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# Combining influenza and COVID-19 vaccination (ComFluCOV) study

**Submission date**
17/03/2021

**Recruitment status**
No longer recruiting

**Registration date**
30/03/2021

**Overall study status**
Completed

**Last Edited**
30/06/2025

**Condition category**
Infections and Infestations

[_] Prospectively registered
[_] 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.

Mass vaccination against COVID-19 started in the UK in early December 2020 and is likely to continue until mid-2021. Whilst rates of COVID-19 infection have decreased, the emergence of variants of interest and planned easing of lockdown measures has led to predictions of potential resurgence of infection from autumn 2021. The duration of protection of the current COVID-19 vaccines is unknown but it may be that further booster doses will be required in 9 to 12 months' time with current or potentially strain-modified vaccines to afford continued protection into the autumn. The timing of the booster doses is likely to coincide with seasonal influenza vaccination, which is usually September to February. Delivering COVID-19 and influenza vaccines at separate appointments will cause significant logistical challenges therefore it would be desirable to immunise with both vaccines at the same appointment, in different arms.

The ComFluCOV trial will determine the safety, as well as the immune responses, to administration of the currently approved COVID-19 vaccines at the same time as the recommended influenza vaccines from the 2020/21 season.

Participants who are having their second COVID-19 vaccine will be randomised into two groups; one group will receive the influenza vaccine and the other group will receive saline (placebo) at the same time as the COVID-19 vaccine. Participants will not know whether they receive the influenza vaccine or the placebo. After 3 weeks participants who received the influenza vaccine will receive the saline injection and participants who received the saline injection will receive the influenza vaccine. Participants will be followed up for a further 3 weeks after the second injection. We hope to recruit 504 participants into the trial. The trial will be conducted in at least 5 UK NHS centres. The trial is expected to take about 6 months to complete.

Who can participate?
Adult health volunteers who have received one dose of either the ChadOx1-nCOV-19 (AstraZeneca/Oxford) vaccine (56 to 90 days prior to trial enrolment) or the BNT162b2 (Pfizer BioNTech) vaccine (28 and 90 days prior to trial enrolment)

What does the study involve?
Participants will be allocated, with an equal chance of receiving either treatment (like tossing a coin), to receive one of the following at the same time as their second COVID-19 vaccine dose:
1. Influenza vaccine (Flucelvax QIV if the participant is less than 65 years old, or FluAd (MF59) if the participant is aged 65 years or older)
2. An inactive, similar in appearance, injection of Sodium chloride 0.9%
Participants will not know which treatment they have received during the study. Participants who do not receive the Influenza vaccine at the same time as their second COVID-19 vaccine dose will receive this vaccine 3 weeks later.

What are the possible benefits and risks of participating?
There are no immediate benefits for participants taking part in this trial. The influenza vaccine may provide protection against influenza infection at a later point in the year, for those who do not routinely receive an influenza vaccine in the autumn.

Side effects and allergic reactions may occur in response to the vaccines. Participants will be encouraged to report any reaction to the study team. These will be reviewed regularly and participants will be contacted if there is any cause for concern. There is a risk of localised bruising and discomfort when having a blood sample taken. Infrequently fainting may occur.

Participants might feel they can modify their COVID-19 risk behaviours on the assumption that they are protected once vaccinated. Participants will be extensively counselled that they should continue to follow all up to date government advice in relation to COVID-19 precautions during the trial. Trial participants can be subjected to unwanted attention from the media. They will therefore be provided with access to a document outlining some suggested media guidance.

Where is the study run from?
University Hospitals Bristol NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
March 2022 to February 2023

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

Who is the main contact?
Dr Rajeka Lazarus, rajeka.lazarus@uhbw.nhs.uk

### Study website
https://comflucov.blogs.bristol.ac.uk/

# Contact information

### Type(s)
Public

**Contact name**
Dr Rajeka Lazarus

**ORCID ID**
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**Contact details**
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# Additional identifiers

**EudraCT/CTIS number**
2021-001124-18

**IRAS number**
297151

**ClinicalTrials.gov number**
Nil known

**Secondary identifying numbers**
IRAS 297151

# Study information

**Scientific Title**
A single-blind, phase IV UK multi-centre randomised controlled trial to determine reactogenicity and immunogenicity of COVID-19 vaccines administered concomitantly with seasonal influenza vaccines

**Acronym**
ComFluCOV

**Study objectives**
The reactogenicity of concomitant administration of COVID-19 and influenza vaccine is no worse than COVID-19 vaccine alone

**Ethics approval required**
Old ethics approval format

**Ethics approval(s)**
Approved 17/03/2021, South Central - Berkshire Research Ethics Committee (Bristol REC centre, Whitefriars, Level 3, Block B, Lewins Mead, Bristol BS1 2NT; +44 (0)207 104 8224, +44 (0)207 104 8270; berkshire.rec@hra.nhs.uk), ref: 21/SC/0100

## Study design
Multicentre triple-blind parallel-group randomized placebo-controlled trial

## Primary study design
Interventional

## Secondary study design
Randomised controlled trial

## Study setting(s)
Other

## Study type(s)
Prevention

## Participant information sheet
Available through https://comflucov.blogs.bristol.ac.uk/

## Health condition(s) or problem(s) studied
Adults receiving the influenza (flu) vaccine who may also need COVID-19 booster vaccines

## Interventions
Study participants will be randomly allocated to receive one of the following at visit 1 at the same time as their second COVID-19 vaccine (either ChadOx1-nCOV-19 (AstraZeneca/Oxford) vaccine or BNT162b2 (Pfizer BioNTech) vaccine):
1. Investigational Medicinal Product (IMP): Influenza vaccine (Flucelvax QIV if the participant is aged <65 years or FluAd (MF59) if the participant is aged ≥65 years)
2. Placebo: Sodium chloride 0.9% injection

Participants, laboratory staff, and clinicians assessing causality will be blinded to the treatment allocation. Randomisation will be performed using a secure internet-based randomisation system ensuring allocation concealment by a member of the local research team. Participants will be allocated in a 1:1 ratio to COVID-19 vaccine plus influenza vaccine or COVID-19 vaccine plus placebo vaccine. The allocation will be computer-generated and will be stratified by age (under 65 years, 65 years or over), type of vaccine (ChAdOx1 or BNT162b2), and centre by an independent BTC CTEU statistician, not involved in the trial, before recruitment begins.

Approximately 3 weeks later participants will receive the other intervention (participants receiving the influenza vaccine at visit 1 will receive the placebo at visit 2, and participants receiving the placebo at visit 1 will receive the influenza vaccine at visit 2)

## Intervention Type
Drug

## Phase
Phase IV

## Drug/device/biological/vaccine name(s)
Influenza vaccines (Flucelvax (QIV), FluAd (MF59) & Flublok (QIVr)) COVID-19 vaccines (ChadOx1-nCOV-19 (AstraZeneca/Oxford) vaccine & 6.1.2 BNT162b2 (Pfizer BioNTech) vaccine)

### Primary outcome measure
1. Incidence of ≥1 solicited systemic reaction measured using an electronic diary completed by participants in the 7 days following visit 1. Solicited systemic adverse events include fever, feverishness, chills, joint pains, muscle pains, fatigue, headache, malaise, nausea, vomiting, and diarrhoea.

### Secondary outcome measures
1. Type and severity of solicited adverse reactions (systemic or local reaction) measured using an electronic diary completed by participants in the 7 days following visit 1
2. Unsolicited adverse reactions measured using an electronic diary completed by participants during trial participation
3. Medically attended events or serious adverse events (SAEs) measured using an electronic diary completed by participants during trial participation
4. Response to the second dose of COVID-19 vaccine measured using anti-spike protein immunoglobulins in blood samples taken at visit 1 and 2
5. Response to the second dose of COVID-19 vaccine measured using neutralising antibodies against SARS-CoV-2 in blood samples taken at visit 1 and 2
6. Response to influenza vaccine measured using haemagglutination inhibition assay in blood samples taken at visits 1, 2, and 3
7. Mucosal immune responses to COVID-19 vaccines in saliva measured using an assay of saliva samples collected at visits 1, 2, and 3
8. Success of participant blinding measured using the participant completed Bang Blinding Index at visit 3
9. Participant willingness to receive concomitant influenza and COVID-19 vaccinations in the future as reported by participants at visit 3
10. Days off work for participants in employment as reported by participants at visit 3

### Overall study start date
01/03/2021

### Completion date
21/02/2023

## Eligibility

### Key inclusion criteria
1. Aged ≥18 years
2. Received one dose of either:
2.1. ChAdOx1 vaccine, 56 to 90 days prior to trial enrolment
2.2. BNT162b2 vaccine, 28 and 90 days prior to trial enrolment
3. Agree to refrain from blood donation in the 7 days following vaccination (at both visits 1 and 2)
4. Willing to allow their General Practitioner (GP) and consultant, if appropriate, to be notified of participation in the trial
5. Willing to allow investigators to discuss their medical history and confirm vaccination status with their GP, and access all medical records when relevant to trial procedures
6. Willing and able to give written informed consent for participation in the trial
7. Able to use and has access to an electronic device (such as a laptop, tablet, or smartphone) to complete trial procedures (such as the e-diary)
8. Able and willing to comply with all trial requirements, in the Investigator’s opinion

### Participant type(s)

Healthy volunteer

## Age group
Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants
756

## Total final enrolment
679

## Key exclusion criteria
Current exclusion criteria as of 07/05/2021:
1. Receipt of any vaccine (licensed or investigational) other than ChAdOx1 or BNT162b2 within 30 days before visit 1
2. Administration of immunoglobulins and/or any blood products within three months before visit 1
3. History of allergic disease or reactions likely to be exacerbated by any component of trial vaccines (for example hypersensitivity to the active substance or any of the SmPC-listed ingredients)
4. Bleeding disorder (e.g., factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following intramuscular injections or venepuncture and any history of cerebral venous sinus thrombosis, acquired or hereditary thrombophilia, heparin-induced thrombocytopenia or antiphospholipid syndrome. Those who have experienced major venous and arterial thrombosis occurring with thrombocytopenia following vaccination with any COVID-19 vaccine should not receive a second dose of COVID-19 Vaccine AstraZeneca.
5. Continuous use of anticoagulants, such as coumarins and related anticoagulants (such as warfarin) or novel oral anticoagulants (such as apixaban, rivaroxaban, dabigatran, and edoxaban)
6. Suspected or known current alcohol or drug dependency
7. Any other significant disease, disorder, or finding which may significantly increase the risk to the participant, affect their ability to participate in the trial, or impair interpretation of the trial data
8. Current, active, and progressive neurological disorders (such as multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion
9. Scheduled elective surgery during trial participation if this interferes with the study protocol
10. Participated in another research trial involving an investigational product in the 12 weeks prior to visit 1, or if receipt of any IMP is planned during the trial period
11. Acute, ongoing respiratory illness (moderate or severe illness, with or without fever) at visit 1
12. Fever (oral temperature >37.8°C) at visit 1

Previous exclusion criteria:
1. Receipt of any vaccine (licensed or investigational) other than ChAdOx1 or BNT162b2 within 30 days before visit 1
2. Administration of immunoglobulins and/or any blood products within three months before visit 1

3. History of allergic disease or reactions likely to be exacerbated by any component of trial vaccines (for example hypersensitivity to the active substance or any of the SmPC-listed ingredients)
4. Bleeding disorder (for example factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular injections or venepuncture
5. Continuous use of anticoagulants, such as coumarins and related anticoagulants (such as warfarin) or novel oral anticoagulants (such as apixaban, rivaroxaban, dabigatran, and edoxaban)
6. Suspected or known current alcohol or drug dependency
7. Any other significant disease, disorder, or finding which may significantly increase the risk to the participant, affect their ability to participate in the trial, or impair interpretation of the trial data
8. Current, active, and progressive neurological disorders (such as multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion.
9. Scheduled elective surgery during trial participation if this interferes with the study protocol
10. Participated in another research trial involving an investigational product in the 12 weeks prior to visit 1, or if receipt of any IMP is planned during the trial period
11. Acute, ongoing respiratory illness (moderate or severe illness, with or without fever) at visit 1
12. Fever (oral temperature >37.8°C) at visit 1

### Date of first enrolment
29/03/2021

### Date of final enrolment
30/05/2021

## Locations

### Countries of recruitment
England

United Kingdom

Wales

### Study participating centre
### Gloucestershire Hospitals NHS Foundation Trust
Victoria Warehouse
The Docks
Gloucester
United Kingdom
GL1 2EL

### Study participating centre
### Great Western Hospitals
Marlborough Road

Swindon
United Kingdom
SN3 6BB

**Study participating centre**
**North Bristol NHS Trust**
Southmead Road
Bristol
United Kingdom
BS10 5NB

**Study participating centre**
**Royal Cornwall Hospitals NHS Foundation Trust**
Treliske
Truro
United Kingdom
TR1 3LJ

**Study participating centre**
**Royal United Hospitals Bath**
Combe Park
Bath, Avon
United Kingdom
BA1 3NG

**Study participating centre**
**University Hospitals Bristol and Weston NHS Foundation Trust**
Trust Headquarters
Marlborough Street
Bristol
United Kingdom
BS1 3NU

**Study participating centre**
**Cardiff Bayside Mass Vaccination Centre**
Olympian Drive
Cardiff
United Kingdom
CF11 0JS

**Study participating centre**
**Rotherham Doncaster and South Humber NHS Foundation Trust**
Tickhill Road Hospital
Balby
Doncaster
United Kingdom
DN4 8QN

**Study participating centre**
**University College London Hospitals**
12 Queen Square
London
United Kingdom
WC1N 3BG

**Study participating centre**
**Newquay Health Centre**
St Thomas' Road
Newquay
United Kingdom
TR7 1RU

**Study participating centre**
**The Alverton Practice**
St Clare Medical Centre
St Clare Street
Penzance
United Kingdom
TR18 3DX

**Study participating centre**
**Knowle House Surgery**
4 Meavy Way
Crownhill
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PL5 3JB

# Sponsor information

### Organisation
University Hospitals Bristol NHS Foundation Trust

### Sponsor details
Research and Innovation
Education & Research Centre Level 3
Upper Maudlin Street
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United Kingdom
BS2 8AE
+44 (0)1173420233
research@uhbw.nhs.uk

### Sponsor type
Hospital/treatment centre

### Website
http://www.uhbristol.nhs.uk/

### ROR
https://ror.org/04nm1cv11

## Funder(s)

### Funder type
Government

### Funder Name
Vaccine Taskforce (VTF)

### 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

### Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

### Intention to publish date
31/08/2022

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Rajeka Lazarus (comFluCOV-trial@bristol.ac.uk). Anonymised trial data will only be made available for sharing outside the ComCOV studies group after publication of the main results of the trial. Thereafter, individual participant data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements, and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods, and analysis of the secondary research, e.g., a protocol for a Cochrane systematic review.

### IPD sharing plan summary
Available on request

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | | 11/11/2021 | 15/11/2021 | Yes | No |
| Other publications | Summary of results for participants version 1.0 | | 17/03/2023 | No | Yes |
| HRA research summary | | | 28/06/2023 | No | No |
| Other publications | implementation | 11/01/2024 | 12/01/2024 | Yes | No |
| Other publications | statistical methodologies implementation | 23/01/2024 | 24/01/2024 | Yes | No |
| Results article | | 23/09/2024 | 25/09/2024 | Yes | No |
| Results article | Secondary outcome investigating SARS-CoV-2-specific mucosal antibody responses | 30/04/2024 | 30/06/2025 | Yes | No |