

Immunopathogenesis of COVID-19

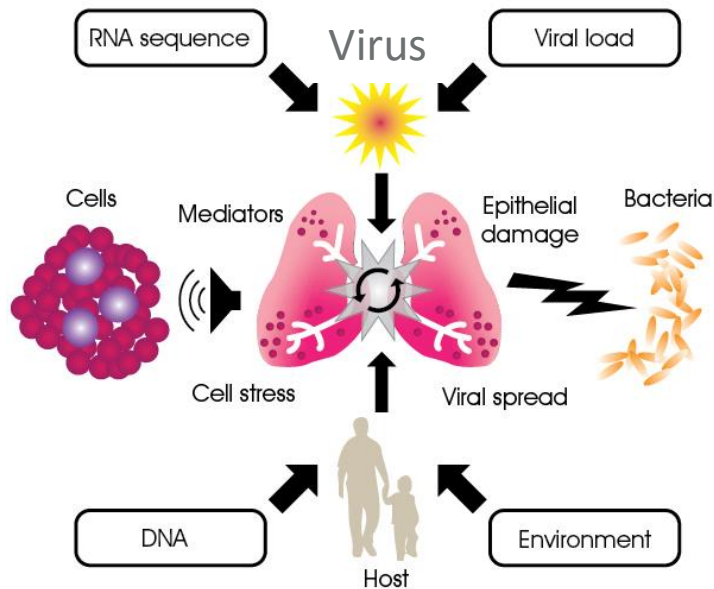
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What determines disease severity?



Need to study host, pathogen and co-pathogen

MOSAIC

255 patients with influenza-like illness
172 (65%) with PCR-confirmed influenza

45 page
booklet
(Flu-CIN)

Extensive clinical
information

Samples from
multiple timepoints

Respiratory, blood
and other samples

8000
sample
biobank

Virology and
genomics

Molecular
bacteriology

Mediators and cellular
immunology

Transcriptomics

Host
genomics

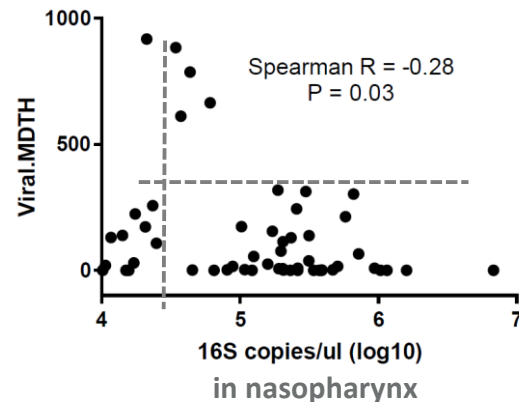
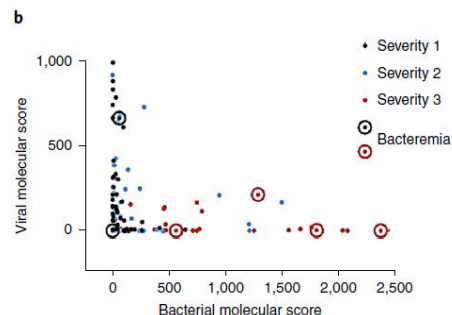
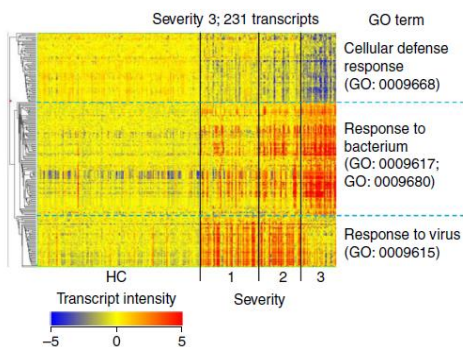
matched healthy controls, ILI controls

*A comprehensive study of the causes of
severe pandemic influenza*

21,000,000 data points

Progression of whole-blood transcriptional signatures from interferon-induced to neutrophil-associated patterns in severe influenza

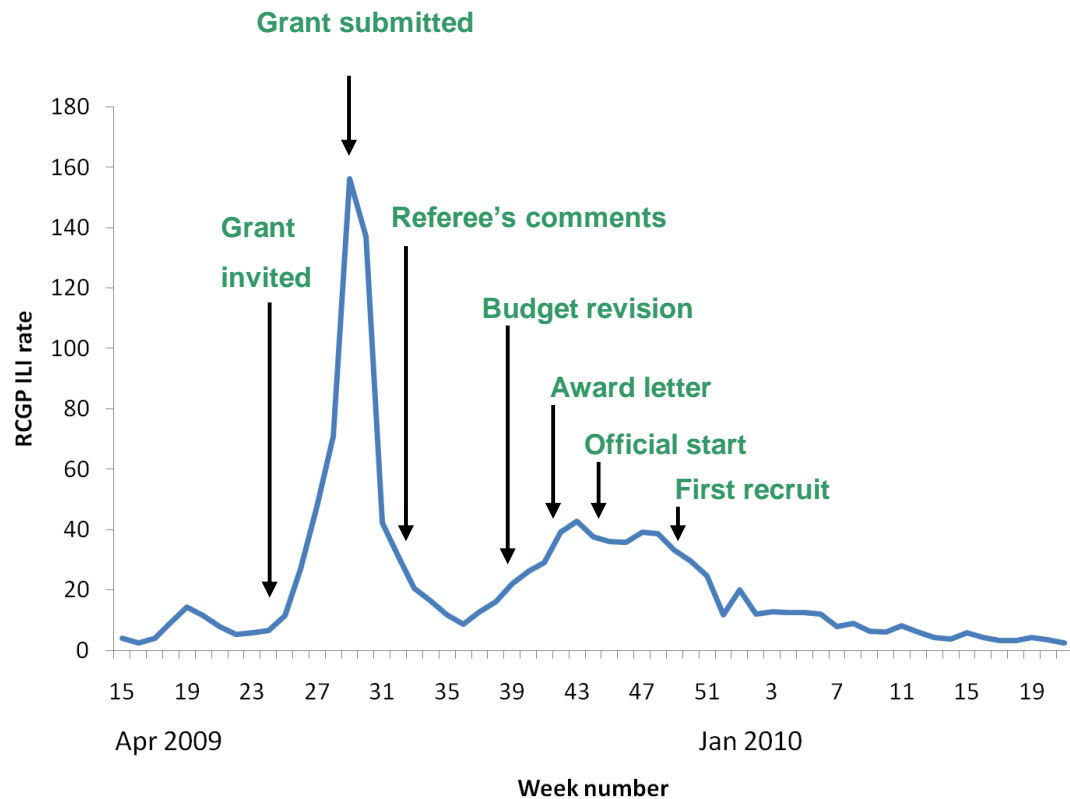
Jake Dunning^{1,8}, Simon Blankley², Long T. Hoang¹, Mike Cox³, Christine M. Graham², Philip L. James³, Chloe I. Bloom², Damien Chaussabel⁴, Jacques Banchereau⁵, Stephen J. Brett⁶, MOSAIC Investigators⁷, Miriam F. Moffatt³, Anne O'Garra^{2*} and Peter J. M. Openshaw^{1*}



Conclusions:

1. 'Viral' signal is only in those with low NPA bacterial load
2. 'Bacterial' signal is not seen in those with low NPA bacterial load

MOSAIC Timelines



ISARIC preparedness platform



Kenny Baillie

- Developed in the wake of the flu pandemic
- Uses WHO-approved clinical data tool from MOSAIC
- Sleeping platform, launched 2011
- Pre-agreements in place with >200 UK hospitals



Calum Semple



BILL & MELINDA
GATES *foundation*



Calum Semple

CO-CIN and ISARIC-4C

77 933

Number of patients (all tiers)

75 522

Number of patients (Tier 0)

697

Number of patients (Tier 1)

1 714

Number of patients (Tier 2)



Tier 0

- Demographic data
- Outcome
- Comorbidities



Tier 1

Single biological sample set:

- Plasma/serum
- Nasal swabs
- Urine + Stool



Tier 2

- Serial biological sample sets

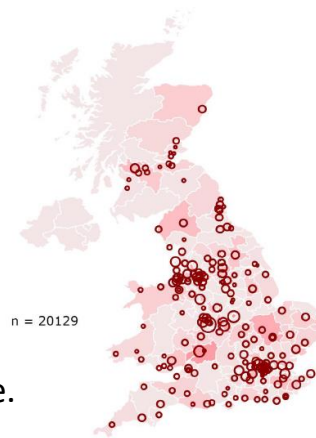
https://isaric4c.net/sample_access.html

Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study

- People of all ages admitted to 208 hospitals in the UK
- Patient data collected and uploaded from start of admission by **2648** frontline NHS clinical and research staff and volunteer medical students

22nd April 2020:

- **20,133 patients** with confirmed SARS-CoV-2
- **34%** of cases in the UK
- **Median age:** 73 years, Male/Female 60/40
- **Outcome:**
 - 41% discharged alive
 - 26% died
 - 34% still in hospital at reporting date.



*Annemarie
Docherty*



Calum Semple



Kenny Baillie



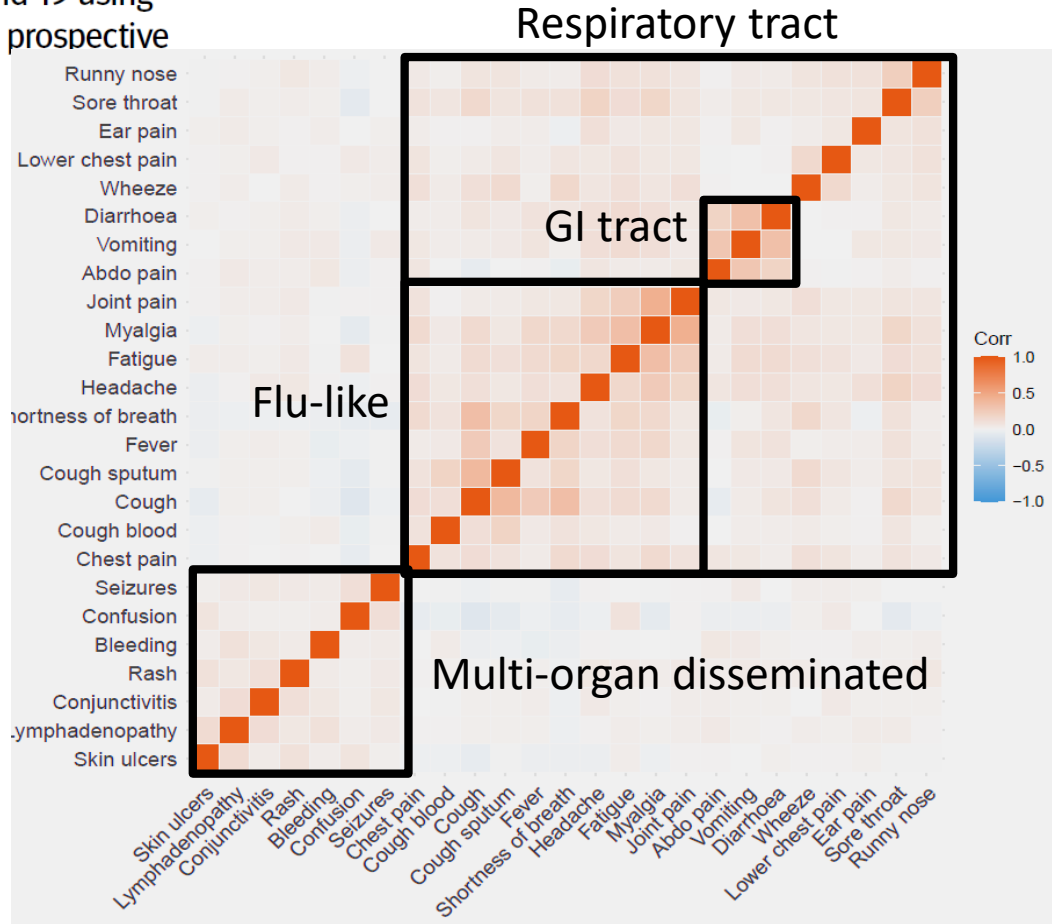
Peter Openshaw

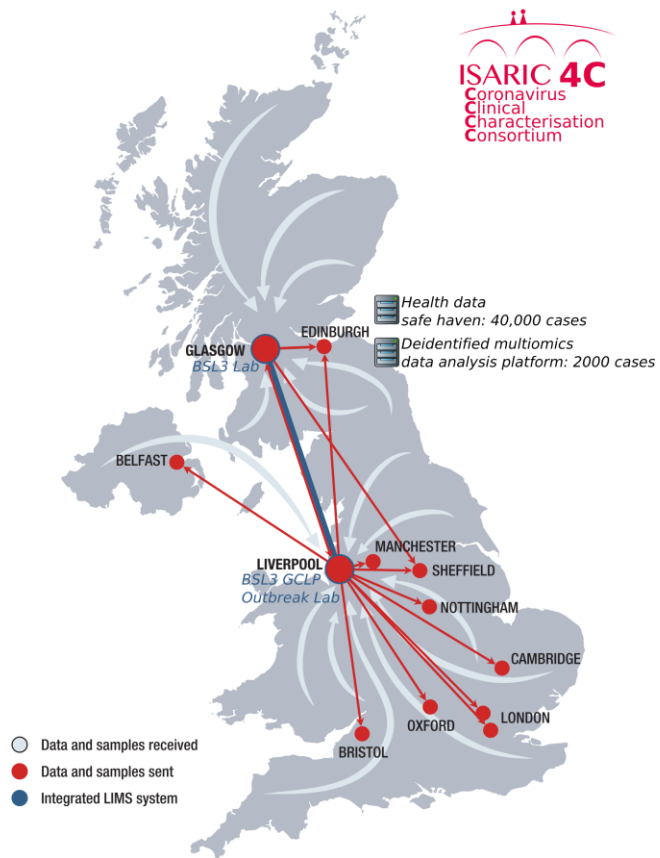
Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study

the **bmj**

doi:[10.1136/bmj.m1985](https://doi.org/10.1136/bmj.m1985)

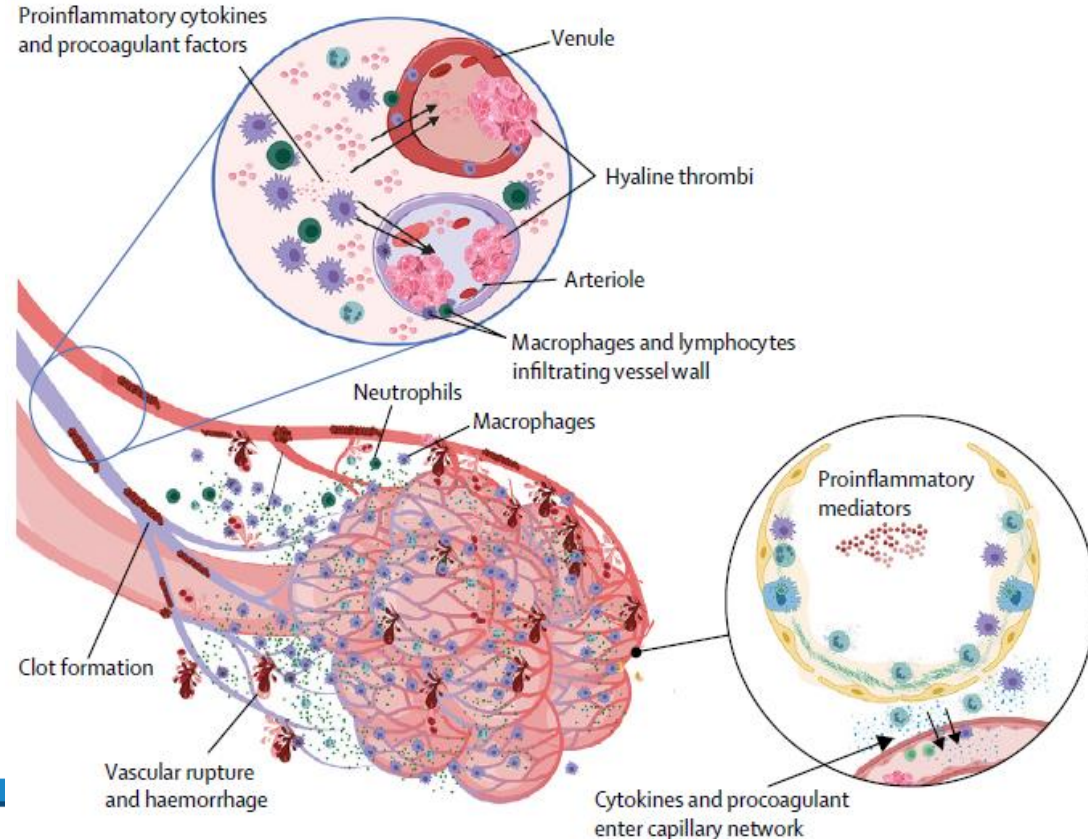
<http://dx.doi.org/10.1136/bmj.m1985>





Potential mechanisms

- Diffuse alveolar damage attracts macrophages and neutrophils
- Hyaline deposition, endothelial infection/injury and secretion of inflammatory mediators
- Microthrombi incompletely cleared by fibrinolysis (D-dimer)
- Progressive occlusion of small vessels, right ventricular stress



Genetic mechanisms of critical illness in Covid-19

E Païro-Castineira, S Clohisey, L Klaric, A Bretherick, K Rawlik... The GenOMICC Investigators, The ISARIC-4C Investigators, The Covid-19 Human Genetics Initiative, ... PJM Openshaw, MG Semple, V Vitart, JF Wilson, J. Kenneth Baillie

Steroids benefit those with respiratory failure, but may harm milder cases. Severity is largely immune-mediated and is strongly heritable

Genome-wide association study, 2244 critically-ill Covid-19 were ancestry-matched to UK Biobank; confirmed in GWAS comparisons with two other population control groups

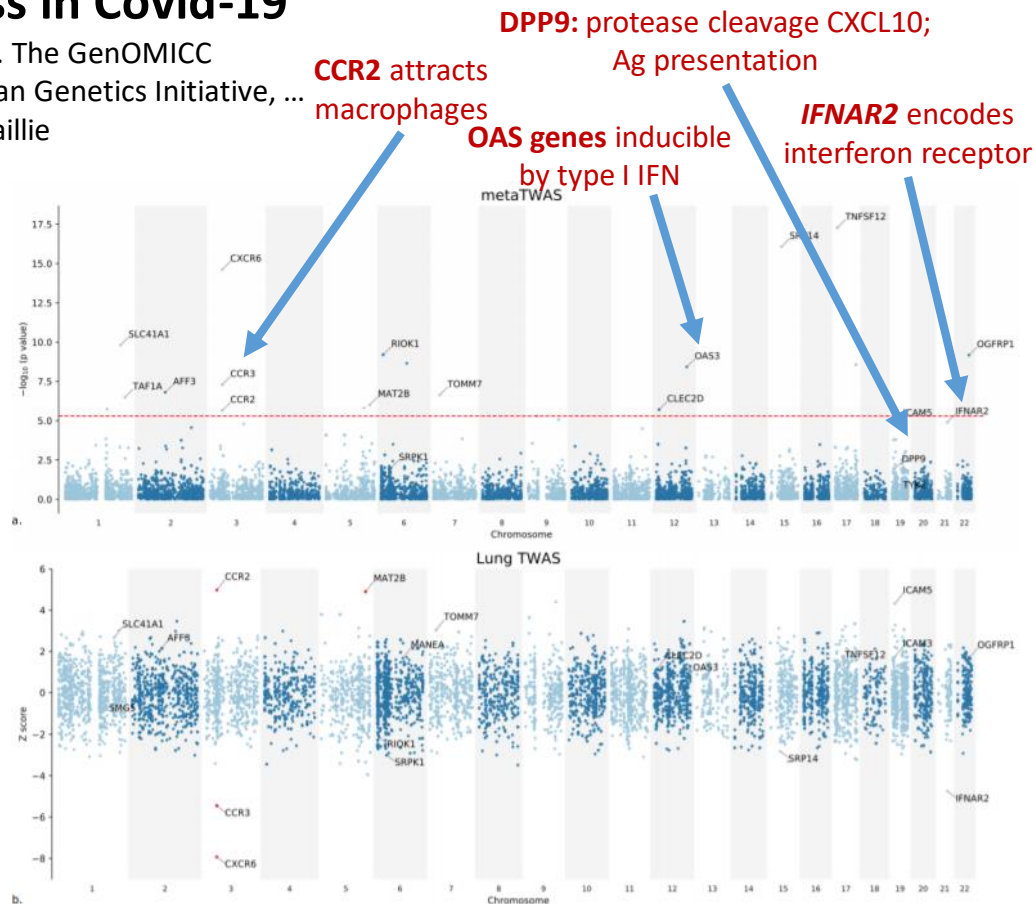
Found three novel associations:

1. Chr19p13.3 ($p = 3.98 \times 10^{-12}$) dipeptidyl peptidase 9 (DPP9)
2. Chr12q24.13 ($p = 1.65 \times 10^{-8}$) antiviral restriction enzyme activators (OAS1, OAS2, OAS3)
3. Chr21q22.1 ($p = 4.99 \times 10^{-8}$) interferon receptor IFNAR2

Also confirmed 3p21.31 locus (rs73064425, $p = 4.77 \times 10^{-30}$).

Evidence of a causal link from low expression of IFNAR2 and high expression of TYK2 to life-threatening disease.

Transcriptome-wide association in lung tissue of the monocyte/macrophage chemotactic receptor CCR2 with severe Covid-19



INFLAMMAGE study, EMINENT consortium

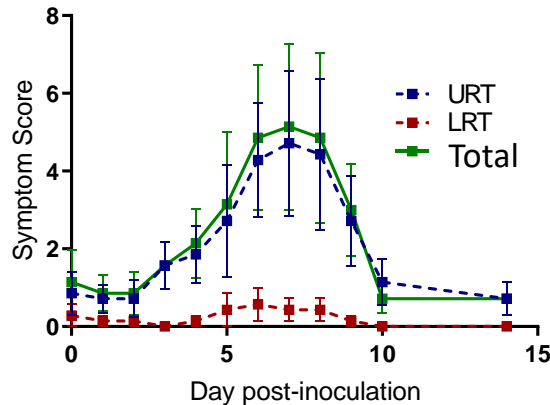
Symptom scores

Effect of age on
outcome of RSV
human challenge

Viral load (qPCR)

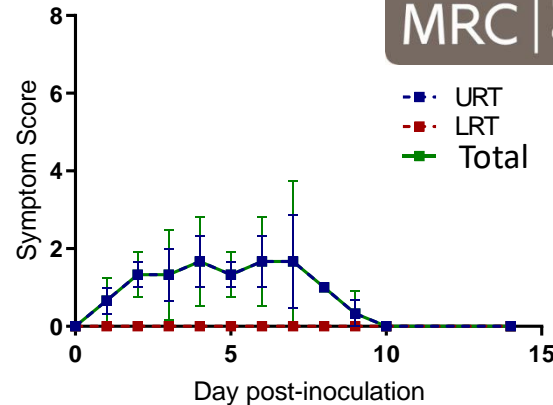
Dr Chris Chiu et al.

Elders 61-71y



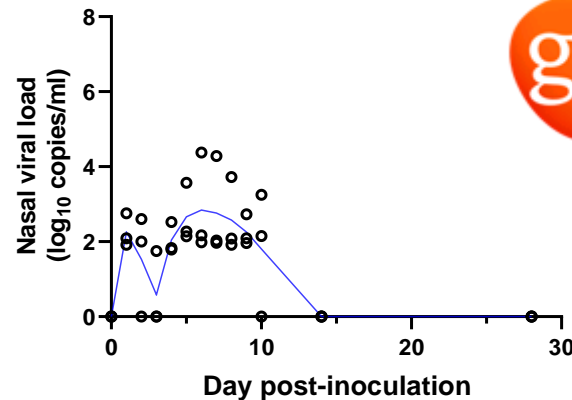
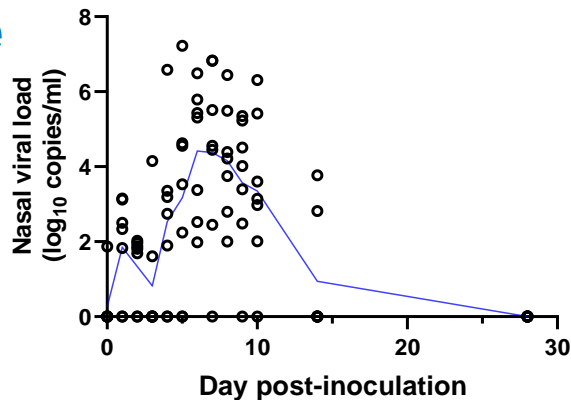
Adults 24-52y

B)



MRC

Medical
Research
Council



Acknowledgements

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- Graham Cooke
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- Dan Solanki
- Seema Vekaria
- Emma Smith

ISARIC

- 2648 frontline volunteers
- ISARIC outbreak lab volunteers
- Kenny Baillie
- Calum Semple
- Ewen Harrison
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- Shona Moore
- Antonia Ho

Thank you

To the patients and their relatives