

# Comparing COVID-19 vaccine schedule combinations – stage 2

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<b>Registration date</b> 26/03/2021	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 11/04/2023	<b>Condition category</b> Infections and Infestations	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

COVID-19 is a condition caused by the coronavirus (called SARS-CoV-2) that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people do not have symptoms but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough among other symptoms. This can develop into pneumonia. Pneumonia is a chest infection where the small air pockets of the lungs, called alveoli, fill with liquid and make it more difficult to breathe.

Multiple vaccines against COVID-19 have been shown to be effective in phase III 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 where 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 likely to be made available to the Department of Health and Social Care (DHSC) for population use, including COVID-19 mRNA Pfizer Vaccine BNT162b2, Oxford/AstraZeneca ChAdOx1, COVID-19 Vaccine Moderna and Novavax NVX-CoV2373, with the potential to add additional vaccines at a later date. Furthermore, as the UK introduction of COVID-19 vaccines has used an extended (up to 12 weeks) interval between the first and second dose of vaccine, this study will evaluate combinations of vaccines with an 8-12-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 different vaccines. Participants will be allocated at random (rather like a flip of a coin) to receive a dose of the same vaccine (homologous) or a dose of a different vaccine to the one they received as part of the national rollout (heterologous). Between five and seven 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. Participants undergo tests to check their blood count is ok (not anaemic), and tests to check that levels of blood salts, liver and kidney function are normal. If a participant were to test positive for the virus causing COVID-19 they are asked to attend for an extra visit. Participants will also need to complete an online diary for up to 28 days following their vaccination. The trial will take 1 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.

### What are the possible benefits and risks of participating?

Participants 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 for vaccines based on the spike protein, it is likely that 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. It is anticipated that this will apply to the Novavax vaccine if it is approved. Participants may benefit from a slightly early receipt of a boost dose vaccine.

The risks and side effects of the proposed study procedures are:

1. Localised bruising and discomfort associated with blood samples
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.

Added 19/04/2021:

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.

Where is the study run from?

Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital (UK)

When is the study starting and how long is it expected to run for?

March 2020 to September 2023

Who is funding the study?

1. National Institute for Health Research (NIHR) (UK)
2. Collaboration for Epidemic Preparedness Innovations (CEPI) (UK)
3. UK Vaccine Task Force (UK)

Who is the main contact?

Iason Vichos

info@ovg.ox.ac.uk

## Contact information

### Type(s)

Public

### Contact name

Mr Iason Vichos

### Contact details

Oxford Vaccine Centre  
Centre for Clinical Vaccinology & Tropical Medicine  
University of Oxford  
Churchill Hospital  
Oxford  
United Kingdom  
OX3 7LE  
+44 (0)1865 611400  
info@ovg.ox.ac.uk

### Type(s)

Scientific

### Contact name

Dr Matthew Snape

### Contact details

Oxford Vaccine Centre  
Centre for Clinical Vaccinology & Tropical Medicine  
University of Oxford  
Churchill Hospital  
Oxford  
United Kingdom  
OX3 7LE  
+44 (0)1865 611400  
info@ovg.ox.ac.uk

# Additional identifiers

## Clinical Trials Information System (CTIS)

2021-001275-16

## ClinicalTrials.gov (NCT)

Nil known

## Protocol serial number

OVG 2021/01

# Study information

## Scientific Title

A single-blind, randomized, phase II UK multi-centre study to determine the reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules – stage 2

## Acronym

Com-COV2

## Study objectives

1. To determine whether the immune response to immunisation with a heterologous boost of a COVID-19 vaccine is non-inferior to that observed following immunisation with a homologous boost, in participants seronegative to SARS CoV-2 nucleocapsid IgG at enrolment
2. To assess the safety of heterologous boost COVID-19 vaccines
3. Further characterisation of immunogenicity of heterologous & homologous boost schedules\*
4. Reactogenicity and safety of heterologous & homologous boost schedules of COVID-19 vaccines
5. Evaluation of immunogenicity, safety & reactogenicity of COVID-19 vaccines in participants seropositive for SARS-CoV-2 nucleocapsid IgG at enrolment

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Not provided at time of registration

## Study design

Single-blind randomized study

## Primary study design

Interventional

## Study type(s)

Prevention

## Health condition(s) or problem(s) studied

COVID-19 (SARS-CoV-2 infection)

## Interventions

Method of randomization: block randomization (blocks of 6 and 12 in the general cohort, blocks of 6 in the immunology cohort).

ChAdOx1-nCoV-19 groups (n = 525) (participants who had their prime dose of this vaccine through the national rollout) will be split into two groups:

1. Immunology group (n = 75) - heterologous boost with either COVID-19 Vaccine Moderna (n = 25), Novavax, NXM-CoV2373 (n = 25), or homologous boost (n = 25), at Day 56-84 post prime. Follow up at days 7, 14, 28, 56, 112, 294 post-boost.
2. General group (n = 450) - heterologous boost with either COVID-19 Vaccine Moderna (n = 150), Novavax, NXM-CoV2373 (n = 150), or homologous boost (n = 150), at Day 56-84 post prime. Follow up at days 28, 56, 112, 294 post-boost.

BNT162b2 groups (n = 525) (participants who had their prime dose of this vaccine through the national rollout) will be split into two groups:

1. Immunology group (n = 75) - heterologous boost with either COVID-19 Vaccine Moderna (n = 25), Novavax, NXM-CoV2373 (n = 25), or homologous boost (n = 25), at Day 56-84 post prime. Follow up at days 7, 14, 28, 56, 112, 294 post-boost.
2. General group (n = 450) - heterologous boost with either COVID-19 Vaccine Moderna (n = 150), Novavax, NXM-CoV2373 (n = 150), or homologous boost (n = 150), at Day 56-84 post prime. Follow up at days 28, 56, 112, 294 post-boost.

### **Intervention Type**

Biological/Vaccine

### **Phase**

Phase II

### **Drug/device/biological/vaccine name(s)**

AstraZeneca COVID-19 vaccine AZD1222 (ChAdOx1 nCoV-19), Pfizer BioNTech (BNT162b2), COVID-19 Vaccine Moderna, Novavax, NVX-CoV2373

### **Primary outcome(s)**

The immune response to immunisation with a heterologous or homologous boost of a COVID-19 vaccine in participants seronegative to SARS CoV-2 nucleocapsid IgG at enrolment, measured with immunogenicity (quantity of anti-spike immunoglobulins measured with ELISA) at Day 28

### **Key secondary outcome(s)**

1. The safety of heterologous boost COVID-19 vaccines, measured with numbers of serious adverse events and adverse events of special interest recorded throughout the study.
2. Further characterisation of the immunogenicity of heterologous and homologous boost schedules, measured with:
  - 2.1. Anti-spike immunoglobins measured with ELISA on days 0, 7, 14, 56, 112, 294
  - 2.2. Neutralising antibodies against SARS-CoV-2 measured with ELISA on days 0, 14, 28, 56, 112, 294
  - 2.3. Anti-nucleocapsid immunoglobins measured with ELISA on days 0, 56, 112, 294 - Updated 01/06/2021: measured on days 0, 28, 112, 294
  - 2.4. Pseudo-neutralising antibodies measured with ELISA on days 0, 14, 28, 56, 112, 294
  - 2.5. Cellular immune responses by enzyme-linked immune absorbent spot (ELISpot) on days 0, 14, 28, 56, 112, 294
  - 2.6. Cellular immune responses by intracellular cytokine staining (ICS) (Th1/Th2) on days 0, 14
3. Reactogenicity and safety of heterologous and homologous boost schedules of COVID-19

vaccines, measured with:

- 3.1. Solicited local reactions and solicited systemic reactions recorded in participant electronic diaries at 7 days after immunisation
- 3.2. Unsolicited reactions recorded in participant electronic diaries at 28 days after immunisation
- 3.3. Medically attended adverse events recorded in participant electronic diaries up to 3 months post boost
- 3.4. Laboratory safety measures (full blood count and biochemical tests) at baseline and days 0, 7, 28
4. Evaluation of the immunogenicity, safety and reactogenicity of COVID-19 vaccines in participants seropositive for SARS-CoV-2 nucleocapsid IgG at enrolment, measured with immunogenicity, safety and reactogenicity endpoints as outlined above throughout the study

### **Completion date**

01/09/2023

## **Eligibility**

### **Key inclusion criteria**

1. Participant is willing and able to give written informed consent for participation in the trial
2. Male or female, aged 50 years or above and in good health as determined by a trial clinician. Participants may have well-controlled or mild-moderate comorbidity
3. Has received one dose of the prime/boost schedules being studied via the UK COVID-19 vaccination programme at a timing to allow boost dose given in the trial to fall between days 56-84 post-prime. Evidence of this will be gathered from medical history and/or medical records.
4. Female participants 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. In the Investigator's opinion, is able and willing to comply with all trial requirements
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)**

Healthy volunteer

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Sex**

All

### **Total final enrolment**

1072

### **Key exclusion criteria**

1. Receipt of any vaccine (licensed or investigational) within 30 days before enrolment (1 week for licensed seasonal influenza vaccine or pneumococcal vaccine)
2. Previous receipt of two or more COVID-19 vaccine doses
3. 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 other than ChAdOx1 nCoV-19)
4. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
5. Any confirmed or suspected immunosuppressive or immunodeficient state; asplenia; recurrent severe infections and use of immunosuppressant medication within the past 6 months, except topical steroids or short-term oral steroids (course lasting  $\leq 14$  days)
6. History of anaphylaxis, 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), as specified in the UK Immunisation 'Green Book' COVID-19 vaccine chapter
7. Pregnancy, lactation or willingness/intention to become pregnant within 3 months post boost vaccine
8. Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ). This does not include recurrence prophylaxis treatment in those who have no evidence of active disease e.g. hormonal therapy in hormone-sensitive cancers.
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, rheumatological 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 (e.g. history of SARS-CoV-2 detection by PCR or antibody to SARS-CoV-2)
16. Significant renal or hepatic impairment
17. Scheduled elective surgery requiring overnight admission and/or general anaesthetic during the trial
18. Participant with a life expectancy of less than 6 months
19. Participants who have participated 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

**Date of first enrolment**

19/04/2021

**Date of final enrolment**

21/05/2021

## **Locations**

**Countries of recruitment**

United Kingdom

England

**Study participating centre****Centre for Clinical Vaccinology & Tropical Medicine**

University of Oxford

Churchill Hospital

Oxford

United Kingdom

OX3 7LA

**Study participating centre****St Georges University Hospital NHS Foundation Trust**

Blackshaw Road

Tooting

London

United Kingdom

SW17 0TQ

**Study participating centre****Sheffield Teaching Hospitals**

Royal Hallamshire Hospital

Glossop Road

Sheffield

United Kingdom

S10 2RX

**Study participating centre****Guy's and St Thomas' NHS Foundation Trust**

Department of Infection

St Thomas Hospital

Westminster Bridge Road

London

United Kingdom

SE1 7EH

**Study participating centre****The Newcastle upon Tyne Hospitals NHS Foundation Trust**

Royal Victoria Infirmary

Newcastle upon Tyne  
United Kingdom  
NE1 4LP

**Study participating centre**  
**University College London Hospitals**  
250 Euston Road  
London  
United Kingdom  
NW1 2PG

**Study participating centre**  
**Hull University Teaching Hospitals NHS Trust (HUTH)**  
Hull Royal Infirmary  
Anlaby Road  
Hull  
United Kingdom  
HU3 2JZ

**Study participating centre**  
**University Hospitals Birmingham NHS Foundation Trust (UHB)**  
Queen Elizabeth Hospital Birmingham  
Mindelsohn Way  
Birmingham  
United Kingdom  
B15 2TH

**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**  
**Oxford University Hospital Foundation Trust**  
John Radcliffe Hospital  
Headley Way  
Headington

Oxford  
United Kingdom  
OX3 9DU

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

## Sponsor information

**Organisation**  
University of Oxford

**ROR**  
<https://ror.org/052gg0110>

## Funder(s)

**Funder type**  
Government

**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

## Funder Name

UK Vaccine Task Force

## Funder Name

Collaboration for Epidemic Preparedness

# 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?
<a href="#">Results article</a>	Immunogenicity, safety, and reactogenicity results	06/12/2021	10/12/2021	Yes	No
<a href="#">Results article</a>	Persistence of immune response	05/04/2023	11/04/2023	Yes	No
<a href="#">Participant information sheet</a>	version V4.0	15/06/2021	24/06/2021	No	Yes
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes
<a href="#">Protocol file</a>	version V4.0	15/06/2021	24/06/2021	No	No
<a href="#">Protocol file</a>	version 6.1	22/09/2021	27/09/2021	No	No
<a href="#">Protocol file</a>	version 7.1	20/07/2022	08/09/2022	No	No
<a href="#">Protocol file</a>	version 7.2	20/10/2022	14/11/2022	No	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes