

Lasten akuutti uloshengitysvaikeus ja virusinfektiot

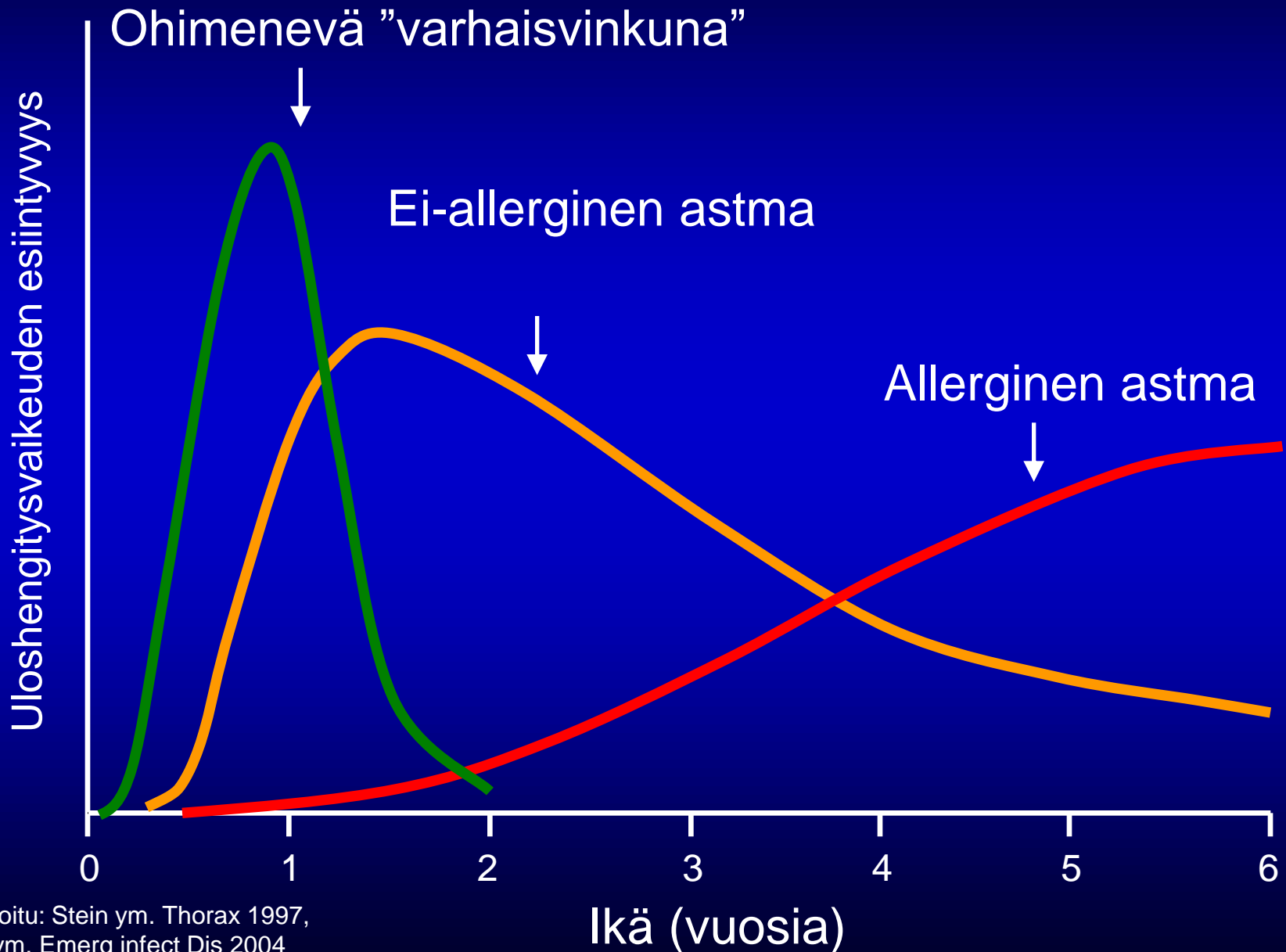
Tuomas Jartti

Dosentti, lastenlääkäri, lastenallergologi

TYKS, Lastenkliniikka

Ei sidonnaisuuksia

Pikkulasten uloshengitysvaikeuden luokittelu



Questions

1. What are the limitations in **the definition** of bronchiolitis?
2. **Why** new viral risk markers for asthma are needed?
3. What are the developments in **viral diagnostics** for acute wheezing?
4. Is there **a link** between viral etiology of wheezing and development of asthma?
5. Which factors are linked to **HRV** associated wheezing?

1. What are the limitations in **the definition** of bronchiolitis?

USA and UK definitions for bronchiolitis

- Age < 2 years
- Clinical definition
(dyspnea / wheezing / crackles)
- Diagnostic tests are not necessary

(American Academy of Pediatrics 2006,
Scottish Intercollegiate Guidelines Network 2006)

Limitations in the definition

- The ignorance of
 - **viral etiology,**
 - **atopy status and**
 - **number of wheezing episodes or chronicity of symptoms**



**Risk
factors
of
asthma**

(Castro-Rodriguez AJRCCM 2000, Korppi Acta Paediatr 2008)

- These factors probably explain differences in the clinical outcomes of trials and treatment practises

(Chavasse Arch Dis Child 2002, Christakis Pediatrics 2005)

Opinion:

A diagnosis of **bronchiolitis** (<6-12months):

- no prolonged cough,
- no major risk factors of asthma AND
- 1st episode of dyspnea / wheezing / crackles

➔ **Less likely** to benefit from asthma medication

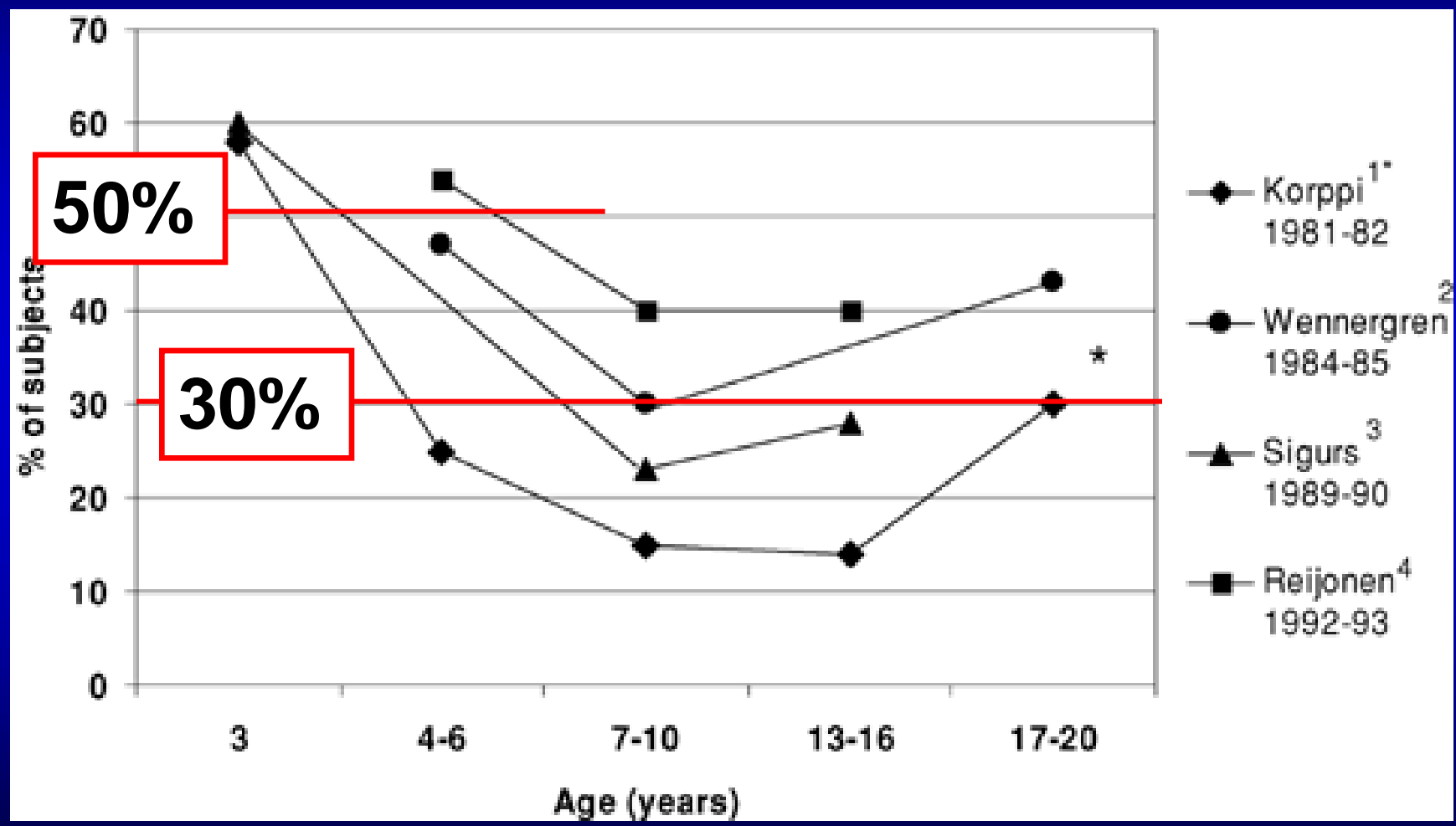
A diagnosis of **acute or recurrent wheezing:**

- chronic respiratory symptoms OR
- major risk factors of asthma

➔ **May benefit** from asthma medication

2. **Why** new viral risk markers for asthma are needed?

Hospitalization for bronchiolitis has been linked to asthma up to age 27 years



Piippo-Savolainen & Korppi Acta Paediatr 2007,
Ruotsalainen et al. Allergy 2010

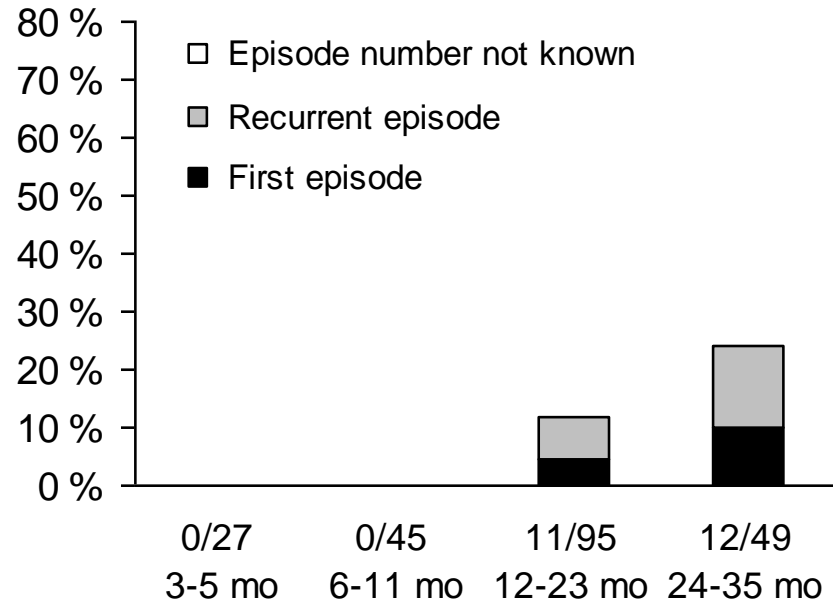
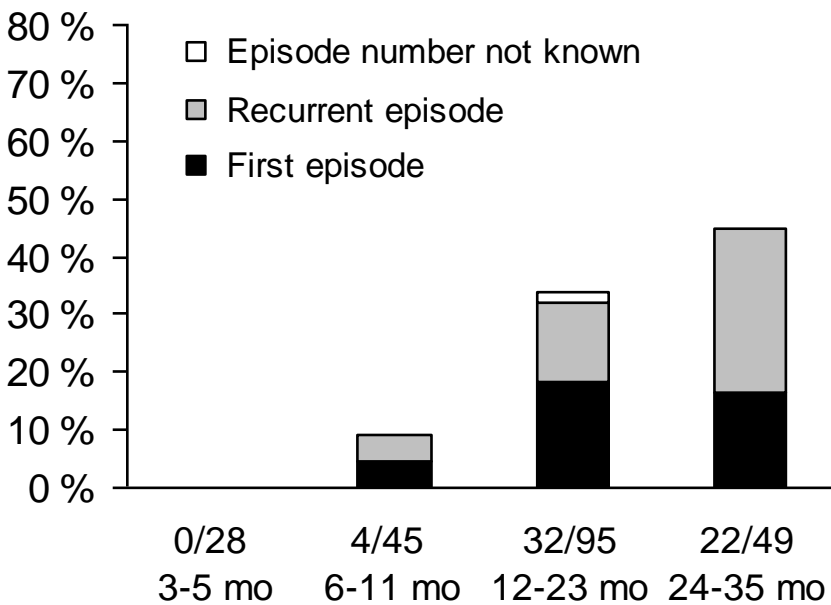
Early wheezing is an independent risk factor of adulthood asthma

The risk is **further increased** if a child has:

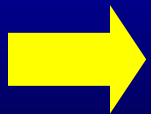
- Parental asthma
- Atopy related factors: aeroallergen sensitization, atopic dermatitis, eosinofilia
- Recurrent wheezing at age <2 years
- Decreased lung function (severity of wheezing)
- Human rhinovirus (**HRV**) associated wheezing

Ruotsalainen et al. Allergy 2010,
Malmström et al. Thorax 2011

Any sensitization (left) and aeroallergen sensitization (right) develop slowly



Jartti et al. PIDJ 2009 (VINKU-study, Figs), Illi et al. Lancet 2006 (German MAS)



Viral (or bacterial) detection may be a useful tool for the early identification of high risk children for asthma.

3. What are the developments in **viral diagnostics** for acute wheezing?

Discovery of respiratory viruses: new wave during 21st century due to molecular methods

Influenza virus 1933

Coxsackie virus 1948

Echovirus 1951

Adenovirus 1953

RSV 1956

Rhinovirus 1956

Parainfluenza virus 1956

Coronavirus 1965

Torque Teno virus 1997

Metapneumovirus 2001

Coronaviruses: SARS, NL63 & HKU1 2002-2005

Bocavirus 2005

Polyomaviruses: KI & WU 2007

Rhinovirus C & D groups 2007-



1930 1940 1950 1960 1970 1980 1990 2000 2010

The virus etiology of childhood wheezing over 5 decades

Reference	N	Methods					Detection rate (%)										Total
		Cu	Ag	Sero	PCR	RSV	HRV	EV	PIV	Flu	AdV	CV	MPV	HBoV	PyV		
Tyrrell (1965)	225	+				8	3	5	4	0	4						27
Glezen (1971)	855	+				9	2	1	8	1	2						25
Horn (1975)	1515	+				3	12	3	3	2	1						23
Mitchell (1976)	267	+		+		4	6	1	1	1	3						14
Henderson (1979)	1851	+				7	1		6		2						21
Horn (1979)	554	+				2	13	4	4	2	1						26
Carlsen (1984)	256	+	+	+		5	13		4	2	3	2					29
Jennings (1987)	204	+	+	+		6	1	5	0	3	2						19
Rylander (1996)	181	+	+			12	6	1	7		2						26
Freymuth (1999)	132	+	+		+	21	47	10	4	5	5	5					82
Papadopoulos (2002)	118				+	53	21		3	3	8	3					74
Rawlinson (2003)	179	+	+		+	7	79		1	2			2				88
Jartti et al (2004), Allander et al (2007), Kantola et al (2008)	293	+	+	+	+	27	24	25	6	2	5	1	4	19	5		95
Söderlund-Venermo et al (2009)																	
Nieminen et al. (2012), unpubl	121				+	31	91	5	18	2	5	5	8	20			100

Jartti Astma- ja allergiapäivät 2012



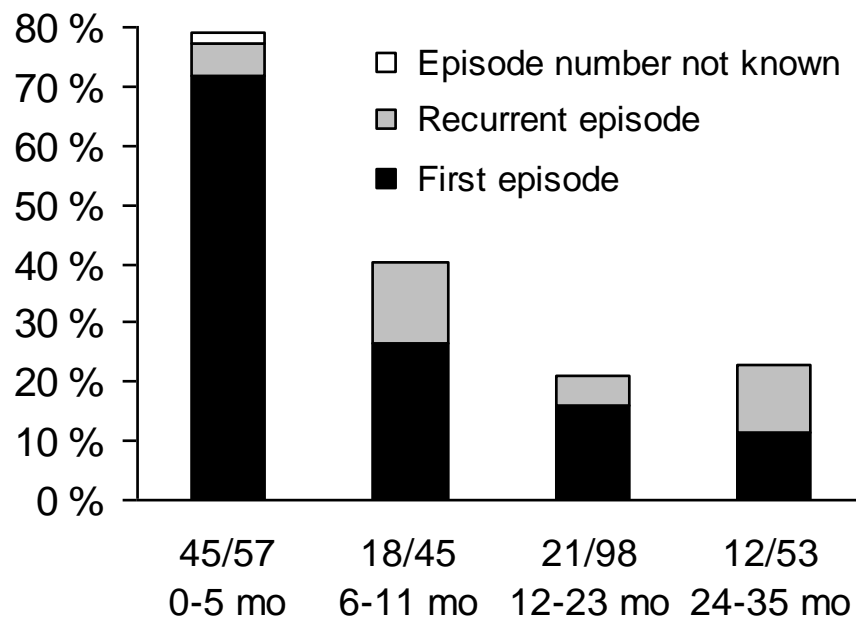
Viral wheeze is really viral wheeze

Bronchiolitis / early wheezing:

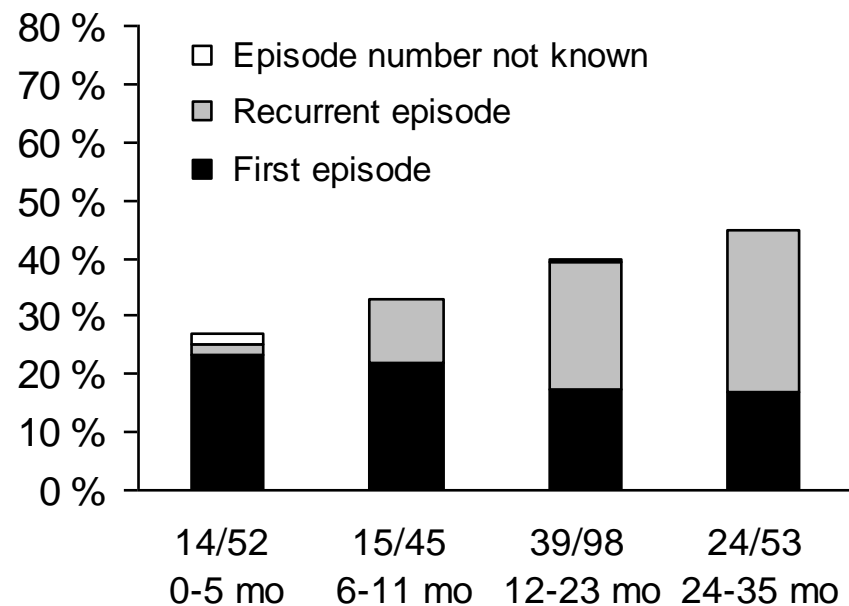
RSV dominates in infants aged <12 months

HRV dominates in children aged ≥ 12 months

RSV, $P < 0.0001$ for trend



HRV, $P = 0.035$ for trend

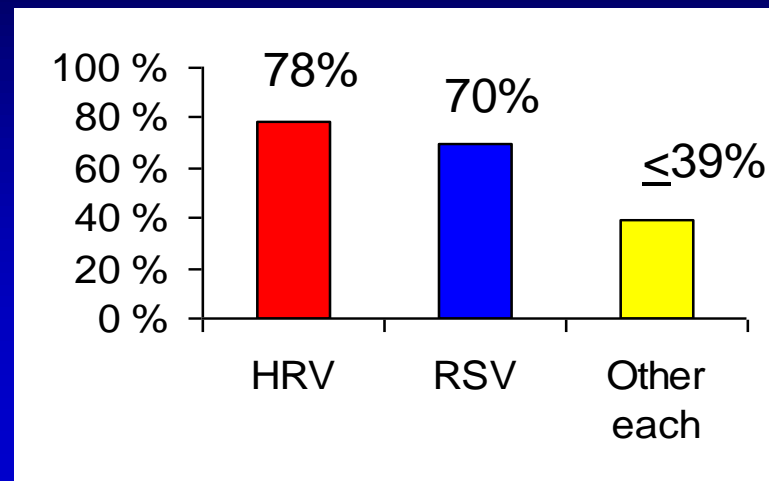


Bronchiolitis is particularly associated with HRV in predisposed children aged <12 months

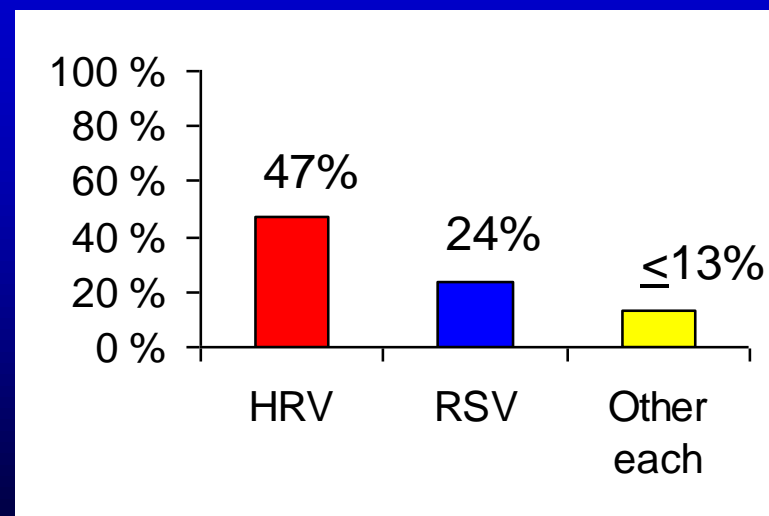
Infants with parental asthma/allergy & ≥ 5 mod-sev. resp. infections during 1st yr of life (236 samples in 27 infants, 2 year study period)



Wheezed at least once with



Wheezing episodes associated with

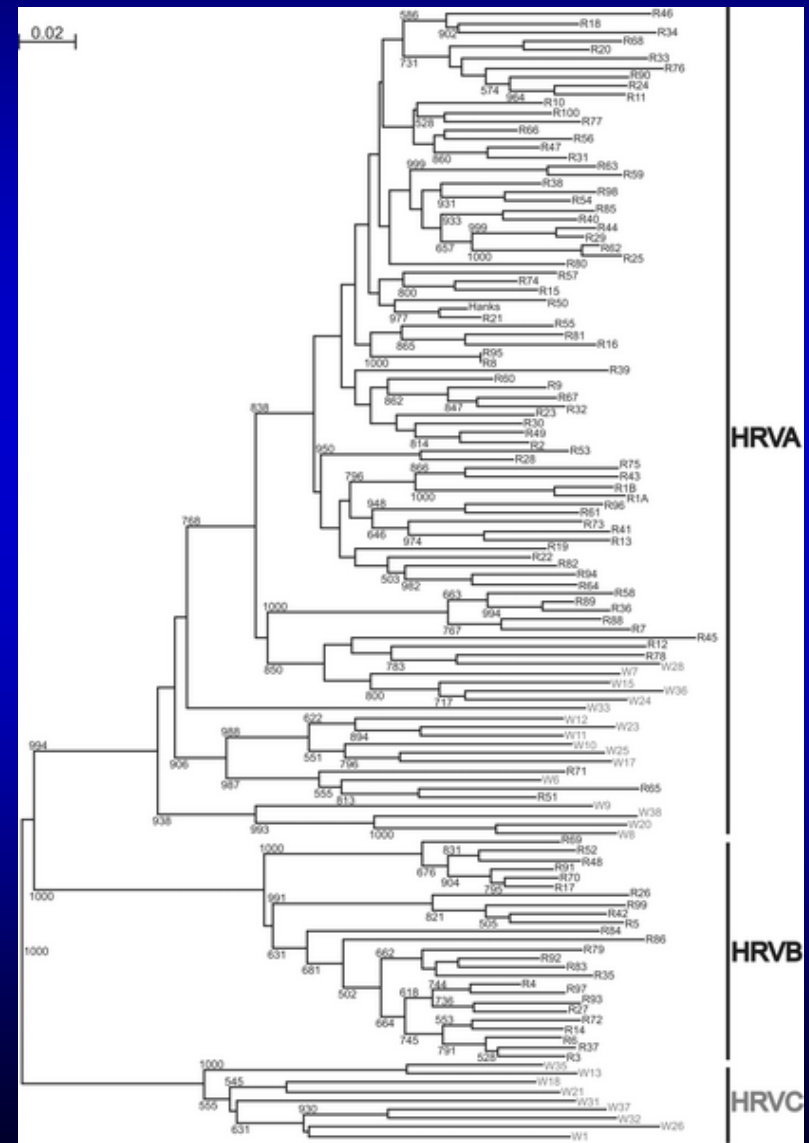


HRVs are highly diverse, HRV-C and HRV-D recently discovered

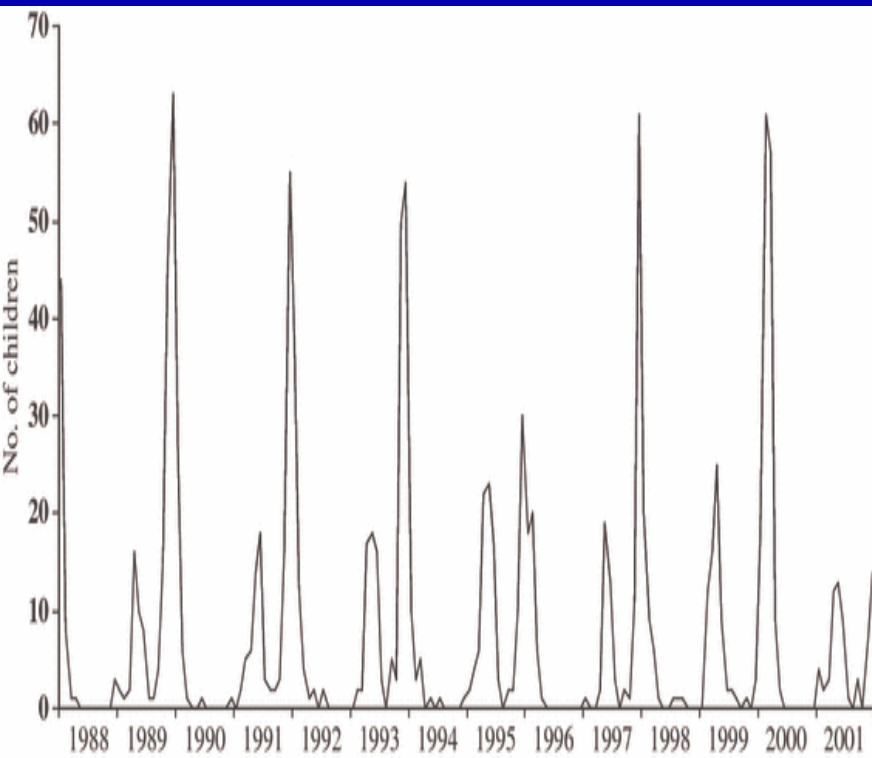
HRV: Subgroups A, B, C and D,
100 serotypes, >150 genotypes

RSV: Single serotype with 2
major antigenic subgroups A
and B, ≥ 12 genotypes

Lee et al. PlosONE 2007,
Sato et al. J Clin Microbiol 2005
Palmenberg et al. Science 2009

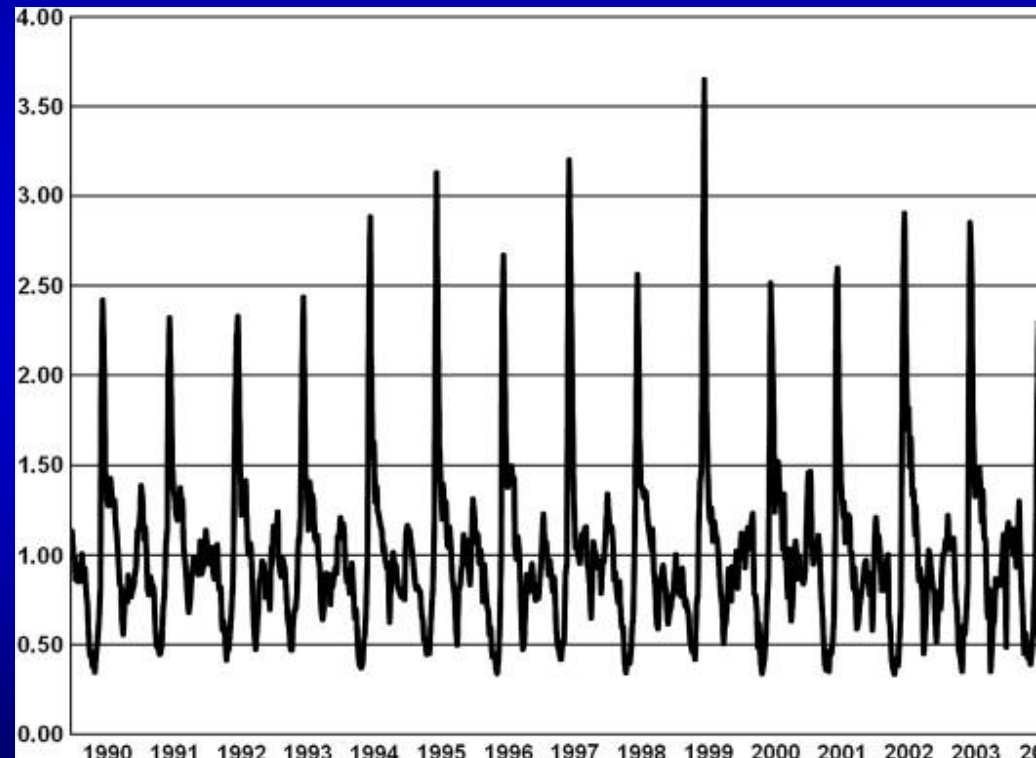


Laboratory-confirmed **RSV** infections in children in Finland during 1988–2001



Valkonen et al. Allergy 2010

September epidemics of asthma, probably mainly caused by **HRV**, in Canada during 1990 –2004



Sears & Johnston
J Allergy Clin Immunol 2007

4. Is there **a link** between viral etiology of wheezing and development of asthma?

Long-term follow-up studies on HRV and RSV induced wheeze

RSV vs non-RSV/ctrl

- Stein Lancet 1999
- Piippo-Savolainen
Pediatr Int 2007
- Hyvärinen Acta
Paediatr 2007
- Valkonen Allergy 2009

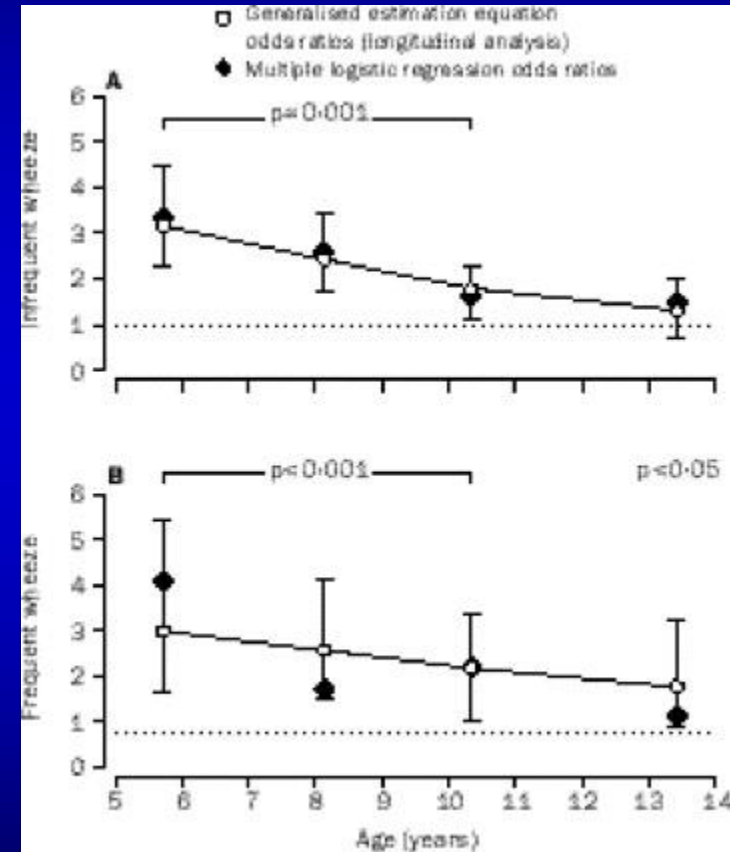
HRV vs RSV/non-HRV

- Kotaniemi-Syrjänen JACI 2003
 - Hyvärinen PPul 2005
- Lemanske JACI 2005
 - Jackson JACI 2008
- Lehtinen JACI 2007
 - Lukkarinen unpubl.
- Kusel JACI 2007
- Midulla ERJ 2011

4.1. **RSV vs non-RSV/ctrl**
bronchiolitis:
link to asthma?

LRTI <3 years and infrequent (top) and frequent (bottom) wheeze

	6 yr	8 yr	11 yr	13 yr
RSV	3.2 *	2.5 *	1.7	1.4
Neg test	1.5	1.3	1.6	1.9 †
RSV	4.3*	1.9	2.4	1.4
Neg test	1.9	2.3	2.0	2.1 ‡



OR adjusted for sex, maternal education, family history of asthma, allergy skin tests at yr 6, birthweight, and current maternal smoking

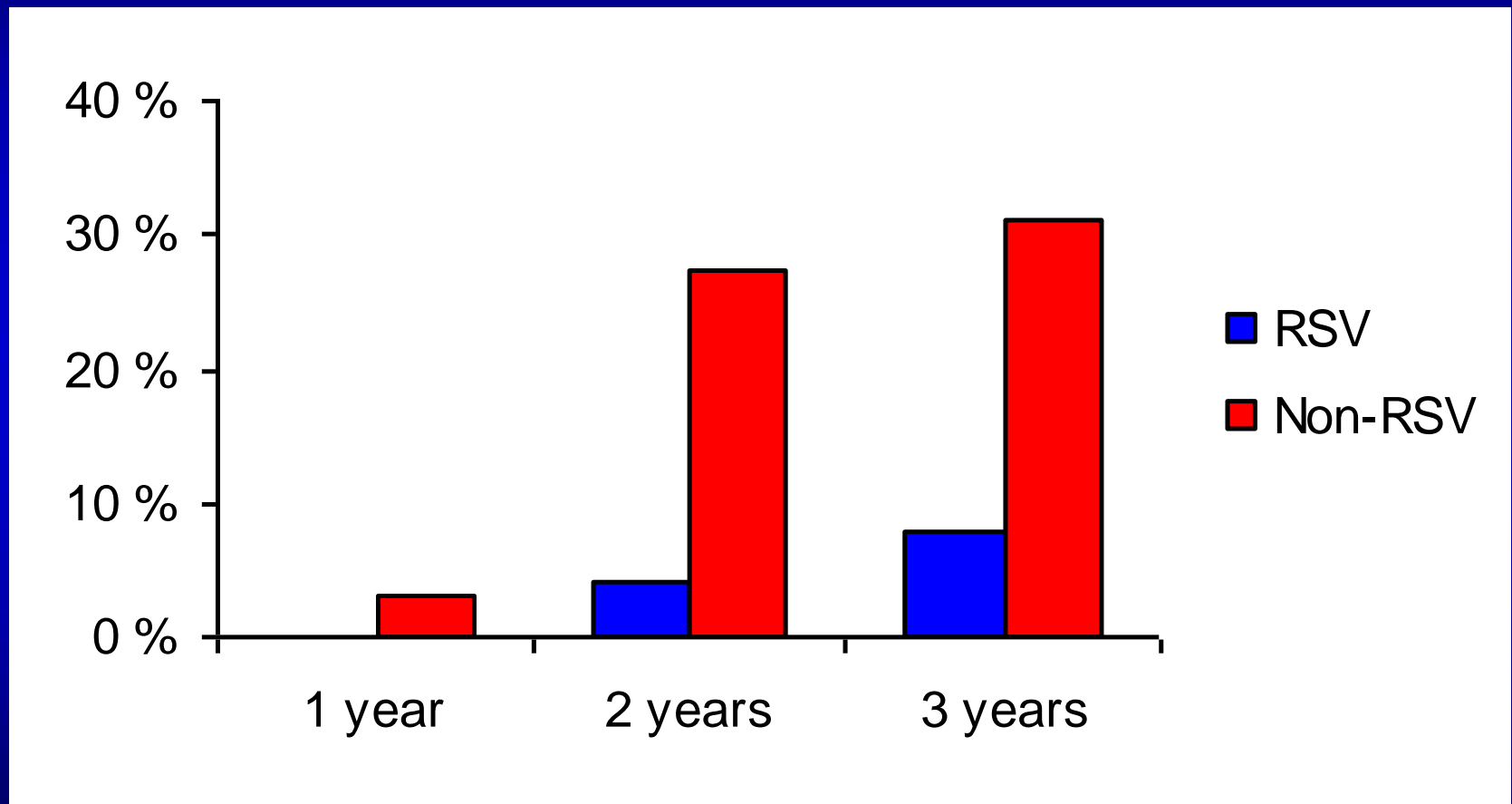
Adult asthma after non-RSV vs RSV induced bronchiolitis: 20-year prospective follow-up

- N = 54, hospitalization for bronchiolitis at age <2 years
- Re-studied at median age 19 years
- Outcome: adult asthma; 2 definitions
- In the non-RSV group, asthma was present in 41-50% (vs 18-27% in RSV group). In adjusted analysis, non-RSV etiology increased asthma risk by both strict (**OR 8.3**) and less strict (**OR 7.9**) criteria

Lung function and BHR 11 years after hospitalization for bronchiolitis

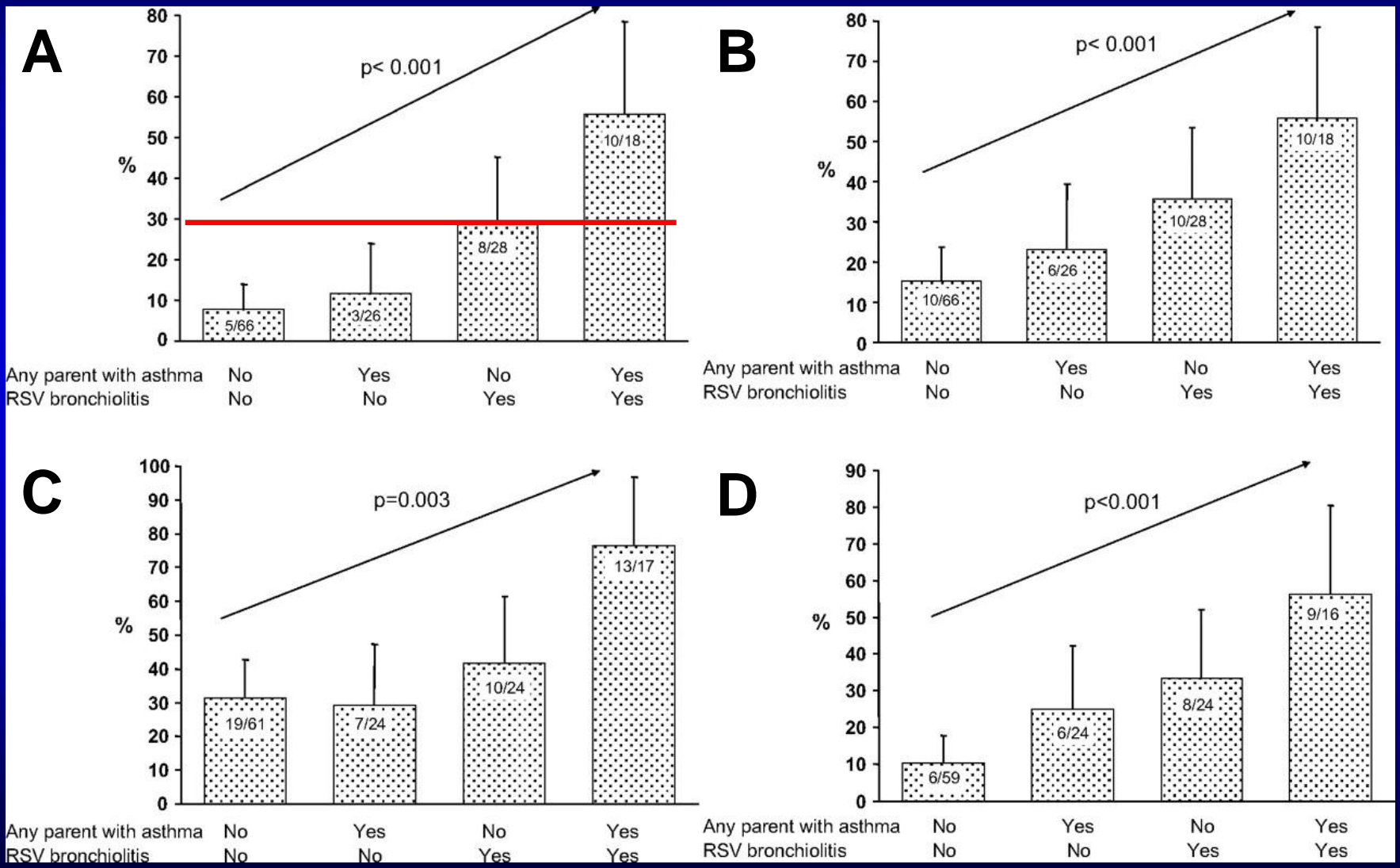
- **Forced vital capacity:**
 - RSV 94% vs non-RSV 100%
- **Bronchial hyperresponsiveness:**
 - **early sensitization (OR 12.6)**
 - maternal smoking during pregnancy (OR 4.6)
 - early atopic dermatitis (3.5)

Recurrent wheezing requiring long-term asthma medication during first 1, 2, and 3 years after the hospitalization for RSV vs non-RSV bronchiolitis



RSV: n = 75, non-RSV: n = 69

RSV-bronchiolitis at age ≤ 6 mo is associated with (A) asthma, (B) allergic rhinoconjunctivitis, (C) aeroallergen sensitization and (D) perennial allergen sensitization at age 18 years



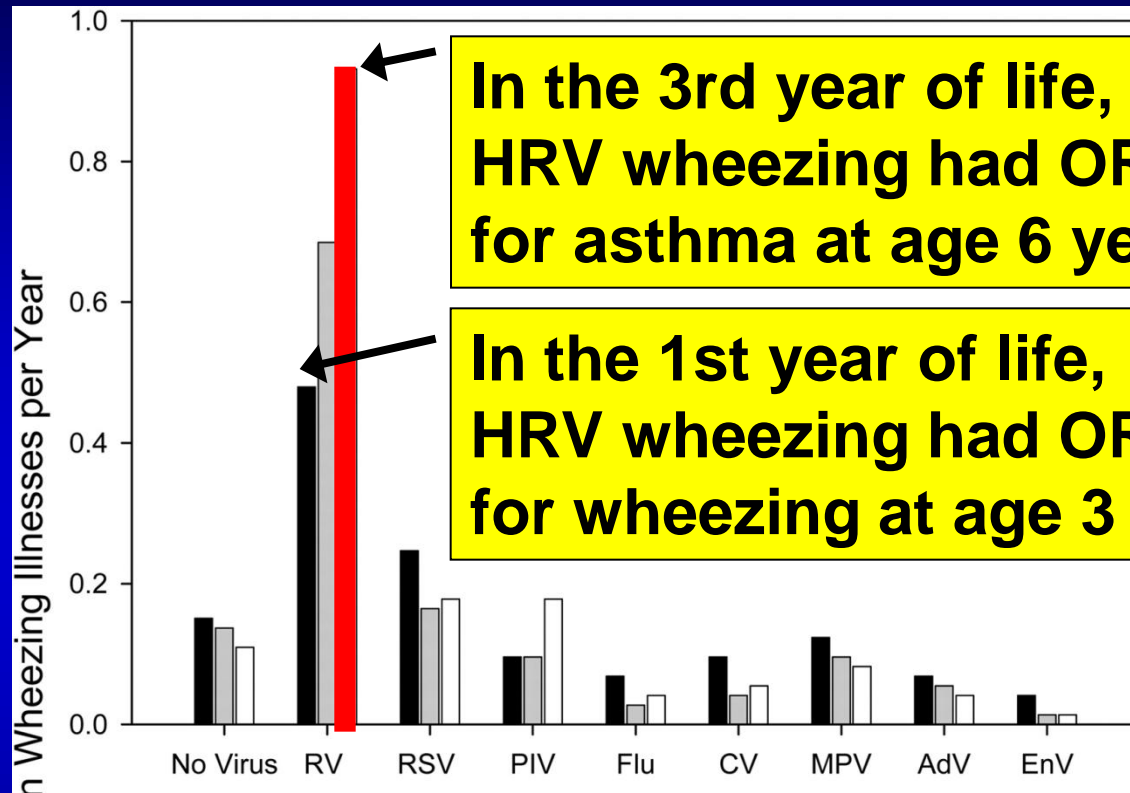
4.2. **HRV vs RSV/non-HRV** bronchiolitis/wheeze: link to asthma?

The first report on the link between HRV bronchiolitis and asthma

Kotaniemi-Syrjänen et al. J Allergy Clin Immunol 2003

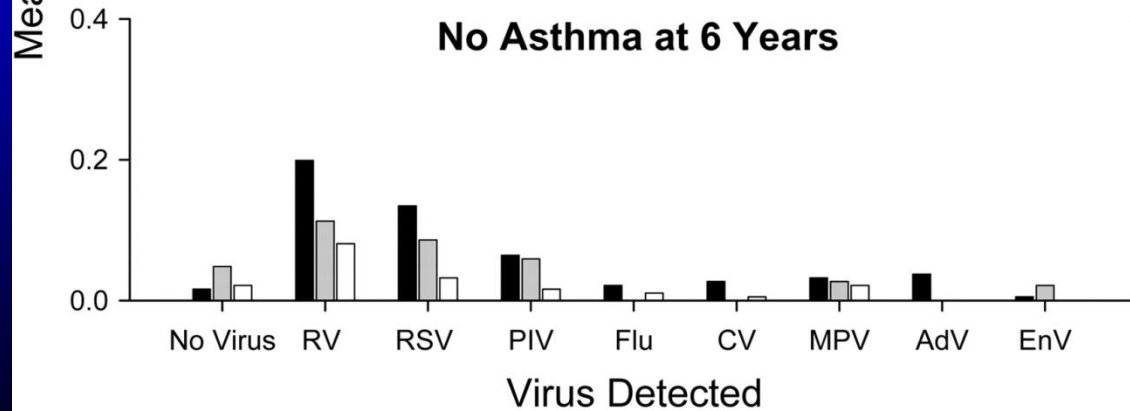
- Population based, hospitalized
- Age <2 years
- n = 66, 27 (41%) had asthma at school-age
- **OR 4.1 for school-age asthma in HRV group** (compared to non-HRV, adjusted for age, sex, and atopic dermatitis)

HRV wheezing during the 1st 3 yrs of life is highly associated with asthma at age 6 yrs



In the 3rd year of life, HRV wheezing had OR 25.6 for asthma at age 6 years

In the 1st year of life, HRV wheezing had OR 10 for wheezing at age 3 years



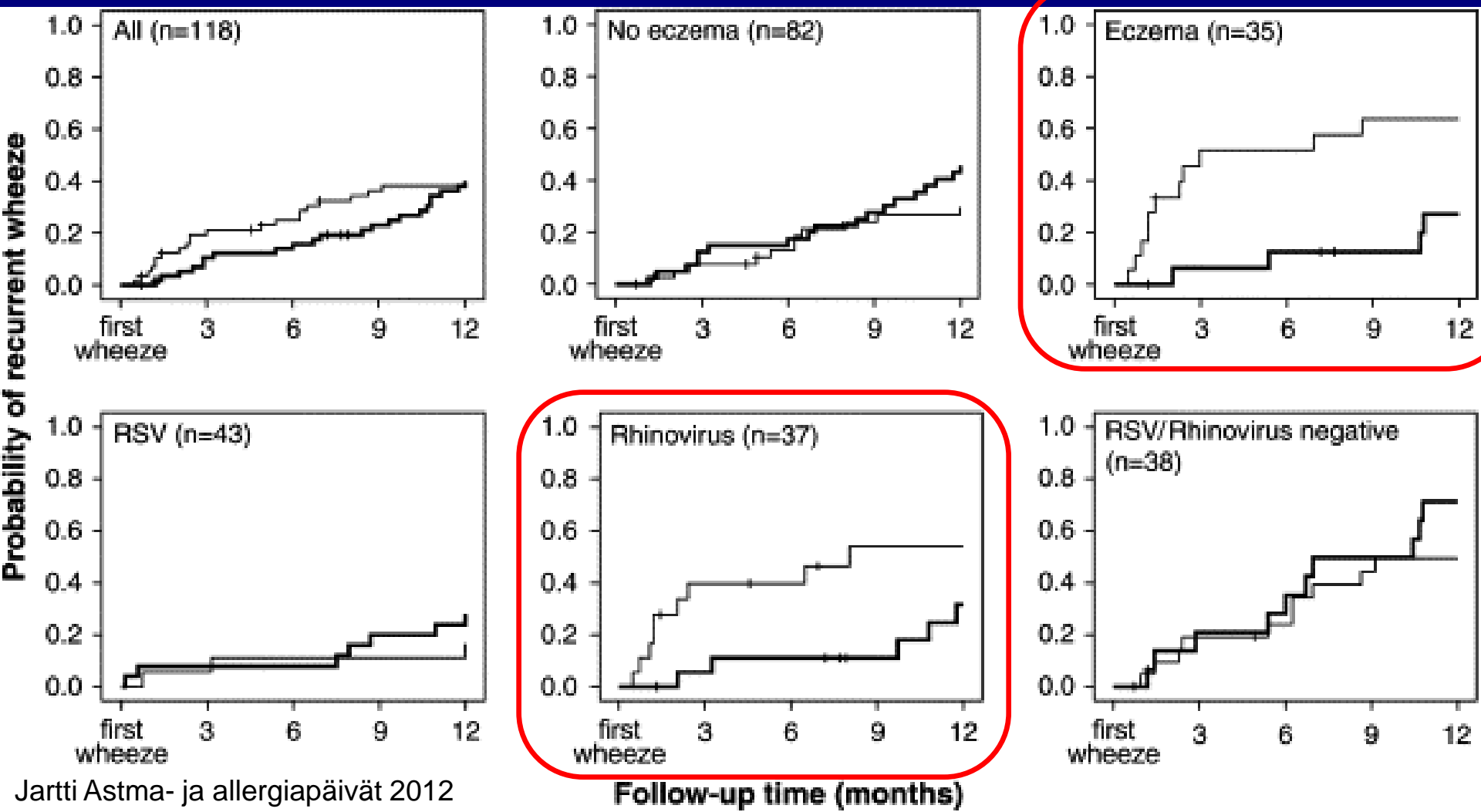
Lemanske et al.
J Allergy Clin Immunol 2005

Jackson et al.
Am J Respir Crit Care Med 2008

Predictors of current wheeze at 5 years of age in relation to time of atopic sensitization (OR)

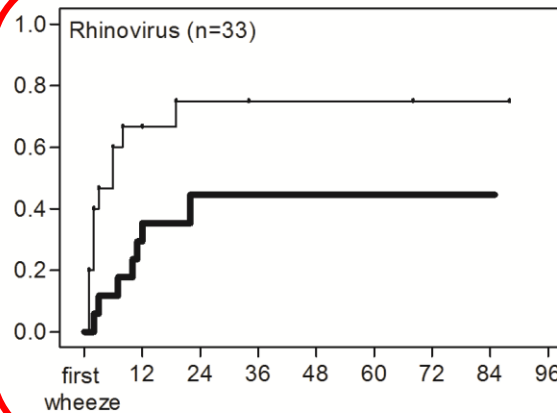
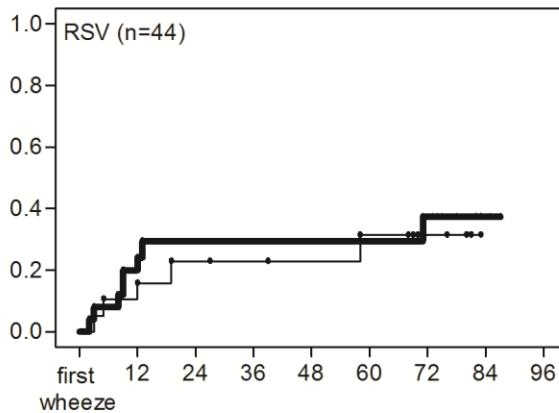
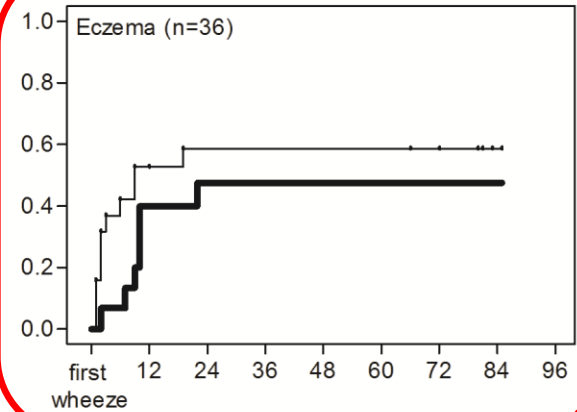
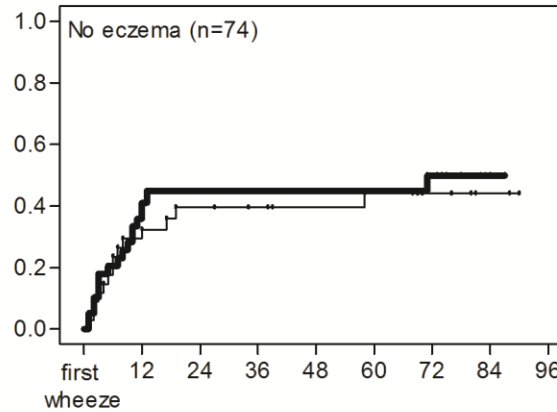
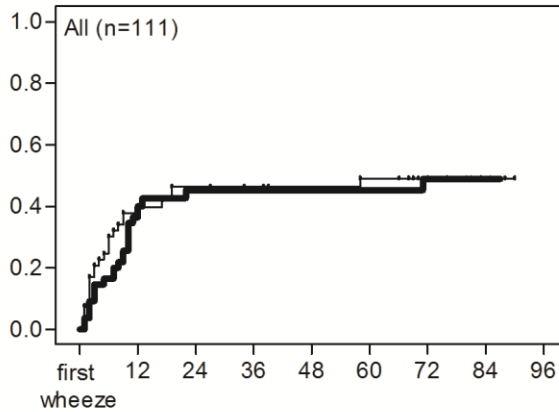
Any wheezy LRI associated with	Never atopic	Atopic by age of 2 yrs	Atopic after age 2 yrs
HRV or RSV	0.8	4.1	0.9
HRV	1.6	3.2	2.1
RSV	1.6	3.6	N ↓

VINKU study: the 1-year outcome of the 1st wheezy episode at age <3 years



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VINKU study: the 5-year outcome of the 1st wheezy episode at age <3 years



Bold line = prednisolon
Thin line = placebo

Follow-up time (months)

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Lukkarinen et al. unpublished

VINKU study: the 5 year outcome of the 1st wheezy episode at age <3 yrs

- Independent risk factors for asthma:
 - **HRV: HR 4.5** (compared to RSV)
 - other than RSV/HRV etiology: HR 3.3
 - any sensitization: HR 3.3
 - age <1 year: HR 2.3
- **Prednisolone treatment was associated with a 54% lower probability of asthma in HRV group *post hoc*** (non-adjusted HR 0.34; adjusted HR 0.15)

One year outcome of HRV bronchiolitis (1st episode) at age <12 months

- Outcome = recurrent wheezing, i.e. ≥ 2 physician-verified episodes of wheezing during a one year follow-up
- n = 313, all hospitalized
- Results: risk factors for recurrent wheezing:
 - B-eos count $>0.4 \times 10^9$, OR 4.9
 - **HRV, OR 4.0**
 - Family history for asthma, OR 2.7
 - CRP < 0.8 mg/dl, OR 1.9
 - Absence of lung consolidation, OR 1.7

Is there **a link** between viral etiology of wheezing and development of asthma?

- Any virus (vs healthy): 5 fold risk (~30%)
- Non-RSV (vs RSV): 0 - 4.5 fold risk
- **HRV** (vs RSV/non-HRV): **3-10 (- 25) fold risk**

5. Which factors are linked to **HRV**-bronchiolitis?

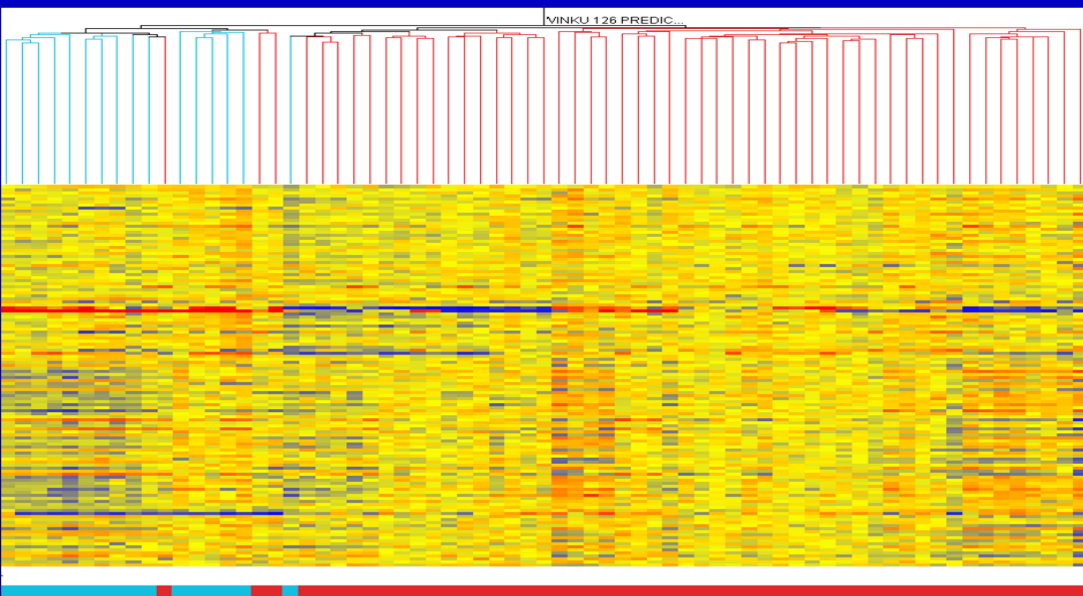
Early HRV associated wheezing is likely to be associated with..

- Atopy, B-eosinofilia, atopic dermatitis, increased FeNO (Jartti et al. PIDJ 2006, Rakes et al. AJRCCM 1999, Korppi et al. PIDJ 2004, Kusel et al. JACI 2007, Jackson AJRCCM 2011)
- Low IFN- γ level (IFN- γ and - λ in adults) (Copenhaver et al. AJRCCM 2004, Contoli et al. Nat Med 2006, Massage et al. Proc Acad Sci USA 2008)
- Asthma (Miller et al. J Infect Dis 2007)
- Epithelial damage *in vitro* (Jakiela et al. AJRCMB 2008)
- Response to corticosteroid? (Lehtinen et al. JACI 2007, Lukkarinen et al. Unpublished)

Transcriptional profiles correlate with HRV and RSV etiology and disease severity in children bronchiolitis

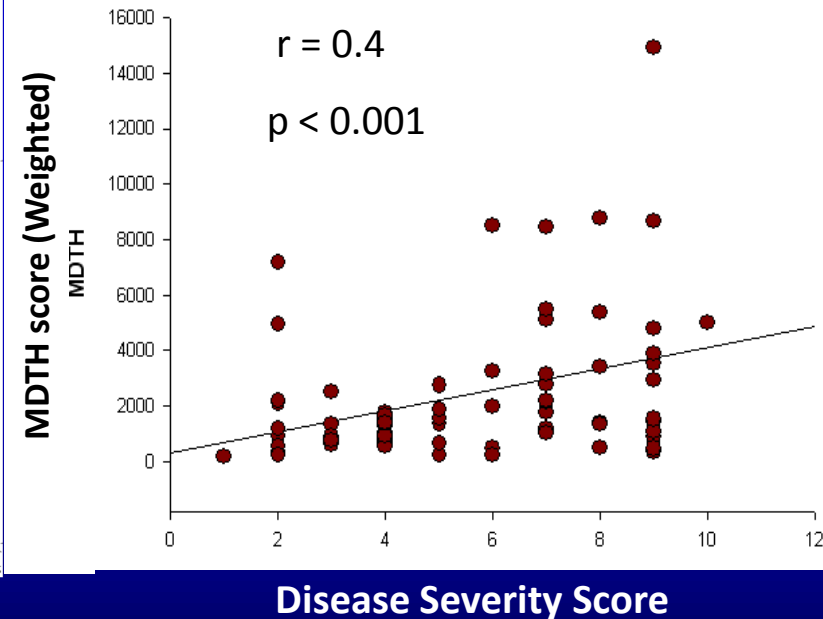
Dimo B, Jartti T, Ramilo O, Mejias A, et al.

Unsupervised Cluster Analysis



Predictor genes discriminate RSV vs HRV with 94% accuracy

Correlations: CRSS and MDTH



Lopuksi

- **Rinovirus liittyy yleisesti** akuuttiin uloshengitysvaikeuteen, erityisesti atoopikoilla (20%-80%)
- **Bronkioliitti lisää astmariskiä**, mutta riski on korkeampi RSV-negatiivisilla lapsilla, ja **korkein rinovirus-positiivisilla lapsilla**
- Rinovirusalttius liittyy moniin **astmaan kytkeytyviin tekijöihin**, esim. atopia, eosinofilia, matala IFN- γ taso ja hengitystie-epiteelivaurio.