZ N = 130,765	BNT-BNT N = 130,765
(Continued from previous page)				
2	6095 (2.4%)	4005 (2.4%)	2845 (2.2%)	2735 (2.1%)
3+	6630 (2.6%)	4360 (2.6%)	2780 (2.1%)	2380 (1.8%)
Region				
East of England	55,955 (21.7%)	38,525 (22.8%)	28,340 (21.7%)	28,340 (21.7%)
Midlands	62,190 (24.1%)	40,340 (23.8%)	33,535 (25.6%)	33,535 (25.6%)
London	5590 (2.2%)	5715 (3.4%)	2650 (2.0%)	2650 (2.0%)
North East and Yorkshire	48,920 (19.0%)	30,425 (18.0%)	23,490 (18.0%)	23,490 (18.0%)
North West	24,590 (9.5%)	14,535 (8.6%)	11,005 (8.4%)	11,005 (8.4%)
South East	13,740 (5.3%)	9020 (5.3%)	6540 (5.0%)	6540 (5.0%)
South West	46,600 (18.1%)	30,640 (18.1%)	25,205 (19.3%)	25,205 (19.3%)
JCVI priority group				
3 (75+)	81,150 (31.5%)	72,855 (43.1%)	52,895 (40.5%)	54,300 (41.5%)
4 (70+ or clinically extremely vulnerable)	103,575 (40.2%)	58,180 (34.4%)	50,920 (38.9%)	46,700 (35.7%)
5 (65+)	34,040 (13.2%)	17,635 (10.4%)	16,195 (12.4%)	16,095 (12.3%)
6 (16–65 and clinically vulnerable)	38,820 (15.1%)	20,535 (12.1%)	10,755 (8.2%)	13,665 (10.5%)
See Supplementary Table S1 for further details on variable definitions. Equivalent data for the three-dose cohort are provided in Supplementary Table S5 . Data are n (%) after rounding to the nearest 5. AZ, AZD1222; BNT, BNT162b2. CKD, chronic kidney disease; JCVI, Joint Committee on Vaccination and Immunisation; RRT, renal replacement therapy.				
Table 1: Baseline characteristics of two-dose vaccination cohort.				

Similar discrepancies between AZ–AZ and BNT–BNT recipients were observed for more severe outcomes. Overall incidence rates for COVID-19-related hospitalisation were 9.4 per 1000 person-years in AZ–AZ recipients and 5.7 per 1000 person-years in BNT–BNT recipients (fully adjusted HR 1.59 [1.43–1.77]). COVID-19-related deaths occurred at a rate of 1.7 per 1000 person-years in AZ–AZ recipients and 1.1 per 1000 person-years in BNT–BNT recipients (fully adjusted HR 1.44 [1.12–1.85]). Where event counts were sufficient to enable estimation, discrepancies for both outcomes were consistent across time periods and modelling strategies, including in the matched sub-cohort ([Supplementary Table S8](#)). Non-COVID-19 deaths occurred at a marginally higher rate in AZ–AZ than BNT–BNT recipients (fully adjusted HR 1.09 [1.02–1.16]).

COVID-19-related outcomes were markedly more common in RRT recipients than people with CKD3, with intermediate incidence among people with CKD4–5 ([Supplementary Table S9](#)). Specifically, following AZ–AZ, SARS-CoV-2 infection, COVID-19-related hospitalisation, and COVID-19-related death occurred at 3-fold, 7-fold, and 9-fold higher incidence rates in kidney transplant versus CKD3 subgroups, with comparable discrepancies among BNT–BNT recipients. For SARS-CoV-2 infection and COVID-19-related hospitalisation, comparative effectiveness estimates for BNT–BNT versus AZ–AZ were highly consistent across kidney disease subgroups, including transplant and dialysis recipients (HRs of 1.2–1.7 in favour of BNT–BNT; [Fig. 2](#)). Subgroup-specific estimates for COVID-

19-related deaths were generally non-significant (i.e., CIs crossed 1), albeit constrained by low event counts in individual subgroups. The discrepancy in non-COVID-19 deaths observed for the overall cohort appears to be driven by individuals with CKD3 (fully adjusted HR 1.11 [1.03–1.19]); no significant differences were observed for people with CKD4–5 or in RRT recipients (in contrast to the significant discrepancies in COVID-19-related outcomes in these subgroups).

Comparative effectiveness after BNT162b2 third dose

Follow-up for the three-dose cohort spanned periods of Delta and Omicron dominance between September 2021 and May 2022 ([Supplementary Fig. S1B](#)). There were 27,320 SARS-CoV-2 infections, 3360 COVID-19-related hospitalisations, 325 COVID-19-related deaths, and 3420 non-COVID-19 deaths across a median follow-up time of 146 [IQR 127–160], 182 [170–182], 182 [170–182], and 182 [170–182] days, respectively ([Fig. 1](#)). A total of 25,105 (92%) SARS-CoV-2 infections occurred on or after 15th December 2021, when Omicron became the dominant variant in England. The proportion of SARS-CoV-2 infections occurring during the Omicron era rose across time periods from 330/1535 (21%) in days 1–14 to 6940/7915 (88%) in days 15–70 and >99% thereafter.

Full model outputs for the three-dose cohort are provided in [Supplementary Table S10](#). Across the overall follow-up period, SARS-CoV-2 infections occurred at a similar rate in AZ–AZ–BNT versus BNT–

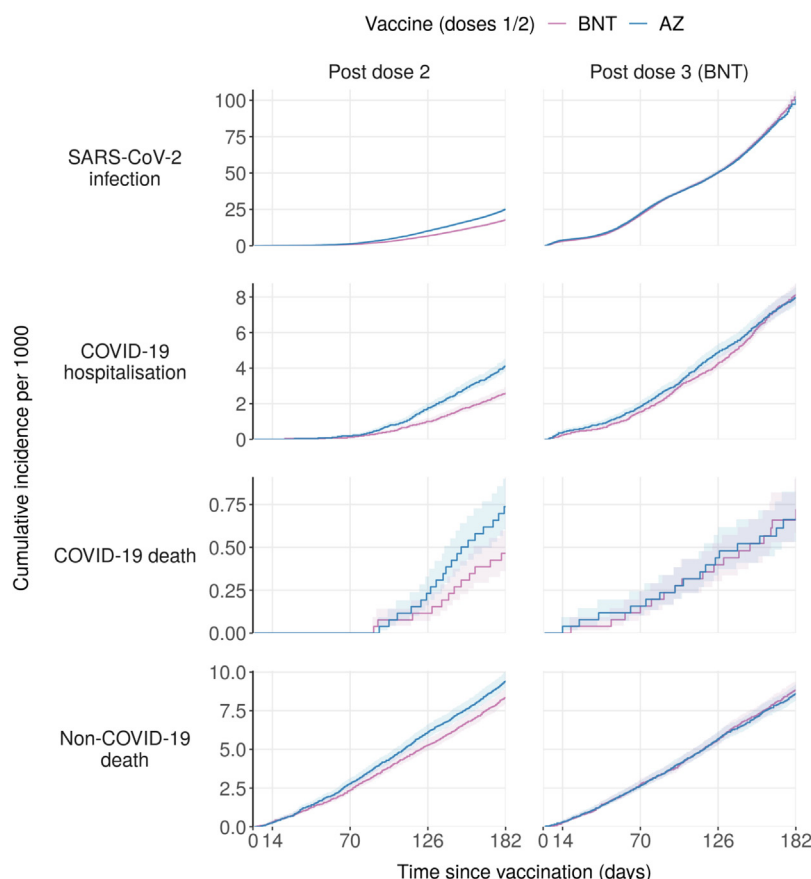


Fig. 1: Cumulative incidence rates by vaccine group. Kaplan-Meier estimates of cumulative incidence in matched two-dose and three-dose sub-cohorts. Kaplan-Meier steps are delayed until ≥ 5 events occur in compliance with re-identification minimisation requirements in OpenSAFELY. Data for the matched sub-cohorts are shown here to minimise confounding associated with key matching variables; see [Supplementary Fig. S2](#) for equivalent plots relating to the unmatched cohorts. Numbers at risk at days 0, 15, 71, and 127 are provided in [Supplementary Tables S8](#) (two-dose cohort) and [S10](#) (three-dose cohort). AZ, AZD1222 (AstraZeneca); BNT, BNT162b2 (Pfizer/BioNTech).

BNT–BNT recipients (156.2 vs 166.4 per 1000 person-years, respectively; fully adjusted HR 0.96 [0.93–0.98]; [Figs. 1 and 2](#)). When broken down by time period, infections initially occurred at a higher rate in AZ–AZ–BNT recipients (fully adjusted HRs of 1.25 [1.13–1.39] and 1.06 [1.01–1.11] for days 1–14 and 15–70, respectively), while the inverse was true from day 71 onwards, resulting in approximate parity across the overall study period. Findings were similar across modelling strategies, supporting equivalent protection for AZ–AZ–BNT versus BNT–BNT–BNT across the study period (e.g., HR of 0.99 [0.96–1.02] for the matched sub-cohort; [Supplementary Table S10](#)).

COVID-19-related hospitalisations occurred at a rate of 19.1 per 1000 person-years in AZ–AZ–BNT recipients and 19.0 per 1000 person-years in BNT–BNT–BNT recipients (fully adjusted HR 1.01 [0.95–1.09]). As observed for SARS-CoV-2 infection, hospitalisations were initially more common among AZ–AZ–BNT

recipients, but reached parity across the overall study period ([Figs. 1 and 3](#)). COVID-19-related deaths occurred at a rate of 1.9 per 1000 person-years in AZ–AZ–BNT recipients and 1.8 per 1000 person-years in BNT–BNT–BNT recipients (fully adjusted HR 1.15 [0.92–1.45]). Likewise, non-COVID-19 deaths occurred at a similar rate across the two vaccine groups (fully adjusted HR 0.97 [0.90–1.04]).

When analyses were stratified by kidney disease subgroup, we observed markedly higher event rates in RRT recipients than individuals with CKD3–5 ([Supplementary Table S11](#)). In particular, SARS-CoV-2 infection, COVID-19-related hospitalisation, and COVID-19-related death occurred at 3-fold, 6-fold, and 13–14-fold higher incidence rates in kidney transplant versus CKD3 subgroups. However, no clinically important differences in event rates were observed between AZ–AZ–BNT versus BNT–BNT–BNT recipients for any outcome in any subgroup ([Fig. 2](#)), including transplant and dialysis recipients.

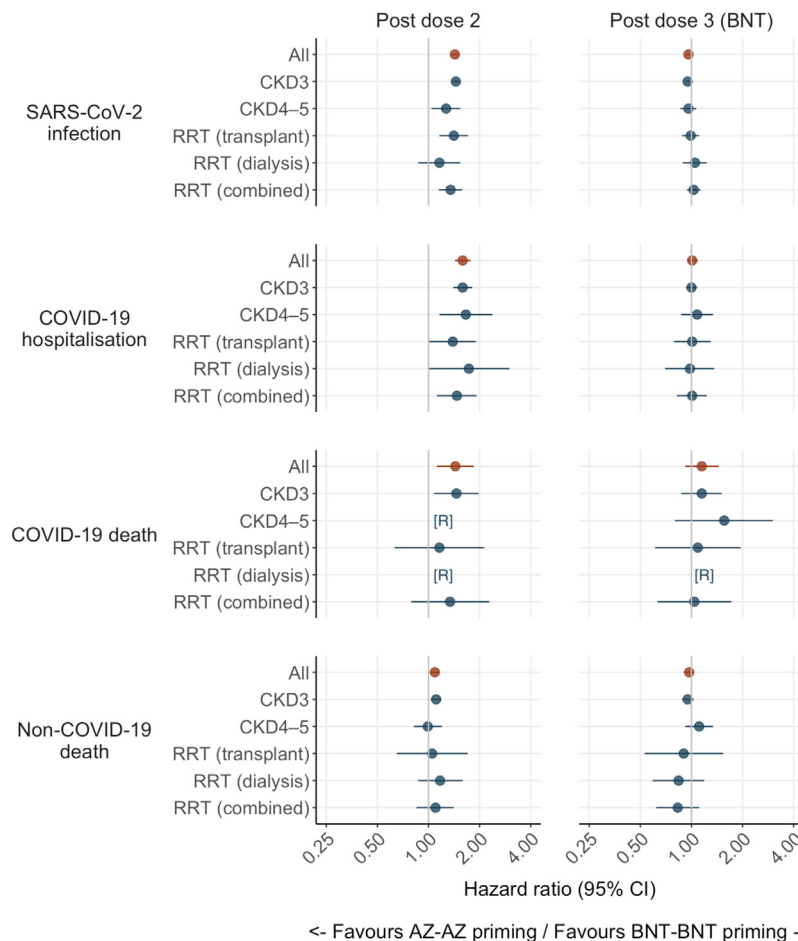


Fig. 2: Hazard ratios for the comparative effectiveness of two- and three-dose schedules in kidney disease subgroups. See [Supplementary Tables S9](#) (two-dose cohort) and [S11](#) (three-dose cohort) for associated population sizes and incidence rates. AZ, AZD1222; BNT, BNT162b2; CI, confidence interval; CKD, chronic kidney disease; [R], redacted due to low event counts in one or both vaccine groups; RRT, renal replacement therapy.

Discussion

Optimising the use of available COVID-19 vaccines among people with kidney disease is crucial to reduce the burden of morbidity and mortality in this vulnerable population. The present study suggests that a two-dose series of BNT conferred stronger protection than AZ against SARS-CoV-2 infection, COVID-19-related hospitalisation, and COVID-19-related death among people with kidney disease in England during the Delta wave of the pandemic. These findings were consistent across CKD3, CKD4-5, transplant and dialysis subgroups. By contrast, after administration of BNT as a third dose, AZ- and BNT-primed individuals exhibited similar risks of COVID-19 during a period dominated by the Omicron variant.

Our findings are consistent with previous immunology studies that reported higher antibody levels following BNT-BNT versus AZ-AZ,¹⁷⁻¹⁹ including

studies in dialysis and kidney transplant recipients.^{6,20} Higher effectiveness for BNT-BNT versus AZ-AZ has also been reported during the Delta wave in study populations not restricted to individuals with kidney disease.^{21,22} One study of solid organ transplant recipients in England showed no reduction in SARS-CoV-2 infection rates relative to unvaccinated individuals following AZ-AZ or BNT-BNT, and a reduction in post-infection mortality for AZ-AZ but not BNT-BNT.²³ In addition, previous cohort studies focusing on people receiving haemodialysis have documented no clear differences in effectiveness or post-infection progression between BNT-BNT and AZ-AZ.^{8,24} By contrast, we found that people receiving RRT (dialysis or kidney transplant) were less likely to experience SARS-CoV-2 infection and COVID-19-related hospitalisation following BNT-BNT versus AZ-AZ. In contrast to previous studies, we limited enrolment to periods of

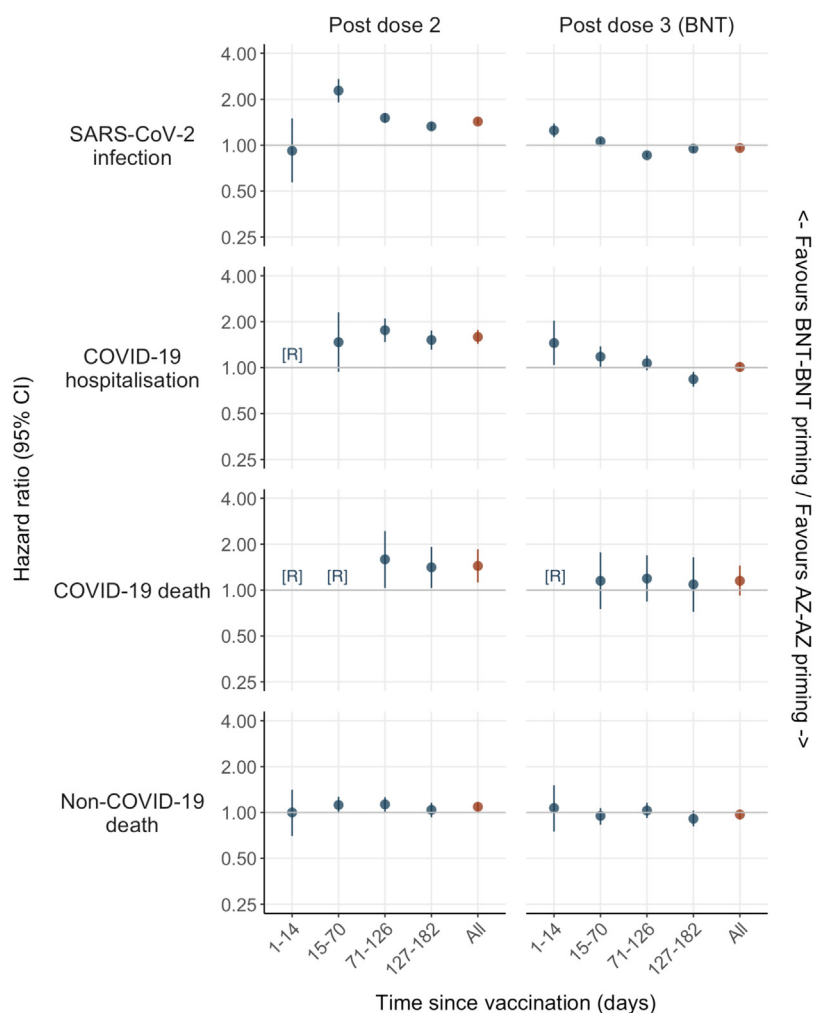


Fig. 3: Hazard ratios for the comparative effectiveness of two- and three-dose schedules. See [Supplementary Tables S8](#) (two-dose cohort) and [S10](#) (three-dose cohort) for associated population sizes and incidence rates. AZ, AZD1222; BNT, BNT162b2; CI, confidence interval; [R], redacted due to low event counts in one or more groups.

concomitant AZ and BNT usage. We also harnessed primary care data linkages to identify detailed comorbidity data and reduce confounding of comparative effectiveness estimates.

The administration of BNT as a third dose appeared to compensate for the discrepancies in protection between AZ- and BNT-primed individuals. This finding is consistent with observational and clinical studies of third-dose immunogenicity in healthy adults^{17,25} and individuals with kidney disease,^{7,9,26} as well as vaccine effectiveness data from the general population.²⁷ One previous study explored short-term vaccine effectiveness of BNT as a third dose following AZ or BNT priming among haemodialysis recipients, reporting increased protection against Omicron infection for boosted compared with unboosted individuals and no significant differences according to primary vaccine group.²⁸ We

show the equivalent effectiveness of AZ–AZ–BNT versus BNT–BNT–BNT to persist for up to 182 days against infection, COVID-19-related hospitalisation, and COVID-19-related death. The higher rates of SARS-CoV-2 infection and COVID-19-related hospitalisation observed after AZ–AZ versus BNT–BNT persisted from days 1–14 after the third dose of BNT, consistent with a lag of 1–2 weeks while the additional dose takes effect. Interestingly, towards the end of follow-up in the three-dose cohort, these outcomes were more frequent in BNT–BNT–BNT than AZ–AZ–BNT recipients, potentially indicative of a more durable long-term protection in the heterologous vaccine group.

Although comparative effectiveness estimates were consistent across kidney disease subgroups of varying severity, we observed markedly higher event rates in transplant and dialysis recipients compared with

individuals with CKD3–5, particularly for severe outcomes. This likely reflects the greater baseline vulnerability of RRT recipients to COVID-19⁴ alongside lower immunogenicity and absolute effectiveness per vaccine dose.²⁹ A recent randomised trial compared several strategies aiming to enhance immunogenicity among kidney transplant recipients who remain seronegative after multiple RNA vaccine doses, including administration of a double RNA vaccine dose, heterologous vaccination, and temporary discontinuation of immunosuppressive therapy before vaccination. However, these approaches induced seroconversion rates comparable to that of a standard RNA vaccine dose.³⁰ Overall, these findings highlight the benefits of repeated COVID-19 vaccination in RRT recipients, while emphasising the need for alternative strategies (e.g. pre-exposure prophylaxis with monoclonal antibodies) that might reduce the burden of disease in this vulnerable population.

Outpatient treatment with monoclonal antibodies and antivirals has increasingly been deployed to mitigate the risk of disease progression after SARS-CoV-2 infection in high-risk groups. In the UK, such treatments were available in community settings from December 2021, reaching ~33% coverage among individuals with renal disease (including CKD4–5) and solid organ transplant recipients who were infected between December 2021 and April 2022.³¹ These treatments may have reduced the risk of disease progression following SARS-CoV-2 infection among a small subset of AZ–AZ–BNT and BNT–BNT–BNT recipients in the three-dose cohort of the present study.³²

Our study is strengthened by the scale and representativeness of the OpenSAFELY-TTP database,³³ offering the statistical power to explore endpoints such as COVID-19-related hospitalisation and death. The unique use of a gold-standard registry of people receiving treatment for end-stage kidney disease (the UKRR) enabled us to reduce misclassification of treatment modality (e.g. ~65% of the kidney transplant subgroup in this study also had a prior dialysis code in their primary care record) and provided a valuable opportunity to audit vaccine implementation and performance within this high-risk population. The integration of UKRR data within OpenSAFELY allows novel linkages to be made with primary care and COVID-19-related outcome data, forming the key foundation for the present analysis.

Several limitations of our study should be highlighted. First, given the higher rates of COVID-19-related outcomes following AZ–AZ than BNT–BNT, we cannot rule out the potential influence of selection bias in the three-dose cohort. To mitigate the potential influence of hybrid immunity (which would have been more common in AZ-primed individuals), we opted to exclude individuals if they had any evidence of SARS-CoV-2 infection between doses 1 and 3. The resulting cohort may therefore be

unrepresentative of the initial population of AZ–AZ recipients, introducing a bias towards individuals who responded more robustly to the two-dose series or had a lower exposure risk post-vaccination. Second, the phased vaccine roll-out in England imposed constraints on our analyses. Individuals over 80 years of age, many of whom would have been eligible for this study, were excluded given that BNT had been widely distributed to this age group before AZ became available. Thus, our findings may not be generalisable to older adults with kidney disease. Third, despite careful measures to control for confounding, residual biases may have contributed to the observed discrepancies between vaccine groups. Among people with CKD3, deaths from causes other than COVID-19 were more common in AZ–AZ than BNT–BNT recipients, potentially reflecting greater underlying frailty in this population that was not captured by the clinical covariates (e.g. reflecting easier transport of AZ to individuals unable to attend vaccination centres in person). Undiagnosed COVID-19 may also have contributed to this pattern if it played a causal role in the medium- or long-term pathway to mortality (e.g. by exacerbating existing morbidities) but was not mentioned on death certificates. Notably, the discrepancy in non-COVID-19 deaths was much smaller than that observed for COVID-19-related outcomes and was not apparent in people with CKD4–5 or in RRT recipients. Finally, an assessment of immunogenicity would provide valuable context to our estimates of comparative effectiveness, but was beyond the scope of the present study.

Overall, BNT–BNT conferred stronger protection than AZ–AZ among people with kidney disease in England. However, our study serves as an important demonstration of the value of heterologous BNT following AZ (and likely heterologous RNA vaccine booster doses more broadly), suggesting these doses have the capacity to close the gap in immunity observed after prior doses. In settings such as the UK, RNA vaccines have been offered to vulnerable populations across multiple booster campaigns. However, targeted measures to improve the uptake of these doses may be beneficial, particularly in minority ethnic groups and in deprived areas that have been persistently linked with lower COVID-19 vaccine coverage.^{34,35} In countries where RNA vaccines make up a portion of the COVID-19 vaccine supply, allocating available RNA vaccine doses to high-risk individuals may help reduce the overall burden of COVID-19-related disease.

Contributors

Conceptualisation: EPKP, FL, SL, DN, and LAT; Methodology: EPKP, EMFH, WJH, JT, BZ, BG, JACS, DN, and LAT; Software: EPKP, EMFH, and WJH; Formal analysis, EPKP and EMFH; Data curation: AM, SS, RS, BG, and DN; Writing—original draft, EPKP; Writing—review & editing, EMFH, WJH, EJC, FL, SL, VM, BM, MS, SS, RS, DN, and LAT; Visualisation, EPKP and WJH; Supervision, DN and LAT; Project administration: EPKP, AM, DN, and LAT; Funding acquisition, EPKP, BG, DN, and LAT.

Data sharing statement

Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared. Access to the underlying identifiable and potentially re-identifiable pseudonymised electronic health record data is tightly governed by various legislative and regulatory frameworks, and restricted by best practice. The data in OpenSAFELY is drawn from General Practice data across England where TPP is the data processor. TPP developers initiate an automated process to create pseudonymised records in the core OpenSAFELY database, which are copies of key structured data tables in the identifiable records. These pseudonymised records are linked onto key external data resources that have also been pseudonymised via SHA-512 one-way hashing of NHS numbers using a shared salt. Bennett Institute for Applied Data Science developers and PIs holding contracts with NHS England have access to the OpenSAFELY pseudonymised data tables as needed to develop the OpenSAFELY tools. These tools in turn enable researchers with OpenSAFELY data access agreements to write and execute code for data management and data analysis without direct access to the underlying raw pseudonymised patient data, and to review the outputs of this code. All code for the full data management pipeline – from raw data to completed results for this analysis – and for the OpenSAFELY platform as a whole is available for review at github.com/OpenSAFELY.

Ethical approval

This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the London School of Hygiene & Tropical Medicine's Ethics Board (reference 21863).

Information governance

NHS England is the data controller for OpenSAFELY-TPP; TPP is the data processor; all study authors using OpenSAFELY have the approval of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant. Patient data has been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts.

The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent.

Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

This project includes data from the UKRR derived from patient-level information collected by the NHS as part of the care and support of kidney patients. We thank all kidney patients and kidney centres involved. The data are collated, maintained, and quality assured by the UKRR, which is part of the UK Kidney Association. Access to the data was facilitated by the UKRR's Data Release Group after consultation with the UK Kidney Association Patient Council. UKRR data are used within OpenSAFELY to address a limited number of critical audit and service delivery questions related to the impact of COVID-19 on patients with kidney disease.

Code availability

Data management was performed using Python, with analysis carried out using R 4.0.2. Code for data management and analysis, as well as codelists, are archived online (<https://github.com/opensafely/ckd-coverage-ve>).

Declaration of interests

EPKP has been employed as a consultant by the WHO Strategic Advisory Group of Experts on Immunization Working Group on COVID-19 Vaccines. WJH and VM have received research funding from the National Institute for Health and Care Research (NIHR). EJC has received research funding (paid to the institution) from Kidney Research UK and partner charities and patient associations. FL is employed as Policy Director of Kidney Care UK, which has received funding from AstraZeneca, Pfizer, Novartis, and GSK, and honoraria (paid to the institution) from AstraZeneca, Novartis, and University College London for invited talks and meeting attendance. FL is Lay Chair of the West Herts Hospital Organ Donation committee; Vice Chair of the Lister Hospital Kidney Patients' Association; and member of the International Society for Nephrology patient liaison advisory group. SL has received medical writing fees from the UK Kidney Association and Vascular Society of Great Britain and Ireland; freelance employment as Deputy Editor for Kidney Care UK's Kidney Matters magazine; and support for conference attendance from the UK Kidney Association. SL is Chair of the UK Kidney Association Patient Council and member of the Guy's and St Thomas' Kidney Patients' Association. BMK is also employed by NHS England as a specialist pharmacist adviser. AM has received consultancy fees from Induction Healthcare and is a member of the Royal College of General Practitioners' health informatics group and the NHS Digital GP data Professional Advisory Group. BG's work on better use of data in healthcare more broadly is currently funded in part by: the Bennett Foundation, the Wellcome Trust, NIHR Oxford Biomedical Research Centre, NIHR Applied Research Collaboration Oxford and Thames Valley, the Mohn-Westlake Foundation; all Bennett Institute staff are supported by BG's grants on this work. BG is a Non-Executive Director at NHS Digital. DN is the UK Kidney Association's Director of Informatics Research. LAT has received research funding from the Medical Research Council (MRC), Wellcome, and NIHR; has consulted for Bayer in relation to an observational study of chronic kidney disease (unpaid); is a member of four non-industry funded (NIHR/MRC) trial advisory committees (unpaid); and is a member of the Medicines and Healthcare products Regulatory Agency expert advisory group (Women's Health). The authors disclose no other competing interests.

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Appendix. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanepe.2023.100636>.

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