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Evaluating a full or fractional third dose of COVID-19 vaccines in previously vaccinated adults

Submission date
21/01/2022

Recruitment status
No longer recruiting

Registration date
17/03/2022

Overall study status
Completed

Last Edited
17/03/2022

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Coronavirus Disease 2019 (COVID-19) is an acute respiratory disease caused by a coronavirus (SARS-CoV-2). In January 2020 the World Health Organisation (WHO) declared the Covid-19 outbreak an international public health emergency that has now become a global pandemic. The symptoms of Covid-19 vary considerably from person to person and range from mild to severe. Many people do not develop any symptoms of disease, whereas older adults and those with serious underlying medical conditions may be at risk of severe symptoms and even death. Globally, so far, there have been over 270 million confirmed cases of Covid-19 and over 5 million deaths. Although there are some treatments that have been shown to somewhat reduce the severity of the disease, there is currently no cure for Covid-19. Vaccinations remain an effective method to reduce severe infection and the likelihood of hospitalisation. Several vaccines against Covid-19 have been approved for in different countries around the world. Other vaccines are still being tested in clinical trials and may be available in the future.
A large proportion of the population has now received their first two vaccinations against Covid-19, which we refer to as a “prime-boost” course. These vaccines have been shown to be effective at preventing severe disease, however, it is uncertain how long this immune protection will last. With new variants (the same virus but with different mutations) of the Covid-19 virus emerging, it is important to make sure that population immunity is maintained and people are protected against the Covid-19 virus.
Booster vaccines have been shown to be a promising way to increase immune response and protection against Covid-19 infection, particularly in high-risk groups. Due to increased demand and shortage of vaccine supplies, many Governments are struggling to provide booster vaccinations to large populations over a short time period. The aim of this study is to see whether a half dose of booster vaccine will provide the same amount of protection as a full dose vaccine when given as a third dose booster. Giving half a dose of vaccine means that twice the number of people will be able to be vaccinated against Covid-19, which could reduce supply chain problems and shortages of vaccines.
Booster vaccines given at a lower dose, following two doses of primary vaccine, may not only increase protection in those with decreasing immunity but could potentially provide an equal and long-lasting response as those vaccinated with a full dose of booster vaccine. Considering

the challenges in immunizing large populations, especially due to supply issues and lack of stock, it is essential to develop more flexible vaccination protocols, where doses used are from different authorized vaccines. In this study, we will use different or 'heterologous' combinations of vaccines which could also reduce reliance on a single supply chain of vaccination.

Who can participate?
Adults that are aged 18 years of age or older are suitable to take part if they have received 2 doses of Sinovac/Butantan, at least 4 months (120 days) prior to administration of booster.

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 visit 1: a fractional dose of Pfizer/Wyeth or AstraZeneca /Fiocruz vaccines, or full dose AstraZeneca/Fiocruz vaccine at least 4 months (120 days) after they have received 2 doses of Sinovac/Butantan.
Following vaccination, you will be provided with a thermometer, ruler, access to an electronic diary, and a contact card with 24-hour phone numbers of the study team.
In the electronic diary, you will be required to record your temperature and any symptoms that you experience from the day of vaccination until day 7. This includes documenting any symptoms which you may have as a result of the vaccine.
You will also be asked to provide a blood sample initially and then at the subsequent visits which will be used to verify that your immune system has responded to the study booster vaccination. At each visit, the maximum amount of blood that will be collected from you will be 50 ml (about 4 tablespoons).

What are the possible benefits and risks of participating?
You will not necessarily get any direct benefit from the study but the vaccinations you receive will offer you some form of further protection against Covid-19, however, if you receive a half dose there is no guarantee of how much protection it will offer. If you receive the full dose of the AstraZeneca/Fiocruz vaccine then you will benefit from increased protection against the Covid-19 virus. The information obtained from the study could help influence further vaccination schedules and government policy and if the reduced dose vaccinations result in a good immune response then this may mean that in the future there will be increased vaccination availability for others which will help in the fight against Covid-19.
There are possible risks and adverse effects that you might experience from participating in the study. You will be monitored for these throughout the duration of the study. You should contact the responsible researcher if you think that you are experiencing adverse effects or a change in your health. Possible risks and discomforts are detailed below; however, there may be other risks and adverse effects that are not yet known.
Blood collection may result in slight pain and occasional bruising at the site at which the needle is inserted. Occasionally some people may feel light-headed at the time of blood collection and may even faint when having blood taken.

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

When is the study starting and how long is it expected to run for?
December 2021 to December 2022

Who is funding the study?
Coalition for Epidemic Preparedness Innovations (CEPI) (UK)

Who is the main contact?
Prof. Dr. Sue Ann Costa Clemens, sue.costaclemens@paediatrics.ox.ac.uk
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
OVG 21/06

Study information

Scientific Title
A Phase 4, single blind, randomised controlled trial to assess the immunogenicity, safety and reactogenicity of a third heterologous full or fractional booster dose Covid-19 vaccine in previously vaccinated adults

Study objectives
1. A fractional dose of AstraZeneca/Fiocruz or Pfizer/Wyeth or full dose AstraZeneca/Fiocruz given to adults at least 4 months (120 days) after two doses of Sinovac/Butantan, induces a seroresponse (4- fold rise) in at least 80% of seropositive participants.
2. The fractional dose of AstraZeneca/Fiocruz and Pfizer/Wyeth as a booster regimen is well-tolerated in adults who have received 2 doses of the Sinovac/Butantan.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/01/2022, Oxford Tropical Research Ethics Committee (University of Oxford Research Services, Research Governance, Ethics and Approvals Boundary Brook House, Churchill Drive. Oxford OX3 7GB, UK; +44 (0)1865 282106; oxtrec@admin.ox.ac.uk), ref: 8-22

Study design
Multicentre interventional single-blinded randomized controlled trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
The administration of fractional dose of Pfizer/Wyeth or AstraZeneca/Fiocruz vaccines for prevention of COVID-19 when used as an additional dose in adults aged 18 years or older who have received 2 doses of Sinovac/Butantan, at least 4 months (120 days) prior to administration of booster.

Interventions
Study participants will be randomly allocated to receive one of the following at visit 1: a fractional dose of Pfizer/Wyeth or AstraZeneca/Fiocruz vaccines, or full dose AstraZeneca /Fiocruz vaccine given at least 4 months (120 days) after two doses of Sinovac/Butantan.

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 1:1:1 ratio.

Intervention Type
Biological/Vaccine

Phase
Phase IV

Drug/device/biological/vaccine name(s)
ChadOx1-nCOV-19 (AstraZeneca/Fiocruz) vaccine, 6.1.2 BNT162b2 (Pfizer/Weyth) vaccine

Primary outcome(s)

1. Sororesponse is measured using anti-Spike IgG seroresponse rate (SRR)* in the fractional and full dose arms. *SRR is defined as: 4-fold rise in GMTs at 28 days post study vaccine from baseline among participants with detectable Ab titers pre-booster; OR detectable Ab titres at 28 days post study vaccine among participants with no pre-dose detectable titres.
2. Safety and reactogenicity are measured using an electronic diary completed by participants in the 7 days following visit 1and up to 28 days if unsolicited adverse events occur. Solicited systemic adverse events include fever, chills, joint pains, muscle pains, fatigue, headache, nausea, and loss of appetite. Occurrence of SAEs and AESIs will be followed throughout the Trial.

Key secondary outcome(s))
1. Humoral immune response measured using geometric mean titre (GMT) and geometric mean fold rise (GMFR) for binding neutralizing antibody titres at day 0, day 28 and day 182.
2. Humoral immune response measured using seroresponse rate (SRR) based on neutralising antibody titres at day 0, day 28 and day 182.
3. Cellular immune responses measured by ELISpot and ICS (Th1/Th2) at day 0, day 28 and day 182.

Completion date
01/12/2022

Eligibility

Key inclusion criteria
1. Males or females aged 18 years old or above.
2. Participants willing and able to comply with the study procedure.
3. Participants willing and able to provide informed consent prior to screening.
4. Participants who received two Sinovac/Butantan vaccine doses at least 4 months (120 days) prior to enrolment in this study, with a dose interval between each Sinovac/Butantan dose of 14-28 days (+ 7 days).
5. For females of childbearing potential: willingness to practice continuous effective contraception during the study and a negative pregnancy test on the day(s) of screening and vaccination.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria

1. Participants with fever >37.5 °C (axillary) or any acute disease at baseline (Day 1) or within the 3 days prior to randomization. Febrile participants with mild diseases may be enrolled at the investigator's discretion.
2. Participants with a recent history of COVID-19 (≤ 4 weeks prior to visit 1), laboratory confirmed.
3. Participants with a history of serious vaccine-related adverse reaction or serious allergic reaction (e.g., anaphylaxis) to any study vaccine component, as described in the last summary of product characteristics for Sinovac/Butantan, AstraZeneca/Fiocruz or Pfizer/Wyeth.
4. Participants with a known bleeding disorder that, in the investigator's opinion, would contraindicate intramuscular injection.
5. Participants with any progressive or serious neurological disorder, seizure disorder or history of Guillian-Barré syndrome.
6. Participants given treatment with immunosuppressant therapy within the last 90 days, including cytotoxic agents or systemic corticosteroids or planned receipt during the study period. If a short-term cycle of immunosuppressant systemic corticosteroid dose has been used to treat acute disease, the participant should not be enrolled in the study until corticosteroid therapy has been discontinued for at least 15 days prior to the first study vaccination. In case the participant has been on an immunosuppressant dose of a depot, intramuscular or intra-articular corticosteroid, 60 days should be waited for their enrolment in the study. Inhaled/nebulized, intra-articular, intrabursal or topical (skin or eyes) corticosteroids are allowed.
7. Participants with autoimmune diseases, other than: Hashimoto thyroiditis, vitiligo, psoriasis, discoid lupus and the like; HIV-positive participants and/or in treatment for HIV;
8. Participants given any other investigational product within the 30 days prior to Day 1 or who intend to take part in another clinical trial at any time during this study conduction.
9. Participants given any other licensed vaccine within 14 days prior to enrolment in this study or who plan to receive any vaccine up to 28 days after vaccination.
10. Participants given treatment with Rituximab or any other anti-CD20 monoclonal antibody within 9 months prior to Day 1 or planned during the study period.
11. Administration of intravenous immunoglobulins and/or any blood products within 3 months prior to enrolment or planned dosing during the study period.
12. Participants with any condition that, in the investigator's opinion, could interfere with the status primary objectives or represent an additional risk for the participant.
13. Participants who have received any other vaccine for Covid-19 other than two Sinovac /Butantan doses.

Date of first enrolment
01/03/2022

Date of final enrolment
01/06/2022

Locations

Countries of recruitment
Brazil

Colombia

Study participating centre

CEPClin
Ponciano Barbosa, 282 - Cidade Alta
Natal
Brazil
59025-050

Study participating centre
Instituti Evandro Chagas
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Coalition for Epidemic Preparedness Innovations (CEPI)

Results and Publications

Individual participant data (IPD) sharing plan
The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 (or local equivalent regulations, [such as Brazilian General Data Protection Law (LGPD) in Brazil]) which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

IPD sharing plan summary

Not expected to be made available