Ανασκόπηση βρογχιολίτιδας

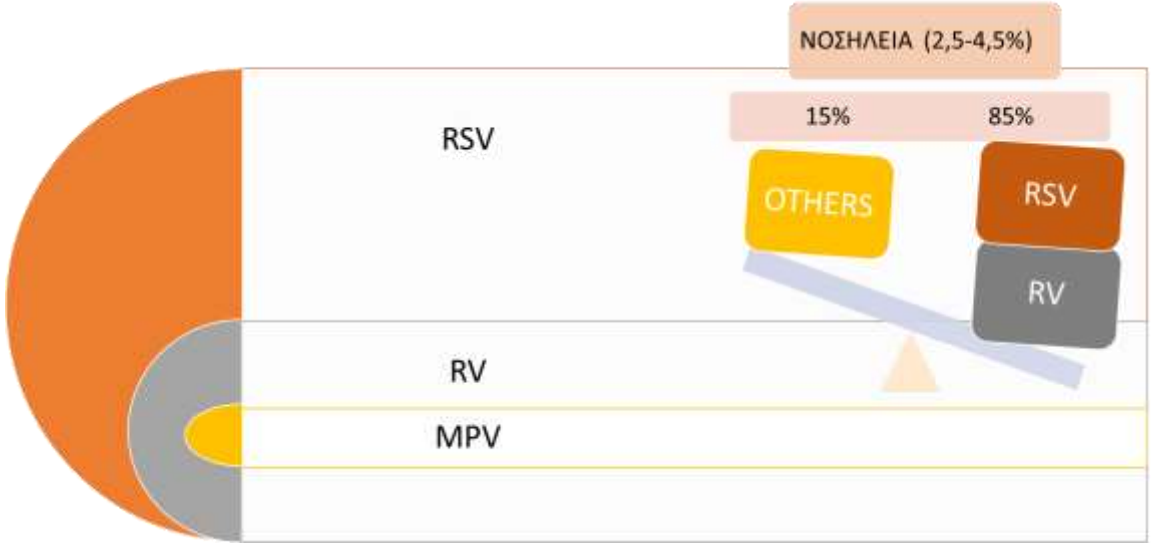
Αθηνά Παπαδοπούλου

Παιδοπνευμονολόγος -παιδοαλλεργιολόγος

Δήλωση σύγκρουσης συμφερόντων : καμμία

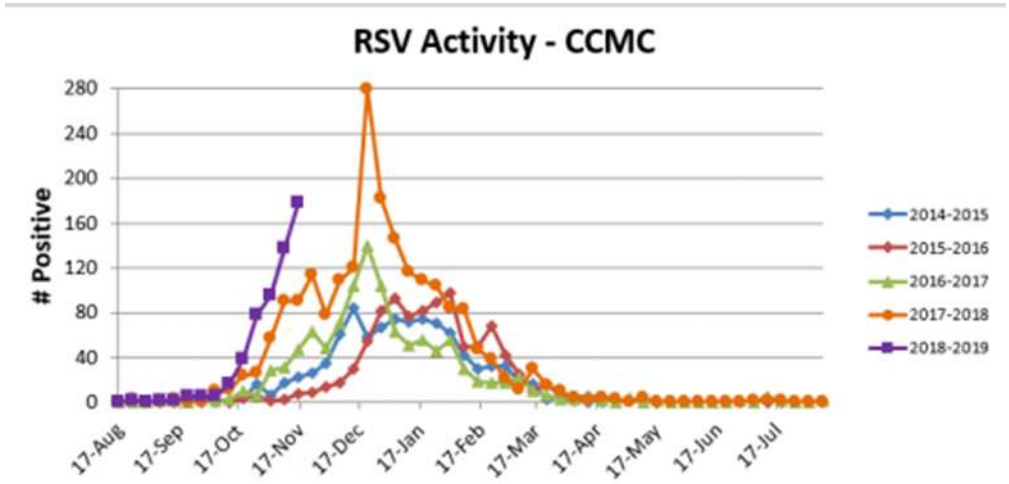
Η Επιδημία του χειμώνα

- Υψηλή νοσηρότητα και θνητότητα στην βρεφική ηλικία
- Respiratory syncytial virus (RSV) είναι υπεύθυνος για το 75% των περιπτώσεων.
- Η βρογχιολίτιδα κυρίως αντιμετωπίζεται κατ' οίκον με υποστηρικτική θεραπεία. Όμως 2.4%–4.6% αυτών έχει ανάγκη νοσηλείας .
- Διεθνώς 3.2 εκατ/χρ νοσηλείες σε παιδιά <5χρ (45% <6 μ).
- Κυρίως σε μέσου και χαμηλού εισοδήματος χώρες



Infants <18m 50% RSV , 40% RV
children >18m RV 60% and EV 30%

RSV (A,B)

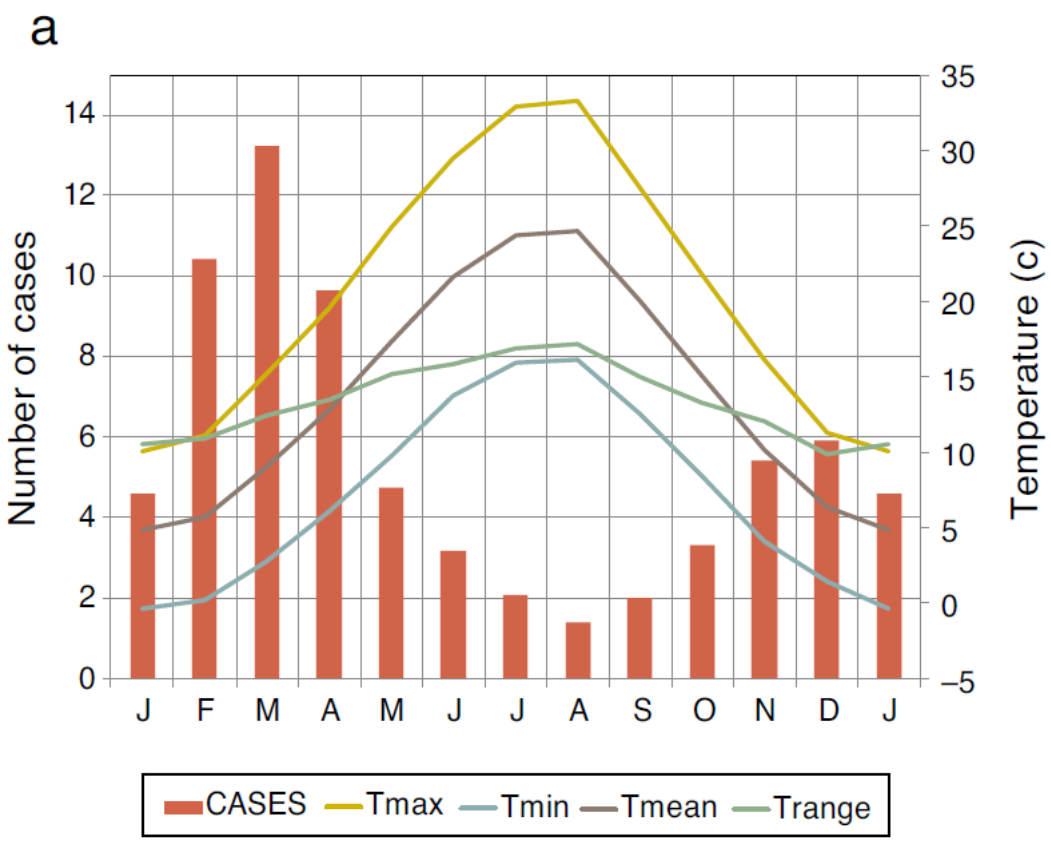


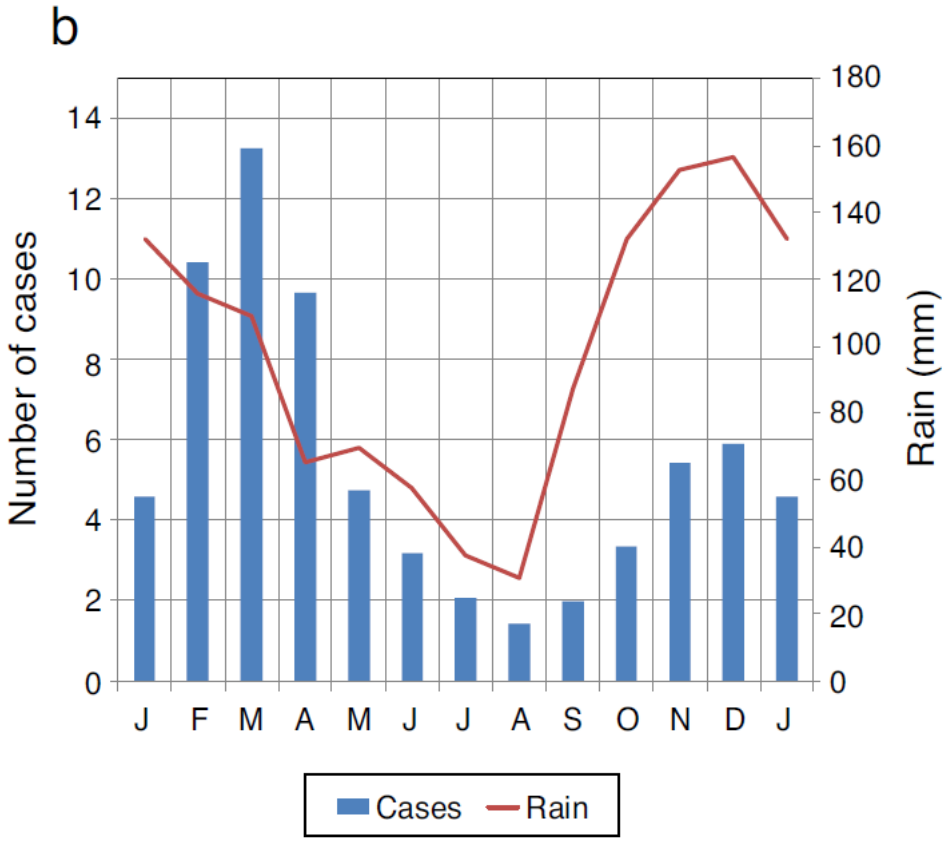
- Οκτ-Ιουν (κορύφωση Ιαν-Μαρτ)
- Ανάλογα με υγρασία (βορεια /τροπικά)
- Επώαση 5-8 μέρες
- Μετάδοση 2 μ πριν και 14 μετά (ανοσοκαταστολή >6 εβδ)
- Μεταδίδεται με χονδρά σταγονίδια (επιζούν 1 ώρα στα χέρια και 24ώρες σε σκληρές επιφάνειες)
- Πρωτολοίμωξη 60% , επαναλοίμωξη 20%
- όλα τα βρέφη μέχρι την ηλικία των 5 ετων (50% χ2)
- RSV + αλλοι ιοί (RV, MPV, Boca, Influenza) βαρύτερη νόσος

Όχι μόνο τον χειμώνα…

- RSV κυρίως τους χειμερινούς μήνες
- Human metapneumovirus (hMPV) που κυρίως προσβάλει λίγο μεγαλύτερα παιδιά κυρίως την Άνοιξη.
- Human rhinoviruses (hRV) and human parainfluenza virus type 3 (hPIV3) κυριαρχεί το φθινόπωρο και την Άνοιξη

Impact of meteorological factors on the emergence of bronchiolitis in North-western Greece.
Tsabouri S, et al.





increasing influenza virus survival in aerosols, and increasing influenza and RSV survival on surfaces

increasing the amount of virus that is deposited on surfaces.

Allergol Immunopathol (Madr). 2017.

Impact of meteorological factors on the emergence of bronchiolitis in North-western Greece.
Tsabouri S, et al.

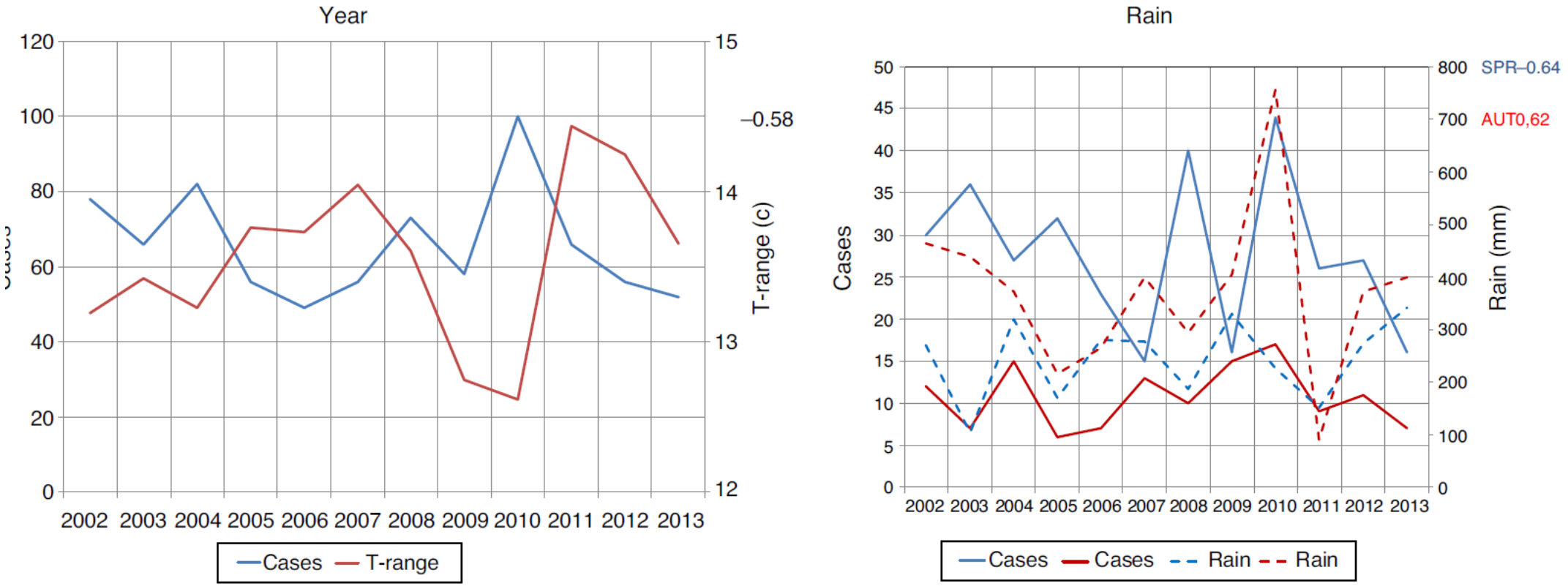


Figure 2 The inter-annual variations of AEB cases and (a) *T*-range and (b) autumn and spring rainfall.

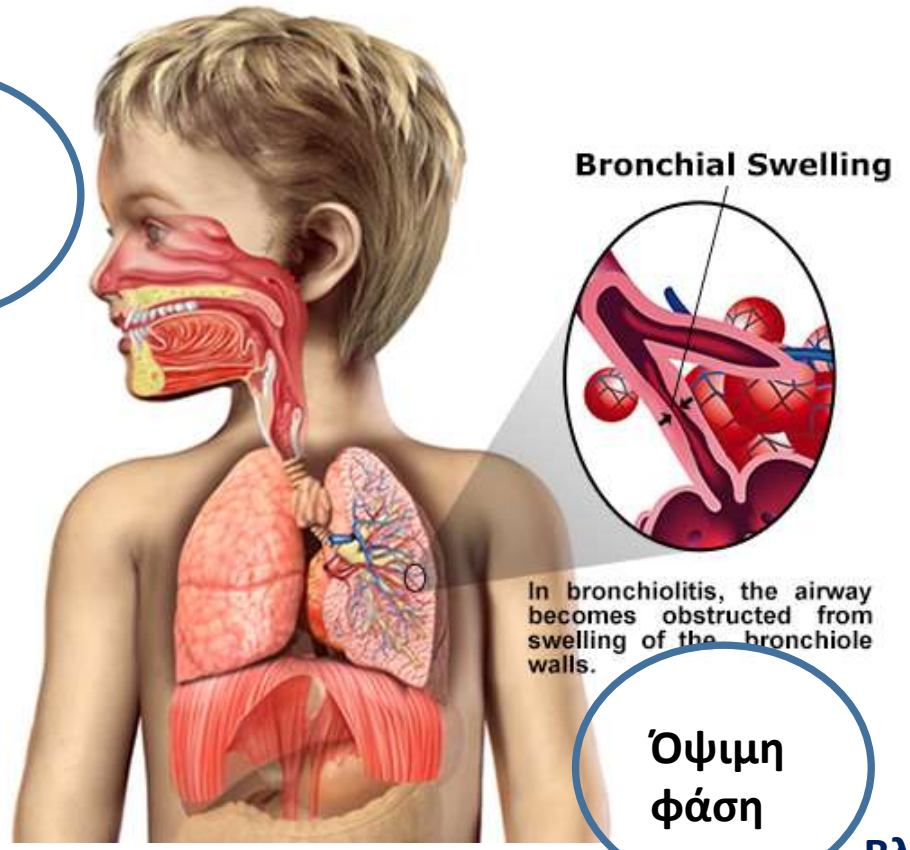
Allergol Immunopathol (Madr). 2017.

Τυπική

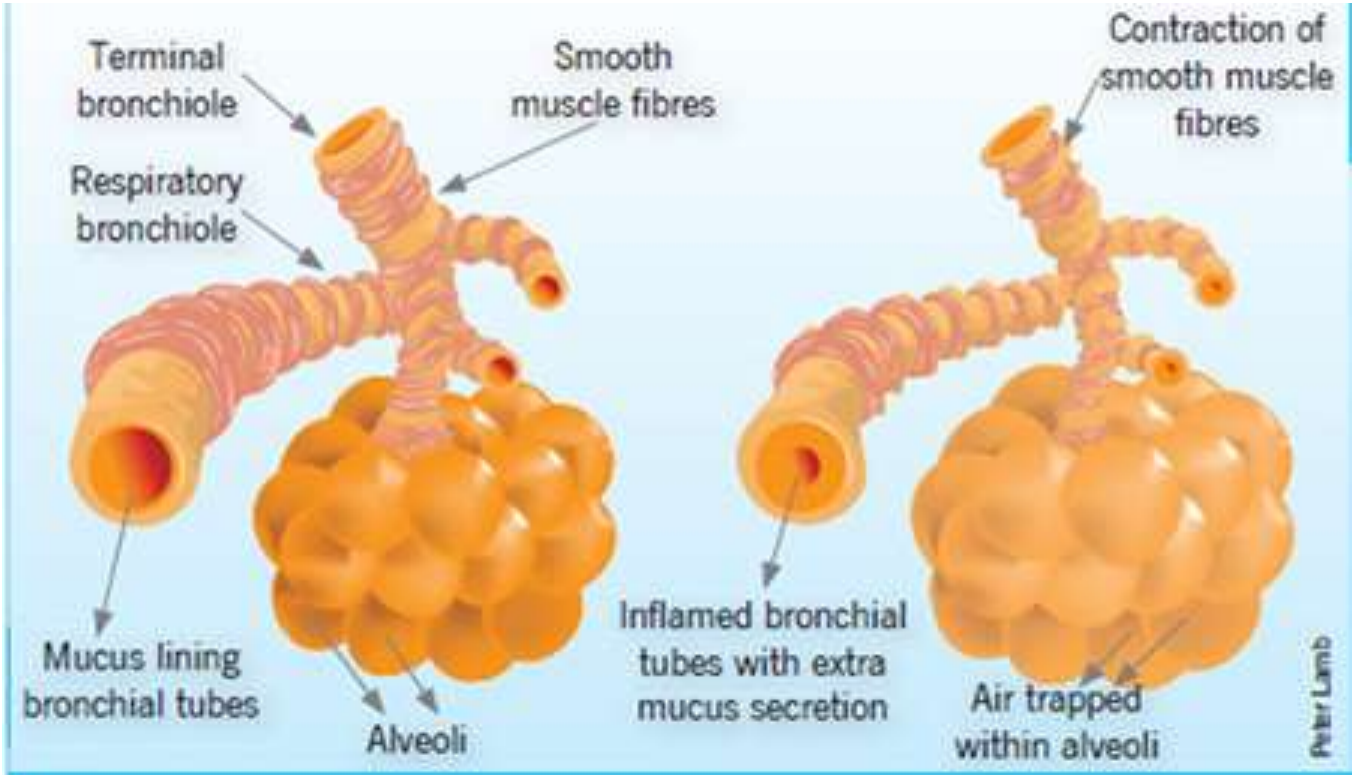
Συμμετοχή κατώτερου

Λοίμωξη ανώτερου αναπνευστικού

Πρώιμη φάση



Όψιμη φάση



Βλέννη +
Κυτ συγκρίματα +
ινική

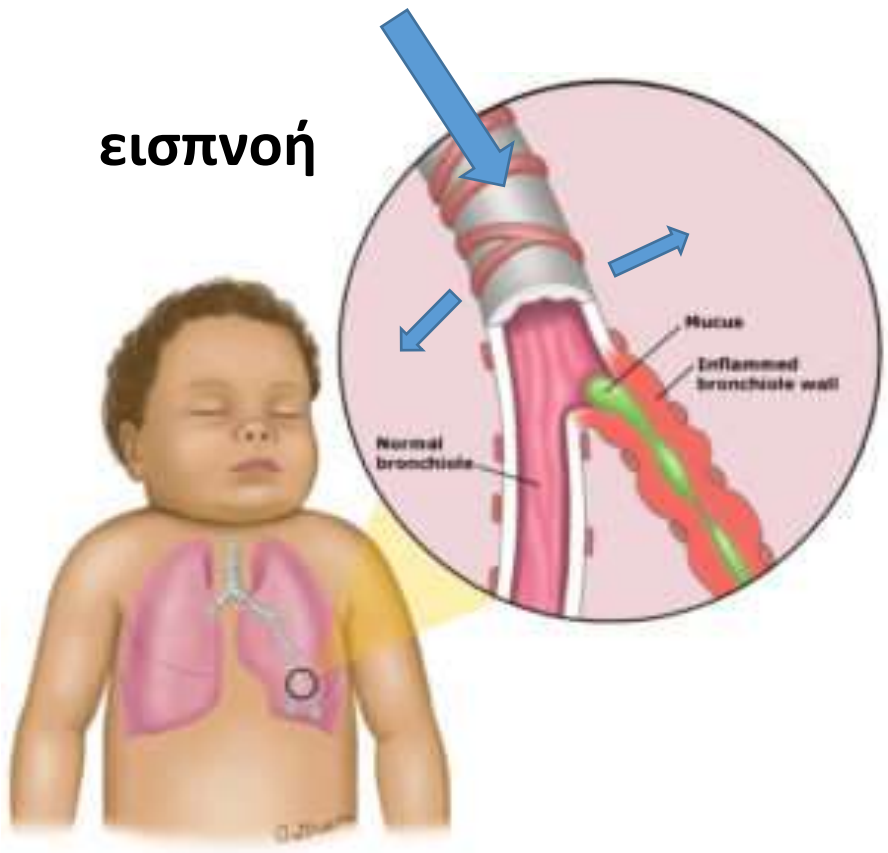
απόφραξης περιφερικών αεραγωγών και αναπνευστικής δυσχέρειας

40%	2 εβδ
18%	3 εβδ
10%	4 εβδ

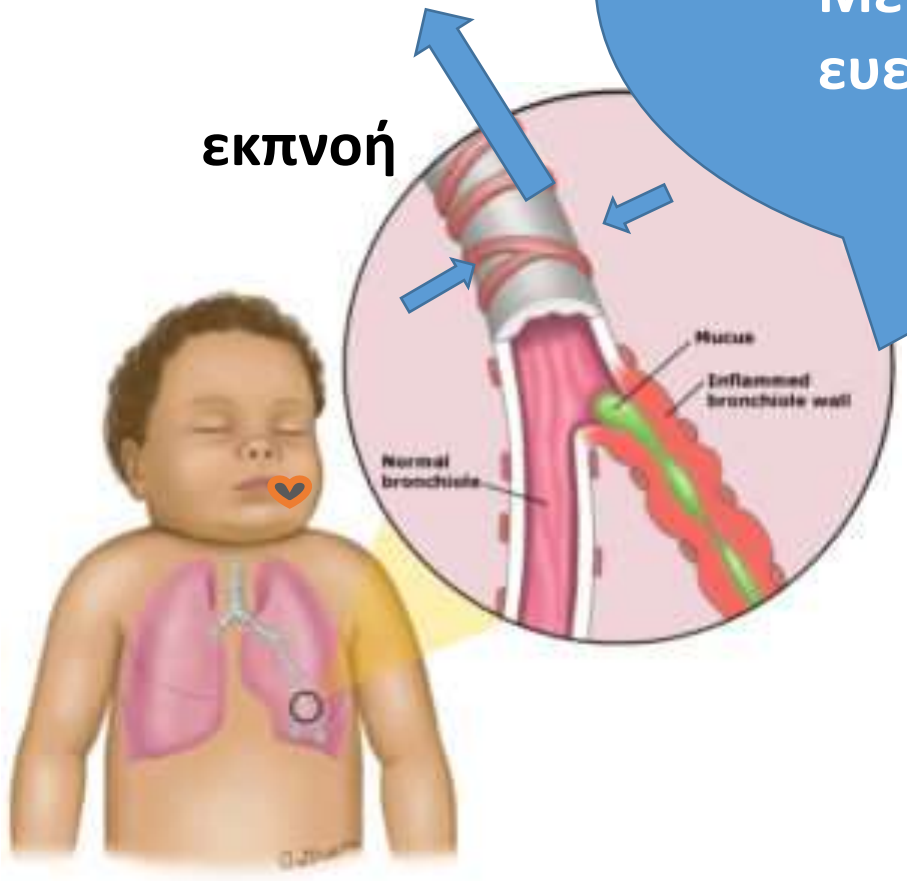
Συριγμός (υψηλής συχνότητας μουσι

ΒΡΕΦΗ
- **Μικρότερη διάμετρο**
- **Μεγαλύτερη ευενδοτότητα**

εισπνοή



εκπνοή



Respiratory Distress Assessment Instrument score

TABLE 1. The RDAI score*

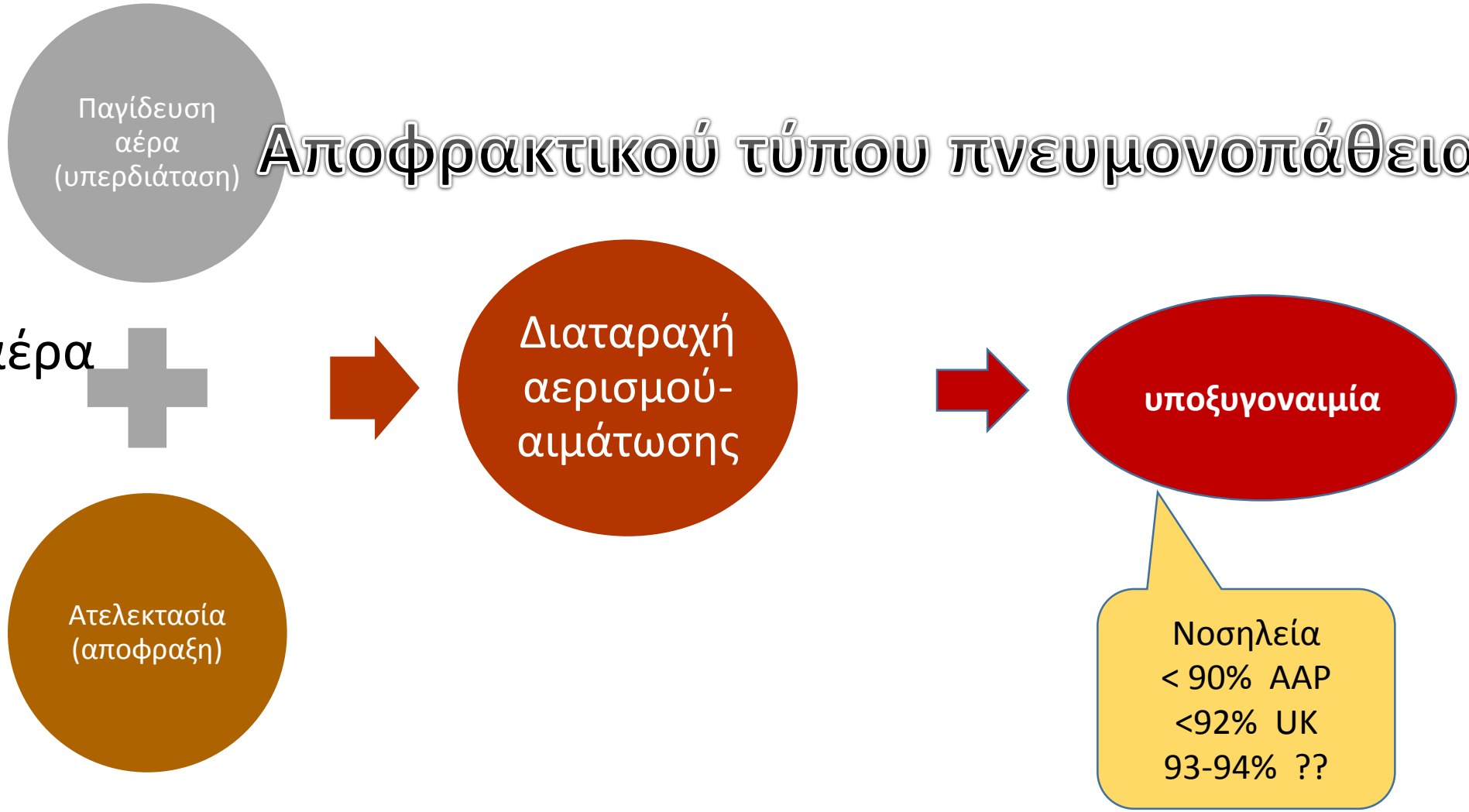
	Points					
	0	**1**	**2**	**3**	**4**	**Maximum**
Wheezing						
Expiration	None	End	1/2	3/4	All	4
Inspiration	None	Part	ALL	—	—	2
Lung fields	None	≤2 of 4	≥3 of 4	—	—	2
Retractions						
Supraclavicular	None	Mild	Moderate	Marked	—	3
Intercostal	None	Mild	Moderate	Marked	—	3
Subcostaal	None	Mild	Moderate	Marked	—	3
Total						17

*Both wheezing and retractions are scored. The RDAI score is the sum of the row scores, with total range 0 to 17; higher scores indicate more severe disease.

Howard M. Corneli, Pediatr Emer Care 2012

Φλεγμονή (οίδημα-εκκρίσεις- υπολείμματα)

- >> R
- > FRC
- Παγίδευση αέρα
- Ατελεκτασία

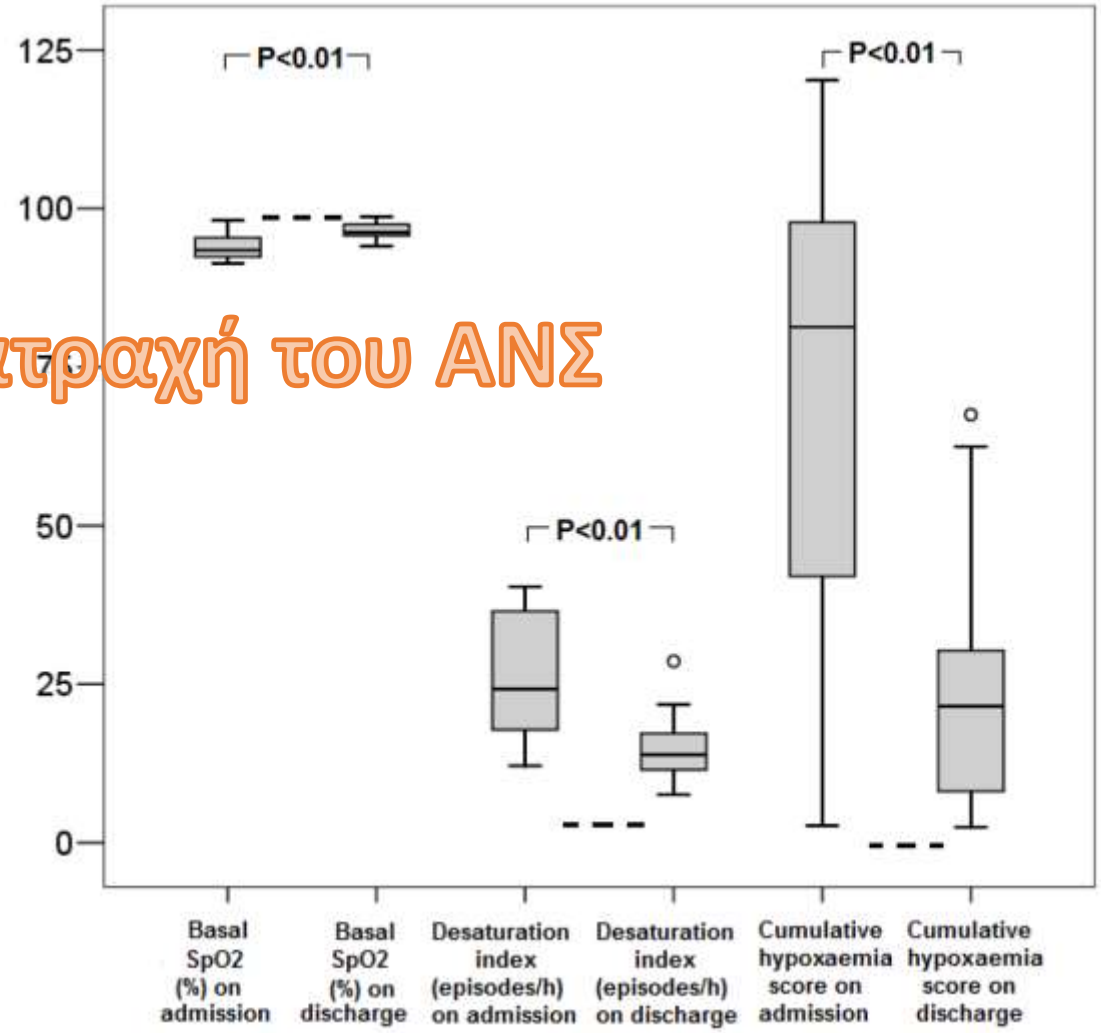


Infants with viral bronchiolitis demonstrate two distinct patterns of nocturnal oxyhaemoglobin desaturation.

Kaditis AG, Acta Paediatr. 2015

Variables	Bronchiolitis n = 21	UAO n = 11	Control infants n = 21	P value
Age, mo	2.7 (1-9.8)	2.6 (1-11.1)	2.8 (1-11.1)	0.49
Gender, male (%)	14 (66.7)	8 (72.7)	14 (66.7)	0.93
Days of bronchiolitis symptoms	[illegible]	NA	NA	NA
RDAI score	4 (2-7)	NA	NA	NA
SpO_2 while awake (%)*	96 (91-98)	97 (96-98)	99 (97-100)	<0.001
Oximetry recording duration (min)	454 (353.6-682)	588 (492.8-690.8)	507 (307.4-678.2)	0.16
Nocturnal basal SpO_2 (%)*†	93.7 (91.1-96.8)	96.9 (95.3-98.1)	98.7 (96.9-99.3)	<0.001
Nocturnal oxygen desaturation (≥3%) of haemoglobin index (episodes/hour)*	23.3 (10.3-46.6)	15.5 (5.4-36.4)	3.1 (0.3-5.5)	<0.001
Nocturnal cumulative hypoxaemia score*†	75.8 (19.2-120.7)	17.1 (1.9-46.1)	0.8 (0.1-2.6)	<0.001

απνοιες οφείλονται σε διατραχή του ΑΝΣ



bronchiolitis risk score

- being ≤2 months of age;
- Having apnea; oxygen saturation of <90%;
- signs of increased work of breathing [including nasal flaring, grunting, and retractions];
- dehydration and/or
- poor feeding

Freire et al, as part of the Pediatric Emergency Research Networks, addressed this knowledge gap by analyzing data that were collected from 38 emergency departments
Pediatrics. 2018

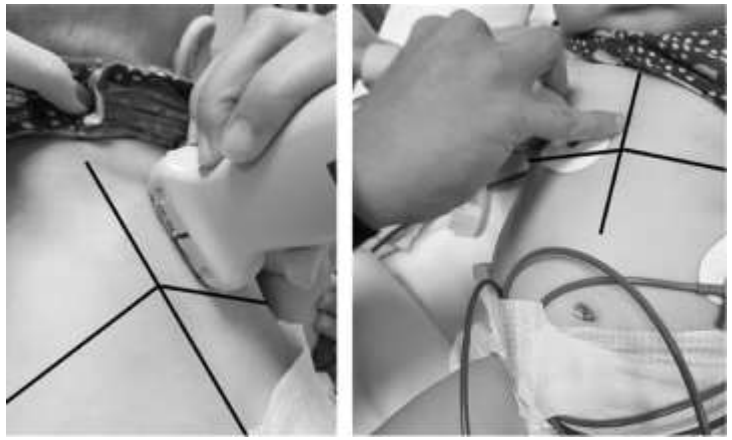
Υποκείμενη νόσο (ΒΠΔ, ΣΚ)

Περιοριστικού τύπου πνευμονοπάθεια

α/α θωρακα. Πότε;;

- Η νόσος είναι σοβαρή ή εξαιρετικά σοβαρή (βλ. ενότητες 6.1. και 6.2 καθώς και Πίνακα 2)
- Η νόσος είναι ήπιας ή μέτριας βαρύτητας, αλλά υπάρχει ιστορικό καρδιοπάθειας, χρόνιας πνευμονοπάθειας, ανοσοανεπάρκειας ή υποψία μυοκαρδίτιδας
- Η νόσος είναι ήπιας ή μέτριας βαρύτητας αλλά συντρέχουν λόγοι που καθιστούν το επεισόδιο άτυπο, όπως:[14]
  - Υψηλός πυρετός >39-40°C
  - Απουσία πρόδρομων συμπτωμάτων από το ανώτερο αναπνευστικό σύστημα
  - Συχνές υποτροπές, ιδιαίτερα εάν δεν υπάρχει προηγούμενος ακτινογραφικός έλεγχος
- Η κατάσταση του βρέφους εμφανίζει αδικαιολόγητη επιμονή της κλινικής εικόνας, απρόβλεπτη επιδείνωση ή πιθανολογείται εισαγωγή στη Μονάδα Εντατικής Θεραπείας (ΜΕΘ).

ultrasound in infants with bronchiolitis



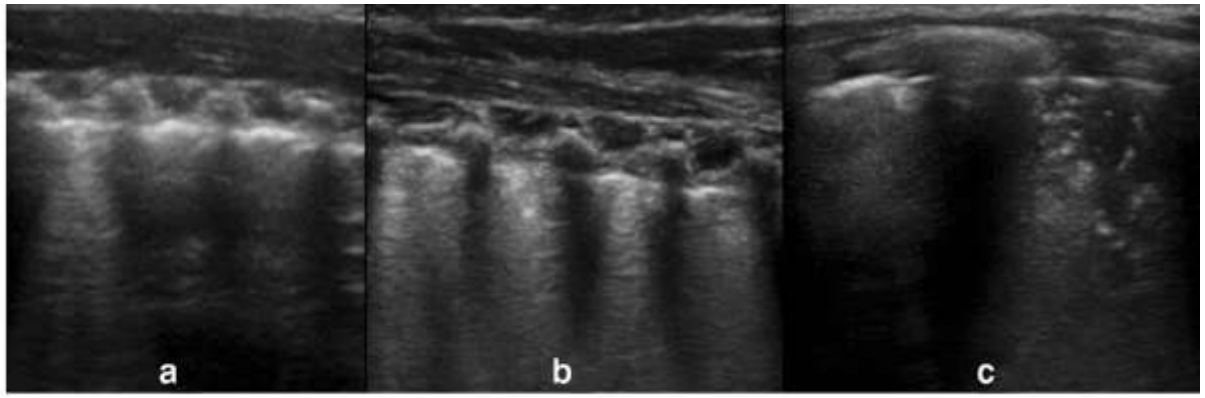
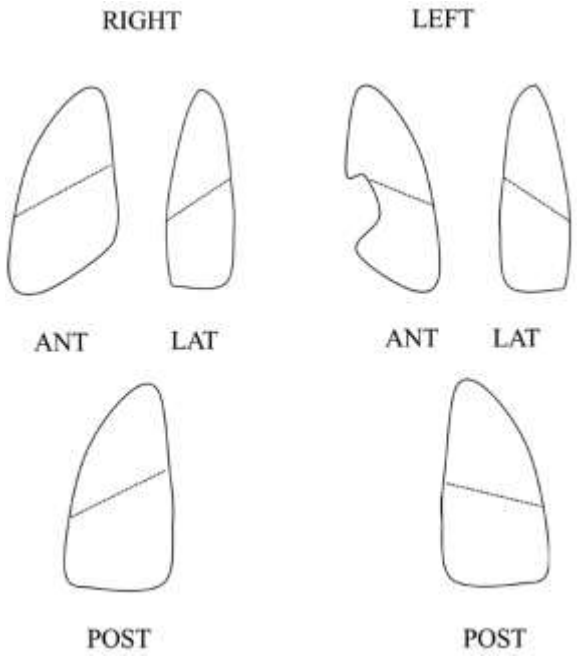
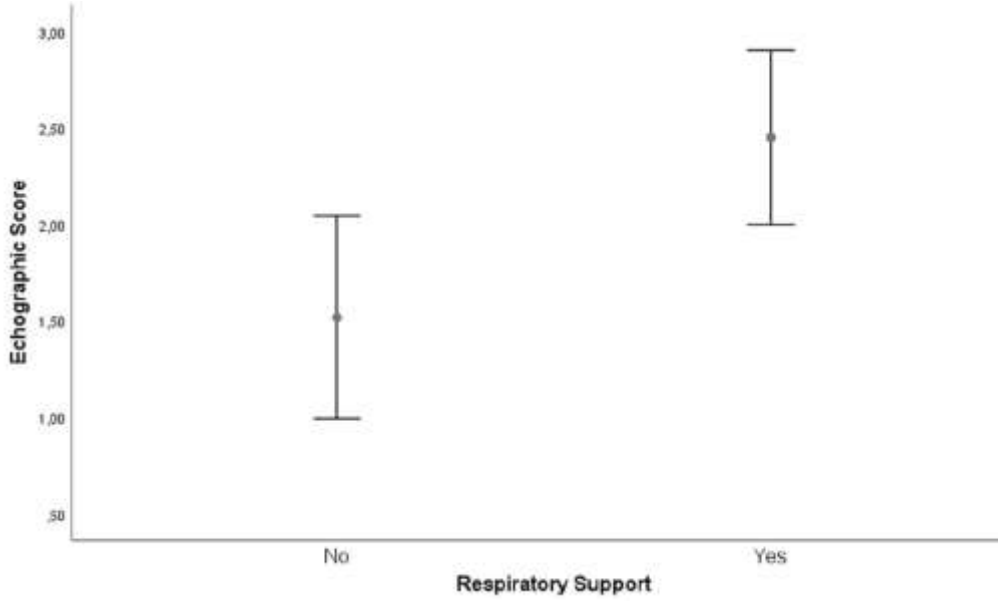


Fig. 3 Ultrasound score: **a** mild interstitial syndrome, **b** white lung, **c** subpleural consolidation > 1 cm





Maria Chiara Supino European Journal of Pediatrics 2019

Hubble D, Osborn GR. Acute Bronchiolitis in Children. Br Med J. 1941; 1: 107-126.1

Bronchiolitis was described as an inflammatory "*respiratory obstruction caused by mucus in the bronchioles" presenting "with a slight temperature, pharyngeal cough and some gastrointestinal upset", followed by a phase when "bronchioles become plugged with exudate and the clinical picture is dominated by obstructive dyspnea. Respiratory distress is then very marked... Cough is always incessant and disturbing."*

Ralston SL et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics 2014*

Bronchiolitis is now according to the American Academy of Pediatrics (AAP) "*a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing… characterized by acute inflammation, edema and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm.*

Βρογχιολίτιδα περιλαμβάνει πολλές νόσους

(όπως πυρετός ή άσθμα)

Η διάγνωση παραμένει κλινική αλλά πολλοί φαινότυποι

Κλινική εικόνα

- Συριγμός
- Λίγη ή πολύ παγίδευση αέρα
- Βήχας , ΒΥΑ
- Σπάνιες ή άφθονες εκκρίσεις
- Συνύπαρξη πνευμονίας ατελεκτασίας ή RDS

Διαφορετικοί μηχανισμοί (άφθονές καλές μελέτες)

ή

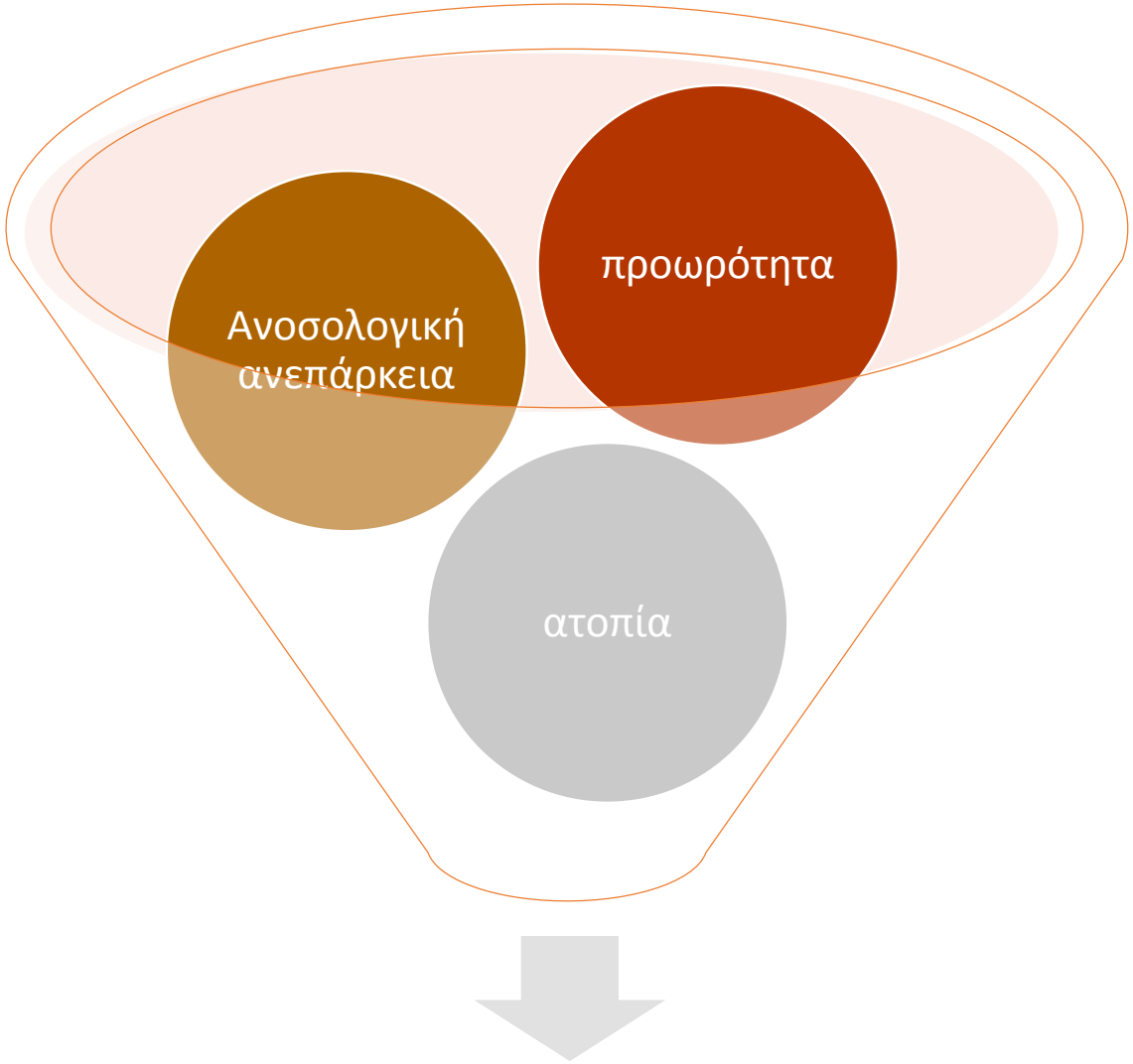
Διαφορετικοί ιοί που δρούν διαφορετικά σε κάθε ηλικία με διαφορετική φλεγμονώδη αντίδραση

The wheezy legacy of infant bronchiolitis
Fabio Midulla

The question is still open.
Is it RSV that causes bronchial hypersensitivity and the development of asthma or rather, does the virus identify those infants that have a genetic predisposition for the development of recurrent wheeze and asthma?

Editorial Thorax 2019

Παράγοντες κινδύνου / αφαίρεση μάσκας



Αυξημένο κίνδυνο βρογχιολίτιδας

The Syndrome we agreed to call bronchiolitis
FP. Polack, RT. Stein, A.Custovic

…severely-ill hosts who are frequently “unmasked” by the pathogen include children with a specific at-risk background: premature infants with bronchopulmonary dysplasia, children with atopic backgrounds, and future asthmatics.

J Infect Dis. 2019

Ανταπόκριση στην θεραπεία

Paediatric Research in Emergency Departments International Collaborative (PREDICT). Australasian Bronchiolitis Guideline. 2016
National Institute for Health and Care Excellence (NICE) bronchiolitis guideline 2017
AAP 2016

In 2016, the Paediatric Research in Emergency Departments International Collaborative (PREDICT) published the Australasian Bronchiolitis Guideline to provide a single source evidence-based framework for the diagnosis and management of infants in EDs and paediatric inpatient units. The translation of this guideline into practice represents a significant challenge, as it largely provides guidance on what not to do.

http://www.predict.org.au/download/Australasian-bronchiolitis-guideline.pdf

Διάσταση απόψεων μεταξύ μελετών και ιατρικών πρακτικών

- Πολλές υψηλής αξίας μελέτες δείχνουν την έλλειψη ωφέλειας από την χρήση πολλών θεραπευτικών επιλογών “nothing works.”

- Η αίσθηση ότι κάτι πρέπει να κάνεις τουλάχιστον για ψυχολογικούς λόγους.
- Η δυσκολία να αποποιηθείς πρακτικές που εφαρμόζονταν για χρόνια
- Η αίσθηση ότι αυτές οι παλιές πρακτικές ωφελούν αρκετά παιδιά. one-size doesn't fit-all

UK, USA και SWISS studies

- full compliance with the guideline did not change with **18%** of Trusts compliant before publication of the guideline in 2015 and **19%** fully compliant with the guideline in 2017

- routinely testing hospitalized infants for respiratory viruses significantly decreased between 2015 and 2017
  - 40% reported ordering a chest radiograph (CXR),

- Reduced use of nebulised bronchodilators and hypertonic saline and provision of parental written guidance.
  - 38% prescribed bronchodilators

Barr R. Change in viral bronchiolitis management in hospitals in theUK after the publication of NICE guideline.Journal of Clinical Virology (2018)
Parikh K, Hall M, Teach SJ. Bronchiolitis management before and after the AAP guidelines. Pediatrics 2014;
Barben J et al. Management of acute bronchiolitis:can evidence based guidelines alter clinical practice? Thorax 2008;
Jessica Gold et al 2018

Preschool respiratory hospital admissions following infant bronchiolitis: a birth cohort study

Φυσική πορεία

Patients: bi
followed up
Methods: V
wheezing a
had been a
hazard regr
factors inclu
condition.
Results: 16
these, 21.7
8% without
The associa
wheezing a
for URTI an
Conclusion
to fivefold r
respiratory
a subsequent respiratory hospital admission by age 5 years.

Table 2 Percentage of children with at least one respiratory admission, before 5 years of age, in those with previous infant bronchiolitis admissions and those without

	Infants admitted with bronchiolitis	No admission for bronchiolitis in infancy
Respiratory condition admission	21.7 (21.0 to 22.3)	7.62 (7.56 to 7.69)
Asthma admission	4.27 (3.96 to 4.58)	0.880 (0.856 to 0.903)
LRTI admission	6.77 (6.38 to 7.15)	2 (1.97 to 2.04)
URTI admission	11.9 (11.4 to 12.4)	4.75 (4.70 to 4.81)
Wheezing admission	4.84 (4.51 to 5.17)	0.884 (0.860 to 0.908)

Helen Skirrow, et al Arch Dis Child 2018

Severe bronchiolitis profile and recurrent wheeze by age 3y

1016 infants with bronchiolitis defined according to the American Academy of Pediatrics.

Profile A: infants with a history of eczema and of breathing problems, elevated blood eosinophil, Haemophilus or Moraxella dominant microbiota and, most of them infected by RV

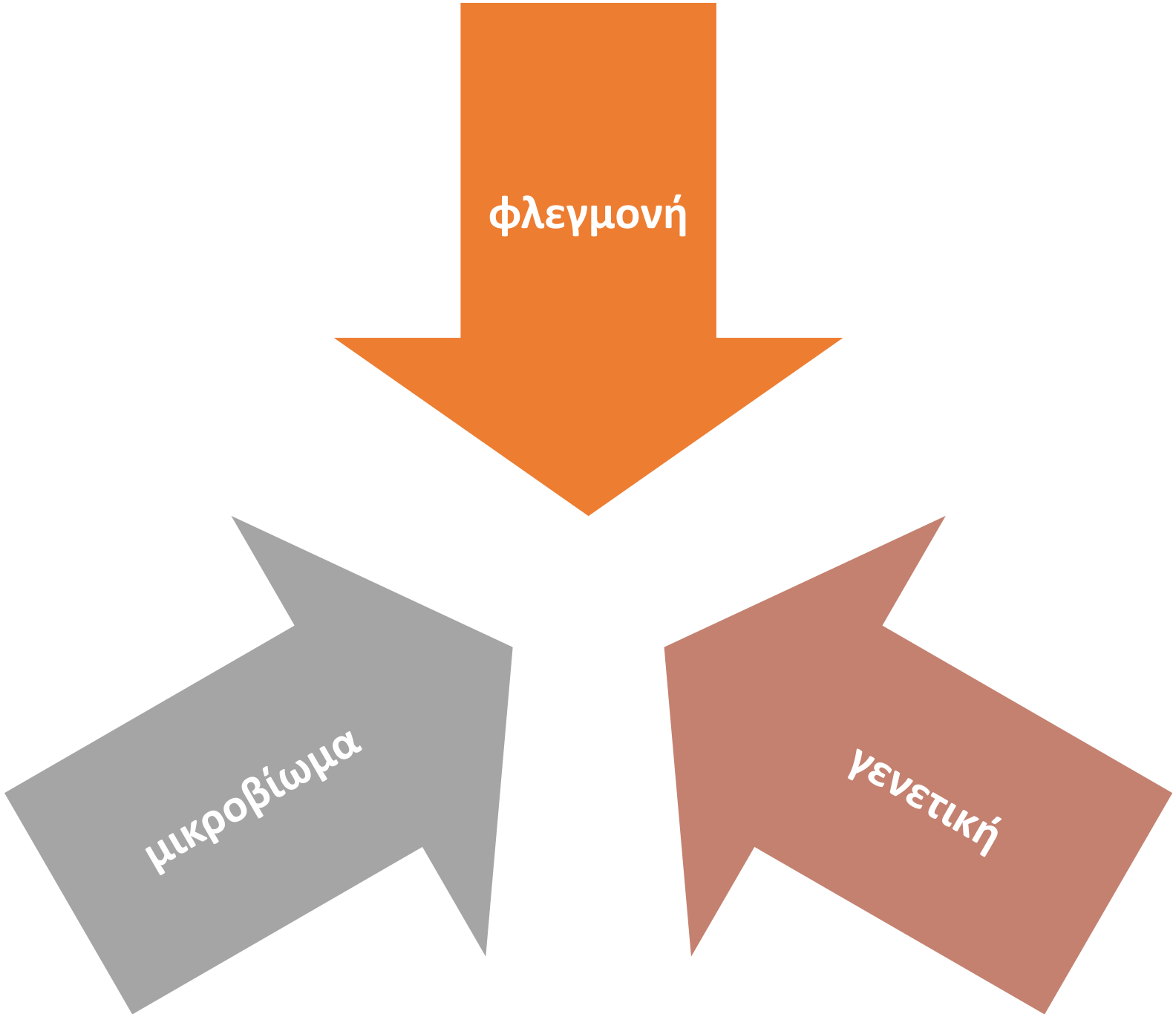
Profile B: mainly infants with RSV bronchiolitis, with a less predominant history of breathing problems or eczema.

Profile C: younger infants with the most severe bronchiolitis, most of whom were infected by RSV.

The RR to develop RW after 3 years of follow-up was high in infants from profile A, moderate in infants from profile C and low in infants from profile B.

Asthma was associated only to profile A.

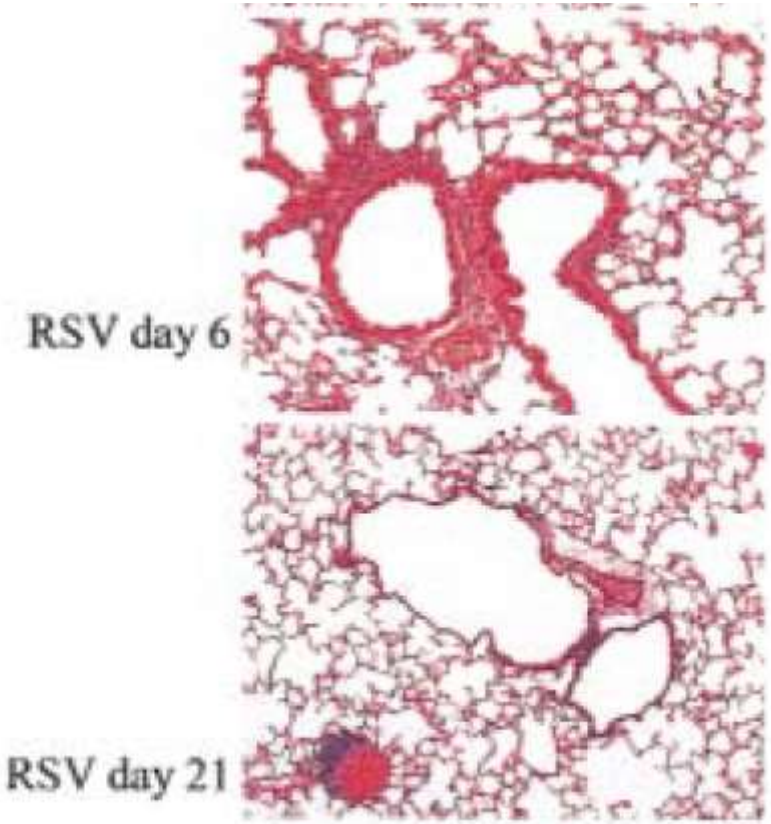
Dumas O. J Allergy Clin Immunol 2019

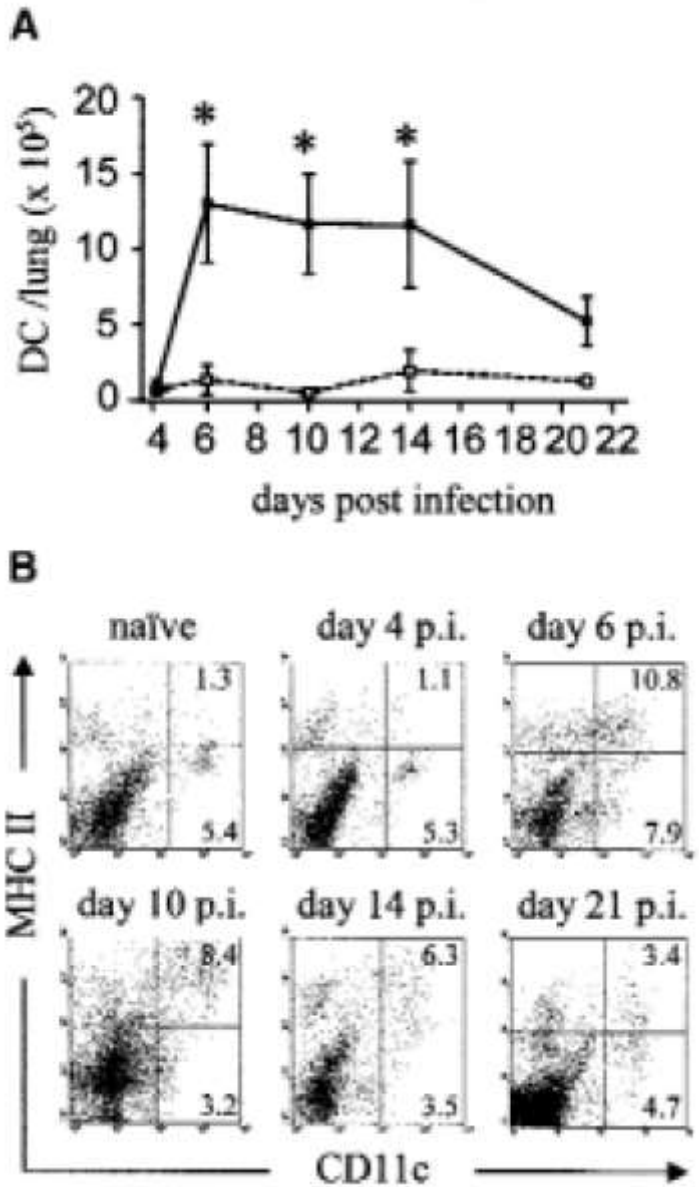

φλεγμονή
μικροβίωμα
γενετική

Διαφορετική φλεγμονώδης διεργασία

- Abs-virus complex
- Th2-mediated bronchoconstriction
- direct viral injury of the small airways (T Killers)
- innate inflammation (macrophases/defencins of surfanctan and TLR)
- airways plugging due to debris and mucus production (IL 8 neutrophils elastase, MPO, MPt)

Φλεγμονή –Δενδριτικα κύτταρα



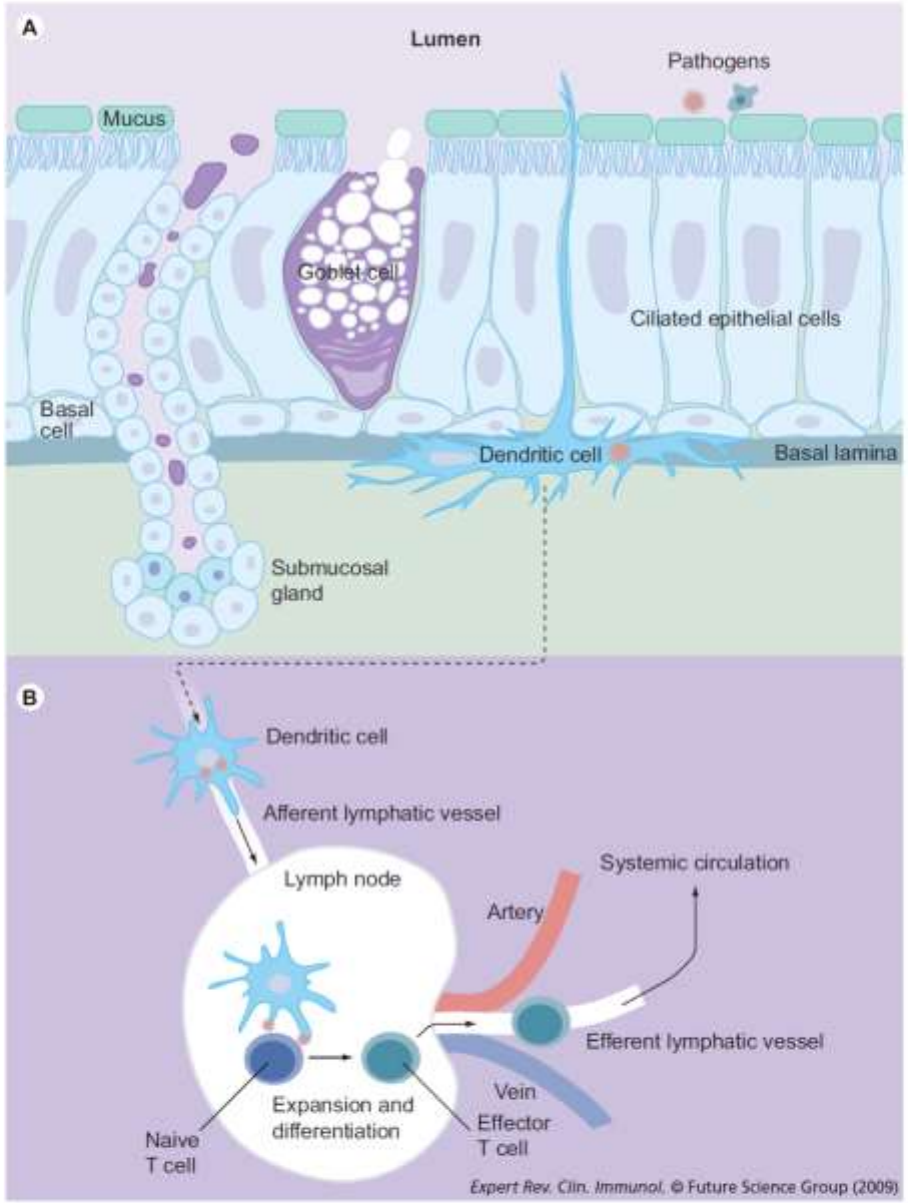


RSV infection results in sustained increases in numbers of mature dendritic cells in the lung. These might well contribute to the development of intense airway inflammation and airway hyperresponsiveness after RSV infection

Berger M. J Allergy Clin Immunol 2004

Dendritic cells in viral bronchiolitis

- Ακρογωνιαίος λίθος της ανοσολογικής απάντησης σε ιούς. Κύριος συνομιλητής
- Φυσική ανοσία με την παραγωγη IFNς τυπου-1
- Επίκτητη ανοσία με την ρύθμιση των CD4 T λεμφοκυττάρων



P. Maggina. Expert Rev Clin Immunol 2009

Dendritic cells in viral bronchiolitis

Table 1. Comparison of the effects of different respiratory viruses on dendritic cell function and immune response.

Virus	Infection of DCs	Maturation of DCs	Cytokine production	Type I IFN production	CD4 T-cell stimulation
RSV	Yes	Yes	Impaired +	Yes	Impaired ++
MPV	Yes	No	Impaired ++	Yes	Impaired +
RV	Yes	?	Impaired	Yes	Impaired
PIV	Yes	Yes	Impaired ++	Yes	Impaired ++
FLU	Yes	Yes	Not impaired in low MOI	Yes	Not impaired
AdenoV	Yes	?	Impaired	Yes	Impaired
CoV	No	No	Not impaired	Poor ?	Not impaired

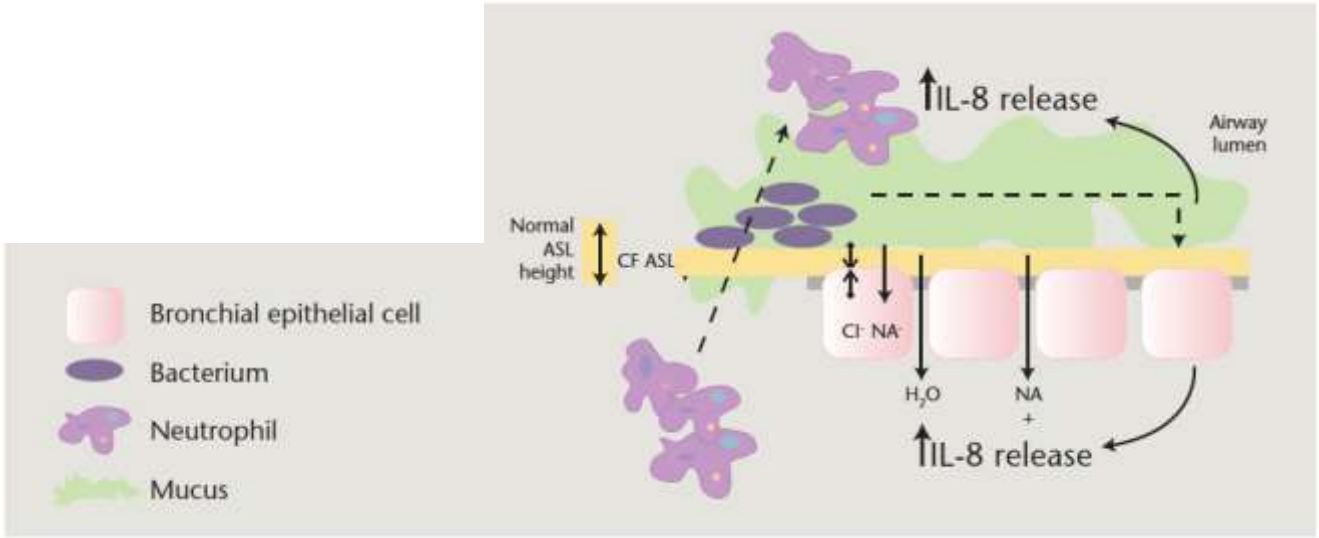
+: Impaired to a high degree; ++: Impaired to a very high degree; ?: Not clearly established.
AdenoV: Adenovirus; CoV: Coronavirus; DC: Dendritic cell; FLU: Influenza virus; IFN: Interferon; MOI: Multiplicitiy of infection; MPV: Metapneumovirus; PIV: Parainfluenza virus; RSV: Respiratory syncytial virus; RV: Rhinovirus.

P. Maggina. Expert Rev Clin Immunol 2009

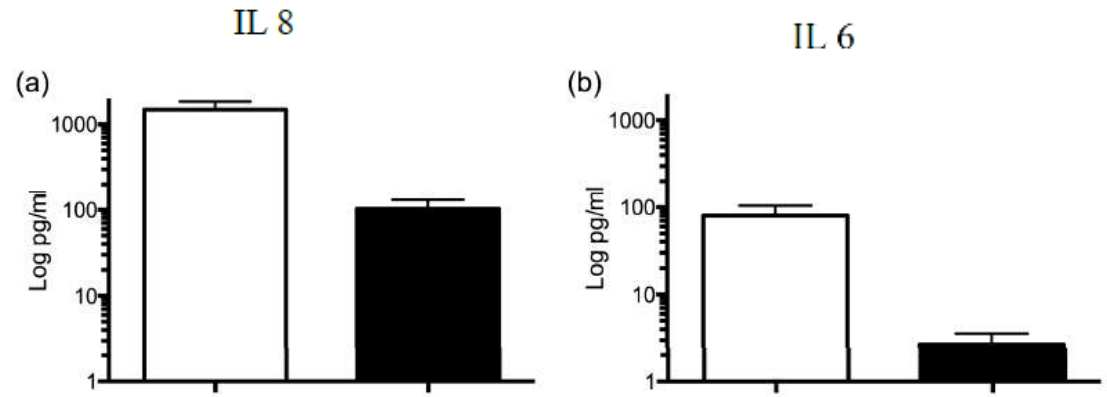
Φλεγμονή

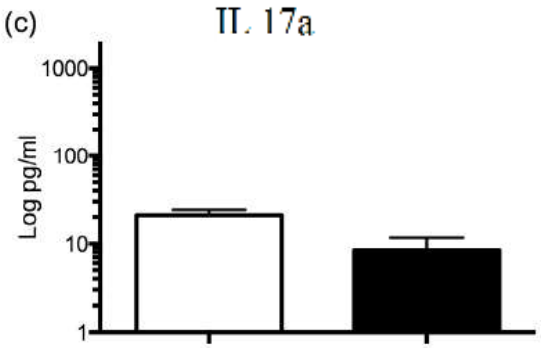
- IL 8 (neutrophil chemotactic factor,)
  - Ουδετεροφιλία
  - Αυξημένη επιβίωση ουδετεροφίλων
- myeloperoxidase και human neutrophil elastase
- Secretions /cough
- neutrophil numbers correlate with IL-8 levels and that both IL-8 levels and neutrophil numbers correlate closely with symptom severity
- lung sections of fatal cases of infant bronchiolitis show abundant accumulation of neutrophils and macrophages in the airways

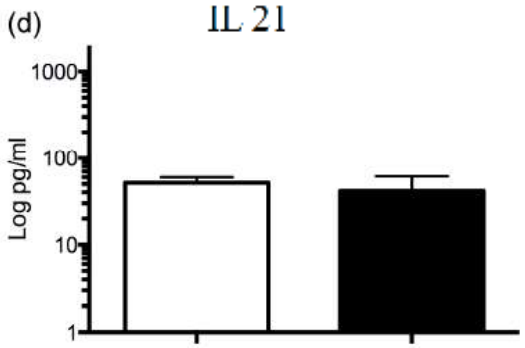
- IL6 and IL17 pro-inflammatory cytokine
- IL-17 acts in concert with TNF and IL-1
- ?protection or increase in allergy and remodeling

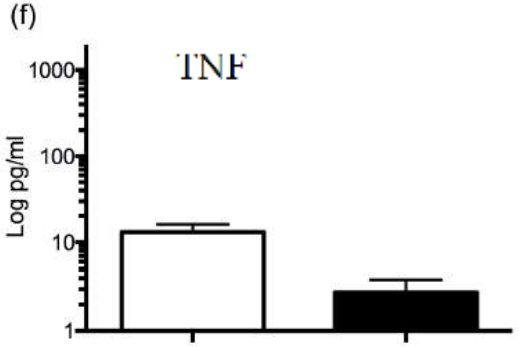


Cytokine responses in primary and secondary respiratory syncytial virus Infections









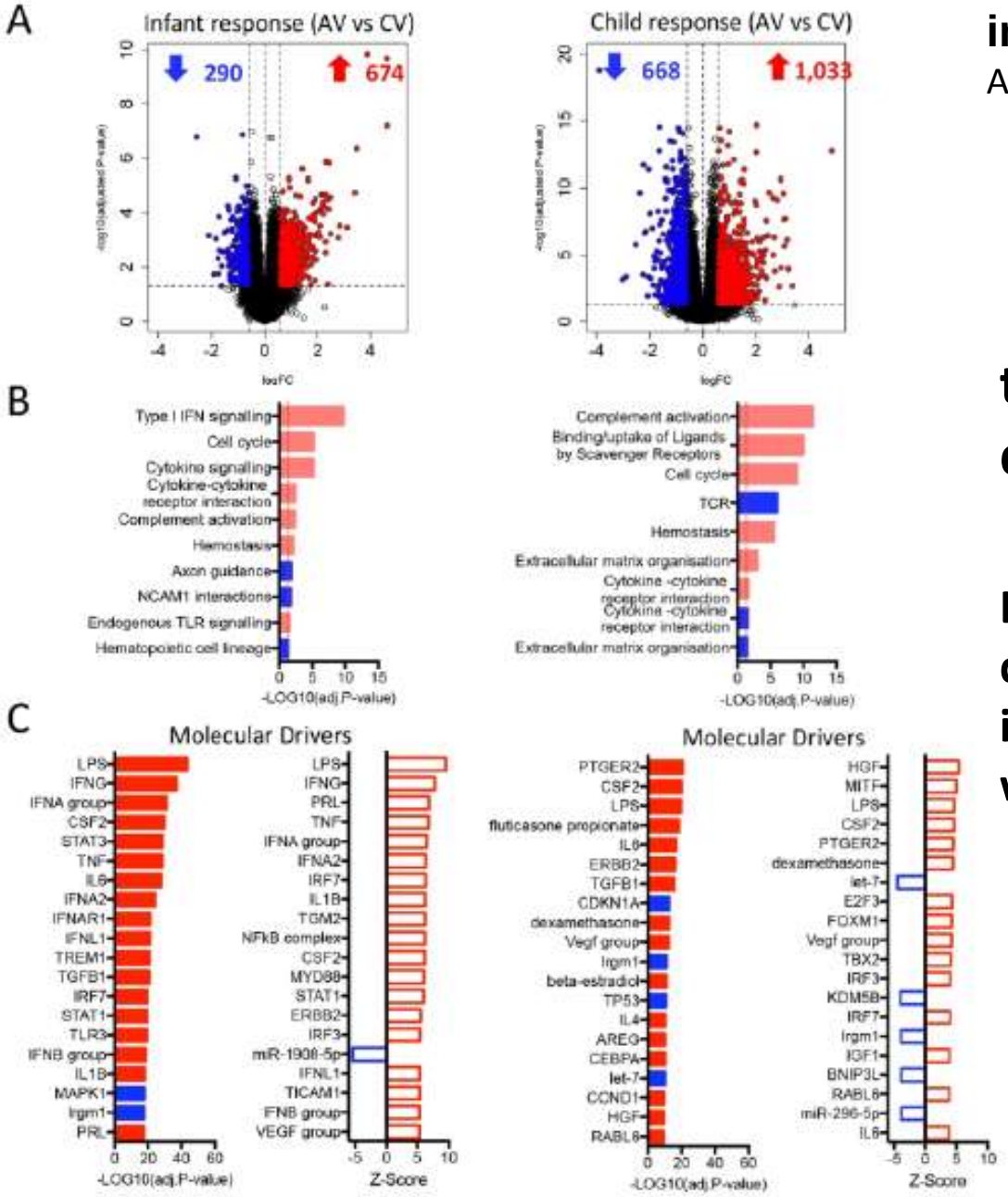
RSV positive Infants
RSV positive Siblings

Levels of IL-8 and IL-6 were significantly lower during the secondary infections

Mark L Everard . Pediatric Research 2016

Personalised transcriptomics reveals heterogeneous immunophenotypes in children with viral bronchiolitis

Anya C Jones,Patrick G Holt *University of Western Australia*



the most prominent differences were firstly the dominance of type 1 IFN

Local airway mucosal responses were comparable qualitatively in infants/children, dominated by interferons type 1-3, but the magnitude of upregulation was multi-fold higher in infants than children.

AJRCCM 2018

Personalised transcriptomics reveals heterogeneous immunophenotypes in children with viral bronchiolitis

Anya C Jones,……Patrick G Holt *University of Western Australia*

Infant response

- dominated by monocyte-associated hyper-upregulated type 1 interferon signalling/**pro-inflammatory pathways** (drivers: TNF, IL6, TREM1, IL1B),

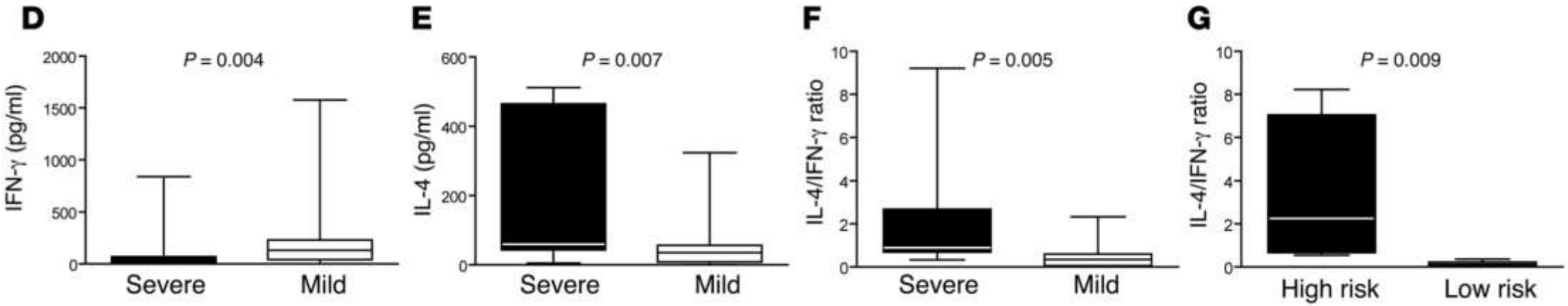
Children response

- combination of inflammation (PTGER2, IL6) plus **growth/repair/remodelling** pathways (ERBB2, TGFB1,AREG, HGF) coupled with **Th2 and NK-cell** signaling
- subset of older children demonstrate infant-equivalent hyper-upregulation of interferon pathways.

- IFNL υπερ-εκφρασή/ δυσλειτουργία έχει συσχετιστεί με μαζική φλεγμονώδη αντίδραση και τελικά καταστροφή του αναπνευστικού επιθηλίου
- Αυξημένη έκφραση πολλών κιτοκινών οδηγεί σε ενισχυμένη φλεγμονή
- Παρουσία μικρού αριθμού NK cell στο περιφερικό αίμά και στους αεραγωγούς έχει συσχετιστεί με σοβαρότερη κλινική εικόνα RSV (μειωμένη κυτταροτοξικότητα και απομάκρυνσή του ίού)

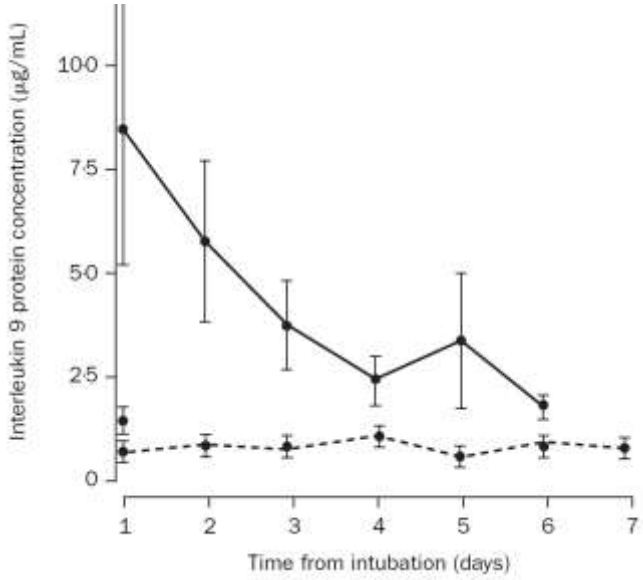
AJRCCM 2018

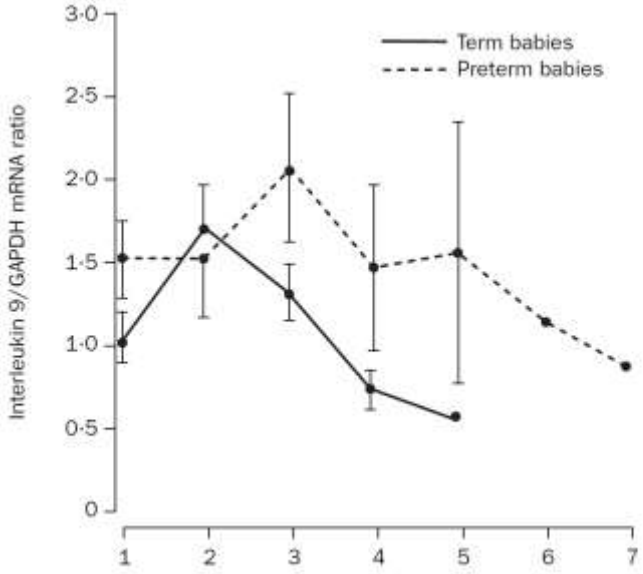
Severe RSV bronchiolitis and TH2 polarization



J Clin Invest. 2015

Severe RSV bronchiolitis in the U.K. has been linked to IL-9 levels (BHR)





Term preterm

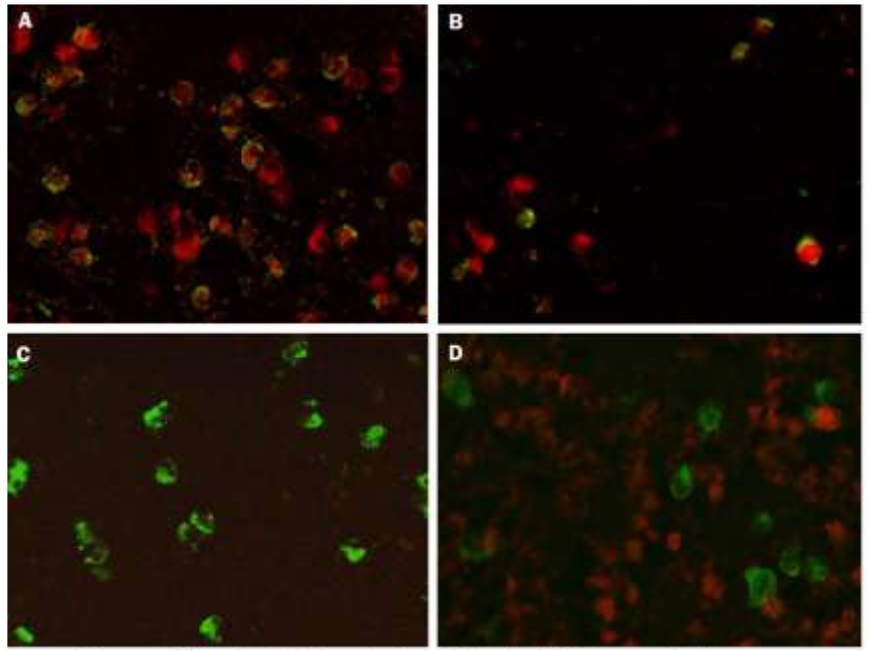
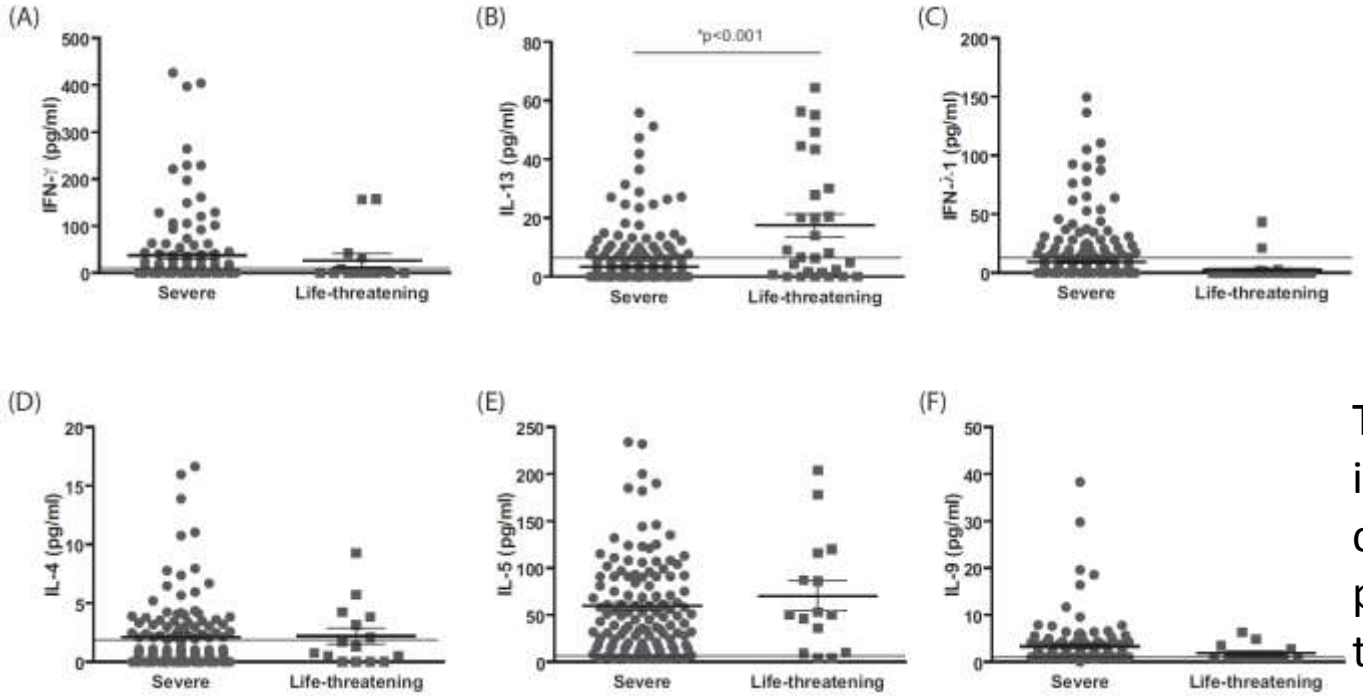


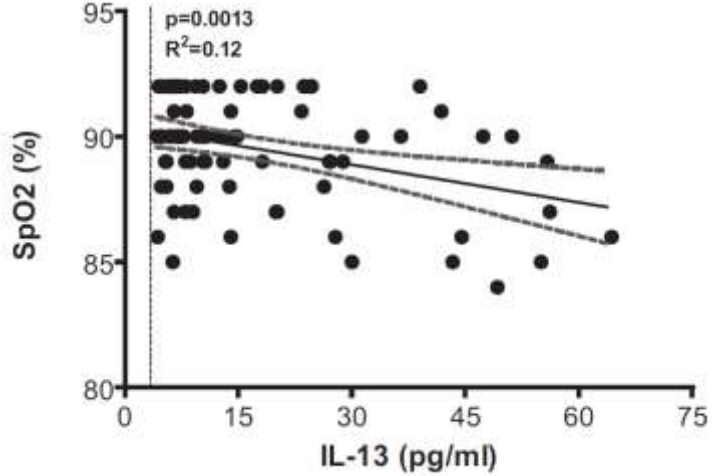
Figure 3: **Immunohistochemical localisation of interleukin 9 expression in bronchoalveolar lavage cells**

McNamara PS[1], Flanagan BF, Baldwin LM, Newland P, Hart CA, Smyth RL Interleukin 9 production in the lungs of infants with severe respiratory syncytial virus bronchiolitis. Lancet. 2004

Interleukin-13 associates with life-threatening rhinovirus (RV) infections in infants and young children

	All rhinovirus + patients $n = 347$	Severe disease O_2 saturation 88-93% $n = 315$ (90.78%)	Life-threatening disease O_2 saturation <87% $n = 32$ (9.22%)
Laboratory variables			
IL 13, pg/mL (mean, range)	4.93 (0.001-31.33)	3.42 (0.001-31.33)	17.31 (0.001-27.83)
IFNλ_1, pg/mL (mean, range)	8.98 (0.001-96.3)	9.15 (0.001-96.3)	2.55 (0.001-43.35)



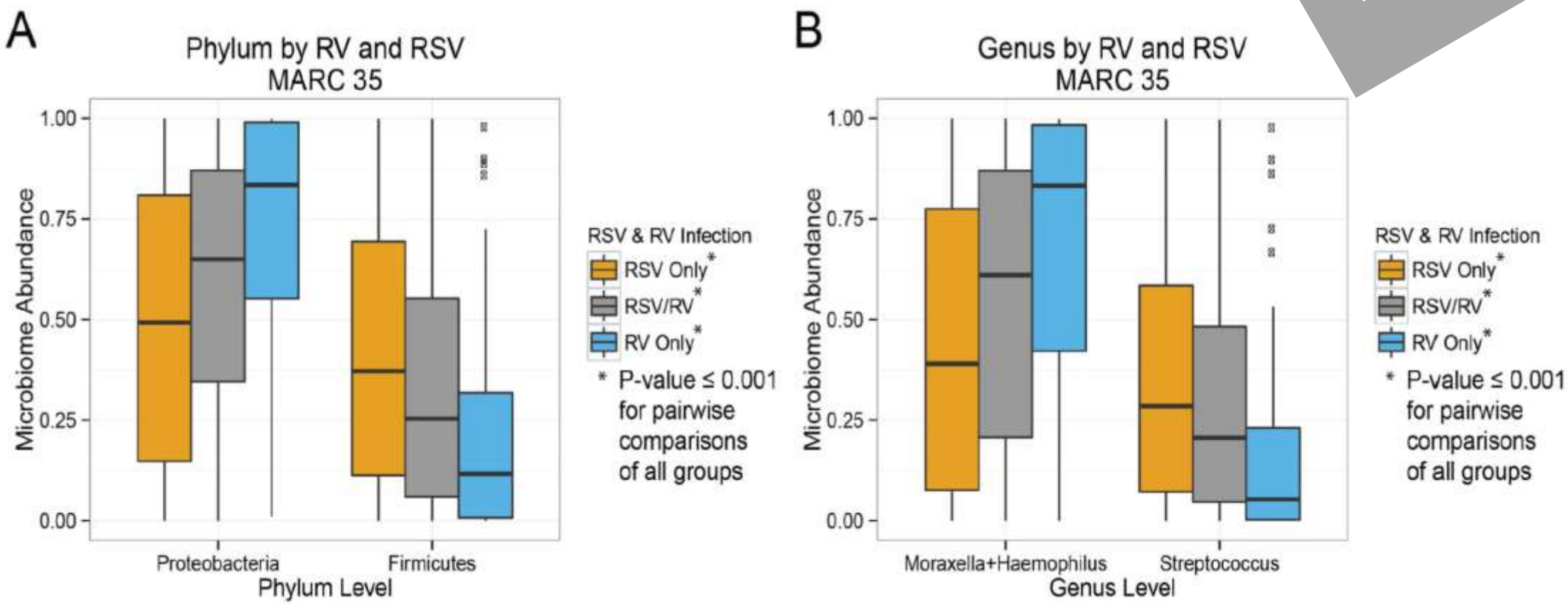


This cytokine down-regulates macrophage activity, thereby inhibits the production of pro-inflammatory cytokines and chemokines. This cytokine is found to be critical to the pathogenesis of allergen-induced asthma but operates through mechanisms independent of IgE and eosinophils

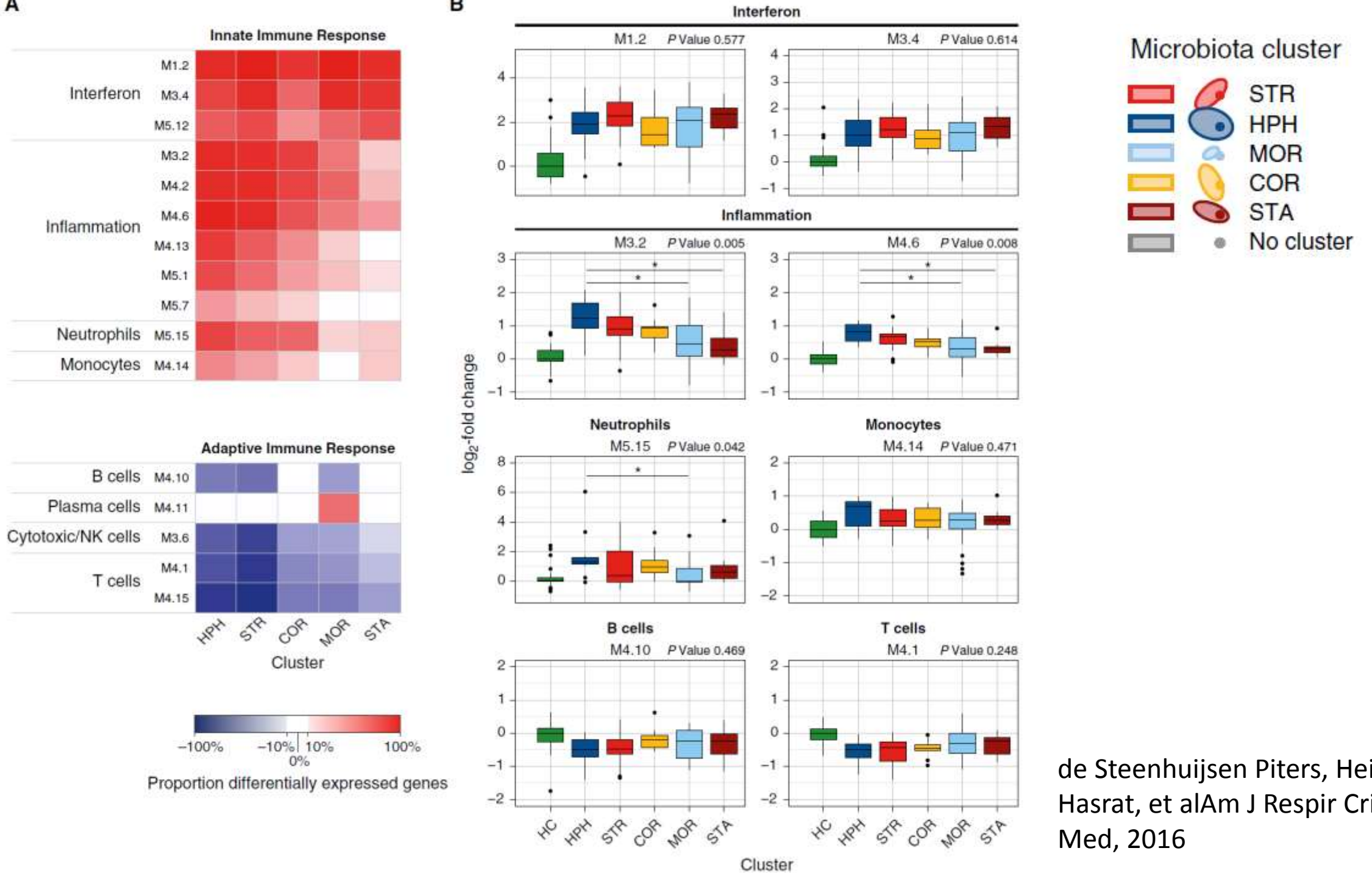
Mauricio T. Caballero, Pediatric Pulmonology 2018

Respiratory syncytial virus and rhinovirus severe bronchiolitis are associated with distinct nasopharyngeal microbiota

μικροβίωμα

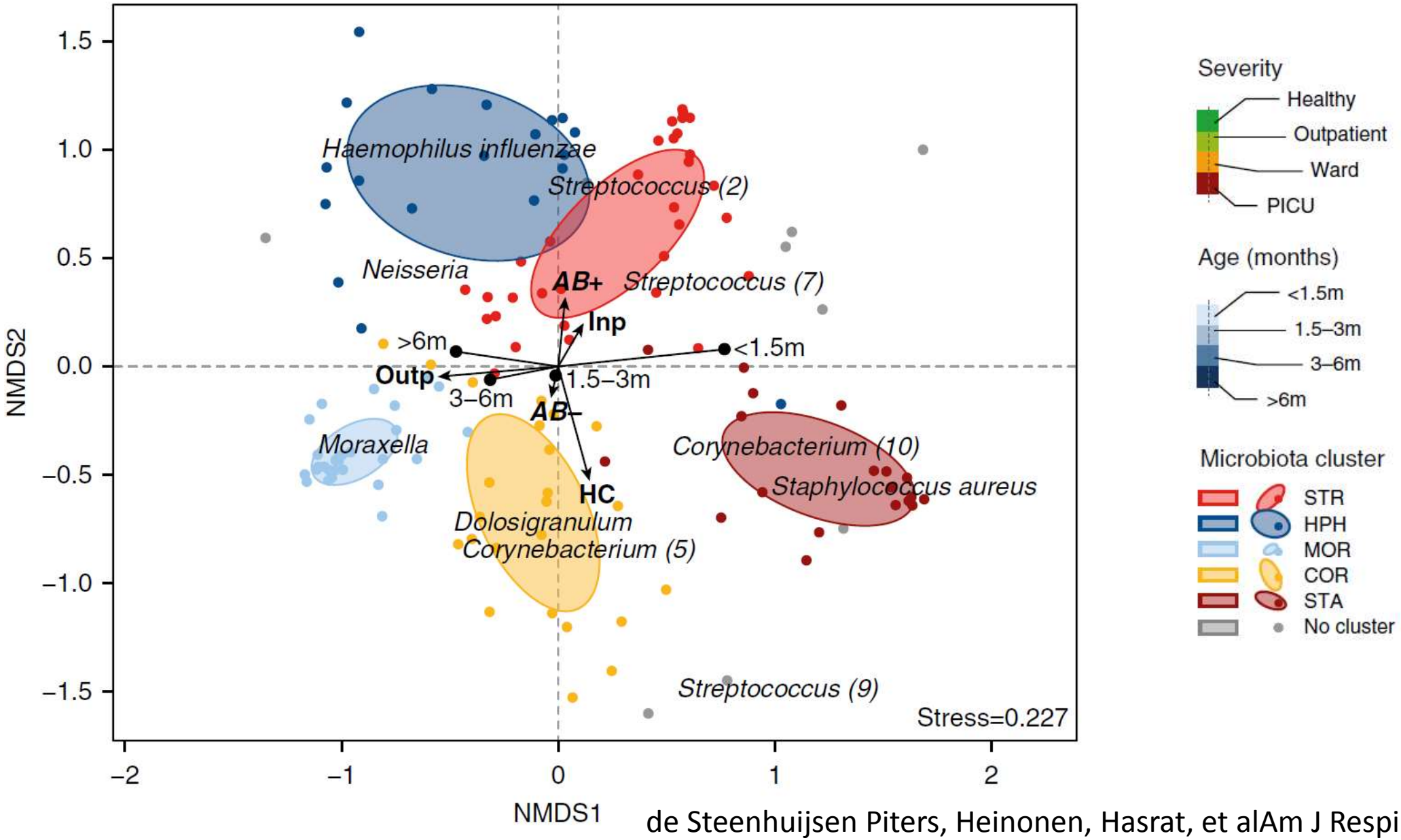


JACI 2017



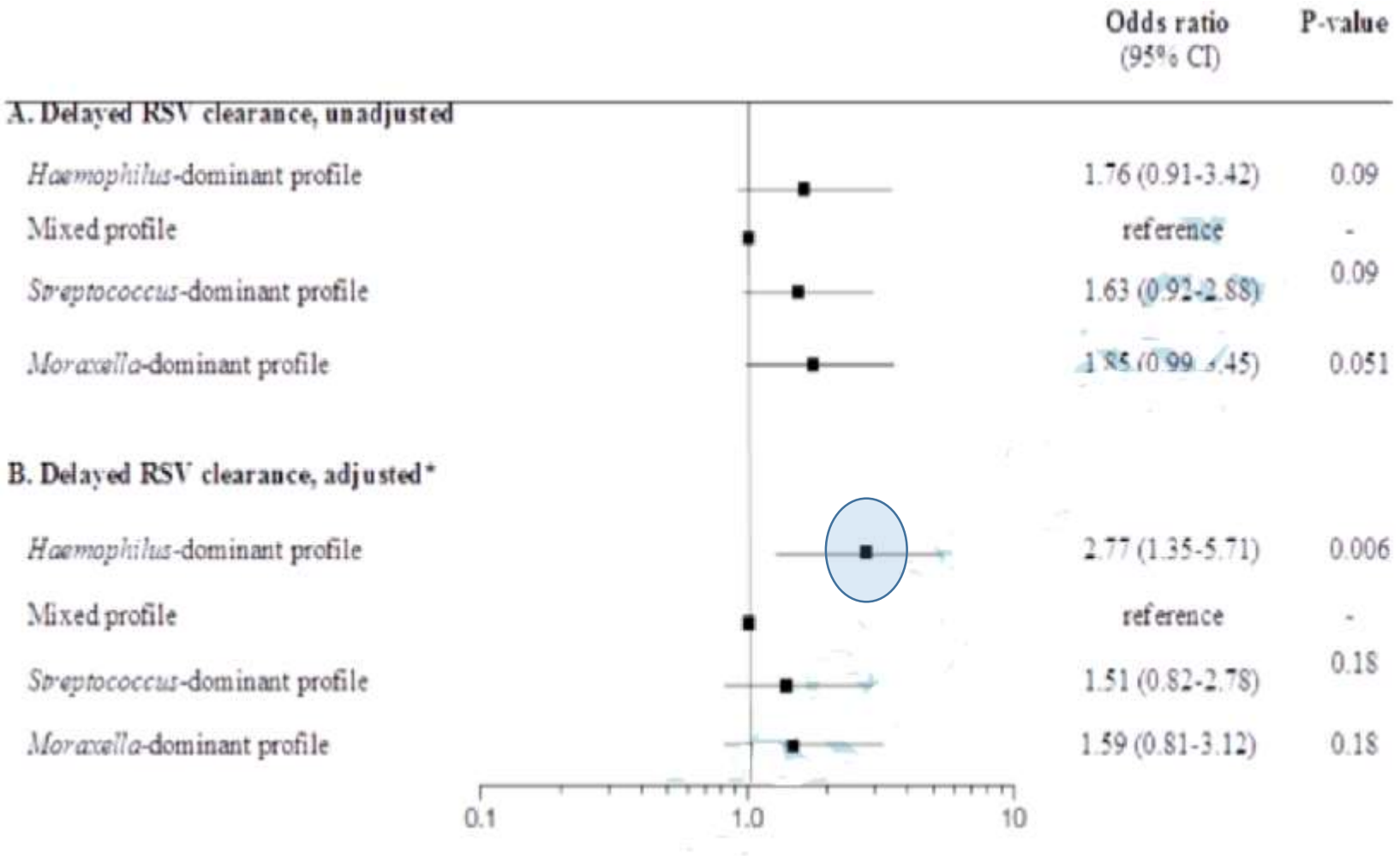
de Steenhuijsen Piters, Heinonen, Hasrat, et alAm J Respir Crit Care Med, 2016

Nasopharyngeal microbiota might modulate the host immune response, potentially affecting clinical disease severity.



de Steenhuijsen Piters, Heinonen, Hasrat, et alAm J Respir Crit Care Med, 2016

Haemophilus-dominant nasopharyngeal microbiota is associated with delayed clearance of respiratory syncytial virus in infants hospitalized for bronchiolitis



JM Mansbach, J Infect Dis. 2019

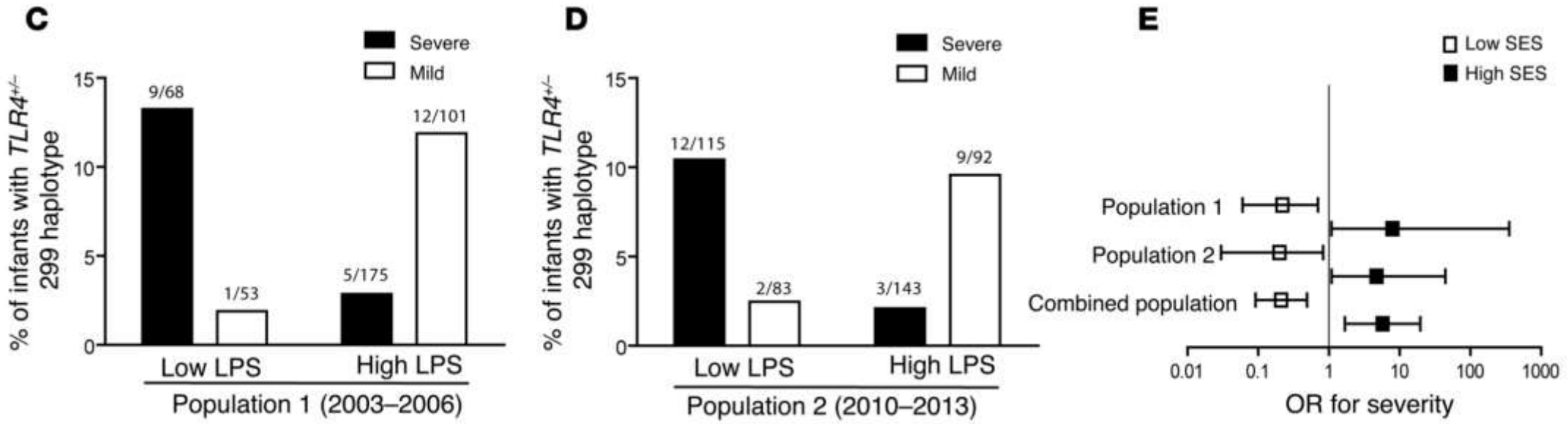
Γενετική

- Υψηλό ποσοστό παιδιών από Navajo, και Alaska χρειάζονται νοσηλεία (υψηλότερο από κάθε άλλη περιοχή της Αμερικής και ακόμα και από τα παιδιά χαμηλού κοινωνικοοικονομικου περιβάλλοντος αναπτυσομένων χωρών.

- Παιδιά στα οποία η χρήση προφύλαξης έναντι RSV δεν μπορεί να τα προφυλάξει

TLR4 genotype of the individual and environmental exposure to LPS

infants with a TLR4+/- genotype born at term experience an exorbitant ~90% hospitalization rate when visiting an emergency department with respiratory symptoms.



In middle-class urban and suburban populations, infants with loss-of-function single nucleotide polymorphisms in Asp299Gly and/or Thr399Ile (TLR4+/-) experience exaggerated Th2 responses in the respiratory tract during RSV infection and are not protected by the administration of RSV-specific mAb when premature.

Caballero MT..TLR4 genotype and environmental LPS mediate RSV bronchiolitis through Th2 polarization. J Clin Invest. 2015

Transcriptome

children with RSV infection had overexpression of neutrophil-related genes and suppression of B cell, T cell, lymphoid lineage, and antimicrobial response genes while those with rhinovirus infection had a higher expression of cytotoxic/natural killer (NK) cell genes.

compared to mild-to-moderate infection, severe RSV infection was associated with an overexpression of neutrophil and inflammation genes as well as an under-expression of T cell, cytotoxic and plasma cell genes, indicating the important contribution of host immune response to the clinical course

Epigenome

gene expression regulators (NK cells)
epigenetic regulation pathways of host defense against respiratory infections differ by causative virus

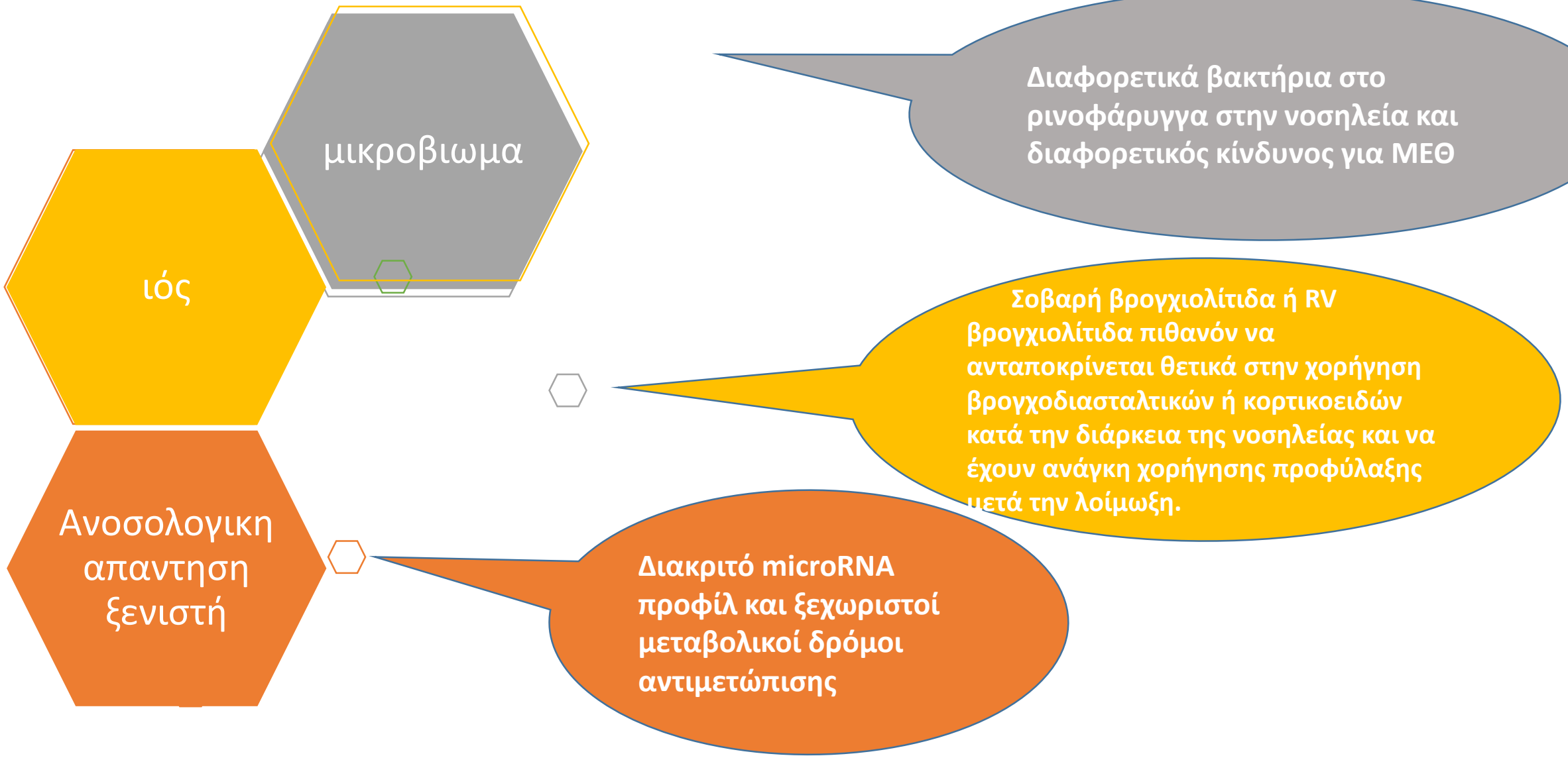
Viral Genotype

microbiome

Metabolome

Metabolomic analyses of urine in children with bronchiolitis discriminated those prone to recurrent wheezing as having a greater involvement of the citric acid cycle
Barlotta A. J Infect Dis. 2018

Ετερογένεια της βρογχιολίτιδας



Hasegawa K, Dumas O, Hartert TV, Camargo CA Jr. Advancing our understanding of infant bronchiolitis through phenotyping and endotyping: clinical and molecular approaches. Expert Rev Respir Med 2016;10(8):891–899