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Supplementary appendix

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AZD1222-induced neutralising antibody activity against SARS-CoV-2 Delta VOC

Emma C Wall*[1,2], Mary Wu*[1], Ruth Harvey*[3], Gavin Kelly[1], Scott Warchal[1], Chelsea Sawyer[1], Rodney Daniels[3], Lorin Adams[3], Philip Hobson[1], Emine Hatipoglu[4], Yenting Ngai[4], Saira Hussain[1], Karen Ambrose[1], Steve Hindmarsh[1], Rupert Beale[1,4,6], Andrew Riddell[1], Steve Gamblin[1], Michael Howell[1], George Kassiotis[1,5], Vincenzo Libri[2,4] Bryan Williams [2,4], Charles Swanton[1,4], Sonia Gandhi*[1,4], David LV Bauer*[1,6]

Affiliations

1. The Francis Crick Institute, 1 Midland Road, London, UK
2. National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre and NIHR UCLH Clinical Research Facility, London, UK
3. Worldwide Influenza Centre, The Francis Crick Institute, 1 Midland Road, London, UK
4. University College London, Gower Street, London
5. Department of Infectious Disease, St Mary's Hospital, Imperial College London, London, UK
6. Genotype-to-Phenotype UK National Virology Consortium (G2P-UK)

*These authors contributed equally to this work.

Lead Authors: George Kassiotis George.Kassiotis@crick.ac.uk, Charles Swanton charles.swanton@crick.ac.uk, Sonia Gandhi sonia.gandhi@crick.ac.uk, and David LV Bauer david.bauer@crick.ac.uk

Correspondence to: David LV Bauer david.bauer@crick.ac.uk

Contents

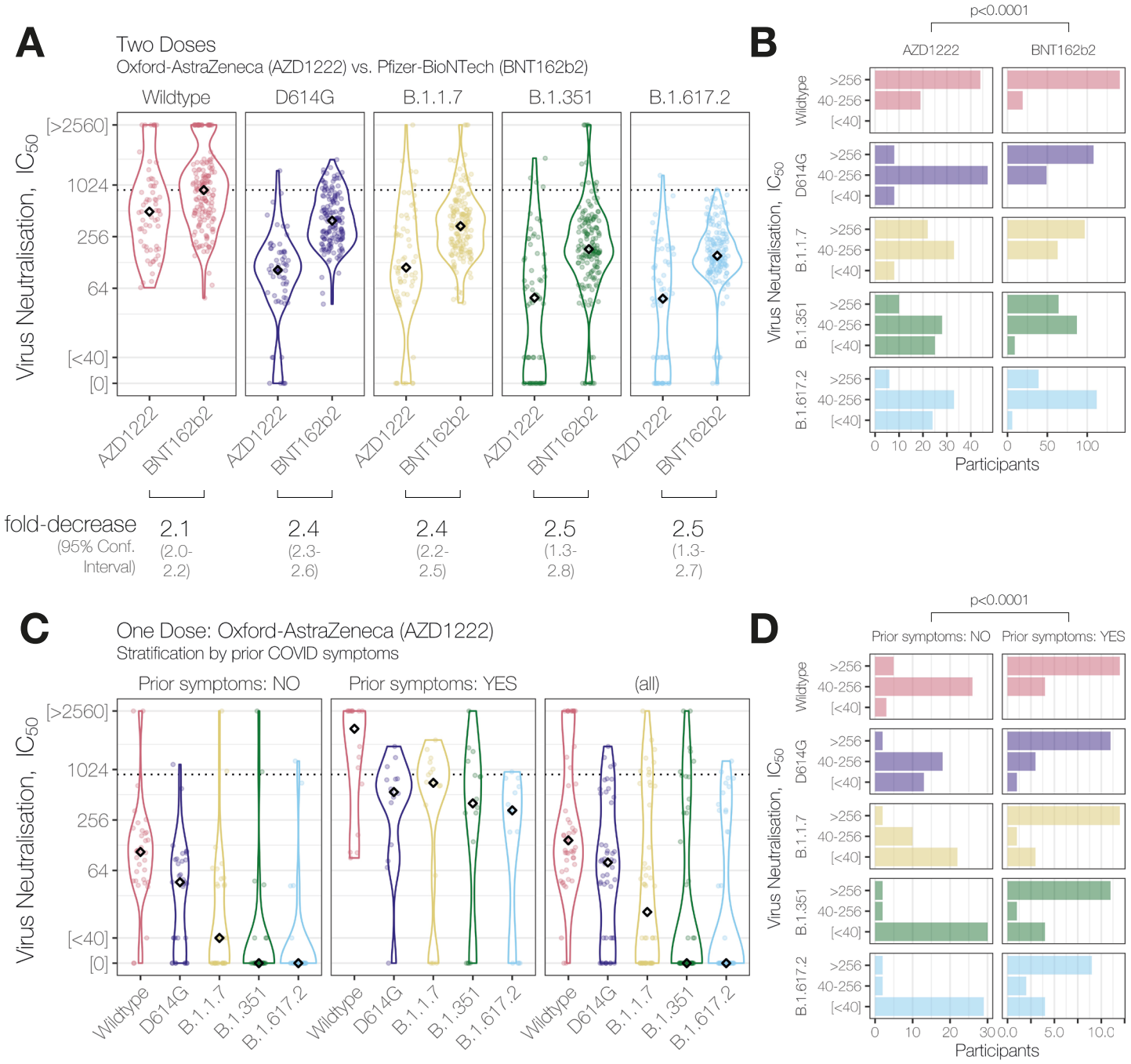

Figure 1. Neutralising antibody activity against SARS-CoV-2 variants of concern B.1.617.2 and B.1.351 elicited by partial or full vaccination with ChAdOx1 nCoV-19 (AZD1222, Oxford-AstraZeneca) and effect of reported prior COVID symptoms. (**A**) Neutralising antibody titres (NAbTs) against five SARS-CoV-2 strains from 63 study participants who had received 2 doses of AZD1222, compared to 159 participants who had received 2 doses of BNT162b2. NAbTs are expressed as serum fold-dilution required to achieve 50% virus neutralisation (IC_{50}), and shown (**B**) grouped into 3 response levels. (**C**) NAbTs from 50 participants following 1 dose of AZD1222, stratified according to participants' report of prior COVID symptoms, and (**D**) grouped into 3 response levels.

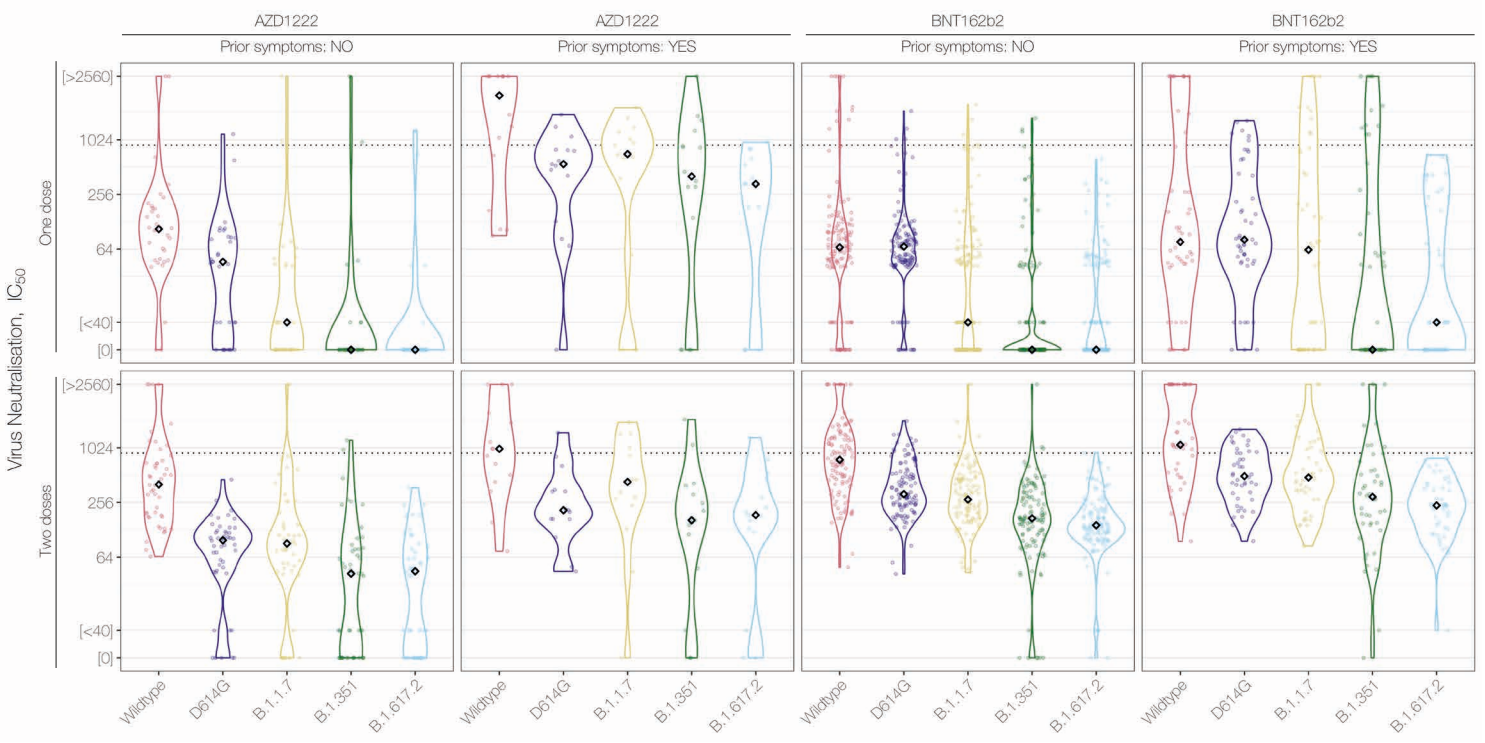

Figure 2. NAbT responses stratified by Vaccine Type, number of doses, and self-reported prior COVID symptoms. Data from this study and from (Wall, Wu, et al., Lancet, 2021)[10].

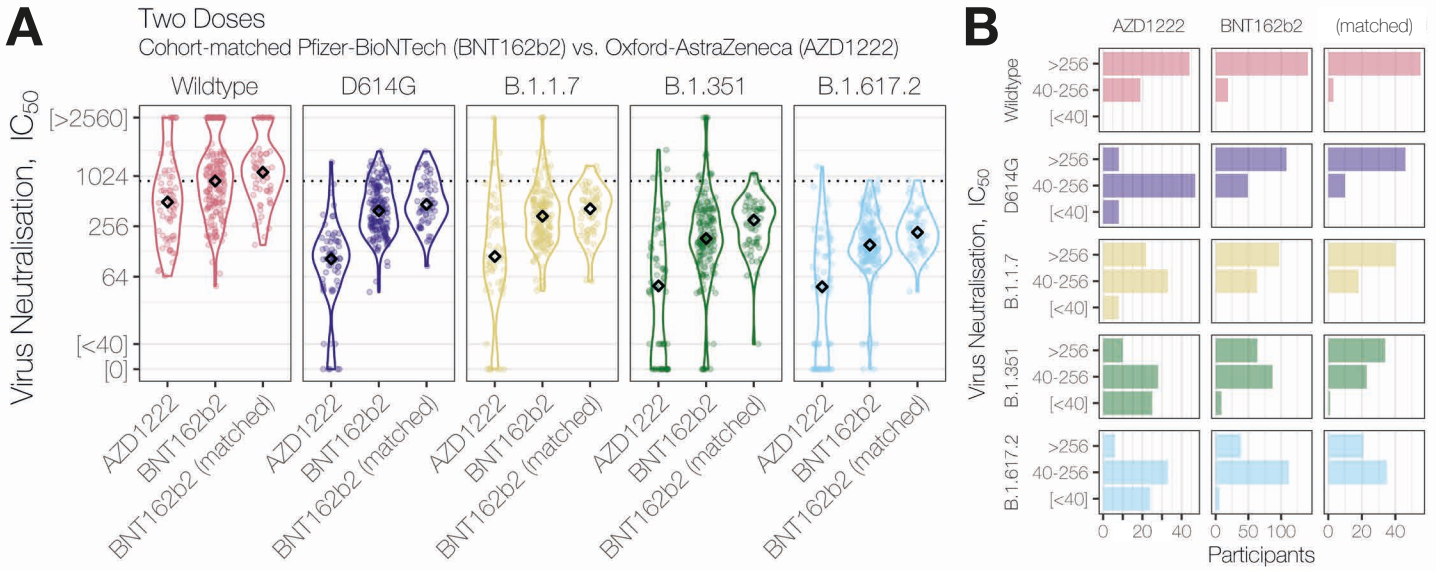

Figure 3. Neutralising antibody responses of AZD1222 recipients vs. cohort-matched BNT162b2 recipients. (**A**) Neutralising antibody titres (NAbTs) against five SARS-CoV-2 strains from study participants who had received 2 doses of AZD1222, comparised to participants who had received 2 doses of BNT162b2, and a matched subset of BNT162b2 recipients selected to match characterisitcs of AZD1222 cohort (single study site, age<50 years, dose interval > 40 days), see Table 1. NAbTs are expressed as serum fold-dilution required to achieve 50% virus neutralisation (IC_{50}), and shown (**B**) grouped into 3 response levels.

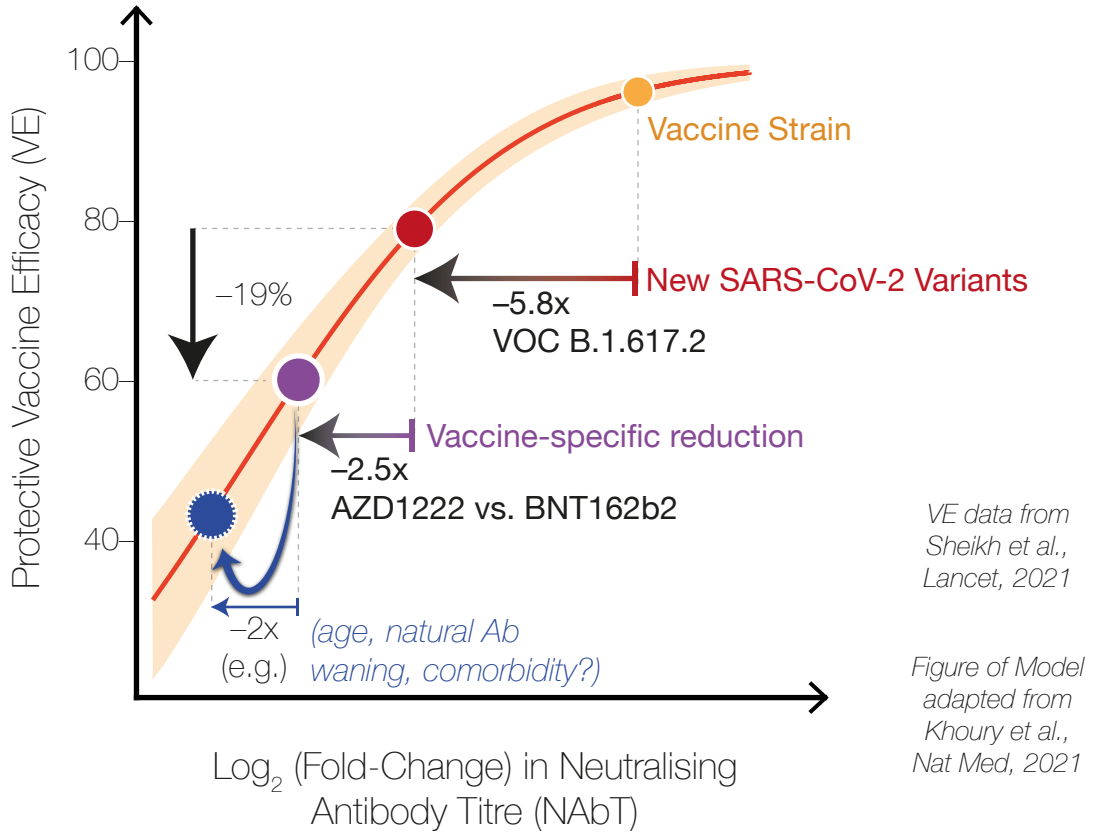

Figure 4. Schematic illustrating correlates between neutralising antibody titres against SARS-CoV-2 and vaccine efficacy (VE). Schematic based on the model of Khoury et al., overlayed with our laboratory measurements of neutralising antibody titres (NAbTs) against SARS-CoV-2 and observed real-world VE data from Sheikh et al., illustrating the relationship between NAbTs and VE. When NAbTs begin at a high level (e.g. against variants with spike proteins similar to the Wild-type spike in first-generation vaccines), small changes in NAbsTs have a small effect on VE. However, when titres begin from a lower level, such as from a cumulative effect of VOCs and vaccine type, small additional changes in NAbTs (e.g. due to age, antibody waning, immune status) now have a larger effect on VE.

Site = Crick
Age < 50 years
Dose Interval > 40 days

	AZD1222			**BNT162b2** (Cohort-Matched Subset)		**BNT162b** (Wall, Wu et al., Lancet, 2021)		
	Unique Participants n = 106		**P-Value**			**Unique Participants** n = 250		**P-Value**
	First Dose	**Second Dose**		**Second Dose**	**P** (vs AZD1222)	**First Dose**	**Second Dose**	
	Mean/Count (SD/%)	*Mean/Count (SD/%)*		*Mean/Count (SD/%)*		*Mean/Count (SD/%)*	*Mean/Count (SD/%)*	
	n = 50	n = 63		n = 58		n = 149	n = 159	
Site			0.87		0.34			0.052
Crick	49 (98%)	62 (98.4%)		58 (100%)		95 (63.8%)	84 (52.8%)	
UCLH	1 (2%)	1 (1.6%)		0 (0%)		54 (36.2%)	75 (47.2%)	
Age			0.23		0.74			0.812
	37.3 (8.6)	35.3 (8.7)		35.8 (7.8)		42.7 (11.9)	43.1 (11.6)	
Sex			0.62		0.14			0.041
Female	34 (68%)	40 (63.5%)		44 (75.9%)		109 (73.2%)	99 (62.3%)	
Male	16 (32%)	23 (36.5%)		14 (24.1%)		40 (26.8%)	60 (37.7%)	
BMI			0.68		0.60			0.870
	23.8 (3.9)	23.5 (3.8)		23.7 (5.1)		24.9 (5.4)	24.9 (5.6)	
Ethnicity (Grouped)			0.04		0.13			0.362
All White Bkgs.	42 (84%)	42 (66.7%)		47 (81%)		123 (82.6%)	125 (78.6%)	
All S. Asian Bkgs.	0 (0%)	9 (14.3%)		2 (3.4%)		5 (3.4%)	11 (6.9%)	
All Other Bkgs.	7 (14%)	11 (17.5%)		9 (15.5%)		21 (14.1%)	23 (14.5%)	
(No response)	1 (2%)	1 (1.6%)		0 (0%)				

Table 1. A second initial analysis of the Legacy study (University College London Hospital and the Francis Crick Institute)

Ordered Logistic Regression IC50_binned ~ Strain * VaccineType

Factor	Coef.	S.E.	Wald Z	Pr(>|Z|)
Strain (vs. Wildtype)				
D614G	-2.5880	0.3894	-6.65	<0.0001
B.1.1.7	-1.6845	0.3816	-4.41	<0.0001
B.1.351	-3.5941	0.4058	-8.86	<0.0001
B.1.617.2	-3.7118	0.4000	-9.28	<0.0001
Vaccine Type (vs. AZD1222)				
BNT162b2	1.1504	0.3663	3.14	0.0017
Interactions (Strain * Vaccine Type)				
D614G * BNT162b2	1.3893	0.4902	2.83	0.0046
B.1.1.7 * BNT162b2	0.1391	0.4802	0.29	0.7721
B.1.351 * BNT162b2	1.1529	0.4951	2.33	0.0199
B.1.617.2 * BNT162b2	0.7467	0.4872	1.53	0.1254

ANOVA

Wald Statistics Response: IC50_binned

Factor	Chi-Square	d.f.	P
Strain (incl. Higher Order Factors)	230.21	8	<.0001
Vaccine Type (incl. Higher Order Factors)	144.86	5	<.0001
Interaction	13.00	4	0.0113

Table 2. Ordered logistic regression model and ANOVA of effect of strain and vaccine type on neutralising antibody response following 2-dose vaccination (Relates to Figure 1B).

Ordered Logistic Regression IC50_binned ~ Strain * PriorCOVIDsymptoms

Factor	Coef.	S.E.	Wald Z	Pr(>|Z|)
Strain (vs. Wildtype)				
D614G	-0.9181	0.4349	-2.11	0.0347
B.1.1.7	-1.7536	0.4695	-3.74	0.0002
B.1.351	-3.1014	0.6196	-5.01	<0.0001
B.1.617.2	-3.0659	0.6206	-4.94	<0.0001
Prior COVID Symptoms (vs. those without)				
With COVID Symptoms	2.0380	0.6474	3.15	0.0016
Interactions (Strain * Symptoms)				
D614G * Symptoms	0.7486	0.9235	0.81	0.4175
B.1.1.7 * Symptoms	1.4876	0.9444	1.58	0.1152
B.1.351 * Symptoms	2.4180	1.0096	2.39	0.0166
B.1.617.2 * Symptoms	1.9735	1.0019	1.97	0.0489

ANOVA

Wald Statistics Response: IC50_binned

Factor	Chi-Square	d.f.	P
Strain (incl. Higher Order Factors)	44.35	8	<.0001
COVID Symptoms (incl. Higher Ord. Factors)	89.98	5	<.0001
Interaction	7.55	4	0.1096

Table 3. Ordered logistic regression model and ANOVA of effect of strain and self-reported prior COVID symptoms on neutralising antibody response following 1-dose AZD1222 vaccination (Relates to Figure 1D).

Methods

Clinical cohort

Two prospective cohorts of Legacy participants were established in January 2021 (NCT04750356). Participants were included if they were an employee of either UCLH or the Francis Crick Institute and had submitted at least one sample for RT-qPCR occupational health testing for COVID-19 using the Crick testing pipeline. Participants consisted of patient-facing healthcare workers at UCLH, who had received at least one dose of a currently licensed COVID-19 vaccine and Crick staff. Participants were sampled at approximately 3 weeks post-vaccination and invited for follow-up visits at approximately 6 and 12 weeks. All participants were sampled at each visit with additional nasopharyngeal RT-qPCR for SARS CoV-2 (in addition to their occupational health testing) to exclude concurrent active infection, blood was collected for serological assays. Participants were analysed by vaccine type, vaccine dose number, date since vaccine dose, and self-reported prior COVID-19 symptoms.

Serological Analysis and Live-virus Neutralisation

All serological analysis, including live-virus neutralisation assay, were performed exactly as previously described (**Wall, Wu et al., *Lancet*, 2021**)[10]

Data analysis, statistics

Study data were collected and managed using REDCap electronic data capture tools hosted at University College London[8,9]. Data were exported from REDCap into R for visualisation and analysis. IC50 values above the quantitative limit of detection of the assay (>2560) were recoded as 5120; IC_{50} values below the quantitative limit of the assay (< 40) but within the qualitative range were recoded as 10 and data below the qualitative range (i.e. no response observed) were recoded as 5. These changes do not affect any statistical parameters considered in the analysis and we do not perform analyses that consider that consider the absolute value of the points – i.e. rank-based analyses are used instead: statistical significance of the difference in median viral neutralisation IC_{50} values between different strains was performed using a paired Wilcoxon Ranked sum test. *p*-values reported have not been corrected for multiple testing. Fold-changes in median NAbTs (and 95% confidence intervals) between BNT162b2 and AZD1222 cohorts were determined using bootstrap statistics using the '*boot'* package in R, specifying vaccine type using the *strata* option. All graphs were generated using the '*ggplot2'* package. Analyses of stratified NAb responses by strain, vaccine type, and COVID symptoms of participants, were carried out using the *prop.test* function of the '*stats'* package in R, and ordered logistic regression using the *lrm* function of

the Regression Modeling Strategies (‘*rms*’) package in R, using the formula IC50 ~Strain*VaccineType or IC50 ~Strain*COVIDsymptoms , and *p*-values were calculated using the Wald Chi-Square test. Analysis of variance was carried out using the *anova* function in R.

Data Sharing

All data (anonymised) and full R code to produce all figures and statistical analysis presented in this manuscript are freely-available online on Github: https://github.com/davidlvb/Crick-UCLH-Legacy-AZ-VOCs-2021-06

Ethics

The Legacy study was approved by London Camden and Kings Cross Health Research Authority (HRA) Research and Ethics committee (REC) IRAS number 286469 and sponsored by University College London.

Role of the funding source

This work was undertaken at UCLH/UCL who received a proportion of funding from the National Institute for Health Research (NIHR) University College London Hospitals Department of Health’s NIHR Biomedical Research Centre (BRC). EW, VL and BW are supported by the Centre’s funding scheme. This work was supported jointly by the BRC and core funding from the Francis Crick Institute, which receives its funding from Cancer Research UK, the UK Medical Research Council, and the Wellcome Trust. DLVB is additionally supported by the Genotype-to-Phenotype National Virology Consortium (G2P-UK) via UK Research and Innovation and the UK Medical Research Council. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data and the final responsibility to submit for publication.

Contributors Statement

Emma C Wall - Investigation, Data Curation, Writing - original draft. Has access to & has verified underlying data.
Mary Wu - Investigation, Methodology, Resources, Writing – review & editing, Conceptualization
Ruth Harvey - Investigation, Methodology, Resources, Writing – review & editing, Conceptualization
Gavin Kelly - Formal Analysis, Validation
Scott Warchal - Software, Methodology, Formal Analysis
Chelsea Sawyer - Software, Methodology, Formal Analysis
Rodney Daniels - Investigation
Lorin Adams - Investigation
Philip Hobson - Investigation
Emine Hatipoglu - Project administration, Conceptualization
Yenting Ngai - Project administration, Conceptualization
Saira Hussain - Investigation, Resources
Karen Ambrose - Supervision, Software, Methodology

Steve Hindmarsh - Supervision, Software, Methodology
Rupert Beale - Writing – review & editing, Conceptualization
Andy Riddell - Supervision, Methodology
Steve Gamblin - Project administration, Conceptualization
Michael Howell - Project administration, Supervision, Writing – review & editing, Conceptualization
George Kassiotis - Writing – review & editing, Conceptualization
Vincenzo Libri - Funding acquisition, Project administration
Bryan Williams - Funding acquisition, Project administration, Writing – review & editing, Conceptualization
Charles Swanton - Supervision, Funding acquisition, Project administration, Writing – review & editing, Conceptualization. Has access to & has verified underlying data.
Sonia Gandhi - Supervision,Funding acquisition, Methodology, Project administration, Writing – review & editing, Conceptualization. Has access to & has verified underlying data.
David LV Bauer - Methodology, Formal Analysis, Visualization, Writing - original draft, Conceptualization. Has access to & has verified underlying data.

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Supplementary References

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