

# Potential public health impact of RSV vaccines

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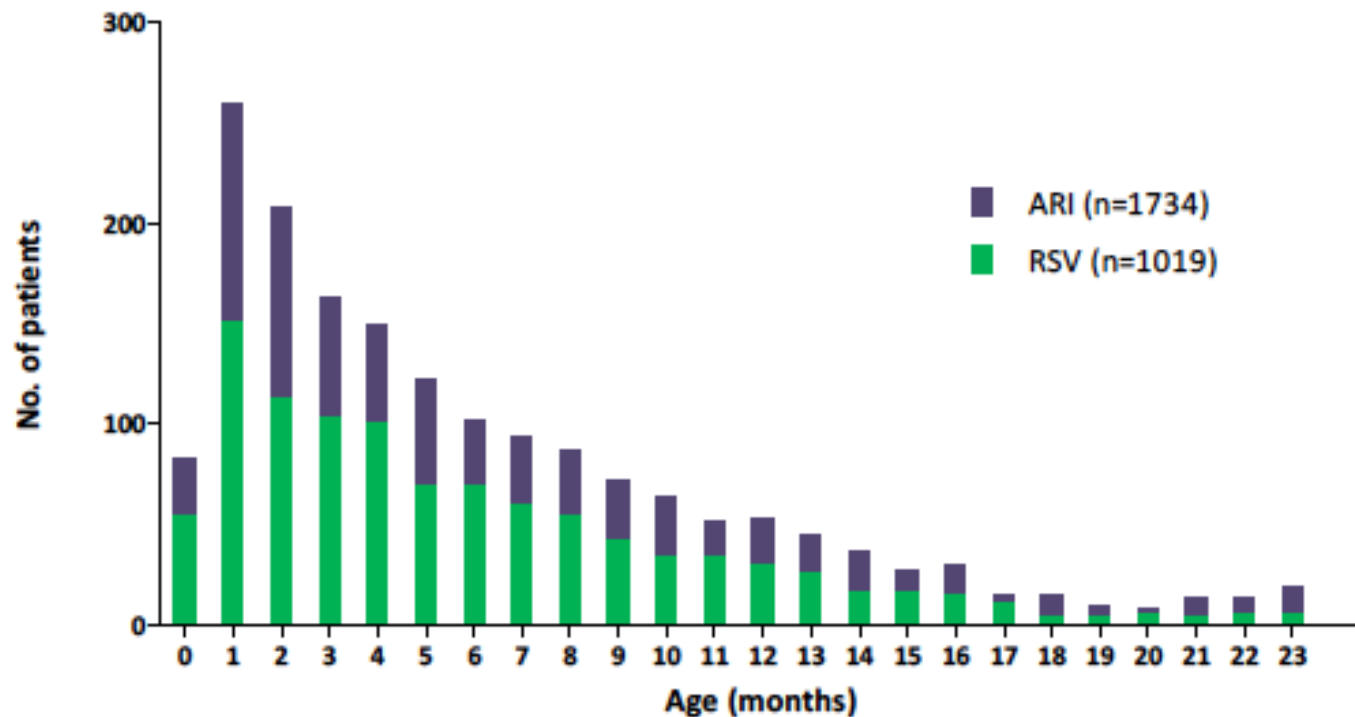
# RSV is...

- The leading cause of hospitalization in infants and in many high-income countries; >2 million medical visits annually in US children U5
- The cause of >33 million cases of ALRI, 3.4 million cases of severe ALRI, and 160,000 global deaths (2005 estimates)



# Burden of RSV is largely postneonatal

## A. HOSPITALIZATIONS



# RSV Vaccine and mAb Snapshot

## 62 candidates total; 19 in clinical trials

TARGET INDICATION: P = PEDIATRIC M = MATERNAL E = ELDERLY T = TBD

	PRECLINICAL				PHASE 1		PHASE 2	PHASE 3	MARKET APPROVED
LIVE-ATTENUATED/ CHIMERIC	AmVac Sendai virus	Intravacc Delta-G RSV	Meissa Vaccines RSV	Sanofi Pasteur RSV	LID/NIAID/NIH <sup>P</sup> RSV LID ΔM2-2	LID/NIAID/NIH <sup>P</sup> RSV D46 cpΔM2-2	MedImmune, LID/NIAID/NIH <sup>P</sup> RSV cps2		
	Codagenix RSV	LID/NIAID/NIH PIV1-3/RSV	Pontificia Universidad Catolica de Chile BCG/RSV	St. Jude Hospital SeV/RSV	LID/NIAID/NIH <sup>P</sup> RSV ΔNS2 Δ1313	MedImmune, LID/NIAID/NIH <sup>P</sup> RSV Medi ΔM2-2			
WHOLE-INACTIVATED	NanoBio RSV								
PARTICLE-BASED	AgilVax VLP	Fraunhofer VLP	Ruhr-Universität Bochum VLP	University of Massachussetts VLP	Novavax <sup>P</sup> RSV F Nanoparticle			Novavax <sup>M</sup> RSV F Nanoparticle	Maternal
	Artificial Cell Technologies Peptide microparticle	Georgia State University VLP	TechnoVax VLP	VBI Vaccines RSV F eVLP				Novavax <sup>E</sup> RSV F Nanoparticle	
	DBV Technologies/INRA RSV N/F rings	Mucosis BLP RSV pre-F	University of Massachussetts VLP	VLP Biotech VLP					
SUBUNIT	Advaccine Biotech RSV G+CSA	Instituto de Salud Carlos III RSV F protein	NIH/NIAID/VRC RSV pre-F Protein	University of Saskatchewan RSV F protein	University of Illinois RSV F protein	GlaxoSmithKline <sup>M</sup> RSV post-F Protein	GlaxoSmithKline <sup>M</sup> RSV F protein	Maternal	
	GlaxoSmithKline RSV F protein	Janssen Pharmaceutical RSV pre-F Protein	PeptiVir RSV peptides	University of Georgia RSV G protein	Immunovaccine/ <sup>E</sup> VIB DPX-RSV-SH Protein	MedImmune <sup>E</sup> RSV F protein			
NUCLEIC ACID	CureVac RNA	GlaxoSmithKline RNA	Inovio Pharmaceuticals DNA	Ruhr-Universität Bochum DNA					
GENE-BASED VECTORS	AlphaVax Alphavirus	GenVec Adenovirus	University of Pittsburg Adenovirus		Bavarian Nordic <sup>T</sup> MVA	Janssen Pharmaceutical <sup>P</sup> Adenovirus			
	Emergent BioSolutions MVA	Ruhr-Universität Bochum Adenovirus	Vanderbilt University Alphavirus		GlaxoSmithKline <sup>P</sup> Adenovirus	Vaxart <sup>E</sup> Adenovirus			
COMBINATION/IMMUNO-PROPHYLAXIS	Biomedical Research Models DNA prime, particle boost	Fudan University DNA+protein combo	UCAB/mAbXience Anti-F mAb				MedImmune <sup>P</sup> Anti-F mAb	Regeneron <sup>P</sup> Anti-F mAb	MedImmune <sup>P</sup> Synagis

Infant

Infant

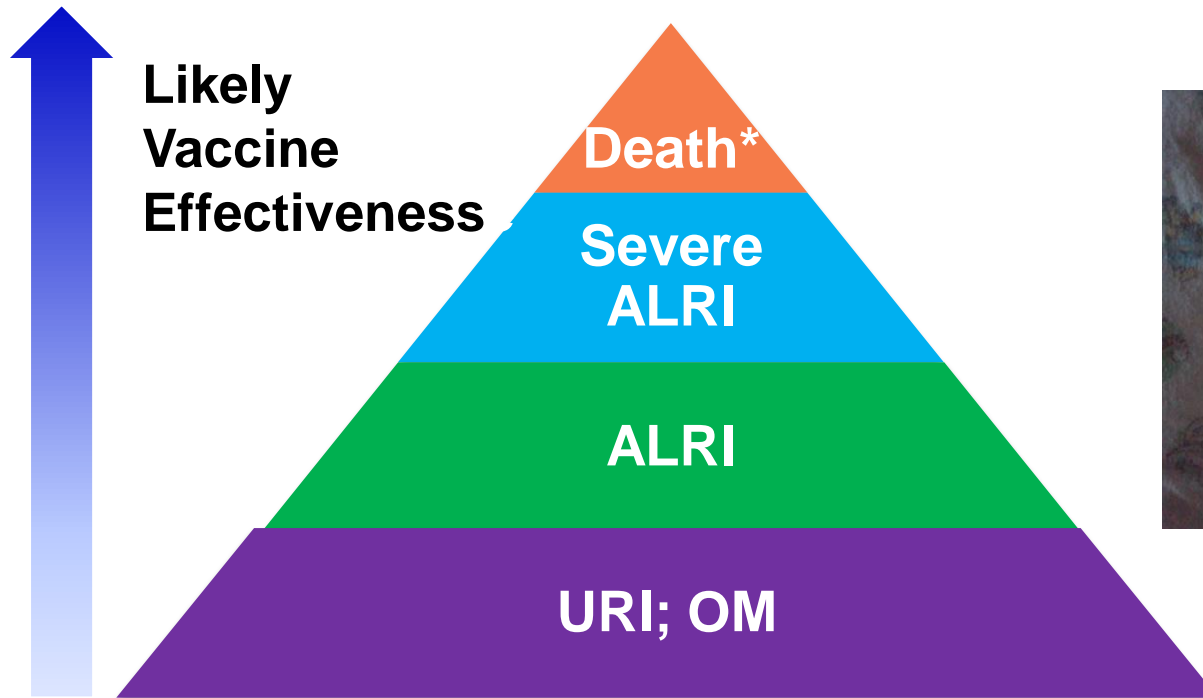
Infant

UPDATED: SEPTEMBER 23, 2016

<http://www.path.org/vaccineresources/details.php?i=1562>



# What type of acute RSV illness are we trying to prevent?



**The spectrum of acute RSV illness in children**

\* PERCH: RSV+ CFR=2.8%; 7.2% of all severe/very severe deaths

# RSV vaccine efficacy: focus on RSV LRTI

RSV+

LRTI

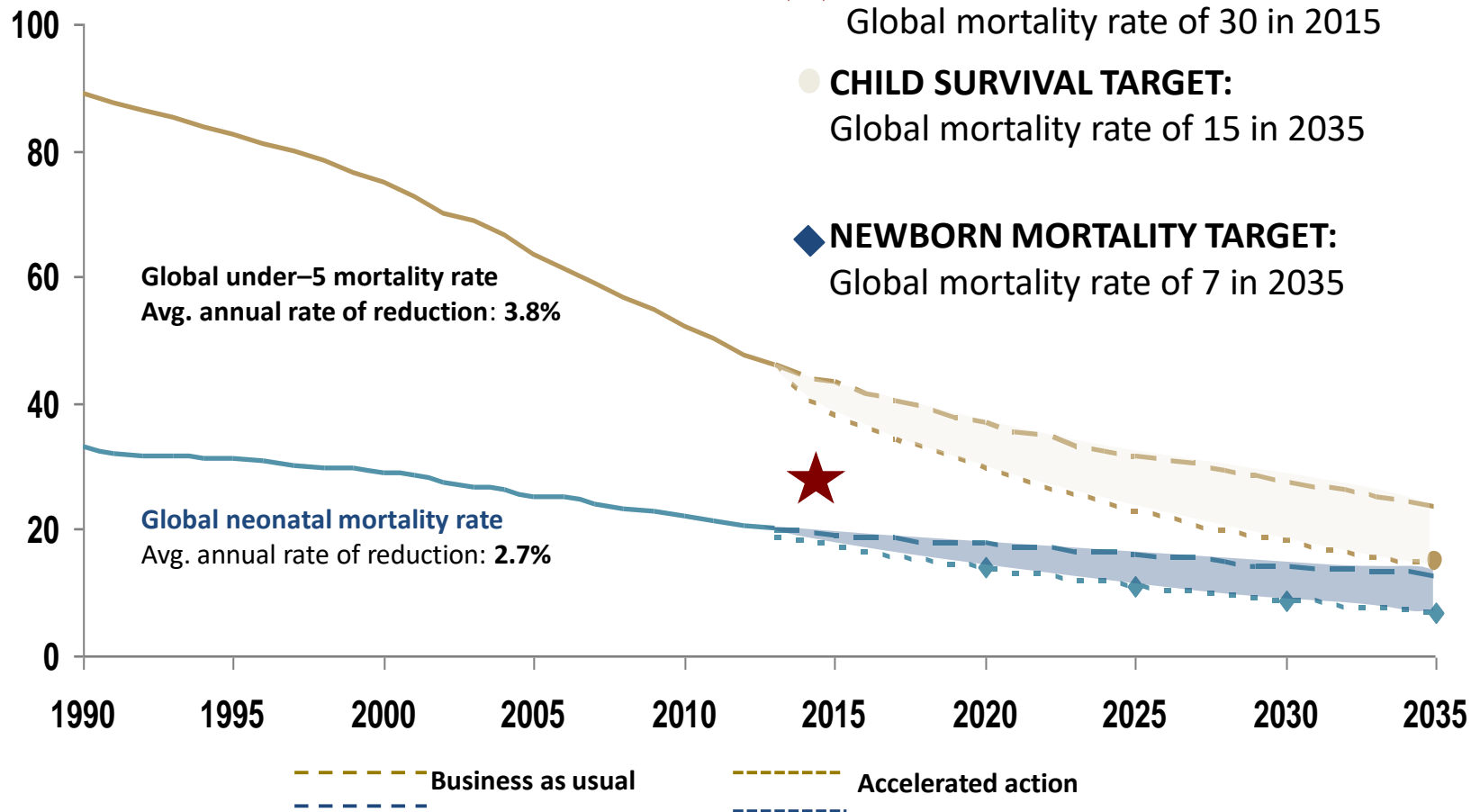
Pulse ox  
or other  
severity  
measure

Severe RSV LRTI	Very Severe RSV LRTI
<p>An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory <b>AND</b> clinical criteria below:</p> <p><b><u>Laboratory criterion</u></b> RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples.</p> <p><b><u>Clinical criteria</u></b> Respiratory Infection defined as Cough or Difficulty Breathing</p> <p><b>AND</b></p> <p>LRTI defined as FAST BREATHING by WHO criteria <b>OR</b> SpO2 &lt; 95%</p> <p><b>AND</b></p> <p>≥ 1 OF THE FOLLOWING FEATURES OF SEVERE DISEASE:</p> <p><b>Pulse oximetry &lt; 93%</b> <b>AND/OR</b> lower chest wall in-drawing</p>	<p>An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory <b>AND</b> clinical criteria below:</p> <p><b><u>Laboratory criterion</u></b> RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples.</p> <p><b><u>Clinical criteria</u></b> Respiratory Infection defined as Cough or Difficulty Breathing</p> <p><b>AND</b></p> <p>LRTI defined as FAST BREATHING by WHO criteria <b>OR</b> SpO2 &lt; 95%</p> <p><b>AND</b></p> <p>≥ 1 OF THE FOLLOWING FEATURES OF VERY SEVERE DISEASE:</p> <p><b>Pulse oximetry &lt; 90%</b> <b>AND/OR</b> Inability to feed <b>AND/OR</b> Failure to respond/unconscious</p>



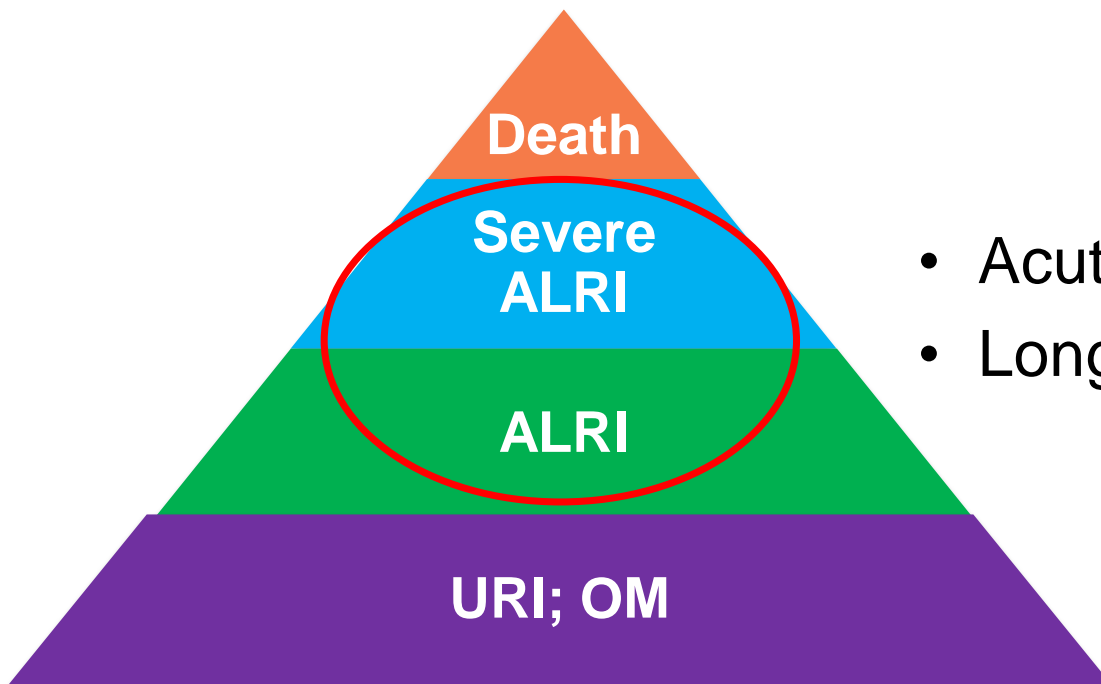
# Infant mortality is declining

Mortality rate per 1,000 live births



# The potential public health impact of RSV vaccines: focus on prevention of RSV ALRI

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- Acute indirect effects
- Long-term effects



# Acute indirect effects: viral-bacterial interactions

- RSV- pneumococcal interactions
- RSV and the microbiome



# Efficacy of PCV9 against pneumonia South Africa, HIV-uninfected Children

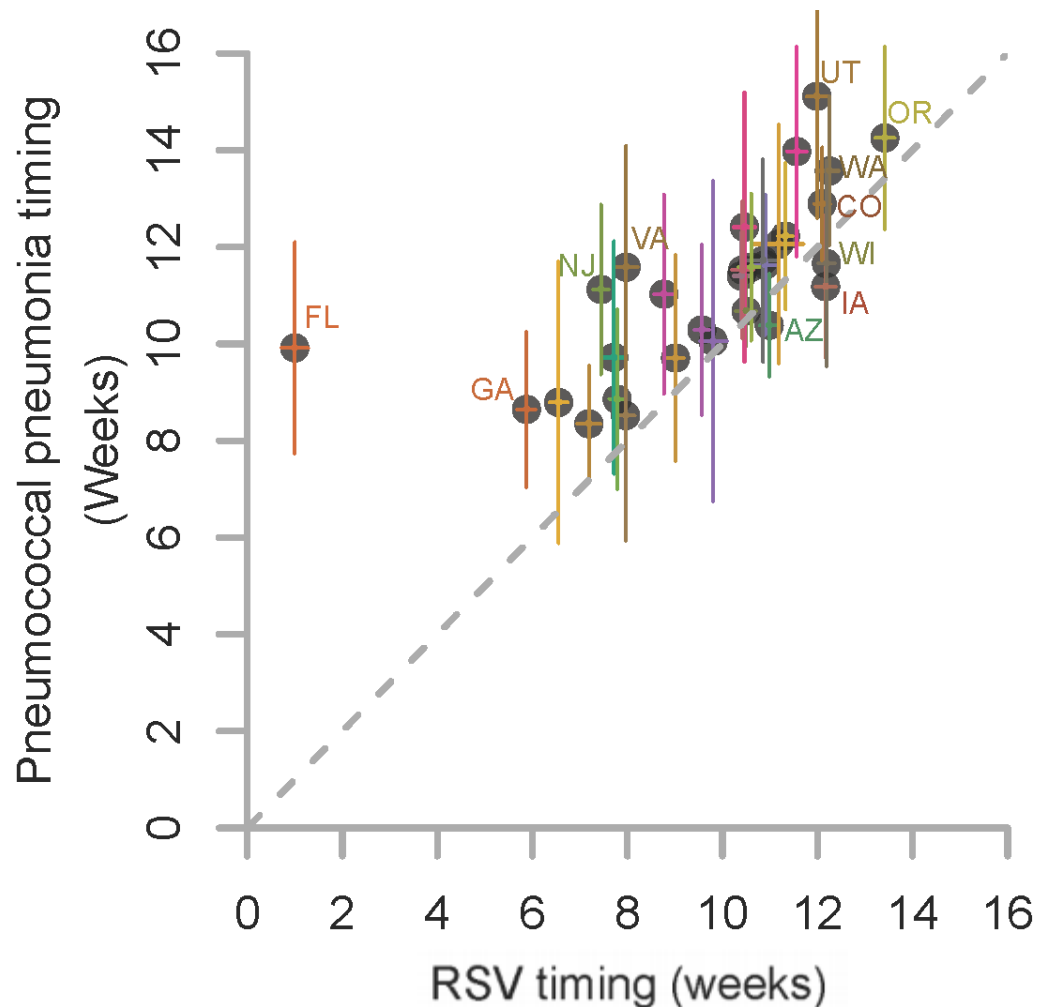
A role for *Streptococcus pneumoniae* in virus-associated pneumonia

Shabir A Madhi<sup>1</sup>, Keith P Klugman<sup>1,2</sup> & The Vaccine Trialist Group

Nature Med 2004

	PCV-9 (n= 17,065)	Placebo (n=17,086)	VE (95% CI)	P-value
First Episode of Pneumonia	348	452	23 (11, 33)	<0.001
Alveolar Consolidation	119	158	25 (4, 40)	0.02
Influenza A	21	32	34 (-14, 62)	0.1
RSV	64	94	32 (6, 50)	0.02
PIV 1-3	16	27	41 (-10, 68)	0.09

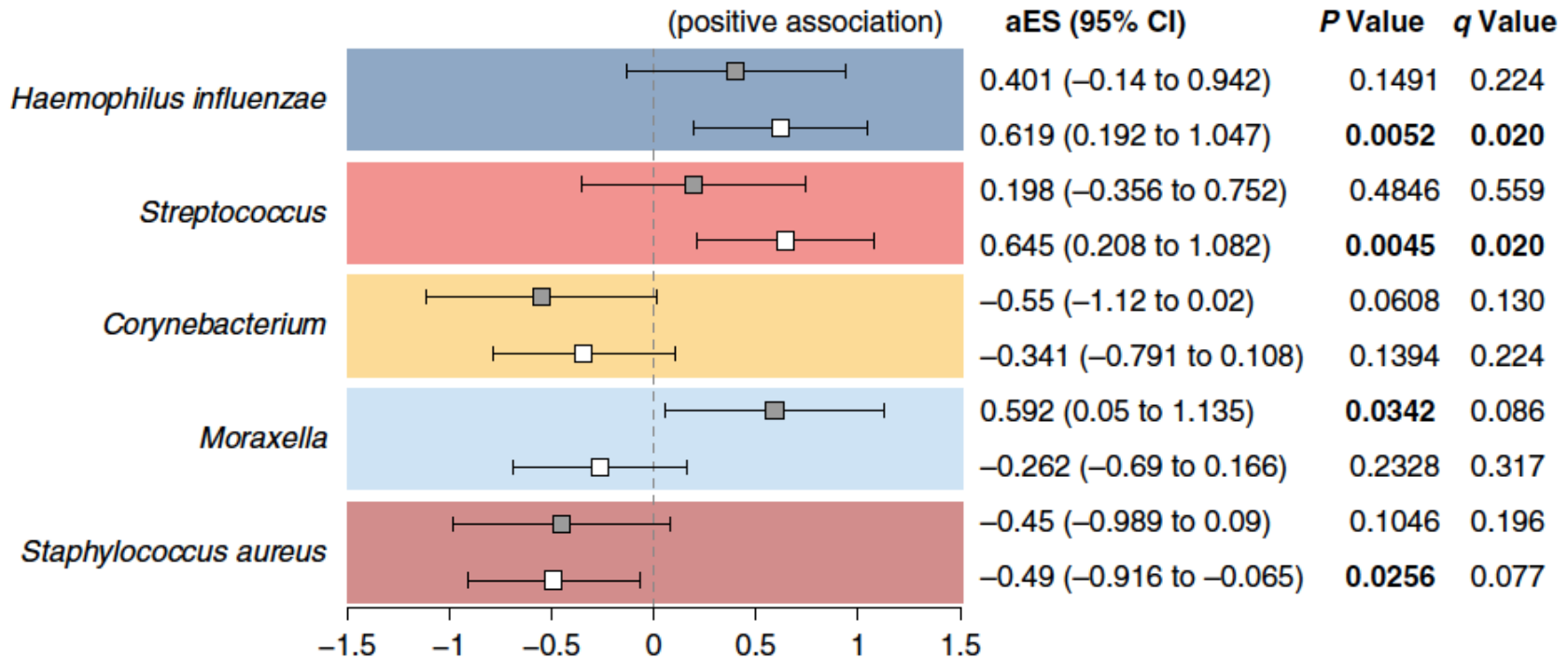
# Correlation between RSV hospitalizations & pneumococcal pneumonia hospitalizations




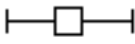
Average epidemic timing of pneumococcal pneumonia lagged behind RSV by 1.5 wks



# Interactions between RSV, nasal microbiome, and host response

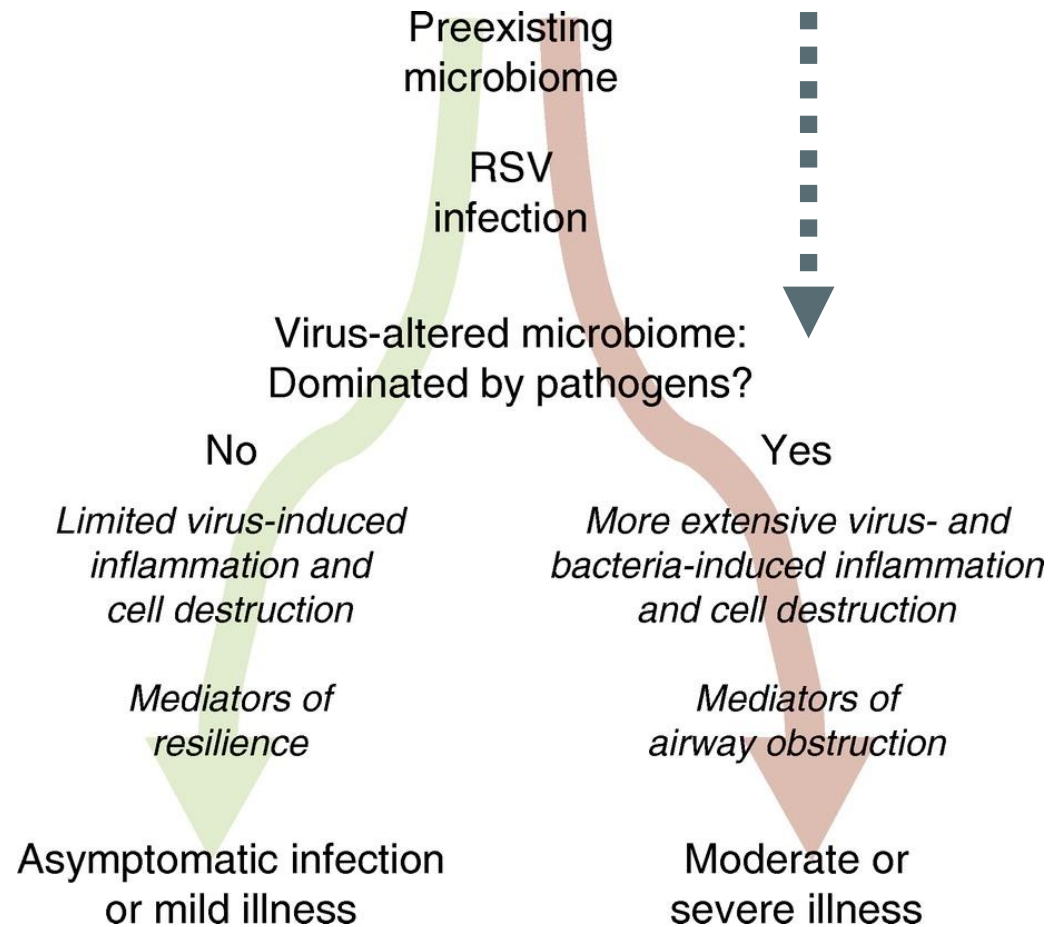


“Infants within HI and Strep enriched clusters mounted a distinct inflammatory response... [with] overexpression of genes related to TLR signaling and neutrophil recruitment and activation”

 **Outpatients**  
 **Inpatients**

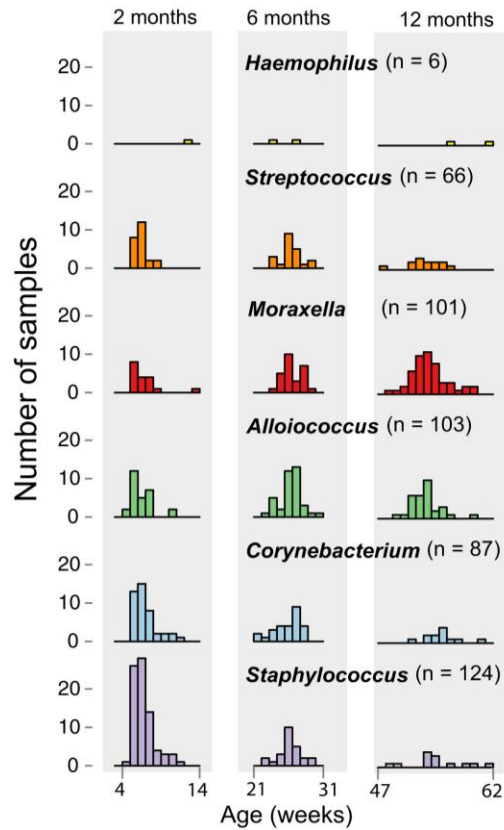


# Postulated interactions between RSV, the respiratory microbiome, & disease severity

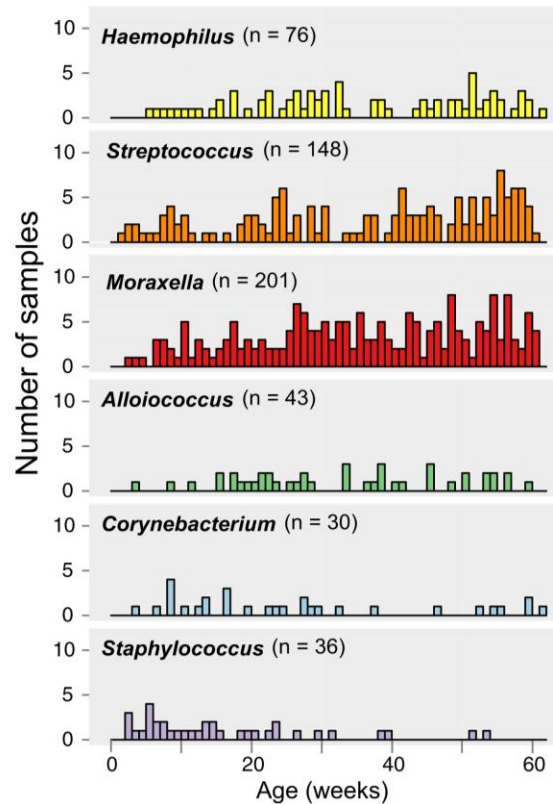


# Changes in infant respiratory microbiome over time and with illness

## C Healthy samples



## D Acute respiratory infections (ARI)



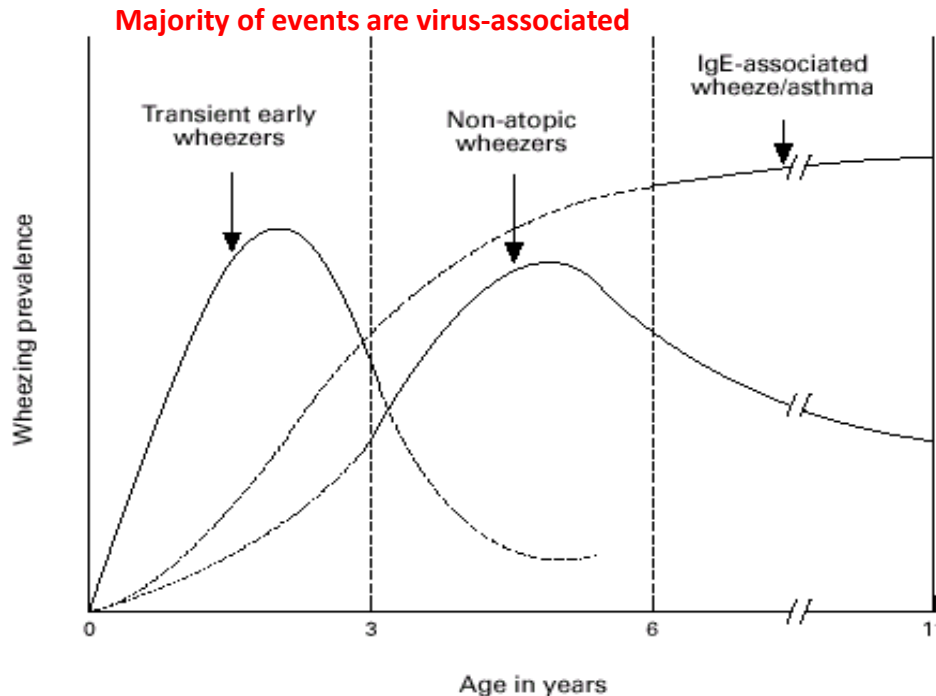
## E Association with ARI

	Adjusted for virus
-	
<b>11</b> (5.2 - 25) $p = 1.9e-9$	<b>12</b> (4.2 - 35) $p = 3.2e-6$
<b>2.0</b> (1.4 - 2.9) $p = 8.6e-5$	<b>1.6</b> (1.1 - 2.5) $p = 2.5e-2$
<b>1.8</b> (1.3 - 2.3) $p = 1.7e-4$	<b>2.2</b> (1.5 - 3.2) $p = 2.8e-5$
<b>0.41</b> (0.27 - 0.61) $p = 1.3e-5$	<b>0.43</b> (0.26 - 0.72) $p = 1.1e-3$
<b>0.38</b> (0.24 - 0.62) $p = 8.2e-5$	<b>0.35</b> (0.20 - 0.62) $p = 2.8e-4$
<b>0.29</b> (0.19 - 0.44) $p = 7.1e-9$	<b>0.37</b> (0.23 - 0.58) $p = 1.8e-5$

# **RSV and long-term effects on lung health**



# Wheezing in early life



- Primary risk for transient early wheeze is viral ALRI, not family history of allergy or asthma
- 60% of wheezing children under 3 years are transient early wheezers\*
- Burden of transient early wheeze itself is believed to be substantial—better metrics needed



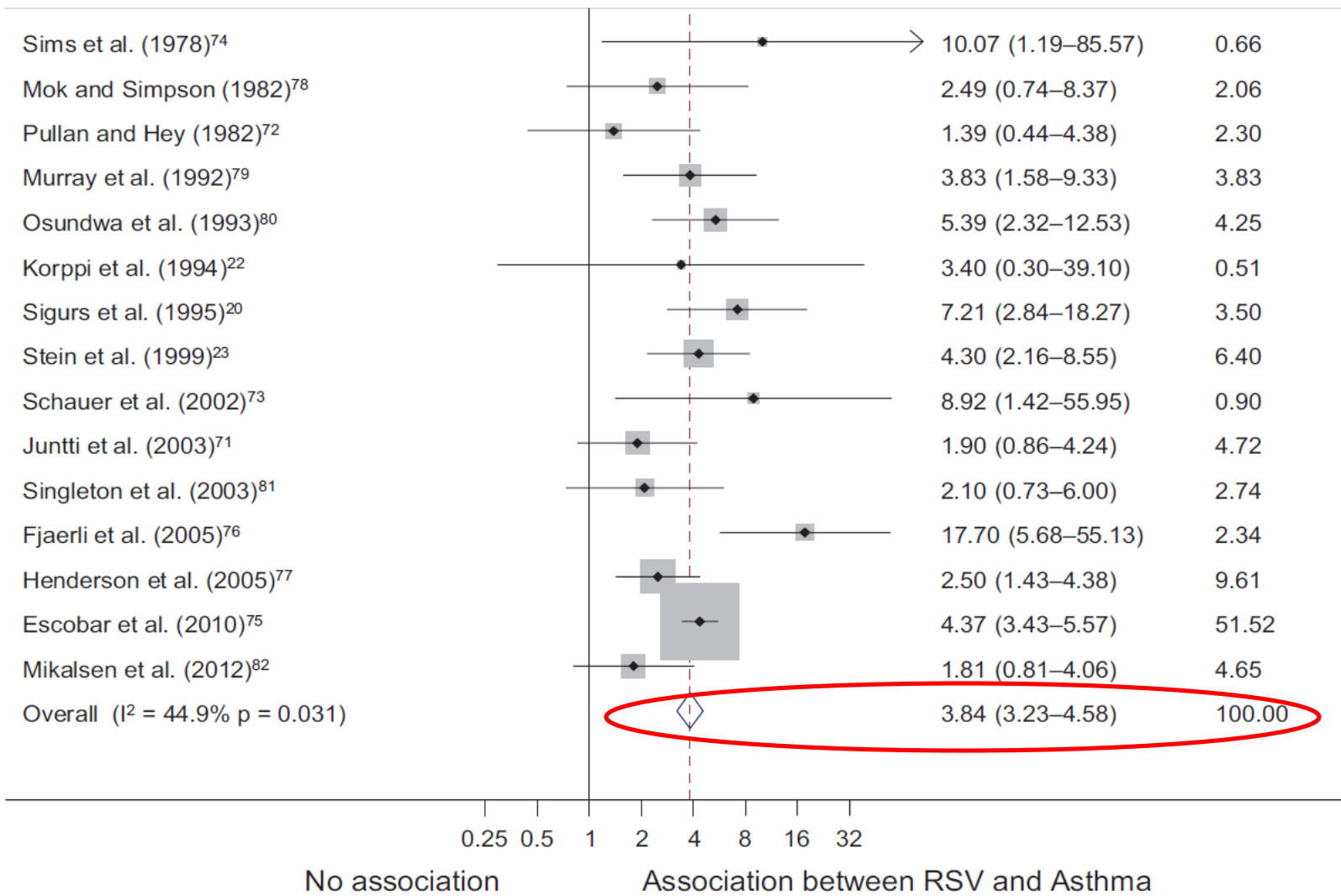


## **Evidence for links between early RSV disease and long-term lung health**

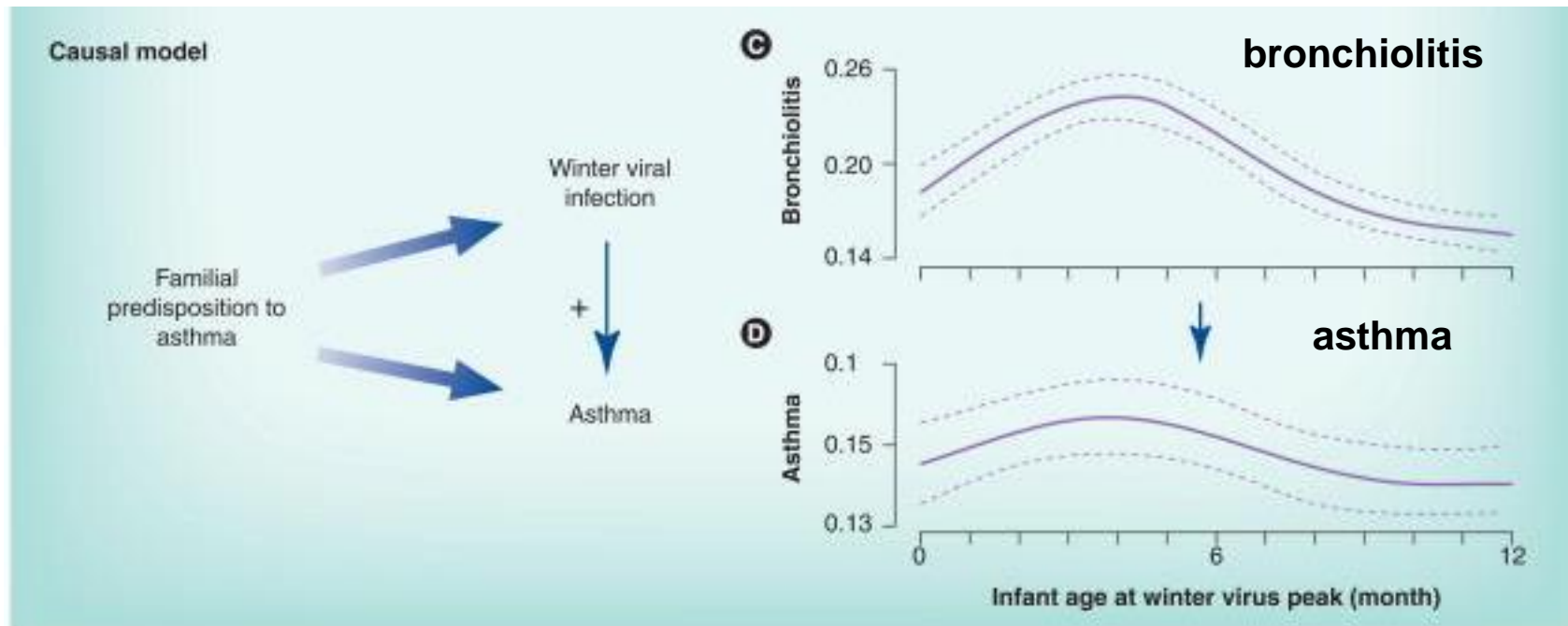
- Ecologic
- Intervention-based



# RSV associated with increased asthma risk consistently in all studies



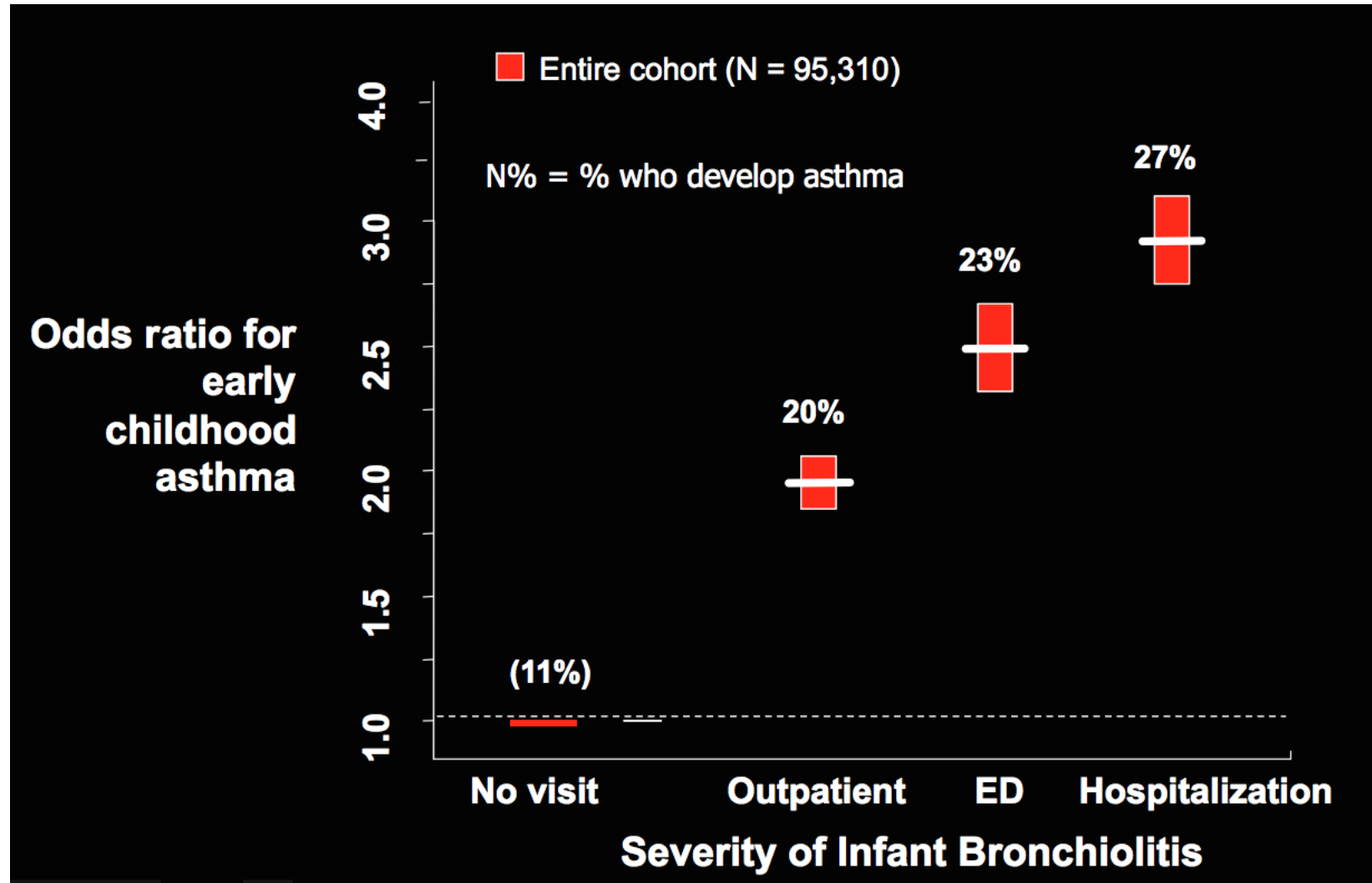
# Winter viral infections in the causal pathway for asthma



- Infants who were 4 months of age at the peak of winter viral season were more likely to develop both clinical bronchiolitis and childhood asthma at 5-6 years
- Risk of asthma shifted in any given year with the shift in the peak of the winter viral peak, such that infants born approximately 4 months prior to the first winter viral peak ...were at the highest risk of developing childhood asthma

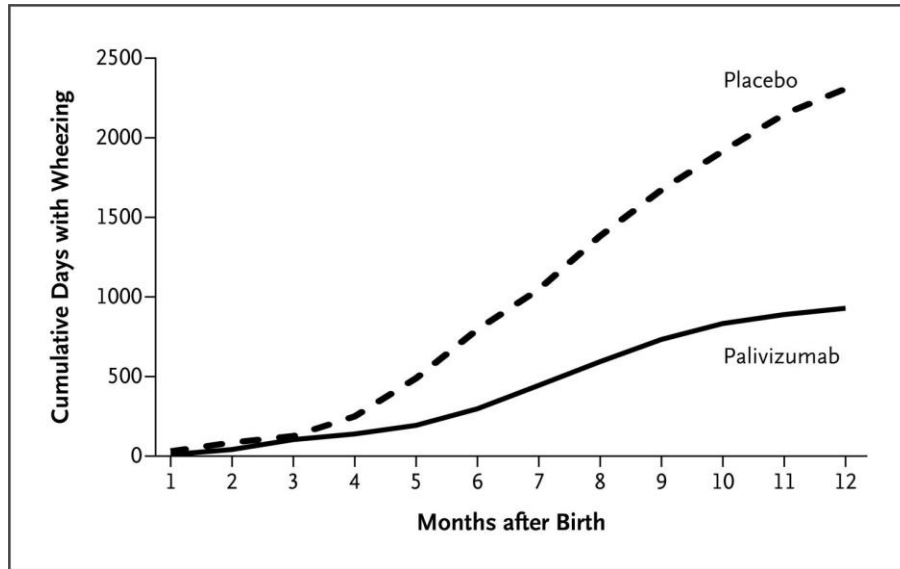


# Dose response relationship between asthma and RSV severity



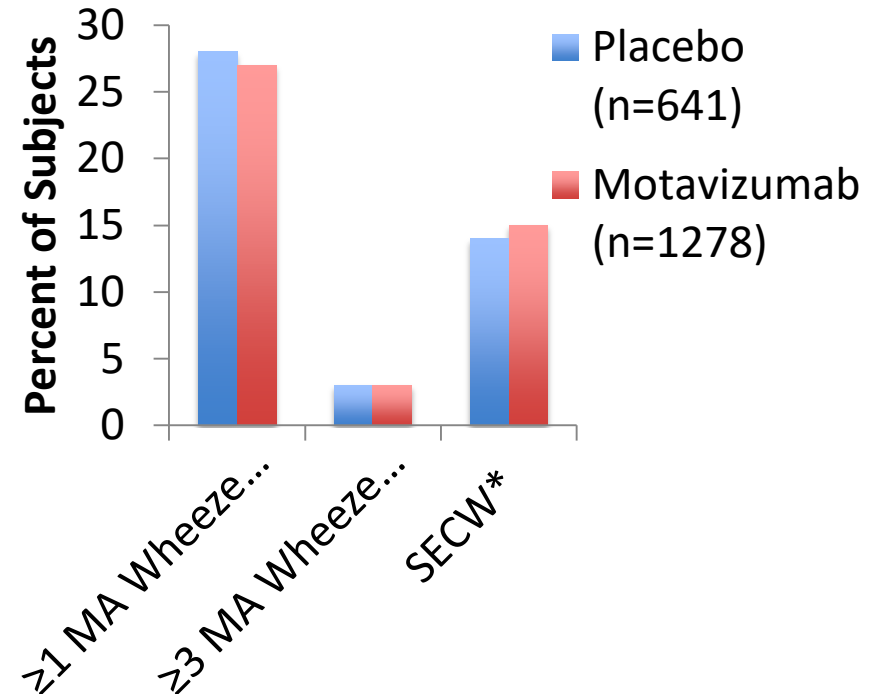
# RSV and wheezing: intervention studies

## Palivizumab in healthy late preterm



- Followed to 1 year
- Parent reported illness

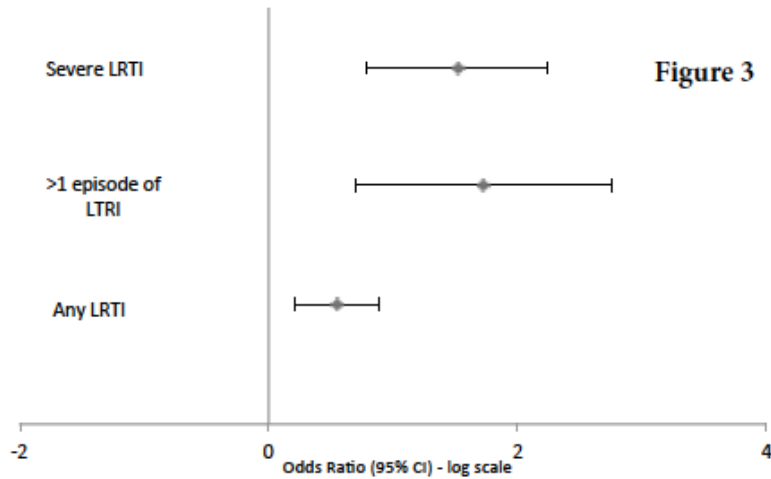
## Motavizumab in healthy term



- Followed to 3 years
- Medically-attended illness

# Beyond wheezing: Abnormal lung fcn in 1-yr-olds after ALRI in infancy

OR of increased RR (>50.6 breaths/minute)



- Children enrolled in the Drakenstein Child Health Study (n=648)
  - All episodes of ALRI assessed
  - Lung function measured at 6 weeks and 1 year
- Any ALRI associated with increased RR; repeated ALRI associated with diminished  $V_T$ , increased LCI (evidence of small airways disease)
- Abnormalities observed even when lung function was normal at 6 weeks



# How can we properly value RSV vaccines?

- Include assessments of all-cause pneumonia and ALRI during RSV vaccine efficacy assessments
  - Pathogen-pathogen interactions
  - Pathogen replacement
- Establish cohorts during efficacy trials that could be followed for long-term wheezing/ lung function outcomes
- Embrace the likely heterogeneity of impact of RSV vaccination on these indirect outcomes
  - Host factors and environmental factors will determine burden of these outcomes and may determine the impact of RSV LRI prevention on these outcomes
  - Heterogeneity of impact on these outcomes likely to be greater than heterogeneity in prevention of severe RSV ALRI
  - Data should be obtained from multiple settings; models should take heterogeneity into account



Thank you

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