Imperial College London

ReSViNET meeting, Accra, Ghana
Wednesday 13th November 2019

Immunological responses at different stages of infection

Peter Openshaw

Imperial College London

p.openshaw@imperial.ac.uk

@p_openshaw

Imperial College London

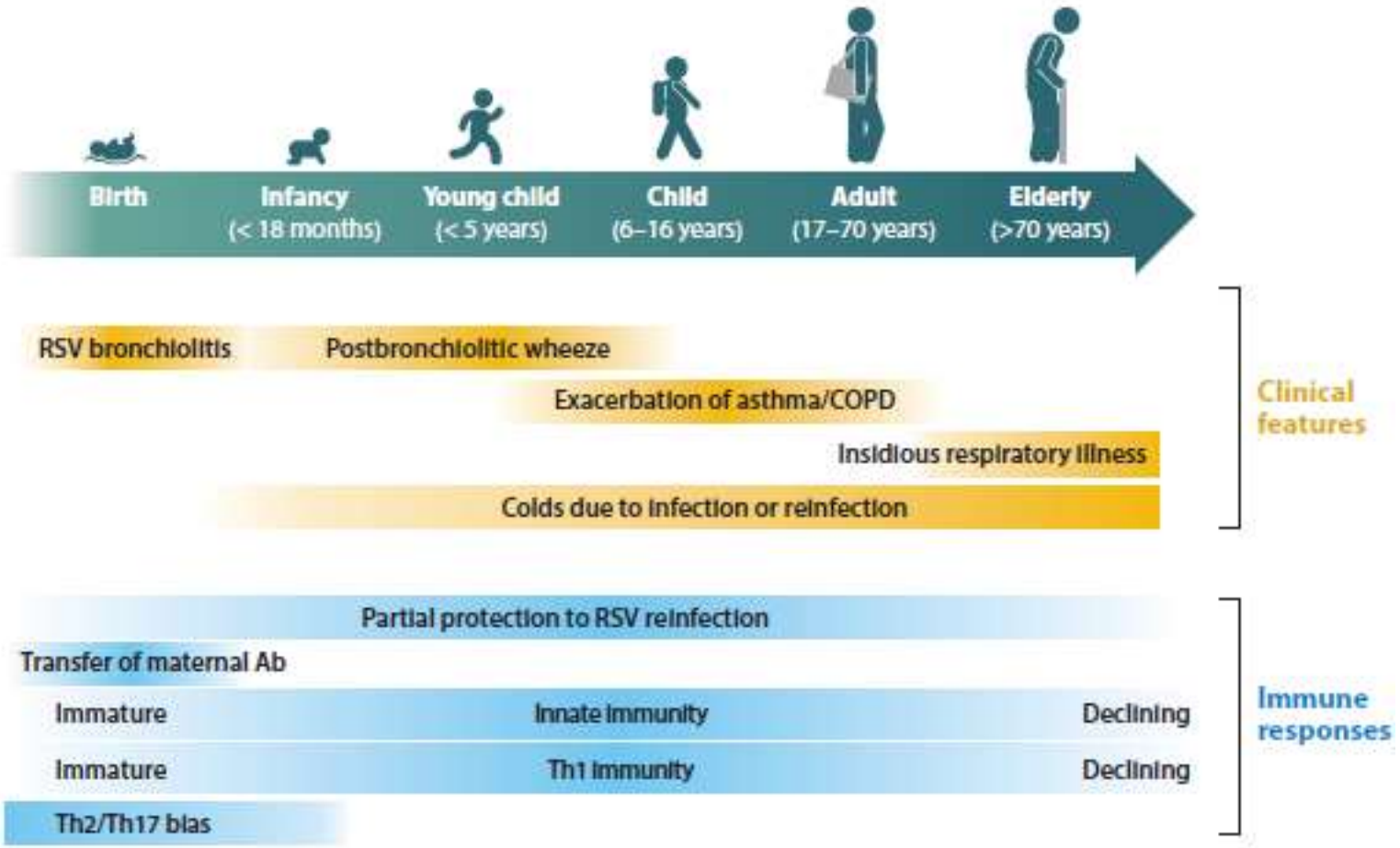
Declaration of interests

Grants from MRC and EU; NIHR Senior Investigator fund, Biomedical Research Centre (BRC) and Health Protection Research Unit (HPRU); Wellcome Trust; MRC Global Challenge Research Fund; EMINENT Consortium supported by MRC/GSK

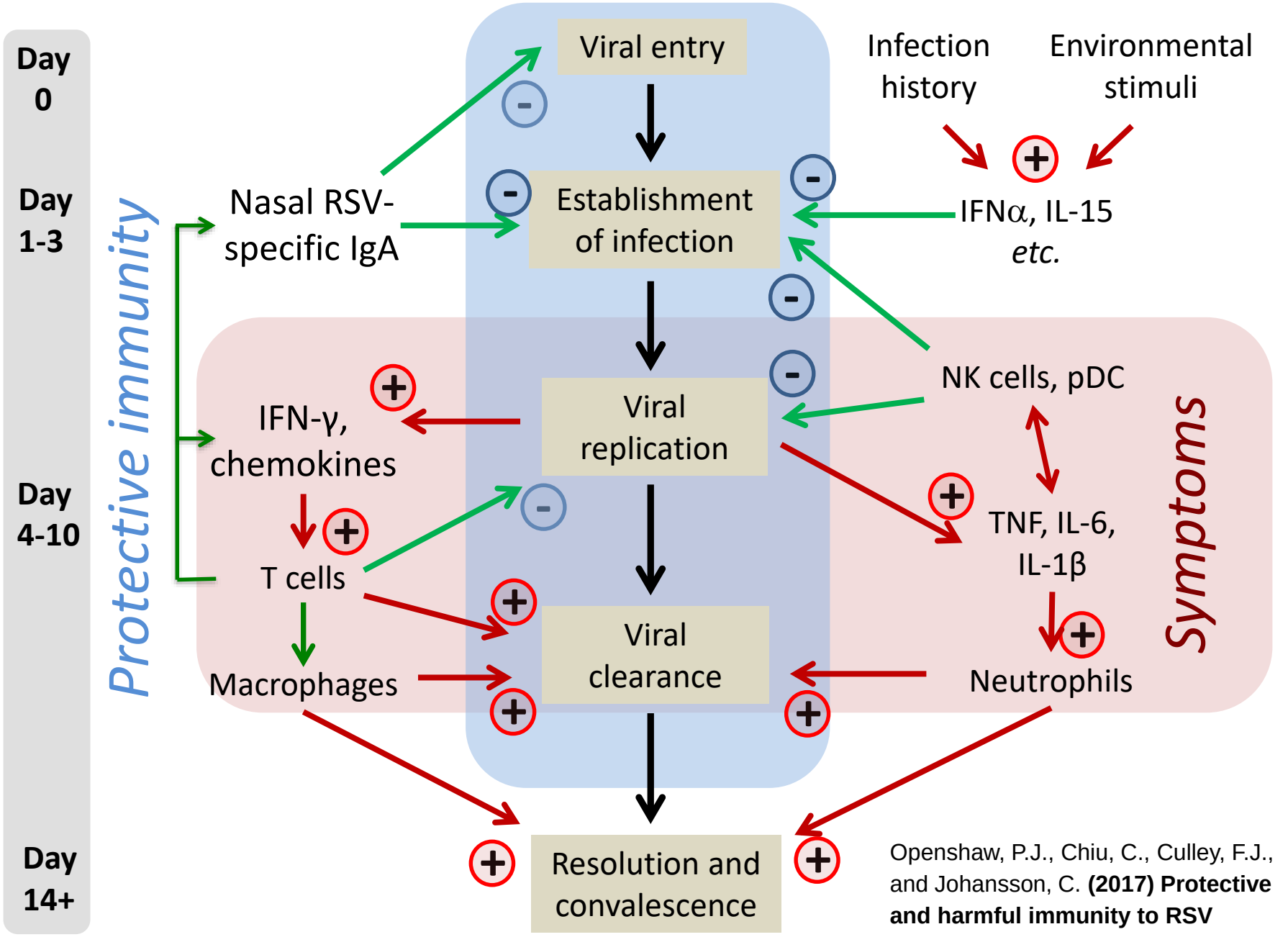
Fees from European Respiratory Society; non-financial support as Past-President and Trustee of BSI; Advisory Boards: Janssen/JnJ, Cephid, Pfizer and Sanofi

Committees: Vice-Chair/ Member, NERVTAG (Emerging Respiratory Virus Threats Group; Department of Health), UK

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



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

Imperial College London

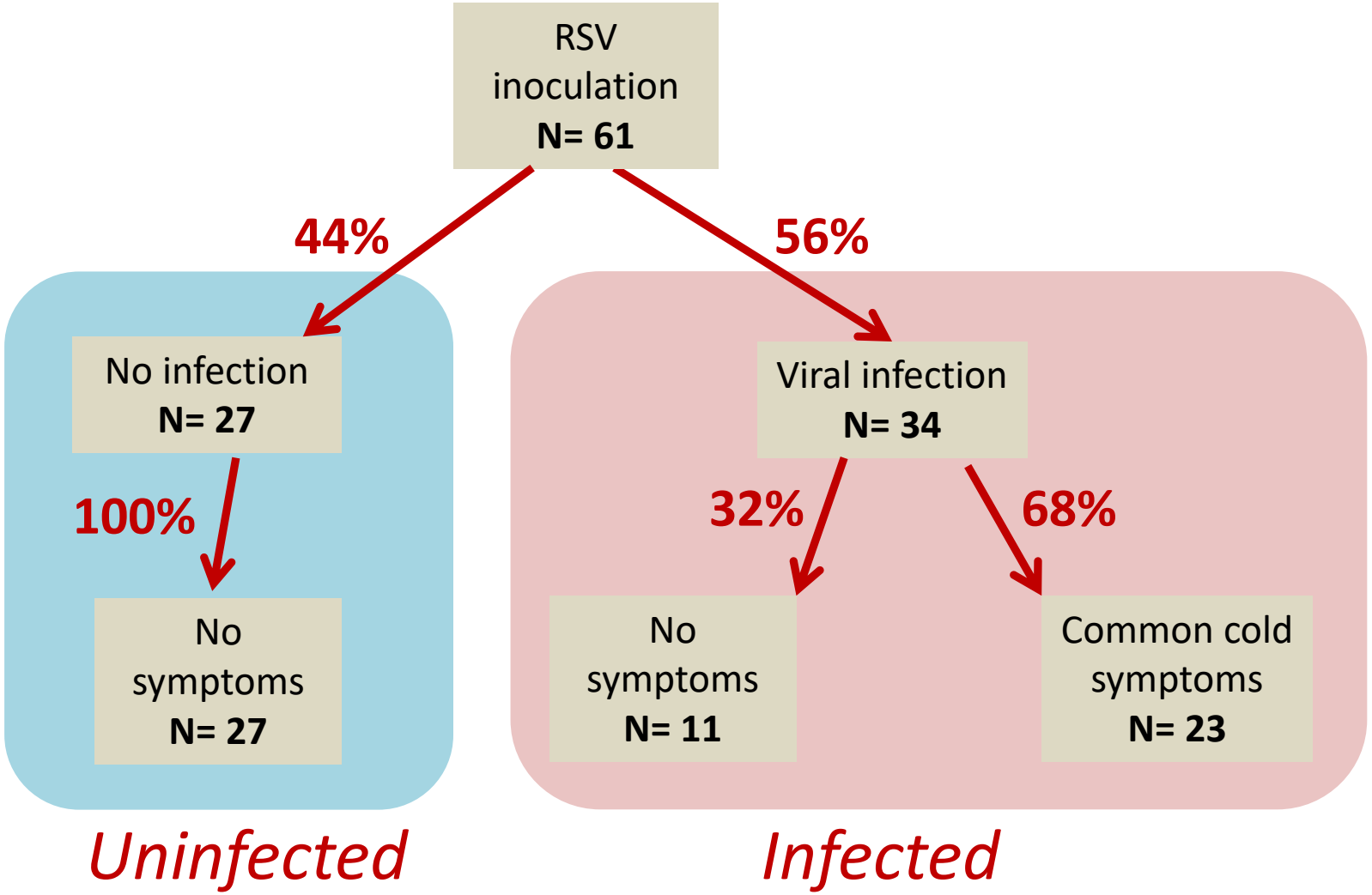
Inoculation of volunteers with RSV

- **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

Infection rates and colds



No difference between males and females

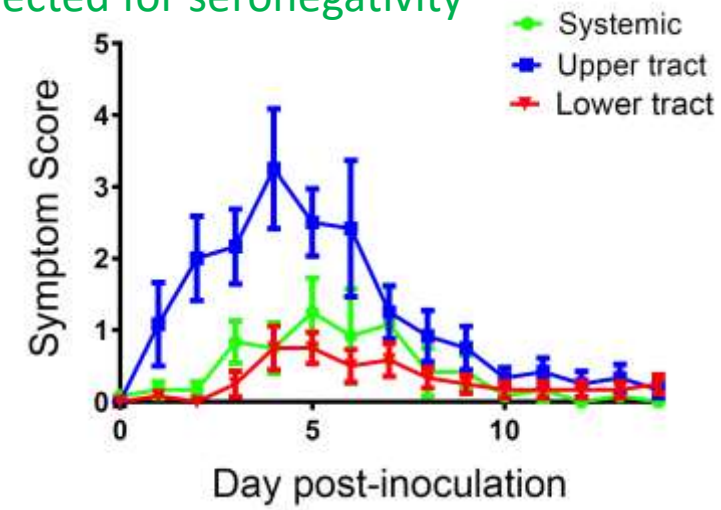
No relationship between age and infection rate or colds

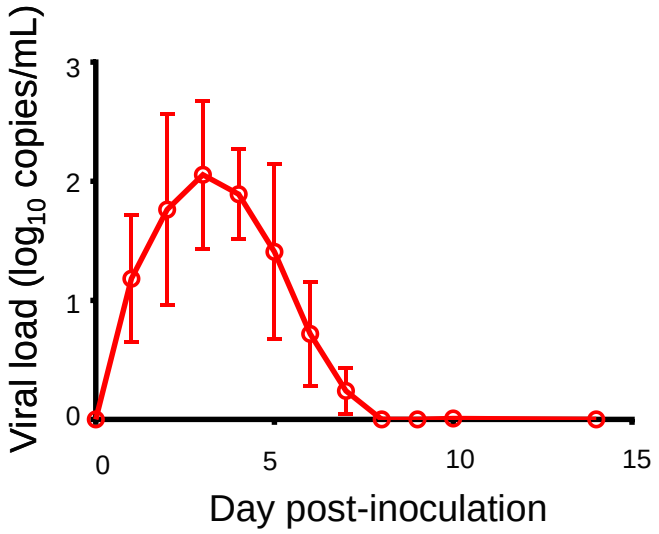
Imperial College London

Symptoms & viral load: comparing RSV and flu

Pre-selected for seronegativity

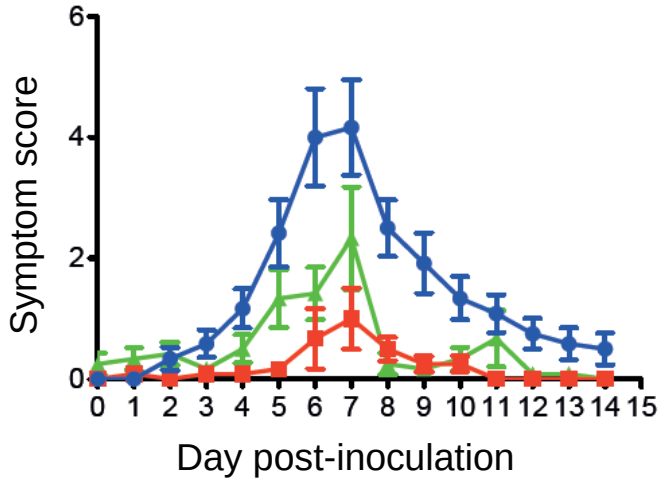
Influenza

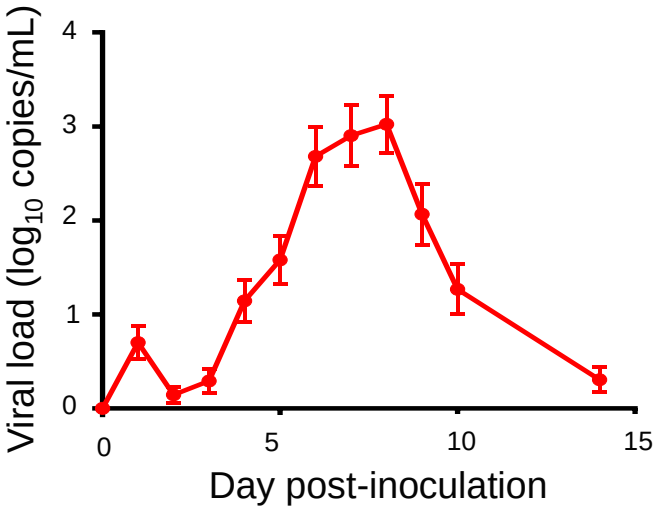




Not pre-selected for seronegativity

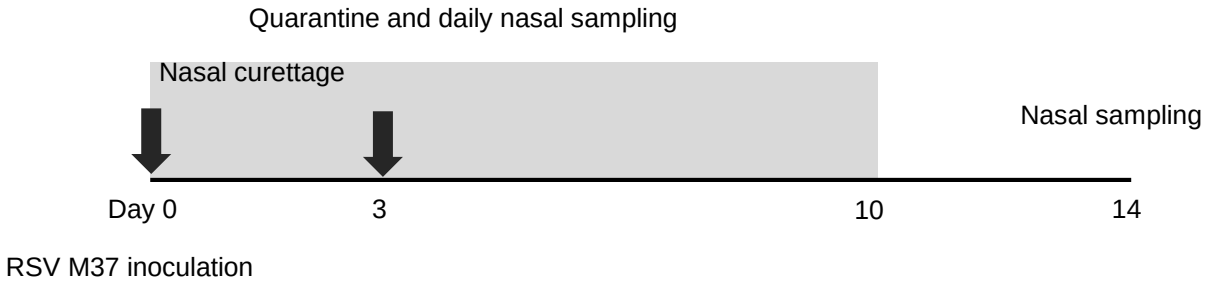
RSV

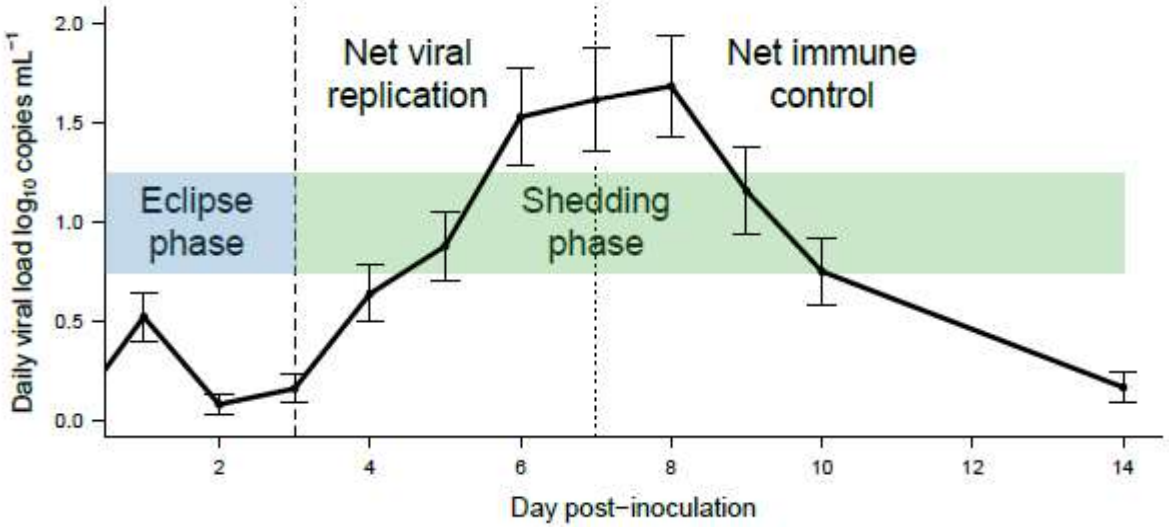




Imperial College London

RSV infection of adult volunteers





Imperial College London

Nasal Mucosal Sampling

Nasosorption

- CE-marked
- Simple to use
- Undiluted mucosal fluid

- Allows measurement of:
  - Cytokines and chemokines
  - Antibodies
  - Viral load
  - Microbiome

Thwaites RS, Jarvis HC, Singh N, Jha A, Pritchard A, Fan H, Tunstall T, Nanan J, Nadel S, Kon OM, Openshaw PJ, Hansel TT **(2018)** Absorption of Nasal and Bronchial Fluids. *J. Vis. Exp. 2018* (131), e56413, doi:10.3791/56413

Imperial College London

RSV-specific CD8+ T cells

Trm cells in the airway

- Associated with reduction in severity of RSV disease
- Preferentially retained in convalescence

T cells only appear only transiently in blood

- Frequency too low to correlate with protection

NATURE COMMUNICATIONS | DOI: 10.1038/ncomms10224

Received 26 Oct 2015 | Accepted 16 Nov 2015 | Published 21 Dec 2015

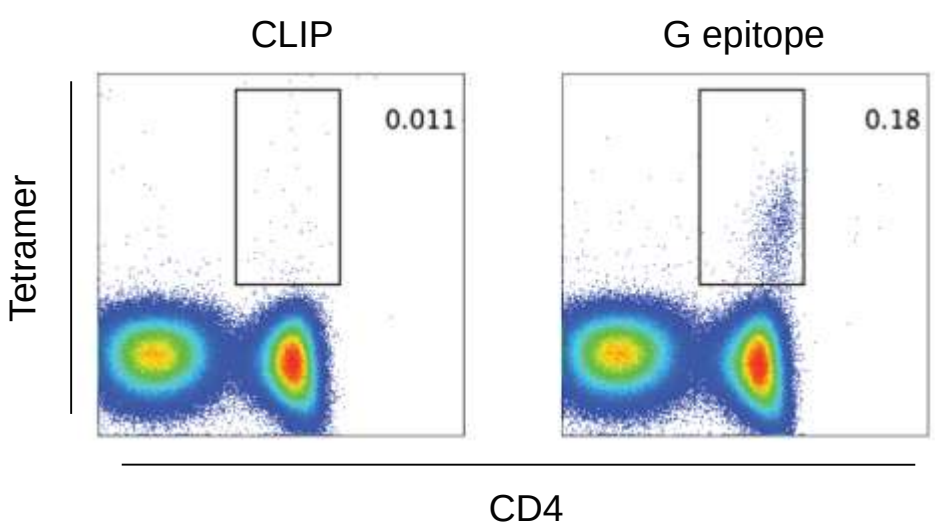
DOI: 10.1038/ncomms10224 OPEN

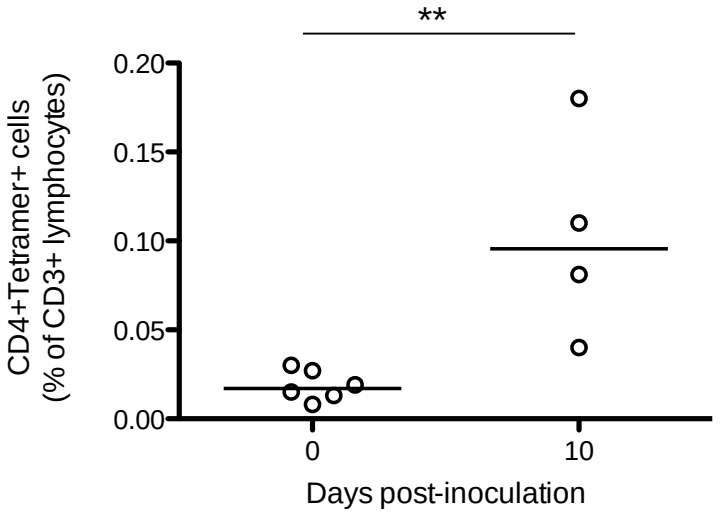
RSV-specific airway resident memory CD8+ T cells and differential disease severity after experimental human infection

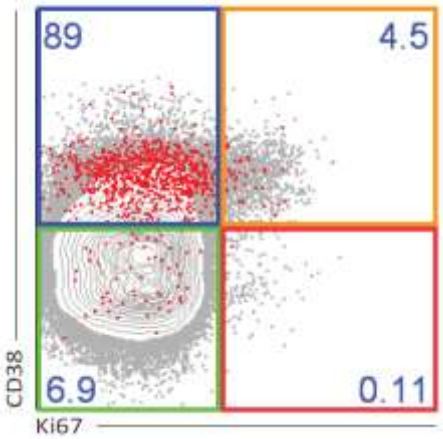
Agnieszka Jozwik[1], Maximillian S. Habibi[1], Allan Paras[1], Jie Zhu[1], Aleks Guvenel[1], Jaideep Dhariwal[1], Mark Almond[1], Ernie H.C. Wong[1], Annemarie Sykes[1], Matthew Maybeno[2], Jerico Del Rosario[1], Maria-Belen Trujillo-Torralbo[1], Patrick Mallia[1], John Sidney[2], Bjoern Peters[2], Onn Min Kon[1], Alessandro Sette[2], Sebastian L. Johnston[1], Peter J. Openshaw[1] & Christopher Chiu[1]

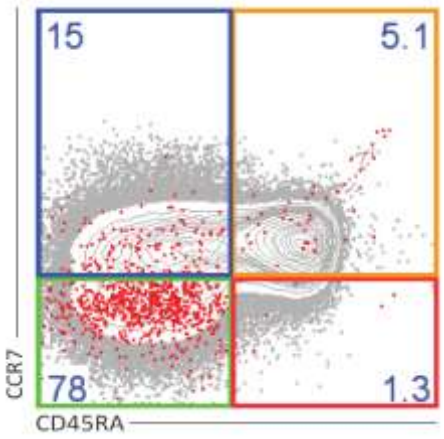
Imperial College London

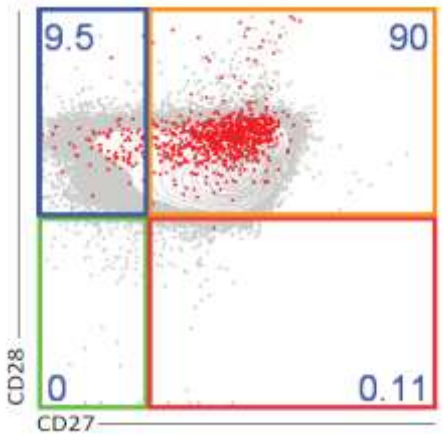
Tetramer labelling of RSV-specific CD4+ T cells

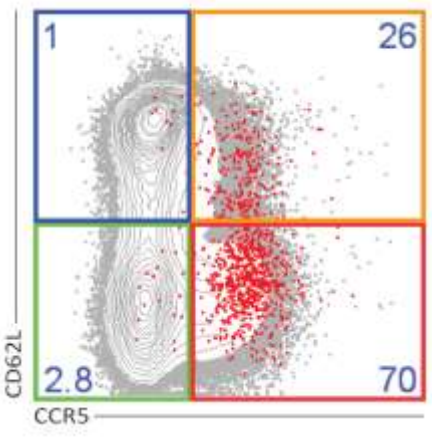






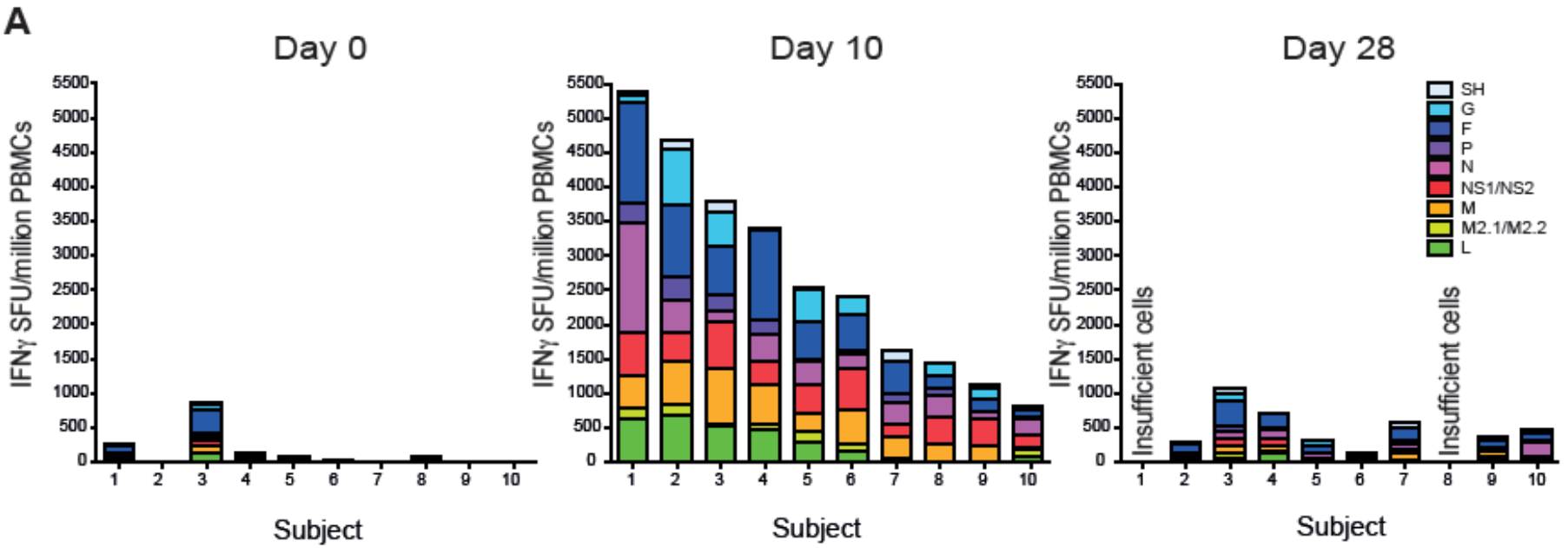






Imperial College London

CXCL10-associated recruitment of airways-resident CD4+ T-cells in controlled human RSV infection

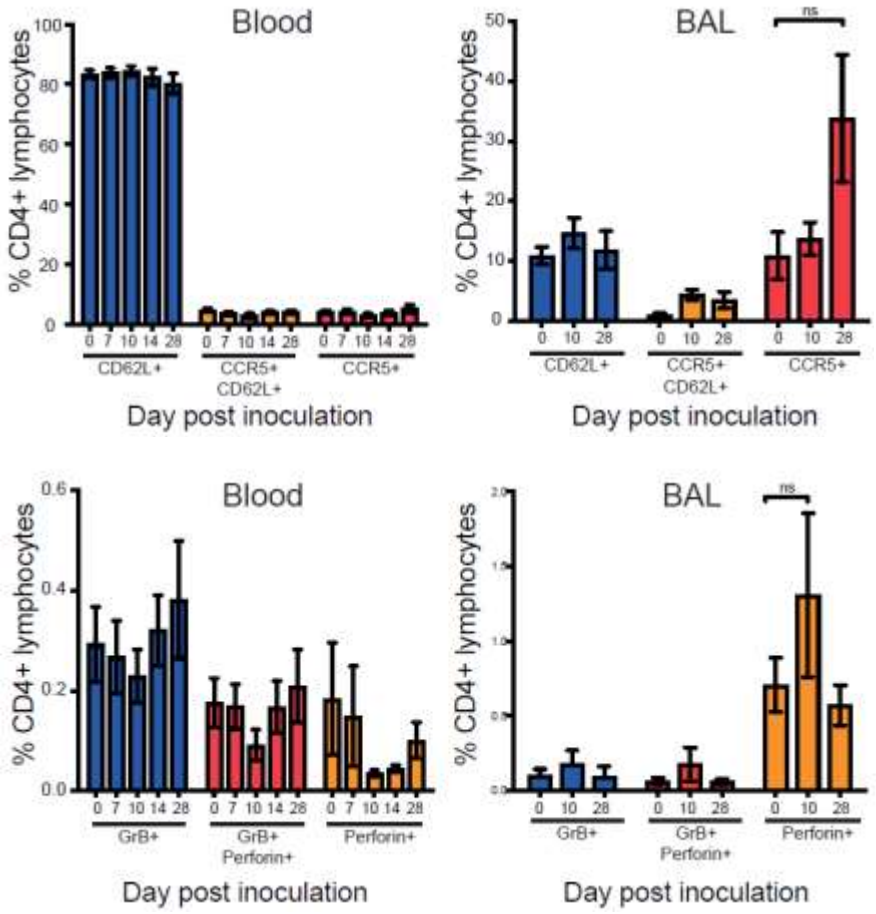


Immunodominant CD4+ T-cell epitopes in the surface F and G proteins.
Fresh PBMCs from RSV-infected individuals (n=10) were assayed by IFN-γ ELISpot using overlapping peptides covering the RSV proteome. ELISpot responses to peptide pools at days 0, 10 and 28 post-infection are arranged according to the originating protein

Aleks Guvenel, Agnieszka Jozwik, Stephanie Ascough, … Peter J. Openshaw and Christopher Chiu (JCI *in press* 2019)

Imperial College London

CXCL10-associated recruitment of airways-resident CD4+ T-cells in controlled human RSV infection



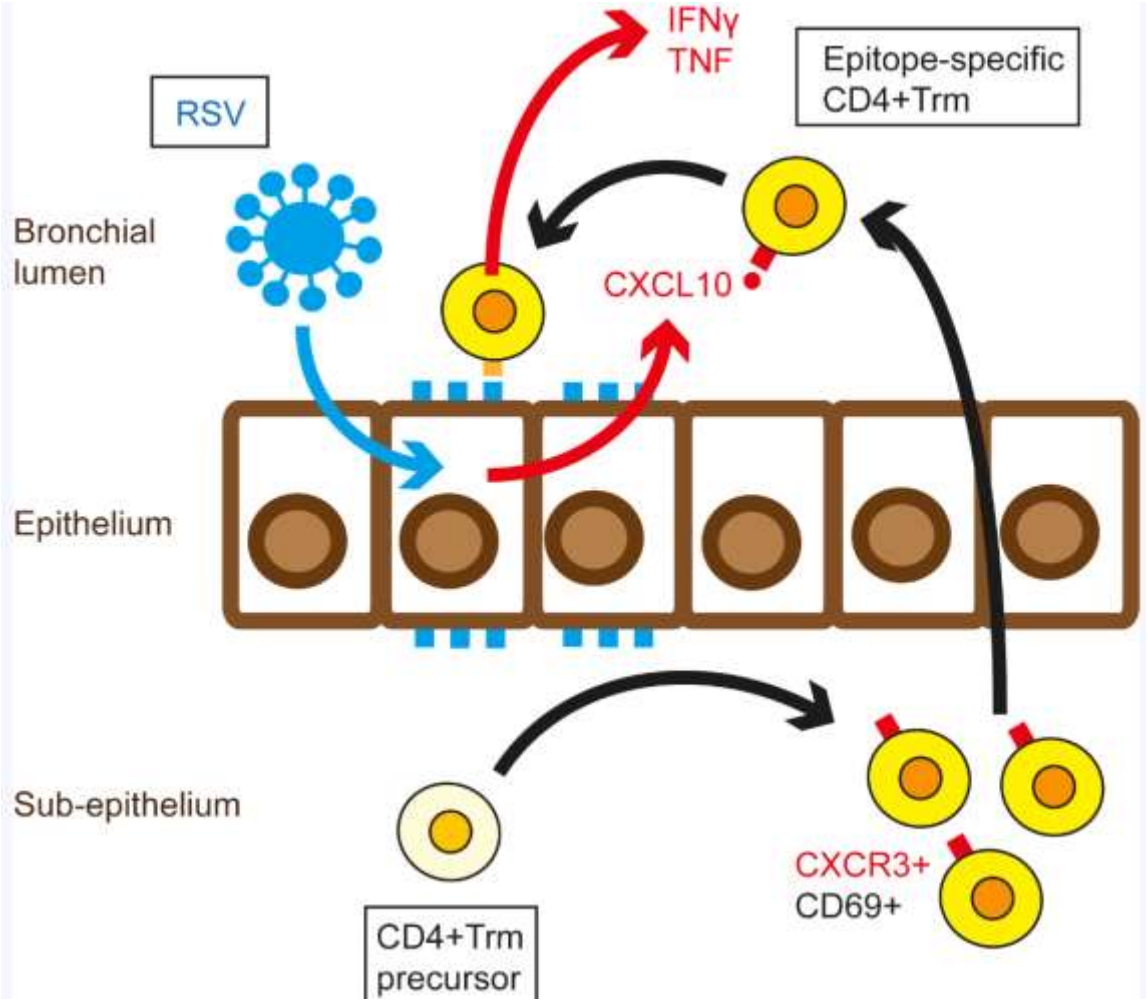
CD69+ resident memory CD4+ T-cells in BAL exhibit advanced differentiation

Whole blood/PBMCs (n=10) and BAL (n=5) from RSV-infected volunteers co-stained with anti-CD3, CD4, CD62L, CXCR5, GzmB, perforin and CD69 and CD103. Lung cells mostly Trm phenotype.

Aleks Guvenel, Agnieszka Jozwik, Stephanie Ascough, … Peter J. Openshaw and Christopher Chiu (JCI in press 2019)

Imperial College London

CXCL10-associated recruitment of airways-resident CD4+ T-cells in controlled human RSV infection



Aleks Guvenel, Agnieszka Jozwik, Stephanie Ascough, … Peter J. Openshaw and Christopher Chiu (JCI *in press* 2019)

Imperial College London

RSV disease in volunteers

1. RSV infection challenge is feasible in adults over a range of ages, including elders (who seem more symptomatic)

2. Allows deep investigation of the mucosal response, its role in protection and in pathogenesis

3. Uniquely allows the prospective and sequential evaluation of the responses over the time-course of disease, including the prior state of the mucosa

Imperial College London

The infection challenge team

Chris Chiu
Steff Ascough
Maximillian Habibi
Aleks Guvenel

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

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

Alessandro Sette
Bjoern Peters
John Sidney

Rafi Ahmed
Jens Wrammert
Xander de Haan

Thank you!

wellcome trust

gsk

Platform foR European Preparedness Against (Re-)Emerging Epidemics
PREPARE

MRC Medical Research Council

NHS National Institute for Health Research