Version history

V0.1	Drafted by WW	
V0.2	Edited by AMW	Edits related to analysis decisions for second vaccine dose analysis.
V0.3	Edited by AMW, CLMS, WW, AA, SD, SJK	Edits related to various comments from the group.
V0.4	Edited by SI	Edits related to updated first and second vaccine dose study designs, expansion of outcomes list and rewrites.
V0.5	Edited by AMW, VW	Edits related to refocus on myo/pericarditis, simplified analyses due to low available event counts
V0.6	Edited by AMW, VW, CLMS, WW, AA, FT, SI	Edits related to various comments from the group.

AUTHORS

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TITLE

COVID-19 vaccination and risk of myocarditis and pericarditis.

BACKGROUND

A few case series have reported a temporal association between the second dose of COVID-19 vaccination with Pfizer-BioNTech and Moderna mRNA vaccines and myocarditis or myopericarditis. The patients affected were mostly males, younger than 50 years old and had an illness of chest pain associated with fever and with a rise in cardiac specific troponins that later fully recovered.[1–3] In some patients, cardiac magnetic resonance imaging (MRI) demonstrated typical findings of myocarditis.

Whilst this illness appears self-limiting, it is important to understand its frequency because these vaccines are currently the backbone of the COVID-19 vaccine control program in younger people.

In addition, it is important to clarify whether the risk of events seen after the second vaccination dose is similar or different to the risk after the first vaccination dose.

Myocarditis and pericarditis are rare conditions. We will conduct this study through analyses of linked healthcare data from the populations of England and Wales (total populations of around 57 million and 3 million respectively). The very large population size is needed to detect sufficient numbers of these rare health conditions for analyses to be statistically robust. In addition, the linked health data come from mutiple sources (e.g. primary care, secondary care, death registries, COVID testing and vaccination data), providing comprehensive information for defining the exposure of interest (vaccination), the outcome of interest (myocarditis or pericarditis), key characteristics of the population (e.g., age, sex, ethnicity) and other important comorbidities (e.g. prior COVID infection).

RESEARCH HYPOTHESES

There is a higher risk of myocarditis or pericarditis after COVID-19 vaccination than before or without vaccination, that varies with vaccine type and by first or second vaccination dose

DATA SOURCES

NHS Digital TRE for England (up to latest release)

- 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 dispensing data;
- COVID-19 vaccination data.

Wales (SAIL Databank)

- Primary care data: Welsh Longitudinal General Practice dataset (WLGP)
- Secondary care data: Patient Episode Dataset for Wales (PEDW)
- Pillar 1 and 2 COVID-19 infection laboratory testing data.
- COVID C20 (all people alive and resident in Wales from 01/01/20) and C16 (counterfactual from 01/01/16 to end 2019) total population cohorts 3.2M. Censored by migration out of Wales and death.
- Consolidated mortality dataset for COVID-19 electronic cohort (C20) using data from four separate mortality data sources (Welsh Demographic Service Dataset (WDSD) – population spine weekly flows, ONS - monthly and daily flows (ADDE and ADDD), and records from the MPI (Master Patient Index) - daily flows (CDDS)).

- Research ready version of the community dispensing data: RRDA_WDDS
- Research ready version of COVID-19 vaccination data: RRDA_CVVD

Other available data sources such as CENW (for ethnicity variable) in Wales will be added depending on the availability to the project.

RESEARCH QUESTIONS

1. What are the age- and sex- specific incidences of myopericarditis in 2018-2019 (before the pandemic) and in 2020-2021 (during the pandemic)?
2. In people who have had first or second dose of COVID-19 vaccination compared with people who have not, are there higher rates (expressed as hazard ratios with time since vaccination) of fatal or non-fatal myocarditis and/or pericarditis (i.e. combined outcome) with each vaccine?

STUDY POPULATION

Population for incidence of events (recorded in HES) during 2018-2021

Follow-up period: events in 2018, 2019, 2020 and 2021.

For England, the whole population of England, estimated by the mid-2019 population from ONS (or later mid-year population estimate, if/when available).

For Wales, the all those who were residing in Wales between 2016 and 2019 will form the counterfactual cohort for these analysis, and all residents at the start of 2020 up to 30 June 2021 (*current coverage updated monthly*) will be used as a current population.

Population for COVID-19 vaccination analyses

The CDC first reported a possible association between myocarditis and the second COVID-19 vaccination dose on 17/05/2021.

Follow-up period:

- Primary analysis: 08/12/20 to date of latest data release
- Secondary analysis: 08/12/20 to 17/05/21

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

- An age of ≥12 can be calculated on 8th December 2020;
- Known sex;
- Be present in the primary care extract (ie, have a record);
- Alive on 8th December 2020.

Enumerate and exclude the following individuals:

- 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 mixed vaccine types where the second dose was given before 7th May 2021

Enumerate those with mixed vaccine types where the second dose was given after 7th May 2021. If numbers are low, exclude these individuals from the second dose analysis.

All individuals satisfying the eligibility constraints above are included in the first dose analysis. A subset of this population, only those who have had their first dose vaccination, are eligible for the second dose analysis.

EXPOSURES

- AstraZeneca
    - dose number (first or second)
- Pfizer
    - dose number (first or second)
- Moderna
    - dose number (first or second)

OUTCOMES

Primary outcome: defined as combined myocarditis or pericarditis recorded in "any position" in hospital admissions (HES APC or SUS in England and PEDW in Wales) or death records.

Secondary outcomes: If counts are adequate, we will also explore combined myocarditis or pericarditis recorded in "first position" in hospital admissions (HES APC or SUS in England and PEDW in Wales) or death records.

Myocarditis	
I51.4	Myocarditis, unspecified
I40*	Acute myocarditis
I41*	Myocarditis in diseases classified elsewhere
Pericarditis	
I30*	acute pericarditis

STATISTICAL METHODS

Primary analysis:

- For the first dose analysis, follow-up will begin on 08/12/2020 and be censored at the first of: death, the outcome event, receipt of another vaccine type, second dose vaccination or the end of the follow-up period.
- For the second dose analysis, the individual-specific follow-up will begin on date of first dose vaccination and be censored at the first of: death, the outcome event, or the end of the follow-up period.

We will split the follow-up time for each individual into periods before and after exposure (COVID-19 vaccination of a given vaccine type and dose number) and further into time periods since exposure if event counts allow (eg, 1-7 days, 8-14 days, >14 days) (see Appendix 1) .

Separate analyses will be performed for Pfizer, Oxford/AstraZeneca and Moderna vaccinations (if event counts allow).

Exposure and outcomes are listed above. When vaccination and outcome co-occur on the same day, we assume that vaccine occurs first. We will enumerate these occurrences. We will tabulate numbers of outcome events, person-years of follow-up and rates of events before and with time since exposure.

We will fit survival models (Cox PH models) with start and end times as defined above. This will allow us to estimate the hazard ratios for events of different types before and after exposure, and by time since exposure when event numbers allow.

For computational efficiency, Cox models will be fitted to datasets including all people with the outcome event, all vaccinated people and a random subset (for example, 10%) of people without the outcome event, with analyses incorporating inverse probability weights (for example, 10) for data from people in the random sample, and confidence intervals derived using robust standard errors.

Cox models will be performed separately in the England and Wales resource (where events counts allow), and hazard ratios pooled using inverse-variance weighted meta-analysis. Heterogeneity will be assessed using the I2 statistic.

Confounders

We will perform analyses adjusted for potential confounders as follows:

1. unadjusted;
2. adjustment for age, sex and region (for England only)
3. adjustment for age, sex, region, deprivation, ethnicity, prior covid and prior history of myo/pericarditis.

Confounders will be defined as detailed below from records on or before the time at which individuals enter the follow-up period in each analysis (ie, the start of follow-up or, in analyses of second vaccine dose, the date of first vaccine dose).

covariate	type	description	source
sex	categorical	Two categories: Male, Female	England: GDPPR, HES APC, HES OP, HES AE Wales: C19_COHORT16, C19_COHORT20
age	continuous	Age in years on index date.	England: GDPPR, HES APC, HES OP, HES AE Wales: C19_COHORT16, C19_COHORT20
region	categorical	Ten categories: East of England, London, Midlands, North East and Yorkshire, North West, South East, South West, Scotland, Wales, missing	England: GDPPR, ons_chd_geo_locations Wales: C19_COHORT16, C19_COHORT20
deprivation	categorical	Six categories: deciles_1_2, deciles_3_4, deciles_5_6,	England: GDPPR, IMD Wales: C19_COHORT16,

		deciles_7_8, deciles_9_10, missing	C19_COHORT20 (WIMD)
ethnicity	categorical	Six categories: Asian or Asian British, Black or Black British, Mixed, Other Ethnic Groups, White, Unknown or missing or, for pooled analyses with Wales, use 5 categories: Asian, Black, Mixed, Other and White	England: GDPPR, HES APC, HES OP, HES AE Wales: Ethnicity_spine
prior myo or pericarditis	binary	1 if ever recorded prior to index date, 0 otherwise	England: HES APC, SUS Wales: PEDW
prior covid infection	binary	1 if ever recorded prior to index date, 0 otherwise	England: GDPPR, HES APC, SUS, SGSS Wales: PEDW, WLGP

Missing data
Missing indicator categories will be used for potential confounders with missing values (eg, ethnicity, deprivation and region).

Analyses on subgroups or with interactions
Event numbers are likely to be too low to investigate post-vaccination hazard ratios at time periods since vaccination (eg, 1-7 days, 8-14 days, >14 days) by age group and/or sex. We will investigate three models of interest:

A. estimate post-vaccination hazard ratios at time periods since vaccination (eg, 1-7 days, 8-14 days, >14 days or 1-7 days, >7 days) across all ages and both sexes
   i. unadjusted;
   ii. adjusted for age, sex and region
   iii. adjusted for age, sex, region, deprivation, ethnicity, prior covid and prior history of myo/pericarditis.

B. estimate post-vaccination hazard ratios across the whole time period since vaccination with interaction with age group (<40, 40-69 and 70+).
   ii. adjusted for age, sex and region
   iii. adjusted for age, sex, region, deprivation, ethnicity, prior covid and prior history of myo/pericarditis.

C. estimate post-vaccination hazard ratios across the whole time period since vaccination (across all ages) with interaction with sex

ii. adjusted for age, sex and region

iii. adjusted for age, sex, region, deprivation, ethnicity, prior covid and prior history of myo/pericarditis.

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Appendix 1: splitting follow up according to time since the start of follow up and since exposure.

Definitions
Time scale – days since start of follow-up

Outcome of interest – time to event D (T_D, I_D)

Exposure of interest – binary exposure E (COVID vaccination) measured at T_E with indicator I_E, parameterised as days since T_E, categorised for example into E1 = 0-13.999 E2=14-27.999; E3=28-41.999; E4=42-55.999; E5=56-70 days (although time interval may change depending on analysis and the number of events of different types)

Administrative Censoring time – set as day T_C

For individuals without exposure and without event then T_D=T_C, I_D = 0, T_E=T_C, I_E=0 (e.g., individual 1 in table below)

For individuals without exposure and with event at time *t* then T_D=*t*, I_D = 1, T_E=*t*, I_E=0 (e.g. individual 2 in table below)

For individuals with exposure at T_E and without event then: (1) split follow-up time at T_E, and (2) split follow-up time>T_E at T_E+14; T_E+28; T_E+42; T_E+56 and then censor at earliest of T_E+70 or T_C (e.g., individual 3 in table below)

For individuals with exposure at T_E and event at T_D, then first (1) split follow-up time at T_E, and then (2) split follow-up time>T_E at T_E+14; T_E+28; T_E+42; T_E+56 and then censor at earliest of T_E+70 or T_D (e.g., individual 4 in table below)

In example I have set T_C = 300

id	T_E	T_D	T_C	T0	T1	I_E	I_D	E1	E2	E3	E4	E5
1	300	300	300	0	300	0	0	0	0	0	0	0
2	47	47	300	0	47	0	1	0	0	0	0	0
3	35	300	300	0	35	0	0	0	0	0	0	0
3	35	300	300	35	49	1	0	1	0	0	0	0
3	35	300	300	49	63	1	0	0	1	0	0	0
3	35	300	300	63	77	1	0	0	0	1	0	0
3	35	300	300	77	91	1	0	0	0	0	1	0
3	35	300	300	91	105	1	0	0	0	0	0	1
4	105	136	300	0	105	0	0	0	0	0	0	0
4	105	136	300	105	129	1	0	1	0	0	0	0
4	105	136	300	129	136	1	1	0	1	0	0	0

Cox model in R:
Coxph(Surv(T0, T1, I_D) ~ E1+E2+E3+E4+E5)