Risk Factors for Recurrent Early Wheezing in Childhood: Viral Infections

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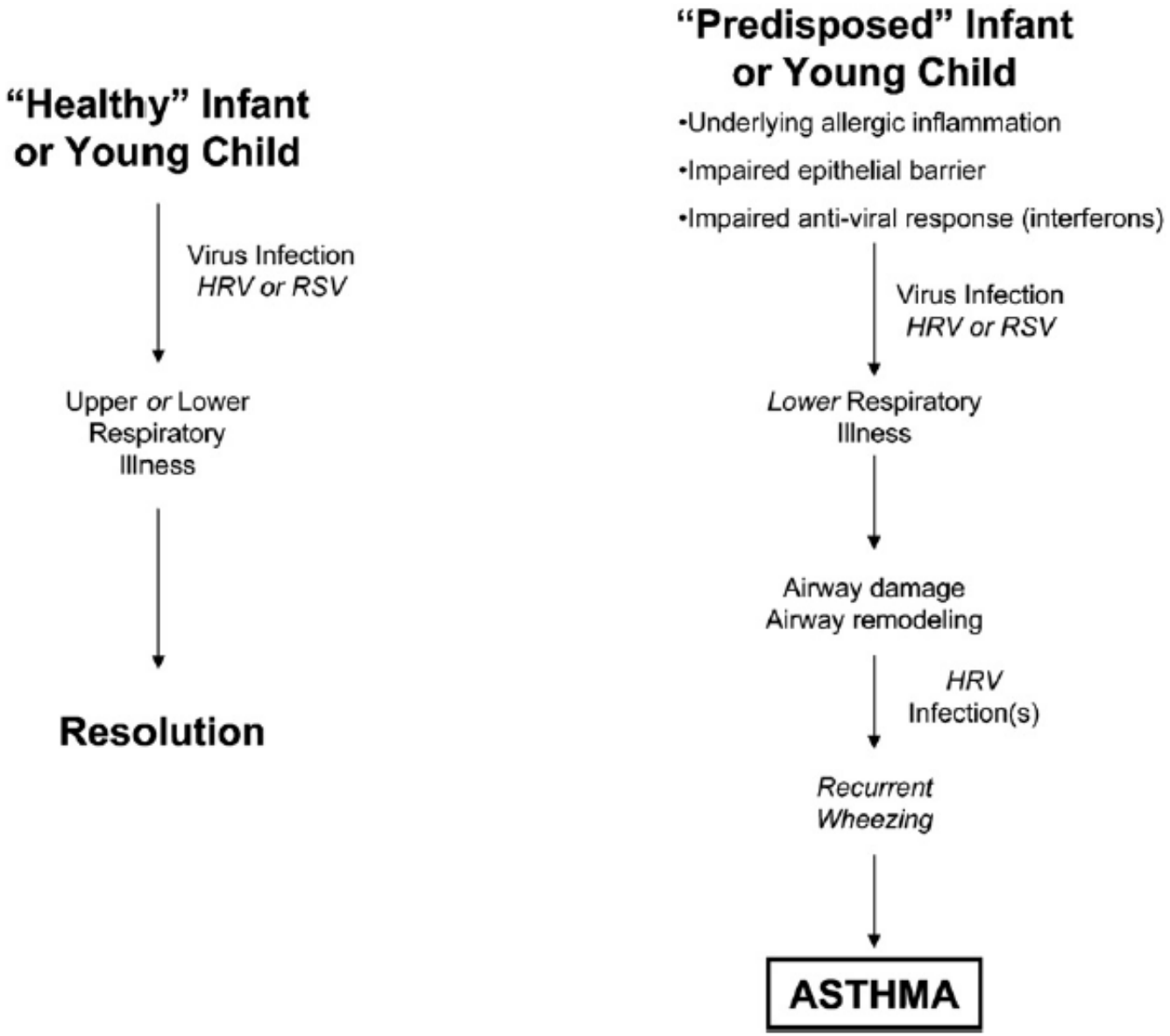


Jackson & Lemanske, *Immunology & Allergy Clin of North America,* 2010

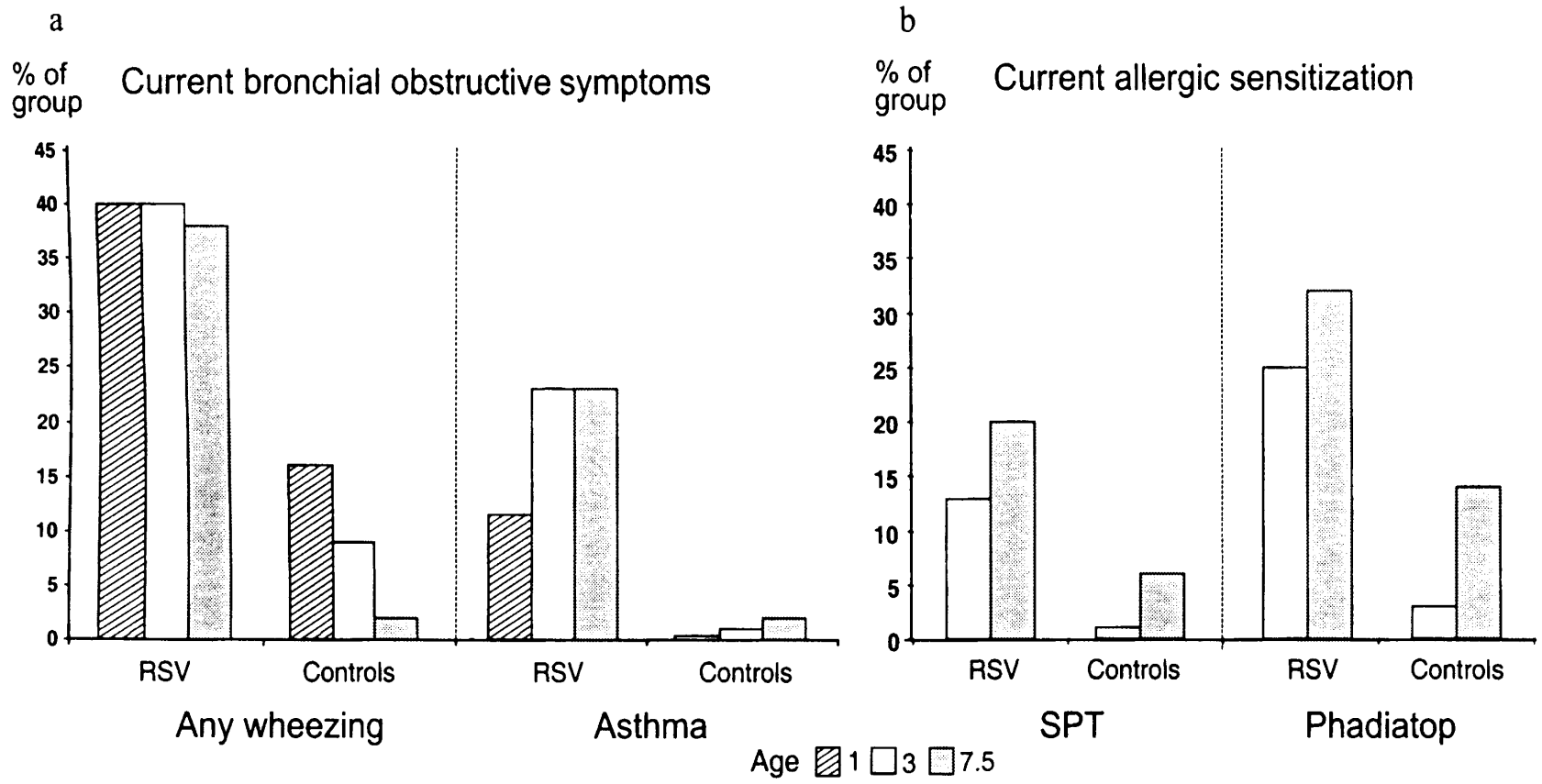
Viral Infections and Asthma

20% of all children have at least 1 episode of LRI associated with wheezing in the first year of life, and 70% of these are associated with viral infections

Wright, A.L. et al. Am.J.Epidemiol. 129:1232, 1996.

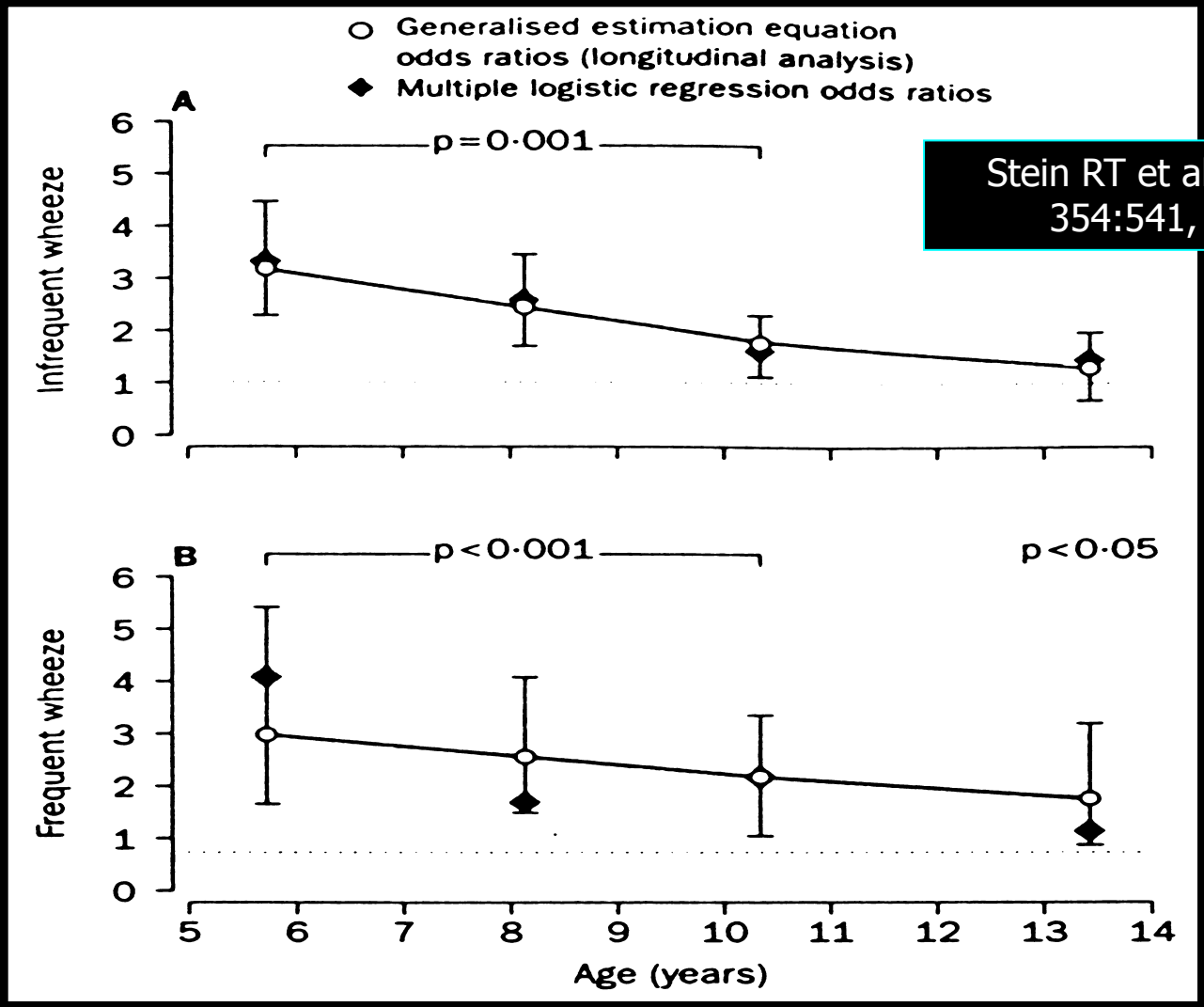

RSV

Respiratory Syncytial Virus Bronchiolitis in Infancy Is an Important Risk Factor for Asthma and Allergy at Age 7



Sigurs N et al. AJRCCM 161:1501, 2000

RSV Infections and Recurrent Wheezing



Stein RT et al. Lancet 354:541, 1999

Viral Pathogens other than RSV

Prevalence of Common Common Respiratory Viral Infections

Common colds

1. Rhinoviruses
2. Coronaviruses (winter)
3. Parainfluenza viruses
4. Enteroviruses (summer)
5. Influenza A, B, C (winter)
6. RSV (winter)
7. Metapneumoviruses (winter)
8. Bocavirus (winter?)

Wheezing Infants

1. RSV (winter)
2. Rhinoviruses
3. MPV (winter)
4. Coronaviruses
5. Parainfluenza viruses
6. Influenza viruses
7. Adenoviruses
8. Bocavirus (winter?)

Rhinovirus

Viruses other than RSV: *Rhinovirus*

- RV infections leading to hospitalization during infancy were an early predictor of the subsequent development of asthma.

Kotaneimi-Syrjanen A. et al. JACI 111:66, 2003

- Significant association between wheezing outpatient RV (and RSV) illnesses in infancy and persistent wheezing at 5 years of age
  - These findings were restricted to those children with early allergic sensitization (≤ 2 yrs of age)
  - Multivariate analyses using other risk factors eliminated association with asthma

Kusel MM et al. JACI 119:1105, 2007

COAST

Childhood Origins of ASThma

A prospective study in a high risk cohort designed to evaluate the interactions among age, patterns of immune dysfunction, and virus infections with respect to the subsequent development of asthma and allergic diseases

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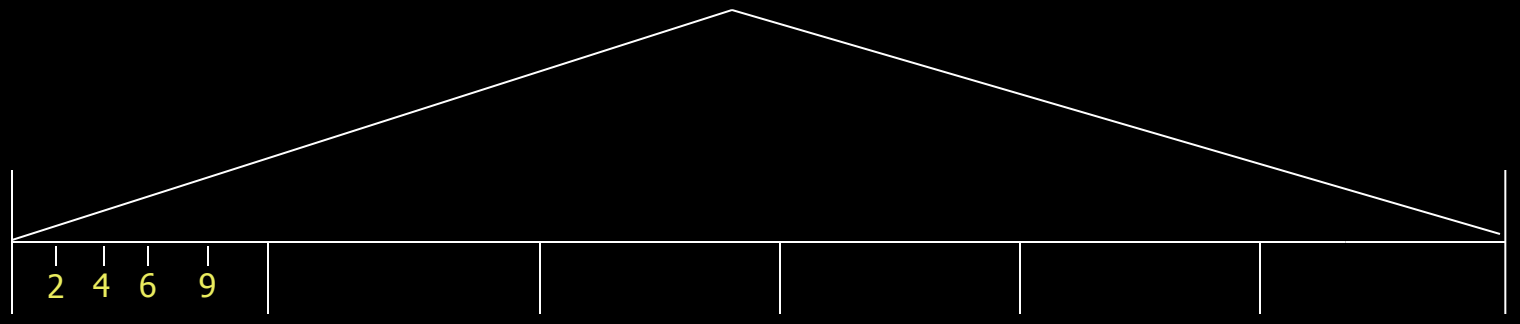
Funded by the NHLBI

Research Design and Methods

- Target enrollment: 300 families
- At least one parent with allergies or asthma
- Prospective (developmental) evaluation of
  - Immune system
    - Child (annually from birth) and parent
    - Cytokine response profiles; antigen-specific IgE
  - Respiratory infections (nasal aspirates)
  - Wheezing phenotypes (questionnaires)
  - Airway physiological evaluation (ages 4-7 yrs)
    - Impulse oscillometry, spirometry, eNO, meth. challenge
  - Environmental evaluation (diet, allergens, pets)
  - Genotype evaluation
- Minimum 12-14 year follow-up

COAST Evaluations

Nasal lavage specimens collected
at symptomatic illnesses



Nasal Washes collected at
"Well Child Visits"

Persistent
Wheezing
Evaluation

[JACI 116:571, 2005]

Asthma Evaluation
[AJRCCM 178:667, 2008]

Timing, severity & etiology of respiratory
illnesses determined throughout childhood

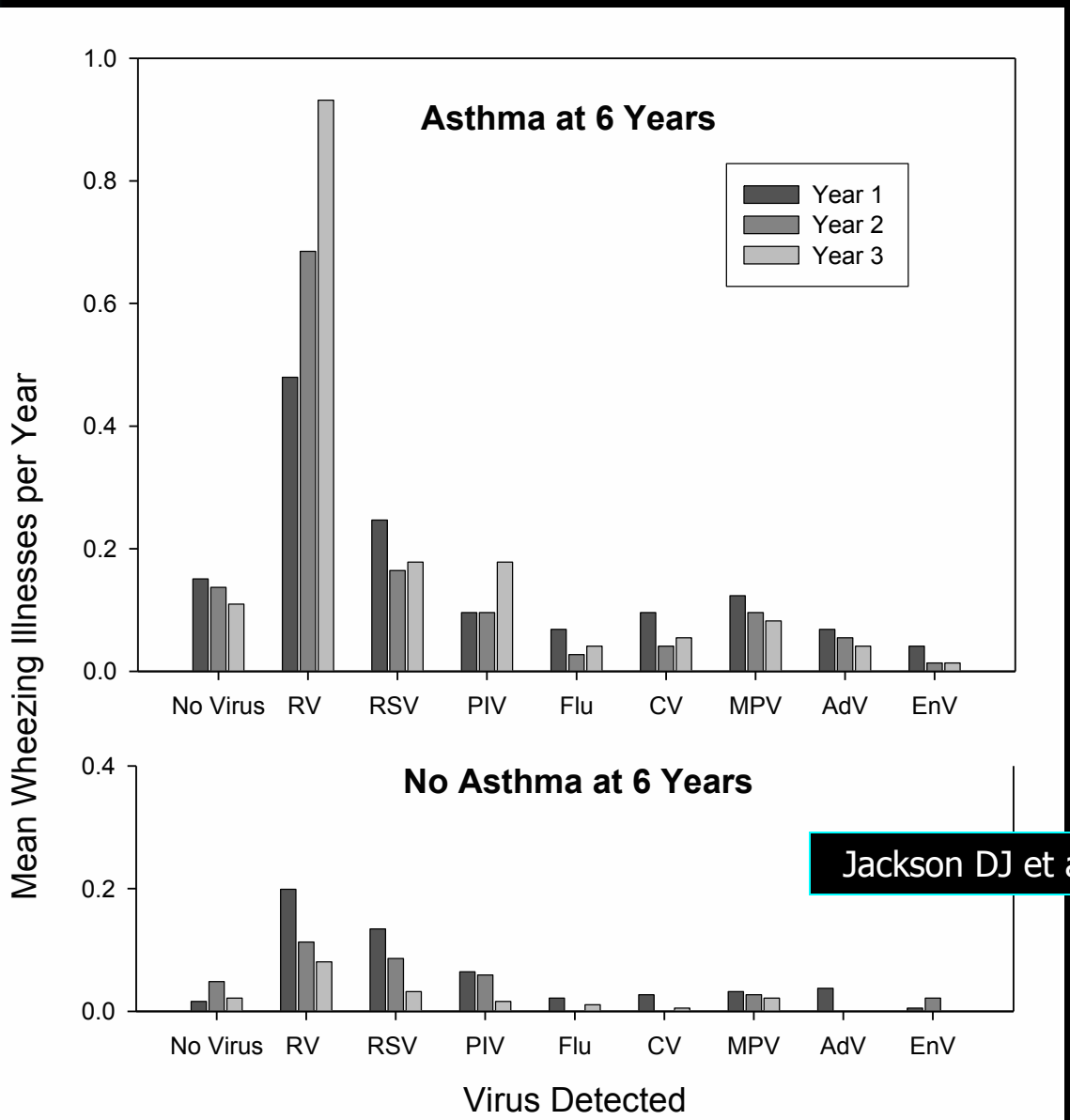
Risk Factors for Third Year Wheezing

- Passive smoke exposure (OR=2.1)
- Older siblings (OR=2.5)
- Allergic sensitization to food protein at age 1 year (OR=2.0)
- Any moderate to severe respiratory illness without wheezing during infancy (OR=3.6)
- At least one wheezing illness during infancy with:
  - RSV (OR=3.0)
  - Non RV/RSV pathogens (OR=3.9) during infancy
  - Rhinovirus (RV, OR=10)
- *When viral etiology was considered, first-year wheezing illnesses caused by RV infection were the strongest predictor of subsequent third year wheezing (OR = 6.6; p<0.0001).*

Lemanske RF et al. JACI 116:571, 2005

What viral infections in early life are associated with the development of asthma at age 6 years?

Etiology of Wheezing Illnesses in Early Childhood

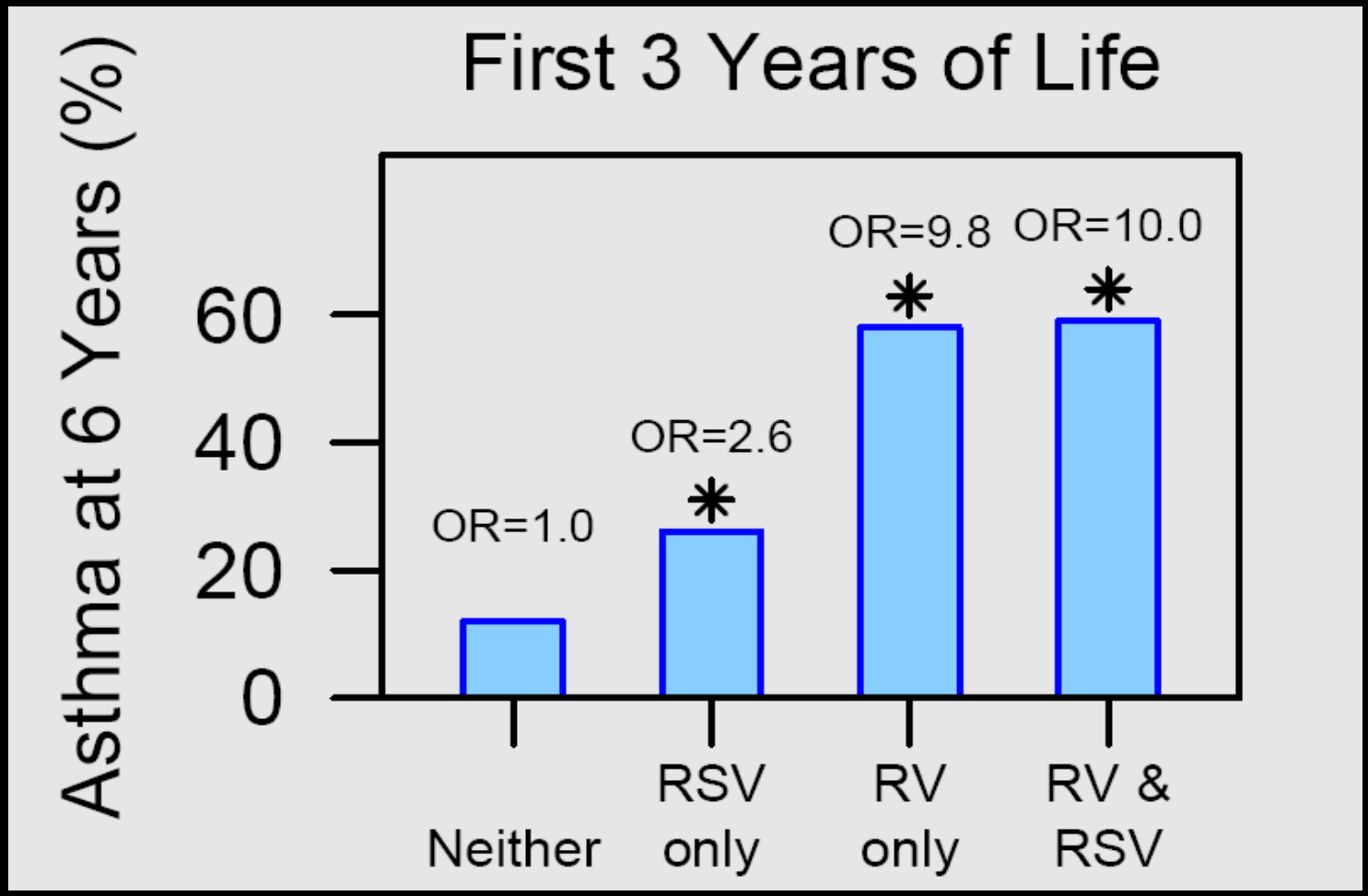


RV Rhinovirus
RSV Respiratory syncytial virus
PIV Parainfluenza
Flu Influenza
CV Coronavirus
MPV Metapneumovirus
AdV Adenovirus
EnV Enterovirus

Jackson DJ et al. AJRCCM, 178:667, 2008

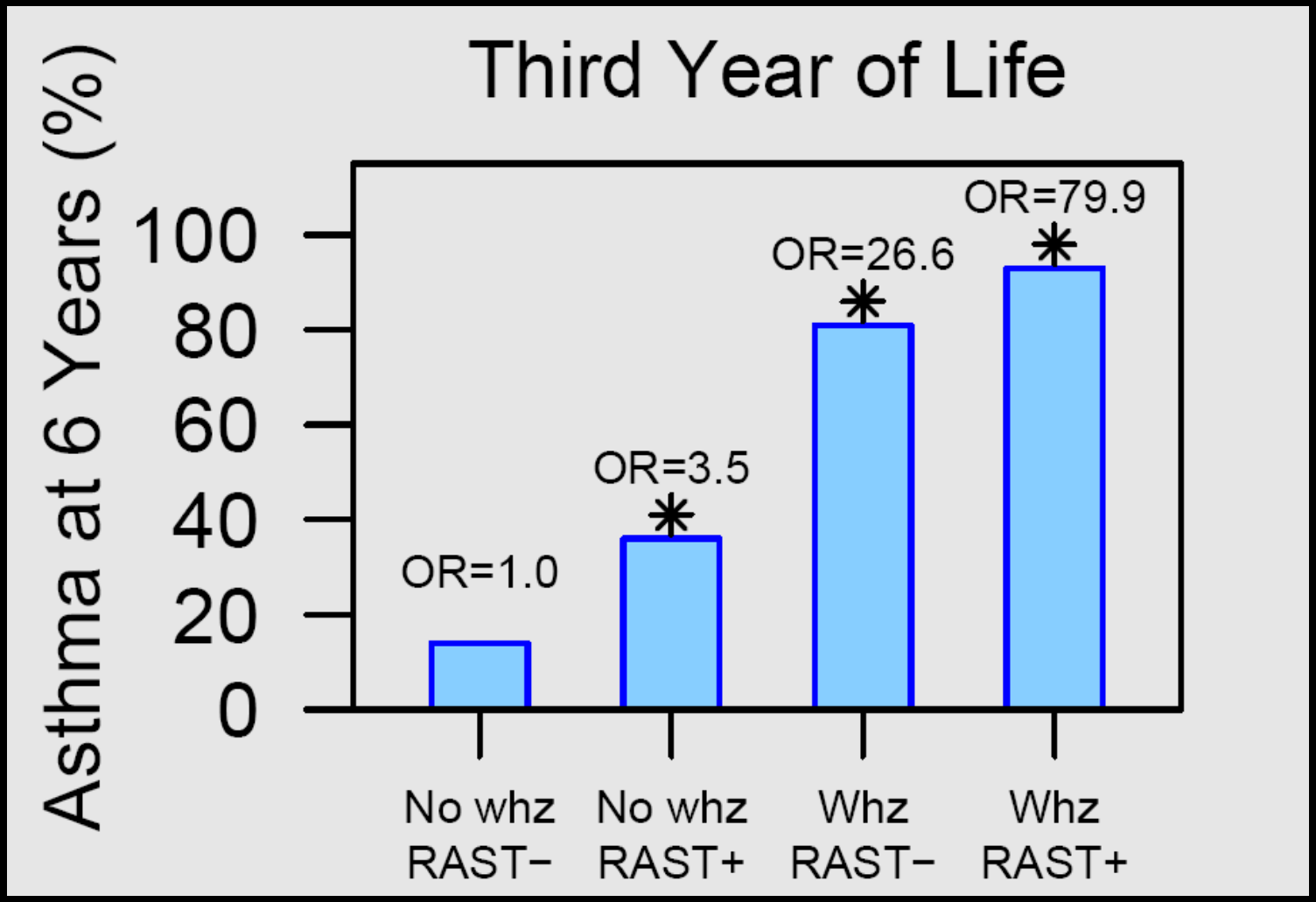
Did RV or RSV wheezing illnesses during years 1-3 impact the risk of asthma at age 6?

RV Wheezing vs. RSV Wheezing in First 3 Years and Asthma at Age 6 Years



Jackson DJ et al. AJRCCM, 178:667, 2008

RV Wheezing & Allergic Sensitization in Year 3 and Asthma at Age 6 Years

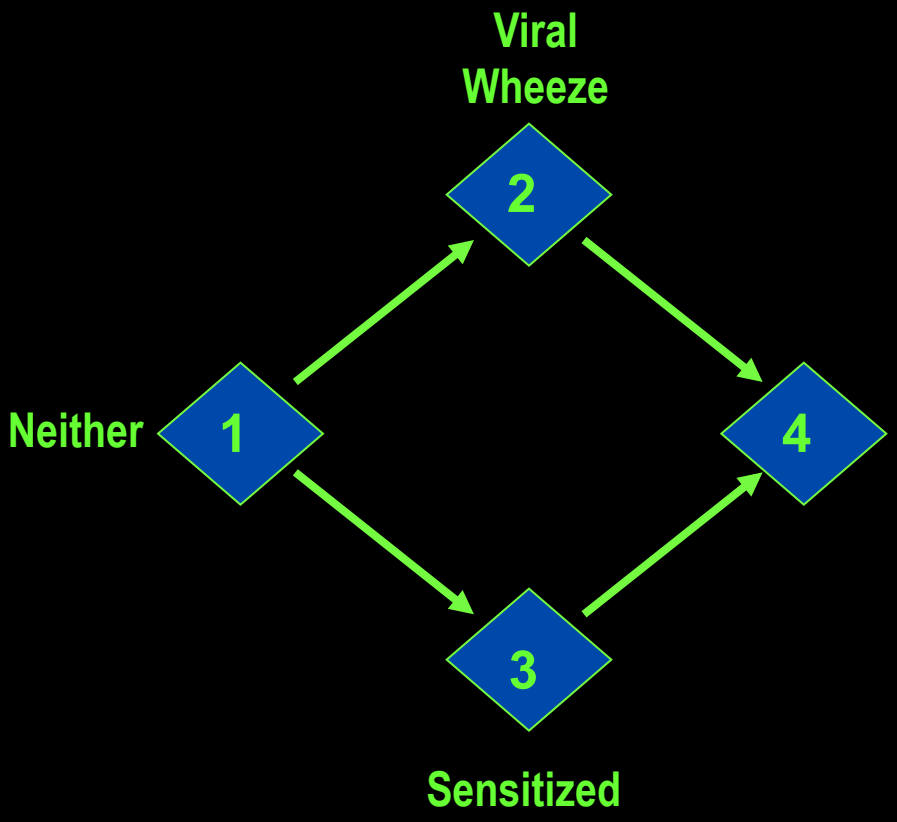


Jackson DJ et al. AJRCCM, 178:667, 2008

Which comes first?

Allergic sensitization or wheezing illnesses?

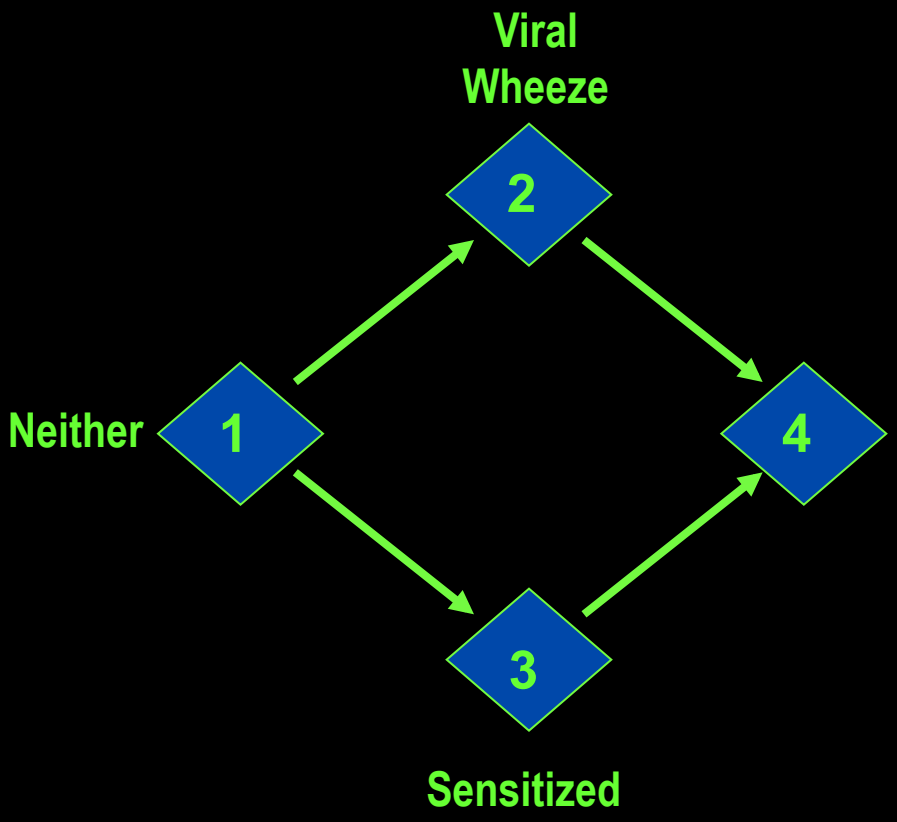
Does sensitization lead to viral wheezing, or does viral wheezing lead to sensitization?



- COAST cohort
- Ages 0 – 6 yrs
- Does sensitization lead to viral wheezing, or does viral wheezing lead to sensitization?
- Analysis of transitions between 4 states.

Jackson et al. AJRCCM, in press

Does sensitization lead to viral wheezing, or does viral wheezing lead to sensitization?



If viral wheeze causes sensitization:

$2 \rightarrow 4 > 1 \rightarrow 3$

If sensitization causes viral wheeze:

$3 \rightarrow 4 > 1 \rightarrow 2$

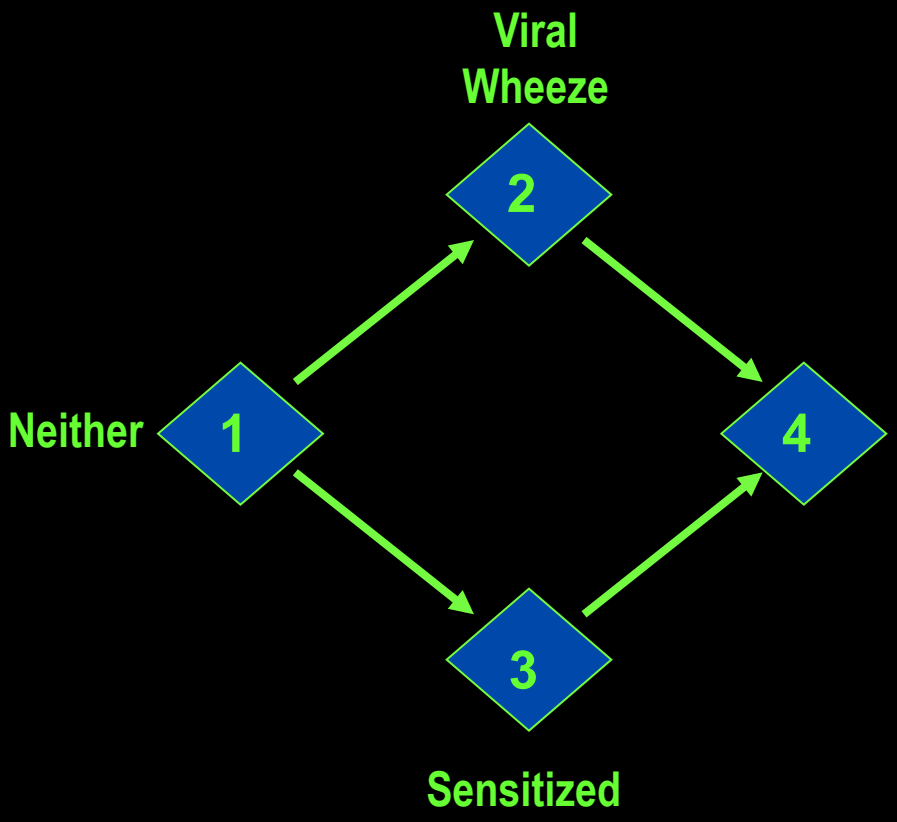
No causality:

$2 \rightarrow 4 = 1 \rightarrow 3$

$3 \rightarrow 4 = 1 \rightarrow 2$

Jackson et al. AJRCCM, in press

Sensitization Leads to Viral Wheeze
(the reverse does not appear to be true)

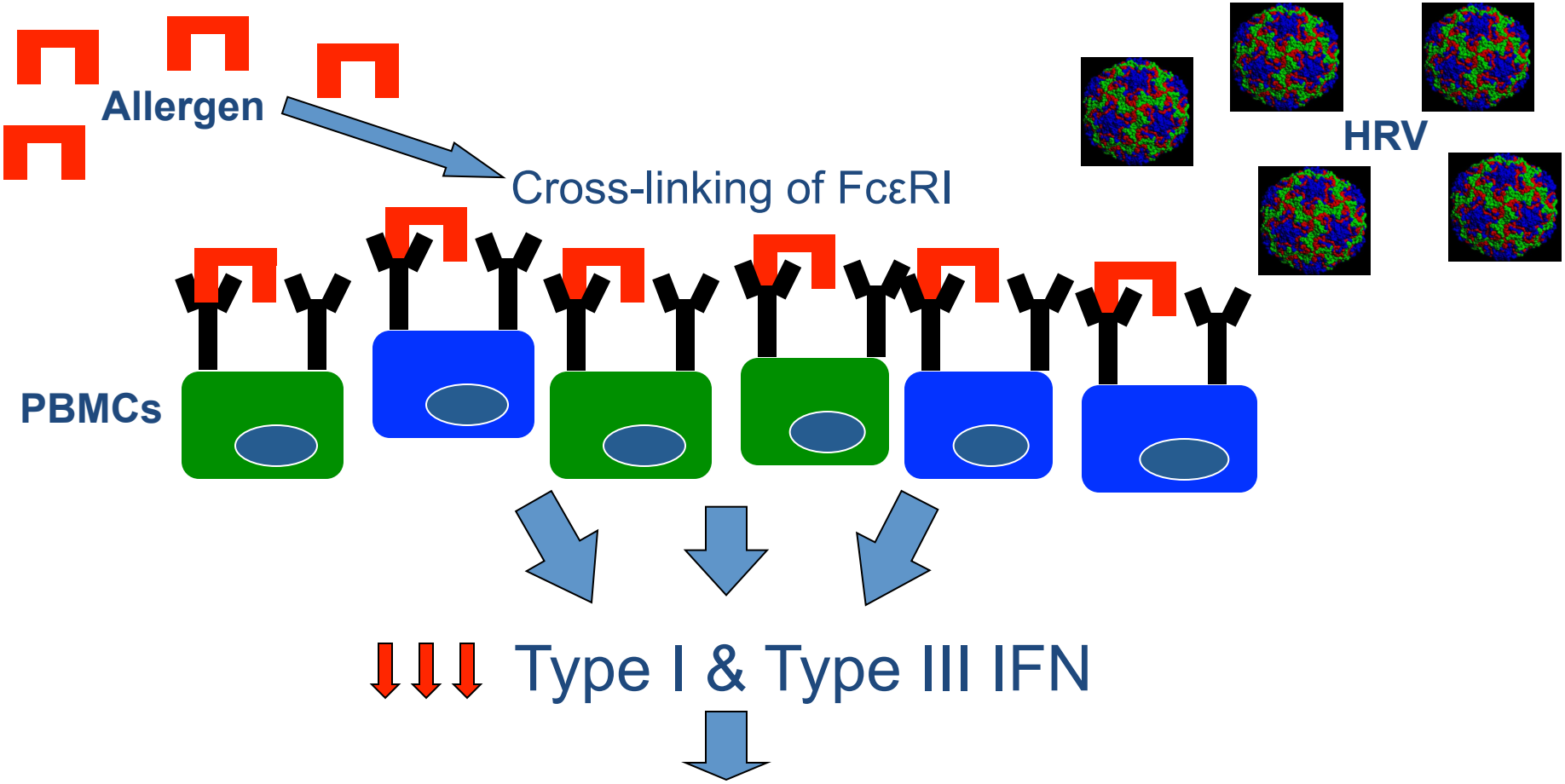


Virus	Ratio $\frac{3\rightarrow4}{1\rightarrow2}$	Ratio $\frac{2\rightarrow4}{1\rightarrow3}$
Any	1.9* (1.2, 3.1)	0.75 (0.49, 1.1)
HRV	2.4* (1.4, 4.3)	0.69 (0.41, 1.2)
RSV	1.6 (0.9, 2.9)	0.8 (0.52, 1.3)

Jackson et al. AJRCCM, in press

How does allergic sensitization alter the host response to viral respiratory infections?

Hypothesis: Allergy Inhibits Innate Immune Responses



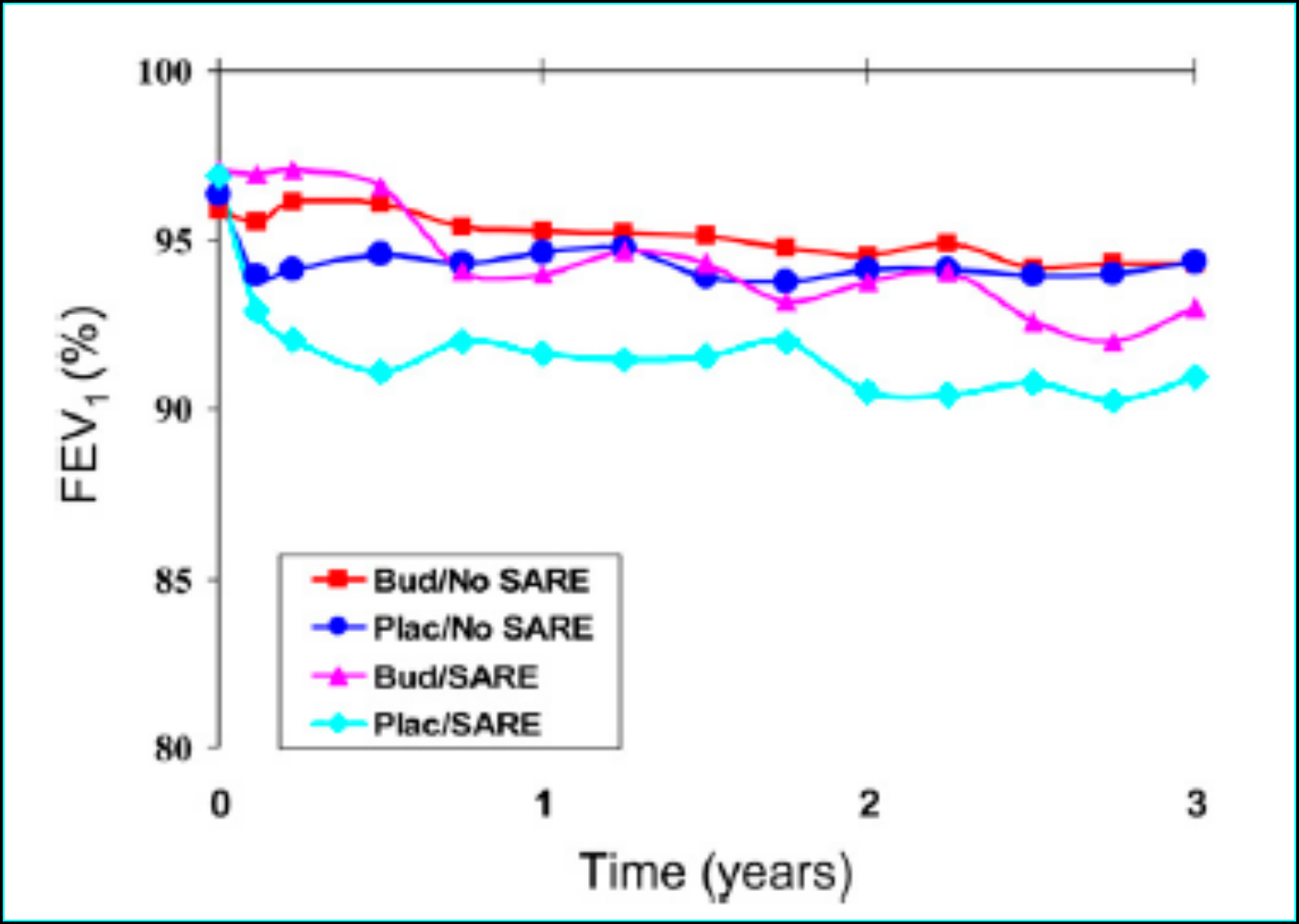
More frequent and severe virus-induced wheezing

Prolonged inflammation

Possible airway remodeling and/or loss of lung function

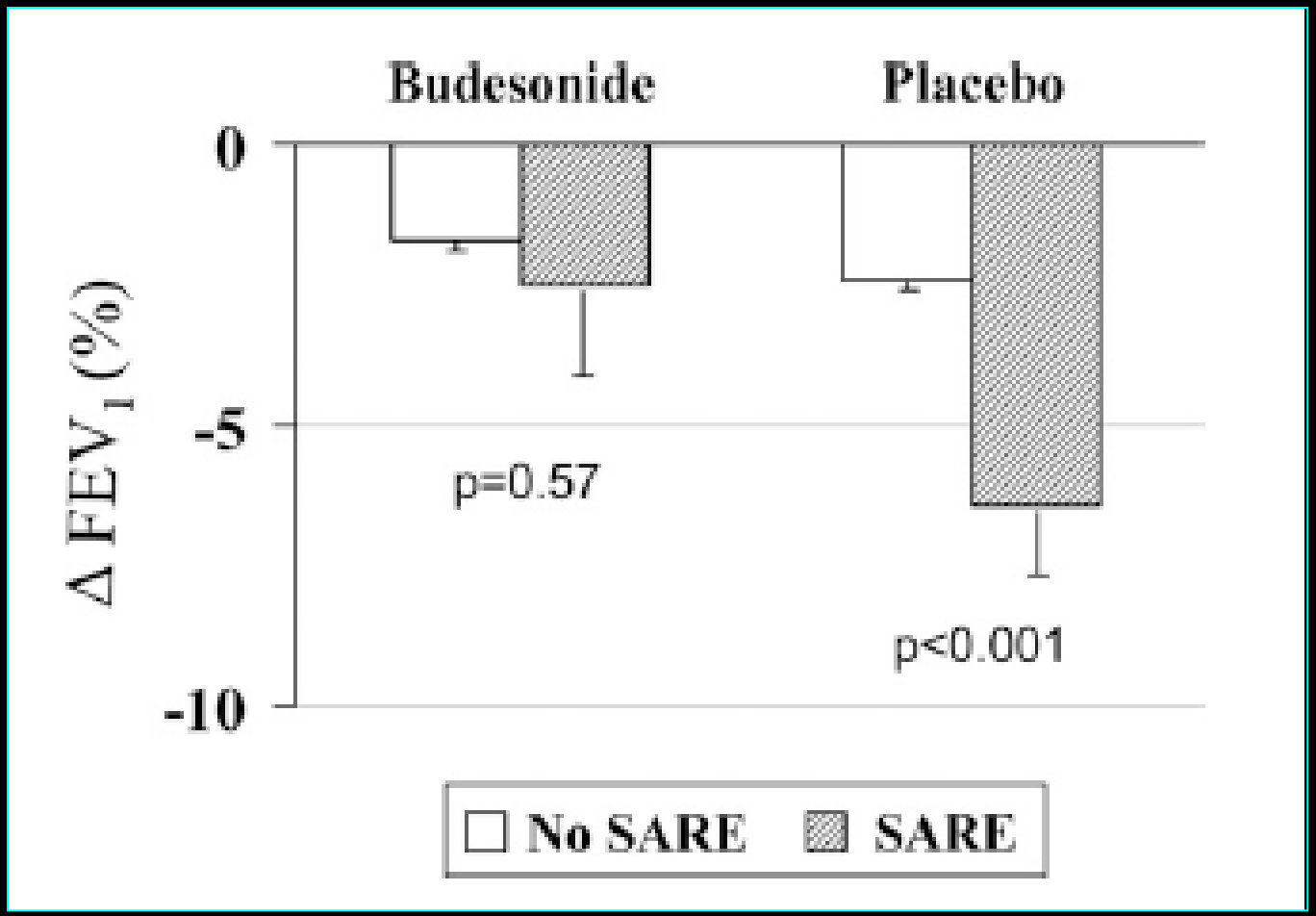
Do wheezing RV infections in early life influence subsequent lung function?

Effect of Treatment on SARE-related Changes in Post-bronchodilator FEV_1



O' Byrne PM et al. AJRCCM 179:19, 2009

Mean 3 Year Change in Post-bronchodilator FEV_1

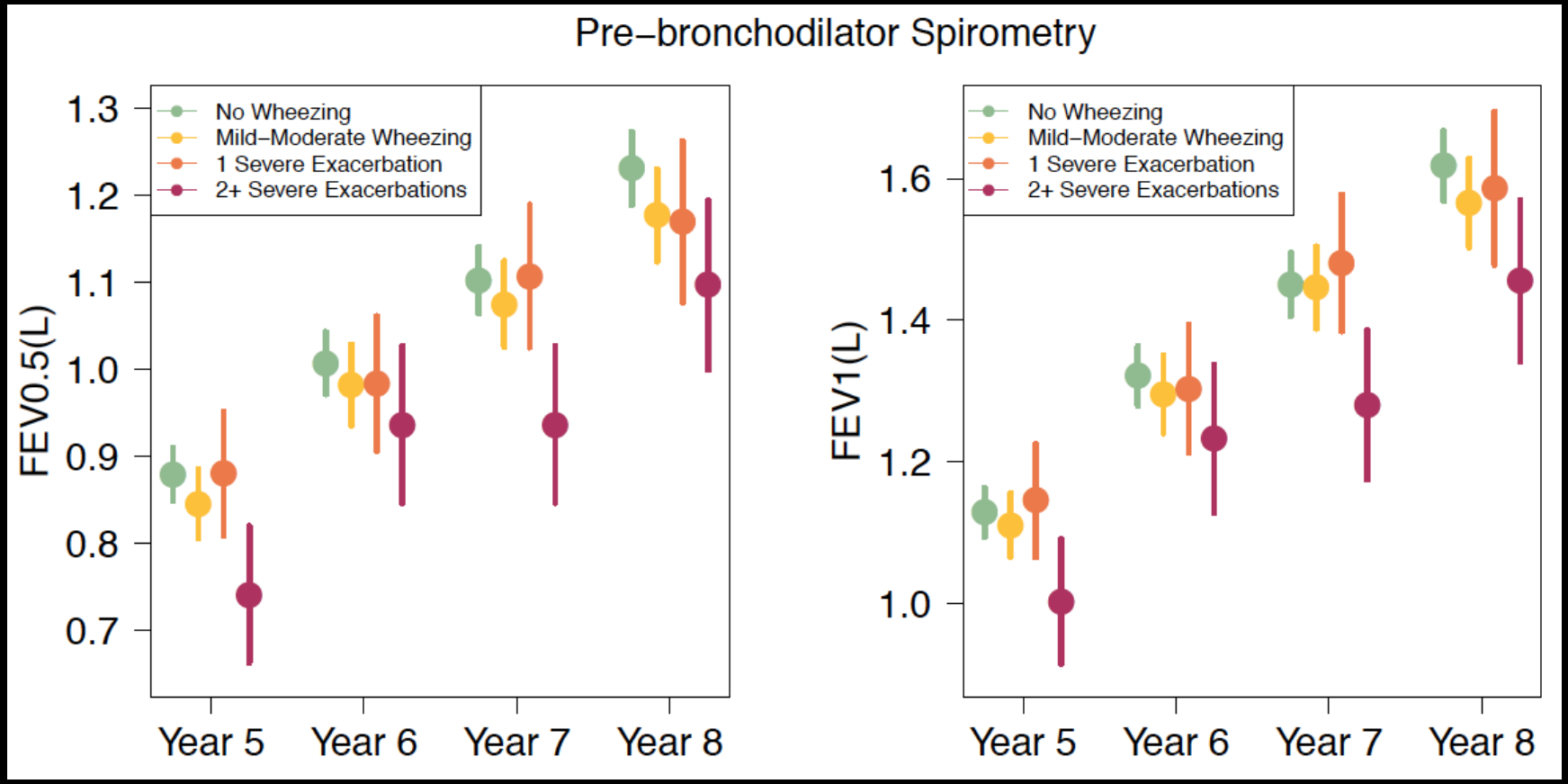


O' Byrne PM et al. AJRCCM 179:19, 2009

Influence of Viral Etiology for Wheezing on Lung Function

Guilbert T et al. JACI 128:532, 2011

Effects of Asthma Exacerbation Severity on Lung Function



Mechanisms

Do wheezing RV infections in early life *cause* asthma?

Host Factors

↓ antiviral responses

↓ lung function

Genetic polymorphisms

Asthma

Abnormal Host

Mechanisms

- Airway epithelial cells[1]
  - Normal: apoptosis
  - Asthma: viral replication
- Immune dysregulation[1-4]
  - Altered innate immune responses
    - Type 1-3 interferons (α, β, γ, λ)
  - Fc ε R1 numbers and bridging on antigen-presenting cells[4]
- Genetic polymorphisms[5]
  - CD14_159 and Toll 3 receptors

1. Contoli M et al. Nat Med 12:1023, 2006

2. Wark PA et al. J Exp Med 201:937, 2005

3. Copenhaver CC et al. AJRCCM 170:175, 2004

4. Gill M et al. JI 184:5999, 2010

5. Hewson CA et al. J Virol 79:12273, 2005

6. Martin AC et al. AJRCCM 173:617, 2006

Normal Host

Asthma

Virus Factors

Lung/Airway damage

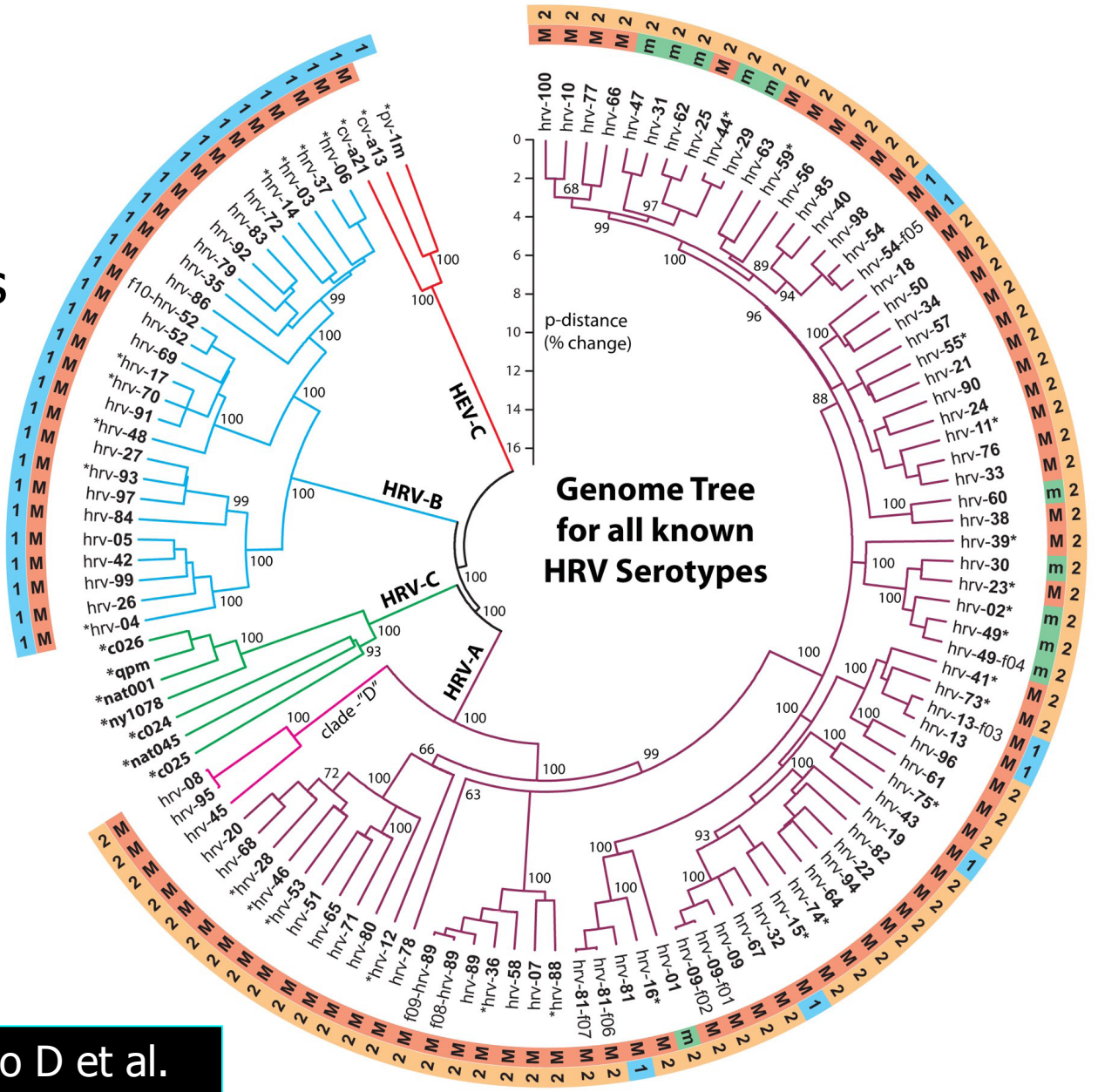
Virulent strains?

Virus Factors: Rhinovirus

- Rhinoviruses are the most prevalent human pathogen
- May produce a range of respiratory tract illnesses
- Seasonal: early fall and late spring in temperate climates
- Until recently, 101 strains identified and categorized genetically into 2 groups: A and B
- Recently, a new Group C has been identified
- Virulence patterns currently under investigation

Lee W-M et al. PLoS ONE 10:966, 2007

Sequencing and Analyses of All Known Human Rhinovirus Genomes Reveals Structure and Evolution



Palmenberg A and Spiro D et al.
Science 2009;324:55-59

HRV-C and Asthma Exacerbations

- Prospective population-based surveillance[1]

  Nashville TN and Rochester NY

  1052 children age <5 yrs hospitalized with ARI or fever

  HRV-C vs. HRV-A:

  - ↑ discharge diagnosis of asthma (55% vs 36%, *P* = .022)

- ED Asthma Study (2-16 y/o)[2]

  Perth, Australia

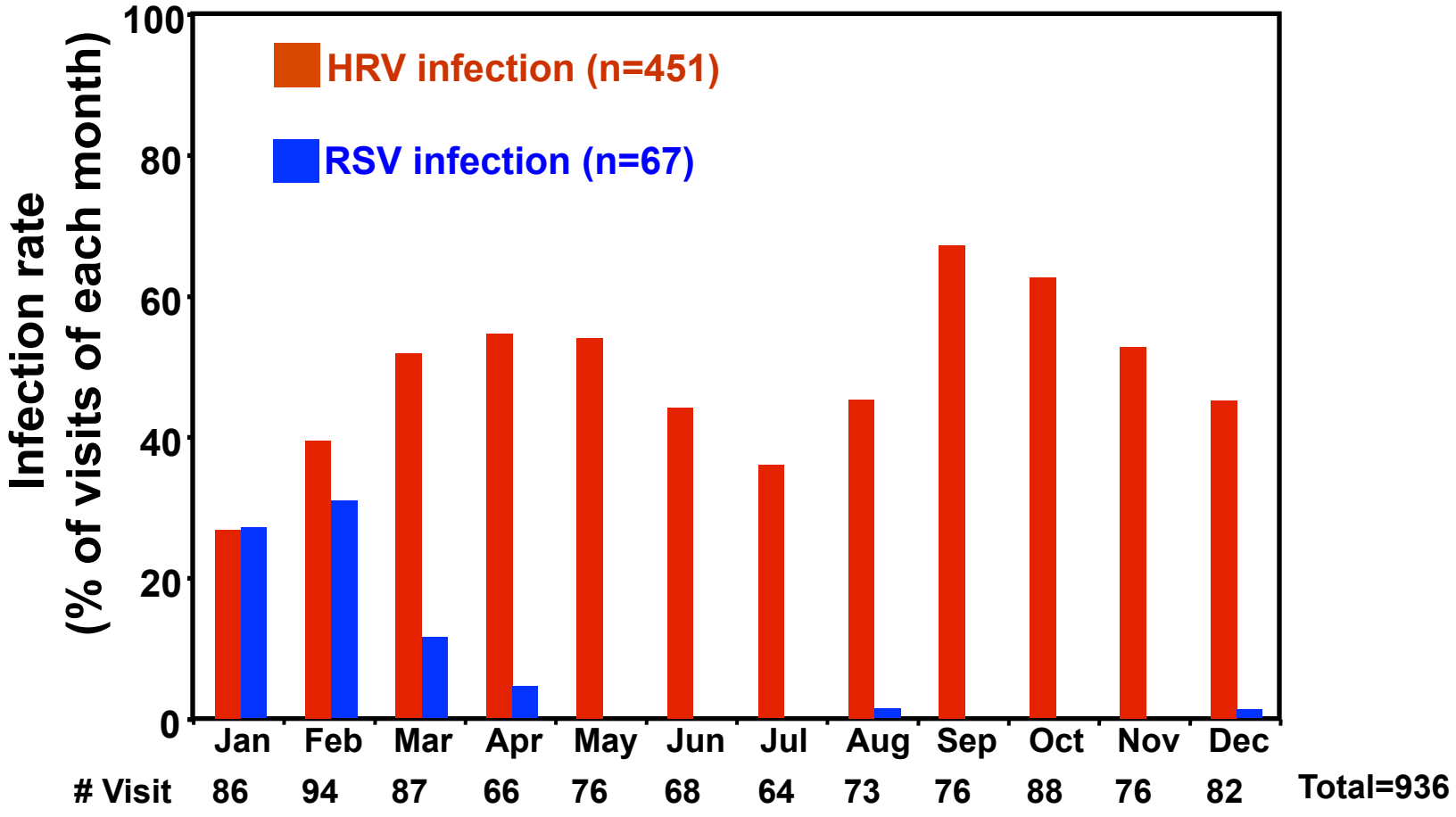
  HRV C detected in 59% of children:

  - ↑ severity in HRV C vs. A or B

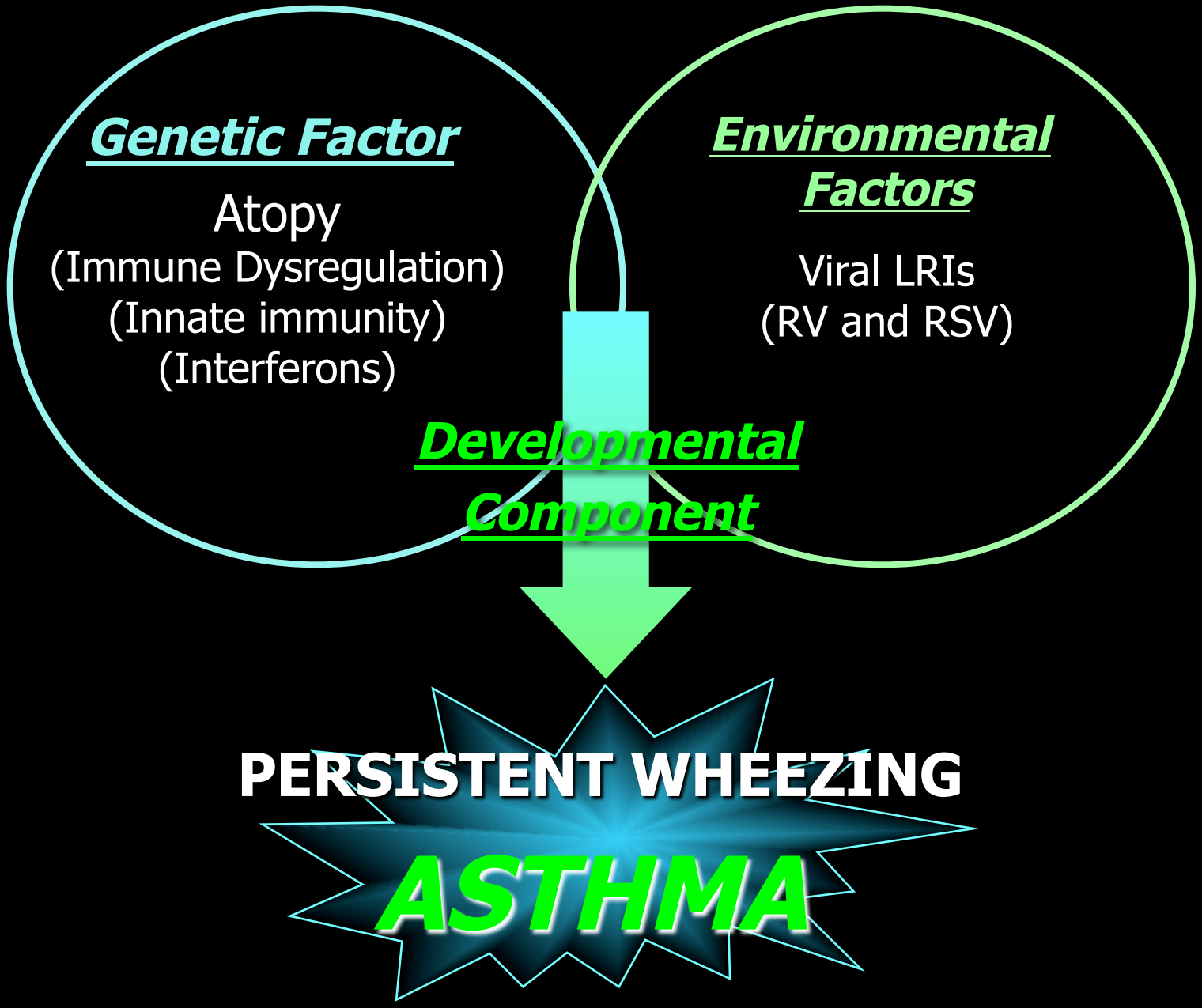
1 Miller EK et al. JACI 2009
2 Bizzintino J et al. ERJ 2011

HRV infections and illnesses in COAST during infancy

HRV infection of infant occurs year-round.



HRV Strain Virulence


Genetic Factor
Atopy
(Immune Dysregulation)
(Innate immunity)
(Interferons)
Environmental Factors
Viral LRIs
(RV and RSV)
Developmental Component
PERSISTENT WHEEZING
ASTHMA

COAST Personnel

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