The ABCs of Rhinovirus Infections and Asthma

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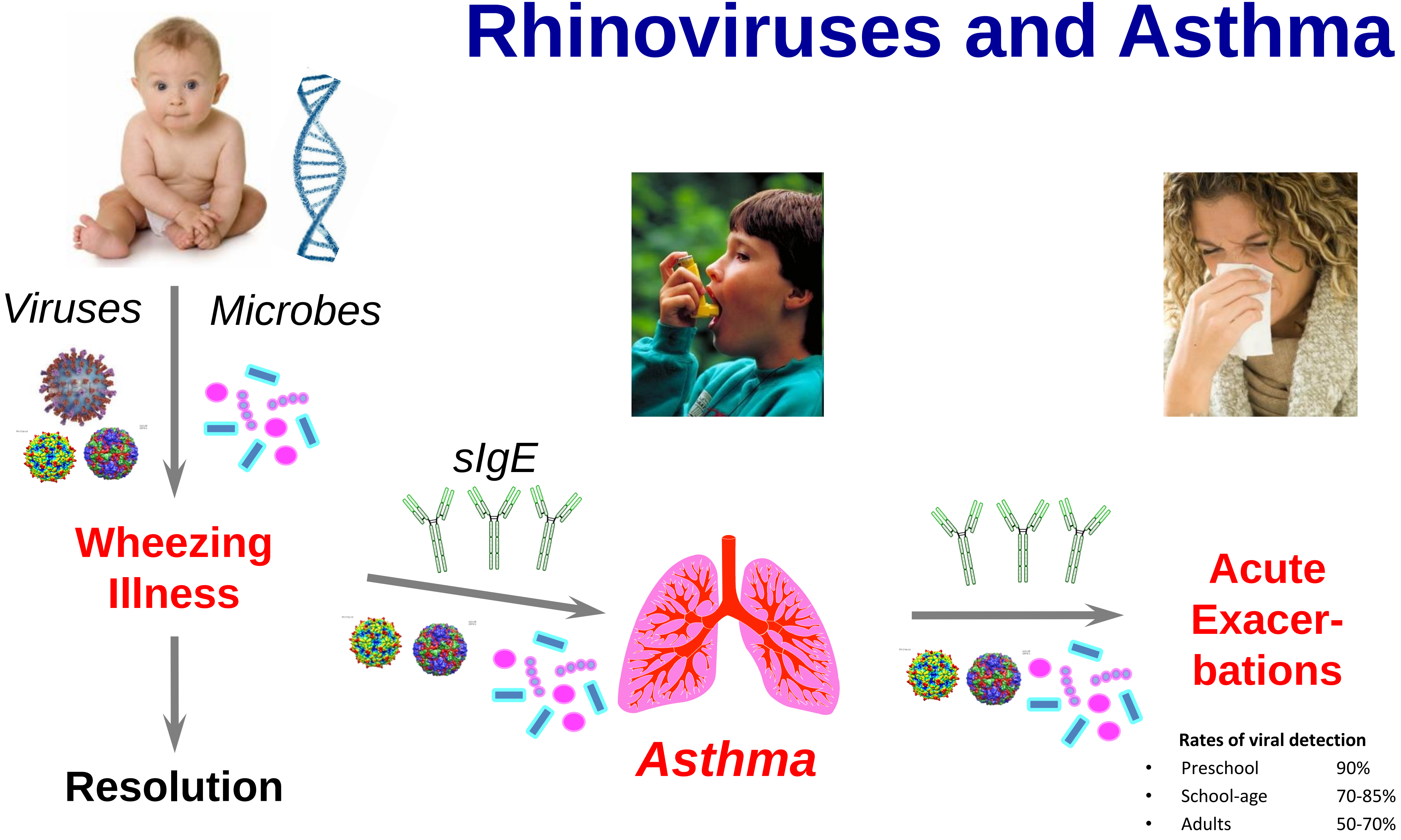
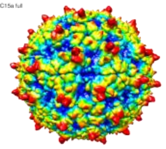
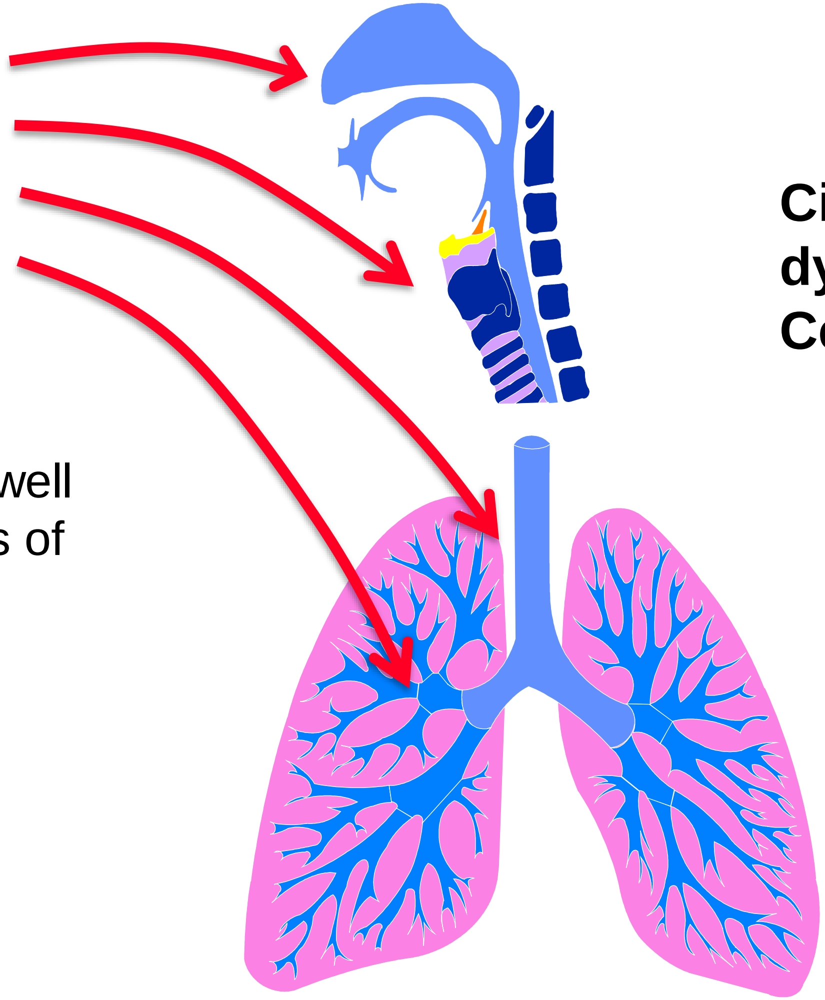
Rhinoviruses and Asthma

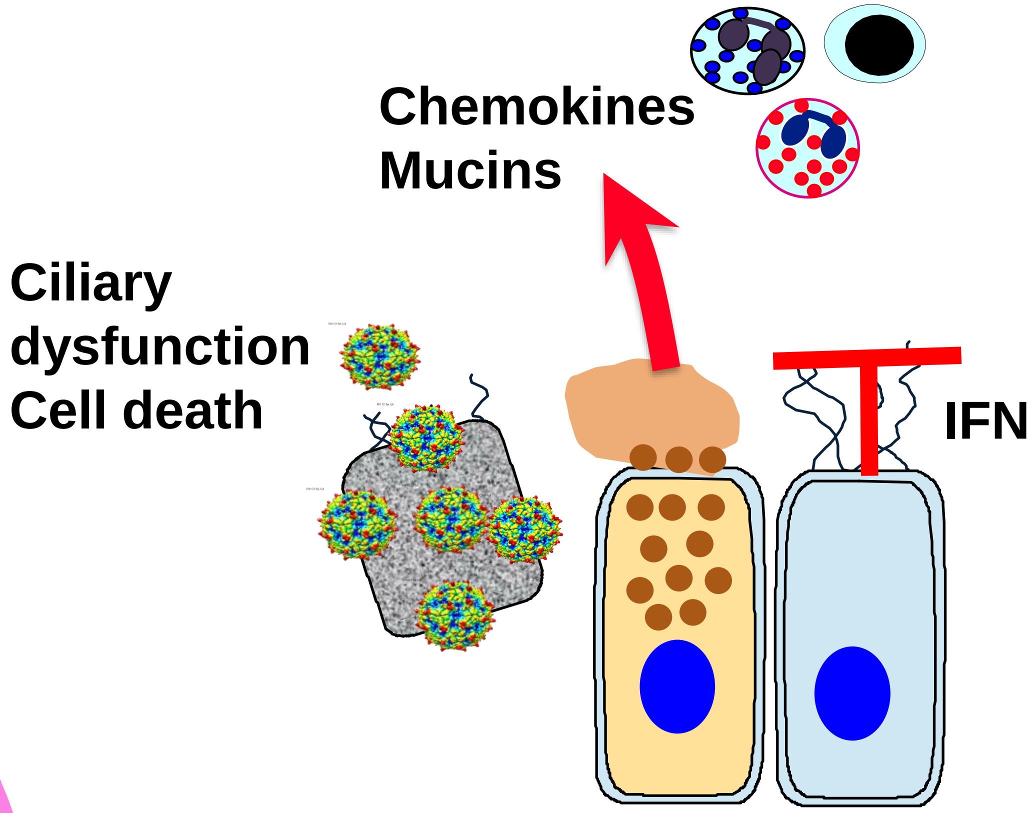


How do RV infections provoke asthma?



Ciliated airway epithelial cells





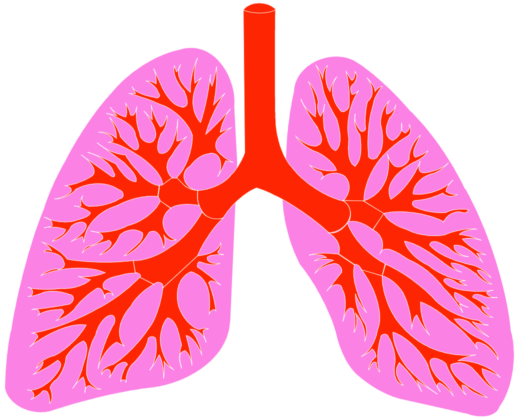
- RV have adapted very well to grow at temperatures of the lower airways[1]
- In adults, 50% of RV infections extend to the lower airway[2]

1. *McFadden ER Jr et al, J Appl Physiol 1985*
2. *Mosser AG et al, AJRCCM 2005*
3. *Nakagome K et al JACI 2017*
4. *Essaidi-Laziosi M et al JACI 2018*

Most RV Infections Do Not Cause Exacerbations

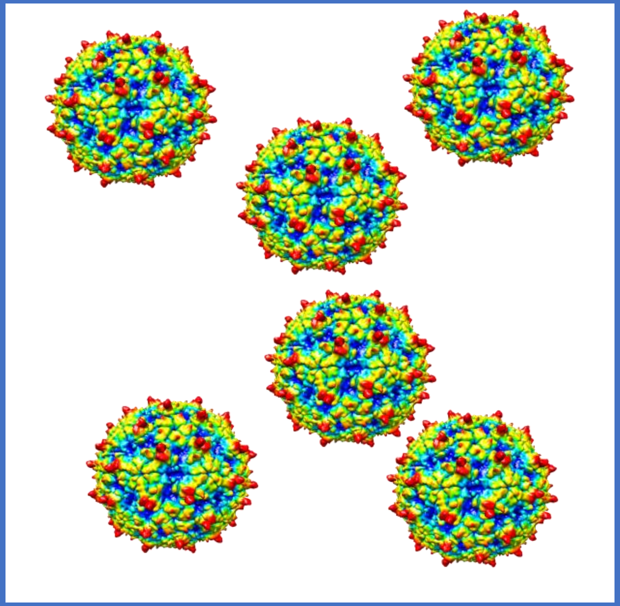
URI
(Just a cold)

<30%

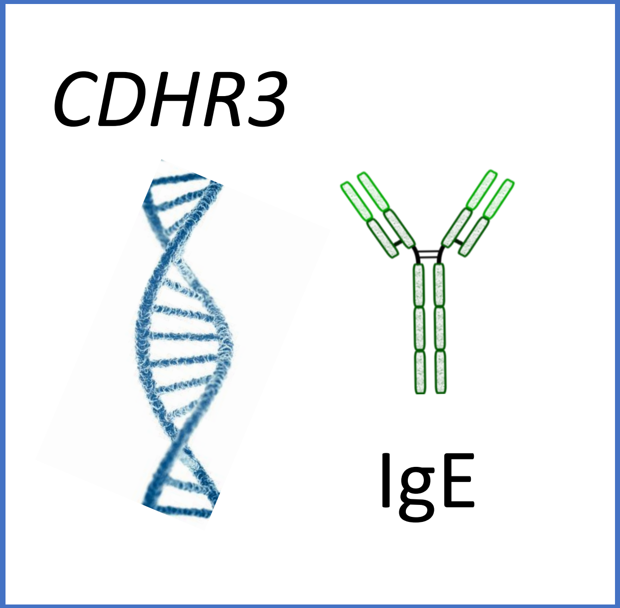


Exacerbation

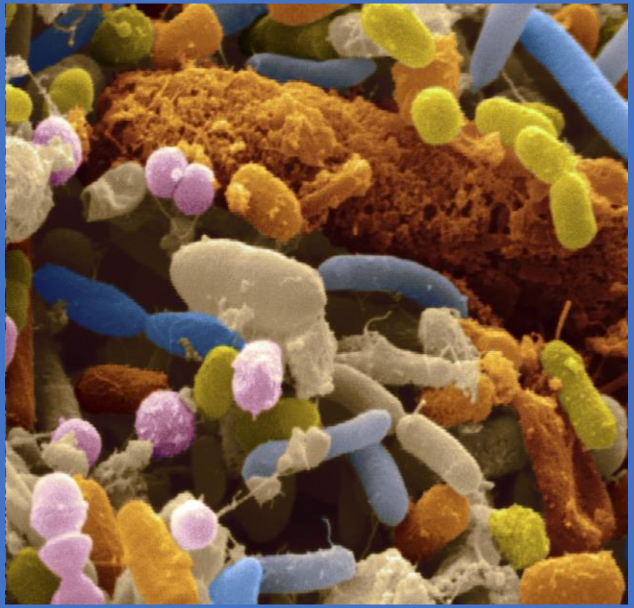
What are the risk factors for RV-induced exacerbations?



Viruses



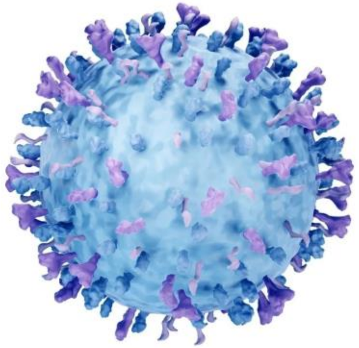
Host



Bacteria

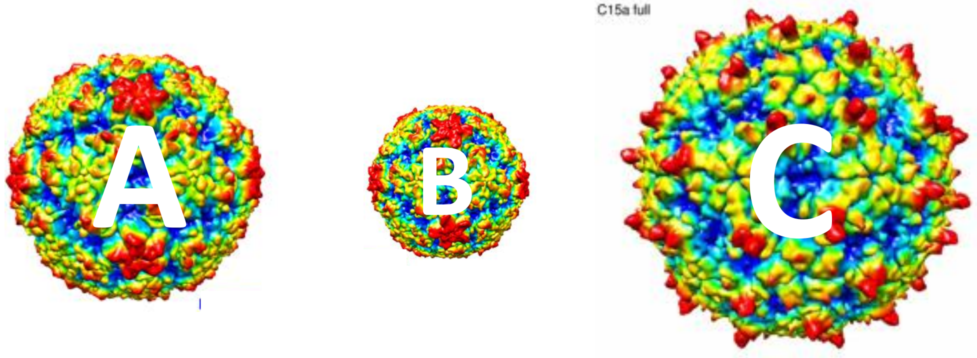
Viruses that Commonly Cause Wheezing

Respiratory Syncytial Virus (RSV)

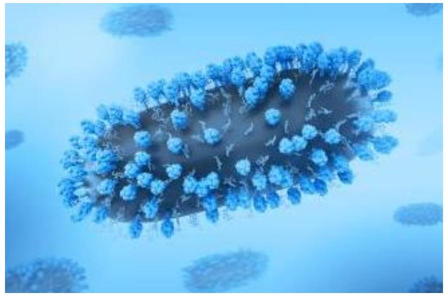


- Most common cause of bronchiolitis through age 1 yr
- Risk factors:
  - Young age
  - Prematurity, SGA
  - Winter birth
  - Prenatal smoke
  - Daycare and older sibs

Rhinoviruses

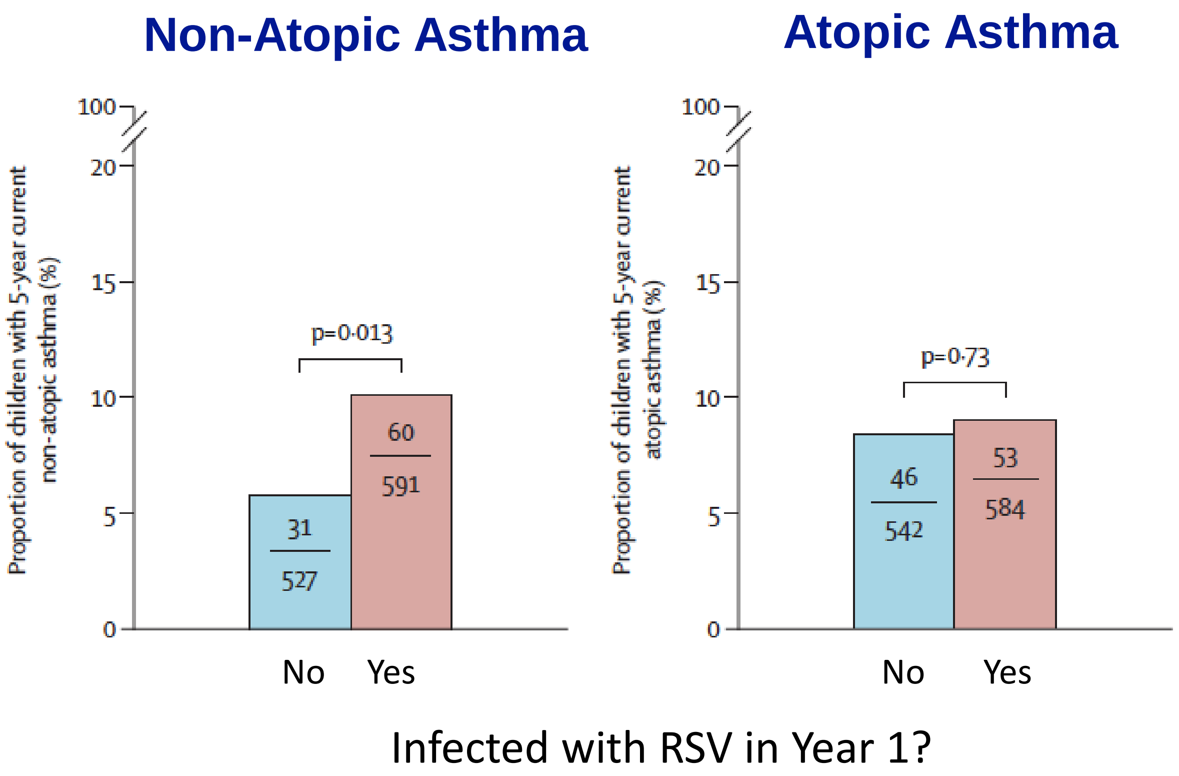


Wang X et al. Lancet 2024
Dallagiacoma et al. Lancet Reg Health - Europe 2025



RSV Infection During Infancy and Childhood Asthma

- INSPIRE birth cohort study
  - 1741 term infants with virology
  - 1371 (70%) with 5-year follow-up
  - 54% of children were infected in the first year
- Not being infected with RSV during infancy → 26% lower risk of current asthma (adjusted RR 0.74, 95% CI 0.58–0.94, p=0·014).



Rosas-Salazar et al., Lancet 2023

RSV Intervention Studies and Asthma Outcomes

Citation	Study design	Intervention	Effects on Asthma
Hasson HO, Vaccines 2024	Retrospective population-based cohort study, 4503 preterm infants	Palivizumab	No effects on asthma or related healthcare utilization in preschoolers
Scheltema NM, Lancet Respir Med 2018	Randomized controlled trial, 429 healthy preterm infants	Palivizumab	No differences in physician-diagnosed asthma or FEV 0.5 at age 6
Mochizuki H, AJRCCM 2017	Prospective multicenter observational cohort study of 444 preterm infants	Palivizumab	Reduced recurrent wheeze but not asthma at age 6
O'Brien KL, Lancet Respir Med 2015	Phase 3, double-blind, placebo-controlled, randomized trial, 2127 Native American Infants 36 weeks gestation	Motivizumab	No effect on rates of medically-attended wheezing in children ages 1-3 years

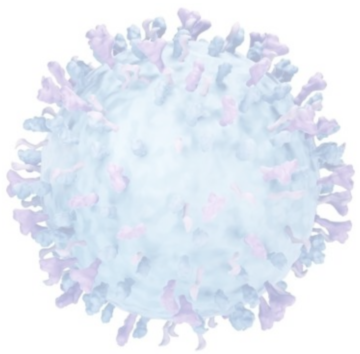
New approaches for preventing severe RSV illnesses in term babies[1]

- Prenatal RSV vaccine
- Nirsevimab

[1]*Percenka C et al, Lancet 2024*

Viruses that Commonly Cause Wheezing

Respiratory Syncytial Virus (RSV)



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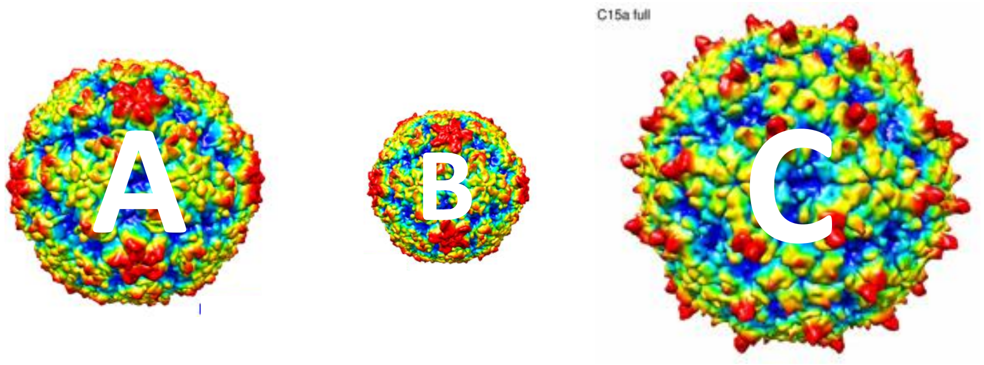
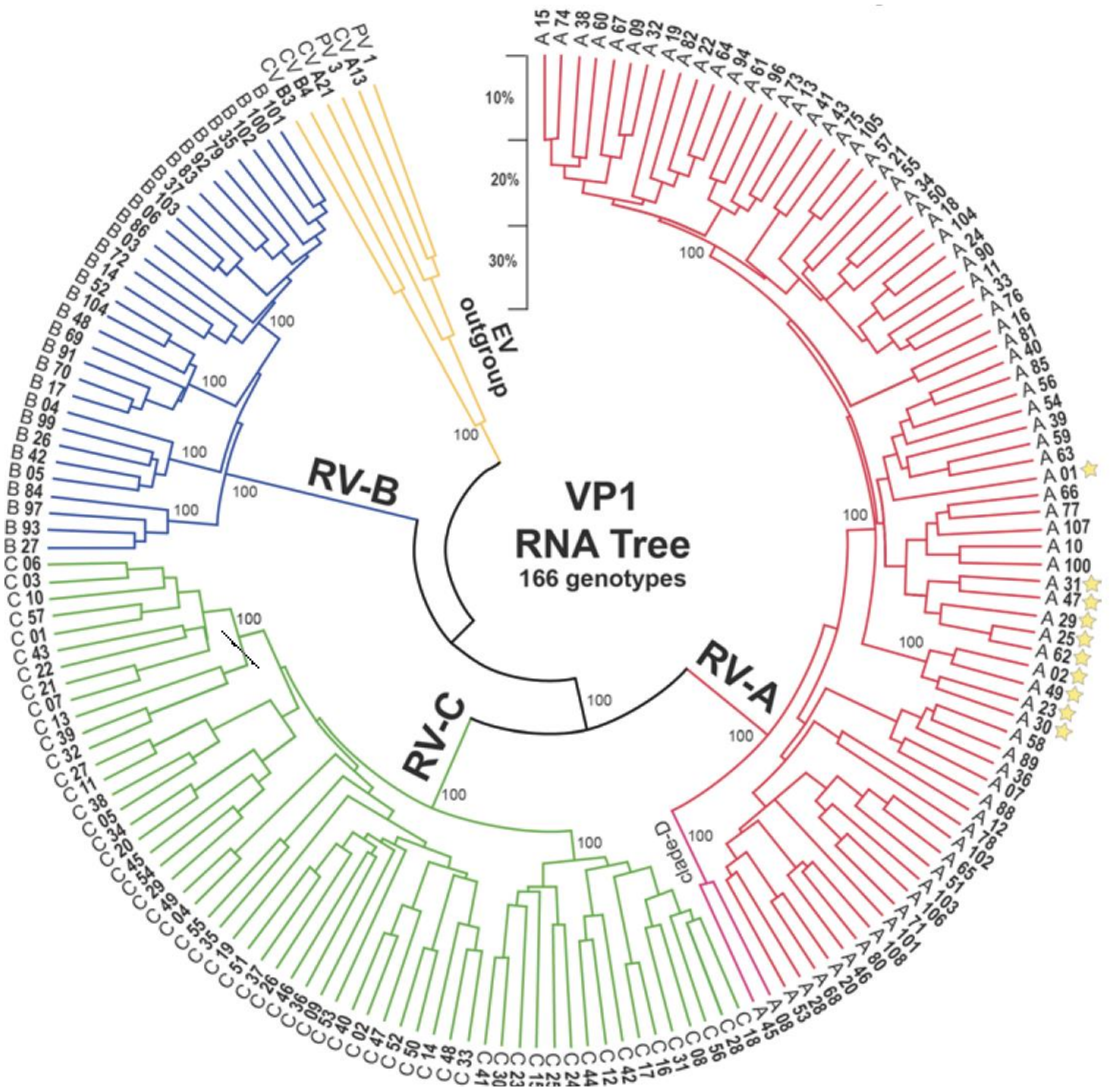
Wang X et al. Lancet 2024
Dallagiacoma et al. Lancet Reg Health - Europe 2025

Rhinoviruses



- Common cold viruses
- Most common cause of wheezing after age 1 year
  - Exacerbations of asthma & COPD
- Risk factors

Jackson and Gern. JACI-Pract 2022
Miranda-Katz M et al. JACI 2026



Rhinovirus Epidemiology

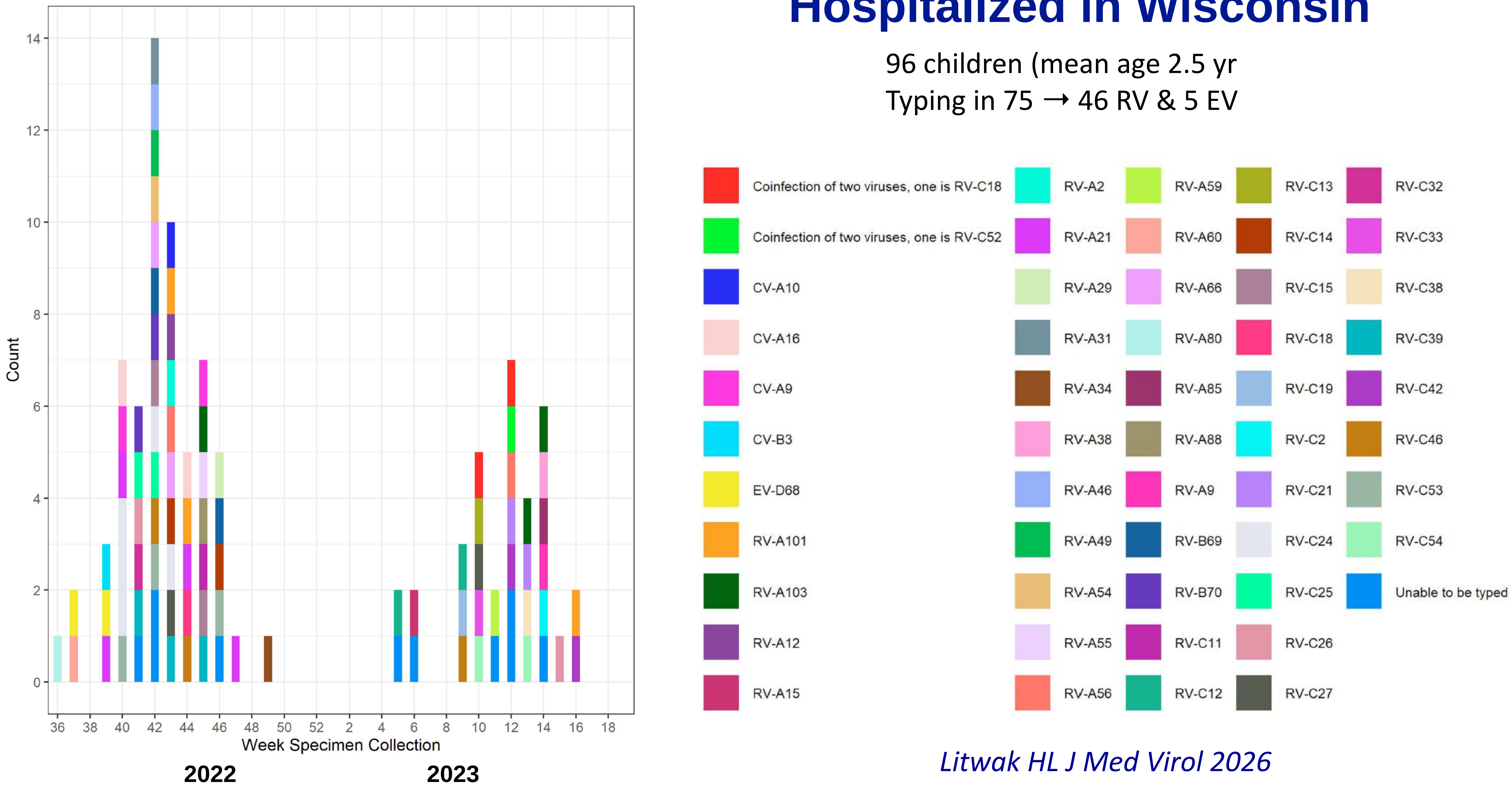
- Over 170 types
- Virulence:
  - RV-C > RV-A >> RV-B
- 20-30 types circulate in a community during a Spring or Fall Season
- Multiplicity is a challenge for developing vaccines or therapeutics

Palmenberg A, Field's Virology 2026

RVs and EVs in Children Hospitalized in Wisconsin

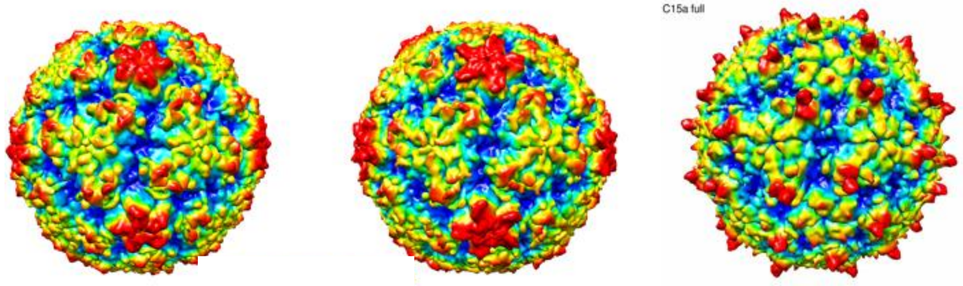
96 children (mean age 2.5 yr

Typing in 75 → 46 RV & 5 EV



Litwak HL J Med Virol 2026

RV Species



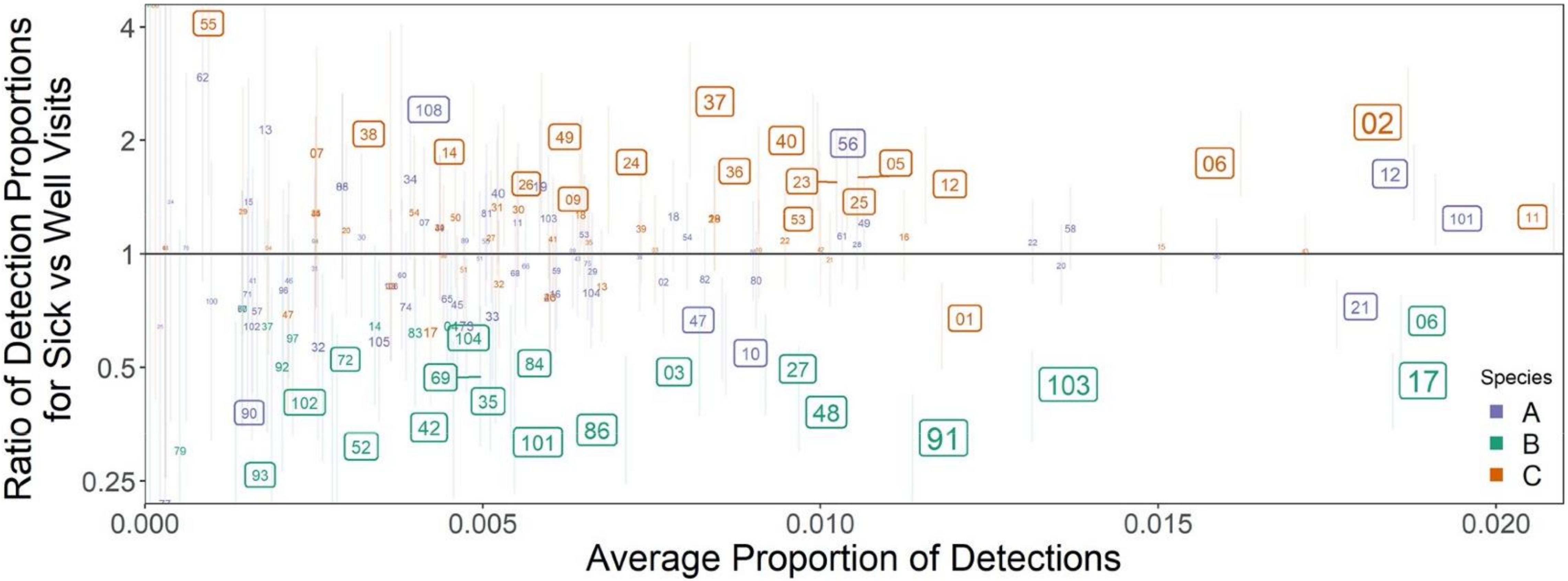
A B C

Yury Bochkov

- Pooled analysis of RV diagnostic information from 14 study cohorts located in the US, Finland and Australia
  - RV-positive samples (n=10,185)
  - Partial sequencing to identify RV species and type
- Research questions
  - Which RV species and types are more prevalent & virulent?
  - How does age influence rates of illnesses?

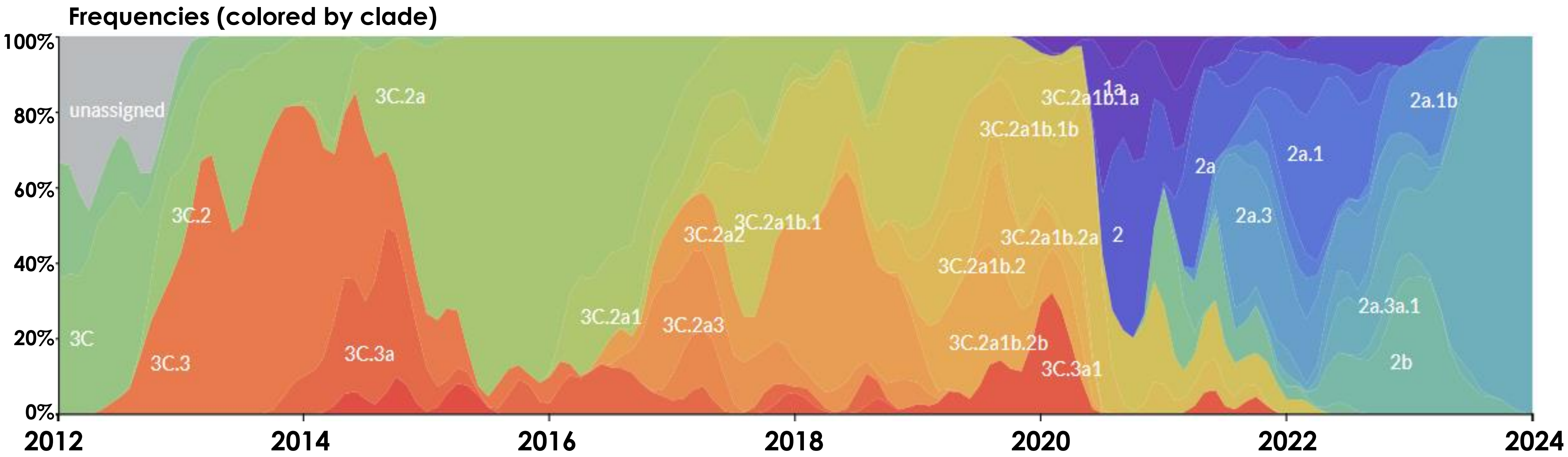
Choi T et al. AJRCCM 2021

Detection Frequency and Virulence of RV Species and Types



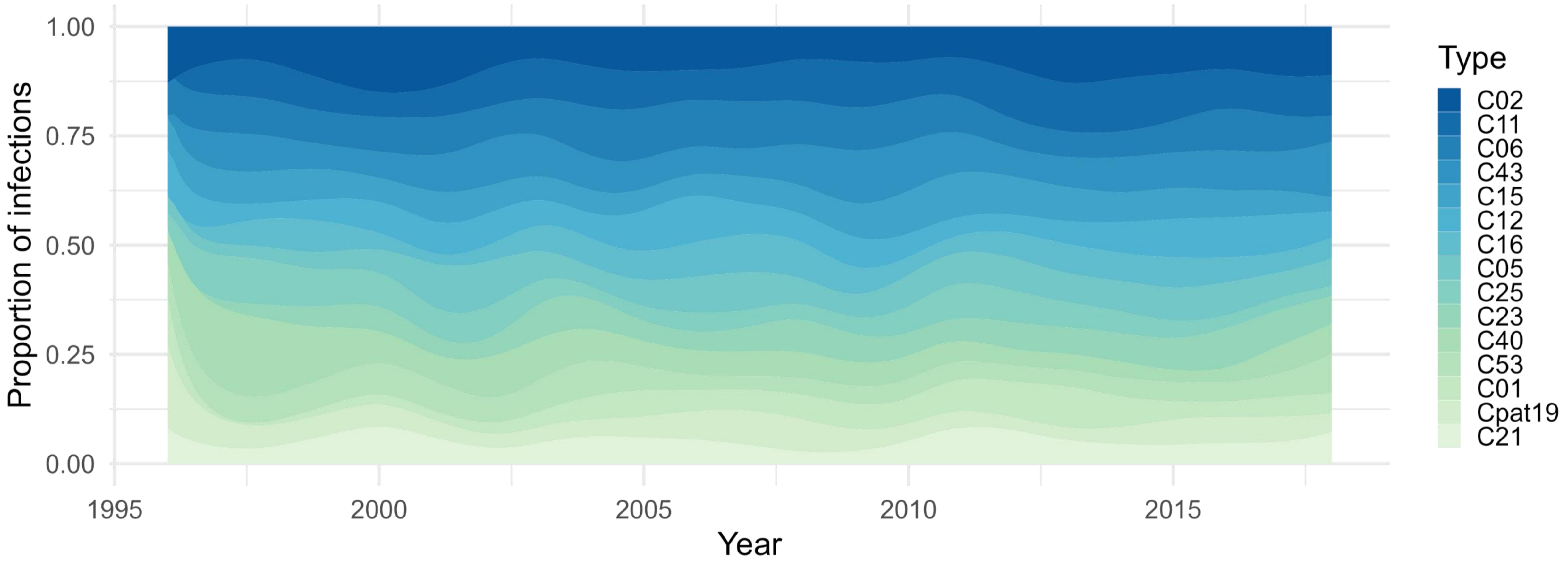
Choi T et al. AJRCCM 2021

Circulation Pattern of Influenza A



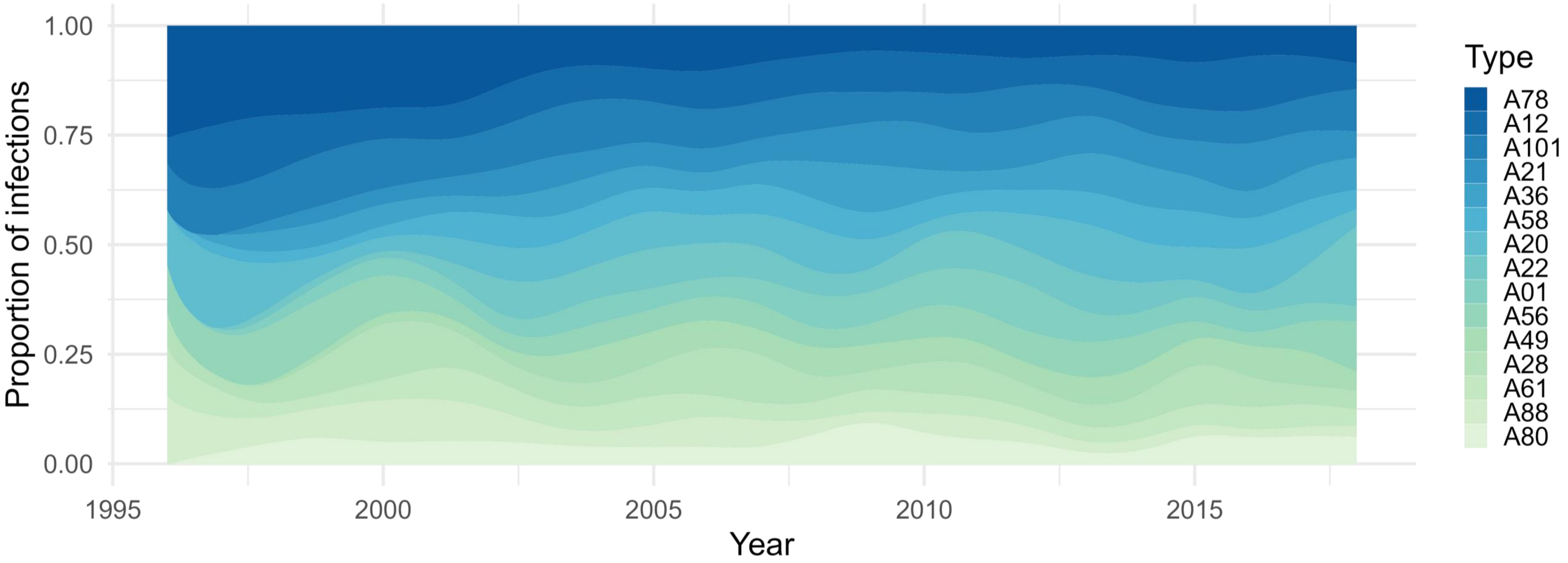
Nextstrain.org

Stability of Top 15 Circulating RV-C Types



Gao D and Wilson J, JACI 2026

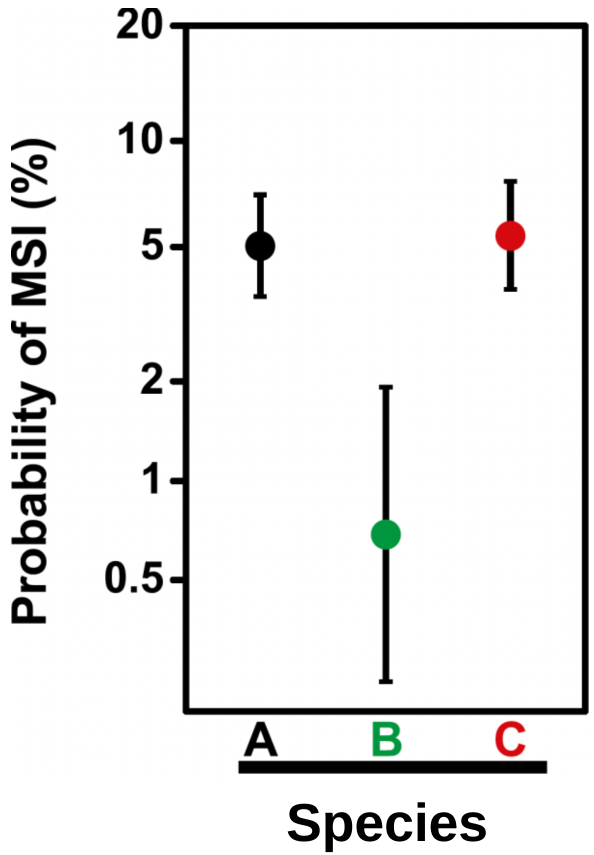
Stability of Top 15 Circulating RV-A Types



Gao D and Wilson J, JACI 2026

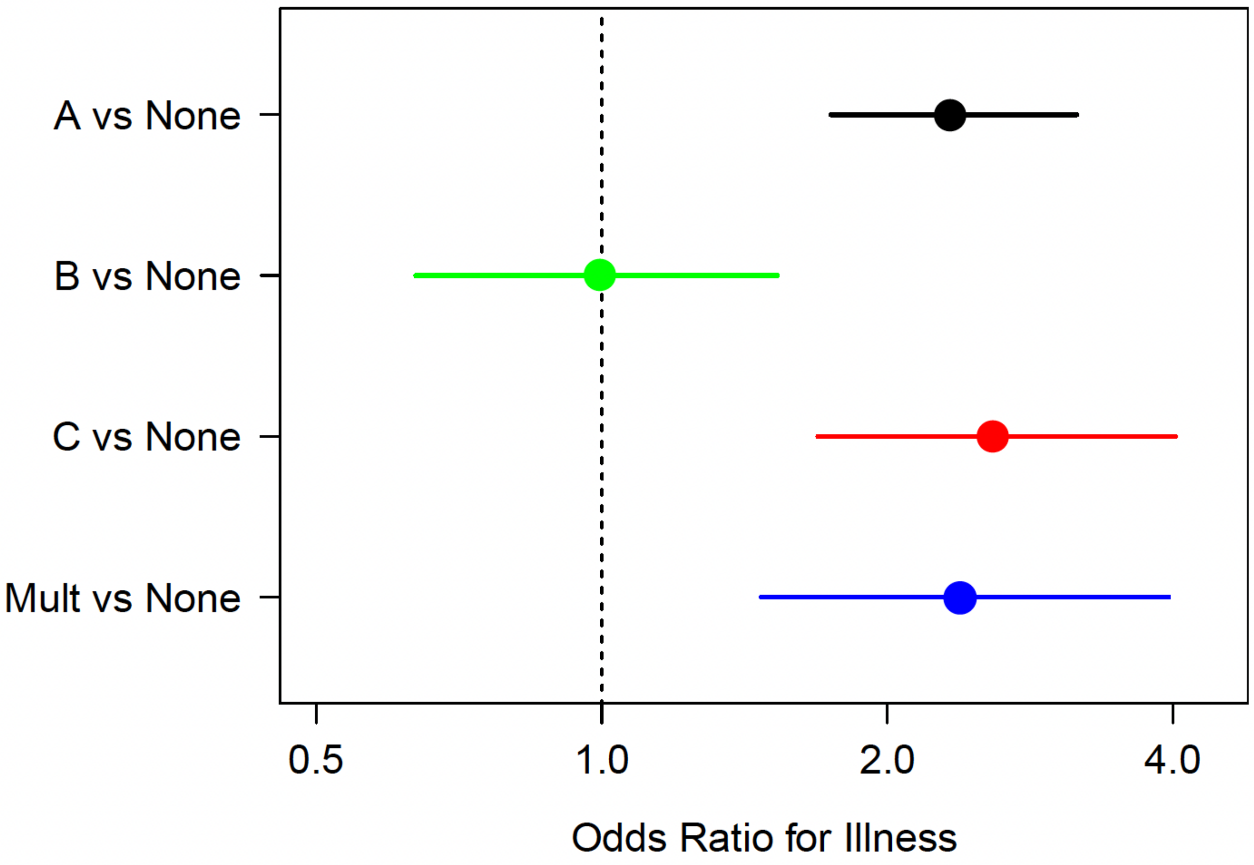
RV-A and RV-C are More Virulent

COAST Birth Cohort
Age 0-1 Yr



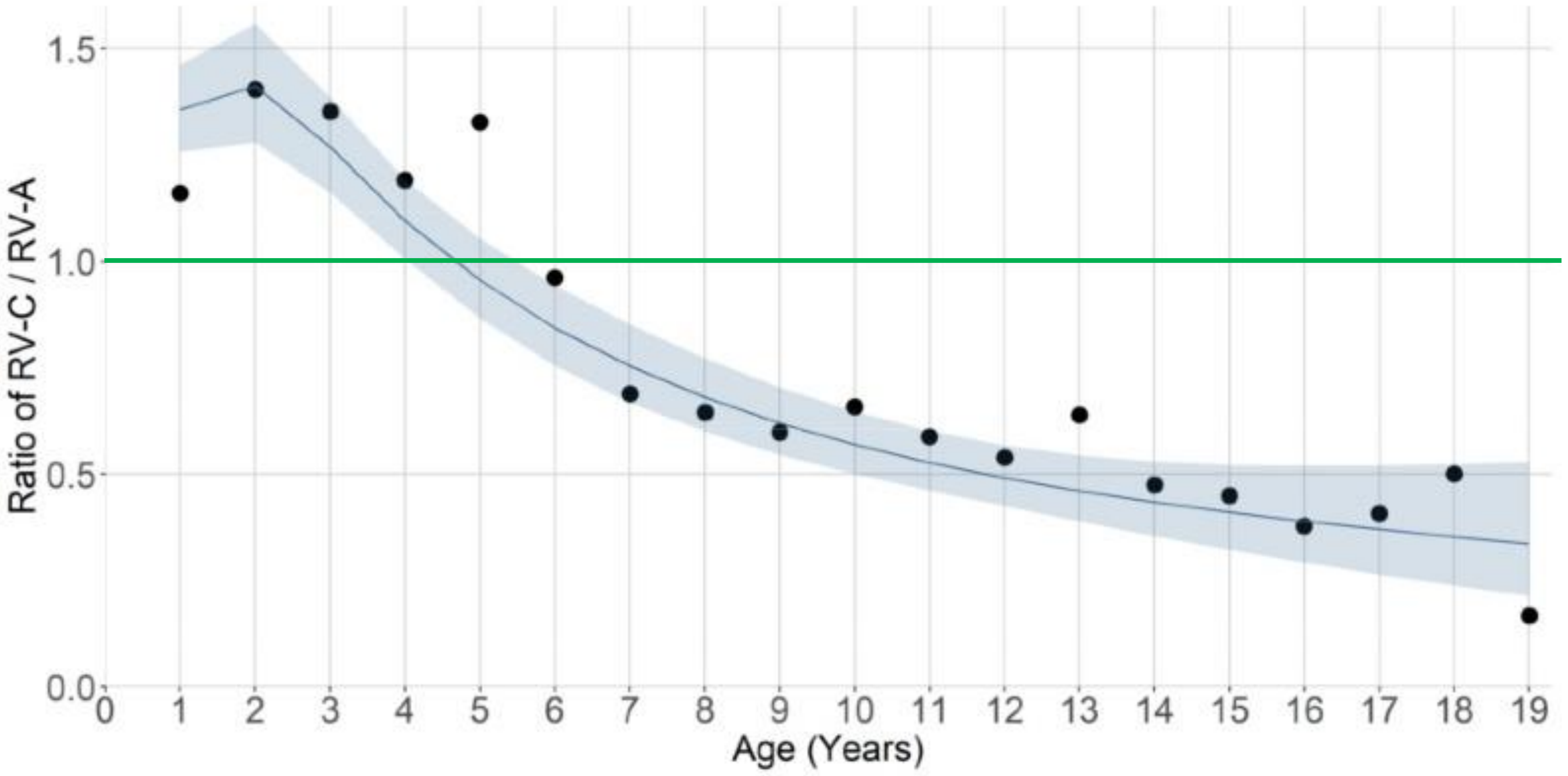
Lee WM et al. AJRCCM 2012

RhinoGen Study
Age 4-12 Yr



Bashir H et al. JACI 2018

RV-C Infections are Most Common in Preschoolers

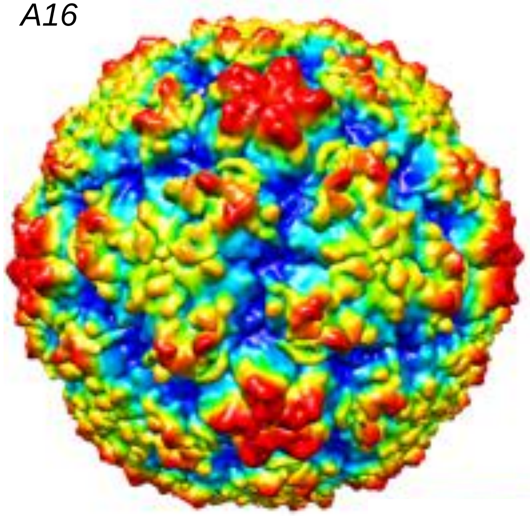


Choi T et al. AJRCCM 2021

Summary: Rhinovirus Species

RV-A
N~80

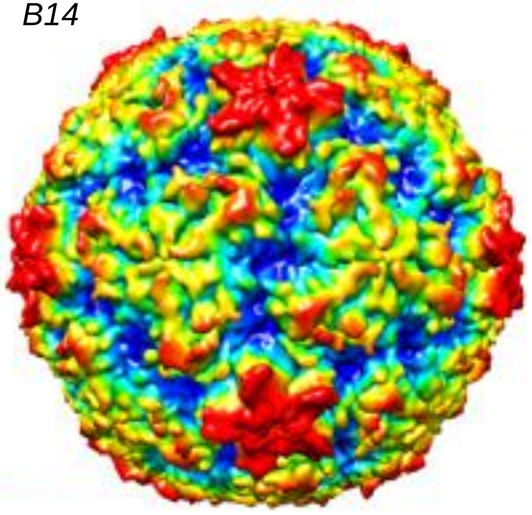
A16



Asymptomatic
URI
LRI

RV-B
N~30

B14

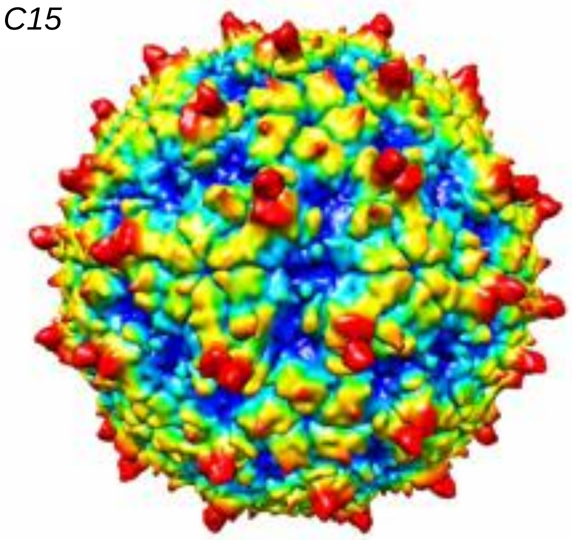


Asymptomatic
URI

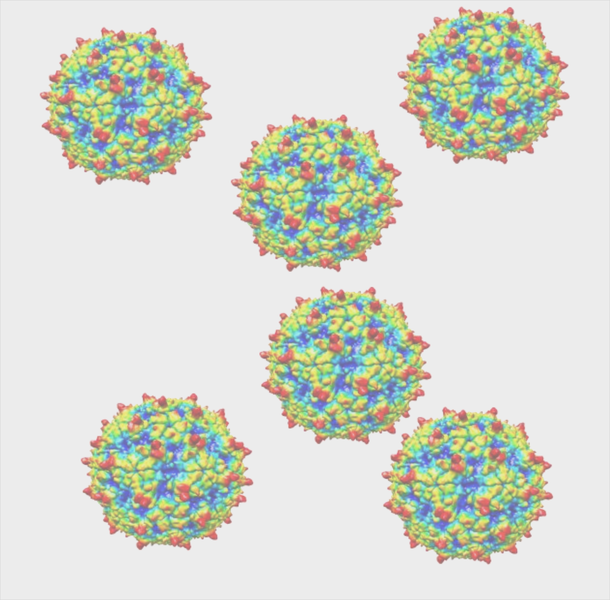
RV-C
N~60

Common & Rare

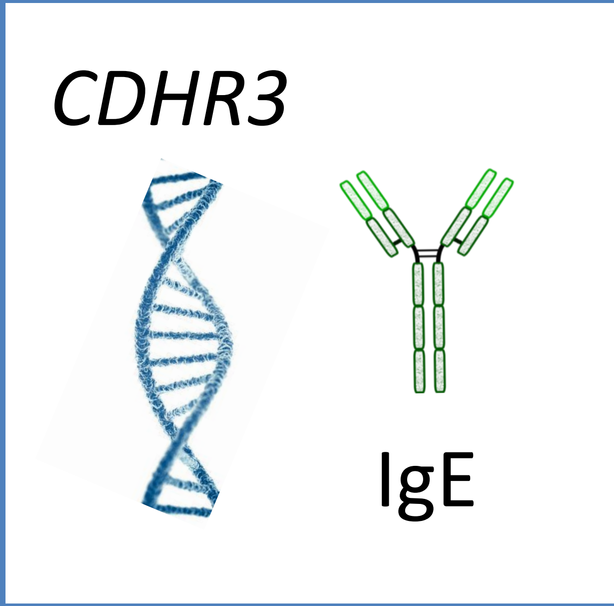
C15



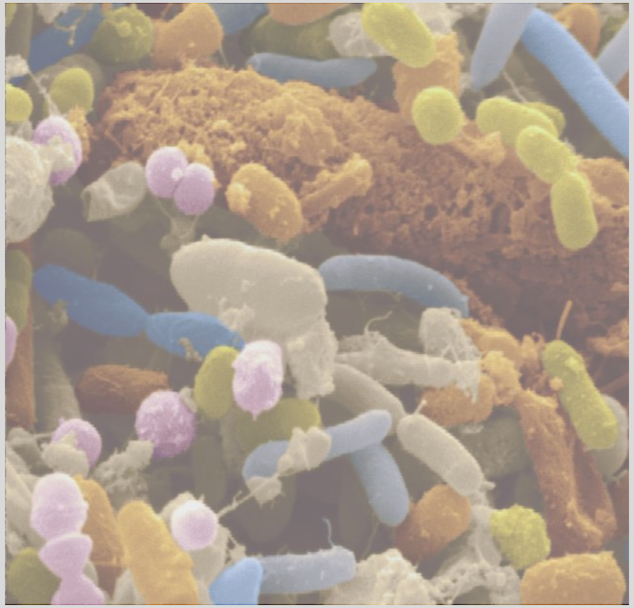
Asymptomatic
URI
LRI
Young children



Viruses

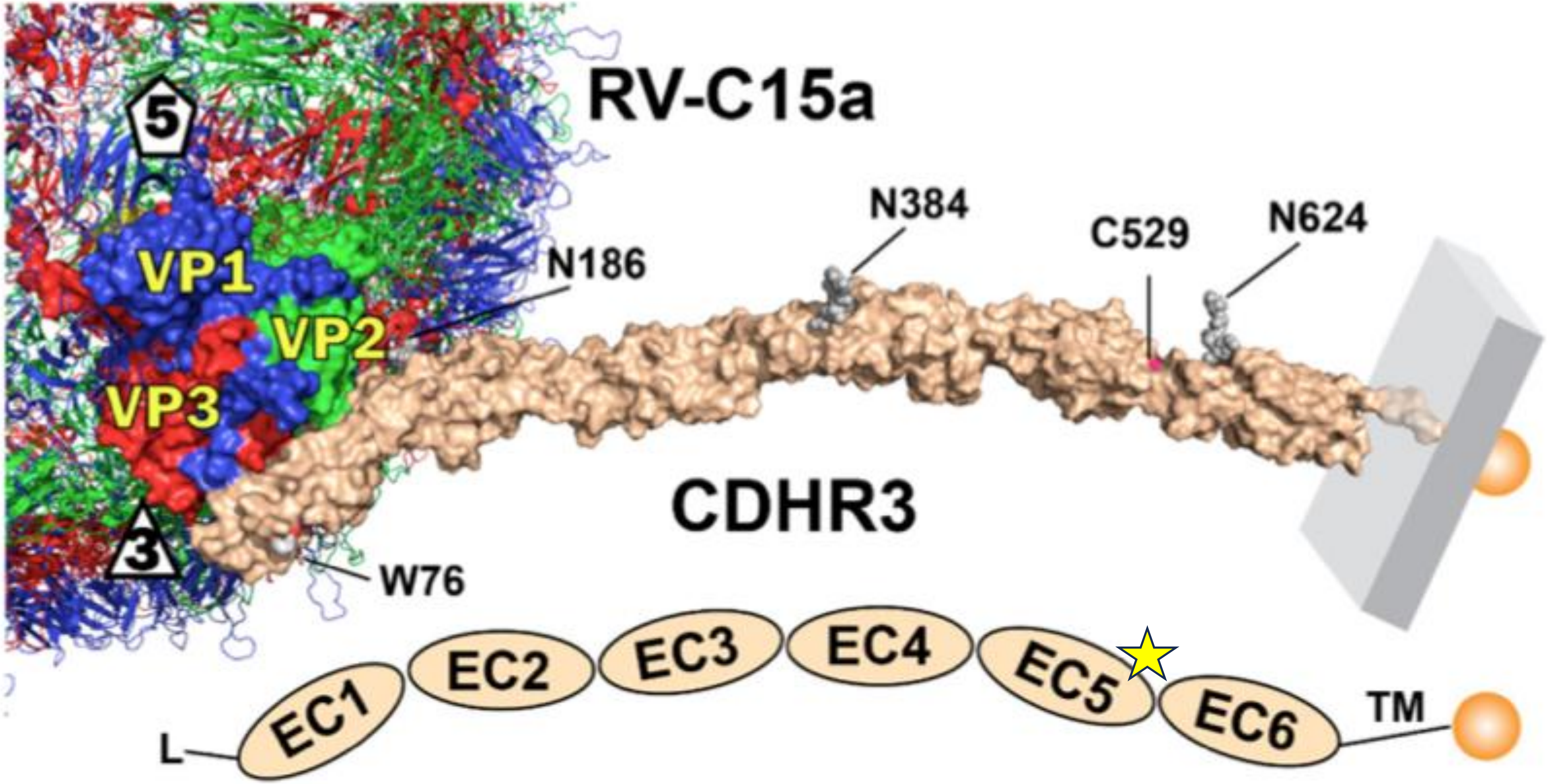


Host



Bacteria

Risk Factor: CDHR3 Genetics

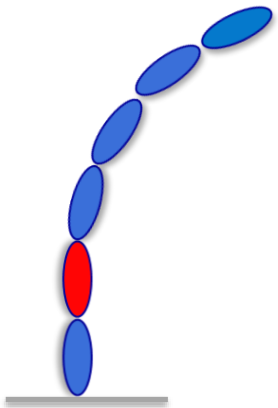


Lee W and Palmenberg A et al. Viruses 2021
Sun and Palmenberg et al. PNAS 2020

CDHR3 Genetic Variation Influences RV-C Replication

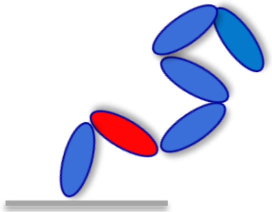
Expression on cell surface

Y_{529}



High (asthma risk)

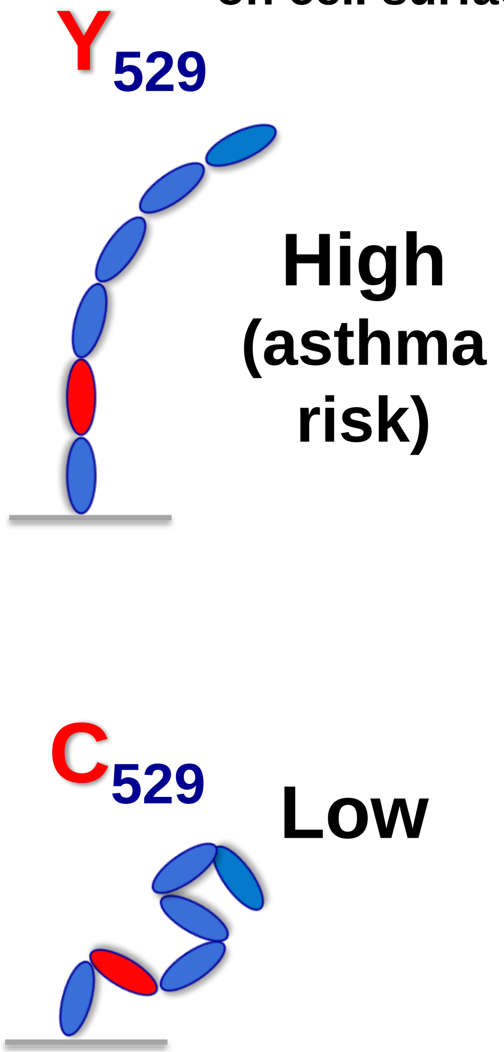
C_{529}



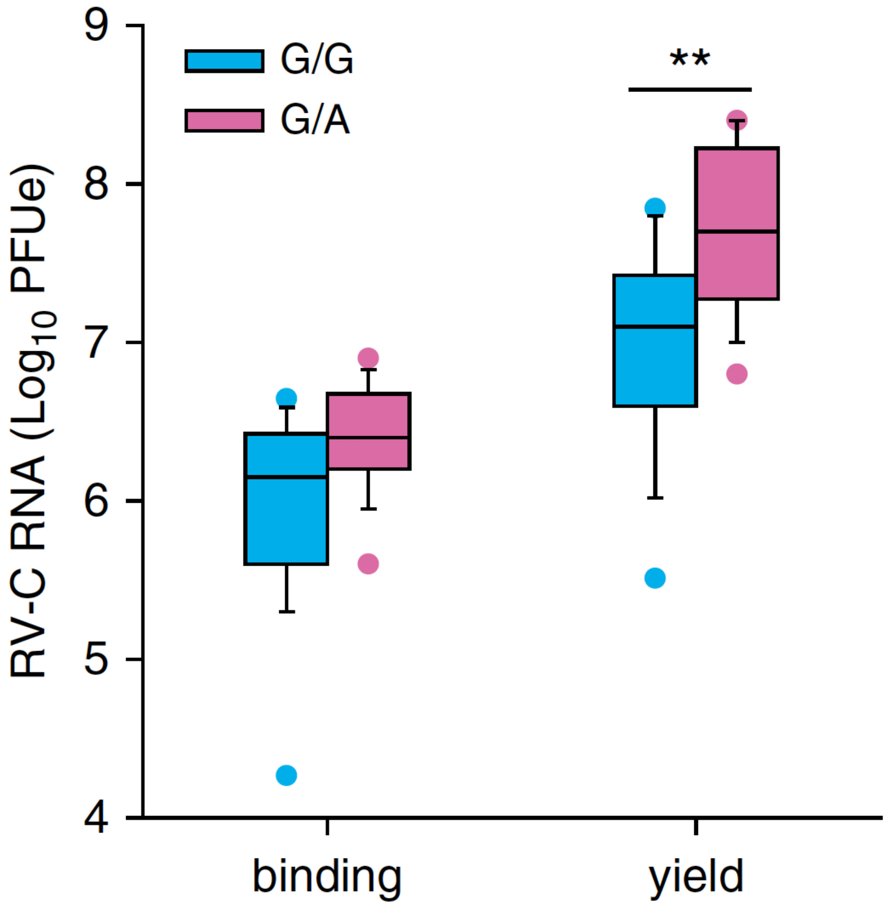
Low

CDHR3 Genetic Variation Influences RV-C Replication

Expression on cell surface

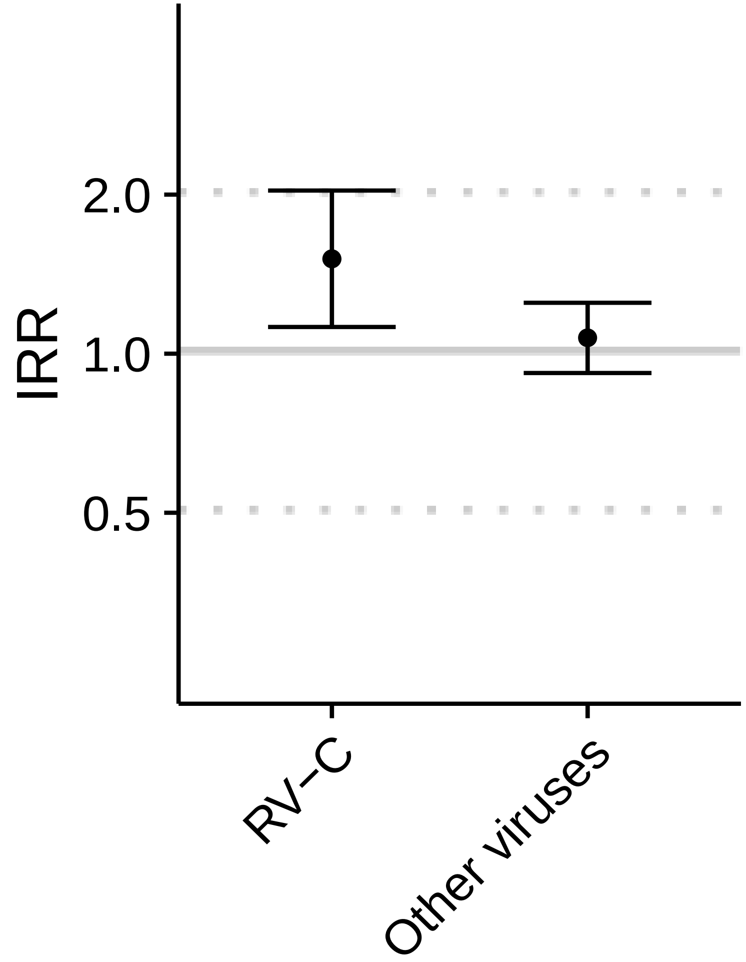


RV Replication in Culture



Basnet S. et al. AJRCMB 2019

COAST and COPSAC Birth Cohorts



Bonnelykke K. et al. AJRCCM 2019

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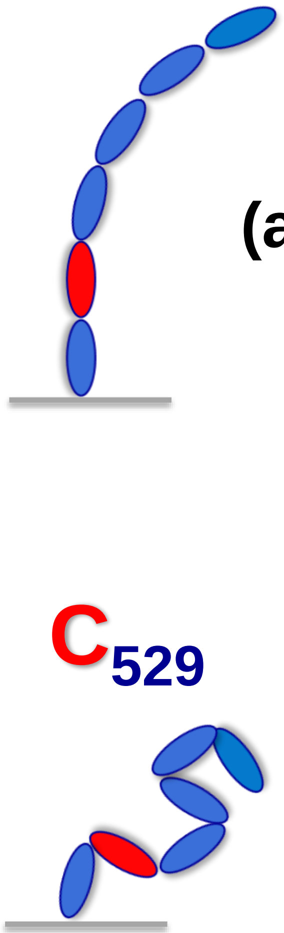
Y529

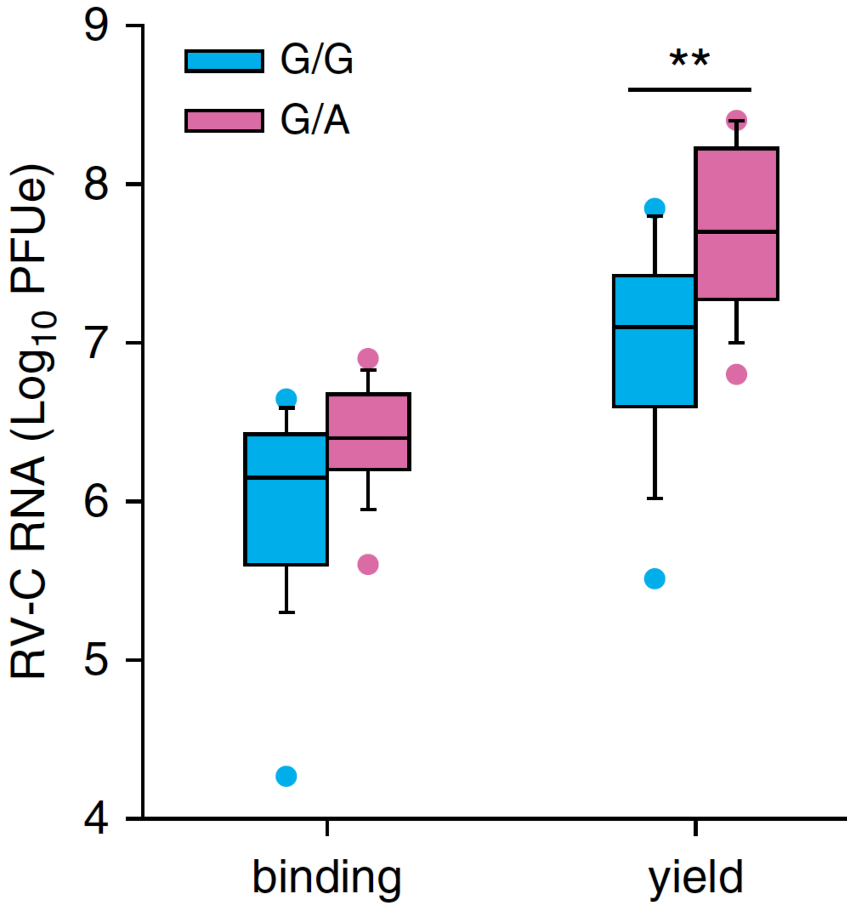


High (asthma risk)

C529

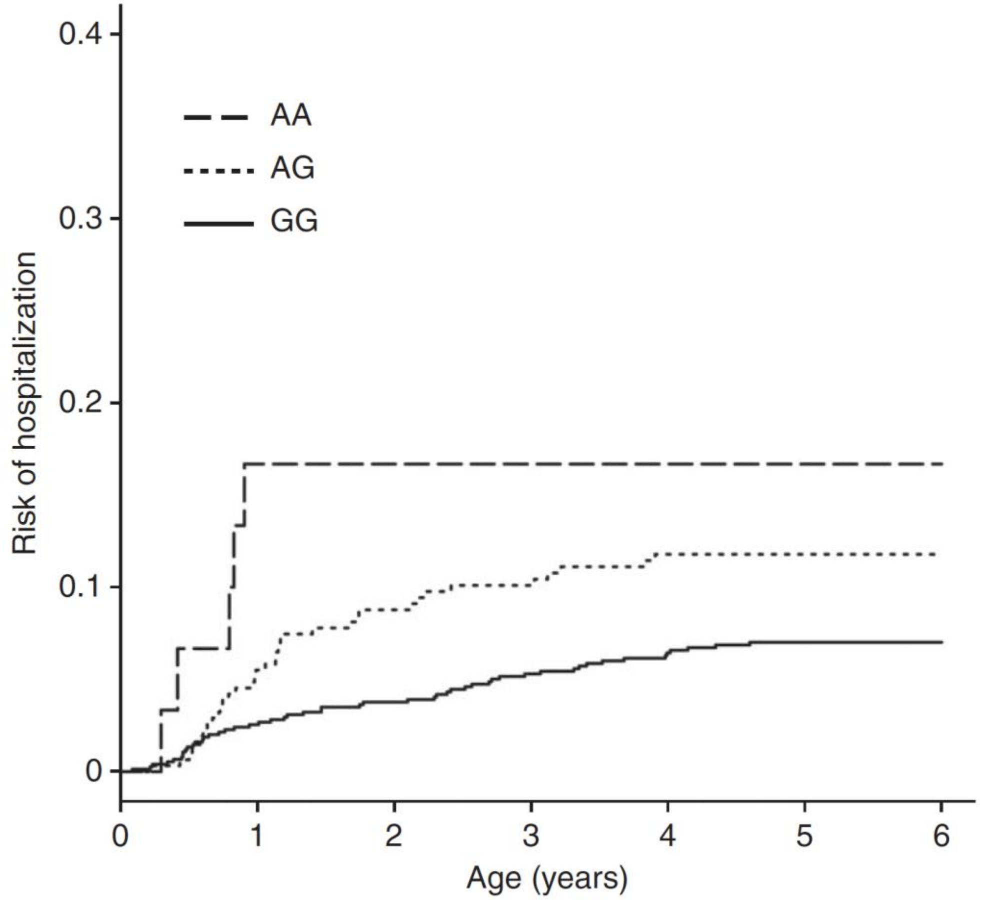
Low

RV Replication in Culture

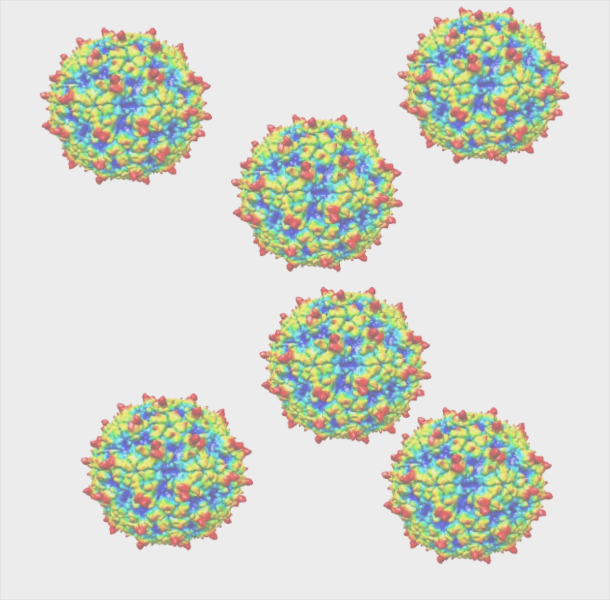


Basnet S. et al. AJRCMB 2019

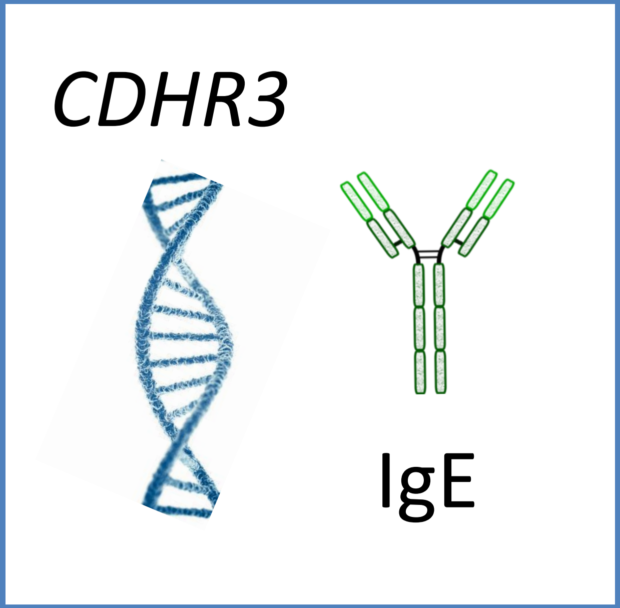
Asthma Hospitalization



Bonnelykke K. et al. Nat Gen 2014



Viruses



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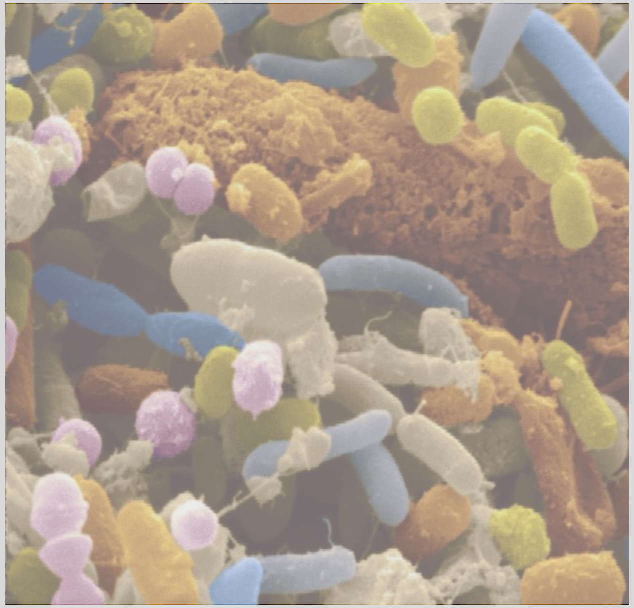
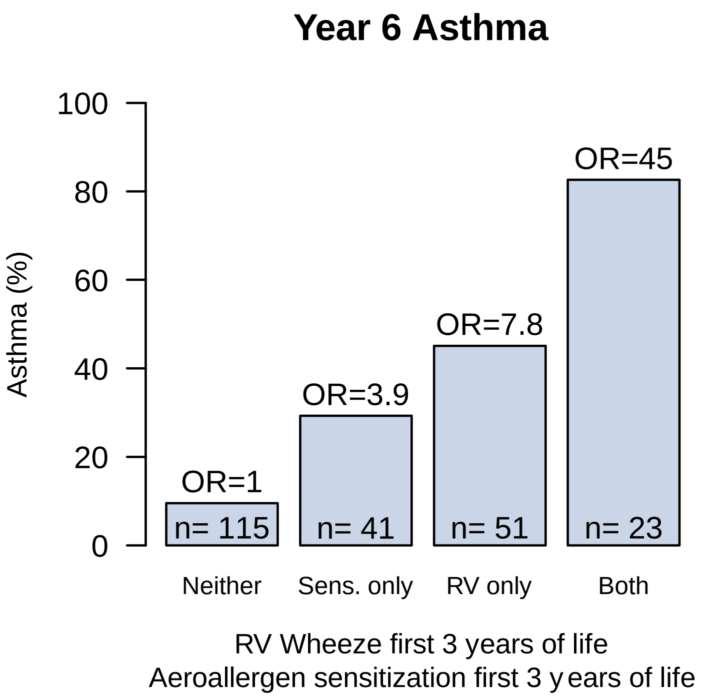
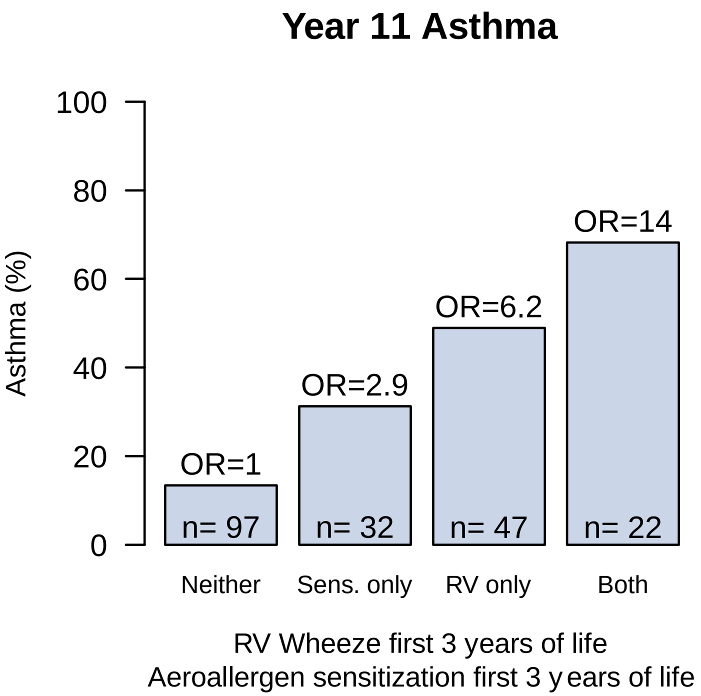


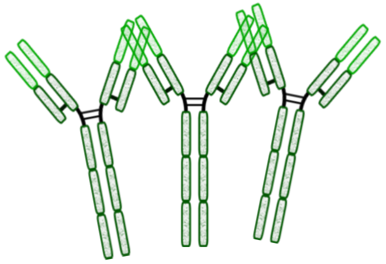
Bacteria

Early Life Allergic Sensitization, RV Wheezing, and Asthma Risk

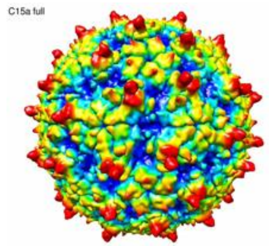
Rubner FJ, et al. JACI 2017
Jackson D, et al, AJRCCM 2012



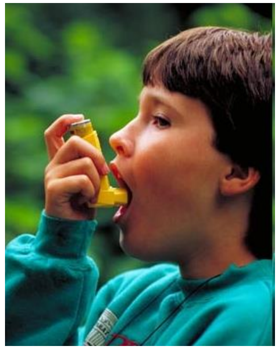




sIgE



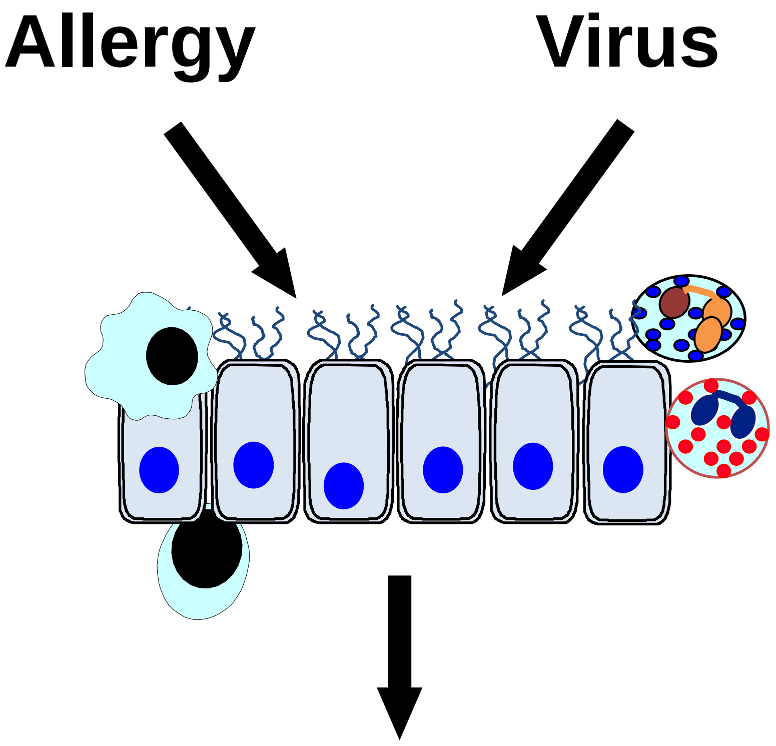
Wheezing Illness



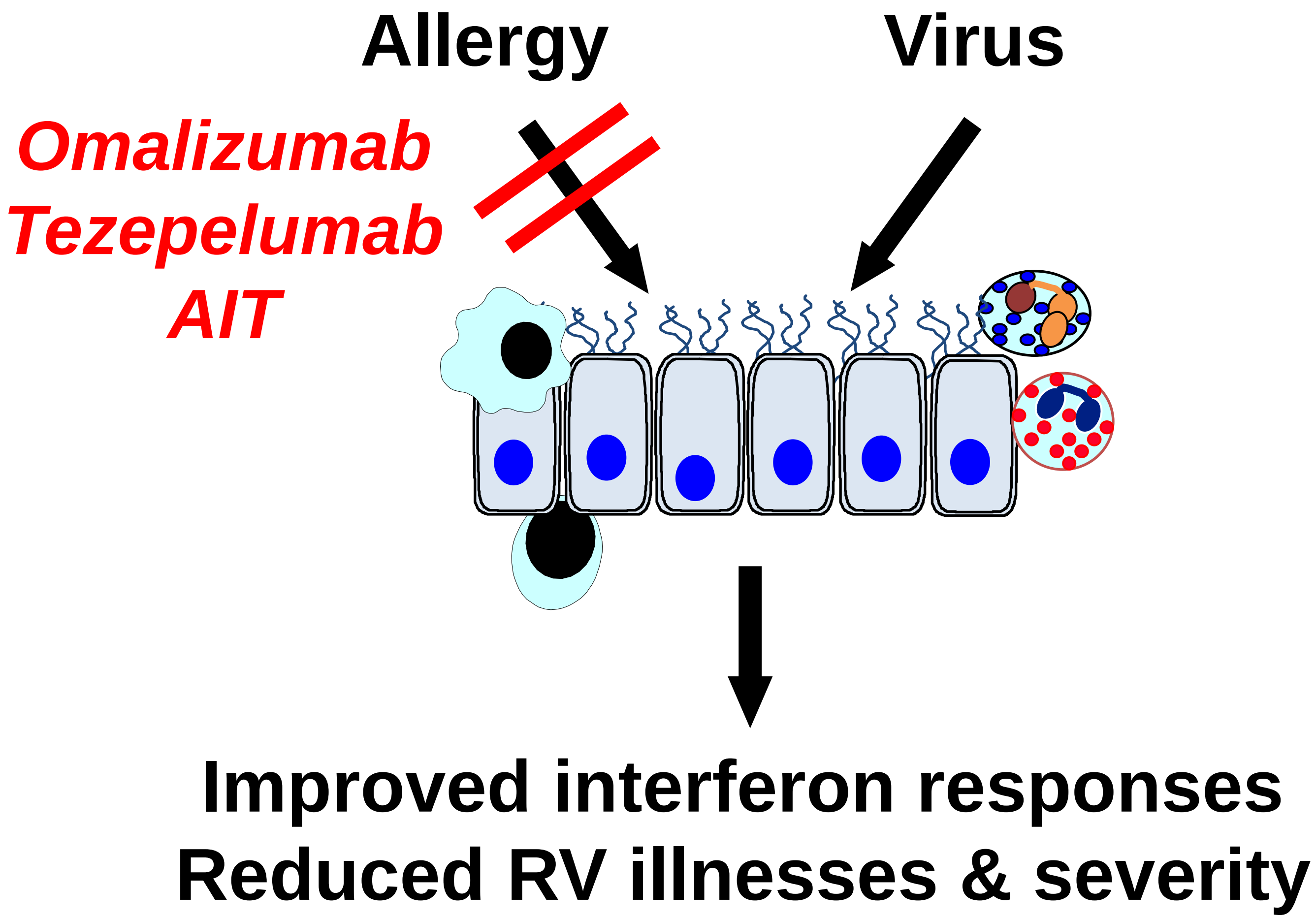
Asthma

Hazard Ratio 2.4* (1.4, 4.3)

Allergy Increases Susceptibility to RV



Impaired antiviral response &
Increased illness severity



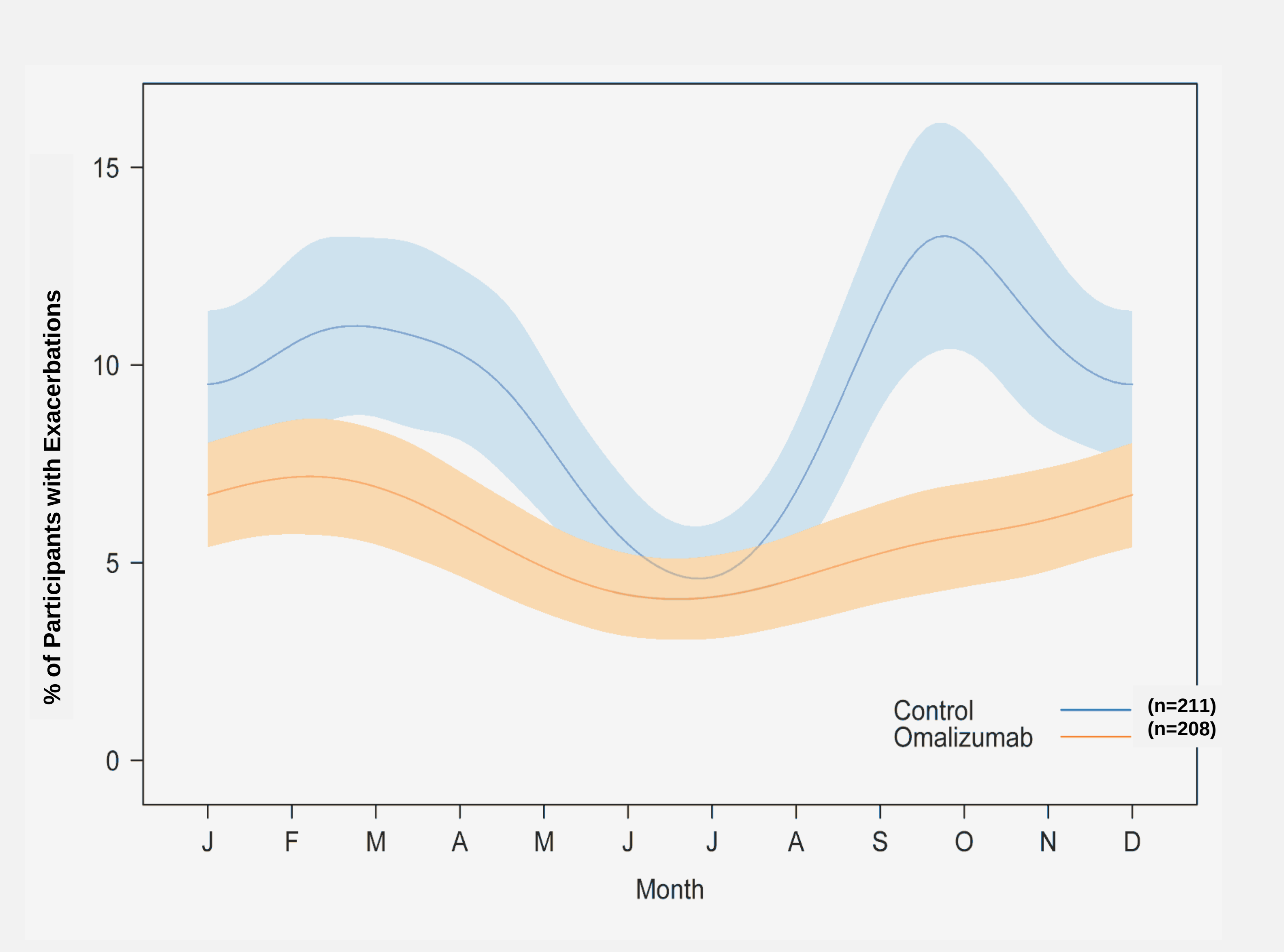
Does treating allergic inflammation reduce virus-induced wheezing illnesses?

- Omalizumab
- Tezepelumab
- Allergen immunotherapy

Omalizumab Reduced Seasonal Asthma Exacerbations

Omalizumab effects:

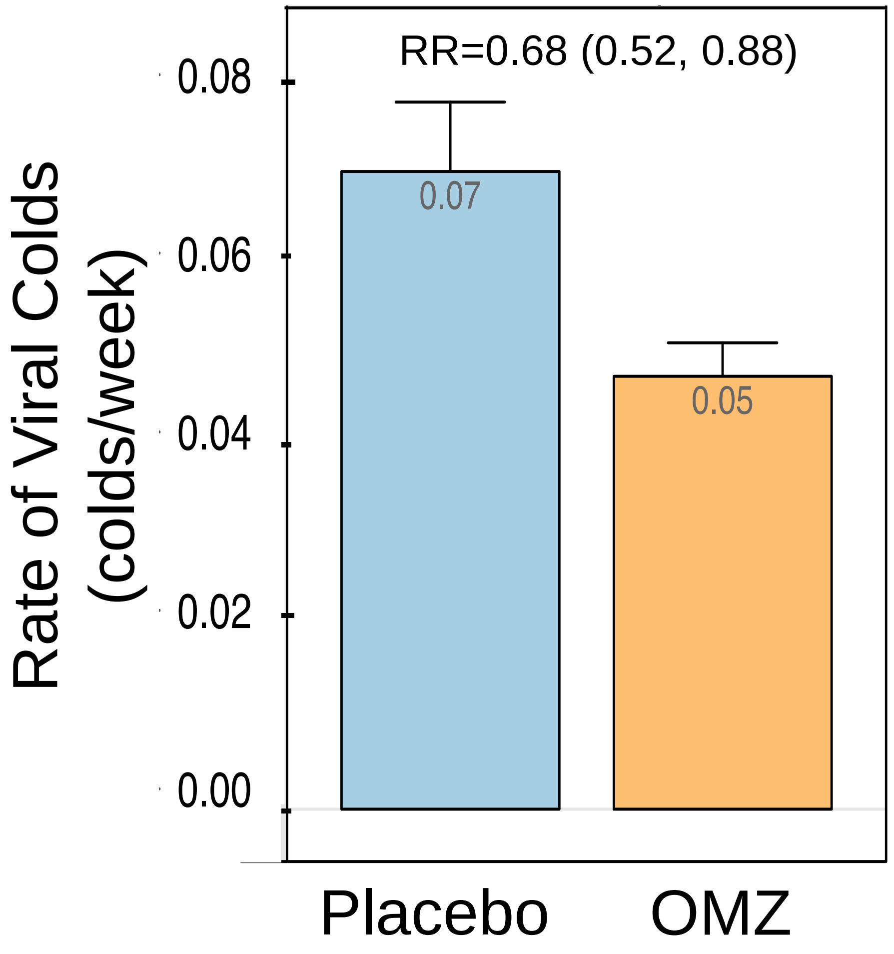
- Reduced days with symptoms by 25% (p<0.001)
- Reduced exacerbations (30% vs. 49% P<0.001)
- Post hoc: reduced fall and spring exacerbations



Busse WW et al, NEJM 2011

OMZ Reduces RV Infections & Colds

- Weekly nasal mucus specimens during the fall season analyzed for RV
- Symptom diaries
- OMZ effects (vs. placebo)
  - ↓ RV detection by 30%
  - ↓ Viral colds by 32%
  - ↓ Duration of viral shedding (0.9 days, $p=0.04$)
  - ↓ Peak viral shedding (0.4 log unit, $p<0.05$)

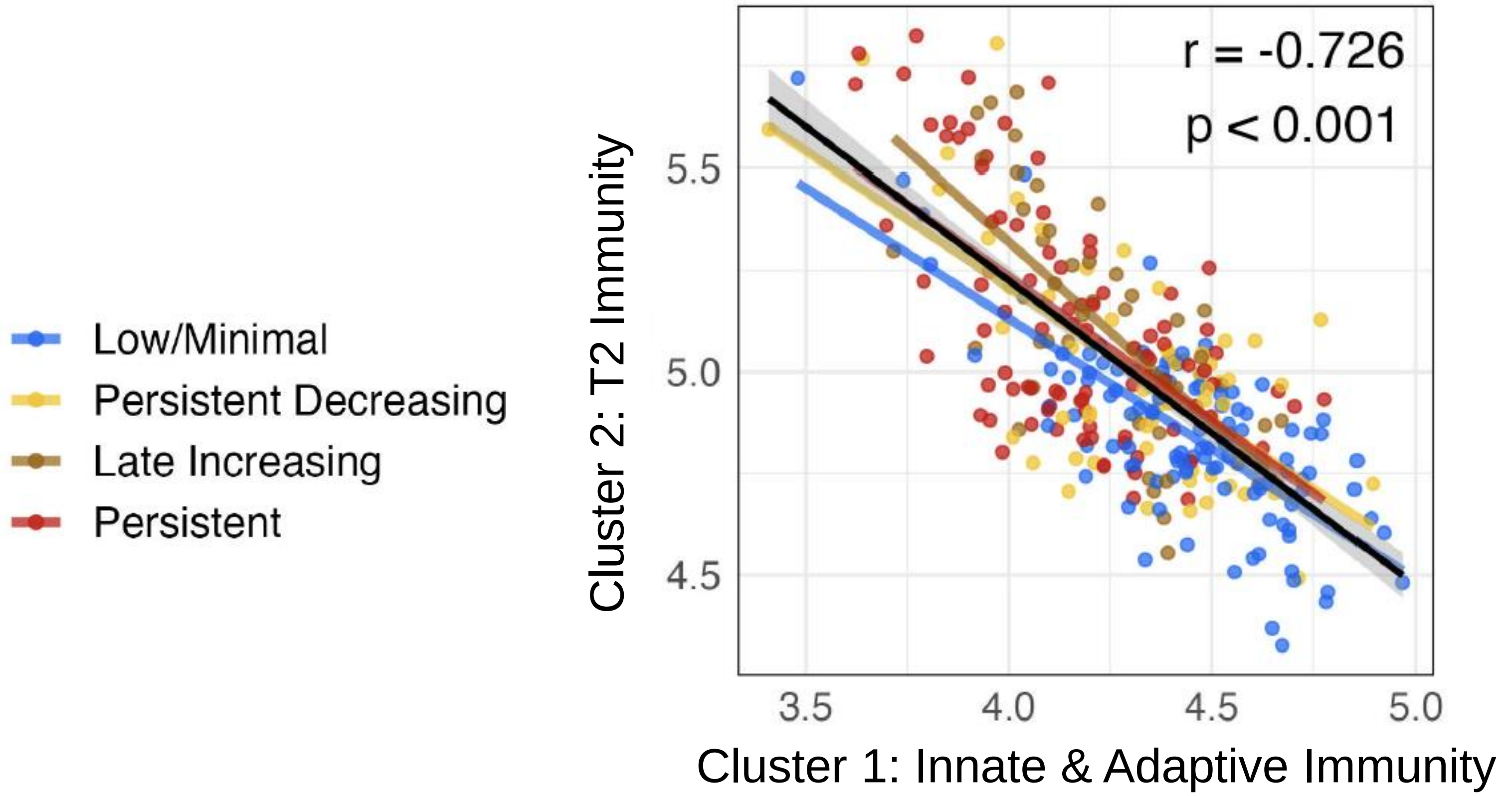


Esquivel A et al AJRCCM 2017

T2 Inflammation is Inversely Related to Antiviral Responses

- URECA birth cohort
  - High-risk families
  - n=485 to age 11
- Rhinitis phenotypes
  - Longitudinal symptom patterns age 0-11 years
- Nasal cell gene expression age 11 years

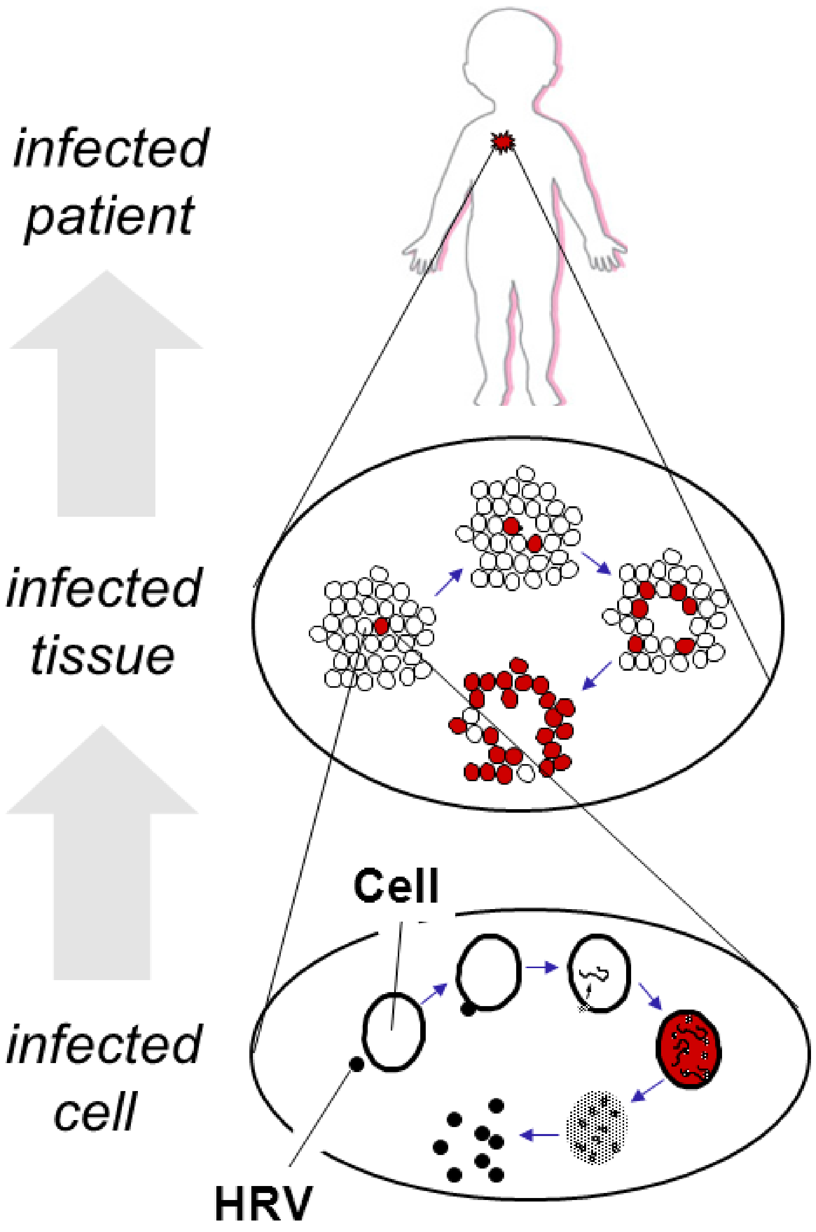
Nasal Cell Gene Expression in URECA (age 11 yr)



Ramratnam S and Altman M et al, JACI 2024

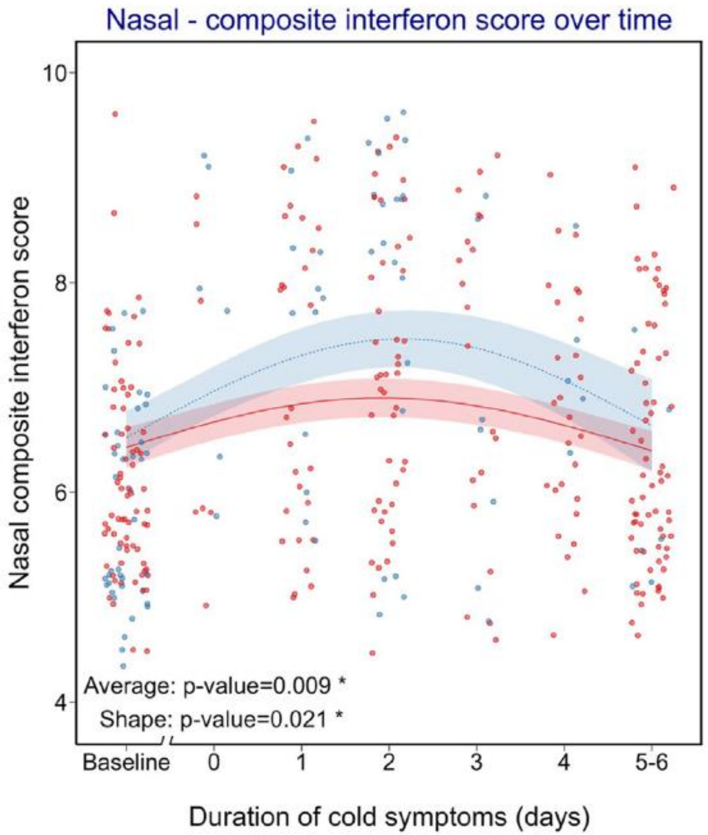
Immune Response

- The epithelial response to RV may be critical to limiting severity of illnesses
  - Brisk early response → mild illness
  - Delayed response → replication and spread → more severe illness
  - Role of allergy



Nasal Cell Interferon Gene Expression Scores are Greater During Exacerbations

- 108 children ages 6-17 years with exacerbation-prone asthma
- 154 cold events
  - 64% of colds were virus+ (most often RV)
  - 47 exacerbations, 107 URI only
- Nasal cell gene expression:
  - Baseline & cold visits
- Interferon score = average expression of 93 interferon-related genes



Gaberino C et al. JACI 2025

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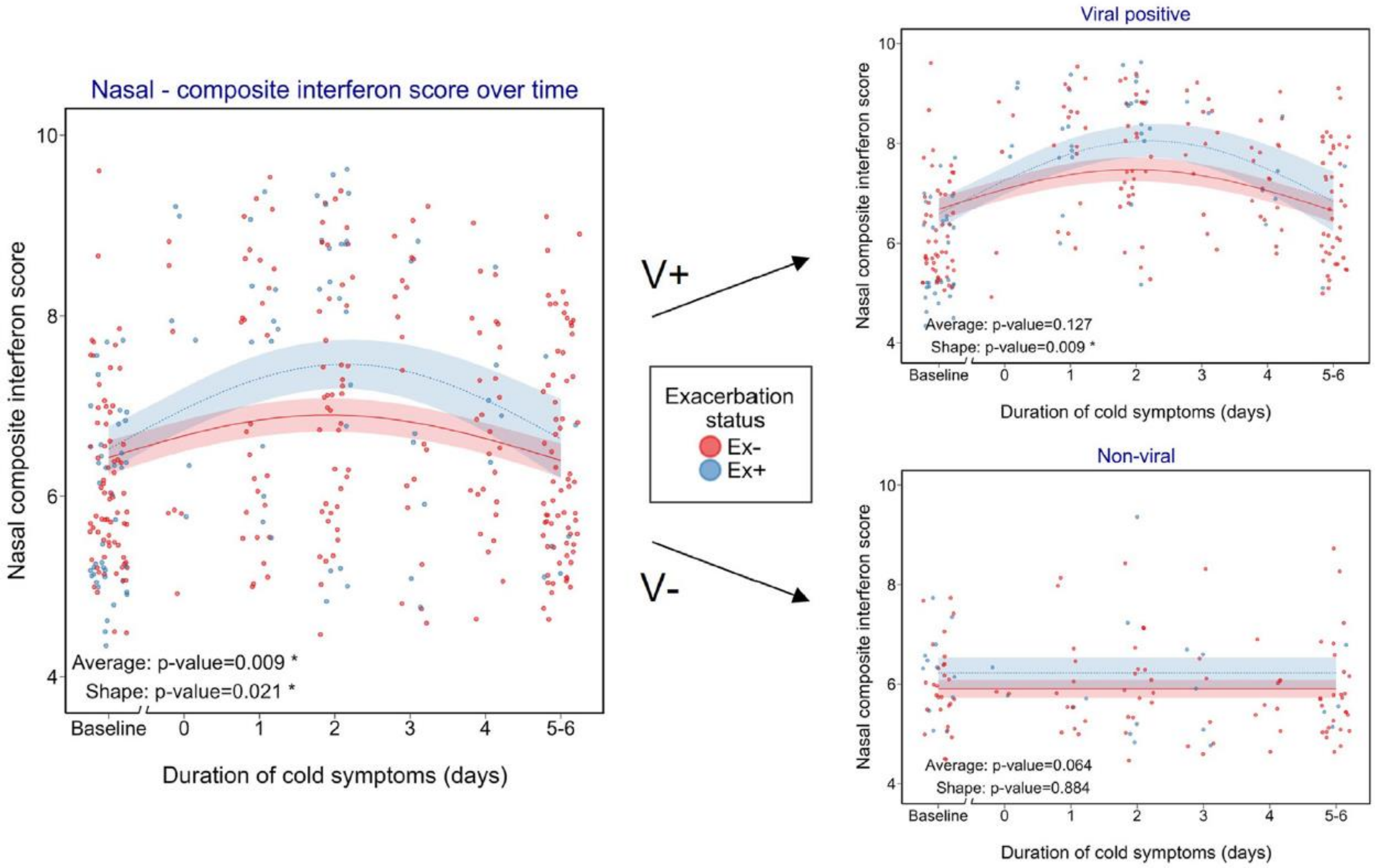
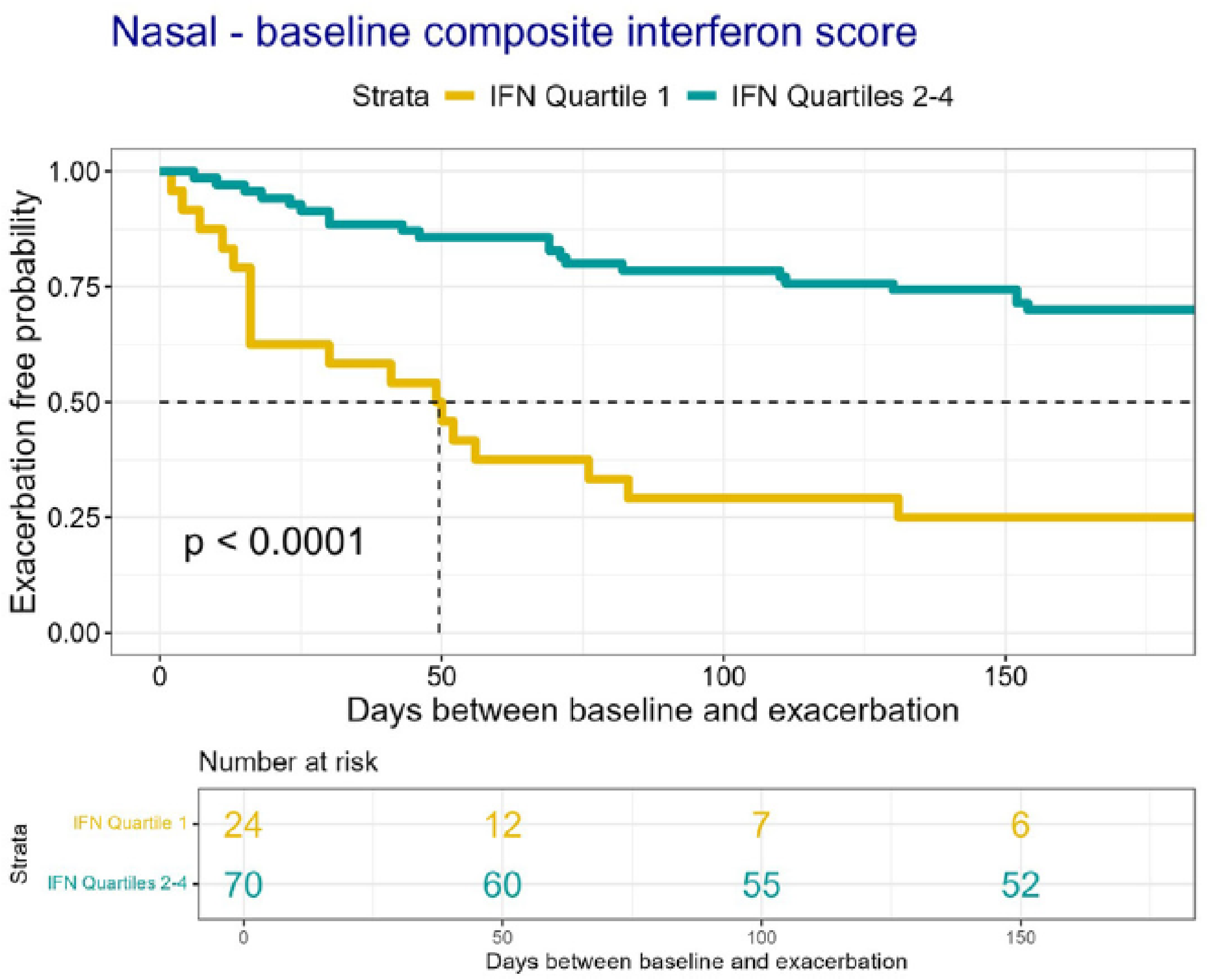


Gaberino C et al. JACI 2025

Baseline IFN Score Predicted Exacerbations

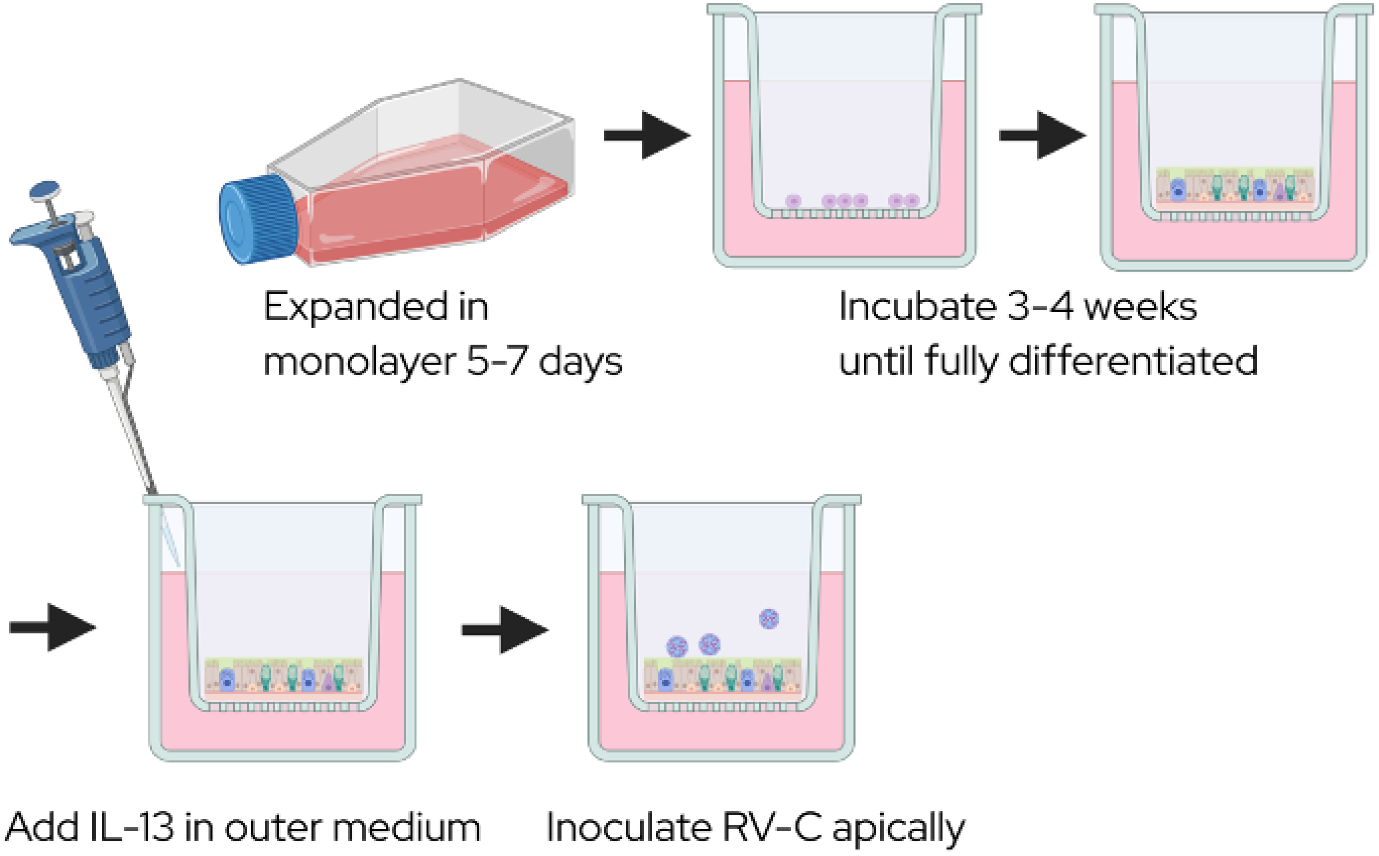


Gaberino C et al. JACI 2025

Aya Konno-Yamamoto

How does allergic inflammation affect RV-C replication & spread?

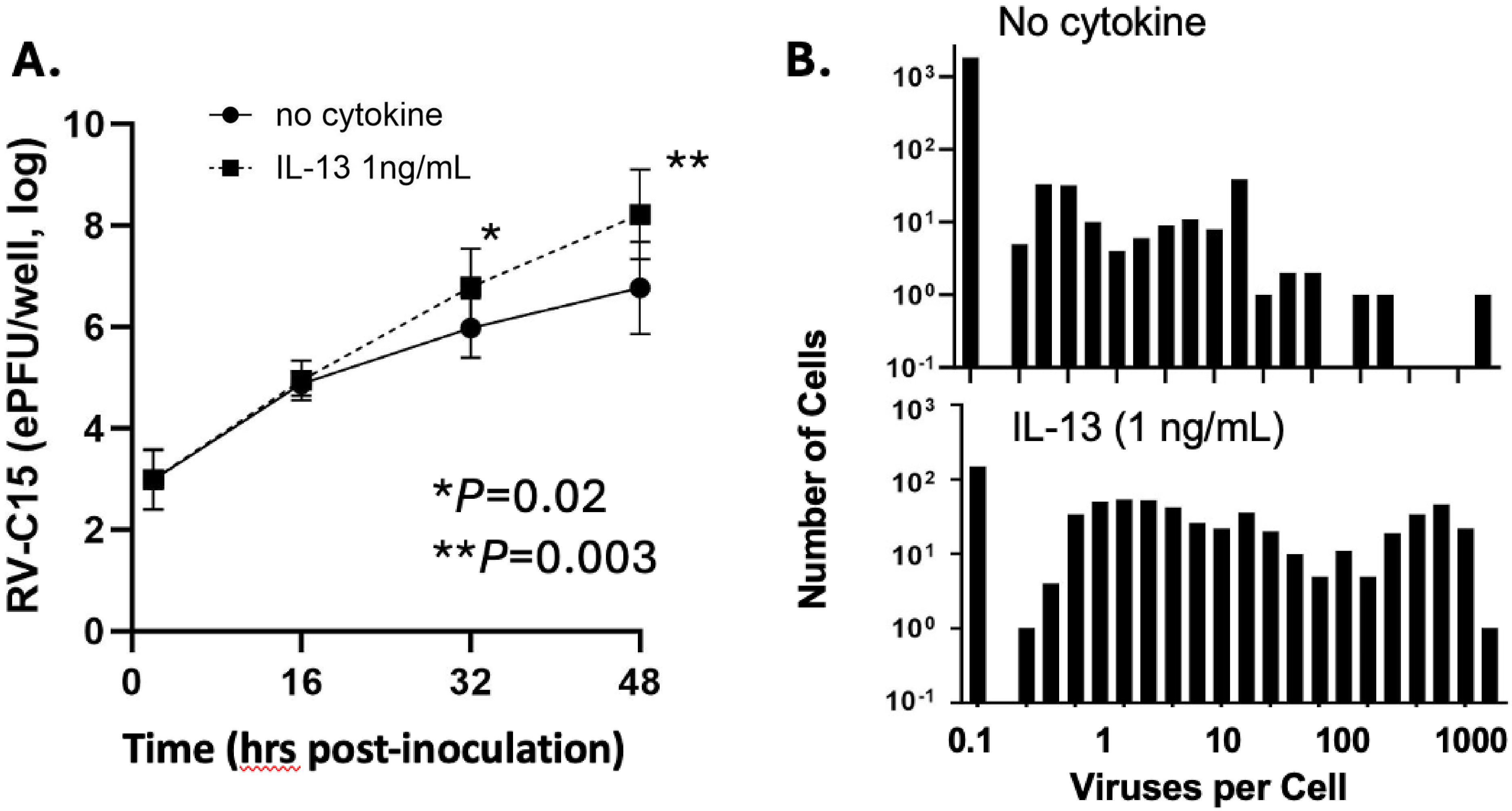
- Of the T2 cytokines, IL-13 induces the greatest changes in epithelial gene expression
- Previous studies showed inconsistent effects of IL-13 on RV replication[1-3]
- Higher doses of IL-13 can skew cell differentiation and reduce ciliated cells

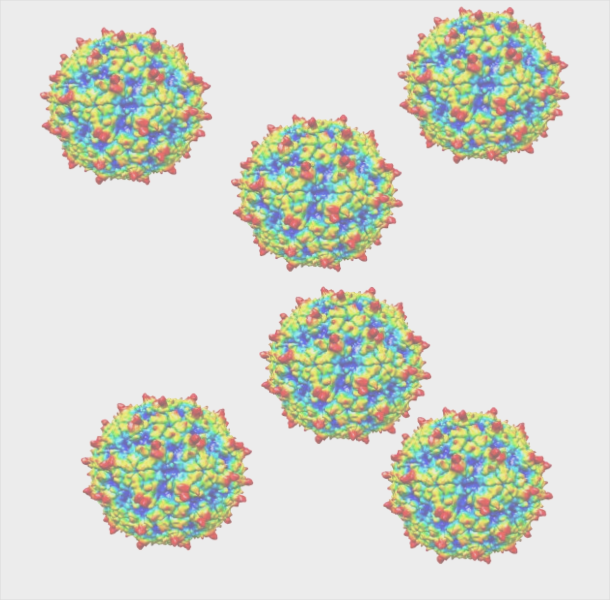


1 ng/mL (close to EC50)

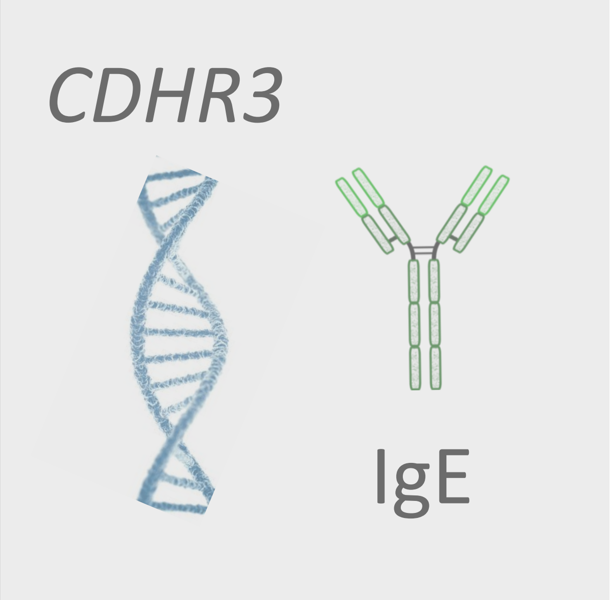
1. Lachowicz-Scroggins et al. AJRCMB 2010
2. Jakiela B et al. AJRCMB 2014
3. Contoli M et al. Allergy 2015

IL-13 pretreatment increases RV replication
(n=9, 3 donors)

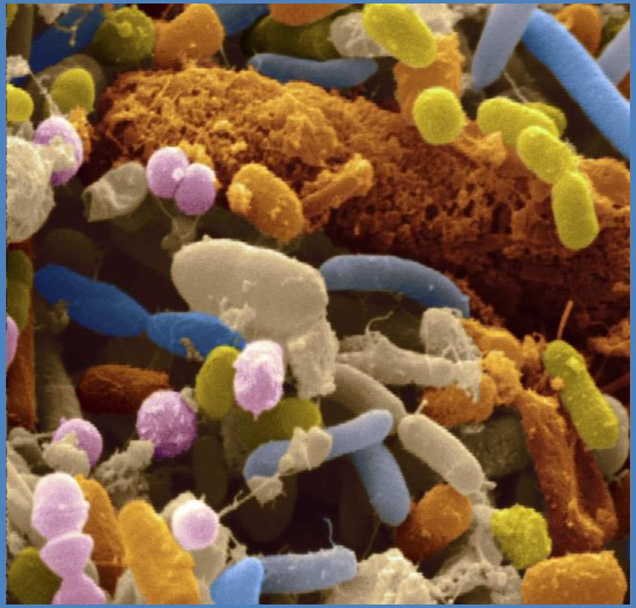




Viruses



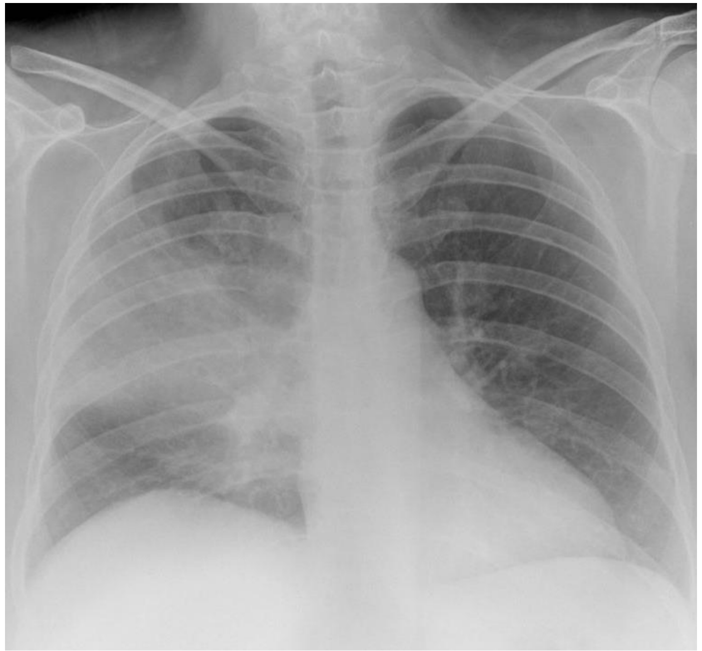
Host



Bacteria

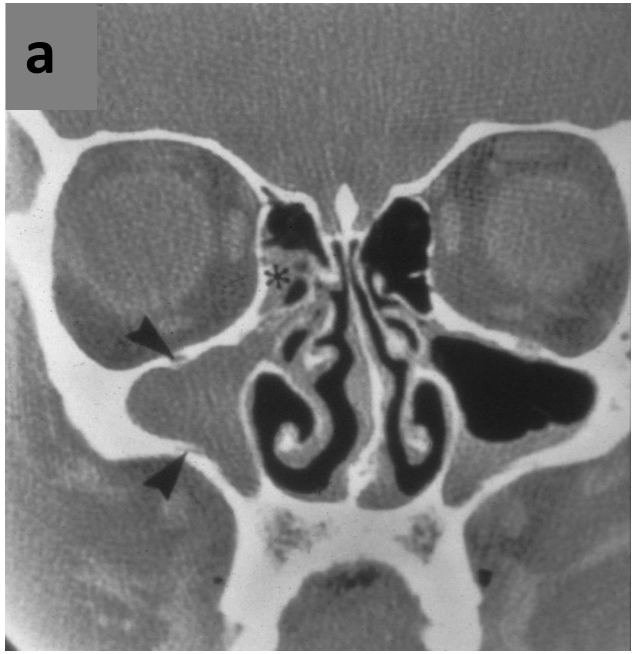
Interactions Between RVs and Bacteria

Pneumococcal Pneumonia



https://radiopaedia.org/cases/pneumococcal-pneumonia

Bacterial Sinusitis



Otitis Media

https://medicine.uiowa.edu/iowaprotocols/otitis-media

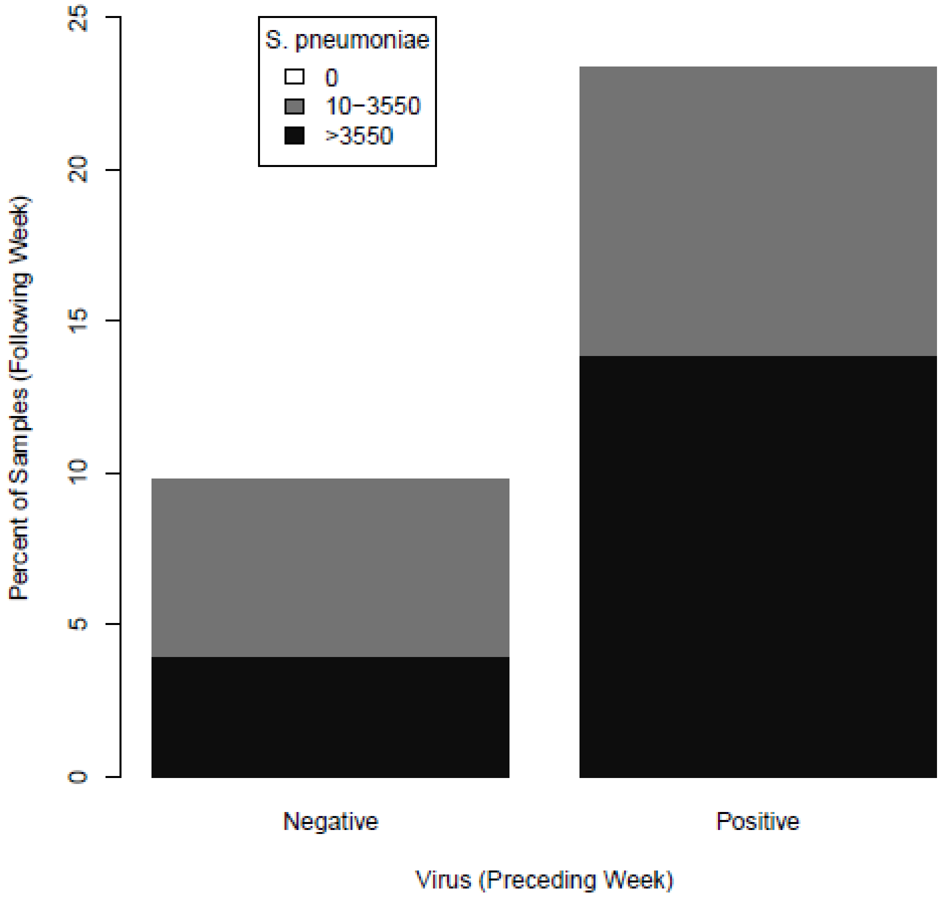
Hypothesis: RV-bacteria interactions contribute to severity of URI and exacerbations of asthma

Do Bacterial Pathogens Modify Viral Illnesses?

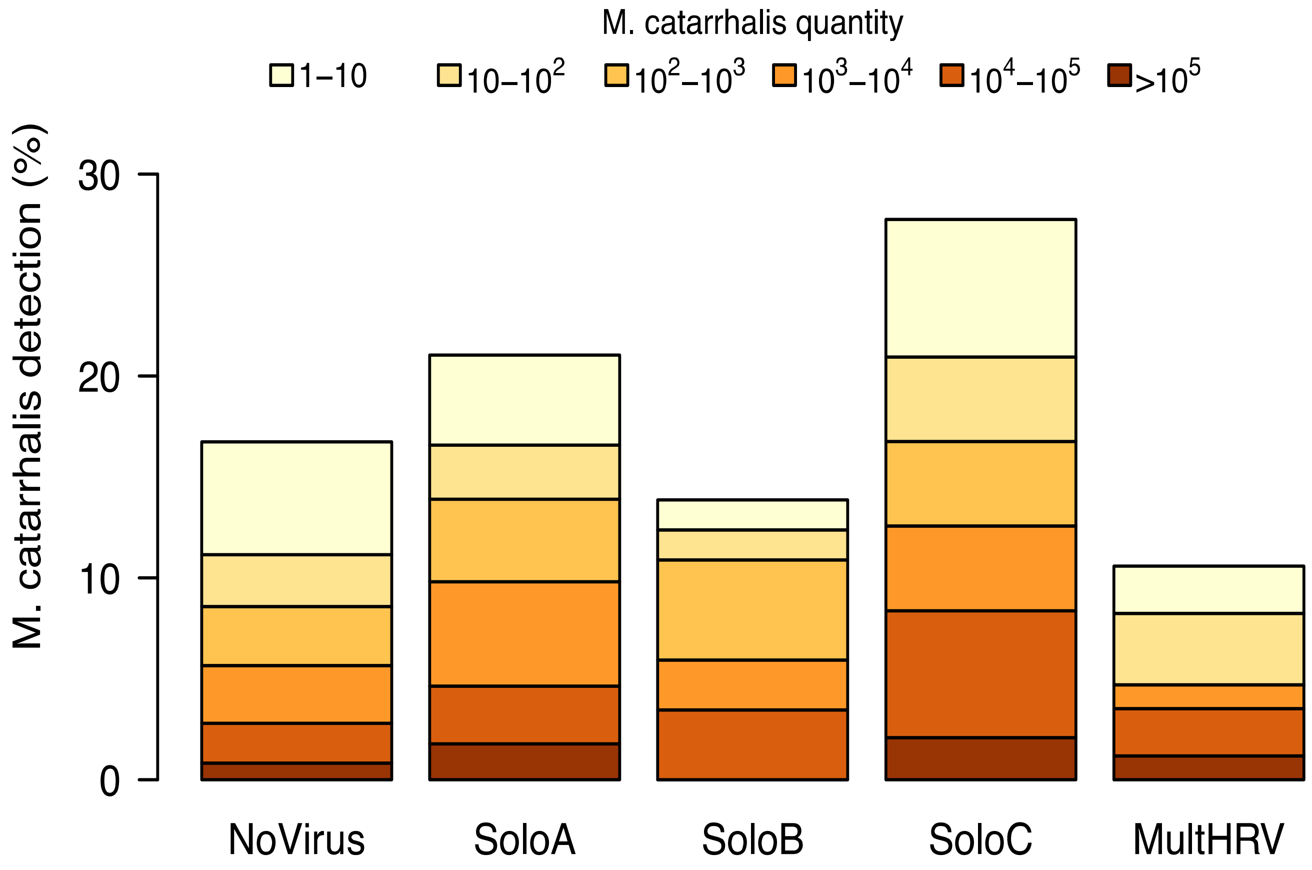
- 309 children (166 with asthma) ages 4-12 years
- Weekly nasal mucous samples (n=1420) during September cold season
  - Common respiratory viruses and RV species
  - *H. flu, S. pneumo, and M catarrhalis* (qPCR)
- Daily symptom diaries
  - Cold and asthma symptoms (none, mild, mod, sev)
  - Moderate asthma exacerbations
    - At least moderate asthma symptoms <u>and</u>
    - Increased albuterol use <u>or</u> 20% decrease in peak flow.

Kloepfer et al J Allergy Clin Immunol 2014

Virus Precedes Detection of Bacterial Pathogens

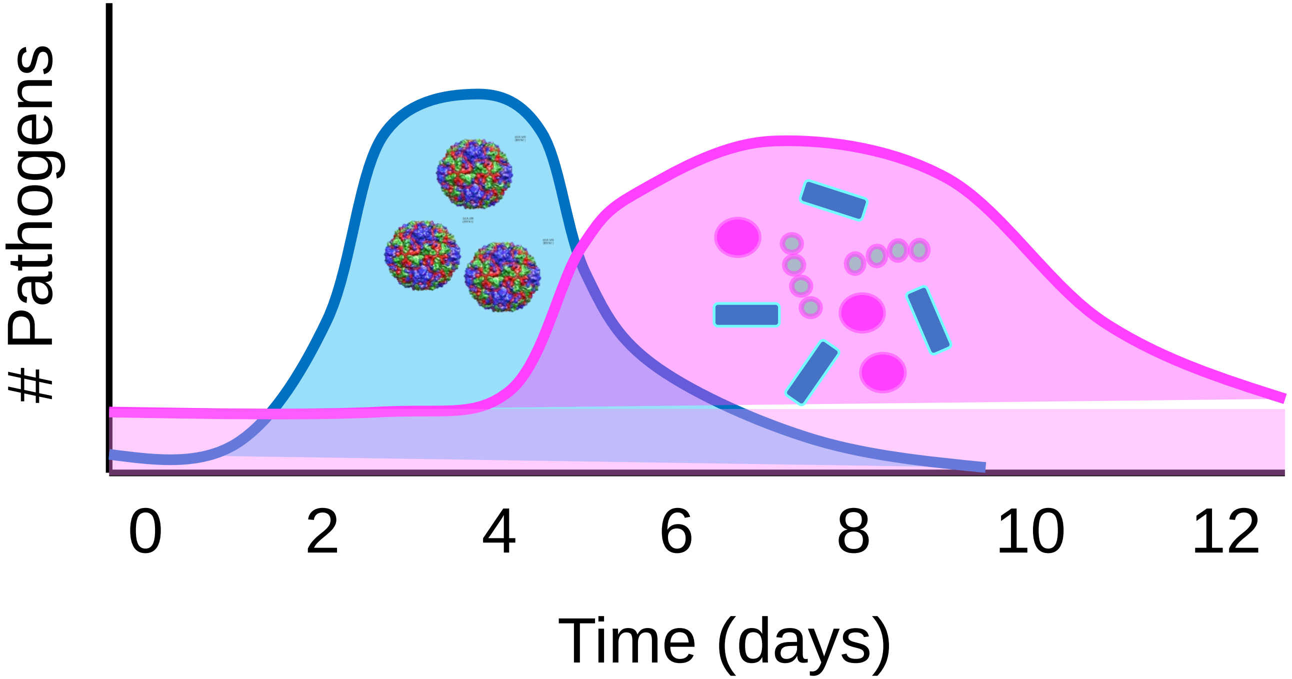


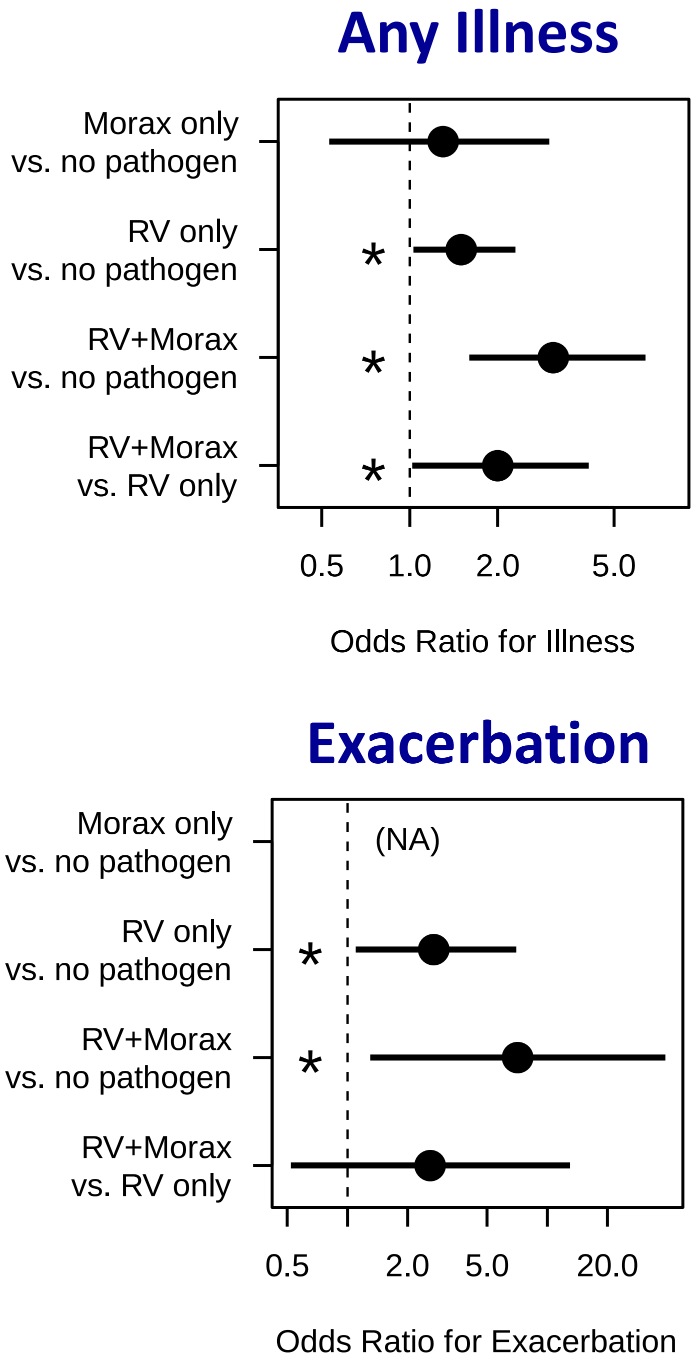
Kloepfer et al J Allergy Clin Immunol 2014



Bashir H et al, J Allergy Clin Immunol 2018

Sequential Appearance of RV and Bacterial Pathogens





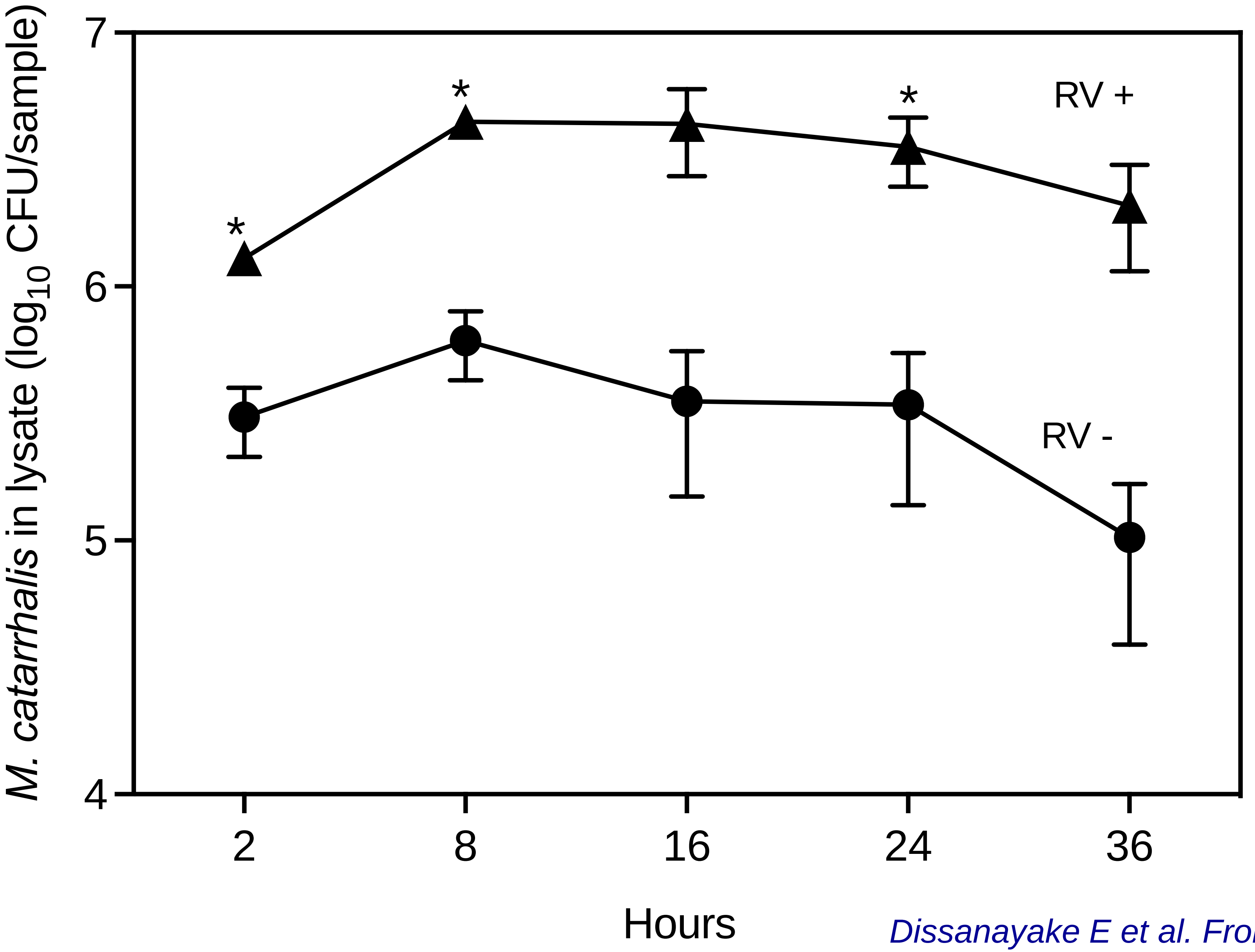
Kloepfer et al J Allergy Clin Immunol 2014

In Vitro Model of RV Infection and M. Catarrhalis

- Hypothesis: RV infection and Moraxella interact to promote epithelial damage
- Methods
  - Airway epithelial cells differentiated at air-liquid interface
  - RV infection followed by Moraxella (clinical isolates)
- Outcomes:
  - Moraxella binding to airway epithelial cells
  - Epithelial cell responses
    - Moraxella binding and proliferation
    - Cell death
    - Induction of pro-inflammatory cytokines

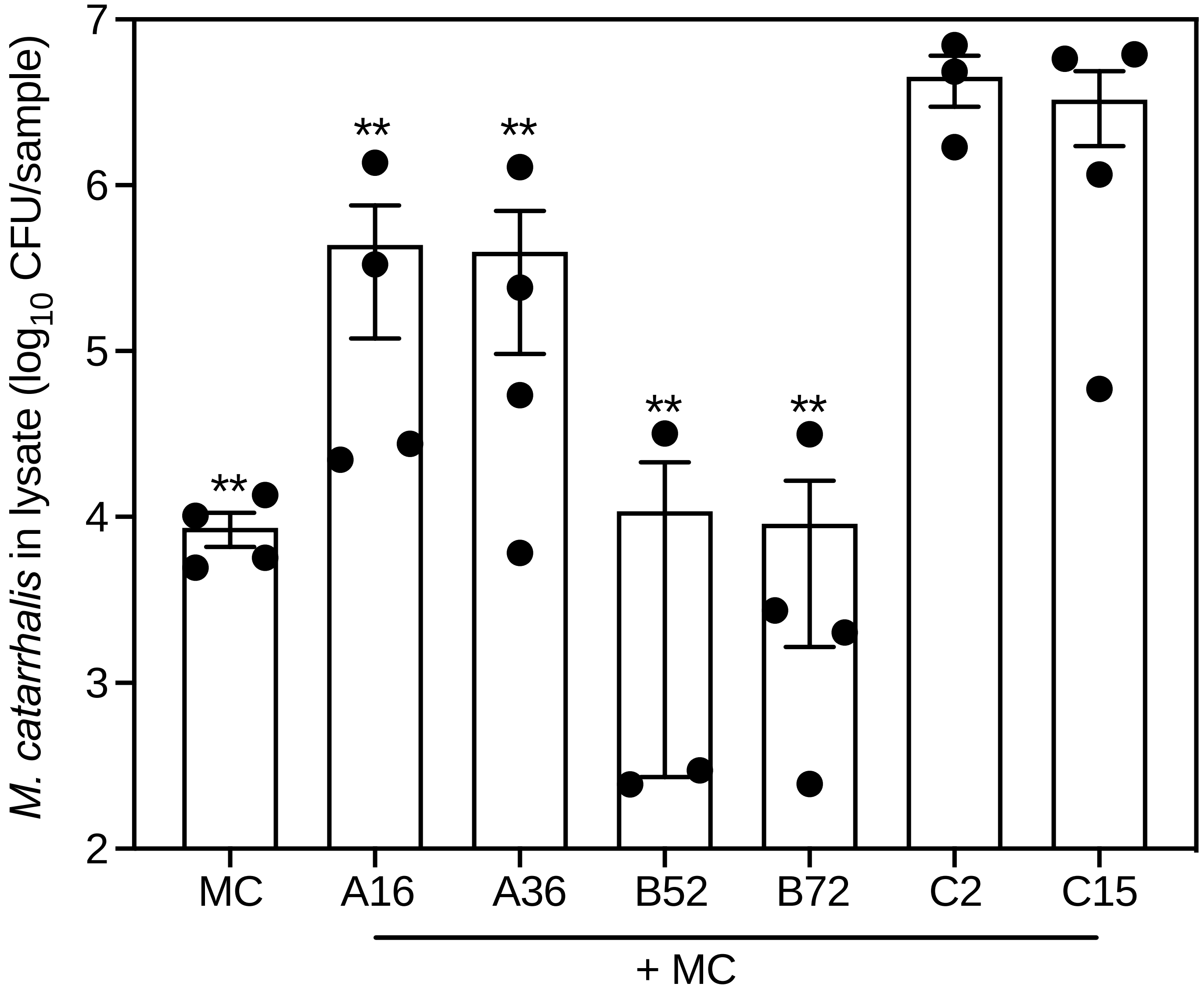
Eishika Dissanayake

RV-C15 for 16 h → *M. catarrhalis* added to ALI cultures for 2-36 h



Dissanayake E et al. Front Cell Infect Biol 2023

RV-C and RV-A Induce M. catarrhalis Adhesion



Dissanayake E et al. Front Cell Infect Biol 2023

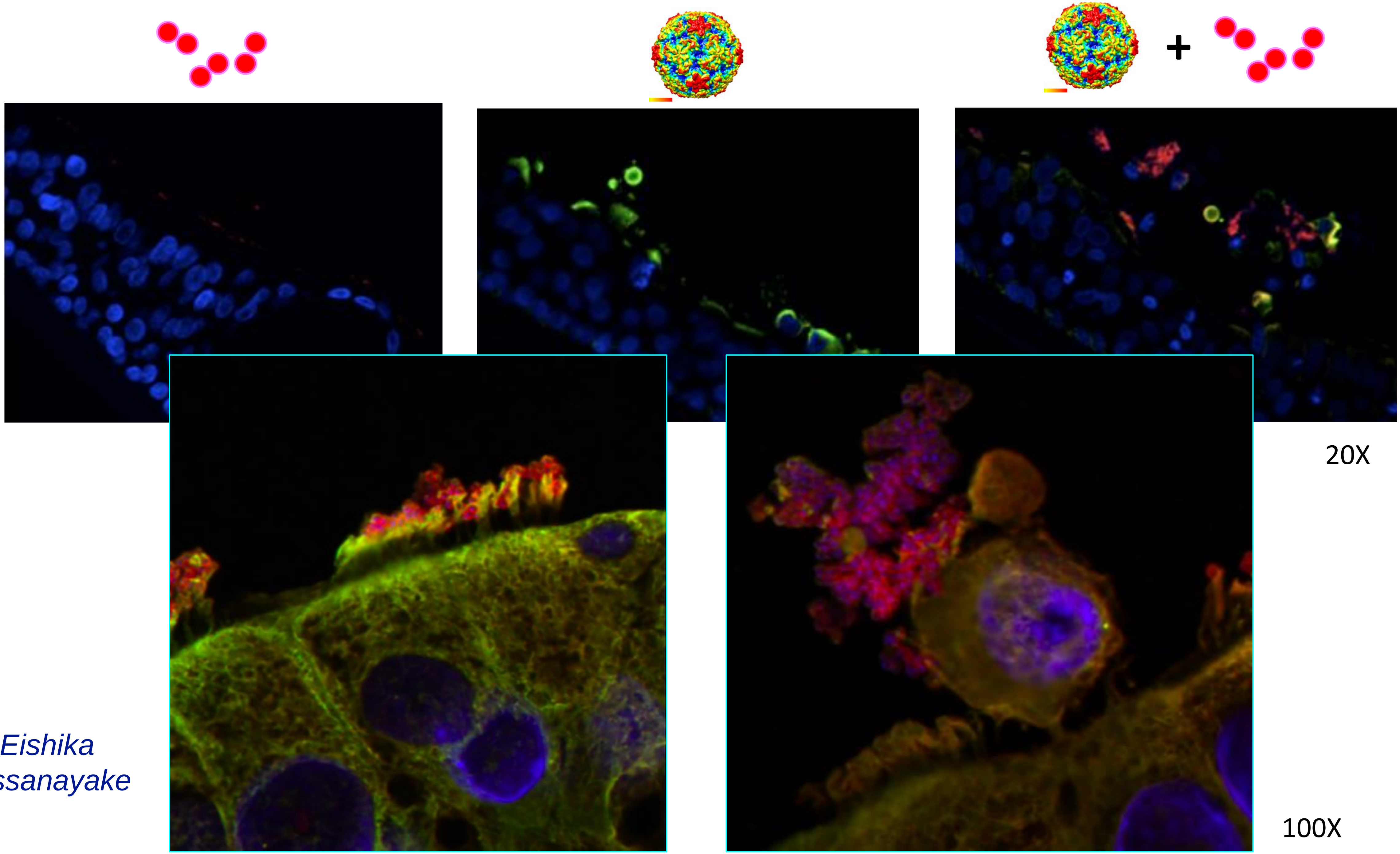
*P value vs C2

Moraxella did not affect:

- Epithelial barrier integrity
- Ciliary function
- Cytokine or chemokine production
- Cell viability

What is the nature of the RV-Moraxella-epithelial cell interaction?

- Are the bacteria invasive?
- With which cells do the bacteria interact?
  - Immunofluorescent staining



Eishika Dissanayake

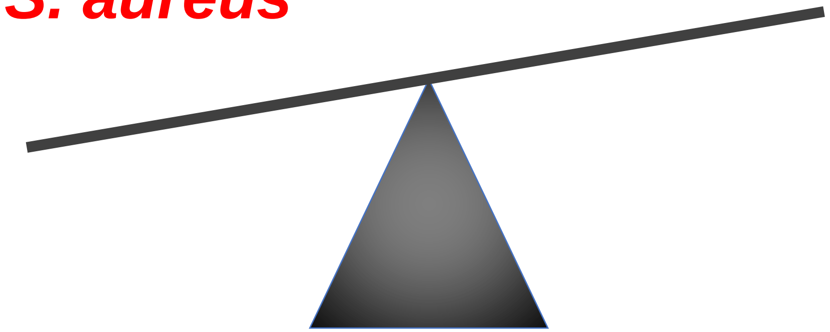
Viral Wheeze and Microbial Balance

Pathogens

M. catarrhalis
H. Influenzae
S. Pneumoniae
S. aureus

Commensals

D. pigrum
Corynebacteria
S. epidermidis



Teo M et al, Cell Host & Microbe 2015
Tang H and Lang A et al, JACI 2020

Viral Wheeze and Microbial Balance

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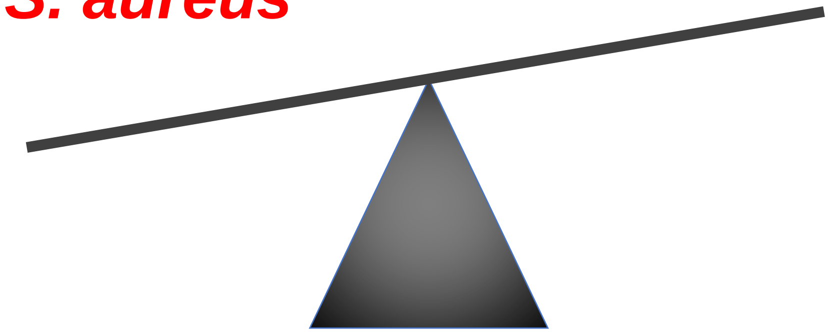
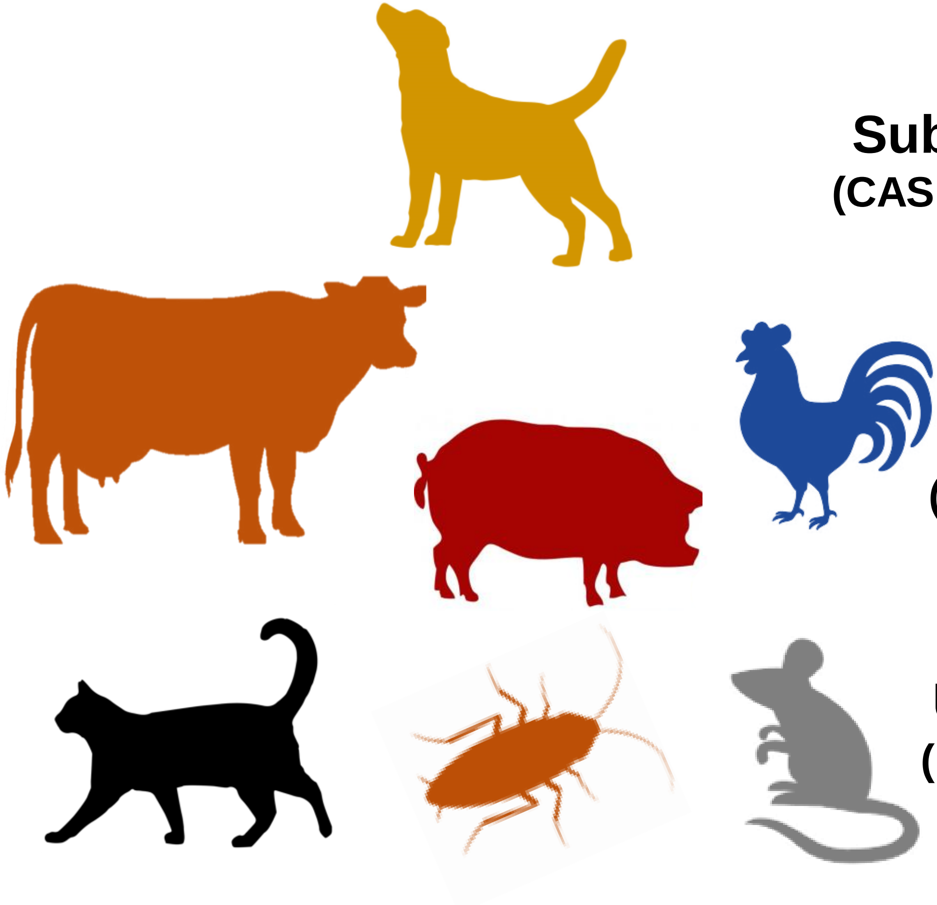


Teo M et al, Cell Host & Microbe 2015
Tang H and Lang A et al, JACI 2020

Early Life Exposures that Lower the Risk of Viral Illness



Suburban
(CAS, COAST)

Farm
(PARSIFAL, WISC)

Urban
(URECA)

Gern JE et al JACI 113:307-314, 2004
Brownell J et al. unpublished
Lynch SV and Wood RA et al. JACI 2014

Dolosigranulum pigrum in the Upper Respiratory Tract is Associated With Health

Author, Year	Population	Sample	Association
Laufer, 2011	Children (<7 yr)	Nasal swab	↓ abundance in acute otitis media ↓ abundance with *Streptococcus pneumoniae* carriage
Liu, 2015	Adults (>18 yr)	Nasal swab	↓ abundance with *Staphylococcus aureus* carriage
Escapa, 2018	Adults (18-40 yr)	Nasal swab	
Khamash, 2019	Neonates	Nasal swab	
Wagner Mackenzie, 2021	Adults (>18 yr)	Nasal swab	
Accorsi, 2020	Infants (<1 yr)	Nasal swab	↓ abundance with increased risk of *S. aureus* acquisition
Teo, 2015	Infants (<1 yr)	NP aspirate	↓ abundance with acute respiratory infection symptoms
Kelly, 2017	Children (<2 yr)	NP swab	
Hasegawa, 2017	Children (<5 yr)	Nasal swab	
de Koff, 2021	Children (<2 yr)	NP swab	
de Steenhuijsen Piters, 2022	Children (<2 yr)	NP swab	
Lappan, 2018	Children (<5 yr)	NP swab	↓ abundance in acute otitis media
Gan, 2019	Adults (>18 yr)	Nasal swab	↓ abundance in chronic rhinosinusitis
De Boeck, 2021	Adults (18-65 yr)	NP swab	
Tang, 2021	Children (< 2 yr)	Nasal lavage	↓ abundance with increased risk of wheezing illness
Patel, 2023	Children (<5 yr)	NP swab	↓ abundance with *S. pneumoniae* colonization

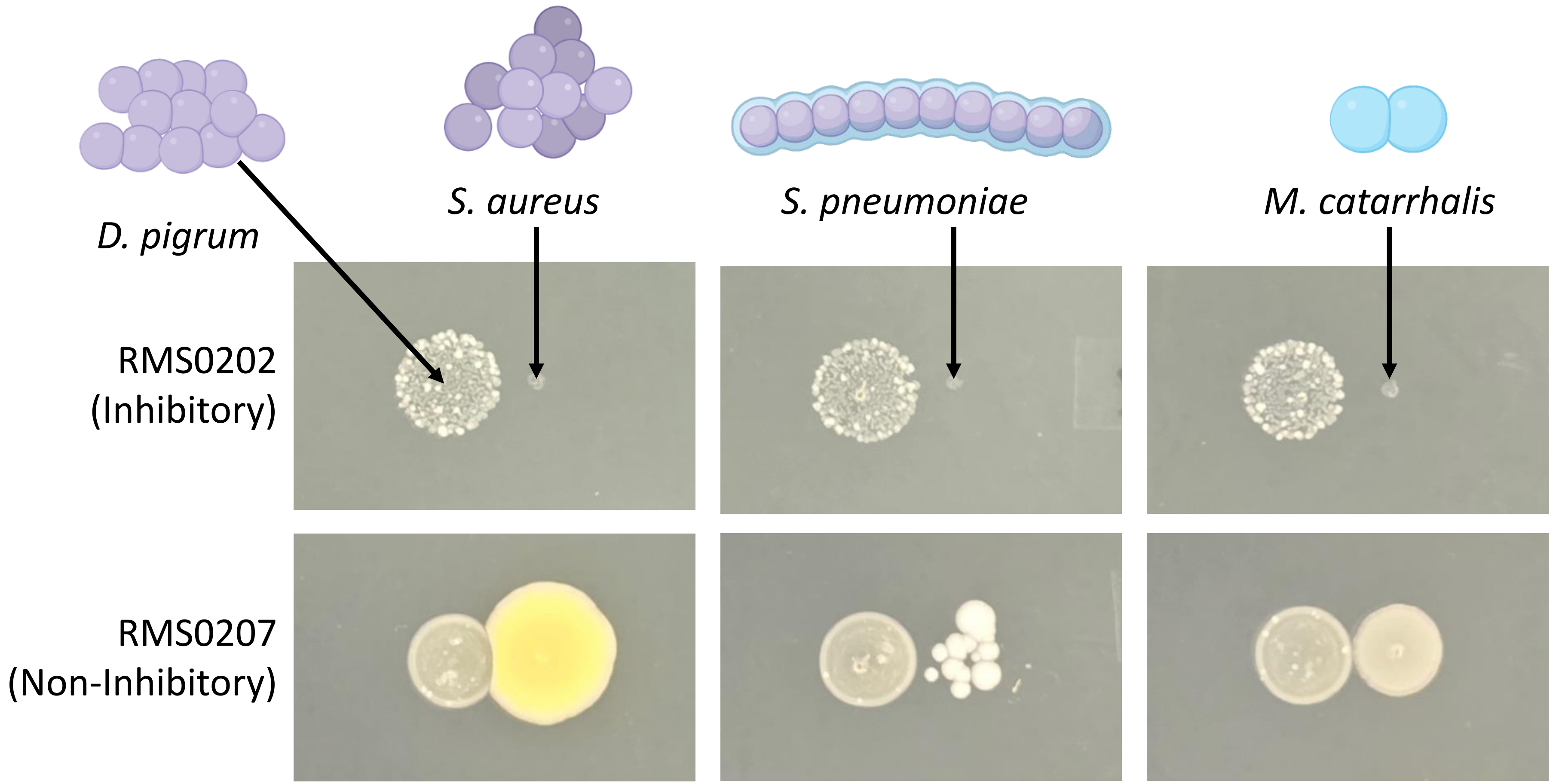
Table adapted from: Stubbendieck et al. 2024. PLOS Pathogens.

Reed Stubbendieck
Oklahoma State U.

Dolosigranulum pigrum

- Only one species in the genus
- Common in healthy young children
- Facultative anaerobe (doesn't grow well with standard plates)

Dolosigranulum pigrum Can Inhibit Pathobiont Growth *In Vitro*



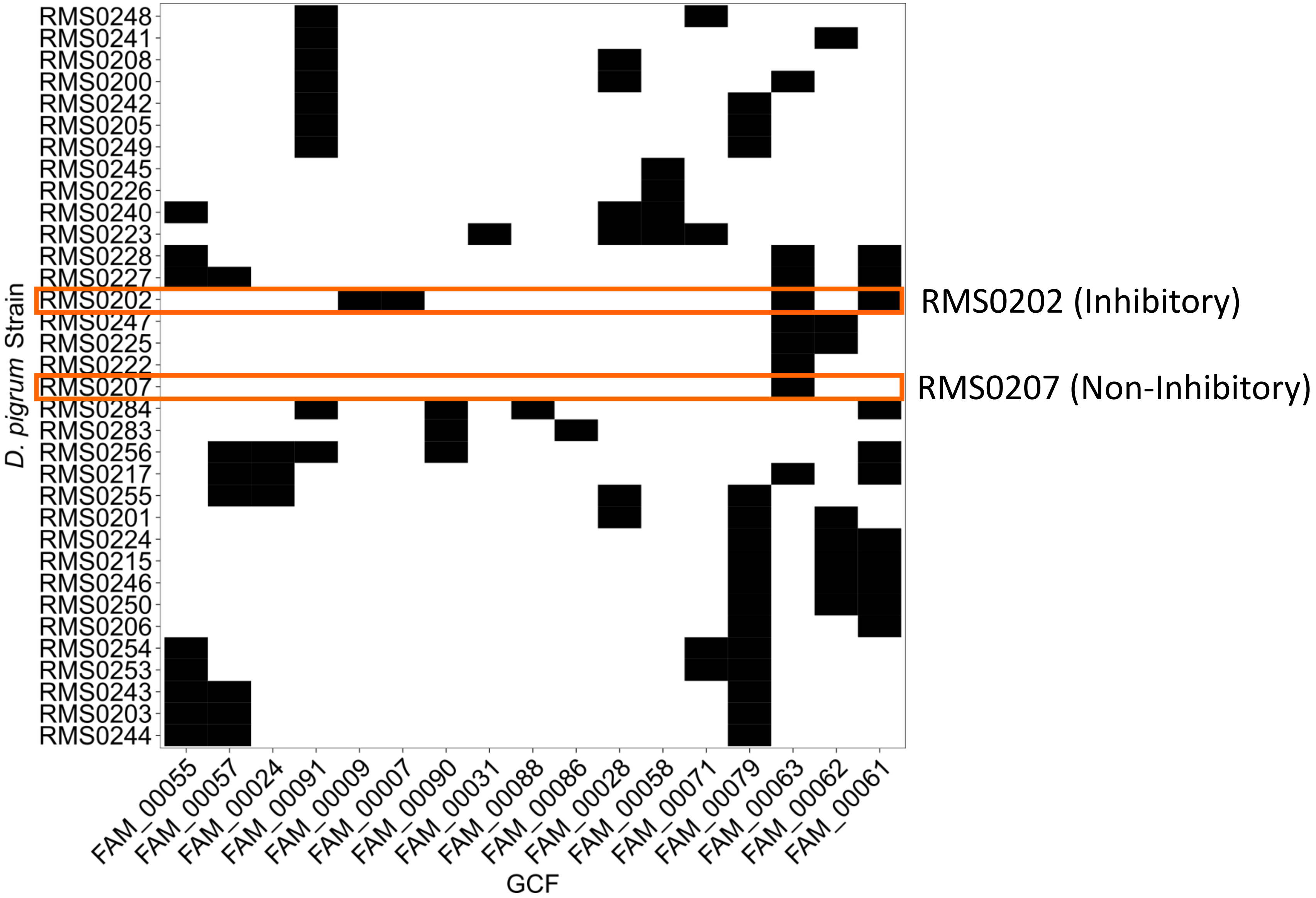
Madeline Reichert

Luke Myers

Do some *D. pigrum* strains encode BGCs for secondary metabolites that inhibit pathobionts?

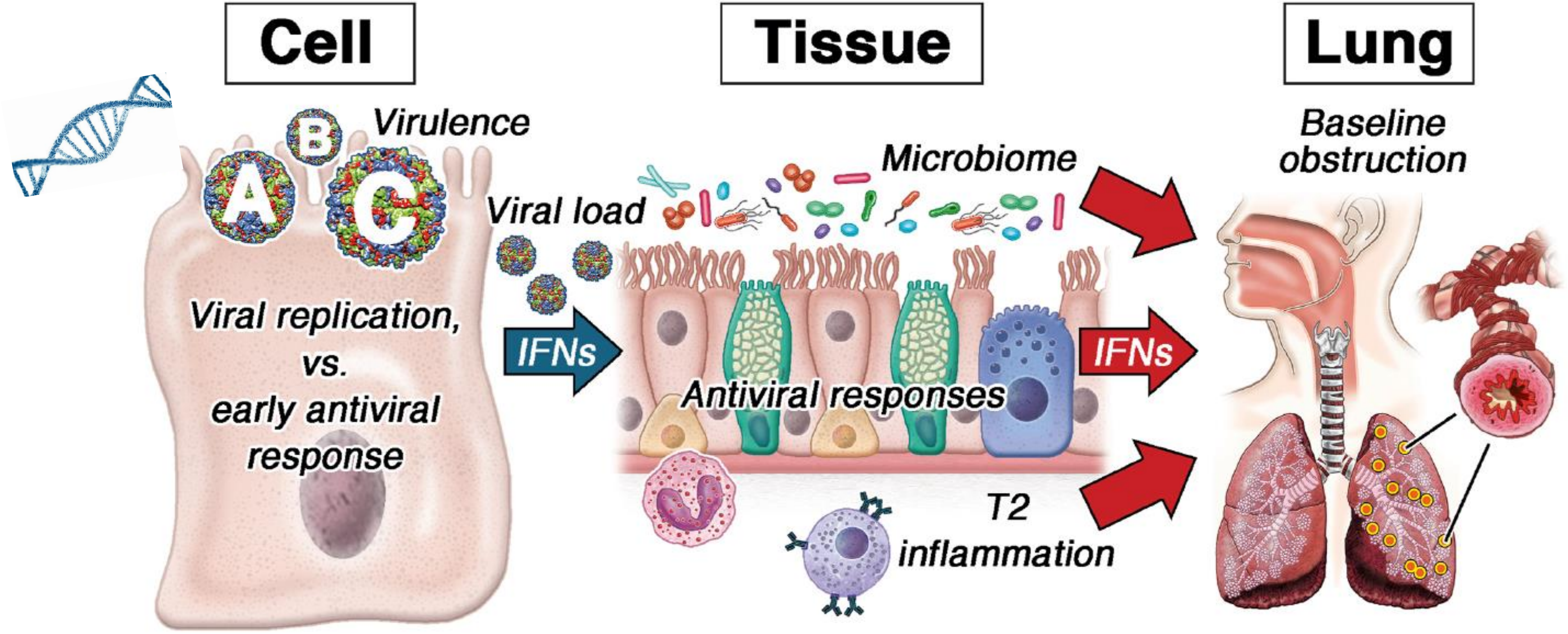
Unpublished Data

Dolosigranulum pigrum Strains Encode Variable BGCs



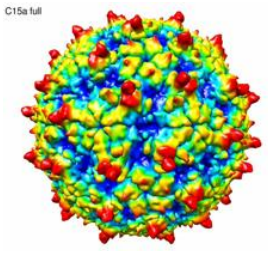
Unpublished Data

Conclusions



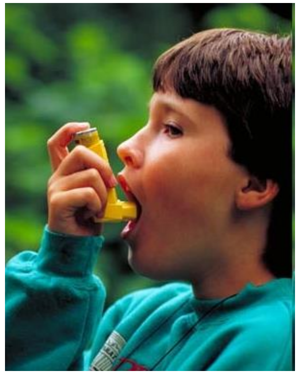
Implications for Treatment

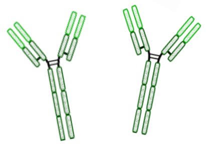
Viruses



- Target viruses that are more common and more virulent with vaccines or antivirals

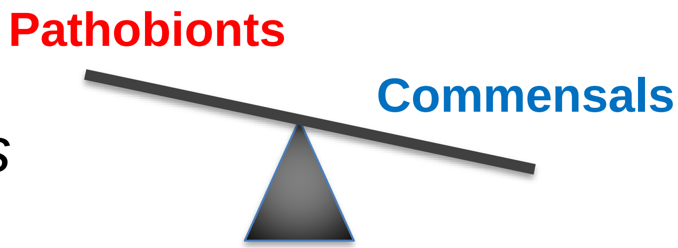
Host





- Identify children at risk for more severe disease
  - Epithelium cellular responses
- Treat allergic inflammation

Microbes



- Determine how bacterial pathogens promote severe RV illnesses
- Commensals as probiotics?

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  - NIAID, NHLBI, NICHD
- UW Institute for Molecular Virology
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  - Eishika Dissanayake
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  - Kris Grindle
  - Tressa Pappas
  - Christine Seroogy
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