Imperial College London

Les Pensières, Annecy, France
29th November, 2018

Pathogenesis and impact of respiratory viruses

Peter Openshaw

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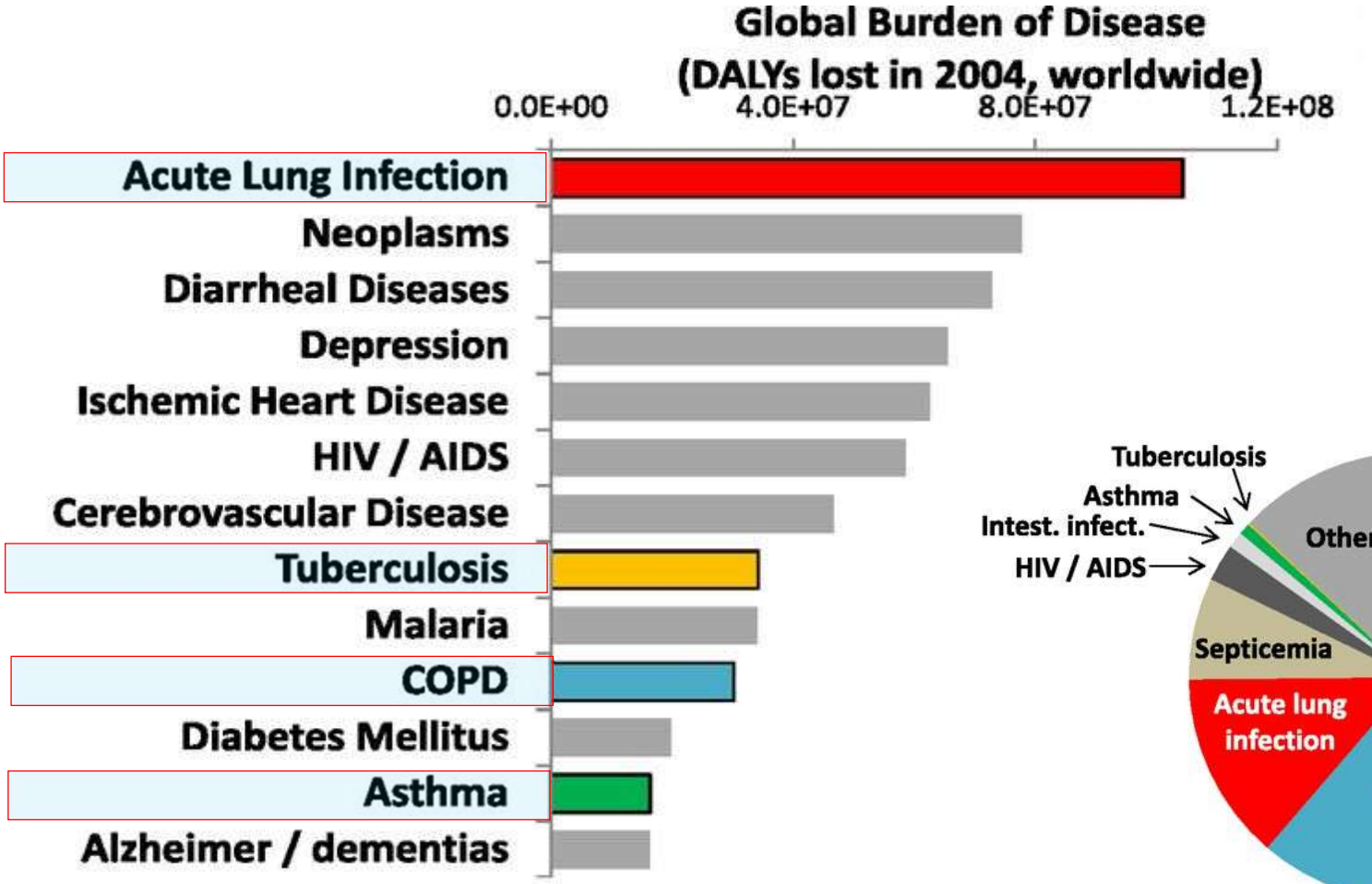
Respiratory Infection and the Impact of Pulmonary Immunity on Lung Health and Disease

Joseph P. Mizgerd[1]

Am J Respir Crit Care Med Vol 186, Iss. 9, pp 824–829, Nov 1, 2012



Deaths due to infection or lung disease (US, 2005)

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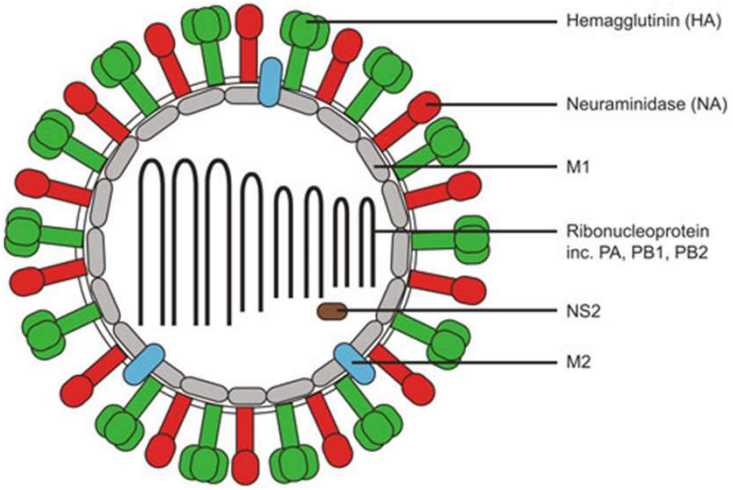
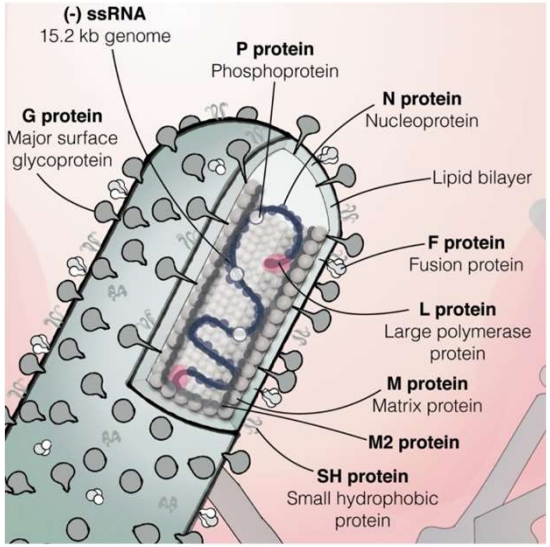
Influenza vs respiratory syncytial virus

Influenza



- No re-infection by same strain
- Imperfect vaccines:
  - Vaccine-induced immunity rapidly wanes
  - Mainly homotypic immunity
  - Annual vaccination required

RSV



- Recurrent re-infection with similar strains
- No vaccine
  - Poor immunogenicity
  - Vaccine-enhanced disease
  - Very active research field

Lambert, et al. *Front Immunol* (2014)


Human
RSV bronchiolitis

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RSV interference with host immune response

Non-structural proteins

- NS1 disrupts IRF3 binding to the IFNβ promoter
- NS2 protein binds RIG-I, blocking innate signalling
- NS1/2 enhance degradation of STAT2, terminating innate response
- NS1/2 inhibits cDC maturation, inhibiting APC functions

Surface glycoproteins

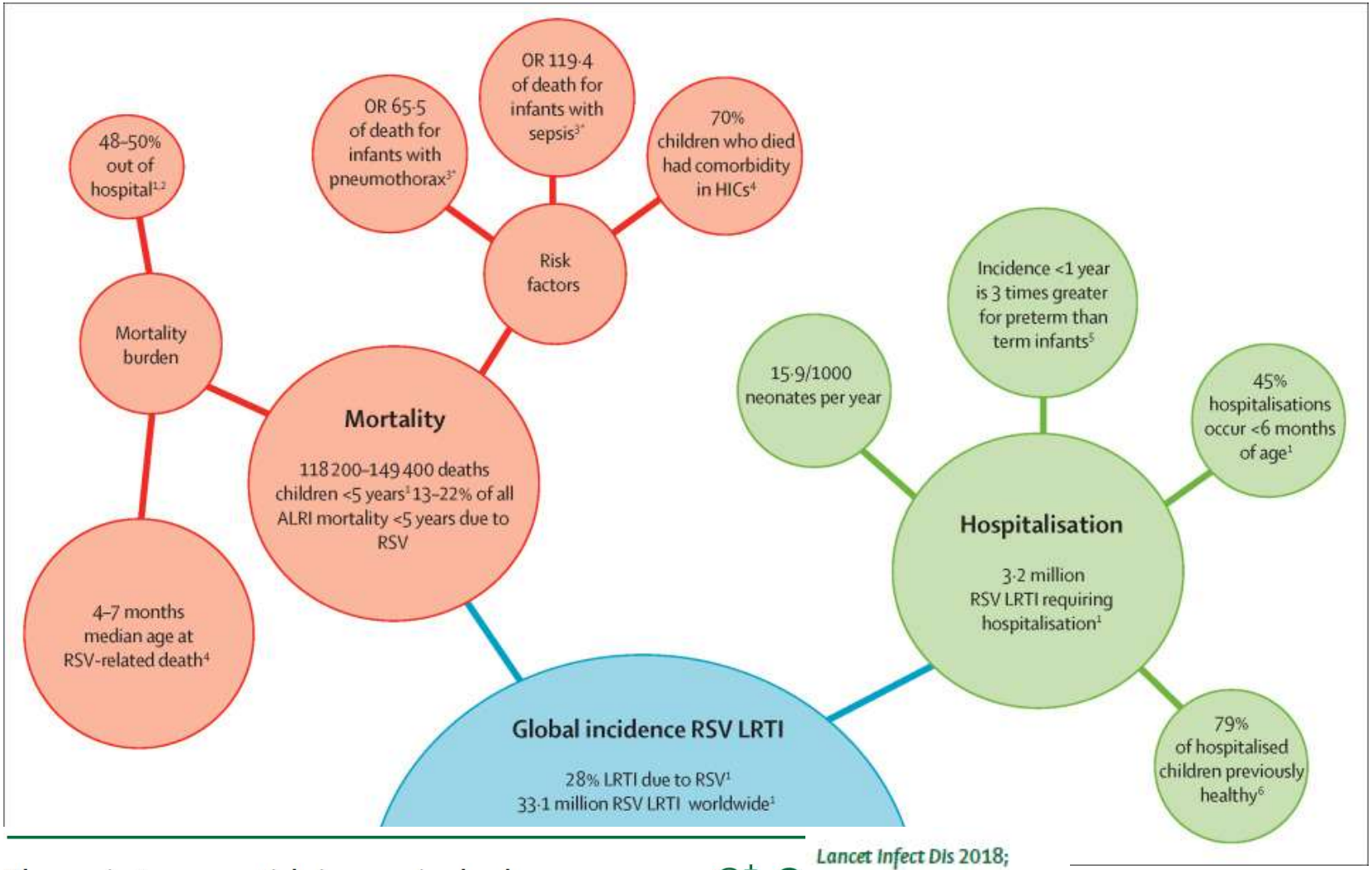
- G protein binds to CX3CR1 on pDC/cilliated cells
- Secreted G acts as a decoy for antibody
- F binds to TLR4, possibly causing innate desensitisation

Internal proteins

- N disrupts the synapse between CD4 and CD8 cells

Openshaw, P.J., Chiu, C., Culley, F.J., and Johansson, C. **(2017)**
Protective and harmful immunity to RSV infection *Annu Rev Immunol 35*, 501–32

Global burden of RSV in children under 5 years of age



The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates

Natalie I Mazur, Deborah Higgins, Marta C Nunes, José A Melero, Annefleur C Langedijk, Nicole Horsley, Ursula J Buchholz, Peter J Openshaw, Jason S McLellan, Janet A Englund, Asuncion Mejias, Ruth A Karron, Eric AF Simões, Ivana Knezevic, Octavio Ramilo, Pedro A Piedra, Helen Y Chu, Ann R Falsey, Harish Nair, Leyla Kragten-Tabatabaie, Anne Greenough, Eugenio Baraldi, Nikolaos G Papadopoulos, Johan Vekemans, Fernando P Polack, Mair Powell, Ashish Satav, Edward E Walsh, Renato T Stein, Barney S Graham, Louis J Bont; in collaboration with Respiratory Syncytial Virus Network (ReSViNET) Foundation

Lancet Infect Dis 2018; 18: e295–311

Published Online June 15, 2018

http://dx.doi.org/10.1016/S1473-3099(18)30292-5

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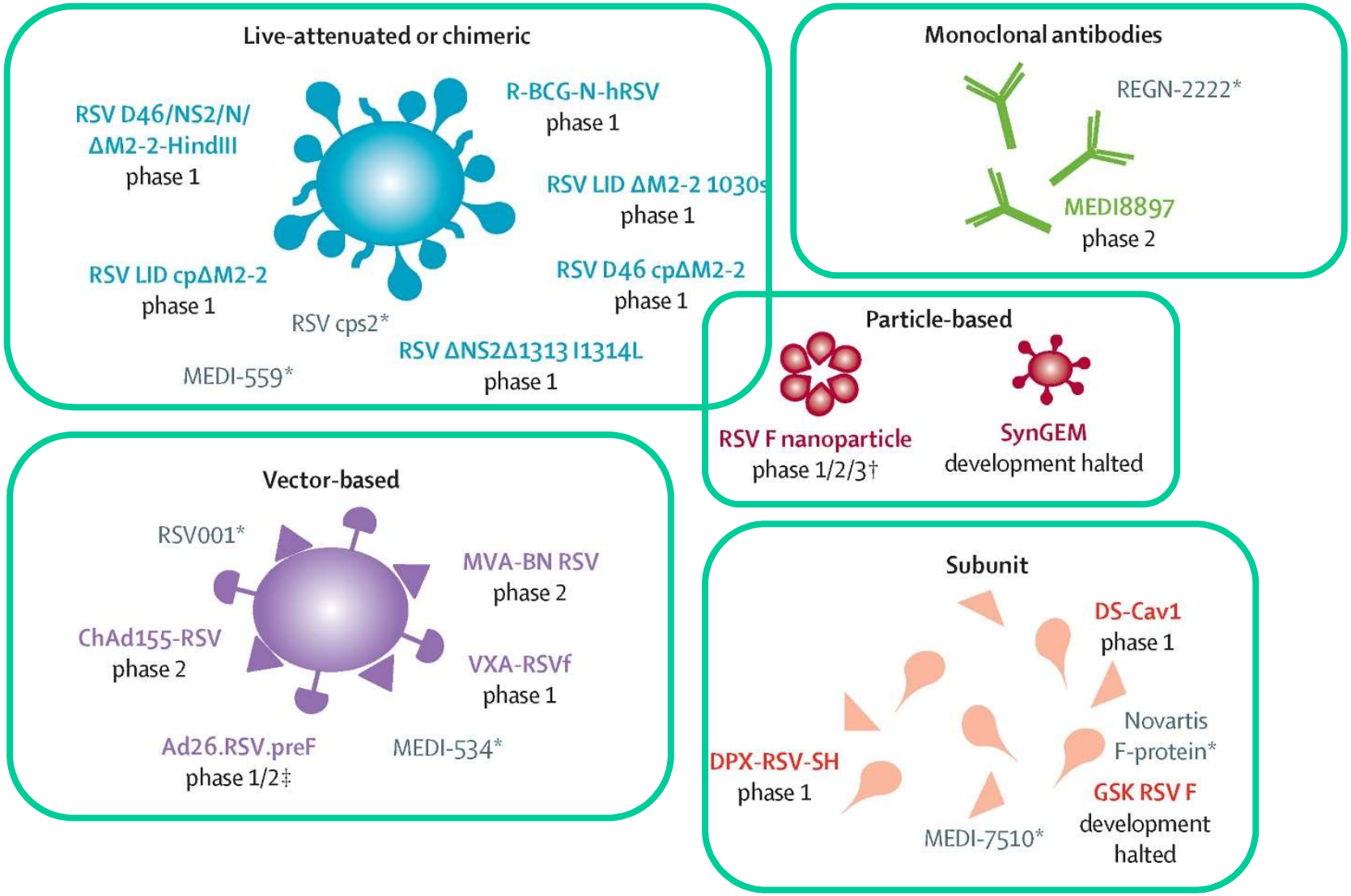
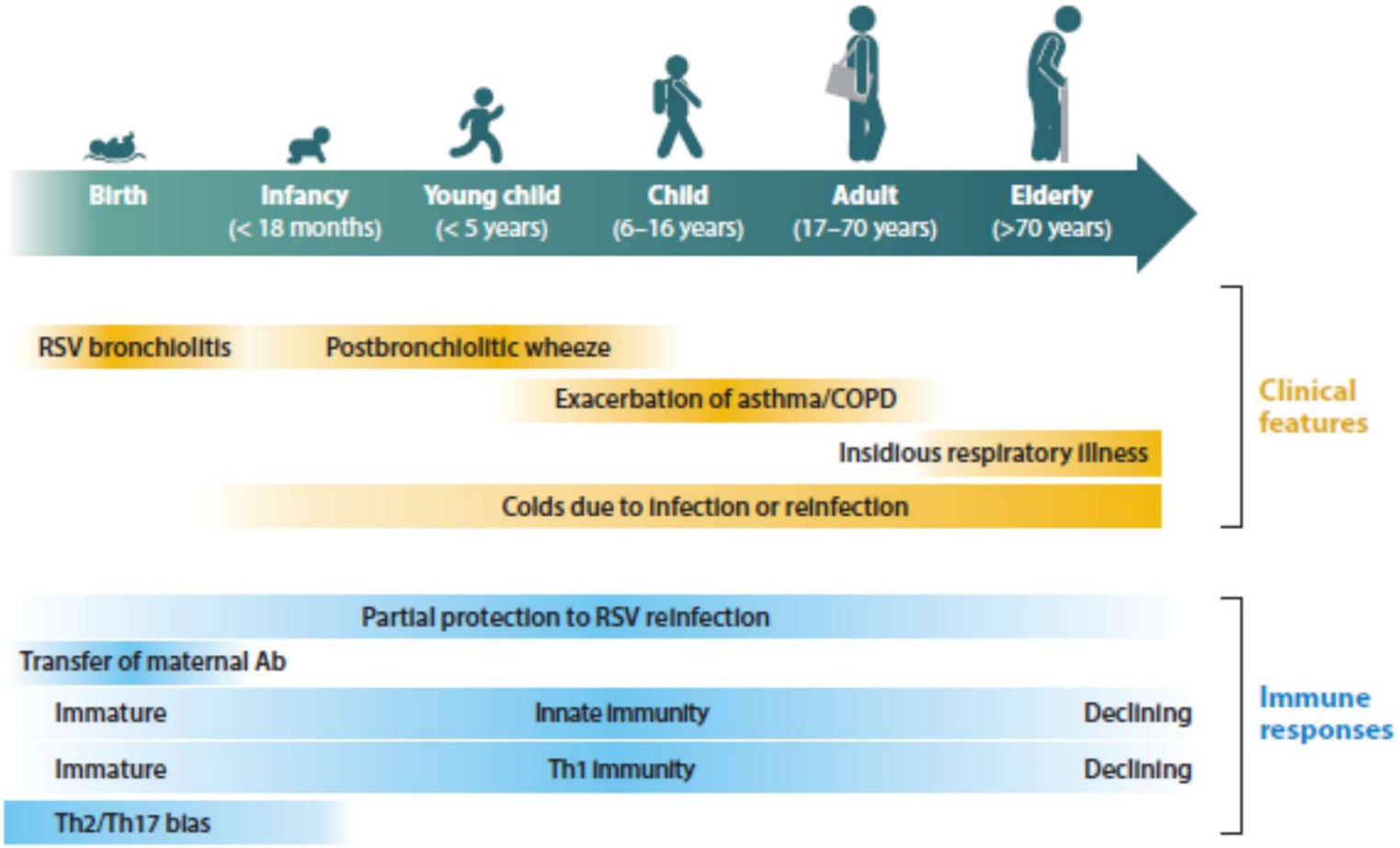


Age and RSV disease



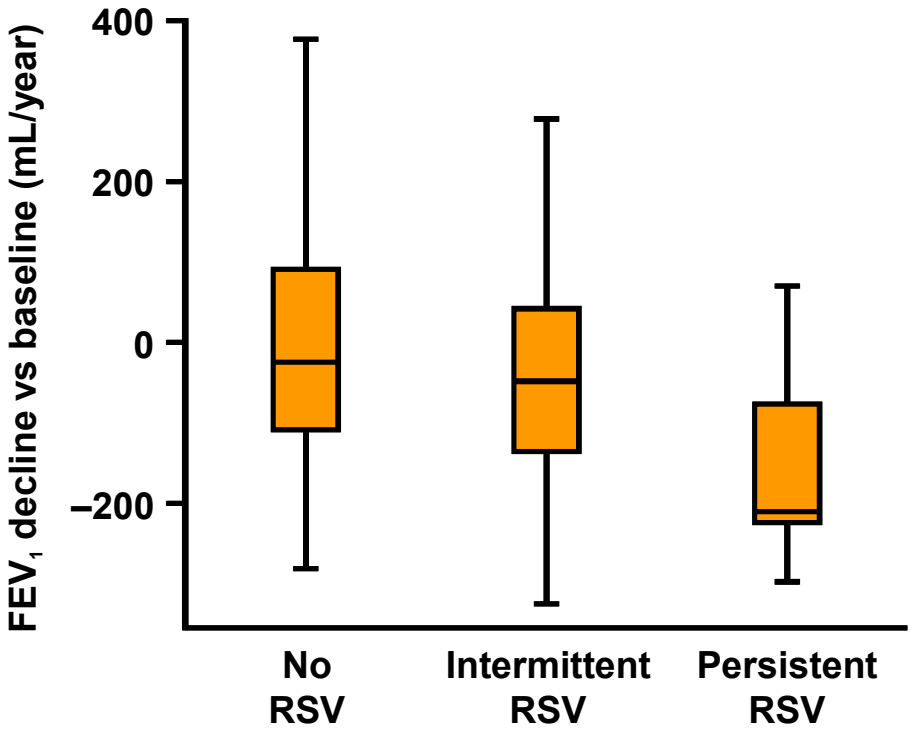
Openshaw, P.J., Chiu, C., Culley, F.J., and Johansson, C. **(2017)**
Protective and harmful immunity to RSV infection *Annu Rev Immunol 35*, 501–32

Respiratory Syncytial Virus, Airway Inflammation, and FEV_1 Decline in Patients with Chronic Obstructive Pulmonary Disease

Am J Respir Crit Care Med Vol 173. pp 871–876, 2006

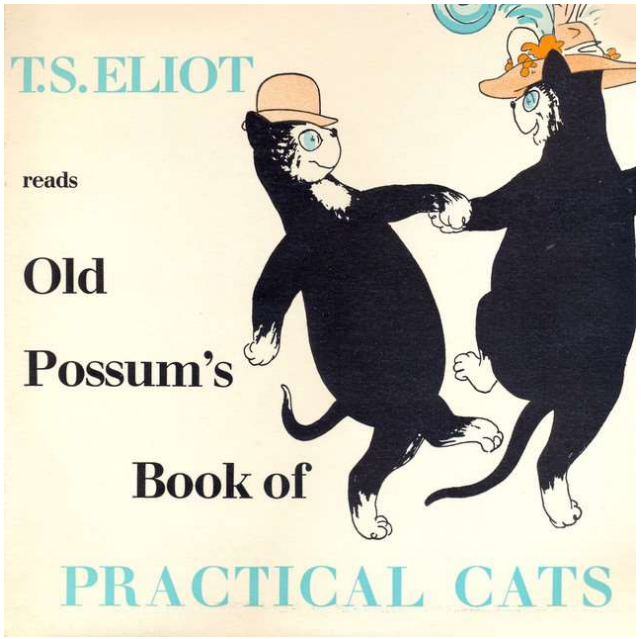
Tom M. A. Wilkinson, Gavin C. Donaldson, Sebastian L. Johnston, Peter J. M. Openshaw, and Jadwiga A. Wedzicha

- 88 COPD patients (from East London)
- Prospective study, 14-month duration
- Daily diary cards
- Sputum samples every 3 months
  - 272 samples collected
    - quantitative microbiology
    - RSV by qualitative PCR
- 34 patients were RSV negative throughout (RSV free)
- 42 patients had RSV detected in one or more samples, but not all sputa (intermittent RSV)
- 12 patients were RSV positive in all their samples ('persistent' RSV)



FEV_1 = forced expiratory volume in 1 second

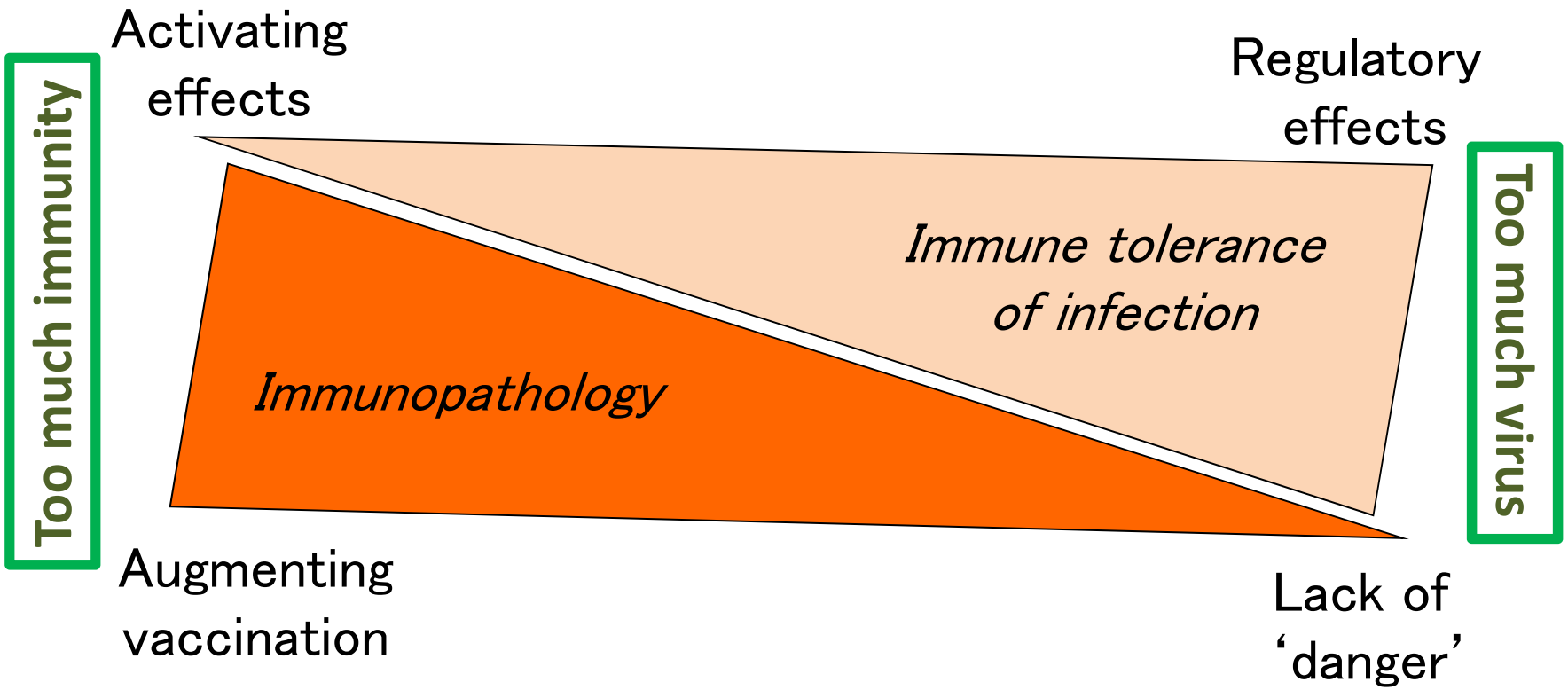
RSV: the ‘hidden paw’



Macavity's a Mystery Cat: he's called the Hidden Paw—
For he's the master criminal who can defy the Law.
He's the bafflement of Scotland Yard, the Flying Squad's despair:
For when they reach the scene of crime—Macavity's not there!

Antiviral B cell and T cell immunity in the lungs

Christopher Chiu & Peter J Openshaw



VOLUME 16 NUMBER 1 JANUARY 2015 NATURE IMMUNOLOGY

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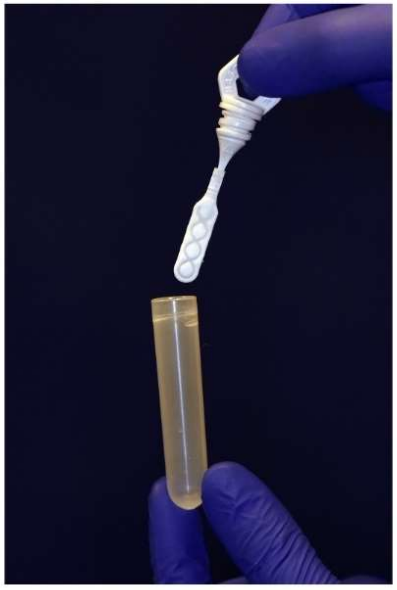
RSV load and immune mediator levels in nasal mucosal lining fluid

- 55 infants with bronchiolitis, one hospital, 2016/17 season.
- 30 were RSV infected:
  - 18 ‘moderate’ (ward care)
  - 12 mechanically ventilated ‘severe’

Up to 13 samples per patient



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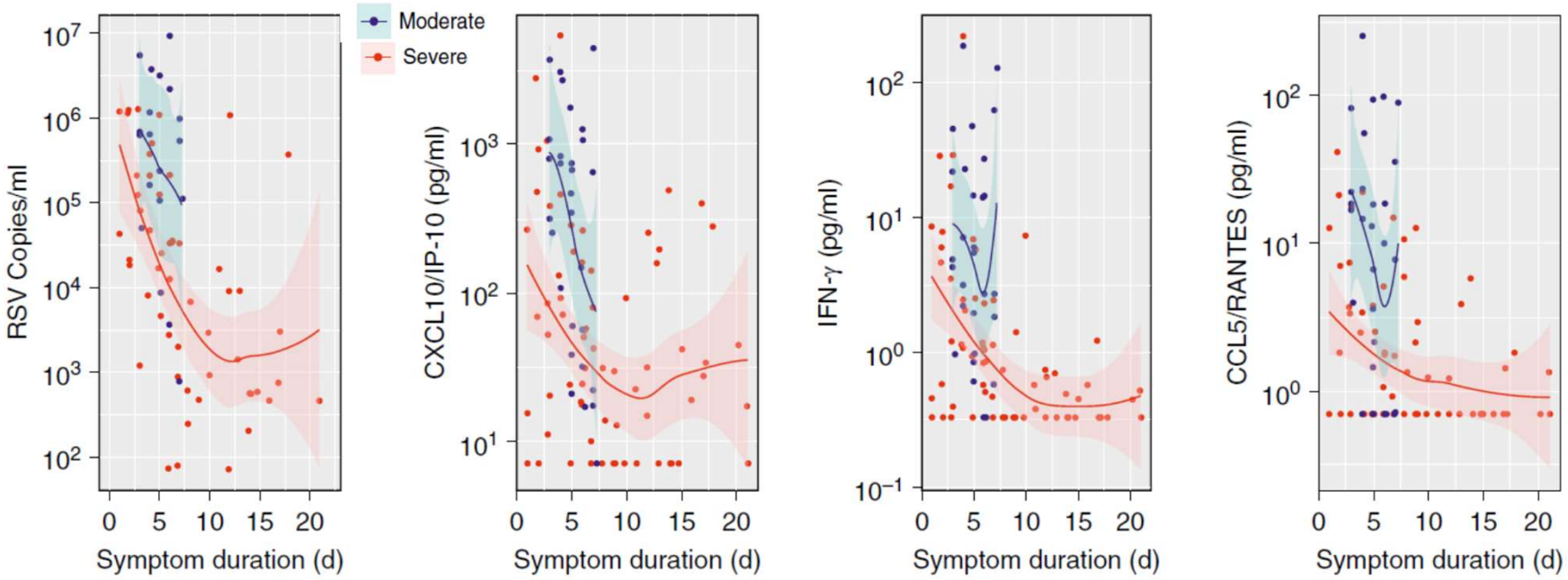
RSV load and immune mediator levels in nasal mucosal lining fluid



Compared to moderately ill children, those with **severe** RSV bronchiolitis have:

- **Lower** nasal viral loads
- **Reduced**, IP-10/CXCL10, CCL5 and IFNγ levels

Thwaites RS, … Rapeport G, Hansel TT, Nadel S, Openshaw PJ. **(2018)** Reduced Nasal Viral Load and IFN Responses in Infants with RSV Bronchiolitis and Respiratory Failure. Am J Respir Crit Care Med. 2018 doi: 10.1164/rccm.201712-2567OC

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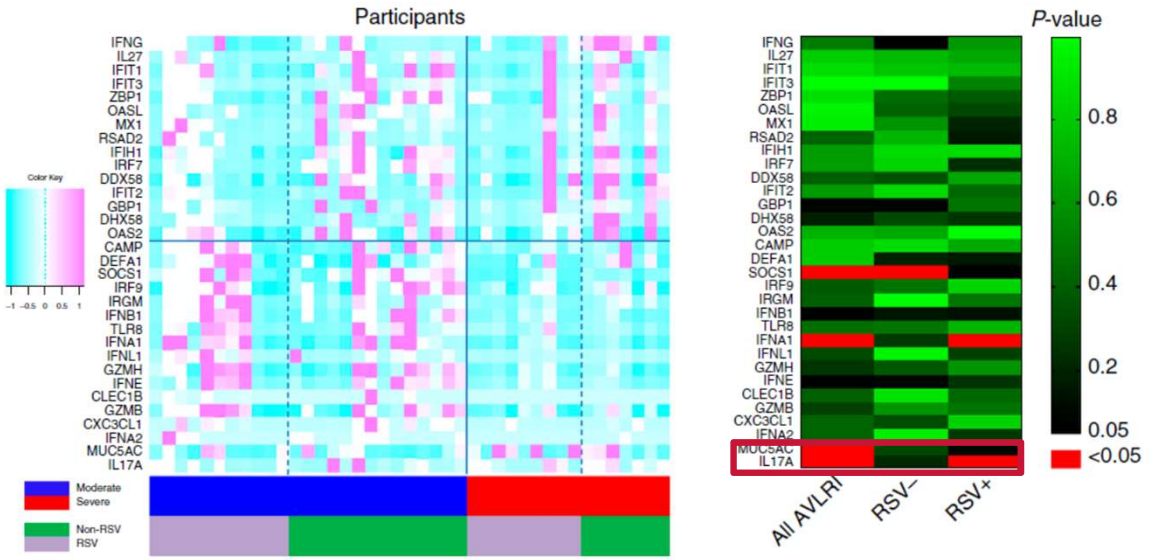
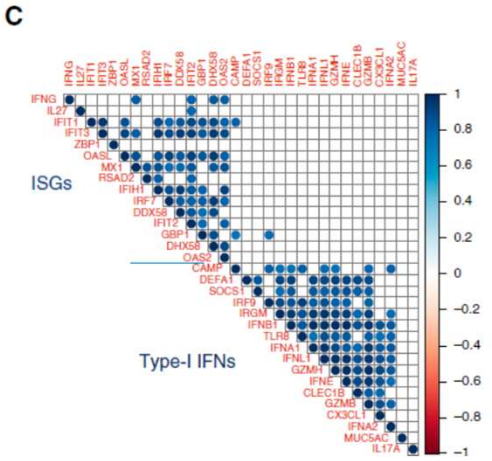
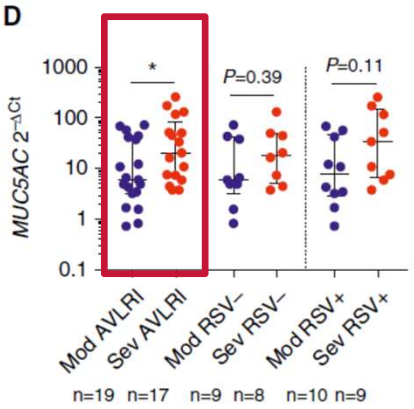
Gene expression in mucosal samples at enrolment

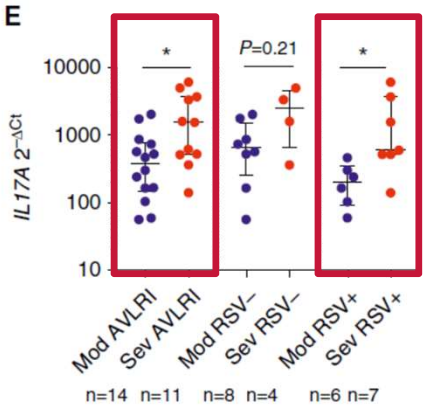


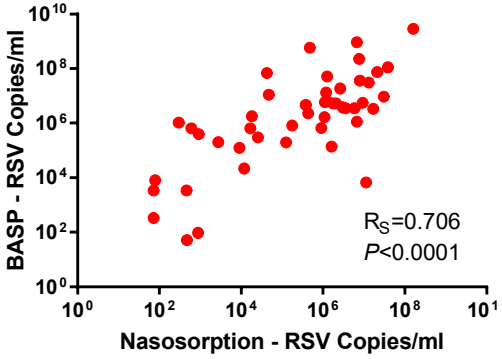
Compared to moderately ill children, those with **severe** bronchiolitis have:

increased
MUC5AC and *IL17A*



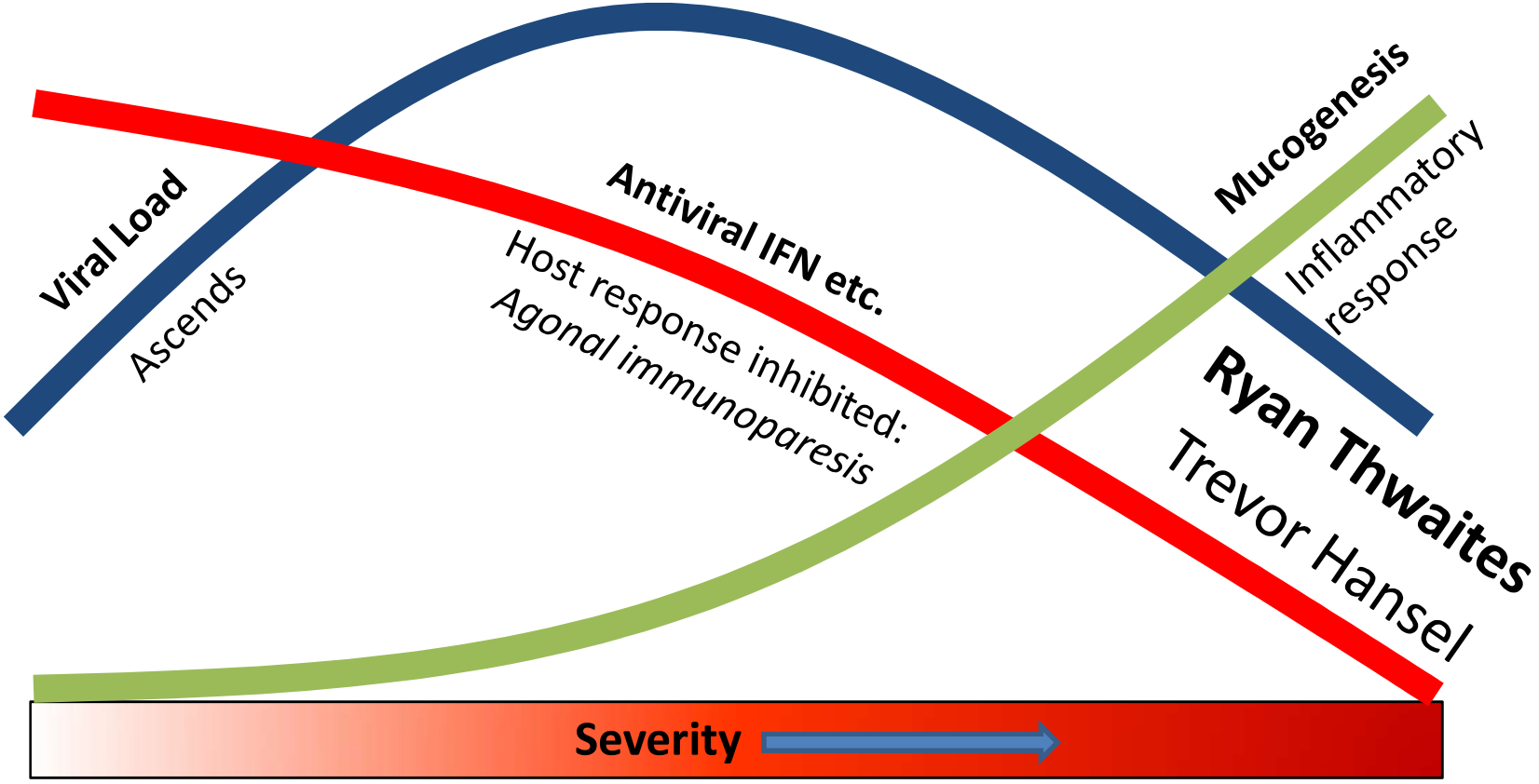






Infantile viral lung infection

Pathogenesis progresses through stages



Mild
(Community)

Moderate
(Hospitalised)

Severe
(Respiratory Failure)

The relationship between viral load and interferon breaks down in severe disease, where mucus production mediates airway plugging and respiratory failure

Infant study group

St Mary's Hospital

Cally Feather

Marwa Ghazaly

Farhana Abdulla

Simon Nadel

Imperial College London

Ryan Thwaites

Trevor Hansel

PULMOCIDE
INHALED RESPIRATORY MEDICINE

Kaz Ito

Matthew Coates

Lyndsey Cass

Garth Rapeport

Charing Cross

Alison Cox

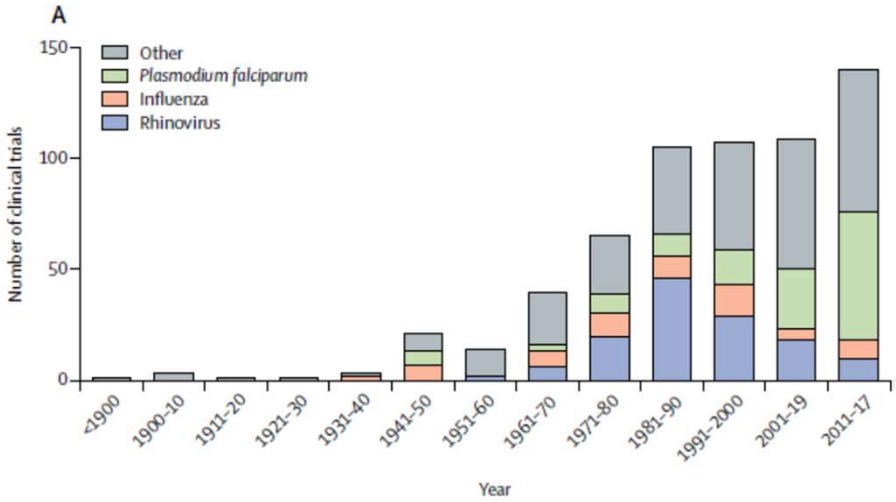
Panos Pantelidis

Pinglawathee Madona

David Muir

Experimental infection of human volunteers

Meta Roestenberg, Marie-Astrid Hoogerwerf, Daniela M Ferreira, Benjamin Mordmüller, Maria Yazdanbakhsh



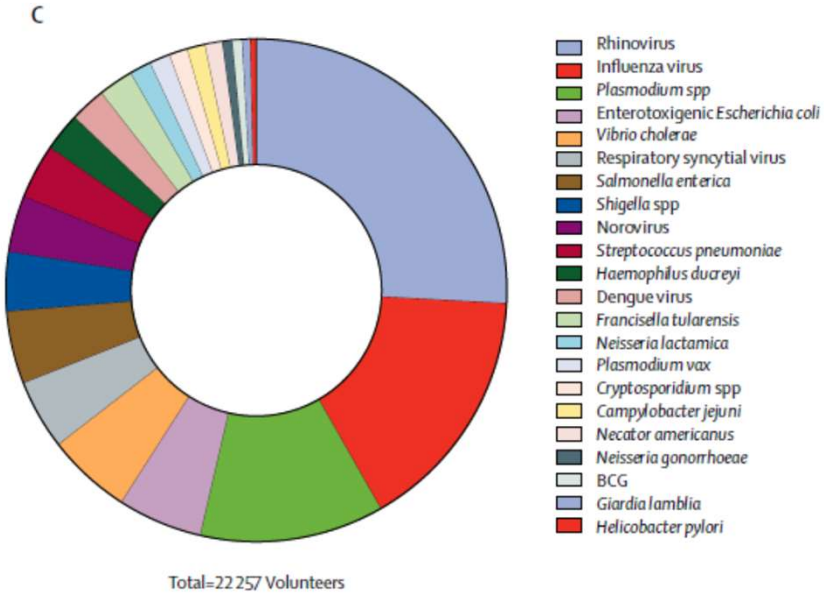
Lancet Infect Dis 2018

Published Online
June 8, 2018
http://dx.doi.org/10.1016/
S1473-3099(18)30177-4

NIH researchers infect volunteers with the flu virus in an ongoing effort to improve vaccines. AP PHOTO/CHARLES DHAR

Studies that intentionally infect people with disease-causing bugs are on the rise

By Jon Cohen | May. 18. 2016 , 3:00 AM



Total=22 257 Volunteers

HIC-Vac

The network

www.hic-vac.org

£3m, 4 yr MRC-funded network to:

Support, develop and advocate the use of Human Infection Challenge, to…

- Improve understanding of infections and the diseases they cause
- Enhance the development of new/better vaccines/treatments for LMIC infections

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MRC Medical Research Council

GCRF

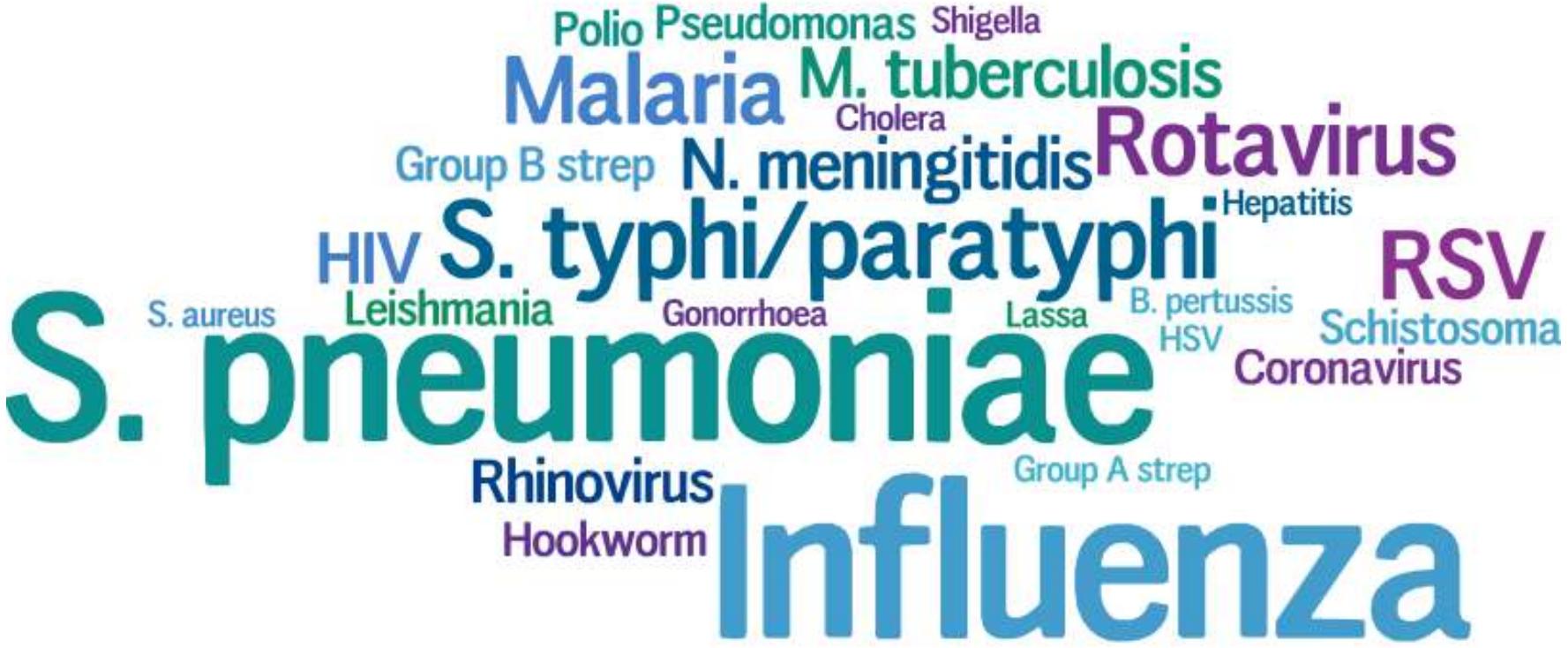
BBSRC bioscience for the future

University of Oxford

Network Management Board

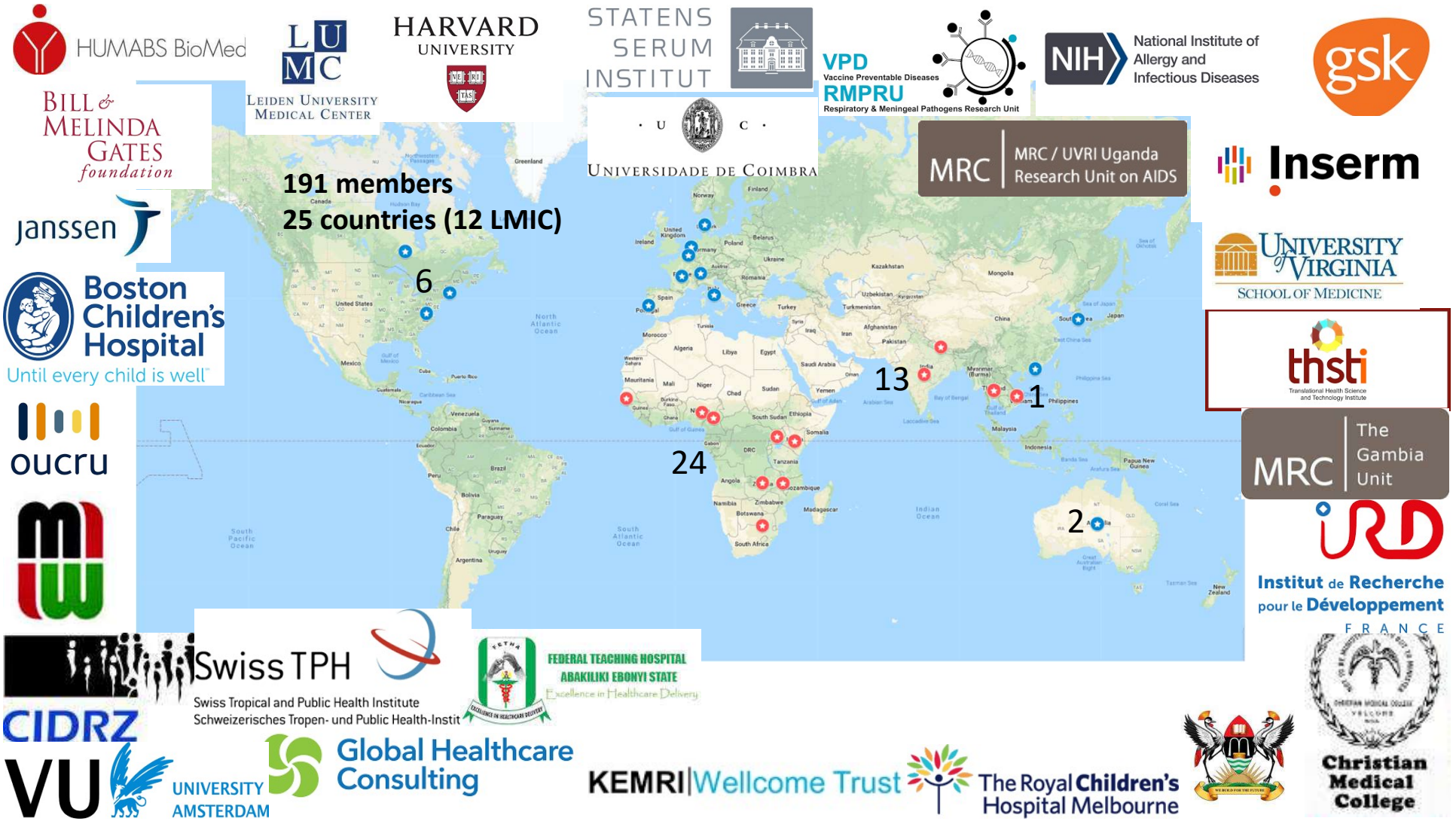
Name	Surname	Institution
Peter	Openshaw	Imperial College London (**Director**)
Andrew	Pollard	University of Oxford (**Deputy Director**)
Stephen	Gordon	Liverpool School of Tropical Medicine & Malawi-Liverpool-Wellcome Trust Clinical Research Programme
Cherry	Kang	Translational Health Science and Technology Institute, India
Daniela	Ferreira	Liverpool School of Tropical Medicine
Robert	Read	University of Southampton
Meta	Roestenberg	Leiden University Medical Center
John	Tregoning	Imperial College London

Human challenge network focus:



UK Members (n=114)

Non-UK Members: n=77



Membership

Total members September, 2018: 191, 25% LMIC

1. **Investigators (74)**: Independent current HIC studies
2. **Associates (69)**: Work with Investigators (Postdoc *etc.*)
3. **Affiliates (48):** Others interested in HIC studies

What we provide:

- Eligibility to apply for HIC-Vac funding
- Invitations to meetings and events
- Profile on website – networking and collaborations
- HIC-Vac mailing list for network notices

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Inoculation of volunteers with RSV

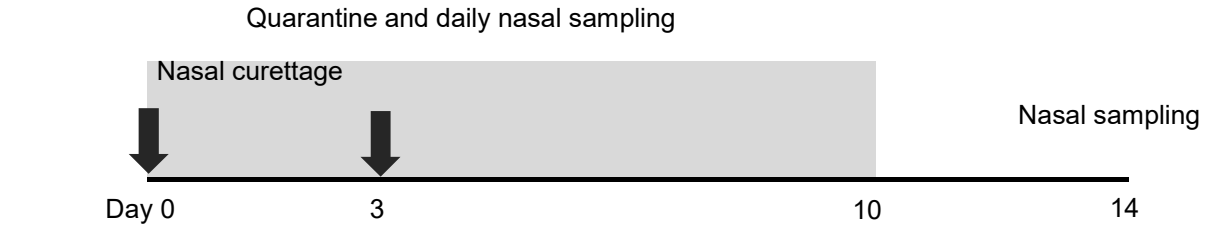
- **Healthy**, aged 18 – 55 years
- Intranasal 10^4 pfu RSV A **Memphis 37**
- Keep in seclusion from D-1 to D10
- Intensive daily sampling
- Follow-up:
  - day 14 (airway)
  - day 28 (airway and blood)

Dr Max Habibi
and Chris Chiu

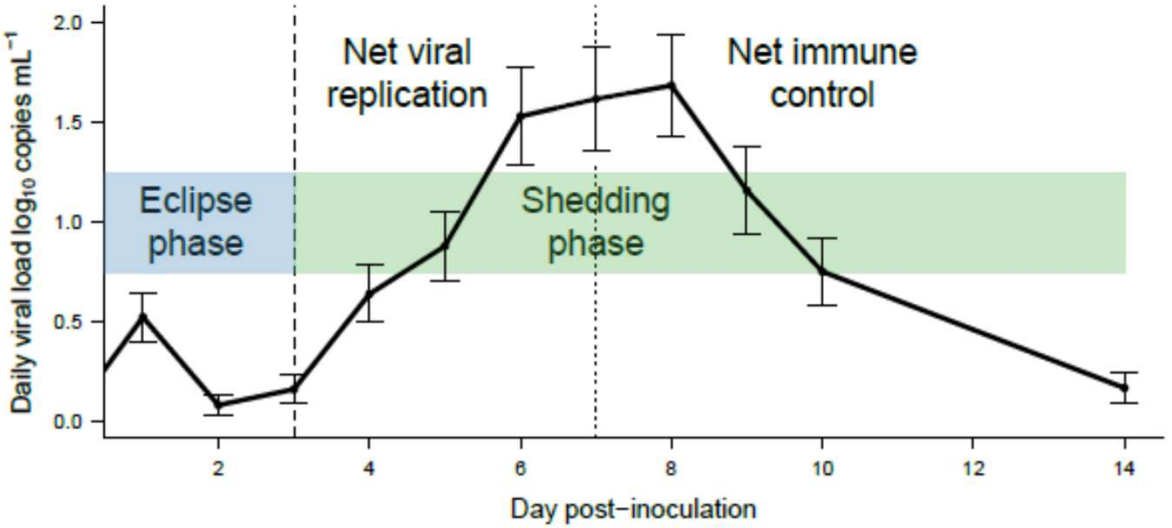
wellcome trust

Imperial College London

RSV infection of adult volunteers



RSV M37 inoculation



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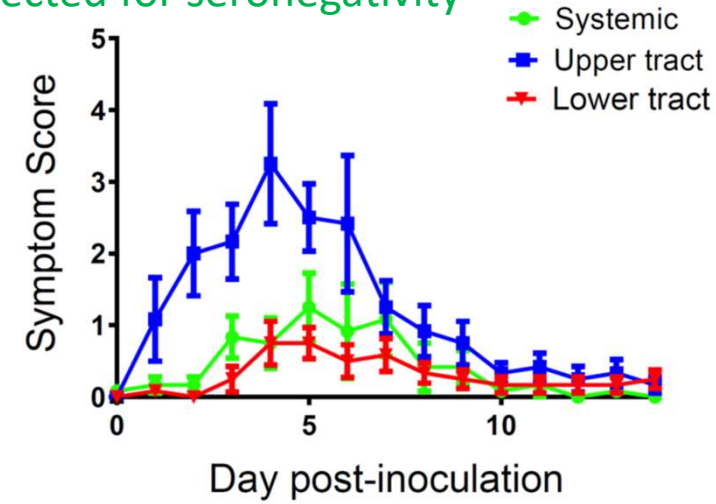
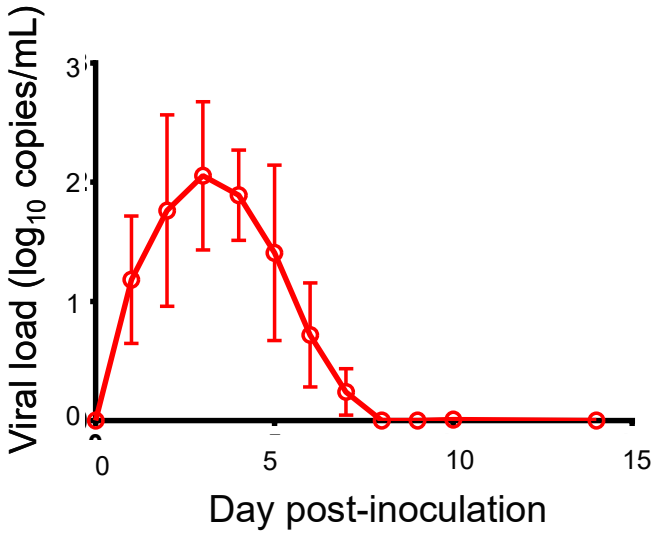
Symptoms & viral load: comparing RSV and flu

Pre-selected for seronegativity

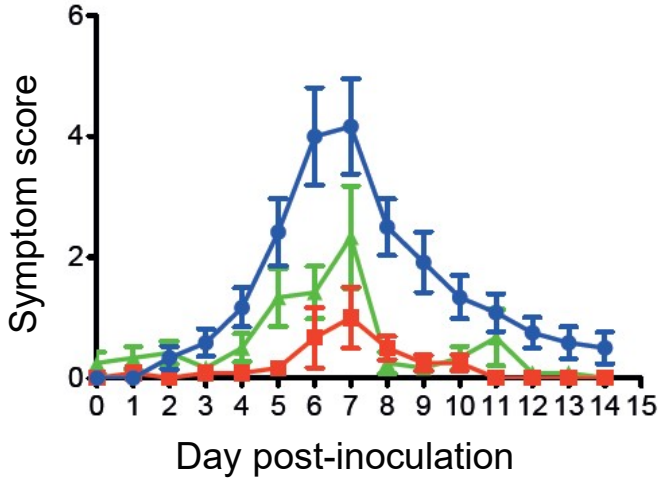
Influenza

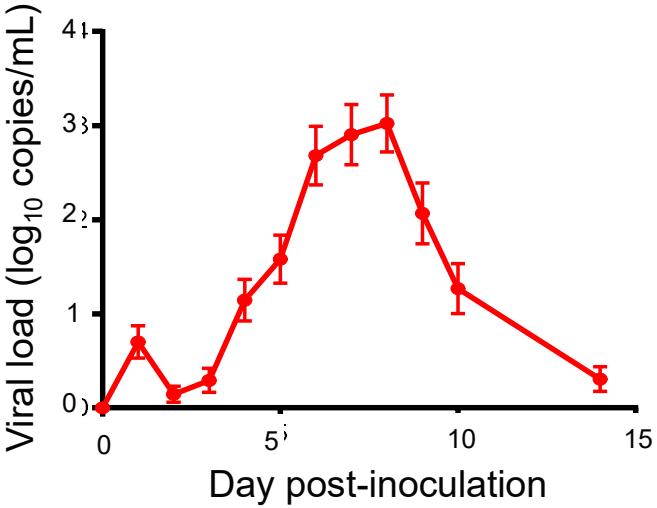




Not pre-selected for seronegativity

RSV





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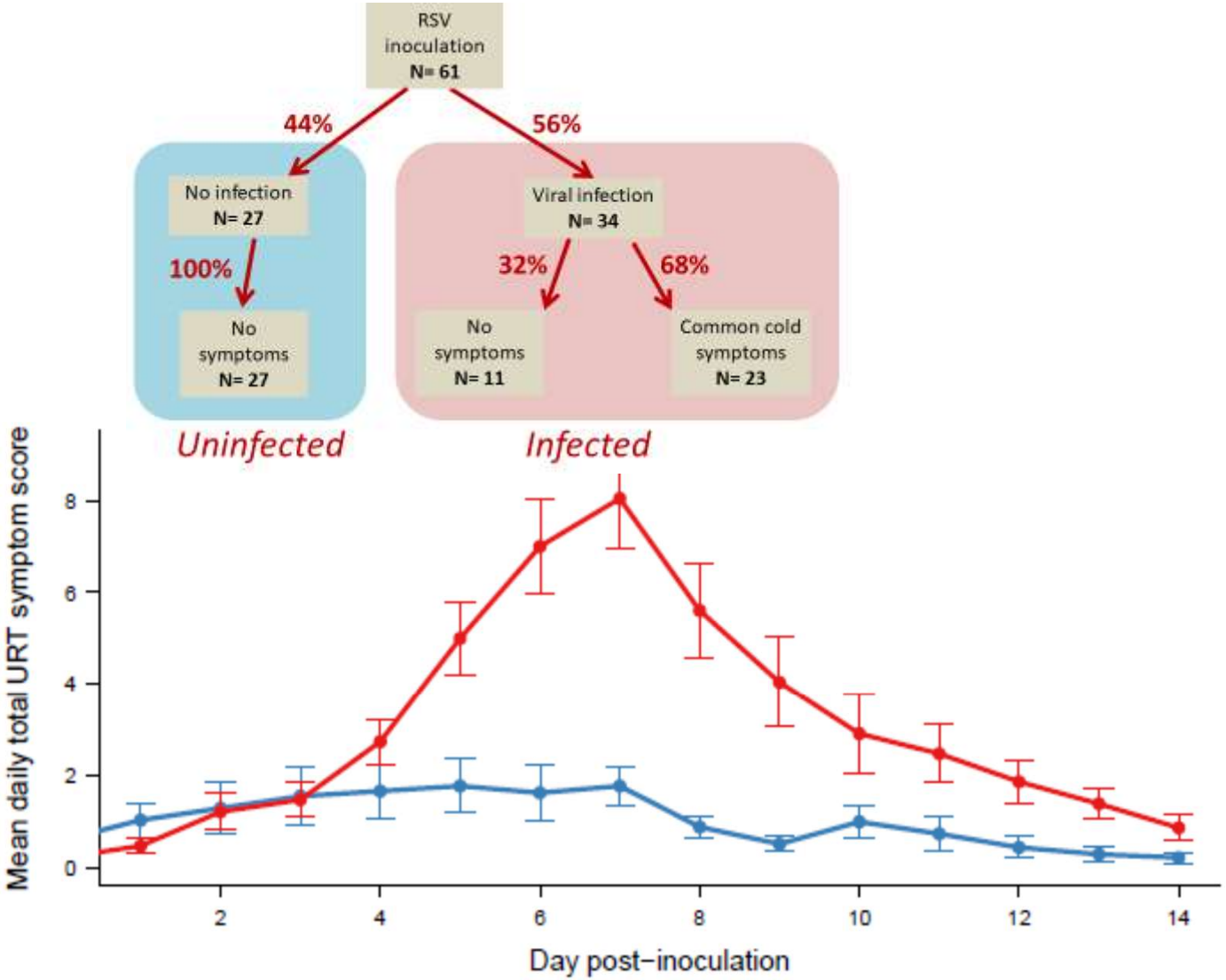
Outcome of RSV inoculation in 61 adults



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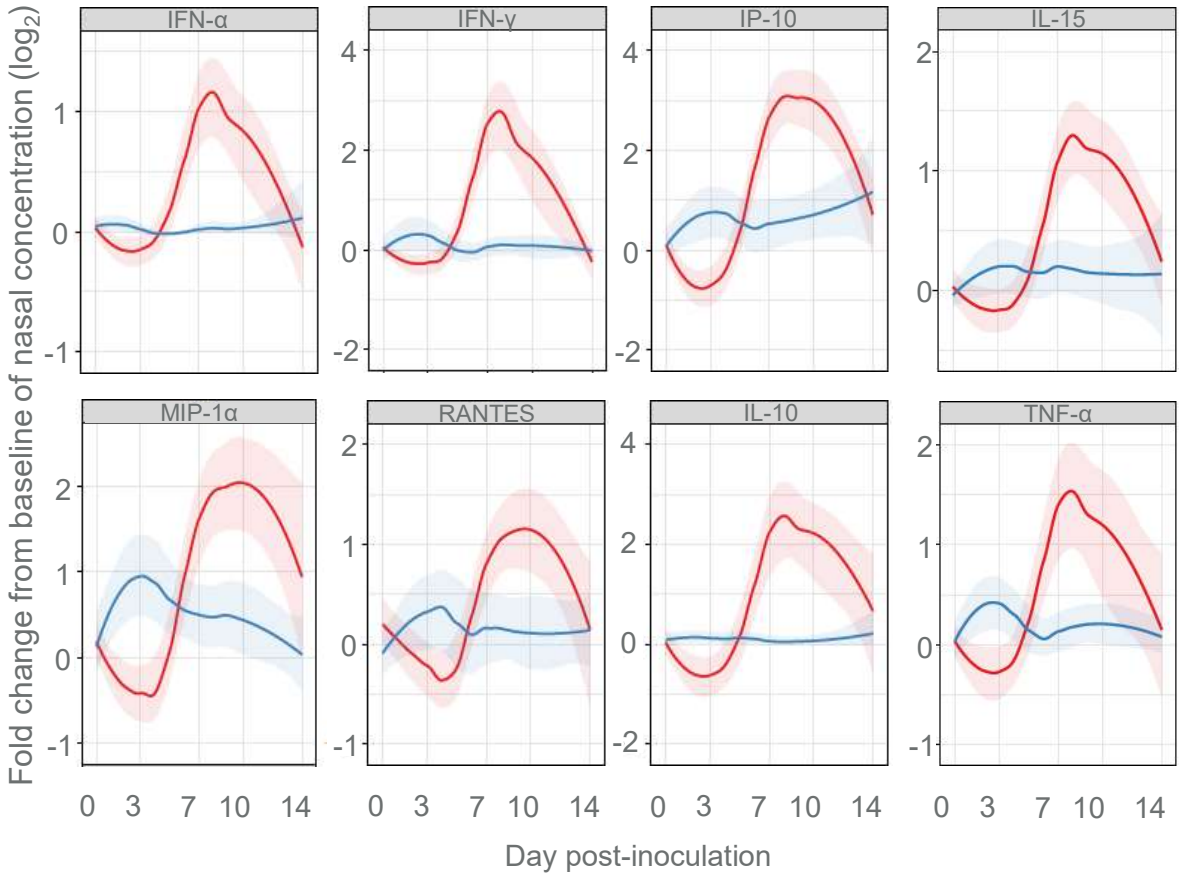
The silent phase is vital in understanding outcome



Host shows a response: virus defeated

Host mediators supressed: virus succeeds

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The infection challenge team

Chris Chiu
Maximillian Habibi
Agnieszka Jozwik
Aleks Guvenel

Hannah Jarvis
Onn Min Kon
Jai Dhariwal
Annemarie Sykes
Mark Almond
Ernie Wong
Patrick Mallia
Seb Johnston

Allan Paras
Zoe Gardener
Steff Ascough
Anakin Ung
Jie Zhu
Jerico Del Rosario
Hiromi Uzu
Helen Piotrowski
Jennifer Brimley
Belen Trujillo-Torralbo

Alessandro Sette
Bjoern Peters
John Sidney

Rafi Ahmed
Jesus Wrammert
Xander de Haan

Thank you

wellcome trust

PREPARE

MRC Medical Research Council

NHS National Institute for Health Research