# Version history

|  |  |  |
| --- | --- | --- |
| V1 | 03/11/21 | VW provided skeleton protocol |
| V2 | 06/12/21 | TLN circulates protocol to CCU002 working group |
| V3 | 11/01/22 | TLN amends protocol following comments |
| V4 | 12/01/22 | Tracked changes removed, edits to ‘enumerate and exclude’ subsection of Study Population section, edits to ‘Primary analysis’ subsection of Main Analysis section, and Follow-up section added |
| V5 | 18/01/22 | TLN amends protocol following comments |
| V6 | 08/02/22 | TLN tracked changes removed; TLN updated confounders |
| V6 | 28/03/22 | SI clarified covariate exclusion criterion from discussions of JS and AMW |
| V6 | 30/03/22 | TLN amends confounder section to add HES as a data source  TLN amends outcome section to add primary care as a data source |
| V6 | 31/03/22 | SI added lay summary.  TLN amends outcome section to add SUS as a data source  TLN updates confounder 17 – history of all venous thromboembolic events |
| V7 | 31/03/22 | TLN tracked changes removed, cosmetic changes |
| V8 | 10/05/22 - 11/05/22 | TLN minor changes to:   1. Study population section 2. Confounder section 3. Missing data section |
| V9 | 25/05/22 | TLN minor changes   1. Removal of splitting up time appendix 2. Change to definition of LSOA covariate 3. Change to 20 controls per case 4. Removal of examination of I2 and Q statistics 5. Additional minor changes to text |
| V10 | 09/06/22 | TLN edits:   1. Restriction of analysis to England only 2. Minor edit to Main Analyses section 3. Minor edit to Follow-up section 4. Minor edits to Missing Data section |
| V11 | 26/04/23 | SI updated the Follow-up and Main Analyses sections. Changes were made to censoring conditions and sampling strategy to address memory limitations. The Exposures, and Outcomes sections were expanded to include the primary course for booster and composite outcomes. Outputs section was also minorly updated. |

# Authors

COVID IMPACT UK

# Title

First, second and booster dose COVID-19 vaccination and the risks of arterial and venous vascular events

# Lay summary

There were reported cases of venous and arterial blood clots in unusual locations, such as the cerebral veins, low platelet levels, as well as inflammation of the heart, after various doses of COVID-19 vaccination. We will study the associated risks of arterial and venous vascular events with vaccine dose (first, second and booster) and type (AstraZeneca, Pfizer, Moderna) using population-level data. We will study all adults alive in England at the start of vaccine rollout 8th December 2020 with data included in the NHS Digital Trusted Research Environment for England.

We will compare the risk of developing one of these conditions among people who have had a particular COVID-19 vaccine dose and type with the risk in those who are eligible for the dose and type in question. We will account for other differences, such as age, sex, ethnic group and previous medical history, that might affect the risk of these conditions.

This research will provide reliable information about any risks associated with COVID-19 vaccines to medicine regulators, the UK Departments of Health, health professionals, and the public. It will be important to understand not only whether there is an increased risk with a COVID vaccine but also the size of any increased risk and whether it only applies to particular groups of people. It will also be important to understand how any risk compares with the benefits of the vaccine, which are known to be substantial.

# Research hypotheses

The risks of arterial and venous vascular events may differ after second dose COVID-19 vaccination compared with first dose. These risks may also differ by vaccine type. The risks of such events may also differ after booster compared with second dose, and these risks may differ according to whether first and second dose were mRNA vaccines.

# Research questions

How do rates of arterial and venous vascular incident events compare\* (quantified as hazard ratios with time since vaccination) in people who:

(a) have had first dose COVID-19 vaccination compared with people who have not,

(b) have had second dose COVID-19 vaccination compared with people who have had first dose,

and

(c) have had booster dose COVID-19 vaccination compared with people who have had second dose?

\*Note that a person can contribute their time prior to vaccination to the unexposed group and their time after vaccination to the exposed group.

Research question (a) has already been partially addressed in a previous analysis1 but we will repeat here to incorporate additional vaccines, several more months of population-wide data from the UK vaccination programme since our previous analyses, and to ensure consistency in analysis approach for the comparison with second vaccination and booster results.

Analyses for (a) and (b) will be stratified by vaccine type for first and second dose (AstraZeneca, Pfizer or Moderna). Analyses for (c) will be stratified according to whether first and second doses were mRNA or non-mRNA vaccines and according to the booster vaccine (Pfizer or Moderna)

What is the absolute excess risk of certain outcomes in particular subgroups after first dose, second dose and booster dose vaccination? (Absolute excess risk is calculated using the estimated background risk pre-pandemic - see Main Analyses).

# Data sources

*(All data will be used up to the latest available stable release of data)*

***NHS Digital TRE for England***

* Primary care data (GP Data for Pandemic Planning and Research via General Practice Extraction Service, GPES);
* Secondary Use Service (SUS) hospital data;
* Pillar 1 and Pillar 2 COVID-19 infection laboratory testing data;
* Hospital episode statistics Admitted Patient Care (HES APC);
* Office of National Statistics (ONS) death registration records;
* Community drug dispensing data;
* COVID-19 vaccination data.

# Study population

Follow-up period:

* Primary analysis: 8th December 2020 (date of start of vaccine rollout) to the date of latest data release (i.e., study end date)

Patients will be included if they meet ALL the following criteria:

* An age of ≥18 and <111 can be calculated on 8th December 2020;
* Known sex;
* Have a record in the primary care extract;
* Alive on 8th December 2020.
* Not known to be living outside of England

Enumerate and exclude the following individuals:

* those vaccinated before 8th December 2020
* those with second vaccine dose before first vaccine dose
* those with an interval between first and second vaccine dose of <21 days
* those with a second vaccine dose but no first vaccine dose
* those with booster dose before first or second vaccine dose
* those with a booster dose but no first and second vaccine dose
* those with an interval between second vaccine dose and booster dose of < 3 months
* those with a third vaccine dose before first or second vaccine dose
* those with a third vaccine dose but no first and second vaccine dose
* those with mixed first and second vaccine types where the second dose was given before 7th May 2021

Additional notes:

* All individuals satisfying the eligibility constraints above are included in the first dose analysis. A subset of this population, only those who have received a first dose vaccination, are eligible for the second dose analysis. A further subset, only those who have received a first and second dose, are eligible for the booster dose analysis.

# Follow-up

Follow-up will start on:

* First-dose analyses: 8/12/20 for all individuals in the first-dose analyses
* Second-dose analysis: Date of first-dose vaccination (individual index dates)
* Booster analysis: Date of second-dose vaccination (individual index dates)

All follow-up will end at the earliest of:

* Death
* Outcome event
* Receipt of another vaccine type to that under study
* 26 weeks since the studied vaccination
* Study end date

# Exposures

First dose analysis: AstraZeneca, Pfizer, Moderna

Second dose analysis:

|  |  |
| --- | --- |
| First dose | Second dose |
| AstraZeneca | AstraZeneca |
| Pfizer | Pfizer |
| Moderna | Moderna |

Booster dose analysis:

|  |  |
| --- | --- |
| First & Second dose | Booster |
| AstraZeneca & AstraZeneca | Pfizer or Moderna |
| (Pfizer & Pfizer) OR (Moderna & Moderna) | Pfizer or Moderna |
| AstraZeneca & AstraZeneca | Pfizer |
| AstraZeneca & AstraZeneca | Moderna |
| (Pfizer & Pfizer) OR (Moderna & Moderna) | Pfizer |
| (Pfizer & Pfizer) OR (Moderna & Moderna) | Moderna |
| (AstraZeneca & AstraZeneca)  OR (Pfizer & Pfizer) OR (Moderna & Moderna) | Pfizer |
| (AstraZeneca & AstraZeneca)  OR (Pfizer & Pfizer) OR (Moderna & Moderna) | Moderna |
| (AstraZeneca & AstraZeneca)  OR (Pfizer & Pfizer) OR (Moderna & Moderna) | Pfizer or Moderna |

Cell counts for other vaccine type combinations will be examined to ensure the above reflects the majority of the data.

Description of exposed vs unexposed group for each component of the analysis:

|  |  |  |
| --- | --- | --- |
| Analysis | Exposed group | Unexposed group |
| First dose (AstraZeneca) | Person-time for individuals after their first dose of AstraZeneca | Person-time for individuals who are unvaccinated and person-time for individuals prior to their first dose of any vaccine |
| First dose (Pfizer) | Person-time for individuals after their first dose of Pfizer |
| First dose (Moderna) | Person-time for individuals after their first dose of Moderna |
| Second dose (AstraZeneca) | Person-time for individuals after their second dose of AstraZeneca (who received a first dose of AstraZeneca) | Person-time between first and second vaccinations for individuals who have received a first dose of AstraZeneca |
| Second dose (Pfizer) | Person-time for individuals after their second dose of Pfizer (who received a first dose of Pfizer) | Person-time between first and second vaccinations for individuals who have received a first dose of Pfizer |
| Second dose (Moderna) | Person-time for individuals after their second dose of Moderna (who received a first dose of Moderna) | Person-time between first and second vaccinations for individuals who have received a first dose of Moderna |
| Pfizer/Moderna booster dose (vs. non-mRNA previous doses) | Person-time for individuals after their booster vaccination (Pfizer or Moderna) who have received a first and second dose of AstraZeneca | Person-time between second and booster vaccinations for individuals who have received a first and second dose of AstraZeneca |
| Pfizer/Moderna booster dose (vs. mRNA previous doses) | Person-time for individuals after their booster vaccination (Pfizer or Moderna) who have received EITHER (1) a first and second dose of Pfizer OR (2) a first and second dose of Moderna | Person-time between second and booster vaccinations for individuals who have received EITHER (1) a first and second dose of Pfizer OR (2) a first and second dose of Moderna |
| Pfizer booster dose (vs. non-mRNA previous doses) | Person-time for individuals after their Pfizer booster vaccination who have received a first and second dose of AstraZeneca | Person-time between second and booster vaccinations for individuals who have received a first and second dose of AstraZeneca |
| Moderna booster dose (vs. non-mRNA previous doses) | Person-time for individuals after their Moderna booster vaccination who have received a first and second dose of AstraZeneca | Person-time between second and booster vaccinations for individuals who have received a first and second dose of AstraZeneca |
| Pfizer booster dose (vs. mRNA previous doses) | Person-time for individuals after their Pfizer booster vaccination who have received EITHER (1) a first and second dose of Pfizer OR (2) a first and second dose of Moderna | Person-time between second and booster vaccinations for individuals who have received EITHER (1) a first and second dose of Pfizer OR (2) a first and second dose of Moderna |
| Moderna booster dose (vs. mRNA previous doses) | Person-time for individuals after their Moderna booster vaccination who have received EITHER (1) a first and second dose of Pfizer OR (2) a first and second dose of Moderna | Person-time between second and booster vaccinations for individuals who have received EITHER (1) a first and second dose of Pfizer OR (2) a first and second dose of Moderna |
| Moderna booster dose (vs. any previous doses) | Person-time for individuals after their Moderna booster vaccination who have received both first and second doses of one of AstraZeneca/Pfizer/Moderna | Person-time between second and booster vaccinations for individuals who have received both first and second doses of one of AstraZeneca/Pfizer/Moderna |
| Pfizer booster dose (vs. any previous doses) | Person-time for individuals after their Pfizer booster vaccination who have received both first and second doses of one of AstraZeneca/Pfizer/Moderna | Person-time between second and booster vaccinations for individuals who have received both first and second doses of one of AstraZeneca/Pfizer/Moderna |
| Pfizer/Moderna booster dose (vs. any previous doses) | Person-time for individuals after their Pfizer/Moderna booster vaccination who have received both first and second doses of one of AstraZeneca/Pfizer/Moderna | Person-time between second and booster vaccinations for individuals who have received both first and second doses of one of AstraZeneca/Pfizer/Moderna |

# Outcomes

Primary analysis will consider the following 11 outcomes in hospital admissions (HES APC or SUS in England), primary care data or death records. By default, we will use codes recorded in first position. For rare outcomes, we will use any position.

Fatal or non-fatal:

Arterial thrombotic events (as a composite and separately):

1. Acute myocardial infarction (MI)
2. Ischaemic stroke (ischaemic or unclassified stroke, spinal stroke or retinal infarction)
3. Composite arterial (any of AMI, ischaemic stroke or other arterial embolism)

Venous thrombo-embolic events (as a composite and separately):

1. Pulmonary embolism (PE)
2. Lower limb deep venous thrombosis (DVT)
3. Intracranial venous thrombosis (ICVT)
4. Portal vein thrombosis
5. Composite venous (any of PE, DVT, ICVT or portal vein thrombosis)

Thrombocytopenic haematological events

1. Any thrombocytopenia (idiopathic, primary, secondary or unspecified)

Other vascular outcomes

1. Haemorrhagic stroke (intracerebral or subarachnoid)
2. Mesenteric thrombus (for which available codes do not distinguish between arterial or venous causes)
3. Myocarditis
4. Pericarditis

# Potential confounders

Similar to the first dose vaccination paper1 (Covariates section), covariates for first dose analysis will be defined as follows:

1. Age on 8/12/20

Latest recorded in primary care (and if not available in primary care, HES) before 8/12/20

1. Sex
2. Ethnicity

As defined after mapping from latest recorded LSOA before 8/12/20

1. Region
2. Deprivation from the Index of Multiple Deprivation (IMD)

Latest recorded in primary care before 8/12/20

1. Smoking status

Any record in primary care, SUS and/or hospital admission data before 8/12/20 (7-18)

1. History of diabetes
2. History of depression
3. History of obesity
4. History of cancer
5. History of chronic obstructive pulmonary disease (COPD)
6. History of chronic kidney disease (CKD)
7. History of liver disease
8. History of dementia
9. History of stroke
10. History of MI
11. History of all venous thromboembolic events (DVT, ICVT, portal vein thrombosis, PE)
12. History of thrombophilia
13. Number of unique diseases in SNOMED-CT for the year before 8th December 2020 from primary care records
14. Major surgery in the year before 8th December 2020 from hospital admissions records
15. History of SARS-CoV2 infection before the 8th December 2020: ascertained using established algorithms that combine information from: a) national laboratory data, b) primary care diagnoses, c) hospital admissions, d) critical care treatments, e) national mortality data3

Prior medication from community dispensing data (binary variable yes/no) in the three months before the 8th December 2020:

1. Antiplatelets
2. Antihypertensives
3. Lipid lowering agents
4. Oral anticoagulants
5. Combined oral contraceptives
6. Hormone replacement therapy

With the exception of sex and ethnicity, covariates for the second dose analysis will be re-defined using an index date of first vaccination.

With the exception of sex and ethnicity, covariates for the booster analysis will be re-defined using an index date of second vaccination.

# Codelists

<https://github.com/BHFDSC/CCU002_02/blob/main/phenotypes/phenotypes.csv>

# Main analyses

Descriptive statistics will be used to describe the demographic and clinical characteristics of the baseline cohort.

Primary analysis:

* First-dose analysis: follow-up will begin on 8/12/20 and be censored at first of death, outcome event, receipt of another vaccine type, second dose vaccination or study end date
* Second-dose analysis: individual specific follow-up period will begin on date of first dose vaccination and be censored at first of death, outcome event, third dose vaccination, booster vaccination, receipt of a different vaccine type to first dose or study end date
* Booster analysis: individual specific follow-up period will begin on date of second dose vaccination and be censored at first of death, outcome event, third (non-booster) dose, non-Pfizer and non-Moderna booster\* or study end date

\* see Follow-up section for clarification

We will split follow-up time for each person into periods before and after COVID-19 vaccination (first dose, second dose or booster depending on analysis and analyse separately by vaccine type as per Exposures section), and into time periods since vaccination defined in days (time periods: [0,7), [7,14), [14,28), [28,84), [84,168), [168, end of follow-up). We will tabulate numbers of outcome events (see: Outcomes), person-years of follow-up and rates of events before and with time since exposure. If any of these time periods contains no events, we will collapse the time periods after COVID-19 vaccination into [0,28) and [28, end of follow-up) prior to analysis. When vaccination and outcome occur on the same day, we will enumerate these occurrences and assume that vaccination happens first. In general, when the number of outcome events after vaccination is too small, we will either compress the time periods or reduce the number of covariates to ensure the models fit (firstly trying time period compression and secondly changing to a ‘core’ covariate set e.g. covariates 1-6 see: Potential Confounders.)

We will fit Cox regression models with calendar time scale using the start of study date (8/12/20) as the origin for first dose, second dose and booster analyses. This will ensure that all analyses account for changes with calendar time in rates of the outcome event. Using this approach, we will estimate hazard ratios for events of different types before and after exposure, and by time since exposure.

For computational efficiency, Cox models will be fitted to datasets including all people with the outcome event (i.e. the cases) and a random sample of people without the outcome event equal to twenty times the number of people with the outcome event (i.e. the controls) whenever possible, and ten times should memory limitations necessitate. Analyses will incorporate inverse probability weights for people without the outcome event. For example, consider a sample of N people, X of whom have the outcome. Suppose we sample 20X people without the outcome, so that the proportion of sampled people without the outcome is 20X/(N-X). The inverse probability weight is therefore (N-X)/20X for each person without the outcome and 1 for each person with the outcome. If 20X>=N-X, we will analyse the whole sample. Confidence intervals will be derived using robust standard errors.

Potential confounders (see: Potential Confounders) will be based on data recorded before the start of follow-up in each analysis. All models will be stratified by region so that risk sets are constructed within region, hence accounting for between-region variation in the baseline hazard.

We will estimate: (i) age and sex adjusted and (ii) maximally adjusted HRs. We will exclude potential confounders with ≤2 post-exposure outcome event-of-interest at any level. For smoking, we will try merging the categories ‘Ex smoker’ and ‘Current smoker’ into “Ever smoker” before exclusion. For deprivation, we will try merging the deciles into quintles before exclusion (1-2, 3-4, 5-6, 7-8, 9-10).

Second dose vaccination effects will be compared with first dose vaccination effects by plotting hazard ratios against time from each analysis side by side on the same graphic. See Appendix 1: Proposed Outputs.

As per previous analyses2, absolute excess risk (in time intervals since vaccination) of particular outcomes for subgroups of interest will be calculated by applying hazard ratios to calculated incidence rates from 2019 data, within strata defined by age and sex, and subtracting these baseline rates. Population excess risk will be calculated as a weighted average of the stratum-specific excess risks, and plotted graphically by outcome or groups of outcome. These calculations will also be stratified by vaccine type (see Exposures).

Proposed outputs for this project are included as Appendix 1: proposed outputs.

# Sensitivity analyses

## Subgroup analyses

If possible, we will repeat the main analysis (1st dose, 2nd dose and booster separately) to estimate stratified post-exposure hazard ratios for the composite venous and composite arterial outcomes by including exposure-covariate interaction terms for the following covariates:

* Age group (18-39 / 40-59 / 60-79 / 80-110)
* Sex (male / female)
* Ethnicity (White / Asian or Asian British / Black or Black British / Mixed / Other Ethnic Groups)
* Prior history of outcome (prior history of outcome / no prior history of outcome)
* Prior history of COVID-19 infection

# Missing data

Individuals with missing age or sex are excluded from the analysis by the study definition. We will include missing categories for smoking, ethnicity and deprivation. Individuals with missing region will not be analysed. All other covariates are defined using the presence versus absence of specific codes in the EHRs, so have no identifiable missing values. We will not use multiple imputation.

# Appendix 1: proposed outputs

**Main paper**

Table 1: Baseline characteristics – split by All, Venous composite, Arterial composite

Table 2: Event counts, person-years and incidence rates

Fig 1: Dose 1: Maximally-adjusted hazard ratios for various cardiovascular events by time since vaccination with ChAd0x1 or BNT162b2

Fig 2: Dose 2: Maximally-adjusted hazard ratios for various cardiovascular events by time since vaccination with ChAd0x1 or BNT162b2

Fig 3: Booster: Maximally-adjusted hazard ratios for various cardiovascular events by time since vaccination among individuals who received a primary course of ChAdOx1, mRNA-1273 or BNT162b

**Supplementary Material**

**Supplementary tables:**

* Main analyses hazard ratios, maximally- and age/sex/region- adjusted, for all vaccine-outcome combinations, for each dose
* Subgroup analyses hazard ratios, maximally-adjusted, for all subgroup-vaccine-outcome combinations specified in the section “SENSITIVITY ANALYSES: Subgroup analyses“
* Documentation of which analyses required noncase:case ratio of 10 instead of 20.

Supplementary figures:

* Population flow diagram
* Other vaccine-outcome combinations indicated on section “EXPOSURES”
* Subgroup analyses: Maximally-adjusted hazard ratios, for all subgroup-vaccine-outcome combinations specified in the section “SENSITIVITY ANALYSES: Subgroup analyses“

**REFERENCES**

1. medRxiv 2021.08.18.21262222; doi: <https://doi.org/10.1101/2021.08.18.21262222>.
2. medRxiv 2021.11.22.21266512; doi: <https://doi.org/10.1101/2021.11.22.21266512>
3. medRxiv 2021.11.08.21265312; doi: <https://doi.org/10.1101/2021.11.08.21265312>