

Human infection challenge in the UK: past, present and future

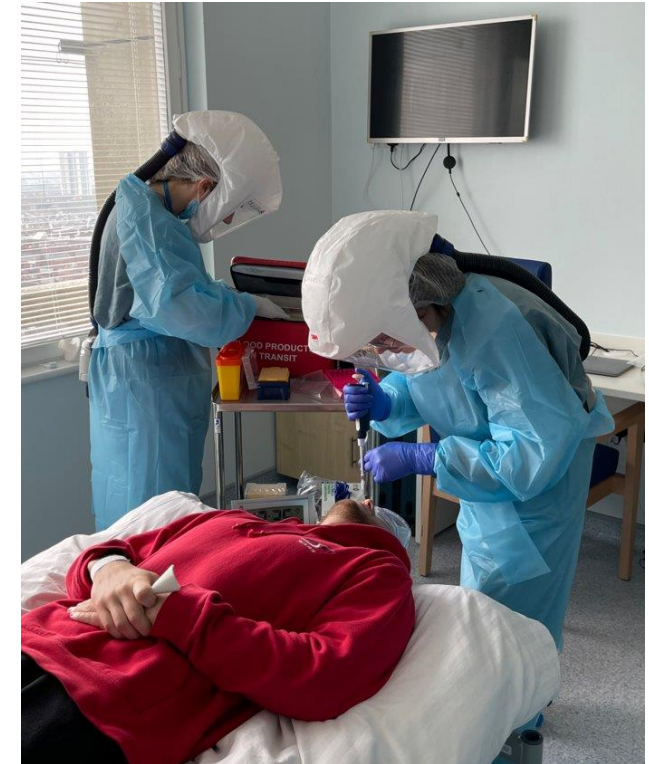
Dr Emma Smith PhD
Imperial College London

March 2021: UK performs first SARS-CoV-2 challenge study

- Extensive public support & interest: ~27,000 potential volunteers registered online
- Screened for seronegative status (natural infection and vaccination)
- 53% infection rate using **10 TCID₅₀** inoculum dose

Nature Medicine 28:1031–1041 (2022)

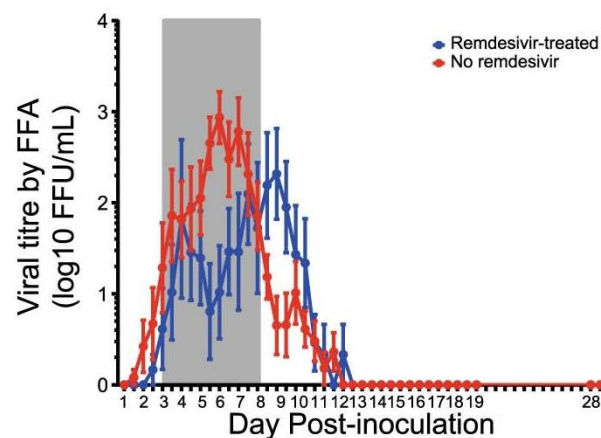
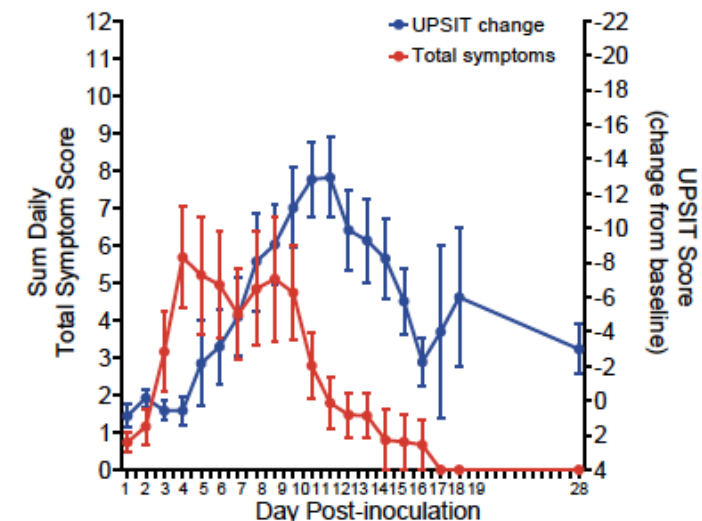
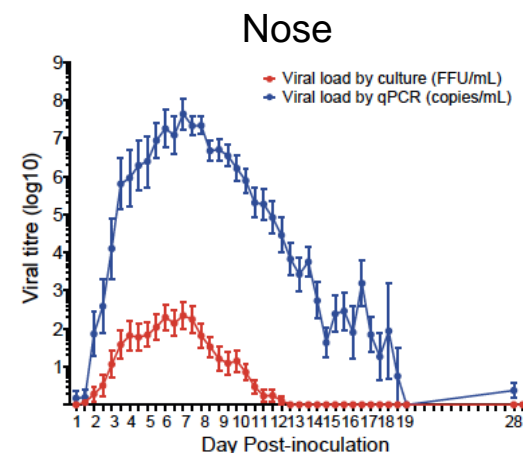
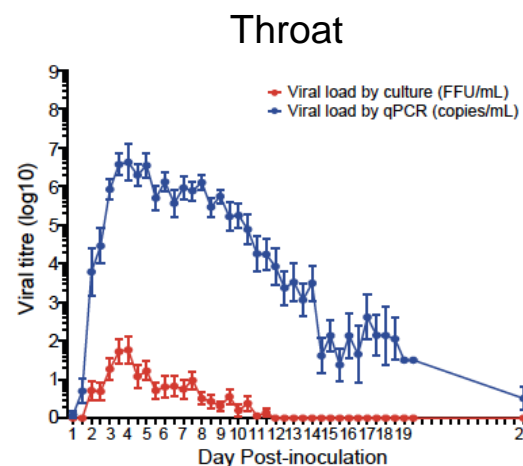
<https://www.nature.com/articles/s41591-022-01780-9>



Killingley, Mann... Chiu *et al.*

Viral & clinical headlines

- Short incubation (40h, variable)
- Rapid onset VL in throat
- Peak VL higher in nose
- **Very abundant viral shedding**
- Mild symptoms
- Remdesivir had little benefit
- Frequent smell disturbance
- Full recovery in all cases



- Long history of human challenge in the UK
 - Supportive regulatory and ethical approvals environment
 - NHS and clinical trial infrastructure
 - Political engagement and advocacy
 - Funding support
 - Expertise and collaboration
-

- Jenner and smallpox (1796), John Hunter and venereal diseases (1760s).
- Unethical studies: prisoners, disabled children etc.
- Nuremburg code (1947), Declarations of Geneva ('48) and Helsinki ('64).
- Common Cold Unit (MRC, 1946-90): colds, 'flu, ARIs – causes, transmission, treatment efficacies.

“One woman, also a teacher, volunteered six times in eleven years:

‘Time flew, sewing, reading, going on the occasional walk. It was a complete break from the world, a time to return to the freedom of childhood without its restraints.’ ”

- Legal
 - Not regulated as a investigative medicine (MHRA)
 - Research Ethics Committees are experienced and knowledgeable
-

- Multi-centre trials
- Government funded clinical support for clinical trials
- Immediate and long-term paid-for care for any health impacts
- Large population without health insurance



COVID-19: The UK's national enablers



Prof Sir Jonathan Van-Tam
Former Deputy Chief
Medical Officer



Prof Dame Sally Davies
Former CMO



Prof Sir Mark Walport
Former head, UKRI



Prof Sir Chris Whitty
Chief Medical Officer



Prof Sir Patrick Vallance
Chief Scientific Advisor



Dame Kate Bingham
Head of Vaccine TF



UK Research
and Innovation

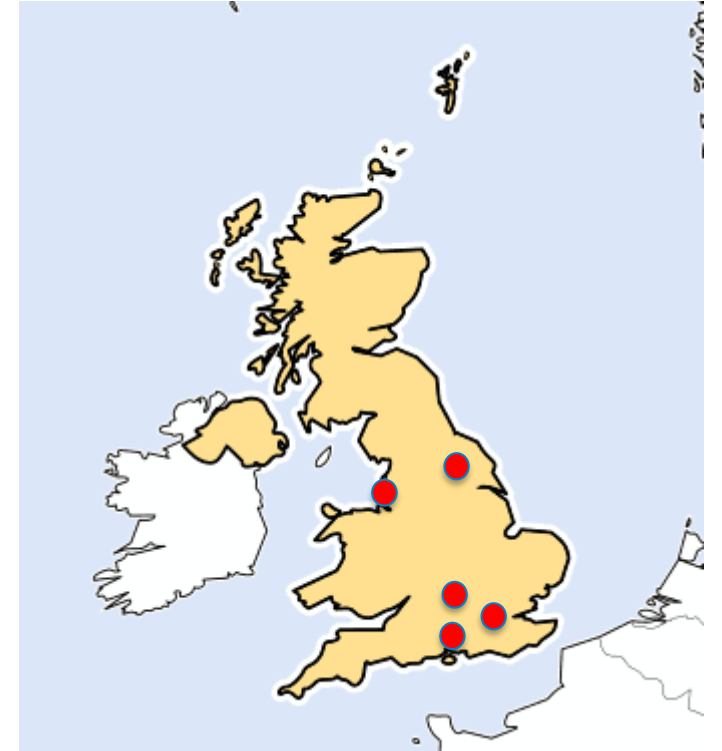


Established models:

- Typhoid/paratyphoid
- Malaria
- Whooping cough (*Pertussis*)
- Meningitis (*Neisseria lactamica*)
- Flu
- RSV
- Rhinovirus
- *Streptococcus pneumoniae*
- BCG (tuberculosis)

Newly developed models:

- Leishmania
- Non-typhoidal *Salmonella*



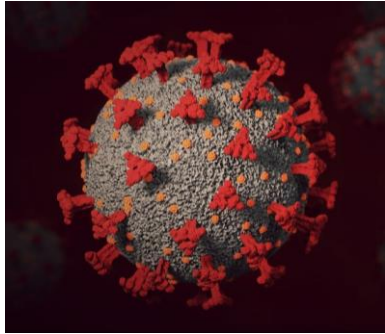
£3.5m, 6 year MRC & BBSRC-funded network (current funding Wellcome Trust)

Support, develop and advocate the use of human infection challenge studies, in order to:

- Improve understanding of infectious diseases
- Enhance the development of vaccines & treatments for diseases of global importance

Outputs: building a community, expertise sharing, funding and supporting early career researchers, underpinning new model development, engaging with regulators/CMC/industry/ethics bodies to develop and enhance frameworks, public engagement.

Future directions



Pandemic planning



Biobanking &
resource sharing



Challenge
specific training



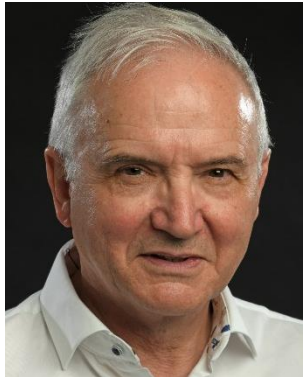
Challenge agent
manufacture



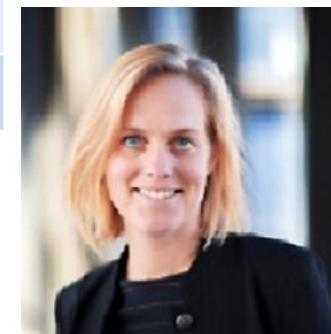
Vaccine
development
utility



Global legal,
regulatory and
ethical
frameworks



Name	Surname	Institution
Peter	Openshaw	Imperial College London (Director)
Andrew	Pollard	University of Oxford (Deputy Director)
Malick	Gibani	Imperial College London
Stephen	Gordon	Liverpool School of Tropical Medicine & Malawi-Liverpool-Wellcome Trust Clinical Research Programme
Cherry	Kang	CMC Vellore
Daniela	Ferreira	Liverpool School of Tropical Medicine
Robert	Read	University of Southampton
Meta	Roestenberg	Leiden University Medical Center
Patricia	Njuguna	PATH



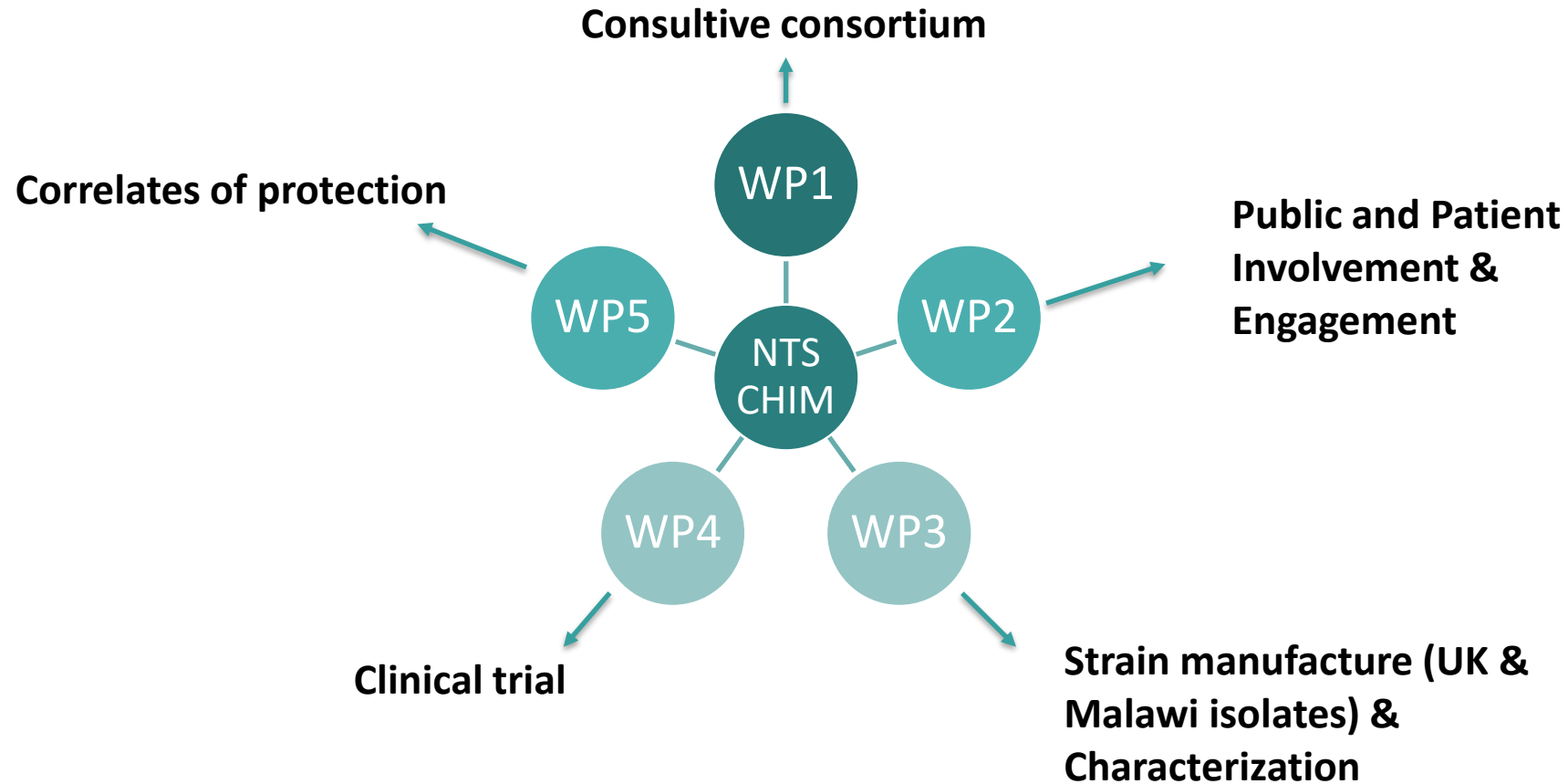
Setting up a new human infection challenge model: non-Typhoidal *Salmonella* (NTS)

Utilising collaborative networks

Imperial College
London



Study set-up





Consent
Medical history
Examination
Blood test
Urine Sample
Pregnancy test
Questionnaire
Ultrasound scan
Consent quiz
Letter to GP

Screening

Pre-Challenge

Continued consent
Issue study pack



Study plan

Challenge

Daily blood & stool cultures

Day 0 to 7
Inpatient
Quarantine

Treatment
if severe gastroenteritis
or other treatment
criteria*

Treatment
at Day 14 if not
diagnosed

Daily blood & stool cultures

Day 8 to 14
Daily Visits

Treatment

Salmonella diagnosis

Criteria: Temperature $\geq 38^{\circ}\text{C}$ for ≥ 12 hrs or positive
blood culture for *Salmonella* Typhimurium
May occur at any point from Day 0 to Day 14
Treatment started at time of diagnosis

Medical review
Blood sample
Stool sample
Questionnaire

Day 28

Clearance
cultures

Day 90

Follow up visit
Medical review
Blood sample
Questionnaire

Follow up visit
Medical review
Blood sample

Day 180

Day 365

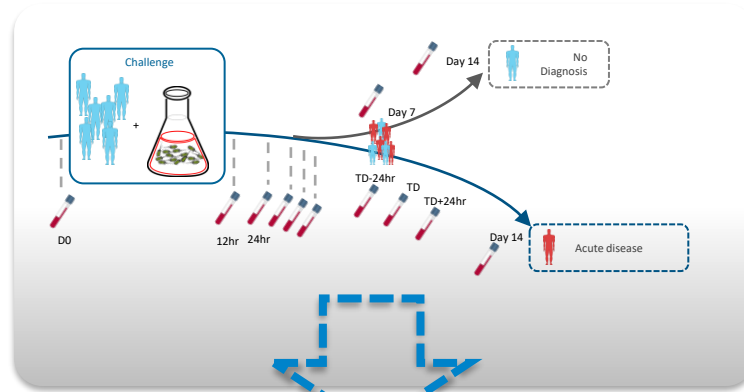
Follow up visit
Medical review
Blood sample

Accelerating vaccine development

- Primary aim to develop a model for future vaccine assessment
- Opportunity to:
 - Study host-pathogen interactions in closely monitored environment
 - Compare clinical response to different pathovariants of *S. Typhimurium* (diarrhogenic vs. invasive strains)
 - Define correlates of protection

Vaccines

Typoid (VI Capsular Polysaccharide)-Tetanus Toxoid Conjugate Vaccine
Typbar TCV PFS
For intramuscular use only



Diagnostics

Which Sample? Which Target? Which Method? What Issues?

- Can it be made more cost effective?
- Can we use Genomics for Optimize Media?
- Can we identify new Antibodies?
- Can we make better Antibody?
- Will it work combined with bio-led culture?
- Is identifying DNA sensitive enough?
- Standard Protocols or Best Practices?
- Is it too Expensive?

Disease Pathogenesis

ColB
PliA
PliB

Omics

Metabolomics/Proteomics

Genomics

Transcriptomics

Cellular Immunity

Flow cytometry plot showing $CD14^+$ vs $CD14^+$ cells.

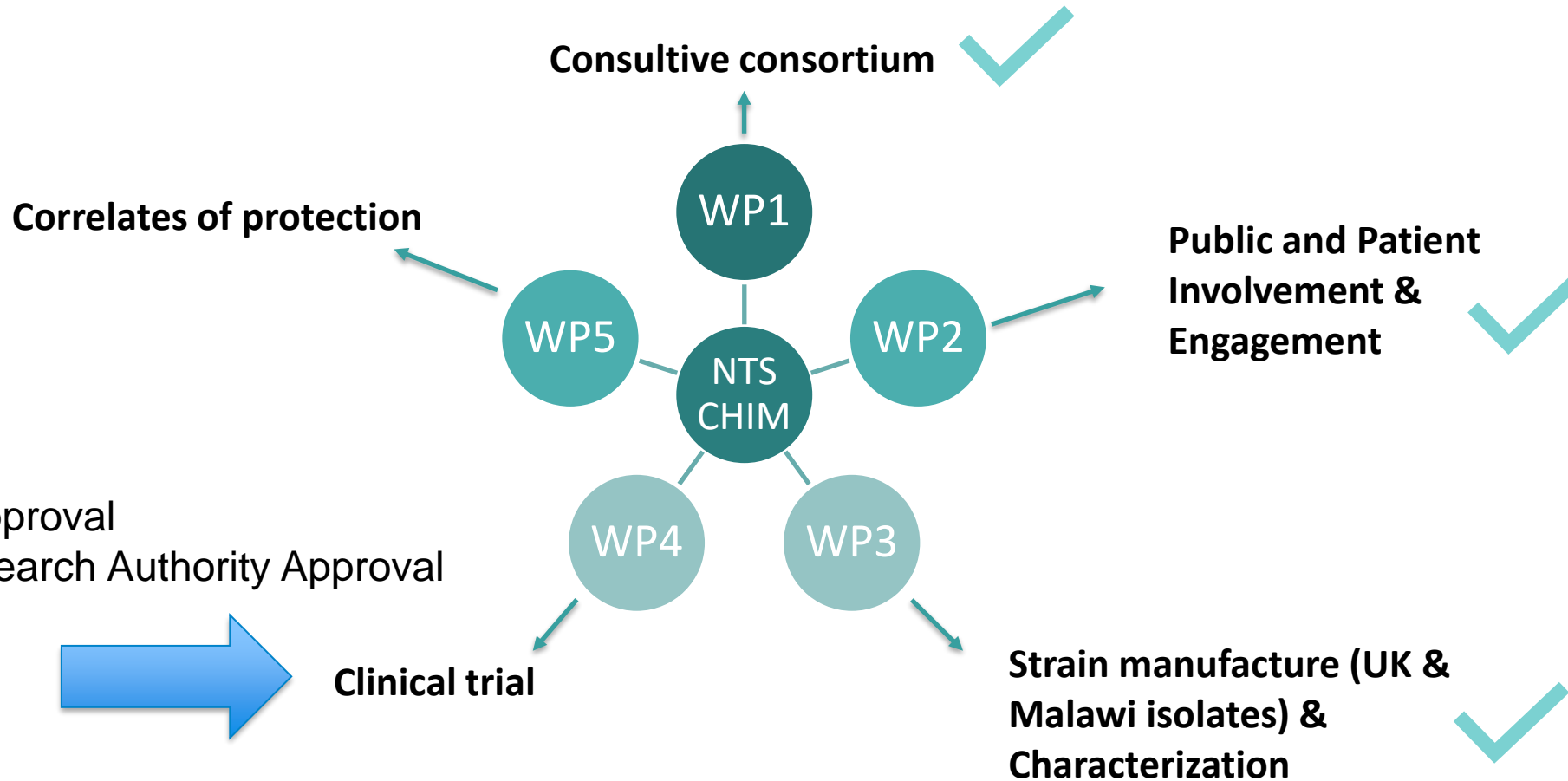
Serology & Cytokines

IFN-gamma (log₂ FC) vs Timepoint

log₁₀ ELISA units/mL vs Timepoint

- Microbiome
- Shedding & transmission

Study set-up



- Sponsor Approval
- Health Research Authority Approval

- Chants study team (Imperial College London):
 - Dr Malick Gibani, Prof Graham Cooke, Dr Chris Smith, Robert Varro, Anna Rydlova
 - Collaborators: Prof Chris Chiu (Imperial), Dr Robert Choy (PATH), Prof Jay Hinton (University of Liverpool), Prof Andrew J Pollard (University of Oxford), Prof Melita Gordon (Malawi-Liverpool-Wellcome Trust Clinical Research Programme).
 - Funding: Wellcome Trust

