Imperial College London

3rd Feb 2019
ASM Melbourne, Australia
Virtual presentation

ISG
Influenza Specialist Group

Developments in RSV vaccines

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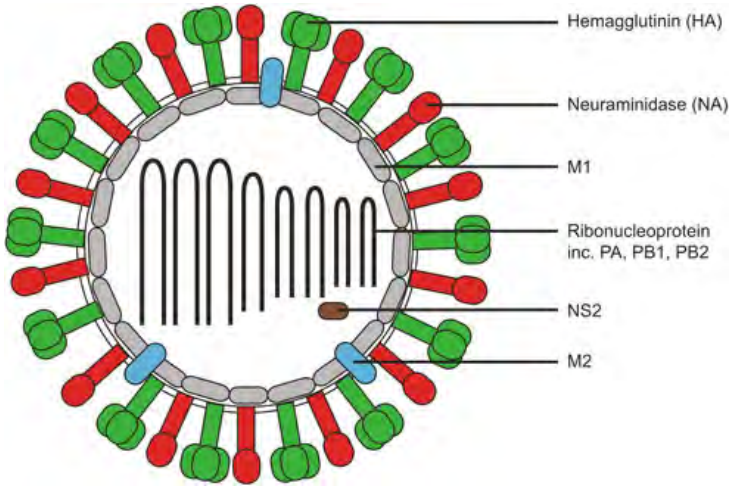
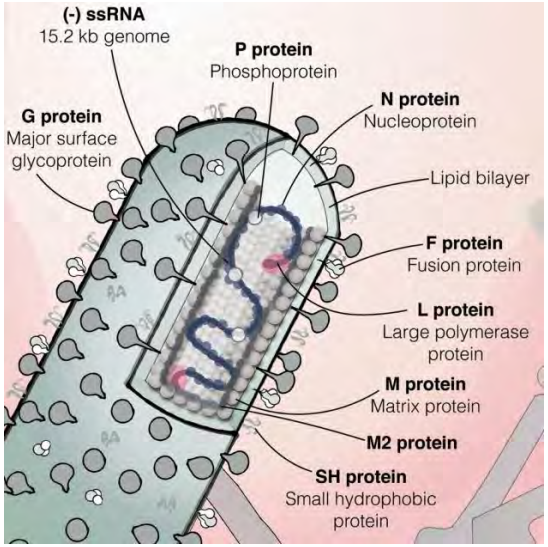
Influenza vs respiratory syncytial virus

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)

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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

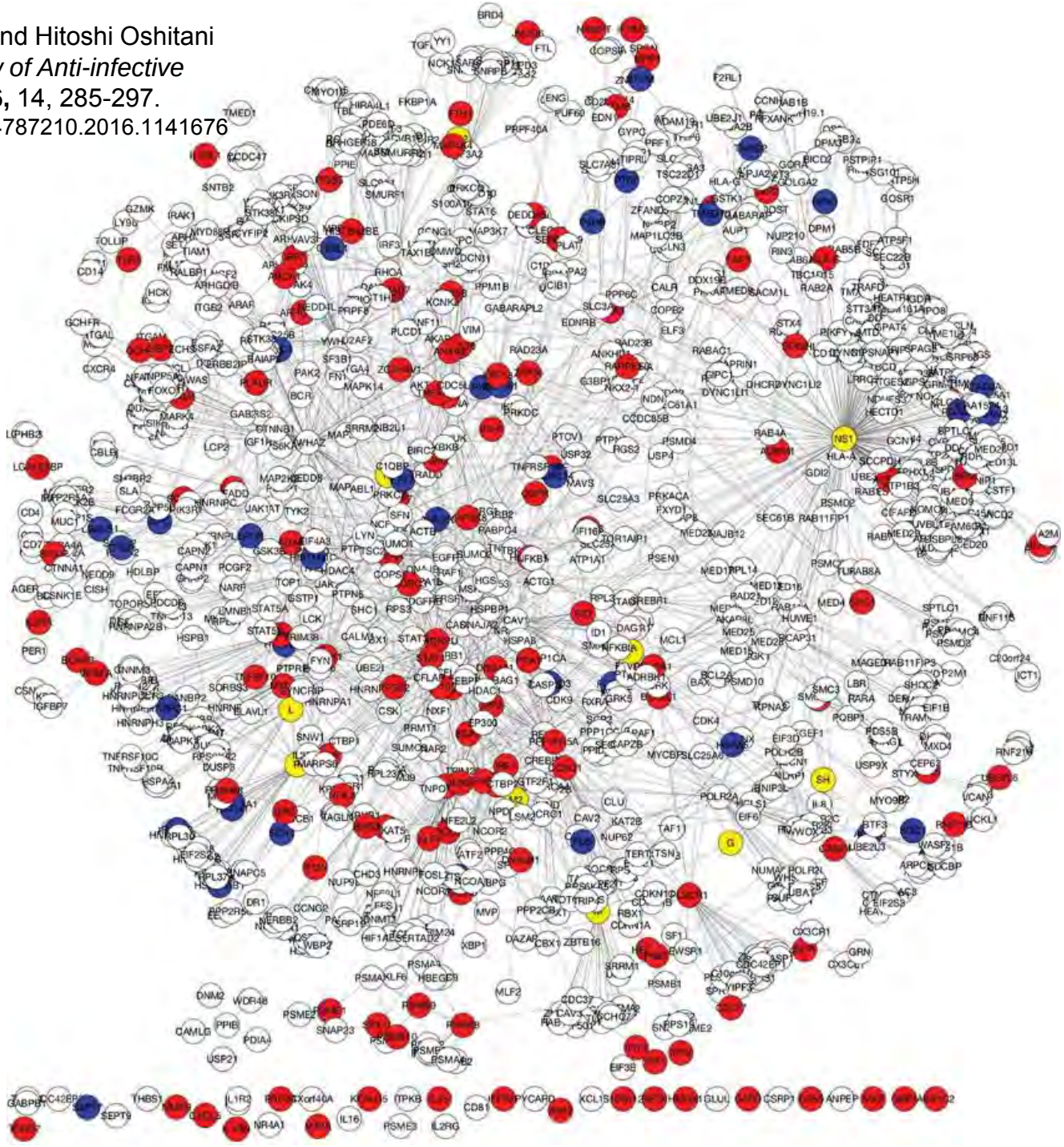
- G protein binds to CX3CR1 on pDC/cilliated cells
- Secreted G acts as a decoy for antibody
- F binds to TLR4, possibly causing innate desensitisation

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

Clyde Dapat and Hitoshi Oshitani
Expert Review of Anti-infective Therapy **2016,** 14, 285-297.
DOI: 10.1586/14787210.2016.1141676



RSV-host interaction network

The network contains 1,254 proteins (nodes) and 1,989 interactions (edges), which was constructed using HIPPIE and VirHostNet databases and visualized using Cytoscape.

Yellow nodes represent RSV proteins

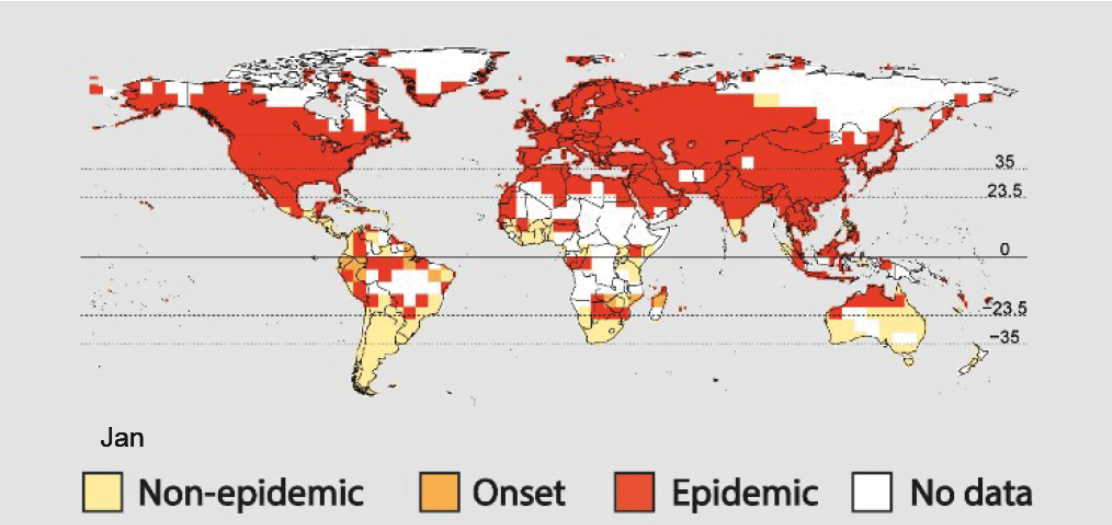
Red nodes indicate upregulated host factors and blue nodes represent downregulated host factors during RSV infection.

Gray nodes represent disconcordant expression level of host factors between and among transcriptome and proteome datasets.

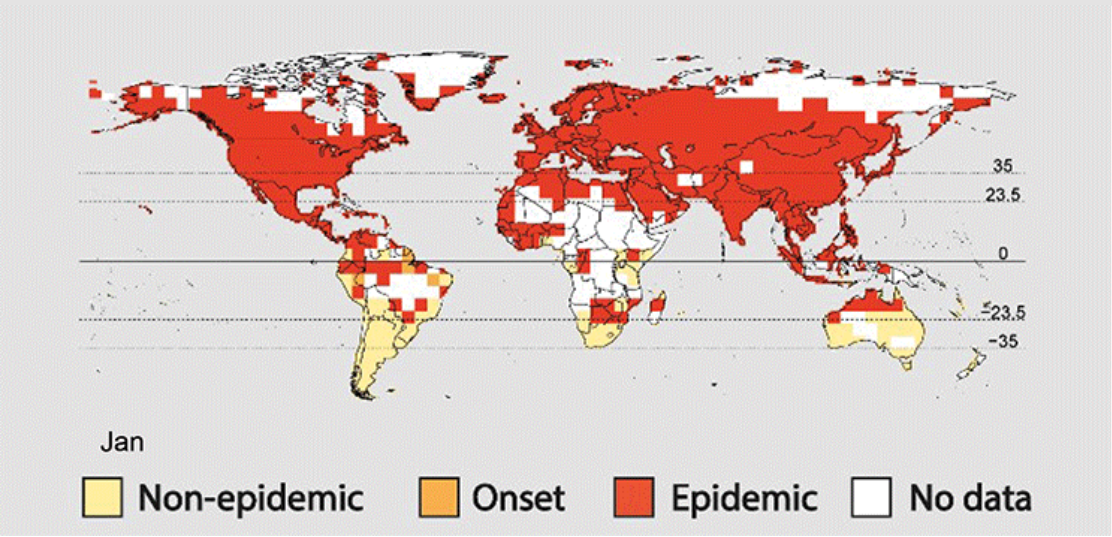
White nodes represent protein interactors identified from the databases.

Global changes in RSV and flu prevalence month by month

RSV



Flu



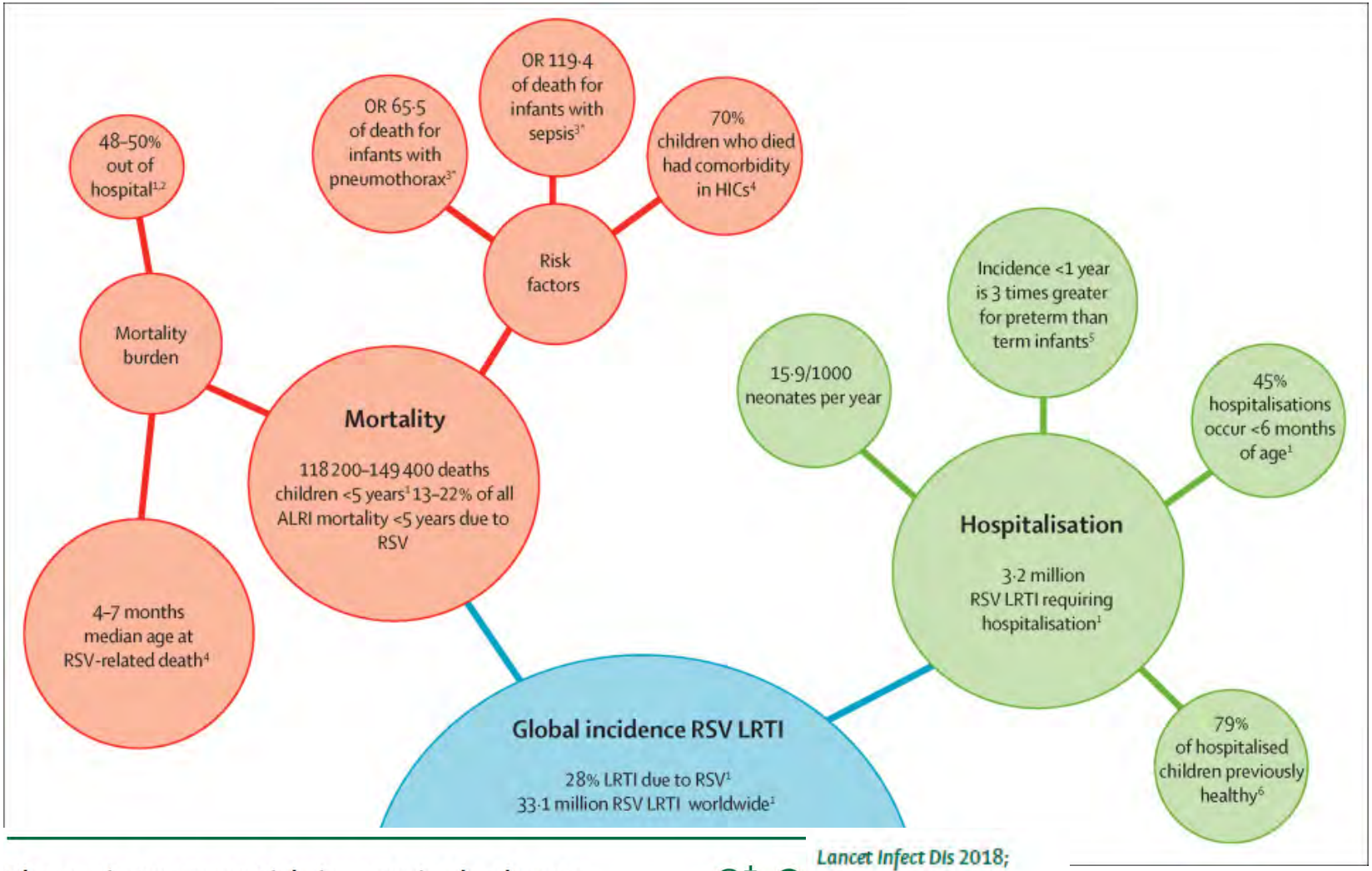
RESCEU
REspiratory Syncytial virus Consortium in EUrope

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

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

ORIGINAL ARTICLE

Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants

Maarten O. Blanken, M.D., Maroeska M. Rovers, Ph.D., Jorine M. Molenaar, M.D., Pauline L. Winkler-Seinstra, M.Sc., Adam Meijer, Ph.D., Jan L.L. Kimpen, M.D., Ph.D., and Louis Bont, M.D., Ph.D., for the Dutch RSV Neonatal Network

Double-blind, 429 healthy preterm infants born (33 to 35 weeks)
Monthly palivizumab (214 infants) or placebo (215 infants) in RSV season

Treatment reduced RSV-related hospitalization from 5.1% to 0.9% (P = 0.01).

Palivizumab caused 61% (95% CI 56 to 65) reduction parent-reported wheezing days in the first year of life [1.8% vs. 4.5%]
Funded by Abbott Laboratories

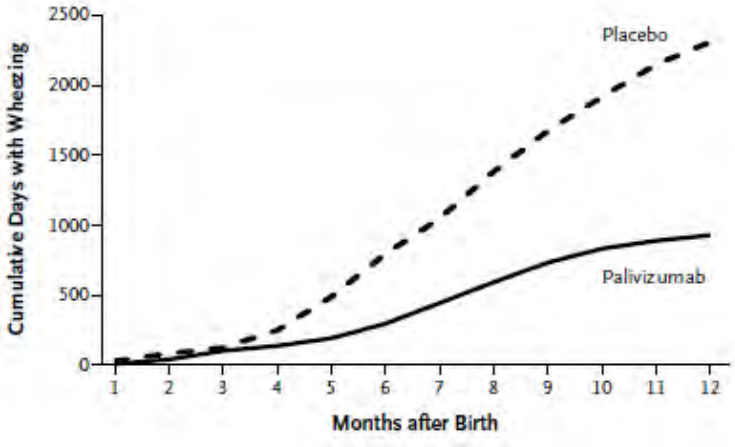


Figure 2. Cumulative Wheezing Days for 429 Preterm Infants during the First Year of Life.
P<0.001 for the comparison between palivizumab and placebo with the use of Poisson regression.

Table 3. Infants with Wheezing.*

Variable	Palivizumab (N=214)	Placebo (N=215)	Absolute Reduction†	Relative Risk Reduction (95% CI)†
Any wheezing — no. of infants (%)	66 (30.8)	101 (47.0)	16.2	34 (14–53)
Wheezing episodes — no.	137	266	129	48 (32–62)
Recurrent wheezing — no. of infants (%)	24 (11.2)	45 (20.9)	9.7	47 (14–80)

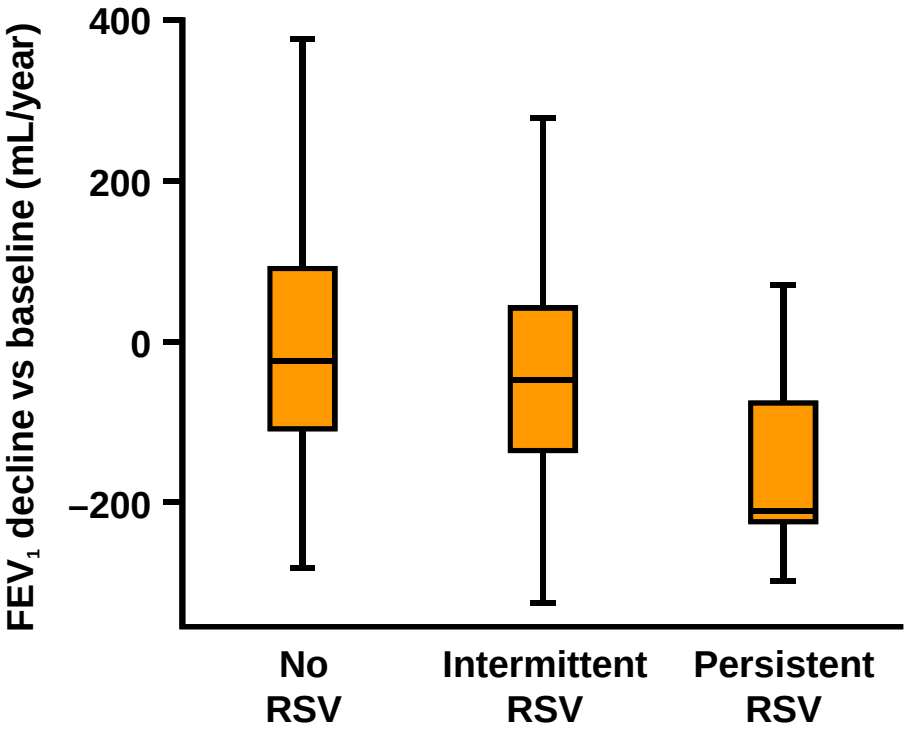
N Engl J Med 2013;368:1791-9.
DOI: 10.1056/NEJMoa1211917

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)



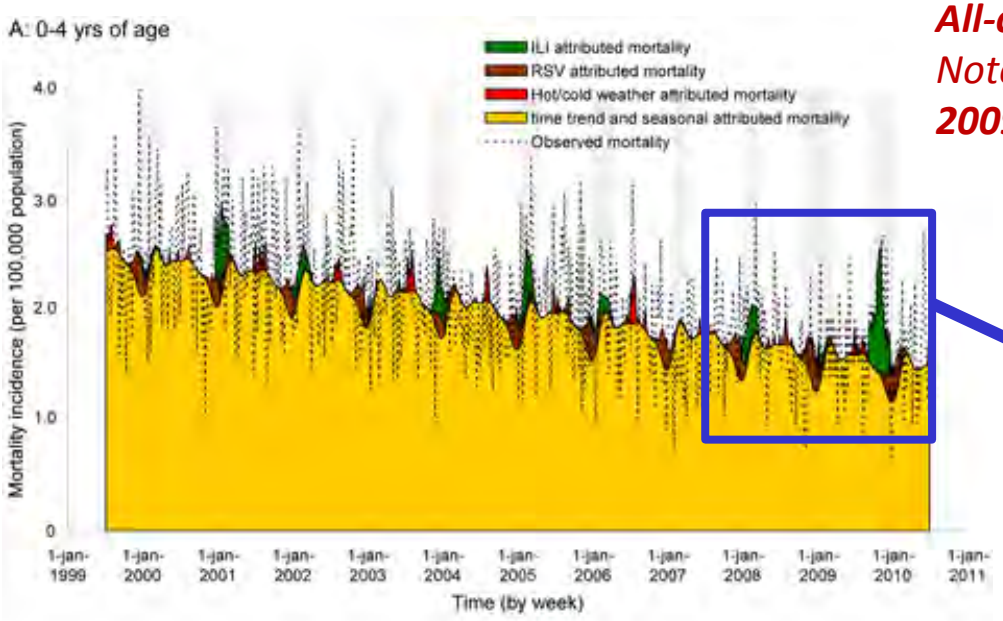
FEV_1 = forced expiratory volume in 1 second

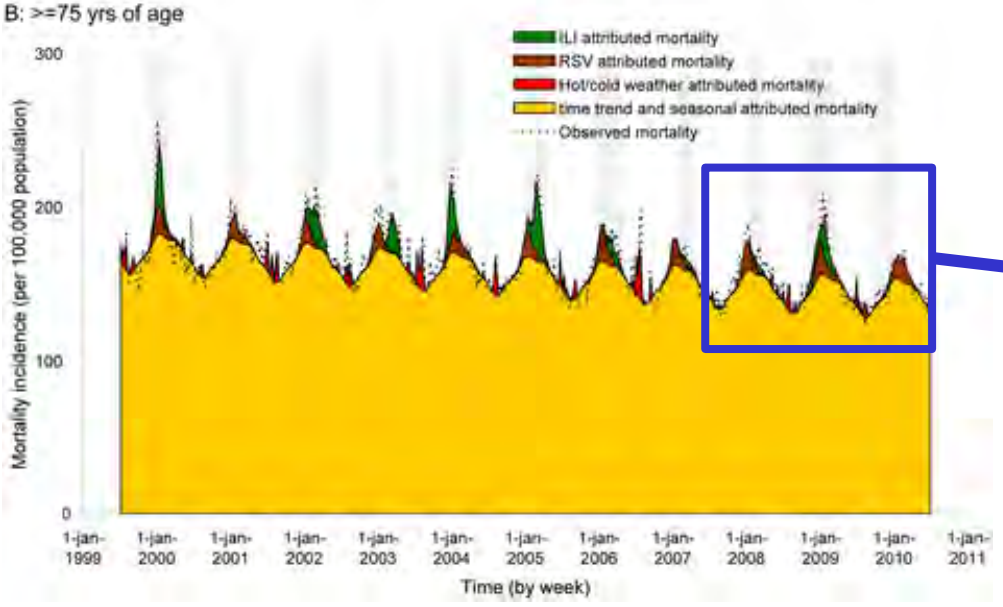
RSV-related deaths according to age

Age (years)	All influenza	RSV
<1	**39**	**335**
1-4	**91**	**32**
5-49	**1061**	**641**
50-64	**3084**	**1816**
≥65	**39977**	**11199**
Total	44252	14028

Thompson WW et al. JAMA 2003;289(2):179–86

OPEN ACCESS Freely available online PLoS one

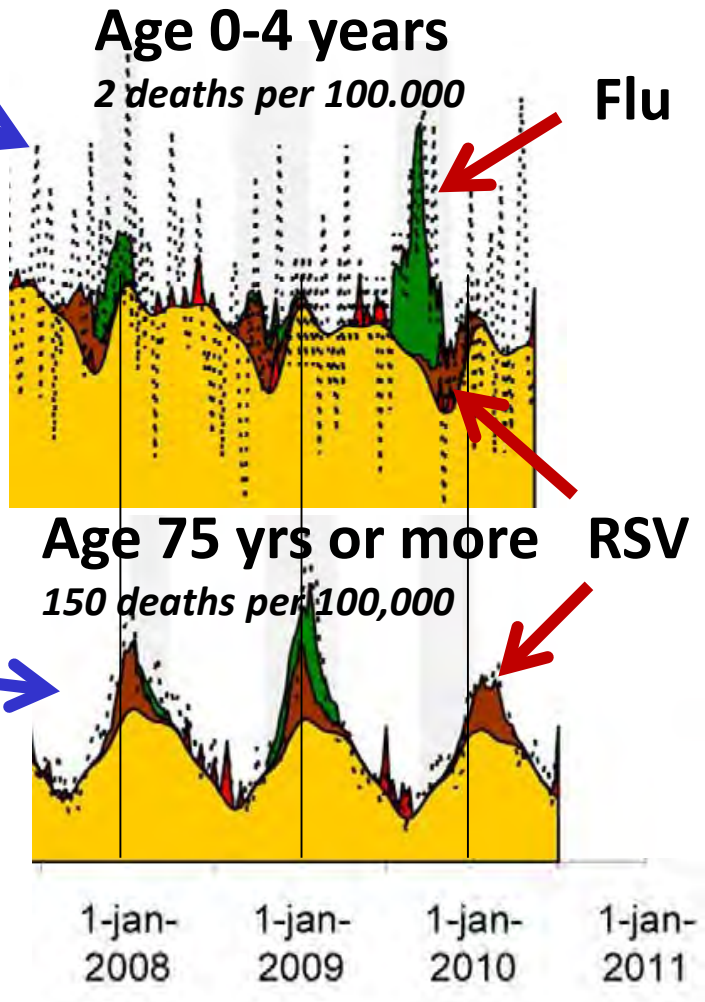




All-cause mortality (1999-2010) 16.5 million Dutch

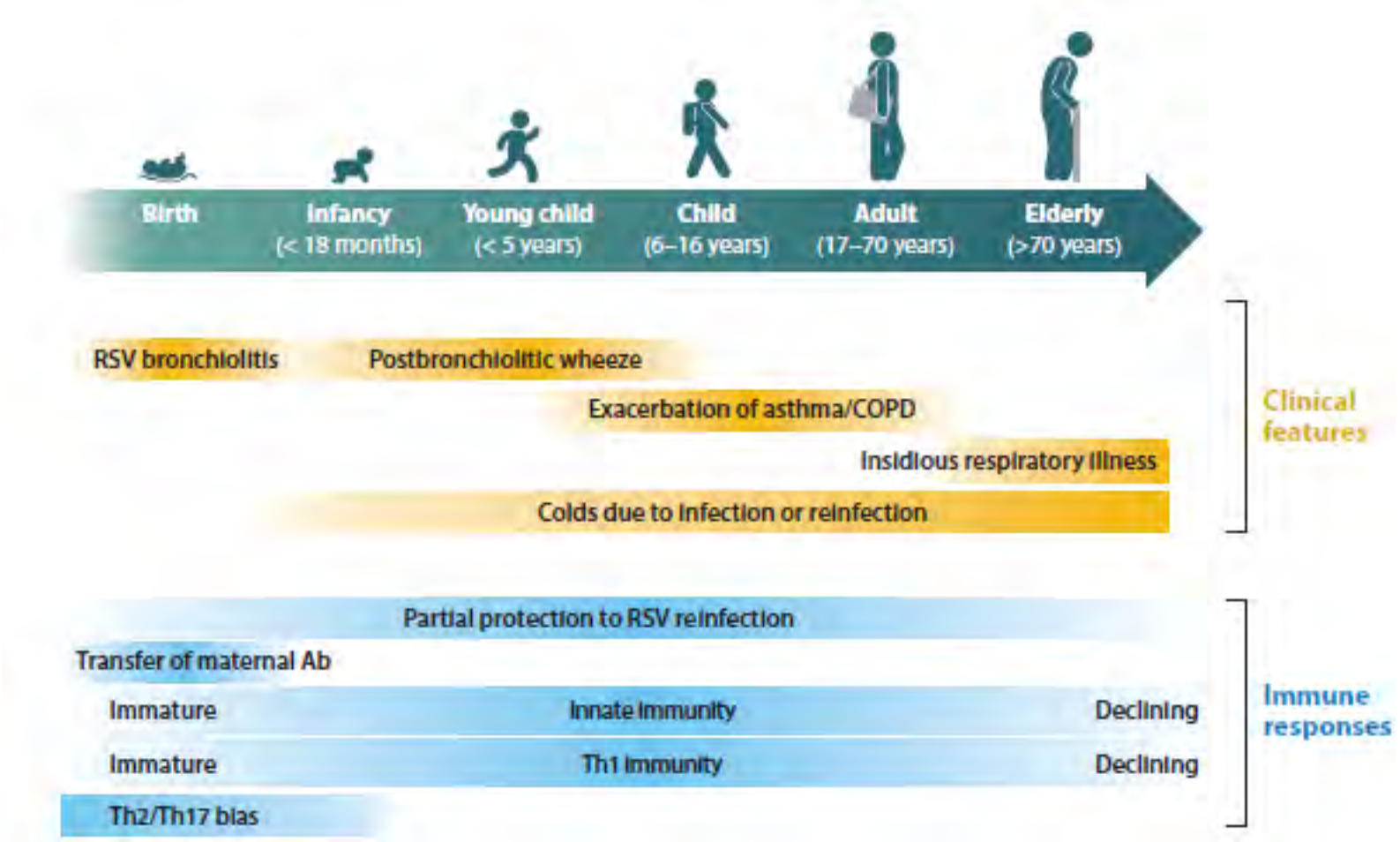
Note decrease of 39% in neonatal deaths over 10 years

***2009:** est. 612 influenza deaths, 77 in children 0-4yrs.*



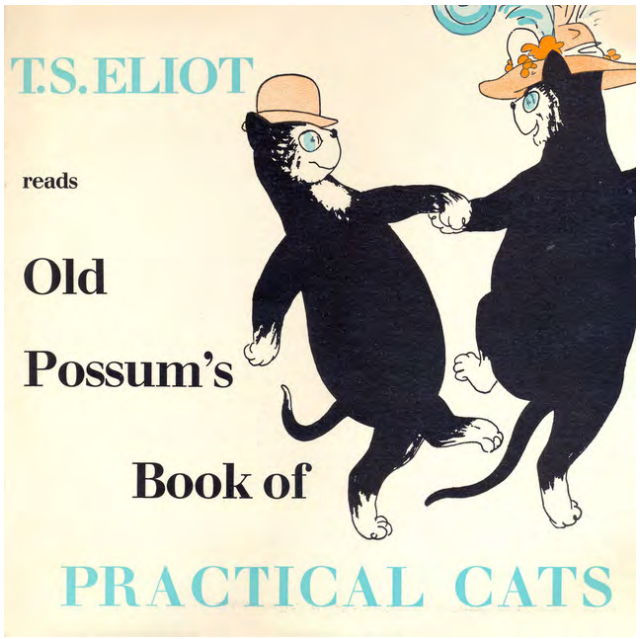
Citation: van den Wijngaard CC, van Asten L, Koopmans MPG, van Pelt W, Nagelkerke NJD, et al. (2012) Comparing Pandemic to Seasonal Influenza Mortality: Moderate Impact Overall but High Mortality in Young Children. PLoS ONE 7(2): e31197. doi:10.1371/journal.pone.0031197

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

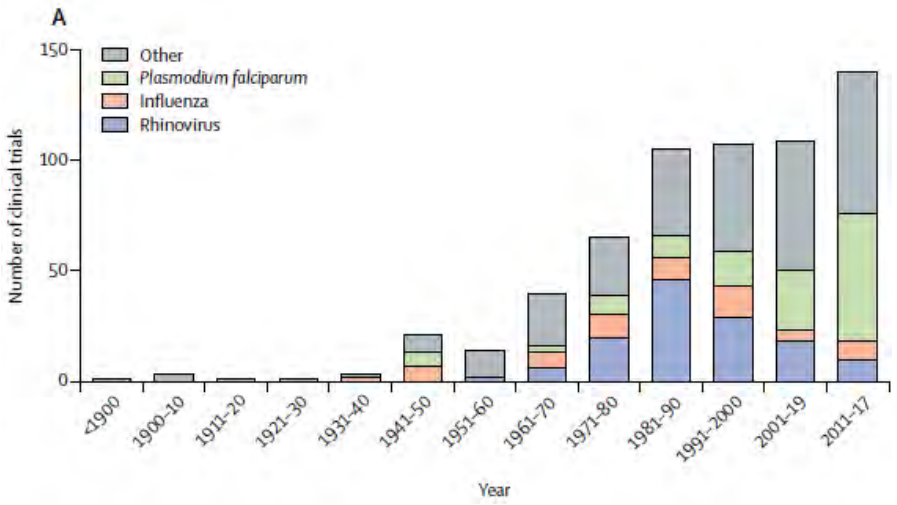
RSV: the ‘hidden paw’



He's outwardly respectable. (They say he cheats at cards.)
And his footprints are not found in any file of Scotland Yard's.
And when the larder's looted, or the jewel-case is rifled,
Or when the milk is missing, or another Peke's been stifled,
Or the greenhouse glass is broken, and the trellis past repair –
Ay, there's the wonder of the thing! *Macavity's not there!*

Experimental infection of human volunteers

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

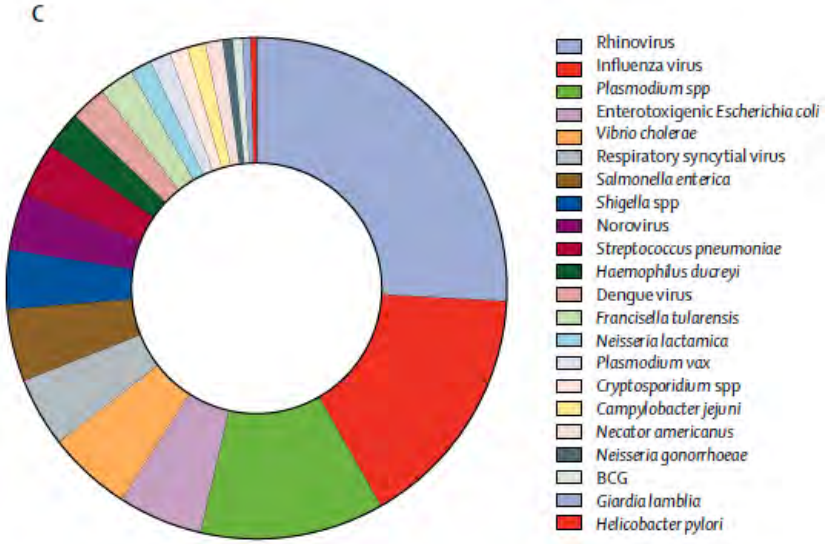


Lancet Infect Dis 2018

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

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

Imperial College London

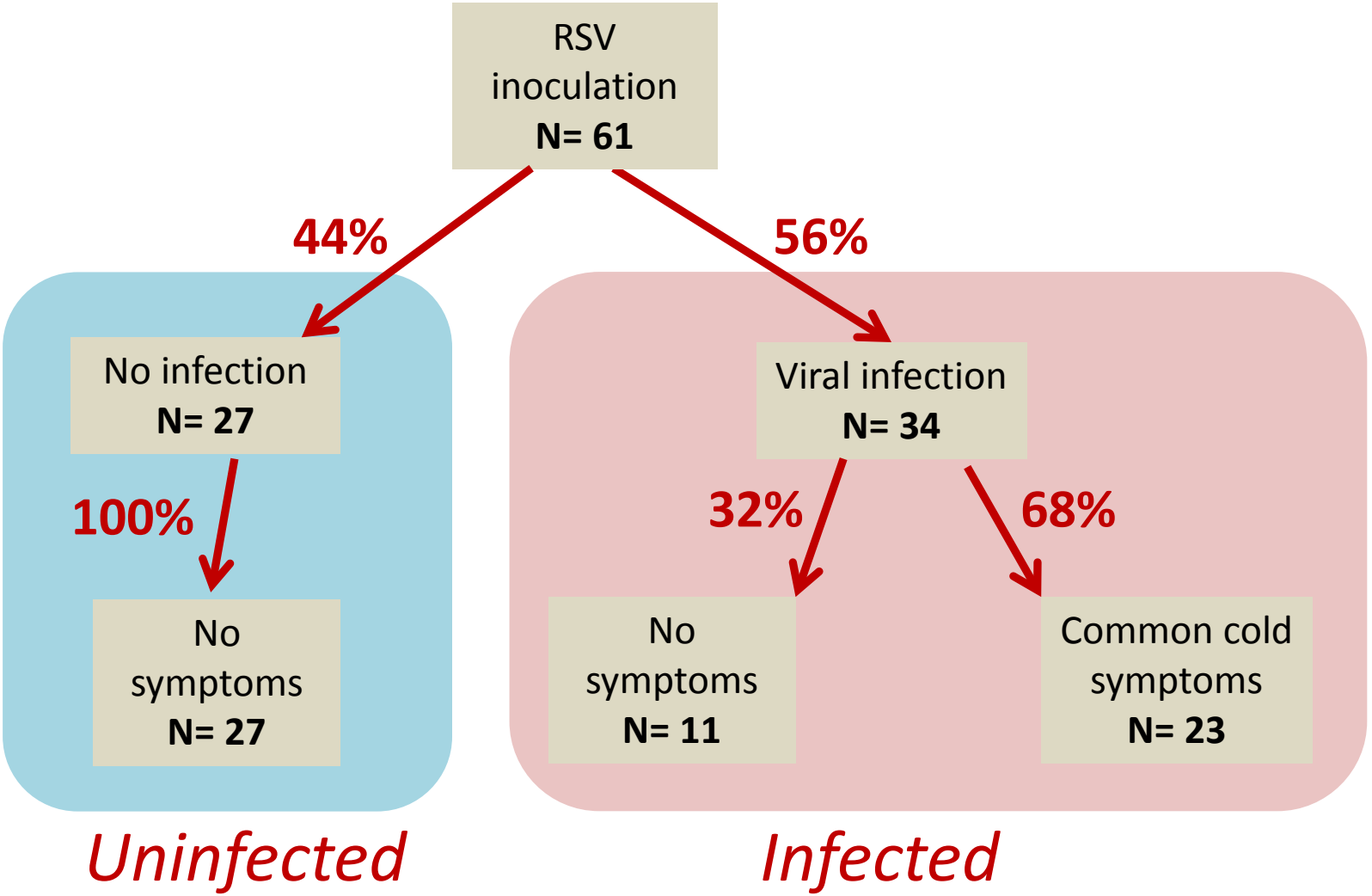
Inoculation of volunteers with RSV

- **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

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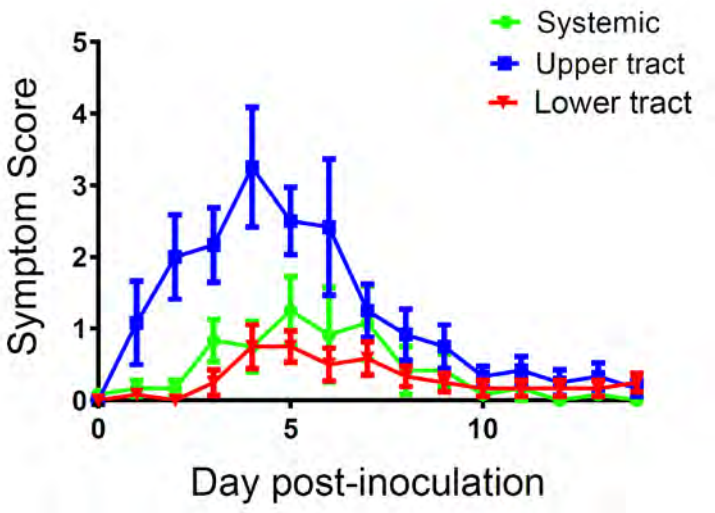
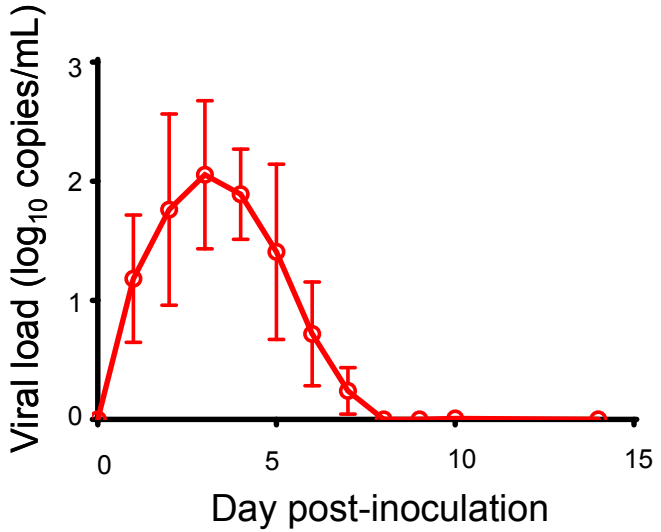
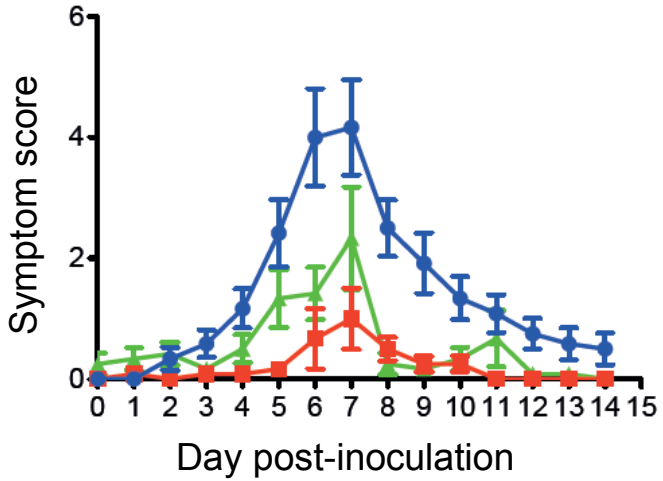
Symptoms & viral load: comparing RSV and flu

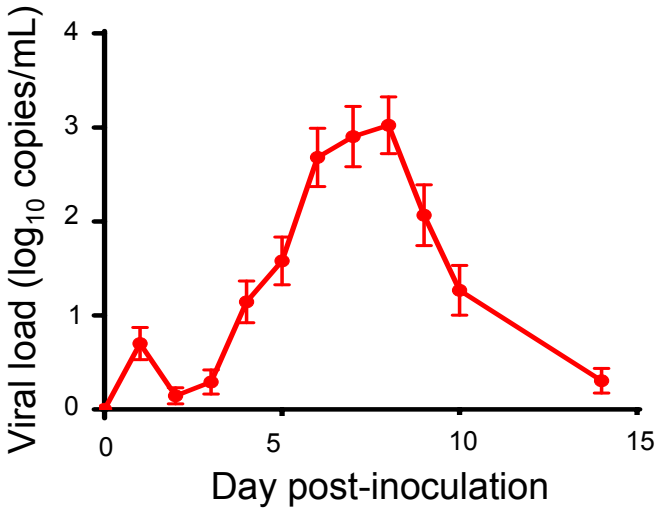
Influenza





RSV





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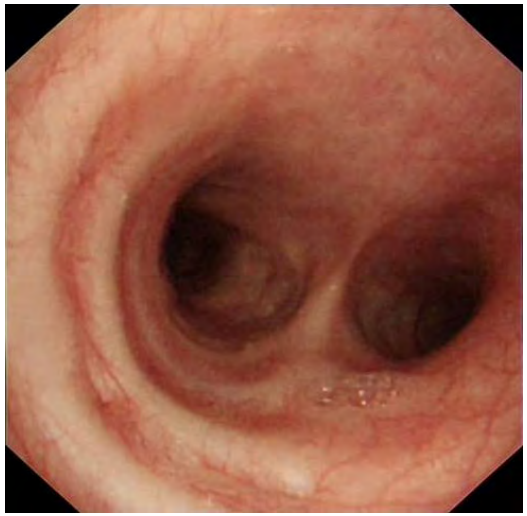
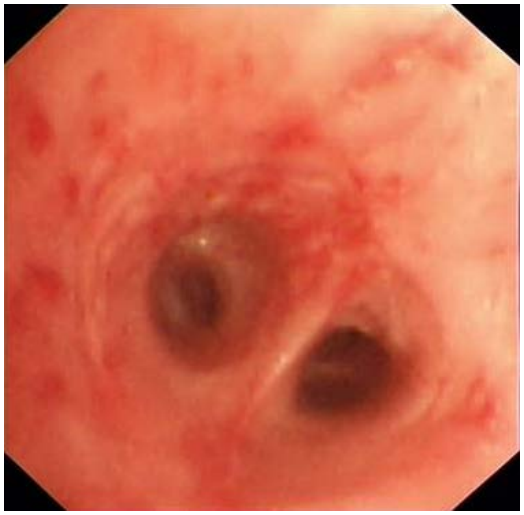
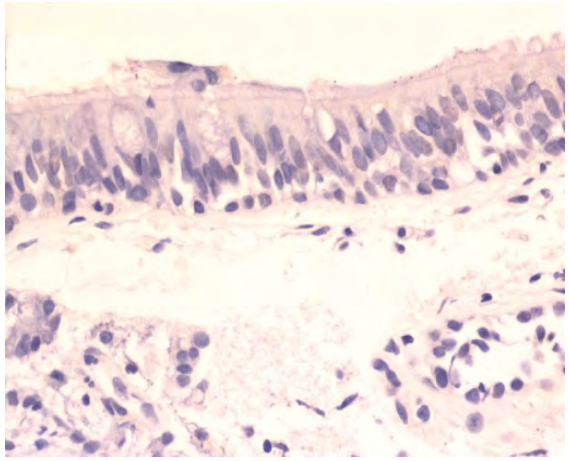
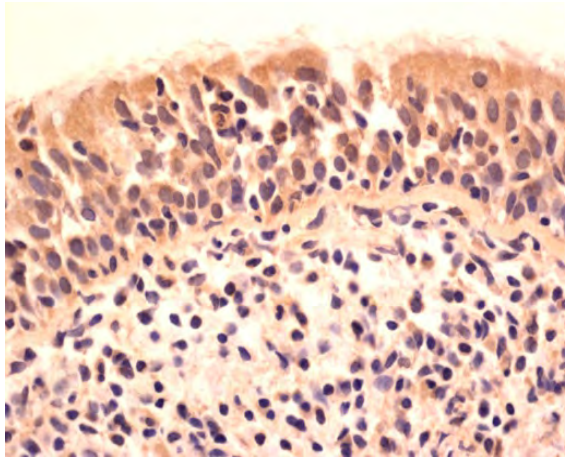
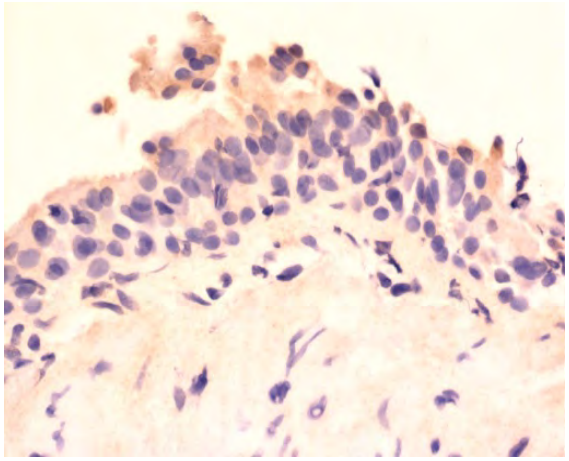
Lower airway inflammation after RSV challenge

Day 0 | Day 10 | Day 28

RSV antigen by immunohistochemistry

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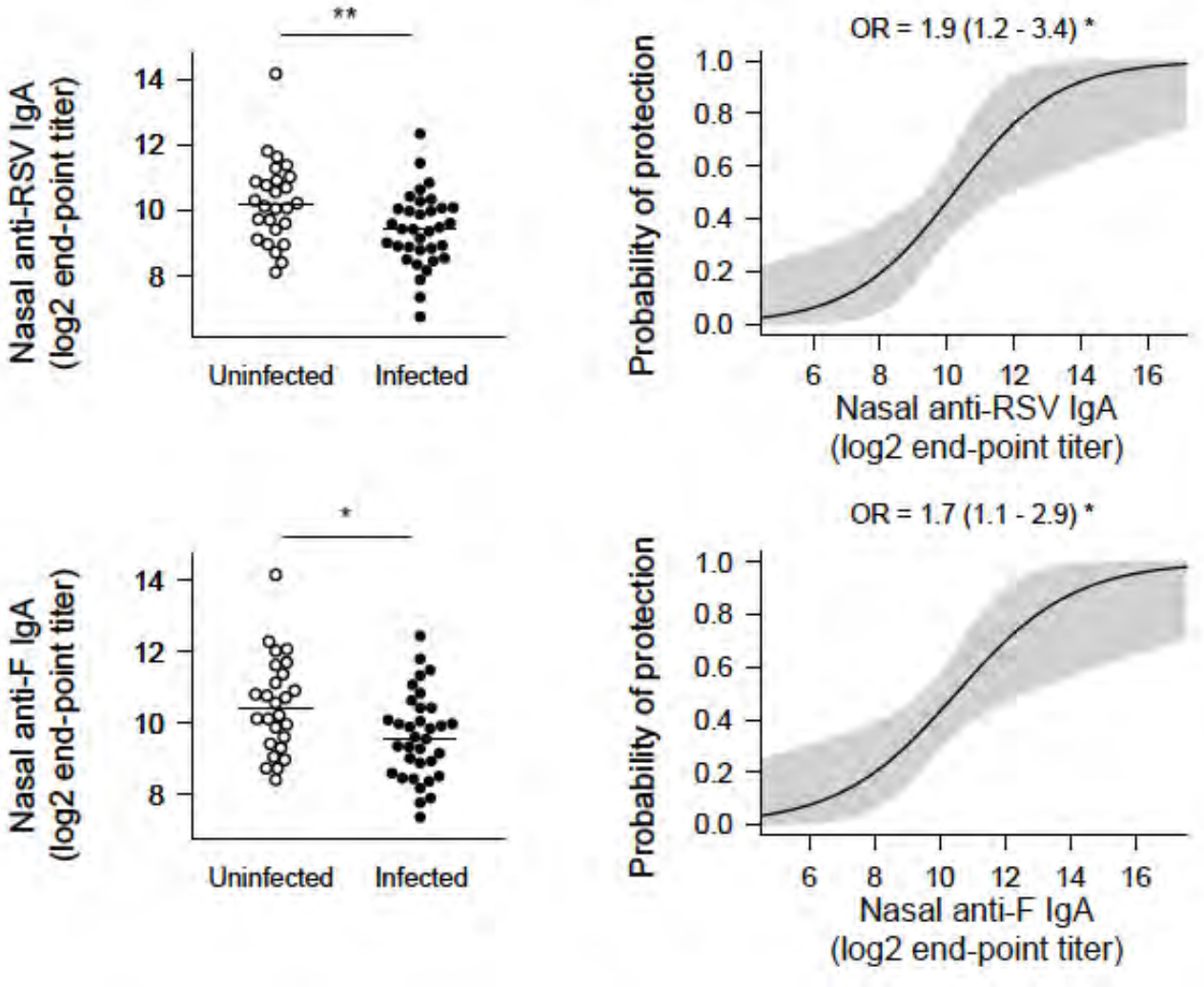
RSV-specific nasal IgA as a correlate of protection



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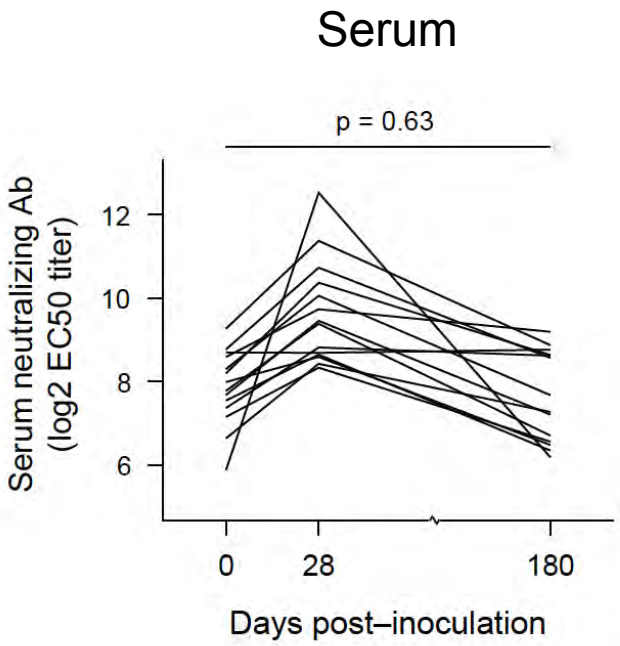
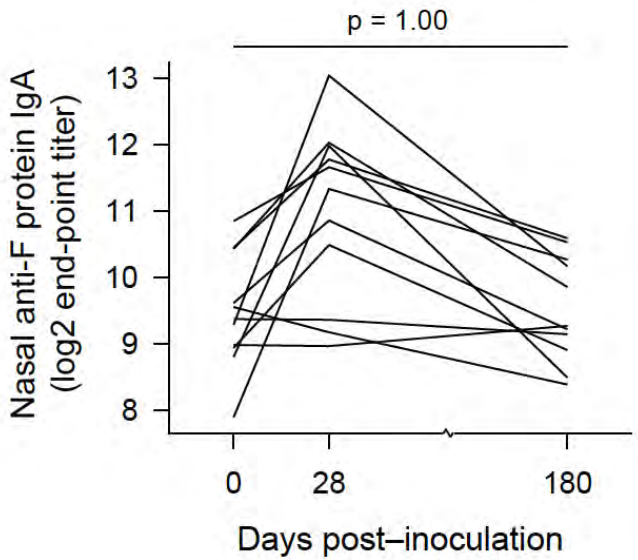
Anti-RSV antibodies are poorly maintained



Anti-RSV
Serum PRNT50



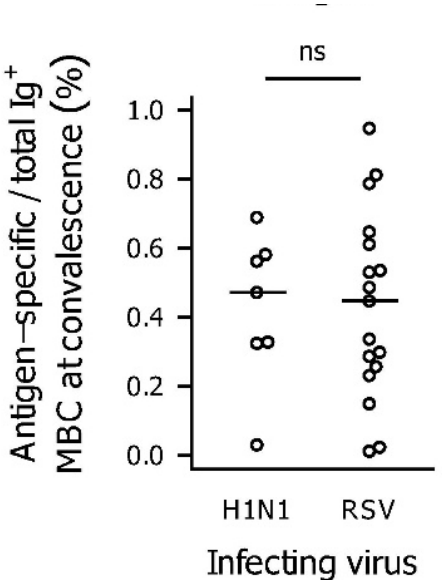
Anti-RSV
Nasal IgA

Habibi Ms *et al* (**2015)** Impaired Antibody-mediated Protection and Defective IgA B Cell Memory in Experimental Infection of Adults with RSV. Am J Respir Crit Care Med. PMID: 25730467

Impaired Antibody-mediated Protection and Defective IgA B-Cell Memory in Experimental Infection of Adults with Respiratory Syncytial Virus

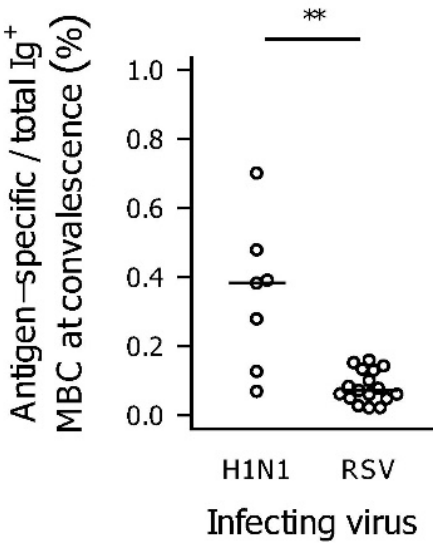
Maximillian S. Habibi[1], Agnieszka Jozwik[1], Spyridon Makris[1], Jake Dunning[1], Allan Paras[1], The Mechanisms of Severe Acute Influenza Consortium Investigators*, John P. DeVincenzo[2], Cornelis A. M. de Haan[3], Jens Wrammert[4,5], Peter J. M. Openshaw[1‡], and Christopher Chiu[1‡]

IgG MBC



RSV and H1N1 both induce IgG memory B cells

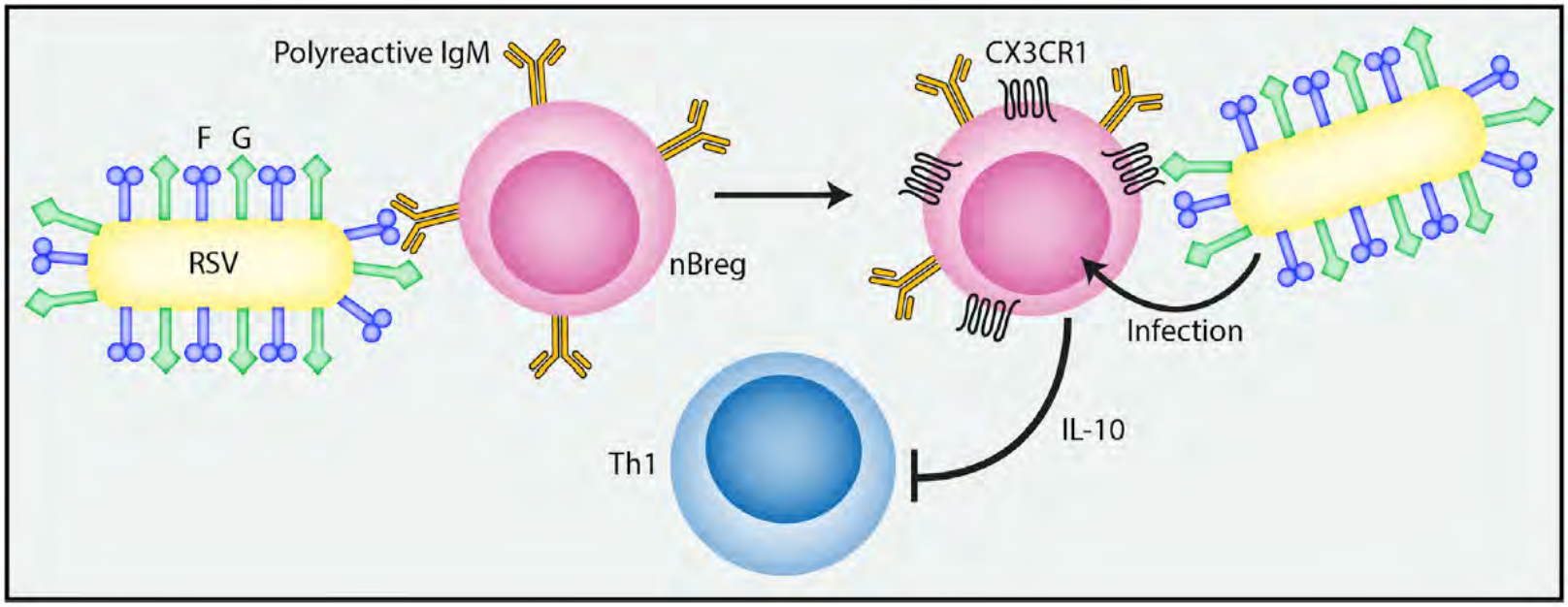
IgA MBC



RSV infection does <u>not</u> induce IgA memory B cells

Habibi Ms *et al* (**2015**) Impaired Antibody-mediated Protection and Defective IgA B Cell Memory in Experimental Infection of Adults with RSV. Am J Respir Crit Care Med. PMID: 25730467

RSV Takes Control of Neonatal Breg Cells: Two Hands on the Wheel



Respiratory Syncytial Virus Infects Regulatory B Cells in Human Neonates via Chemokine Receptor CX3CR1 and Promotes Lung Disease Severity

Dania Zhivaki,[1,2] Sébastien Lemoine,[3,4] Annick Lim,[5] Ahsen Morva,[1] Pierre-Olivier Vidalain,[6] Liliane Schandene,[7] Nicoletta Casartelli,[8,9] Marie-Anne Rameix-Welti,[10,11] Pierre-Louis Hervé,[12] Edith Dériaud,[3,4] Benoit Beitz,[13] Maryline Ripaux-Lefevre,[13] Jordi Miatello,[14,15,16] Brigitte Lemercier,[5] Valerie Lorin,[17,18] Delphyne Descamps,[12] Jenna Fix,[12] Jean-François Eléouët,[12] Sabine Riffault,[12] Olivier Schwartz,[8,9] Fabrice Porcheray,[13] Françoise Mascart,[7,19] Hugo Mouquet,[17,18] Xiaoming Zhang,[20] Pierre Tissières,[14,15,16] and Richard Lo-Man[1,21,*]

Immunity *46*, 301–314, February 21, 2017

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Mechanisms of immediate/early protection in the nose

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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
Jens Wrammert
Xander de Haan

wellcome trust

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

MRC Medical Research Council

NHS National Institute for Health Research

The perfect vaccine

NHS choices

Imperial College London

What do we want in an RSV vaccine?

Better than natural immunity

- Durable B cell responses
- Deletion vectors (abolish immune modulation?)
- Adjuvants

Mucosal immunity

- Antiviral IgA
- Local CD8+ T cells

Not just for infants

- Sibs may be transmitters
- Maternal (carer's…) vaccines may have a role
- Target the elderly

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

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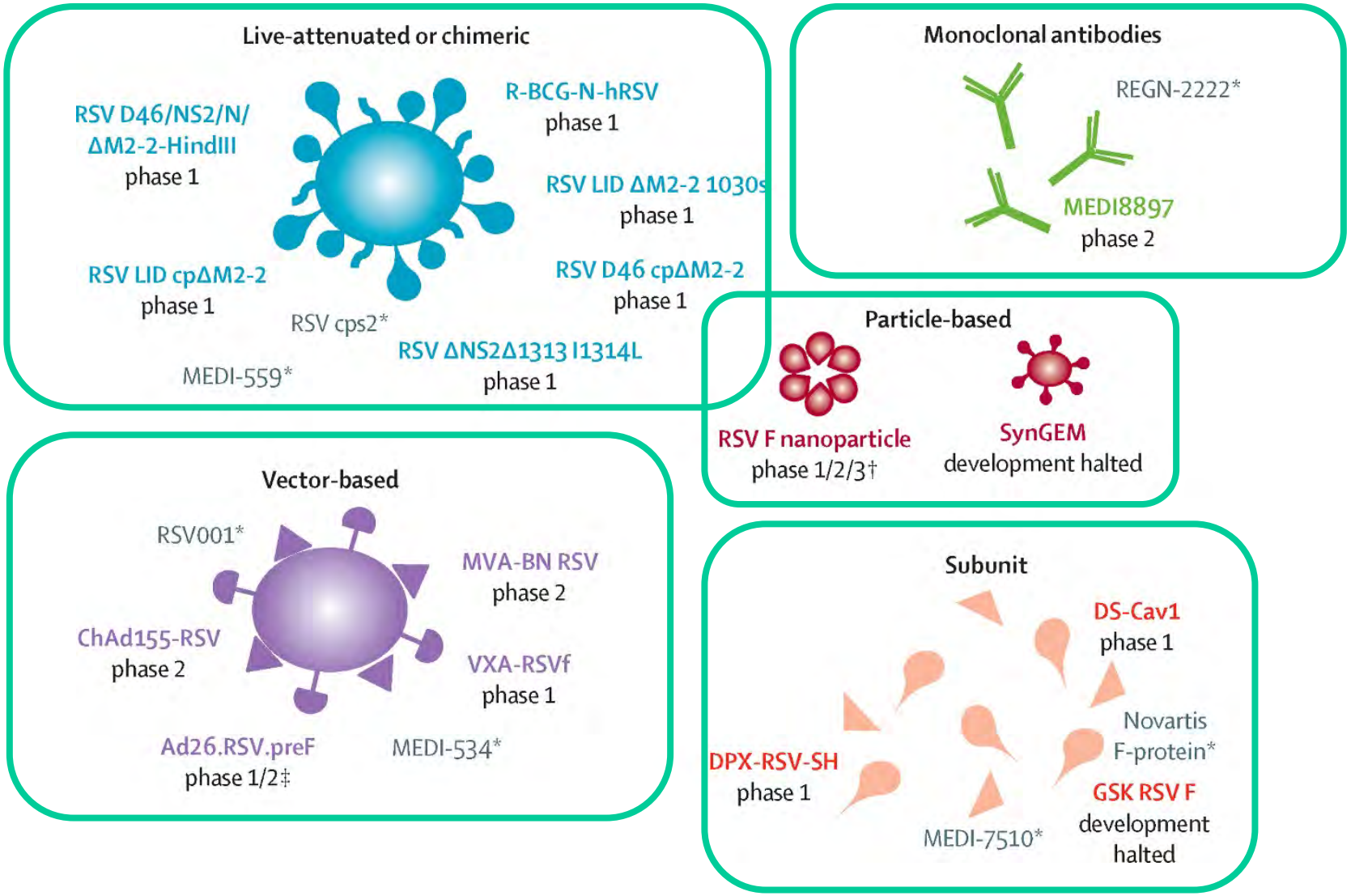
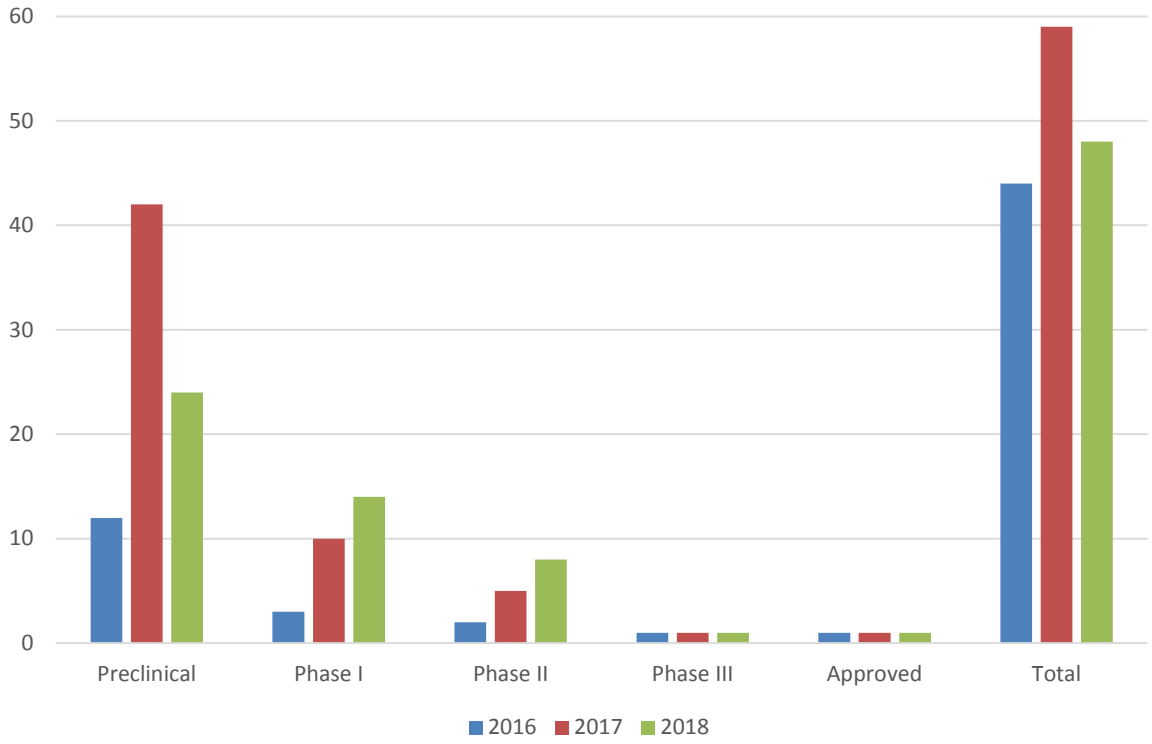


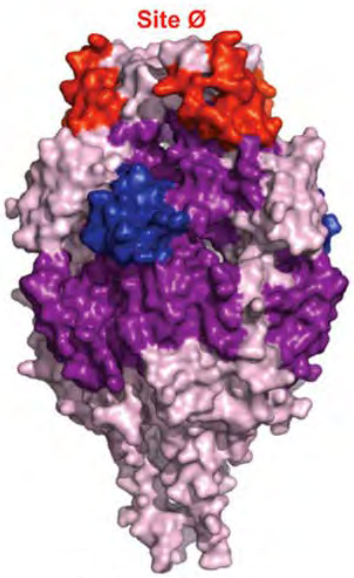
Vaccine pipeline for RSV



Year	Preclinical	Phase I	Phase II	Phase III	Approved	Total
2016	12	3	2	1	1	44
2017	42	10	5	1	1	59
2018	24	14	8	1	1	48

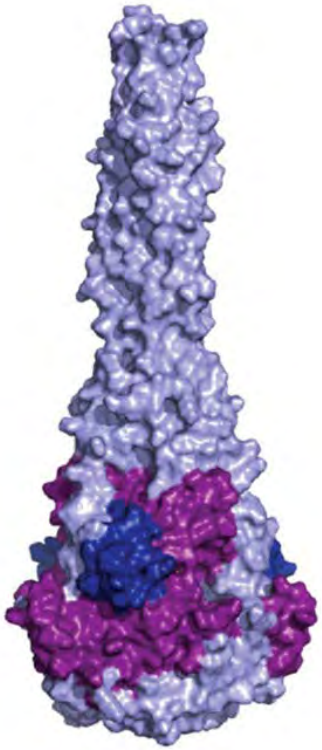
Data from: http://vaccineresources.org/details.php?i=1582 and https://goo.gl/VdrKFK

Neutralising Ab vs pre-F

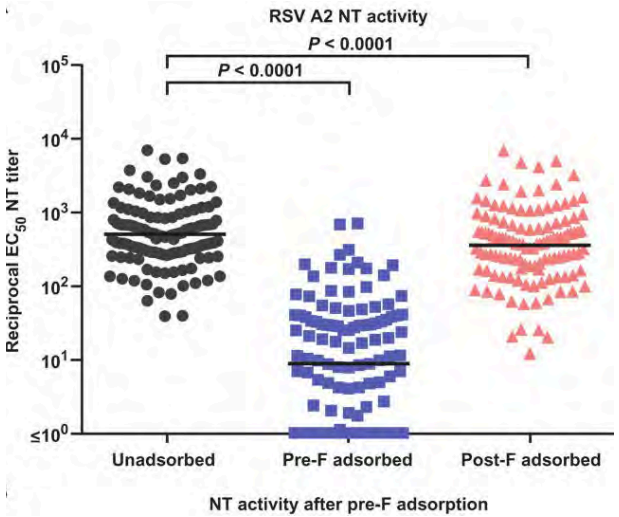


Prefusion RSV F

Site II



Postfusion RSV F



McLellan JS Science 2013 *etc.*

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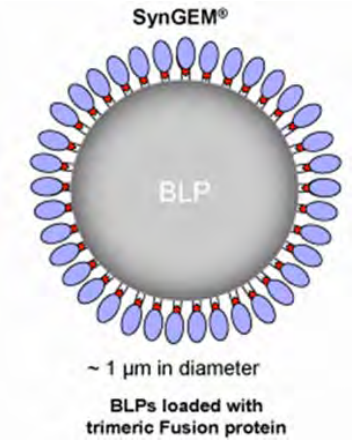
Openshaw/Chiu:
MUCOSIS intranasal RSV vaccine



Wellcome Trust Translation Fund
2016-2018

Bacteria-like particles (*Lactobacillus*), coated with pre-fusion RSV F protein

Delivered by nasal spray

First in man **immunogenicity** and **protection** against challenge in adult volunteers

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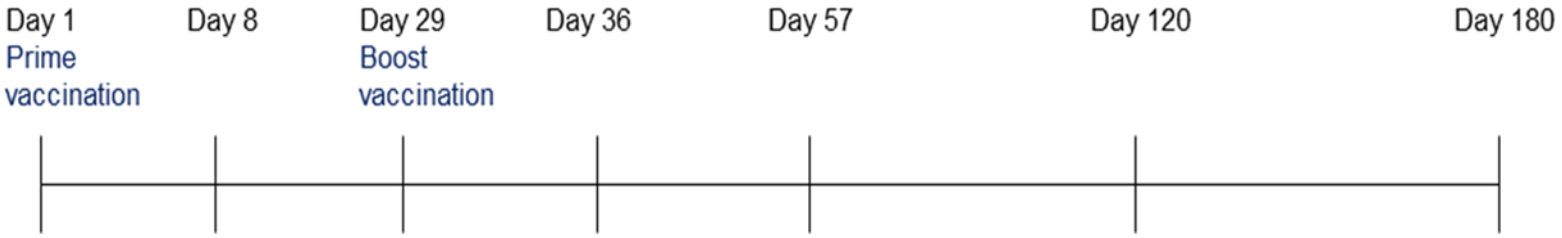
Study protocol



Route of administration: intranasal using VaxInator device

Two doses levels of SynGEM selected for clinical testing on the basis of pre-clinical studies;

Dose 1: 140 µg F/ 2mg BLP (18 participants)
Dose 2: 350 µg F/ 5mg BLP (18 participants)
Placebo: PBS + 2.5% glycerol (12 participants)

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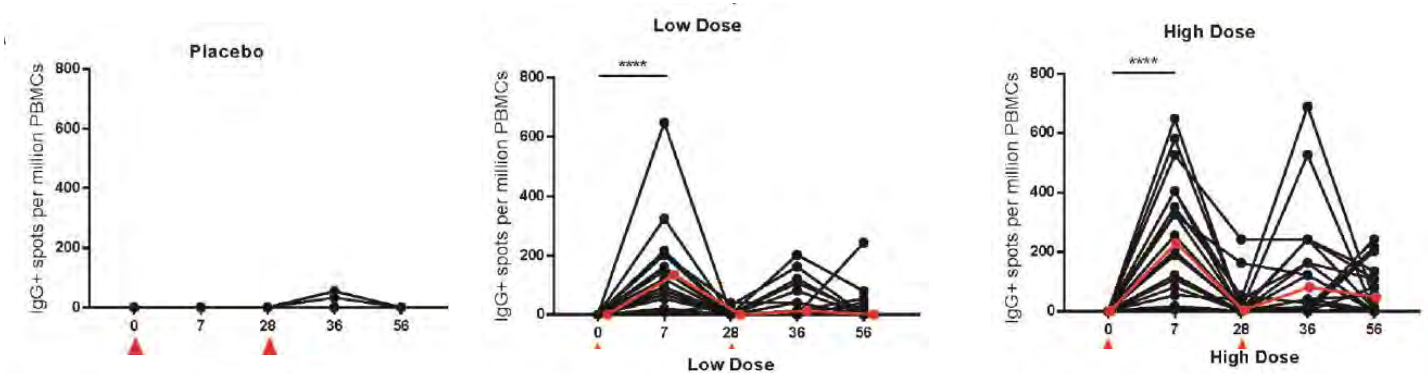
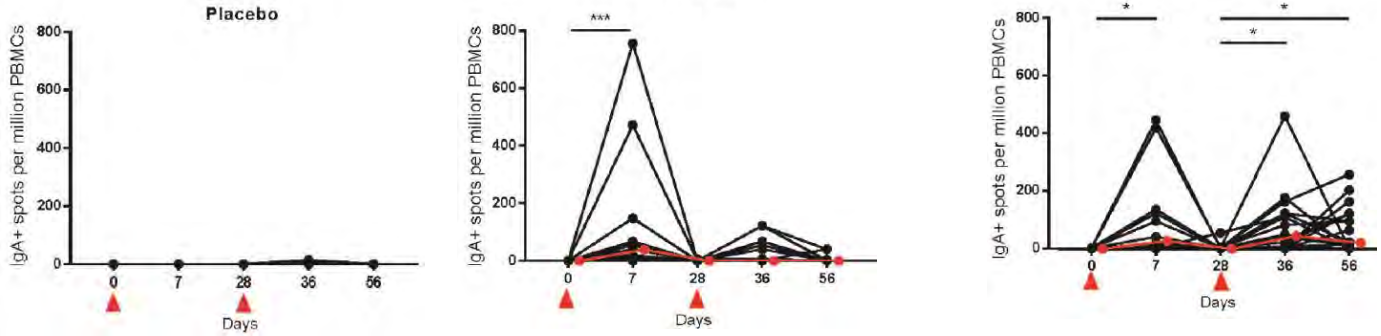
Acute antibody secreting cells in the peripheral blood

IgG



IgA



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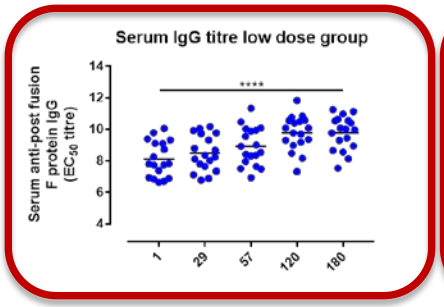
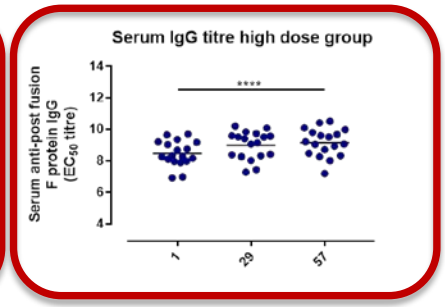
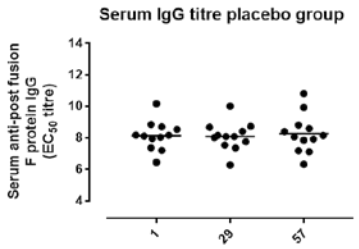
Serum F-specific IgG increases following vaccination

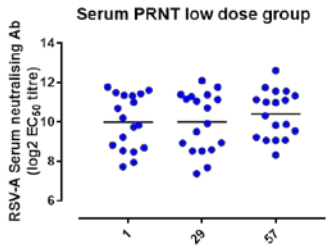
- **Increase in F-specific IgG** against both pre- and post-fusion proteins

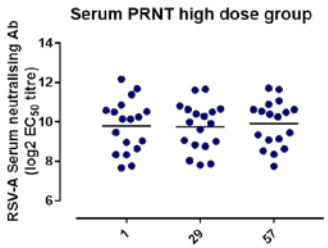


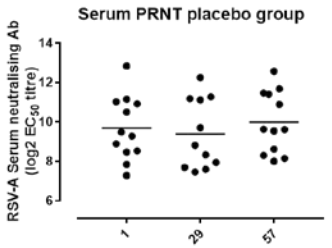




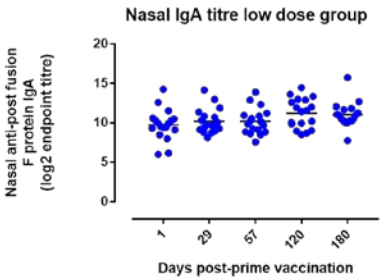
- **No increase in** RSV A **neutralising Ab** titres following SynGEM vaccination

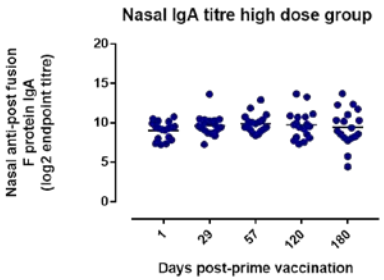


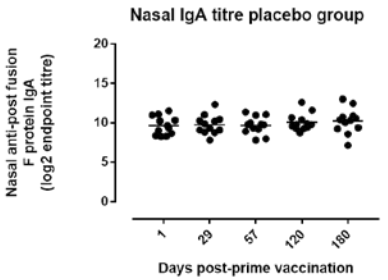




- **No increase** in pre- or post-fusion **F specific IgA** responses







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Conclusions

- Zoe Gardener
- Steff Ascough
- Iris Vlachantoni
- Suzie Paterson

Intranasal SynGEM induces:

- serum IgG (pre- and post-fusion F)
- **no** serum neutralising **or** mucosal IgA
- boosts responses to epitopes shared between pre- and post-fusion F *(not to antigenic site Ø)*
- early antibody secreting cell response in blood (IgG+ and IgA+ plasmablasts)
- weak memory B cell response

Stephanie Ascough[1,2]†, Iris Vlachantoni[2]†, Mohini Kalyan[1,2], Bert-Jan Haijema[3], Sanna Wallin-Weber[3], Margriet Dijkstra-Tiekstra[3], Muhammad S Ahmed[4], Roberto Grimaldi[3], Qibo Zhang[4], Kees Leenhouts[3], Peter J Openshaw[2]* and Christopher Chiu[1]* [1] Section of Infectious Diseases and Immunity, Department of Medicine, Imperial College London, UK. [2] Section of Respiratory Infections, National Heart and Lung Institute, Imperial College London, UK. [3] Mucosis B.V., represented by trustee Mr. Holtz LLM, Bout Advocaten, Groningen and Virtuvax B.V., The Netherlands. **AJRCCM** *in press*

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

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.

Gregory M. Glenn, MD

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."

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RSV vaccines

Pre-fusion F vaccines may be best

Local IgA production may be important

Live attenuated vaccines progressing (slowly)

Maternal immunisation has advantages

Problems remain:

- Incrementing natural Ab in seropositive adults
- No clear candidates for younger infants
- Understanding of protective immunity incomplete

Interventions to interrupt RSV disease