hVIVO

part of Open Orphan plc

The worlds first Covid-19 Human Challenge Trial

Le Club Phase 1

17th of June, 2022

Robin Rogiers, Director Clinical Delivery & Innovation hVIVO

Company Overview

Open Orphan

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- Acquired in January 2020
- World Leader in Human Challenge Trials with Onsite Virology Labs
- FluCamp: tech-enabled volunteer and patient recruitment platform

Venn Life Sciences part of Open Orphan plc

- Acquired in June 2019
- Early Clinical Drug Development Services
- Biometric services

hVIVO Capability Venn Life Sciences Capability

CMC	Preclinical	Phase I	Challenge Study	Lab Services	Phase II	Biometrics	Regulatory

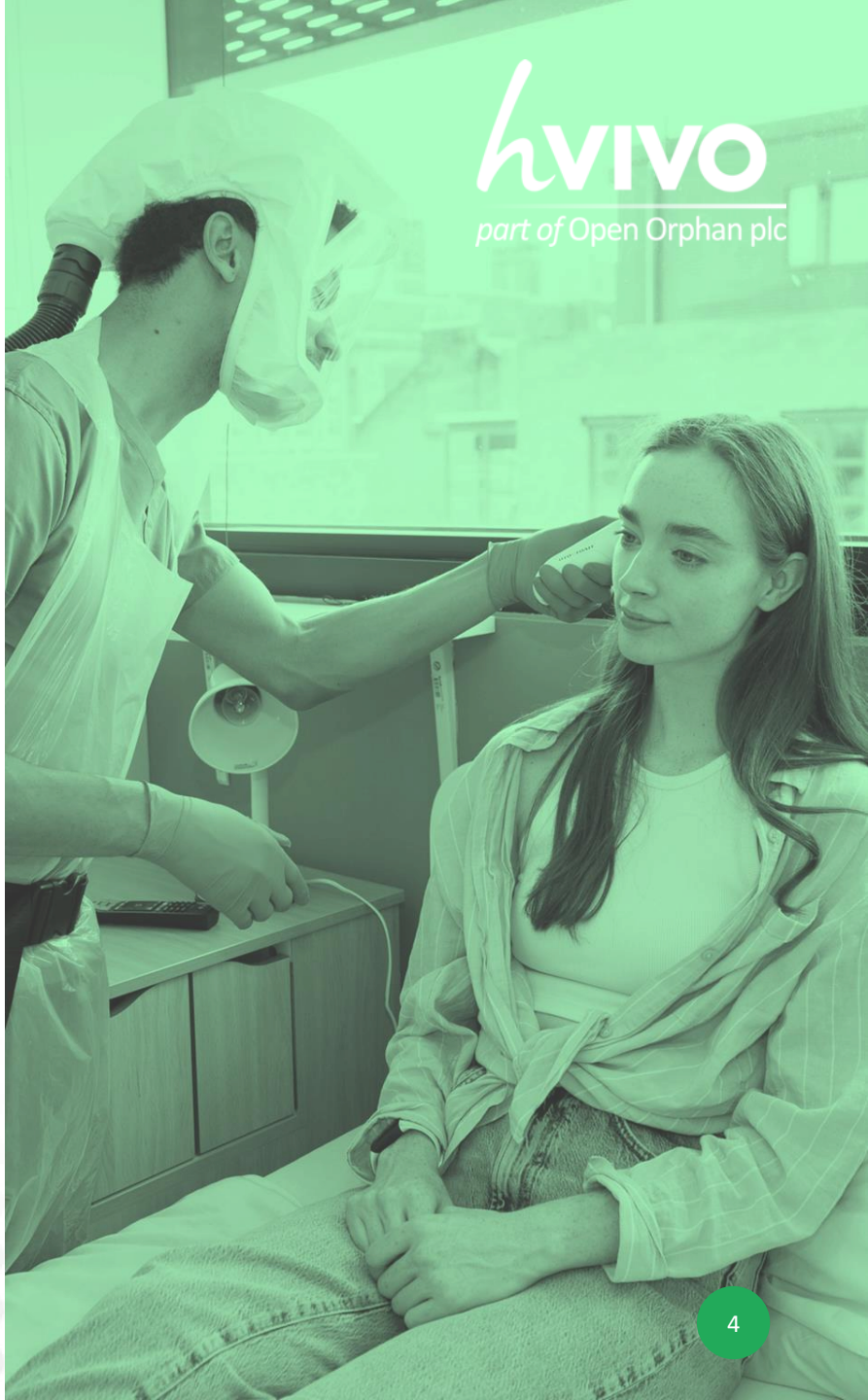
…offering full end-to-end services for key biopharma clients

Introduction: Controlled Human Infection Considerations

- Challenge organisms:
  - Close to wild-type and pathogenic
  - Adapted and/or attenuated from wild-type with less or no pathogenicity
  - Genetically modified in some manner (GMO)

- Specifically designed clinical facilities/procedures:
  - Quarantine unit - isolation rooms
  - Cross-contamination between subjects and/or staff
  - “Reversed-barrier nursing”

- Challenge study design aspects:
  - Characterisation trial: open label design
    - Fundamental scientific research
  - Vaccine / prophylactic / therapeutic IMP trials: double blind design
    - Proof of concept, dose finding studies,…



Wanted: Volunteers to be infected with the coronavirus

Researchers are hoping so-called 'challenge trials' will offer solutions to the pandemic.

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THE WALL STREET JOURNAL.

Researchers Infect Volunteers With Coronavirus, Hoping to Conquer Covid-19

So-called challenge trials have long been used to study infections, but so far only the U.K. is doing them for Covid-19

The Economist

Science & technology | A calculated risk

Why scientists are deliberately infecting volunteers with covid-19

"Human challenge trials" may help answer important questions quickly

FINANCIAL TIMES

World's first trial of deliberate coronavirus infection is approved

Challenge study in London will provide platform for future vaccine development

CORONAVIRUS

Scientists win approval to infect healthy volunteers with Covid for trial

THE TIMES

NEWS

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Health

UK plan to be first to run human challenge Covid trials

By Michelle Roberts
Health editor, BBC News online

HEALTH AND SCIENCE

UK will soon expose volunteers to Covid in world's first 'human challenge' study

CNBC

Business

Open Orphan gets final go-ahead for Covid-19 human trial

abc NEWS VIDEO LIVE SHOWS GUNS IN AMERICA JAN. 6

UK asks for volunteers to be exposed to COVID-19 for research

An ethics committee approved the trials, which will start within a month.

The NEW ENGLAND JOURNAL of MEDICINE

SARS-CoV-2 Human Challenge Studies — Establishing the Model during an Evolving Pandemic

Garth Rapeport, M.B., B.Ch., Emma Smith, Ph.D., Anthony Gilbert, M.B., B.Ch., Andrew Catchpole, D.Phil., Helen McShane, F.Med.Sci., and Christopher Chiu, B.M., B.Ch., Ph.D.

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Focus	Potential impact	Practically Possible with CHIM	Accelerated by CHIM
Relative protective efficacy of SARS-CoV-2 vaccines	Using licensed vaccines as a benchmark, new vaccines can be directly and rapidly compared for prioritization. Field studies to determine relative efficacy would be unfeasibly large and subject to unavoidable confounding.	X	
Effect of vaccination on viral shedding from the nose (transmission blockade)	**Preventing infection in the upper respiratory tract and viral shedding is critical to preventing transmission but cannot be practically assessed in field studies.**	X	
Comparative efficacy of vaccines with different modes of action	**Different vaccine platforms may induce distinct mechanisms of protection that are assessable only in a controlled study, given noncomparable immune readouts.**	X	
Vaccine-mediated correlates of protection in immunized participants	Vaccine-induced markers that correlate strongly with protection from challenge infection can be validated as measures for vaccine licensure of new vaccine candidates in lieu of determining efficacy in a phase 3 trial.	X	
Nimble selection of optimal vaccine dose and dosing regimen, including heterologous combinations	Rapid attainment of data in small cohorts allows comparative analysis and avoids failed phase 3 trials.		X
Booster-vaccine efficacy against variants of concern (VOCs)	**Challenge viruses made using VOCs enable testing of homologous and heterologous protection.**	X	

https://www.nejm.org/doi/full/10.1056/NEJMp2106970

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Focus	Potential impact	Practically Possible with CHIM	Accelerated by CHIM
Durability of antiviral action as prophylaxis	Challenge infection at different time points after administration of monoclonal antibody or antiviral agents will determine how long they are effective.	X	
Rapid determination of efficacy of antivirals	**Human challenge has a well-established role in antiviral evaluation and can use very small sample sizes to accelerate their development**		X
Appropriate dosing for antivirals, next-generation monoclonal antibodies, and combination approaches	Rapid, small studies nimbly assess efficacy of dosing and regimen adjustments.		X

https://www.nejm.org/doi/full/10.1056/NEJMp2106970

In exceptional cases:

- Support for emergency use of an investigational vaccine
- Efficacy basis for licensure

Need for SARS-CoV-2 challenge model

- Allows for rapid determination of efficacy without confounding factors commonly seen in hospital setting
- Potential to support efficacy claims for licensure/support emergency use
- No different approach from the standard viral challenge models – but less scientific knowledge on the disease (anno 2020):
  - Long term serious consequences?
  - (lack of) treatment options?

But…

Is it ethical to conduct a SARS-CoV-2 Human challenge trial?

WHO criteria on ethical acceptability of SARS-CoV-2 Human Challenge Studies

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World Health Organization

Table 1
Eight criteria for SARS-CoV-2 challenge studies.

Scientific and ethical assessments		
Criterion 1	Scientific justification	SARS-CoV-2 challenge studies must have strong scientific justification
Criterion 2	Assessment of risks and potential benefits	It must be reasonable to expect that the potential benefits of SARS-CoV-2 challenge studies outweigh risks
Consultation and coordination		
Criterion 3	Consultation and engagement	SARS-CoV-2 challenge research programmes should be informed by consultation and engagement with the public as well as relevant experts and policy-makers
Criterion 4	Coordination	SARS-CoV-2 challenge study research programmes should involve close coordination between researchers, funders, policy-makers and regulators
Selection criteria		
Criterion 5	Site selection	SARS-CoV-2 challenge studies should be situated where the research can be conducted to the highest scientific, clinical and ethical standards
Criterion 6	Participant selection	SARS-CoV-2 challenge study researchers should ensure that participant selection criteria limit and minimize risk
Review and consent		
Criterion 7	Expert review	SARS-CoV-2 challenge studies should be reviewed by a specialized independent committee
Criterion 8	Informed consent	SARS-CoV-2 challenge studies must involve rigorous informed consent

(https://www.sciencedirect.com/science/article/pii/S0264410X20313955?via%3Dihub)

WHO Advisory Group – Recommendations for SARS-CoV-2 challenge trials anno 2020:

- An incremental 2 step strategy should be applied:
  - **Step 1:** Characterisation / Dose-escalation study
  - **Step 2:** Studies to investigate the level of protection and preliminary efficacy of vaccines/antivirals
- Volunteers should be restricted to healthy individuals, proposed between 18–25 years of age
  - *How predictive is this model for the general population?*
- Studies should be performed in High-Level Isolation Units
- Legal Quarantine (Compulsory Isolation)
  - *Can this be enforced?*
- GMP manufacturing under BSL-3 capability
- **No consensus on the need for rescue treatment**

UK COVID-19 Challenge Programme

- Funded by the UK Government through the UK Vaccine Task Force
- The Human Challenge Programme is a partnership between
  - Imperial College London
  - hVIVO, part of Open Orphan
  - Department for Business, Energy and Industrial Strategy (BEIS) – UK government
  - Royal Free London NHS Foundation Trust
- Supported by "Clinical Advisory Network" with expertise in virology, epidemiology and vaccinology
  - University of Southampton
  - University of Oxford
  - University College London
  - University of Liverpool
  - Wellcome Trust
  - MHRA
- Aim to establish a Covid-19 Human Challenge model
  - SARS-CoV-2 Characterisation Study
  - Antiviral / vaccine studies
  - Fundamental research studies

Timelines

Decisions based on the knowledge present at that time

Sep 2020	Jan 2021 – Feb 2021	Feb 2021
Start of GMP manufacturing	Animal Study	Approval Characterisation study
Mar 2021	**July 2021**	**July 2022**
First volunteer enters Quarantine	Last Volunteer leaves Quarantine	Final Full Analysis Characterisation study

Regulators and ethics

- **Scientific Advise: MHRA and EMA**
  - Manufacturing of Challenge Agent
  - Non-clinical Development Challenge Agent
    - Animal model relevance and translation to humans
  - Study Design
    - Ethical considerations
    - Safety measurements
    - Rescue therapy:
      - Remdesivir pre-emptively – did not have market authorisation
      - Triggering of rescue medication with monoclonal antibodies (Regeneron)

UK Research Ethics Committee's review of the global first SARS-CoV-2 human infection challenge studies

Hugh Davies, On behalf of the HRA Specailist Research Ethics Committee

- **UK Health Research Authority (HRA)**
  - Specialist 'ad hoc' Research Ethics Committee (REC)
- **Composition**
  - Expert and lay members of UK RECs
  - Experience review Clinical Trials of Investigational Medicinal Products or phase I studies in healthy volunteers
  - Experience of vaccine studies
- **Assessment based on WHO Advisory**
- **Extensive and very detailed informed consent process**
- **'Could these research questions be equally well answered by less intrusive studies?'**

Davies H Journal of Medical 10.1136/medethics-2021-107709

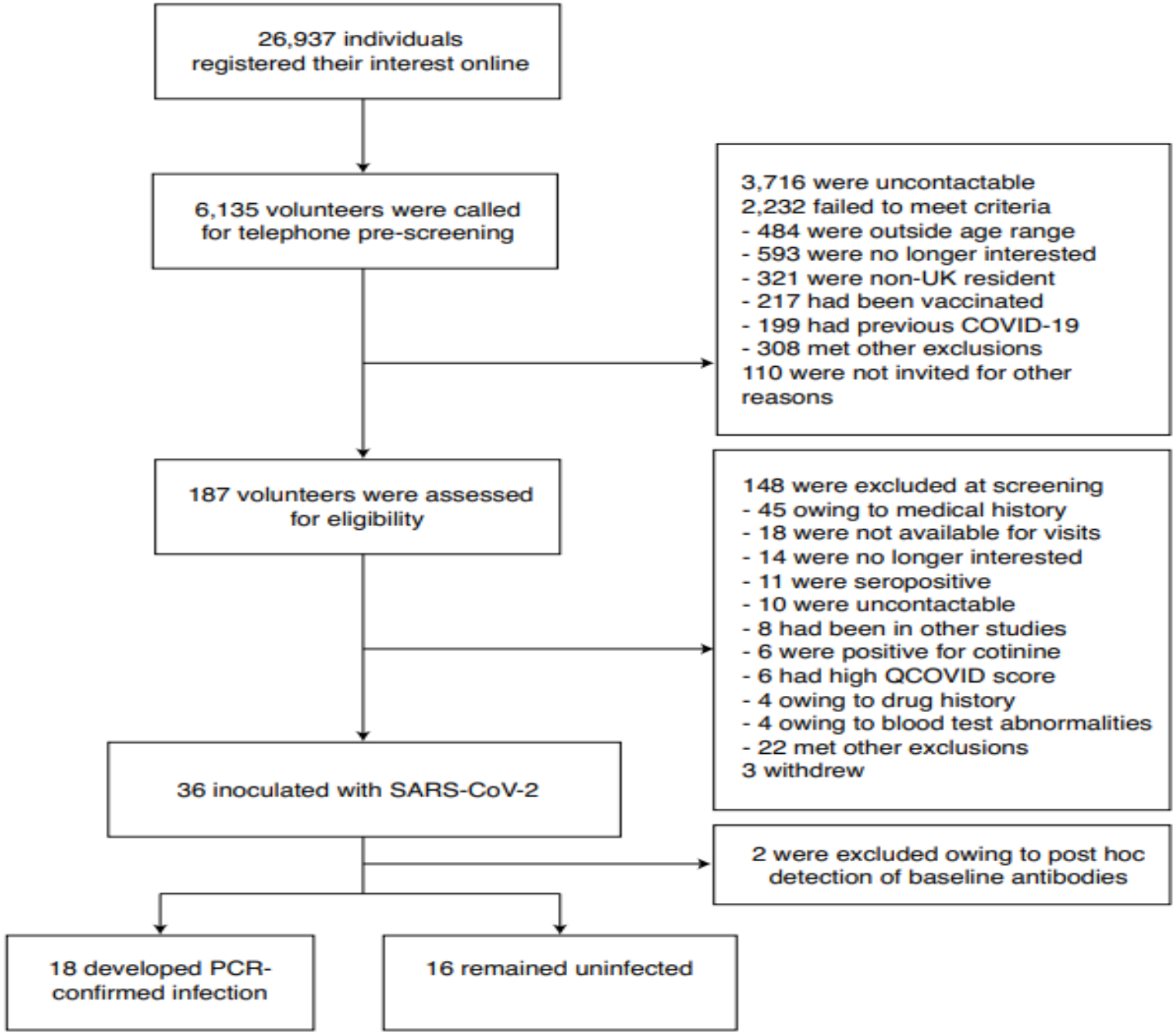
SARS-CoV-2 Characterisation Study

part of Open Orphan plc

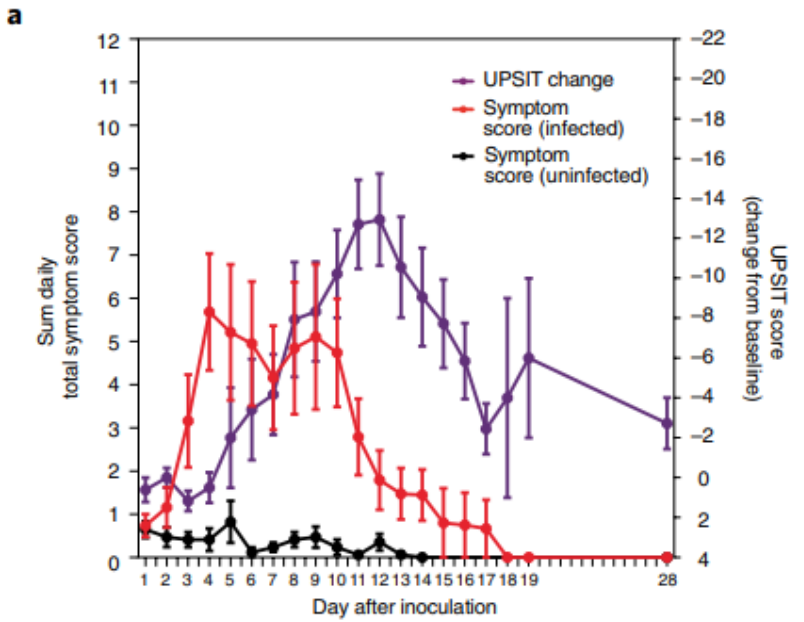
- Title:
  - *A dose finding human experimental infection study in healthy subjects using a GMP-produced SARS-COV-2 wild type strain(SARS-CoV-2 Characterisation Study)*
- Chief Investigator: Chris Chiu, Imperial College London
- SARS-CoV-2 Challenge virus Administered intranasally
- Healthy volunteers aged between 18 and 30 years inclusive, BMI up to 28, non-smokers
- Dose escalation study
  - 1x10^1 TCID50
  - 1x10^2 TCID50
  - 1x10^3 TCID50
- Sentinel groups at each dose level
- Safety Review Committee after every 10 subjects

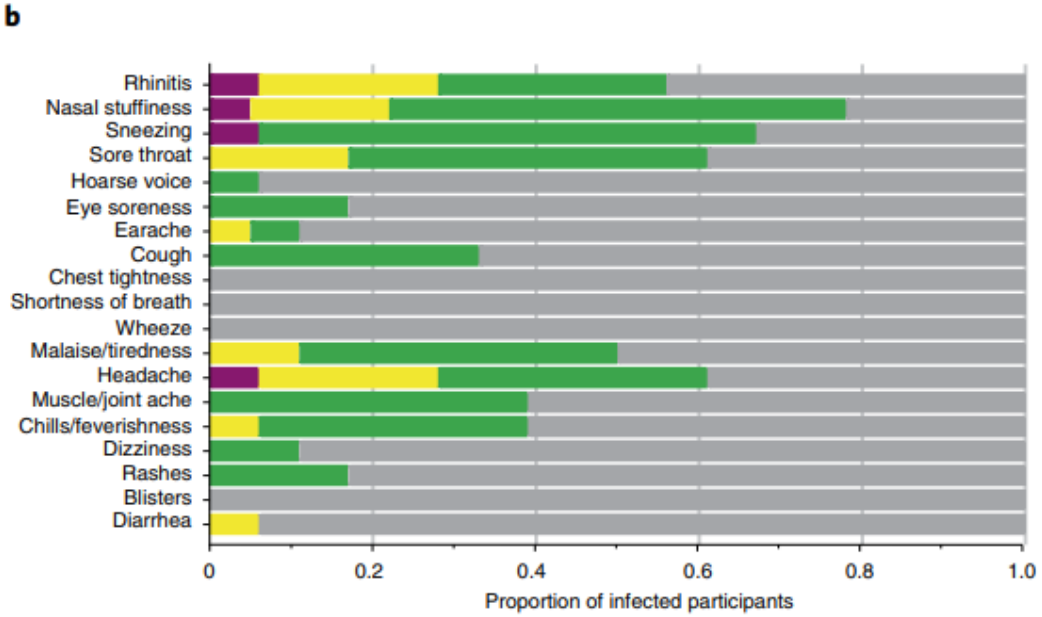
- Endpoints
  - Evaluate the safety of wild type SARS-CoV-2 challenge in healthy participants
  - To identify an inoculum dose that safely induces laboratory confirmed infection in ≥50% participants
- Performed at Royal Free Hospital, London
  - BSL-4 Quarantine Unit
  - Close proximity to ICU

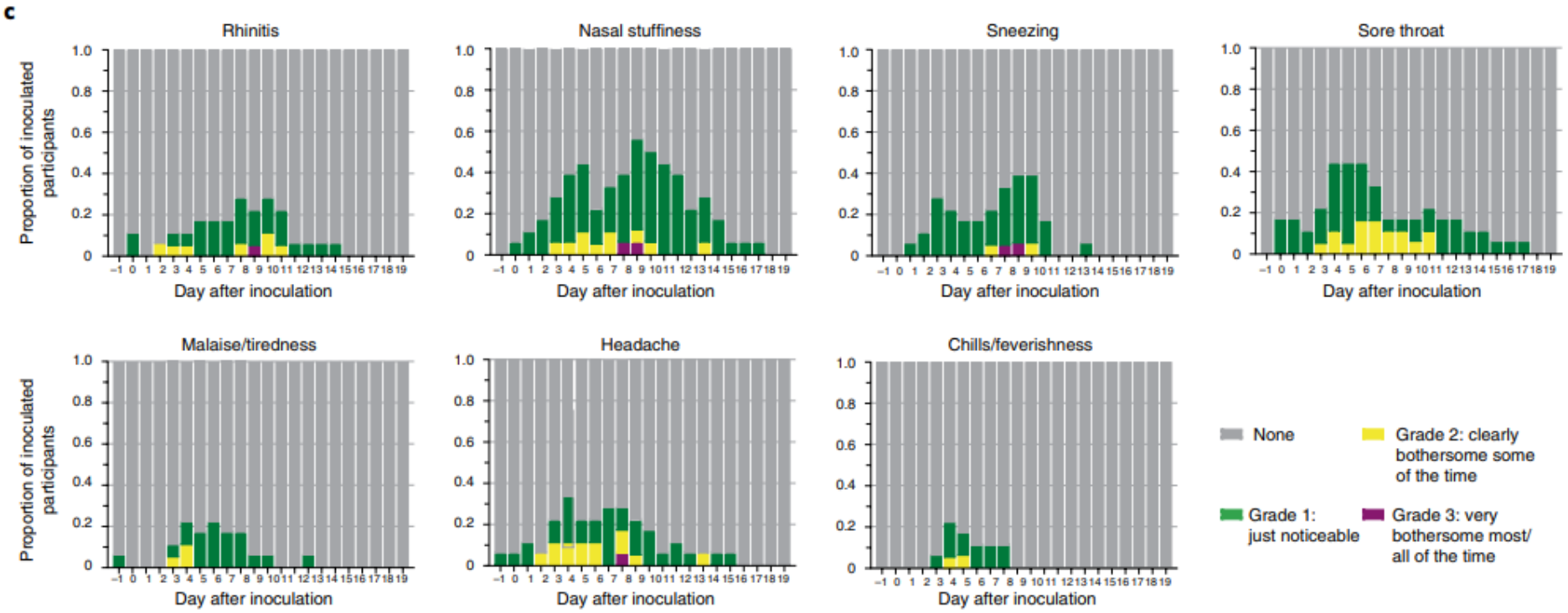
Recruitment



Symptoms


a
UPSIT change
Symptom score (infected)
Symptom score (uninfected)
Sum daily total symptom score
UPSIT score (change from baseline)
Day after inoculation


b
Rhinitis
Nasal stuffiness
Sneezing
Sore throat
Hoarse voice
Eye soreness
Earache
Cough
Chest tightness
Shortness of breath
Wheeze
Malaise/tiredness
Headache
Muscle/joint ache
Chills/feverishness
Dizziness
Rashes
Blisters
Diarrhea
Proportion of infected participants


c
Rhinitis
Nasal stuffiness
Sneezing
Sore throat
Malaise/tiredness
Headache
Chills/feverishness
Proportion of inoculated participants
Day after inoculation
None
Grade 1: just noticeable
Grade 2: clearly bothersome some of the time
Grade 3: very bothersome most/ all of the time

Trial Outcome

36 seronegative and unvaccinated volunteers were inoculated safely

- Between 18 and 29 years old

No safety concerns noted, no Serious Adverse Events

- Most frequent symptoms in upper respiratory tract
- Peak symptoms at 112h post-inoculation
- No quantitative correlation between viral load and symptoms
- 67% of infected volunteers reported some form of smell disturbance, anosmia was the symptom with longest duration

No clinical need for rescue therapy or hospital transfer

- 6 volunteers were treated with pre-emptive Remdesivir as part of the adaptive protocol design; no difference in viral load or qPCR between treated and untreated individuals; no difference in symptomatology between remdesivir treater or untreated participants

Timing, duration and expression of infection as can be expected

- Viral shedding begins within 2 days after exposure, viral load was higher in nasopharynx than oropharynx though peaked later, viable virus detected up to 12 days after inoculation

Challenge model well tolerated

- 53% became infected, viral load peaking 5d after inoculation

Study status on 17 JUN 2022

- Subjects in follow-up phase until 1 year after inoculation
- See Clinicaltrial.Gov for more information

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What is next?

- Conversion to seropositive model
  - Data is with subjects screened to have no detectable antibodies to SARS-CoV-2
  - Large part European population aged 12 or over are now fully vaccinated
- Delta virus manufacturing on behalf of Imperial College London (sponsored by Wellcome Trust)
- Use of challenge trials in future development of
  - New / booster vaccines
  - Treatment options
- Re-infection Human Challenge trial - University of Oxford

Useful guidances

- WHO. Human challenge trials for vaccine development: regulatory considerations. 2016.
- WHO. Guidelines on clinical evaluation of vaccines: regulatory expectations.
- WHO. Key criteria for the ethical acceptability of COVID-19 human challenge studies. WHO Working Group for Guidance on Human Challenge Studies in COVID-19, 6 May 2020.
- WHO. Feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental COVID-19 infection and illness in healthy young adult volunteers. Report from the WHO Advisory Group on Human Challenge Studies, 2 December 2020.

Useful literature

- Killingley, B., Mann, A.J., Kalinova, M. et al. Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. Nat Med 28, 1031–1041 (2022).
- Davies H UK Research Ethics Committee's review of the global first SARS-CoV-2 human infection challenge studies *Journal of Medical Ethics* Published Online First: 05 October 2021. doi: 10.1136/medethics-2021-107709
- I. Bekeredjian-Ding, W. Van Molle, M. Baay, P. Neels, C. Conrad, A. van Diepen, *et al.* Human challenge trial workshop: focus on quality requirements for challenge agents, Langen, Germany *Biologicals*, 66 (2020), pp. 53-61
- M. Baay, P. Neels SARS-CoV-2 controlled human infection models: ethics, challenge agent production and regulatory issues *Biologicals*, 67 (2020), pp. 69-74
- M. Baay, P. Neels Controlled human infection to speed up SARS-CoV-2 vaccine development *Front Immunol*, 12 (2021), p. 658783
- Rapeport G, Smith E, Gilbert A, Catchpole A, McShane H, Chiu C. SARS-CoV-2 human challenge studies — establishing the model during an evolving pandemic. *N Engl J* Med 2021;385:961-964.
- Kuiper VP, Rosendaal FR, Kamerling IMC, Visser LG, Roestenberg M. Assessment of risks associated with severe acute respiratory syndrome coronavirus 2 experimental human infection studies. *Clin Infect Dis* 2021;73(5):e1228-e1234.

Upcoming free webinar

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Date: 21 June 2022 **Time:** 15:00 - 16.00 BST (GMT+1)

How regulators view Human Challenge Trial Results

by **Bruno Speder**

VP Regulatory Affairs, at hVIVO

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Questions?

Robin Rogiers

Director, Clinical Delivery & Innovation, hVIVO

Mobile: +44 777 658 7576

Email: R.Rogiers@hvivo.com