OpenSAFELY Protocol: Short-term safety of COVID-19 vaccines in England 2020/21 – neurological events

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Amendments

The table below specifies the version history of the protocol and the rationale for any changes.

Version, Date	Change	Rationale
v2.0	**Comments from External Collaborators.** This revision incorporated comments from external collaborators.	Due to timelines, comments from external collaborators were incorporated after locking v1.0.
v3.0	**Secondary analyses**. The matched (historical and concurrent) cohort study was updated to a cohort study with a time-updated exposure variable	Vaccine uptake was significantly higher than anticipated at the time of writing the study, meaning that concurrent matching was no longer considered feasible to implement.
v3.0	**Exclusion Criteria.** Removed acute disseminated encephalomyelitis (ADEM) from the list of exclusion criteria (both cohort and SCCS)	Following advice from clinical neurologists, it was decided to remove ADEM.

Contents

Background

Safe and effective vaccination is vital for the public health response to the COVID-19 pandemic. The COVID-19 pandemic has prompted rapid vaccine development and roll-out.[1] Three vaccines are in use in the UK: Pfizer BioNTech and Moderna COVID-19 vaccines, which use an mRNA platform, and AstraZeneca COVID-19 vaccine, which uses an adenovirus vector platform. By 2 June 2021, approximately 14.7 million first doses of Pfizer/BioNTech and 24.5 million first doses of AstraZeneca COVID-19 vaccines had been administered in the UK. The Moderna COVID-19 vaccine was introduced later in the UK, on 13 April 2021. Vaccine eligibility in the UK has been prioritised by older age, health and social care occupation, and underlying health conditions (**Appendix A**).

Each vaccine demonstrated a reassuring safety profile in large clinical trials before licensing for use.[2, 3] However, even large clinical trials have limited power to detect rare adverse outcomes which may be detected when the vaccine is rolled out to the general population. In addition, when vaccinating a large population, baseline rates of disease mean that vaccination will occasionally coincide with the onset of illness, and vaccine confidence may be undermined by this whether these events are genuine adverse effects of the vaccine or not.[4, 5] Once vaccines are approved for general use, post-licensing vaccine safety surveillance remains important for vaccine safety and public confidence. National COVID-19 vaccine safety surveillance combines analysis comparing 'Yellow Card' reporting of possible adverse events to expected event rates, analysis of possible adverse outcomes in electronic health records using the Clinical Practice Research Datalink, and active surveillance of selected cohorts under-represented in trials.[6] These aim to rapidly detect and strengthen potential safety signals, but do not adjust for confounding. Any potential safety signals detected require further epidemiological investigation to assess the likelihood of a causal relationship between the vaccine and any potential adverse event.

Pre-specified potential outcomes of interest for surveillance included Bell's palsy, transverse myelitis and Guillain-Barré syndrome. Bell's palsy is an acute palsy of the facial nerve, causing temporary weakness or paralysis of one side of the face.[7] Bell's palsy has previously been investigated as a potential outcome of influenza vaccination, and found to be associated with an intranasal influenza vaccination (which is now no longer in use).[8] In the Pfizer BioNTech COVID-19 vaccine trials, among non-serious unsolicited adverse events, there was a numerical imbalance of four cases of Bell's palsy in the vaccine group compared with no cases in the placebo group, although the four cases in the vaccine group do not represent a frequency above that expected in the general population.[9]

Transverse myelitis is a focal inflammation of the spinal cord, with a characteristic clinical presentation of bilateral motor and sensory symptoms corresponding to the level of the spinal cord inflammation.[10]. Very rare events of neuroinflammatory disorders were reported following vaccination with AstraZeneca COVID-19 vaccine, although a causal relationship was not established. Published study findings describe three cases of transverse myelitis among AstraZeneca COVID-19 vaccine trial participants: one had received the control vaccine, the other had previously unrecognised multiple sclerosis and the third was considered by an independent neurological committee possibly associated with the vaccine but to be most likely to be an idiopathic, short segment, spinal cord demyelination, although an association with the vaccine could not be ruled out.[11] The high-profile pausing of the trial for safety review may have affected vaccine confidence and reporting of transverse myelitis in vaccine recipients.[12]

Guillain-Barré syndrome (GBS) is an autoimmune disease affecting the peripheral nerves, which causes acute and progressive weakness with sensory changes. It is commonly post-infectious,

following acute respiratory or gastrointestinal infection.[13] An excess risk of GBS was found after swine flu vaccination in 1976, but there is a higher rate of GBS after influenza-like-illness than after seasonal influenza vaccination.[14]

A number of reports of Bell's palsy, transverse myelitis and Guillain-Barré syndrome had been reported following vaccination (Table 1). Surveillance analyses in the UK suggest that an association of each of these events with COVID-19 vaccination is possible, but further epidemiological investigation is needed to establish whether or not these events are associated with vaccination, once adjusted for potential confounders such as demographics and underlying health conditions.

Table 1: Yellow card spontaneous reports of selected acute neurological events following Pfizer BioNTech or AstraZeneca COVID-19 vaccination* in the UK, by 2 June 2021

	Pfizer BioNTech COVID-19 vaccine n	**AstraZeneca COVID-19 vaccine** n
Bell's palsy	264	391
Facial nerve disorder	3	4
Facial paralysis	194	230
Guillain-Barré syndrome	38	283
Miller Fisher syndrome	-	16
Other acute polyneuropathy	1	6
Transverse myelitis	17	63
Number of first doses given	c.14.7 million	c.24.5 million

*Moderna vaccination data not shown due to smaller number of doses given with shorter follow up time for reporting

This study aims to investigate whether there is any association between any of the three brands of vaccine widely used in England and each of the following neurological events: Bell's palsy, transverse myelitis, and Guillain-Barré syndrome.

Objectives

Primary Objectives

The primary objective is to investigate separately for each of the Pfizer BioNTech, AstraZeneca and Moderna COVID-19 vaccines whether there is an association between vaccination and each of the following neurological events: Bell's palsy, transverse myelitis, and Guillain-Barré syndrome.

Secondary Objective

A secondary objective is to understand the extent to which self-controlled case series (SCCS) and cohort study designs differ in their estimations of associations of COVID-19 vaccination with the short-term acute outcomes. The purposes of this comparison are: to assess the robustness of findings from SCCS analysis; to inform design of future studies of COVID-19 vaccine safety; and to aid interpretation of findings from other observational vaccine safety studies.

Methods

Data source

We will use data from general practice (GP) records, obtained from the GP software provider TPP, which represent approximately 40% of the population in England, linked to: (1) NHSE/NHSX hospital inpatient activity data sets and emergency care data sets from Secondary Uses Service (SUS) data extracts for ascertaining study outcomes; (2) Office for National Statistics (ONS) death data, including cause of death; (3) NHSE data on healthcare worker status (available only for vaccinated individuals); and (4) NHSE/NHSX Second Generation Surveillance System (SGSS) data on SARS-CoV-2 test results to ascertain a history of COVID-19 infection.

The data will be accessed, linked and analysed through OpenSAFELY, a new data analytics platform created on behalf of NHS England to address urgent questions relating to the epidemiology and treatment of COVID-19.[15] For more information on the OpenSAFELY data platform, please see **Appendix B**.

Study Design

Primary analysis for each outcome will use a self-controlled case series (SCCS) design. Secondary analysis will use a cohort study design with both historical and concurrent comparator groups.

SCCS is a case-only design which compares incidence of events within the same individual across different time periods. An SCCS design is suited to the study of acute outcome events and transient effects of precisely-timed exposures. It is particularly valuable for observational studies of vaccine safety, since people who receive vaccines typically differ from those who are eligible but unvaccinated, by characteristics which are unavailable in routinely recorded electronic health records, such as attitudes to health and health-care, health behaviours and healthcare access. This can result in confounding of observational studies of vaccine safety (sometimes known as the 'healthy vaccinee' effect as vaccinees tend to have better outcomes overall than non-vaccinees).[16] Since self-controlled case series compare incidence of events within the same individual, the SCCS design implicitly controls for confounding by fixed individual characteristics, even for characteristics which are unmeasured.[17]

The SCCS design requires several assumptions, including that the exposure is not (appreciably) affected by outcome events.[17] If this is violated (for example, if vaccination is hastened by hospital admission, or delayed during investigation for acute neurological symptoms), the design is vulnerable to reverse causality bias. It may also be confounded by time-varying characteristics if these cannot be adequately adjusted for: and comparison of time post-vaccination to periods before vaccine introduction may be susceptible to confounding by trends over time in the outcomes or their ascertainment.

Secondary analysis will comprise a cohort study with a time-updated exposure variable ~~both historical and concurrent comparator groups~~. A cohort study design can be a useful complement to investigate the robustness of findings from SCCS analysis in safety studies, since they have a different profile of biases (**Table 2**).[18] The cohort study will not be susceptible to reverse causality, but will be susceptible to confounding by both fixed and time-varying characteristics (particularly the 'healthy vaccinee effect'). A cohort study with a concurrent comparator group can control for any

confounding by trends over time in the outcomes, but may be particularly susceptible to confounding when vaccine uptake is high and unvaccinated individuals are increasingly atypical. For new vaccination programmes, confounding may be reduced by selecting a historical unvaccinated comparator group (individuals who meet vaccine eligibility criteria during a recent time period before vaccination was available), as unvaccinated historical controls have not been selected by their attitudes, behaviour or healthcare access.[19] However, as with the self-controlled case series, a cohort study with a historical comparator group is also susceptible to confounding by trends over time in the outcomes comparing pre- and post-vaccination periods, which can be better addressed in a cohort study with concurrent controls.

Some of these biases can also be evaluated in a cohort study with a time-updated exposure variable, which unlike a cohort study with matched concurrent controls, would not suffer from difficulties in finding matches as vaccine uptake increases. Although a time-updated cohort study is potentially subject to time-varying confounding, this is suspected to be of relatively modest strength given the nature of the outcomes included here. For these reasons, it was decided to move ahead only with a cohort study with a time-updated exposure variable as part of the secondary analyses.

The strengths and limitations of the originally planned study ~~each~~ designs are summarised in **Table 2**. The overall effect of the combined bias and patterns of confounding is difficult to predict, and one of the aims of this study is to compare the estimates from each study design to aid interpretation of other COVID-19 vaccine safety studies.

Table 2: Strengths and limitations of the selected study designs

Design	Key strengths	Key limitations
Primary analysis: Self-controlled case series	● Not susceptible to selection bias or confounding by time-invariant characteristics (such as fixed attitudes or access to healthcare).	● Susceptible to reverse causality (if the outcome affects the probability of exposure). ● May be susceptible to confounding by trends over time (in analyses using a comparison period prior to the introduction of the vaccination programme)
Cohort study (historical comparator group)	● Not susceptible to reverse causality. ● Confounding by 'healthy vaccinee effect' attenuated (compared to cohort study with concurrent comparator group) since controls are not selected on basis of vaccination status, only vaccine eligibility criteria.	● Somewhat susceptible to confounding due to 'healthy vaccinee effect' (compared to SCCS) ● Susceptible to confounding by trends over time pre-compared to post-vaccination period
Cohort study (concurrent comparator group)	● Not susceptible to reverse causality. ● Less susceptible to confounding by trends over time (compared to cohort study with historical controls, or SCCS with comparison	● Susceptible to between person confounding due to 'healthy vaccinee effect'. ● High vaccine uptake could deplete comparator group, particularly among older adults who have high vaccine

	period before the introduction of vaccination).	coverage. The healthy vaccine effect could have a strong confounding effect and estimates of effect modification by age may be particularly affected.

Study Population

The eligible primary study population will comprise all adults (aged 18 years or over) registered at a practice using TPP software. Inclusion and exclusion criteria are summarised in **Table 3**. Individuals will be required to have at least one year's continuous registration prior to the study start date to ensure that outcome event codes represent new incident outcomes rather than retrospective recording of past events.[20] Patients with missing age or a recorded age under 18 years or over 105 years, missing sex, or missing postcode (used to identify care home residence) will be excluded. Individuals who receive a COVID-19 vaccine of unclear brand (unspecified or more than one brand specified on the same date) will be excluded from SCCS, and censored from the vaccination date in cohort study analysis. Women with evidence of pregnancy during the 9 months prior to baseline will also be excluded, as national guidance on vaccination of pregnant women was initially cautious and has evolved during the study period.

The national vaccination programme began on 8 December 2020, and this will be the study start date for the cohort study analysis vaccinated group and concurrent comparator group. The study start date for SCCS and cohort study historical control group is 1 July 2020, selected to provide some pre-vaccination comparison period while minimising changes over time in ascertainment of outcomes. During the period March 2020 to June 2020 primary care contacts and hospitalisations for many non-COVID conditions were considerably depressed compared to the same period in 2019, but were considerably recovered for many acute severe physical conditions by the start of July 2020.[21, 22] The study end date for both designs will be three weeks prior to the latest SUS linkage on the date of data extraction, to allow for reasonably complete recording of hospitalisations.[23, 24]

To ensure that only new incident events are recorded as study outcomes, for each outcome of interest we will exclude individuals with a diagnosis of the outcome of interest in the year prior to the study start date.

Among individuals with an existing diagnosis of chronic neurological disease which can cause repeated episodes of transverse myelitis, discrete episodes of transverse myelitis may be managed directly in specialised outpatients and may not be individually recorded in primary care. Individuals with a diagnosis of multiple sclerosis, neuromyelitis optica, or acute disseminated encephalomyelitis (ADEM) at baseline will be excluded from analyses of transverse myelitis. Individuals diagnosed with any of these conditions during the study will have follow up censored at the date of diagnosis in the main analysis. We will similarly exclude or censor follow-up at diagnosis of chronic inflammatory demyelinating polyneuropathy (CIPD) for the analysis of Guillain-Barré syndrome.

Table 3: Summary of primary study population inclusion and exclusion criteria

	Inclusion / Exclusion Criteria
Inclusion criteria	Aged 18 - 105 years old AND Continuously registered in TPP for at least one year before study start date
Exclusion criteria	Missing age or a recorded age under 18 years or over 105 years on 31 March 2021, missing sex, or missing care home status or unknown IMD OR (for all analyses) ● received a COVID-19 vaccine of unspecified or unclear brand (excluded from SCCS, censored from cohort study)

	• a record of the outcome of interest in the year prior to study start date • evidence of pregnancy in the 9 months prior to study start date OR (for transverse myelitis analysis) • a diagnosis of multiple sclerosis, or neuromyelitis optica~~, or acute disseminated encephalomyelitis (ADEM)~~ OR (for Guillain-Barré syndrome analysis) • a diagnosis of chronic inflammatory demyelinating polyneuropathy (CIPD)

Study Measures

Exposure

The exposure of interest is the brand-specific first dose of vaccination against COVID-19. Each vaccine brand will be analysed separately, with first dose of brand-specific vaccination compared to absence of vaccination in the main analysis. A secondary analysis will compare first dose of AstraZeneca to first dose of Pfizer BioNTech vaccine.

Vaccination status will be determined from the 'vaccination table' in the TPP primary care record, Vaccination type and date are recorded using SNOMED codes together with dictionary of medicines and devices "dm+d" codes. Vaccine type will be categorised as AstraZeneca, Pfizer BioNTech, Moderna or unspecified/unclear (for exclusion from SCCS and censoring vaccine eligibility in cohort study analysis). The details of all administered vaccinations are automatically sent to every person's GP, as well as being recorded in the National Immunisation Management Service.

All COVID-19 vaccines currently in use in the UK require a two-dose regimen. In the main analysis we will disregard second doses. Individuals will be considered vaccinated from the first dose of vaccine, and the vaccine brand will be based on the first dose given.

For secondary analysis, we will also explore second dose of vaccination. A second dose will be defined as a second record of vaccination at least 21 days after the first dose, and will be assumed to be the same brand as the first dose unless otherwise specified. In SCCS analysis, days 5-42 post second dose of vaccination will censor the first dose risk window and start a separate risk window. A pre-exposure window will only be included for second dose vaccination after the risk window from the first dose has ended. In cohort analysis we will consider a second dose of the same brand of vaccine as a separate exposure category, with the exposure modelled in a time-updated fashion. We will describe the number of individuals for whom the second dose of vaccine is unclear (unspecified or more than one brand recorded on the same day) or discordant (second dose of vaccine is different brand from the first dose), and depending on numbers may consider sensitivity analysis or quantitative bias analysis exploring the possible impact of vaccine brand misclassification.

Outcomes

The study outcomes of interest are Bell's palsy, transverse myelitis, or Guillain-Barré syndrome, incident during the study period.

Bell's palsy has previously been found to be predominantly recorded in primary care with good completeness within 6 weeks.[7] Primary care recording has been found to have a high positive predictive value.[25] Hospital admission records will be used to supplement ascertainment, using the ICD-10 code recommended by the Brighton Collaboration case definition.[26] Patients may also present to emergency departments without requiring hospital admission, and the diagnosis of Bell's palsy is included in the selected reference set of diagnoses recorded in emergency care.[27, 28] Bell's palsy, and so will be ascertained from the first record in any of primary care, emergency care, hospital admission or mortality records.

Acute transverse myelitis will be defined specifically, and the study definition will not include other myelitis or broader conditions which may include myelitis. The Brighton Collaboration definition of acute myelitis has been reviewed to identify ICD-10 codes for transverse myelitis, but codes for other acute myelitis not specified as transverse myelitis will not be included as outcome events in this study.[29] Similarly, myelitis may accompany encephalitis or be part of clinically isolated syndrome: encephalomyelitis and clinically isolated syndrome will not be included as outcome events. Repeated episodes of transverse myelitis may be part of acute disseminated encephalitis and encephalomyelitis (ADEM), multiple sclerosis, or neuromyelitis optica, and for patients with these conditions, transverse myelitis episodes may not be recorded separately. Patients with ADEM, multiple sclerosis or neuromyelitis optica will be censored at diagnosis with any of these conditions. Transverse myelitis is not included in the restricted reference set of diagnosis codes that may be recorded in the emergency care dataset, and will be ascertained from the first record in any of primary care, hospital admission, or mortality records.[28]

The study definition of Guillain-Barré syndrome (GBS) will include Miller Fisher syndrome and other GBS subtypes. The ICD-10 code for ascertainment is consistent with the Brighton-Collaboration case definition.[30] Guillain-Barré syndrome is a specialist diagnosis unlikely to be confirmed within an emergency care attendance, and patients presenting to emergency care with Guillain-Barré syndrome would be expected to require hospital admission for investigation and treatment. This outcome will be ascertained from the first record in any of primary care, hospital admission, or mortality records, but not from emergency care records.

For each study outcome, an incident outcome will be defined as occurring on the date of the first diagnosis recorded during follow up, in any data source. A single episode of illness may result in more than one code being recorded at multiple points of follow up. Only the first recorded diagnosis of a study outcome during the study period will be included. After this, individuals will not be eligible for another incident episode of the same study outcome during the study.

Table 4: Codelists for study outcomes

	Primary care (CTV3)		Hospital and mortality records (ICD-10)	Emergency Care (SNOMED simple reference set)
Bell's palsy	2BR6. 2BR7. F31.. F310. F31z. X009n X00jD	O/E -cranial nerve 7-palsy-LMN O/E -cranial 7 -paralysis -LMN Disorder of facial nerve Bell's palsy Facial nerve disorder NOS Facial neuropathy Inflammatory facial neuropathy	G51.0 Bell palsy	193093009 Bell's palsy (disorder)

	X76nD Facial weakness, lower motor neurone XE18F Bell's palsy &/or facial palsy Y6712 Facial nerve disorders		
Transverse myelitis	https://www.opencodelists.org/codelist/opensafely/transverse-myelitis/2020-09-23	G37.3 Acute transverse myelitis	N/A
Guillain Barré syndrome	F370. Acute infective polyneuritis F3700 Guillain-Barre syndrome F3701 Post-infectious polyneuritis F370z Acute infective polyneuritis NOS F37z. (Toxic or inflamm neuropathy NOS) or (polyneuropathy unspec) Fyu7B [X]Inflammatory polyneuropathy, unspecified X00AV Miller-Fisher variant of Guillain-Barre syndrome X00CG Demyelinating sensorimotor neuropathy XE18N Acute infective polyneuritis (& [Guillain-Barre syndrome])	G61.0 Guillain-Barré syndrome	N/A

Covariates

Factors associated with COVID-19 vaccine eligibility, access and uptake were considered as potential confounders for all outcomes if they could also affect access to healthcare to investigate and diagnose the outcome. On this basis, potential confounders for all outcomes include:

- age
- geographical area (categorised by Sustainability and Transformation Partnership)
- care home residence
- sex
- ethnicity
- index of multiple deprivation quintile
- calendar time (as ascertainment was expected to be affected by the pandemic effect on health-seeking behaviour and health services)

Risk factors for the outcome were considered as potential confounders for that outcome if they could affect vaccine eligibility, uptake, or timing (as detailed in **Appendix C**). Potential confounders for specific outcomes are summarised in **Table 4**. All covariates will be assessed at the study start date other than age (which will be assessed on 31 March 2021 for consistency with vaccine eligibility).

Table 4: Outcome-specific risk factors considered as potential confounders

Outcome	Potential confounders in cohort study analysis
Bell's palsy [31]	• Diabetes mellitus • HIV • Hypertension • Systemic inflammatory or autoimmune disorders combining: ankylosing spondylitis, antiphospholipid syndrome, Behçet disease, mixed

	connective tissue disease, rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren syndrome, systemic lupus erythematosus, and sarcoidosis.
Transverse myelitis [29]	● HIV ● Systemic inflammatory or autoimmune disorders combining: ankylosing spondylitis, antiphospholipid syndrome, Behçet disease, mixed connective tissue disease, rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren syndrome, systemic lupus erythematosus, and sarcoidosis. ● A recent diagnosis of incident cancer ● A history of haematological cancer
Guillain-Barré syndrome [30, 32]	● Systemic lupus erythematosus ● A recent diagnosis of incident cancer ● A history of haematological cancer ● HIV

We will ascertain a history of COVID-19 infection on the vaccination date (or index date for matched controls in the cohort analysis) using a positive test result in SGSS.

Statistical Analysis

Self-controlled case series

The primary analysis for all prespecified outcomes will use a self-controlled case series design, which uses conditional Poisson regression to calculate incidence rate ratios comparing time periods for the same individual, with time windows defined relative to the individual's vaccination date. A separate analysis will be conducted for each of AstraZeneca, Pfizer BioNTech and Moderna COVID-19 vaccine brands.

Eligible individuals will be included in self-controlled case series analyses if they have experienced both the exposure (brand-specific first dose of COVID-19 vaccination) and the outcome of interest. The main analysis will be an unadjusted analysis using conditional Poisson regression. All potential confounders are considered fixed individual characteristics within the short time frame of the study, and are innately controlled for by the study design. Due to the potential changes in ascertainment over time during the study period, including any delay in recording of events in GP records after longer hospital admissions towards the end of the study period, we will adjust for weekly period effect to account for this. We will then additionally explore a history of COVID-19 infection by the vaccination date as a potential effect modifier, by stratification. We will also explore for effect modification by age, grouped as 16—39, 40—64 and 65—105 years (subject to sufficient numbers in each age group).

The main risk window of interest for post-vaccination exposure will be 4—28 days after first dose vaccination for Bell's palsy and acute transverse myelitis and 4—42 days after first dose vaccination for Guillain-Barré syndrome. The Brighton Collaboration recommended risk window for each of facial nerve palsy, acute myelitis and Guillain-Barré syndrome as possible reactions to inactivated or subunit vaccines is 5-28 days for primary analysis and 2-42 days for secondary analysis.[26, 29, 30] However, the association of intranasal adjuvanted influenza vaccination with Guillain Barre syndrome had a longer risk period, and so we have selected the extended risk window for primary analysis of

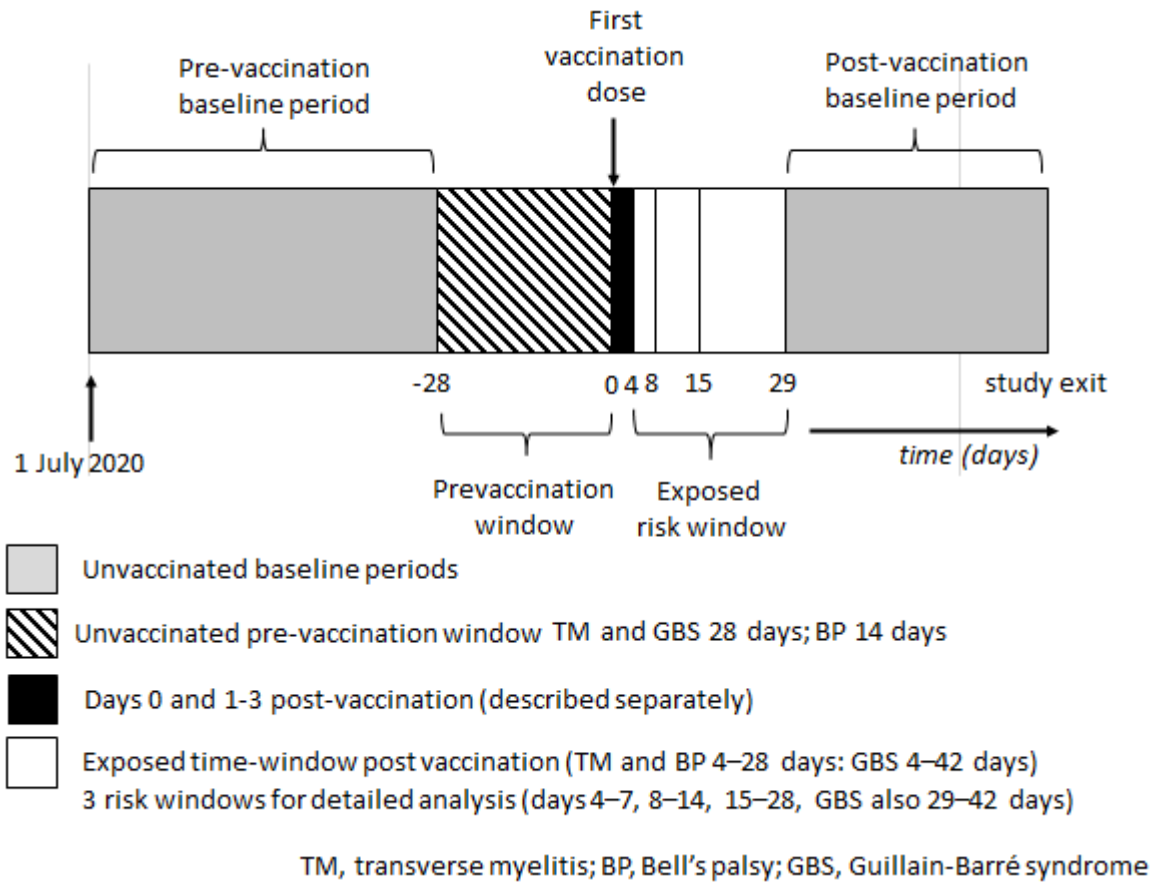
Guillain-Barré syndrome. We will also consider a sensitivity analysis extending the post-vaccination risk window for GBS according to findings from the cohort study.

SCCS designs assume that occurrence of an outcome event (Bell's palsy, transverse myelitis or Guillain-Barré syndrome) should not alter the probability of subsequent exposure (to COVID-19 vaccination).[17, 33] This may be violated through deferral of vaccination while unwell, under investigation for unexplained symptoms, or recovering from the outcome event. To minimise this, we will exclude a pre-exposure window of four weeks for transverse myelitis and Guillain-Barré syndrome, and two weeks for Bell's palsy.

The unexposed time period will run from the study start date of 1 July 2020 to the start of the pre-exposure window, combined with follow up time from the end of the post-vaccination risk window until the end of study follow up.

The incidence may not be constant over the risk window, so if there are sufficient cases we will also break down the exposed period into risk windows of 1-3, 4-7, 8-14, 5-28 and (for GBS) 29-42 days for a more detailed description of the risk period. We will describe the number of events on the day of vaccination separately, to exclude opportunistic recording of outcomes on the day of vaccination from the main analysis.[25]

Figure 1: Illustration of time-windows for self-controlled case series (main analysis)



TM, transverse myelitis; BP, Bell's palsy; GBS, Guillain-Barré syndrome

An SCCS design assumes that outcome events do not influence the length of observation period. This assumption may be violated by excess mortality following the study outcomes. This would be unexpected for these study outcomes, but we will describe the number of individuals who died within 42 days of the outcome event, and check for event-dependent censoring of observation time by describing time from event to end of observation in two histograms according to whether observation times are censored or not.[33] Depending on findings, we will consider whether to exclude all individuals who died within 42 days of the outcome event (if there are a small number of deaths), or use an extension of the SCCS model to take the distribution of intervals from event to end of observation into account.[34]

The SCCS design also assumes that recurrent outcome events are independent, that is, the chance of a second event is not influenced by having a first event.[17] The study definition of an incident event means that recurrence cannot occur within the study period.

Sensitivity Analyses

We will conduct sensitivity analyses to assess the robustness of the primary analysis to our assumptions.

Restricting the baseline comparison window to post-vaccination time

Inclusion of pre-vaccination time (particularly prior to 8 December 2020) includes time in which individuals were not eligible for the exposure. To reduce confounding by trends in outcomes over time, a sensitivity analysis will compare the main risk window to post-vaccination follow-up time, without any comparison to the pre-vaccination period.

Varying pre-exposure excluded window

We will describe the interval between vaccination and outcome for each outcome, using a histogram (an 'exposure-centred interval plot') to assess the suitability of the length of the pre-exposure window for each outcome, and may conduct sensitivity analyses varying the length of the pre-exposure window in response to these.[33] In addition, depending on the effect of acute illness on deferral or non-uptake of vaccination, exclusion of the pre-exposure window may in fact introduce bias. We will therefore conduct a sensitivity analysis in which the pre-exposure window is not excluded from the baseline comparison period.

Extending the risk window following vaccination

It is possible that potential adverse events may take longer than 28 or 42 days to manifest and be diagnosed.[8] Depending on post-vaccination rates observed in the cohort study, we may also extend the post-vaccination risk window to 42 days for Bell's palsy and transverse myelitis, and 90 days for GBS.

Unspecified or conflicting vaccine brand

We will describe the number of individuals with unspecified brand of vaccination, and individuals who receive a second dose of vaccine of a different brand to the first dose. Depending on numbers, we may conduct sensitivity analyses to additionally include individuals with unspecified vaccine brand in each brand-specific analysis, and to censor follow up at second vaccination dose if the second dose of vaccine is a different brand to the first dose.

Excluding healthcare workers

Transverse myelitis and GBS may result in time off work or even prevent return to work. This could introduce reverse causation in SCCS, which will include healthcare workers eligible for vaccination due to their work if they have an underlying health condition. A linked dataset is available with healthcare worker status for vaccine recipients, and this will be used to exclude healthcare workers from a sensitivity analysis.

Cohort study

A secondary analysis for all outcomes will use a ~~matched~~ cohort study design analysed using a ~~conditional~~ Poisson regression model. We will analyse each vaccine brand and outcome separately, comparing people vaccinated with the relevant brand of vaccine to those not vaccinated. We will split the comparator time into two different groups: (1) unvaccinated time before the availability of the vaccine; and (2) unvaccinated time after the availability of the vaccine, as outlined below. Vaccinated time for each brand will be compared to both of these reference groups in turn. ~~each of two separate comparator groups: one concurrent, and one historical, for each outcome.~~ Patients will be followed from the 1 July 2020 until the outcome or censor date, whichever comes first. This follow-up time will consequently be categorised into exposure periods of interest, as follows:

1. **Unvaccinated, vaccine not available :** Index until 8 December 2020, outcome, or censoring, whichever comes first.
2. **Unvaccinated, vaccine available:** 8 December 2020 until outcome or censoring, whichever comes first. Note, this excludes risk periods after a vaccine dose (3 and 4 below)
3. **Vaccinated, one dose:** First vaccine dose until 28 days (42 for GBS), outcome, or censoring, or second vaccine dose, whichever comes first.
4. **Vaccinated, two doses:** Second vaccine dose until 28 days (42 for GBS), outcome or censoring, whichever comes first.

Patients' exposure status will change over time. The risk categories of interest, 3 and 4, will be compared both to unvaccinated person time when the vaccine was not available [1], as well as unvaccinated time when the vaccine was available [2], broadly corresponding to a historical and a concurrent comparator group.

We will use lexis expansion to adjust for calendar time to take any period effects on outcome ascertainment into account.

~~Eligible individuals who are vaccinated with the relevant brand will be matched to up to 10 concurrent and historical controls by age (80+, 75-79, 70-24, 65-69 and <65 years) and area (STP).~~

~~Unvaccinated individuals will be eligible to be concurrent controls from 8 December 2020, and the index date will be the vaccination date. Individuals will be eligible to be historical controls from 1 July 2020. The index date for concurrent controls will be the vaccinated individual's vaccination date, and 160 days prior to the vaccination date (the difference between 1 July and 8 December) for the historical controls~~. Individuals will exit the study at the earliest of: study outcome, death, leaving the practice, study end date, or (for analyses of transverse myelitis) diagnosis of ~~ADEM~~, multiple sclerosis or neuromyelitis optica. Vaccinated individuals will be eligible to become controls until their vaccination date. ~~Follow up of controls will be censored at vaccination (with any brand of COVID-19 vaccine, including Moderna or unspecified/unclear brand).~~

We will explore for potential confounding by age, sex, care home residence, deprivation, and additionally by relevant underlying health conditions at baseline for each outcome (**Table 4**).

To explore for potential confounding by ethnicity, we will assess the association of vaccination with each outcome with and without adjustment for ethnicity in a complete case analysis. If there is evidence of confounding by ethnicity, we will analyse the final model as a complete case analysis, excluding individuals with missing ethnicity.

Finally, we will explore for effect modification by age, grouped as 16-39, 40-64 and 65-105 years.

Among vaccinated individuals, we will describe rates of each outcome over time following vaccination, which may be used to inform the length of the post-vaccination risk window in SCCS sensitivity analysis.

Sensitivity analyses

Restricted to vaccination in 2021

The initial vaccination programme in December targeted individuals at highest risk and in particular settings. The additional deployment of the AstraZeneca vaccine in early January, increasing vaccine supply and reducing cold chain requirements, was followed by vaccination of less highly-selected individuals. We will therefore restrict to individuals vaccinated after 1 January 2021 for a sensitivity analysis with lower power and shorter duration of post-vaccination follow up, but which may be less subject to confounding by unmeasured characteristics.

~~**Excluding women with evidence of pregnancy**~~

~~We are unable to reliably identify the timing of current pregnancies to time-update pregnancy status during the study. We will describe the number of completed pregnancy outcomes (livebirths, stillbirths, miscarriages and terminations) during the cohort study with concurrent controls, using primary care records. Depending on numbers, we will consider the need for sensitivity analysis excluding individuals with any record of a completed pregnancy during the study.~~

~~**Length of follow-up for the concurrent comparator group**~~

~~We will describe length of follow up for the concurrent comparators by age group. For age groups with high vaccine coverage and depletion of available controls, we will consider the need for sensitivity analysis censoring follow up of these age groups to reduce the 'healthy vaccinee' confounding effect. We will also censor follow up of individuals and concurrent controls aged under 30 years on 7 April 2021 and individuals and controls aged under 40 years on 7 May 2021, since from these dates individuals of these ages were offered Pfizer or Moderna but not AstraZeneca vaccine.~~

Quantitative bias analysis

Depending on results, we may also consider quantitative bias analysis to describe the potential difference in confounding between analysis with concurrent and historical comparator groups, and to describe the extent of residual confounding that would be required to explain any observed association.

Secondary analyses

For both SCCS and cohort study designs, we will undertake the following secondary analyses.

Relative safety of the two different vaccines

When two products are in use as alternatives for the same population, a head-to-head comparison can reduce residual confounding.[18]

In the UK, the Pfizer BioNTech COVID-19 mRNA vaccine was available sooner than the AstraZeneca COVID-19 adenovirus vector vaccine, and was delivered to the highest priority individuals, including targeting by setting such as hospital inpatients. During the time in which both vaccinations have been available, the different cold chain requirements and batch sizes have resulted in the delivery of different vaccination brands by setting, which is also likely to result in confounding of a head-to-head comparison, with confounding varying geographically due to different local delivery plans. In addition, a head-to-head comparison of vaccine brands may miss any safety issues common to both vaccine brands. Despite its potential advantages for reducing confounding by indication, a head-to-head comparison of the vaccine brands has therefore not been selected for main analysis.

As a secondary analysis we will use a ratio-of-ratios approach to compare the relative safety of the two vaccine brands, with the *a priori* hypotheses that the Pfizer BioNTech vaccine will have a greater association with Bell's palsy than the AstraZeneca COVID-19 vaccine, and the AstraZeneca COVID-19 vaccine a greater association with transverse myelitis and GBS than the Pfizer BioNTech vaccine. This analysis will be limited to vaccinations from 1 January 2020 (the period from which both vaccines were available), and will be interpreted with caution due to the likelihood of confounding by indication.

Second dose of vaccination

Depending on the number of eligible individuals who received a second dose of vaccination during follow up, we will consider the second dose of vaccination as a separate exposure. In cohort study analysis, vaccine exposure will be categorised as a time-updated variable considering unvaccinated, first dose, or second dose received. In SCCS analysis, days 5-42 post second dose of vaccination will censor the first dose risk window and start a separate risk window, as described in more detail in 'Exposure' above.

Software and Reproducibility

Data management will be performed using Python and Google BigQuery, with analysis carried out using Stata 16.1 MP. The codelists, and code for data management and analysis are archived online https://github.com/opensafely/covid-vaccine-safety-research.

Administrative

Information Governance

NHS England is the data controller; TPP is the data processor; and the key researchers on OpenSAFELY are acting on behalf of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment, which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant;[35, 36] patient data have been pseudonymized for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymized datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is through a virtual private network (VPN) connection; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; and only aggregate statistical outputs leave the platform environment following best practice for

anonymization of results such as statistical disclosure control for low cell counts.[37] The OpenSAFELY research platform adheres to the data protection principles of the UK Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR) 2016. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organizations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure.[38] Together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

Ethics

We received ethics approval to conduct the data linkage and analyses by the London - City & East Research Ethics Committee on the 2nd of April 2020 (REC reference: 20/LO/0651) and LSHTM Ethics Board (ref 21863). No further ethical or research governance approval was required by the University of Oxford but copies of the approval documents were reviewed and held on record.

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The views expressed are those of the authors and not necessarily those of the NIHR, NHS England, Public Health England or the Department of Health and Social Care.

Conflict of Interests

Members of the OpenSAFELY collaboration employed by Oxford University are listed in the author affiliations, above. None of the study authors were directly involved in the development of the Oxford AstraZeneca vaccine. Public Health England Immunisation and Countermeasures Division has

provided vaccine manufacturers with post-marketing surveillance reports which the companies are required to submit to the UK Licensing Authority in compliance with their Risk Management Strategy, and a cost recovery charge is made for these reports. IJD has received unrestricted research grants and holds shares in GlaxoSmithKline (GSK). EW has received payments from AZ for providing training, unrelated to the submitted work. BG has received research funding from the Laura and John Arnold Foundation, the NHS National Institute for Health Research (NIHR), the NIHR School of Primary Care Research, the NIHR Oxford Biomedical Research Centre, the Mohn-Westlake Foundation, NIHR Applied Research Collaboration Oxford and Thames Valley, the Wellcome Trust, the Good Thinking Foundation, Health Data Research UK (HDRUK), the Health Foundation, and the World Health Organization; he also receives personal income from speaking and writing for lay audiences on the misuse of science. TS was Chair/Co-Chair of the United Kingdom Research and Innovation / National Institute for Health Research COVID-19 Rapid Response and Rolling Funding Initiatives, was an Advisor to the UK COVID-19 Therapeutics Advisory Panel and is a member of the UK Medicines and Healthcare Products Regulatory Agency COVID-19 Vaccines Benefit Risk Expert Working Group.

Appendix A: UK COVID-19 vaccine prioritisation

COVID-19 vaccination in the UK was prioritised according to advice from the Joint Committee on Vaccination and Immunisation (**Table A1**).

Table A1: Priority groups for vaccination advised by the Joint Committee on Vaccination and Immunisation (reproduced from the Green Book provisional guidance, 5 December 2020 update)[39]

Priority group	Risk group
1	Residents in a care home for older adults Staff working in care homes for older adults
2	All those 80 years of age and over Frontline Health and social care workers
3	All those 75 years of age and over
4	All those 70 years of age and over Clinically extremely vulnerable individuals (not including pregnant women and those under 16 years of age)
5	All those 65 years of age and over
6	Adults aged 16 to 65 years in an at-risk group*
7	All those 60 years of age and over
8	All those 55 years of age and over
9	All those 50 years of age and over

* 'at-risk' groups comprise individuals with any of: chronic respiratory disease including severe asthma, chronic heart disease including atrial fibrillation, peripheral vascular disease, a history of venous thromboembolism, chronic kidney disease, chronic liver disease, stroke, transient ischaemic attack, cerebral palsy, Down's syndrome, or other chronic neurological conditions which may compromise respiratory function, diabetes mellitus, immunosuppression due to disease or treatment including any history of haematological malignancy, morbid obesity, severe mental illness, adult carers, and younger adults in residential care settings. Eligibility for people with learning disability was widened in February 2020.

Appendix B: The OpenSAFELY data platform

OpenSAFELY provides a secure software interface allowing the analysis of pseudonymised primary care patient records from England in near real-time within the I vendor's highly secure data centre, avoiding the need for large volumes of potentially disclosive pseudonymised patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimises any risk of re-identification. Similarly pseudonymised datasets from other data providers are securely provided to the I vendor and linked to the primary care data. Descriptions of OpenSAFELY have been previously published,[40] and more information can be found on https://opensafely.org/.

Primary care records retrieved from the TPP SystmOne electronic health record system include diagnoses (Read 3 CTV3 and SNOMED coded), prescriptions (dictionary of medicines and devices, dm+d coded), basic sociodemographics and vital signs for 22 million individuals – approximately 40% of the English population. Data extracted by SystmOne have previously been used in medical research, as part of the ResearchOne dataset.[41]

All data is held in a secure research environment hosted by TPP, which is a Tier 3 data centre, accredited to NHS Digital standards for centrally hosted clinical systems (ISO 27001 standard and IG Toolkit version 2). We received ethics approval to conduct the data linkage and analyses by the London – City & East Research Ethics Committee on the 2nd of April 2020 (REC reference: 20/LO/0651) and LSHTM Ethics Board (ref 21863). No further ethical or research governance approval was required by the University of Oxford but copies of the approval documents were reviewed and held on record.

Appendix C: Consideration of outcome-specific risk factors as possible confounders

For each outcome, risk factors for the outcome were considered as potential confounders if they could affect vaccine eligibility, uptake, or timing.

Bell's palsy

Risk factors for Bell's palsy include diabetes mellitus, HIV, hypertension, amyloidosis, sarcoidosis, Sjögren syndrome, Lyme disease, parotid nerve tumours, and pregnancy.[31]

Risk factors for Bell's palsy that are also indications for vaccination and will therefore be considered as possible confounders are **diabetes mellitus** and **HIV**. Hypertension is a risk factor for Bell's palsy and not itself an indication for vaccination, but **raised blood pressure** is a risk factor for cardiovascular and cerebrovascular events which are an indication for vaccination, and will be considered as a potential confounder. **Systemic inflammatory or autoimmune conditions** such as amyloidosis, sarcoidosis or Sjögren syndrome are not themselves indications for vaccination, but would typically result in vaccine eligibility due to immunosuppressing medications, and will therefore also be combined for consideration as possible confounders.

Lyme disease and **parotid nerve tumours** are not indications for vaccination, and were not considered likely to considerably affect vaccine uptake, and so will not be considered as confounders. **Pregnancy** is a risk factor for Bell's palsy and a contraindication to vaccination and therefore a possible confounder. However, identification of pregnancy status in primary care or hospital admission records relies heavily on records of delivery or other outcomes of completed pregnancy, and therefore identification of pregnancy was therefore not considered feasible for this study.

Bell's palsy is **seasonal**. Vaccination has been delivered over a single year winter-summer, and the pre-vaccination comparison season for SCCS and historical controls is summer/autumn, and so the SCCS and historical controls analyses may be vulnerable to confounding by seasonality despite adjustment for calendar time during the study. We considered including a comparison period from recent years to match the vaccination seasons, but the changes in outcome incidence since the onset of the COVID-19 pandemic (for example due to physical distancing and changes in circulation of non-COVID respiratory viruses) and ascertainment (due to healthcare attendance, access, and coding) suggest that outcome incidence in previous winters would not be a useful comparison period. The cohort study comparison to concurrent controls should be less vulnerable to confounding by season.

Transverse myelitis

Transverse myelitis may be idiopathic, post-infectious, due to systemic inflammation, or due to multifocal central nervous system disease.[10] Incidence varies with age. Multiple sclerosis is more common in women but otherwise there is no known gender, ethnic or genetic predisposition to acute transverse myelitis.[29]

A wide range of bacterial and viral infections may cause transverse myelitis, and one study found a recent infection in 12% of cases of acute and subacute myelopathy.[29] Acute infections which may not be severe were considered unlikely to affect vaccination outside the excluded pre-vaccination window, and also particularly unlikely to be well-ascertained in primary care records during a

COVID-19 pandemic. **HIV** is a chronic infection which is an indication for vaccination, and so will be considered as a potential confounder.

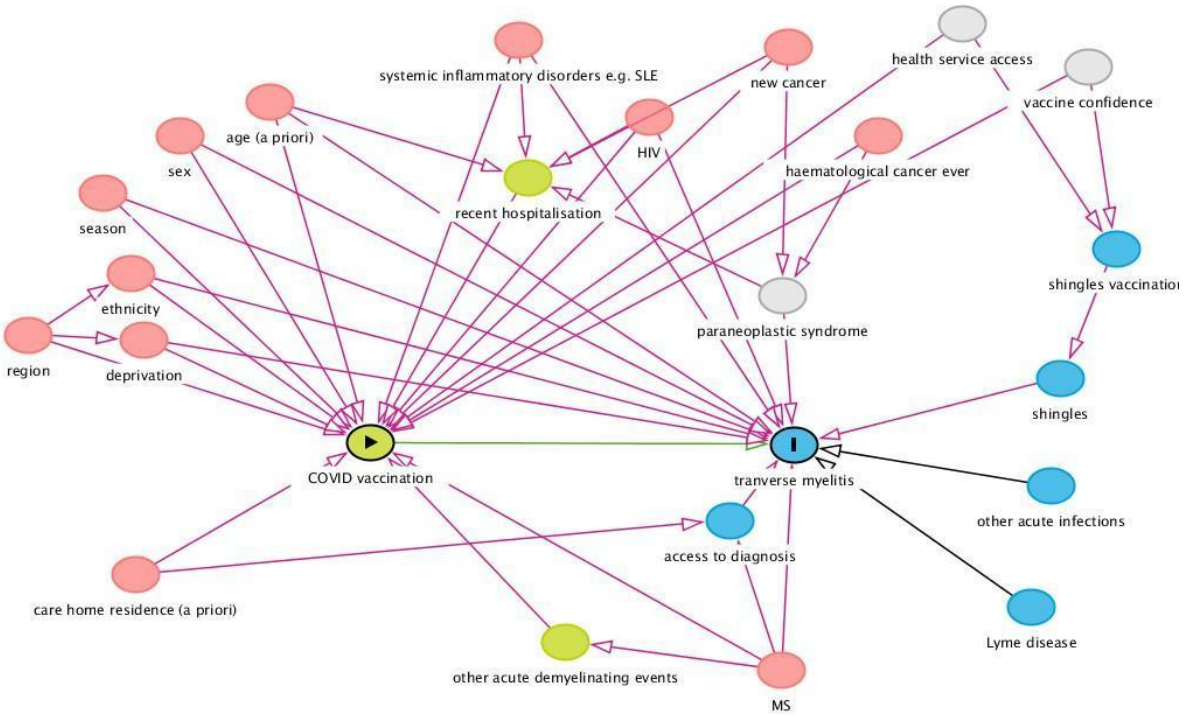
Systemic inflammatory or autoimmune disorders associated with transverse myelitis include ankylosing spondylitis, antiphospholipid syndrome, Behçet disease, mixed connective tissue disease, rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren syndrome, and systemic lupus erythematosus.[29] These, or their treatment with immunosuppressing medication, were indications for vaccination in the 'at-risk' group and will be combined to explore for confounding.

Transverse myelitis may also be a manifestation of paraneoplastic syndrome.[29] A known diagnosis of cancer may affect vaccine uptake, while any history of haematological cancer is an indication for vaccination. A **recent first diagnosis of cancer** and (separately) **any history of haematological cancer** will be explored as potential confounders.

Other chronic conditions associated with acute myelitis such as thyroid disease were not indications for COVID-19 vaccination, and considered unlikely to confound any association between vaccination and transverse myelitis.

Finally, central nervous system disorders including ADEM, multiple sclerosis and chronic neuromyelitis optica spectrum disorder may cause episodes of transverse myelitis.(20) Since a known diagnosis of these chronic neurological diseases may preclude investigation and diagnosis of a discrete episode of transverse myelitis, patients with **ADEM, multiple sclerosis or neuromyelitis optica spectrum disorder at baseline will be excluded** from analyses of transverse myelitis, and follow up will be censored at diagnosis of any of these conditions.

Figure 1: Directed acyclic graph (DAG) for vaccination and transverse myelitis, generated using www.daggity.net [42]



Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is more common in men, and with increasing age.[30] **Cancer**, particularly **Hodgkin's lymphoma**, is a risk factor for GBS.[30] A known diagnosis of cancer may affect vaccine uptake, while any history of haematological cancer is an indication for vaccination. A **recent first diagnosis of cancer** and (separately) **any history of haematological cancer** will be explored as potential confounders. **HIV** infection is associated with GBS and is an indication for vaccination, and will be considered a potential confounder.[30] **Systemic lupus erythematosus** is also a risk factor for GBS, and its treatment with immunosuppressing medications is an indication for vaccination, and so this will also be considered a potential confounder.[32] As with Bell's palsy, GBS is **seasonal** and the SCCS and historical controls analyses may be vulnerable to confounding by seasonality despite adjustment for calendar time during the study.

An estimated two-thirds of cases of Guillain-Barré syndrome follow a recent **acute diarrhoeal or respiratory infectious illness**, such as *Campylobacter jejuni* infection or influenza.[30] Severe infectious illness (particularly fever with respiratory symptoms) may result in some delay to vaccination uptake, but these conditions are not otherwise criteria for or contraindications to vaccination, and so any confounding effect is expected to be small. Short-term illnesses which are typically self-managed at home are particularly unlikely to be recorded in primary care records during the COVID-19 pandemic, and any recorded diagnosis is likely to reflect health-seeking behaviour or other underlying health conditions or frailty. The study will therefore not attempt to ascertain or adjust for short-term infectious illnesses.

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