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Effectiveness of COVID-19 booster vaccines against covid-19 related symptoms, hospitalisation and death in England

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19 Abstract

20 Booster vaccination with mRNA vaccines have been offered to adults in England starting on 14 September
21 2021. We used a test-negative case-control design to estimate the relative effectiveness of a booster dose of
22 BNT162b2 (Pfizer-BioNTech) compared to only a 2-dose primary course (at least 175 days after the second
23 dose) as well as compared to unvaccinated individuals from 13 September 2021 to 5 December 2021, when
24 Delta variant was dominant in circulation. Outcomes were symptomatic COVID-19 and hospitalisation. The
25 relative effectiveness against symptomatic disease 14-34 days after a BNT162b2 or mRNA-1273 (Moderna)
26 booster after a ChAdOx1-S (Astrazeneca) and BNT162b2 as a primary course ranged from around 85 to 95%.
27 Absolute VE ranged from 94-97% and was similar in all age groups. Limited waning was seen 10+ weeks after
28 the booster. Against hospitalisation or death absolute effectiveness of a BNT162b2 booster ranged from
29 around 97% to 99% in all age groups irrespective of the primary course with no evidence of waning up to 10
30 weeks. This study provides real world evidence of significant increased protection from the booster vaccine
31 dose against mild and severe disease irrespective of the primary course.

32

33 Introduction

34 Real world effectiveness data has demonstrated high levels of short-term protection by COVID-19 vaccines
35 against clinical disease and, more so, against severe outcomes including hospitalization and death ¹⁻⁷.
36 Nevertheless, there is evidence that protection against symptomatic disease wanes over time ^{8,9}. Booster
37 doses have now been implemented in the UK and elsewhere in order to combat the rise in COVID-19 cases and
38 the additional threat of the winter 2021 influenza season.

39 We recently reported that vaccine effectiveness against symptomatic disease peaked in the early weeks after
40 the second dose and then fell to 47.3 (95% CI 45 to 49.6) and 69.7 (95% CI 68.7 to 70.5) by 20+ weeks against
41 the Delta variant for ChAdOx1-S (AstraZeneca) and BNT162b (Pfizer-BioNTech)), respectively. Vaccine
42 effectiveness against severe disease outcomes remained high up to 20+ weeks after vaccination in most
43 groups, nevertheless, greater waning was seen in older adults and those with underlying medical conditions
44 compared to young, healthy adults ⁸.

45 In the UK, COVID-19 booster vaccines were introduced on 14 September 2021. Using evidence from the COV-
46 BOOST trial, which demonstrated that the mRNA vaccines provide a strong booster effect with low
47 reactogenicity, regardless of the vaccine given in the primary course , the UK Joint Committee on Vaccination
48 and Immunisation (JCVI) recommended either a BNT162b2 or a half dose (50µg) of mRNA-1273 (Moderna)
49 vaccine to be given as a booster dose no earlier than 6 months after completion of the primary vaccine course
50 ^{10,11}. In this initial phase of the UK booster programme the following groups were eligible: all adults over 50
51 and those 16-49 years with underlying health conditions that put them at higher risk of severe COVID-19, adult
52 carers and adult household contacts (aged 16 or over) of immunosuppressed individuals, and healthcare
53 workers.

54 In this study, we aimed to estimate the effectiveness of the BNT162b2 and mRNA-1273 booster
55 vaccines against symptomatic disease, hospitalisation and death in adults in England. Table 1 outlines the main
56 findings and implications for policy of our study.

57 Results

58 Descriptive statistics and characteristics

59 From 13 September 2021 to 5 December 2021 there were a total of 893,845 eligible tests in those aged 18
60 years and over, with a test date within 10 days of their symptom onset date and had linked to the National
61 Immunisation Management system, with a 91.04% match rate. Of these 278,096 (31.1%) were
62 unvaccinated 223,198 received ChAdOx1-S 175 days post a second dose, 171,079 received BNT162b2 175 days
63 post a second dose. Of those that had received a booster dose 89,019 received a ChAdOx1-S primary course
64 and 132,453 received a BNT162b2 primary course. Of the 343,955 positive cases included in the analysis,
65 4,377 (1.27%) were hospitalised for any reason (excluding injuries) within 14 days of the test. A description of
66 the eligible tests is given in supplementary table 1.

68 Vaccine effectiveness for symptomatic disease

69 An overall effect on the proportion of cases and controls can be seen from around day 7 after the booster dose
70 and stabilises at day 11 (Extended Data Figure 1). In individuals aged 18 to 49 where the primary course was
71 ChAdOx1-S vaccine, relative to those that had received only two doses, effectiveness against symptomatic
72 disease peaked at 14-35 days post the BNT162b2 booster at 89.6% (95% confidence interval 88.6-90.4) and
73 95.3% (95% confidence interval 91.8-97.3) after the mRNA-1273 booster (table 2 & figure 1). In individuals
74 where BNT162b2 was the primary course, relative vaccine effectiveness 14-34 days a BNT162b2 booster was
75 82.8% (81.8-83.7) and after a mRNA-1273 booster 90.9% (84.5-94.7). Relative vaccine effectiveness with the

76 BNT162b2 booster decreased slightly in the 35-69 day and 70+ day periods (later follow-up was not available
77 for mRNA1273). The same analysis in individuals aged 50 years and over gave similar results (table 2 & figure
78 1).

79 In the secondary analysis, which used the 2-6 day period post the booster dose as the baseline results were
80 similar to the primary analysis (table 2 & Extended Data Figure 2). In the analysis using the unvaccinated
81 individuals as the baseline, the booster dose was associated with an absolute VE from 14-34 days after a
82 BNT162b2 booster of 94.4% (95% confidence interval 94.1-94.7) following either a ChAdOx1-S or BNT162b2
83 primary course in individuals 50 years and older. With an mRNA-1273 booster, absolute vaccine effectiveness
84 was 97.0 (95% CI 96.0-97.8) after a ChAdOx1-S primary course and 94.8% (95%CI 92.7-96.3%) BNT162b2
85 primary course (table 3 & Extended Data Figure 3).

86 Vaccine effectiveness for hospitalisation and death

87 High levels of protection were also seen against hospitalisation in both age groups. In individuals aged 50 years
88 and over, the vaccine effectiveness 14-34 days after a BNT162b2 booster dose, relative to unvaccinated
89 individuals, was 99.2% (98.6 to 99.5) where the primary course was ChAdOx1-S. and 98.6% (98.0 to 99.0)
90 where BNT162b2 was used as the primary course.

91 A similar high protection was seen in the younger age group with a vaccine effectiveness estimate of 97.5%
92 (93.3 to 99.1) where the primary course was ChAdOx1-S and 98.8% (97.2 to 99.5) where BNT162b2 was used
93 as the primary course. (table 3 & figure 2). There was little evidence of any waning in vaccine effectiveness
94 against hospitalisation up to 69 days after the booster.

95 Vaccine effectiveness against death in individuals 50 years and over 14-34 days after a BNT162b2 booster
96 dose relative to the unvaccinated was 97.8 (95% confidence interval 94.4-99.1) after a ChAdOx1-S primary
97 course and 98.7% (97.4 to 99.4) where the primary course was BNT162b2 (table 4 & figure 2)

99 Intervals between dose 2 and the booster dose

100 After assessing the distribution of intervals between dose 2 and the booster dose for cases and controls by age
101 group and manufacturer, the interval between dose 2 and booster was split into three periods: 25-29, 30 to 34
102 and 35 or more weeks (Extended Data Figure 4). Due to the roll out of the vaccine programme, there were
103 more individuals who had received a second dose of BNT162b2 at an earlier timepoint, therefore, the majority
104 of the individuals who had the longest interval between dose 2 and the booster had a BNT162b2 primary
105 course. Analyses by interval between dose 2 and dose 3 were thus restricted to those who received BNT162b2
106 as the primary course.

108 A shorter interval between dose 2 and the booster of 25-29 weeks compared to the baseline interval of 35
109 weeks or more was associated with an increased adjusted odds ratio of 1.54 (95% confidence interval 1.35-
110 1.76) for becoming a symptomatic case. This was also seen in the 30-34 week interval, adjusted odds ratio 1.32
111 (1.12-1.56). Although remaining high the adjusted VE estimates reduced from 95.6% (95% confidence interval
112 94.9-96.1) in the 35 weeks or more interval to 93.2% (95% confidence interval 92.8-93.6) in the shortest
113 interval between dose 2 and the booster (supplementary table 2). A test for the interaction effect of age was
114 not significant (p=0.15).

115 Discussion

117 This study provides evidence of a significant increase in protection against symptomatic COVID-19 disease
118 after a booster dose of BNT162b2 or mRNA-1273 vaccines, during the period when the Delta variant was the

dominant strain in the UK. Very high levels of protection were seen against hospitalisation or death with a BNT162b2 booster. Vaccine effectiveness of a booster dose was very similar irrespective of the vaccine used in the primary course. A longer interval between dose 2 and the booster doses was associated with small improvements in vaccine effectiveness¹².

These findings suggest that the booster offers very high levels of protection against mild and severe disease. While a small amount of waning in protection against symptomatic disease is seen from 10 weeks after the booster, there is no clear evidence of waning against severe disease up to 10 weeks after the booster. Given the recent deployment of the booster programme in the UK, further follow-up is needed to understand how protection changes longer term against both mild and severe disease. The slightly lower relative VE estimates of the booster in individuals with BNT162b2 as a primary course compared to the ChAdOx1-S in the primary analysis is due to the different baseline with higher VE after 2 doses of BNT162b2 as compared to ChAdOx1-S⁸. When using unvaccinated controls, there was little difference in observed vaccine effectiveness of the booster dose with either primary course. We also observed a peak in testing at day 1 after the booster dose which is likely to be reactogenicity effects so shortly after the vaccine, as has been reported previously¹³. The improved vaccine effectiveness with a longer interval between dose 2 and the booster suggests that there will be some benefit in delaying booster doses. Nevertheless, this improvement was only small and has to be balanced with the reduced protection among those that have received just two doses (where protection may have waned), compared to protection from the booster even with a relatively short interval. This finding was also similar to the reduced effectiveness among those that had a shorter interval between dose 1 and 2^{8,14}. Furthermore, similar findings are also seen with history of prior infection whereby a longer interval between infection and vaccination was associated with increased protection¹⁵.

In Israel, a booster programme began in July 2021. Bar-On et al reported an adjusted rate ratio of 11.3 (10.4-12.3) against confirmed infection in booster dose recipients compared to those who received only 2 doses (equivalent to relative vaccine effectiveness of 91.2%)¹⁶. This is slightly higher than the relative vaccine effectiveness that we report, which could reflect lower 2 dose vaccine effectiveness in the comparison group in Israel where a greater degree of waning has previously been reported^{9,17,18}. Even greater protection has been reported in Israel against severe disease.^{16,19} We were unable to find other studies reporting vaccine effectiveness of a third dose where ChAdOx1-S was used as the primary course or where mRNA-1273 was used as the booster.

This is an observational study with a number of possible biases and should be interpreted with caution. The imperfect sensitivity PCR testing could cause misclassification of both cases and controls, in a test negative case control analysis, which could attenuate vaccine effectiveness estimates. Many individuals will also have been previously infected so the VE measured is in the context of a population where many might have already had natural exposure. We adjust for measured confounders, however, there may be residual confounding that we could not account for. Nevertheless, the similarity of the VE estimates using those with two doses and no booster as the baseline and using the 2-6 day period post booster as the baseline suggests that residual confounding is small. Use of the unvaccinated as a comparator to obtain absolute effectiveness is most susceptible to residual confounding as the totally unvaccinated population may differ in many ways to those who have had vaccine doses, many of which could lead to underestimation of VE⁸. Despite this potential underestimation, using the unvaccinated comparator the absolute VE estimates were over 93%. Due to small we are only able to report the early effects of the booster programme and it is not yet clear how long protection against COVID-19 following booster vaccination will last.

For the analysis by interval between dose 2 and dose 3, it should be noted that those that had a longer interval between dose 2 and dose 3 are likely to have had a shorter interval between dose 1 and dose 2. As these will be colinear it is not possible to adjust for interval between dose 1 and 2 in this analysis. In these analyses, we were unable to report on the half dose (50µg) of mRNA-1273 vaccine due to low numbers as the majority of booster doses given in this period were BNT162b2. We were unable to assess the VE in all those targeted for a booster dose such as individuals with underlying health conditions, adult carers and adult household contacts of immunosuppressed individuals due to small numbers and difficulty identifying these individuals with the dataset.

Our study provides real world evidence of significant increased protection from the booster dose against symptomatic disease and hospitalisation in those aged over 50 year of age irrespective of which primary course was received. This indicates that a high level of protection is achieved among older adults who are more vulnerable to severe COVID-19. This will be important in the 2021 to 2022 winter period when COVID-19 is likely to co-circulate alongside other respiratory viruses, including seasonal influenza virus.

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Author Contributors: JLB, NA, and MR designed the study and developed the protocol and analysis plan. NA, FK and JS cleaned and analysed the data. JS drafted the manuscript. All authors contributed to the study design and revised the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. JLB and MR are the guarantors.

Competing Interests Statement: No conflicts of interests to declare

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Figure 1: Vaccine Effectiveness estimates (95% CI) against symptomatic disease in time intervals post booster according to primary course in individuals aged a) 18 to 49 years b) 50 years and over: Dose 2 at 175 days as baseline

Figure 2: Vaccine Effectiveness estimates (95% CI) in time intervals post booster according to primary course a) against hospitalisation in individuals aged 18 to 49 years b) against hospitalisation in individuals aged 50 years and over c) against death in individuals aged 50 years and over: Unvaccinated as baseline

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254 **Table 1: Policy Summary**

Background	Following evidence of waning protection after a primary course of COVID-19 vaccines, booster doses are now being offered in the UK and elsewhere. There is limited evidence on the effectiveness of booster doses.
Main findings and limitations	<p>We observed a significant increase in protection against symptomatic COVID-19 disease with the Delta variant after a booster dose of an mRNA vaccine irrespective following a primary course of two doses of either BNT162b2 or ChAdOx1-S. There was limited waning by 10+ weeks after vaccination. A longer interval between primary course and booster vaccination was associated with small improvements in vaccine effectiveness.</p> <p>Very high levels of protection (97-99%) were seen against hospitalisation or death with a BNT162b2 booster with no evidence of waning up to 9 weeks after the booster.</p> <p>This is an observational study and there may be residual confounding that could not be accounted for. There may also be misclassification due to imperfect sensitivity of PCR testing.</p>
Policy implications	COVID-19 booster vaccination programmes are likely to result in substantial reductions in cases, hospitalisations and deaths with COVID-19. There is some benefit of a longer interval between primary course and booster vaccination, however, this needs to be balanced with reduced protection among those that have only received two doses.

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260 **Table 2: Vaccine effectiveness against symptomatic disease for the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) booster vaccines in England**
261 **by age group. Table values are VE (95% CI).**

Age Group	Primary Course (175+ days post dose 2)	Booster manufacturer	Interval since Booster	Controls	Cases	rVE (175+ days post dose 2 baseline)	rVE (dose 3: 2-6 days post booster baseline)	VE (unvaccinated base)
18-49 years	Unvaccinated			125,353	126,940			
	ChAdOx1-S	None		61,022	45,988	Baseline		44.7 (43.7 to 45.6)
	ChAdOx1-S	Any	0-1 days	2,111	1,407	16.8 (10.8 to 22.4)		54.5 (51.2 to 57.6)
	ChAdOx1-S	Any	2-6 days	3,947	2,467	22.3 (18.0 to 26.3)	Baseline	57.2 (54.8 to 59.4)
	ChAdOx1-S	BNT162b2	7-13 days	3,984	736	76.1 (74.1 to 78)	69.3 (66.2 to 72.0)	86.8 (85.7 to 87.9)
	ChAdOx1-S	BNT162b2	14-34 days	7,174	561	89.6 (88.6 to 90.4)	86.6 (85.2 to 87.9)	94.3 (93.8 to 94.8)
	ChAdOx1-S	BNT162b2	35-69 days	2,927	319	84.4 (82.4 to 86.1)	79.9 (77.2 to 82.3)	91.6 (90.5 to 92.5)
	ChAdOx1-S	mRNA-1273	7-13 days	635	98	81.3 (76.8 to 84.9)	75.9 (70.0 to 80.6)	89.7 (87.2 to 91.7)
	ChAdOx1-S	mRNA-1273	14-34 days	342	13	95.3 (91.8 to 97.3)	93.9 (89.4 to 96.5)	97.4 (95.5 to 98.5)
	BNT162b2	None		79,181	29,489	Baseline		65.3 (64.7 to 65.9)
	BNT162b2	Any	0-1 days	2,800	839	25.6 (19.4 to 31.3)		73.7 (71.5 to 75.7)
	BNT162b2	Any	2-6 days	6,186	2,046	21.0 (16.7 to 25.1)	Baseline	71.8 (70.3 to 73.3)
	BNT162b2	BNT162b2	7-13 days	8,797	825	77.9 (76.2 to 79.5)	72 (69.5 to 74.4)	92.1 (91.5 to 92.7)
	BNT162b2	BNT162b2	14-34 days	20,595	1,614	82.8 (81.8 to 83.7)	78.2 (76.5 to 79.7)	93.9 (93.6 to 94.2)
	BNT162b2	BNT162b2	35-69 days	16,703	1,707	77.7 (76.4 to 78.9)	71.7 (69.6 to 73.7)	92.1 (91.6 to 92.5)
	BNT162b2	BNT162b2	70 + days	194	22	78.1 (65.8 to 86)	72.3 (56.6 to 82.3)	92.0 (87.5 to 94.8)
	BNT162b2	mRNA-1273	7-13 days	397	49	77.4 (69.6 to 83.3)	71.4 (61.3 to 78.9)	91.9 (89.0 to 94.0)
	BNT162b2	mRNA-1273	14-34 days	290	14	90.9 (84.5 to 94.7)	88.5 (80.3 to 93.3)	96.7 (94.4 to 98.1)
50 years and older	Unvaccinated			10,322	15,481			
	ChAdOx1-S	None		55,808	60,380	Baseline		39.4 (37.4 to 41.3)
	ChAdOx1-S	Any	0-1 days	4,284	4,212	12.3 (8.3 to 16.2)		46.9 (44.0 to 49.6)
	ChAdOx1-S	Any	2-6 days	7,924	7,762	13.9 (10.9 to 16.8)	Baseline	47.7 (45.3 to 50.0)
	ChAdOx1-S	BNT162b2	7-13 days	8,887	2,514	74.8 (73.6 to 75.9)	70.7 (69.1 to 72.3)	84.7 (83.8 to 85.5)
	ChAdOx1-S	BNT162b2	14-34 days	16,437	1,691	90.8 (90.3 to 91.3)	89.4 (88.7 to 90.0)	94.4 (94.1 to 94.7)
	ChAdOx1-S	BNT162b2	35-69 days	5,432	703	88.3 (87.3 to 89.2)	86.4 (85.2 to 87.5)	92.8 (92.2 to 93.4)

ChAdOx1-S	mRNA-1273	7-13 days	1,275	317	78.9 (76.1 to 81.4)	75.5 (72.2 to 78.5)	87.2 (85.4 to 88.7)
ChAdOx1-S	mRNA-1273	14-34 days	770	44	95.2 (93.4 to 96.4)	94.4 (92.4 to 95.9)	97 (96.0 to 97.8)
BNT162b2	None		38,673	23,736	Baseline		61.2 (59.8 to 62.5)
BNT162b2	Any	0-1 days	2,753	1,792	-0.7 (-7.3 to 5.5)		61 (58.2 to 63.5)
BNT162b2	Any	2-6 days	6,474	3,747	14 (10.1 to 17.8)	Baseline	66.6 (64.8 to 68.2)
BNT162b2	BNT162b2	7-13 days	9,094	1,812	71.4 (69.8 to 72.9)	66.7 (64.5 to 68.8)	88.9 (88.2 to 89.5)
BNT162b2	BNT162b2	14-34 days	22,158	2,352	85.6 (84.9 to 86.3)	83.3 (82.2 to 84.2)	94.4 (94.1 to 94.7)
BNT162b2	BNT162b2	35-69 days	15,931	2,119	81.9 (80.8 to 82.8)	78.9 (77.5 to 80.2)	92.9 (92.5 to 93.3)
BNT162b2	BNT162b2	70 + days	165	20	82.1 (71.3 to 88.8)	79.2 (66.6 to 87.0)	93 (88.8 to 95.6)
BNT162b2	mRNA-1273	7-13 days	440	86	74.4 (67.6 to 79.7)	70.2 (62.2 to 76.5)	89.9 (87.3 to 92)
BNT162b2	mRNA-1273	14-34 days	374	39	86.8 (81.5 to 90.5)	84.6 (78.5 to 89.0)	94.8 (92.7 to 96.3)

VE: vaccine effectiveness compared to zero doses, rVE: relative vaccine effectiveness compared to dose 2 (either 175+ days post dose 2 with no booster or 175+ days post dose 2 and 2-6 days after he booster).

Table 3: Vaccine effectiveness against hospitalisation for the BNT162b2 (Pfizer-BioNTech) booster vaccines in England by age group. Table values are VE (95% CI).

Age Group	Primary Course (175+ days post dose 2)	Booster manufacturer	Interval since Booster	Controls	Cases	VE (unvaccinated base)
18-49 years	Unvaccinated			111,292	1,366	Baseline
	ChAdOx1-S	None		42,032	171	85.7 (82.9 to 88.1)
	ChAdOx1-S	Any	0-1 days	1,244	5	89.2 (73.7 to 95.5)
	ChAdOx1-S	Any	2-6 days	2,181	6	93.0 (84.2 to 96.9)
	ChAdOx1-S	BNT162b2	7-13 days	2,498	6	93.8 (86.1 to 97.3)

50 years and older	ChAdOx1-S	BNT162b2	14-34 days	4,284	4	97.5 (93.3 to 99.1)
	ChAdOx1-S	BNT162b2	35-69 days	1,279	2	94.7 (78.7 to 98.7)
	BNT162b2	None		70,347	72	94.8 (93.3 to 96.0)
	BNT162b2	Any	0-1 days	2398	6	89.9 (77.3 to 95.5)
	BNT162b2	Any	2-6 days	5275	3	97.8 (93.1 to 99.3)
	BNT162b2	BNT162b2	7-13 days	7552	2	98.9 (95.8 to 99.7)
	BNT162b2	BNT162b2	14-34 days	16531	5	98.8 (97.2 to 99.5)
	BNT162b2	BNT162b2	35-69 days	8697	2	99.1 (96.4 to 99.8)
	Unvaccinated			9093	719	Baseline
	ChAdOx1-S	None		41992	807	85.6 (83.7 to 87.3)
	ChAdOx1-S	Any	0-1 days	2877	47	87.3 (82.7 to 90.7)
	ChAdOx1-S	Any	2-6 days	5151	47	93.9 (91.6 to 95.5)
	ChAdOx1-S	BNT162b2	7-13 days	6029	24	97.6 (96.3 to 98.4)
	ChAdOx1-S	BNT162b2	14-34 days	9664	14	99.2 (98.6 to 99.5)
	ChAdOx1-S	BNT162b2	35-69 days	2130	1	99.7 (98.1 to 100.0)
	BNT162b2	None		36093	424	92.1 (90.8 to 93.2)
	BNT162b2	Any	0-1 days	2469	27	93.0 (89.4 to 95.3)
	BNT162b2	Any	2-6 days	5743	43	95.5 (93.7 to 96.7)
	BNT162b2	BNT162b2	7-13 days	7843	21	98.5 (97.6 to 99.0)
	BNT162b2	BNT162b2	14-34 days	17393	45	98.6 (98.0 to 99.0)
	BNT162b2	BNT162b2	35-69 days	8424	19	98.7 (97.8 to 99.2)

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Table 4: Vaccine effectiveness against death for the BNT162b2 (Pfizer-BioNTech) booster vaccines in England in individuals aged 50 years and over. Table values are VE (95% CI).

Primary Course (175+ days post dose 2)	Booster manufacturer	Interval since Booster	Controls	Cases	VE (unvaccinated base)
Unvaccinated			7470	107	Baseline
ChAdOx1-S	None		25641	191	82.8 (76.9 to 87.2)
ChAdOx1-S	Any	0-1 days	1476	5	91.7 (79.0 to 96.7)
ChAdOx1-S	Any	2-6 days	2610	10	92.8 (85.7 to 96.4)
ChAdOx1-S	BNT162b2	7-13 days	2956	5	97.2 (92.9 to 98.9)
ChAdOx1-S	BNT162b2	14-34 days	3716	5	97.8 (94.4 to 99.1)
ChAdOx1-S	BNT162b2	35-69 days	302	0	
BNT162b2	None		30263	127	90.2 (86.5 to 92.8)
BNT162b2	Any	0-1 days	1888	13	84.4 (71.1 to 91.6)
BNT162b2	Any	2-6 days	4298	7	96.9 (93.0 to 98.6)
BNT162b2	BNT162b2	7-13 days	5775	10	97.1 (94.1 to 98.5)
BNT162b2	BNT162b2	14-34 days	11286	9	98.7 (97.4 to 99.4)
BNT162b2	BNT162b2	35-69 days	2063	1	99.2 (94.2 to 99.9)

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ACCELERATED ARTICLE PREVIEW

Methods

Study Design

We used a test-negative case-control design to estimate vaccine effectiveness of a booster dose of BNT162b2 vaccine against PCR-confirmed symptomatic disease and hospitalisation. We compared vaccination status in symptomatic adults over 18 years of age with PCR-confirmed SARS-CoV-2 infection with the vaccination status in individuals who reported symptoms but had a negative SARS-CoV-2 PCR test. As mRNA-1273 vaccine, as a primary course, was not made available until later in the vaccine programme insufficient time had elapsed for a booster dose to be indicated in this group. Study protocol available in supplemental appendix.

Ethical approval

Surveillance of covid-19 testing and vaccination is undertaken under Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002 to collect confidential patient information (www.legislation.gov.uk/ukxi/2002/1438/regulation/3/ made) under Sections 3(i) (a) to (c), 3(i)(d) (i) and (ii) and 3(3). The study protocol was subject to an internal review by the Public Health England Research Ethics and Governance Group and was found to be fully compliant with all regulatory requirements. As no regulatory issues were identified, and ethical review is not a requirement for this type of work, it was decided that a full ethical review would not be necessary.

Data Sources

Vaccination data

The National Immunisation Management System (NIMS) (1) 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 14 December 2021. The information used from NIMS was all dates of COVID-19 vaccination, vaccine manufacturer for each dose. Demographic data such as sex, date of birth, ethnicity, and residential address was extracted. Addresses were used to determine index of multiple deprivation quintile and were also linked to Care Quality Commission registered care homes using the unique property reference number. NIMS also contained data on geography (NHS region), risk groups status, clinically extremely vulnerable, and health/social care worker.

Booster doses were identified as being a third dose 175 days or more after a second dose and given after 13th September 2021. Individuals with four or more doses of vaccine, a mix of vaccines in their primary schedule or less than 19 days between their first and second dose were excluded.

COVID-19 testing data

SARS-CoV-2 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, who is a contact of a confirmed case, for care home staff and residents or anyone who has self-tested positive using a lateral flow device. Initially data on all positive and negative tests for the period 08 December 2020 to 05 December 2021 were extracted for individuals aged ≥ 18 years (age as of August 31st 2021). 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 these are likely to be false negatives. Positive and negative tests within 90 days of a previous positive test were also excluded. Participants contributed a maximum of one randomly chosen negative test result 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. A small number of

positive samples where sequencing was done and they were found not to be the Delta variant were excluded. Finally, only samples taken from 13 September 2021 (week 37, 2021) were retained for analysis.

Testing data were linked to NIMS on 14 December 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 NIMS denominator file included information on potential confounding variables related to targeted populations.

Hospitalisations

Testing data were linked to the Emergency Care Dataset (ECDS) to assess vaccine effectiveness against hospitalisation using data extracted on 15 December 2021. We included emergency care attendances among symptomatic cases within 14 days of the positive test, which were not injury related, and resulted in an inpatient admission. ECDS data include 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. Data were extracted on 15 December 2021 with cases included if tested by 26 November 2021 to allow for lags in hospitalisation.

Data management and linkage was carried out using Microsoft SQL Server Management Studio 18.

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. 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 (5 year bands), sex, index of multiple deprivation (quintile), ethnic group, care home residence status, geographic region (nhs region), period (calendar week of onset), health and social care worker status, clinical risk group status, clinically extremely vulnerable, severely immunosuppressed, and previously testing positive. These factors were all considered potential confounders so were included in all models. To assess the importance of previously testing positive a sensitivity analysis was done excluding those previously testing positive for the comparison of the booster vaccine to unvaccinated.

Analyses were stratified by which primary doses had been received, ChAdOx1-S or BNT162b2 and any mixed primary courses were excluded.

Vaccine effectiveness against symptomatic disease was assessed for each primary course of vaccine in intervals in days post the booster dose. The BNT162b2 and mRNA-1273 booster doses were combined in the 0-1 and 2-6 days post booster periods. Subsequent periods (7-13, 14-34, 35-69 and 70+ days) were analysed separately. There was insufficient data in the last two periods for the mRNA-1273 booster.

Vaccine effectiveness against hospitalisation and death was assessed in the combined 0-1 and 2-6 days post booster and in the 7-13, 14-34 and 35-69 days post the BNT162b2 booster vaccine. All analysis were stratified by 18 to 49 and over 50 years of age apart from the deaths analysis which was only reported for individuals 50 years and over due to small numbers in under 50 year olds.

In the primary analysis, those that had received the booster were compared to individuals who had received two primary doses with at least 175 days prior to the onset but with no booster dose recorded. In secondary analyses, we also compare to completely unvaccinated individuals and to the 2-6 day period

after the booster was received. The 2-6 day period was selected after plotting the data on case and control numbers after the booster dose and to avoid days 0 and 1 post booster when vaccine reactogenicity may affect the case-control ratio (figure 1). The analyses comparing to two doses or the 2-6 day post booster period measures relative effectiveness to two doses, whilst the comparison to unvaccinated is absolute effectiveness of two doses and a booster. In the analysis comparing to unvaccinated we also assessed the remaining effectiveness of two doses at least 175 days (25 weeks) post second dose.

Among individuals who received BNT162b2 as their primary course, an additional analysis was undertaken estimating the odds of testing positive in shorter intervals between dose 2 and booster (25-29 and 30-34 weeks) relative to the longest interval (35 or more weeks). A test for the interaction effect of age was also performed. Vaccine effectiveness compared to unvaccinated was also stratified by the interval between dose 2 and the booster.

Data Availability Statement: No additional data available. Data cannot be made publicly available for ethical and legal reasons, i.e. public availability would compromise patient confidentiality as data tables list single counts of individuals rather than aggregated data. Databases used in this study include the National Immunisation Management System (NIMS), Unified Sample Database and the Emergency Care Dataset (ECDS).

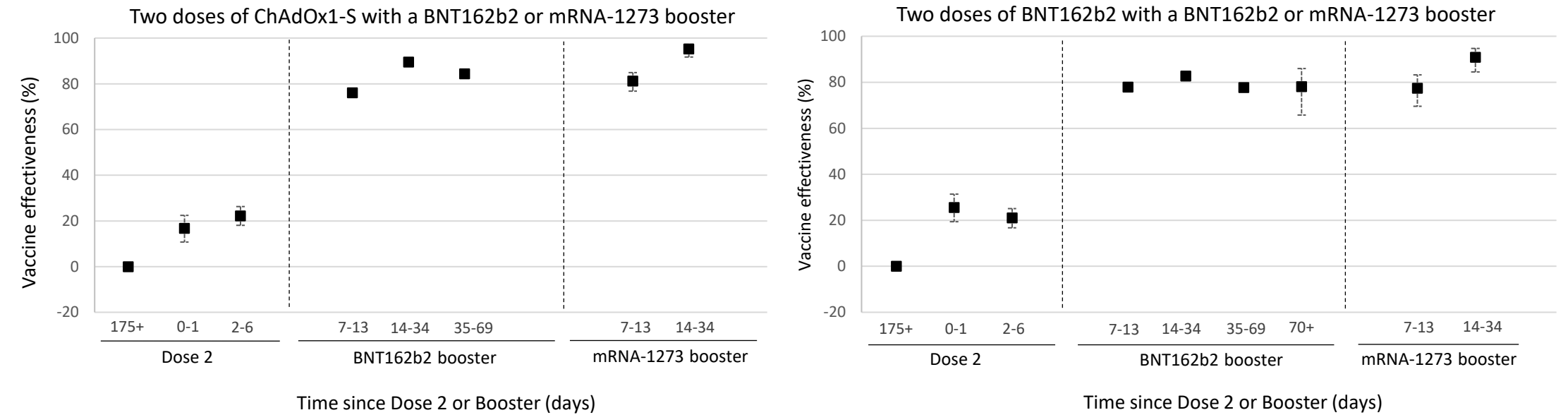
Code availability Statement: Model fitting code is available on our GitHub site <https://github.com/UKHSAGithub/StataCode.git>

References

- (1) NHS England. National COVID-19 and Flu Vaccination Programmes [Available from: <https://www.england.nhs.uk/contact-us/privacy-notice/national-flu-vaccination-programme/>. Accessed 11/01/2022)

Figure 1. Vaccine Effectiveness estimates (95% CI) against symptomatic disease in time intervals post booster according to primary course in individuals aged a) 18 to 49 years b) 50 years and over: Dose 2 at 175 days as baseline.

a) 18-49 years



b) 50+ years

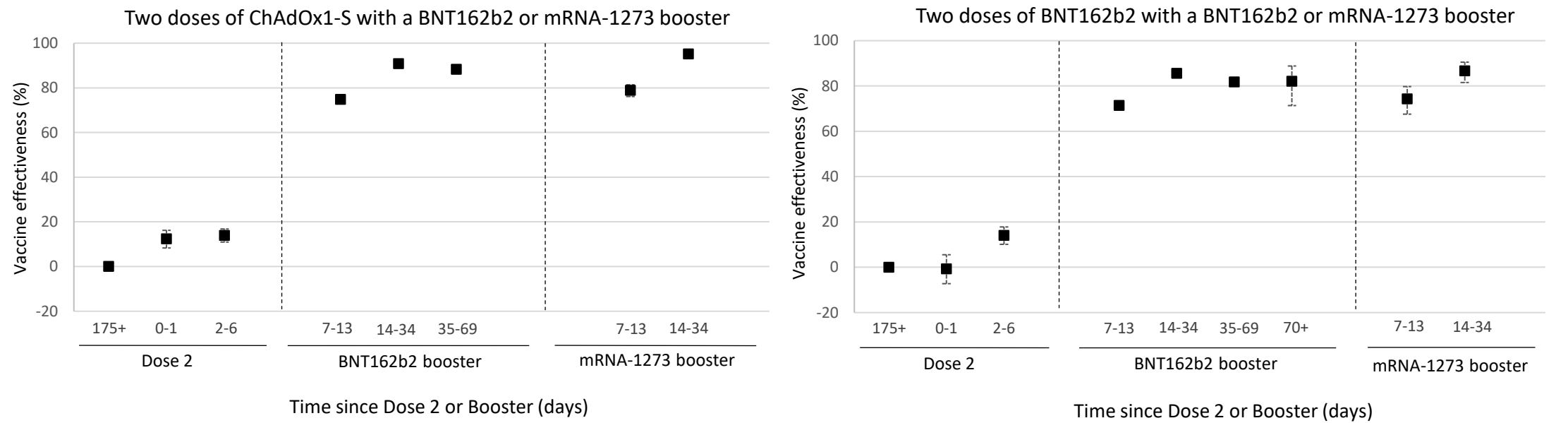
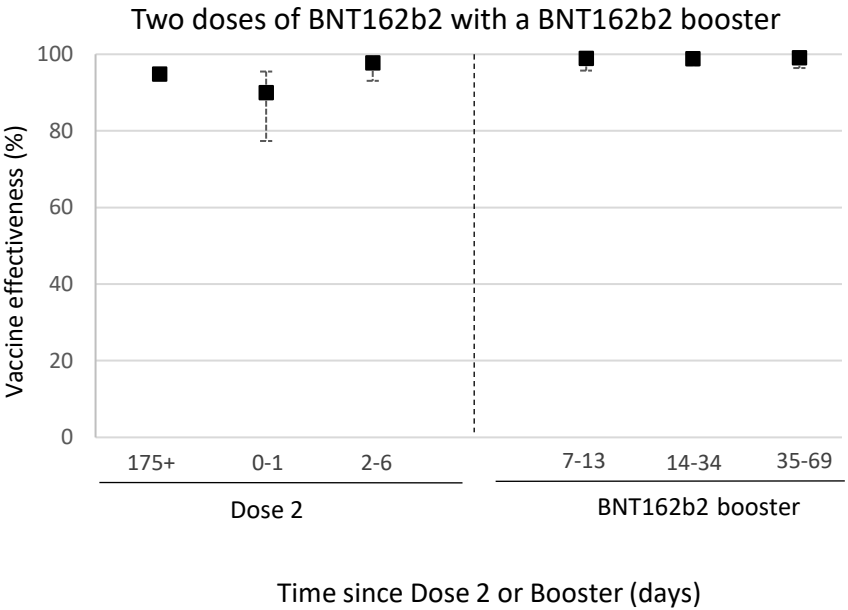
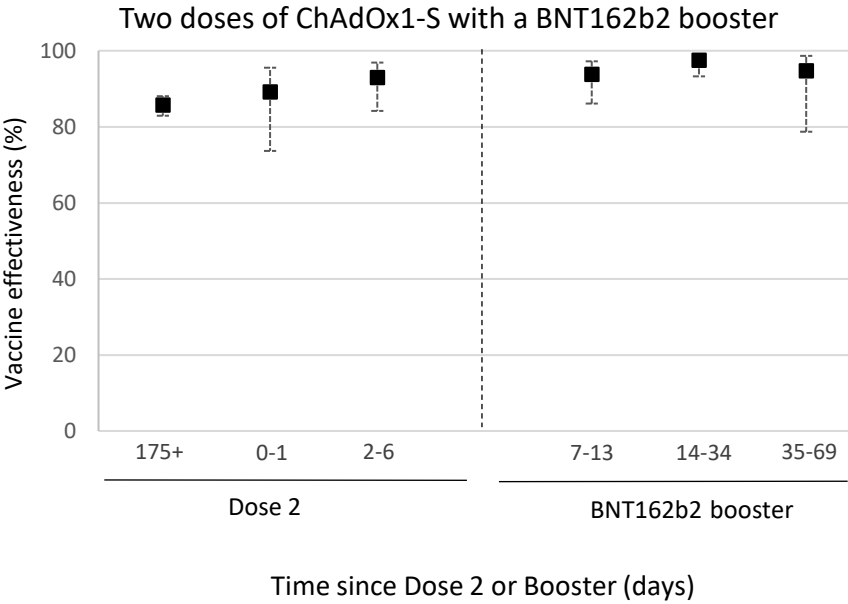
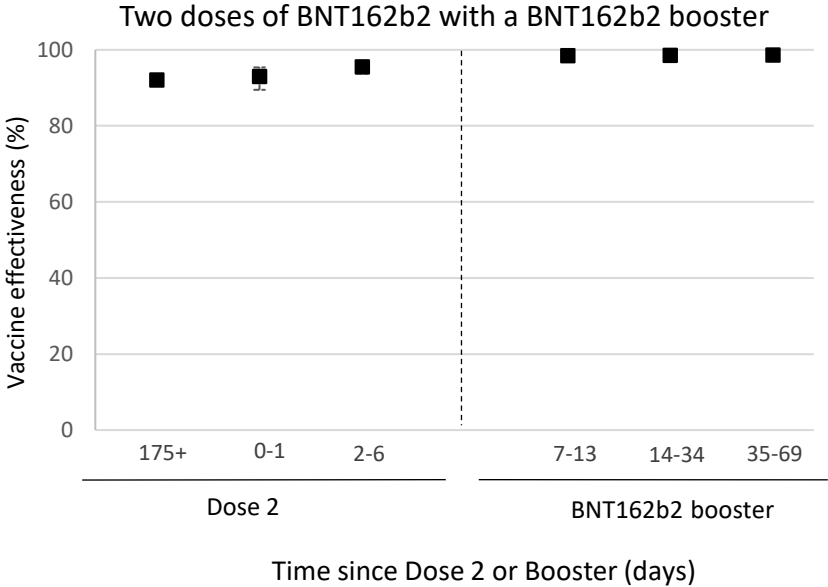
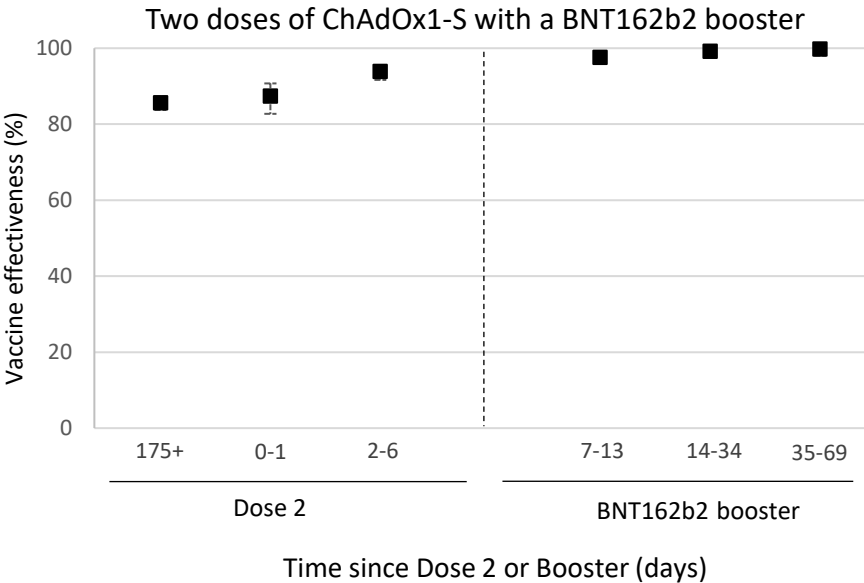


Figure 2. Vaccine Effectiveness estimates (95% CI) in time intervals post booster according to primary course a) against hospitalisation in individuals aged 18 to 49 years b) against hospitalisation in individuals aged 50 years and over c) against death in individuals aged 50 years and over: Unvaccinated as baseline.

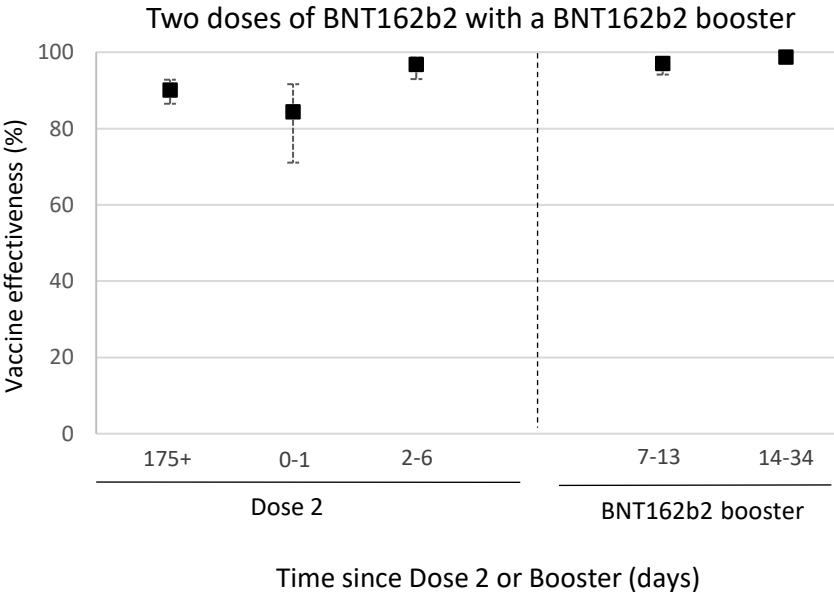
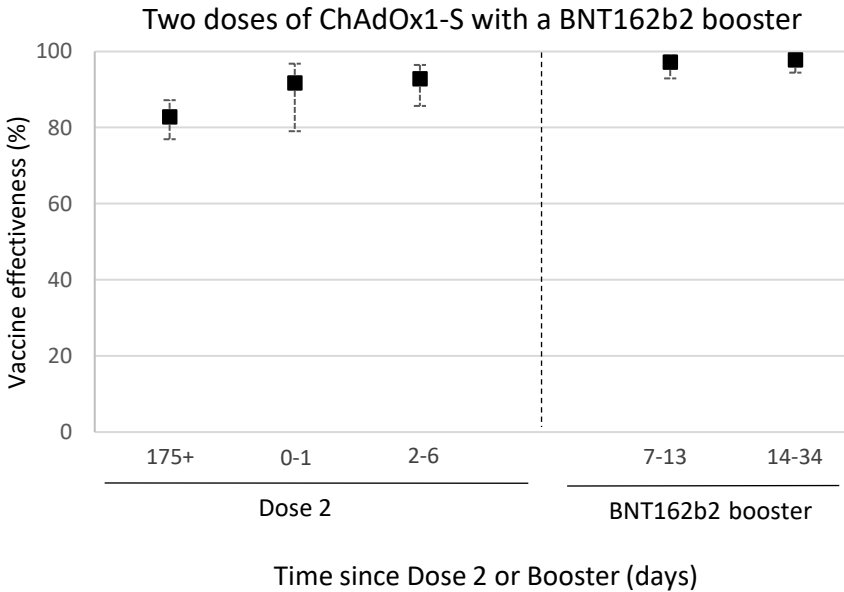
a) VE against hospitalisation:18-49 years



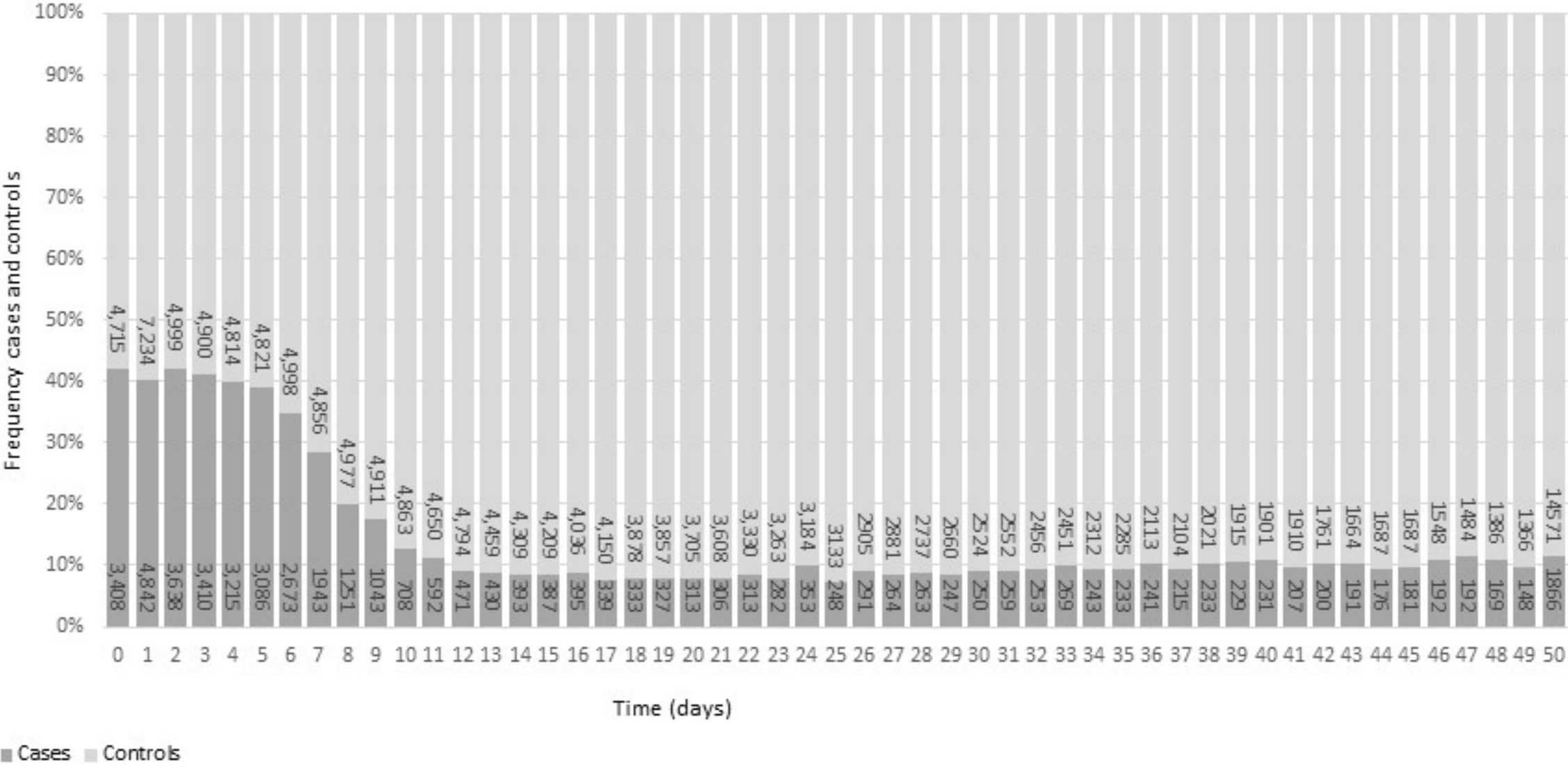
b) VE against hospitalisation: 50+ years



c) VE against death: 50+ years

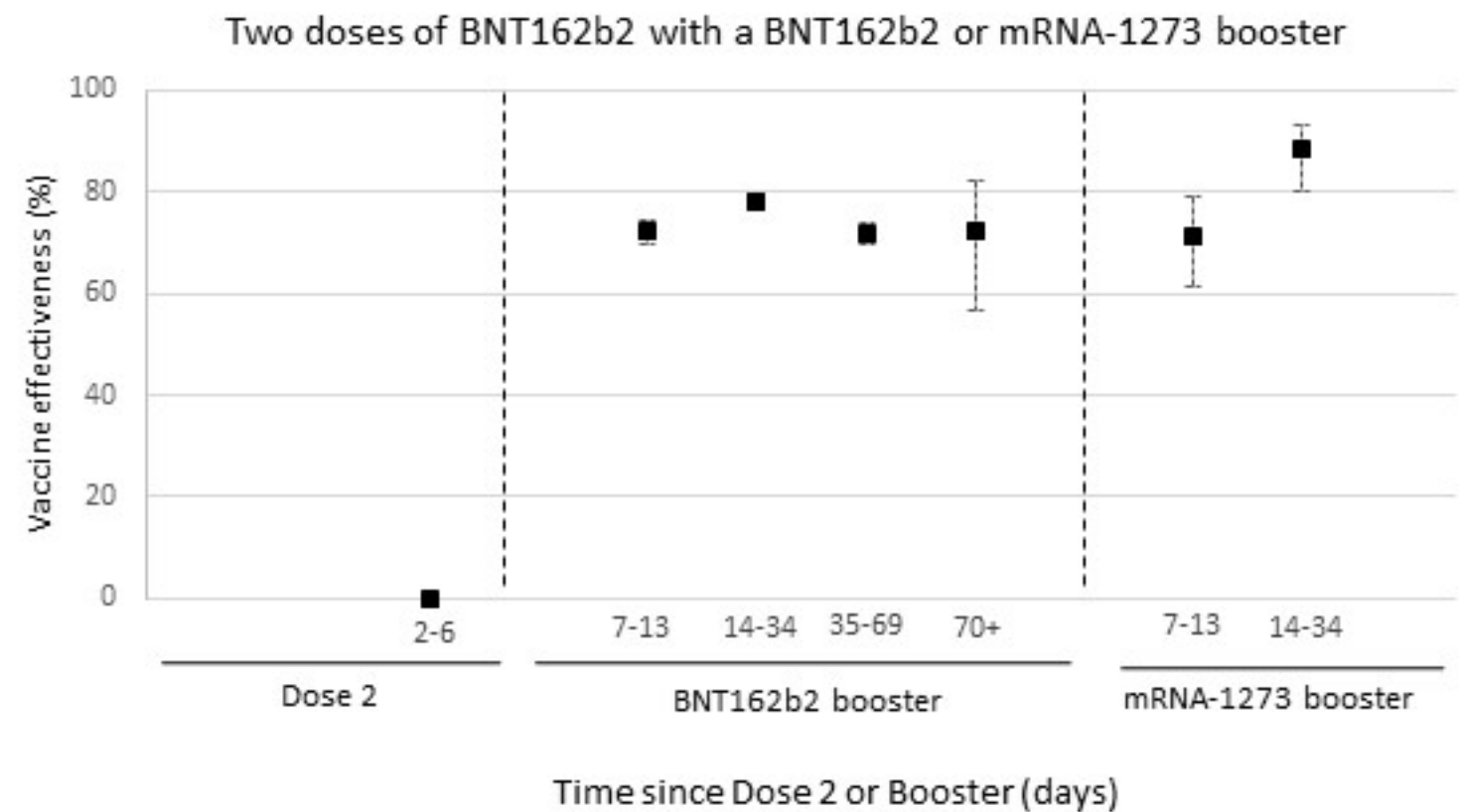
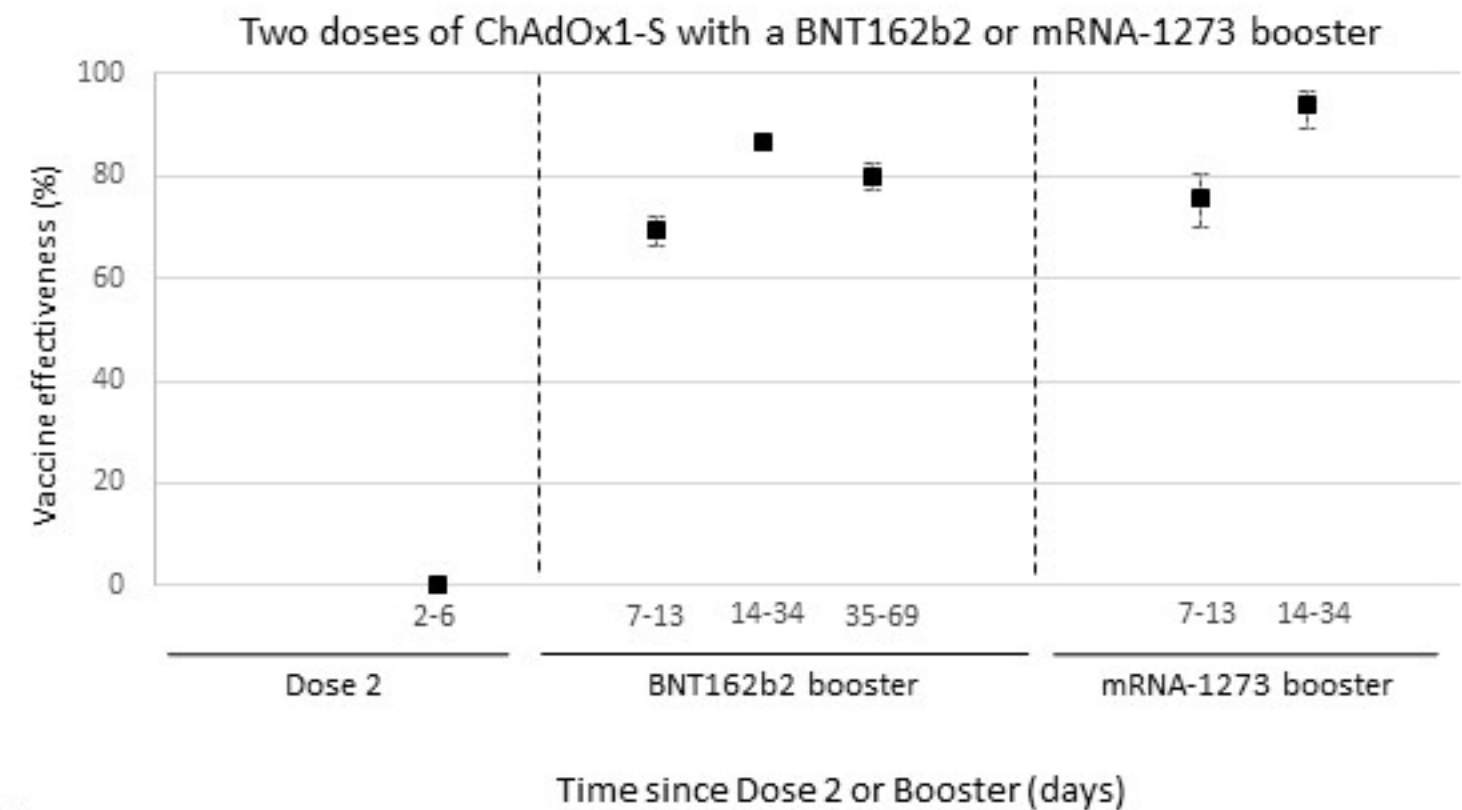


Extended Data Figure 1. Frequency and total numbers of cases and controls by time interval (days) from symptom onset date to date of booster vaccine.

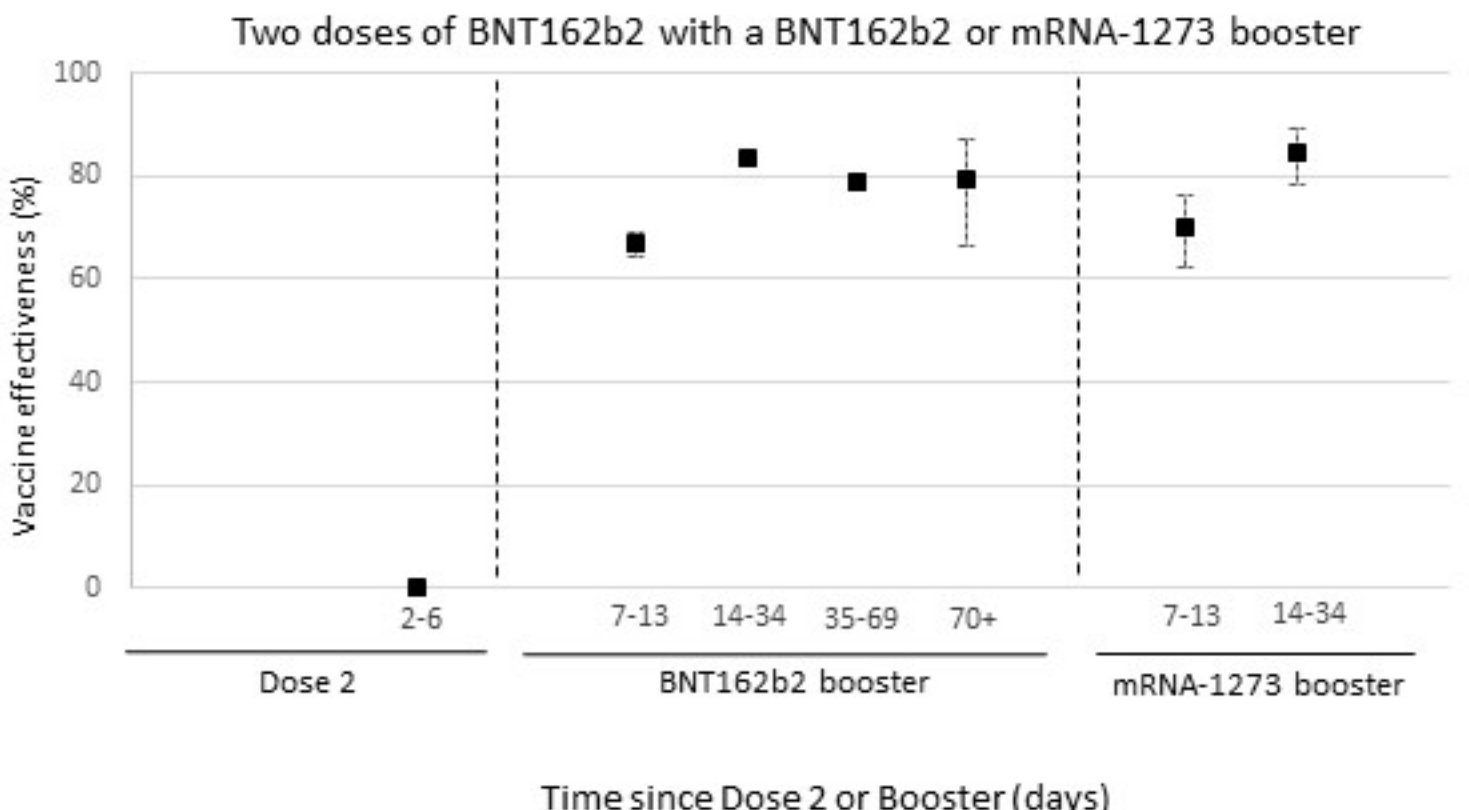
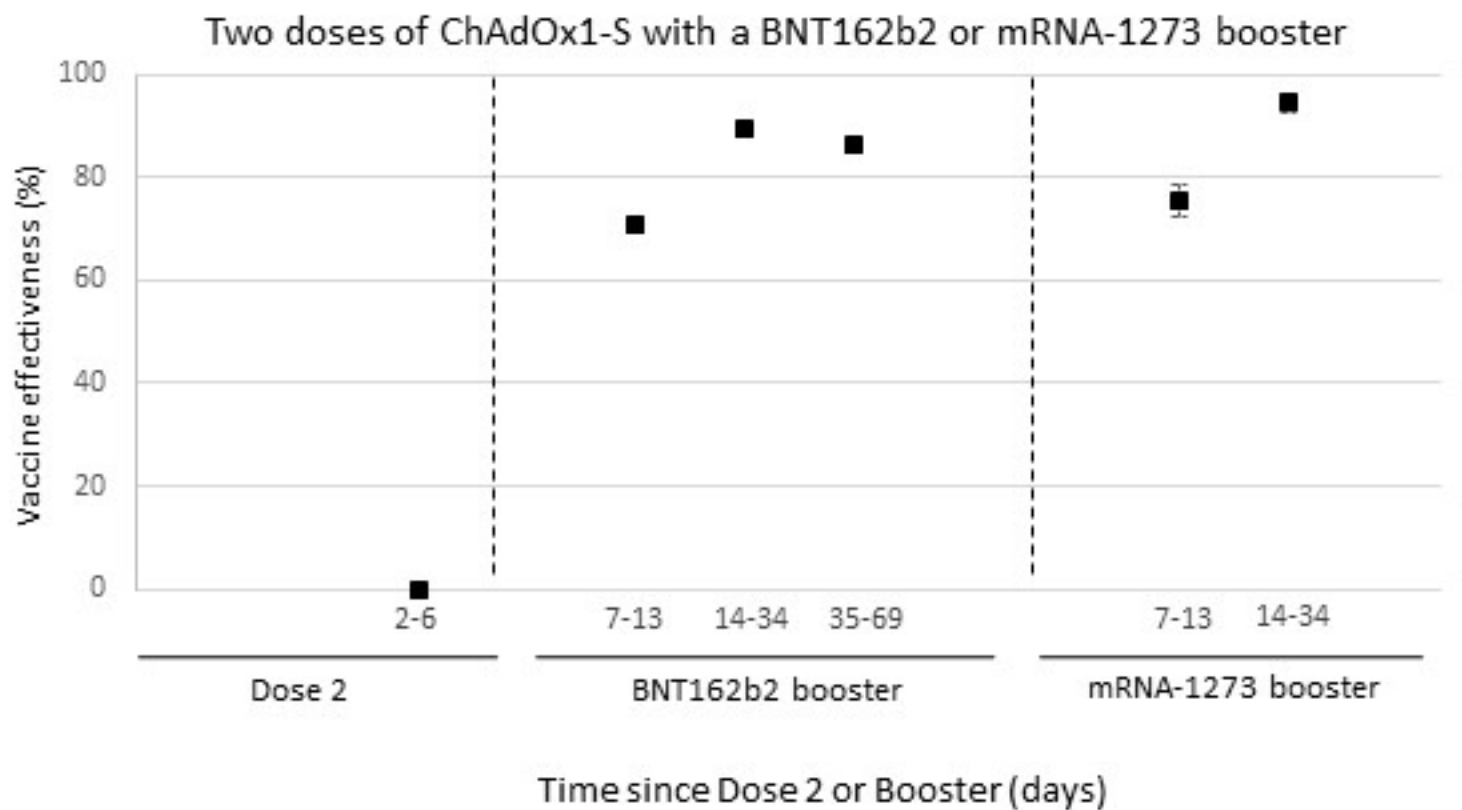


Extended Data Figure 2. Vaccine Effectiveness estimates against symptomatic disease in time intervals post booster according to primary course in individuals aged 18 to 49 years. Dose 3 at 2-6 days baseline.

a) 18-49 years

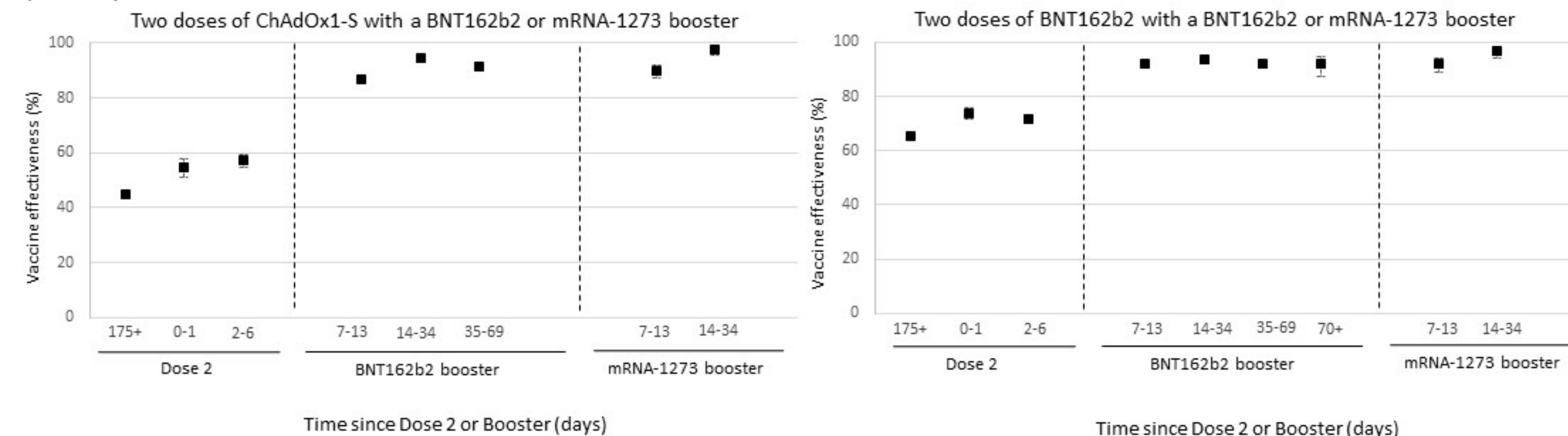


b) 50+ years

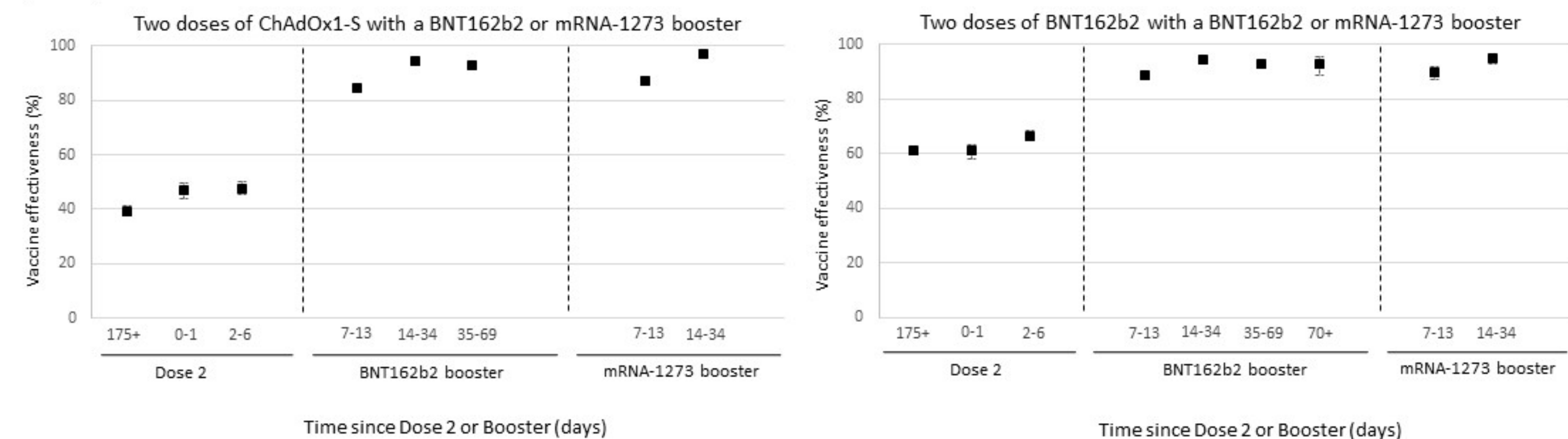


Extended Data Figure 3. Vaccine effectiveness estimates against symptomatic disease in time intervals post booster according to primary course in individuals aged 18 to 49 years: Dose 3 at unvaccinated baseline.

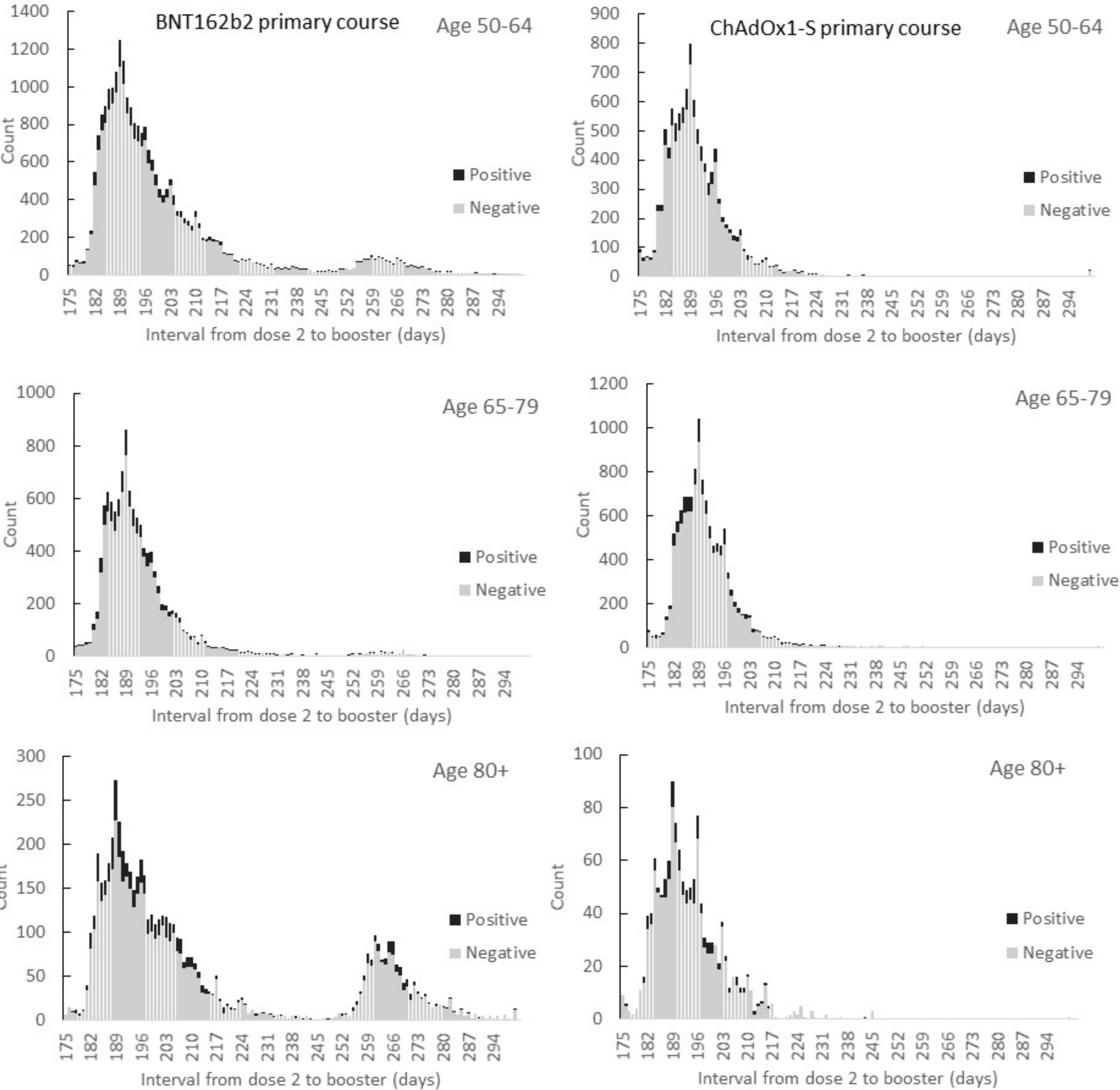
a) 18-49 years



b) 50+ years



Extended Data Figure 4. The distribution of intervals between the second dose and the booster dose for cases and controls by age group and manufacturer.



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n/a Confirmed

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- ☒ ☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☐ ☒ The statistical test(s) used AND whether they are one- or two-sided
Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- ☐ ☒ A description of all covariates tested
- ☒ ☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- ☐ ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- ☐ ☒ For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
Give P values as exact values whenever suitable.
- ☒ ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- ☒ ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- ☒ ☐ Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated

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This work is carried out under Regulation 3 of The Health Service (Control of Patient Information) (Secretary of State for Health, 2002)(3) using patient identification information without individual patient consent. Data cannot be made publicly available for ethical and legal reasons, i.e. public availability would compromise patient confidentiality as data tables list single counts of individuals rather than aggregated data. Databases used in this study include the National Immunisation Management System (NIMS), Unified Sample Database and the Emergency Care Dataset (ECDS).

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Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Test negative case control design that compares the vaccination status in COVID-19 positive and negative cases using quantitative data.
Research sample	English resident population
Sampling strategy	none- whole population of England
Data collection	Routinely collected data: National COVID-19 vaccine register and national COVID-19 testing data. These data are used for clinical management and disease surveillance purposes
Timing	08 December 2020 to 19 November 2021
Data exclusions	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 these are likely to be false negatives. Positive and negative tests within 90 days of a previous positive test were also excluded. Participants contributed a maximum of four 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. A small number of positive samples where sequencing was done and they were found not to be the Delta variant were excluded. Finally, only samples taken from 13 September 2021 (week 37, 2021) were retained for analysis.
Non-participation	no participants were involved in the stud
Randomization	No randomization was needed as this is an observational study

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	age (5 year bands), sex, index of multiple deprivation (quintile), ethnic group, care home residence status, geographic region (nhs region), period (calendar week of onset), health and social care worker status, clinical risk group status, clinically extremely vulnerable, severely immunosuppressed, and previously testing positive
Recruitment	Observation study using routinely collected data as part of the UK COVID-19 testing and vaccination programme
Ethics oversight	Surveillance of covid-19 testing and vaccination is undertaken under Regulation 3 of The Health Service (Control of Patient

Information) Regulations 2002 to collect confidential patient information (www.legislation.gov.uk/uksi/2002/1438/regulation/3/made) under Sections 3(i) (a) to (c), 3(i)(d) (i) and (ii) and 3(3). The study protocol was subject to an internal review by the Public Health England Research Ethics and Governance Group and was found to be fully compliant with all regulatory requirements. As no regulatory issues were identified, and ethical review is not a requirement for this type of work, it was decided that a full ethical review would not be necessary.

Note that full information on the approval of the study protocol must also be provided in the manuscript.