Uptake, effectiveness, and comparative safety of new COVID-19 vaccines by age, sex, region, ethnicity, comorbidities, medication, deprivation, risk level and evidence of prior COVID infection.

Research Protocol

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1.0	13.12.2020	JHC	First issue sent to co-applicants
1.1	14.12.2020	JHC	Comments from KK, CC, FZ, PT,PW
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2 Study Team

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3 Background

On 11 March 2020, the World Health Organization (WHO) declared a global COVID-19 pandemic, which has since affected millions of patients globally with major health, social and economic consequences. This prompted the rapid development and licensing of several vaccines for use in the general population. Policy makers, health care professionals and the general public need timely information about the uptake, effectiveness and safety profile of these new vaccines in the real world setting to satisfy regulatory requirements and inform operational decisions about the use and distribution of vaccines in the pandemic situation. In order to obtain fully informed consent from patients for vaccination it is also necessary to provide an understanding of the risk of COVID-19 as well as the risks and benefits of the COVID-19 vaccinations [1]. COVID-19 vaccinations are being tested in randomised clinical trials with 5,807 adult participants receiving the Oxford-AstraZeneca DNA vaccination [2], 21,720 receiving the mRNA BioNTec/Pfizer vaccine[3], and 15,210 receiving the Moderna mRNA vaccine[4]. These trials are necessarily designed to establish efficacy and safety but are insufficiently powered to detect rare adverse or unintended effects or heterogeneity within subgroups of subjects. If a new vaccine has a serious adverse profile (even if the risk is rare), then a risk-benefit evaluation may lead to withdrawal of the vaccine in the interests of public safety. This will be a difficult decision in the context of the COVID-19 pandemic, especially if few alternative vaccines or effective preventative measures are available. For example, a swine flu vaccine developed in 1976 in America was withdrawn after 30% of the US population had been vaccinated because the vaccine appeared to be associated with an eight-fold increase in the incidence of Guillain Barre Syndrome, although on further analyses, this may have been an effect of the influenza virus itself [5].

When any new vaccine or drug is launched onto the market, it is necessary to undertake post-marketing surveillance to evaluate the uptake, effectiveness and safety of the treatment in the general population [6]. This is because people recruited to trials can differ in characteristics from the rest of the population (for example, only 12% of the participants in the Oxford-AstraZeneca vaccine trial were aged 55 and over), limiting the generalisability of trial findings to children or older patients with more co-morbidities or in multi-ethnic populations. Whilst the Federal Drug Administration (FDA) has not recommended pre-selection of vaccine trial participants to those without prior COVID-19 infection (since pre-vaccination screening is unlikely to happen in practice [7]), some but not all trials have excluded such patients. For example, the BioNTec/Pfizer mRNA vaccine trial [3] excluded those who had already had a positive COVID-19 test. Therefore the safety of the vaccine amongst those with

prior infection is unknown [3]. However, in the UK implementation plan, the vaccine will be administered also in those who have previously had COVID-19. Additionally, rare events (for example, events occurring in fewer than 1: 10,000 patients) are unlikely to be captured in trial populations due to limitations of sample size and trial duration. In the Pfizer trials, outcomes were only measured over seven days after the second dose. However, when an intervention is likely to be used in billions of people, the numbers affected by rare events could be substantial in the longer term. Evaluation of safety is particularly important when the roll out is rapid and at scale, as is the case with the deployment of the COVID-19 vaccines with over 10 million patients already vaccinated as of 1st Feb 2021. Whilst the first COVID-19 vaccination was administered in the UK on 8th Dec 2020, vaccines have now been licensed in other countries and are likely to rapidly extend to a global population over the coming months.

Established approaches for the evaluation of the safety of new drugs largely rely on the statistical analysis of routinely collected health data. These data contain both recording of the exposure (i.e. vaccination) and relevant outcomes (i.e. adverse or unintended events), taking account of other confounding variables which might be associated with either the exposure or the outcomes of interest. These analyses can be complex, especially with a new disease such as COVID-19 which is not yet completely understood and where effects of the disease itself may be confounded with potential effects of a vaccine to prevent it. It is also complex where a risk stratified approach to prioritisation of vaccination according to the risk of severe outcomes from COVID-19 is being used [8]. Fortunately, the UK has some of the most advanced and highest quality comprehensive electronic health record systems internationally, particularly in general practice (GP) where nearly all clinicians have been routinely recording health care events and vaccinations received electronically for over 20 years. Medical research databases derived from these systems, such as QResearch, have been linked at individual level to secondary care data including mortality, cancer registry, hospital admissions, intensive care and, COVID-19 test data and used for pharmacovigilance studies [9-15] and thus provide a rich source of data to enable the robust evaluation of the safety of COVID-19 vaccinations.

In addition to safety monitoring, it is essential to monitor vaccine uptake since new interventions tend to be initially adopted at different rates by different segments of society for example based on socioeconomic position, educational level, and ethnic group rather than need or ability to benefit. The 'inverse equity hypothesis' anticipates that this will exacerbate health inequalities in the short term [16]. Uptake in the most deprived and in ethnic minority groups tends to be much lower until high levels of coverage have been achieved in the wealthier groups [16]. Even then, uptake rarely fully reaches levels achieved in the least disadvantaged groups. This effect has been reported for various screening programs and interventions over the last 20 years [16]. Therefore, the mass COVID-19 vaccination programme could not only exacerbate existing health inequalities regarding uptake of the vaccination but could also compound inequalities for deprived and ethnic minority groups who are already known to be at higher risk of severe outcomes from COVID-19 infection [8].

We will therefore undertake a near real time rapid independent evaluation of the uptake and safety of the new COVID-19 vaccinations in the general population during the COVID-19 pandemic using the QResearch database linked to mortality, hospital and COVID-19 vaccination, infection and outcome information.

3.1 Aims

The aim is to develop a system which can be used for rapid assessment of uptake of the vaccination programme in different groups and of the safety and effectiveness of the new COVID-19 vaccines by examining effectiveness and risks of a range of serious outcomes among people receiving the different vaccines and unvaccinated patients. We will achieve this through the analysis of linked electronic health records held on the QResearch database.

3.2 Objectives

The primary objective is to rapidly establish uptake and to evaluate the overall and comparative safety and effectiveness profiles of the new COVID-19 vaccines in the general population.

The secondary objectives are:

(A) To determine vaccine uptake by vaccine type and subgroups including age, sex, ethnicity, deprivation, region, co-morbidities (including transplants), medication use and QCovid risk score and prior COVID-19 status. This will include analyses of patients where two different vaccinations may have been used in an individual.

(B) To determine vaccine safety by vaccine type and time since vaccination and by subgroups including age, sex, ethnicity, deprivation, region, care home status, household size, co-morbidities[8] (including transplants), medication use, QCovid risk score[8] and prior COVID-19 status (including new variants of concern).

(C) To estimate vaccine effectiveness by evaluating the risk and severity of a COVID-19 diagnosis by vaccine type, time since vaccination and following one or two doses of vaccination and by previous COVID-19 positivity status.

(D) Specific analyses of patient wait list for solid-organ transplantation or recipients of a solid organ transplant will be undertaken to analyse these extremely vulnerable populations who are known to respond sub-optimally to other viral vaccines and have a high risk of poor outcomes from COVID-19.

3.3 Inclusion criteria

All patients of all ages will be included in the analyses since all patients are eligible to be considered for COVID-19 vaccination or likely to become so over time.

3.4 Exclusion criteria

Patients will be excluded if they have had three or mode vaccines or a combination of more than one vaccine type.

3.5 Data sources and settings

Our main analyses will be based on the QResearch database linked to the following datasets to improve ascertainment of exposures, confounders and outcomes:

- Pillar 1 and 2 testing data (PHE SGSS)
- Civil registration data (NHS Digital)
- HES care data (NHS Digital)
- Intensive Care National Audit and Research Centre Case Mix Programme (ICNARC)
- Cancer registry, SACT & Radiotherapy (PHE)
- COVID-19 Vaccine uptake data from the National Immunisation Database (NIMS, NHS Digital)
- COVID-19 vaccination adverse events (NIMS, NHS Digital)
- Occupation data (ONS)
- National Blood and Transplant Data (NHSBT)

3.6 Study Design

We will utilise a variety of study designs including a cohort study design nested self-controlled case-series and nested case control analysis.

3.7 Statistical Analysis of Vaccine Uptake

Outcomes:

For the vaccine uptake analyses, the main outcomes of interest are at least one COVID-19 vaccination dose administered in the study period. The study period will be from 8th December 2020 (date of first vaccination in England) to the latest date for which linked data are available

Descriptive analyses:

We will undertake descriptive analyses to calculate vaccine uptake rates overall, by type and by population subgroup. We will describe the numbers having two vaccination doses of the same vaccine, and the numbers having two different vaccinations and the number of days between each dose. We will present Kaplan-Meier curves. Results will be presented for vaccine priority groups and by dates when vaccination was introduced for each group.

Regression analyses:

We will use Cox regression analyses to calculate adjusted rate ratios (95% CI) for uptake of vaccination by age, sex, ethnicity, deprivation, region, co-morbidity and prior COVID-19

infection. We will check for proportional hazard and extend to using Royston-Palmar models to account for time varying hazard ratios if proportional hazards assumption not valid. Patients will enter the analysis period on 8th Dec 2020 and will be censored on the date on which they leave, die or the latest date for which data are available. Results will be also presented for vaccine priority groups and by dates when vaccination was introduced for each group.

3.8 Statistical analysis of vaccine effectiveness

Outcomes:

For the effectiveness analyses, the outcomes of interest are occurrence and severity of a COVID-19 diagnosis following one or two doses of COVID-19 vaccination compared with those who have not received the vaccination

- Laboratory confirmed SARS-CoV-2 infection (excluding those with a positive test within 7 days of vaccination)
- COVID-19 hospitalisation, defined as hospitalisation within 14 days of a positive COVID test)
- COVID-19 admission to intensive care, define as admission to intensive care during a COVID-19 hospitalisation
- COVID-19 related mortality, defined as COVID on the death certificate or death from any cause within 28 days of a laboratory confirmed COVID infection.

Exposure definition:

For the Oxford vaccine, the date on which patients are likely to have a significant immune response is in the second week post vaccination. However, a positive symptomatic test result in this time window is likely to reflect a virus acquired a week or so earlier. Hence patients will be considered to be unexposed (i.e not vaccinated) from 1st Dec 2020 to day 20 post vaccination. Patients will be considered to be exposures (vaccinated) from day 21 post vaccination to the end of the study period.

For the Pfizer vaccine, patients will be considered to be unexposed for 1st Dec to Day 8 post vaccination. Patients will be considered to be exposure from Day 9 post vaccination to the study end date

Descriptive analyses:

We will present outcomes by subgroups of age, sex, ethnicity, deprivation, geographical region, household size and in those previously infected by COVID.

Regression analyses:

We will undertake a time varying Royston-Palmer regression analyses to determine unadjusted and adjusted hazard ratios for the occurrence of each outcome in vaccinated versus unvaccinated individuals with vaccination treated as a time varying exposure.
Patients will enter the analyses on 8th Dec 2020 (date on which first vaccines became available in the UK). Each patient vaccinated will be matched by age and sex to a person not vaccinated on that date. Vaccinated patients will be censored on the earliest of date of outcome of interest, death, end of the study period or last date for which data are available at the time of the analysis. Unvaccinated patients will be censored on the earliest of date of vaccination, date of outcome of interest, death, end of the study period or last date for which data are available at the time of the analysis.

Analyses will be adjusted for factors associated with increased risk of severe COVID outcomes as determined by the recent QCovid algorithm[8] which is being used for vaccine prioritisation along with the recommendations from the Joint Committee on Vaccination and Immunisation. These are listed below.

3.9 Statistical analysis of vaccine safety

Outcomes:

For the safety analyses, the outcomes of interest include occurrence of any of the serious adverse events of special interest, all-cause mortality and cause-specific mortality listed in Table 1. These include events previously highlighted in relation to vaccine safety or because they have been identified as specific events in the Oxford Vaccine Protocol or are events which need to be monitored by the European Medicines Agency (EMA) Designated Medical Event, FDA, the UK's Medicines Health Regulatory Authority vaccine clinical trials, post-marketing surveillance and the emerging scientific literature [3]. Table 1 includes an indicative list which will evolve as the vaccinations are rolled out and further information becomes available.

Exposure definition:

Patients will be considered as exposed from the date of their first vaccination.

Descriptive analysis:

For the vaccine safety analysis, we will examine for increased risk of potentially vaccine related serious outcomes by examining the incidence of specific outcomes in the -29-1 days prior to vaccination, the day of vaccination and 1-7; 8-14; 15-21; 22-28 days post vaccination days and compare to the incidence of the same outcomes within an equivalent time period in the unvaccinated subjects. We will also compare background rates for the adverse events of interest in the 5 years prior to the pandemic and the first year of the pandemic. We will undertake analyses by vaccination type, as more vaccines become available.

Regression analyses:

For our main safety analyses, we will undertake a self-controlled case series approach since this was originally developed to assess adverse events to vaccination [17]. It can be used to determine the relative incidence of the outcome of interest for exposed time periods (i.e. following vaccination) compared to unexposed periods in individuals who have the outcome of interest. Inference is within individuals and hence covariates which do not change over the study period are implicitly controlled for. For each outcome, we will select the patients within the study cohort with the outcome during the study period and ascertain dates when they had the vaccination doses. We will use conditional Poisson regression to estimate relative rate ratios and adjust for age in 5-year bands. We will then determine the relative rate ratios for each vaccination dose during the pre-defined periods above, following vaccination compared with baseline unexposed period (prior to vaccination) during each person's observation time. We will also consider excluding a period prior to vaccination in an event in that period changes likelihood of receiving vaccination.

In addition, we will determine incidence rates of the outcomes of interest per 100,000 person-years in vaccinated and unvaccinated patients using Poisson regression. Background incidence rates will be determined for comparison. For unvaccinated patients at each time point, we will use a pseudo vaccination date as a reference point – this will be the median date on which vaccinated patients receive their vaccine. There is scope for confounding by indication since those patients with comorbidities and considered as clinically vulnerable may be more likely to have adverse events and are also most likely to be in the risk group requiring early vaccination. People with previous allergies or anaphylaxis are being encouraged to wait for later vaccination types rather than the Pfizer one. Therefore, we will adjust analyses for underlying co-morbidity including indications for earlier vaccination.

3.10 Confounding factors associated with increased risk of poor outcomes from COVID-19 infection

- **Demographics:** age, sex, ethnicity, deprivation, domicile (residential care; homeless; neither)
- **Cardiovascular conditions**: atrial fibrillation, heart failure, stroke, peripheral vascular disease, coronary heart disease, congenital heart disease
- **Diabetes:** type 1 and type 2 and interaction terms for type 2 diabetes with age
- **Respiratory conditions**: asthma, rare respiratory conditions (cystic fibrosis, bronchiectasis or alveolitis), COPD, pulmonary hypertension or pulmonary fibrosis
- **Cancer**: blood cancer, chemotherapy, lung or oral cancer, marrow transplant, radiotherapy,
- **Neurological conditions** cerebral palsy, Parkinson's disease, rare neurological conditions (motor neurone disease, multiple sclerosis, myasthenia, Huntington's chorea), epilepsy, dementia, learning disability, severe mental illness
- **Other**: smoking status, liver cirrhosis, osteoporotic fracture, rheumatoid arthritis or SLE, sickle cell disease, immunosuppression; venous thromboembolism, solid organ transplant, renal failure (CKD3, CKD4, CKD5) +/- dialysis or transplant.
- **Medication**: 4+ GP prescriptions in the last 6 months for oral steroids long-acting beta-agonists; or leukotrienes, immunosuppressants.

3.11 Plans for addressing missing data

For all analyses, we will initially conduct complete case investigations. We will also carry out analysis to account for clustering at GP level. We will subsequently evaluate the models in multiply imputed data. Under the 'missing at random assumption', we will use multiple imputation with chained equations to generate 5 imputed datasets, where values for ethnicity, body mass index (BMI), Townsend deprivation quintile and smoking status are imputed [18-21]. Imputation models will include all exposure and outcome variables; statistical models will be developed on each of the 5 imputed datasets and estimates pooled using Rubin's rules.

QResearch provides the largest primary care resource covering 1500 GP practices nationally with a population of 12.5 million currently registered patients. It is linked to the ICNARC CMP database, which covers all ICUs in England – making it the largest available database in the UK with which to complete this work.

Data will be analysed using STATA (version 16). Our study will be conducted and be reported in line with the RECORD and STROBE guidelines for observational studies using routinely collected health data.

3.12 Limitations of study design, data sources, and analytic methods

Limitations of our study include potential lack of formal adjudication of diagnoses (e.g. comorbidities on Read codes), potential for misclassification of outcomes, information bias and potential bias due to missing data. Our study is not randomised and so has limited utility for determining vaccine effectiveness compared with a conventional trial. However, in the absence of very large-scale post marketing randomised trials, observational assessment of the risk of COVID-19 diagnoses and outcomes of COVID infection following vaccination will provide some useful information, albeit with a cautious interpretation.

4 Patient benefit and involvement

Enhanced independent patient safety monitoring accounting for detailed comorbidities and medications, increasing public confidence across multiple subgroups. Data to drive equity of access to vaccination and inform clinical decision making with patients. This project is intended to inform national policy development on vaccination development and strategy and is complementary to MHRA required activities.

We will ask our PPI panel for their perspectives on the relevance of our research questions, which will help us ensure that our research is looking at questions that are clear and important to the wider community. We will also ask panellists for their advice about other questions that could be included in our research. This will be guided by our PPI panel, but

questions we anticipate working on with them include helping us identify groups in which we should explore vaccine uptake or groups who might be worried about vaccine safety, for example those in high-risk categories or who have had COVID-19. The panel may also suggest investigating whether the time between vaccine doses affects how well it works or whether side-effects develop.

We will work with our PPI panel to develop the role of PPI in this project, seeking their views on how they can shape and inform the development and reporting of this project.

Panellists will help us write about our research, to ensure that our findings are communicated in a way that is accessible and relevant. They will be invited to review material intended for publication to explain the project or to report findings from the research. We will work with our PPI team to co-create publications which are intended for a lay audience, to make sure these are both clear and accessible as well as interesting and informative. For example, this lay summary was written with three lay advisers, who were supportive of the importance and necessity of this project. In particular, working with PPI advisers from different ethnic and social backgrounds will be important when considering the implications of findings, as well as helping us communicate about these. Incorporating these considerations will improve the reach and impact of the research.

5 Appendix

Table 1: Adverse events of interest related to COVID-19 vaccination. Information includes the unique ID for each code groups used when interrogating either GP records (using Read or SNOMED) or hospital records (using ICD-10).

ID	Event	Read/Snomed Code group ID	ICD-10	Source
General	Sudden death	n/a	n/a	MHRA
	Unplanned ICU admission	n/a	n/a	n/a
	Adult Respiratory Distress Syndrome	n/a	n/a	n/a
Autoimmune or inflammatory				
	Anaphylaxis	301	13058	EMA
	Angioedema	13079	13080	EMA
	Autoimmune thyroiditis	6148	11312	MHRA
	Autoimmune hepatitis	6149	6295	EMA
	Primary Biliary Cirrhosis	6089	13483	FDA
	Cholangitis	6082	13495	FDA
	Type 1 diabetes	1913	1940	FDA
	Multisystem inflammatory syndrome	13068	13067	MHRA
	Rhabdomyolysis	606	2740	EMA
	Addison's disease	6088	13484	FDA
	Autoimmune myocarditis/cardiomyopathy	2221	13488	FDA
	Goodpasture syndrome	1831	n/a	FDA
	Pernicious anaemia	75	13485	FDA
	Sarcoidosis	6501	13486	FDA

	Gout	74	13059	JHC
	Sjögren's syndrome	72	13487	FDA
	Vasculitis	7582	13498	FDA
Musculoskeletal				
	Dermatomyositis/polymyositis	73	13490	FDA
	Mixed connective tissue disorder	7649	1977	FDA
	Polymyalgia rheumatic	7911	13491	FDA
	Non-rheumatoid or Psoriatic arthropathy	7580	13494	FDA
	Scleroderma and systemic sclerosis	71	13492	FDA
	Spondyloarthritis and ankylosing spondylitis,	6090	13493	FDA
	Systemic lupus erythematosus	70	1976	FDA
	Rheumatoid arthritis	68	1975	MHRA
Gastrointestinal	Acute liver injury or hepatic failure	1333	13061	EMA; EU-ADR
	Jaundice	1841	13060	EU-ADR
	Acute Pancreatitis	1317	2442	EMA; EU-ADR
	Coeliac disease	47	1979	FDA
	Crohn's disease	45	1978	FDA
	Ulcerative colitis	46	1980	FDA
	Transplant refection or failure	134947	13496	
Renal	Acute kidney injury	2742	2466	EMA; EU-ADR
Blood	Aplastic anaemia/pancytopenia	1313	13073	EMA; EU-ADR
	Haemolytic anaemia	1314	13062	EMA; EU-ADR
	thrombocytopenia	6154	13074	EMA
	Neutropenia/agranulocytosis	1312	13075	EMA; EU-ADR
Neurological	Bell's palsy	1316	13069	MHRA;
	Encephalitis and myelitis	13078	13071	MHRA, FDA
	Guillain Barre syndrome	1318	13066	MHRA;
	Narcolepsy	13081	13072	MHRA
	Optic neuritis	13082	13083	EMA; MHRA
	Myasthenia gravis	1822	11194	EMA, FDA
	Reye's syndrome	13076	13077	EMA
	Multiple sclerosis	38	11193	MHRA
Skin	Bullous eruption including Stevens Johnson	619	3305	EMA
	Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis	2423 or 6139		FDA
	Erythema nodosum	13499	13500	FDA
Cardiovascular	Myocardial infarction	20	1950	MHRA;
	Arrythmias including ventricular fibrillation	1205	24444	EMA; EU-ADR
	Myocarditis or pericarditis	2220	13084	MHRA
	Venous thromboembolism	368	1935	JHC

	Stroke	272	1929	MHRA
Respiratory	Pulmonary fibrosis	6502	11197	EMA
	Pulmonary hypertension	7608	11211	EMA

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