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Comparing coronavirus (COVID-19) vaccine schedule combinations

Submission date
29/01/2021

Recruitment status
No longer recruiting

Registration date
03/02/2021

Overall study status
Completed

Last Edited
14/11/2022

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Multiple vaccines against COVID-19 have shown efficacy on phase 3 studies, and several of these have been granted approval for use. There are likely to be significant logistical challenges immunising large portions of the population. There would be significant advantages to having flexible immunisation programmes whereby the second vaccine dose is not necessarily the same as the first dose.

The main aim of this study is to determine the safety as well as the immune responses to a variety of combinations of schedules for receiving the first dose (prime) and second dose (boost) of candidate COVID-19 vaccines that will potentially be deployed in the UK. The vaccines to be studied in this protocol will primarily be determined by those made available to the Department of Health and Social Care (DHSC) for population use, and in the first instance are the COVID-19 mRNA Vaccine BNT162b2 and the Oxford/AstraZeneca ChAdOx1, with the potential to add additional vaccines at a later date.

Furthermore, given the UK introduction of COVID-19 vaccines has utilised an extended (up to 12 weeks) interval between the first and second dose of vaccine, this study will evaluate combinations of vaccines with a 12 week, as well as 4 week, dosing interval.

Additional objectives of the study are to characterise COVID-19 infections experienced during the study by participants and to look at the immune response to those infections.

Who can participate?
Adult volunteers aged at least 50 years, including those who have other medical conditions, as long as those conditions are mild or moderate in severity and are well controlled at the time of volunteering for the study. Individuals of all ethnicities are eligible to be recruited, with the recruitment of those identifying as Black and Minority Ethnic particularly encouraged, in order to try to reflect the diversity of the UK population.

What does the study involve?
This trial will be studying combinations of two different vaccines. As more new SARS-CoV-2 vaccines become available, more vaccines may be included in the trial and so the total number of participants may increase.

Participants will be allocated, at random, (rather like a flip of a coin) to receive one dose of one approved vaccine and a second dose of either the same approved vaccine or a dose of a different approved vaccine. Participants will also be allocated at random to the timing of receiving these doses, some will get a boost dose four weeks after the first dose (prime) and some will get a boost after twelve weeks.

Between 5 and 9 routine blood tests will be taken over the course of a year to look at the immune responses to the vaccine depending on the group a participant is in. Participants may also be asked for a nasal fluid sample at each visit. Participants might also be asked to attend for a repeat blood test if there were any safety concerns. If a participant were to test positive for the virus causing COVID-19 they be asked to attend for an extra visit. Participants will also need to complete an online diary for up to 28 days following each of the two vaccinations

The trial will take one year to complete per participant (from the time the first dose of vaccine is given).

The study team will not be offering diagnostic COVID-19 testing as part of this trial, but it is important that participants in this trial access COVID-19 testing outside of the trial following normal government guidance. If a participant receives the two doses of COVID-19 vaccines in this trial, this participant will not know which two vaccines they have received until the end of the trial. Unless specifically advised by the study team, a trial participant would not be eligible to receive any further vaccine doses via the government vaccination scheme.

Due to changes in rules affecting national and international travel, as well as event attendance, and concerns about the disadvantage to participants from being unable to access details of their vaccination status, as of 22nd June 2021 (28 days after the last trial participant has received their boost dose) an amendment to allow the unblinding of all participants will be implemented. This will allow for recording of participants vaccination status on medical records and the NHS app. (added 18/06/2021)

What are the possible benefits and risks of participating?
Participants in this study should have a lower risk of COVID-19 disease than unimmunised individuals. Although the heterologous prime/boost schedules have not been tested or approved as yet, the UK ‘Green Book’ guide to immunisation notes that ‘as both the vaccines are based on the spike protein, it is likely the second dose will help to boost the response to the first dose’, therefore it is expected that those in the heterologous group will receive some protection (Public Health England 2020a). Participants may benefit from early receipt of an approved vaccine, should their age/risk group not be eligible for routine vaccination before the end of the trial.

The risks and side effects of the proposed study procedures are:
1. Localised bruising and discomfort associated with blood draws
2. Localised discomfort associated with mucosal fluid sampling
3. Possible allergic reactions to vaccines (rare but can be serious)
4. Side effects from receiving vaccines such as pain in the vaccination site and flu-like symptoms for a short period afterwards (e.g. muscle aches and chills)
5. There is a theoretical risk of Antibody-Dependent Enhancement, also known as Vaccine

Associated Enhanced Disease. This is where having a vaccine can alter the immune response to an infection it is protecting against and make inflammation in the body worse. This has not yet been seen in any previous trials of COVID-19 vaccines but remains a theoretical risk.
6. Participants may alter their behaviour in relation to COVID-19 risks and precautions on the assumption that they are completely protected from the vaccines received in the trial. Participants will be advised to follow all current COVID-19 government advice.
7. Participants may receive unwanted media attention from participating in the trial
8. Following reports of blood clots with lowered platelets following immunisation with the AstraZeneca vaccine a review has been undertaken by the MHRA and the EMA (European Medicines Agency). The reports were into a very rare type of blood clot in the brain, known as cerebral venous sinus thrombosis (CVST), and in some other organs together with low levels of platelets (thrombocytopenia) that might be associated with vaccination with the AstraZeneca vaccine. Up to and including 31 March 2021 there have been 79 UK reports of these blood clots and unfortunately 19 people died. By 31 March 2021 20.2 million doses of the AstraZeneca vaccine had been given in the UK. This means the overall risk of these blood clots is extremely rare, approximately 4 people in a million who receive the vaccine. All participants in this study will be provided with up-to-date information from regulators on this finding. Participants will be advised to be aware of possible signs and symptoms of blood clots and to have a low threshold to contact trial teams if experiencing these or other symptoms.

(added 04/05/2021)
9. There is some initial evidence from those participants boosted at 28 days, that those participants receiving different vaccines for their prime and boost doses might have some of the listed side-effects more commonly and possibly a bit more severely in the first 24 hours following vaccination. We do not know if this will be the case in participants receiving their boost dose at 84 days.
We would like to try to find out whether there is anything that can be done to reduce these side-effects. To do this, for participants who are due to receive their boost vaccine dose 84 days after their prime vaccine dose, there will be an option to be randomised again either to take paracetamol preventatively for the first 24 hours (with the first dose as soon as is convenient after vaccination), or to take paracetamol only if you feel you need to take it for any symptoms experienced. Dosing should be as indicated in the instructions for this over-the-counter medication and it is important not to exceed the maximum stated dose. We would not supply you with this paracetamol, but would ask you to source it yourself. Taking part in this sub-study is optional, and you do not have to agree.

Where is the study run from?
Oxford Vaccine Group (UK)

When is the study starting and how long is it expected to run for?
From October 2020 to November 2022

Who is funding the study?
National Institute for Health Research (UK) and the UK Vaccine Task Force (UK)

Who is the main contact?
Com-COV Study Project Manager
info@ovg.ox.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Com-COV study team

Contact details
Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)
Churchill Hospital
Old Road
Headington
Oxford
United Kingdom
OX3 7LE
+44 (01865) 611400
info@ovg.ox.ac.uk

Type(s)
Public

Contact name
Ms Com-COV study team

Contact details
Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)
Churchill Hospital
Old Road
Headington
Oxford
United Kingdom
OX3 7LE
+44 (01865) 611400
info@ovg.ox.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2020-005085-33

Integrated Research Application System (IRAS)
291055

Central Portfolio Management System (CPMS)
48289

Protocol serial number
OVG2020/03

Study information

Scientific Title
A single-blind, randomised, phase II UK multi-centre study to determine reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules

Acronym
Com-COV

Study objectives
The immune response in COVID seronegative participants to immunisation with heterologous prime/boost COVID-19 vaccines regimens (boosted at 28 days) is non-inferior to that observed following immunisation with approved homologous prime-boost regimens (boosted at 28 days).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/01/2021, South Central - Berkshire Research Ethics Committee (Bristol REC Centre, Whitefriars, Level 3, Block B, Lewins Mead, Bristol, BS1 2NT), ref: 21/SC/0022

Primary study design
Interventional

Study design
Multi-centre single-blind phase II randomized parallel study

Study type(s)
Prevention

Health condition(s) or problem(s) studied
COVID-19 (SARS-CoV-2 infection)

Interventions
A total of 820 participants, consisting of an immunology cohort who will receive their booster vaccine dose after 28 days (n=100) and a general cohort (n=720). Half of the general cohort participants (n=360) will receive their booster vaccine after 28 days, and half will receive their booster vaccine after 84 days. Both cohorts will be stratified by study sites.

All doses are given by intramuscular injection. The dose of ChAdOx1 nCOV-19 is 0.5 ml, the dose of BNT162b2 is 0.3 ml.

Within the immunology cohort (n=100) participants will be randomised using stratified block randomisation 1:1:1:1 with a block size of 4 to the following arms receiving their booster vaccine dose after 28 days:
1. Prime ChAdOx1 nCOV-19, Boost ChAdOx1 nCOV-19
2. Prime ChAdOx1 nCOV-19, Boost BNT162b2
3. Prime BNT162b2, Boost BNT162b2
4. Prime BNT162b2, Boost ChAdOx1 nCOV-19

Within the general cohort participants (n=720) will be randomised using stratified block randomisation 1:1:1:1:1:1:1:1 with random block sizes of 8 or 16 to the following arms:
1. Prime ChAdOx1 nCOV-19, Boost ChAdOx1 nCOV-19 (28 day boost)
2. Prime ChAdOx1 nCOV-19, Boost BNT162b2 (28 day boost)
3. Prime BNT162b2, Boost BNT162b2 (28 day boost)
4. Prime BNT162b2, Boost ChAdOx1 nCOV-19 (28 day boost)
5. Prime ChAdOx1 nCOV-19, Boost ChAdOx1 nCOV-19 (84 day boost)
6. Prime ChAdOx1 nCOV-19, Boost BNT162b2 (84 day boost)
7. Prime BNT162b2, Boost BNT162b2 (84 day boost)
8. Prime BNT162b2, Boost ChAdOx1 nCOV-19 (84 day boost)

The duration of follow-up will be one year from the first vaccination for each participant.

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
ChAdOx1 nCOV-19 vaccine, tozinameran vaccine

Primary outcome(s)
Immunogenicity of COVID-19 vaccines boosted at day 28 in seronegative participants measured using serum level of anti-spike immunoglobulins using ELISA at 56 days

Key secondary outcome(s)
1. Immunogenicity of COVID-19 vaccines in seronegative participants across all dosing intervals measured using serum level of anti-spike immunoglobulins using ELISA at 4 weeks post-boost (56 days for 28-day boost cohort and 112 days for 84-day boost cohort)
2. Safety of heterologous prime-boost COVID-19 vaccines measured using the incidence of serious adverse events and adverse events of special interest measured by electronic diary card and participant reporting throughout the study
3. Further characterisation of immunogenicity measured using the following:
3.1. Anti-spike immunoglobulins using ELISA at 4 weeks post-boost (56 days for 28-day boost cohort and 112 days for 84-day boost cohort)
3.2. Anti-spike immunoglobulins using ELISA at baseline, 7, 28, 35, 84, 112, 182, and 364 days
3.3. Neutralising antibodies against SARS-CoV-2 using viral neutralizing assay at baseline, 28, 56, 84, 112, 182, and 364 days
3.4. Anti-nucleocapsid immunoglobulins by immunoassay at baseline, 28, 56, 84, 112, 182, and 364 days
3.5. Pseudo neutralising antibodies at baseline, 28, 56, 84, 112, 182, and 364 days
3.6. Cellular immune responses by ELISpot at baseline, 14, 28, 42, 56, 84, 112, 182, and 364 days
3.7. Cellular immune responses by intracytoplasmic cytokine staining (ICS) (Th1/Th2) at baseline, 14, and 42 days
4. Reactogenicity and safety measured using the following:
4.1. Solicited local reactions measured by electronic diary card at 7 days after each immunisation
4.2. Solicited systemic reactions measured by electronic diary card at 7 days after each immunisation
4.3. Unsolicited reactions at 28 days after each immunisation
4.4. Medically attended adverse reactions measured by electronic diary card at up to 3 months

post-boost
4.5. Changes from baseline in laboratory safety measures at baseline, 28, 35, 56, 84, and 112 days
5. Immunogenicity, safety, and reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 IgG at baseline, measured using the following:
5.1. Anti-spike immunoglobulins using ELISA at 4 weeks post-boost (56 days for 28-day boost cohort and 112 days for 84-day boost cohort)
5.2. Anti-spike immunoglobulins using ELISA at baseline, 7, 28, 35, 84, 112, 182, and 364 days
5.3. Neutralising antibodies against SARS-CoV-2 using viral neutralizing assay at baseline, 28, 56, 84, 112, 182, and 364 days
5.4. Anti-nucleocapsid immunoglobulins by immunoassay at baseline, 28, 56, 84, 112, 182, and 364 days
5.5. Pseudo neutralising antibodies at baseline, 28, 56, 84, 112, 182, and 364 days
5.6. Cellular immune responses by ELISpot at baseline, 14, 28, 42, 56, 84, 112, 182, and 364 days
5.7. Cellular immune responses by ICS (Th1/Th2) at baseline, 14, and 42 days
5.8. Incidence of serious adverse events and adverse events of special interest recorded throughout the study
5.9. Solicited local reactions measured by electronic diary card at 7 days after each immunisation
5.10. Solicited systemic reactions measured by electronic diary card at 7 days after each immunisation
5.11. Unsolicited reactions measured by electronic diary card at 28 days after each immunisation
5.12. Medically attended adverse reactions measured by electronic diary card at up to 3 months post-boost
5.13. Changes from baseline in laboratory safety measures at baseline, 28, 35, 56, 84, and 112 days
6. Characterisation of COVID-19 infections experienced following administration of vaccine, and the immune response to those infections, measured using: serum levels of anti-spike and anti-nucleocapsid immunoglobulins, and neutralising and pseudo-neutralising antibodies; cellular immune response by ICS; and ELISpot Genome sequencing of SARS-CoV-2 viruses isolated from infected participants between the prime dose, and within 1 week of a participant being found to be SARS-CoV-2 positive by external testing

Completion date
05/11/2022

Eligibility

Key inclusion criteria
1. Aged ≥50 years
2. In good health or have well-controlled or mild-moderate comorbidity, as determined by a trial clinician
3. Willing and able to give written informed consent for participation in the trial
4. Those of childbearing potential must be willing to ensure that they or their partner use effective contraception from 1 month prior to first immunisation continuously until 3 months after boost immunisation
5. Able and willing to comply with all trial requirements, in the Investigator's opinion
6. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
7. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures
8. Agreement to refrain from blood donation during the course of the study

Participant type(s)
All

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
830

Key exclusion criteria
1. Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)
2. Prior or planned receipt of an investigational or licensed vaccine or product likely to impact on the interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines)
3. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
4. Any confirmed or suspected immunosuppressive or immunodeficient state, asplenia, recurrent severe infections, or use of immunosuppressant medication within the past 6 months, with the exception of topical steroids or short-term oral steroids (course lasting ≤14 days)
5. History of allergic disease or reactions likely to be exacerbated by any component of study vaccines (e.g. hypersensitivity to the active substance or any of the SmPC-listed ingredients of the Pfizer vaccine)
6. Any history of anaphylaxis
7. Pregnancy, lactation, or willingness/intention to become pregnant within 3 months post boost vaccine
8. Current diagnosis of or treatment for cancer (with the exception of basal cell carcinoma of the skin and cervical carcinoma in situ)
9. Bleeding disorder (e.g. factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
10. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran, and edoxaban)
11. Suspected or known current alcohol or drug dependency
12. Any other significant disease, disorder, or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data
13. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness (mild/moderate well-controlled comorbidities are allowed)
14. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell’s palsy will not be an exclusion criterion
15. History of laboratory-confirmed COVID-19 prior to enrolment (history of SARS-CoV-2 detection by PCR or antibody to SARS-CoV-2)
16. Significant renal or hepatic impairment
17. Scheduled elective surgery during the trial

18. Life expectancy of <6 months
19. Participation in another research trial involving an investigational product in the past 12 weeks
20. Insufficient level of English language to undertake all study requirements in the opinion of the Investigators
21. If at Visit 1 Screening & Vaccination the volunteer has either of the following, they will not be enrolled that day, however, they may be considered for enrolment later in the trial; if they recover in sufficient time:
21.1. Acute respiratory illness (moderate or severe illness with or without fever)
21.2. Fever (oral temperature >37.8°C)

Date of first enrolment
08/02/2021

Date of final enrolment
28/02/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford Vaccine Group
Centre for Clinical Vaccinology & Tropical Medicine
University of Oxford
Churchill Hospital
Oxford
United Kingdom
OX3 7LE

Study participating centre
NIHR WTCRF
University Hospital Southampton NHS Foundation Trust
Southampton
United Kingdom
SO16 6YD

Study participating centre
St Georges University Hospital NHS Foundation Trust
Blackshaw Road
Tooting
London

United Kingdom
SW17 0QT

Study participating centre
North Bristol NHS Trust
Southmead Hospital
Southmead Road
Westbury-on-Trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
University of Nottingham Health Service
Cripps Health Centre
University Park
Nottingham
United Kingdom
NG7 2QW

Study participating centre
Liverpool School of Tropical Medicine
Accelerator Research Clinic
Clinical Sciences Accelerator
1 Daulby Street
Liverpool
United Kingdom
L7 8XZ

Study participating centre
UCLH
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
University Hospitals Birmingham NHS Foundation Trust (UHB)
Queen Elizabeth Hospital
Mindelsohn Way
Birmingham

United Kingdom
B15 2TH

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
UK Vaccine Task Force

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available. Summary data only will be published. No identifiable personal data will be used.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/08/2021	10/08/2021	Yes	No
HRA research summary			26/07/2023	No	No
Interim results article	early results of reactogenicity data	01/05/2021	18/05/2021	Yes	No
Interim results article	Exploratory analysis	08/06/2022	13/06/2022	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 9.2	20/09/2021	27/09/2021	No	No
Protocol file	version 10.2	20/07/2022	08/09/2022	No	No
Protocol file	version 10.3	20/10/2022	14/11/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes