Impact of vaccination on SARS-CoV-2 cases in the community: a population-based study using the UK's COVID-19 Infection Survey

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Abstract (250-300 words; currently 299 words)

Objectives To assess the effectiveness of COVID-19 vaccination in preventing SARS-CoV-2 infection in the community.

Design Prospective cohort study.

Setting The UK population-representative longitudinal COVID-19 Infection Survey.

Participants 373,402 participants aged ≥16 years contributing 1,610,562 RT-PCR results from nose and throat swabs between 1 December 2020 and 3 April 2021.

Main outcome measures New RT-PCR-positive episodes for SARS-CoV-2 overall, by self-reported symptoms, by cycle threshold (Ct) value (<30 versus ≥30), and by gene positivity (compatible with the B.1.1.7 variant versus not).

Results Odds of new SARS-CoV-2 infection were reduced 65% (95% CI 60 to 70%; P<0.001) in those ≥21 days since first vaccination with no second dose versus unvaccinated individuals without evidence of prior infection (RT-PCR or antibody). In those vaccinated, the largest reduction in odds was seen post second dose (70%, 95% CI 62 to 77%; P<0.001).There was no evidence that these benefits varied between Oxford-AstraZeneca and Pfizer-BioNTech vaccines (P>0.9).There was no evidence of a difference in odds of new SARS-CoV-2 infection for individuals having received two vaccine doses and with evidence of prior infection but not vaccinated (P=0.89). Vaccination had a greater impact on reducing SARS-CoV-2 infections with evidence of high viral shedding Ct<30 (88% reduction after two doses; 95% CI 80 to 93%; P<0.001) and with self-reported symptoms (90% reduction after two doses; 95% CI 82 to 94%; P<0.001); effects were similar for different gene positivity patterns.

Conclusion Vaccination with a single dose of Oxford-AstraZeneca or Pfizer-BioNTech vaccines, or two doses of Pfizer-BioNTech, significantly reduced new SARS-CoV-2 infections in this large community surveillance study. Greater reductions in symptomatic infections and/or infections with a higher viral burden are reflected in reduced rates of hospitalisations/deaths, but highlight the potential for limited ongoing transmission from asymptomatic infections in vaccinated individuals.

Registration The study is registered with the ISRCTN Registry, ISRCTN21086382.

Introduction

On 8 December 2020, the UK was the first country to start a COVID-19 vaccination programme following the emergency use authorisation of the PBNT162b2 messenger RNA (mRNA) vaccine (Pfizer-BioNtech) by UK's Medicines & Healthcare Products Regulatory Agency (MHRA)[1]. Additional COVID-19 vaccines have since been approved, including the Oxford-AstraZeneca adenovirus-vector vaccine, ChAdOx1 nCOV-19[2], and more recently an mRNA-based COVID-19 vaccine developed by Moderna, mRNA-1273[3]. To date, most vaccinated individuals in the UK received one or two doses of the Pfizer-BioNTech or Oxford-AstraZeneca vaccines.

Initially, those in care homes, over 80 years old, and frontline health and social care workers were prioritised for vaccination[4]. Clinically vulnerable people and those ≥70 years were the next priority groups, followed by remaining adults in decreasing age order. As of 14 April, over 32 million (62%) UK adults had received at least one COVID-19 vaccine dose[5], and mostly one dose only following the extension of the dosing interval to 12 weeks to maximise initial coverage[6].

Large randomised trials estimated efficacy against symptomatic laboratory-confirmed COVID-19 infection of 70% (95% CI 55% to 81%) after two Oxford-AstraZeneca doses[7], and 95% (95% CI 90% to 98%) after two Pfizer-BioNTech doses[8]. Whilst trials provide unbiased effect estimates, trial participants may differ from the general population in many ways, and so it is essential to assess effectiveness in the community, particularly given differences between real-world vaccine deployment and the licenced dosing schedule. Comparing vaccine effectiveness in the community is also important as the trials used different outcome definitions (e.g. start of at-risk period 14 vs 7 days after the second dose) and populations (e.g. smaller proportion >55 years in the Oxford-AstraZeneca vaccine trial (12%[7] vs 42% for Pfizer-BioNtech[8])).

Furthermore, both trials were largely conducted before the SARS-CoV-2 variant, B.1.1.7, became dominant[9]. This variant is more transmissible and potentially also more severe[10-12]. Concerns have been raised that some of its defining mutations may affect the efficacy of vaccines and natural infection-derived immunity to (re)infection. A subset of 8,534 participants from the initial Oxford-AstraZeneca trial were followed for a longer period to assess protection against different viral variants, but large uncertainty meant it was difficult to conclude whether efficacy was lower against B.1.1.7 (70%, 95%CI 44% to 85%) than other lineages (82%, 95%CI 70% to 89%)[13].

Ongoing assessment of the effectiveness of different vaccines across different subgroups is critical – especially amongst older adults, where more limited evidence from Oxford-AstraZeneca trials has resulted in several countries deciding not to use this vaccine in the elderly despite vaccination shortages and increasing infections. Real-world studies are starting to appear, with an analysis from Israel estimating 92% (95%CI 88 to 95%) effectiveness against symptomatic PCR-confirmed infection ≥7 days after the second Pfizer-BioNTech dose[14]. Another study assessing the early effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccine in older adults (≥70 years) in England showed a single dose of either vaccine was ~60% and ~80% effective against symptomatic laboratory-confirmed infection and hospitalisation respectively[15]. The evidence on effectiveness against asymptomatic infection is limited, with one study among healthcare workers from Oxfordshire, UK, showing a 64% (95% CI 50 to 74%) reduction in any SARS-CoV-2 PCR-positive result following a single Pfizer-BioNTech or Oxford-AstraZeneca dose[9]. Another study among 3,950 healthcare workers, first responders, and other essential and frontline workers from the US estimated 80% (95%CI 59 to 90%) and 90% (95%CI 68 to 97%) vaccine effectiveness 14 or more days after 1 or 2 doses of the Pfizer-BioNTech or Moderna vaccines respectively[16]. Most recently, a study in 10,412 residents of long-

term care facilities showed 65% and 68% protection against SARS-CoV-2 PCR-positive results 28-42 days after vaccination with Oxford-AstraZeneca and Pfizer-BioNtech vaccines respectively[17].

However, existing studies have either investigated defined sub-populations[9 16 17] or have relied on results from symptomatic testing programmes[14 15], potentially leading to bias from vaccination status influencing test-seeking behaviour of cases not requiring healthcare. Large community-based studies where testing is done in a systematic manner (independent of both vaccination status and symptoms) are lacking. We therefore used the Office for National Statistics (ONS) COVID-19 Infection Survey (CIS) – a large community-based survey of individuals aged 2 years and older living in randomly selected private households across the UK – to assess the effectiveness of Pfizer-BioNTech and Oxford-AstraZeneca vaccines against any SARS-CoV-2 PCR positive test performed in the survey[18], where RT-PCR tests were done on a fixed schedule, irrespective of symptoms, vaccine status and prior infection. We assessed vaccine effectiveness based on overall RT-PCR positivity, and split according to self-reported symptoms, cycle threshold (Ct) value (<30 versus ≥30) as a surrogate for viral load, and gene positivity pattern (compatible with B.1.1.7 or not).

Methods

Study participants

The Office for National Statistics (ONS) COVID-19 Infection Survey (CIS) is a large household survey with longitudinal follow-up (ISRCTN21086382, https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey/protocol-and-information-sheets) (details in[18]). Private households are randomly selected on a continuous basis from address lists and previous surveys to provide a representative sample across the UK. Following verbal agreement to participate, a study worker visited each selected household to take written informed consent for individuals aged 2 years and over. Parents or carers provided consent for those aged 2-15 years; those aged 10-15 years also provided written assent.

Individuals were asked about demographics, behaviours, work, and vaccination uptake (https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey/case-record-forms). At the first visit, participants were asked for (optional) consent for follow-up visits every week for the next month, then monthly for 12 months from enrolment. At each visit, enrolled household members provided a nose and throat self-swab following instructions from the study worker. From a random 10-20% of households, those 16 years or older were invited to provide blood monthly for antibody testing.

Laboratory testing

Swabs were couriered directly to the UK's national Lighthouse laboratories (Glasgow and the National Biocentre in Milton Keynes (to 8 February 2021)) where samples were tested within the national testing programme using identical methodology. The presence of three SARS-CoV-2 genes (ORF1ab, nucleocapsid protein (N), and spike protein (S)) was identified using real-time polymerase chain reaction (RT-PCR) with the TaqPath RT-PCR COVID-19 kit (Thermo Fisher Scientific, Waltham, MA, USA), analysed using UgenTec Fast Finder 3.300.5 (TagMan 2019-nCoV assay kit V2 UK NHS ABI 7500 v2.1; UgenTec, Hasselt, Belgium). The assay plugin contains an assay-specific algorithm and decision mechanism that allows conversion of the qualitative amplification assay raw data into test results with little manual intervention. Samples are called positive if either N or ORF1ab, or both, are detected. The S gene alone is not considered a reliable positive[18], but could accompany other genes (ie, one, two, or three gene positives).

Blood samples were couriered directly to the University of Oxford, where they were tested for the SARS-CoV-2 antibody using an ELISA detecting anti-trimeric spike IgG[19]. Before 26 February 2021, the assay used fluorescence detection as previously described (positivity threshold 8 million units)[19]. After this, it used a commercialised CE-marked version of the assay, the Thermo Fisher OmniPATH 384 Combi SARS-CoV-2 IgG ELISA (Thermo Fisher Scientific, Waltham, MA, USA), with the same antigen and a colorimetric detection system (positivity threshold 42 ng/ml monoclonal antibody unit equivalents, determined from 3840 samples run in parallel).

Inclusion and exclusion criteria

This analysis included participants aged 16 years or over (i.e. those who theoretically could have received vaccination), and all visits with positive or negative swab results from 1 December 2020 to 3 April 2021.

Vaccination status

Participants were asked about their vaccination status at visits, including type, number of doses and date(s). Participants from England were also linked to administrative records from the National Immunisation Management Service (NIMS). We used records from NIMS where available, otherwise

records from the survey, since linkage was periodic and NIMS does not contain information about vaccinations received abroad or in Northern Ireland, Scotland, and Wales. Where records were available in both, agreement on type was >98% and on dates >95% within ±7 days.

SARS-CoV-2 infection episodes

PCR-positive results may be obtained at multiple visits after infection, so we grouped positive tests into 'episodes'. Whole genome sequencing is available on only a subset of positives, and only a subsample provide monthly blood samples for antibody status, so positive episodes were defined using study PCR results. Based on the World Health Organisation (WHO) definition of re-infection as positive tests occurring at least 90 days after the onset of primary infection[20], but also incorporating multiple consecutive negative tests, we defined the start of a new 'infection episode' as the date of either: i) the first PCR-positive test in the study (not preceded by any PCR-positive test); ii) a PCR-positive test after 4 or more consecutive negative tests; or iii) a PCR-positive test at least 90 days after the start of a previous infection episode with one or more negative tests immediately preceding this. Positive episodes were used to classify exposure groups and outcomes (see below).

Exposures

At each study visit, a participant was classified into one of seven different exposure groups based on current vaccination status, and study antibody and PCR tests, as follows:

i) Visits from participants ≥21 days before first vaccination, including those currently with no vaccination date, with no prior PCR/antibody-positive (as defined below) ("Not vaccinated, not previously positive, ≥21 days before vaccination");
ii) Visits from participants 1 to 21 days before first vaccination with no prior PCR/antibody-positive ("Not vaccinated, not previously positive, 1-21 days before vaccination")
iii) Visits 0 to 7 days following a first vaccination ("Vaccinated 0-7 days ago");
iv) Visits 8 to 20 days following a first vaccination ("Vaccinated 8-20 days ago");
v) Visits 21 days or more following a first vaccination ("≥21 days after 1st dose, no second dose");
vi) Visits after second vaccination, ≥21 days following first vaccination ("Post second dose");
vii) Visits from participants previously PCR/antibody-positive and not (yet) vaccinated ("Not vaccinated, previously positive").

As antibody status before vaccination is not available for all participants, we defined prior positivity by having either a positive antibody measurement or PCR-positive episode >45 days before the visit date. The choice of 45 days was arbitrary, but designed to exclude ongoing infections acquired previously being misattributed to current visits. Information about self-reported or linked positive SARS-CoV-2 PCR or lateral flow tests outside the study was not considered. Visits from vaccinated individuals (groups (iii)-(vi)) were defined irrespective of previous positivity. Visits from the same participant were classified in different groups depending on their status at each visit. As very few visits occurred after a second Oxford-AstraZeneca dose (3,613, 3.5% of all visits ≥21 days after first Oxford-AstraZeneca dose), this group was pooled with Oxford-AstraZeneca one dose only in analyses of vaccine type. We chose these vaccination status categories empirically based on the odds of infection episodes when modelling days since first vaccination as a continuous effect, allowing for non-linearity by using restricted cubic splines (**Supplementary Figure 1**).

Outcomes

Analysis was based on visits, since these occur independently of symptoms and are therefore unbiased. Only the first test-positive visit in the first new positive infection episode starting after 1 December was used, dropping all subsequent visits in the same infection episode, to avoid misattributing ongoing PCR-positivity to visit characteristics. Primary analysis included all first new positive infection episodes. Secondary analyses considered the impact of vaccination on infection severity, by classifying positives by cycle threshold (Ct) value (<30 or ≥30) and self-reported symptoms. For each positive test, a single Ct was calculated as the arithmetic mean across detected genes (Spearman correlation>0.98), then the minimum value was taken across positives in the infection episode to reflect the greatest measured viral burden within an episode. To allow for pre-symptomatic positives being identified in the survey, any self-reported symptoms at any visit within 0 to 35 days after the index positive in each infection episode were included (questions elicit symptoms in the last 7 days at each visit). Finally, positive infection episodes were classified as compatible with the B.1.1.7/VOC202012/01 SARS-CoV-2 variant (those positive at least once for ORF1ab+N across the episode and never S-positive) and those that were incompatible (ORF1ab+N+S or ORF1ab+S or N+S at least once). B.1.1.7/VOC202012/01 has deletions in the S gene leading to S gene target failure, and ORF1ab+N positivity only remains a good proxy for B.1.1.7/VOC202012/01 from whole-genome sequencing from mid November 2020[21]. Positives where only a single N or single ORF1ab gene were detected were excluded from this secondary analysis.

Confounder

The following potential confounders were adjusted for in all models as potential risk factors for acquiring SARS-CoV-2 infection: geographic area and age in years (see below), sex, ethnicity, index of multiple deprivation (percentile, calculated separately for each country in the UK)[22-25], working in a care-home, having a patient-facing role in health or social care, presence of long-term health conditions, household size, multigenerational household, rural-urban classification[26-28], direct or indirect contact with a hospital or care-home, smoking status, mode of travel to work, work location, and visit frequency. Details are shown in **Supplementary Table 1**. Analysis was based on complete cases (>99% observations) (**Supplementary Table 2**).

Statistical analysis

Associations between the different exposure groups and outcome (first positive test in an infection episode vs test-negative) were evaluated with generalised linear models with a logit link. Robust standard errors were used to account for multiple visits per-participant. To adjust for substantial confounding by calendar time and age, with non-linear effects of age which are also different by region, we included both as restricted cubic splines with knots at the 20%, 40%, 60%, and 80% percentiles of unique values and interactions between these splines and region/country (regions for England and country for Northern Ireland, Scotland and Wales). Furthermore, given previous observations of different positivity rates by age over time[18], we added a tensor spline to model the interaction between age and calendar time with the restriction that the interaction is not doubly non-linear[29]. We considered effect modification by age of vaccination by fitting this same model, but also including an interaction between vaccine exposure group and age <75 vs ≥75 years, or long-term health conditions. Pairwise comparisons of the five exposure groups were performed using Tukey adjustments for the pairwise comparisons.

Patient and public involvement

Members of the general public contributed to participant materials. Question wording was tested with members of the general public and amended based on their feedback. No members of the

public were asked to advise on interpretation or writing up of results. Results will be disseminated to relevant communities through news media.

Results

PCR-positive episodes and vaccination status

From 1st December 2020 to 03rd April 2021, 373,402 individuals provided 1,610,562 RT-PCR results from nose and throat swabs in the COVID-19 Infection Survey (median [IQR] 3 [2 to 4]), of which 12,525 (0.8%) were the first positive in an infection episode and 1,598,037 (99.2%) were negative. Of 12,525 PCR-positives, 10,636 (85%) occurred in those ≥21 days before vaccination with no prior PCR/antibody-positive, 613 (5%) in those 1 to 21 days before vaccination with no prior PCR/antibody-positive, 238 (2%) in those first vaccinated 0 to 7 days ago, 421 (3%) in those first vaccinated 8 to 20 days ago, 417 (3%) in those vaccinated ≥21 days ago having received only one dose, 72 (1%) in those having received 2 vaccine doses, and 83 (1%) in those not vaccinated but previously PCR/antibody-positive.

Very few new infection episodes occurred in vaccinated individuals with evidence of previous infection (i.e. prior PCR or antibody test positive) before vaccination (seven in those vaccinated 0 to 7 days ago, seven in those vaccinated 8 to 20 days ago, 11 in those ≥21 days after 1st dose with no second dose, and six in those post second dose [**Supplementary Table 3**]) so these were classified based on vaccination history alone. Of the 19,756 individuals who received a second vaccine dose, 3,437 (17%) had this 21 days after first vaccination, while the remainder received a second dose median 59 days (IQR 36 to 71) later.

Ct values (inversely related to viral load) of new infections increased with increasing time from first vaccination and number of doses (**Figure 1; Supplementary Table 4**). The highest Ct values were in those who had received two vaccine doses, with a similar distribution to those not vaccinated but previously PCR/antibody-positive. Ct values were lowest in those not vaccinated and not previously PCR/antibody-positive. The percentage of PCR-positive cases self-reporting symptoms was highest in those not vaccinated and not previously PCR/antibody-positive, and lowest in those with two vaccine doses and those not vaccinated but previously PCR-/antibody-positive (**Figure 2**). Well-recognised COVID-19 symptoms (cough, fever, loss of taste/smell) were most commonly reported in unvaccinated individuals and not previously PCR/antibody-positive, while other self-reported symptoms occurred similarly across all vaccine exposure groups.

Impact of vaccination on new infections

In unadjusted analyses, the percentage of positive PCR tests remained stable over the first 20 days following vaccination, but decreased from 21 days onwards regardless of having received one or two doses (**Supplementary Figure 2**). Adjusting for multiple potential confounders, the odds of a new PCR-positive, with or without symptoms, were reduced by 55% (95% CI 49 to 60%) in those 8 to 20 days after vaccination versus those not vaccinated or previously PCR/antibody-positive and ≥21 days before vaccination, with no evidence of a difference versus those vaccinated 0 to 7 days ago (P=0.204). Odds were reduced 65% (95% CI 60 to 70%; P<0.001) in those ≥21 days since first vaccination with no second dose, significantly more than those vaccinated 8 to 20 days ago (P=0.004) (**Figure 3A, Supplementary Table 5;** coefficients for all factors in **Supplementary Table 6**). Odds of testing positive were reduced 72% (95% CI 69 to 74%) 1 to 21 days before first vaccination and 62% (57 to 67%) 0 to 8 days post vaccination versus those not vaccinated or previously PCR/antibody-positive and ≥21 days before vaccination.

In those vaccinated, the largest reduction in odds was seen in those post second vaccine dose (70%, 95% CI 62 to 77%; P<0.001); however, there was no evidence this differed compared with having received only one dose ≥21 days previously (P=0.889). There was no evidence that reductions in

odds of testing positive differed between having received two vaccine doses and not being vaccinated but previously PCR/antibody-positive (P=1.00) (**Supplementary Table 5**).

The benefits associated with vaccination were much greater for infection episodes with Ct<30 as evidence of high levels of viral shedding compared with Ct≥30 (**Figure 3B**), with a 88% reduction (95% CI 80 to 93%; P<0.001) in odds of testing positive with Ct<30 post-second dose, a marginally greater reduction compared with one dose ≥21 days ago (P=0.050) and with no evidence of difference versus those not vaccinated but previously PCR/antibody-positive (P=1.00). Similarly, benefits associated with vaccination were much greater for self-reported symptomatic infection episodes (**Figure 3C**), with an 90% reduction (95% CI 82 to 94%; P<0.001) in odds of testing positive post-second dose with self-reported symptoms, significantly greater than with one dose ≥21 days ago (P=0.012) (**Supplementary Table 5**), but again without evidence of difference versus those not vaccinated but previously PCR/antibody-positive (P=0.992). In comparison, the reduction in odds of new infection episodes with no self-reported symptoms was 49% (95% CI 31 to 62%; P<0.001) post-second dose. Whilst overlapping, positives with Ct<30 also differed to positives reporting symptoms e.g. 4377 (35%) of all positives had Ct <30 and symptoms reported, and 2,332 (19%) had Ct<30 and no symptoms reported (**Supplementary Table 4**). Effects of vaccination on infections compatible and incompatible with the B.1.1.7 variant appeared similar, but small numbers of positives in the latter group led to large uncertainty in estimates (**Figure 3D; Supplementary Table 5**).

Impact of vaccination type on new infections

There was no evidence that reductions in odds of new infections differed between the Pfizer-BioNTech and Oxford-AstraZeneca vaccine (**Figure 4A; Supplementary Table 7**) whether the vaccine was received 0 to 7 days ago (P=0.965), 8 to 20 days ago (P=1.00), or ≥21 days ago (P=0.998 for Pfizer-BioNTech ≥21 days ago, one dose only, vs Oxford-AstraZeneca ≥21 days ago, one or two doses). There was also no evidence that reductions in odds of new infections differed between those post second Pfizer dose and those not vaccinated but previously PCR/antibody-positive (P=1.00). Effects were similar considering infections with Ct<30 and ≥30 (**Figure 4B**), and with and without self-reported symptoms (**Figure 4C**), with the impact of both vaccines attenuated for infections with Ct≥30 and without self-reported symptoms.

Impact of age on reductions in new infections post vaccination

There was evidence of differences in the effect of vaccination on new infection between those aged under or over 75 years (global heterogeneity for all vaccination terms P=0.014), with the reduction in odds of new infections post-vaccination being slightly greater in those aged ≥75 (**Figure 6A**). The greatest numeric difference was in those ≥21 days since first vaccination with no second dose, where reductions in odds were 76% in those aged ≥75 (95% CI 68% to 82% reduction) and 62% in those <75 (95% CI 56 to 67%) (interaction P=0.002). There was no evidence of differences in the effect of vaccination on new infection between those reporting or not reporting long-term health conditions (global heterogeneity for all vaccination terms P=0.840).

Discussion

Principal findings

The results from this large community surveillance study show that vaccination against COVID-19 significantly reduced the odds of individuals testing PCR-positive with a new SARS-CoV-2 infection, with greatest reductions in new infections with Ct<30 and self-reported symptoms, and in those who had received 2 vaccine doses. Reductions afforded by vaccination were similar to those provided by natural immunity. The protective effect of vaccination was attenuated in infections with Ct≥30 and without self-reported symptoms. There was no evidence of any difference in effectiveness between Pfizer-BioNTech and Oxford-AstraZeneca vaccines, or in those with long-term health conditions. We observed greater reductions in new infections in those aged ≥75 years versus those under 75.

Strengths and weaknesses of the study

The main study strength is its design as a large-scale community survey recruiting from randomly selected private residential households, providing a representative sample of the UK general population. Participants are tested regardless of symptoms, allowing us to additionally consider vaccine effectiveness against infection without reported symptoms. The availability of Ct values allowed us to compare vaccine impact on viral loads, using Ct as a proxy[30]. Scheduled visits provide an unbiased sampling frame which we exploited for our logistic regression, rather than having to censor individuals at last tests in the study using time-to-event analyses, and assume all infections between visits were identified. Participants were asked about demographics, behaviours, and work, allowing us to control for a wide range of potential confounders that are unavailable in record linkage studies performed to date.[15]

The design also has limitations, particularly with individuals tested initially at weekly and then monthly visits. Any positive episodes occurring between visits will be missed, leading to contamination of the "not vaccinated, no previous PCR/antibody-positive" groups, possibly diluting the effect of vaccination. Because participants can only test positive at scheduled visits, some of the "new" positives episodes may in fact have occurred sometime previously; we therefore stratified time from vaccination to reduce the impact of this. Older infections would be expected to have a higher Ct values, so this may also partly explain the differences between positives with Ct<30 and ≥30, at least shortly after vaccination. Imperfect sensitivity of SARS-CoV-2 PCR tests may bias absolute risk, but would result in unbiased relative risk provided that misclassification is non-differential to vaccination status and all non-cases are correctly classified (i.e. 100% specificity). PCR test specificity is likely very high[12 18], and therefore any bias here is expected to be small. Due to relatively small numbers of infections post-vaccination, power to detect differences between vaccine types and differential vaccine effectiveness in subgroups was relatively low.

An important potential issue with observational studies evaluating vaccine effectiveness is that individuals are not supposed to be vaccinated if they recently tested positive, and individuals may reduce their number of contacts in response to the knowledge that they will soon receive a vaccination. Interestingly, we found that 613 individuals tested positive 1 to 21 days before receiving their vaccination – due to the design and logistics of the survey they may have received their test results after the date of vaccination – suggesting that ensuring social distancing at vaccination locations remains important. The reduced risk observed in the 21 days prior and 0-7 days after vaccination is likely due to this reverse causality, specifically changes in behaviour due to either receiving the vaccination invitation letter or knowledge that individuals from their age or risk group are about to get vaccinated in their area, rather than a biological effect. Because a reduction in contacts in the week before vaccination will also reduce the likelihood of testing positive in the

following week, it will be important for future studies trying to evaluate the effectiveness of vaccination to carefully construct the appropriate comparator. Here we used study visits from those that are not vaccinated, not previously positive, ≥21 days before vaccination as comparator to overcome these issues when estimated the impact of the vaccination itself.

Comparison with other studies

Our estimated effect of two vaccine doses on symptomatic infections is similar to other studies which have considered this outcome[9 14-16,17], but is slightly lower than that reported in the key Phase III clinical trials[7 8]. The clinical trials had a more intensive testing schedule, whereas we may have missed some infections due to monthly testing in the majority of participants. Another explanation could be differences with our general population sample, in particular our vaccinated participants being, on average, older due to their prioritisation in the UK's vaccine rollout[4], combined with decreased immunological competence (immunosenescence) in an older population[31] (although we did not identify any loss of benefit in older individuals in subgroup analyses). Higher Ct in infections identified post vaccination has also been demonstrated in older adults in care homes[17]. Our estimated effectiveness is also slightly lower than studies in healthcare workers[9 16]; these studies had antibody tests in the majority of participants so were likely able to identify previous infection more accurately, avoiding misclassification in our control "not vaccinated, no previous PCR/antibody-positive" group. Our estimated reduction in risk of infection for those not vaccinated but previously PCR/antibody positive was slightly lower than the ~80% (95% CI 75.4 to 84.5%) estimated elsewhere[32].

Consistent with two recent studies[9,13], we found vaccination to be as effective against the B.1.1.7 variant as non-B.1.1.7 variants. Our study supports this in a broader population, including positives from individuals not reporting symptoms and for the Pfizer-BioNTech vaccine in addition to the Oxford-AstraZeneca vaccine. Our study had good power to estimate vaccine effectiveness against the B.1.1.7 variant as it was conducted over the period when B.1.1.7 became dominant in the UK. This is particularly relevant as the variant has now been detected in over 40 countries worldwide[33 34], and the major Phase III vaccine trials were conducted before this strain was dominant[7 8]. We observed a slightly greater reduction in new infection episodes in those vaccinated and aged ≥75 years, compared with those <75 years, potentially due to the combination of vaccination with reduced social contact in the former group. We currently do not have evidence of the vaccine being less effective in older individuals as seen elsewhere with natural re-infections[32], although would note that, as described above, vaccine effectiveness also includes a non-biological behavioural component and there may be compensation for lower biological activity in older individuals with lower behavioural risk.

Explanations and implications

Similar to other studies[7 9 16], we found greater reductions in new positives after two vaccine doses compared with one dose, particularly in reducing infections with self-reported symptoms and low Ct/high viral load. In the UK, the interval between vaccine doses was extended to 12 weeks to maximise initial coverage and reduce hospitalisations/deaths; our findings highlight the importance for increased protection of individuals getting the second vaccine dose. Nonetheless, the significant reduction in positivity after only one dose supports the decision to maximise initial vaccination coverage.

While some infections, particularly those with Ct≥30, could represent historical infections contracted prior to vaccination, given the timescales and prior negatives post vaccination, some will

undoubtedly reflect new infections after vaccination. Together with other evidence, this suggests that vaccination does not completely prevent infection following virus exposure, yet minimises progression to more severe infection[14]. The fact that vaccinated individuals can still be infected, even if predominantly with lower viral burden/asymptomatic infections, means that onwards transmission remains a possibility, albeit at lower efficiency[35]. Maintaining measures such a social distancing may therefore still be needed to control virus spread until enough of the population is vaccinated.

We have also shown two vaccine doses to be as effective as prior natural infection. This could be an important consideration during policy development over COVID-status certification or "COVID passports", and supports considering both prior PCR/serological testing and vaccination data for this[36].

Unanswered questions and future research

Looking forward, one key question will be whether immunisation offers long-term protection against COVID-19. A recent study showed the rate of waning and longevity of neutralising antibodies varies greatly amongst individuals with prior COVID-19 infection and suggested that, if similar rates of waning are seen after vaccination, annual vaccine administration is likely needed[37].

Overall, we have shown COVID-19 vaccination to be effective in reducing the number of new SARS-CoV2 infections, with the greatest benefit received after two vaccinations, and against symptomatic and high viral burden infections, and no difference between the Pfizer-BioNTech and Oxford-AstraZeneca vaccine.

Summary box:

What is already known on this topic

- Large randomised trials have shown high efficacy of Oxford-AstraZeneca and Pfizer-BioNTech vaccines against symptomatic laboratory-confirmed SARS-CoV-2 infection
- The effectiveness of these vaccines in the real world against any SARS-CoV-2 infection, including those without symptoms is less clear, especially among the elderly that were underrepresented in the Oxford-AstraZeneca trial

What this study adds

- SARS-CoV-2 infections fall substantially after a first dose of either vaccine; two doses of the Pfizer-BioNTech vaccine provided even greater protection, to a similar degree as previous infection with SARS-CoV2
- Vaccination and previous infection were most effective at reducing symptomatic infections, and infections with high viral burden, with lower reductions in infections not causing symptoms and with lower viral burden.
- Both vaccines appear to be highly effective against infections compatible with B.1.1.7

Contributors: The study was designed and planned by ASW, JF, JB, JN, IB, ID and KBP and is being conducted by ASW, IB, RS and ER. This specific analysis was designed by ASW, KBP, PCM, NS, DWE, TH, DC, TEAP, K-DV, and EP. EP, KBP, OG, and JJ contributed to the statistical analysis of the survey data. HVS conducted analysis of the RT-PCR data. EP, ASW and KBP drafted the manuscript. All authors contributed to interpretation of the study results, and revised and approved the manuscript for intellectual content. KBP and ASW are the guarantors and accept full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author (KBP) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure from at www.icmje.org/coi_disclore.pdf and declare: DWE declares lecture fees from Gilead, outside the submitted work; EP, PCM, NS, DWE, JIB, DC, TEAP, ASW, and KBP are employees of the University of Oxford, but not involved in the development or production of the vaccine; JIB act as an unpaid advisor to HMG on Covid but does not sit on the vaccine task force and it not involved in procurement decisions, sits on the Board of OSI who has an investment in Vaccitech who have a royalty from the Oxford-AstraZeneca vaccine when, if ever, it makes a profit; HVS reports personal fees from BioSpyder Technologies, Inc, outside the submitted work; ASW besides funding mentioned above, also received grants from Medical Research Council UK during the conduct of the study; there are no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study received ethical approval from the South Central Berkshire B Research Ethics Committee (20/SC/0195).

Data sharing: Data are still being collected for the COVID-19 Infection Survey. De-identified study data are available for access by accredited researchers in the ONS Secure Research Service (SRS) for accredited research purposes under part 5, chapter 5 of the Digital Economy Act 2017. For further information about accreditation, contact Research.Support@ons.gov.uk or visit the SRS website.

Transparency The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study design being reported, no important aspects of the study have been omitted, and any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Results of individual tests were communicated to the participants. Overall study results were disseminated through the preprint of the study. Findings were disseminated in lay language in the national and local press.

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REFERENCES

1. Medicines and Healthcare Products Regulatory Agency. Vaccine BNT162b2: conditions of authorisation under Regulation 174 2020, 2020. https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/conditions-of-authorisation-for-pfizerbiontech-covid-19-vaccine#vaccine-bnt162b2--conditions-of-authorisation-under-regulation-174--2-december-2020-amended-on-30-december-2020-28-january-2021-and-30-march-2021
2. Medicines and Healthcare products Regulatory Agency. Regulatory approval of COVID-19 Vaccine AstraZeneca, 2020. https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca
3. Medicines and Healthcare products Regulatory Agency. Regulatory approval of COVID-19 Vaccine Moderna, 2021. https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna
4. Joint Committee on Vaccination and Immunisation. Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination, 30 December 2020. https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020/joint-committee-on-vaccination-and-immunisation-advice-on-priority-groups-for-covid-19-vaccination-30-december-2020
5. Public Health England. Vaccinations in United Kingdom 2021 [Available from: https://coronavirus.data.gov.uk/details/vaccinations.
6. Saad-Roy CM, Morris SE, Metcalf CJE, et al. Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes. *Science* 2021 doi: 10.1126/science.abg8663
7. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020;383(27):2603-15. doi: 10.1056/NEJMoa2034577
8. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397(10269):99-111. doi: 10.1016/s0140-6736(20)32661-1
9. Lumley SF, Rodger G, Constantinides B, et al. An observational cohort study on the incidence of SARS-CoV-2 infection and B. 1.1. 7 variant infection in healthcare workers by antibody and vaccination status. medRxiv, 2021. https://www.medrxiv.org/content/10.1101/2021.03.09.21253218v1
10. Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science* 2021 doi: 10.1126/science.abg3055
11. Davies NG, Jarvis CI, Edmunds WJ, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. *Nature* 2021 doi: 10.1038/s41586-021-03426-1
12. Walker AS, Vihta KD, Gethings O, et al. Increased infections, but not viral burden, with a new SARS-CoV-2 variant. medRxiv, 2021. https://www.medrxiv.org/content/10.1101/2021.01.13.21249721v1
13. Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *The Lancet* 2021 doi: https://doi.org/10.1016/S0140-6736(21)00628-0
14. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med* 2021 doi: 10.1056/NEJMoa2101765
15. Bernal JL, Andrews N, Gower C, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. MedRxiv, 2021. https://www.medrxiv.org/content/10.1101/2021.03.01.21252652v1
16. Centers for Disease Control and Prevention. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among

Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021. MMWR Morb Mortal Wkly Rep 2021;70:495-500.
17. Shrotri M, Krutikov M, Palmer T, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of Long-Term Care Facilities (VIVALDI study). *MedrXiv* 2021;https://doi.org/10.1101/2021.03.26.21254391
18. Pouwels KB, House T, Pritchard E, et al. Community prevalence of SARS-CoV-2 in England from April to November, 2020: results from the ONS Coronavirus Infection Survey. *Lancet Public Health* 2021;6(1):e30-e38. doi: 10.1016/s2468-2667(20)30282-6
19. National SARS-CoV-2 Serology Assay Evaluation Group. Performance characteristics of five immunoassays for SARS-CoV-2: a head-to-head benchmark comparison. *Lancet Infect Dis* 2020;20(12):1390-400. doi: 10.1016/s1473-3099(20)30634-4
20. Pan American Health Organisation. Interim guidelines for detecting cases of reinfection by SARS-CoV-2, 2020. https://www.paho.org/en/documents/interim-guidelines-detecting-cases-reinfection-sars-cov-2
21. Public Health England. Investigation of novel SARS-CoV-2 variants of concern, 2020. https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201
22. Ministry of Housing CLG. English indices of deprivation 2019, 2019. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019
23. Statistics for Wales. Welsh Index of Multiple Deprivation (full Index update with ranks): 2019, 2019. https://gov.wales/welsh-index-multiple-deprivation-full-index-update-ranks-2019
24. Scottish Government. Scottish Index of Multiple Deprivation 2020, 2020. https://www.gov.scot/collections/scottish-index-of-multiple-deprivation-2020/
25. Northern Ireland Statistics and Research Agency. Northern Ireland Multiple Deprivation Measure 2017 (NIMDM2017), 2017. https://www.nisra.gov.uk/statistics/deprivation/northern-ireland-multiple-deprivation-measure-2017-nimdm2017
26. Northern Ireland Statistics and Research Agency. Urban- Rural Geography Documents (2015), 2017. https://www.nisra.gov.uk/support/geography/urban-rural-classification
27. Department for Environment FRA. Rural Urban Classification, 2016. https://www.gov.uk/government/collections/rural-urban-classification
28. Scottish Government. Scottish Government Urban Rural Classification 2016, 2018. https://www.gov.scot/publications/scottish-government-urban-rural-classification-2016/pages/2/
29. Harrell Jr FE. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis: Springer 2015.
30. Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Euro Surveill* 2020;25(32) doi: 10.2807/1560-7917.Es.2020.25.32.2001483
31. Cox LS, Bellantuono I, Lord JM, et al. Tackling immunosenescence to improve COVID-19 outcomes and vaccine response in older adults. *Lancet Healthy Longev* 2020;1(2):e55-e57. doi: 10.1016/s2666-7568(20)30011-8
32. Hansen CH, Michlmayr D, Gubbels SM, et al. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet* 2021;397(10280):1204-12. doi: 10.1016/s0140-6736(21)00575-4
33. Global report investigating novel coronavirus haplotypes. B.1.1.7, 2021.
34. Chaillon A, Smith DM. Phylogenetic analyses of SARS-CoV-2 B.1.1.7 lineage suggest a single origin followed by multiple exportation events versus convergent evolution. *Clin Infect Dis* 2021 doi: 10.1093/cid/ciab265
35. Lee LYW, Rozmanowski S, Pang M, et al. An observational study of SARS-CoV-2 infectivity by viral load and demographic factors and the utility lateral flow devices to prevent transmission.

http://modmedmicro.nsms.ox.ac.uk/wp-content/uploads/2021/01/infectivity_manuscript_20210119_merged.pdf
36. Cabinet Office. Government asks for views on Covid-19 certification, 2021. https://www.gov.uk/government/news/government-asks-for-views-on-covid-19-certification
37. Chia WN, Zhu F, Ong SWX, et al. Dynamics of SARS-CoV-2 neutralising antibody responses and duration of immunity: a longitudinal study. *Lancet Microbe* 2021 doi: 10.1016/s2666-5247(21)00025-2

Figure 1: Distribution of Ct values of new positive episodes by vaccination status. Numbers to the right of violins show number of positive episodes in each. Boxplot inside violin shows the median, and upper and lower quartiles of the distribution. Values given in **Supplementary Table 4**.

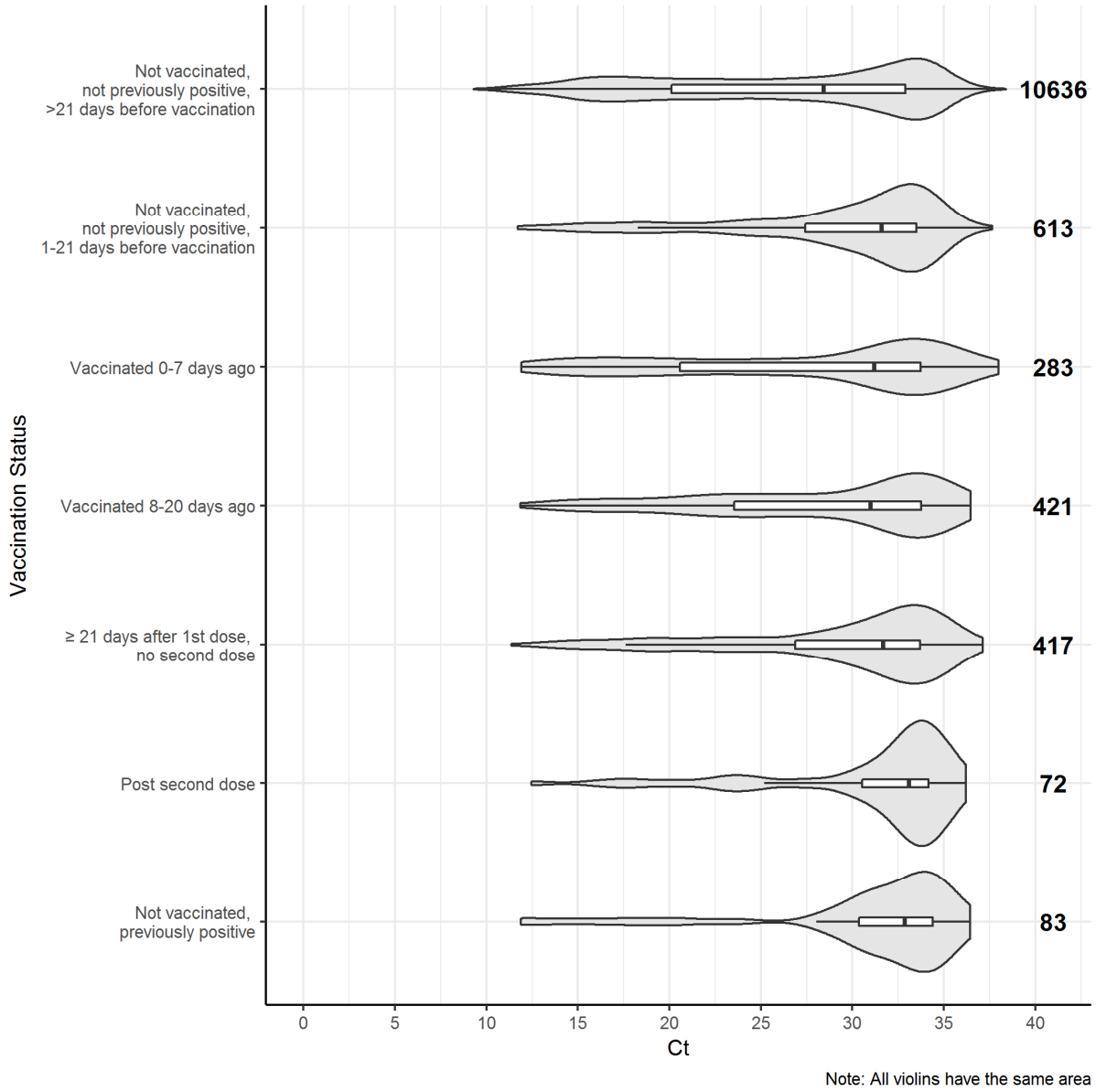


Figure 2: Percentage of symptoms in new positive episodes by vaccination status. Values given in **Supplementary Table 4**.

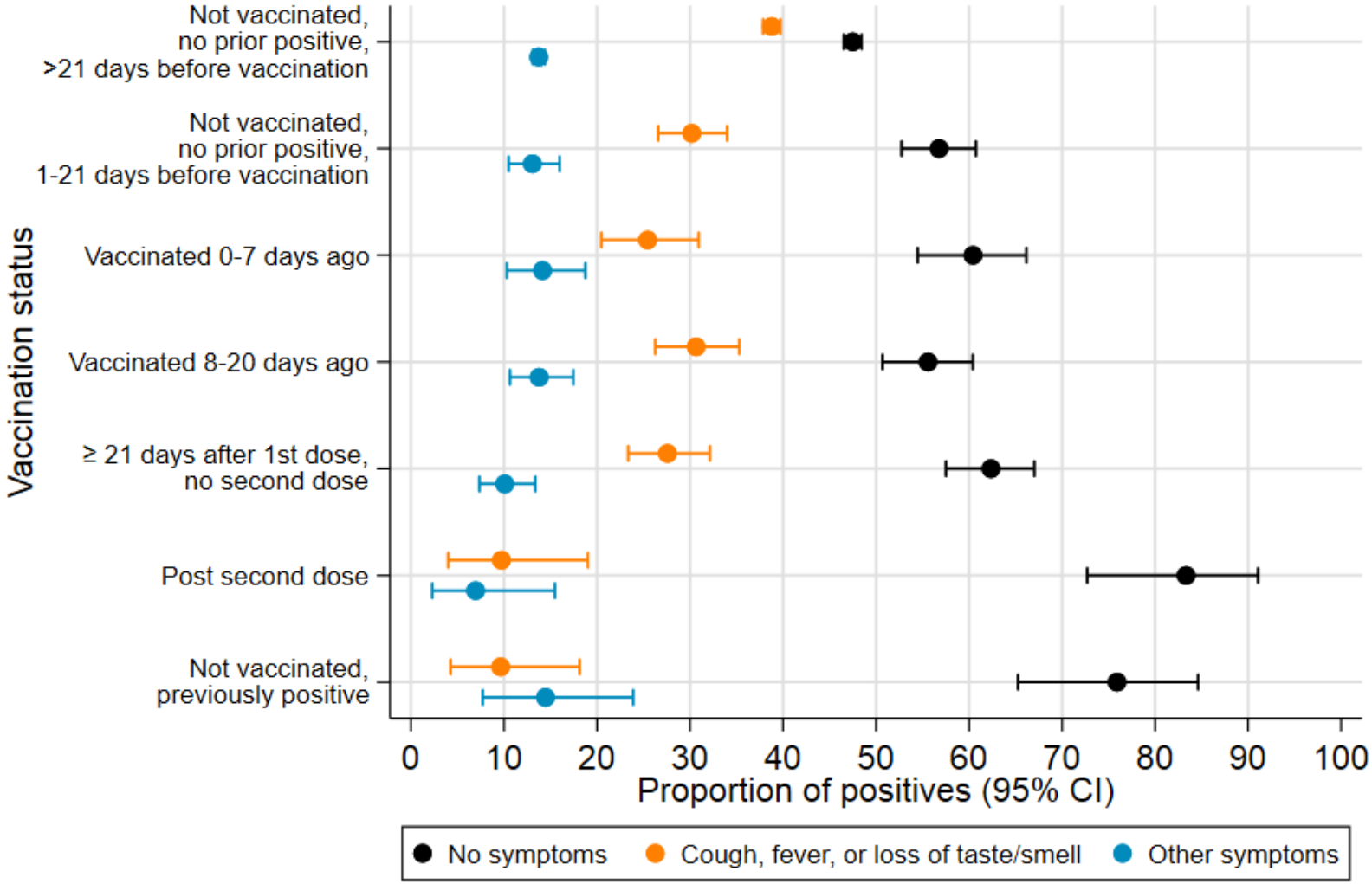
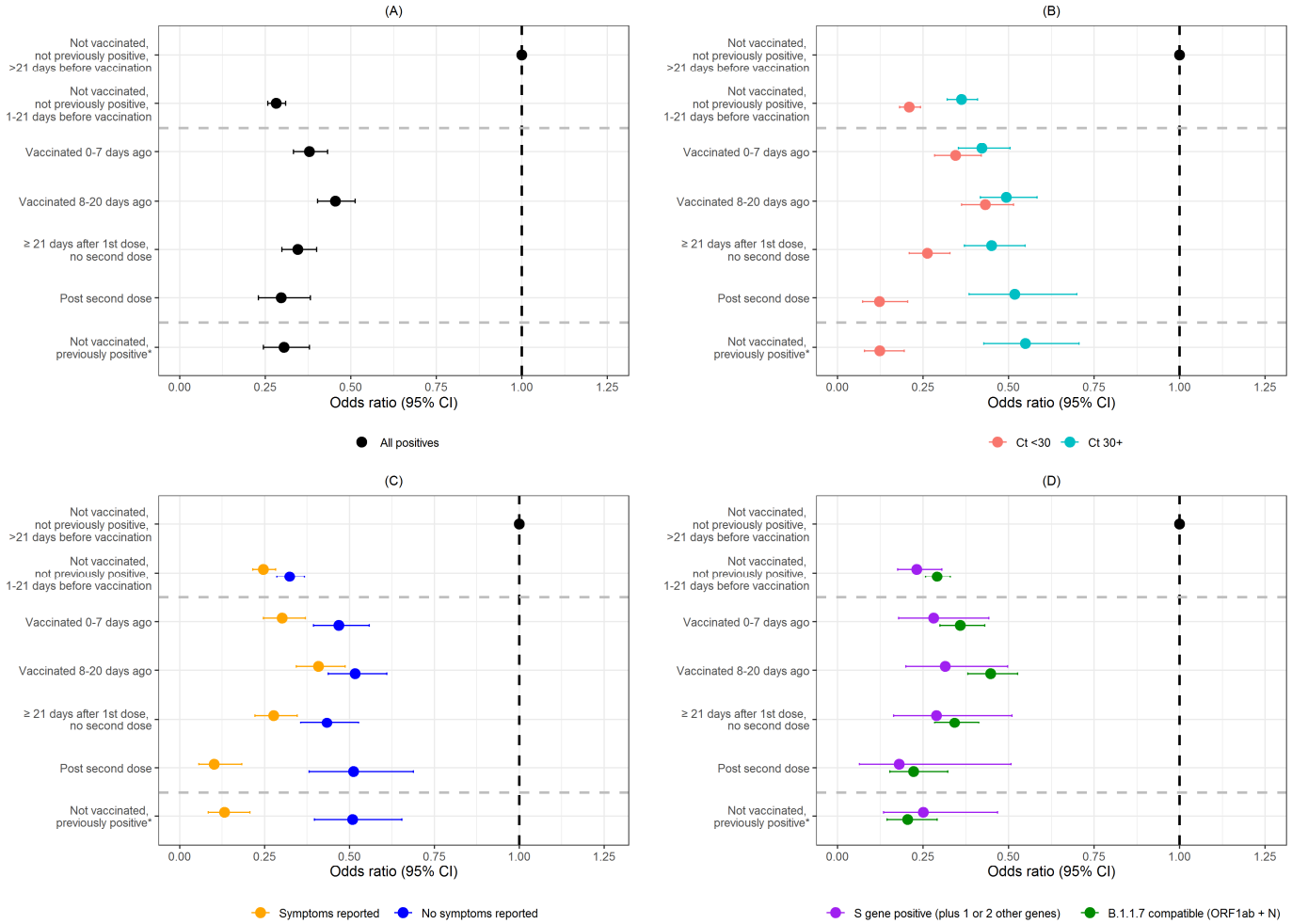
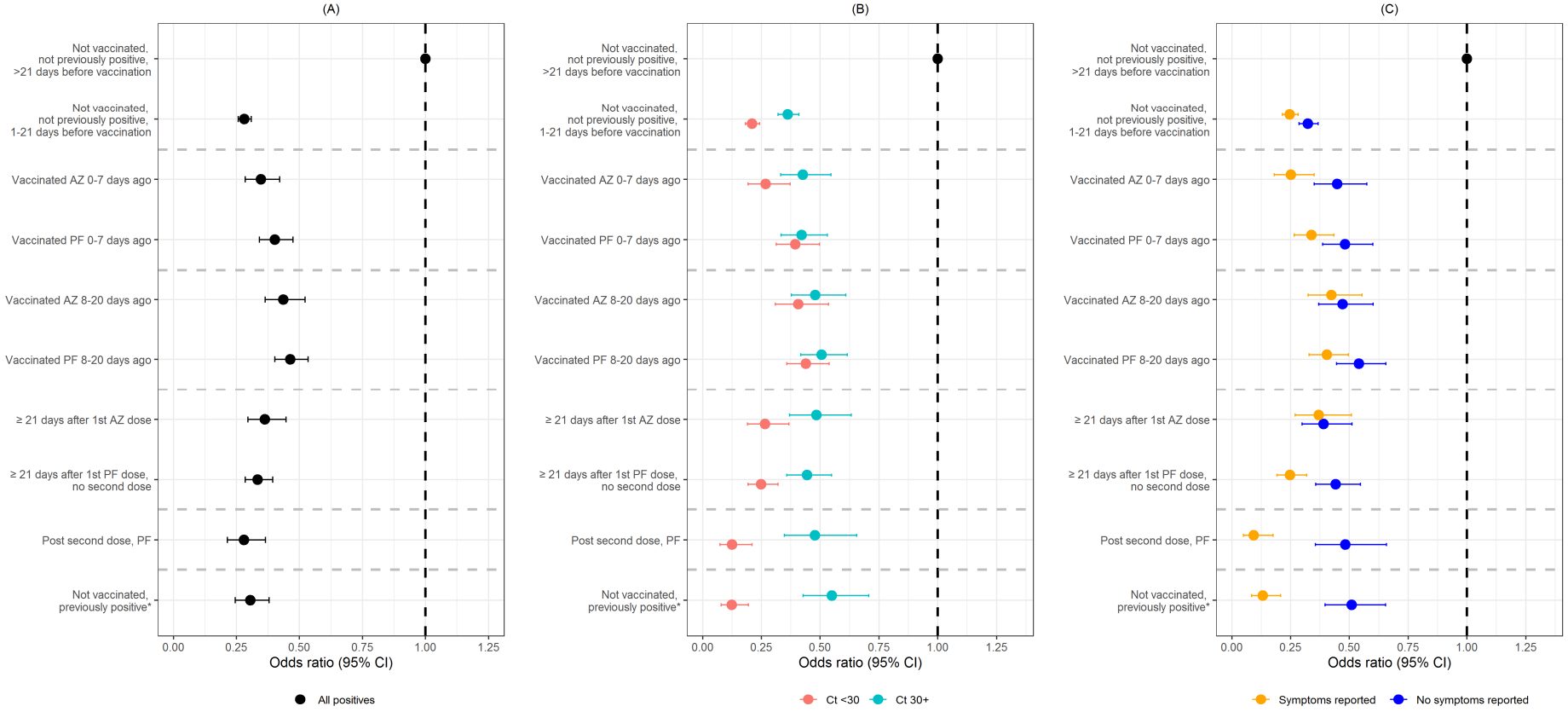


Figure 3: Adjusted odds ratios (95% CIs) for the effect of vaccination and prior positivity on: all positives (A), and positives split by Ct<30 or ≥30 (B), self-reported symptoms (C), and gene positivity pattern (D). All odds ratios are compared to the reference category of "Not vaccinated, not previously positive and ≥21 days before vaccination"



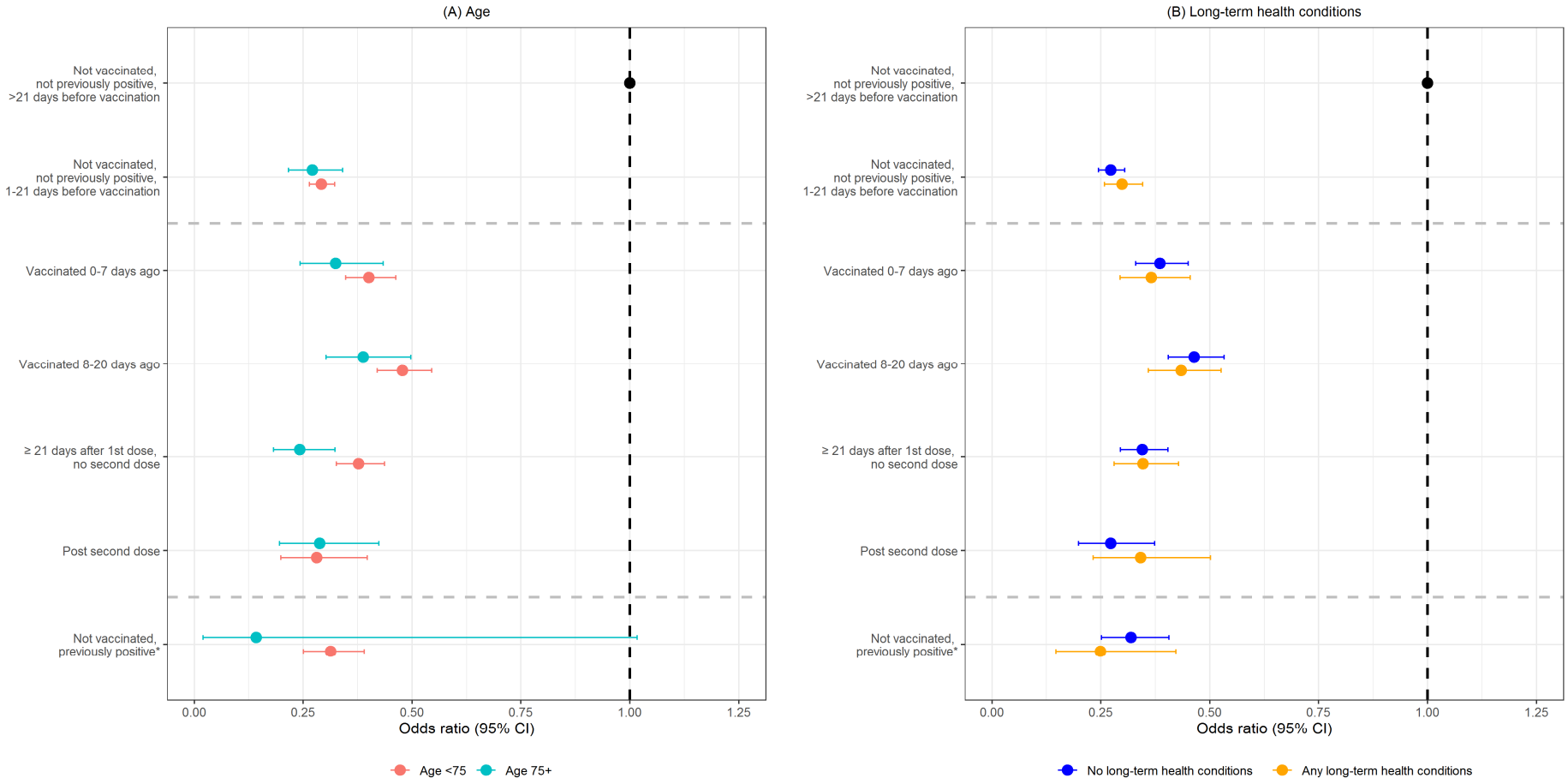
* Not vaccinated, but with a positive antibody result in the study >45 days previously or a previous positive episode in the study
Note: Odds ratios given in **Supplementary Table 5**.

Figure 4: Adjusted odds ratios (95% CIs) for the effect of vaccination split by vaccine type and prior positivity on: all positives (A), and positives split by Ct<30 or ≥30 (B), self-reported symptoms (C). All odds ratios are compared to the reference category of "Not vaccinated, not previously positive and ≥21 days before vaccination"



* Not vaccinated, but with a positive antibody result in the study >45 days previously or a previous positive episode in the study
Note: Odds ratios given in **Supplementary Table 7**.

Figure 5: Adjusted odds ratios (95% CIs) for the effect of vaccination split by age <75 or 75+ (A) and long-term health conditions (B) on all positives. All odds ratios are compared to the reference category of "Not vaccinated, not previously positive and ≥21 days before vaccination"



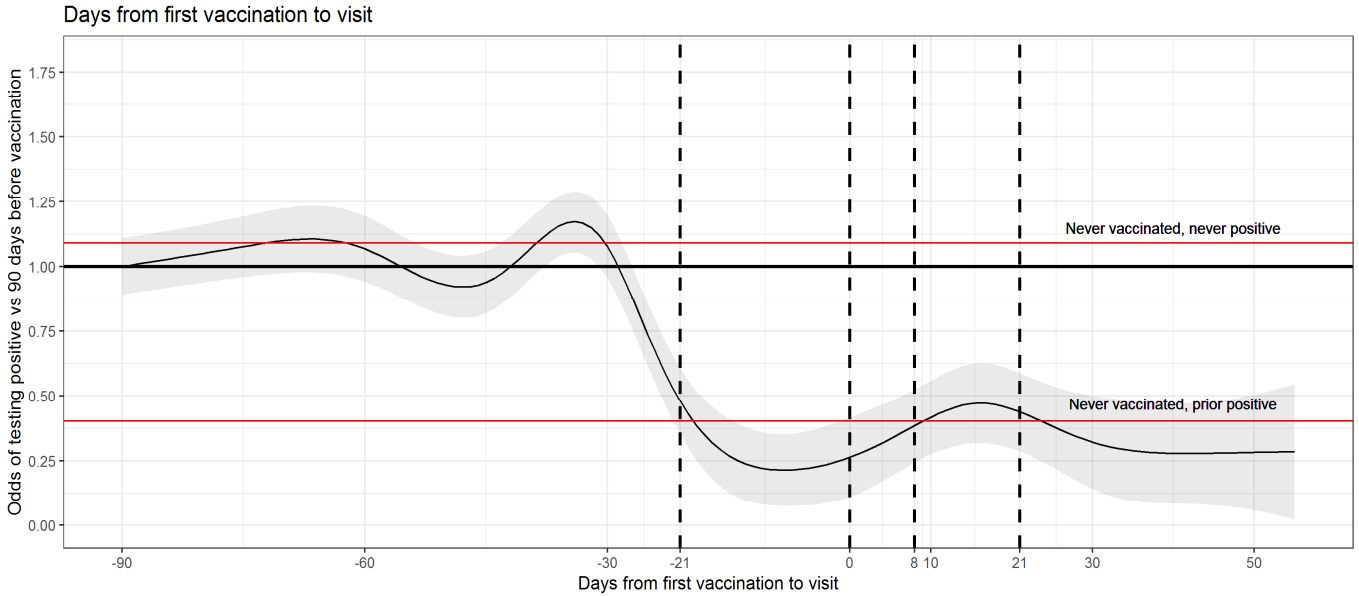
* Not vaccinated, but with a positive antibody result in the study >45 days previously or a previous positive episode in the study

Note: Heterogeneity p-values for vaccination categories: Age p-value = 0.014, long-term health conditions p-value = 0.84

Supplementary Material

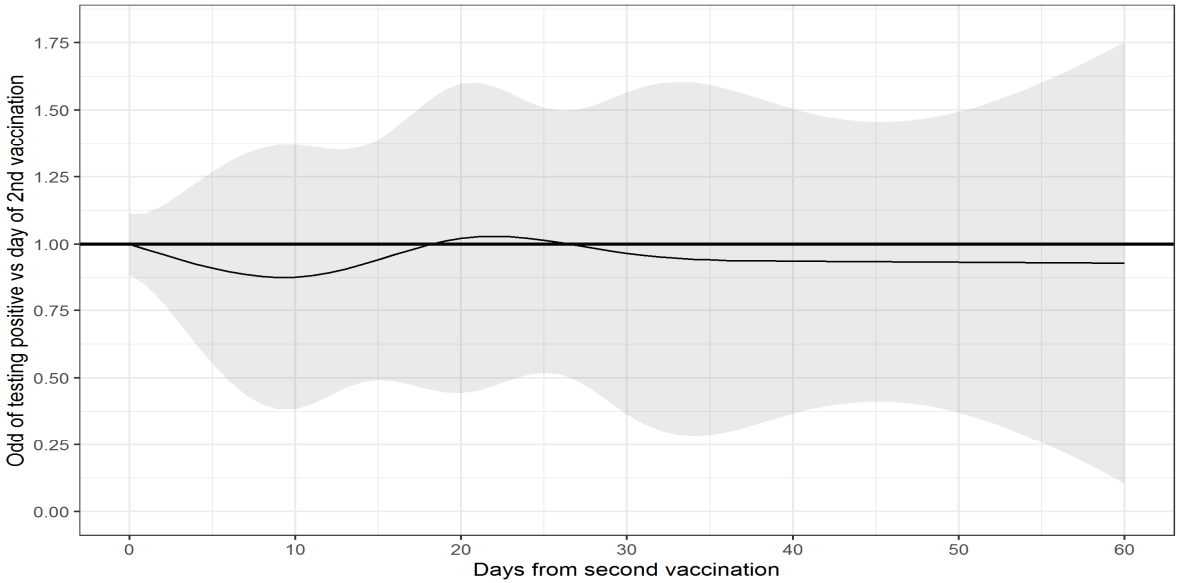
Supplementary Figure 1: Estimated effect of days since from vaccination on odds of testing positive on a continuous scale

(A) Days from first vaccination to visit

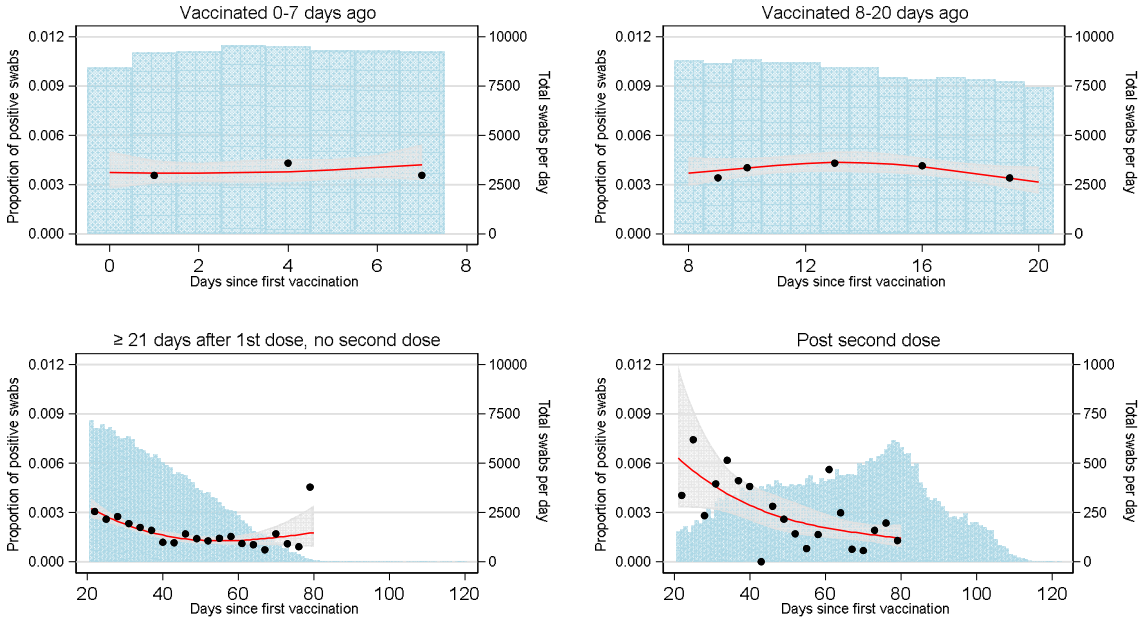


Note: arbitrarily categorised in main analysis at dashed lines as shown.

(B) Days from second vaccination to visit



Supplementary Figure 2: Observed proportion of positives and numbers of visits over days from vaccination



Note: observed proportion of positives grouped over every 3 days since vaccination (black dots) with fit of restricted natural cubic spline (fit to each study day) with 3 knots at the 10th,50th and 90th percentile of the unique values of study day (red line) and 95% confidence intervals. Number of individuals on each vaccination day (denominator of the proportions) is shown by the blue bars

Supplementary Table 1: Characteristics of visits included in analysis

Characteristic [number missing]	Negative, n (%) or median (IQR)	Positive, n (%) or median (IQR)	Total, n (%) or median (IQR)
Female [0]	855557 (54)	6739 (54)	862296 (54)
White ethnicity [0]	1495987 (94)	11308 (90)	1507295 (94)
Age [0]	55 (40, 68)	49 (35, 61)	55 (40, 68)
Region [0]			
London	286273 (18)	3240 (26)	289513 (18)
North_West_England	174907 (11)	1545 (12)	176452 (11)
North_East_England	55224 (3)	463 (4)	55687 (3)
Yorkshire	121570 (8)	796 (6)	122366 (8)
West_Midlands	109536 (7)	851 (7)	110387 (7)
East_Midlands	94210 (6)	726 (6)	94936 (6)
South_East_England	194479 (12)	1477 (12)	195956 (12)
South_West_England	122743 (8)	601 (5)	123344 (8)
East_England	152881 (10)	1238 (10)	154119 (10)
Northern_Ireland	50223 (3)	353 (3)	50576 (3)
Scotland	150824 (9)	712 (6)	151536 (9)
Wales	85167 (5)	523 (4)	85690 (5)
Household size group [0]			
One	299678 (19)	1974 (16)	301652 (19)
Two	755152 (47)	4974 (40)	760126 (47)
Three	250638 (16)	2366 (19)	253004 (16)
Four	207042 (13)	2229 (18)	209271 (13)
Five_plus	85527 (5)	982 (8)	86509 (5)
Multigenerational households [0]	77956 (5)	782 (6)	78738 (5)
Rural-urban classification [0]			
major_urban	568812 (36)	5638 (45)	574450 (36)
urban_city_town	672738 (42)	4858 (39)	677596 (42)
rural_town	173257 (11)	1070 (9)	174327 (11)
rural_village	183230 (11)	959 (8)	184189 (11)
IMD [0]	6 (3, 8)	5 (3, 8)	6 (3, 8)
ever_care_home_worker [0]	17814 (1)	247 (2)	18061 (1)
ever_patientfacing_hcw [0]	61015 (4)	759 (6)	61774 (4)
ever_personfacing_socialcare [0]	18306 (1)	217 (2)	18523 (1)
ever_lthc [0]	424662 (27)	2873 (23)	427535 (27)
Visit frequency [0]			
>14 days	1180787 (74)	9583 (77)	1190370 (74)
<=14 days	336544 (21)	1887 (15)	338431 (21)
Enrolment	80706 (5)	1055 (8)	81761 (5)
Smoking status [0]			
Non-smoker	1445978 (90)	11383 (91)	1457361 (90)
Tobacco smoker	117345 (7)	824 (7)	118169 (7)
Only vape	34714 (2)	318 (3)	35032 (2)
Contact hospital [6930]			
No	1244932 (78)	9374 (75)	1254306 (78)
Yes, I have	215278 (13)	1952 (16)	217230 (13)
No, but someone in HH	130953 (8)	1143 (9)	132096 (8)
Contact carehome [9710]			

Characteristic [number missing]	Negative, n (%) or median (IQR)	Positive, n (%) or median (IQR)	Total, n (%) or median (IQR)
No	1537731 (96)	11849 (95)	1549580 (96)
Yes, I have	29899 (2)	353 (3)	30252 (2)
No, but someone in HH	20779 (1)	241 (2)	21020 (1)
Work location/ distancing [5890]			
Working from home	405151 (25)	3169 (25)	408320 (25)
Elsewhere, easy to maintain 2m	168400 (11)	1372 (11)	169772 (11)
Elsewhere, relatively easy to maintain 2m	76038 (5)	793 (6)	76831 (5)
Elsewhere, difficult to maintain 2m	60043 (4)	683 (5)	60726 (4)
Elsewhere, very difficult to maintain 1m	101385 (6)	1273 (10)	102658 (6)
Furloughed	66153 (4)	914 (7)	67067 (4)
Unemployed	101045 (6)	887 (7)	101932 (6)
Student	63369 (4)	629 (5)	63998 (4)
Retired	550596 (34)	2772 (22)	553368 (34)
Work travel [5931]			
Not travelling to work	940183 (59)	5917 (47)	946100 (59)
On foot/bike	125077 (8)	1123 (9)	126200 (8)
Car/taxi	444083 (28)	4534 (36)	448617 (28)
Train/bus	63531 (4)	767 (6)	64298 (4)
Other	19262 (1)	154 (1)	19416 (1)

Supplementary Table 2: Populations included in the models.

Model	Positive swabs, n (%*)	Negative swabs, n (%*)	Total, n (%*)
Outcome: All positives	12,406 (99)	1,582,078 (99)	1,594,484 (99)
Outcome: Positives based on Ct values			
Ct <30	6,656 (99)	1,587,828 (99)	1,594,484 (99)
Ct 30+	5,750 (99)	1,587,828 (99)	1,594,484 (99)
Outcome: Positives based on symptoms			
Core	6,287 (99)	1,588,197 (99)	1,594,484 (99)
Adjusted	6,119 (99)	1,588,197 (99)	1,594,484 (99)
Outcome: Positives based on Ct pattern			
OR+N+S, OR+S, or N+S	1,926 (99)	1,592,558 (99)	1,594,484 (99)
OR+N	6,543 (99)	1,587,941 (99)	1,594,484 (99)

*Percentage of swabs with complete data for all variables included in model (complete cases)

Supplementary Table 3: Vaccination status at visits by previous swab or antibody positivity >45 days previously

Vaccination Status	No prior study swab or antibody positive >45 days ago	Prior swab or antibody positive >45 days ago	Total
Not vaccinated, no prior positive, >21 days before vaccination	992152 (100) [10636]	0 (0) [0]	992152 (100) [10636]
Not vaccinated, no prior positive, 1-21 days before vaccination	166895 (100) [613]	0 (0) [0]	166895 (100) [613]
Vaccinated 0-7 days ago	71582 (97) [276]	2155 (3) [7]	73737 (100) [283]
Vaccinated 8-20 days ago	103680 (97) [414]	3528 (3) [7]	107208 (100) [421]
≥21 days after 1st dose, no second dose	206676 (96) [406]	8296 (4) [11]	214972 (100) [417]
Post second dose	28870 (94) [66]	1857 (6) [6]	30727 (100) [72]
Not vaccinated, previously positive	0 (0) [0]	24871 (100) [83]	24871 (100) [83]

Supplementary Table 4: Characteristics of new positives by vaccination status

	Vaccination Status							
	Not vaccinated, no prior positive, >21 days before vaccination	Not vaccinated, no prior positive, 1-21 days before vaccination	Vaccinated 0-7 days ago	Vaccinated 8-20 days ago	≥21 days after 1st dose, no second dose	Post second dose	Not vaccinated, previously positive*	P-value**
N (%)	10636 (85)	613 (5)	283 (2)	421 (3)	417 (3)	72 (1)	83 (1)	
Minimum Ct, median (IQR)	28.4 (20.1-32.9)	31.6 (27.4-33.5)	31.2 (20.6-33.7)	31.0 (23.5-33.8)	31.7 (26.9-33.7)	33.1 (30.5-34.2)	32.9 (30.2-34.4)	<0.001
Ct pattern								
OR+N+S, OR+N, OR+S	1703 (16)	57 (9)	21 (7)	25 (6)	20 (5)	3 (4)	9 (11)	
OR+N	5572 (52)	335 (55)	148 (52)	232 (55)	245 (59)	32 (44)	32 (39)	<0.001
Other single/double	3361 (32)	221 (36)	114 (40)	164 (39)	152 (36)	37 (51)	42 (51)	
Symptoms								
None	5051 (47)	348 (57)	171 (60)	234 (56)	260 (62)	60 (83)	63 (76)	
Yes, other	1461 (14)	80 (13)	40 (14)	58 (14)	42 (10)	5 (7)	12 (14)	<0.001
Yes, cough/fever	4124 (39)	185 (30)	72 (25)	129 (31)	115 (28)	7 (10)	8 (10)	
Ct/ symptoms combination								
Ct <30 and symptoms reported	3968 (37)	130 (21)	71 (25)	123 (29)	74 (18)	5 (7)	6 (7)	
Ct <30 and no symptoms reported	1997 (19)	103 (17)	56 (20)	69 (16)	83 (20)	11 (15)	13 (16)	
Ct 30+ and symptoms reported	1617 (15)	135 (22)	41 (14)	64 (15)	83 (20)	7 (10)	14 (17)	
Ct 30+ and no symptoms reported	3054 (29)	245 (40)	115 (41)	165 (39)	177 (42)	49 (68)	50 (60)	
Visit with prior negative result post vaccination	-	-	269 (95)	399 (95)	401 (96)	70 (97)	-	

* positive antibody result in the study >45 days previously or a previous positive episode in the study.

**p-values from Kruskal-Wallis test across vaccination status groups.

Note: showing n (col %) or median IQR

Supplementary Table 5: Odds ratios (95% confidence intervals) from adjusted models

Model	Not vaccinated, no prior positive, 1-21 days before vaccination		Vaccinated 0-7 days ago			Vaccinated 8-20 days ago			≥21 days after 1st dose, no second dose			Post second dose			Not vaccinated, previously positive		
	OR (95% CI)	P-value vs baseline	OR (95% CI)	P-value vs baseline	Pairwise p-value	OR (95% CI)	P-value vs baseline	Pairwise p-value	OR (95% CI)	P-value vs baseline	Pairwise p-value	OR (95% CI)	P-value vs baseline	Pairwise p-value	OR (95% CI)	P-value vs baseline	Pairwise p-value
All positives																	
Unadjusted	0.34 (0.31, 0.37)	<0.001	0.36 (0.32, 0.40)	<0.001	0.995	0.36 (0.33, 0.40)	<0.001	1.000	0.18 (0.16, 0.20)	<0.001	<0.001	0.22 (0.17, 0.27)	<0.001	0.716	0.31 (0.25, 0.38)	<0.001	0.258
Adjusted	0.28 (0.26, 0.31)	<0.001	0.38 (0.33, 0.43)	<0.001	0.001	0.45 (0.40, 0.51)	<0.001	0.204	0.35 (0.30, 0.40)	<0.001	0.004	0.30 (0.23, 0.38)	<0.001	0.889	0.30 (0.24, 0.38)	<0.001	1.000
Ct value																	
Mean Ct <30	0.21 (0.18, 0.24)	<0.001	0.35 (0.28, 0.42)	<0.001	<0.001	0.43 (0.36, 0.51)	<0.001	0.408	0.26 (0.21, 0.33)	<0.001	<0.001	0.12 (0.07, 0.20)	<0.001	0.050	0.12 (0.08, 0.19)	<0.001	1.000
Mean Ct ≥30	0.36 (0.32, 0.41)	<0.001	0.42 (0.35, 0.50)	<0.001	0.671	0.49 (0.42, 0.58)	<0.001	0.731	0.45 (0.37, 0.55)	<0.001	0.965	0.52 (0.38, 0.70)	<0.001	0.962	0.55 (0.43, 0.71)	<0.001	1.000
Symptoms																	
Symptoms reported	0.25 (0.21, 0.28)	<0.001	0.30 (0.25, 0.37)	<0.001	0.521	0.41 (0.34, 0.49)	<0.001	0.122	0.28 (0.22, 0.35)	<0.001	0.012	0.10 (0.06, 0.18)	<0.001	0.012	0.13 (0.08, 0.21)	<0.001	0.992
No symptoms reported	0.32 (0.29, 0.37)	<0.001	0.47 (0.39, 0.56)	<0.001	0.002	0.52 (0.44, 0.61)	<0.001	0.961	0.43 (0.36, 0.53)	<0.001	0.539	0.51 (0.38, 0.69)	<0.001	0.902	0.51 (0.40, 0.65)	<0.001	1.000
Ct pattern																	
ORF1ab+N+S, N+S, ORF1ab+S	0.23 (0.18, 0.30)	<0.001	0.28 (0.18, 0.44)	<0.001	0.984	0.32 (0.20, 0.50)	<0.001	1.000	0.29 (0.16, 0.51)	<0.001	1.000	0.18 (0.06, 0.51)	0.001	0.975	0.25 (0.13, 0.47)	<0.001	0.998
OR+N	0.29 (0.26, 0.33)	<0.001	0.36 (0.30, 0.43)	<0.001	0.335	0.45 (0.38, 0.53)	<0.001	0.335	0.34 (0.28, 0.41)	<0.001	0.084	0.22 (0.15, 0.32)	<0.001	0.225	0.21 (0.14, 0.29)	<0.001	1.000

*Pairwise p-value: p-value testing whether the OR for each vaccine status group is different to the vaccine status group below; so respectively "Vaccinated 0 to 7 days ago, 1 dose" vs "Not vaccinated, no prior positive, 1-21 days before vaccination", "Vaccinated 8 to 20 days ago" vs "Vaccinated 0 to 7 days ago", "Vaccinated ≥ 21 days ago, 2 doses" vs "Vaccinated ≥ 21 days ago, 1 dose" and "Not vaccinated, but swab or antibody positive >45 days ago" vs "Vaccinated ≥ 21 days ago, 2 doses".

Note: all odds ratios are compared to the reference category of **Not vaccinated, no prior positive (>45 days ago), >21 days before vaccination.** Results shown graphically in **Figure 3**.

Supplementary Table 6: Odds ratios (95% confidence intervals) for main effects[1] from adjusted model with all positives as outcome

Term	Odds ratio	95% CI		P-value
Contact care home				
No	1			
No, but someone in HH	1.34	1.18	1.53	<0.001
Yes, I have	1.28	1.14	1.44	<0.001
Contact hospital				
No	1			
No, but someone in HH	1.11	1.04	1.18	0.001
Yes, I have	1.29	1.23	1.36	<0.001
Vaccination status				
Not vaccinated, no prior positive, >21 days before vaccination	1			
Not vaccinated, no prior positive, 1-21 days before vaccination	0.28	0.26	0.31	<0.001
Vaccinated 0 to 7 days ago	0.38	0.33	0.43	<0.001
Vaccinated 8 to 20 days ago	0.46	0.41	0.52	<0.001
≥21 days since 1st vaccination, no second dose	0.35	0.30	0.40	<0.001
Post second dose	0.30	0.23	0.39	<0.001
Not vaccinated, prior positive	0.31	0.25	0.39	<0.001
Ethnicity				
White	1			
Non-White	1.15	1.08	1.23	<0.001
Ever care home worker				
No	1			
Yes	1.16	1.00	1.34	0.051
Ever reported long-term health conditions				
No	1			
Yes	0.99	0.95	1.04	0.819
Ever patient facing healthcare worker				
No	1			
yes	1.54	1.41	1.69	<0.001
Ever person-facing social care worker				
No	1			
Yes	1.34	1.16	1.55	<0.001
Household size				
One	1			
Two	1.00	0.95	1.05	0.947
Three	1.18	1.10	1.26	<0.001
Four	1.32	1.23	1.42	<0.001
Five_plus	1.40	1.28	1.52	<0.001
IMD score	0.96	0.95	0.97	<0.001
Multigenerational household				
No	1			
Yes	0.95	0.87	1.03	0.192

Term	Odds ratio	95% CI		P-value
Sex				
Male	1			
Female	0.99	0.95	1.03	0.591
Smoking status				
Non-smoker	1			
Only vape	1.02	0.91	1.14	0.778
Tobacco smoker	0.80	0.74	0.86	<0.001
Visit frequency				
>14 days since last first	1			
<=14 days since last visit	0.58	0.55	0.61	<0.001
Enrolment	1.08	1.01	1.16	0.024
Work location distancing				
Working from home	1			
Elsewhere, difficult to maintain 2m	1.27	1.15	1.39	<0.001
Elsewhere, easy to maintain 2m	0.96	0.89	1.03	0.281
Elsewhere, relatively easy to maintain 2m	1.19	1.08	1.30	<0.001
Elsewhere, very difficult to maintain 1m	1.41	1.30	1.53	<0.001
Furloughed	1.74	1.61	1.88	<0.001
Retired	1.10	1.02	1.19	0.020
Student	0.98	0.87	1.10	0.750
Unemployed	1.12	1.03	1.21	0.006
Work travel				
Not travelling to work	1			
Car/taxi	1.40	1.32	1.50	<0.001
On foot/bike	1.16	1.08	1.26	<0.001
Other	1.02	0.87	1.21	0.772
Train/bus	1.28	1.17	1.40	<0.001
Rural urban classification				
Major urban area	1			
Urban city/town	0.86	0.81	0.91	<0.001
Rural town	0.79	0.73	0.85	<0.001
Rural village	0.68	0.63	0.74	<0.001

[1]Interactions included in model: study day by age, study day by region, age by region

Supplementary Table 7: ORs from vaccine split by type

		All positives	Ct value		Symptoms	
Model		Adjusted	Ct <30	Ct ≥30	Symptoms reported	No symptoms reported
Not vaccinated, no prior positive, 1-21 days before vaccination	OR (95% CI)	0.28 (0.26, 0.31)	0.21 (0.18, 0.24)	0.36 (0.32, 0.41)	0.25 (0.21, 0.28)	0.32 (0.29, 0.37)
	P-value vs baseline	<0.001	<0.001	<0.001	<0.001	<0.001
Vaccinated with AZ 0-7 days ago	OR (95% CI)	0.35 (0.28, 0.42)	0.27 (0.19, 0.37)	0.43 (0.33, 0.55)	0.25 (0.18, 0.35)	0.45 (0.35, 0.57)
	P-value vs baseline	<0.001	<0.001	<0.001	<0.001	<0.001
	Pairwise p-value	0.566	0.909	0.956	1.00	0.244
Vaccinated with PF 0-7 days ago	OR (95% CI)	0.40 (0.34, 0.47)	0.39 (0.31, 0.50)	0.42 (0.33, 0.53)	0.34 (0.27, 0.43)	0.48 (0.39, 0.60)
	P-value vs baseline	<0.001	<0.001	<0.001	<0.001	<0.001
	Pairwise p-value	0.965	0.576	1.00	0.877	1.00
Vaccinated with AZ 8-20 days ago	OR (95% CI)	0.44 (0.36, 0.52)	0.41 (0.31, 0.54)	0.48 (0.38, 0.61)	0.42 (0.32, 0.55)	0.47 (0.37, 0.60)
	P-value vs baseline	<0.001	<0.001	<0.001	<0.001	<0.001
	Pairwise p-value	0.999	1.00	0.998	0.945	1.00
Vaccinated with PF 8-20 days ago	OR (95% CI)	0.46 (0.40, 0.53)	0.44 (0.36, 0.54)	0.51 (0.42, 0.62)	0.40 (0.33, 0.50)	0.54 (0.45, 0.65)
	P-value vs baseline	<0.001	<0.001	<0.001	<0.001	<0.001
	Pairwise p-value	1.00	1.00	1.00	1.00	0.992
≥21 days after 1st AZ dose	OR (95% CI)	0.36 (0.30, 0.45)	0.26 (0.19, 0.37)	0.48 (0.37, 0.63)	0.37 (0.27, 0.51)	0.39 (0.30, 0.51)
	P-value vs baseline	<0.001	<0.001	<0.001	<0.001	<0.001
	Pairwise p-value	0.465	0.118	1.00	1.00	0.432
≥21 days after 1st PF dose, no second dose	OR (95% CI)	0.33 (0.28, 0.39)	0.25 (0.19, 0.32)	0.44 (0.36, 0.55)	0.25 (0.19, 0.32)	0.44 (0.36, 0.55)
	P-value vs baseline	<0.001	<0.001	<0.001	<0.001	<0.001
	Pairwise p-value	0.998	1.00	1.00	0.288	0.995
Post second PF dose	OR (95% CI)	0.28 (0.21, 0.36)	0.12 (0.07, 0.21)	0.48 (0.35, 0.66)	0.09 (0.05, 0.17)	0.48 (0.36, 0.66)
	P-value vs baseline	<0.001	<0.001	<0.001	<0.001	<0.001
	Pairwise p-value	0.954	0.244	1.00	0.078	1.00
Not vaccinated, prior positive	OR (95% CI)	0.30 (0.24, 0.38)	0.12 (0.08, 0.19)	0.55 (0.43, 0.71)	0.13 (0.08, 0.21)	0.51 (0.40, 0.65)
	P-value vs baseline	<0.001	<0.001	<0.001	<0.001	<0.001

	Pairwise p-value	1.00	1.00	0.999	0.996	1.00

*Pairwise p-value: p-value testing whether the specified OR vaccine status is different to the vaccine status group below
Note: all odds ratios are compared to the base category of Not vaccinated, not positive > 45 days ago), >21 days before vaccination. Results shown graphically in Figure 4.