Imperial College London

Webinar
7th August, 2019

The value of human challenge studies in accelerating vaccine development

Peter Openshaw

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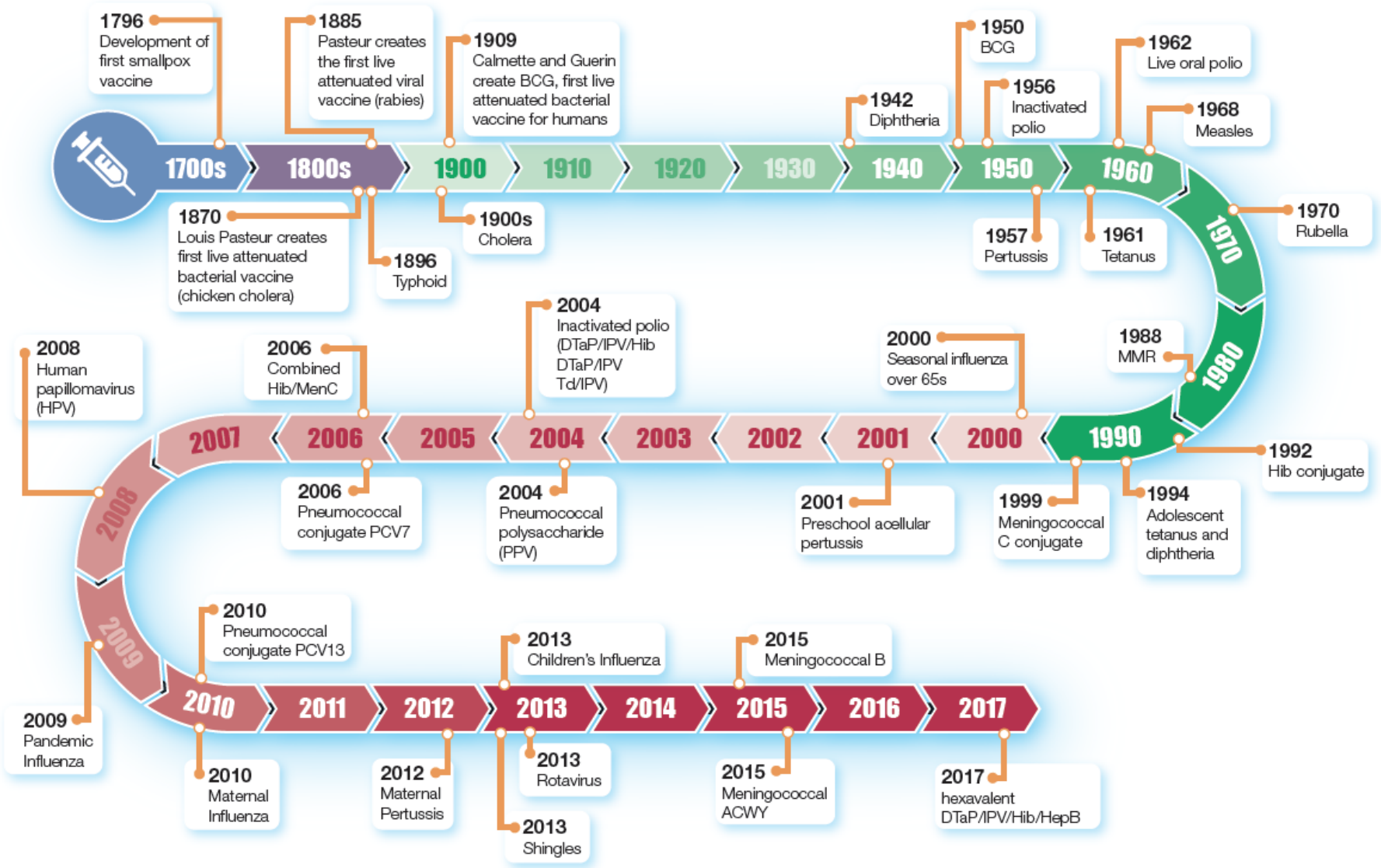
p.openshaw@imperial.ac.uk

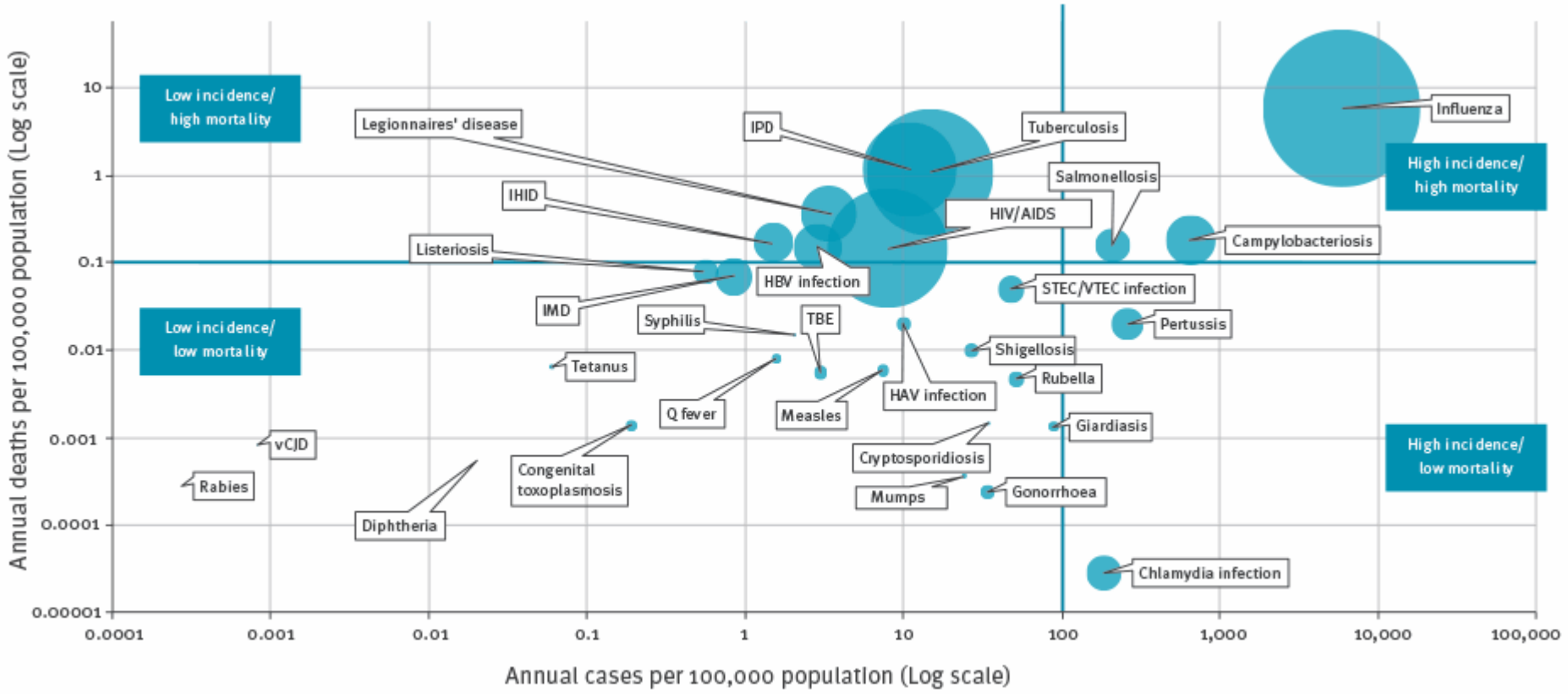
Public Health England

Historical vaccine development and introduction of routine vaccine programmes in the UK



https://www.gov.uk/government/publications/vaccination-timeline

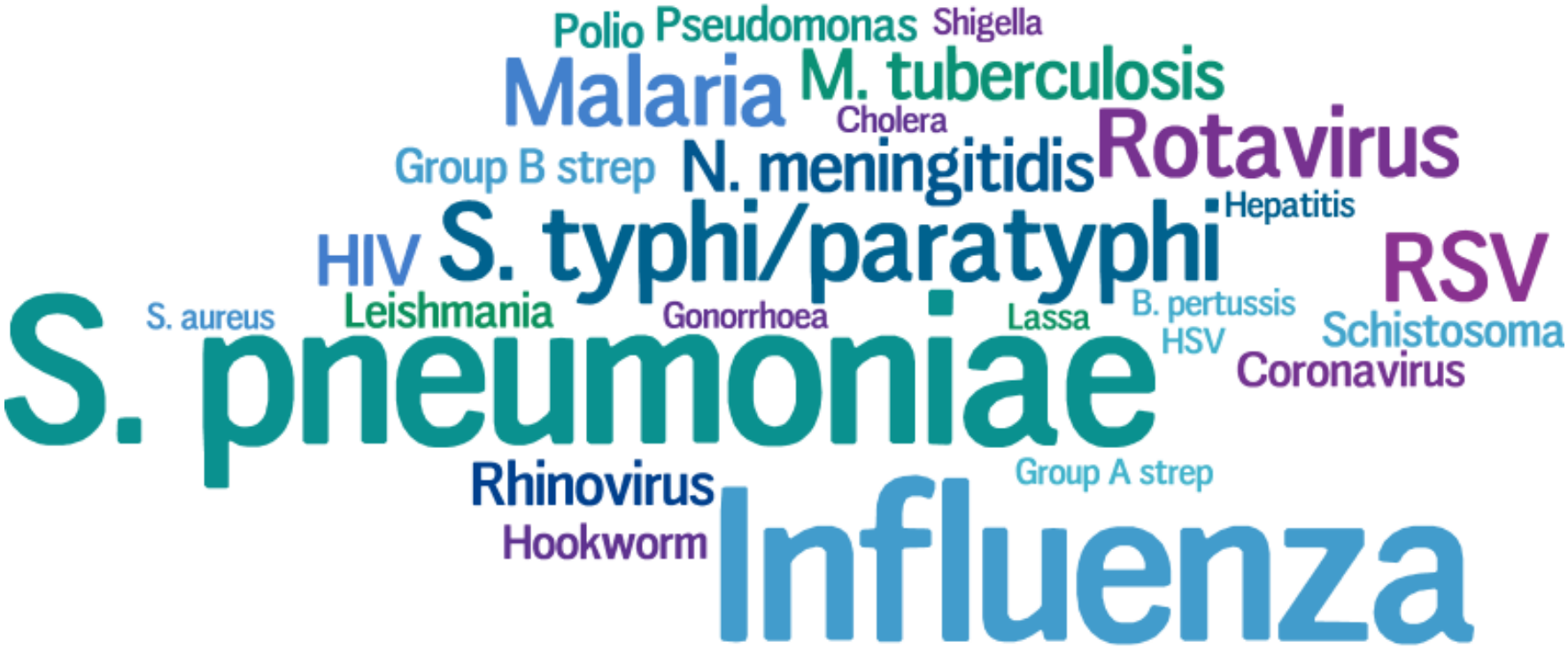
Burden of selected infectious diseases (mortality and incidence) EU/EEA countries, 2009–2013



The diameter of the bubble reflects the number of DALYs per 100,000 population per year

Cassini Alessandro, *et al* on behalf of the BCoDE consortium. Impact of infectious diseases on population health using incidence-based DALYs:
results from the Burden of Communicable Diseases in Europe study 2009 to 2013.
Euro Surveill. 2018;23(16):pii=17-00454. https://doi.org/10.2807/1560-7917.ES.2018.23.16.17-00454

Pathogens we'd like new or better vaccines against…



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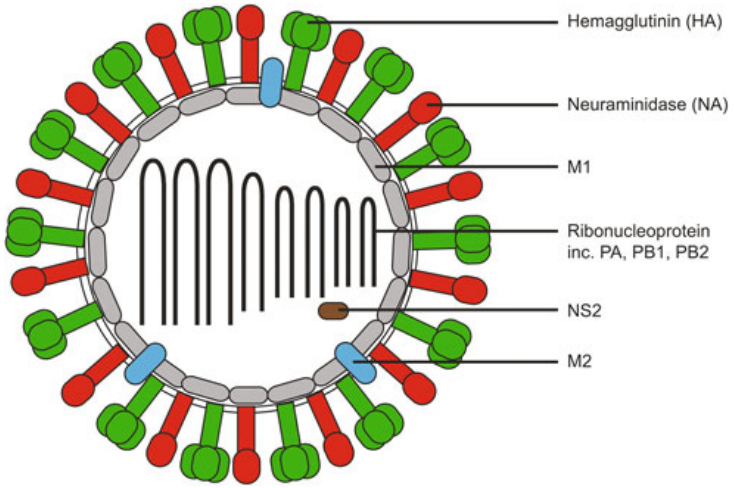
Influenza vs respiratory syncytial virus

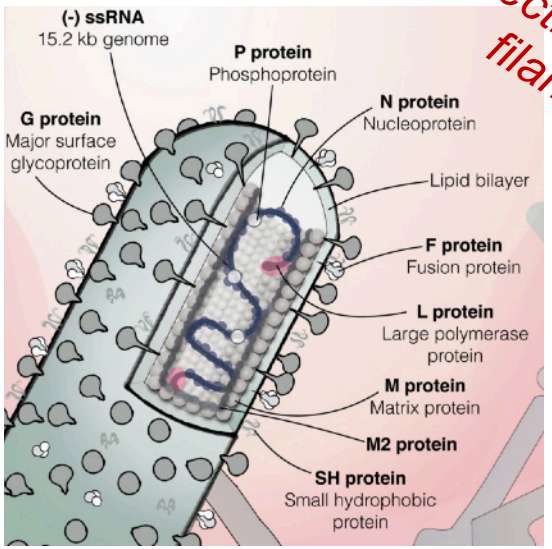
Influenza



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

RSV

Infectious form is filamentous



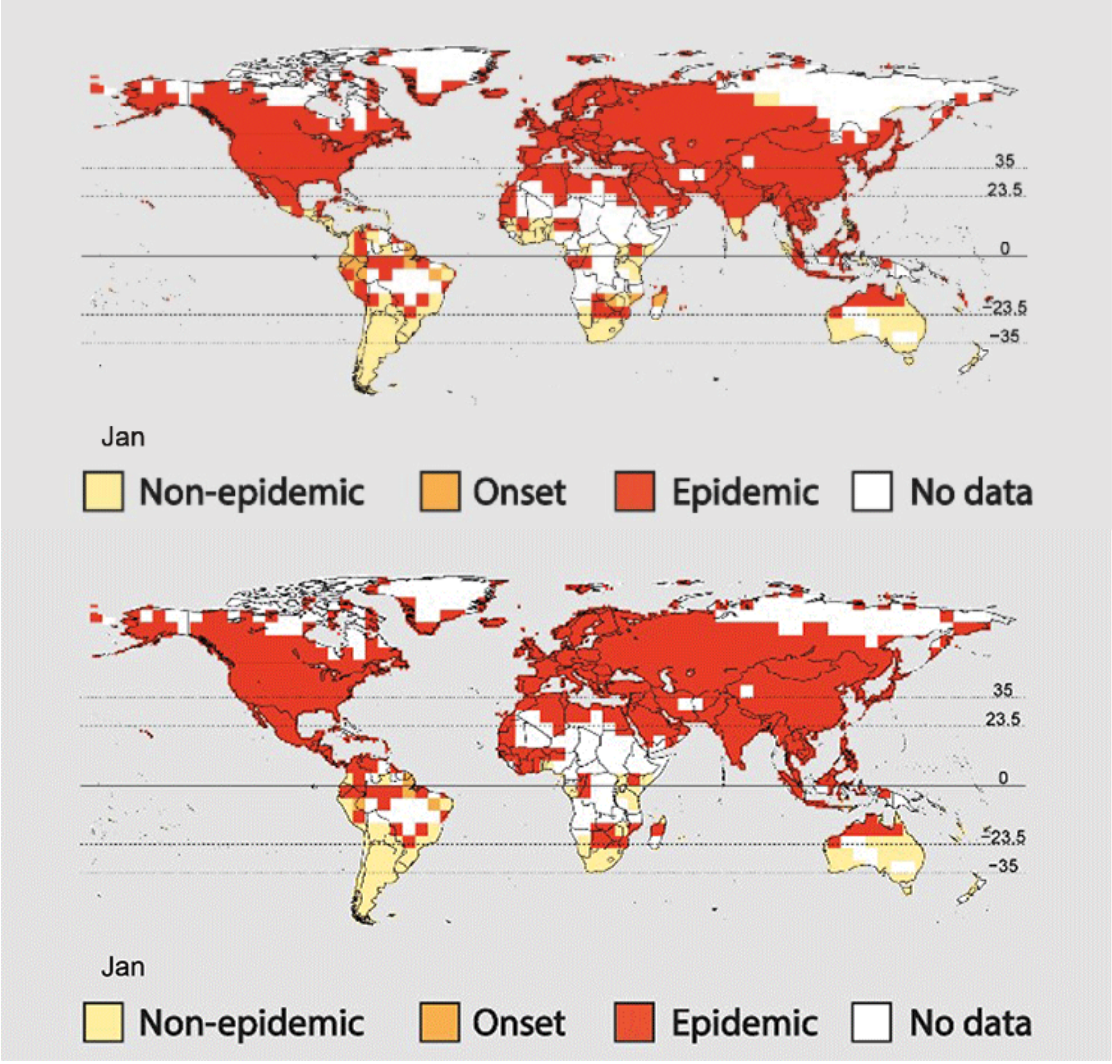
- Recurrent re-infection with similar strains
- No vaccine
  - Poor immunogenicity
  - Vaccine-enhanced disease
  - Very active research field

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

Global changes in RSV and flu prevalence month by month

RSV

Flu



RESCEU
REspiratory Syncytial virus Consortium in EUrope

WP1 – Systematic literature review on RSV and current estimates of burden of disease

D1.10 Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and meta-pneumovirus: a systematic analysis

Lead contributor	**Harish Nair (University of Edinburgh)**
	Harish.nair@ed.ac.uk

Thanks to Sophie Sagawe for animation

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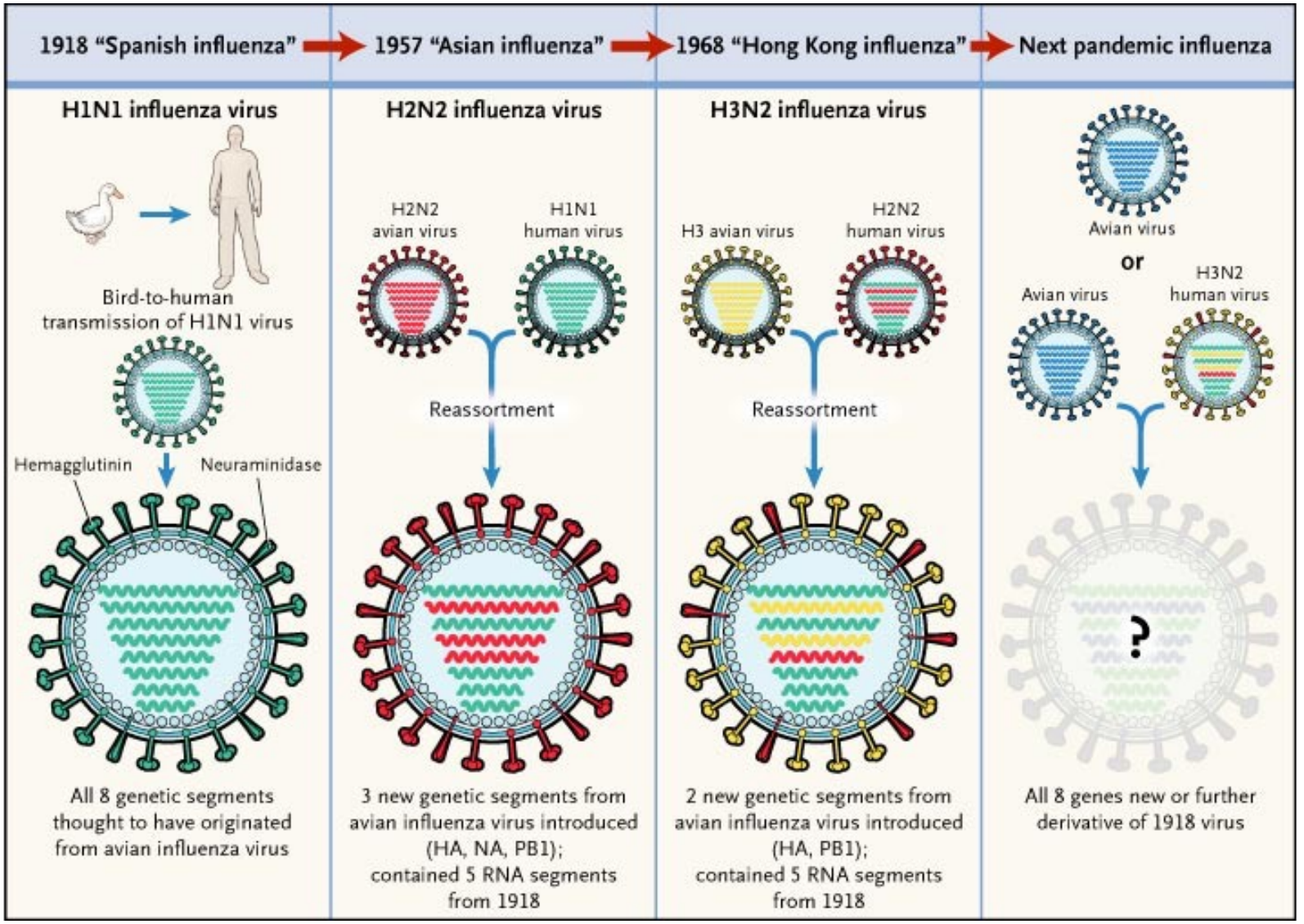
Edith Schiele died of flu on 28 October 1918, 6 months pregnant. Egon Schiele died 3 days after his wife and child, aged 28 yrs

Gustav Klimt ‘Death and Life’ 1910

Egon Schiele 1890 –1918

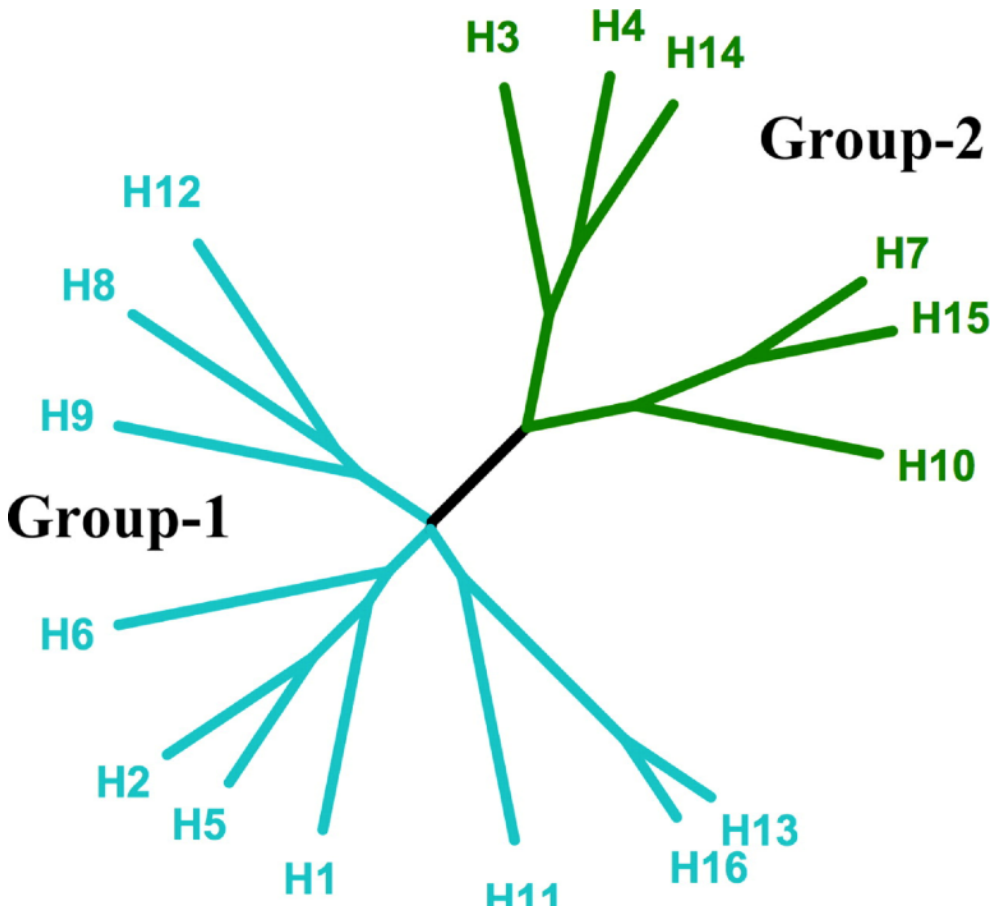
Evolution of new flu strains



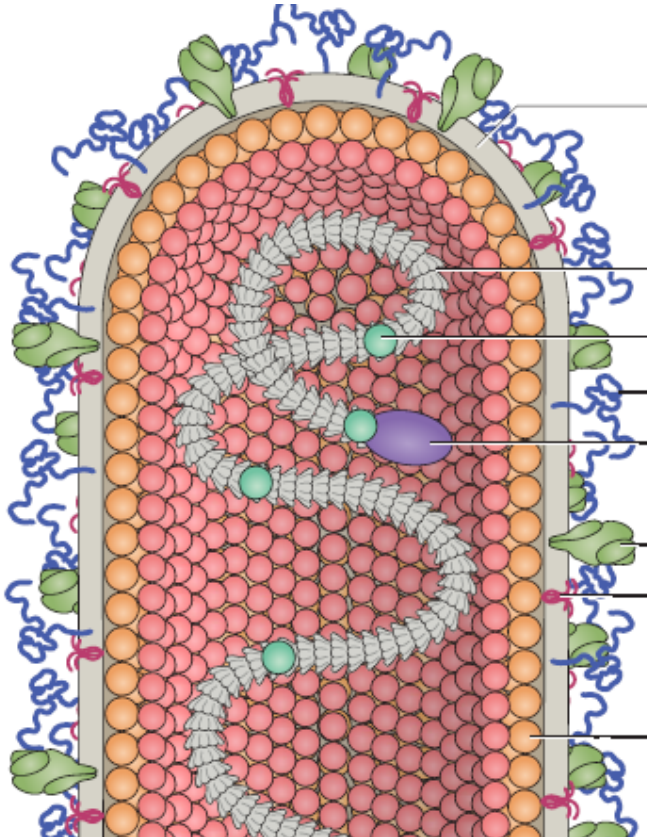
Belshe (2005) NEJM 353:2209-2211

Influenza & antigenic variation

- Influenza A & B
- Seasonal
  - 3-5 million severe cases
  - 250,000 – 500,000 deaths per annum
- Pandemic
  - Influenza A(H1N1)2009
- *Strain-specific immunity*
- *Antigenic drift & shift*
  - 3-4 strains per vaccine
  - Annual reformulation



Respiratory Syncytial Virus



- **Genus:** *Orthopneumovirus*
  Family: *Pneumoviridae*
  Order: *Mononegavirales*
- Single stranded, negative sense RNA virus
- ~ 15,200 nucleotides
- Transcribed into 11 subgenomic mRNAs

Respiratory syncytial virus entry and how to block it

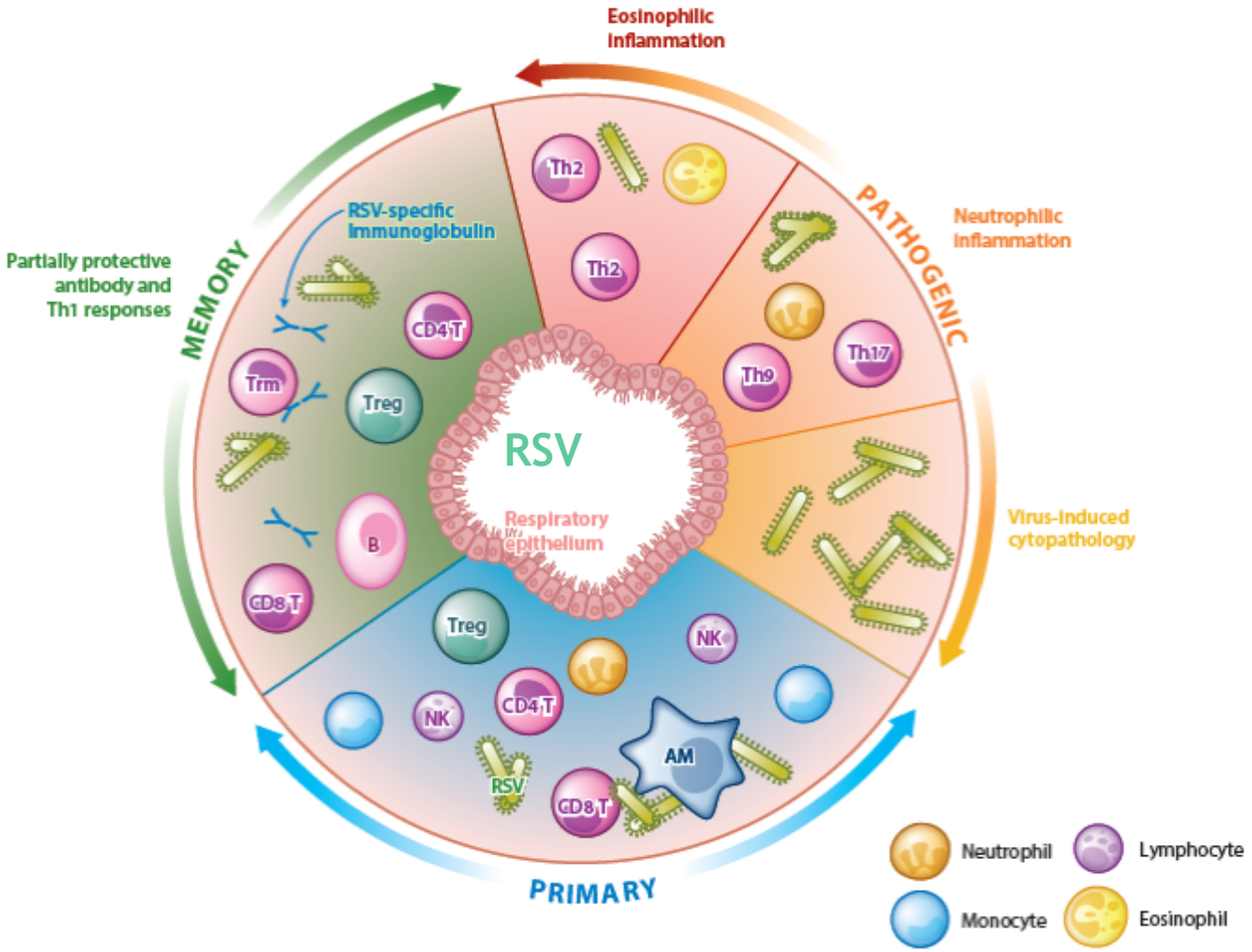
https://doi.org/10.1038/s41579-019-0149-x

Michael B. Battles[1] and Jason S. McLellan[2]*

NATURE REVIEWS | MICROBIOLOGY

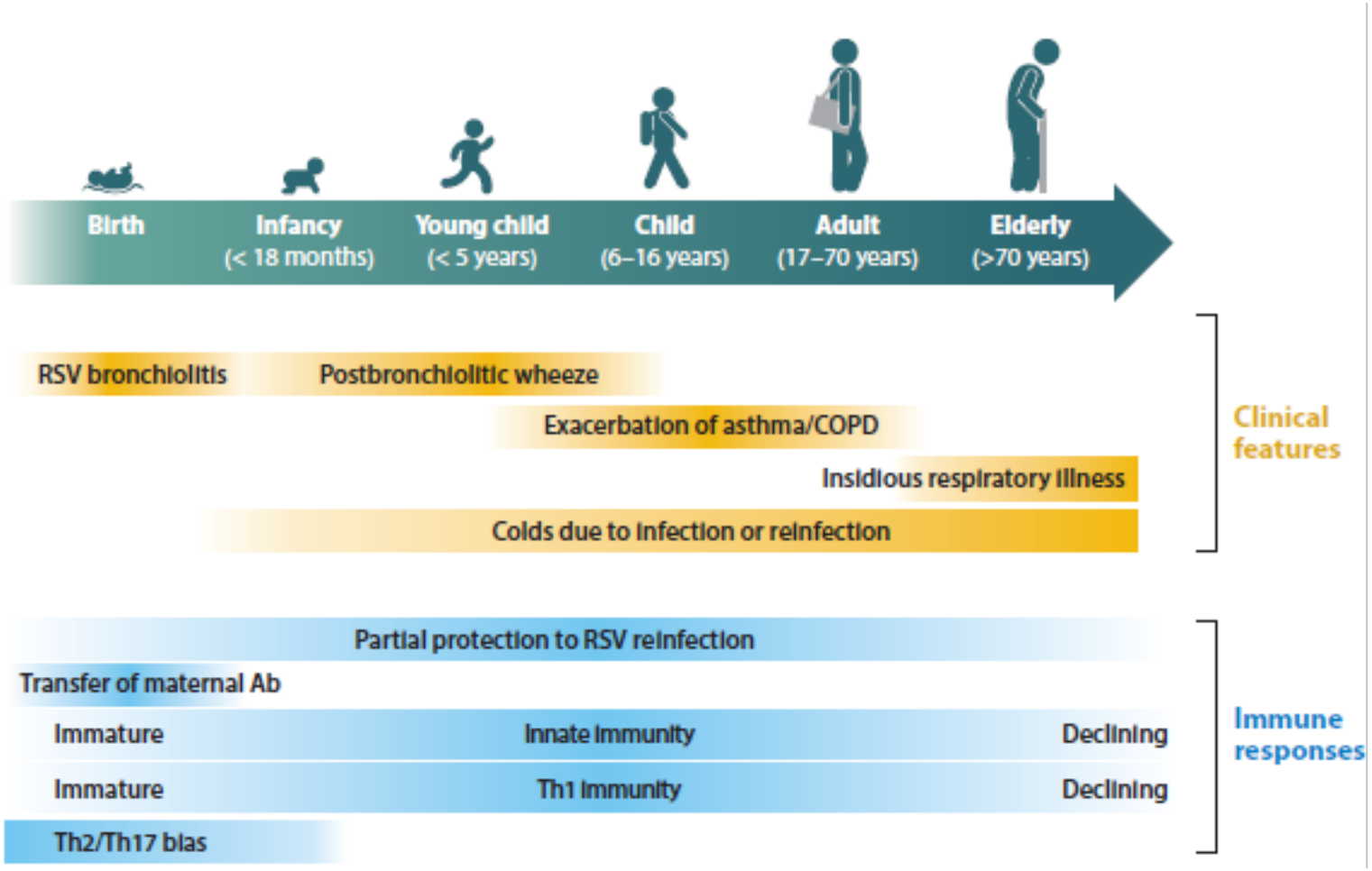
2019

Protective and harmful immune responses to RSV infection



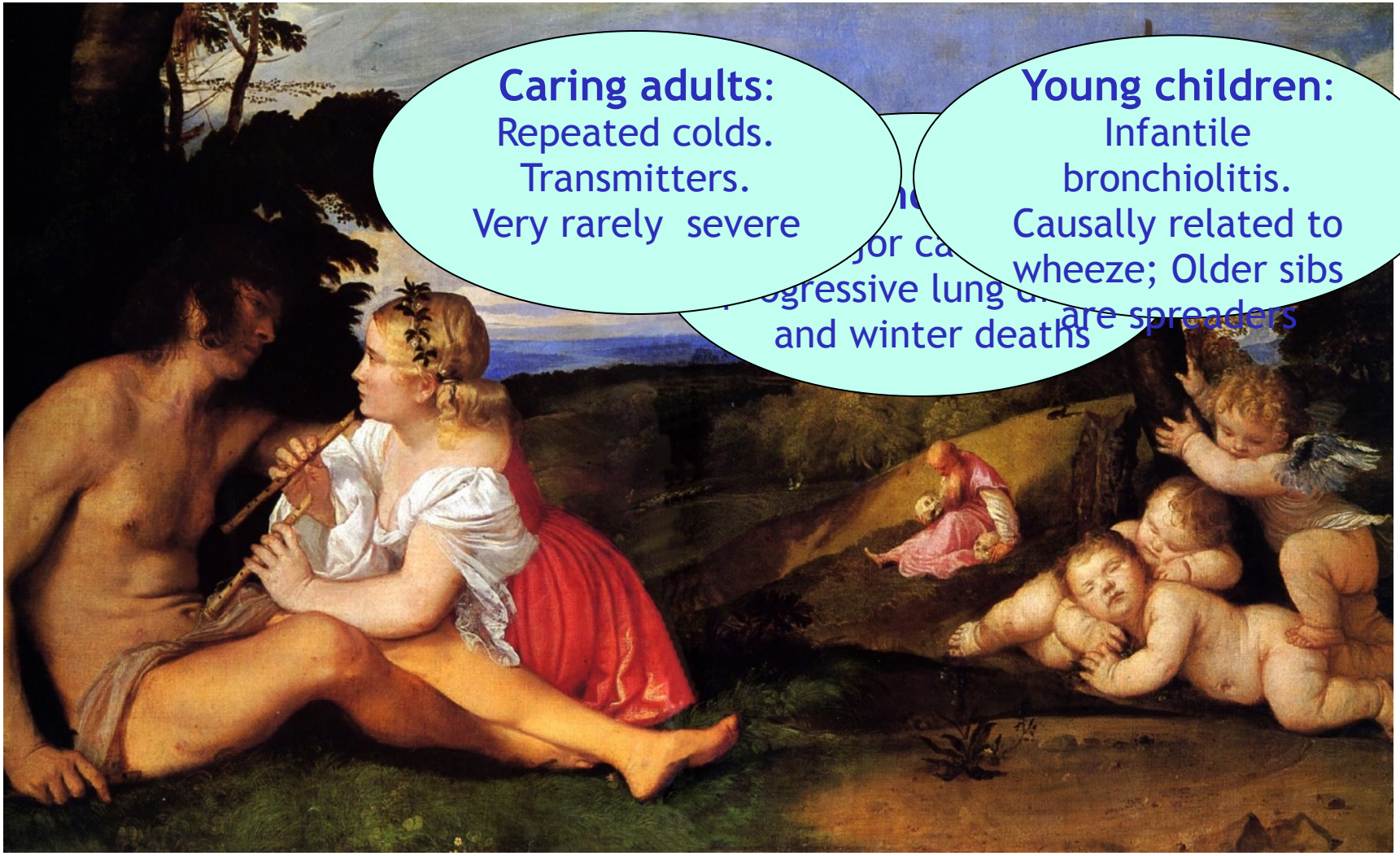
Openshaw, P.J., Chiu, C., Culley, F.J., and Johansson, C. **(2017)** *Annu Rev Immunol 35*, 501–32

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 through the ages



Three ages of man, Titian, National Gallery of Scotla

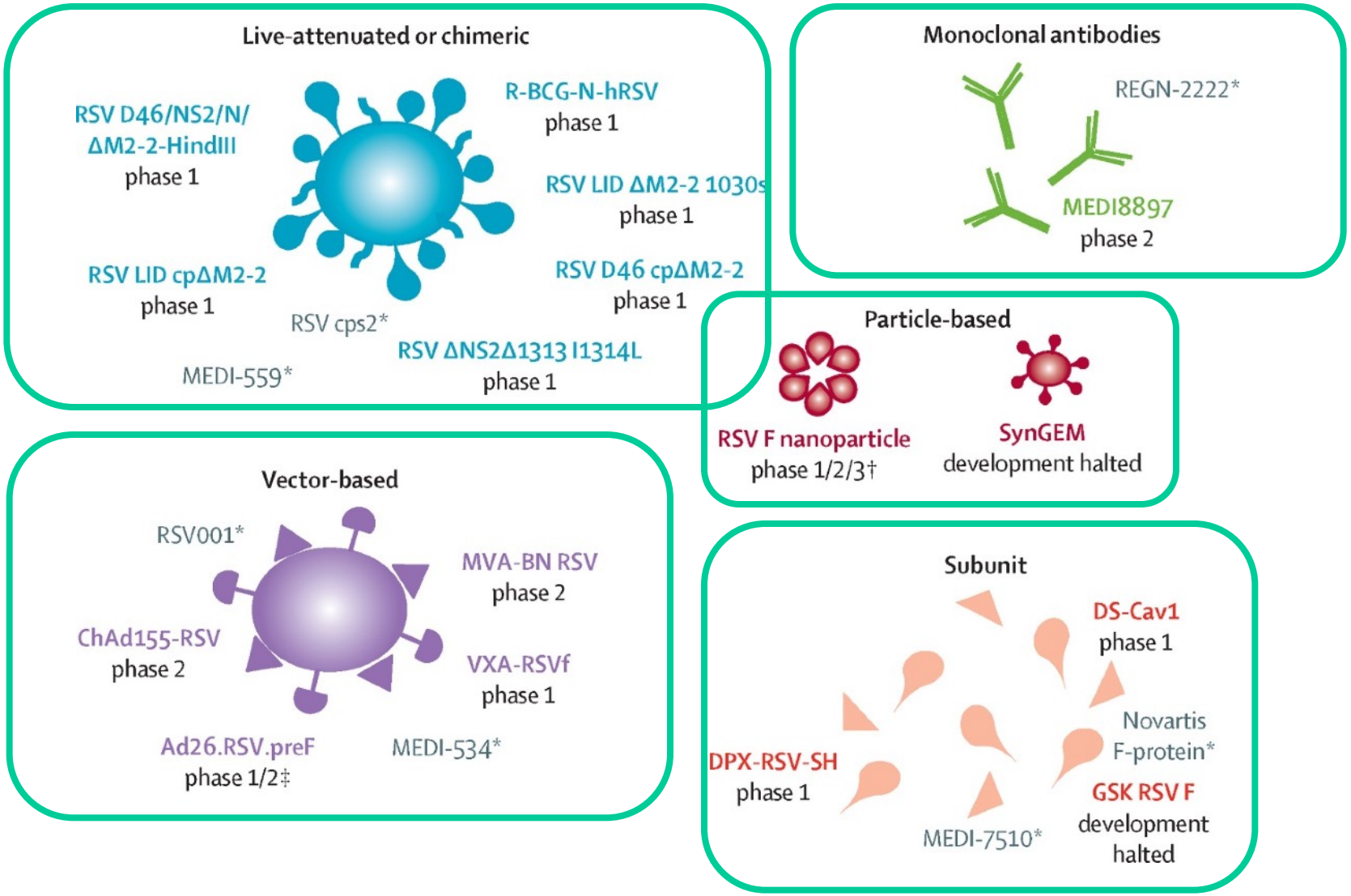
The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates

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



Another Investigational Vaccine Fails to Reduce RSV Infections

OCTOBER 12, 2017

Kenneth Bender

The latest investigational vaccine to be unsuccessful in targeting respiratory synctial virus (RSV) demonstrated immunogenic activity in older adults — without reducing their rate of infection.

Ann Falsey, MD (pictured), University of Rochester, New York, and colleagues reported results from a phase 2 clinical trial of a candidate vaccine (MED17510) containing the postfusion F protein of the RSV virus. The formulation also contained an adjuvant for the target population of older adults, who can be affected by the illness but have compromised response to vaccines from natural immunosenescence.

The F protein has been used with other RSV candidate vaccines as it is on the viral envelope, mediates viral entry into the host cell, and has previously been shown susceptible to serum neutralizing activity. There has yet to be a successful vaccine candidate against RSV, however. The most effective intervention has been use of monoclonal antibody palivisumab (Synagis), to bind postfusion F protein to prevent RSV disease in infants.

Faley and colleagues reported finding the candidate vaccine did promote an immunogenic response, but did not protect the older adults cohort from illness. The incidence of confirmed RSV illness occurring at least 14 days after dosing was 1.7% and 1.6% in the vaccine and placebo groups, respectively.

Novavax Nears Maternal Immunization Results for RSV Vaccine

JANUARY 18, 2019

Kevin Kunzmann

@NotADoctorKevin

Gregory M. Glenn, MD

The state of maternal immunization is much different now than from when Gregory M. Glenn, MD, first started in healthcare. It was a widely studied field, but still not as practiced in pregnant women.

Now, Glenn, president of Research & Development for Novavax Inc., and his team of investigators are at the cusp of revolutionary development for maternal vaccines.

The Maryland-based clinical-stage vaccine company intends to share data in the following weeks on its first clinical trial of an investigative respiratory syncytial virus (RSV) vaccine in third-trimester pregnant women. Its findings and eventual successive studies could alter the scope of care for RSV, the most common cause of bronchiolitis and pneumonia in children younger than 1 year old in the US.

The trial—which has been ongoing for 4 years and has assessed the potential vaccine in about 3000 treatment-eligible pregnant subjects in that time—has been carried out by teams comprised of RSV, vaccination, and maternity-care specialists across 11 countries. "This is an incredible number of people working on a trial," Glenn told *MD Magazine®*. "And because they're on the front line, they are extremely excited at the prospect of having a vaccine for infants."

Goals and design

THE Prepare TRIAL

Primary objective

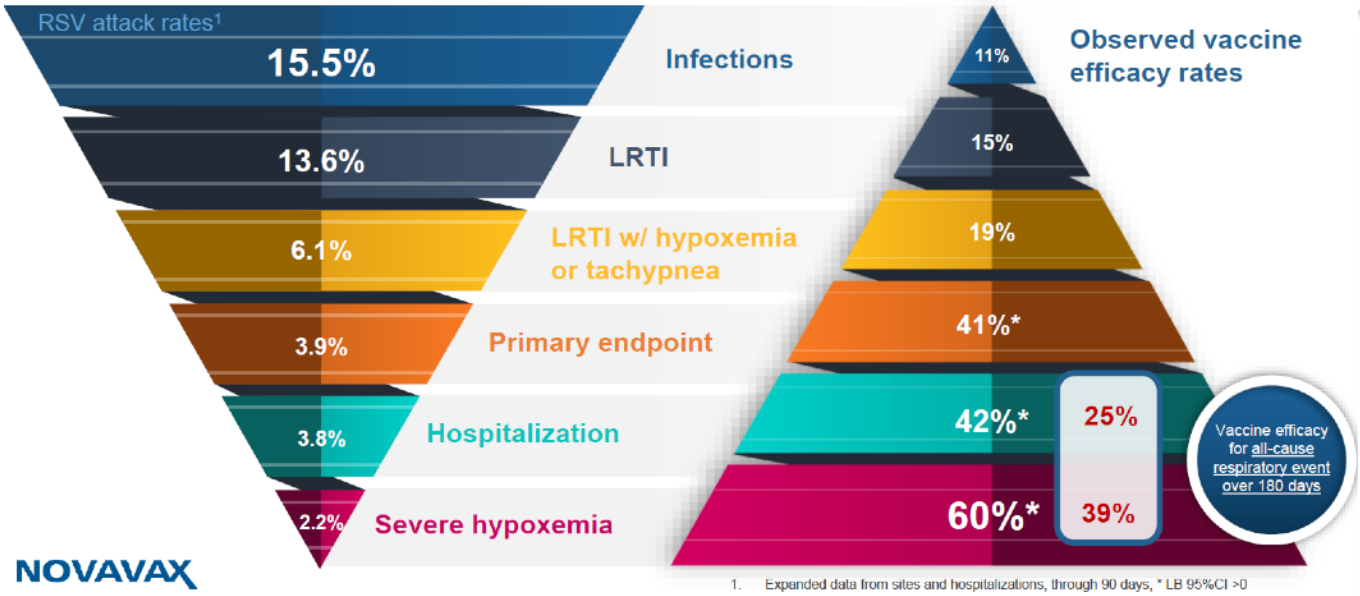
Determine the efficacy of maternal immunization with the RSV F vaccine against medically significant symptomatic RSV lower respiratory tract infection (LRTI) through 90, 120, 150 and 180 days of life in infants.

Design	Randomized, Observer-Blind, Placebo-Controlled	
	Number of Participants	• 4,636 third trimester pregnant women randomized 2:1 (vaccine:placebo)
	Length of Study Participation	• Maternal Participants: up to 9 months • Infant Participants: 1 year after delivery
	Dosing	• 1 intramuscular (IM) Injection of RSV F Vaccine or Placebo at 28-36 weeks Estimated Gestational Age (EGA)
	Safety Assessment	• Through 6 months post-partum in mothers • Through 1 year in infants

	Efficacy Assessment	• Active/passive surveillance in mothers and infants
		  • Confirmation of RSV infection by RT-PCR
		  • Medically significant tachypnea or pulse oximetry
		  • Confirmation of LRTI
		  • Data collected at clinical sites or from both site and hospitalization records

Novavax update
28th Feb 2019

Vaccine impact on all-cause respiratory disease



NOVAVAX

1. Expanded data from sites and hospitalizations, through 90 days, * LB 95%CI >0

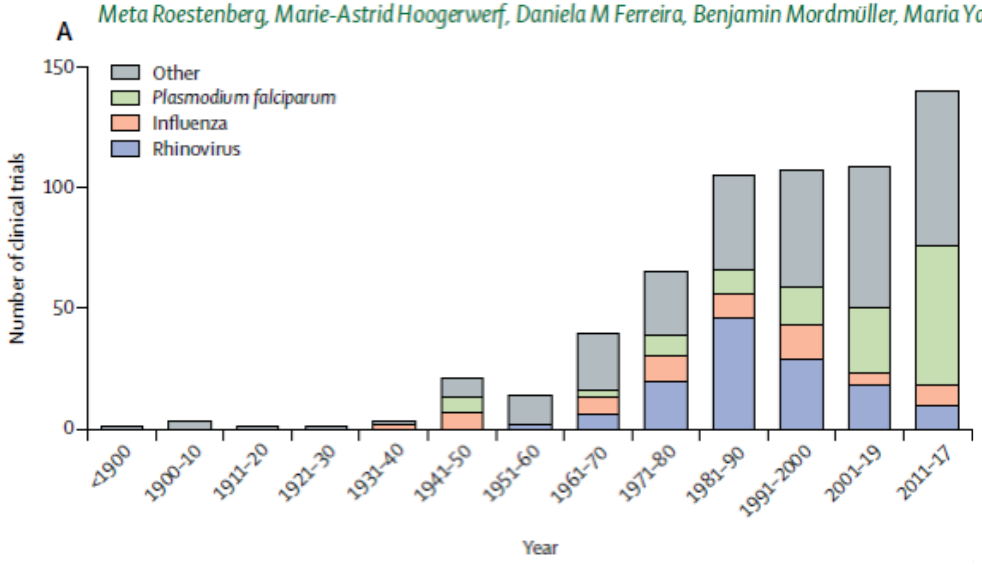
Challenge models

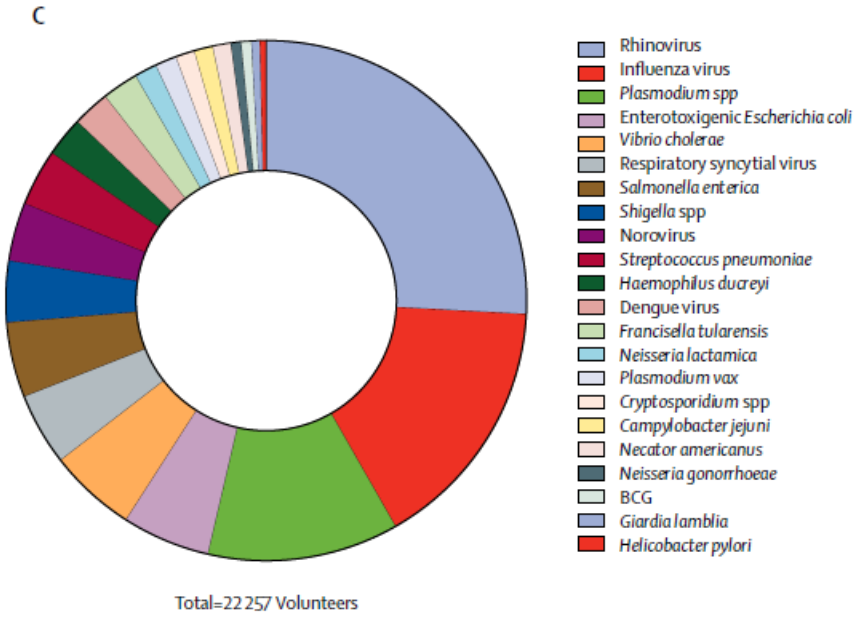
Experimental infection of human volunteers

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





Human Infection Challenge (HIC)

- A **Human Infection Challenge** is a carefully managed research study during which volunteers are purposefully exposed to an infection, in a safe way and with healthcare support.

- HIC studies are a valuable tool for understanding the underlying immunological response to infection, and enabling, accelerating and de-risking the development of novel drugs and vaccines.

- There are robust ethical review processes in place to protect the safety of volunteers.

What is HIC-Vac?

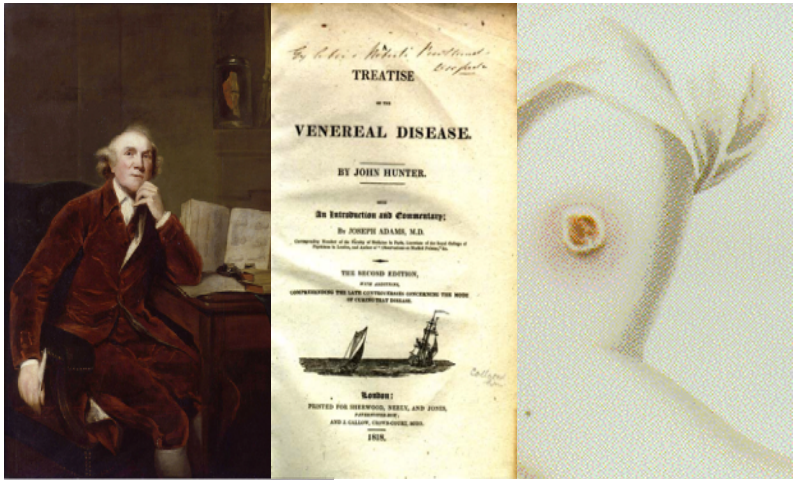
£3m, 4 year MRC & BBSRC-funded network

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

- The UK has **unique strengths**
- Extensive **infrastructure**
- **Need and utility is great**: new vaccines, rapid advances in immunological understanding
- **Strong commercial buy-in**
- All our investigators work on **LMIC** diseases and/or have **LMIC** collaborators

Experimental Human Infection Models "are on the rise"



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SHARE

1K

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

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

Our shared objectives

NETWORKING

- Create an interactive, supportive network of investigators
- Form bridges between the UK and LMICs
- Exchange of eligible volunteers between programmes

UNDERPINNING

- Facilitate and support regulatory and ethical structures
- Enhance and support applications to science funders
- Enhance public understanding of HIC in the UK/LMICs
- Enable and de-risk phase III vaccine studies

Networking

Total members May, 2019: 275, ~25% LMIC

1. **Investigators (91)**: Independent current HIC studies
2. **Associates (97)**: Work with Investigators (Postdoc *etc.*)
3. **Affiliates (87):** 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

Catalyst activities: Pump-priming awards

AIMS:

- *Develop and improve HIC studies*
- *Enhance and support applications to science funders*
- *Enable and de-risk phase III vaccine studies*

June 2018: Awarded 9 pump-priming projects

- 14 out of 15 applications were scored fundable.
- Awards were up to £100,000
- 4 led by PIs in LMICs (Zambia, The Gambia, Kenya)
- Cover a range of pathogens (flu, SV, rotavirus, typhoid, schistosomiasis)
- Industry partners involved

Regulatory & ethical frameworks

Events

Academy of Medical Sciences Regulatory workshop

- Output: report published

Activities

•Working with the Wellcome Trust to implement points in AMS report and developing funder's principles

•A new joint initiative with Wellcome Trust and Bill & Melinda Gates Foundation: Global Health Network platform

- Sharing information
- Developing training programmes

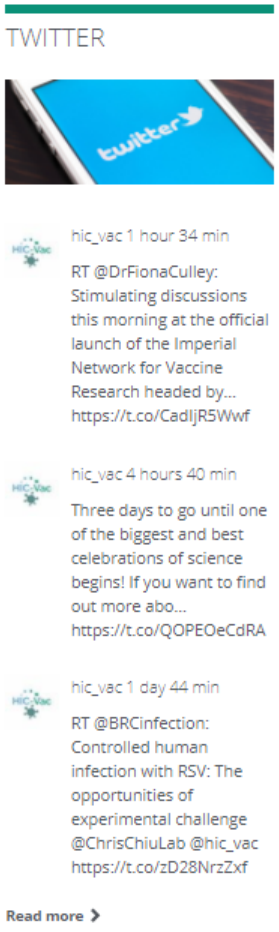
THE GLOBAL HEALTH NETWORK
Enabling research by sharing knowledge

Find out more

www.hic-vac.org

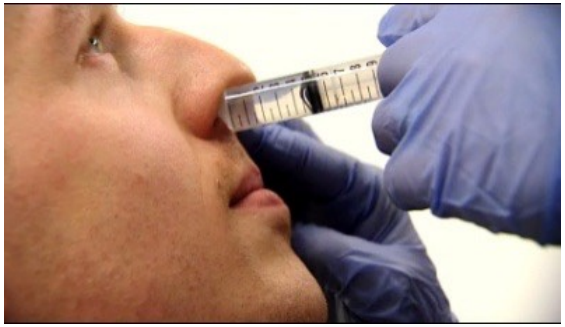
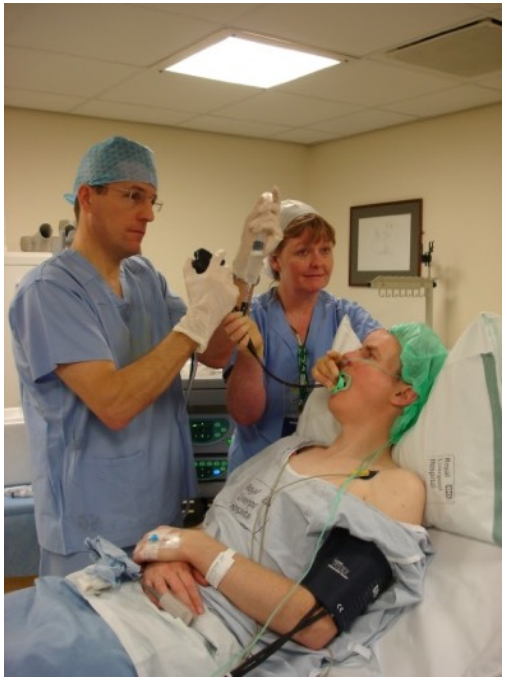
Join us on Twitter

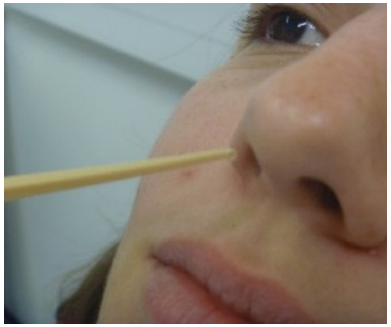
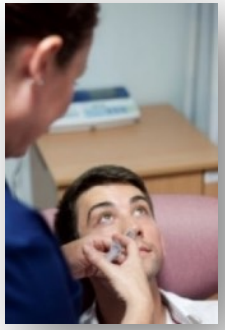
@hic_vac

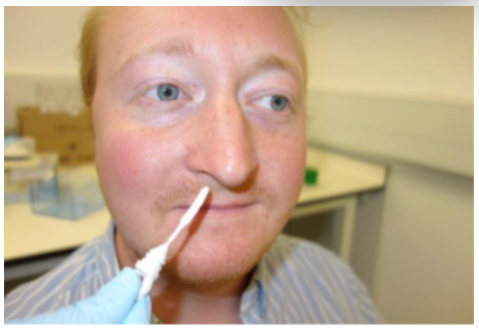
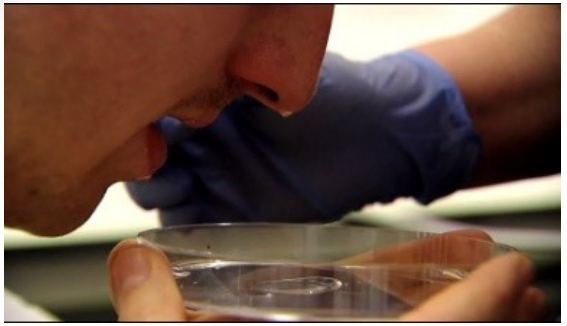


Volunteers are willing to do a lot…



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Infection of adult volunteers

- **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

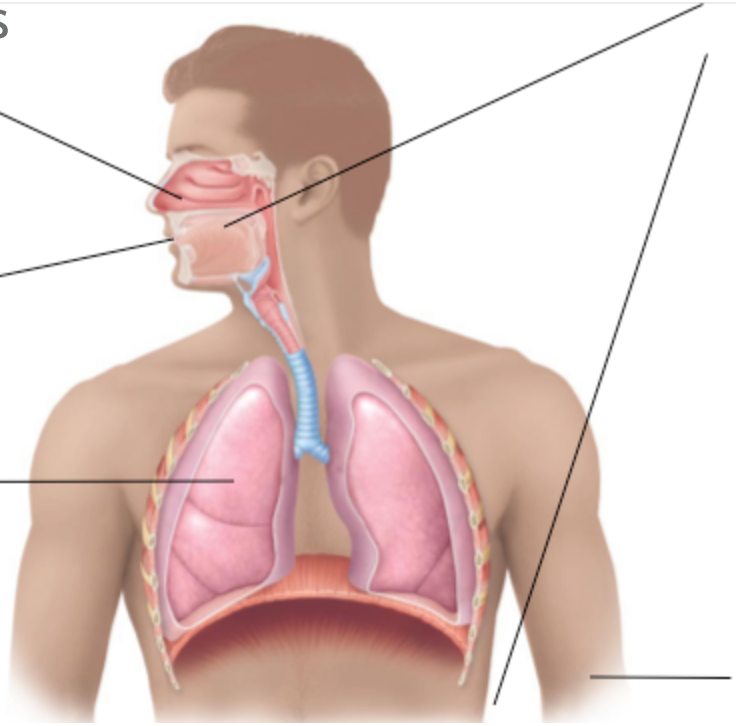
Imperial College London

Samples Taken before and during infection

Nasal
SAM, wash, scrapes
(AMC & IC)

Breathomics
(AMC)

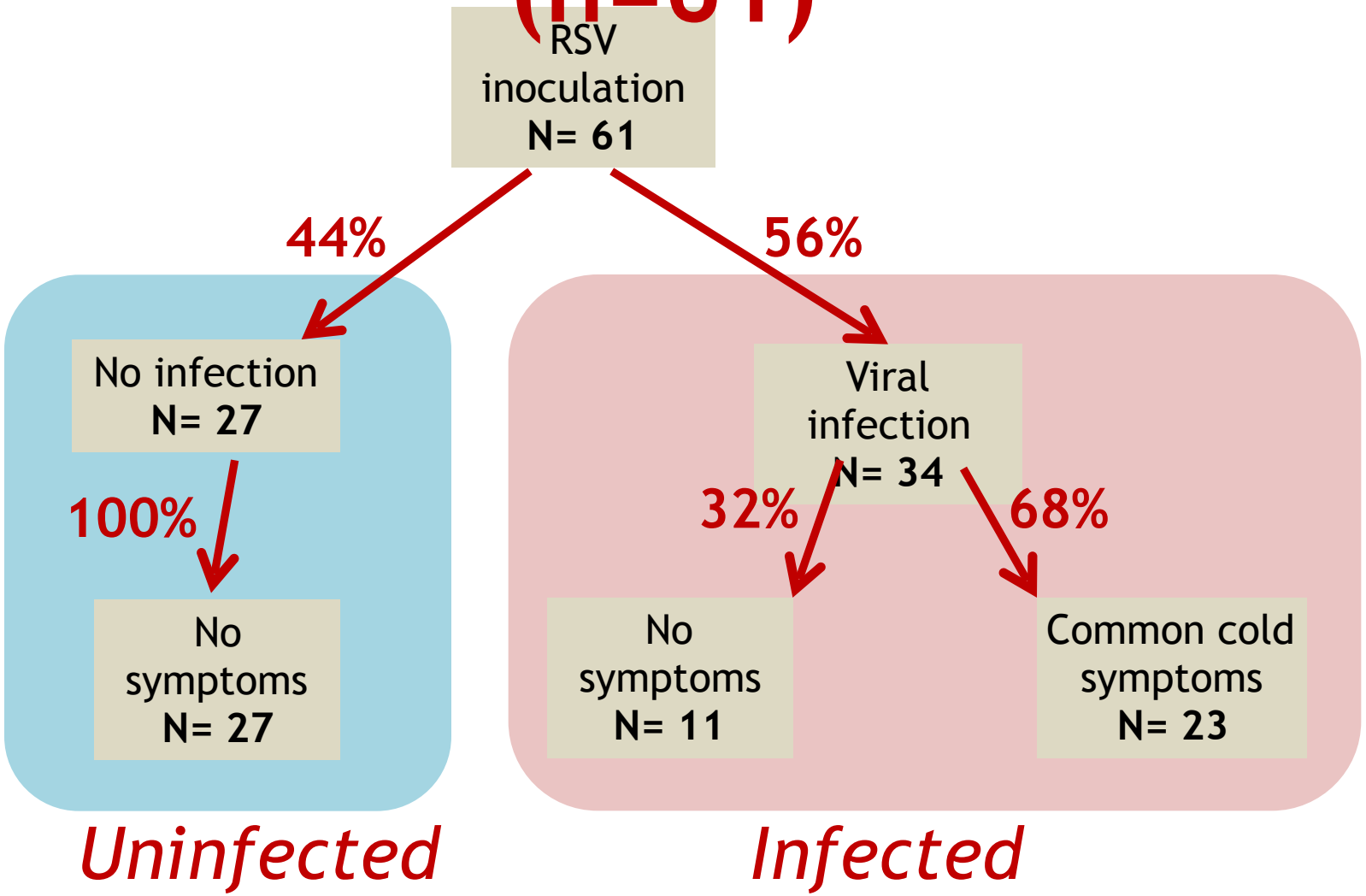
Bronchial
Brushings,
BAL, biopsies,
secretions
(AMC & IC)



Microbiome swabs
(AMC)

Blood
PBMC, serum, plasma
(Split, AMC, IC)

Infection rates and colds (n=61)



No difference between males and females
No relationship between age and infection rate or colds

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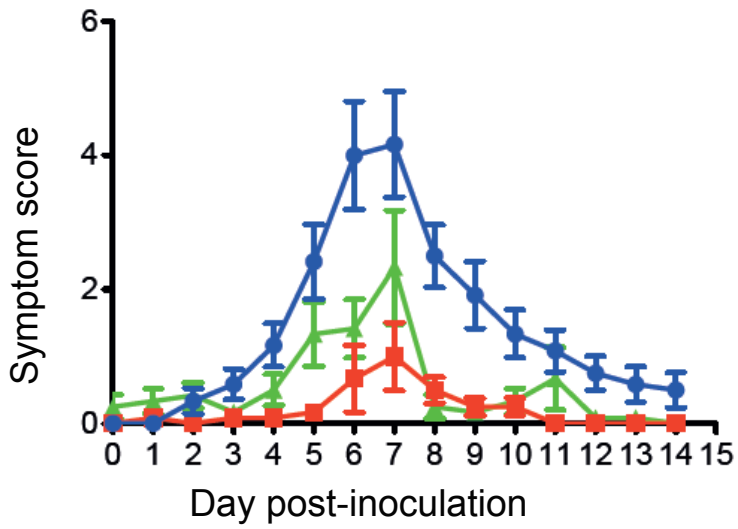
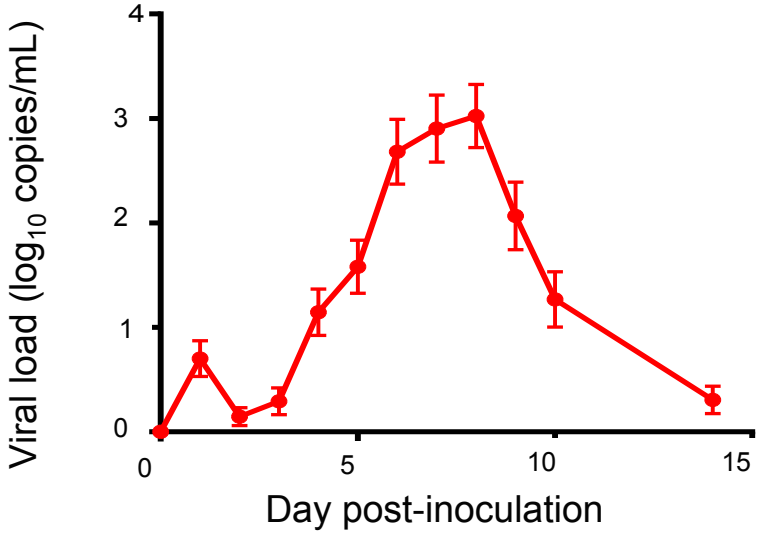
Symptoms & viral load: RSV challenge





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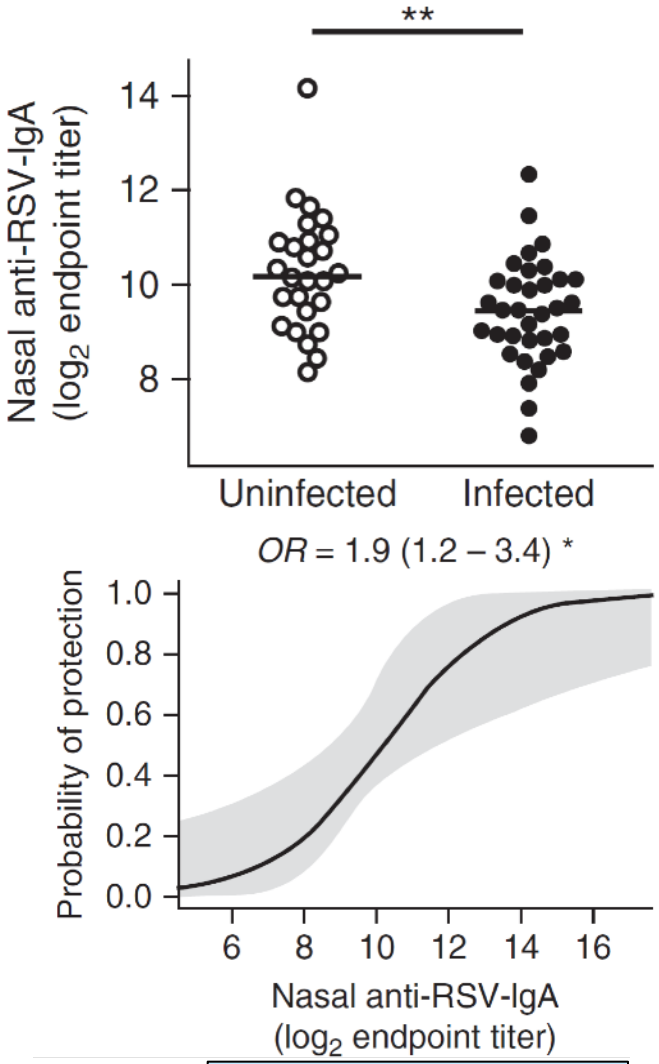
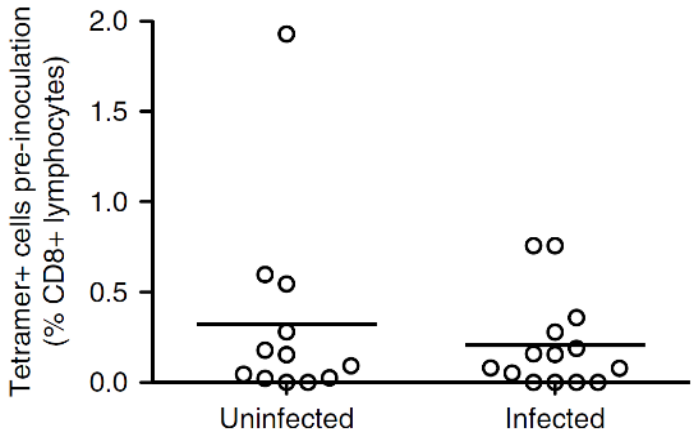
What prevents infection?



Habibi et al. *AJRCCM* (2015)

- Very high nasal antibody titres offer some protection
- High probability of protection would require supernatural titres



Jozwick et al. *Nat Comms* (2015)

- $CD8^+$ T_{RM} influence severity, but not rate of infection

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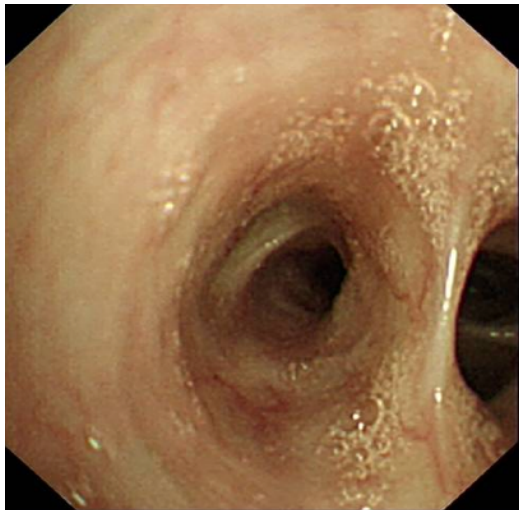
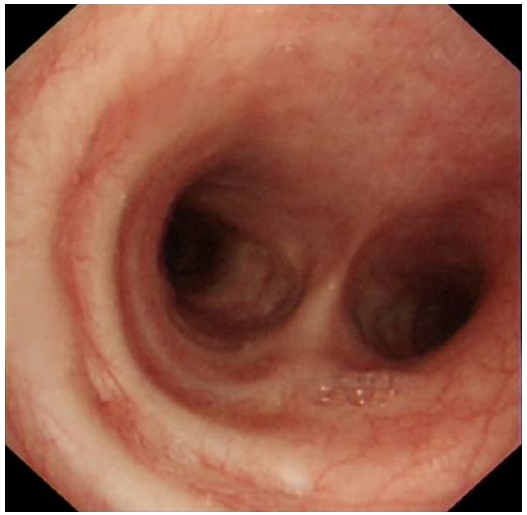
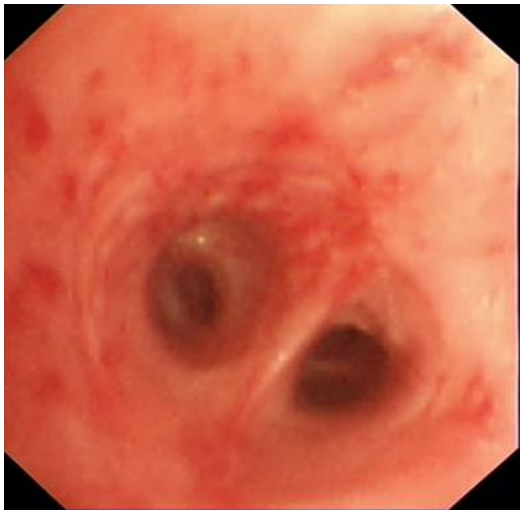
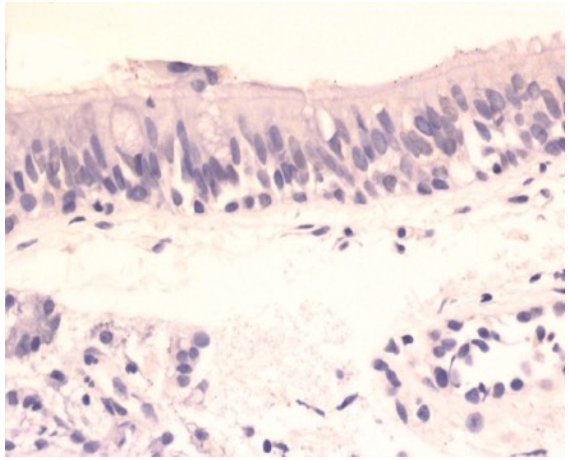
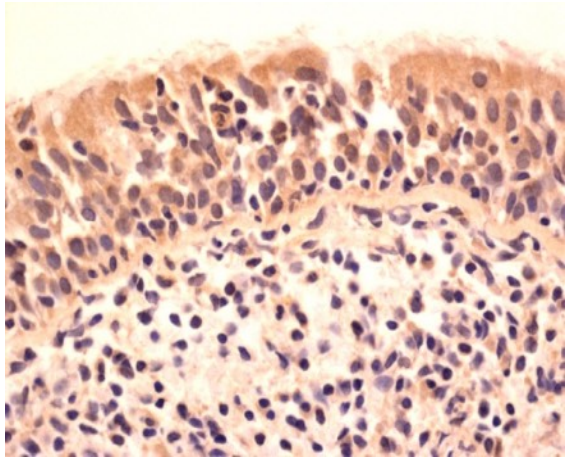
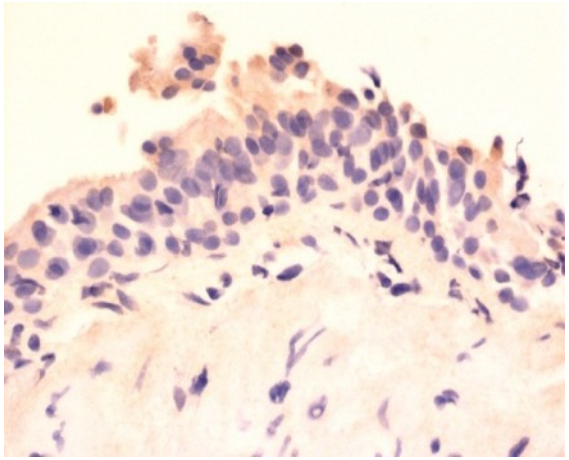
Lower airway inflammation after RSV challenge

Day 0 | Day 10 | Day 28

RSV antigen by immunohistochemistry

INFLAMMAGE: clinical and inflammatory endpoints reflective of infective COPD exacerbation

- Infective exacerbations in COPD
  - In COPD, around 11% of hospitalisations are caused by respiratory syncytial virus (RSV)[1]
  - RSV impact on health care is similar to (or possibly greater than) influenza[1]
  - Repeated exacerbations reduce life expectancy[2]
- New endpoints that reflect druggable pathways are needed
- A human translational model with novel endpoints can aid the field
  - Establishment of biomarkers that correlate with infective exacerbations
  - Identification of novel druggable disease pathways (dysregulated during infection)
  - Provide a COPD-like human model for early proof of efficacy studies

INFLAMMAGE will extend the experimental human RSV infection studies established at Imperial College to investigate the pulmonary response to RSV infection in older adult smokers and non-smokers

[1]Fleming DM *et al*, *BMC Infect Dis* **15**:443, 2015
[2]Soler-Cataluna *et al.*, *Thorax* **60**:925, 2015

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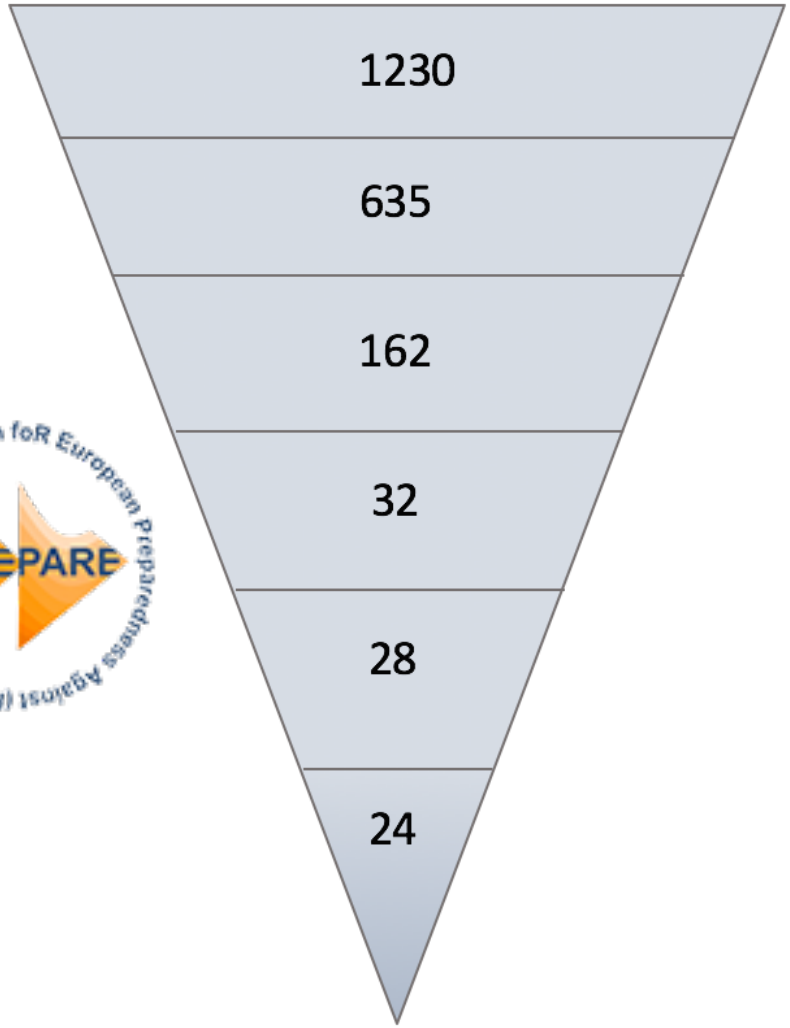
Volunteer rrecruitment – May 2015 to November 2016



Responded to posters/adverts

Pre-screened

Screened for seronegativity

Safety screening

Suitable for enrollment in study

Enrolled in the study

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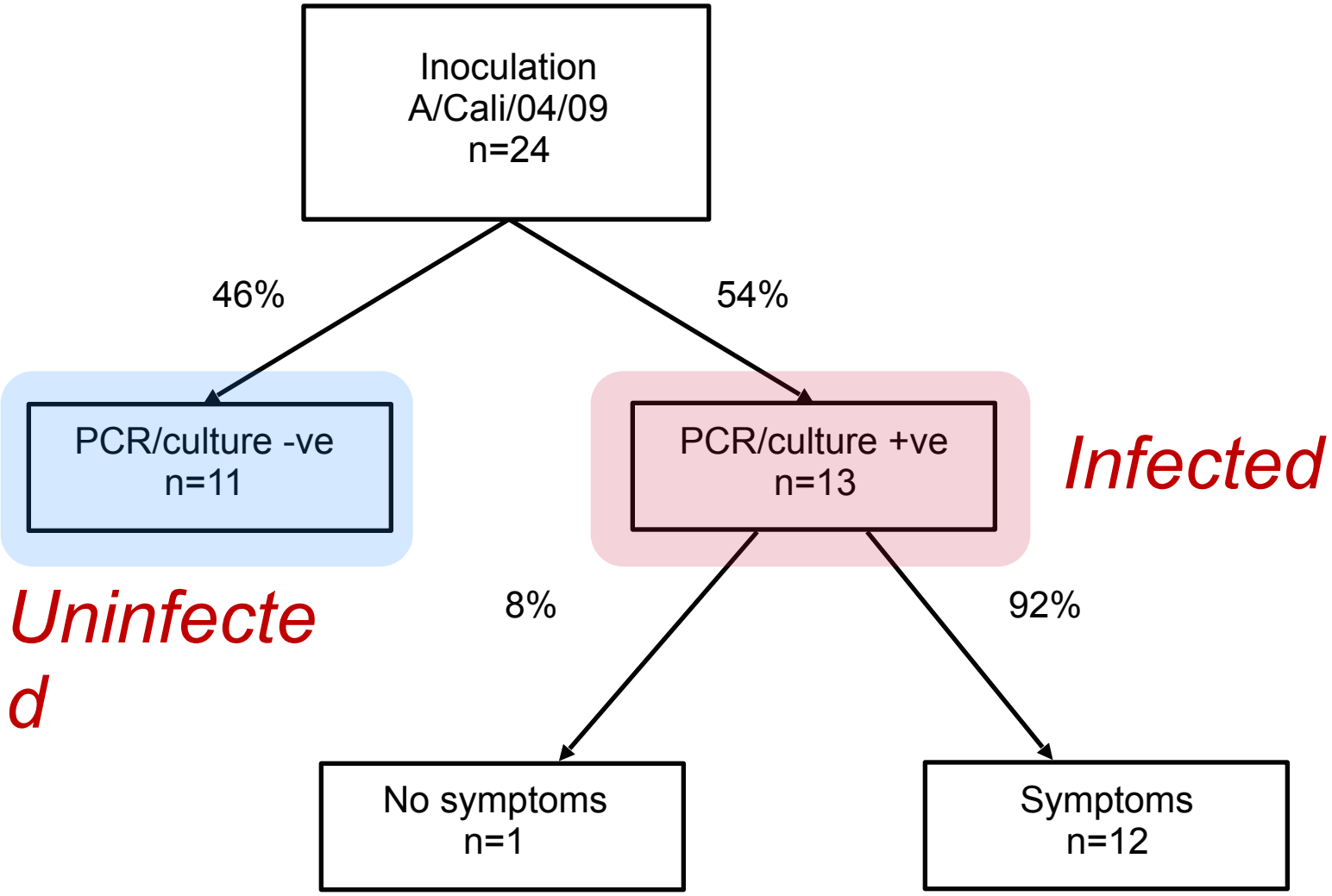
Infection rate after pH1N1 influenza challenge



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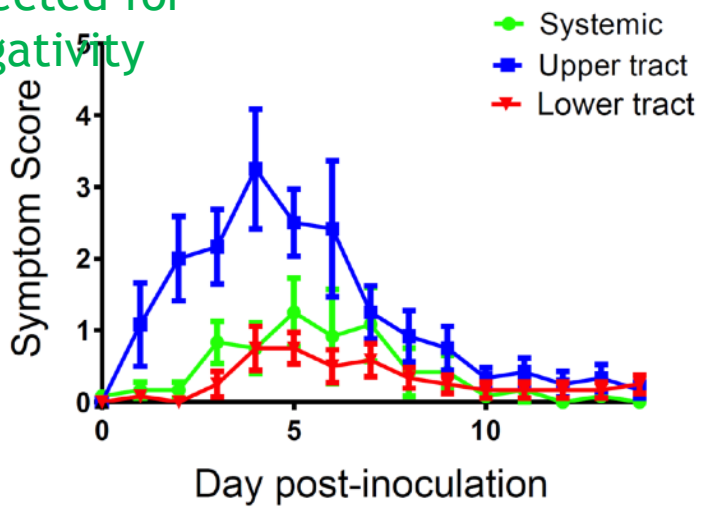
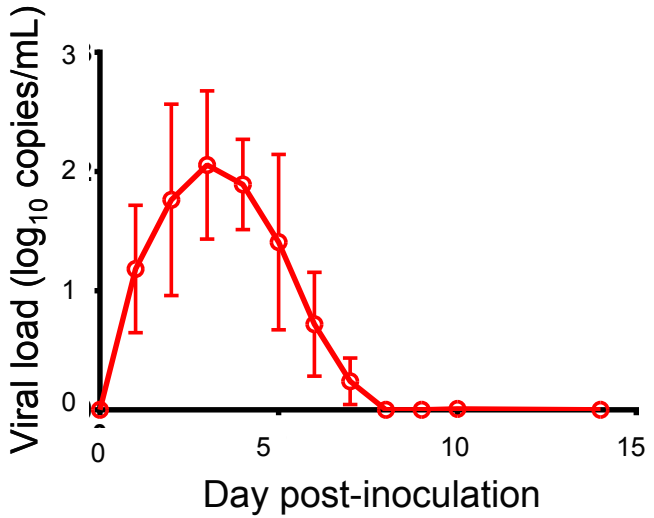
Symptoms & viral load: comparing RSV and flu

Pre-selected for seronegativity

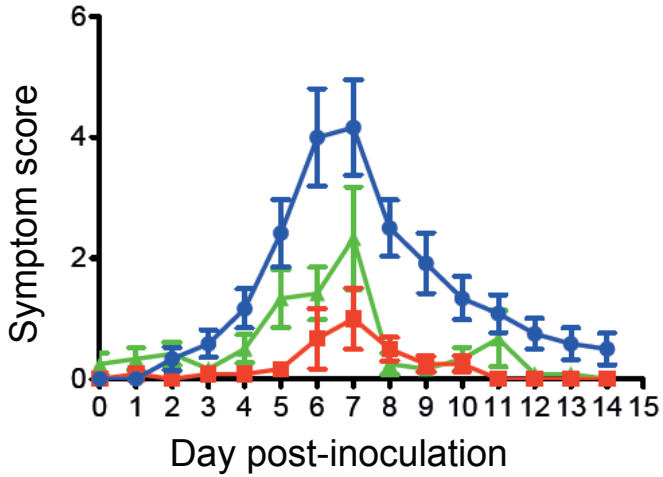
Influenza

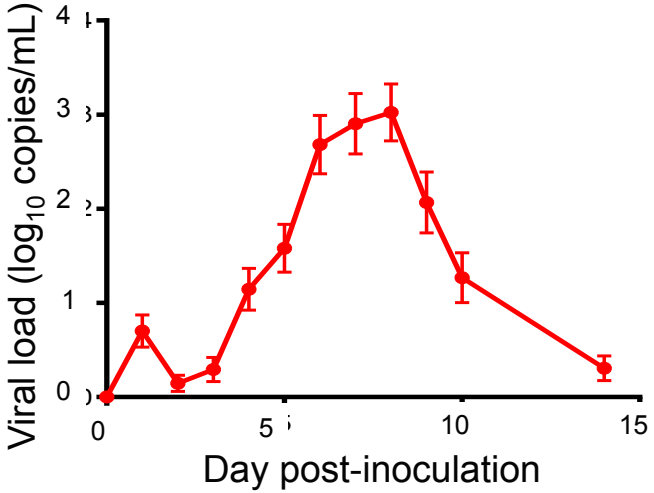




Not pre-selected for seronegativity

RSV





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pH1N1 challenge

- About 80% of volunteers are already immune
- Human pH1N1 challenge has (so far) been safe
  - Allows for multiple compartment sampling
  - Allows alignment of transcriptomic analyses with viral kinetics
- Great heterogeneity of outcome
  - Despite seronegativity, 11/24 were resistant to infection
  - Range of symptom severity/onset & viral loads

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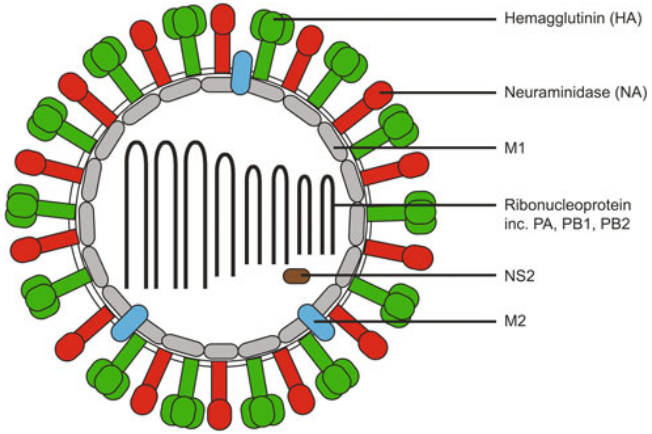
Influenza vs respiratory syncytial virus

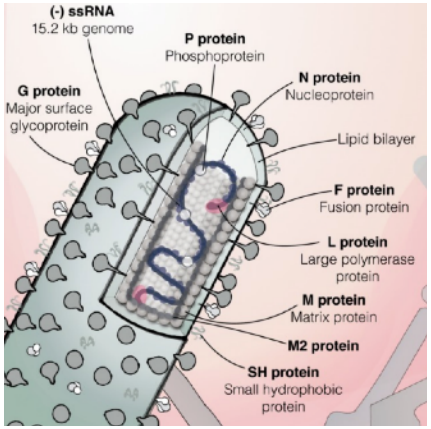
Influenza



Many volunteers excluded during selection

- **Symptoms** in most infected volunteers
  Rapid onset; peak day 3-4
- **Lung inflammation** in lung peaks on d7
- **T cells** peak:
  - Blood d7
  - BAL: d7 then decline
- **B cell** response strong and long-lasting

RSV



Volunteer selection is relatively simple

- **No symptoms** in 1/3rd of infected volunteers
  Delayed onset; peak day 7
- **Lung inflammation** in lung continues to d28
- **T cells** peak:
  - Blood d10
  - BAL: continue to accumulate on d28
- **B cell** response weak and transient

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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 Johnst

Allan Paras
Zoe Gardener
Steff Ascough
Anakin Ung
Jie Zhu
Jerico Del Rosario
Hiromi Uzu
Helen Piotrowski
Jennifer Brimley
Belen Trujillo-Tor
A Sett
Bj rn Pet s
John Sidney

Rafi Ahmed
Jens Wrammert
Xander de Haan

Thank you

wellcome trust

PREPARE

MRC Medical Research Council

NHS National Institute for Health Research