Potential public health impact of RSV vaccines

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December 2016

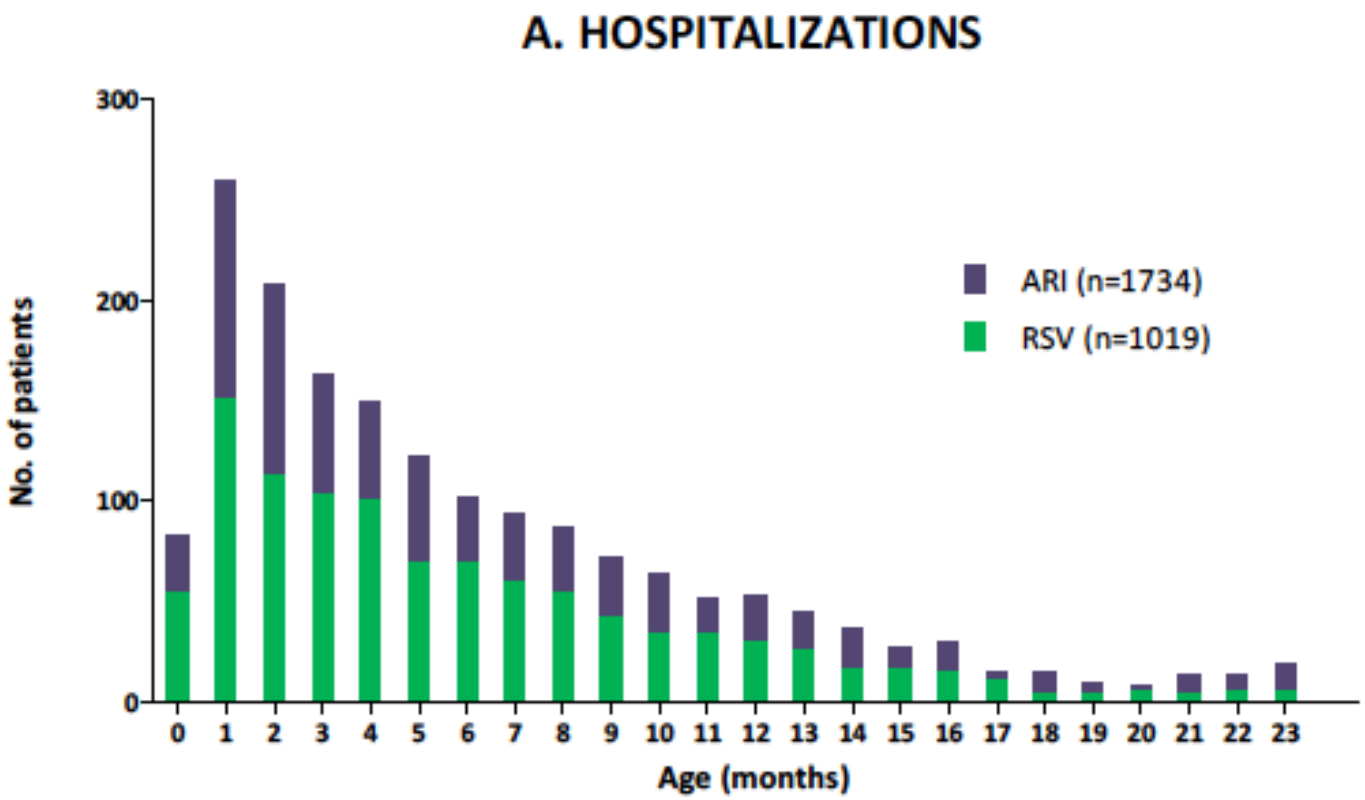
RSV is…

- 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)

1. Hall CB. N Engl J Med. 2009 Feb 5;360(6):588-98.
2. Nair H. Lancet. 2010 May 1;375(9725):1545-55.

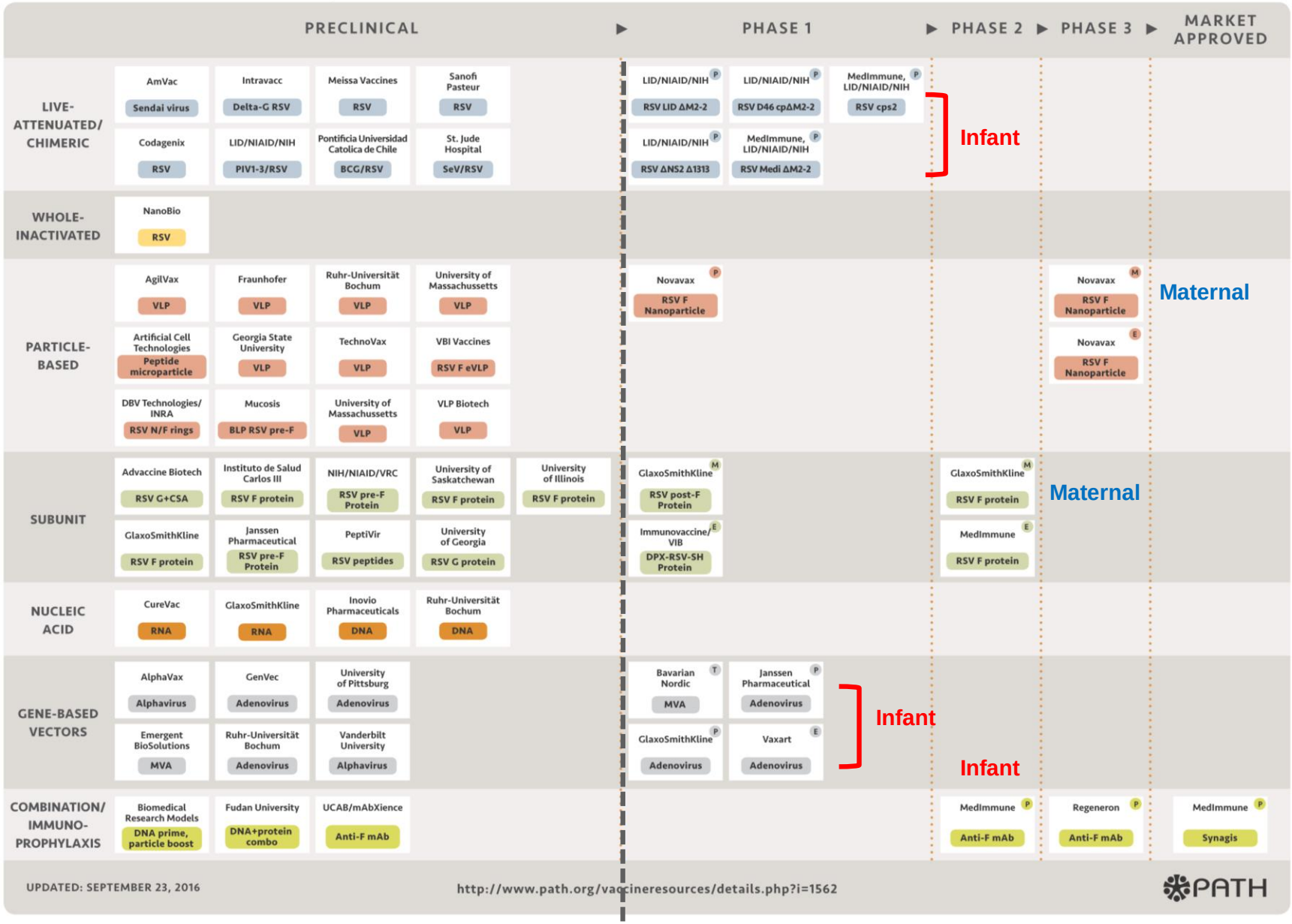
Burden of RSV is largely postneonatal



Ferolla FM et al. Am J Respir Crit Care Med. 2013 May 1;187(9):983-90.

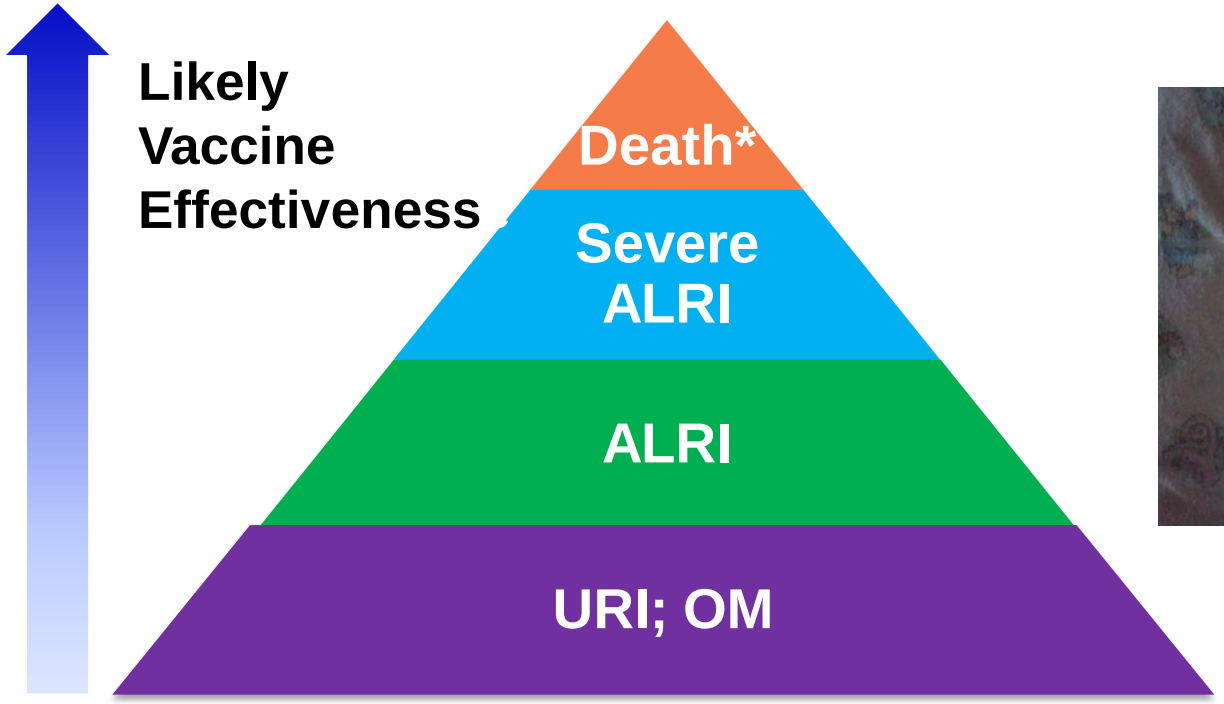
RSV Vaccine and mAb Snapshot

62 candidates total;19 in clinical trials



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

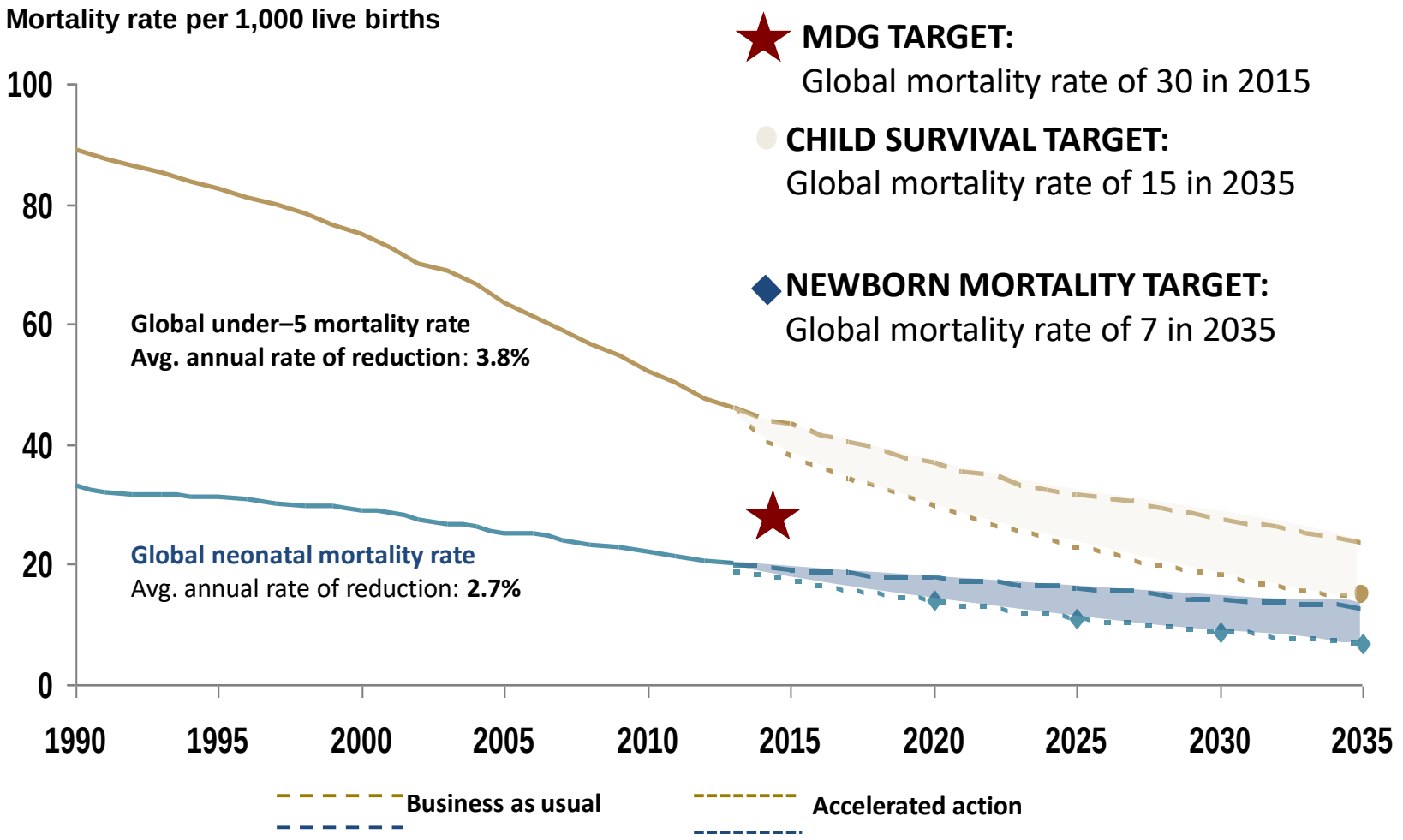
* PERCH: RSV+ CFR=2.8%; 7.2% of all severe/very severe deaths

RSV vaccine efficacy: focus on RSV LRTI

	Severe RSV LRTI	Very Severe RSV LRTI
	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 **AND** clinical criteria below:	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 **AND** clinical criteria below:
RSV+	***Laboratory criterion*** RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples.	***Laboratory criterion*** RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples.
	Clinical criteria Respiratory Infection defined as Cough or Difficulty Breathing	***Clinical criteria*** Respiratory Infection defined as Cough or Difficulty Breathing
	AND	**AND**
LRTI	LRTI defined as FAST BREATHING by WHO criteria **OR** SpO2 < 95%	LRTI defined as FAST BREATHING by WHO criteria **OR** SpO2 < 95%
	AND	**AND**
Pulse ox or other severity measure	≥ 1 OF THE FOLLOWING FEATURES OF SEVERE DISEASE: **Pulse oximetry < 93%** **AND/OR** lower chest wall in-drawing	≥ 1 OF THE FOLLOWING FEATURES OF VERY SEVERE DISEASE: **Pulse oximetry < 90%** **AND/OR** Inability to feed **AND/OR** Failure to respond/unconscious

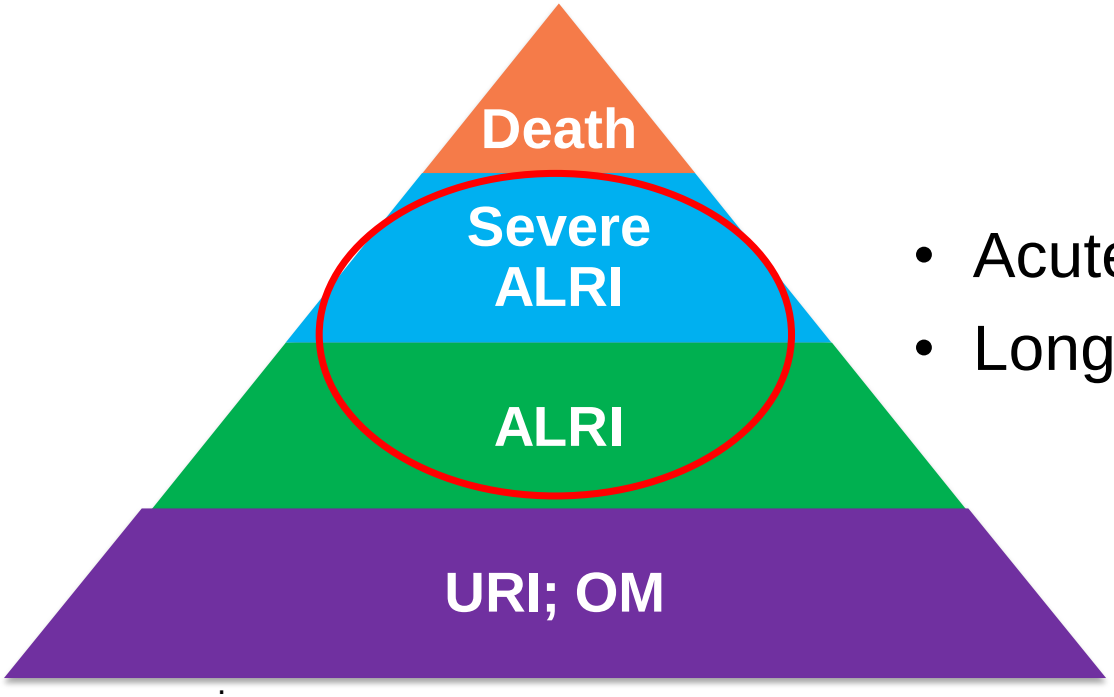
Modjarrad K et al, Vaccine 2015 Jun 20. pii: S0264-410X(15)00767-7.

Infant mortality is declining



Source: The Lancet Every Newborn Series, Lawn JE et al. Lancet, 2014 (1)

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



- 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

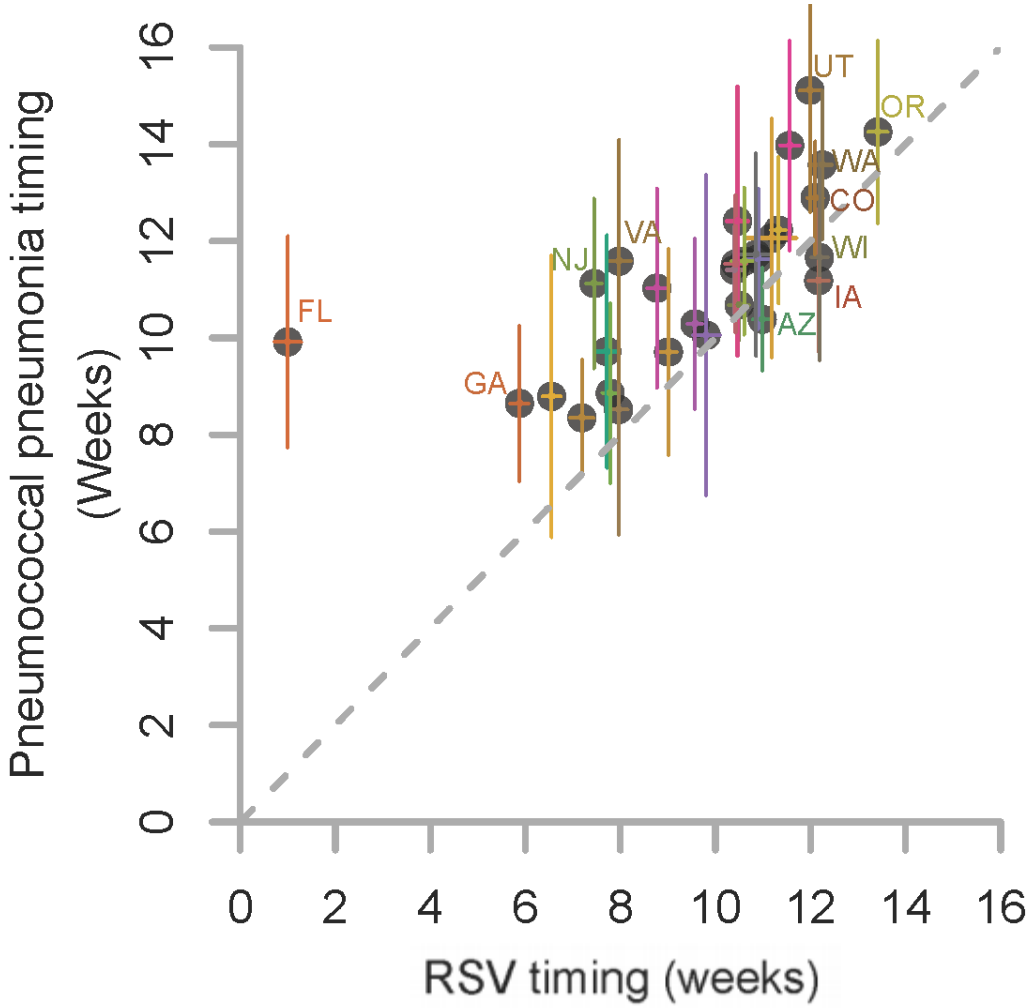
A role for *Streptococcus pnemoniae* in virus-associated pneumonia

Shabir A Madhi[1], Keith P Klugman[1,2] & 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

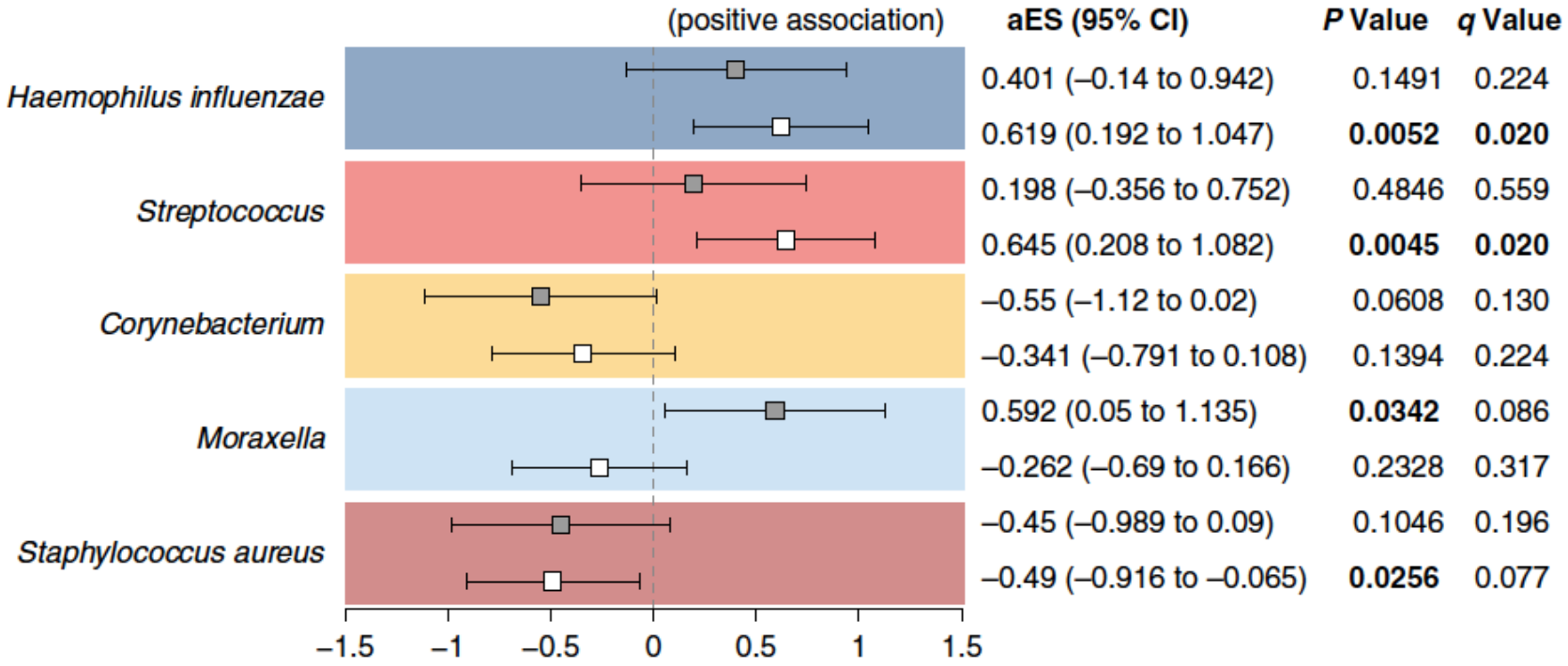
Correlation between RSV hospitalizations & pneumococcal pneumonia hospitalizations



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

Weinberger et al. 2015

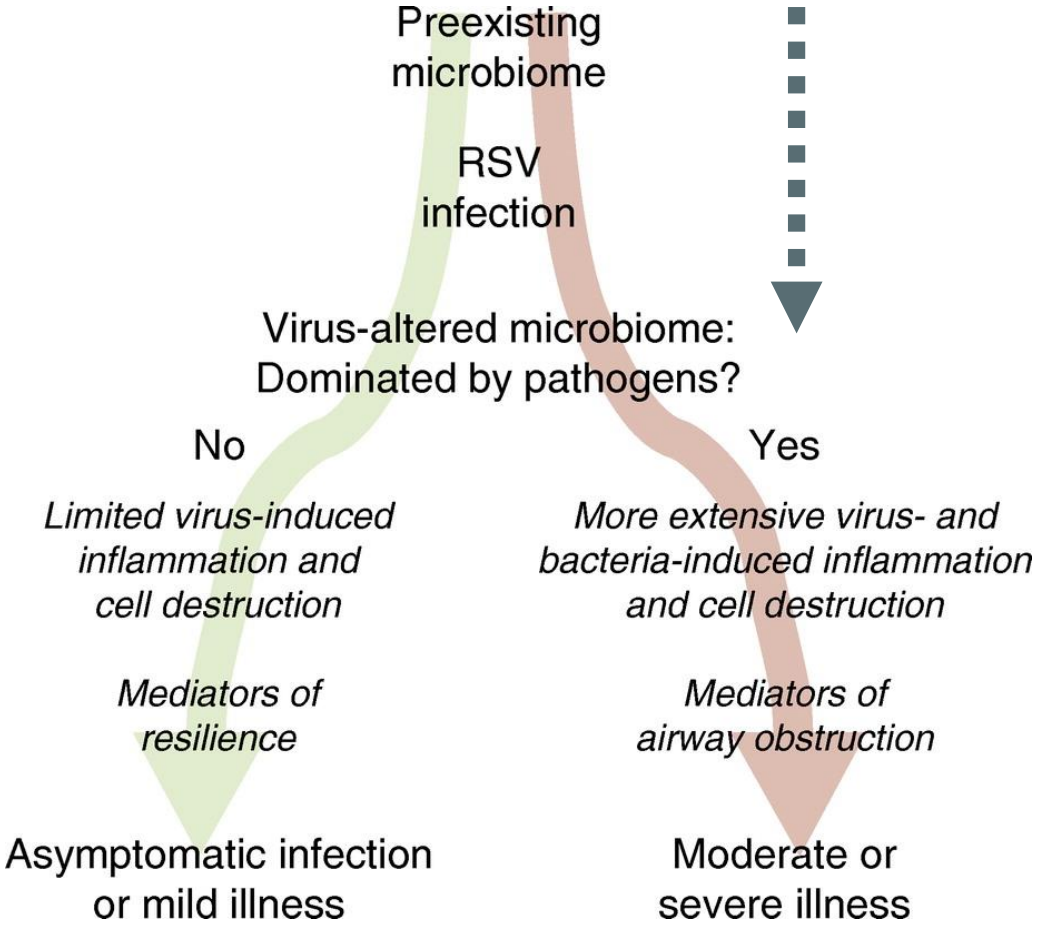
Interactions between RSV, nasal microbiome, and host response



"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"

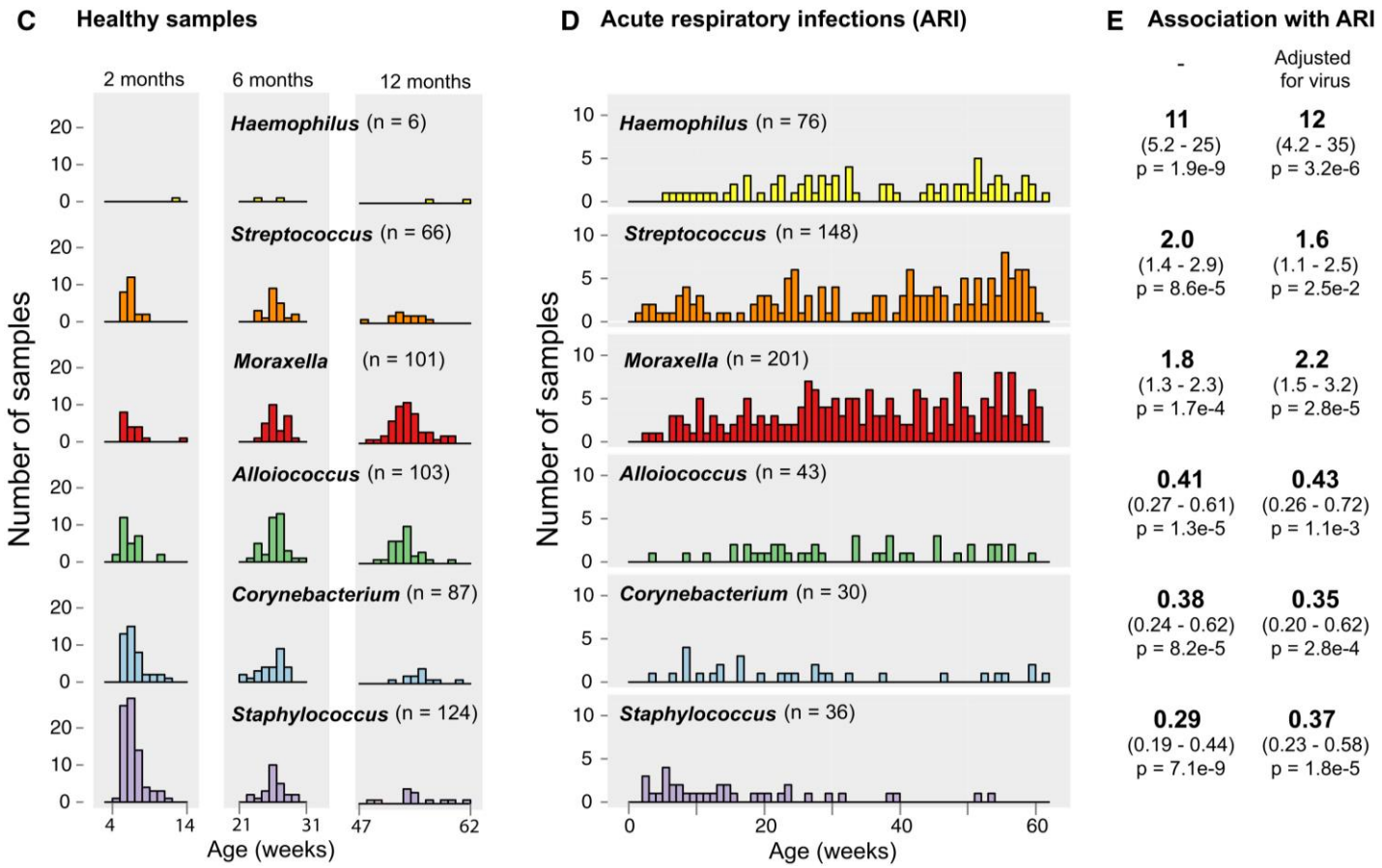
de Steenhuijsen Piters WA et al Am J Respir Crit Care Med. 2016 Nov 1;194(9):1104-1115.

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



Gern JE Am J Respir Crit Care Med. 2016 Nov 1;194(9):1044-1045

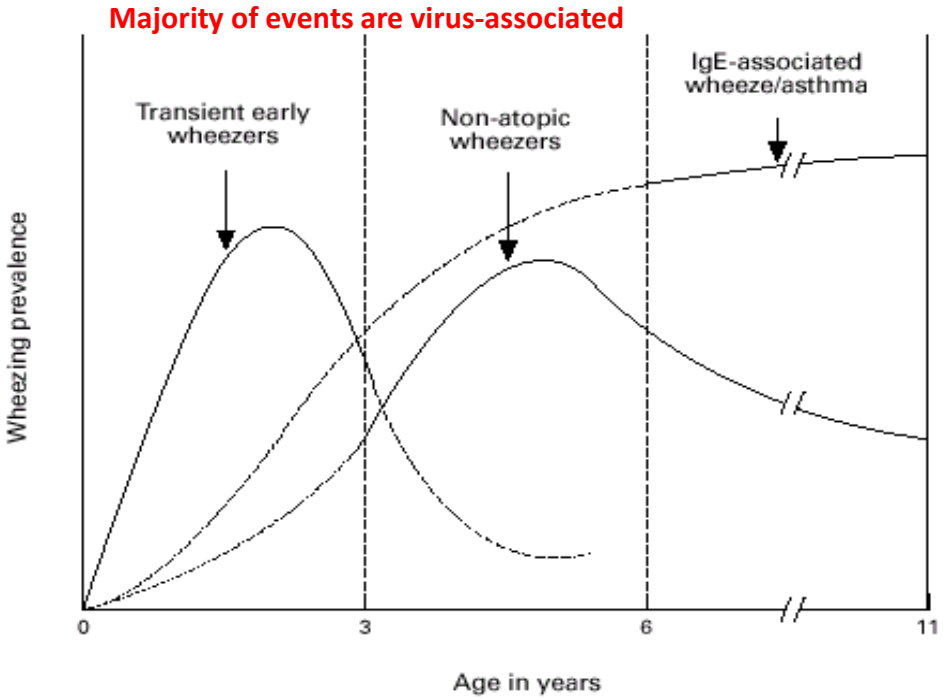
Changes in infant respiratory microbiome over time and with illness



Cell Host & Microbe 2015 17, 704-715DOI: (10.1016/j.chom.2015.03.008)

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

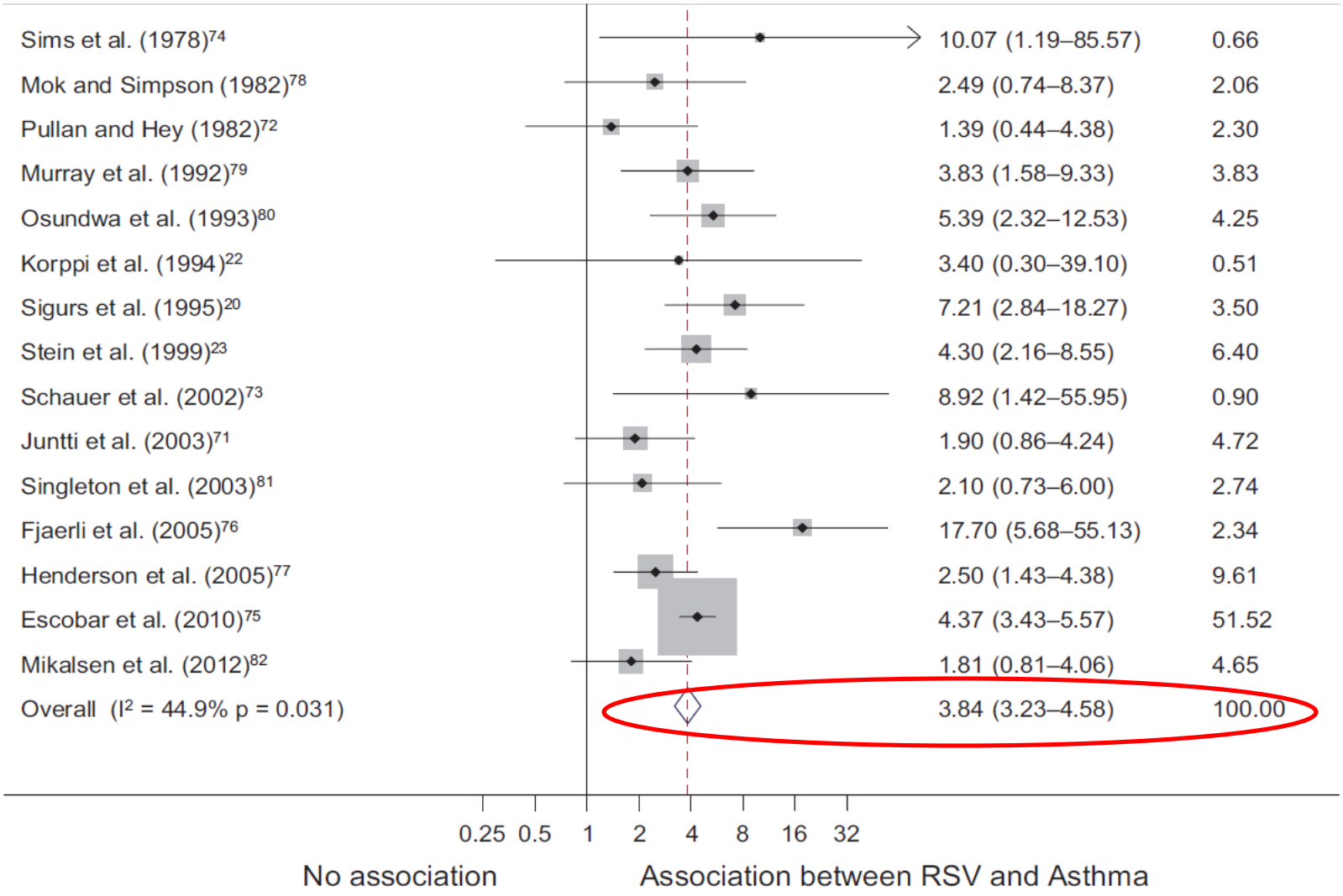
* US data

Stein RT et al. Lancet 1999

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

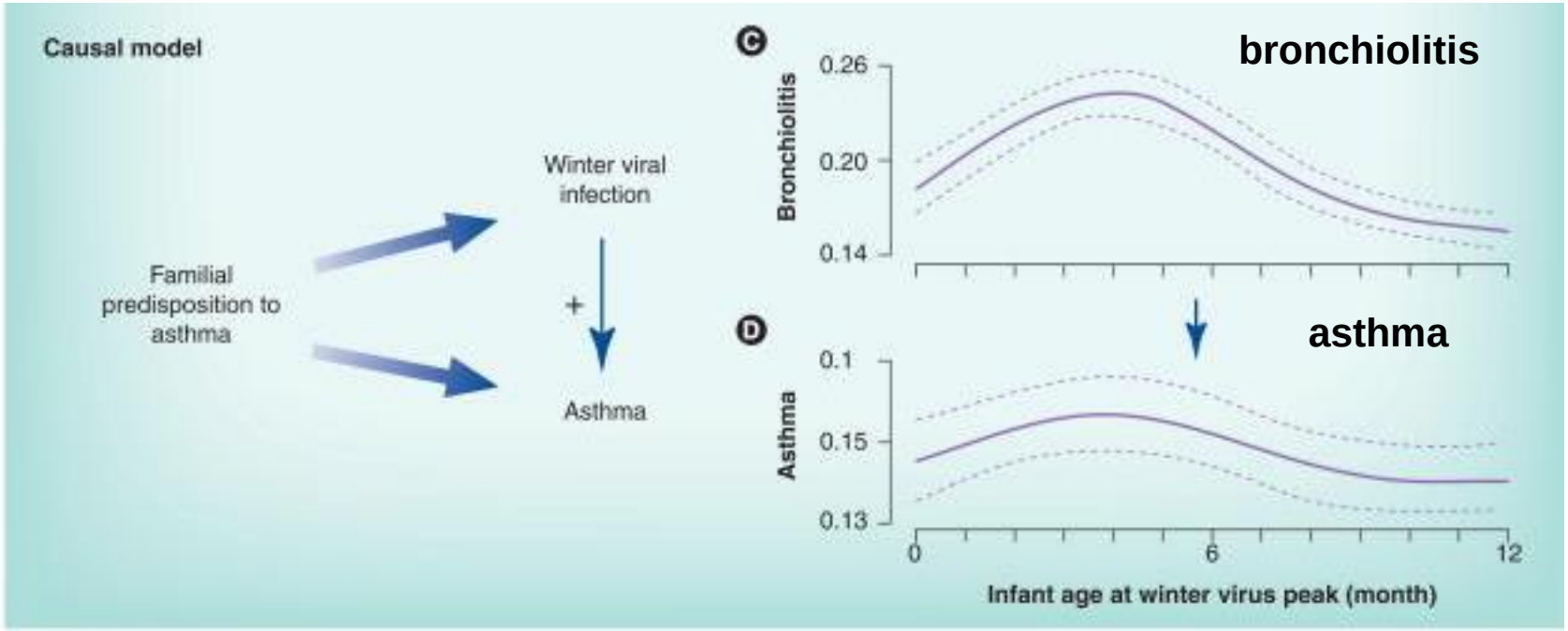
- Ecologic
- Intervention-based

RSV associated with increased asthma risk consistently in all studies



Regnier SA et al. *Pediatr Infect Dis J* 2013;32:820-26.

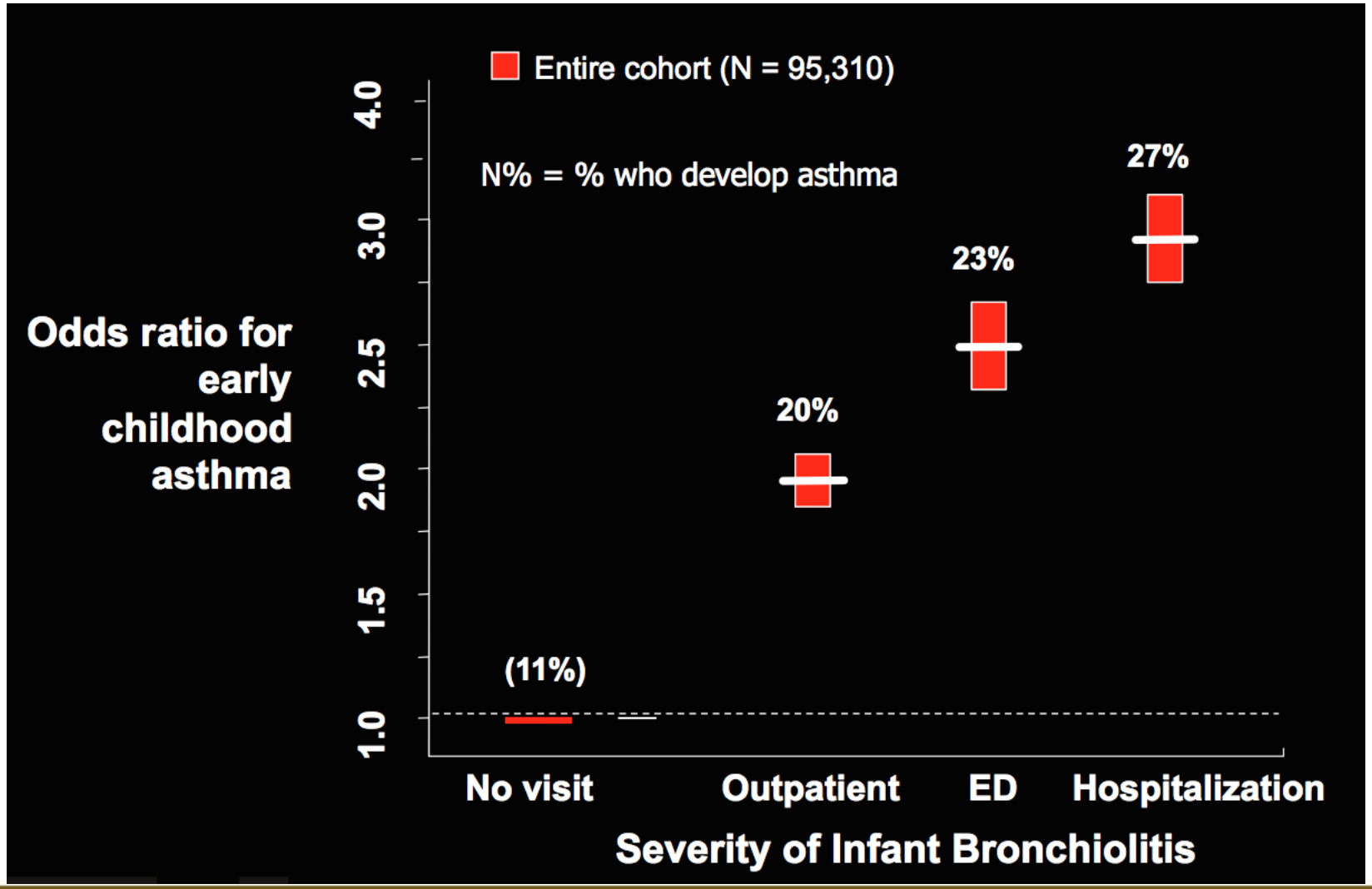
Winter viral infections in the causal pathway for asthma



- 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

Wu P. Expert Rev Anti Infect Ther. 2011 Sep;9(9):731-45.

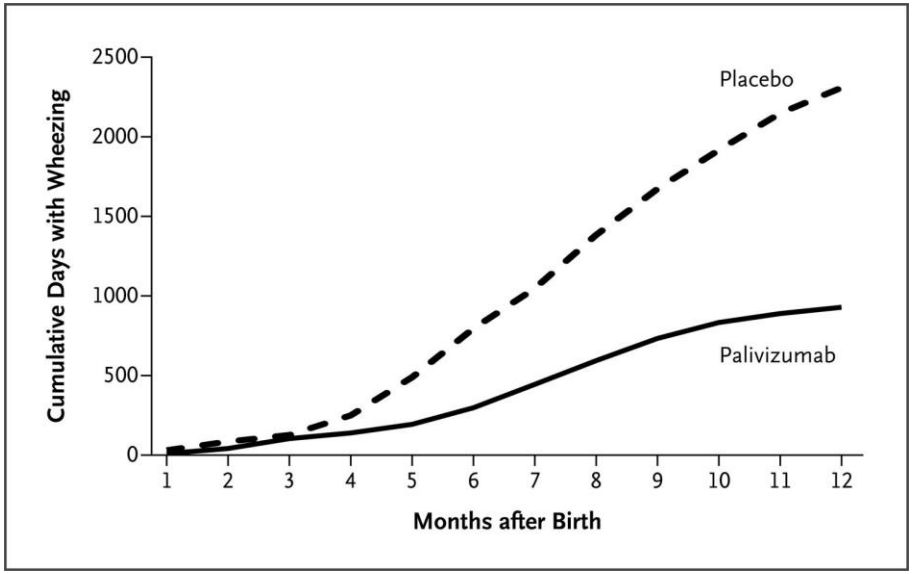
Dose response relationship between asthma and RSV severity



Carroll K et al. *J Allergy Clin Immunol* 2009;123(5):1055-61.

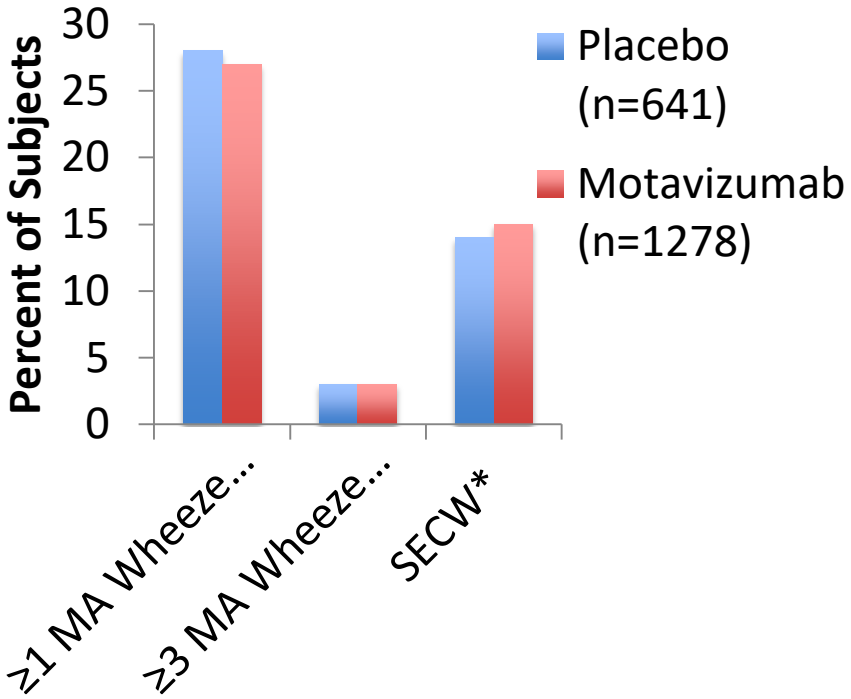
RSV and wheezing: intervention studies

Palivizumab in healthy late preterm



- Followed to 1 year
- Parent reported illness

Motavizumab in healthy term



- Followed to 3 years
- Medically-attended illness

Blanken MO et al. N Engl J Med 2013;368:1791-1799

O'Brien KL Lancet Infect Dis. 2015 Dec;15(12):1398-408.

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

OR of increased RR (>50.6 breaths/minute)

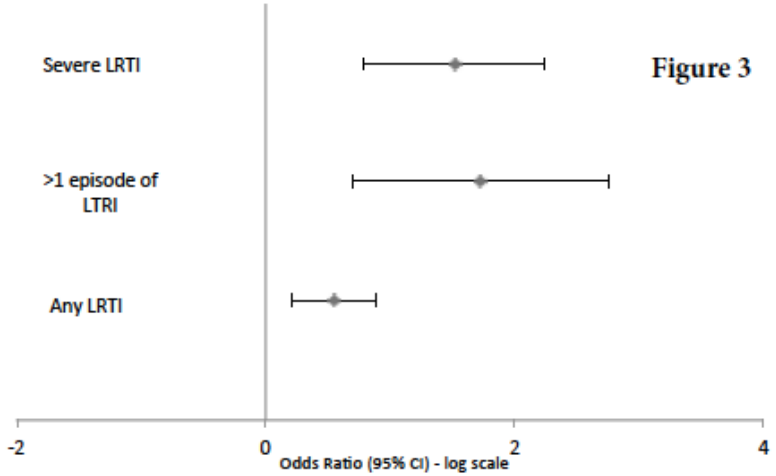


Figure 3

- 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

Gray DM. Am J Respir Crit Care Med. 2016 Aug 10

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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