ISRCTN12348322 https://doi.org/10.1186/ISRCTN12348322

Comparing COVID-19 vaccine schedule combinations in adolescents (Com-COV3)

Submission date
15/09/2021

Recruitment status
No longer recruiting

Registration date
16/09/2021

Overall study status
Completed

Last Edited
09/05/2024

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
Since early 2020, COVID-19 has spread around the world. Over 130,000 people in the UK and over 4 million people worldwide have died with COVID-19 (by August 2021). It has made many more people seriously unwell.
Widespread vaccination is helping to save lives, reduce the severity of illness and reduce the spread of the disease. Most adults in the UK have now been vaccinated. By early August 2021, over 88% of adults in the UK had received at least one dose of vaccine.
The vaccination programme in the UK has so far focussed on adults because older adults are more likely to suffer from severe disease or die from COVID-19 than younger people. Although children and young people usually do not become very unwell with COVID-19, some do develop serious illness and a few have died. Young people with COVID-19 occasionally develop a serious inflammatory condition called paediatric multisystem inflammatory syndrome (PIMS-TS). In England, in the first year of the pandemic (until the end of February 2021), 251 under-18-year-olds (about 20 per million) were admitted to intensive care with COVID-19, and 25 (about 2 per million) died; 309 (about 26 per million) developed PIMS-TS.
Vaccinating young people may reduce their risk of severe disease and reduce their chance of missing time in education whilst isolating.
Cohort A of this study will determine the side effect profile, and the immune responses, following schedules using BNT162b2 as a first dose (administered in this study or in the community), and a second dose administered at least 8 weeks later of either BNT162b2 (full or one- third dose) or NVXCoV2373 (full dose). When enrolment to Cohort A of the study commenced, young people aged 12 to 17 years were being invited to receive one dose of the Pfizer-BioNTech vaccine, and many had already been given this. Individuals who had received one dose of the Pfizer-BioNTech vaccine in the community were eligible to enrol in the study at least 8 weeks afterwards.
Following the JCVI recommendation on 29th November 2021 that all 12- to 15-year-olds should be offered a second dose of the BNT162b2 vaccine, the study design was amended to focus on the immune response to BNT162b2. After this date, participants were randomised 1:1 to either full or one-third dose BNT162b2 for their second vaccination. Participants were no longer randomised to the Novavax arm of the study in order to prioritise the arms of the study that were likely to be more policy relevant. This did not reflect any concern regarding the safety or immunogenicity of the Novavax vaccine.

A further review of the study design was undertaken following an interim analysis and on 3rd February 2022, the study Trial Steering Committee advised to stop recruitment for Cohort A. It was also decided to add a new cohort to the study to investigate possible strategies for a third dose of the COVID-19 vaccine in adolescents, following the JCVI's recommendation of a third dose to 16- and 17-year-olds (22nd December 2021).
Cohort B of this study will determine the side effect profile and the immune responses to a third dose of COVID-19 vaccination in adolescents, given at least three months after completion of a two-dose schedule (two full doses of BNT162b2 given at least 8 weeks apart). Participants will be randomised to receive 30µg BNT162b2, 10µg BNT162b2 (given as 0.1ml of adult formulation), 10µg BNT162b2 (given as 0.2ml of paediatric formulation), NVXCov2373 (full dose) or two doses of 4CMenB (Meningococcal Group B vaccine, control group). The control group will be offered Pfizer-BioNTech Comirnaty (Original/Omicron BA.1) 15 µg/15 µg (0.3ml) vaccine 6 months after enrolling in the study.

Who can participate?
Cohort A: This cohort will enrol young people aged 12 to 16 years from various sites in the UK.
Cohort B: This cohort will enrol young people aged 12 to 15.5 years from various sites in the UK.

What does the study involve?
COHORT A
All participants will receive their first immunisation with a standard dose of the Pfizer-BioNTech vaccine. This may either be given in the study, or it may have been given in the community before enrolment in the study.
A second dose of the COVID-19 vaccine will be given at least 8 weeks after the first. The type and dose of vaccine given to each participant will be decided using a process called “randomisation”.
The second dose of vaccine will be one of the following three possibilities:
1. A full standard dose of the Pfizer-BioNTech vaccine
2. A third of a standard dose of the Pfizer-BioNTech vaccine
3. A full standard dose of the Novavax vaccine

Each participant who receives their first vaccine in the study or in the community will have a total of six or five blood tests, respectively, during the course of the study to assess their immune response to the vaccines.
Please note that Participants not randomised by 29th November 2021 will only be randomised to:
1. A full standard dose of the Pfizer-BioNTech vaccine
2. A third of a standard dose of the Pfizer-BioNTech vaccine

COHORT B
The second part of the study (Cohort B) will investigate various options for a third dose booster in adolescents aged 12 to 15.5 years who have already received two doses of BNT162b2 30µg. It will include arms to compare 10µg BNT162b2 administered as either paediatric or adult formulation. For direct comparison, the study will include a blinded control group, receiving a MenB vaccine (which is of similar reactogenicity to COVID-19 vaccines). The rapidly changing situation, with respect to the proportion of the population previously infected and dominant circulating COVID-19 variants, makes it preferable to use randomised rather than historical controls.

What are the possible benefits and risks of participating?
On 15th November 2021 16- and 17-year-olds in the UK were deemed eligible for a second dose of the Pfizer-BioNTech vaccine and on 29th November 2021 this was extended to all adolescents

12 years and over. However, only people aged 16 and older (and participants at increased risk of COVID-19, or household contacts of immunocompromised individuals, based on JCVI and 'Green Book' guidelines current on 13th September 2021) are eligible to receive a third dose of a COVID-19 vaccine. Participation in this study will provide 12- to 15-year-olds with the opportunity to receive a third dose of a COVID-19 vaccine, which may boost their immune response to previous doses. The results of this study may be used to guide future decisions about how best to vaccinate young people against COVID-19. By taking part in the study, participants will also have contributed to this.

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?
September 2021 to September 2024

Who is funding the study?
1. National Institute for Health Research (NIHR) (UK)
2. UK Vaccine Task Force (VTF) (UK)
3. Novavax (USA)
4. CEPI (Cohort B)

Who is the main contact?
Emma Plested, info@ovg.ox.ac.uk

Study website
https://comcovstudy.org.uk

Contact information

Type(s)
Public

Contact name
Mrs Emma Plested

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

EudraCT/CTIS number
2021-004267-27

IRAS number
304450

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 304450, CPMS 50491

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 in adolescents

Acronym
Com-COV3

Study objectives
Current hypothesis as of 25/05/2022:
Cohort A:
1. To evaluate the reactogenicity of heterologous boost at least 8 weeks following BNT162b2 prime vaccine administered to adolescents.
2. To characterise immunogenicity of heterologous and homologous second dose schedules of COVID-19 vaccines

Cohort B:
1. To evaluate the reactogenicity of homologous and heterologous boost (third dose) given to adolescents at least 3 months after a two-dose schedule of BNT162b2
2. To determine whether the immune response with BNT162b2 (10 µg, 0.1 ml adult formulation) is non-inferior to that with BNT162b2 (10 µg, 0.2 ml paediatric formulation)
3. To characterise immunogenicity of heterologous and homologous third dose schedules of COVID-19 vaccines when compared with unimmunized controls

Cohorts A and B:
1. To assess safety of heterologous second and third dose COVID-19 vaccines
2. Characterisation of frequency of anti-SARS-CoV-2 nucleocapsid IgG seropositivity at enrolment, and subsequent seroconversion through the study
3. To assess reactogenicity and safety of heterologous and homologous second and third dose schedules of COVID-19 vaccines
4. To evaluate immunogenicity, safety and reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 nucleocapsid IgG at enrolment, compared with seronegative

———

Previous hypothesis:
1. To evaluate the reactogenicity of heterologous boost at least 8 weeks following BNT162B2 prime vaccine administered to adolescents.
2. To assess safety of heterologous boost COVID-19 vaccines
3. To characterise immunogenicity of heterologous & homologous boost schedules

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/09/2021, Berkshire Research Ethics Committee (Easthampstead Baptist Church, South Hill Road, Bracknell, RG12 7NS, UK; +44 (0)207 104 8224; berkshire.rec@hra.nhs.uk), ref: 21/SC/0310

Study design
Single-blinded randomized controlled phase II multi-centre

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
https://comcovstudy.org.uk/comcov3pis

Health condition(s) or problem(s) studied
Prevention of COVID-19 infection in adolescents between 12-16 years of age

Interventions
Current interventions as of 24/10/2023:

COHORT A:
All participants will receive their first immunisation with a standard dose of Pfizer-BioNTech (BNT162b2) vaccine, a dose of 30 µg (0.3 ml). This may either be given in the study, or it may have been given in the community before enrolment in the study. A second dose of the COVID-19 vaccine, given at least 8 weeks after the first, will be one of the following three possibilities:
1. A full standard dose of the Pfizer-BioNTech vaccine
2. A third of a standard dose of the Pfizer-BioNTech vaccine
3. A standard dose of Novavax NVXCoV2373, dose of 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)
Participants not yet randomised by 29/11/2021 will only be randomised to
1. A full standard dose of the Pfizer-BioNTech vaccine
2. A third of a standard dose of the Pfizer-BioNTech vaccine
All vaccines will be administered intramuscularly according to specific SOPs.
A computer-generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1 to the three groups using block randomisation (random block sizes of 3 and 6). Participants not yet randomised by 29/11/2021 will be randomised 1:1 using block randomisation (random sizes of 2 and 4).
Follow-up is for 10 months.

COHORT B:
The second part of the study (Cohort B) will investigate various options for a third dose booster in adolescents aged 12 to 15.5 years who have already received two doses of BNT162b2 30 µg. It will include arms to compare 10 µg BNT162b2 administered as either paediatric or adult formulation. For direct comparison, the study will include a blinded control group, receiving a MenB vaccine (which is of similar reactogenicity to COVID-19 vaccines). The rapidly changing situation, with respect to the proportion of the population previously infected and dominant circulating COVID-19 variants, makes it preferable to use randomised rather than historical controls.

We aim to recruit 310 participants aged 12 to 15½ years, who have already received two standard doses of the Pfizer vaccine in the community. They will be randomised into five groups, each of which will be given a different vaccine schedule. The options for the third dose of the COVID-19 vaccine we will investigate are:
1. A full dose of the adult Pfizer vaccine
2. A one-third dose of the adult Pfizer vaccine
3. A full dose of the paediatric Pfizer vaccine
4. A full dose of the Novavax vaccine

The fifth group in the study will be given their third dose of the COVID-19 vaccine (Pfizer-BioNTech Comirnaty (Original/Omicron BA.1)) later in the study than the other groups. This 'control group' will improve our understanding of the immune responses in the other groups.

Following approval of Substantial Amendment 13, the randomisation ratio for Cohort B has been changed from 1:1:1:1:1 to 1:3:3:1:1 to prioritise recruitment to study arms 2 and 3 (i.e., the fractional dose BNT162b2 10µg adult and paediatric formulation groups) to achieve the participant numbers required to meet the study's co-primary endpoint of non-inferiority between the two BNT162b2 fractional dose groups

All vaccines will be administered intramuscularly according to specific SOPs.

Follow-up is for 10 months.

———

Previous interventions from 09/06/2023 to 24/10/2023:

COHORT A:
All participants will receive their first immunisation with a standard dose of Pfizer-BioNTech (BNT162b2) vaccine, a dose of 30 µg (0.3 ml). This may either be given in the study, or it may have been given in the community before enrolment in the study. A second dose of the COVID-19 vaccine, given at least 8 weeks after the first, will be one of the following three possibilities:
1. A full standard dose of the Pfizer-BioNTech vaccine
2. A third of a standard dose of the Pfizer-BioNTech vaccine
3. A standard dose of Novavax NVXCoV2373, dose of 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)

Participants not yet randomised by 29/11/2021 will only be randomised to
1. A full standard dose of the Pfizer-BioNTech vaccine
2. A third of a standard dose of the Pfizer-BioNTech vaccine

All vaccines will be administered intramuscularly according to specific SOPs.

A computer-generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1 to the three groups using block randomisation (random block sizes of 3 and 6). Participants not yet randomised by 29/11/2021 will be randomised 1:1 using block randomisation (random sizes of 2 and 4).

Follow-up is for 10 months.

COHORT B:
The second part of the study (Cohort B) will investigate various options for a third dose booster in adolescents aged 12 to 15.5 years who have already received two doses of BNT162b2 30 µg. It will include arms to compare 10 µg BNT162b2 administered as either paediatric or adult formulation. For direct comparison, the study will include a blinded control group, receiving a MenB vaccine (which is of similar reactogenicity to COVID-19 vaccines). The rapidly changing situation, with respect to the proportion of the population previously infected and dominant circulating COVID-19 variants, makes it preferable to use randomised rather than historical controls.

We aim to recruit 380 participants aged 12 to 15½ years, who have already received two standard doses of the Pfizer vaccine in the community. They will be randomised into five groups, each of which will be given a different vaccine schedule. The options for the third dose of the COVID-19 vaccine we will investigate are:
1. A full dose of the adult Pfizer vaccine
2. A one-third dose of the adult Pfizer vaccine
3. A full dose of the paediatric Pfizer vaccine
4. A full dose of the Novavax vaccine

The fifth group in the study will be given their third dose of the COVID-19 vaccine (Pfizer-BioNTech Comirnaty (Original/Omicron BA.1)) later in the study than the other groups. This 'control group' will improve our understanding of the immune responses in the other groups.

Following approval of Substantial Amendment 13, the randomisation ratio for Cohort B has been changed from 1:1:1:1:1 to 1:3:3:1:1 to piroritise recruitment to study arms 2 and 3 (i.e., the fractional dose BNT162b2 10µg adult and paediatric formulation groups) to achieve the participant numbers required to meet the study's co-primary endpoint of non-inferiority between the two BNT162b2 fractional dose groups

All vaccines will be administered intramuscularly according to specific SOPs.

Follow-up is for 10 months.

———

Previous intervention as of 24/11/2022:

COHORT A:
All participants will receive their first immunisation with a standard dose of Pfizer-BioNTech (BNT162b2) vaccine, a dose of 30 µg (0.3 ml). This may either be given in the study, or it may have been given in the community before enrolment in the study. A second dose of the COVID-19 vaccine, given at least 8 weeks after the first, will be one of the following three possibilities:
1. A full standard dose of the Pfizer-BioNTech vaccine
2. A third of a standard dose of the Pfizer-BioNTech vaccine

3. A standard dose of Novavax NVXCoV2373, dose of 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)

Participants not yet randomised by 29/11/2021 will only be randomised to
1. A full standard dose of the Pfizer-BioNTech vaccine
2. A third of a standard dose of the Pfizer-BioNTech vaccine

All vaccines will be administered intramuscularly according to specific SOPs.

A computer-generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1 to the three groups using block randomisation (random block sizes of 3 and 6). Participants not yet randomised by 29/11/2021 will be randomised 1:1 using block randomisation (random sizes of 2 and 4).

Follow-up is for 10 months.

COHORT B:
The second part of the study (Cohort B) will investigate various options for a third dose booster in adolescents aged 12 to 15.5 years who have already received two doses of BNT162b2 30 µg. It will include arms to compare 10 µg BNT162b2 administered as either paediatric or adult formulation. For direct comparison, the study will include a blinded control group, receiving a MenB vaccine (which is of similar reactogenicity to COVID-19 vaccines). The rapidly changing situation, with respect to the proportion of the population previously infected and dominant circulating COVID-19 variants, makes it preferable to use randomised rather than historical controls.

We aim to recruit 380 participants aged 12 to 15½ years, who have already received two standard doses of the Pfizer vaccine in the community. They will be randomised into five groups, each of which will be given a different vaccine schedule. The options for the third dose of the COVID-19 vaccine we will investigate are:
1. A full dose of the adult Pfizer vaccine
2. A one-third dose of the adult Pfizer vaccine
3. A full dose of the paediatric Pfizer vaccine
4. A full dose of the Novavax vaccine

The fifth group in the study will be given their third dose of the COVID-19 vaccine (Pfizer-BioNTech Comirnaty (Original/Omicron BA.1)) later in the study than the other groups. This 'control group' will improve our understanding of the immune responses in the other groups.

All vaccines will be administered intramuscularly according to specific SOPs.

Follow-up is for 10 months.

———

Previous intervention from 25/05/2022 to 24/11/2022:

COHORT A:
All participants will receive first immunisation with a standard dose of Pfizer-BioNTech (BNT162b2) vaccine, dose of 30 µg (0.3 ml). This may either be given in the study, or it may have been given in the community before enrolment in the study. A second dose of COVID-19 vaccine, given at least 8 weeks after the first, will be one of the following three possibilities:

1. A full standard dose of Pfizer-BioNTech vaccine
2. A third of a standard dose of Pfizer-BioNTech vaccine
3. A standard dose of Novavax NVXCoV2373, dose of 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)

Participants not yet randomised by 29/11/2021 will only be randomised to
1. A full standard dose of Pfizer-BioNTech vaccine
2. A third of a standard dose of Pfizer-BioNTech vaccine

All vaccines will be administered intramuscularly according to specific SOPs.

Computer-generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1 to the three groups using block randomisation (random block sizes of 3 and 6). Participants not yet randomised by 29/11/2021 will be randomised 1:1 using block randomisation (random sizes of 2 and 4).

Follow up is for 10 months.

COHORT B:
The second part of the study (Cohort B) will investigate various options for a third dose booster in adolescents aged 12 to 15.5 years who have already received two doses of BNT162b2 30 µg. It will include arms to compare 10 µg BNT162b2 administered as either paediatric or adult formulation. For direct comparison, the study will include a blinded control group, receiving a MenB vaccine (which is of similar reactogenicity to COVID-19 vaccines). The rapidly changing situation, with respect to proportion of population previously infected and dominant circulating COVID-19 variants, makes it preferable to use randomised rather than historical controls.

We aim to recruit 380 participants aged 12 to 15½ years, who have already received two standard doses of Pfizer vaccine in the community. They will be randomised to 5 groups, each of which will be given a different vaccine schedule. The options for the third dose of COVID-19 vaccine we will investigate are:
1. A full dose of adult Pfizer vaccine
2. A one-third dose of adult Pfizer vaccine
3. A full dose of paediatric Pfizer Vaccine
4. A full dose of Novavax vaccine

The fifth group in the study will be given their third dose of COVID-19 vaccine later in the study than the other groups. This 'control group' will improve our understanding of the immune responses in the other groups.

All vaccines will be administered intramuscularly according to specific SOPs.

Follow up is for 10 months.

———

Previous intervention as of 08/12/2021:
All participants will receive first immunisation with a standard dose of Pfizer-BioNTech (BNT162b2) vaccine, dose of 30 µg (0.3ml). This may either be given in the study, or it may have been given in the community before enrolment in the study. A second dose of COVID-19 vaccine, given at least eight weeks after the first, will be one of the following three possibilities:

1. A full standard dose of Pfizer-BioNTech vaccine
2. A third of a standard dose of Pfizer-BioNTech vaccine
3. 4. A standard dose of Novavax NVXCoV2373, dose of 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)

Participants not yet randomised by 29th November 2021 will only be randomised to
1. A full standard dose of Pfizer-BioNTech vaccine
2. A third of a standard dose of Pfizer-BioNTech vaccine

All vaccines will be administered intramuscularly according to specific SOPs.

Computer generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1 to the three groups using block randomisation (random block sizes of 3 and 6). Participants not yet randomised by 29th November will be randomised 1:1 using block randomisation (random sizes of 2 and 4).

Follow up is for 10 months.

———

Previous intervention as of 19/11/2021:
All participants will receive first immunisation with a standard dose of 30 µg (0.3ml) of Pfizer-BioNTech (BNT162b2) vaccine. This may either be given in the study, or it may have been given in the community before enrolment in the study. A second dose of COVID-19 vaccine, given at least eight weeks after the first, will be one of the following four possibilities:

1. A full standard dose of Pfizer-BioNTec vaccine
2. A third of a standard dose of Pfizer-BioNTec vaccine
3. A standard dose of Novavax NVXCoV2373, dose of 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)

All vaccines will be administered intramuscularly according to specific SOPs.

Computer generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1 to the three groups using block randomisation (random block sizes of 3 and 6).

Follow up is for 10 months.

Previous intervention as of 27/10/2021:
All participants will receive first immunisation with a standard dose of Pfizer-BioNTech (BNT162b2) vaccine, dose of 30 µg (0.3ml) and 15 µg (0.15ml). This may either be given in the study, or it may have been given in the community before enrolment in the study. A second dose of COVID-19 vaccine, given at least eight weeks after the first, will be one of the following four possibilities:

1. A full standard dose of Pfizer-BioNTec vaccine
2. A third of a standard dose of Pfizer-BioNTec vaccine
3. A half standard dose of Moderna COVID-19 vaccine, dose of 50 µg (0.25ml)
4. A standard dose of Novavax NVXCoV2373, dose of 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)

All vaccines will be administered intramuscularly according to specific SOPs.

Computer generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1:1 to the four groups using block randomisation (random block sizes of 4 and 8).

Follow up is for 12 months.

Previous intervention:
All participants will receive first immunisation with a standard dose of Pfizer-BioNTech (BNT162b2) vaccine, dose of 30 µg (0.3ml) and 15 µg (0.15ml). This may either be given in the study, or it may have been given in the community before enrolment in the study. A second dose of COVID-19 vaccine, given at least eight weeks after the first, will be one of the following four possibilities:

1. A full standard dose of Pfizer-BioNTec vaccine
2. A half standard dose of Pfizer-BioNTec vaccine
3. A half standard dose of Moderna COVID-19 vaccine, dose of 50 µg (0.25ml)
4. A standard dose of Novavax NVXCoV2373, dose of 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)

All vaccines will be administered intramuscularly according to specific SOPs.

Computer generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1:1 to the four groups using block randomisation (random block sizes of 4 and 8).

Follow up is for 12 months.

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
Pfizer BioNTech (BNT162b2), Moderna COVID-19 vaccine, Novavax, NVXCoV2373

Primary outcome measure
Current primary outcome measure as of 25/05/2022:
Solicited systemic reactions measured by self-report 7 days after booster immunisation in Cohort A or 7 days after third dose in Cohort B

Previous primary outcome measure:
Solicited systemic reactions measured by self-report 7 days after booster immunisation

Secondary outcome measures
Current secondary outcome measures as of 25/05/2022:
1. Serious adverse events and adverse events of special interest will be collected throughout the

study
2. Cellular immune responses by ELISpot on days 0 and 56 post-prime and days 14, 132 and 236 post-boost for Cohort A and days 0, 28, 84, 182, 210 in Cohort B
3. Anti-spike immunoglobulins measured by blood test at days 0 and 56 post-prime and days 132 and 236 post-boost for Cohort A and days 0, 84 and 182 in Cohort B
4. Anti-nucleocapsid immunoglobulins measured by blood test at days 0, 56, 140 and 238
5. Cellular immune responses measured by ELISpot at days 0, 56, 70, 140 and 238
6. Solicited local reactions collected by self-report at 7 days after prime and boost immunisation in Cohort A and 7 days post third dose in Cohort B
7. Unsolicited reactions collected by self-report at 28 days after prime and boost immunisation in Cohort A and 28 days post third dose in Cohort B

_____

Previous secondary outcome measures as of 19/11/2021:
1. Serious adverse events and adverse events of special interest will be collected throughout the study
2. Anti-spike immunoglobulins measured by blood test at D0*, 56, 70, 84, 140, 238
3. Anti-nucleocapsid immunoglobulins measured by blood test at D0*, 56**, 140, 238
4. Cellular immune responses measured by ELISpot at D0*, 56, 70, 140, 238
5. Solicited local reactions and unsolicited reactions collected by self-report at 7 days and 28 days, respectively, after prime* and boost immunisation
*Only for participants receiving their first dose of COVID-19 vaccine in the study
**Only for participants receiving their first dose of COVID-19 vaccine in the community

_____

Previous secondary outcome measures:
1. Serious adverse events and adverse events of special interest will be collected throughout the study
2. Anti-spike immunoglobulins measured by blood test at D0*, 56, 70, 84, 182, 364
3. Anti-nucleocapsid immunoglobulins measured by blood test at D0*, 56** 182, 364
4. Cellular immune responses measured by ELISpot at D0*, 56, 70, 182, 364
5. Solicited local reactions and unsolicited reactions collected by self-report at 7 days and 28 days, respectively, after prime* and boost immunisation
*Only for participants receiving their first dose of COVID-19 vaccine in the study
**Only for participants receiving their first dose of COVID-19 vaccine in the community

Overall study start date
14/09/2021

Completion date
30/09/2024

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 25/05/2022:
For Cohort A:
1. Aged 12 to 16 years (inclusive) at enrolment

For Cohort B:
1. Aged 12 to 15.5 years (inclusive) at enrolment
2. Already received two doses of 30 µg BNT162b2, the second dose received at least 91 days prior to randomisation

For Cohorts A and B:
1. In good health as determined by a trial clinician. Participants may have well-controlled or mild to moderate comorbidity, as long as this would not render them considered as belonging to a 'high-risk' cohort at particular need of additional doses of COVID-19 2. Able and willing (in the Investigator's opinion) to comply with all study requirements
3. Registered with a GP, and willing to allow the investigators to discuss the participant's medical history with their General Practitioner and access all medical records when relevant to study procedures
4. Parent/legal guardian/participant is willing and able to give written informed consent for participation in the trial. Parent/legal guardian to provide informed consent for participants under the age of 16. Participants aged 16 years will be assumed to be able to provide consent for themselves, however parental support will be encouraged and investigators will reserve the right to refuse enrolment if concerns arise.

_____

Previous participant inclusion criteria as of 19/11/2021:
1. Parent/legal guardian/participant is willing and able to give written informed consent for participation in the trial
2. Aged 12 to 16 years inclusive at enrolment
3. In good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity, as long as this would not render them considered as belonging to a 'high - risk' cohort at particular need of 2 doses of COVID-19 vaccine (see exclusion criteria below) as part of the national roll out
4. Able and willing (in the Investigator's opinion) to comply with all study requirements
5. Registered with a GP, and willing to allow the investigators to discuss the participant's medical history with their General Practitioner and access all medical records when relevant to study procedures

_____

Previous participant inclusion criteria:
1. Parent/legal guardian/participant is willing and able to give written informed consent for participation in the trial
2. Aged 12 to 16 years inclusive at enrolment
3. In good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity, as long as this would not render them eligible for 2 doses of COVID-19 vaccine (see exclusion criteria below) as part of the national roll out
4. Able and willing (in the Investigator's opinion) to comply with all study requirements
5. Registered with a GP, and willing to allow the investigators to discuss the participant's medical history with their General Practitioner and access all medical records when relevant to study procedures

Participant type(s)
Healthy volunteer

Age group

Child

Lower age limit
12 Years

Upper age limit
16 Years

Sex
Both

Target number of participants
148 Cohort A, 310 Cohort B

Total final enrolment
429

Key exclusion criteria
Current participant exclusion criteria as of 24/11/2022:
For Cohort A:
1. Previous receipt of more than one dose of a COVID-19 vaccine, or a COVID-19 vaccine other than BNT162b2

For Cohort B:
1. Previous receipt of more than two doses of a COVID-19 vaccine, or a COVID-19 vaccine other than BNT162b2 30 µg
2. Previous receipt of the 4CMenB vaccine
3. Participants in Cohort A are not eligible to be enrolled into Cohort B unless they received two full doses of BNT162b2 in Cohort A, and they have completed the Cohort A day 236 study visit. At this point they are eligible to enrol in Cohort B, in which case they will be treated as a new participant and receive a new, unrelated, participant number.

For Cohorts A and B:
1. Belonging to a 'high- risk' cohort advised to receive additional doses of a COVID-19 vaccine (participants at increased risk of COVID-19, or household contacts of immunocompromised, based on JCVI and 'Green Book' guidelines current on 28/02/2022).
2. First-degree relative of study team member
3. 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)
4. 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/IB-listed ingredients of any study vaccine). This includes latex and polyethylene glycol/macrogol (PEG).
5. Pregnancy, lactation or unwillingness to practice effective contraception from enrolment to 3 months post-study vaccination (for post-menarcheal females only)
6. Malignancy requiring receipt of immunosuppressive chemotherapy or radiotherapy for treatment of solid organ cancer/haematological malignancy within the 6 months prior to consent
7. Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
8. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin)

or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
9. Any serious chronic illness requiring hospital specialist supervision
10. Congenital cardiovascular conditions
11. Severe and/or uncontrolled respiratory disease, gastrointestinal disease, liver disease, renal disease, rheumatological disease, and neurological illness (mild/moderate well-controlled comorbidities are allowed)
12. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis)
13. Significant renal or hepatic impairment
14. Scheduled elective surgery requiring overnight admission and/or general anaesthetic during the trial
15. Insufficient level of English language to undertake all study requirements in the opinion of the Investigators
16. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
17. Participants who have participated in another research trial involving an investigational product in the past 12 weeks (see exclusion criteria above for enrolment into Cohort B after participation in Cohort A of this study)
18. Note that a prior history of confirmed or suspected COVID-19 is NOT an exclusion criterion for this study, provided the participant otherwise satisfies the health screening criteria for the study

———

Previous participant exclusion criteria from 25/05/2022 to 24/11/2022:
For Cohort A:
1. Previous receipt of more than one dose of a COVID-19 vaccine, or a COVID-19 vaccine other than BNT162b2

For Cohort B:
1. Previous receipt of more than two doses of a COVID-19 vaccine, or a COVID-19 vaccine other than BNT162b2 30 µg
2. Participants who received their second dose of COVID-19 vaccine in Cohort A of this study are not eligible to enrol in Cohort B

For Cohorts A and B:
1. Belonging to a 'high- risk' cohort advised to receive additional doses of a COVID-19 vaccine (participants at increased risk of COVID-19, or household contacts of immunocompromised, based on JCVI and 'Green Book' guidelines current on 28/02/2022).
2. First-degree relative of a study site staff member
3. 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)
4. 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/IB-listed ingredients of any study vaccine). This includes latex and polyethylene glycol/macrogol (PEG).
5. Pregnancy, lactation or unwillingness to practice effective contraception from enrolment to 3 months post study vaccination (for post-menarcheal females only)
6. Malignancy requiring receipt of immunosuppressive chemotherapy or radiotherapy for treatment of solid organ cancer/haematological malignancy within the 6 months prior to consent
7. Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of

significant bleeding or bruising following IM injections or venepuncture
8. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
9. Any serious chronic illness requiring hospital specialist supervision
10. Congenital cardiovascular conditions
11. Severe and/or uncontrolled respiratory disease, gastrointestinal disease, liver disease, renal disease, rheumatological disease, and neurological illness (mild/moderate well-controlled comorbidities are allowed)
12. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis)
13. Significant renal or hepatic impairment
14. Scheduled elective surgery requiring overnight admission and/or general anaesthetic during the trial
15. Insufficient level of English language to undertake all study requirements in opinion of the Investigators
16. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
17. Participants who have participated in another research trial involving an investigational product in the past 12 weeks
18. Note that a prior history of confirmed or suspected COVID-19 is NOT an exclusion criterion for this study, provided the participant otherwise satisfies the health screening criteria for the study

---

Current participant exclusion criteria as of 19/11/2021:
1. Previous receipt of more than one dose of a COVID-19 vaccine, or a COVID-19 vaccine other than BNT162b2
2. Belonging to a 'high risk' cohort advised to receive 2 doses of a COVID-19 vaccine (participants at increased risk of COVID-19, or household contacts of immunocompromised, based on JCVI and 'Green Book' guidelines current as of 13th September 2021).
3. First degree relative of a study site staff member
4. 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)
5. 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/IB-listed ingredients of any study vaccine). This includes latex and polyethylene glycol/macrogol (PEG)
6. Pregnancy, lactation or unwillingness to practice effective contraception from enrolment to 3 months post booster vaccination, for post-menarcheal females only
7. Malignancy requiring receipt of immunosuppressive chemotherapy or radiotherapy for treatment of solid organ cancer/haematological malignancy within the 6 months prior to consent.
8. Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
9. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
10. Any serious chronic illness requiring hospital specialist supervision
11. Congenital cardiovascular conditions
12. Severe and/or uncontrolled respiratory disease, gastrointestinal disease, liver disease, renal disease, rheumatological disease, and neurological illness (mild/moderate well controlled

comorbidities are allowed)
13. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis)
14. Significant renal or hepatic impairment
15. Scheduled elective surgery requiring overnight admission and/or general anaesthetic during the trial
16. Insufficient level of English language to undertake all study requirements in opinion of the Investigators
17. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
18. Participants who have participated in another research trial involving an investigational product in the past 12 weeks
19. Note that a prior history of confirmed or suspected COVID-19 is NOT an exclusion criterion for this study, provided the participant otherwise satisfies the health screening criteria for the study

Previous participant exclusion criteria:
1. Previous receipt of more than one dose of a COVID-19 vaccine, or a COVID-19 vaccine other than BNT162b2
2. Belonging to a cohort advised to receive 2 doses of a COVID-19 vaccine (participants at increased risk of COVID-19, or household contacts of immunocompromised, based on JCVI and 'Green Book guidelines).
3. First degree relative of a study site staff member
4. 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)
5. 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/IB-listed ingredients of any study vaccine). This includes latex and polyethylene glycol/macrogol (PEG)
6. Pregnancy, lactation or unwillingness to practice effective contraception from enrolment to 3 months post booster vaccination, for post-menarcheal females only
7. Malignancy requiring receipt of immunosuppressive chemotherapy or radiotherapy for treatment of solid organ cancer/haematological malignancy within the 6 months prior to consent.
8. Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
9. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
10. Any serious chronic illness requiring hospital specialist supervision
11. Congenital cardiovascular conditions
12. Severe and/or uncontrolled respiratory disease, gastrointestinal disease, liver disease, renal disease, rheumatological disease, and neurological illness (mild/moderate well controlled comorbidities are allowed)
13. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis)
14. Significant renal or hepatic impairment
15. Scheduled elective surgery requiring overnight admission and/or general anaesthetic during the trial
16. Insufficient level of English language to undertake all study requirements in opinion of the Investigators
17. Administration of immunoglobulins and/or any blood products within the three months

preceding the planned administration of the vaccines
18. Participants who have participated in another research trial involving an investigational product in the past 12 weeks
19. Note that a prior history of confirmed or suspected COVID-19 is NOT an exclusion criterion for this study, provided the participant otherwise satisfies the health screening criteria for the study

Date of first enrolment
20/09/2021

Date of final enrolment
30/06/2023

Locations

Countries of recruitment
England

United Kingdom

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

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

Study participating centre
Southampton General Hospital
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
St George's Hospital
St George's University Hospitals NHS Foundation Trust
Blackshaw Road
Tooting
London
United Kingdom
SW17 0QT

Study participating centre
Noah’s Ark Children’s Hospital for Wales
Public Health Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

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

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Addenbrooke's Hospital
Cambridge Biomedical Campus
Hills Road
Cambridge
United Kingdom
CB2 0AU

Study participating centre
Manchester University NHS Foundation Trust
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre

Alder Hey Children's Hospital NHS Foundation Trust
Eaton Road
Liverpool
United Kingdom
L12 2AP

Study participating centre
Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Sheffield Children's NHS Foundation Trust
Clarkson Street
Broomhall
Sheffield
United Kingdom
S10 2TQ

Study participating centre
Leeds Teaching Hospitals NHS Trust
Trust Headquarters
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Sponsor information

Organisation
University of Oxford

Sponsor details
Clinical Trials Research Governance
Joint Research Office
1st floor, Boundary Brook House
Churchill Drive, Headington
Oxford
England
United Kingdom
OX3 7GB
+44 (0)1865 289885
ctrg@admin.ox.ac.uk

Sponsor type
University/education

Website
http://www.ox.ac.uk/

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
Novavax

Funder Name
UK Vaccine Task Force (VTF)

Results and Publications

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

Intention to publish date
30/07/2023

Individual participant data (IPD) sharing plan
Current IPD sharing plan as of 24/10/2023:
Individual participant data will be made available when the trial is complete, upon requests directed to the trial's Chief Investigator Angela Minassian (angela.minassian@bioch.ox.ac.uk) or upon written approval of the sponsor. After approval of a proposal, data can be shared through a secure online platform. All data shared will be anonymised. The type of data available upon request includes datasets generated during and/or analysed during the current study.

Previous IPD sharing plan:
The datasets generated during and/or analyzed during the current study will be available upon requests directed to Angela Minassian (angela.minassian@bioch.ox.ac.uk) or upon written approval of the sponsor.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 5.1	21/12/2021	06/01/2022	No	No
Protocol file	version 6.0	18/01/2022	04/02/2022	No	No
Protocol file	version 7.1	09/05/2022	25/05/2022	No	No
Protocol file	version 8.0	22/09/2022	24/11/2022	No	No
Protocol file	version 9.0	19/12/2022	09/06/2023	No	No
HRA research summary			28/06/2023	No	No
Results article		17/06/2023	20/07/2023	Yes	No
Protocol file	version 10.0	31/08/2023	24/10/2023	No	No
Protocol file	version 11.0	13/12/2023	23/02/2024	No	No