Supplementary Appendix

Supplement to: Andrews N, Tessier E, Stowe J, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. N Engl J Med. DOI: 10.1056/NEJMoa2115481

This appendix has been provided by the authors to give readers additional information about the work.

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Supplementary Section 1: Methods

Study Design

We used a test-negative case-control design to estimate vaccine effectiveness of two doses of ChAdOx1-S, BNT162b2 and mRNA-1273 COVID-19 vaccines against PCR-confirmed symptomatic disease, hospitalisation within 14 days of PCR confirmation, and death within 28 days of PCR confirmation. The analysis was stratified to assess vaccine effectiveness against the Delta and Alpha variants over the period that they were circulating. In brief, we compared vaccination status in symptomatic adults with PCR-confirmed SARS-COV-2 infection for each outcome of interest with vaccination status in adults who reported symptoms but had a negative SARS-COV-2 PCR test.

Data Sources

National Immunisation Management System

The National Immunisation Management System (NIMS) contains demographic information on the whole population of England who are registered with a GP in England and is used to record all COVID-19 vaccinations. These data were accessed on 04 October 2021. The information used from NIMS was all dates of COVID-19 vaccination, vaccine manufacturer for each dose, date of death and demographic data (see section on covariates).

COVID-19 testing data

SARS-CoV-2 Testing Polymerase-chain-reaction (PCR) testing for SARS CoV-2 in the United Kingdom is undertaken by hospital and public health laboratories, as well as by community testing with the use of drive through or at-home testing, which is available to anyone with symptoms consistent with Covid-19 (high temperature, new continuous cough, or loss or change in sense of smell or taste), is a contact of a confirmed case, for care home staff and residents or who has self-tested as positive using a lateral flow device. Regular COVID-19 lateral flow testing is available to all members of the population. Data on all positive PCR tests between 08 December 2020, and 01 October 2021 were extracted. Data on all recorded negative community tests were also extracted for this period. Any negative tests taken within 7 days of a previous negative test, or where symptoms were recorded, with symptoms within 10 days of symptoms for a previous negative test were dropped as these likely represent the same episode. Negative tests taken within 21 days before a positive test were also excluded as there is a high chance of these being false negatives. Participants contributed a maximum of three randomly chosen negative test results in the follow-up period. Data were restricted to persons who had reported symptoms and gave an onset date. Only persons who had undergone testing within 10 days after symptom onset were included in order to account for reduced sensitivity of PCR testing beyond this period. To aim to estimate vaccine effectiveness in fully susceptible people, we excluded all test results with a previous positive PCR or antibody test result for the same individual. Children younger than 16 years of age as of March 31, 2021, were excluded.

Identification of Variants and assignment of cases to Alpha and Delta analyses

Sequencing is undertaken at a network of laboratories, including the Wellcome Sanger Institute, where a high proportion of samples have been tested, and whole-genome sequences are assigned to UKHSA definitions of variants based on mutations. Genotyping based on known mutations is also used to identify known variants in addition to full sequencing. Spike gene target status on PCR is a second approach for identifying each variant. Approximately 60% of Pillar 2 Community testing in the UK is carried out by laboratories using the TaqPath assay (Thermo Fisher Scientific) which test for three gene targets: spike (S), nucleocapsid (N), and open reading frame 1ab (ORF1ab). In December 2020, the Alpha variant was noted to be associated with negative testing on the S target, so S target–

negative status was subsequently used as a proxy for identification of the variant. S target-positive status has been used as a proxy for the delta variant since mid-May 2021. [1]

Prior to May 2021, the Alpha variant was the main COVID-19 variant circulating in the UK after which time the Delta variant predominated. Cases were assigned to Alpha or Delta variant first on whole-genome sequencing, second on the spike gene (S-gene) target status third, for cases where sequencing or S-gene testing was not done, based on time-period. Full details of numbers assigned to Alpha and Delta (or neither) by time period are given in Supplementary table S1. The assignment aimed to ensure a high proportion (over 90%) of cases included in the analyses would be the correct variant.

We previously used an earlier cut of this data to estimate the effectiveness of vaccines against the Delta variant compared to the Alpha variant.[2]

Linkage of testing data to NIMS

Testing data were linked to NIMS on 05 October 2021 using combinations of National Health Service number (a unique identifier for each person receiving medical care in the United Kingdom), date of birth, surname, first name, and postcode using deterministic linkage with >95.5% uniqueness. The percentage linkage success was compared between cases and controls, by demographic features (gender, ethnicity, age) and by period.

Hospital and mortality outcomes in positive cases

Individuals testing positive were linked to the Emergency Care Dataset (ECDS) on 05 October 2021 using NHS number and date of test. We included emergency care attendances in symptomatic cases within 14 days of the positive test, which were not injury related and resulted in an inpatient admission. ECDS data includes hospital admissions through NHS emergency departments in England but not elective admissions. Only first attendances in the 14-day period were selected if a person had more than one admission from Emergency Care. To allow for delays in the ECDS data flow, only cases and controls tested by 17 September 2021 were included. A sensitivity analysis was conducted using only admissions with COVID-19 or respiratory SNOMED CT codes as described in Public Health England's Emergency department: weekly bulletin.[3]

When assessing effectiveness against death within 28 days of a positive test, data in NIMS on deaths provided by NHS Digital was used which had death registrations up until 03 October 2021. To allow for delays in the deaths data due to registration delays and for all cases to have 28 days follow-up, only cases and controls tested by 03 September 2021 were included.

Covariates

We extracted sex, date of birth, ethnicity, and geography (NHS region) from the testing data. The linked NIMS data were used to determine index of multiple deprivation from addresses and this also contained flags to identify those who were clinically vulnerable (CEV), in a clinical risk group (at risk), a healthcare worker , and a care home resident. Further details of these flags are given below.

- CEV flag: this is provided by NHS Digital and is a record of vulnerable patients thought to be at high risk of complications from COVID-19.[4] This CEV flag was updated at a number of time points since the end of November 2020 and individuals were counted as CEV if they had this flag at any time point.

- At risk flag: this is provided by NHS Digital and is based on a list of NHS numbers extracted from the Electronic Health Record (EHR) based on the national SNOMED coded specification. This includes between 16 and 65 years of age who are in a clinical risk group and also those coded as a carer within the Electronic Staff Record (ESR). [5]
- Healthcare worker (HCW) flag: this is provided by the NHS Business Services Authority for all staff who are directly employed by the NHS organizations using the ESR.
- Care home resident flag: this is generated from the NHS England and Improvement Master Patient Index and uses a Unique Property Reference Numbers and NHS-addresses linked to care home Care Quality Commission addresses. An Individual is given this flag if they have ever lived in a care home since the beginning of the vaccine programme and is updated monthly.

Statistical analysis

Analysis was by logistic regression with the PCR test result as the dependent variable where those testing positive are cases and those testing negative controls. In analyses for hospitalization and death those testing positive and being hospitalized or testing positive and dying were cases and those testing negative were controls. Vaccination status was included as an independent variable and effectiveness defined as 1- odds of vaccination in cases/odds of vaccination in controls. Vaccine effectiveness was adjusted in logistic regression models for age, sex, index of multiple deprivation, ethnic group, care home residence status (for analyses including adults aged >=65 years), geographic region, period (calendar week), health and social care worker status (for analyses with adults aged <65 years), and clinical risk group (only available for <65 year-olds) or a clinically extremely vulnerable group (any age). For deaths, the period was modelled using a cubic spline due to smaller numbers. These factors were also considered potential confounders so were included in all models.

Analyses were stratified by age-group according to the timing of vaccination in the general population as described in Supplementary table S2 and Supplementary table S4. Within age 65 years and above the analyses were also further stratified for those flagged as being in a clinically extremely vulnerable and within age 40-64 for those flagged as being either clinically extremely vulnerable or in a risk group.

Vaccine effectiveness was assessed for each vaccine and by intervals after vaccination of at least 28 days' post first dose, and at least 14 days post second dose. To assess potential waning, intervals of 1 week (7-13 days), 2-9 weeks, 10-14 weeks, 15-19 weeks and over 20 weeks post second dose were used. For the earliest vaccinated groups, (65+ year olds) the last period was further stratified into 20-24 and 25+ weeks. An additional analysis was done in the 80 years an older group according to interval between doses (≤28 days, ≥56 days) for the hospitalisation outcome. Where sample size was very small and VE estimates highly imprecise, estimates are not presented. This mainly affected the 1-week interval after the second dose and for longer intervals after the second dose effectiveness against Alpha and in younger ages effectiveness against Delta. Waning was not assessed for age 16-39 as there was insufficient follow-up time in this group.

Missing data

There was very little missing data in the final dataset with 0.11% missing gender, <0.01% missing region. 7.1% were missing IMD due to missing address details. These data were dropped from the analysis.

Supplementary Section 2: Tables and Figures

Table S1. Assignment of positives cases to Alpha and Delta analyses

Variant sequenced/ S-gene status												
Week year	nk / nk	nk / pos	nk / neg	other / nk	other / pos	other / neg	Alpha / nk	Alpha / pos	Alpha / neg	Delta / nk	Delta / pos	Delta / neg
50-53 2020	2760	793	1144	3	35	1	17	0	46	0	0	0
1-14 2021	228749	24508	222905	455	2651	218	12952	49	62001	12	10	0
15-17 2021	1726	82	1247	79	90	13	1218	2	5595	139	410	0
18-20 2021	2609	446	355	68	81	14	1304	0	2573	474	3191	2
21-25 2201	24674	36349	677	97	27	7	799	3	1106	11569	21396	5
26-39 2021	431901	484231	380	1069	983	0	30	0	25	48328	62050	10

Included as Alpha
Included as Delta
Other/not known
Period not included for that strain

Notes

Over all weeks 71346/71616 (99.6%) of S-gene negatives that were sequenced were Alpha so S-gene negative is highly predictive of Alpha.
From weeks 15 to 39 87047/88233 (98.7%) of S-gene positives that were sequenced were Delta, so in this period S-gene positive is highly predictive of Delta
In weeks 50-53 59% were S-gene negative when done so not known S-gene/sequencing could not be assigned
In weeks 1-17 91% were S-gene negative when done so not knowns were assigned Alpha
In weeks 21-39 99% were S-gene positive when done so not known S-gene/sequencing could be assigned as Delta

Table S2. Analysis sets by age and outcomes

Age at March 31st 2021	Case outcome (all control outcomes are symptomatic infection)	Period for cases / controls included (Alpha)*	Period for cases/controls included (Delta)**	Period in which first vaccination dose is given if vaccinated at onset
80+	Symptomatic infection	Onset 08 Dec 2020 – 27 Jun 2021	Onset from 12 Apr 2021 and tested by 01 Oct 2021	08 Dec 2020 – 03 Jan 2021
	Hospitalisation within 14 days of test in a symptomatic case	Onset 08 Dec 2020 – 27 Jun 2021	Onset from 12 Apr 2021 and tested by 17 Sep 2021	08 Dec 2020 – 03 Jan 2021
65+	Symptomatic infection	Onset 04 Jan 2021 – 27 Jun 2021	Onset from 12 Apr 2021 and tested by 01 Oct 2021	04 Jan 2021 onwards
	Hospitalisation within 14 days of test in a symptomatic case	Onset 04 Jan 2020 – 27 Jun 2021	Onset from 12 Apr 2021 and tested by 17 Sep 2021	04 Jan 2021 onwards
	Death within 28 days of test in a symptomatic case	Onset 04 Jan 2021 – 27 Jun 2021	Onset from 12 Apr 2021 and tested by 03 Sep 2021	04 Jan 2021 onwards
40-64	Symptomatic infection	Onset 01 Feb 2021-27 Jun 2021	Onset from 12 Apr 2021 and tested by 01 Oct 2021	Feb 1 2021 onwards
	Hospitalisation within 14 days of test in a symptomatic case	Onset 01 Feb 2021-27 Jun 2021	Onset from 12 Apr 2021 and tested by 17 Sep 2021	Feb 1 2021 onwards
16-39	Symptomatic infection	Onset 10 May 2020-27 Jun 2021	Onset from 10 May 2021 and tested by 01 Oct 2021	10 May 2021 onwards
	Hospitalisation within 14 days of test in a symptomatic case	Onset 10 May 2020-27 Jun 2021	Onset from 10 May 2021 and tested by 17 Sep 2021	10 May 2021 onwards
16+ (All)	Symptomatic infection	Onset 04 Jan 2021 – 27 Jun 2021	Onset from 12 Apr 2021 and tested by 01 Oct 2021	04 Jan 2021 onwards

	Hospitalisation within 14 days of test	Onset 04 Jan 2020 – 27 Jun 2021	Onset from 12 Apr 2021 and tested by 17 Sep 2021	04 Jan 2021 onwards
	Death within 28 days of test	Onset 04 Jan 2021 – 27 Jun 2021 or for 80+ cohort 08 Dec 2021-27 Jun 2021	Onset from 12 Apr 2021 and tested by 03 Sep 2021	04 Jan 2021 onwards if aged <80 or 08 Dec 2021-03 Jan 2021 if aged 80+

*27 Jun is for test negative controls and test positive cases if sequencing or s-gene target failure is done, otherwise 02 May is used before which >80% of those tested positive were Alpha

**12 Apr is for test negative controls and test positive cases if sequencing or s-gene target failure is done , otherwise 24 May is used after which >80% of those tested positive were Delta

Table S3. Descriptive characteristics of all tests by NIMS linkage status.

		Unlinked to NIMS		Linked to NIMS	
		n	%	n	%
	Total	1,050,309	14.8	6,056,673	85.2
Gender	Male	572,795	54.5	2,633,816	43.5
	Female	473,591	45.1	3,416,100	56.4
Ethnicity	African	29,989	2.9	92,316	1.5
	Another Asian background	17,415	1.7	77,226	1.3
	Another Black background	4,040	0.4	10,499	0.2
	Another ethnic background	14,705	1.4	45,239	0.7
	Arab	7,762	0.7	25,265	0.4
	Bangladeshi	8,426	0.8	51,923	0.9
	Caribbean	13,008	1.2	49,111	0.8
	Chinese	6,352	0.6	29,570	0.5
	Indian	32,393	3.1	211,308	3.5
	Mixed or multiple ethnic groups	31,741	3.0	128,913	2.1
	Pakistani	25,952	2.5	155,139	2.6
	Prefer not to say	63,525	6.0	200,627	3.3
	White	795,001	75.7	4,979,537	82.2
Region	East of England	105,487	10.0	663,816	11.0
	London	194,746	18.5	866,349	14.3
	Midlands	191,947	18.3	1,173,103	19.4
	North East and Yorkshire	161,081	15.3	1,016,867	16.8
	North West	150,394	14.3	865,738	14.3
	South East	149,075	14.2	887,941	14.7
	South West	97,561	9.3	582,847	9.6

Table S4. Descriptive characteristics of positive and negative test results in individuals tested for SARS-CoV-2 in England for the study population.*

		Overall		Positive		Negative	
		n	%	n	%	n	%
	Test Result	**6,056,673**	**100.0**	**1,706,743**	**28.2%**	**4,349,930**	**71.8%**
Vaccination status	Unvaccinated	855,743	14.1%	358,682	21.0%	497,061	11.4%
	ChAdOx1-S 1 dose	76,420	1.3%	23,846	1.4%	52,574	1.2%
	ChAdOx1-S 2 doses	2,376,037	39.2%	642,003	37.6%	1,734,034	39.9%
	BNT162b2 1 dose	393,425	6.5%	155,353	9.1%	238,072	5.5%
	BNT162b2 2 doses	2,133,769	35.2%	474,035	27.8%	1,659,734	38.2%
	mRNA-12731 dose	32,875	0.5%	12,309	0.7%	20,566	0.5%
	mRNA-12732 doses	176,235	2.9%	37,695	2.2%	138,540	3.2%
	Mixed course or dose1-2 interval <19 days	12169	0.2%	2,820	0.2%	9,349	0.2%
Age Group	80+	74,289	1.2%	22,412	1.3%	51,877	1.2%
	65-79	329,812	5.4%	85,951	5.0%	243,861	5.6%
	40-64	2,269,993	37.5%	625,278	36.6%	1,644,715	37.8%
	16-39	3,382,579	55.8%	973,102	57.0%	2,409,477	55.4%
Gender	Female	3,416,100	56.4%	884,254	51.8%	2,531,846	58.2%
	Male	2,633,816	43.5%	820,477	48.1%	1,813,339	41.7%
	Missing	6,757	0.1%	2,012	0.1%	4,745	0.1%
Ethnicity	African	92,316	1.5%	29,719	1.7%	62,597	1.4%
	Another Asian background	77,226	1.3%	23,730	1.4%	53,496	1.2%
	Another Black background	10,499	0.2%	3,526	0.2%	6,973	0.2%
	Another ethnic background	45,239	0.7%	12,532	0.7%	32,707	0.8%
	Arab	25,265	0.4%	7,192	0.4%	18,073	0.4%
	Bangladeshi	51,923	0.9%	19,343	1.1%	32,580	0.7%
	Caribbean	49,111	0.8%	18,743	1.1%	30,368	0.7%
	Chinese	29,570	0.5%	6,185	0.4%	23,385	0.5%
	Indian	211,308	3.5%	58,670	3.4%	152,638	3.5%
	Mixed or multiple ethnic groups	128,913	2.1%	38,254	2.2%	90,659	2.1%
	Pakistani	155,139	2.6%	51,696	3.0%	103,443	2.4%

	Prefer not to say	200,627	3.3%	57,288	3.4%	143,339	3.3%
	White	4,979,537	82.2%	1,379,865	80.8%	3,599,672	82.8%
NHS Region	East of England	663,816	11.0%	171,149	10.0%	492,667	11.3%
	London	866,349	14.3%	233,730	13.7%	632,619	14.5%
	Midlands	1,173,103	19.4%	349,557	20.5%	823,546	18.9%
	North East	1,016,867	16.8%	321,589	18.8%	695,278	16.0%
	North West	865,738	14.3%	266,965	15.6%	598,773	13.8%
	South East	887,941	14.7%	219,904	12.9%	668,037	15.4%
	South West	582,847	9.6%	143,845	8.4%	439,002	10.1%
	Unknown	12	0.0%	4	0.0%	8	0.0%

*aged 80 and above and either unvaccinated at the time of onset or first vaccinated before January 4th, 2021 with onset December 8th, 2020-September 3rd, 2021 or aged 16 and above and unvaccinated prior to January 4th, 2021 with onset January 4th 2021-September 3rd, 2021.

Table S5. Counts by variant, hospitalisations and deaths for positive SARS-CoV-2 tests among individuals in England for the study population.

		All	16-39	40-64	65-79	80+
Variant	**Alpha**	544,468	260,843	242,057	31,798	9,770
	Delta	1,125,257	696,120	368,921	51,922	8,294
	Other or unknown	37,018	16139	14,300	2,231	4348
Outcome	**Number of hospitalisations**	22,575	5,239	10,618	4,184	2,534
	Number of deaths	6,336	83	930	1,209	2,195

Table S6. Vaccine effectiveness against Alpha and Delta symptomatic disease, hospitalisation and death for BNT162b2, ChAdOx1-S and mRNA-1273 in England. Table values are VE (95% CI) or VE (total cases, total controls when VE is 100%).

			Symptomatic disease (tested by Sep 3rd)		Hospitalisation (tested by Aug 13th)		Death (tested by July 29th)	
Age	Vaccine	Dose*	Alpha	Delta	Alpha	Delta	Alpha	Delta
16+	BNT162b2	1	45.9 (44.2 to 47.6)	51.2 (50.7 to 51.7)	85.8 (82.2 to 88.7)	91.1 (89.7 to 92.3)	88.5 (78.5 to 93.8)	88.6 (78.8 to 93.9)
		2	94.9 (93.6 to 95.9)	83.3 (83.1 to 83.5)	97.8 (91.2 to 99.5)	96.6 (96.2 to 96.9)	95.6 (94.4 to 96.5)	95.6 (94.4 to 96.6)
	ChAdOx1-S	1	45.1 (43.4 to 46.7)	46.6 (45.8 to 47.5)	84.0 (80.2 to 87.1)	80.7 (78 to 83)	86.9 (77.5 to 92.4)	86.9 (77.5 to 92.4)
		2	82.1 (79.4 to 84.5)	64.2 (63.9 to 64.5)	95.2 (86.8 to 98.2)	92.5 (92 to 93)	93.2 (91.6 to 94.5)	93.2 (91.7 to 94.5)
	mRNA-1273	1	58.1 (11.7 to 80.1)	64.9 (64 to 65.7)		93.7 (89.9 to 96)		100 (0 cases, 21698 con)
		2		93.6 (93.2 to 93.9)				
	Any	1	45.5 (44.2 to 46.7)	52.2 (51.8 to 52.6)	84.9 (82.3 to 87.2)	87.6 (86.4 to 88.8)	76.7 (70.3 to 81.7)	87.9 (81.6 to 92.1)
		2	89.8 (88.5 to 90.9)	73.9 (73.6 to 74.1)	96.6 (92.2 to 98.5)	94.2 (93.8 to 94.5)	96.1 (89.0 to 98.6)	94.3 (93.0 to 95.3)
16-39	BNT162b2	1		52.5 (52.1 to 53.0)		90.7 (89 to 92.1)		
		2		88.8 (88.6 to 89.0)		99.2 (98.3 to 99.6)		
	ChAdOx1-S	1		49.3 (45.7 to 52.7)		86.1 (66.5 to 94.2)		
		2		59.8 (56.1 to 63.3)		100 (no case, 1165 con)		
	mRNA-1273	1		66.2 (65.3 to 67.0)		93.9 (89.5 to 96.5)		
		2		93.5 (93.0 to 93.9)				
	Any	1		53.9 (53.5 to 54.4)		90.9 (89.4 to 92.3)		
		2		88.8 (88.6 to 89.0)		99.2 (98.5 to 99.6)		
40 to 64	BNT162b2	1	49.4 (45.6 to 53)	43.9 (41.9 to 45.8)	91.8 (83.3 to 96.0)	93.0 (89.5 to 95.4)		
		2	92 (86.7 to 95.2)	78.0 (77.5 to 78.5)	81.5 (19.4 to 95.8)	97.7 (97.3 to 98.1)		
	ChAdOx1-S	1	49.9 (47.2 to 52.5)	33.4 (31.8 to 34.9)	79.8 (71.2 to 85.8)	83.2 (80.3 to 85.7)		
		2	81.9 (76.2 to 86.2)	60.0 (59.4 to 60.7)	82.4 (38.6 to 95.0)	94.3 (93.8 to 94.8)		
	mRNA-1273	1	67.5 (12.7 to 87.9)	53.3 (49.9 to 56.5)		93.6 (82.9 to 97.6)		
		2		91.2 (90.4 to 91.8)				
	Any	1	49.8 (47.4 to 52)	37.8 (36.5 to 39.1)	84.1 (78.0 to 88.5)	86.1 (83.8 to 88.0)		

		2	85.6 (81.6 to 88.7)	63.5 (62.9 to 64.1)	83.1 (53.4 to 93.9)	95.2 (94.7 to 95.6)		
65+	BNT162b2	1	54.8 (50.5 to 58.7)	53.8 (43.8 to 62.0)	79.2 (71.2 to 84.9)	95.4 (85.4 to 98.6)	80.4 (73.8 to 85.3)	81.5 (55.5 to 92.3)
		2	94.3 (90.5 to 96.6)	64.6 (61.9 to 67.2)	100 (0 cases, 10139 con)	94.0 (92.7 to 95.0)	96.6 (90.2 to 98.8)	93.6 (91.2 to 95.4)
	ChAdOx1-S	1	54.8 (50.2 to 58.9)	40.7 (31.4 to 48.8)	79.8 (70.9 to 86.0)	81.6 (69.0 to 89.0)	82.9 (73.1 to 89.1)	82.5 (57.9 to 92.7)
		2	87.8 (81.8 to 91.8)	47.2 (43.2 to 50.9)	96.8 (72.4 to 99.6)	87.7 (85.4 to 89.7)	100 (0 cases, 13030 con)	
	Any	1	54.9 (51.1 to 58.4)	45.5 (38.1 to 52.0)	79.8 (73.3 to 84.7)	87.3 (79.4 to 92.1)	81.3 (75.6 to 85.7)	81.8 (65.2 to 90.5)
		2	91.1 (87.5 to 93.6)	54.5 (51.1 to 57.7)	98.5 (87.2 to 99.8)	90.5 (88.8 to 92.0)	97.2 (91.6 to 99)	92.1 (89.3 to 94.2)
80+ early	BNT162b2	1	56.0 (47.5 to 63.1)		76.1 (61.9 to 85.0)			
		2	81.3 (75.8 to 85.5)	33.5 (16.8 to 46.8)	92.1 (81.7 to 96.6)	80.6 (69.8 to 87.6)		

*dose 1: 28 days after first dose to time of second (if given), dose 2: 14 days after second dose

Table S7. Number of cases and controls (cases; controls) contributing to vaccine effectiveness estimates as shown in Supplementary Table S4.

			Symptomatic disease (tested by Sep 3rd)		Hospitalisation (tested by Aug 13th)		Death (tested by July 29th)	
Age	Vaccine	Dose*	Alpha	Delta	Alpha	Delta	Alpha	Delta
16+	Unvaccinated	0	493602; 2045645	351725; 445531	11109; 2045645	4062; 412352	2267; 2055868	195; 383872
	BNT162b2	1	5126; 69839	131938; 199116	87; 69839	211; 181926	72; 71347	11; 167068
		2	88; 54261	104606; 492329	2; 54261	717; 366948	4; 57238	196; 278436
	ChAdOx1-S	1	5678; 123265	33734; 114854	109; 123265	282; 111679	31; 123265	15; 109188
		2	215; 64178	353203; 677190	5; 64178	2453; 541635	0; 64178	314; 441596
	mRNA-1273	1	8; 1864	12896; 25243	0; 1864	19; 23898		0; 21698
		2		1713; 21583		0; 12456		
	Any	1	10812; 194993	178568; 339213	196; 194993	512; 317503	103; 196501	26; 297954
		2	303; 118439	459249; 1190353	7; 118439	3166; 920571	4; 121416	510; 726472
16-39	Unvaccinated	0		338947; 342028		2346; 301674		
	BNT162b2	1		122808; 173376		172; 156149		
		2		17684; 163273		8; 97081		
	ChAdOx1-S	1		1507; 2337		5; 2059		
		2		783; 1811		1; 1165		
	mRNA-1273	1		11390; 21711		14; 20469		
		2		849; 14919		0; 8086		
	Any	1		135705; 197424		191; 178677		
		2		19316; 179998		9; 106331		
40 to 64	Unvaccinated	0	66092; 309935	46307; 58370	1830; 309935	1535; 52852		
	BNT162b2	1	947; 15351	7172; 16305	8; 15351	28; 15281		
		2	15; 11009	25613; 90333	2; 11009	135; 71763		
	ChAdOx1-S	1	2362; 63440	23178; 72761	43; 63440	197; 71162		
		2	64; 27939	217368; 391099	3; 27939	1038; 306546		
	mRNA-1273	1	5; 1159	1323; 3097	0; 1159	4; 3001		
		2		790; 5868		0; 3795		

	Any	1	3314; 79971	31673; 92163	51; 79971	229; 89444		
		2	79; 38948	243681; 487087	5; 38948	1172; 381992		
65+	Unvaccinated	0	27963; 82268	1854; 2359	2815; 82268	219; 2098	1607; 92491	65; 1888
	BNT162b2	1	1103; 14328	196; 2063	62; 14328	3; 2012	70; 15836	6; 2042
		2	19; 10139	17474; 48333	0; 10139	398; 41857	4; 13116	174; 39737
	ChAdOx1-S	1	1185; 18959	438; 5010	55; 18959	18; 4902	26; 18959	6; 4813
		2	42; 13030	37425; 69149	2; 13030	985; 59827	0; 13030	218; 51046
	Any	1	2288; 33287	637; 7080	117; 33287	21; 6921	96; 34795	12; 6861
		2	61; 23169	54818; 117324	2; 23169	1380; 101570	4; 26146	392; 90784
80+ early	Unvaccinated	0	5509; 15888	207; 290	938; 15888			
	BNT162b2	1	260; 1508		27; 1508			
		2	90; 2977	2550; 5304	6; 2977	149; 4717		

*dose 1: 28 days after first dose to time of second (if given), dose 2: 14 days after second dose

Table S8. Logistic regression estimates for all age analysis for Delta cases, hospitalisations and deaths and Hosmer-Lemeshow goodness of fit assessment by deciles of predicted probability of being a case

Factor	Level	Odds ratio (symptomatic infection)	Odds ratio (hospitalisation)	Odds ratio (death)
health/social care worker	no	base	base	base
	yes	0.90 (0.89-0.91)	0.88 (0.75-1.03)	0.48 (0.18-1.29)
Care home resident	no	base	base	base
	yes	0.82 (0.75-0.90)	1.04 (0.73-1.46)	1.99 (1.37-2.90)
Nhs region	East of England	base	base	base
	London	0.98 (0.97-0.99)	1.19 (1.06-1.33)	0.66 (0.46-0.94)
	Midlands	1.23 (1.22-1.24)	2.10 (1.89-2.32)	1.27 (0.95-1.70)
	North East and Yorkshire	1.39 (1.37-1.40)	2.09 (1.89-2.32)	1.29 (0.96-1.72)
	North West	1.43 (1.41-1.44)	1.81 (1.62-2.01)	1.37 (1.02-1.84)
	South East	0.95 (0.94-0.96)	1.15 (1.03-1.29)	0.73 (0.52-1.02)
	South West	0.93 (0.92-0.94)	1.22 (1.08-1.37)	0.74 (0.52-1.06)
clinically vulnerable	no	base	base	base
	yes	0.97 (0.95-0.98)	2.57 (2.41-2.75)	5.13 (4.31-6.09)
at risk	no	base	base	base
	yes	0.95 (0.94-0.95)	2.19 (2.06-2.32)	1.42 (1.10-1.82)
index of multiple deprivation quintile	1	base	base	base
	2	0.98 (0.97-0.99)	0.95 (0.89-1.01)	0.83 (0.67-1.03)
	3	0.94 (0.93-0.95)	0.85 (0.79-0.91)	0.65 (0.52-0.83)
	4	0.92 (0.92-0.93)	0.77 (0.72-0.83)	0.59 (0.46-0.75)
	5	0.90 (0.89-0.90)	0.68 (0.63-0.74)	0.59 (0.46-0.75)
ethnicity	African	0.88 (0.86-0.90)	1.16 (0.99-1.36)	0.53 (0.21-1.29)
	Another Asian background	0.93 (0.90-0.95)	1.25 (1.00-1.55)	1.35 (0.63-2.90)
	Another Black background	0.94 (0.88-1.00)	1.50 (1.06-2.15)	2.75 (1.06-7.15)
	Another ethnic background	0.80 (0.77-0.82)	1.59 (1.28-1.96)	0.53 (0.17-1.70)
	Arab	0.78 (0.75-0.81)	1.18 (0.89-1.57)	0.40 (0.09-1.72)
	Bangladeshi	1.12 (1.08-1.15)	1.95 (1.59-2.39)	1.18 (0.51-2.74)
	Caribbean	1.11 (1.08-1.14)	1.83 (1.58-2.11)	0.84 (0.46-1.55)
	Chinese	0.61 (0.58-0.63)	1.37 (0.98-1.91)	1.04 (0.26-4.26)
	Indian	0.84 (0.83-0.85)	1.23 (1.09-1.40)	0.94 (0.61-1.45)
	Mixed or multiple ethnic groups	0.94 (0.92-0.95)	1.07 (0.91-1.26)	0.38 (0.12-1.19)
	Pakistani	0.90 (0.88-0.92)	1.43 (1.27-1.61)	1.18 (0.76-1.81)
	Prefer not to say	0.78 (0.77-0.80)	0.98 (0.87-1.10)	0.62 (0.41-0.94)
	White	base	base	base
age (years)	15-19	0.80 (0.78-0.82)	0.02 (0.02-0.03)	1.00 (0.00-0.00)

	20-24	0.77 (0.75-0.78)	0.04 (0.03-0.04)	0.00 (0.00-0.01)
	25-29	0.64 (0.63-0.66)	0.05 (0.05-0.06)	0.01 (0.00-0.01)
	30-34	0.62 (0.60-0.63)	0.07 (0.06-0.08)	0.01 (0.00-0.01)
	35-39	0.69 (0.68-0.71)	0.09 (0.08-0.11)	0.02 (0.01-0.04)
	40-44	0.85 (0.83-0.87)	0.12 (0.11-0.14)	0.03 (0.02-0.05)
	45-49	0.92 (0.90-0.94)	0.15 (0.13-0.17)	0.06 (0.04-0.09)
	50-54	0.89 (0.88-0.91)	0.18 (0.16-0.21)	0.11 (0.07-0.16)
	55-59	0.86 (0.84-0.88)	0.21 (0.19-0.24)	0.16 (0.11-0.23)
	60-64	0.84 (0.82-0.86)	0.27 (0.23-0.31)	0.29 (0.20-0.41)
	65-69	0.89 (0.87-0.92)	0.59 (0.52-0.68)	0.62 (0.46-0.85)
	70-74	base	base	base
	75-79	1.13 (1.09-1.17)	1.49 (1.29-1.72)	1.74 (1.28-2.36)
	80-84	1.23 (1.17-1.29)	1.77 (1.47-2.14)	2.86 (2.09-3.91)
	85-89	1.05 (0.98-1.13)	1.56 (1.22-1.99)	4.18 (3.01-5.81)
	>=90	0.76 (0.69-0.84)	1.42 (1.03-1.95)	4.84 (3.33-7.03)
gender	F	base	base	base
	M	1.31 (1.30-1.31)	1.49 (1.42-1.56)	2.33 (2.00-2.72)
week of onset	14	0.00 (0.00-0.00)	0.01 (0.00-0.03)	1.41 (1.02-1.97)*
	15	0.00 (0.00-0.00)	0.00 (0.00-0.01)	0.50 (0.22-1.15)*
	16	0.00 (0.00-0.01)	0.01 (0.01-0.03)	2.49 (0.78-7.92)*
				* cubic spline
	17	0.01 (0.01-0.01)	0.02 (0.01-0.03)	parameters
	18	0.02 (0.02-0.02)	0.01 (0.01-0.03)	
	19	0.03 (0.03-0.03)	0.05 (0.03-0.07)	
	20	0.06 (0.05-0.06)	0.10 (0.07-0.13)	
	21	0.15 (0.15-0.16)	0.24 (0.19-0.29)	
	22	0.27 (0.27-0.28)	0.38 (0.32-0.45)	
	23	0.35 (0.34-0.35)	0.43 (0.36-0.51)	
	24	0.38 (0.37-0.39)	0.41 (0.35-0.49)	
	25	0.54 (0.53-0.54)	0.54 (0.47-0.63)	
	26	0.68 (0.67-0.69)	0.73 (0.64-0.82)	
	27	0.92 (0.91-0.93)	0.89 (0.79-1.00)	
	28	1.24 (1.22-1.25)	1.20 (1.07-1.34)	
	29	base	base	
	30	1.11 (1.09-1.13)	1.07 (0.94-1.22)	
	31	1.29 (1.27-1.30)	1.30 (1.15-1.47)	
	32	1.40 (1.37-1.42)	1.23 (1.08-1.39)	
	33	1.43 (1.41-1.45)	1.46 (1.30-1.65)	
	34	1.27 (1.26-1.29)	1.54 (1.37-1.74)	
	35	1.03 (1.01-1.04)	1.19 (1.06-1.35)	
	36	0.75 (0.74-0.76)	0.81 (0.71-0.92)	
	37	0.58 (0.57-0.59)	0.62 (0.52-0.75)	
	38	0.60 (0.59-0.61)		
	39	0.64 (0.63-0.65)		
vaccination status	unvacc	base	base	base
	AZ_d1:0-3	0.68 (0.55-0.84)	0.53 (0.16-1.69)	0 deaths
	AZ_d1:4-13	0.78 (0.70-0.86)	0.65 (0.35-1.18)	1.06 (0.15-7.71)
	AZ_d1:14-27	0.50 (0.46-0.53)	0.16 (0.08-0.30)	0 deaths

	AZ_d1:28+	0.53 (0.53-0.54)	0.19 (0.17-0.22)	0.13 (0.08-0.22)
	AZ_d2:0-7	0.51 (0.49-0.52)	0.17 (0.13-0.23)	0.21 (0.08-0.59)
	AZ_d2:7-13	0.35 (0.34-0.36)	0.07 (0.05-0.10)	0 deaths
	AZ_d2:14+	0.36 (0.35-0.36)	0.07 (0.07-0.08)	0.07 (0.05-0.08)
	PF_d1:0-3	1.20 (1.16-1.23)	0.94 (0.74-1.21)	0 deaths
	PF_d1:4-13	0.88 (0.86-0.89)	0.47 (0.39-0.56)	0.51 (0.16-1.62)
	PF_d1:14-27	0.40 (0.40-0.41)	0.09 (0.07-0.12)	0 deaths
	PF_d1:28+	0.49 (0.48-0.49)	0.09 (0.08-0.10)	0.11 (0.06-0.21)
	PF_d2:0-6	0.38 (0.37-0.39)	0.06 (0.04-0.10)	0.11 (0.01-0.76)
	PF_d2:7-13	0.07 (0.07-0.08)	0.01 (0.00-0.02)	0 deaths
	PF_d2:14+	0.17 (0.17-0.17)	0.03 (0.03-0.04)	0.04 (0.03-0.06)
	MD_d1:0-3	1.15 (1.07-1.24)	0.60 (0.27-1.34)	0 deaths
	MD_d1:4-13	0.81 (0.78-0.85)	0.36 (0.21-0.62)	1.27 (0.17-9.27)
	MD_d1:14-27	0.21 (0.20-0.22)	0.08 (0.04-0.19)	0 deaths
	MD_d1:28+	0.35 (0.34-0.36)	0.06 (0.04-0.10)	0 deaths
	MD_d2:0-6	0.23 (0.21-0.24)	0.02 (0.00-0.12)	0 deaths
	MD_d2:7-13	0.04 (0.04-0.05)	0.02 (0.00-0.15)	0 deaths
	MD_d2:14+	0.06 (0.06-0.07)		
Hosmer-Lemeshow goodness of fit	Decile of predicted probability of being a case	Observed/ Expected cases (ratio)	Observed/ Expected cases (ratio)	Observed/ Expected cases (ratio)
	1	8939/9563 (0.93)	14/13 (1.10)	0/0.2 (0.00)
	2	38320/40382 (0.95)	45/45 (0.99)	1/0.7 (1.43)
	3	62328/62455 (1.00)	79/85 (0.93)	1/1.4 (0.71)
	4	81171/80704 (1.01)	107/134 (0.80)	2/2.6 (0.77)
	5	98467/97534 (1.01)	172/201 (0.86)	3/4.5 (0.67)
	6	116152/114096 (1.02)	260/296 (0.88)	7/7.9 (0.89)
	7	131738/129963 (1.01)	363/437 (0.83)	9/13.9 (0.65)
	8	148032/147332 (1.00)	621/673 (0.92)	12/26.2 (0.46)
	9	169338/170144 (1.00)	1220/1199 (1.02)	49/59.3 (0.83)
	10	206482/208794 (0.99)	4697/4495 (1.05)	660/627.4 (1.05)

Table S9. Number of cases and controls (cases; controls) contributing to vaccine effectiveness estimates against symptomatic disease as shown in Table 1 and Supplementary Table S10 (mRNA-1273 VE).

		Weeks post Dose 2					
Vaccine	Age group	1 week	2-9 weeks	10-14 weeks	15-19 weeks	20+ weeks (20-24 weeks for 65+)	25+ weeks
Unvaccinated	16+	351725 ; 445531					
	65+	1854 ; 2359					
	40-64	46307 ; 58370					
	16-39	338947 ; 342028					
ChAdOx1-S	16+	8072 ; 25045	127291 ; 284404	122368 ; 201901	80178 ; 144961	23366 ; 45924	
	65+	39 ; 1511	3090 ; 18879	9762 ; 18768	15737 ; 19282	8383 ; 11589	453 ; 631
	40-64	6194 ; 16409	89337 ; 180719	79973 ; 120590	42824 ; 78396	5234 ; 11394	
	16-39	130 ; 195	659 ; 1512	122 ; 296			
BNT162b2	16+	3317 ; 33997	24519 ; 233114	22901 ; 92724	31498 ; 85083	25688 ; 81408	
	65+	13 ; 913	620 ; 10840	3381 ; 12292	6780 ; 13058	5996 ; 10753	697 ; 1390
	40-64	275 ; 2923	5461 ; 34319	7837 ; 23239	9495 ; 24132	2820 ; 8643	
	16-39	2924 ; 27535	15488 ; 150027	2174 ; 13115	22 ; 131		
mRNA-1273	16+	238 ; 3665	1377 ; 19020	330 ; 2540			
	40-64	60 ; 599	513 ; 3935	274 ; 1922			
	16-39	172 ; 2986	809 ; 14510	40 ; 409			

Table S10. Vaccine effectiveness against Delta symptomatic disease and hospitalisation for mRNA-1273 in England. Table values are VE (95% CI) or VE (total cases, total controls when VE is 100%).

		Weeks post Dose 2		
Outcome	Age group	1 week	2-9 weeks	10-14 weeks
Symptomatic Disease	16+	95.6 (95.0 to 96.2)	93.8 (93.4 to 94.1)	85.6 (83.8 to 87.2)
	40-64	93.5 (91.5 to 95.1)	92.1 (91.3 to 92.8)	87.3 (85.5 to 88.8)
	16-39	95.7 (94.9 to 96.3)	93.5 (93.0 to 94.0)	82.1 (75.2 to 87.1)
Hospitalisation	16+	97.9 (84.9 to 99.7)	100 (0 case, 12035 con)	

Table S11. Vaccine effectiveness against Alpha symptomatic disease among individuals with two doses of ChAdOx1-S, BNT162b2 in England at 1 week, 2-9 weeks and 10+ weeks. Table values are VE (95% CI) or VE (total cases, total controls when VE is 100%).

		Weeks post Dose 2		
Vaccine	Age group	1 week	2-9 weeks	10+
ChAdOx1-S	16+	71.8 (66.2 to 76.5)	82.4 (79.6 to 84.7)	76.2 (49.8 to 88.7)
	65+	78.9 (67.0 to 86.5)	88.2 (82.2 to 92.1)	
	40-64	73.0 (63.6 to 80.0)	81.7 (76.0 to 86.1)	
BNT162b2	16+	90.2 (86.9 to 92.7)	94.9 (93.6 to 95.9)	94.8 (88.4 to 97.7)
	80+	78.3 (67.4 to 85.6)	81.7 (76.1 to 86.0)	67.1 (31.1 to 84.3)
	65+	86.3 (76.4 to 92.1)	94.2 (90.3 to 96.6)	
	40-64	94.7 (85.8 to 98.0)	91.9 (86.5 to 95.2)	

Table S12. Vaccine effectiveness against Alpha hospitalisation among individuals with two doses of ChAdOx1-S, BNT162b2 in England at 1 week, 2-9 weeks and 10+ weeks. Table values are VE (95% CI) or VE (total cases, total controls when VE is 100%).

		Weeks post Dose 2		
Vaccine	Age group	1 week	2-9 weeks	10+ weeks
ChAdOx1-S	16+	89.6 (67.4 to 96.7)	95.1 (86.7 to 98.2)	
	65+	89.7 (19.2 to 98.7)	96.8 (71.8 to 99.6)	100 (0 cases, 874 con)
	40-64	88.2 (12.8 to 98.4)	83.0 (40.5 to 95.2)	100 (0 cases, 282 con)
BNT162b2	16+	96.4 (74.2 to 99.5)	97.7 (90.8 to 99.4)	
	80+	86.6 (57.4 to 95.8)	92.6 (81.6 to 97.0)	87.8 (-15.4 to 98.7)
	65+	89.2 (17.1 to 98.6)	100 (0 cases, 8639 con)	
	40-64	100 (0 cases, 1556 con)	82.1 (21.6 to 95.9)	100 (0 cases, 267 con)

Table S13. Vaccine effectiveness against Alpha deaths among individuals with two doses of BNT162b2 or all vaccines in England at 2+ weeks. Table values are VE (95% CI).

		Weeks post Dose 2
Vaccine	Age group	2 weeks +
BNT162b2	16+	95.6 (94.4 to 96.5)
	65+	96.6 (90.2 to 98.8)
Any	16+	96.1 (89.0 to 98.6)
	65+	97.2 (91.6 to 99.0)

Table S14. Number of cases and controls (cases; controls) contributing to vaccine effectiveness estimates against hospitalisation as shown in Table 2 and Supplementary Table S10.

			Weeks post Dose 2				
Vaccine	Age group	Subgroup	1 week	2-9 weeks	10-14 weeks	15-19 weeks	20+ weeks
Unvaccinated	16+		4062 ; 412352				
	65+	All	219 ; 2098				
		CEV	46 ; 387				
		Not CEV	173 ; 1711				
	40-64	All	1535 ; 52852				
		Risk/CEV group	592 ; 10130				
		Not risk/CEV group	943 ; 42722				
	16-39	All	2346 ; 301674				
ChAdOx1-S	16+		31 ; 24975	520 ; 278747	828 ; 166684	821 ; 79004	284 ; 17200
	65+	All	2 ; 1511	80 ; 18858	262 ; 18689	458 ; 17357	185 ; 4923
		CEV	1 ; 290	34 ; 3198	106 ; 3343	183 ; 3054	93 ; 1202
		Not CEV	1 ; 1221	46 ; 15660	156 ; 15346	275 ; 14303	92 ; 3721
	40-64	All	24 ; 16360	335 ; 176252	422 ; 94055	243 ; 33792	38 ; 2447
		Risk/CEV group	5 ; 2912	186 ; 41173	273 ; 27624	198 ; 15648	30 ; 1552
		Not risk/CEV group					
BNT162b2	16+		2 ; 30880	53 ; 174697	174 ; 78290	295 ; 72026	195 ; 41935
	65+	All	0 ; 912	9 ; 10819	75 ; 12273	173 ; 12437	141 ; 6328
		CEV	0 ; 173	3 ; 2133	40 ; 2439	92 ; 2533	83 ; 1432
		Not CEV	0 ; 739	6 ; 8686	35 ; 9834	81 ; 9904	58 ; 4896
	40-64	All	0 ; 2798	25 ; 31682	49 ; 21018	53 ; 16954	8 ; 2109
		Risk/CEV group	0 ; 1113	21 ; 17143	46 ; 13637	46 ; 11222	6 ; 1122
		Not risk/CEV group	0 ; 1685	4 ; 14539	3 ; 7381	7 ; 5732	2 ; 987
	16-39	All	2 ; 24541	8 ; 94496	0 ; 2584		

MRNA-1273	16+	All	1 ; 3171	0 ; 12035

Table S15. Number of cases and controls (cases; controls) contributing to vaccine effectiveness estimates against death as shown in Table 3.

		Weeks post Dose 2			
Vaccine	Age group	2-9 weeks	10-14 weeks	15-19 weeks	20+ weeks
Unvacc	16+	195 ; 383872			
	65+	65 ; 1888			
ChAdOx1-S	16+	56 ; 269333	100 ; 126863	126 ; 40484	33 ; 5072
	65+	18 ; 18827	60 ; 18461	110 ; 12511	31 ; 1298
BNT162b2	16+	6 ; 127669	42 ; 74176	74 ; 56497	75 ; 20223
	65+	4 ; 11154	31 ; 12707	66 ; 11175	74 ; 4730

Table S16. Vaccine effectiveness against Delta hospitalisation, using only admissions coded as respiratory admission for ChAdOx1-S and BNT162b2 in England. Table values are VE (95% CI) or VE (total cases, total controls when VE is 100%).

		Weeks post Dose 2				
Vaccine	Age group	1 week	2-9 weeks	10-14 weeks	15-19 weeks	20+ weeks
ChAdOx1-S	16+	94.9 (91.9 to 96.7)	96.0 (95.4 to 96.4)	93.4 (92.6 to 94.0)	88.5 (87.0 to 89.7)	82.6 (79.1 to 85.4)
	65+	88.0 (9.8 to 98.4)	91.8 (88.2 to 94.2)	90.8 (88.2 to 92.9)	86.8 (83.4 to 89.5)	83.2 (77.4 to 87.5)
BNT162b2	16+	100 (0 cases, 30880 cont)	99.2 (98.8 to 99.5)	97.7 (97.1 to 98.1)	95.5 (94.7 to 96.2)	93.5 (91.9 to 94.7)
	65+	98.3 (95.8 to 99.3)	96.9 (95.5 to 97.9)	93.4 (91.4 to 94.9)	91.6 (88.5 to 93.8)	

Table S17. Vaccine effectiveness against Delta hospitalisation among individuals with two doses of ChAdOx1-S and BNT162b2 mRNA-1273 in England at 1 week, 2-9 weeks, 10 -14 weeks, 15-19 weeks and 20+ weeks, using test negative hospitalised controls. Table values are VE (95% CI).

		Weeks post Dose 2				
Vaccine	Age group	1 week	2-9 weeks	10-14 weeks	15-19 weeks	20+ weeks
ChAdOx1-S	16+	91.5 (86.2 to 94.8)	93.5 (92.3 to 94.5)	90.2 (88.5 to 91.8)	83.7 (80.2 to 86.7)	77.2 (69.6 to 82.9)
BNT162b2	16+	99.1 (96.4 to 99.8)	98.3 (97.7 to 98.8)	96 (94.9 to 96.8)	93.5 (91.8 to 94.8)	88.1 (84.2 to 91.1)

Table S18. Vaccine effectiveness against Delta symptomatic infection stratified by risk group for ChAdOx1-S and BNT162b2. Table values are VE (95% CI).

			Weeks post Dose 2			
Vaccine	Age group	Subgroup	2-9 weeks	10-14 weeks	15-19 weeks	20+ weeks
ChAdOx1-S	65+	CEV	53.7 (42.2 to 62.9)	43 (30.9 to 53)	37.4 (24.4 to 48.2)	32 (17 to 44.3)
		Not CEV	60.1 (56 to 63.8)	51.5 (47.2 to 55.4)	45 (40.3 to 49.4)	38.9 (33.1 to 44.1)
	40-64	Risk/CEV group	60.7 (59.1 to 62.2)	55.1 (53.4 to 56.8)	50.9 (48.8 to 52.9)	50.2 (47.1 to 53)
		Not risk/CEV group	62.3 (61.6 to 63.1)	58 (57 to 58.9)	56.8 (55.6 to 57.9)	60.9 (58.5 to 63.1)
BNT162b2	65+	CEV	72.3 (63.3 to 79)	59.6 (50.5 to 67)	56.2 (46.9 to 63.9)	44.4 (32.1 to 54.4)
		Not CEV	80.8 (78.1 to 83.1)	71.2 (68.4 to 73.7)	64.5 (61.3 to 67.4)	56.9 (52.8 to 60.6)
	40-64	Risk/CEV group	82.1 (81.1 to 83.1)	75.8 (74.6 to 77)	69.3 (67.8 to 70.7)	64.9 (62.4 to 67.3)
		Not risk/CEV group	85.4 (84.8 to 86)	77.9 (76.9 to 78.9)	74.3 (73 to 75.5)	71.6 (69.5 to 73.5)

Table S19. Number of cases and controls (cases; controls) contributing to vaccine effectiveness estimates against Delta symptomatic infection as shown in Supplementary Table S17.

			Weeks post Dose 2			
Vaccine	Age group	Subgroup	2-9 weeks	10-14 weeks	15-19 weeks	20+ weeks
Unvacc	65+	CEV	268;428			
		Not CEV	1586;1931			
	40-64	Risk/CEV group	9208;11352			
		Not risk/CEV group	37099;47018			
ChAdOx1-S	65+	CEV	432;3201	1472;3352	2338;3262	1616;2588
		Not CEV	2658;15678	8290;15416	13399;16020	7220;9632
	40-64	Risk/CEV group	15539;41434	19263;29543	15986;27770	3220;6896
		Not risk/CEV group	73798;139285	60710;91047	26838;50626	2014;4498
BNT162b2	65+	CEV	116;2139	661;2444	1236;2613	1392;2538
		Not CEV	504;8701	2720;9848	5544;10445	5301;9605
	40-64	Risk/CEV group	2461;17356	4833;13803	6394;16090	1659;4955
		Not risk/CEV group	3000;16963	3004;9436	3101;8042	1161;3688

Figure S1. Total numbers of cases and controls by week.

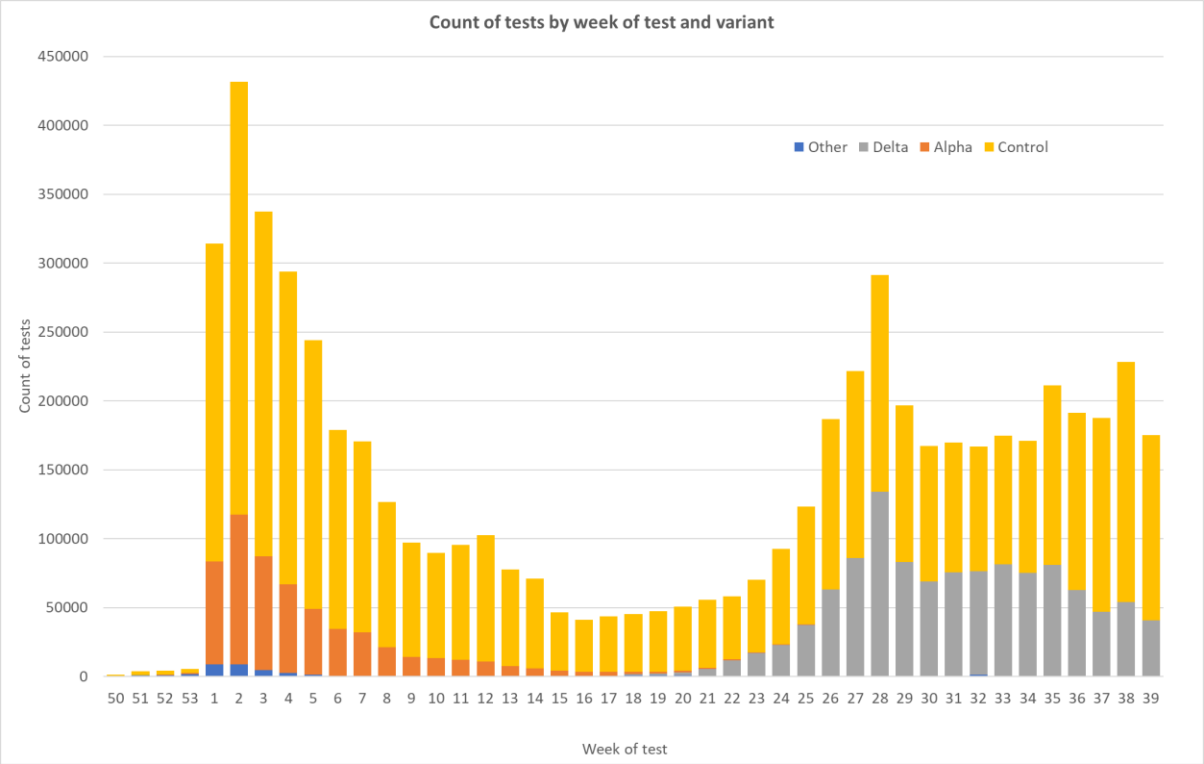


Figure S2. Vaccine effectiveness against hospitalization age ≥ 65, all vaccines combined for intervals afters the second dose with 95% confidence intervals.

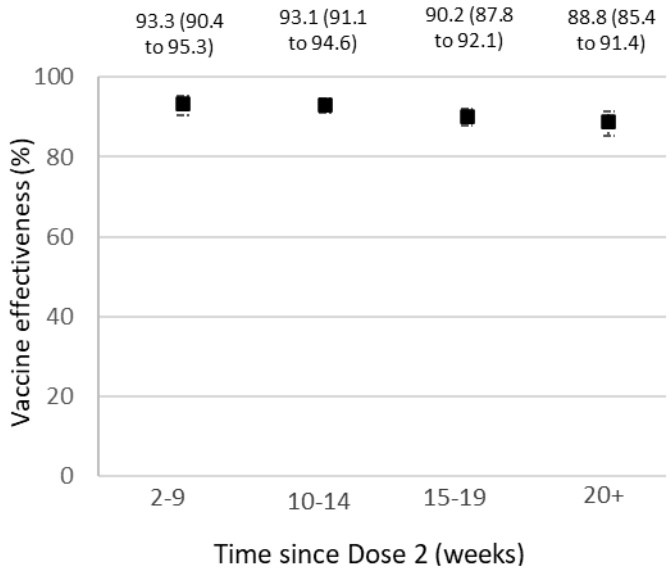


Figure S3. Vaccine effectiveness against Delta hospitalisation using test negative hospitalised controls, with 95% confidence intervals ***.**

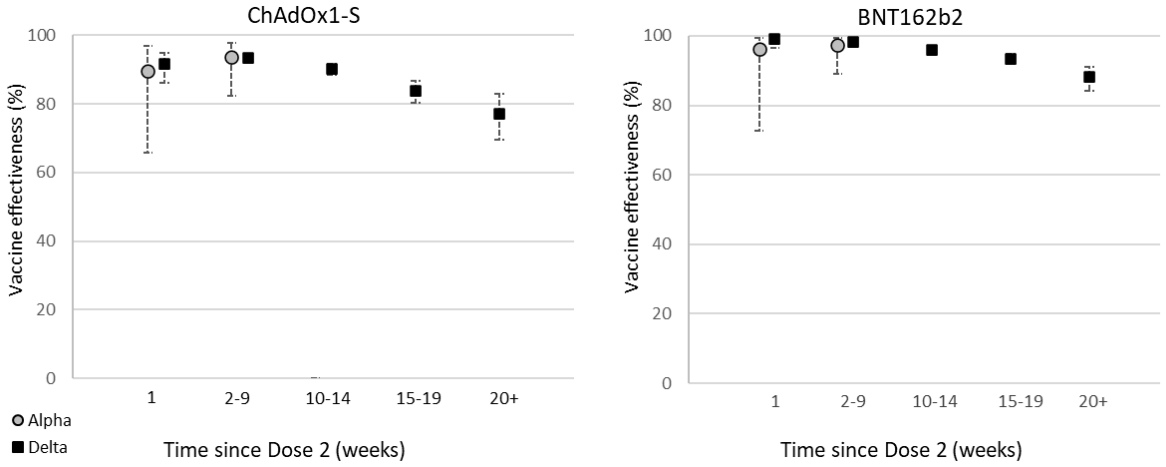
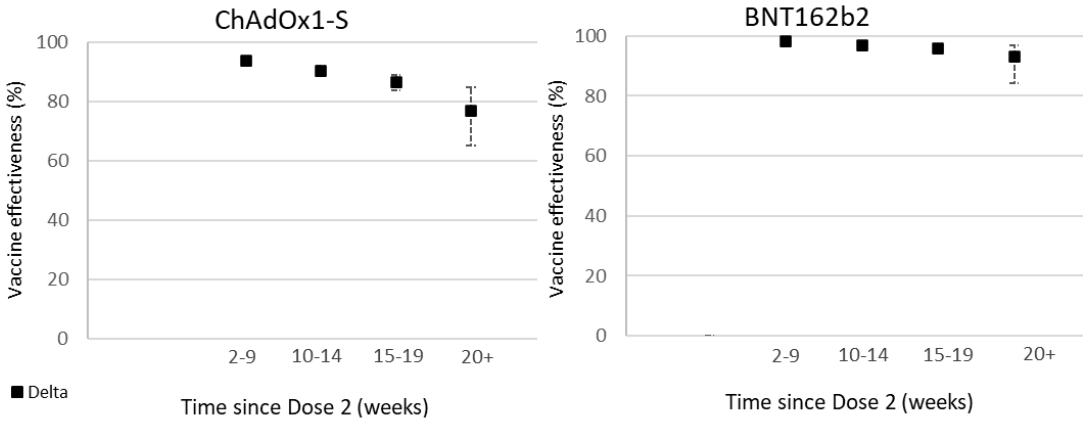
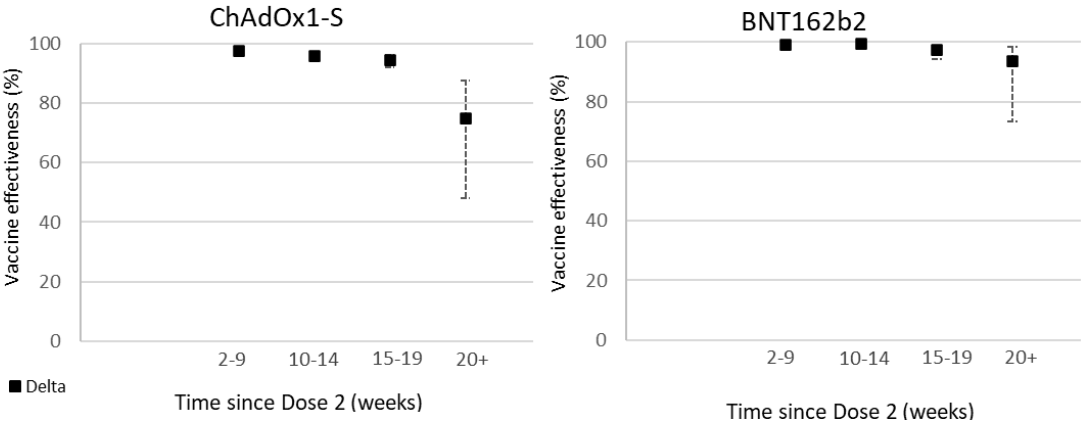


Figure S4. Vaccine effectiveness against Delta hospitalisation (age 40-64 years) by clinical risk group status, with 95% confidence intervals*.

a) In a clinical risk group

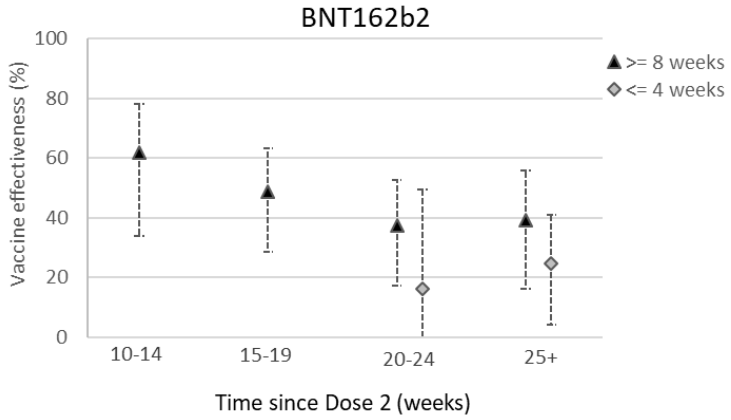


b) Not in a clinical risk group



***** Individuals with an underlying risk group (Risk) include a broad range of chronic conditions as described in The Green Book. [6]

Figure S5. Vaccine effectiveness of BNT162b2 against symptomatic disease (Delta variant) in people aged 80+ with either a short (<= 4 weeks) or long (>= 8 weeks) interval between first and second doses, with 95% confidence intervals.



Supplementary Section 3: Limitations

Main potential sources of bias

i) Sensitivity and specificity of the outcome

Although specificity within symptomatic individuals should be very high for PCR, lack of sensitivity will lead to underestimation of vaccine effectiveness due to outcome misclassification. This is why we restricted samples to those tested within 10 days of onset and did not include negative samples if taken shortly before a positive test. However, the increased use of lateral flow testing devices, with PCR sampling accessed if the lateral flow tests positive is likely to mean an increasing chance of false negative PCR tests and potentially an increasing underestimation of vaccine effectiveness.

ii) Residual confounding

Residual confounding and the possibility this may differ by vaccine and interval after vaccination could be important. Although the test negative design used in symptomatic individuals can help ensure cases and controls are similar in terms of exposure and health care seeking there may remain factors that are all controls associated with both testing behaviour and vaccination. In particular for the outcomes of hospitalization and death our design relies on using and adjusting for factors that may be associated with severe COVID such as age and being clinically extremely vulnerable, but the CEV and risk information is imperfect and there may be factors remaining associated with severe outcomes and vaccination. Failure to adjust for a factor that gave an increased chance of vaccination and the outcome would lead to underestimation of VE. For example, BNT162b2 was less likely to be used in care homes and among individuals in clinical risk groups, in particular housebound individuals, due to challenges in ultra-low temperature storage and delivery. Instead, ChAdOx1-S was more likely to be given to these groups but this vaccine was not given to healthy adults under 40 years of age following a recommendation to use alternative vaccines in this age-group because of the risk of vaccine-induced thrombotic thrombocytopenia. [6] This might mean underestimation of VE for ChAdOx1-S is more likely, and if the use in risk groups was in the early part of the roll out this may also mean residual confounding is greater for the longer intervals after vaccination.

iii) Prior infection,

Over time there will be an increasing number of individuals who would have been infected both prior to and after vaccination. Where they have previously tested positive they will be excluded from the analysis, but many will remain unknown. This means that an increasing proportion of the unvaccinated control group may have some level of protection from natural infection. This will attenuate vaccine effectiveness over time and could lead to overestimation of waning. This impact will be greater where vaccine effectiveness is lower (whether this is related to vaccine type, variant or waning). This will also vary by age as seroprevalence data suggests that there are higher rates of natural infection in younger adults.

iv) selection bias related to use of self-administered lateral flow devices and self-declaration of symptoms.

Selection bias may be an issue if accessing testing is influenced by both vaccination status and knowledge of likely COVID-19 infection status. For example, suppose a vaccinated and unvaccinated person with mild symptoms sought a PCR test with equal probability, but the vaccinated person was more likely to seek a test than the unvaccinated person if they were confident it was COVID-19 (e.g.

because they had done a lateral flow test) then this would bias VE downwards. Similarly, differential use of lateral flow tests prior to PCR in vaccinated and unvaccinated individuals may cause bias, for example if vaccinated individuals stop using lateral flow devices then VE may be overestimated. We also rely on the self-declaration of symptoms when the test is requested and it is likely that some individuals who are not symptomatic declare symptoms in order to access a test. This will attenuate effectiveness if it is lower against asymptomatic infection and, for test-negative controls, may mean they are not matched on exposure to an infectious disease which is one of the strengths of the TNCC design.

Supplementary Section 4: References

1. Public Health England. SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 23. 2021.
2. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. NEJM 2021;385:585-94.
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5. PRIMIS COVID-19. 2021. (Accessed 26/08/2021, at https://www.nottingham.ac.uk/primis/covid-19/covid-19.aspx.)
6. Public Health England. COVID-19: the green book, chapter 14a Coronavirus (COVID-19) vaccination information for public health professionals. 2021.