Changes in the trajectory of Long Covid symptoms following COVID-19 vaccination: community-based cohort study

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Abstract

Objective: To estimate associations between COVID-19 vaccination and Long Covid symptoms in adults who were infected with SARS-CoV-2 prior to vaccination.

Design: Observational cohort study using individual-level interrupted time series analysis.

Setting: Random sample from the community population of the UK.

Participants: 28,356 COVID-19 Infection Survey participants (mean age 46 years, 56% female, 89% white) aged 18 to 69 years who received at least their first vaccination after test-confirmed infection.

Main outcome measures: Presence of Long Covid symptoms at least 12 weeks after infection over the follow-up period 3 February to 5 September 2021.

Results: Median follow-up was 141 days from first vaccination (among all participants) and 67 days from second vaccination (84% of participants). First vaccination was associated with an initial 12.8% decrease (95% confidence interval: -18.6% to -6.6%, p<0.001) in the odds of Long Covid, with the data being compatible with both increases and decreases in the trajectory (+0.3% per week, 95% CI: -0.6% to +1.2% per week, p=0.51) after this. Second vaccination was associated with an 8.8% decrease (95% CI: -14.1% to -3.1%, p=0.003) in the odds of Long Covid, with the odds subsequently decreasing by 0.8% (-1.2% to -0.4%, p<0.001) per week. There was no statistical evidence of heterogeneity in associations between vaccination and Long Covid by socio-demographic characteristics, health status, whether hospitalised with acute COVID-19, vaccine type (adenovirus vector or mRNA), or duration from infection to vaccination.

Conclusions: The likelihood of Long Covid symptoms reduced after COVID-19 vaccination, and there was evidence of a sustained improvement after the second dose, at least over the median follow-up time of 67 days. Vaccination may contribute to a reduction in the population health burden of Long Covid, though longer follow-up time is needed.

Print abstract

Study question: This study sought to estimate associations between COVID-19 vaccination and Long Covid symptoms in adults who were infected with SARS-CoV-2 prior to vaccination.

Methods: We conducted an observational cohort study of 28,356 participants (mean age 46 years, 56% female, 89% white) from the COVID-19 Infection Survey (CIS), a random sample of the UK community population. We included participants who were aged 18 to 69 years and had received at least their first vaccination after test-confirmed infection. Using individual-level interrupted time series analysis, we investigated the presence of Long Covid symptoms at least 12 weeks after infection over the follow-up period 3 February to 5 September 2021.

Study answer and limitations: We found that the likelihood of Long Covid symptoms reduced after COVID-19 vaccination, and there was evidence of a sustained improvement after the second dose, at least over the median follow-up time of 67 days. However, causality cannot be inferred from this observational evidence, and more post-vaccination follow-up time (including the effect of booster doses) is needed.

What this study adds: Our study suggests that vaccination may contribute to a reduction in the population health burden of Long Covid. Further research is needed to understand the biological mechanisms underpinning our results, which may ultimately contribute to the development of therapeutics for Long Covid.

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Suggested figure for print abstract: See Figure 2

Summary box

What is already known on this topic

- COVID-19 vaccines are effective at reducing rates of SARS-CoV-2 infection, transmission, hospitalisation, and death
- The incidence of Long Covid may be reduced if infected after vaccination, but the relationship between vaccination and pre-existing long COVID symptoms is unclear, as published studies are generally small and with self-selected participants

What this study adds

- The likelihood of Long Covid symptoms reduced after COVID-19 vaccination, and there was evidence of a sustained improvement after the second dose, at least over the median follow-up time of 67 days
- There was no evidence of differences in this relationship by socio-demographic characteristics, health-related factors, vaccine type, or duration from infection to vaccination
- Although causality cannot be inferred from this observational evidence, vaccination may contribute to a reduction in the population health burden of Long Covid; further research is needed to understand the biological mechanisms that may ultimately contribute to the development of therapeutics for Long Covid

Introduction

By the end of 2021, there had been nearly 14 million confirmed cases of SARS-CoV-2 in the UK, resulting in 640,000 patients being admitted to hospital and 158,000 deaths with COVID-19, while 90% of the population had received at least one dose of a COVID-19 vaccine [1]. Symptoms may persist for months following infection, defined in UK clinical guidelines [2] as ongoing symptomatic COVID-19 (signs and symptoms from 4 to 12 weeks post-onset) or post-COVID-19 syndrome (more than 12 weeks post-onset). These symptoms are collectively and commonly referred to as Long Covid. Long Covid is characterised by a range of symptoms across organ systems, including fatigue, shortness of breath, and cognitive impairment [3], often with undulating periods of wellness followed by relapse [4-6]. By February 2021, nearly 6% of adults in England may have experienced prolonged symptoms following coronavirus infection since the pandemic began [6], and 1.2 million people in private households in the UK (1.9%) were estimated to be reporting Long Covid symptoms in October 2021, with symptoms having a detrimental impact on the day-to-day activities of two-thirds of these individuals [3].

Population-level immunisation against COVID-19 began in the UK on 8 December 2020, and both adenovirus vector and messenger ribonucleic acid (mRNA) vaccines have demonstrated safety and efficacy in trials [8-11] and real-world effectiveness at reducing rates of infection [12-13], transmission [14], hospitalisation [15] and death [15-16]. Preliminary research suggests that Long Covid symptoms are less common in breakthrough infections [17], but the impact of vaccination on pre-existing Long Covid is less clear. Anecdotal evidence paints a mixed picture of the lived experience following vaccination, with patients describing improvement, deterioration, and no change in their symptoms. An online survey of members of a Long Covid patient advocacy group in the US found that approximately 40% of respondents reported full or partial symptom resolution after they were vaccinated while 14% reported deterioration [18]. A similar survey conducted by UK-based patient group found that over half of participants experienced an improvement in their Long Covid symptoms while a fifth experienced a worsening [19]. Though informative, such studies involve self-selecting groups of participants who may not be representative of the population of interest and lack control groups and long-term follow-up, while others have relied on small sample sizes [20-21]. A quarter of the UK population aged 12 years or over were yet to receive two COVID-19 vaccinations by 5 September 2021, while 16% had not received their first dose [1]. Possible vaccine hesitancy among people with Long Covid symptoms has been identified through social media discourse [22]. There is therefore a need for greater evidence regarding symptomology following vaccination, which may facilitate informed decision-making among individuals with Long Covid.

We used data from the Office for National Statistics (ONS) COVID-19 Infection Survey (CIS), a large, community-based population survey of randomly sampled UK households, to estimate associations between COVID-19 vaccination and Long Covid symptoms in adults who were infected with SARS-CoV-2 prior to vaccination.

Methods

Study data and design

Data were obtained from the CIS (ISRCTN21086382, www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey/protocol-and-information-sheets) [23], a longitudinal survey of individuals aged 2 years or over in randomly sampled UK households (excluding communal establishments such as hospitals, care homes, halls of residence, and prisons).

Enrolment rates were as high as 51% in the initial pilot phase of the CIS from April 2020, when eligible households comprised previous respondents to ONS surveys who had consented to participate in future research. However, as the sample was expanded and transitioned to random selection from address lists in August 2020, the enrolment rate dropped to 12% (see **Supplementary Table 1** for details). Once enrolled into the study, the attrition rate is generally low; using a definition of either formally withdrawing from the study or having not attended the three most recently scheduled follow-up visits, the attrition rate among enrolled CIS participants was less than 1% in 2021.

All participants provided a nose and throat self-swab for polymerase chain reaction (PCR) testing at every follow-up visit. Individuals aged 16 years or older in a random subsample of households (initially 10% but expanded from April 2021), and those in households where another household member previously tested positive for SARS-CoV-2, were invited to provide monthly blood samples for S-antibody testing. Participants also reported whether they had tested positive for the virus or antibodies outside of the study (for example, through national testing programmes).

At every monthly visit since 3 February 2021, all CIS participants were asked whether they would describe themselves as currently experiencing Long Covid, defined as symptoms persisting for at least four weeks from confirmed or suspected coronavirus infection that could not be explained by another health condition. This definition uses self-classification of Long Covid, rather than a pre-specified symptoms list or clinical diagnosis, and thus reflects participants' perception of whether their lived experience is consistent with what they understand of the condition. Participants who responded positively to the Long Covid question were further asked about the extent to which their day-to-day activities were limited as a result, and the presence of 21 individual symptoms as part of their experience of Long Covid (selected on the basis of being among the most commonly reported when the survey question was developed [5, 6, 24]; see **Supplementary Table 2** for the full list).

For participants in England, vaccination information (number of doses, dates, manufacturer) was obtained from self-reported CIS responses and linked National Immunisation Management System (NIMS) records, with NIMS being prioritised where data conflicted. Concordance between self-reported and NIMS data was previously found to be high regarding vaccination type (98%) and date (95% within ±7 days) [12]. Administrative records were not available for participants in Wales, Scotland, and Northern Ireland, so vaccination data for these individuals were taken from the CIS alone.

Inclusion and exclusion criteria

The analysis included CIS participants aged 18 to 69 years on 3 February 2021. Participants were included if they: responded to the survey question on Long Covid at least once up to 5 September 2021 (end of follow-up); received at least one COVID-19 vaccination before or during the follow-up period; and received a positive swab or blood test for SARS-CoV-2, either through the CIS or reported outside of the study, prior to vaccination. We excluded CIS participants remaining unvaccinated by 5 September 2021 because they were likely to differ from those who were vaccinated according to unmeasured characteristics (for example, personal considerations related to vaccine hesitancy).

Infection date

Time of infection was the date of first positive swab or antibody test (ignoring blood tests after first vaccination), or the date when the participant first thought they had COVID-19 that was later confirmed by a positive test, whichever was earlier. Although the CIS question

asks about Long Covid symptoms persisting for at least four weeks from infection, for this analysis we used a longer 12-week threshold, consistent with the UK clinical case definition of post-COVID-19 syndrome [2] and the World Health Organisation's definition of post COVID-19 condition [25]. We therefore excluded any follow-up visits within 12 weeks of infection date.

Follow-up time

Each participant was observed from their first CIS follow-up visit that took place after their first SARS-CoV-2 infection and after the Long Covid question was added to the CIS on 3 February 2021. Follow-up ended on the date of participants' final follow-up visit that took place by 5 September 2021.

Exposures

The exposures of interest were first and second vaccinations of an adenovirus vector (Oxford/AstraZeneca, ChAdOx1 nCoV-19 [AZD1222]) or mRNA (Pfizer/BioNTech, BNT162b2; Moderna, mRNA-1273) COVID-19 vaccine. The recommended interval between the first and second vaccinations was 11 to 12 weeks for most participants in the study sample (having been increased from four weeks on 30 December 2020), with this reduced to eight weeks in May 2021 for people in the top nine vaccination priority groups [26]. For each vaccine dose, we estimated the associated change in outcomes using a binary variable to indicate whether participants had received each dose at each follow-up visit; and a variable equal to the number of days since receiving each dose at each follow-up visit to estimate post-vaccination changes in the outcome trajectory (set to 0 for visits before receiving each dose). This specification implies that any change in the odds of Long Covid occurs instantly following vaccination, but in reality, this may take place over several days or weeks.

Outcomes

The primary outcome at each visit was Long Covid of any severity, with a secondary outcome of Long Covid resulting in activity limitation (day-to-day activities limited "a little" or "a lot" versus "not at all" or no Long Covid); this definition of functional impairment is standardised across UK Government Statistical Service data collections, and is designed to measure disability as defined in the Equality Act 2010. We also evaluated the 10 individual symptoms that were most commonly reported over the follow-up period, and whether the participant was experiencing more than three or five of the 21 symptoms included on the survey. The CIS question relating to activity limitation used wording that

Covariates

As well as time from infection and the exposure variables detailed above to modify the time trajectory of Long Covid, we adjusted for covariates hypothesised to be related to vaccine type and timing [27] and the probability of experiencing Long Covid symptoms [3]: age; sex; white or non-white ethnicity; region/country; area deprivation quintile group; health status; whether a patient-facing health or social care worker; and whether hospitalised with acute COVID-19. We also adjusted for calendar time of infection to control for temporal effects that may be related to the risk of developing prolonged symptoms, such as viral variant (the Alpha and Delta variants were both dominant at different points in the follow-up period) and changes in healthcare practice. Specifications of covariates can be found in **Supplementary Table 3**.

Statistical analysis

We compared covariates between participants receiving adenovirus vector and mRNA vaccines using means and proportions for continuous and categorical variables, respectively. Standardized differences >10% indicated large differences [28].

Associations between exposures and outcomes were estimated using an individual-level interrupted time series approach [29]. For each outcome, we included all exposures and covariates in a binary logistic regression model and estimated robust (clustered) standard errors to account for intra-participant correlation due to having repeated measures. We opted for a linear fit for time since infection as this specification minimised the Bayesian Information Criterion (BIC) compared with higher-order polynomial or spline fits, thus providing a better balance between goodness-of-fit and parsimony **(Supplementary Figure 1)**.

We explored heterogeneity in associations between vaccination and Long Covid by interacting all four exposure variables (change in level and slope after each dose) with each of: age group (18 to <30 years, 30 to <40 years, 40 to <50 years, 50 years to <60 years, ≥60 years); sex; white or non-white ethnicity; area deprivation quintile group; health status; hospitalisation with acute COVID-19; vaccine type (adenovirus vector or mRNA); and duration from infection to first vaccination (modelled as a restricted cubic spline). For each outcome, statistically significant interactions were identified at the 5% level after performing Holm-Bonferroni and Benjamini-Yekutieli corrections to p-values to account for multiple comparisons across exposures and modifiers. All statistical analyses were performed using R version 3.6.

Sensitivity analyses

We restricted the sample firstly to participants with at least one observation before and after each vaccination, and secondly to those with at least three observations after each vaccination. We omitted follow-up visits within the first week after each vaccination, which may have been influenced by post-vaccine side effects. We added CIS participants who remained unvaccinated by their last follow-up visit during the study period (who were excluded from the main analysis). We excluded participants infected before the start of the second wave on 11 September 2020 [30], as mass testing for SARS-CoV-2 was largely unavailable in the first wave and so these infections were likely to have been more severe than the majority included in the analysis. We reset the infection date for 2.5% of participants where this was determined by when the participant first thought they had COVID-19 (later confirmed by a positive test) that was >14 days before a positive swab (the estimated maximum incubation period [31]); these participants may have been reinfected, but only their second infection was validated by means of a positive test, so the infection date was moved forward to the date of this test. Finally, we excluded participants whose infection date was determined by a positive blood test for SARS-CoV-2 antibodies that was obtained before or on the date of their first CIS follow-up visit; the precise timing of infection was unknown for these participants.

Patient and public involvement

NAA contributed to this paper as both a person with lived experience of Long Covid and a public health researcher. She has previously heavily advocated against the separation of ‘identities’ of people with Long Covid who are also scientists, researchers or health professionals. She has also written on patient involvement in Long Covid research and the lessons learnt that could apply to other conditions [32-33]. She contributed to informing this analysis’s concept, design and interpretation.

Although we did not directly involve patients and the public more broadly, the study design was informed by views expressed by patient representatives in monthly meetings attended by DA (the Department of Health and Social Care's Long Covid ministerial roundtable, NHS England's Long Covid national taskforce). These meetings were attended by the founders of three major Long Covid patient support groups in the UK, whose insights on aspects such as the range of Long Covid symptoms experienced and their relapsing/remitting nature informed the data collected and definitions used in this study.

Ethics

Ethical approval for the CIS was obtained from the South Central Berkshire B Research Ethics Committee (20/SC/0195). After verbal agreement to participate, each selected household was visited by a study worker to provide written confirmed consent (from parents/carers for those aged 2 to 15 years; those aged 10 to 15 years also provided written assent). At the first visit, participants could consent for (optional) follow-up visits every week for the next month and then monthly for 12 months or longer.

Results

Description of the study sample

Of 323,685 CIS participants aged 18 to 69 years with at least one visit between 3 February and 5 September 2021, 28,356 had test-confirmed SARS-CoV-2 at least 12 weeks before their final visit and had been vaccinated post-infection, and were therefore included in analysis **(Figure 1)**.

Median time to the final follow-up visit was 169 (interquartile range [IQR]: 141 to 185) days from first visit, and 267 (219 to 431) days from first infection. By design, all study participants received their first vaccination by 5 September 2021, 12,971 (45.7%) after the start of the study period on 3 February. 23,753 (83.8%) participants were double vaccinated by 5 September 2021, 20,335 (71.7%) receiving their second dose after 3 February, with a median time between doses of 72 (61 to 77) days **(Supplementary Figure 2)**. **Supplementary Table 4** shows vaccination status during follow-up by age and health status (two of the main vaccination prioritisation determinants). Participants had a median of 4 (2 to 5) visits over a median of 141 (86 to 173) days after their first dose and, among those double-vaccinated, 2 (1 to 3) visits over 67 (20 to 99) days after their second dose.

At last visit, the mean age of participants was 46 years (standard deviation [SD] 14 years), 55.6% were female, and 88.7% were white **(Table 1)**. Compared with participants receiving an adenovirus vector vaccine, those mRNA vaccinated were on average younger (mean 40 versus 51 years), and more likely to be of non-white ethnicity (13.7% versus 9.4%), resident in London (27.0% versus 22.4%) or Northern Ireland (3.3% versus 1.5%), and a patient-facing health or social care worker (17.1% versus 6.4%).

Long Covid trajectories before and after vaccination

Long Covid symptoms of any severity were reported by 6,729 participants (23.7%) at least once during follow-up. Before vaccination, there was little change in the odds of experiencing Long Covid over time (-0.3% per week, 95% CI: -0.9% to +0.2%, p=0.25) (Table 2). First vaccination was associated with an initial 12.8% decrease (95% CI: -18.6% to -6.6%, p<0.001) in the odds, with the data being compatible with both increases and decreases in the trajectory (+0.3% per week, 95% CI: -0.6% to +1.2% per week, p=0.51) between the first and second doses. Second vaccination was associated with an initial 8.8% decrease (-

14.1% to -3.1%, p=0.003) in the odds, followed by a decrease of 0.8% (-1.2% to -0.4%, p<0.001) per week.

Long Covid resulting in activity limitation was reported by 4,747 participants (16.7%) at least once during follow-up. First vaccination was associated with an initial 12.3% decrease (95% CI: -19.5% to -4.5%, p=0.003) in the odds of activity-limiting Long Covid, followed by an uncertain trajectory (+0.9% per week, 95% CI: -0.2% to +1.9%, p=0.11) until receiving the second dose. Second vaccination was associated with an initial 9.1% decrease (95% CI: -15.6% to -2.1%, p=0.01) in the odds, followed by -0.5% per week (95% CI: -1.0% to +0.05%, p=0.08) until the end of follow-up.

To illustrate the impact of each vaccination, **Figure 2** shows the estimated probability of reporting Long Covid for a study participant receiving their first vaccination 24 weeks after infection and their second dose 12 weeks later. Sensitivity analyses **(Supplementary Figures 3a-i)** were generally consistent with the main results. However, there was stronger evidence of a change to an increasing trend in Long Covid between first and second vaccinations when restricting the sample to participants who received their first dose during the follow-up period 3 February to 5 September 2021 (p<0.001 for Long Covid of any severity, p=0.01 for activity-limiting Long Covid).

Heterogeneity by vaccine type, duration since infection, and participant characteristics

There was no statistical evidence of differences in post-vaccination Long Covid trajectories between participants receiving adenovirus vector and mRNA vaccines **(Table 3, Figure 3)** for either changes in levels (p=0.31 for dose one, p=0.97 for dose two) or slopes (p=0.33 for the change between doses one and two, and p=0.33 for the change after dose two). Vaccination was associated with an initial 14.9% decrease (95% CI: -21.8% to -7.5%, p<0.001) in the odds of Long Covid following first adenovirus vector vaccination, and a numerical 8.9% decrease (95% CI: -18.2% to +1.4%, p=0.09) following first mRNA vaccination, though the data were also compatible with increased odds for the latter. Decreases in the odds after second vaccination were numerically similar between vaccine types, at 8.7% (95% CI: -15.4% to -1.4%, p=0.02) for adenovirus vector and 8.9% (95% CI: -17.6% to +0.7%, p=0.07) for mRNA.

The odds of Long Covid after first vaccination numerically decreased with duration from infection, with estimated numerical decreases of 24.8%, 16.5%, and 4.8% for participants first vaccinated 9, 12, and 15 months after infection **(Supplementary Figures 4a-b)**. However, duration from infection to first vaccination was not a statistically significant moderator of the vaccination-Long Covid relationship **(Supplementary Tables 5a to 5d)**.

There was no statistical evidence of differences in post-vaccination Long Covid trends according to socio-demographic characteristics (age, sex, ethnic group, area deprivation) or health-related factors (self-reported health status not related to COVID-19, whether hospitalised with acute COVID-19) **(Supplementary Tables 5a to 5d)**.

Trajectories of individual symptoms

The odds of experiencing most symptoms, as well as more than three or five symptoms together, initially numerically decreased after each vaccination **(Figure 4)**. After first vaccination, the largest numerical decreases were observed for loss of smell (-12.5%, 95% CI: -21.5% to -2.5%, p=0.02), loss of taste (-9.2%, 95% CI: -19.8% to +2.7%, p=0.13), and trouble sleeping (-8.8%, 95% CI: -19.4% to +3.3%, p=0.15). After second vaccination, the

largest numerical decreases were observed for fatigue (-9.7%, 95% CI: -16.5% to -2.4%, p=0.01), headache (-9.0%, 95% CI: -18.1% to +1.0%, p=0.08), and trouble sleeping (-9.0%, 95% CI: -18.2% to +1.2%, p=0.08).

Similar to Long Covid overall, the odds of experiencing most individual symptoms, and more than three or five symptoms together, numerically decreased after the first vaccination. Trends were generally upwards between the first and second vaccinations, with most returning to a declining or flat trend after the second dose. However, lack of statistical power meant that for most symptoms, the data were compatible with both initial increases and decreases, and with both upward and downward trends, in the likelihood of experiencing symptoms after each vaccination **(Supplementary Table 6)**.

Discussion

In this community-based study of adults aged 18 to 69 years infected with SARS-CoV-2 prior to vaccination, we found that the odds of experiencing Long Covid symptoms that had persisted for at least 12 weeks fell by an average of 13% after receiving a first COVID-19 vaccination. However, it is unclear from the data whether the improvement was sustained until receiving the second vaccination. Receiving a second vaccination was associated with a further 9% decrease in the odds of Long Covid, and there was statistical evidence of a sustained improvement after this, at least over the median follow-up time of 67 days. Similar findings were obtained when focussing on Long Covid severe enough to result in functional impairment.

We found no statistical evidence of heterogeneity in the associations between vaccination and Long Covid symptoms according to vaccine type, duration from infection to first vaccination, socio-demographic characteristics including age, sex, ethnicity, and area deprivation, self-reported health status, and whether hospitalised with acute COVID-19. However, this observational study was unlikely to have been sufficiently powered to detect these associations, particularly given the multiplicity of testing, and absence of evidence does not necessarily imply evidence of absence.

Findings in context

Our results substantially add to existing evidence on the epidemiology of Long Covid after vaccination. A non-controlled study of 900 social media users found that over half had experienced an improvement in symptoms after vaccination while just 7% reported a deterioration [19]. A study of 44 vaccinated patients and 22 unvaccinated controls previously hospitalised with COVID-19 in the UK, which inevitably had limited power to detect clinically relevant effects, found no evidence of vaccination being associated with worsening of Long Covid symptoms or quality of life [20]. A study of 455 self-selected participants in France found reduced symptom burden and double the rate of remission at 120 days post-vaccination compared with unvaccinated controls [21].

COVID-19 vaccination effectively reduces rates of infection [12-13] and transmission [14]. Evidence also suggests that Long Covid incidence is reduced in those infected after vaccination; in a study of 906 mobile phone app users, the odds of having symptoms ≥28 days post-infection was approximately halved in fully vaccinated participants versus unvaccinated controls [17]. Together with our results, these findings suggest that COVID-19 vaccination may reduce the population prevalence of Long Covid by reducing the risk of continuing to experience persistent symptoms in those who already have them when

vaccinated; developing persistent symptoms following breakthrough infections; being infected in the first place; and transmitting the virus following infection.

Our principal finding, of a decrease in the likelihood of experiencing Long Covid symptoms after receiving a second vaccination, supports hypothesised biological mechanisms. People with Long Covid experiencing dysregulation of the immune system may benefit from vaccine-induced diversion of autoimmune processes, while any residual viral reservoir may be destroyed by the antibody response [34]. However, whether this is a long-lasting 'reset' of the immune system remains to be established. Immunological phenotyping suggests differences in those who experience persistent symptoms following SARS-CoV-2 infection compared with healthy controls [35]. The presence of autoantibodies against interferon type-I or autoimmune processes triggered by SARS-CoV-2 through molecular mimicry have been proposed as a manifestation of immune dysregulation in Long Covid, possibly similar to autoimmune rheumatic diseases [36]. Another proposed mechanism is the persistence of viral antigen modifying the immune response months after infection [37]. In this scenario, it is reasonable to hypothesise that COVID-19 vaccination may be beneficial.

The symptom trajectory following the initial fall after first vaccination was unclear, being compatible with both increasing and decreasing odds of Long Covid over time. However, there was evidence of an increasing trend when the sample was restricted to participants vaccinated during the follow-up period. Relapsing symptoms are common in Long Covid [4-6] and persistent symptoms are associated with weak antibody response [38], so it is possible that receiving a first dose alone is insufficient for sustained improvement in some people.

UK government guidelines dictate that people should delay vaccination for four weeks after a positive test for SARS-CoV-2. Given that we only considered follow-up visits beyond 12 weeks of participants' first positive test (as our outcome of interest was Long Covid symptoms at least 12 weeks after infection), it seems unlikely that this guidance would have affected our analysis. The NHS advises patients with ongoing complications of COVID-19 to consult their GP regarding vaccination, so it is possible that some people with Long Covid symptoms may choose to delay vaccination until their symptoms resolve, which would induce an association. However, this is unlikely to have affected our analysis, as there was no evidence that study participants with Long Covid deferred their COVID-19 vaccination relative to those without Long Covid **(Supplementary Figure 5)**. We also acknowledge that our study was observational in nature, so we cannot rule out that the change in symptoms reported by some participants after vaccination may have partly been a placebo effect. We might expect to observe a post-vaccination relapse in some participants whose symptoms initially improved, but our ability to do this was limited by the follow-up available to us (a median of 67 days from the second dose).

Strengths and limitations

With 28,356 adults in our sample, this is the largest study to date internationally on Long Covid and COVID-19 vaccination, and the first to investigate post-vaccine symptom trajectories. The main strength of the study is its use of the CIS, a large survey of approximately half a million people from the community population of the UK with longitudinal follow-up. Random sampling from address lists mitigates against selection bias, while the prospective design means that survey responses are not subject to outcome recall bias (such as participants overestimating the duration of previously experienced symptoms). All CIS participants are swabbed for SARS-CoV-2 at every follow-up visit, irrespective of symptoms, so our study includes asymptomatic as well symptomatic infections.

The study also has limitations. Its observational nature means that causality cannot be inferred, and placebo and side effects of vaccination may have contributed to our findings; however, estimates were robust to excluding follow-up visits within the first week of each vaccination, suggesting that the impact of these effects is likely to be small. Although we adjusted for a wide range of potential confounders, unmeasured factors, such as those related to take-up of a second vaccination, may remain. The observed changes after vaccination could be related to the relapsing-remitting nature of symptoms experienced by many people living with Long Covid [4-6] rather than a causal effect of the vaccine. Future analysis should consider differing patterns of illness, including quantification of the frequency and duration of symptom-free periods after vaccination.

By definition, symptoms are self-reported with no other way to assess them. Together with their impact on daily life, the presence of symptoms is how Long Covid is defined by the World Health Organization [25]. However, attributing symptoms to a previous SARS-CoV-2 infection is likely to be more difficult in the absence of a diagnostic test for Long Covid and likely under-recording in electronic health records [39]. Although all infections in this study were test-confirmed, Long Covid status was self-reported and we did not have data on related healthcare utilisation, so we cannot exclude some participants' symptoms being caused by a medical condition other than COVID-19. Although clinical case definitions for Long Covid exist in the UK [2] and internationally [25], there is lack of consensus over a suitable working definition for research purposes, thus there is potential for inconsistencies in outcome measurement between our study and others on Long Covid. Based on the same data source as that used in this study, the UK Office for National Statistics has previously estimated 12-week prevalence rates from 3% (based on tracking 12 specific symptoms) to 12% (based on self-classification of Long Covid) [40], demonstrating the sensitivity of the estimated prevalence of Long Covid to how it is measured. Nonetheless, the aim of our study was to investigate changes in the illness trajectory after vaccination rather than to estimate the prevalence of Long Covid at a point in time, and our outcome definition was consistent over the study period.

Given the staged roll-out of the vaccination programme in the UK, the main determinant of vaccination timing is age, and thus older study participants tended to have longer post-vaccination follow-up time than younger participants; this may have influenced our analysis of effect modification, whereby we found no evidence of heterogeneity in the post-vaccination trajectory of Long Covid according to age group. The measure of functional impairment recorded on the CIS (day-to-day activities not limited, limited a little, or limited a lot) did not give a detailed indication of the specific ways that participants' lives have been affected by Long Covid or the resulting impact on quality of life. It is possible that the average improvement in Long Covid symptoms and functional impact may wane with time, and longer-term follow-up is required to establish whether the estimated changes after second vaccination are sustained. Follow-up after receipt of a booster dose, now widely available in the UK adult population, is also required. The study sample was restricted to participants aged 18 to 69 years, so our findings may not generalize to children or older adults, nor may they apply to people who had not received a vaccine by 5 September 2021, in particular those who are vaccine-hesitant because of their Long Covid symptoms. Furthermore, symptom data were collected prospectively rather than retrospectively, so parameter estimates relating to changes in the odds of Long Covid may not be generalisable to participants who were vaccinated before the Long Covid question was added to the CIS on 3 February 2021. However, our results were insensitive to including in the study sample

participants who remained unvaccinated by the end of the study period, or excluding those who were vaccinated before the start of the study period.

Conclusions

In summary, we found that COVID-19 vaccination is associated with a decrease in the likelihood of continuing to experience Long Covid symptoms in adults aged 18 to 69 years, and this appeared to be sustained after the second dose. Our results suggest that vaccination of people previously infected may be associated with a reduction in the burden of Long Covid on population health, at least in the first few months following vaccination. Further research is required to evaluate the long-term relationship between vaccination and Long Covid, in particular the impact of the Omicron variant, which has become dominant in the UK, booster doses, now widely available to adults in the population, and reinfections. Studies are also needed to understand the biological mechanisms underpinning any improvements in symptoms following vaccination, which may contribute to the development of therapeutics for Long Covid.

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Footnotes

Contributors: DA, KBP, MG, VN, NAA and ASW conceptualised and designed the study. DA and CB prepared the study data and performed the statistical analysis. All authors contributed to interpretation of the results. DA and CB were responsible for the first draft of the manuscript. All authors contributed to critical revision of the manuscript. All authors approved the final manuscript. The corresponding author 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 form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; KK chairs the Long Covid research-funded group reporting to the Chief Medical Officer, chairs the Ethnicity Subgroup of the UK Scientific Advisory Group for Emergencies (SAGE), and is a Member of SAGE.

Ethical approval: Ethical approval for this study was obtained from the National Statistician's Data Ethics Advisory Committee (NSDEC(20)12). The CIS received ethical approval from the South Central Berkshire B Research Ethics Committee (20/SC/0195).

Data sharing: De-identified study data are available to accredited researchers in the ONS Secure Research Service (SRS) under part 5, chapter 5 of the Digital Economy Act 2017. For further information about accreditation, contact research.support@ons.gov.uk or visit: ons.gov.uk/aboutus/whatwedo/statistics/requestingstatistics/approvedresearcherscheme

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Table 1. Characteristics of study participants at their final follow-up visit, stratified by vaccine type

Characteristic	Category	Full sample (*n* = 28,356)	mRNA vaccinated (*n* = 12,859)	Vector vaccinated (*n* = 15,497)	Standardized difference (%)
Time since infection (days), mean (SD)		308.9 (129.0)	314.9 (132.9)	304.0 (125.4)	8.4
Time since first vaccination (days), mean (SD)		130.7 (55.9)	118.0 (67.8)	141.2 (40.7)	-41.5
Age (years), mean (SD)		45.9 (13.6)	40.1 (14.1)	50.7 (11.1)	-83.4
Sex, *n* (%)	Male	12,596 (44.4)	5,466 (42.5)	7,130 (46.0)	-7.1
	Female	15,760 (55.6)	7,393 (57.5)	8,367 (54.0)	7.1
Ethnic group, *n* (%)	White	25,141 (88.7)	11,097 (86.3)	14,044 (90.6)	-13.6
	Non-white	3,215 (11.3)	1,762 (13.7)	1,453 (9.4)	13.6
Region or country, *n* (%)	North East England	1,133 (4.0)	524 (4.1)	609 (3.9)	0.7
	North West England	3,990 (14.1)	1,774 (13.8)	2,216 (14.3)	-1.4
	Yorkshire and the Humber	2,430 (8.6)	1,028 (8.0)	1,402 (9.0)	-3.8
	East Midlands	1,755 (6.2)	710 (5.5)	1,045 (6.7)	-5.1
	West Midlands	2,204 (7.8)	917 (7.1)	1,287 (8.3)	-4.4
	East of England	2,447 (8.6)	1,044 (8.1)	1,403 (9.1)	-3.3
	London	6,942 (24.5)	3,470 (27.0)	3,472 (22.4)	10.6
	South East England	2,919 (10.3)	1,208 (9.4)	1,711 (11.0)	-5.4
	South West England	1,276 (4.5)	580 (4.5)	696 (4.5)	0.1
	Northern Ireland	657 (2.3)	421 (3.3)	236 (1.5)	11.5
	Scotland	1,376 (4.9)	620 (4.8)	756 (4.9)	-0.3
	Wales	1,227 (4.3)	563 (4.4)	664 (4.3)	0.5
Area deprivation quintile group, *n* (%)	1 (most deprived)	3,825 (13.5)	1,779 (13.8)	2,046 (13.2)	1.8
	2	5,392 (19.0)	2,671 (20.8)	2,721 (17.6)	8.2
	3	5,857 (20.7)	2,633 (20.5)	3,224 (20.8)	-0.8
	4	6,474 (22.8)	2,914 (22.7)	3,560 (23.0)	-0.7
	5 (least deprived)	6,808 (24.0)	2,862 (22.3)	3,946 (25.5)	-7.5
Patient-facing health or social care worker, *n* (%)	Yes	3,190 (11.2)	2,198 (17.1)	992 (6.4)	33.7
Health conditions, *n* (%)	Yes	3,851 (13.6)	1,531 (11.9)	2,320 (15.0)	-9.0
Hospitalisation with acute COVID-19, *n* (%)	Yes	900 (3.2)	359 (2.8)	541 (3.5)	-4.0

Notes: mRNA: messenger ribonucleic acid; SD: standard deviation. The study sample size did not permit disaggregation of ethnicity beyond white and non-white groups. Area deprivation was based on the English Indices of Deprivation 2019, the Welsh Index of Multiple Deprivation 2019, the Scottish Index of Multiple Deprivation 2020, and the Northern Ireland Multiple Deprivation Measure 2017. Health conditions were self-reported rather than clinically diagnosed based on the survey question: “Do you have any physical or mental health conditions or illnesses lasting or expected to last 12 months or more (excluding any long-lasting COVID-19 symptoms)?” Hospitalisation with acute COVID-19 was self-reported rather than derived from medical records.

Table 2. Estimated time trajectories of Long Covid from infection, and changes in trajectories following COVID-19 vaccination

Outcome	Variable	Estimate	SE	P-value	Odds ratio (95% CI)
Long Covid of any severity	Time trajectory (per week)	-0.003	0.003	0.25	0.997 (0.991 to 1.002)
	First vaccination (change in level)	-0.137	0.035	<0.001	0.872 (0.814 to 0.934)
	Second vaccination (change in level)	-0.092	0.031	0.003	0.912 (0.859 to 0.969)
	Time since first vaccination (per week)	0.006	0.005	0.21	1.006 (0.996 to 1.016)
	Time since second vaccination (per week)	-0.011	0.005	0.03	0.989 (0.979 to 0.999)
Activity-limiting Long Covid	Time trajectory (per week)	0.003	0.004	0.44	1.003 (0.996 to 1.010)
	First vaccination (change in level)	-0.131	0.044	0.003	0.877 (0.805 to 0.955)
	Second vaccination (change in level)	-0.096	0.038	0.01	0.909 (0.844 to 0.979)
	Time since first vaccination (per week)	0.006	0.006	0.35	1.006 (0.994 to 1.018)
	Time since second vaccination (per week)	-0.013	0.006	0.03	0.987 (0.976 to 0.998)

Notes: CI: confidence interval; SE: standard error. Estimates and standard errors are on the logit scale. Odds ratios for 'time since first/second vaccination' represent modification of the time trajectory. Estimates and odds ratios are adjusted for age, sex, white or non-white ethnicity, region/country, area deprivation quintile group, health status, whether a patient-facing health or social care worker, whether hospitalised with acute COVID-19, and calendar time of infection.

Table 3. Estimated time trajectories of Long Covid from infection, and changes in trajectories following COVID-19 vaccination, moderated by vaccine type

Outcome	Variable	Estimate	SE	P-value	Odds ratio (95% CI)
Long Covid of any severity	Time trajectory (per week)	-0.004	0.003	0.19	0.996 (0.990 to 1.002)
	First vaccination (change in level)	-0.093	0.055	0.09	0.911 (0.818 to 1.014)
	Second vaccination (change in level)	-0.093	0.051	0.07	0.911 (0.824 to 1.007)
	Time since first vaccination (per week)	0.000	0.008	0.95	1.000 (0.985 to 1.016)
	Time since second vaccination (per week)	-0.004	0.008	0.65	0.996 (0.980 to 1.013)
	Vaccine type: adenovirus vector (versus mRNA)	0.046	0.055	0.40	1.048 (0.941 to 1.166)
	First vaccination interacted with type	-0.069	0.067	0.31	0.934 (0.818 to 1.066)
	Second vaccination interacted with type	0.002	0.064	0.97	1.002 (0.883 to 1.137)
	Time since first vaccination interacted with type	0.009	0.009	0.33	1.009 (0.991 to 1.028)
	Time since second vaccination interacted with type	-0.010	0.010	0.33	0.990 (0.970 to 1.010)
Activity-limiting Long Covid	Time trajectory (per week)	0.002	0.004	0.56	1.002 (0.995 to 1.009)
	First vaccination (change in level)	-0.154	0.070	0.03	0.857 (0.747 to 0.984)
	Second vaccination (change in level)	-0.026	0.064	0.68	0.974 (0.860 to 1.103)
	Time since first vaccination (per week)	0.003	0.010	0.77	1.003 (0.984 to 1.022)
	Time since second vaccination (per week)	-0.013	0.010	0.21	0.987 (0.968 to 1.007)
	Vaccine type: adenovirus vector (versus mRNA)	0.042	0.069	0.54	1.043 (0.911 to 1.195)
	First vaccination interacted with type	0.045	0.087	0.60	1.046 (0.883 to 1.240)
	Second vaccination interacted with type	-0.116	0.080	0.15	0.890 (0.761 to 1.041)
	Time since first vaccination interacted with type	0.004	0.012	0.75	1.004 (0.981 to 1.027)
	Time since second vaccination interacted with type	0.004	0.013	0.73	1.004 (0.980 to 1.029)

Notes: CI: confidence interval; mRNA: messenger ribonucleic acid; SE: standard error. Estimates and standard errors are on the logit scale. Odds ratios for 'time since first/second vaccination' represent modification of the time trajectory. Odds ratios for 'first/second vaccination interacted with type' represent modification of the change in level after first/second vaccination by vaccine type. Odds ratios for 'time since first/second vaccination interacted with type' represent modification of the time trajectory, modified by vaccine type. Estimates and odds ratios are adjusted for age, sex, white or non-white ethnicity, region/country, area deprivation quintile group, health status, whether a patient-facing health or social care worker, whether hospitalised with acute COVID-19, and calendar time of infection.

Figure 1. Study participant flow diagram

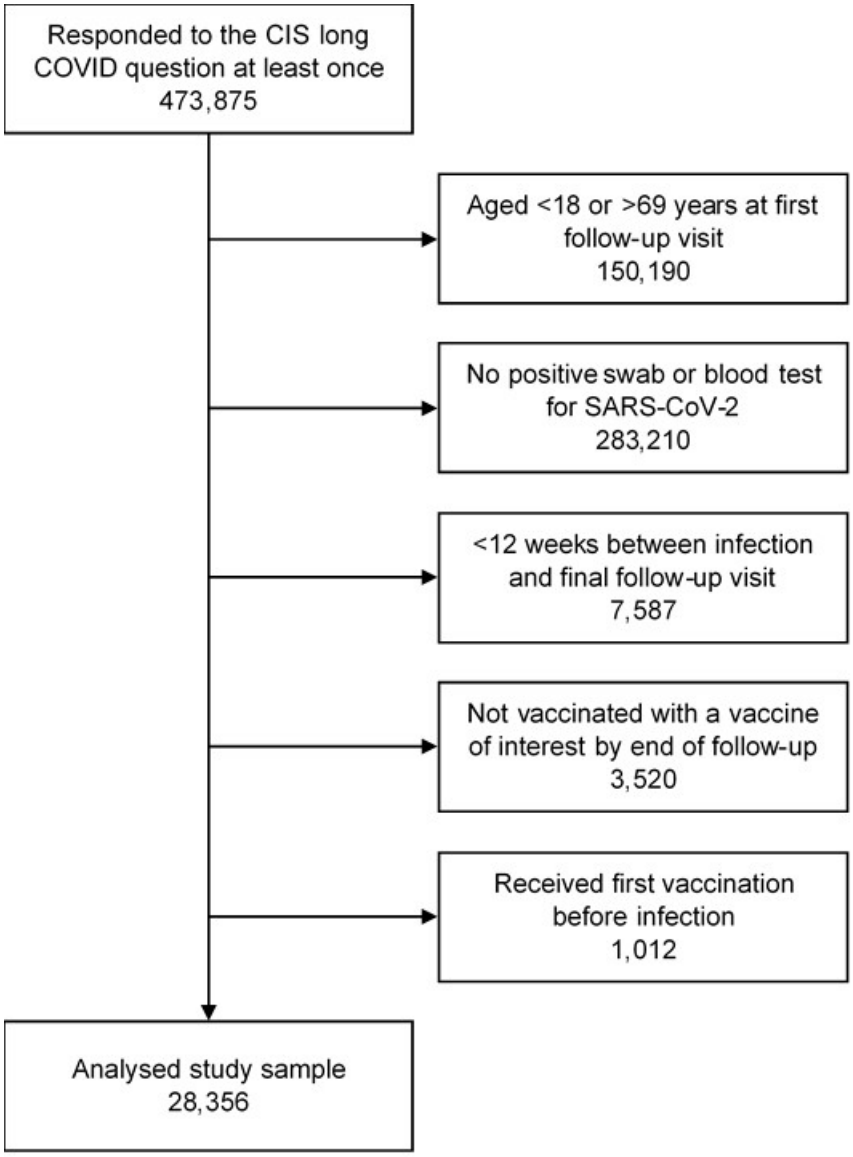
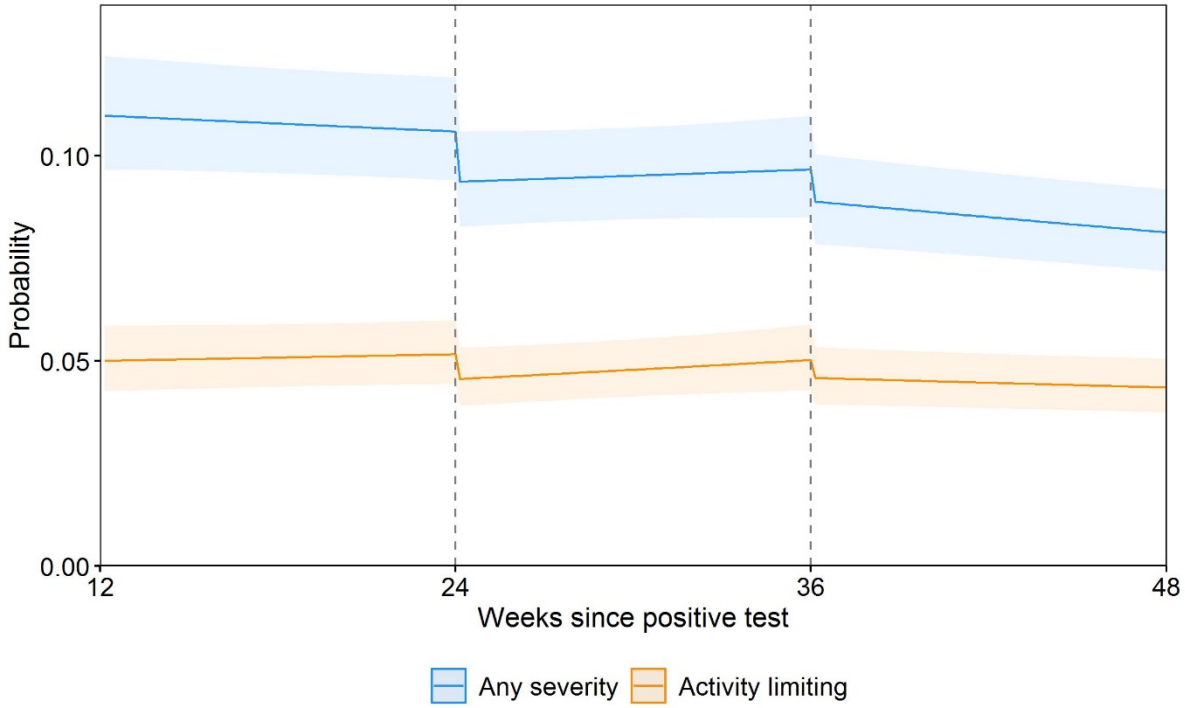
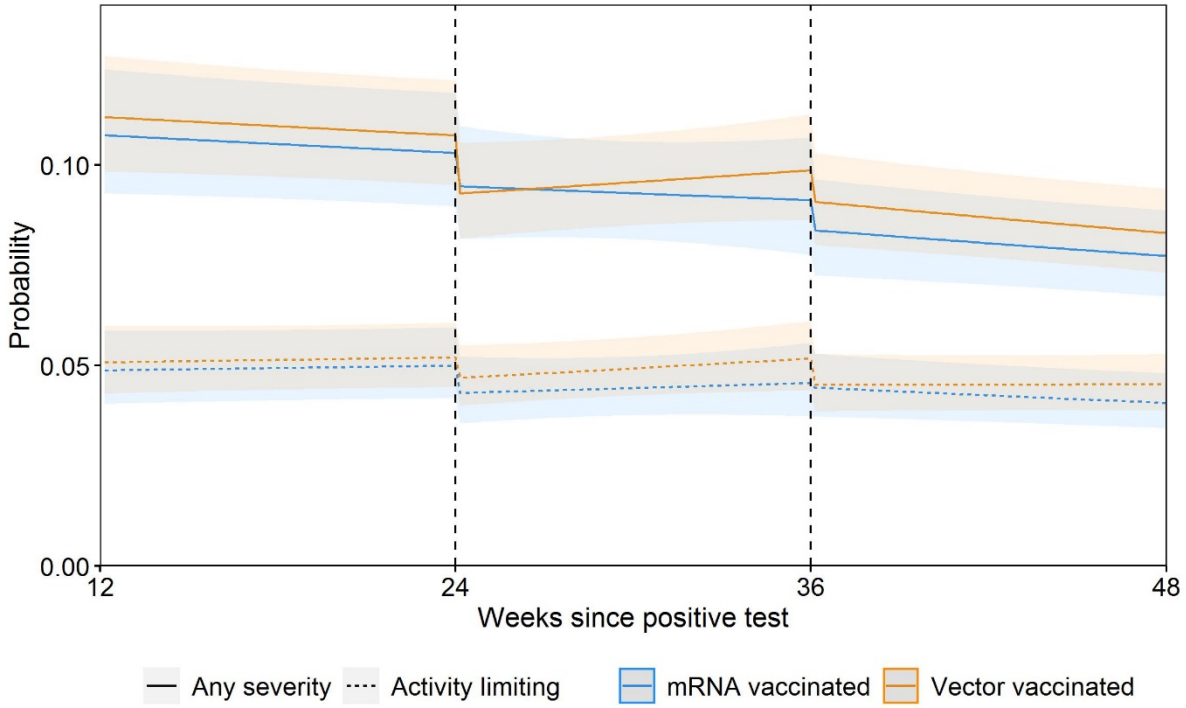


Figure 2. Modelled probabilities of Long Covid for an illustrative study participant who received their first vaccination 24 weeks after infection and their second vaccination 12 weeks later



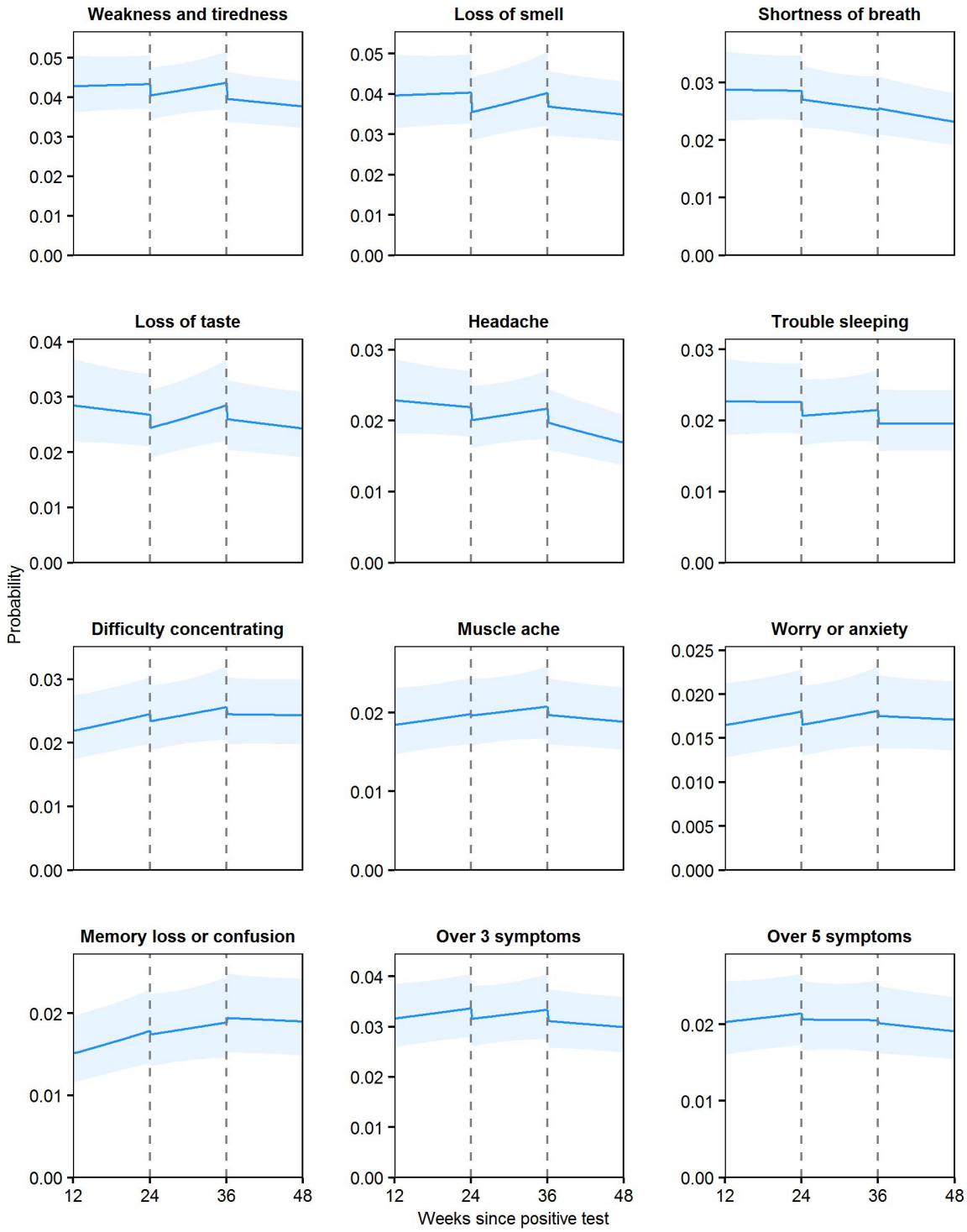
Notes: Probabilities are shown for a participant of approximately mean age (50 years) and in the modal group for other covariates (female, white, living in London, in an area in the least deprived quintile group, not a patient-facing health or social care worker, no pre-existing health conditions, not hospitalised at the acute phase of infection, and infected on 7 September 2020). While the estimated probabilities are specific to this profile, the proportional changes in probabilities after vaccination do not vary across characteristics and can therefore be generalised to other profiles. Dashed lines indicate the timing of vaccination. Shaded areas are 95% confidence intervals.

Figure 3. Modelled probabilities of Long Covid for illustrative study participants who received their first adenovirus vector or mRNA vaccination 24 weeks after infection and their second vaccination 12 weeks later



Notes: mRNA: messenger ribonucleic acid. Probabilities are shown for a participant of approximately mean age (50 years) and in the modal group for other covariates (female, white, living in London, in an area in the least deprived quintile group, not a patient-facing health or social care worker, no pre-existing health conditions, not hospitalised at the acute phase of infection, and infected on 7 September 2020). While the estimated probabilities are specific to this profile, the proportional changes in probabilities after vaccination do not vary across characteristics and can therefore be generalised to other profiles. Dashed lines indicate the timing of vaccination. Shaded areas are 95% confidence intervals.

Figure 4. Modelled probabilities of individual Long Covid symptoms for an illustrative study participant who received their first vaccination 24 weeks after infection and their second vaccination 12 weeks later



Notes: Top 10 most frequently reported symptoms ordered by modelled probability at 12 weeks post-infection. Probabilities are shown for a participant of approximately mean age (50 years) and in the modal group for other covariates (female, white, living in London, in an area in the least deprived quintile group, not a patient-facing health or social care worker, no pre-existing health conditions, not hospitalised at the acute phase of infection, and infected on 7 September 2020). While the estimated probabilities are specific to this profile, the proportional changes in probabilities after vaccination do not vary across characteristics and can therefore be generalised to other profiles. Dashed lines indicate the timing of vaccination. Shaded areas are 95% confidence intervals