



10th December 2024

Respiratory Syncytial Virus

Virology, Epidemiology, Pathogenesis and Global Impact

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Common cold agents *"I contain multitudes"*

Virus	Number of serotypes	% of colds	
Rhinovirus	100+	60	All year (peaks)
Coronaviruses	2	15	All year (peaks)
Influenza viruses	3	<10	Epidemics
Parainfluenza viruses	4	<10	All year (peaks)
Respiratory syncytial virus	2	<10	Epidemics
Adenoviruses	47	<10	Sporadic
Enteroviruses	40+	<10	Sporadic

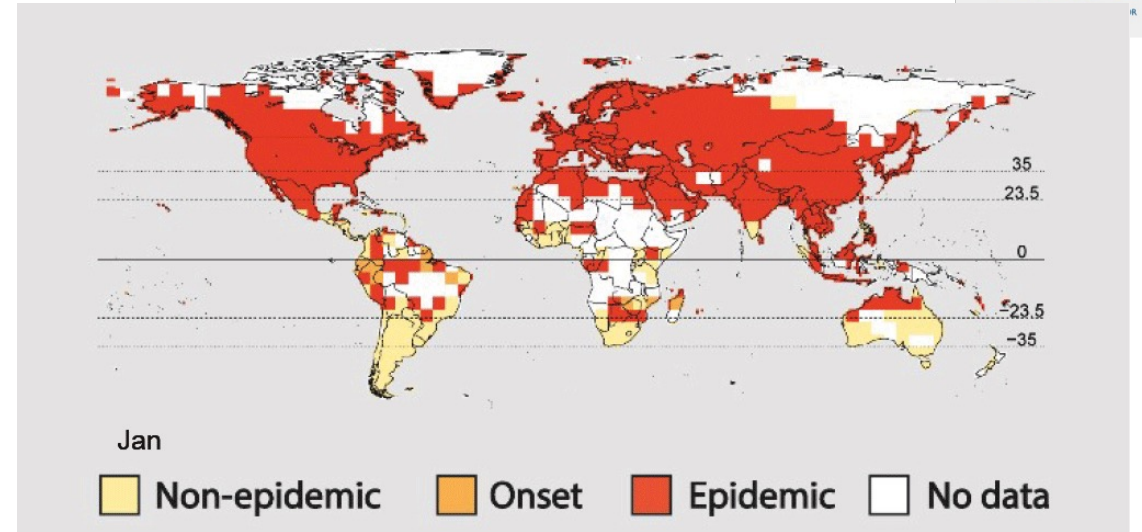
Atypical bacteria	Number of serotypes	% of colds	
Mycoplasma	1	<10	5 yearly cycle
Chlamydia	1	<10	Unknown

Modified from Feigin D, Cherry. Textbook of pediatric infectious diseases (2nd Edn). WB Saunders Co, 1987

Global changes in RSV and flu prevalence month by month



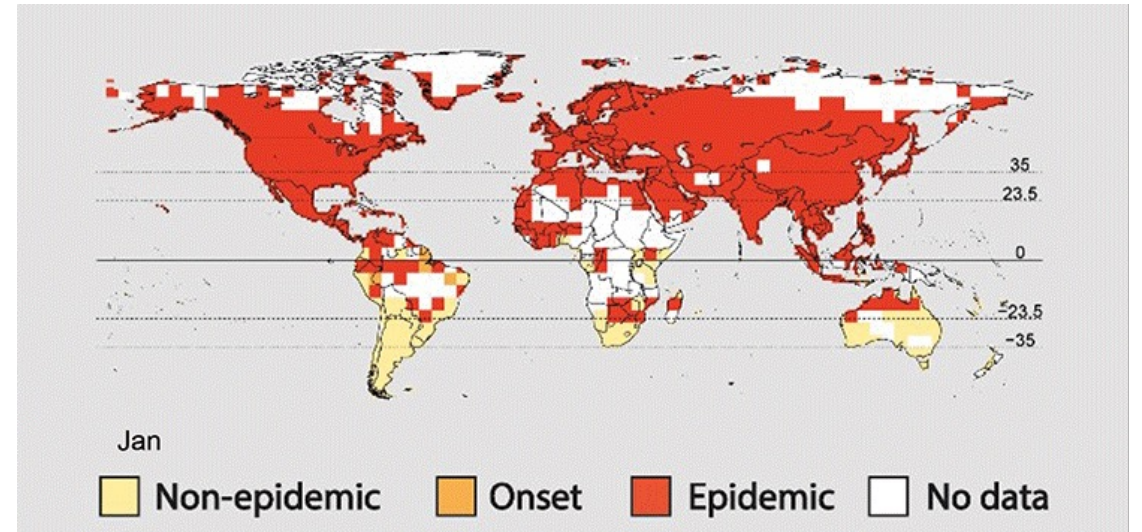
RSV



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

Flu



Respiratory Syncytial Virus

Global pathogen affecting infants, vulnerable adults and frail elderly

- *Each winter, **1 in 6 paediatric beds** are occupied by cases of bronchiolitis*
- ***80% of cases of bronchiolitis** are caused by RSV*
- *Between 2 and 6% of cases of bronchiolitis need paediatric **intensive care***
- *in LMICs, RSV is **2nd only to malaria** in infant mortality*

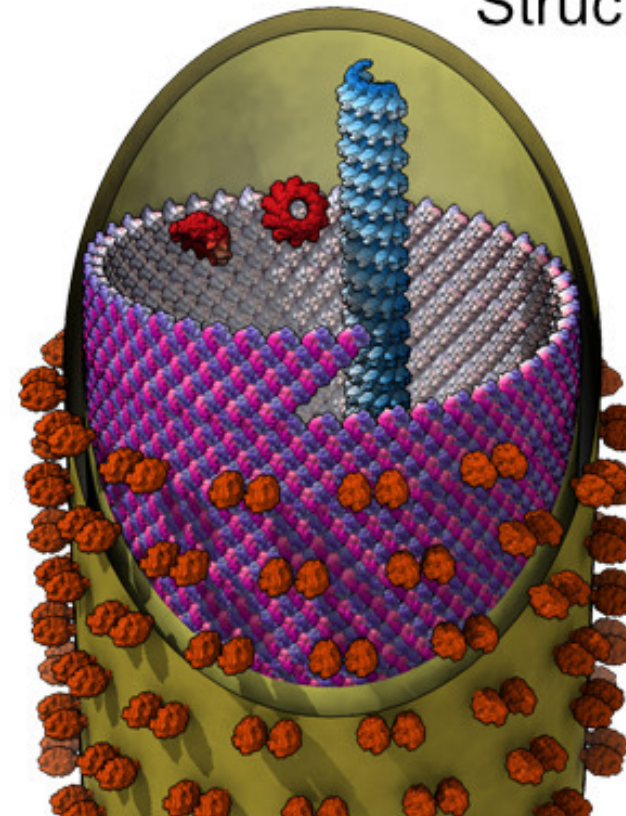
- *In **stem cell transplant** patients, mortality approximately 80%*
- *In **frail elderly** persons, RSV infection has a 10% mortality; winter hospitalization and deaths caused by RSV are **comparable to flu deaths***

There is still no effective vaccine or specific treatment

Respiratory syncytial virus



- Filamentous RNA virus of the *Pneumoviridae* family
- Peaks of severity in early and later life
- Repeated infection with same viral strains ('immunological amnesia')
- Associated with later wheeze and 'asthma'



Structure of Respiratory Syncytial Virus

Matrix Dimers
Glycoproteins
Lipid Envelope
Nucleocapsid
N-RNA Rings

Conley et al/ The EMBO Journal (2022)41:e109728

<https://www.embopress.org/doi/full/10.15252/emj.2021109728>

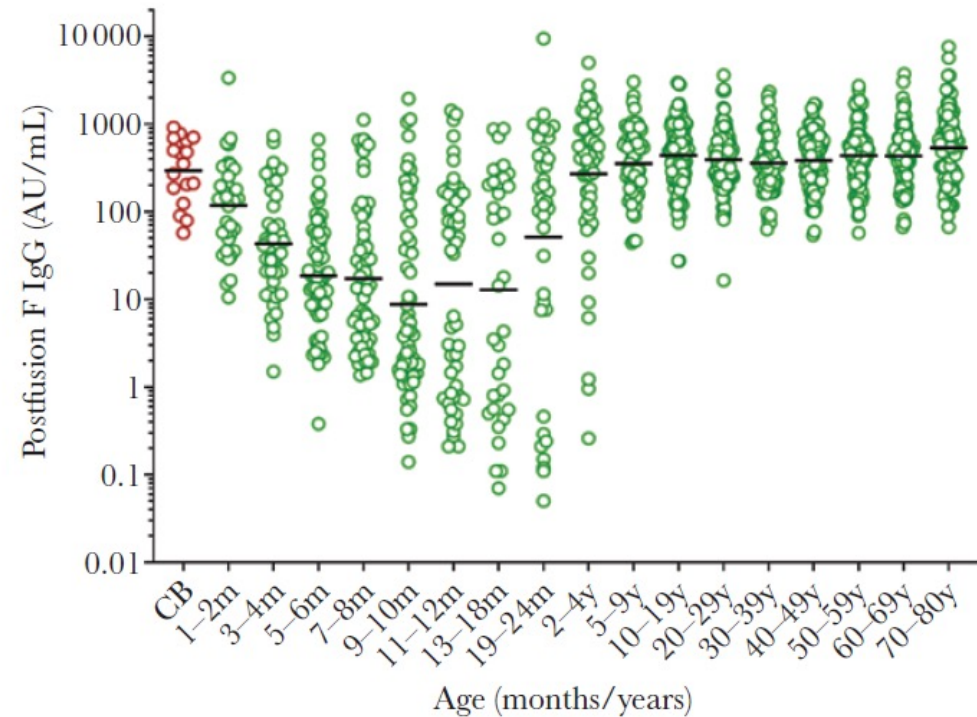
Antibody Responses to RSV: everyone gets infected

A Cross-Sectional Dutch Serosurveillance Study

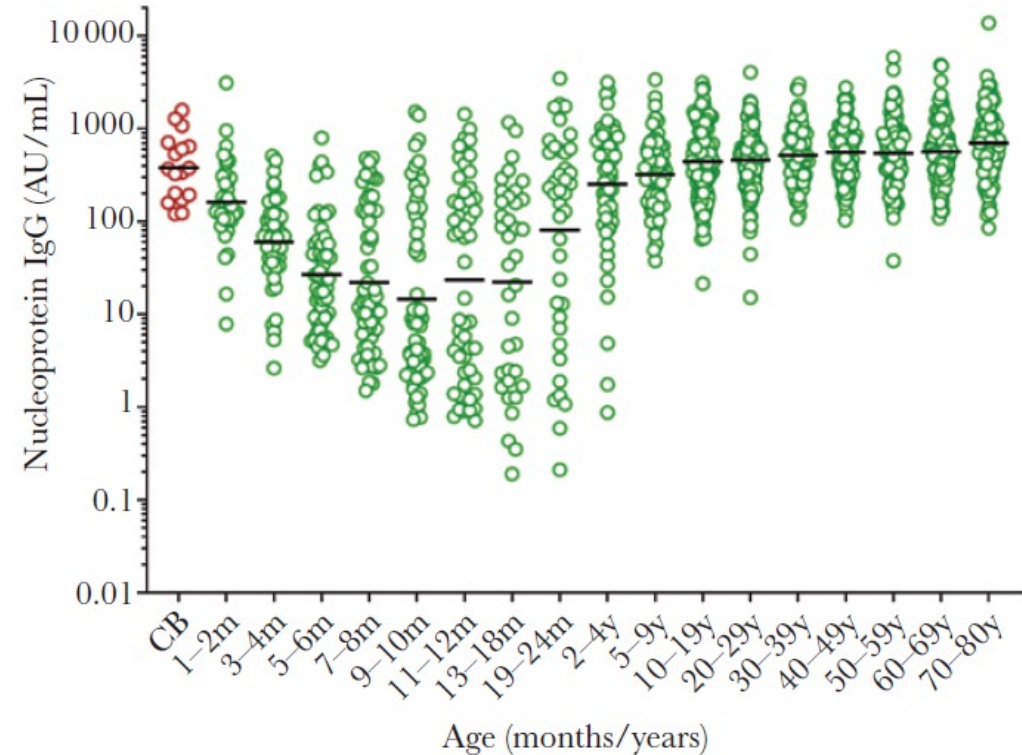


Berbers *et al* J Infect Dis
15;224(2):269-278 (2021)

Postfusion F IgG



Nucleoprotein IgG



Cord blood sera: red circles

2021 Jul 15;224(2):269-278. doi: 10.1093/infdis/jiaa483

RSV interference with host immune response

Non-structural proteins

- NS1 disrupts IRF3 binding to the IFN β promotor
- 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/ciliated cells
- Secreted G acts as a decoy for antibody
- F binds to TLR4, possibly causing innate desensitization

Internal proteins

- N disrupts the synapse between CD4 and CD8 cells

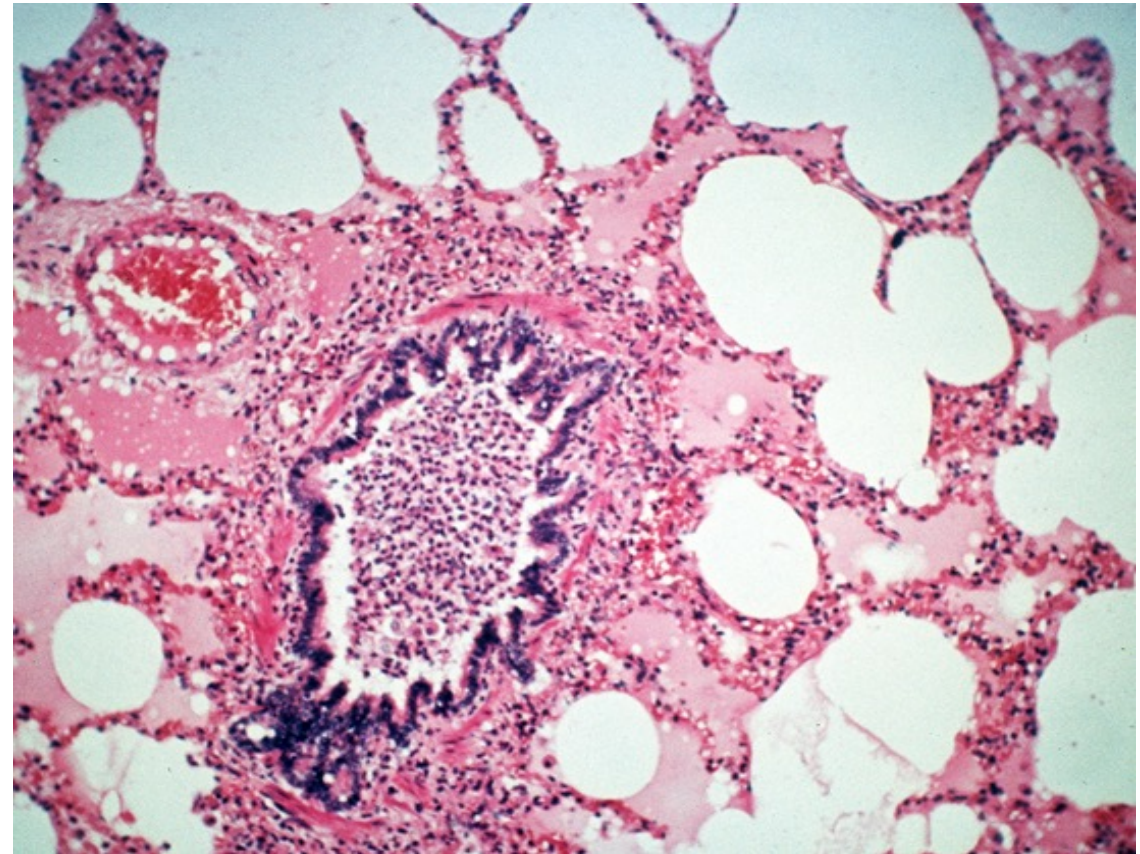
Ab, antibody; IFN- γ ; interferon-gamma; IgA, immunoglobulin A; IgG, immunoglobulin G; IL, interleukin; RSV, respiratory syncytial virus.

Openshaw P et al. Annu. Rev. Immunol. 2017. 35:501–32.

Respiratory syncytial virus (RSV): a scourge from
infancy to old age *Thorax* **2019**;74:986–993.

James Andrew Coultas,¹ Rosalind Smyth,² Peter J Openshaw¹

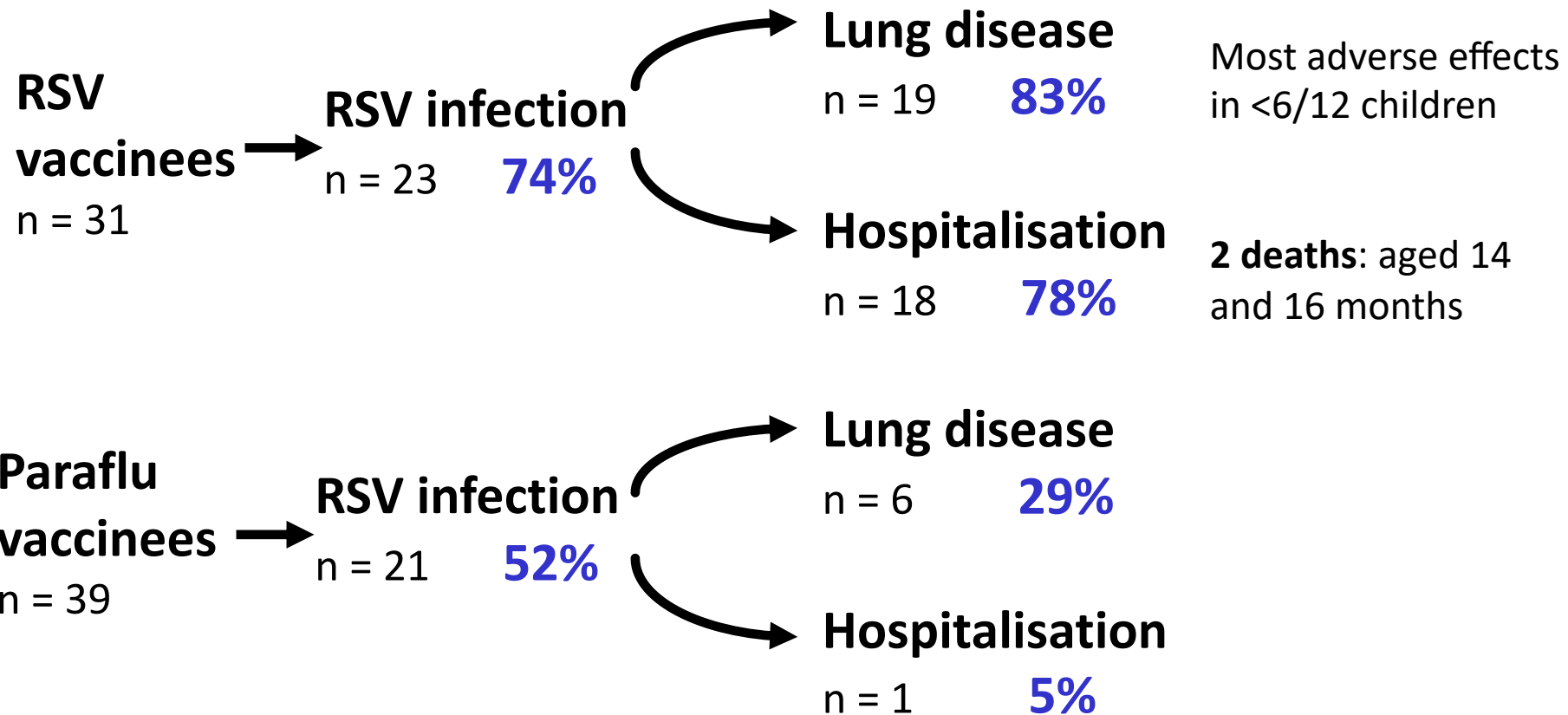
*It's caused by a virus, but it's
an **inflammatory** disease*



Vaccine-enhanced disease

*Lot 100 vaccine 0, 1 and 4 months
0.5ml vaccine i.m.*

*2-7 month deprived infants in Washington DC
5 blood samples, weekly throat/anal swabs*



Ross Otto Hambrick 1965-1966
Victor King 1965-1966



EXPLORE READ LOOK LISTEN **UNDARK** MENU ABOUT



NEWS & FEATURES PRINT

For a Pivotal Vaccine: Trial, Error, and Two Young Lives

The new RSV vaccines are medical milestones. But what is owed to the families who unknowingly helped pave the way?

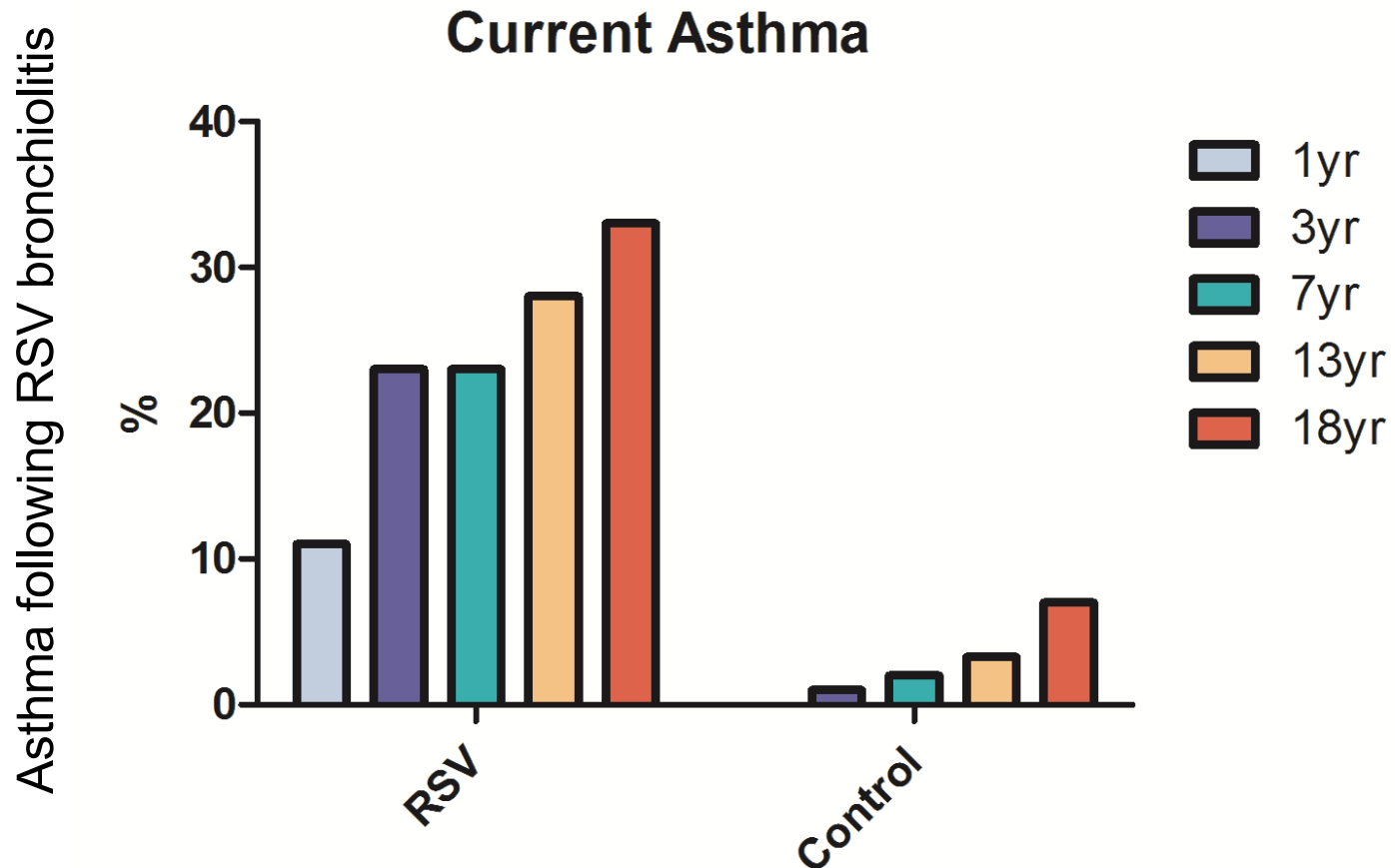
BY MICHAEL SCHULSON
10.09.2023

SHARE >



<https://undark.org/2023/10/09/rsv-vaccine-children-trials>

Long-term effects of early life infection



Sigurs N et al. *Pediatr* 1995; 95:500-05., Sigurs N, et al. *Am J Respir Crit Care Med* 2000;161:1501-07.

Sigurs N, et al. *Am J Respir Crit Care Med* 2005;171:137-41. Sigurs N, et al. *Thorax* 2010;65(12):1045-52

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

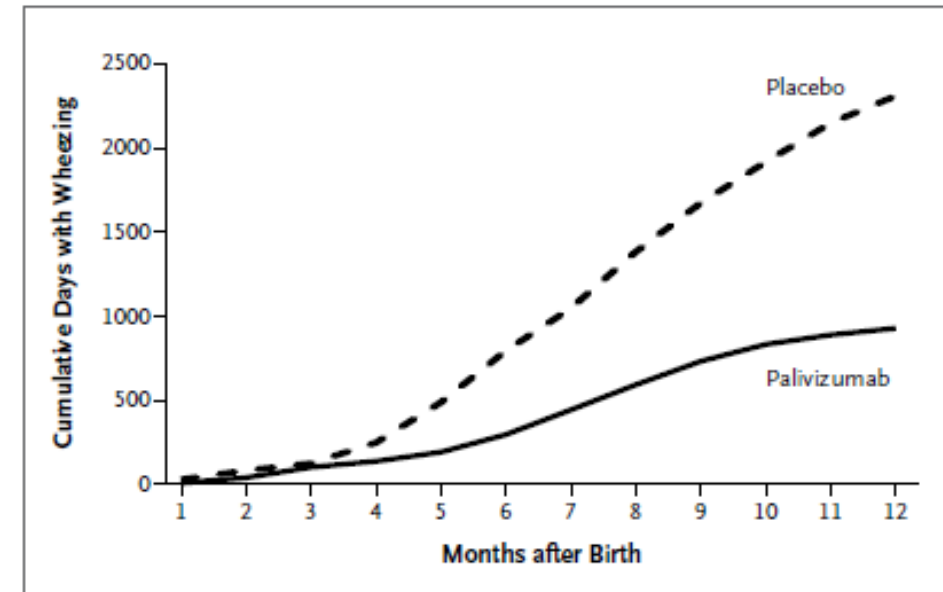


Figure 2. Cumulative Wheezing Days for 429 Preterm Infants during the First Year of Life.

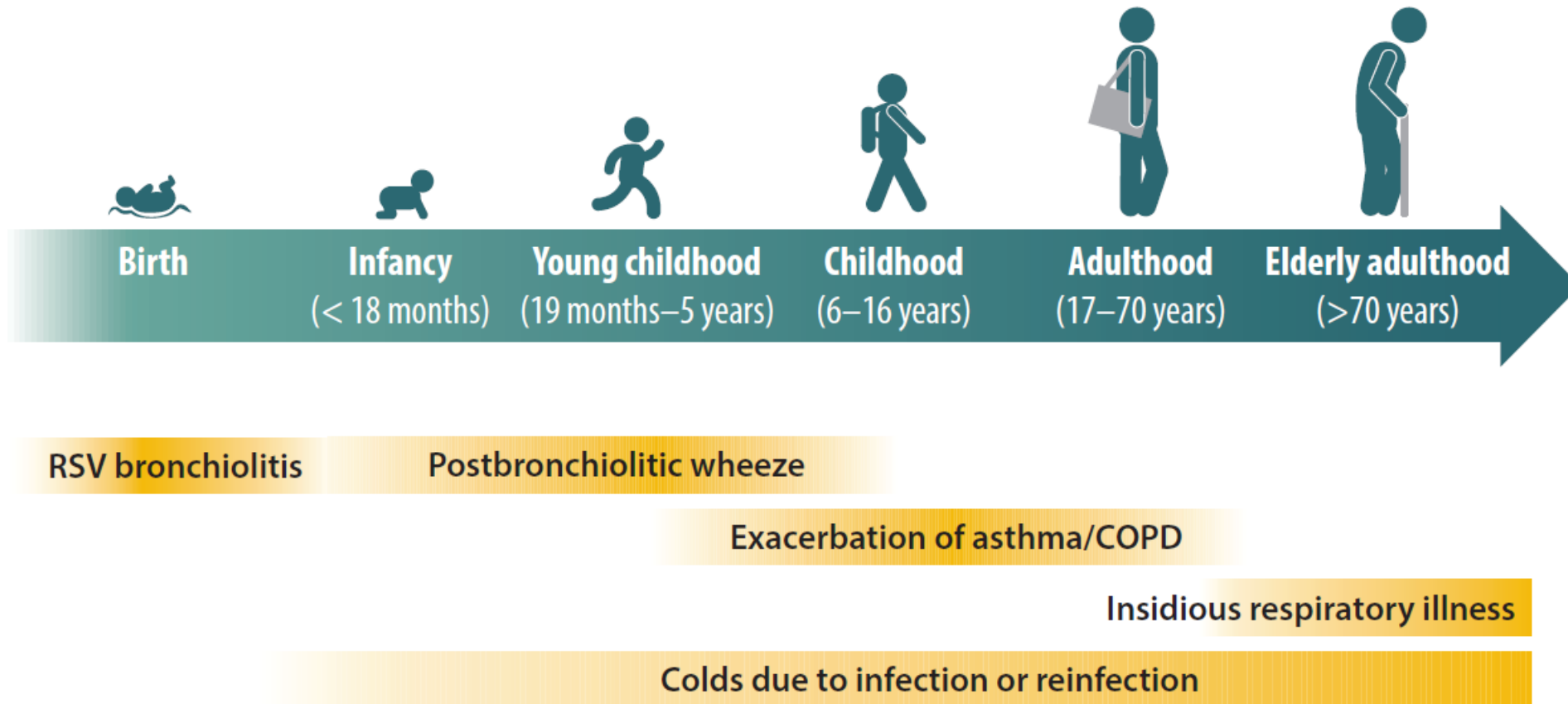
$P < 0.001$ for the comparison between palivizumab and placebo with the use of Poisson regression.

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/NEJMoal211917

RSV affects all ages



The Etiological Role of Common Respiratory Viruses in Acute Respiratory Infections in Older Adults: A Systematic Review and Meta-analysis

Ting Shi,¹ Andrew Arnott,¹ Indre Semogas,¹ Ann R. Falsey,^{3,4} Peter Openshaw,² Jadwiga A. Wedzicha,² Harry Campbell,^{1,6} and Harish Nair,^{1,4,6} for the RESCEU Investigators



<https://doi.org/10.1093/infdis/jiz059>

Review of global RSV-ARI studies in adults aged ≥ 65 years, 1996-2018. Derived rate estimates for 2015, calculated global and regional burdens. Estimated in-hospital deaths due to RSV-ARI by combining hCFR data with hospital admission estimates from hospital-based studies.

Results

- Estimate 1.5m episodes (95% CI 0.3 million–6.9 million) of RSV-ARI in older adults in industrialized countries
- 14.5% of episodes resulted in hosp. admission (n=214 000, 95% CI 100 000–459 000)
- RSV hospital admissions in older adults estimated at 336,000 globally (range 186,000–614,000).
- Estimate about 14 000 in-hospital deaths (5,000–50,000) globally.

The disease burden of RSV-ARI among older adults is substantial



Prof Wisia Wedzicha



- Janssen Pre + Post F serology
- Groningen (6/12 samples sent) – **8** positive (1 overlap with PCR)
- Imperial (6/52 and 6/12 samples sent) -**12** positive (3 overlaps with PCR)

RESCEU: COPD Cohort Study

Dr Dexter J Wiseman Clinical Research Fellow – NHLI, Imperial College London

177 Patients enrolled

1,175 individual visits

188 Exacerbation visits and 222 exacerbation follow-ups

175 Exacerbation visits have had NP swabs tested by GSK

247 'unreported' exacerbations logged on diary cards

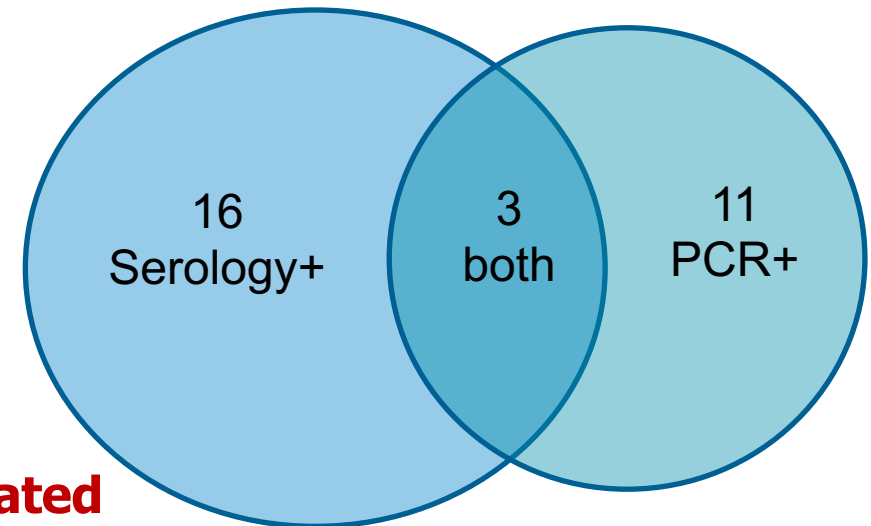
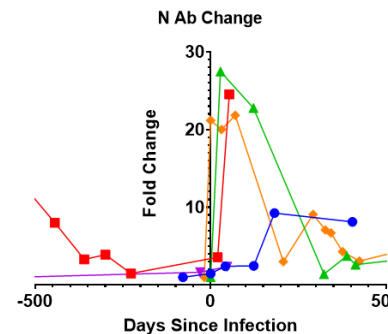


Dr Dexter Wiseman

- 14 PCR positives (including 3 overlaps)
- 19 Serology positives (including 3 overlaps)



27 RSV cases across both cohorts, using serology and PCR



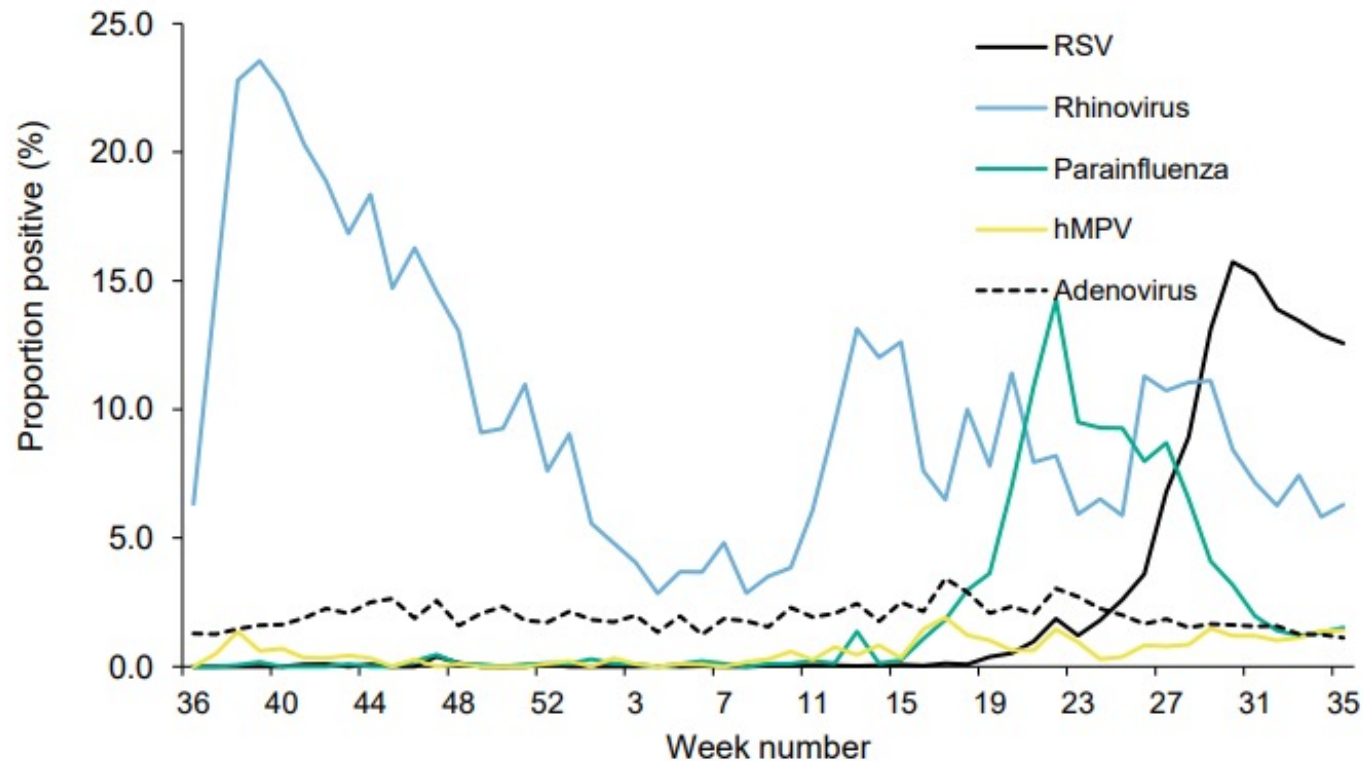
At least 7.4% of COPD exacerbations are RSV-related

<https://www.atsjournals.org/doi/10.1164/rccm.202308-1320OC>

PubMed: [38502541](https://pubmed.ncbi.nlm.nih.gov/38502541/)

UK bounce-back of respiratory viruses after lifting of COVID restrictions

Figure 16: DataMart weekly positivity (%) for other respiratory viruses, England



PHE National flu and COVID-19 surveillance report: 9 September 2021 (week 36)

Experimental infection of human volunteers

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



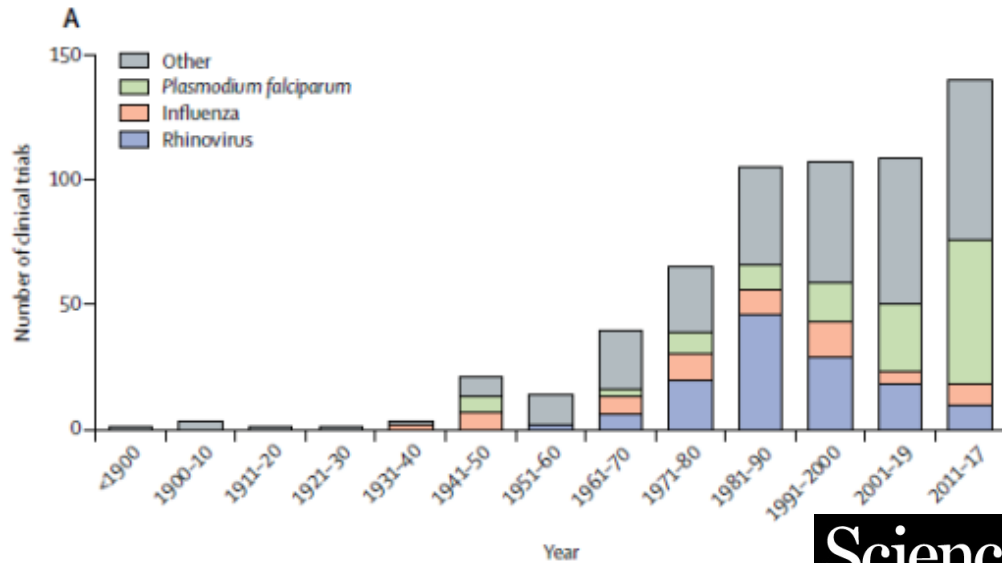
Lancet Infect Dis 2018

Published Online

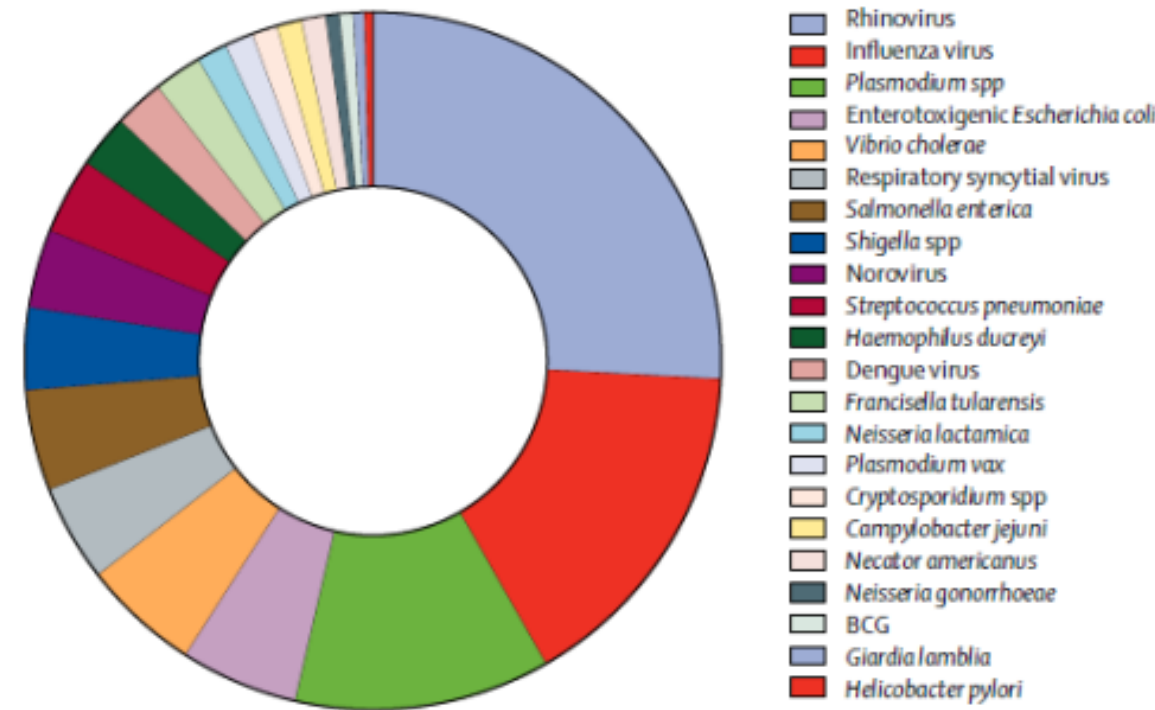
June 8, 2018

[http://dx.doi.org/10.1016/S1473-3099\(18\)30177-4](http://dx.doi.org/10.1016/S1473-3099(18)30177-4)

S1473-3099(18)30177-4



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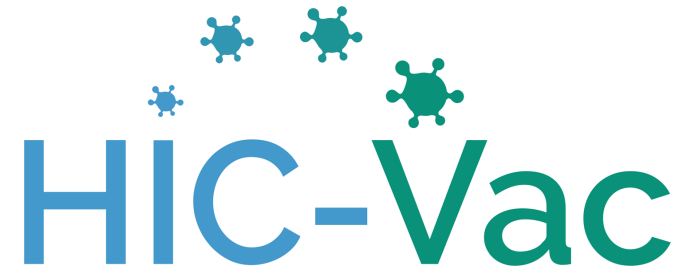
Total=22,257 Volunteers



NH researchers infect volunteers with the flu virus in an ongoing effort to improve vaccines. AP PHOTO/KEVIN MAZUR

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

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



HIC-Vac

Annual Meeting November 2024

*Developing human
infection challenge to
accelerate vaccinology*

540 members, 31% LMIC



Medical
Research
Council

www.hic-vac.org

Distributed £4.8m research fund since 2017



Liverpool, UK: 120 in person, 100 online

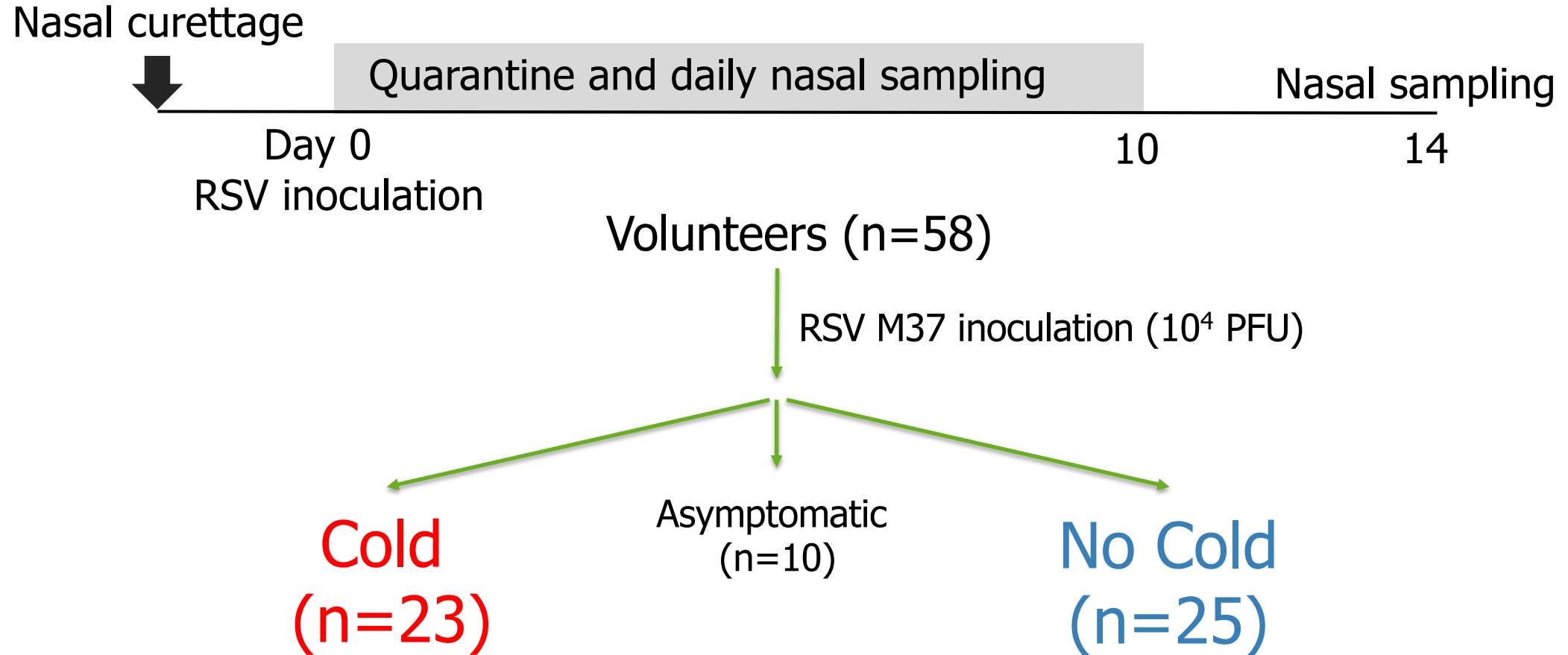
Inoculation of volunteers with RSV



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

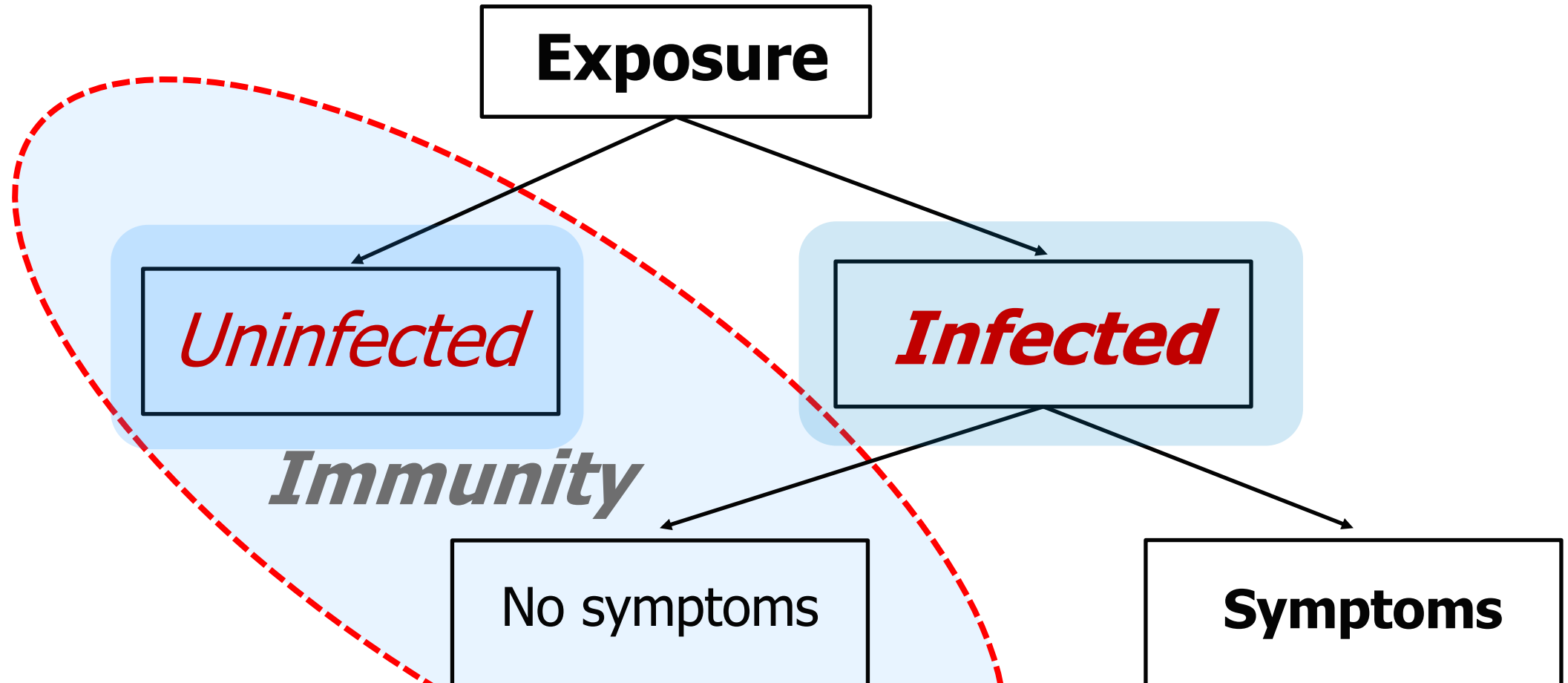
Chris Chiu and Max Habibi

What determines susceptibility?



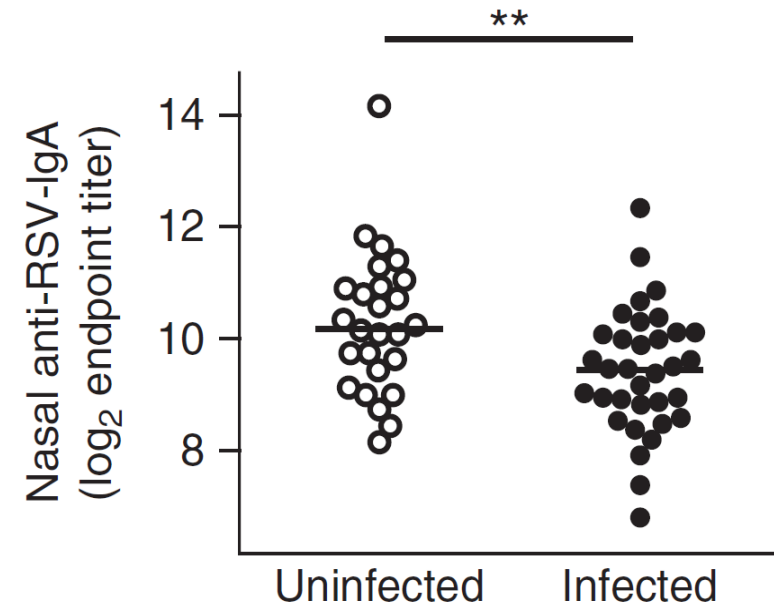
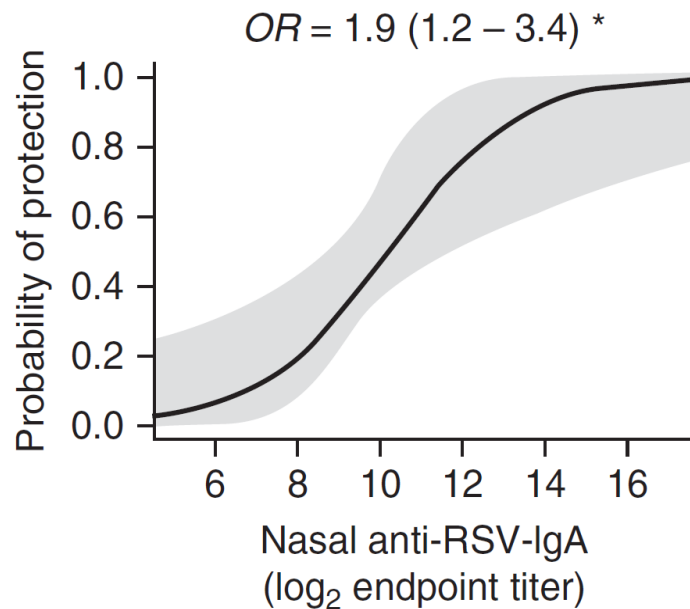
- Human infection challenge model
- Detailed study of complete infection time course

Possible outcomes of RSV exposure

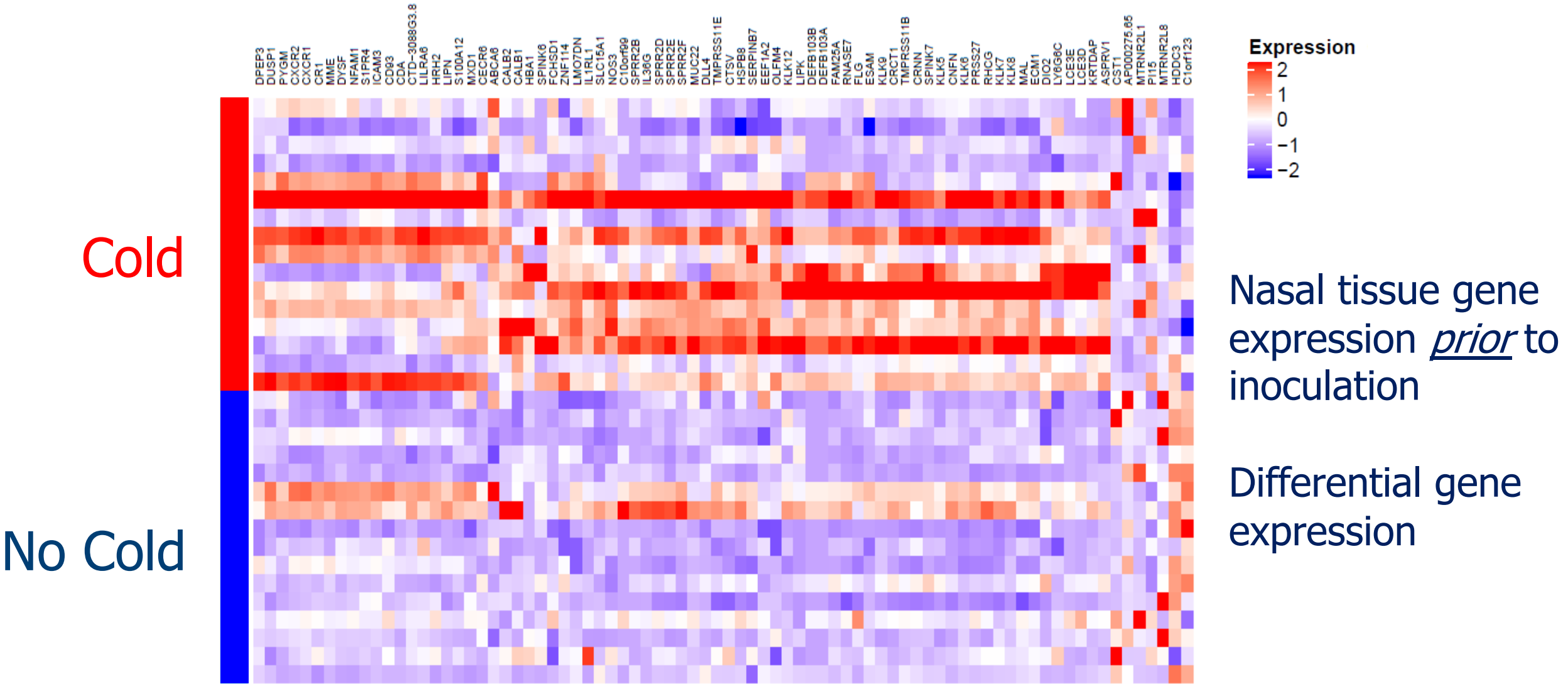


What determines susceptibility?

- Very high nasal antibody levels offer some protection
- High probability of protection would require super-physiologic levels

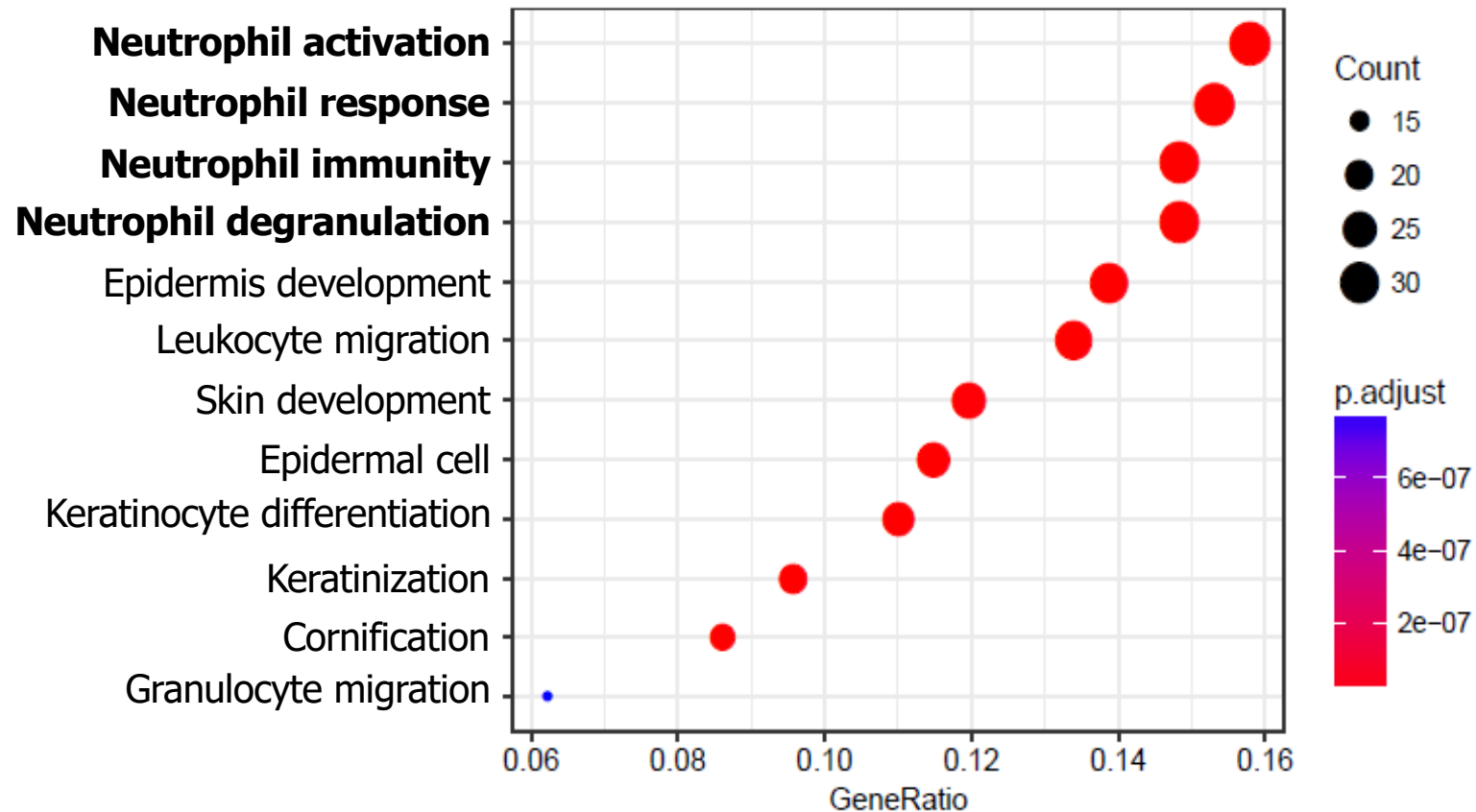


What determines susceptibility?



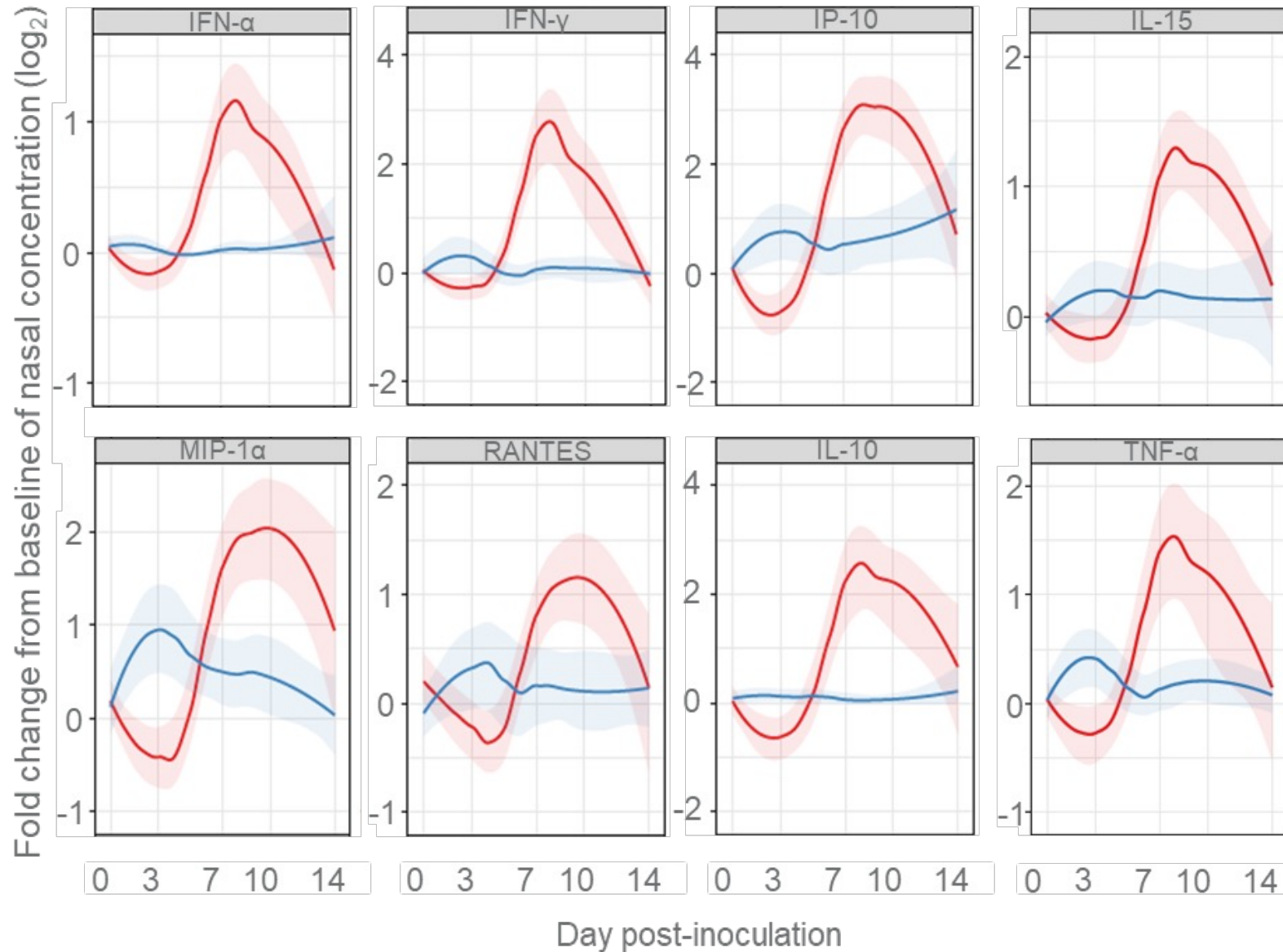
What determines susceptibility?

Biological Processes Enriched: **Cold** vs **No Cold** \\



Elevated neutrophil activation at baseline in **Cold** group

Mucosal response to exposure



No Cold

Host shows an early response:
virus defeated

Cold

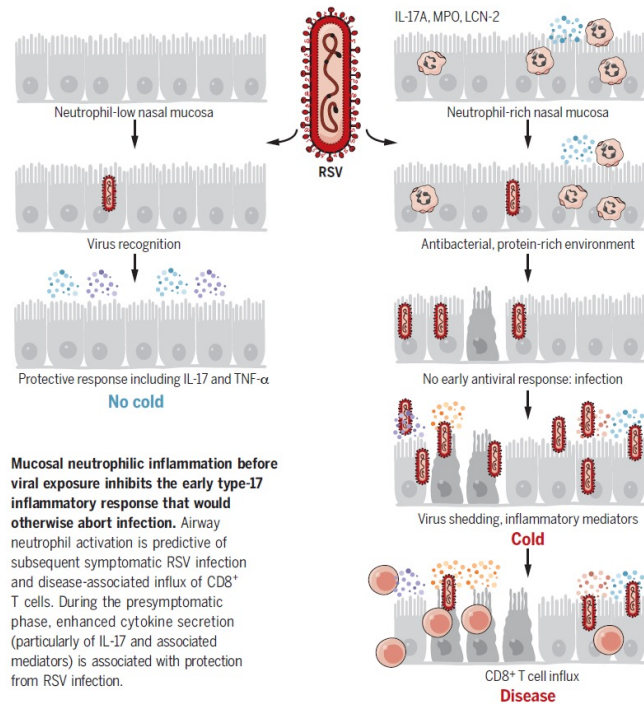
Host mediators suppressed:
virus succeeds

VIRAL INFECTIONS

Neutrophilic inflammation in the respiratory mucosa predisposes to RSV infection

Maximilian S. Habib^{1*}, Ryan S. Thwaites^{1*}, Meiping Chang², Agnieszka Jozwik¹, Allan Paras¹, Freja Kirsebom¹, Augusto Varese¹, Amber Owen¹, Leah Cuthbertson¹, Phillip James¹, Tanushree Tunstall¹, David Nickle³, Trevor T. Hansel¹, Miriam F. Moffatt¹, Cecilia Johansson^{1,†}, Christopher Chiu^{4,†,‡}, Peter J. M. Openshaw^{2,†,‡}

Interpretations...



<https://doi.org/10.1126/science.aba9301>

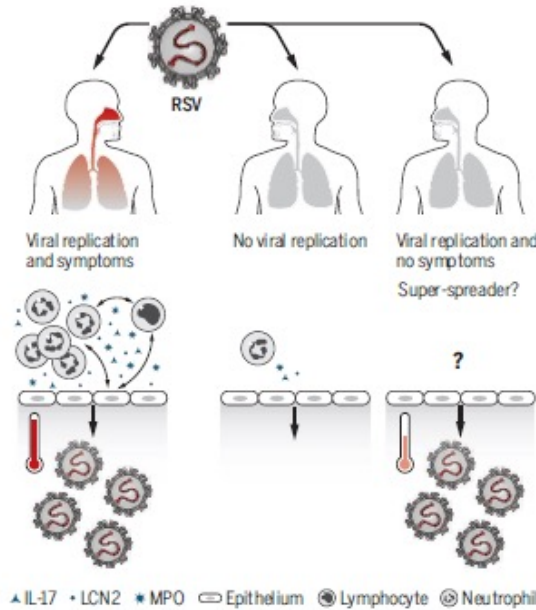
INFECTIOUS DISEASE

Making a bed for viral infections

An inflamed mucosal niche is permissive for symptomatic respiratory syncytial virus infection

By Ananda S. Mirchandani and Sarah R. Walmsley

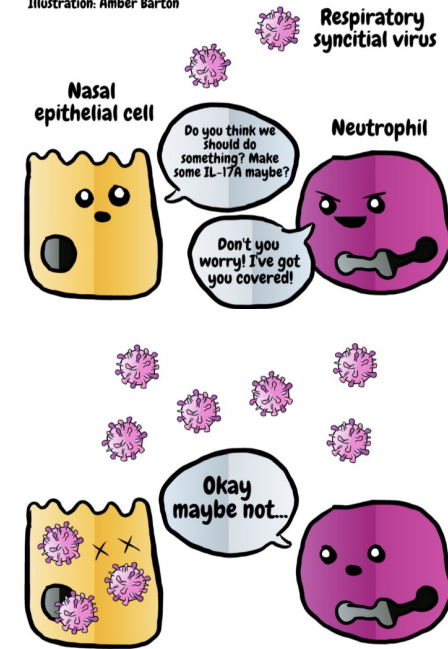
The timing of neutrophil presence in tissues, as well as their activation status, appears to influence levels of the neutrophil-associated proteases lipocalin-2 (LCN2) and myeloperoxidase (MPO).



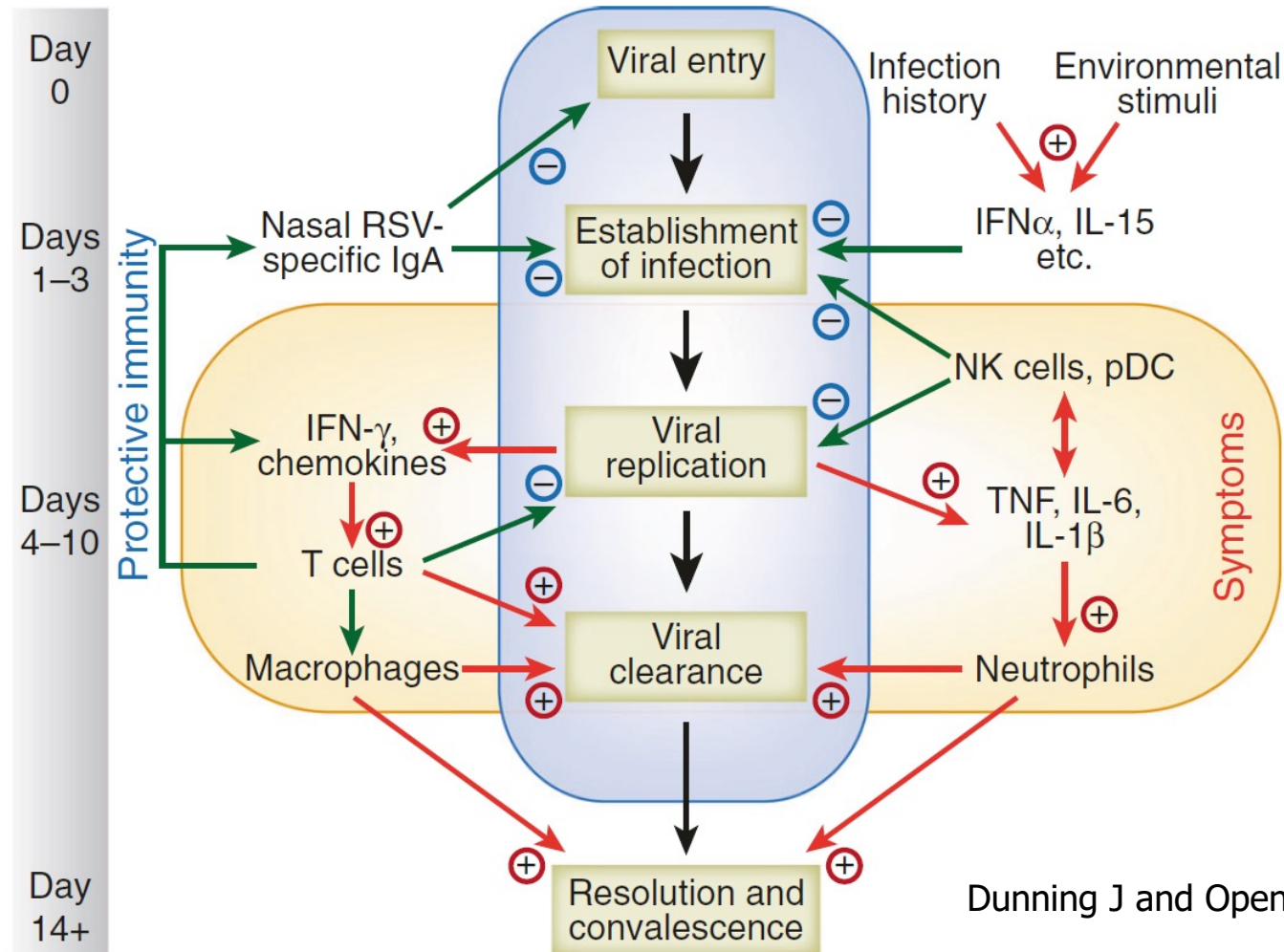
10.1126/science.abe3685

You Retweeted
 amberbarton @amberjoybarton · Oct 9
 After doing a PhD looking at early transcriptomic responses to human challenge I'm very happy to see a paper like this in @ScienceMagazine!

Paper: Habibi et al. 2020
 Science
 Illustration: Amber Barton



Sequential events during RSV virus infection

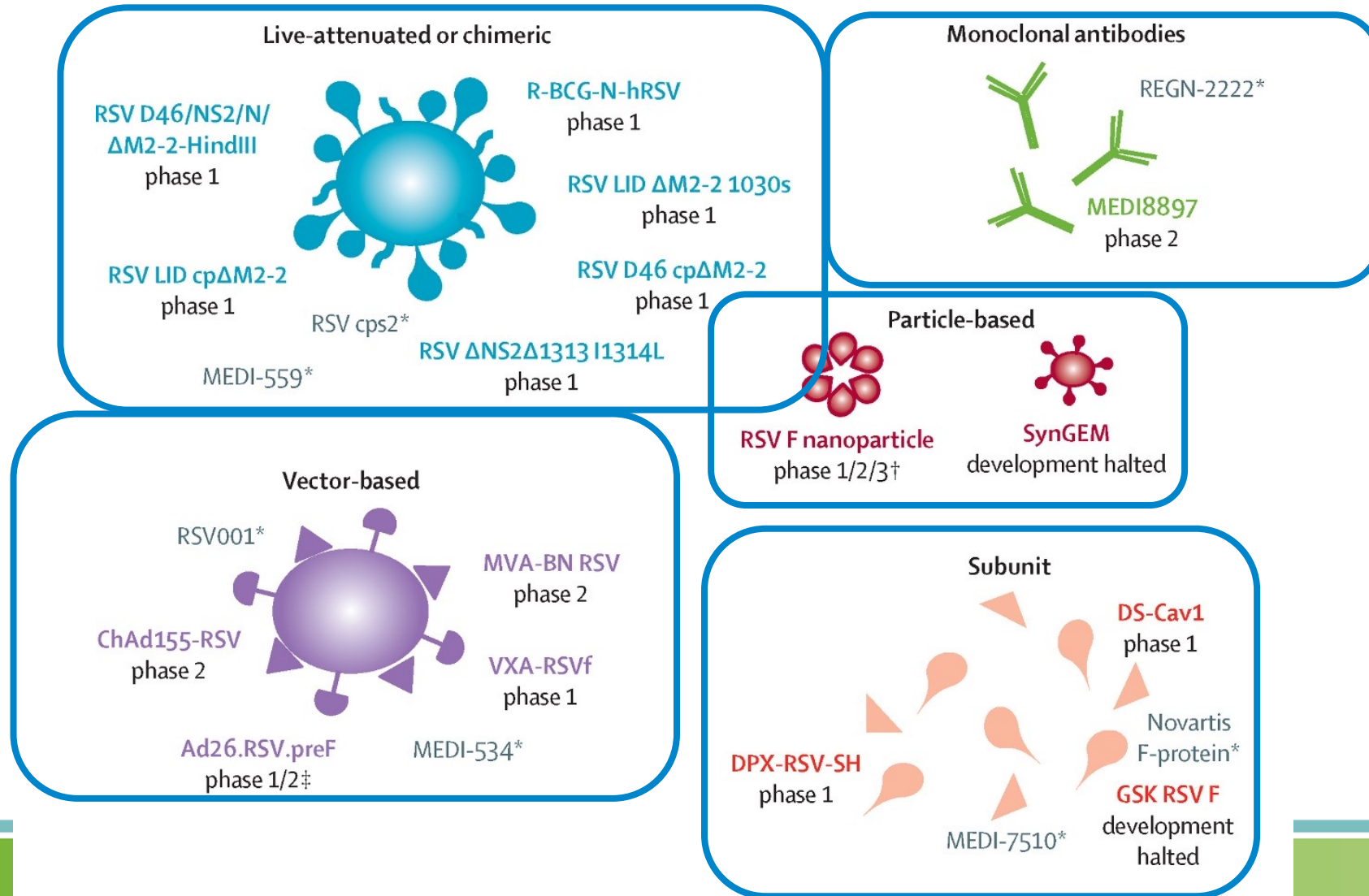


Dunning J and Openshaw P. *Mucosal Immunol* **2020**;13:566–573.

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

S1473-3099(18)30292-5

Serum and mucosal antibody-mediated protection and identification of asymptomatic respiratory syncytial virus infection in community-dwelling older adults in Europe

Deniz Öner, Charlotte Vernhes, Sunita Balla-Jhagjhoorsingh, Annick Moureau, Marjolein ... Christopher C. Butler, Theo J.M. Verheij, Simon B. Drysdale, Joanne G. Wildenbeest, RESCEU Investigators, Andrew J. Pollard, Peter J.M. Openshaw, Louis Bont, Jeroen Aerssens

- Obtained baseline serum RSV-pre- and post-F, RSV-A2 neut IgG, mucosal RSV-pre-F IgA and IgG levels.
- Separated into those with
 - symptomatic RSV-ARTI (N=30)
 - non-RSV (RSV negative) ARTI (N=386)
 - No ARTI (N=338)
 - Asymptomatic RSV infection (serology).

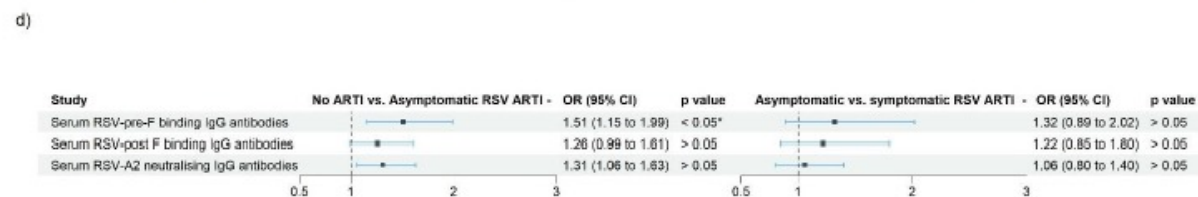
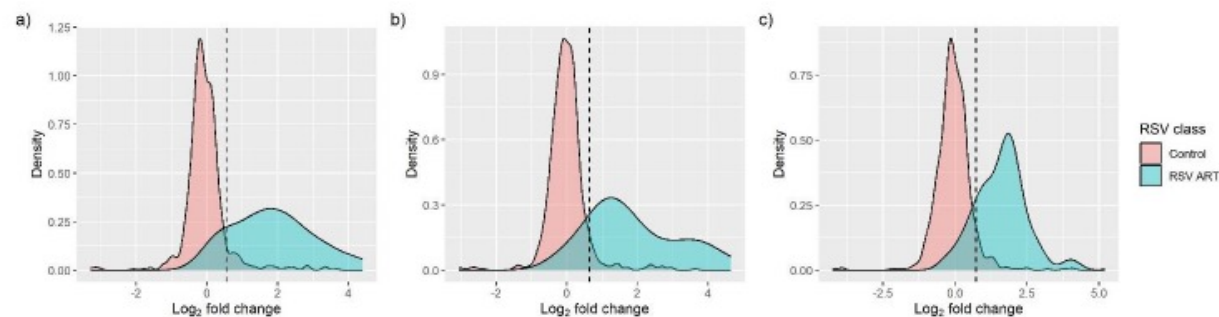
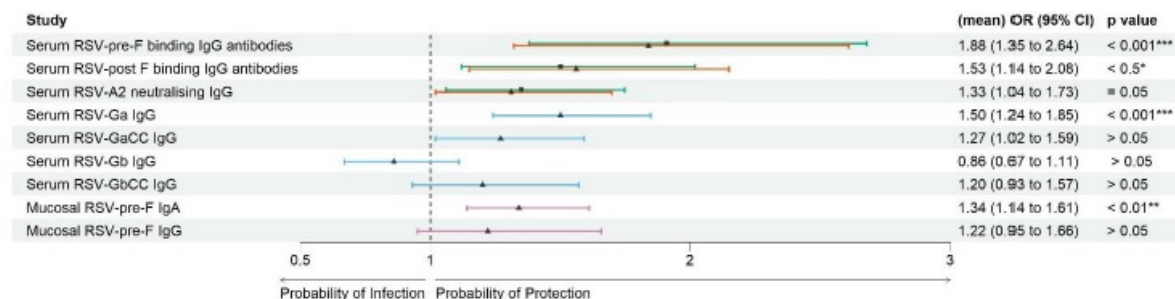
1. Serum RSV-pre-F, RSV-G IgG and mucosal pre-F binding IgA antibodies correlate with protection vs. symptomatic RSV infection.

2. RSV-pre-F IgG antibodies correlate with protection from RSV infection irrespective of symptoms.



Table 1: Clinical and demographic characteristics of the cohort.

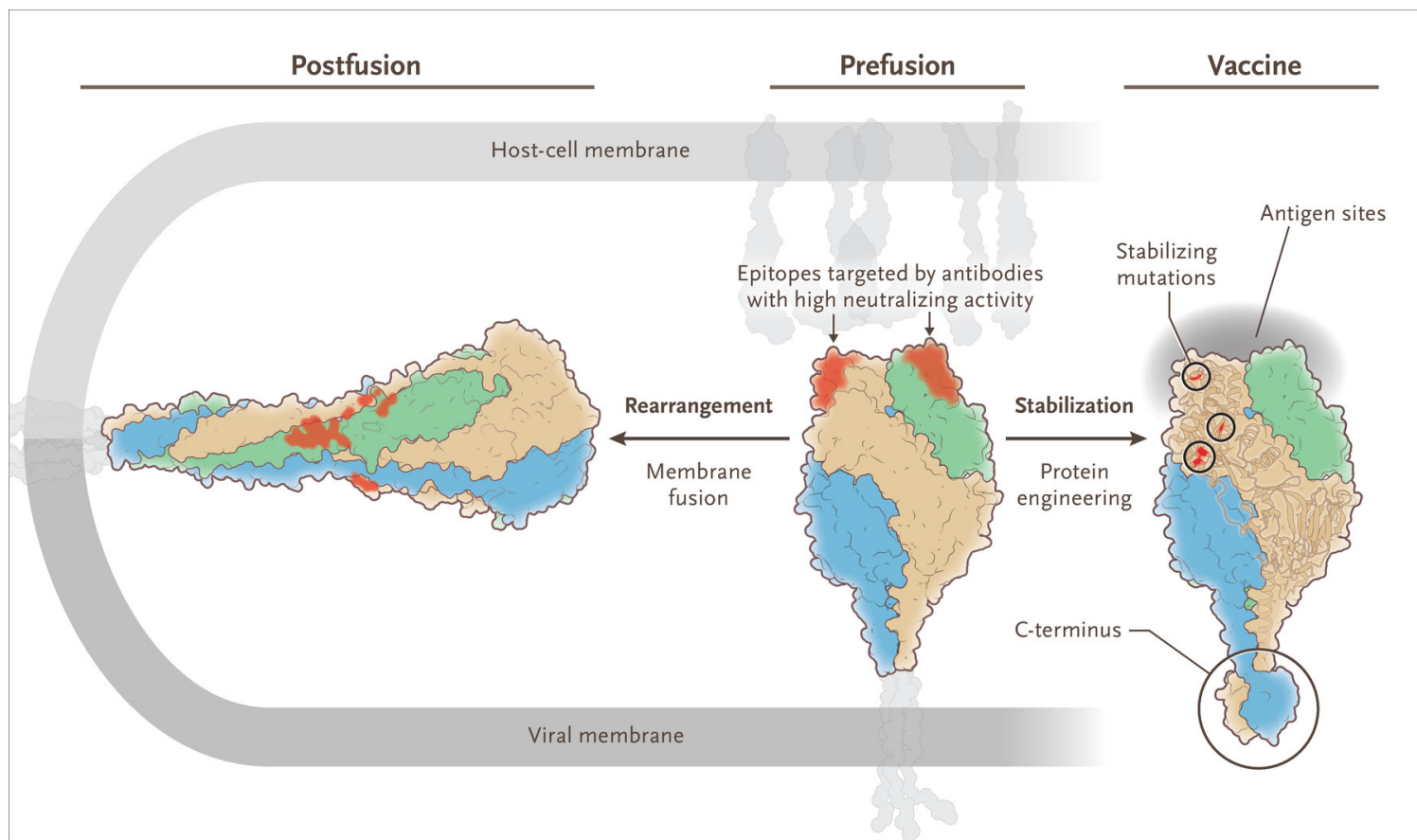
	No ARTI (N=338)	Non-RSV ARTI (N=386)	RSV ARTI (N=30)
Age 75+	186 (55.0%)	200 (51.8%)	18 (60.0%)
Median [Min. Max]	76.0 [60.0. 95.0]	75.0 [60.0. 94.0]	75.5 [64.0. 89.0]



Perspective

The Journey to RSV Vaccines — Heralding an Era of Structure-Based Design

Barney S. Graham, M.D., Ph.D.



"Obtaining RSV preF crystals was difficult, because the unmodified and untethered protein spontaneously rearranges into its highly stable postfusion conformation"

N Engl J Med 2023; 388:579-581

<https://www.nejm.org/doi/full/10.1056/NEJMp2216358>

Nature | Vol 600 | 16 December 2021 | 379

THE NEW WAVE OF VACCINES FOR A KILLER RESPIRATORY VIRUS

“
Things changed
completely when we
began to understand
the main viral protein.”

Respiratory syncytial virus hospitalizes millions of people a year and kills tens of thousands. After decades of failure, four vaccines are now being tested in late-stage trials.

By Kendall Powell

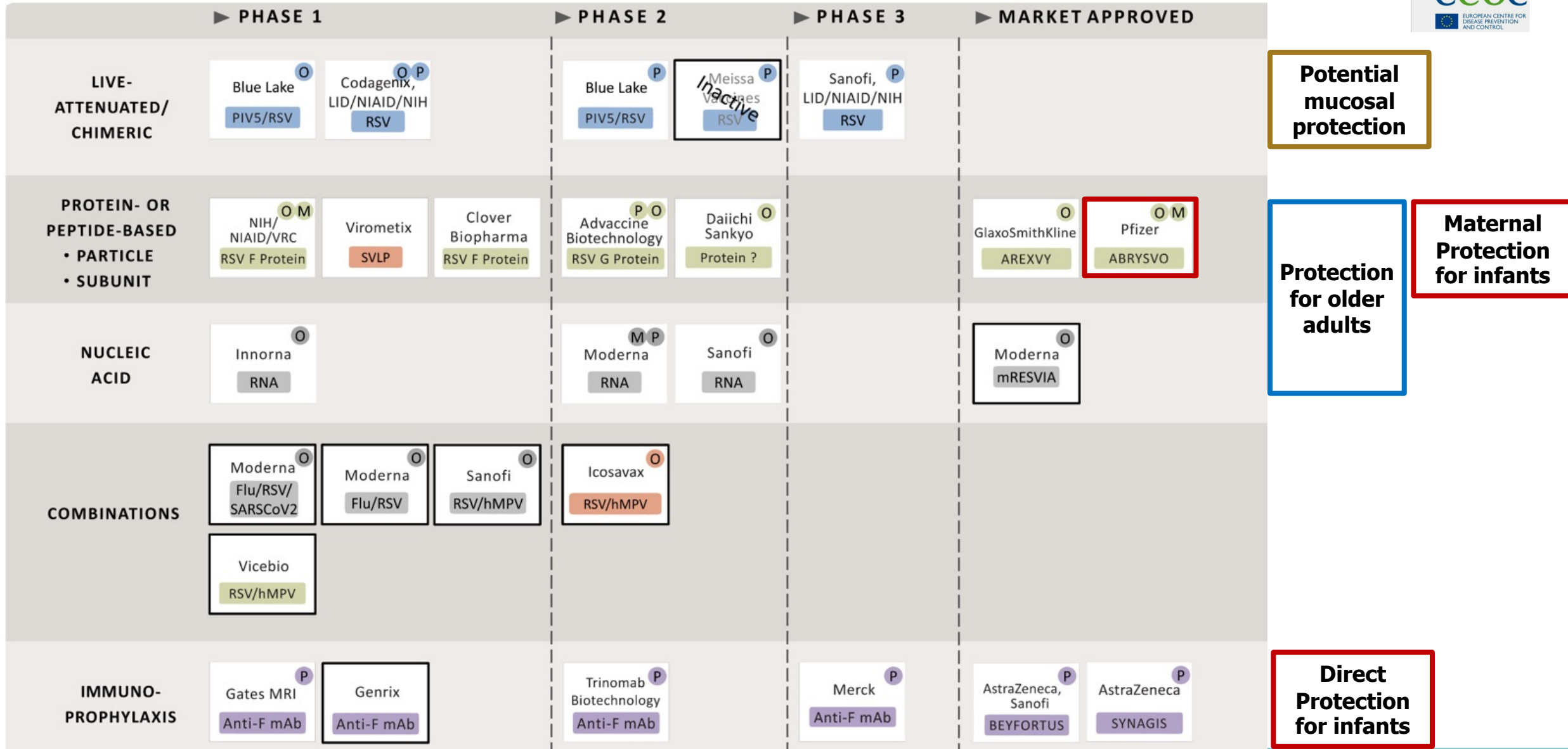
“GSK, Janssen, Moderna and Pfizer now each have global phase III trials under way in tens of thousands of older adults. GSK leads the pack, and Rappuoli says he expects to have interim results in early 2022.”

<https://media.nature.com/original/magazine-assets/d41586-021-03704-y/d41586-021-03704-y.pdf>

RSV Vaccine and mAb Snapshot

TARGET INDICATION: **P** =PEDIATRIC **M** =MATERNAL **O** =OLDER ADULT

PLATFORM KEY: **Blue** =LIVE/CHIMERIC **Orange** =PARTICLE **Green** =SUBUNIT
Grey =NUCLEIC ACID **Purple** =mAb

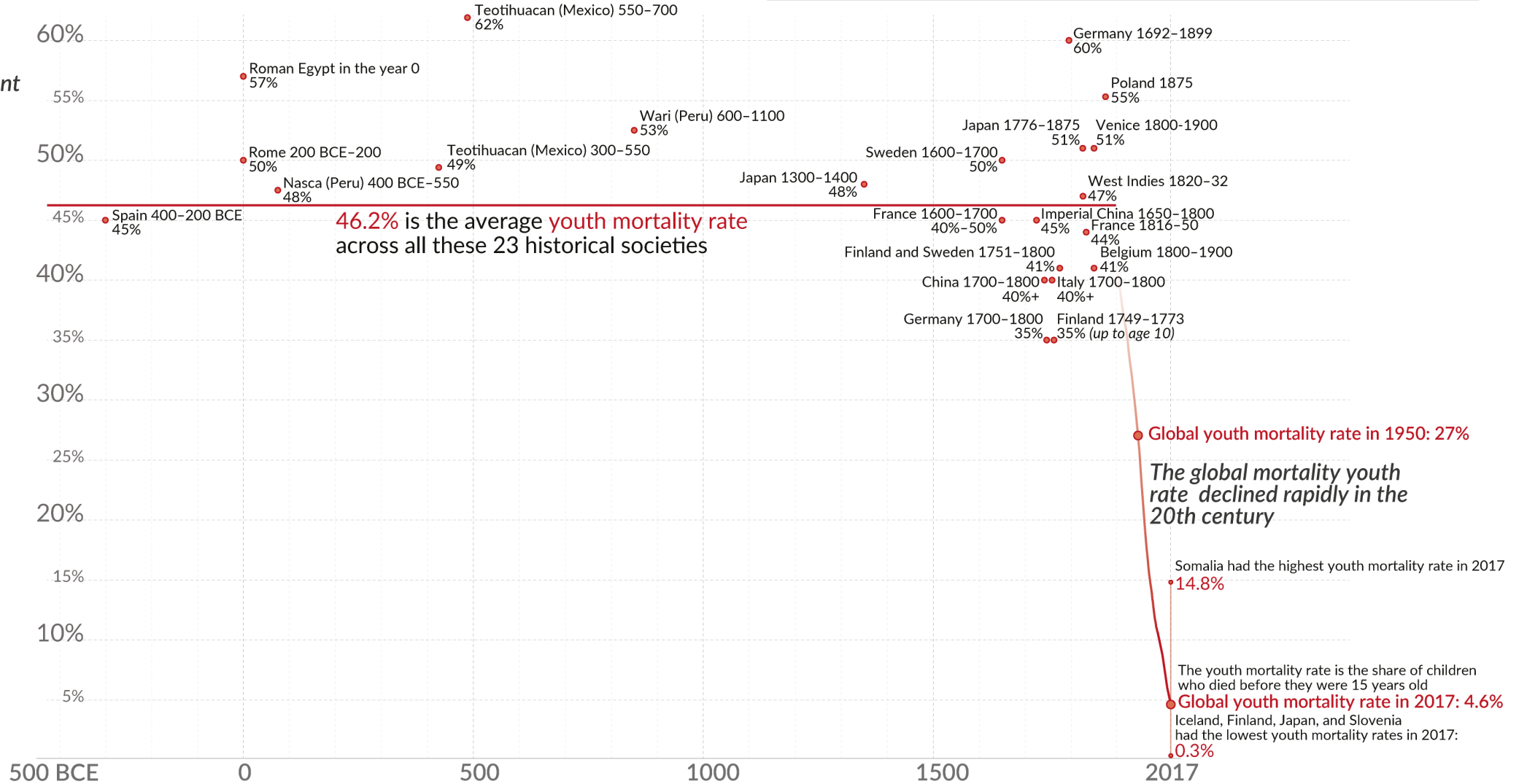


Youth mortality over the last 2400 years

Shown is the share who died as infants or children before reaching the end of puberty (younger than 15)

<https://ourworldindata.org/uploads/2021/03/Youth-mortality-rates-over-last-two-millennia.png>

Average youth mortality rate across 20 different hunter-gatherer societies: **48.8%**



Data sources: the mortality estimates for historical societies are from a large number of independent studies collected in Volk and Atkinson (2013) – *Infant and child death in the human environment of evolutionary adaptation*. Data for 2017 is from the United Nations Inter-agency group for child mortality estimation [IGME]. Global estimates for the 20th century are based on under five mortality from Our World in Data.

Prospects for prevention of RSV disease

Vaccine protection of older adults

- Excellent protection against LRTD
- Will it last many seasons?
- Real-world health benefit is hard to estimate

Vaccines for infants/toddlers

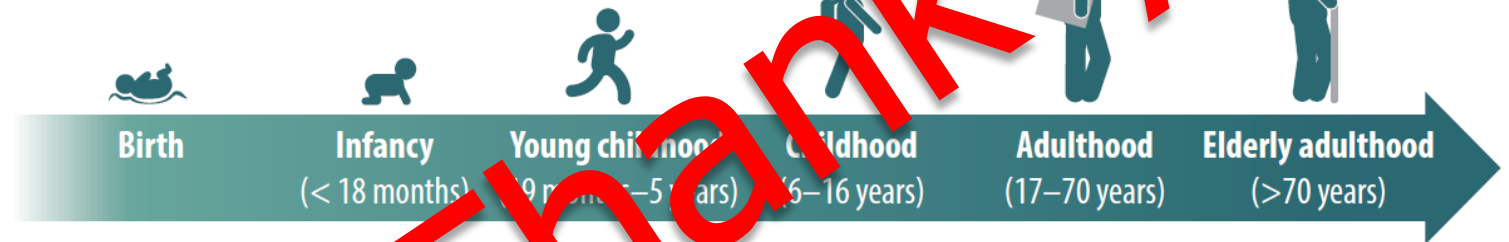
- Live attenuated vaccine might be ideal
- Could follow on from year 1 (after nirsevimab)
- Trials underway- will they reduce transmission in households?

Passive immunity

- Nirsevimab is approved, should replace palivizumab
- Will they reduce childhood wheeze and asthma Dx?
- Might need other of mAbs
- Emergence of resistant strains?

Maternal vaccines

- Protective against infant infection (?4-5 mo.?)
- Premature labour in GSK trials- why?
- Cost effective in LMICs



THANK YOU!