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Comparing COVID-19 vaccine schedule combinations – stage 2

Submission date
12/03/2021

Recruitment status
No longer recruiting

Registration date
26/03/2021

Overall study status
Completed

Last Edited
11/04/2023

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
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?
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Study website
https://comcovstudy.org.uk/

Contact information

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Additional identifiers

EudraCT/CTIS number
2021-001275-16

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
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

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Prevention

Participant information sheet
Patient information material can be found at: https://comcovstudy.org.uk/ , see additional file ISRCTN27841311_PIS_4.0_15 June 2021 (added 24/06/2021)

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 measure
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

Secondary outcome measures
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

Overall study start date
02/03/2020

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

Age group
Adult

Sex
Both

Target number of participants
1050

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 ≤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
England

United Kingdom

Study participating centre
Centre for Clinical Vaccinology & Tropical Medicine
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Sponsor type
University/education

Website
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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

Publication and dissemination plan
1. The protocol can be found at https://comcovstudy.org.uk/
2. Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/09/2023

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