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AZD1222 effectiveness against severe COVID-19 in individuals with comorbidity or frailty: The RAVEN cohort study

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SUMMARY

Objectives: Despite being prioritized during initial COVID-19 vaccine rollout, vulnerable individuals at high risk of severe COVID-19 (hospitalization, intensive care unit admission, or death) remain underrepresented in vaccine effectiveness (VE) studies. The RAVEN cohort study (NCT05047822) assessed AZD1222 (ChAdOx1 nCov-19) two-dose primary series VE in vulnerable populations.

Methods: Using the Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub, linked to secondary care, death registration, and COVID-19 datasets in England, COVID-19 outcomes in 2021 were compared in vaccinated and unvaccinated individuals matched on age, sex, region, and multimorbidity.

Results: Over 4.5 million AZD1222 recipients were matched (mean follow-up ~5 months); 68% were ≥50 years, 57% had high multimorbidity. Overall, high VE against severe COVID-19 was demonstrated, with lower VE observed in vulnerable populations. VE against hospitalization was higher in the lowest multimorbidity quartile (91.1%; 95% CI: 90.1, 92.0) than the highest quartile (80.4%; 79.7, 81.1), and among individuals ≥65 years, higher in the 'fit' (86.2%; 84.5, 87.6) than the frailest (71.8%; 69.3, 74.2). VE against hospitalization was lowest in immunosuppressed individuals (64.6%; 60.7, 68.1).

Conclusions: Based on integrated and comprehensive UK health data, overall population-level VE with AZD1222 was high. VEs were notably lower in vulnerable groups, particularly the immunosuppressed.

Introduction

Despite national social restrictions and other non-pharmaceutical interventions, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused more than 195,000 hospitalizations for coronavirus disease 2019 (COVID-19) and 55,000 deaths

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across the United Kingdom (UK) by December 2020.[1] Development and subsequent approval of vaccines against SARS-CoV-2 had significant impact in reducing the global burden of the COVID-19 pandemic.[2, 3] England and other countries in the UK were among the first in the world to introduce and implement a comprehensive mass vaccination policy, starting in December 2020. The policy originally utilized a homologous two-dose schedule of BNT162b2, AZD1222 (ChAdOx1 nCov-19), or mRNA-1273, all of which demonstrated protection against severe COVID-19 outcomes in clinical trials and real-world vaccine effectiveness (VE) studies throughout the course of the pandemic.[4–16] AZD1222 is one of the most widely administered COVID-19 vaccines worldwide, with more than 3 billion doses having been distributed globally, saving an estimated 6.3 million lives in the first year of vaccine rollout.[2, 17] During the initial vaccine rollout in the UK, compared with other COVID-19 vaccines, AZD1222 was more heavily distributed to older and more vulnerable individuals. This was in part due to beneficial characteristics of AZD1222, including the ability to store at refrigeration temperatures (between 2 and 8 °C), that facilitated easier transportation and longer-term storage. For these reasons, AZD1222 was particularly suitable for use in care homes and administration by general practitioners (GPs).[18]

Administration of COVID-19 vaccines in the UK was the responsibility of the National Health Service (NHS): a comprehensive, state-funded, registration-based health system, which delivers almost all acute primary and specialist medical care. For over 2 years at the height of the pandemic, the NHS provided free nucleic acid amplification testing (NAAT) for SARS-CoV-2 in the community, for care home residents, and for individuals preparing for a hospital procedure. In addition, rapid testing with antigen lateral flow devices were made freely available for home testing and were also employed for emergency admissions to hospital to enable fast-tracking of infected patients admitted via the emergency department. COVID-19 vaccination data were captured in the National Immunization Management System (NIMS) at the point of vaccination, and this information also fed through into primary care medical records. The use of unique NHS numbers for each individual makes the UK ideal for research into COVID-19 vaccines, as pseudonymized NHS numbers can be used to link individual-level data on vaccinations, infections, hospitalizations, and death across electronic health record (EHR) datasets.[19–22]

Like most COVID-19 vaccination strategies, the rollout of COVID-19 vaccines in the UK had the primary aim of minimizing the number of COVID-19 hospitalizations and deaths.[23] Vaccine rollout was phased, initially targeting older individuals and high-risk populations, such as individuals living in care homes, frontline health and social care workers providing care to potentially vulnerable people, and individuals considered to be clinically vulnerable.[23] Notably, recommendations on who should be prioritized for vaccination were broad and based on risk factors such as age and comorbidity, but they did not take into account cumulative risk of multimorbidity, or specific comorbidities/frailty.

While durability of AZD1222 primary series VE has now been demonstrated in several real-world studies, with waning effectiveness against symptomatic disease observed at ~4–6 months,[5,24–26] there is a paucity of data on the long-term protection against severe disease outcomes in the vulnerable populations who were prioritized for vaccination during initial rollout. This is true of all COVID-19 vaccines; while higher risk groups were prioritized for vaccination and are known to have worse prognosis after COVID-19 hospitalization,[27–30] most subsequent assessments of COVID-19 VE have focused on predominantly healthy populations. Despite the extensive digital health systems of the NHS, it is challenging to perform specific assessments of more vulnerable individuals through NHS England (formerly NHS digital) datasets. Therefore, there is a need for sophisticated investigation of VE in individuals who have comorbidities, frailty, or immunosuppression, or who reside in long-term care. Utilizing linked EHR data, a large-scale, retrospective, matched cohort VE study in England (RAVEN [Real-world Oxford/AstraZeneca Vaccine Effectiveness Study in England]; NCT05047822) was conducted to explore the benefit of vaccinating populations at high risk of severe disease. The study investigated VE of the AZD1222 primary series in England throughout 2021, the first year of vaccine rollout; a period that included the height of the pandemic, predominated by SARS-CoV-2 Alpha and Delta variants.[31, 32]

Methods

Study design, population, and eligibility

RAVEN (Real-world Oxford/AstraZeneca Vaccine Effectiveness Study in England; NCT05047822), is a retrospective matched cohort study, which investigated AZD1222 two-dose primary series VE across risk groups. The study population was identified using the Oxford-Royal College of General Practitioners (RCGP) Clinical Informatics Digital Hub (ORCHID),[33] which is the trusted research environment (TRE) hosting the RCGP Research and Surveillance Centre (RSC), one of Europe's oldest sentinel surveillance systems.[34] The RSC works in close collaboration with the UK Health Security Agency and its data were utilized for assessments of COVID-19 vaccine effectiveness across England in UK National Core Studies of COVID-19 vaccine benefit risk, and in European collaborative studies of VE.[35–37] The ORCHID TRE contains comprehensive pseudonymized primary care data for a nationally representative sampling of almost 18 million individuals in England (~32% of the population).[38] These data were collected from participating GP surgeries (in the UK, everyday primary healthcare clinics are referred to as GP surgeries). COVID-19 vaccination status at study entry was a key determinator of eligibility. In this respect, individuals were eligible if: a) they had received a second dose of AZD1222 between January 4, 2021 (the date of first AZD1222 vaccination in England) and December 31, 2021, inclusive; or b) they had no record of COVID-19 vaccination at any given time point through December 31, 2021 (regardless of any subsequent receipt of vaccine). Individuals who had received only one dose of AZD1222 were not eligible for this analysis and individuals who received a third COVID-19 vaccine dose (whether AZD1222 or other) were censored upon receipt of their third dose. The lower age limit for inclusion was 18 years of age (the lower age limit for first-dose vaccination with AZD1222), and the upper age limit was 108 years for males and 112 years for females, as older ages were considered implausible. Individuals with a GP- or NAAT-documented history of SARS-CoV-2 infection prior to vaccination were excluded from the analysis.

Data sources and variables

Effectiveness of the two-dose AZD1222 primary series was assessed against severe COVID-19 outcomes: hospitalization, intensive care unit [ICU] admission, or death. We refer to an ICU synonymously with a critical care unit and an intensive therapy unit. To enable this evaluation, the NHS Data Access Request Service (DARS) was utilized to access secondary care and other data assets, including COVID-19 test results and vaccination data. These national data collections are derived from data used for routine care and for managing commissioned hospital activity in the NHS. Primary care data from the ORCHID database were linked to national datasets approved by DARS, with pseudonymization to enable linking performed by NHS England. Data sources included primary care EHR data curated within the ORCHID dataset, and NHS England data, including secondary care EHR data and national COVID-19 datasets: NIMS, Hospital Episode Statistics (HES), Office for National Statistics (ONS) civil death registrations, COVID-19 Second Generation

Surveillance System (for SARS-CoV-2 testing), and COVID-19 UK community test results. A full list of all variables and their sources is provided in Table S1.

Matching

Vaccinated individuals were exact matched 1:1 to unvaccinated individuals based on the following pre-specified covariates: age (bands: 18–24, 25–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85 years), sex, geographic region (seven regions defined within England), and a single measure of comorbidity burden (the Cambridge Multimorbidity Score [CMMS] quartile; quartile 1: lowest scores, little to no multimorbidity; quartile 4, highest scores, greatest multimorbidity) derived from the overall ORCHID population.[39, 40] Individuals vaccinated with two doses of AZD1222 were matched at their index date (the recorded date of receiving the second AZD1222 dose) to unvaccinated individuals who were eligible for COVID-19 vaccination at the time. The index date for unvaccinated individuals was based on their matched vaccinated counterpart. Dynamic, time-varying matching, based on a previous study,[41] was used to match vaccinated and unvaccinated individuals on a weekly basis, with the intention of mitigating the effect of temporal imbalances in social restrictions/other non-pharmaceutical interventions, testing and infection rates, dominant SARS-CoV-2 variants, and other seasonal factors. Matching was performed with replacement with no upper limit. Matched, unvaccinated individuals who subsequently received an AZD1222 first vaccination could re-enter the study as a vaccinated individual if they received their second dose of AZD1222 during the study period, thus contributing to the study as both an unvaccinated and a vaccinated individual.

Exposure definition

In this study, exposure was defined as receipt of two doses of AZD1222 as a primary series, as recorded in the NIMS. Exposure began from an 'effective vaccination' date, which was 15 days after the second dose (index date) for individuals who had received two doses of AZD1222 as their primary series. This set 15-day timepoint was when a reasonable accrual of protection could be assumed based on clinical trial data. The comparator group comprised individuals without a record of COVID-19 vaccination, and these individuals were considered unexposed from the comparator's index date up until the time at which they received a first dose of any COVID-19 vaccine, or the end of the study period was reached.

Outcomes

VE of the AZD1222 primary series against severe COVID-19 outcomes was assessed via rates of: COVID-19-related hospitalization, ICU admission, and death. COVID-19-related hospitalization did not require a positive test result to be available for this study, but rather was defined as an emergency inpatient admission with an International Classification of Diseases (ICD)-10 primary code for COVID-19 (U071, U072) in HES diagnostic fields upon admission to hospital (DIAG01). COVID-19-related ICU admission was defined as admission to the ICU, during a hospitalization for COVID-19, as defined above. COVID-19-related death was defined as death where COVID-19 was the main underlying cause of death of a patient in or out of hospital, based on an ICD-10 code for COVID-19 in ONS mortality data.

Individuals were followed from the effective vaccination date in vaccinated individuals, or 15 days after the index date in matched unvaccinated individuals, until the earliest occurrence of a censoring event: study end (December 31, 2021), GP surgery deregistration, death, outcome of interest in the absence of death, or vaccination (i.e., a matched unvaccinated individual receiving a first dose, or a matched vaccinated individual receiving a third dose). In outcome-specific analyses, follow-up ended early for individuals experiencing an event of interest. VE was evaluated across all follow-up time, and by time since last dose. Subgroup analyses were performed using the national immunization guide (Green Book) risk groups.[42] Data from primary care medical records were used to assess comorbidity burden (using CMMS quartiles).[39,40] For individuals ≥65 years of age, frailty was defined using the electronic frailty index (eFI), a validated tool that stratifies individuals across a population into quartiles of severity of frailty (fit, mild, moderate, and severe frailty) based on a cumulative deficit model including clinical signs (e.g., Parkinsonism and tremor), symptoms (e.g., visual impairment), diseases, disabilities, and abnormal test values, derived from primary care EHR data.[43,44] Residence in a long-term care facility was also evaluated in a subgroup analysis; while there is no database that holds this specific information on an individual, the population was identified by applying a 'household key' to RSC pseudonymized primary care medical records at the point of extraction from GP surgery systems. This was performed for individuals who: were ≥70 years of age with data available on household; had a median household age of ≥60 years; and had ≥9 residents at their address. This population was verified by linking to the Care Quality Commission register, which lists residences at which a degree of nursing care is provided.

Statistical methods

Poisson regression with offset for time at risk was used to estimate incidence rate ratios (IRRs) to provide estimates of the relative incidence of each outcome in vaccinated compared to unvaccinated individuals. Models were run adjusted for the matching variables (continuous age [3 knot restricted cubic spline; RCS] to allow for non-linearity, CMMS [3 knot RCS], region, and sex) plus the following additional variables: body-mass index, smoking, and other conditions, including the other Green Book Chapter 14a risk groups (chronic respiratory disease, chronic kidney disease [CKD], chronic heart disease and vascular disease, chronic liver disease, chronic neurological disease, diabetes mellitus, severe mental illness, asplenia or dysfunction of the spleen, immunosuppression due to disease or treatment). It should be noted that solid organ transplant patients with kidney transplants were included in the CKD group; therefore, these patients, who would be considered immunosuppressed in a clinical setting, were not captured in the immunosuppression group for this study. Other criteria and sociodemographic data were also adjusted for in the models: influenza vaccination status, ethnicity, Index of Multiple Deprivation (IMD; a measure of socioeconomic status[45]) quintile, propensity to consult (GP consultation count in the year prior to study start), and residence in a long-term residential care facility. For each outcome, VE was calculated as 1-IRR and reported with 95% confidence intervals (95% CIs). Sensitivity analyses were carried out to understand the impact on VE estimates of alternative definitions for the primary outcomes (COVID-19 as a primary or secondary cause of death, or COVID-19 death defined as death from any cause within 28 days of a positive test), choice of effective vaccination date (using follow-up from date of vaccination, and 15 or 22 days after the effective vaccination date), and potential clustering by GP surgery (adjusting for GP surgery as a proxy for unmeasured socio-demographic factors).

Results

Study population

Records of 18,373,714 individuals in England were assessed for eligibility for the RAVEN AZD1222 vaccinated and unvaccinated

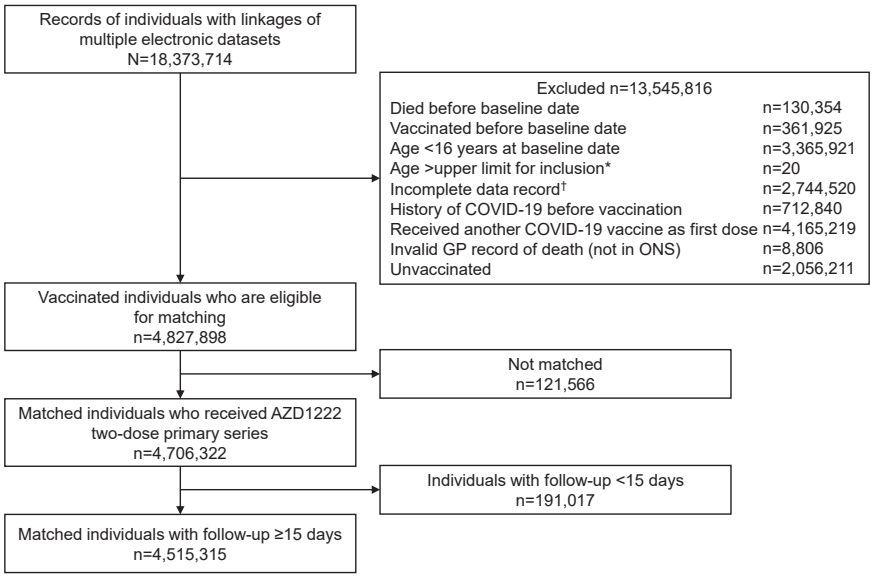

Fig. 1. Enrollment and matching of vaccinated individuals in the RAVEN AZD1222 primary series vaccine effectiveness study. *Upper limit for age: 108 years for males and 112 years for females. †Includes individuals who registered to an included GP surgery within 1 year of baseline, and those who registered over 1 year before baseline but deregistered at or in the year before baseline, or between baseline and the first vaccination, or between their first and second vaccination. COVID-19, coronavirus disease 2019; GP, general practitioner; ONS, Office for National Statistics.

cohorts. Enrollment and matching of vaccinated individuals are shown in Fig. 1. In total, 4,515,315 recipients of an AZD1222 primary series were matched to 4,515,315 unvaccinated individuals. NHS-led vaccination with AZD1222 in England started on January 4, 2021, with the majority of first doses administered by May 2021. Rollout of second doses began in parallel to first doses, based on age cohorts, and were predominantly administered between mid-March and the end of July 2021 (Figs. S1 and S2). Over the study period, the Alpha variant was predominant between December 2020 and May 2021, with the Delta variant rising in prevalence from May to December 2021. The Omicron BA.1 variant was first recognized in November 2021 and was the predominant variant by January 2022 (Fig. S1).

Baseline demographics of individuals in the AZD1222 two-dose and matched-comparator cohorts are shown in Table 1. Sex distribution of the RAVEN cohort was in line with mid-2021 ONS population estimates for individuals aged ≥18 years in England[46] (female 50.8% versus male 51.6%). However, when compared with ONS population estimates for those aged ≥18 years, there were proportionally fewer individuals in study age bands 18–39 years (11% of study population versus 36% of England population) compared with age band 45–64 years (51% of study population versus 33% of England population), reflective of the UK vaccine rollout strategy during the study period. Overall, 57% of individuals were in the CMMS quartiles that indicate the highest levels of comorbidity burden (quartiles 3 and 4). The most common baseline comorbidities in the vaccinated cohort were chronic heart disease (13% of individuals) and diabetes (9% of individuals). Approximately 1% of all individuals in the study were in long-term care. A greater proportion of individuals with IMD Q5 (least deprived) were vaccinated than with IMD Q1 (most deprived). Notably, there were more active smokers in the unvaccinated groups, and individuals who were vaccinated were more likely to have received an influenza vaccination in the two years prior to the study.

Vaccine effectiveness

Mean (standard deviation) follow-up was 156.50 (54.43) days for vaccinated individuals and 154.44 (56.30) days for unvaccinated individuals (i.e., each ~5 months; Table 1). Approximately 13% of potential follow-up time was lost due to initially unvaccinated individuals subsequently being vaccinated, or vaccinated individuals receiving a third-dose booster. Overall VE (95% CI) against severe COVID-19 outcomes during the follow-up period after the effective vaccination date for the two-dose AZD1222 primary series was 84.1% (83.6, 84.6), 90.7% (89.9, 91.5), and 85.9% (84.9, 86.9) against COVID-19-related hospitalization, ICU admission, and death, respectively. VE trended lower in the younger (<40 years) and older (<70 years) age bands, though numbers of events were low for ICU admission and death, limiting interpretation (Fig. 2). VE estimates in sensitivity analyses to understand potential misclassification relating to the effective vaccination date, by using follow-up from the date of vaccination and 15 or 22 days following the effective vaccination date, were consistent with the main VE estimates across severe COVID-19 outcomes (Table S2). In the sensitivity analysis of the influence of additionally adjusting for GP practice (as a proxy for unmeasured socio-demographic factors), VE estimates were also consistent with the main analysis for hospitalization (sensitivity analysis: 84.4 [95% CI: 84.0, 84.9] versus main analysis: 84.1% [95% CI: 83.6, 84.6]), ICU admission (91.0 [95% CI: 90.2, 91.7] versus 90.7 [95% CI: 98.9, 91.5]), and death (86.7 [95% CI: 85.7, 87.6] versus 85.9 [95% CI: 84.9, 86.9]). Sensitivity analysis using a COVID-19 death definition of 'death from any cause within 28 days of a positive test' also showed similar results to the main analysis: 82.0% (95% CI: 80.8, 83.0) versus 85.9% (95% CI: 84.9, 86.9), respectively.

VE across a range of comorbidity and frailty subgroups is shown in Fig. 3. VE of AZD1222 against severe COVID-19 outcomes was higher in individuals in CMMS quartile 1 versus quartile 4 (i.e., with low/no versus highest comorbidity burden). For CMMS quartiles 1 and 4, respectively, VE (95% CI) was 91.1% (90.1, 92.0) and 80.4% (79.7, 81.1) against COVID-19-related hospitalization, 95.7% (94.3, 96.7) and 87.9% (86.7, 89.1) against ICU admission, and 96.0% (93.6, 97.5) and 84.6% (83.4, 85.7) against death.

In the subgroups of individuals aged ≥65 years eligible for analysis by frailty score using eFI, VE of AZD1222 across severe COVID-19 outcomes was higher in those classified as fit than in those with the most severe frailty (Fig. 3). For individuals classified as fit and those with severe frailties, respectively, VE (95% CI) was 86.2% (84.5, 87.6) and 71.8% (69.3, 74.2) against COVID-19-related hospitalization, 91.4% (88.5, 93.7) and 83.1% (76.2, 88.0) against ICU admission, and 91.9% (89.1, 94.0) and 78.9% (76.0, 81.5) against death. Although the

Table 1
Baseline demographics of recipients of the two-dose primary series of AZD1222 and matched unvaccinated individuals in the vaccine effectiveness analysis cohort.

		AZD1222 two-dose matched population vaccine effectiveness analysis cohort		
		Vaccinated	Unvaccinated	SMD
N		4,515,315	4,515,315	
Mean age, years (SD)		56.51 (14.28)	56.35 (14.42)	0.011
Age band, years*	18–24	97,114 (2.2)	97,114 (2.2)	<0.001
	25–34	217,101 (4.8)	217,101 (4.8)	
	35–39	172,798 (3.8)	172,798 (3.8)	
	40–44	437,920 (9.7)	437,920 (9.7)	
	45–49	511,568 (11.3)	511,568 (11.3)	
	50–54	649,723 (14.4)	649,723 (14.4)	
	55–59	631,500 (14.0)	631,500 (14.0)	
	60–64	523,568 (11.6)	523,568 (11.6)	
	65–69	422,522 (9.4)	422,522 (9.4)	
	70–74	425,572 (9.4)	425,572 (9.4)	
	75–79	248,226 (5.5)	248,226 (5.5)	
	80–84	86,738 (1.9)	86,738 (1.9)	
	≥85	90,965 (2.0)	90,965 (2.0)	
Sex*	Female	2,292,789 (50.8)	2,292,789 (50.8)	<0.001
	Male	2,222,526 (49.2)	2,222,526 (49.2)	
Index of multiple deprivation quintile	1 (most deprived)	667,794 (14.8)	1,152,568 (25.5)	0.352
	2	777,101 (17.2)	975,313 (21.6)	
	3	910,275 (20.2)	863,542 (19.1)	
	4	1,002,239 (22.2)	780,148 (17.3)	
	5 (least deprived)	1,157,906 (25.6)	743,744 (16.5)	
Ethnicity	White	3,462,767 (76.7)	2,697,412 (59.7)	0.388
	Asian	245,009 (5.4)	327,455 (7.3)	
	Black	97,011 (2.1)	268,996 (6.0)	
	Mixed	37,681 (0.8)	80,212 (1.8)	
	Other	34,414 (0.8)	82,312 (1.8)	
	Missing	638,433 (14.1)	1,058,928 (23.5)	
BMI	Underweight (BMI <18.5)	77,818 (1.7)	119,825 (2.7)	0.338
	Normal (BMI 18.5–24.9)	1,404,181 (31.1)	1,443,690 (32.0)	
	Overweight (BMI 25–29.9)	1,535,983 (34.0)	1,268,686 (28.1)	
	Obese (BMI 30–39.9)	1,040,099 (23.0)	835,963 (18.5)	
	Severe obesity (BMI >40)	163,851 (3.6)	117,926 (2.6)	
	Not recorded	293,383 (6.5)	729,225 (16.2)	
Smoking status	Never smoked	2,476,823 (54.9)	2,052,106 (45.4)	0.385
	Active smoker	690,979 (15.3)	1,134,448 (25.1)	
	Ex-smoker	1,283,632 (28.4)	1,034,605 (22.9)	
	Not recorded	63,881 (1.4)	294,156 (6.5)	
Region*	East of England	311,773 (6.9)	311,773 (6.9)	<0.001
	London	561,495 (12.4)	561,495 (12.4)	
	Midlands	776,270 (17.2)	776,270 (17.2)	
	Northeast and Yorkshire	534,843 (11.8)	534,843 (11.8)	
	Northwest	705,888 (15.6)	705,888 (15.6)	
	Southeast	991,251 (22.0)	991,251 (22.0)	
	Southwest	633,795 (14.0)	633,795 (14.0)	
Index month	January 2021	14 (0.0)	14 (0.0)	<0.001
	February 2021	1367 (0.0)	1367 (0.0)	
	March 2021	148,209 (3.3)	148,209 (3.3)	
	April 2021	1,160,466 (25.7)	1,160,466 (25.7)	
	May 2021	1,653,185 (36.6)	1,653,185 (36.6)	
	June 2021	1,157,616 (25.6)	1,157,616 (25.6)	
	July 2021	333,147 (7.4)	333,147 (7.4)	
	August 2021	43,566 (1.0)	43,566 (1.0)	
	September 2021	8199 (0.2)	8199 (0.2)	
	October 2021	4286 (0.1)	4286 (0.1)	
	November 2021	3450 (0.1)	3450 (0.1)	
	December 2021	1810 (0.0)	1810 (0.0)	
Cambridge Multimorbidity Score quartile*	1 (lowest)	996,828 (22.1)	996,828 (22.1)	<0.001
	2	935,451 (20.7)	935,451 (20.7)	
	3	935,250 (20.7)	935,250 (20.7)	
	4 (highest)	1,647,786 (36.5)	1,647,786 (36.5)	
Comorbidities	Chronic respiratory disease	184,099 (4.1)	185,132 (4.1)	0.001
	Chronic kidney disease	202,051 (4.5)	166,930 (3.7)	0.039
	Chronic heart disease	567,482 (12.6)	482,956 (10.7)	0.058
	Chronic liver disease	109,101 (2.4)	112,970 (2.5)	0.006
	Chronic neurological disease	302,704 (6.7)	250,433 (5.5)	0.048
	Diabetes	382,605 (8.5)	380,074 (8.4)	0.002
	Severe mental illness	60,897 (1.3)	105,587 (2.3)	0.074
	Asplenia	30,623 (0.7)	18,613 (0.4)	0.036
	Immunosuppression	128,505 (2.8)	84,813 (1.9)	0.064
Influenza vaccination†		2,770,316 (61.4)	645,608 (14.3)	1.11
Long-term care status	In long-term care	52,848 (1.2)	43,998 (1.0)	0.019

(*continued on next page*)

Table 1 (*continued*)

		AZD1222 two-dose matched population vaccine effectiveness analysis cohort		
		Vaccinated	Unvaccinated	SMD
Electronic frailty index category (individuals ≥65 years only)	Fit	580,145 (12.8)	718,412 (15.9)	0.117
	Mild	413,232 (9.2)	327,121 (7.2)	
	Moderate	178,363 (4.0)	144,210 (3.2)	
	Severe	78,109 (1.7)	59,439 (1.3)	
	Missing	24,174 (0.5)	24,841 (0.6)	
	NA (aged <65 years)	3,241,292 (71.8)	3,241,292 (71.8)	
Consultation history (no. GP visits in prior year)	0	2,369,256 (52.5)	2,537,395 (56.2)	0.272
	1–4	434,146 (9.6)	742,372 (16.4)	
	≥5	1,711,913 (37.9)	1,235,548 (27.4)	
Study follow-up (days)	Mean (SD)	156.50 (54.43)	154.44 (56.30)	0.037
	Median (IQR)	174 (157, 185)	173 (154, 184)	
	Min–max	1–318	1–318	

Data are n (%) unless reported otherwise. Analysis cohort includes matched vaccinated and unvaccinated individuals with ≥15 days follow-up after the second-dose vaccination. Individuals with missing ethnicity, deprivation, smoking, or BMI were assigned to missing categories and analyzed using the missing indicator approach.
BMI, body mass index; GP, general practitioner; IQR, interquartile range; NA, not applicable; SD, standard deviation; SMD standardized mean difference.
* Matching variable.
† Within last 2 years.

impact of frailty on VE appears to be substantial, the small number of vaccinated individuals who were either admitted to ICU or died limit conclusive interpretation. Similar to the findings by frailty score, individuals in long-term care had a lower VE than individuals not in long-term care for outcomes of hospitalization and death (Fig. 3). For individuals not in long-term care, and those in long-term care, respectively, VE (95% CI) was 84.7% (84.2, 85.1) and 66.5% (61.6, 70.9) against COVID-19-related hospitalization, 90.7% (89.8, 91.4) and 92.0% (80.4, 96.7) against ICU admission, and 87.0% (86.0, 88.0) and 72.5% (66.8, 77.2) against death.

Across all three severe COVID-19 outcome groups, individuals with immunosuppression showed much lower VE than individuals in the other comorbidity subgroups (Fig. 4). In the no immunosuppression and immunosuppression subgroups, respectively, VE (95% CI) was 85.2% (84.7, 85.7) and 64.6% (60.7, 68.1) against COVID-19-related hospitalization, 91.7% (90.9, 92.4) and 77.4% (71.1, 82.3) against ICU admission, and 87.5% (86.5, 88.4) and 67.6% (60.4, 73.5) against death. VE appeared high across the other comorbidity subgroups, although the VE findings against ICU admission for the asplenia subgroup are not informative due to the small number of severe COVID-19 outcomes. Individuals with severe mental illness had a VE against hospitalization and death similar to that of the overall population (Fig. 4).

AZD1222 primary series VE was durable, being maintained for up to 6 months after the effective vaccination date (Fig. 5). Estimates of VE beyond 6 months have wide CIs due to the limited number of individuals with follow-up beyond 6 months, and thus preclude firm conclusions.

Discussion

Through ORCHID, curation of nationally representative, linked datasets in England has allowed this large-scale study of primary series VE of AZD1222, one of the most widely used COVID-19 vaccines globally.[2,17] The effectiveness of a two-dose AZD1222 primary series against severe COVID-19 outcomes due to early SARS-CoV-2 variants (Alpha and Delta), is confirmed (≥80% against severe COVID-19 outcomes), with durable protection of AZD1222 demonstrated in line with clinical trials and real-world evidence.[3,4,47–49] By utilizing the ORCHID TRE, the RAVEN study has also been able to demonstrate the VE of AZD1222 against lesser studied vulnerable populations. We observed lower VE in the eldest individuals, and individuals with the highest levels of comorbidity and frailty, including in long-term care residents. Despite lower VE, this study demonstrates the benefit of vaccination in these populations.

Findings in context

Recent studies have shown that individuals with immunosuppression, from medical conditions or immunosuppressor drug therapy, are a particularly important cohort to study, as they face a disproportionate risk of severe COVID-19 outcomes compared with the overall

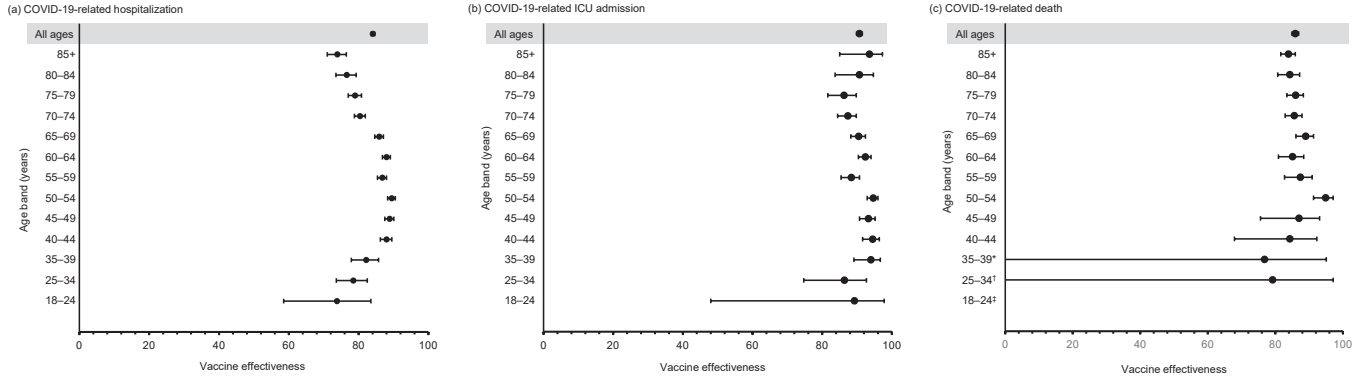

Fig. 2. Effectiveness against severe COVID-19 of a two-dose primary series of AZD1222 by age band: (a) COVID-19-related hospitalization, (b) COVID-19-related ICU admission, and (c) COVID-19-related death. *COVID-19-related death age band 35–39 years 95% CI lower bound: -10.6. †COVID-19-related death age band 25–34 years 95% CI lower bound: -48.2. ‡COVID-19-related death age band 18–24 years has no data: fewer than 5 outcomes reported. CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

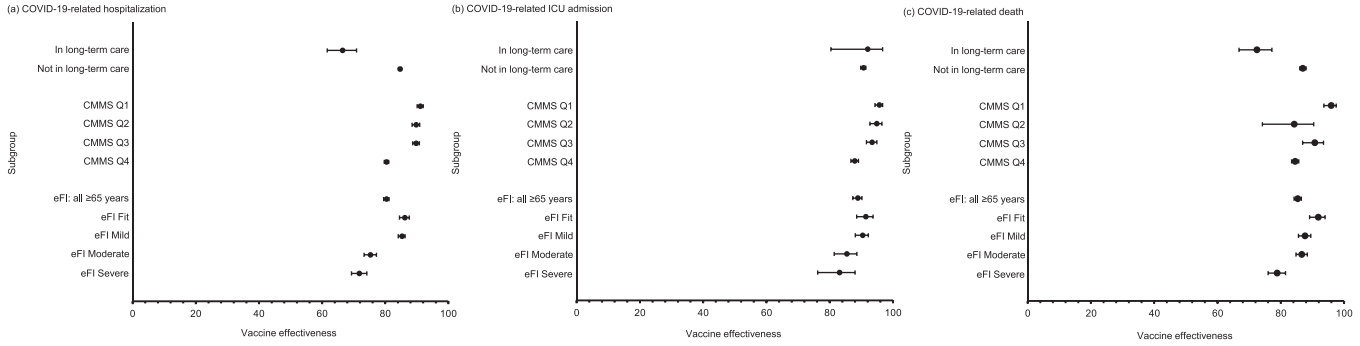

Fig. 3. Effectiveness against severe COVID-19 of a two-dose primary series of AZD1222 by risk groups for comorbidity and frailty: (a) COVID-19-related hospitalization, (b) COVID-19-related ICU admission, and (c) COVID-19-related death. Estimates are fully adjusted vaccine effectiveness estimates (1-IRR) for the entire post-effective vaccination date period for each dose. eFI subgroups exclude 24,172 vaccinated and 24,840 unvaccinated individuals with missing eFI. CMMS is presented by quartile, where Q1 is the lowest CMMS score, and Q4 is the highest CMMS score. CMMS, Cambridge Multimorbidity Score; COVID-19, coronavirus disease 2019; eFI, electronic frailty index; ICU, intensive care unit; IRR, incidence rate ratio; Q, quartile.

population, and may benefit from additional protection.[50–52] Despite making up <1% of the UK population, they represent ~14% of individuals in hospital,[53] and may have worse outcomes and require specialized critical care more often than the general population.[53–55] In RAVEN, individuals with immunosuppression (a heterogenous subgroup with varying levels of immunosuppression due to disease or treatment) attained the lowest VE among the comorbidity subgroups examined. Individuals with immunosuppression were also invited for vaccination earlier than the overall population; however, the magnitude of the reduction in VE was much more pronounced in these individuals than the reductions observed across age groups, which was the key defining factor of the timing of the vaccine rollout strategy. This is in line with recent reports demonstrating that individuals with immunosuppression from various causes can have significantly lower seroconversion rates and reduced VE compared with the overall population.[56–59] In the UK, the JCVI recommended a three-dose primary series for certain individuals with severe immunosuppression in September 2021,[60] three-quarters of the way through the study period. Some individuals who were recommended and subsequently received a third dose as part of an extended primary series will have had their follow-up censored in RAVEN. Since completion of the RAVEN study, updated variant vaccines have been developed and have been shown to be effective as booster doses in the general population.[61,62] However, it is likely that immunocompromised and more vulnerable individuals will still not receive the same level of protection. It will be important to evaluate variant booster vaccines in subgroups of immunocompromised and vulnerable populations to identify the true effectiveness and assess the ongoing need for additional interventions for these individuals.

Individuals with higher CMMS scores and greater frailty were also targeted for earlier vaccination, so average time since effective vaccination date was longer in these individuals, and thus may partly explain the observed lower VE in these groups compared to the overall population in this study. Despite reduced VE in certain subgroups, VE remained high across the overall population and important protection against severe outcomes remained, even in the most vulnerable individuals, which was a key measure of successful vaccine deployment. In the vaccinated cohort, overall VE was maintained at around the same level up to 6 months after effective vaccination date. Beyond this point, there were limited numbers of individuals available for assessment.

While these data report on the AZD1222 primary series, important parallels can be seen with more recent data on the continued utility of COVID-19 vaccines, including booster doses, in protecting vulnerable populations. As of August 31, 2022, 88% of the UK population ≥12 years of age had received at least two doses of a COVID-19 vaccine, and 70% had received at least one additional booster dose,[63] with booster dose recipients having overall better COVID-19 outcomes than those without a booster dose.[64]

Study strengths

The NHS has one of the most mature digital health systems globally, which collects data from hundreds of health and social care providers, and was instrumental in coordinating and tracking distribution of COVID-19 vaccines. COVID-19 mass vaccination programs have proven successful in protecting the general population,

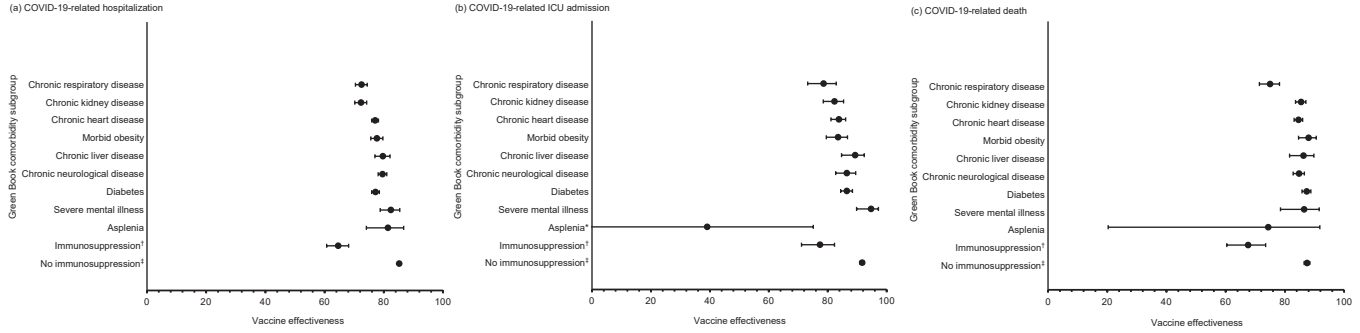

Fig. 4. Effectiveness against severe COVID-19 of a two-dose primary series of AZD1222 by comorbidity subgroup: (a) COVID-19-related hospitalization, (b) COVID-19-related ICU admission, and (c) COVID-19-related death. *COVID-19-related ICU admission 95% CI lower bound: -48.9. †Solid organ transplant patients with kidney transplants were included in the chronic kidney disease group. Therefore, these patients, who would be considered immunosuppressed in a clinical setting, were not captured in the immunosuppression group for this study. ‡Pre-specified subgroup in the statistical analysis plan, not part of the Green Book. CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

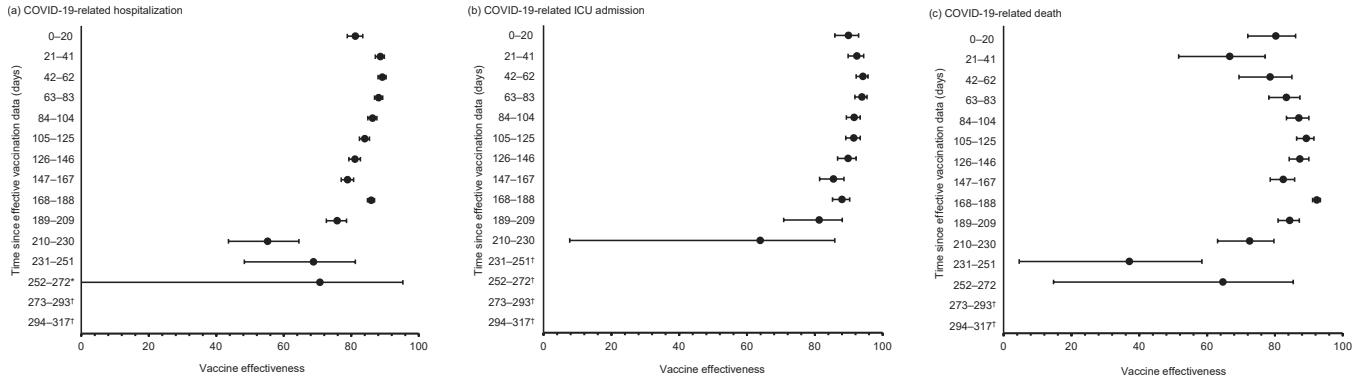

Fig. 5. Effectiveness of a two-dose AZD1222 primary series vaccine by time since effective vaccination date against (a) COVID-19-related hospitalization, (b) COVID-19-related ICU admission, and (c) COVID-19-related death. *COVID-19-related hospitalization time since effective vaccination date 252–272 days 95% CI lower bound: -80.9. †No data: fewer than five severe COVID-19 outcomes reported. CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

but more understanding is needed of how vaccination programs can be reshaped to better protect the most vulnerable populations such as those with comorbidities, frailties, and immunosuppression, and residents of long-term care facilities. As in many countries, individuals at high risk of severe outcomes from COVID-19 were prioritized during vaccine rollout in the UK, with targeted vaccination strategies. Despite extensive data collection and curation by NHS England, limitations in health systems mean that datasets specifically assessing the impact of vaccination for vulnerable individuals are deficient — a situation that is mirrored across the globe. In fact, only approximately 10% of studies captured in the International Vaccine Access Center VIEW-hub include vulnerable populations, and of those, many are subgroups from larger studies of healthier individuals.[65] There is a clear disconnect between prioritizing these groups for protection and ensuring that treatment outcomes in these populations are indeed studied, to measure the impact of such a vaccination strategy.

Through ORCHID, the availability of robust and linked EHR datasets on severe COVID-19 outcomes, and detailed vaccination status for everyone in England made an ideal health system for the assessment of COVID-19 VE with minimal chance of misclassification of exposure or outcomes. Furthermore, ORCHID's flexibility allows curation alongside other datasets, and programming for more granular assessments of unique populations.[39,40,66,67] In RAVEN, stratification by such parameters as CMMS, frailty, immunosuppression, and long-term care status enabled exploration of COVID-19 VE in populations with differing risks of infection and severe disease. For each of these parameters, the depth of data in the ORCHID TRE allows identification and classification of individuals based on pseudonymized diagnostic codes, clinical indicators, or demographic data.[33]

Beyond the unique and well-established digital health systems in the UK, and the flexibility of the ORCHID TRE to assess unique populations, the RAVEN study had strengths in the matching strategy and the representativeness of the base population. The weekly matching strategy controlled for effects of potential calendar time imbalances (e.g., social restrictions/other non-pharmaceutical interventions, infection rates, and dominant SARS-CoV-2 variants) and allowed conditional exchangeability on selected patient characteristics. Use of CMMS as a matching variable (in combination with the other pre-specified match variables) was also important, with demographic data from the study showing reliable matching of individuals from vaccinated and unvaccinated populations across the matching criteria.

Study limitations

Although ORCHID is representative of the overall English population,[38] in this study, AZD1222 primary series VE was estimated only among individuals who had no record of SARS-CoV-2 infection prior to vaccination. While this gives a more accurate estimation of true VE of AZD1222, it may be less representative of real-world protection where individuals may benefit from hybrid immunity. However, testing for SARS-CoV-2 was not widespread in the UK until July 2020, and thus not all infections could have been identified. It is difficult to determine the direction of bias due to misclassified infection, as infection in unvaccinated individuals could offer protection against future infection, but similarly, infection in vaccinated individuals could offer a higher level of protection against future infection than vaccination alone.[68,69] Nonetheless, the magnitude of this effect is likely small, as the study period was before the SARS-CoV-2 Omicron wave in which most individuals were first infected, and during a period where non-pharmaceutical interventions were very much still in place, so the proportion of individuals overall who were infected in the first year of vaccine rollout was relatively low.[32] Further, estimates of VE from RAVEN reflect the distinct population that received AZD1222 in England, particularly at pop-up vaccination centers (due to the beneficial storage characteristics of AZD1222, which allowed for transportation and longer-term storage).[18] Of note, 68% of AZD1222-vaccinated individuals in RAVEN were ≥50 years of age and many had a high comorbidity score (i.e., in CMMS quartiles 3 and 4). Another population that could not be adjusted for was healthcare professionals or other key workers who were prioritized for early vaccination, as employment is not a parameter measured in the source databases. It is possible that the trend towards lower VE in the younger cohorts may have been impacted by high-risk working individuals or individuals with comorbidities who were prioritized for vaccination early in the pandemic.

Interpretation of 'overall' VE estimates in RAVEN is difficult due to the multiple variants (Alpha, Delta, and Omicron from November 2021) circulating during the study period, and the combining of individuals with varying lengths of follow-up from vaccination (average was ~5 months). Interpretation of AZD1222 VE for the rare severe outcomes (ICU admission and death) is also limited due to low numbers in subgroup analyses; thus, conclusive interpretation is not possible.

Policy implications

It is important that more health systems, like ORCHID, are made available to equalize the disconnect between targeting vulnerable individuals for vaccination, and the dearth of research into outcomes for these populations. Systems like ORCHID allow researchers to study the interactions between specific conditions and outcomes, such as the impacts of therapy and severity of disease, and in this case, the impact of COVID-19 vaccination on vulnerable populations. By doing so, it allows further evaluation of policy decisions and a better understanding of how these can be improved in the future.

Ultimately, there is a need to promote care centered around individuals with specific needs, so resources can be appropriately allocated to personalized care plans, to maximize positive outcomes.

The initial UK vaccine rollout aimed to minimize the number of severe COVID-19 outcomes in the population and offered protection to the most vulnerable members of society. The first individuals to be offered COVID-19 vaccines in the UK were those in older age groups, individuals with comorbidities making them vulnerable to respiratory infection, and individuals providing care to the most vulnerable.[23] Similar vaccination strategies were used in other countries; however, the UK strategy was unique in that it prioritized single-dose vaccine rollout above completion of second doses, therefore with prolonged dosing intervals. This strategy afforded more of the population at least some protection than strategies that prioritized completion of the two-dose primary series. This decision was based on preliminary evidence demonstrating BNT162b2 VE of 93% against symptomatic disease early after administration of the first dose,[70] and a trend towards increased protection with a prolonged dosing interval with AZD1222.[71] While other studies and data herein have shown that COVID-19 vaccines, including booster doses, may be less effective in certain populations that are more vulnerable to severe outcomes of COVID-19, such as those with immunosuppression or other comorbidities,[50,72–74] additive strategies such as monoclonal/long-acting antibodies, and antivirals are being used to enhance either protection or aid recovery. Platform studies such as PRINCIPLE (ISRCTN86534580) and PANORAMIC (ISRCTN30448031) are exploring the use of repurposed or novel antiviral agents.[75–79] Learnings from and strategies applied to the management of COVID-19 may be transferable to investigation into seasonal influenza.

Conclusions

In RAVEN, the use of linked data sources and a comprehensive matching strategy enabled a detailed and robust assessment of AZD1222 VE, one of the most common vaccines used as a primary series globally. VE of the AZD1222 primary series was high in the overall population, and subgroup analyses highlighted specific vulnerable groups who may experience lower VE from COVID-19 vaccines, e.g., due to comorbidity, frailty, or immunosuppression; these individuals may benefit from additional preventative or treatment strategies. Access to and use of highly integrated health data systems has been integral to the continued assessment of VE throughout the COVID-19 pandemic, particularly, as demonstrated by RAVEN, through enabling the simultaneous evaluation of both population-level and subgroup VE. Therefore, the continued preservation and enhancement of these data systems is imperative to informing future policy decisions, especially for individuals in high-risk groups.

Ethical approval

The NHS Health Research Authority (HRA), London-Bromley Research Ethics Committee (REC) approved the study to be carried out as mentioned under Integrated Research Application System project identifier 3002559 in May 2021. An amendment to the study was further approved by the HRA REC in September 2021.

Role of the funding source

This study (NCT05047822) was funded by AstraZeneca. DAC, a Royal Academy of Engineering Research Chair, was funded by the NIHR Biomedical Research Centre, Oxford; an NIHR Research Professorship; the InnoHK Centre for Cerebro-cardiovascular Engineering; and the Pandemic Sciences Institute, Oxford. The funder of this study was involved in study design, data interpretation, and writing of the manuscript. The funder had no role in data collection or analysis. The authors had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

Oxford University has entered into a partnership with AstraZeneca for the development of COVID-19 vaccines. **KS, LC, MO, ST, SV, TM, TNT,** and **WM** are employees of AstraZeneca and may own stock/shares. **AJP** was a member of the World Health Organization's Strategic Advisory Group of Experts on Immunization until January 2022 and remains Chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation (JCVI) but does not participate in the JCVI COVID-19 committee. AJP also reports providing advice to Shionogi on COVID-19, and funding from the National Institute for Health Research (NIHR), AstraZeneca, the Bill & Melinda Gates Foundation, Wellcome, the Medical Research Council, the Serum Institute of India, and the Coalition for Epidemic Preparedness Innovations (CEPI); and being a contributor to the intellectual property licensed by Oxford University Innovation to AstraZeneca. **DAC** reports consulting fees from Oxford University Consulting, Bristol Myers Squibb, and grants from UK Research and Innovation, Wellcome Trust, NIHR, Hong Kong ITC, AstraZeneca, and Glaxo Smith Kline (GSK); and patents held by Oxford University Innovation. **JD** is an employee at Momentum data and may own stocks/shares. **FDRH** acknowledges support as Director of the NIHR Applied Research Collaboration Oxford Thames Valley and Theme Lead of the NIHR Oxford University Hospitals Biomedical Research Centre. He also reports fees or expenses for speaking or consultancy from AstraZeneca, Boehringer Ingelheim, Bayer, Bristol Myers Squibb/Pfizer, and Novartis. **GJ** reports ownership of GSK stocks/shares and honoraria form AstraZeneca. **SdeL** reports advisory board membership for AstraZeneca, GSK, Sanofi, and Seqirus (fees paid to University); and receiving university research grants from AstraZeneca, GSK, Sanofi, Seqirus, and Takeda. **ST** reports ownership of GSK stocks/shares. **UH** is an employee at Oxford University and reports membership on a Janssen advisory committee, funding from Seqirus for podcasts, and research funding from Seqirus and AstraZeneca. **WH** resorts partial salary funding from AstraZeneca-sponsored research grants. **AD, AF, DK, KST, MF, MJ, RB, RW, SNA,** and **XF** declare no competing interests.

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Author contributions

AJP, FDRH, MJ, MO, SdeL, ST, TM, TNT, and **WM** conceptualized the study; **FDRH, TM, TNT,** and **WM** contributed to funding acquisition; **KST, SNA, SdeL, TM,** and **WM** contributed study resources; **JD, SV,** and **WM** served as study investigators; **DAC, FDRH, LC, SdeL, ST, TNT,** and **WM** supervised the study; **KS, KST, SNA, WM,** and **XF** provided project administration; **KS** provided project management; **AD, DAC, DK, FDRH, WM, JD, MO, SdeL, ST, SV,** and **TNT** developed the experimental methodology; **MH** and **XF** developed software; **AD** and **JD** contributed to data visualization; **AF, DAC, DK, GJ, RB, RW, SdeL, TM,** and **XF** curated the data; **AD, JD, MJ, RB,** and **SV** conducted formal analyses; **AD, DK, KST, MO,** and **XF** validated the data. All authors reviewed and provided feedback on the manuscript drafts and approved the manuscript for submission. The manuscript was written under the direction of all authors by medical writers funded by the study sponsor.

Data statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/.

AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106129.

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