https://doi.org/10.1038/d41591-022-00013-3

# Effectiveness of BNT162b2 COVID-19 booster vaccine against covid-19 related symptoms and hospitalization in England

Received: 10 December 2021

Accepted: 14 January 2022

Accelerated Article Preview Published online: 14 January 2022

Cite this article as: Andrews, N. et al. Effectiveness of BNT162b2 COVID-19 booster vaccine against covid-19 related symptoms and hospitalization in England. *Nat Med* https://doi.org/10.1038/d41591-022-00013-3 (2022).

**Nick Andrews, Julia Stowe, Freja Kirsebom, Samuel Toffa, Ruchira Sachdeva, Charlotte Gower, Mary Ramsay & Jamie Lopez Bernal**

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

Nick Andrews*[,2], Julia Stowe*[,2], Freja Kirsebom, Samuel Toffa, Ruchira Sachdeva, Charlotte Gower, Mary Ramsay[1,2], Jamie Lopez Bernal [1,2,3]

* These authors contributed equally

**Affiliations:**

1. UK Health Security Agency, London, UK
2. NIHR Health Protection Research Unit in Vaccines and Immunisation, London School of Hygiene and Tropical Medicine, London, UK
3. NIHR Health Protection Research Unit in Respiratory Infections, Imperial College London, London, UK

**Corresponding author:**

Jamie Lopez Bernal
Jamie.LopezBernal2@phe.gov.uk

## Abstract

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

# Introduction

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

We recently reported that vaccine effectiveness against symptomatic disease peaked in the early weeks after 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 the Delta variant for ChAdOx1-S (AstraZeneca) and BNT162b (Pfizer-BioNTech) ), respectively. Vaccine effectiveness against severe disease outcomes remained high up to 20+ weeks after vaccination in most groups, nevertheless, greater waning was seen in older adults and those with underlying medical conditions compared to young, healthy adults [8].

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

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

# Results

## Descriptive statistics and characteristics

From 13 September 2021 to 5 December 2021 there were a total of 893,845 eligible tests in those aged 18 years and over, with a test date within 10 days of their symptom onset date and had linked to the National Immunisation Management system, with a 91.04% match rate. Of these 278,096 (31.1%) were unvaccinated223,198 received ChAdOx1-S 175 days post a second dose, 171,079 received BNT162b2 175 days post a second dose. Of those that had received a booster dose 89,019 received a ChAdOx1-S primary course and 132,453 received a BNT162b2 primary course. Of the 343,955 positive cases included in the analysis, 4,377 (1.27%) were hospitalised for any reason (excluding injuries) within 14 days of the test. A description of the eligible tests is given in supplementary table 1.

## Vaccine effectiveness for symptomatic disease

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

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

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

### Vaccine effectiveness for hospitalisation and death

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

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

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

### Intervals between dose 2 and the booster dose

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

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

## Discussion

This study provides evidence of a significant increase in protection against symptomatic COVID-19 disease 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 effectiveness[12].

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-S [8]. 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 previously [13]. 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 protection[15].

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 ChAOx1-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 VE [8]. 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 difficultly 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.

**Acknowledgements:** We thank the UK Health Security Agency (UKHSA) covid-19 Data Science Team, UKHSA Outbreak Surveillance Team, NHS England, NHS Digital, and NHS Test and Trace for their roles in developing and managing the COVID-19 testing, variant identification and vaccination systems and datasets as well as reporting NHS vaccinators, NHS laboratories, UKHSA laboratories, and lighthouse laboratories; and we thank the Wellcome Sanger Institute and other laboratories involved in whole genome sequencing of COVID-19 samples; and we thank the Joint Committee on Vaccination and Immunisation for advice and feedback in developing this study.

**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

**References**


1. Lopez Bernal, J.*, et al.* Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *The New England Journal of Medicine* **385**, 585-594 (2021).
2. Sharif A. Ismail, T.G.V., Suzanne Elgohari, et al. Effectiveness of BNT162b2 mRNA and ChAdOx1 adenovirus vector COVID-19 vaccines on risk of hospitalisation among older adults in England: an observational study using surveillance data. (2021).
3. Vasileiou, E.*, et al.* Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *The Lancet* **397**, 1646-1657 (2021).
4. Pritchard, E.*, et al.* Impact of vaccination on SARS-CoV-2 cases in the community: a population-based study using the UK's COVID-19 Infection Survey. *medRxiv*, 2021.2004.2022.21255913 (2021).
5. Hyams, C.*, et al.* Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccination at preventing hospitalisations in people aged at least 80 years: a test-negative, case-control study. *The Lancet Infectious Diseases*.
6. Lopez Bernal, J.*, et al.* Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* **373**, n1088 (2021).
7. Pouwels, K.B.*, et al.* Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *medRxiv*, 2021.2008.2018.21262237 (2021).
8. Andrews, N.*, et al.* Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. *MedRxiv*, 2021.2009.2015.21263583 (2021).
9. Goldberg, Y.*, et al.* Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. 2021.2008.2024.21262423 (2021).
10. Alasdair P S Munro, L.J., Victoria Cornelius, Parvinder K Aley, Gavin Babbage et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *The Lancet* (2021).
11. Department of Health & Social Care. JCVI statement regarding a COVID-19 booster vaccine programme for winter 2021 to 2022.
12. Arbel, R.*, et al.* BNT162b2 Vaccine Booster and Mortality Due to Covid-19. *New England Journal of Medicine* **385**, 2413-2420 (2021).
13. Lopez Bernal, J.*, et al.* Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* **373**, n1088 (2021).
14. Amirthalingam, G.*, et al.* Higher serological responses and increased vaccine effectiveness demonstrate the value of extended vaccine schedules in combatting COVID-19 in England. *medRxiv*, 2021.2007.2026.21261140 (2021).
15. Abu-Raddad, L.J.*, et al.* Association of Prior SARS-CoV-2 Infection With Risk of Breakthrough Infection Following mRNA Vaccination in Qatar. *Jama* **326**, 1930-1939 (2021).
16. Bar-On, Y.M.*, et al.* Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *N Engl J Med* **385**, 1393-1400 (2021).
17. Israel, A.*, et al.* Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort. 2021.2008.2003.21261496 (2021).
18. Mizrahi, B.*, et al.* Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. 2021.2007.2029.21261317 (2021).
19. Barda, N.*, et al.* Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *The Lancet* (2021).

**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**

**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 | 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.<br><br>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.<br><br>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. |
| 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. |

**Table 2: Vaccine effectiveness against symptomatic disease for the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) 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 | 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) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 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) |
| 50 years and older | 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) |

**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) |

# 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/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.

## 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 13$^{th}$ 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 $\geq$ 18 years (age as of August 31$^{st}$ 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).

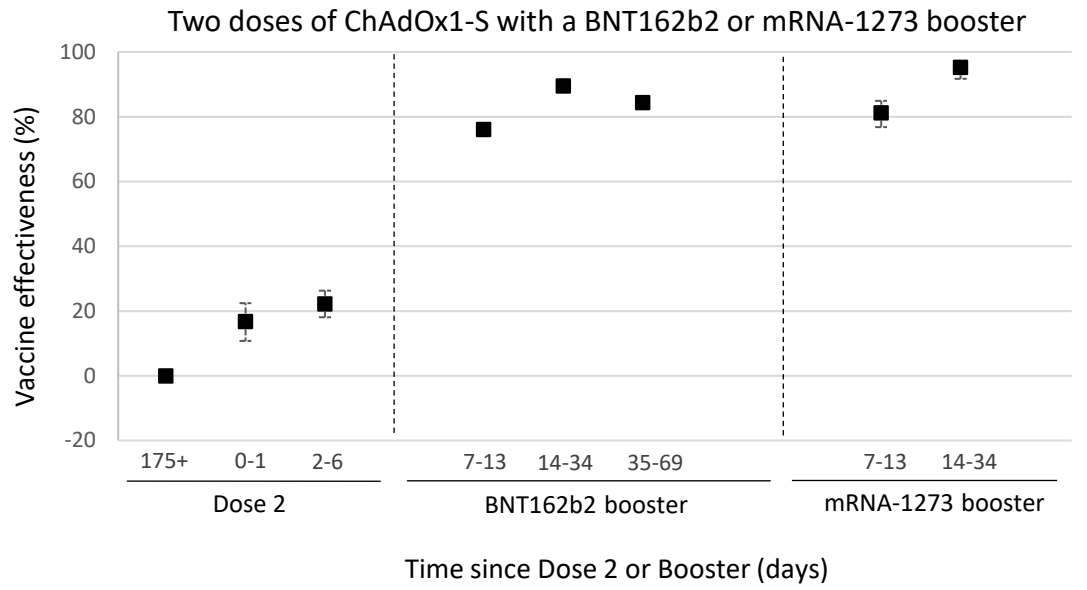
**Code availability Statement**: Model fitting code is available on our GitHub site https://github.com/UKHSAGithub/StataCode.git

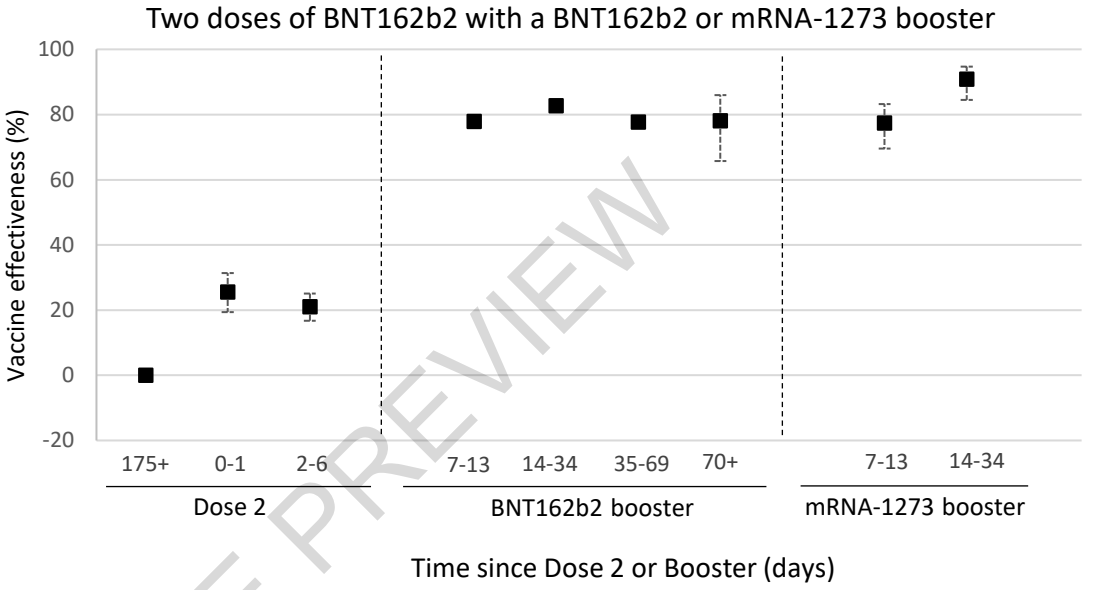
**References**

(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)

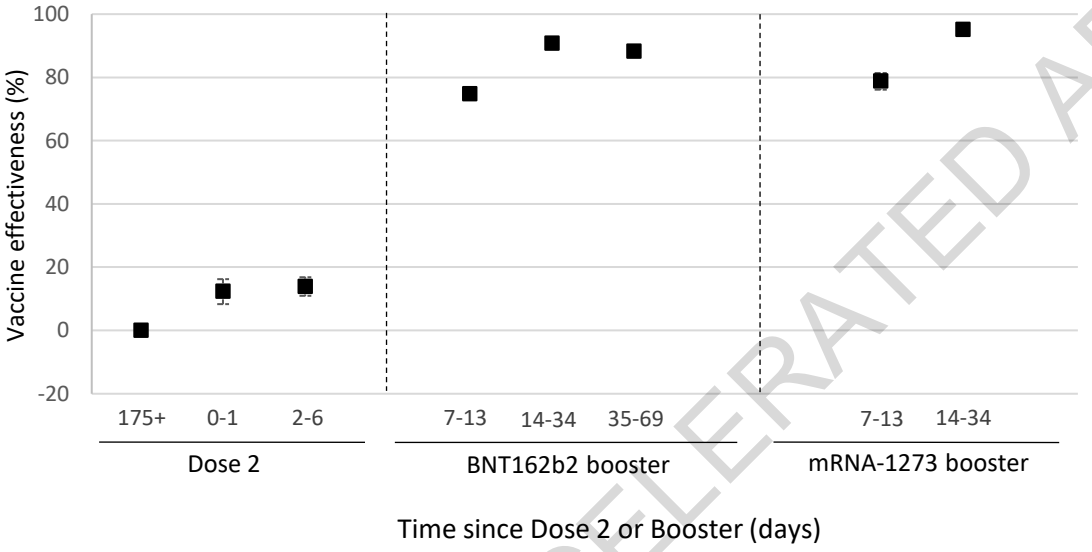
**Figure 1.** Vaccine Effectiveness estimates (95% CI) against symptomatic disease in time intervals post booster according to primary course in individuals aged a) 18 to 49 years b) 50 years and over:  Dose 2 at 175 days as baseline.

**a) 18-49 years**




**b) 50+ years**



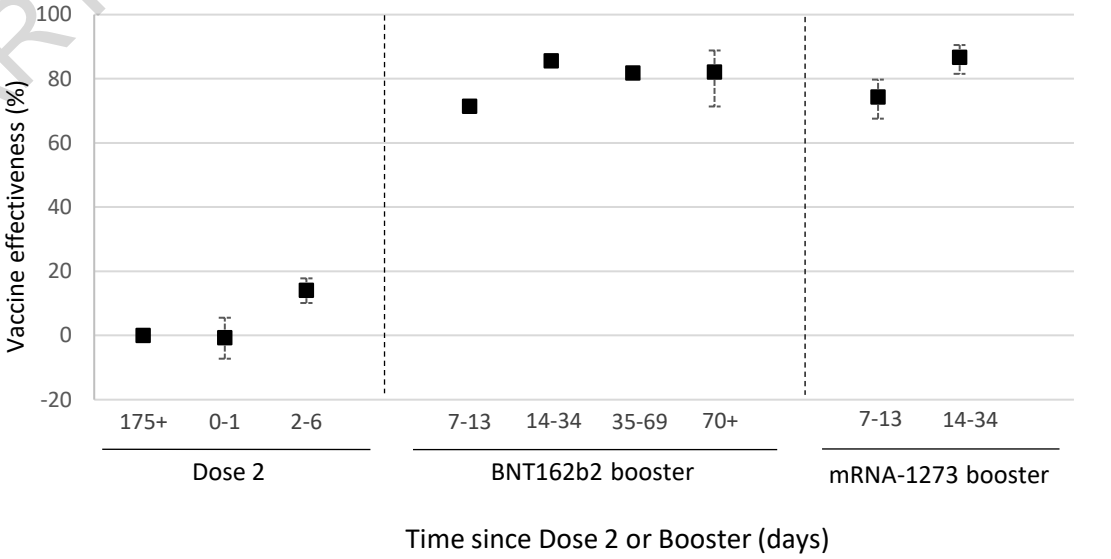
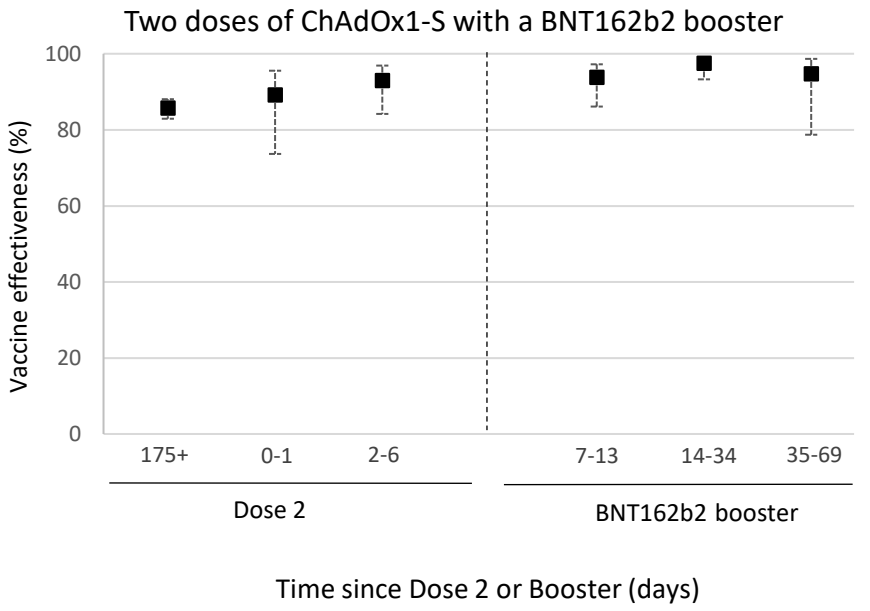
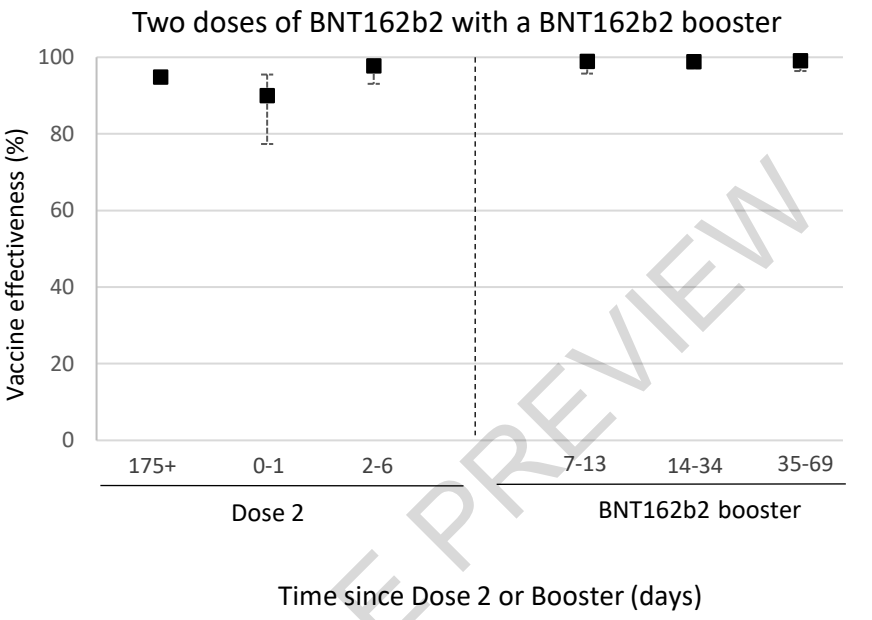



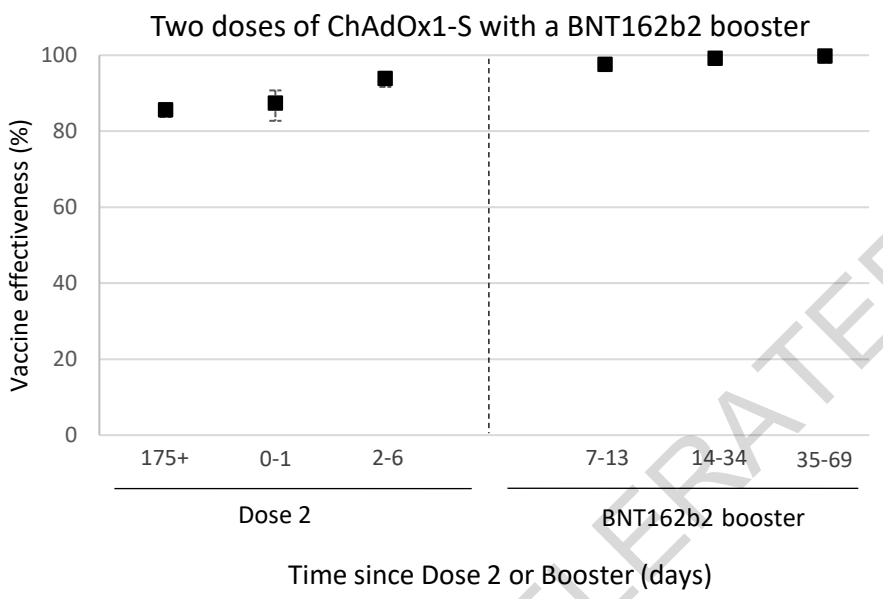
**Figure 2.** Vaccine Effectiveness estimates (95% CI) in time intervals post booster according to primary course a) against hospitalisation in individuals aged 18 to 49 years b) against hospitalisation in individuals aged 50 years and over c) against death in individuals aged 50 years and over: Unvaccinated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

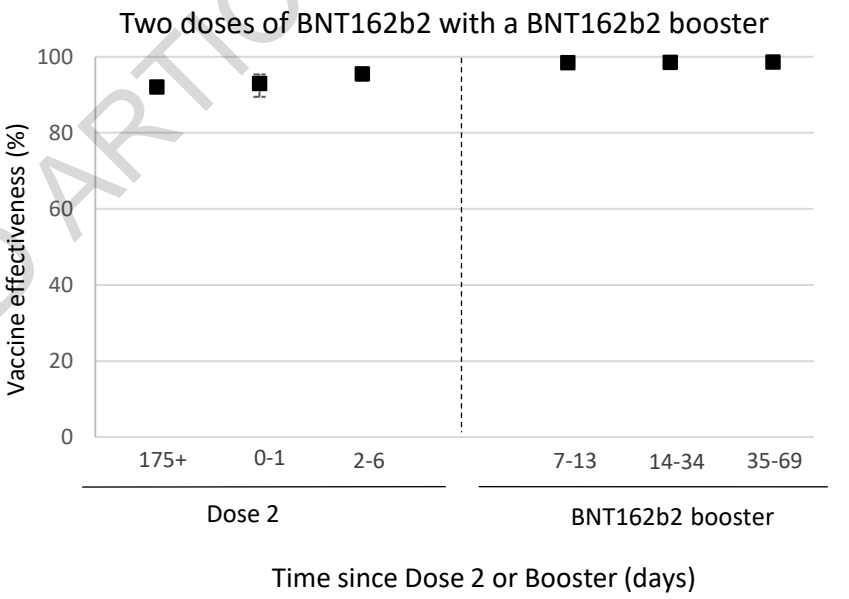
**a) VE against hospitalisation:18-49 years**



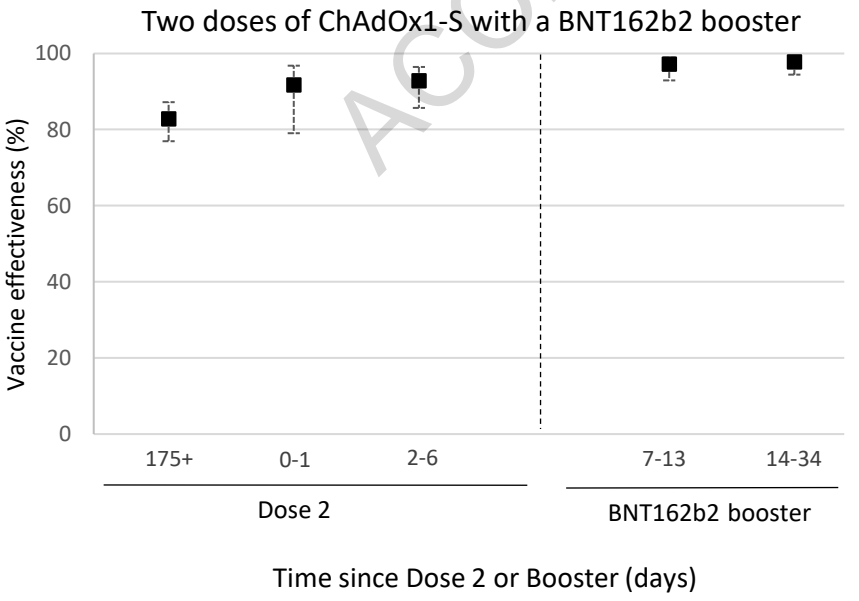



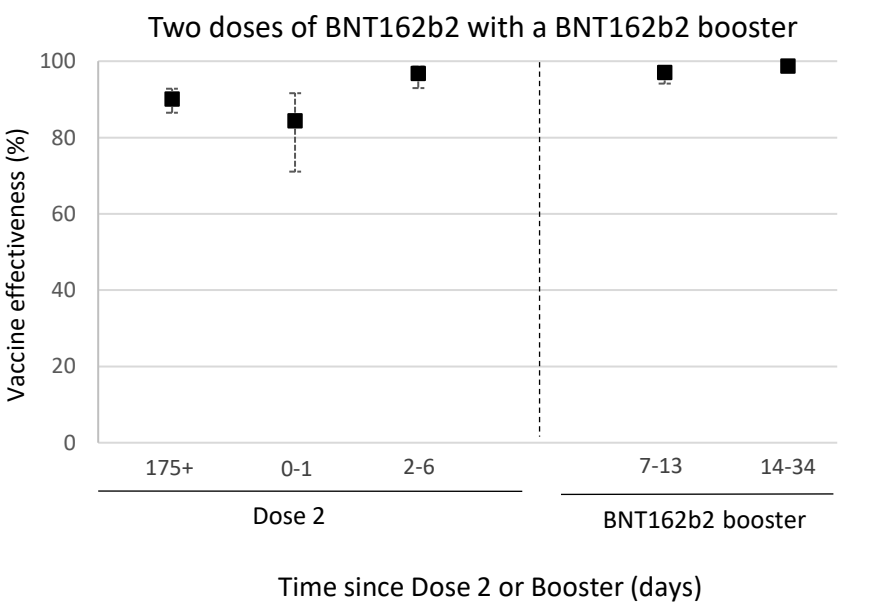

**b) VE against hospitalisation: 50+ years**



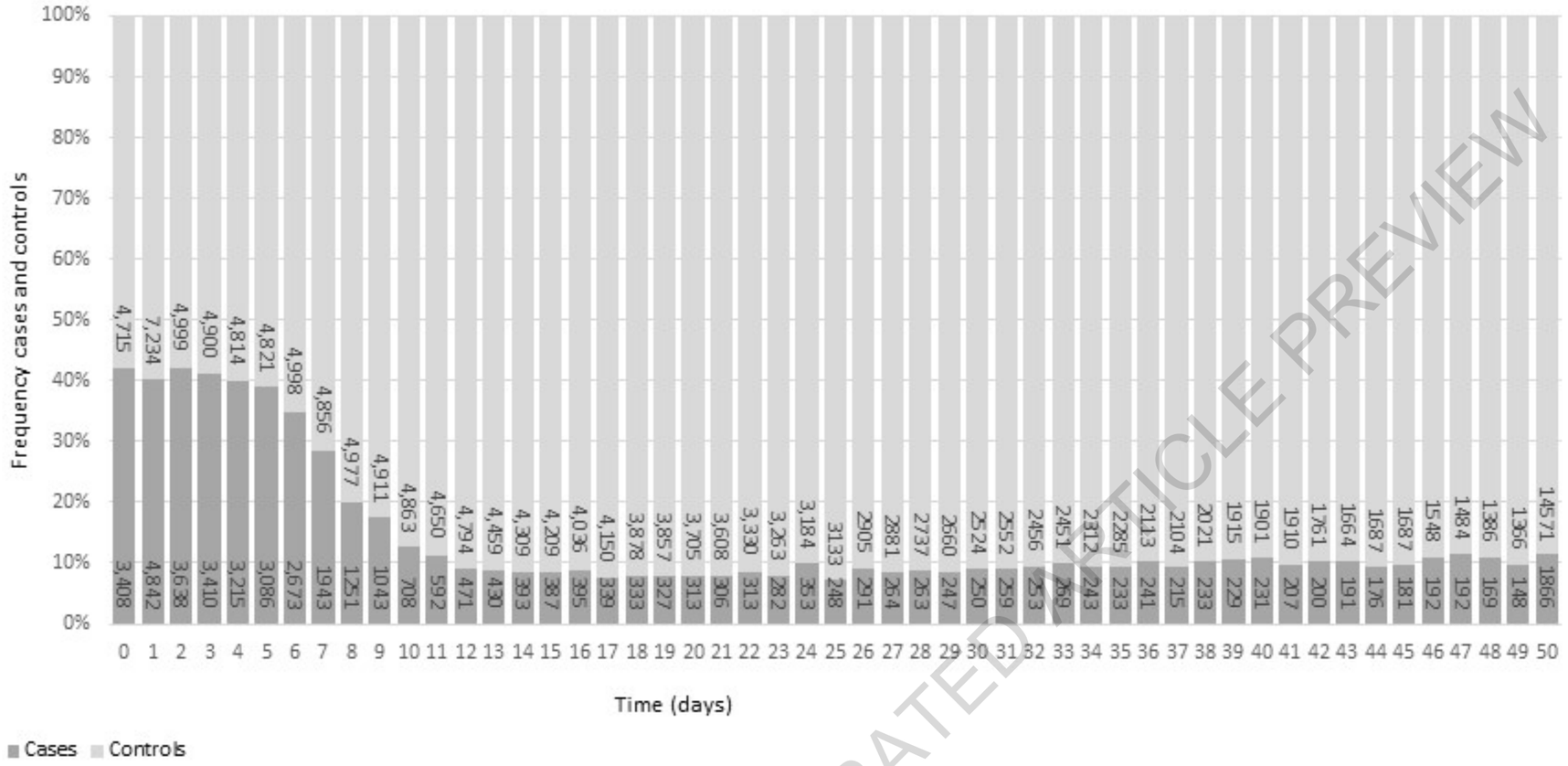




**c) VE against death: 50+ years**



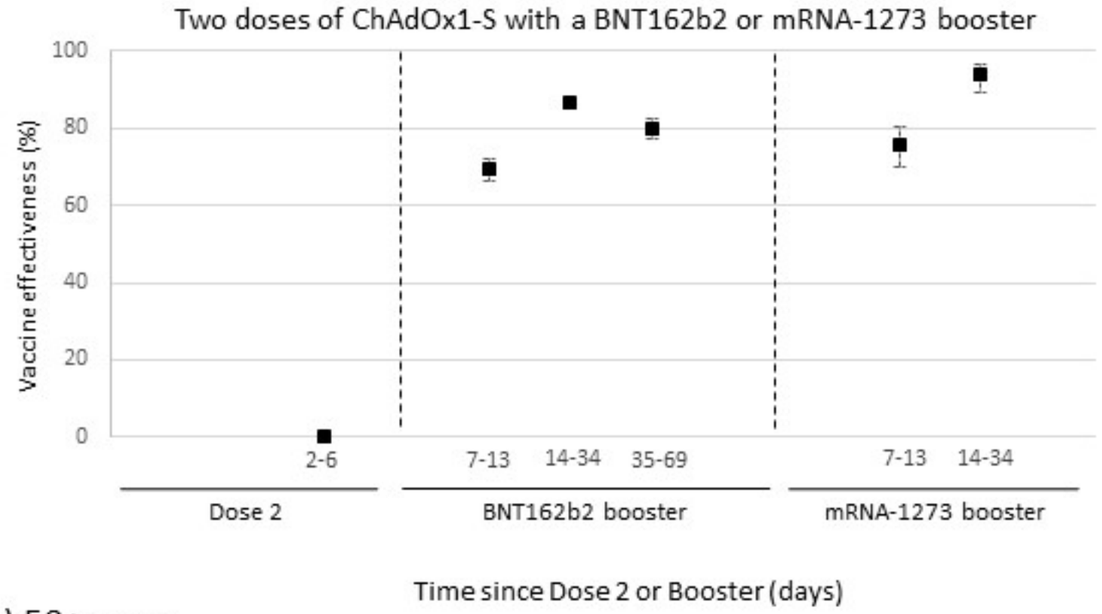



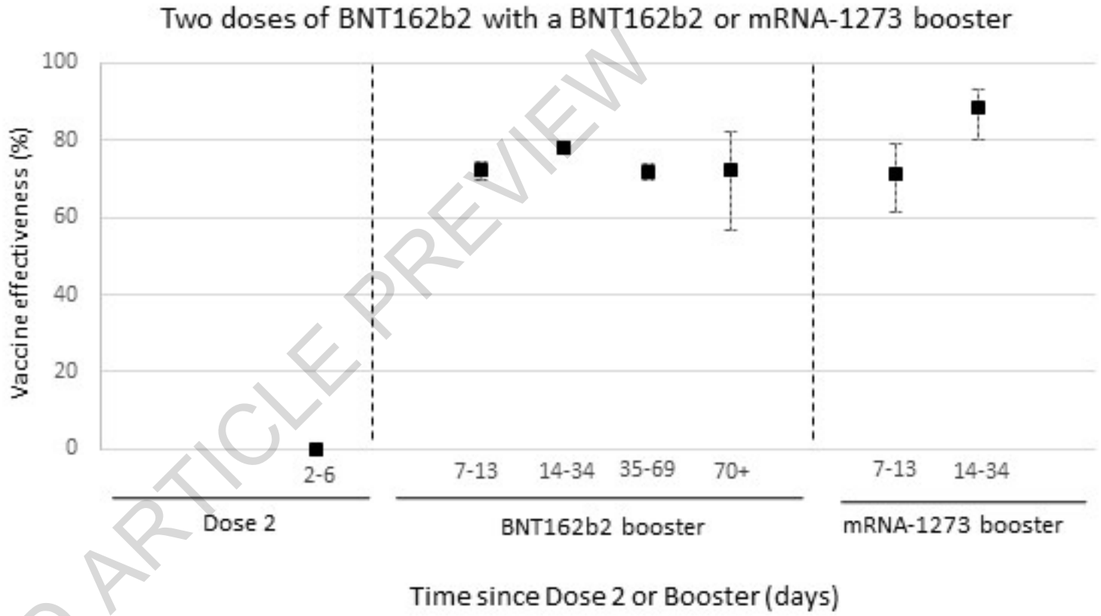
**Extended Data Figure 1.** Frequency and total numbers of cases and controls by time interval (days) from symptom onset date to date of booster vaccine.



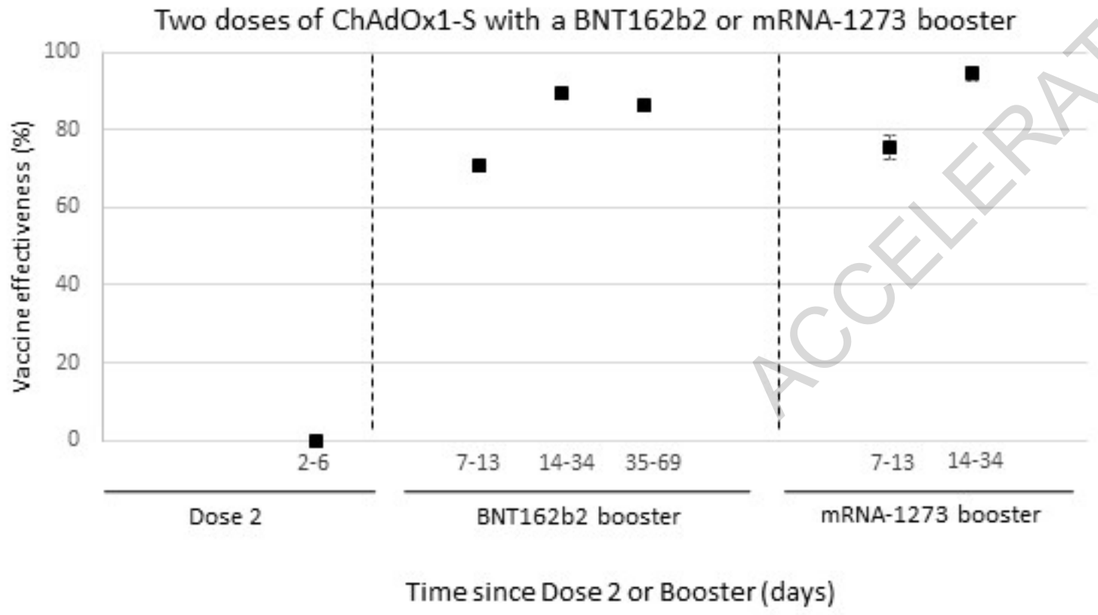
**Extended Data Figure 2.** Vaccine Effectiveness estimates against symptomatic disease in time intervals post booster according to primary course in individuals aged 18 to 49 years. Dose 3 at 2-6 days baseline.

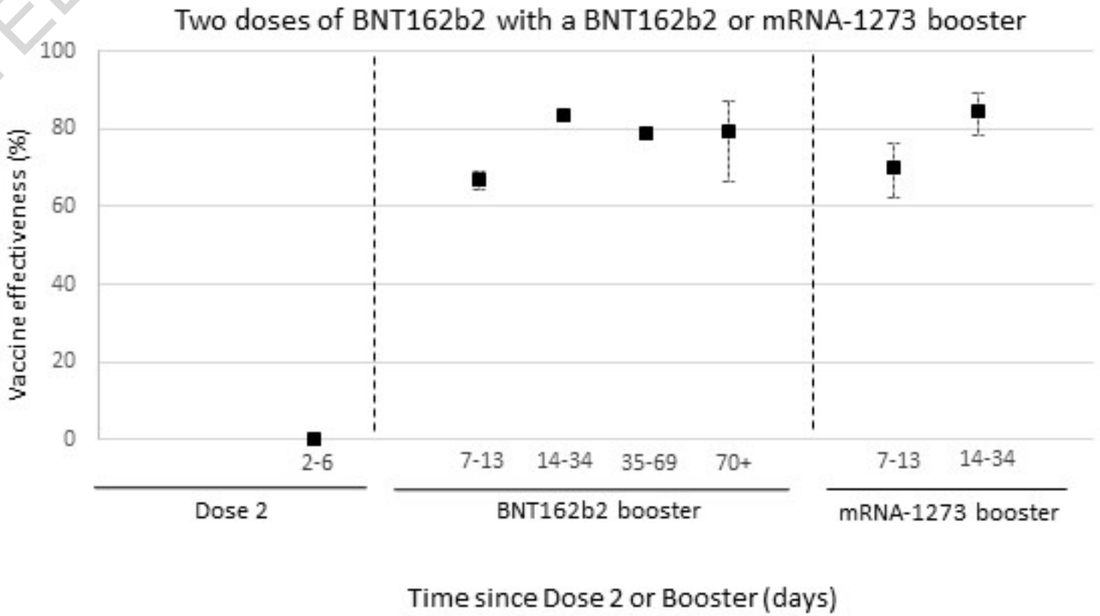
a) 18-49 years



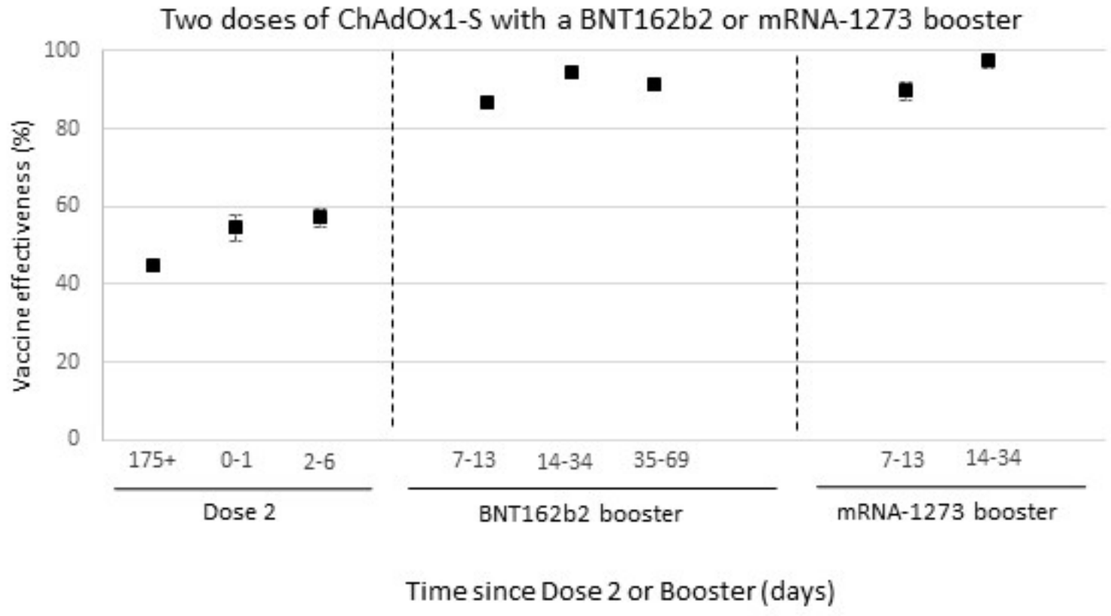

b) 50+ years

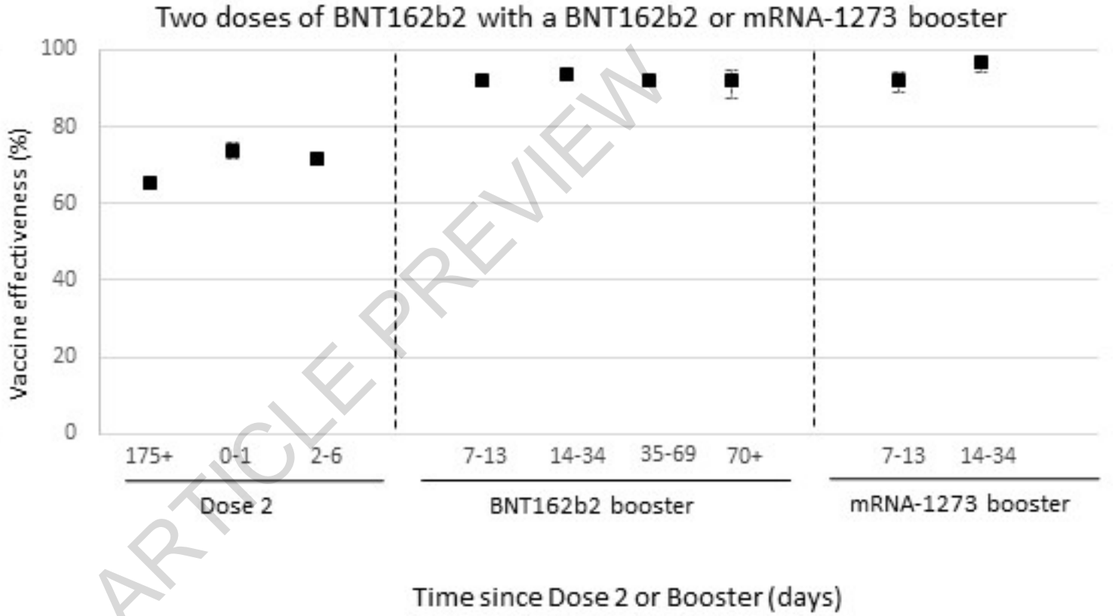


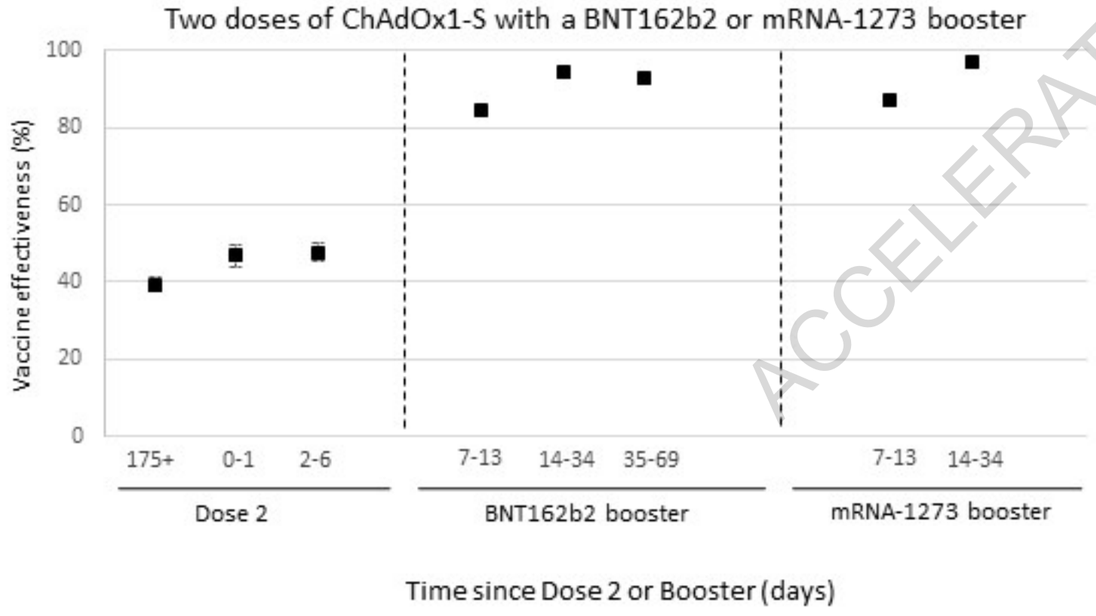
**Extended Data Figure 3.** Vaccine effectiveness estimates against symptomatic disease in time intervals post booster according to primary course in individuals aged 18 to 49 years: Dose 3 at unvaccinated baseline.

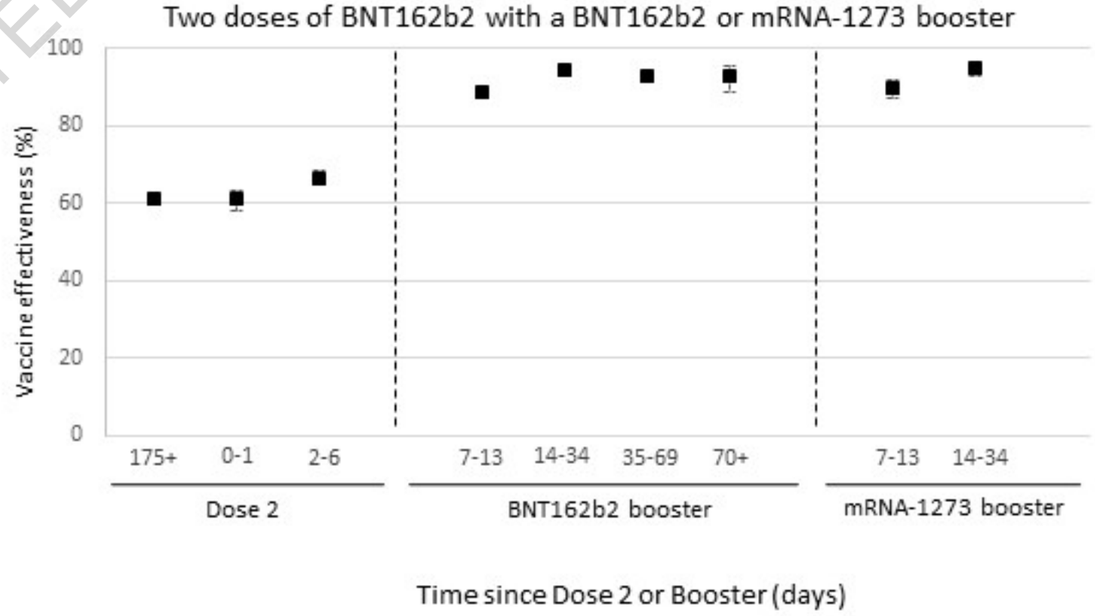
a) 18-49 years



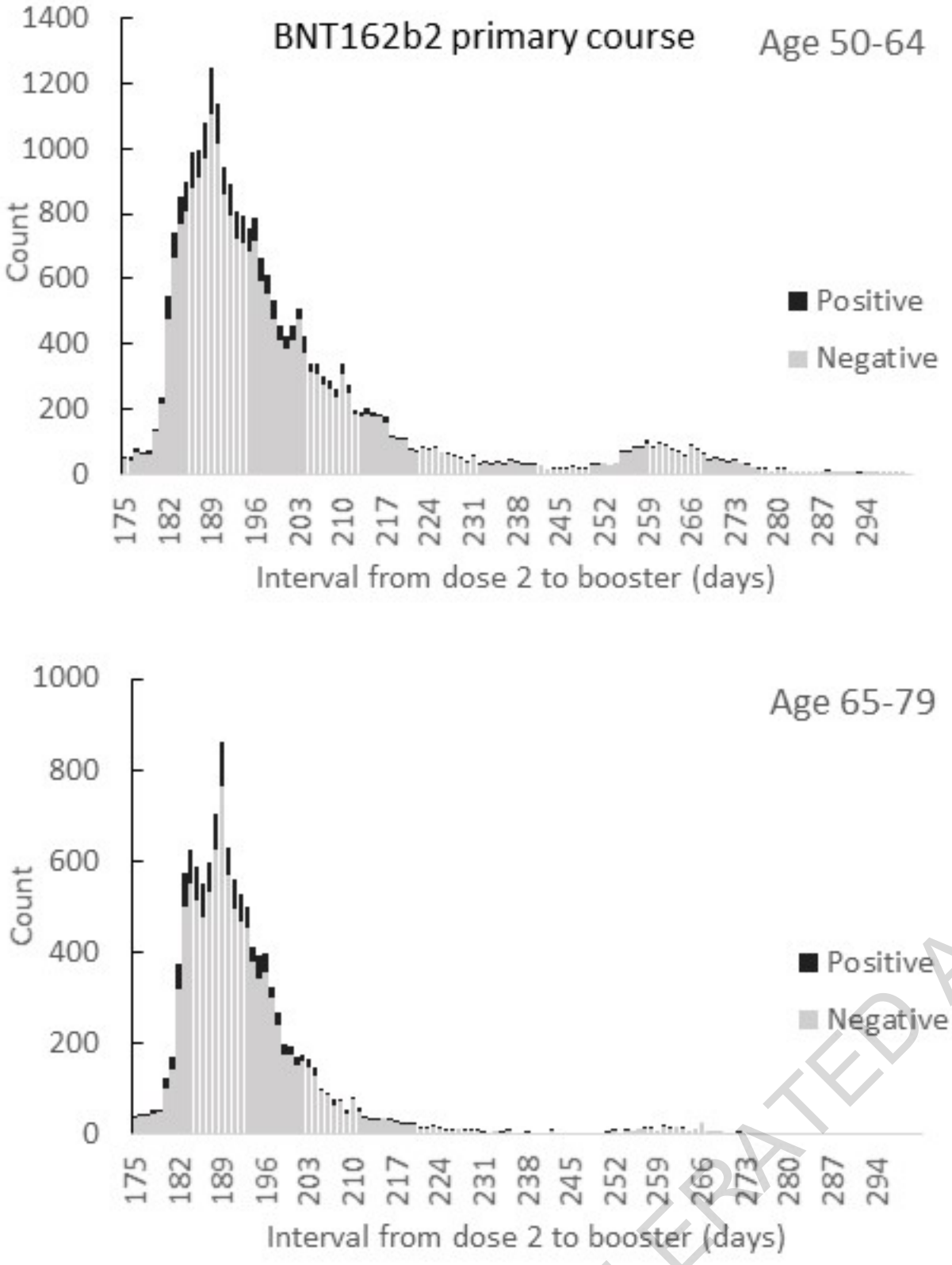



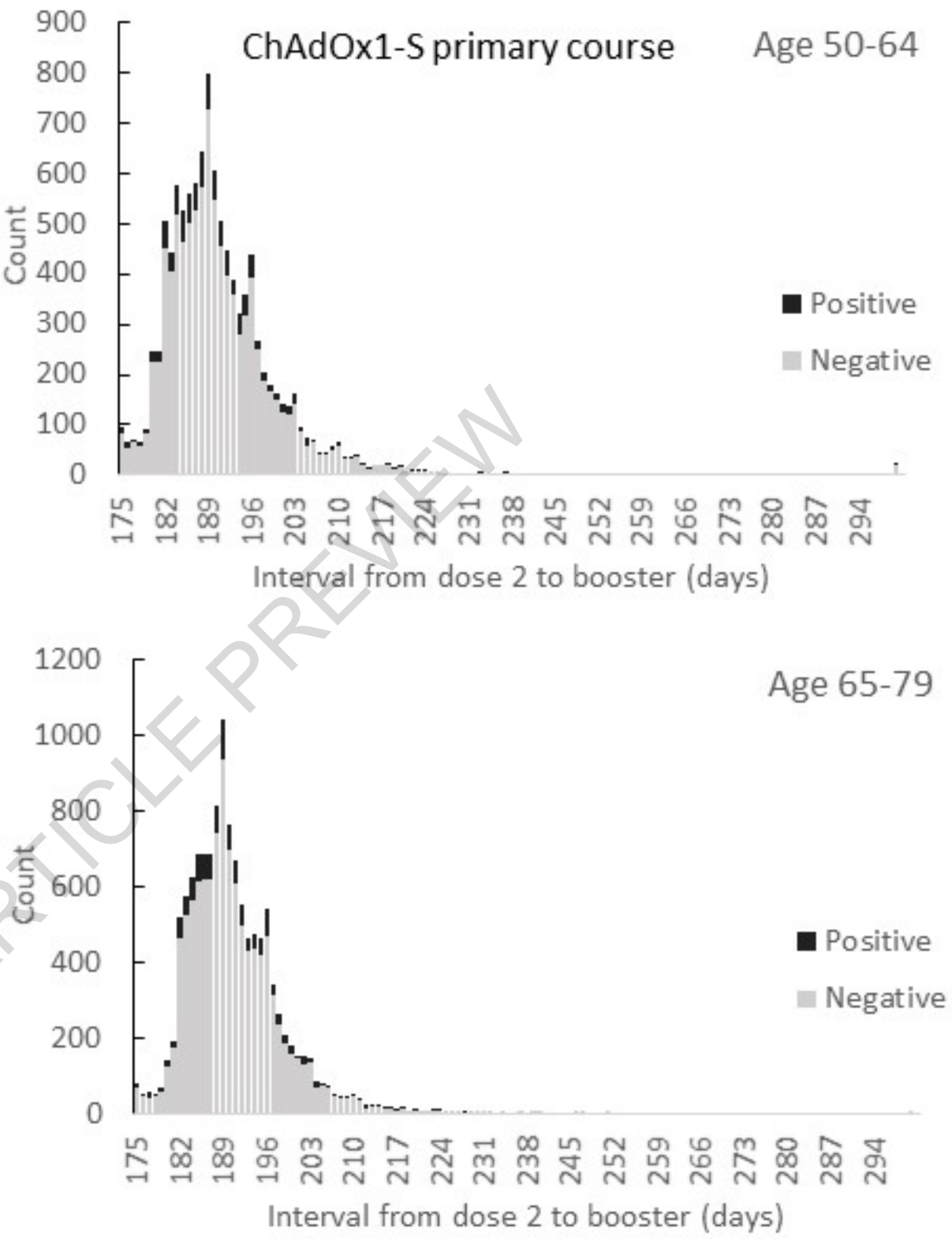

b) 50+ years



**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.

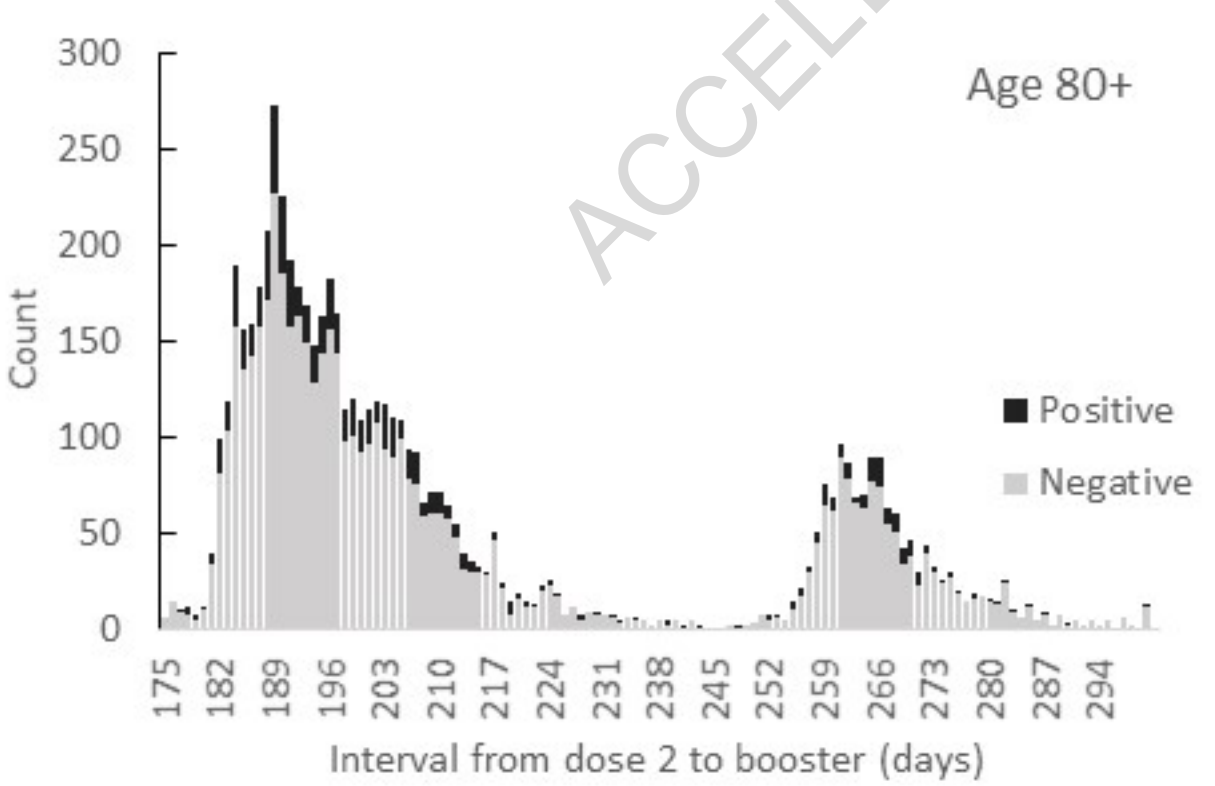


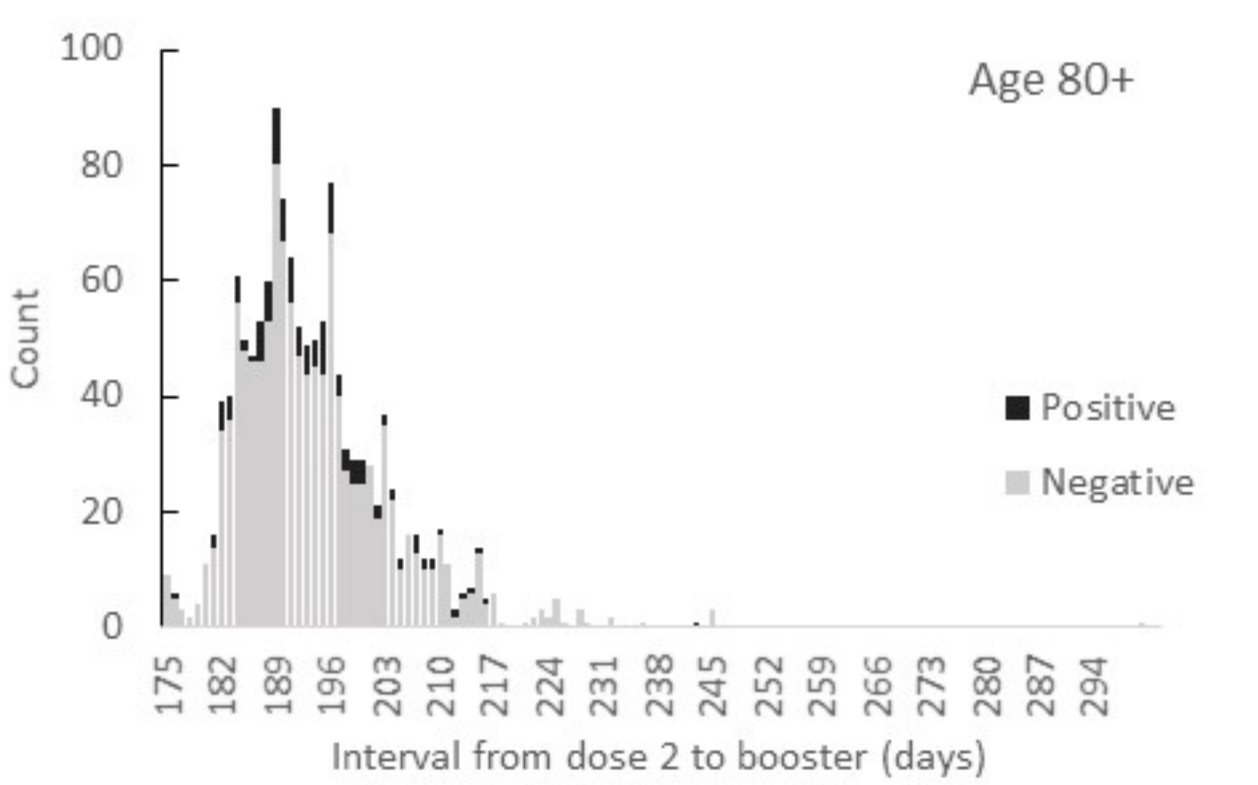









nature portfolio

Corresponding author(s): Jamie Lopez Bernal

Last updated by author(s): Jan 11, 2022

# Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

## Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

| 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<br>*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<br>*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 |

*Our web collection on statistics for biologists contains articles on many of the points above.*

## Software and code

Policy information about availability of computer code

| | |
|---|---|
| Data collection | Custom SQL scripts- Microsoft SQL Server Management Studio 18 |
| Data analysis | Custom SQL and Stata scripts- Microsoft SQL Server Management Studio 18 & Stata 15 |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

## Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

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).

# Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

# 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.

## Materials & experimental systems

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ Antibodies |
| ☒ | ☐ Eukaryotic cell lines |
| ☒ | ☐ Palaeontology and archaeology |
| ☒ | ☐ Animals and other organisms |
| ☐ | ☒ Human research participants |
| ☒ | ☐ Clinical data |
| ☒ | ☐ Dual use research of concern |

## Methods

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ ChIP-seq |
| ☒ | ☐ Flow cytometry |
| ☒ | ☐ 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 |

| | |
|---|---|
| Ethics oversight | 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.