ISRCTN12022293 https://doi.org/10.1186/ISRCTN12022293

Evaluating the persistence of protection of a 3rd dose of COVID vaccine and the safety and induced protection of a 4th dose of COVID-19 vaccines in previously vaccinated adults

Submission date
21/06/2022

Recruitment status
No longer recruiting

Registration date
15/09/2022

Overall study status
Completed

Last Edited
15/09/2022

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:
Vaccines have demonstrated protection against both symptomatic (with noticeable symptoms) and asymptomatic (without noticeable symptoms) COVID-19 (SARS-CoV-2 infection). However, the emergence of new variants (the same virus with some modifications or mutations) of the SARS-CoV-2 virus, and the report of decreased antibodies (a protein used by the immune system to identify specific parts of a foreign object, such as a virus, in order to neutralize it) in vaccinated individuals is a cause for concern (as vaccines are used to stimulate the immune system to produce these antibodies against a specific virus, exactly like the body would it would if exposed to the disease) and further research.

Studies using two doses of inactivated vaccines (a vaccine consisting of particles of a killed virus), such as CoronaVac (Sinovac/Butantan), have shown a drop in the number of antibodies in the blood associated with symptomatic infections. The RHH_001 study carried out in Brazil evaluated a third vaccine dose (booster) in subjects previously vaccinated with two doses of CoronaVac vaccine (Sinovac/Butantan), that was either homologous (the same as the previous type of vaccine received, i.e. an inactivated vaccine) or a heterologous (different to the previous type of vaccine received). The heterologous vaccines were either recombinant vaccines (which use a harmless organism such as yeast to produce sugars or proteins from the surface of viruses to be included in the vaccine and are identified as foreign objects by the immune system), AstraZeneca/Fiocruz or Janssen, or mRNA vaccines (which contain messenger RNA which is able to enter the body's immune cells and provides the protein-assembling machinery inside the cell with the codes to create the antigen protein), Pfizer/Wyeth. The RHH_001 study demonstrated that a third dose can restore immune response against Covid-19 including increasing neutralizing antibodies in the blood. There are no data available about the long-term persistence of some antibodies after a homologous or heterologous third dose in individuals primed with 2 doses of the inactivated vaccine CoronaVac. Those data are however critical for policy making with respect to the eventual need for further doses. Long-term follow-up of participants of study RHH_001 offers a unique opportunity to generate such data.

Because of the rapid decline of antibody neutralising activity and a reduction in vaccine effectiveness after 3 doses against the Omicron variant of the SARS-CoV-2 virus, various regulatory authorities have recommended a 4th vaccine dose, especially for high-risk groups. However, even a homologous 4th dose might not completely restore the level of vaccine protection against the Omicron variant.

This study will assess the immune response to a 4th dose (2nd booster) in individuals who originally received 2 doses of an inactivated vaccine and who have already received a 3rd dose.

Who can participate?
Adults aged 18 years or older, who participated in the RHH_001 study, and who have received a 3rd vaccine dose 6 months or more prior to this study.

What does the study involve?
Participants will be allocated, with an equal chance of receiving either treatment (like tossing a coin), to receive a 4th dose of one of either Pfizer/Wyeth or AstraZeneca/Fiocruz vaccines at the first visit. Following vaccination, participants will be provided with a ruler, access to an electronic diary, and a contact card with 24 h phone numbers of the study team. In the electronic diary, participants will be required to record their temperature, and any symptoms they experience, daily for the 7 days after the vaccination. This includes documenting any symptoms which may be a result of the vaccine.

Participants will also be asked to provide a blood sample initially and then at the subsequent visits, which will be used to verify that their immune system has responded to the study booster vaccination. At each visit, the maximum amount of blood that will be collected from participants will be 50 ml (about 4 tablespoons).

What are the possible benefits and risks of participating?
Study subjects will be informed about whether or not they still have antibodies against the variants of SARS-CoV-2 virus of concern, at 6 months or more after the 3rd dose booster and following 4th dose vaccination (as applicable). This is an expectation of the Brazilian population as part of their participation in such studies.

Furthermore, the contribution of participants to this study is expected to generate evidence-based data for the national and international scientific community for vaccination and public health strategies that are extremely important to fight COVID-19. All subjects participating in part 2 of the study might benefit from receiving the 4th vaccination dose with the potential benefit of added protection.

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?
From March 2022 to July 2023

Who is funding the study?
AstraZeneca (UK) and D'Or Institute for Research and Education (IDOR) (Brazil)

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

Contact information

Type(s)
Scientific

Contact name
Dr Isabela Gonzalez

Contact details
R. Gomes de Carvalho, 1666
Vila Olímpia
Sao Paulo
Brazil
04547-006
+5511996272123
isabela.gonzalez@paediatrics.ox.ac.uk

Type(s)
Scientific

Contact name
Prof Sue Ann Costa Clemens

ORCID ID
https://orcid.org/0000-0001-9576-0878

Contact details
Av. Beira Mar, 406 - Centro
Rio de Janeiro
Brazil
20021-060
+55 21 2262-6523
sue.costaclemens@paediatrics.ox.ac.uk

Additional identifiers

Protocol serial number
13-22

Study information

Scientific Title
Persistence of binding and neutralizing antibodies against SARS-CoV2 strains at 6 months or more after a third dose with recombinant COVID-19 vaccine (AstraZeneca/Fiocruz), mRNA COVID-19 vaccine (Comirnaty, Pfizer/Wyeth), recombinant COVID-19 vaccine (Janssen) or adsorbed inactivated COVID-19 vaccine Coronavac (Sinovac/Butantan) in subjects primed with two Sinovac/Butantan doses – extension of study RHH_001; and assessment of safety and immunogenicity of 4th dose with recombinant COVID-19 vaccine (AstraZeneca/Fiocruz) or mRNA covid-19 vaccine (Comirnaty, Pfizer/Wyeth).

Study objectives
A 4th dose of COVID-19 vaccine (second booster) is non-inferior to a 3rd dose of COVID-19 vaccine in individuals primed with two doses of Sinovac/Butantan inactivated vaccine.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 01/06/2022, National Research Ethics Committee (CONEP) (SRTVN 701, lote D, Edifício PO 700, 3º andar - Asa Norte, Brasília, DF, Brazil; (+61) 33155877; conep@saude.gov.br), ref: 5.444.863
2. Approved 12/05/2022, OxTREC (University of Oxford, Research Services, Research Governance Ethics, and Assurance, Boundary Brook House, Churchill Drive, Oxford OX3 7GB; +44 (0) 1865 (2)82106; oxtrec@admin.ox.ac.uk), ref: 13-22

Study design
Multicenter interventional single-blind randomized trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Severe SARS-CoV-2 infection

Interventions
Study participants will be randomly allocated to receive one of the following at Visit 1: a 4th dose of either Pfizer/Wyeth or AstraZeneca/Fiocruz vaccines, ≥6 months after heterologous or homologous booster in individuals primed with 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 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)
Part 1:
1. Anti-Spike IgG antibody titers of SARS-CoV-2 measured using blood samples collected at ≥6 months after the 3rd vaccine dose

Part 2:
1. Anti-Spike IgG antibody titers of SARS-CoV-2 measured using blood samples collected at ~28 days after the 4th vaccine dose
2. Neutralizing titer (NT) against SARS-CoV-2 (including against relevant variants of concern) measured using blood samples collected at 28 days and 6 months after the 4th vaccine dose (in a sub-set of participants)

Key secondary outcome(s))
Part 1:
1. Neutralizing titer (NT) against SARS-CoV-2 Wuhan strain measured using blood samples collected at ≥6 months after the 3rd vaccine dose
2. Neutralizing titer (NT) against SARS-CoV-2 (including but not limited to delta and omicron variants) measured using blood samples collected at ≥6 months after the 3rd vaccine dose

Part 2:
1. Anti-Spike IgG antibody titers of SARS-CoV-2 measured using blood samples collected at 28 days and 6 months after the 4th vaccine dose
2. Neutralizing titer (NT) against SARS-CoV-2 (including relevant variants of concern) measured using blood samples collected at 28 days and 6 months after the 4th vaccine dose (in a sub-set of participants)
3. Safety measured using the occurrence of local and systemic Adverse Events (AEs) reported within 7 days after study vaccination (per subgroup)
4. Safety measured using the occurrence of unsolicited severe Adverse Events (AEs) reported within 28 days after study vaccination (per subgroup)
5. Safety measured using the occurrence of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) recorded within 28 days and up to 6 months after study vaccination (per subgroup).

Completion date
04/07/2023

Eligibility

Key inclusion criteria
1. Participants in study RHH_001 per-protocol population who were fully evaluable. Participants included in previous neutralization assay subsets will be targeted for enrolment first if operationally feasible.
2. Willing and able to provide informed consent prior to any study procedure
3. Willing and able to comply with the study procedure
4. Received heterologous or homologous third vaccine dose ≥6 months prior to this study
5. For people of childbearing potential:
5.1. Willing to practice continuous effective contraception during the study
5.2. Negative pregnancy test on the day(s) at screening

Additional inclusion criteria for part 2 only:
1. Informed consent to receive 4th vaccine dose, AstraZeneca/Fiocruz or Pfizer/Wyeth
2. No contraindication against AstraZeneca/Fiocruz or Pfizer/Wyeth SARS-C0V-2 vaccine

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Any additional SARS-CoV-2 vaccine after the 3rd dose in study RHH_001
2. Fever >37.5 °C (axillary) or any acute disease at baseline (Day 0) or within the 3 days prior to randomization. Febrile participants with mild diseases may be enrolled at the investigator's discretion once fever has resolved.
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 AstraZeneca/Fiocruz or Pfizer/Wyeth
4. Known bleeding disorder that, in the investigator's opinion, would contraindicate intramuscular injection
5. Any progressive or serious neurological disorder, seizure disorder, or history of Guillian-Barré syndrome
6. 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 ≥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, they should wait 60 days for their enrolment in the study. Inhaled/nebulized, intra-articular, intrabursal or topical (skin or eyes) corticosteroids are allowed.
7. Autoimmune diseases other than: Hashimoto thyroiditis, vitiligo, psoriasis, discoid lupus, and similar diseases.
8. HIV-positive and/or in treatment for HIV
9. Given any other investigational product within the 30 days prior to Day 1, or intending to take part in another clinical trial at any time during this study conduction
10. Given any other licensed vaccine within 14 days prior to enrolment in this study or planning to receive any vaccine up to 28 days after vaccination
11. Given treatment with Rituximab or any other anti-CD20 monoclonal antibody within 9 months prior to Day 1 or planned during the study period
12. Administration of intravenous immunoglobulins and/or any blood products within 3 months prior to enrolment or planned dosing during the study period
13. 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

Temporary exclusion criteria:
1. Participants with a recent history of COVID-19 (≤4 weeks prior to visit 1) will be delayed until 4 weeks after diagnosis

Date of first enrolment
04/07/2022

Date of final enrolment

04/09/2022

Locations

Countries of recruitment
Brazil

Study participating centre
Hospital São Rafael
Av. São Rafael, 2152
Salvador
Brazil
41253-190

Study participating centre
CRIE-UNIFESP
Av. Borges Lagoa, 770
São Paulo
Brazil
04038-001

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Funder Name
D'Or Institute for Research and Education (IDOR)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication.

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
Published as a supplement to the results publication