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SARS-CoV-2 Delta variant dose finding infection study

Submission date 01/03/2023	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 08/03/2023	**Overall study status** Completed	
Last Edited 02/07/2025	**Condition category** Infections and Infestations	

Plain English summary of protocol

Background and study aims
COVHIC002 is a human infection challenge study in which healthy adults aged 18-30 previously vaccinated with an approved COVID-19 vaccine will be administered a SARS-CoV-2 Delta variant virus. The aim is to achieve upper respiratory infection in the majority of challenged individuals with mild or no illness, providing information on the course of SARS-CoV-2 infection and the immune response in vaccinated people. This study will establish an optimised dose and study design that will then be used to evaluate the efficacy of new treatments and vaccine candidates in follow-on trials.

Who can participate?
Healthy adults aged 18-30 years, previously vaccinated with an approved COVID-19 vaccine

What does the study involve?
Participants will stay in a quarantine unit for around 2 weeks and be followed up by the study team for 1 year. Screening and follow-up visits will take place at Imperial College Healthcare NHS Trust and quarantine will take place at the Chelsea and Westminster Hospital.

What are the possible benefits and risks of participating?
Benefits: Participants benefit from receiving financial compensation for their time and inconvenience. Taking part will not improve your health, although you may benefit from a general health check. We hope that this study will support the development of more COVID-19 vaccines/treatments that could help many people around the world. There is a chance you could develop “immunity” against COVID-19, but we don’t know if you will or for how long protection might last.
Risks: The risk from the tests performed in the study (such as blood tests and nasal swabs) is very low, as these tests are not expected to cause more than mild temporary discomfort. Due to inoculating participants with SARS-CoV-2 Delta variant (the virus that causes COVID-19), there is a low risk of severe infection (such as pneumonia or blood clots) and a low risk of developing prolonged symptoms including loss of sense of smell (anosmia) or “long COVID”. The study is designed to ensure these risks are minimised. Volunteers are only eligible if they are previously vaccinated against SARS-CoV-2, young, and healthy, and are carefully selected, with a detailed medical assessment carried out on all potential volunteers before they start the study. An

antiviral therapy is available on standby to any volunteers who develop signs of a more severe infection. The study will start with a low dose of the SARS-CoV-2 Delta virus in a small group of volunteers The research team are available any time day or night and provide access to healthcare if required.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
September 2021 to June 2025

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
318173

Protocol serial number
CPMS 53784, WT 225170/Z/22/Z, IRAS 318173

Study information

Scientific Title
Development of a SARS-CoV-2 Delta variant human infection challenge model (COVHIC002)

Acronym
COVHIC002

Study objectives
This study aims to develop a safe, reproducible SARS-CoV-2 Delta variant human infection challenge model in adult volunteers who are previously vaccinated (with or without previous SARS-CoV-2 infection) to investigate factors associated with susceptibility and protection and permit the future study of vaccines, antivirals and other interventions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/09/2022, Specialist Ad Hoc REC (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, UK; +44 (0)20 7972 2545; specialist.rec@hra.nhs.uk), ref: 22/UK/0001

Study design
Interventional non-randomized study

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
COVID-19

Interventions

This is a dose optimisation study in which increasing titres of Delta variant SARS-CoV-2 (1x101 TCID50, 1x102 TCID50and 1x103 TCID50 or higher, as necessary) will be given via nasal administration to different groups of vaccinated volunteers in order to achieve a ≥50% attack rate (ideally between 50% and 70%), as determined by positive qPCR detection (viral load ≥LLOQ) in respiratory secretions (mid-turbinate swabs and/or throat swabs) at two consecutive timepoints.

A starting dose of 10 TCID50 will be given via intranasal drops to a sentinel group of 3 subjects, followed by a further 3 subjects (total n=6 in first cohort). If the ≥50% target attack rate is not achieved, subsequent cohorts will be selected for low levels of anti-SARS-CoV-2 antibodies and receive escalating doses of SARS-CoV-2.

For initiation of each new dose level, a sentinel group of 3 subjects will be initially assessed for safety and infectivity by the investigators, before proceeding with subsequent inoculations.

The second part will enrol up to 30 vaccinated subjects for challenge with the previously characterised GMP D614G containing wild-type “Wuhan-like” SARS-CoV-2 virus using the optimised conditions established in the first part, for direct comparison with Delta variant infection under identical conditions.

A Data Safety Monitoring Board will review safety and quantitative virology after each cohort and will recommend continuation, dose escalation or de-escalation based on emergent data. A Trial Steering Committee (also known as the Medical Oversight Committee) will provide overall supervision of the project.

Volunteers interested in participating will be asked to register their details on the study website after completing a prescreening questionnaire. These details and questionnaire responses will be downloaded by or sent by email to the research team who will then contact them by phone to confirm the answers they provided on the pre-screening questionnaire and ask further questions pertaining to the full study inclusion/exclusion criteria. If inclusion/exclusion criteria are provisionally met based on answers to these questions, they will then be invited for a pre-screening visit and sent a confirmation email with the visit details and the Participant Information Sheet (PIS).

Pre-Screening visit: The participant information sheet (PIS) and pre-screening ICF will be sent to the participant at least 24 hours prior to the pre-screening visit and they will be encouraged to read these in advance, discuss the study with family and friends and ask questions about the research. During the visit, the PIS and the pre-screening process will be discussed with the participant by the trained study doctor or nurse, to ensure understanding of the risks and unknowns of the study and opportunity to ask further questions. Following informed consent, the following assessments will be completed at the pre-screening visit: Confirmation of name, age, gender, and contact details; Venous blood sampling for Anti-S and Anti-N serology; Optional: Dried blood spot (DBS) capillary sample (by finger prick).

If the volunteer is still deemed to be eligible for the study following the antibody test results, they will then be invited for a full screening visit.

Screening visit: The participant information sheet (PIS) and ICF will be sent to the participant at least 24 hours prior to the screening visit and they will be encouraged to read these in advance. During this visit, the full screening visit process as well as the PIS and ICF will be discussed again with the participant by the study doctor or nurse. A multiple-choice quiz will then be conducted

to check the volunteer's understanding of the study rationale, procedures and risks. If they do not pass the quiz, the study team member will check the incorrect quiz answers and re-review with the volunteer the relevant ICF sections to ensure understanding. When the subject has had enough time to consider their participation in this study, ask any questions they may have, and only when they have agreed to take part will they be asked to read, sign and date the relevant consent form in the presence of the study doctor or nurse who will also sign the consent form. Written consent for screening will be obtained prior to any study procedures. Following informed consent, medical history, examination and screening assessments will be undertaken (see SoA). The volunteer's medical history will be requested from their GP and reviewed to assess suitability. Subjects may be invited for repeat assessment where / if required at the PI's discretion.

Pre-Screening and screening appointments will be conducted at the ICRF, Hammersmith Hospital; ICRRU, St Mary's Hospital, Imperial College Healthcare NHS Trust; or Chelsea and Westminster Clinical Research Facility.

On Day -2, the participant will be admitted to the quarantine unit. Prior to any study specific procedures taking place, participants will have a further opportunity to discuss the research protocol with a trained study team member.

Subjects will remain in the quarantine unit overnight. Subjects with evidence of infection (defined as 2 consecutive viral detections by qPCR after day 1 post-inoculation) will stay overnight for a period of at least 17 days in total, from 2 days before the viral challenge, to at least the 14th day after viral challenge (see discharge criteria). Subjects who remain uninfected will stay overnight for a period of at least 13 days in total, from 2 days before the viral challenge, to at least the 10th day after viral challenge (see discharge criteria). Those who remain uninfected and are discharged on day 10 after inoculation will be required to attend daily visits on Day 11, Day 12, Day 13 and Day 14. This period of confinement has been chosen to eliminate the possibility of subjects in the study transmitting the virus to anyone not involved in the study (i.e. family, household contacts, and the wider community). During the confinement period, all study procedures will take place in the Chelsea and Westminster Hospital confinement facility. During follow up phase
all participants will be required to attend 5 clinic visits on Day 28 (+/- 3 days), Day 90 (+/- 7days), Day 180 (+/- 14 days) and Day 360 (+/- 14 days), as specified in the SoA. They will also have a telephone follow up on Day 21 (+/- 2 days).

At discharge from quarantine, all participants will be provided with lateral flow antigen test kits and RT-PCR swab kits with pre-paid postage and instructions. Participants who become symptomatic during follow-up (up to Day 360) will be instructed to self-perform a lateral flow antigen test and contact the study team. Participants without symptoms who test positive for SARS-CoV-2 in the community (on a lateral flow test or RT-PCR) will also be requested to contact the study team. For those who test positive for SARS-CoV-2, the study team may request the participant attends for Testing Visits. Testing Visit 1 should occur within 5 days of symptom onset and Visit 2 should occur 28 days (+/-7 days) later).

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled visit shown in the SoA (Day 360± 14 days) or the last unscheduled visit as applicable. If a safety visit is required after the last scheduled visit, this will be at the PI's discretion as a duty of care, e.g., repeat spirometry or laboratory tests. These discretionary follow-up visits will not be considered part of the trial data unless they represent follow-up and closure on an AE or serious adverse event (SAE) identified during the trial period. The end of the study is defined as the date of the last visit of the last participant in the study.

Intervention Type
Other

Primary outcome(s)
1. Safety profile as measured by:
1.1. Occurrence of adverse events (AEs) from the viral challenge (Day 0) up to Day 28 follow up.
1.2. Occurrence of serious adverse events (SAEs) from the viral challenge (Day 0) up to Day 28 follow up.
2. Laboratory confirmed infection in ≥50% of participants (ideally ≥70%). Laboratory confirmed infection is defined by: two quantifiable greater than lower limit of quantification (viral load ≥LLOQ) RT-PCR measurements from mid turbinate and/or throat samples, reported on 2 or more consecutive timepoints, starting from Day 2 post-inoculation and up to discharge from quarantine.

Key secondary outcome(s))
1.SARS-CoV-2 breakthrough infection rates and viral dynamics (AUC, peak, duration, incubation period) in upper respiratory samples - qRT-PCR (for SARS-CoV-2 RNA) and cell culture (to for live SARS-CoV-2 virus) are performed daily during quarantine
2. Incidence of symptomatic SARS-CoV-2 breakthrough infection in vaccinated participants and to assess the nature and severity of SARS-CoV-2 induced symptoms (sum, AUC, peak, peak daily, frequency) – symptom diaries are completed three times a day, at baseline, daily during quarantine and at all follow up visits.

Tertiary/Exploratory
1. Safety of the SARS-CoV-2 Delta variant human challenge model – safety laboratory tests, concomitant medications, spirometry, smell (using the UPSIT test), cognition (using the CogAssess app), are measured at baseline, during quarantine and at follow up visits
2. Infection rate, viral dynamics and symptoms of SARS-CoV-2 Delta virus with SARS-CoV-2 pre-Alpha virus challenge
3. SARS-CoV-2 viral dynamics in saliva (AUC, peak, duration, incubation period) - qRT-PCR (for SARS-CoV-2 RNA) is performed from samples collected daily during quarantine
4. SARS-CoV-2 viral infection rates in stool – stool swabs are collected when bowels are opened during quarantine and tested by qRT-PCR
5. Detection of SARS-CoV-2 breakthrough infection by lateral flow antigen tests, which will be tested daily during quarantine
6. Host-pathogen relationship in the SARS-CoV-2 Delta human challenge model (including humoral and cellular immunity, proteomics, transcriptomics, host and viral genomics, microbiome and systems biology) – blood, nasal, throat and stool samples are collected at baseline, during quarantine and at follow up visits
7. Environmental contamination in SARS-CoV-2 Delta-infected participants including during manoeuvres such as singing and reading aloud – air sampling, exhaled breath, hand and surface swabs are collected daily during quarantine and tested by qRT-PCR and cell culture.
8. Changes in the vasculature during SARS-CoV-2 breakthrough infection using an EndoPAT machine, at baseline and during quarantine

Completion date
02/06/2025

Eligibility

Key inclusion criteria
1. An informed consent form has been signed and dated by the participant and the Investigator.
2. Adults age between 18 and 30 years inclusive (at the time of consent)
3. Evidence of having had a complete COVID-19 vaccination course with the last vaccination at least 14 days before enrolment
4. Sero suitable as defined by: positive anti-S AND negative anti-N antibody detection OR positive anti-S AND positive anti-N antibody. Those with an indeterminate anti-N antibody result and no history of laboratory-confirmed SARS-CoV-2 infection may be included or excluded at the CI/PI's discretion on a case-by-case basis. detection (at the CI/PI's discretion).
5. Female participants with a documented menstrual period within 28 days before the inoculation (unless using a contraceptive method that suppressed menstruation as indicated in the study protocol) and willing and able to use contraception as described in the study protocol from 2 weeks before the scheduled date of viral challenge until 6 months after receipt of the final dose of study virus or intervention treatment (whichever occurs last). Negative urine pregnancy tests will be required at screening and on day 0 prior to inoculation. On admission to the quarantine unit a Negative serum beta human chorionic gonadotropin (β-hCG) is required.
6. Men who are willing to use one of the contraception methods described in the study protocol, from the time of the date of viral challenge, until 6 months after receipt of the final dose of study medication (if applicable).
7. In good health with no history of clinically significant medical conditions (as described in Exclusion criteria) that would interfere with subject safety, as defined by medical history, physical examination and routine laboratory tests, ECG, and Chest X-Ray and determined by the Investigator at an admission evaluation.
8. Subjects will have a documented medical history either prior to entering the study and/or following medical history review with the study physician at screening.
9. Willing and able to commit to participation in the study.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
30 years

Sex
All

Total final enrolment
46

Key exclusion criteria
1. History or evidence of any clinically significant or currently active cardiovascular, (including thromboembolic events), respiratory, dermatological, gastrointestinal, endocrine,

haematological, hepatic, immunological, rheumatological, metabolic, urological, renal, neurological, psychiatric illness.
2. Any significant abnormality altering the anatomy or function of the nose or nasopharynx in a substantial way (including loss of or alterations in smell or taste), a clinically significant history of epistaxis within the last 3 months, nasal or sinus surgery within 6 months of inoculation.
3. Clinically active rhinitis (including hay fever) or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of admission to quarantine.
4. History of anaphylaxis and/or a history of severe allergic reaction or significant intolerance to any food or drug, as assessed by the PI.
5. History or presence of alcohol addiction, or excessive use of alcohol or use of drugs of abuse
6. Psychiatric illness including subjects with a history of depression and/or anxiety with associated severe psychiatric comorbidities, for example psychosis. Specifically, (a) Subjects with history of anxiety-related symptoms of any severity within the last 2 years if the Generalized Anxiety Disorder-7 score is > = 4; (b)Subjects with a history of depression of any severity within the last 2 years if the Patient Health Questionnaire-9 score is > = 4
7. Subjects who have smoked > = 5 pack years at any time.
8. Family history of 1st degree relative aged 50 years or less with sudden cardiac or unexplained death
9. Family History of Severe COVID or response to any other viral disease e.g.Guillain–Barré
10. A total body weight of < = 50kg and a BMI < = 18 kg/m2 and > = 28 kg/m2. The upper limit of BMI may be increased to < = 30kg/m2 at the PI's discretion, in the case of physically fit muscular individual
11. Venous access deemed inadequate for the phlebotomy and cannulation demands of the study.
12. Any clinically significant abnormal finding on screening biochemistry, haematology and microbiology blood tests or urinalysis i.e. grade 1 lab abnormalities or above apart from minor deviations which are clinically acceptable and approved by the Principal Investigator
13. A forced expiratory volume in 1 second (FEV1) and a forced vital capacity (FVC) < 80% of predicted value calculated using ATS/ERS guidance
14. Twelve-lead ECG recording with clinically relevant abnormalities as judged by the study physician/PI.
15. History of, or currently active symptoms suggestive of upper or lower respiratory tract infection (including reduced sense of taste and smell, raised body temperature and/or persistent cough) within 6 weeks prior to viral challenge.
16. Presence of cold-like symptoms and/or fever (defined as subject presenting with a temperature reading of > 37.9°C) on Day -2, Day -1 and/or pre-challenge on Day 0.
17. Evidence of any respiratory viruses (on nasopharyngeal swab analysis) prior to challenge virus inoculation on admission to the quarantine unit.
18. Evidence of a live vaccine within 60 days prior to the planned date of viral challenge, a non-live vaccine within 30 days prior to the planned date of viral challenge or intention to receive any vaccination(s) before the day 28 follow-up visit.
19. Receipt of blood or blood products, or loss (including blood donations) of 550 mL or more of blood during the 3 months prior to the planned date of viral challenge or planned during the 3 months after the final visit.
20. Use of certain medications (listed in more detail in the protocol)
21. Prior participation in another human viral challenge study in the preceding 12 months
22. Previous participation in a SARS-CoV-2 vaccine trial of a currently unapproved/unlicensed vaccine in the UK
23. Any nasal sampling procedure in the 6 months before date of expected viral challenge in this study (excluding study tolerance test or routine tests for COVID-19)

24. Subject is mentally or legally incapacitated in the opinion of the Investigator.
25. Females who: Are breastfeeding within 6 months of study commencement, or Had been pregnant within 6 months prior to the study, or Had a positive pregnancy test at any point during screening or prior to inoculation with challenge virus
26. Those in close domestic contact with children under 2 years, the elderly (> 65 years), immunosuppressed persons, or those with chronic respiratory disease
27. Subjects who are currently employed or a first-degree relative of someone employed by the Sponsor or participating site, or any CRO involved in this study.
28. Any other reason that the Investigator considered made the subject unsuitable to participate.
29. Participants with no knowledge of their family history

Date of first enrolment
28/10/2022

Date of final enrolment
07/06/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
NIHR Imperial Clinical Research Facility
Hammersmith Hospital
Du Cane Rd
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W12 0HS

Study participating centre
Chelsea and Westminster Hospital
Chelsea and Westminster Hospital NHS Foundation Trust
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
Oxford Experimental Medicine Clinical Research Facility
Churchill Hospital
Oxford

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OX3 7LE

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository: All data will be collected and generated following written informed consent by study participants. Pseudonymisation of participant-level data will be undertaken, with the pseudonymisation key accessible only to the clinical study team and maintained on an encrypted server. Gene expression data will be deposited in the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) on publication of papers reporting those data and therefore freely available at that point. Whole genome sequence and other pseudonymised data that is classified as sensitive and personal will be deposited in a restricted access repository such

as the European Genome-Phenome Archive (https://ega-archive.org/), which is fully GDPR-compliant and from which data may be downloaded subject to Sponsor-defined access limitations.
The datasets generated during and/or analysed during the current study are/will be available upon request from Professor Christopher Chiu, Department of Infectious Disease, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, United Kingdom. Individual participant data that underlie the results reported in this article after deidentification will be made available for individual participant data meta-analysis beginning 12 months and ending 5 years following article publication upon written request. Additional shareable documents include the Statistical Analysis Plan. Proposals should be directed to c.chiu@imperial.ac.uk.
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication.

IPD sharing plan summary

Stored in publicly available repository, Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 2.0	14/10/2022	07/03/2023	No	No
Protocol file	version 3.0	16/03/2023	14/04/2023	No	No
Protocol file	version 4.0	21/04/2023	04/09/2023	No	No
Protocol file	version 5.0	05/06/2023	04/09/2023	No	No
Protocol file	version 5.1	11/08/2023	04/09/2023	No	No
Protocol file	version 7.0	17/10/2023	05/12/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes