EAVE II

Analysis Plan for first dose vaccine failures in adults

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1 Introduction

Preliminary data suggest the program has led to a substantial fall in severe covid-19 cases requiring hospital admission. We aim to analyse the characteristics of those vaccinated with the first dose of either vaccine and report on the number of COVID 19 related hospitalisations and deaths among them.

2 Aims and objectives

2.1 Aims

To describe the population and clinical characteristics of individuals who are admitted to hospital for or die from COVID-19 following their first COVID-19 vaccine.

2.2 Objectives

We seek to:

a. Identify individuals who have experienced hospitalisation or death due to COVID-19 illness 14 or more days after receiving their first vaccination dose
    i. Report the proportions of people who received a first vaccination dose but who were hospitalised or died due to COVID-19 illness 14 days or more after vaccination overall and by type of vaccination,
    ii. Report on descriptive demographic and clinical characteristics of these individuals compared to others who were vaccinated.
    iii. Explore associations between those characteristics and hospitalisation or death due to COVID-19 illness 14 days or more after vaccination.
b. Report on other causes of hospitalisation and mortality for individuals following their first vaccination.

3 Study Design

3.1 Study design

Open prospective cohort study

3.2 Setting

Scotland

3.3 Population

All adults registered in GP practices across Scotland who have received a first vaccination dose.

3.4 Data sources

- Primary care data: General Practices (n=940) for information on demographics, other population characteristics and vaccination data.
- Vaccination centre data: Vaccines administered in national vaccination centres and data available via the Turas Vaccination Management Tool (TVMT)

- Laboratory test data: RT-PCR laboratory confirmed SARS-CoV-2 infection and data available via the Electronic Communication of Surveillance in Scotland (ECOSS) database
- Secondary care data: Deaths related to COVID-19 illness after a hospital admission.
- Deaths related to COVID-19 from the National Records of Scotland (NRS) database

3.5 Inclusion/exclusion criteria

All adults (aged >= 18 on 8th December 2020) individuals in our dataset who have received a first vaccination dose will be included. Individuals will be followed up until hospitalisation for COVID-19 death.

3.6 Sample size calculations

In this study, we are providing sample size calculations based on Scottish testing and vaccination data due to being the largest UK nation with national coverage data.

As of 18 April 2021, a total of 1.7 million individuals had received a first vaccine against COVID-19 infection and of those 10,115 (0.6%) had subsequently been hospitalised or died from COVID-19 infection.

This gives us the power to detect Hazard Ratios varying 0.5 to 0.9 as shown below:

Power	N	E	HR	SD	Alpha*	Pr(E)
1	1.7e+06	10115	.5	.5	.05	.00595
1	1.7e+06	10115	.6	.5	.05	.00595
1	1.7e+06	10115	.7	.5	.05	.00595
1	1.7e+06	10115	.8	.5	.05	.00595
.999578	1.7e+06	10115	.9	.5	.05	.00595

4 Data and data validation

4.1 Data variables available

We will use pseudonymised individual level linked routinely collected primary, secondary, mortality, laboratory and vaccination healthcare data across Scotland. All data are hosted within a secure environment at Public Health Scotland (PHS), and all analysis will be carried out there. Table 1 lists the groupings of variables available for this study by data source. Outcome data are described in the mortality and hospitalisation category. The rest of the categories contain data on potential confounding factors and effect modifiers.

Table 1: Data items/variables and data sources

Data category	Data item	Data source
Demographic	Sex	GP practice
	Age	GP practice
Socioeconomic	SIMD	GP practice
Other characteristics	Body Mass Index (BMI)	GP practice
	Smoking	GP practice
Geographic	Urban Rural Index (UR6), Health Board	GP practice
Type of residence	Private housing, care home or social housing	GP practice
Clinical diagnoses	Underlying conditions (e.g., asthma, cardiac disease etc.) see Table S2 in Appendix	GP practice
Vaccinations	Vaccine type	GP practice, TVMT
	Vaccine dose	GP practice, TVMT
	Vaccination date	GP practice, TVMT
Laboratory tests	RT-PCR positive SARS-CoV-2	ECOSS
	RT-PCR negative SARS-CoV-2	ECOSS
	Date of RT-PCR test	ECOSS
	Genome sequencing data	PHS
Mortality	Death with COVID-19 as the main cause according to death certificate, or death within 28 days of a positive RT-PCR test for COVID-19 Other causes of Death	NRS
Hospitalisation	Hospitalisation with COVID-19 as the cause in the secondary care datasets Other causes of Hospitalisation	SMR01
History of COVID-19	Prior history of a Hospitalisation for COVID-19 or RT-PCR positive SARS-CoV-2 prior to vaccination date	SMR01, ECOSS

Abbreviations: Scottish Index of Multiple Deprivation (SIMD), Body Mass Index (BMI), Electronic Communication of Surveillance in Scotland (ECOSS), Reverse-transcription polymerase chain reaction (RT-PCR); Turas Vaccination Management Tool (TVMT), Public Health Scotland (PHS), National Records of Scotland (NRS), Scottish Morbidity Record (SMR).

4.2 Constructed variables

To be confirmed, once full analyses list in place

4.3 Consistency and error checking

To be confirmed, once full analyses list in place.

We will remove any individual who is listed as having the dose aged under 18 and will also remove individuals where the data reports the first vaccination was prior to 8th December 2020 or a second dose was received prior to the first dose.

5 Statistical analyses

The following sections are presented separately for each analytical objective.

5.1 Objective

To analyse the association between population and clinical characteristics and RT-PCR positive test, hospitalisation or mortality due to COVID-19 after the first dose of vaccination.

5.1.1 Exposures of interest

Currently licenced COVID-19 vaccines (Pfizer-BioNTech, Oxford-AstraZeneca and Moderna). An individual will be defined as exposed or vaccinated from 14 days post-vaccination onward if they received a single vaccine dose between 8 December 2020 and 18 April 2021. Maximum follow-up time is to be censored at 18 April 2021 which corresponds to the latest event date. Exposed or vaccinated groups will be stratified by time intervals including 14-20, 21-27, 28-34, 35-41 and >42 days post-vaccination, and by the type of vaccine received.

5.1.2 Outcomes of interest

COVID-19 related hospital admission with COVID-19 as the cause of admission recorded between 8th December 2020 and 18th April 2021, which occurred 14 days or more post first vaccination.

Any admission for hospital within 6 days of a RT-PCR test for SARS-CoV-2 infection between 8th December 2020 and 18th April 2021, which occurred 14 days or more post first vaccination.

Any individual with a positive RT-PCR test for SARS-CoV-2 infection during an admission to hospital between 8th December 2020 and 18th April 2021, which occurred 14 days or more post first vaccination.

COVID-19 related death with COVID-19 as the main ICD-10 cause of death recorded on the death certificate (see Table S1), or death from any cause within 28 days of a positive RT-PCR test for SARS-CoV-2 infection, from 8 December 2020 to 18 April 2021, which occurred 14 days or more post first vaccination.

5.1.3 Potential confounders

Age, sex, socio-economic status (SES) measured by quintiles of the Scottish Index of Multiple Deprivation (SIMD), it ranges 1 to 5 (1 refers to most deprived and 5 refers to least deprived), residential settlement measured by the urban/rural 6 fold classification (1 refers to large urban areas and 6 refers to small remote rural areas), the number and types of comorbidities commonly associated with COVID-19 illness (asthma, chronic kidney disease, liver cirrhosis, chronic neurological condition, heart failure, diabetes (type 1 and type 2), dementia, coronary heart disease), risk factors (smoking status, blood pressure, body mass index) and Health Board. Also include size of household and number of PCR tests geographical area also such as health board

5.1.4 Potential effect modifiers

Stratification into different population groups will be considered.

5.1.5 Analytical techniques

We will report descriptive analysis of individuals with hospitalisation or death for COVID-19 illness across exposures of interest and other potential confounders.

We will use time-dependent covariates (taking into account the time since vaccination, time in hospital) in Cox Proportional Hazards models to derive hazard ratios (HR) and 95% confidence intervals (CIs) for hospitalisation or death from COVID-19 illness. Vaccinated individuals hospitalised for COVID-19 or who died for any reason before 14 days post-vaccination will be censored.

5.1.6 Data preparation

1. Compute the number of days to COVID-19 hospitalisations/death and declare the patient as having the event as of that date. The survival time is computed as time between the first vaccination and the date of the event. The censoring code is 1 for them i.e. event of interest.
2. If the event happened within 14 days of vaccination, the censoring code is set to 0.
3. For those with no second dose but no event of interest as of 18th April 2021, the censored time is number of days between date of 1st dose and 18th April 2021 and the respective censoring code is 0

5.1.7 Sub-group analysis

Subgroup analyses by vaccine type, age and sex will be considered.

5.1.8 Corrections for multiple testing

N/A

5.1.9 Sensitivity analysis

To be confirmed.

5.1.10 Other analysis

N/A

5.2 Objective b) Non-COVID18 hospitalisation and mortality following first vaccination.

5.2.1 Outcomes of interest

Death with COVID-19 is not the main ICD-10 cause of death recorded on the death certificate, and death is not within 28 days of a positive RT-PCR test for SARS-CoV-2 infection, from 8 December 2020 to 18 April 2021.

Hospital admission where COVID-19 was not a cause of admission recorded on the SMR01 dataset between 8th December 2020 and 18th April 2021.

5.2.2 Analytical techniques

We will report descriptive analysis of individuals with hospitalisation or death for non COVID-19 illness across exposures of interest and other potential confounders. We will also report rates of events in weekly time periods post vaccination using total time at risk and number of events of interest.

5.3 Missing data

Missing data will be reported as percentages of total or raw number where possible. Single or multiple imputation by chained equations will be considered if possible and sensitivity analysis to examine if the volume of missing data affects the study findings.

5.4 Statistical software

All analyses will be carried out using R/RStudio 3.5.1.

6 Reporting results

6.1 Reporting guidelines and conventions

Results will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and REporting of studies Conducted using Observational Routinely-collected Data (RECORD) (via the COVID-19 extension) guidelines. P-values will be quoted to two decimal places, unless they are less than 0.001 (whereby the p-value will be given as <0.001) or between <0.005 and >0.001, in which case they will be stated to three decimal places. Measures of association will be reported with 95% confidence intervals.

6.2 Dissemination

The analysis will be written in a manuscript and submitted to a peer reviewed journal. We will also seek to provide near real-time reports on vaccine safety, effectiveness and uptake for the various vaccines to the funders and government COVID-19 advisory bodies as appropriate. All codes will be made publicly available via a GitHub repository.

7 Potential useful references

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard [Internet]. Available from: https://covid19.who.int/
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4. Logunov DY, Dolzhikova I V, Shcheblyakov D V, Tukhvatulin AI, Zubkova O V, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet [Internet]. 2021 Feb;397(10275):671–81. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673621002348
5. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99–111.

8 Appendix

Table S1. ICD-10 codes

Code	Description	Category
U07.1	COVID-19, virus identified	U07.1
U07.2	COVID-19, virus not identified	U07.2
Source: https://www.who.int/classifications/icd/COVID-19-coding-icd10.pdf		

Table S2. Medical conditions included from QCovid

Asthma
Chronic Kidney Disease (CKD) – no CKD, CKD3, CKD4, CKD5, unknown
Cirrhosis of the liver
Neurological Condition
Congestive Cardiac Failure
Diabetes
Dementia
Coronary Heart Disease