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Wheezy pre-schoolers: who to treat and with what?

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Wheezy pre-schoolers: current and new treatments

Outline

- what are the links between wheeze and asthma?
- Who requires treatment?
  - Goals of treatment
- What to treat with
- What is the role of “designer” molecules?

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Wheeze in infants and young children

- What is the dilemma?
  - 40% of children in many counties have at least one wheezing episode
  - 80% with severe persistent asthma begin wheezing in y1
  - 70% of pre-schoolers with recurrent wheeze DO NOT proceed to asthma
  - Predictive indices do not help in deciding who to treat
  - ICS, ICS+LABA overused in pre-schoolers

Wheeze in infants and young children

- When is wheeze NOT asthma?
  - CF, BPD
  - Inhaled foreign body
  - Structural airway abnormalities
- When is wheeze asthma?
  - Multiple wheeze phenotypes in infants
    - Unlikely to be associated with asthma
      - Transient wheeze
      - Episodic (viral) wheeze
    - More likely to be associated with asthma
      - Family history of asthma / allergies
      - Personal history of eczema / food allergy
      - Early allergic sensitization

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CAS: Asthma risk only seen in those sensitised early

Type of ARI	Never atopic	Atopic by 2y	Atopic > 2y
Any wLRI 1st year	1.4 (0.4-5.1), 0.6	2.8 (1.1-7.1), 0.03	0.5 (0.1-3.5), 0.5
≥ 2 wLRI 1st year	1.0 (0.1-9.1), 1.0	7.1 (1.3-38.4), 0.02	n/a
Febrile LRI	1.0 (0.2-3.8), 0.9	4.4 (1.7-77.5), 0.002	1.3 (0.2-9.9), 0.8
Febrile wLRI	1.0 (0.3-3.4), 1.0	4.3 (1.7-10.8), 0.002	0.7 (0.1-3.9), 0.7
RSV/RV wLRI	0.8 (0.2-4.0), 0.8	3.3 (1.3-8.1), 0.01	0.9 (0.1-6.4), 0.9

These relationships hold for current asthma at 10y

COAST: Risk of asthma ↑ by aeroallergen sensitization in infancy and if RV wLRI persist beyond y1

[y1: OR ≈ 3, y2: OR ≈ 7, y3: OR ≈ 32]

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[Kusel JACI 2007, ERJ 2012, Jackson COACI 2010]

Wheeze in infants and young children

- Links between wheeze and asthma
  - Low lung function →↑ risk of both wheeze and asthma
  - Viral-induced inflammation → airway damage → asthma risk
  - Wheeze → airway damage → asthma risk

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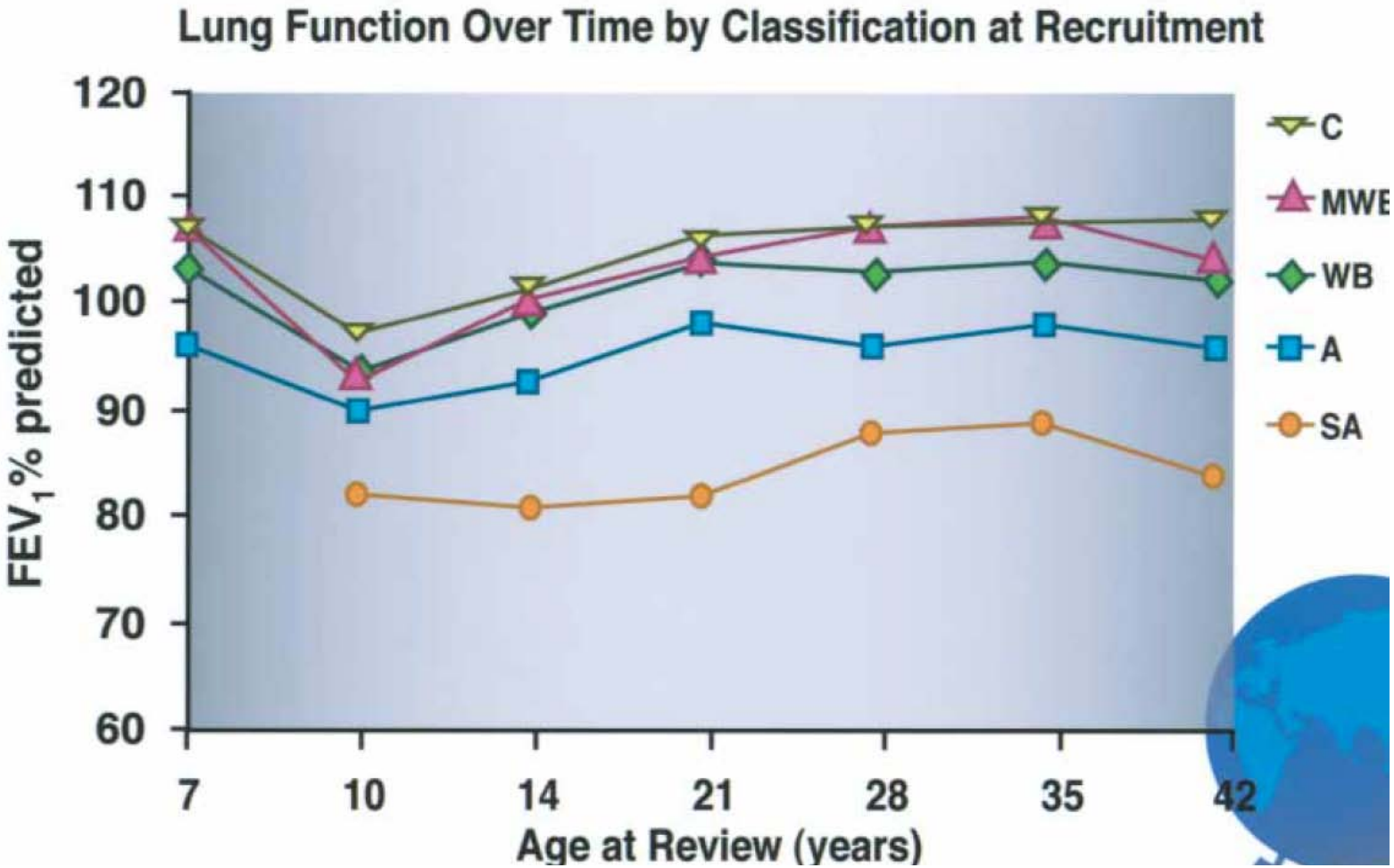
Lung function is low in asthmatics from early life



Phelan JACI 2002

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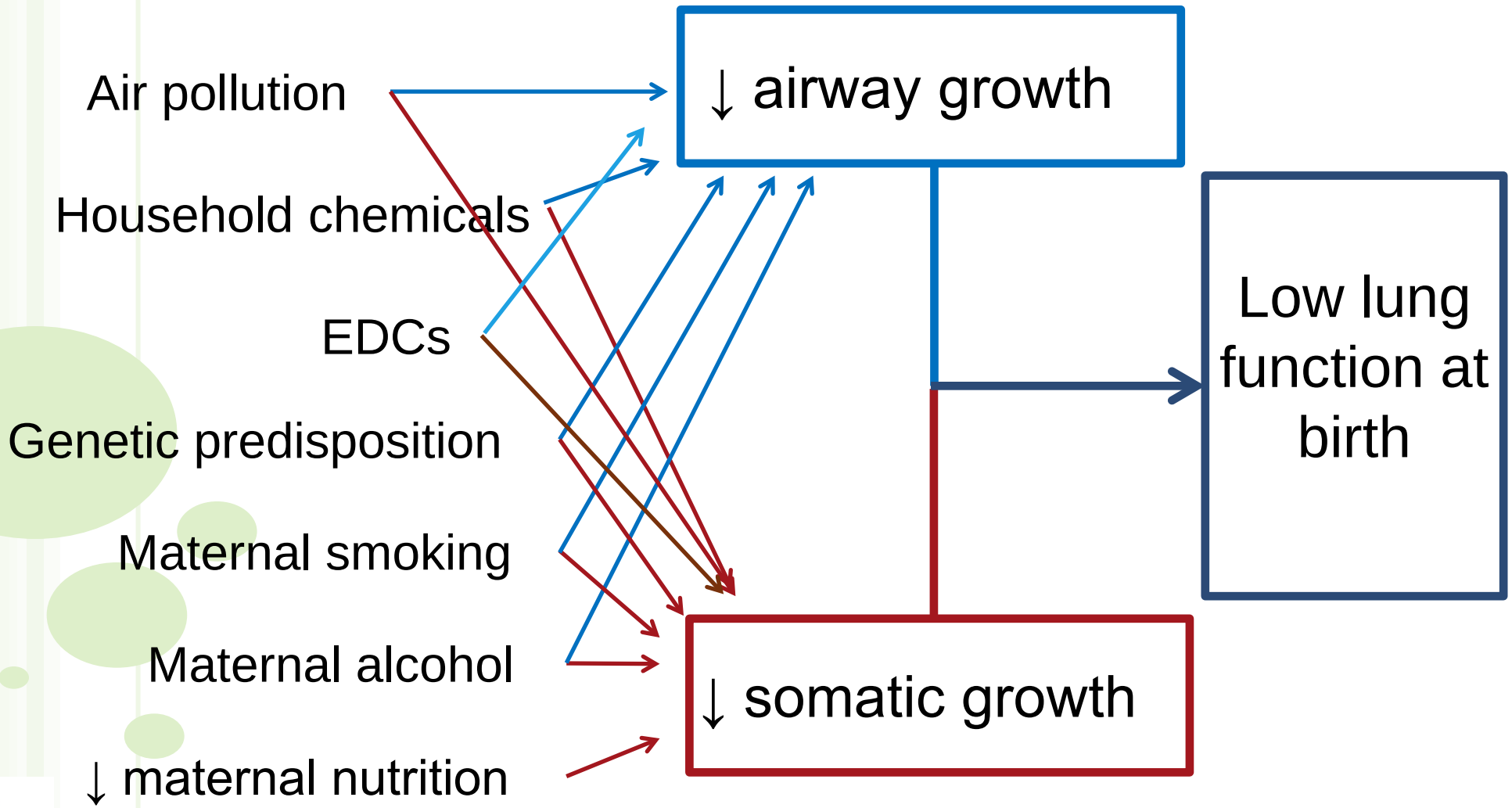
In utero influences on lung function at birth



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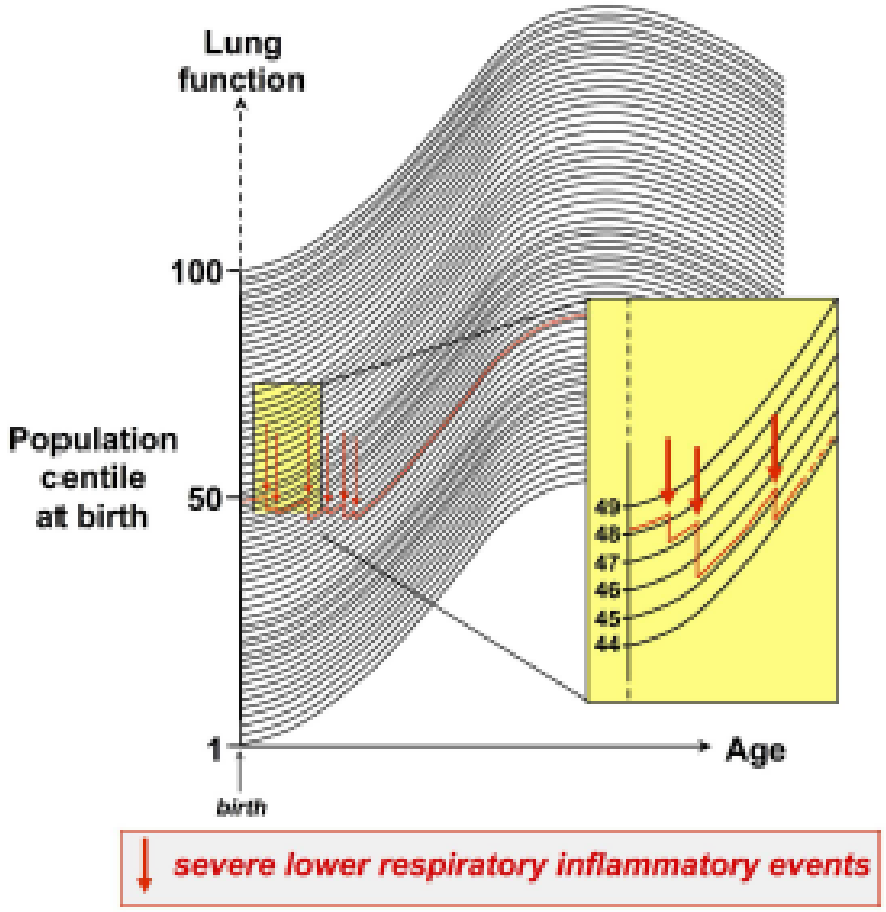
Links between wheeze and asthma

- Lung function tracks from birth
- sLRI may reduce lung growth
- Low lung function ↑ risk of:
  - Further sLRI
  - Chronic lung disease



Walker et al Front Immunol 2014

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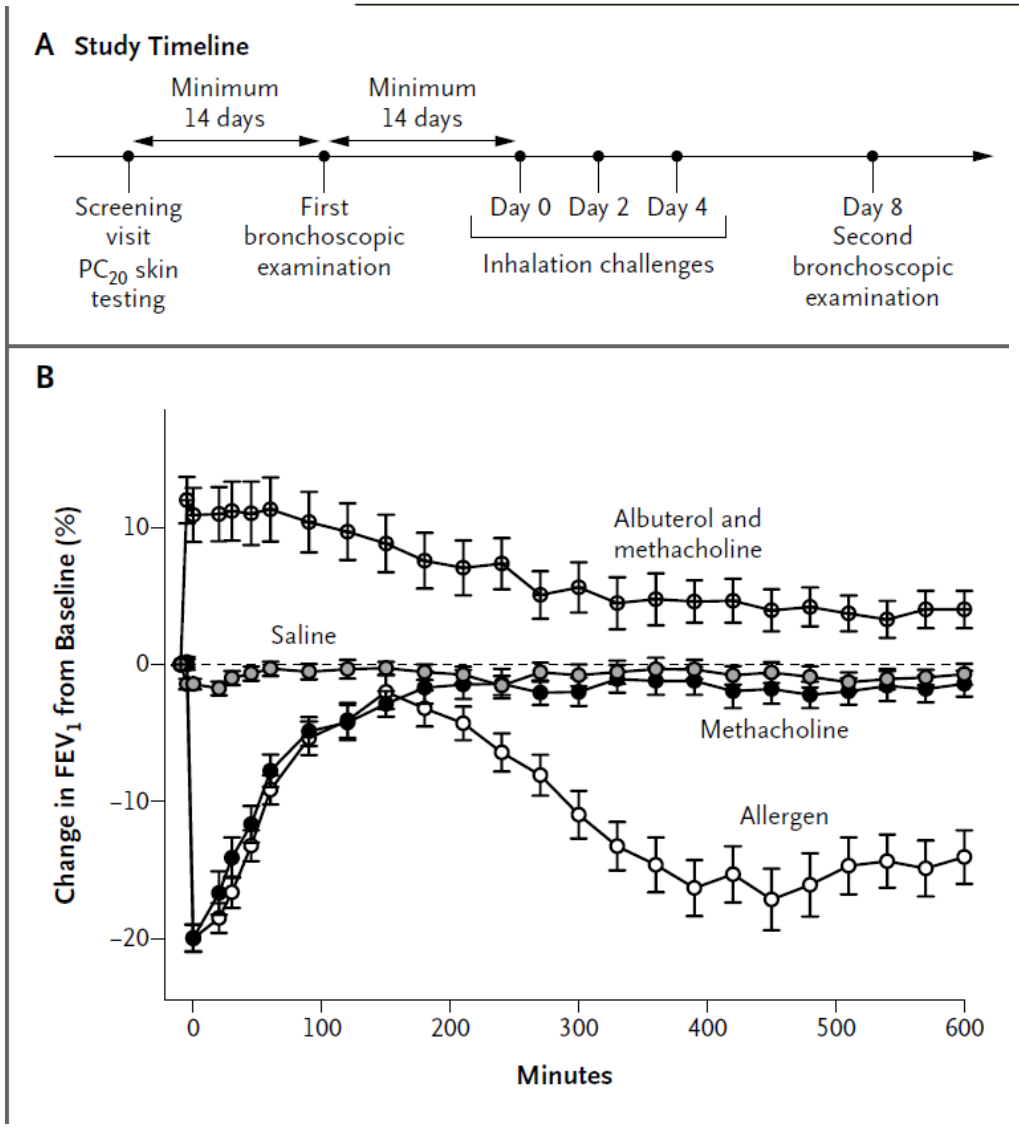
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Bronchoconstriction on Airway Remodeling in Asthma

Christopher L. Grainge, Ph.D., Laurie C.K. Lau, Ph.D., Jonathon A. Ward, B.Sc., Valdeep Dulay, B.Sc., Gemma Lahiff, B.Sc., Susan Wilson, Ph.D., Stephen Holgate, D.M., Donna E. Davies, Ph.D., and Peter H. Howarth, D.M.



Adult atopic asthmatics, 12 per group
Bronchoconstriction induced remodelling independent of cause

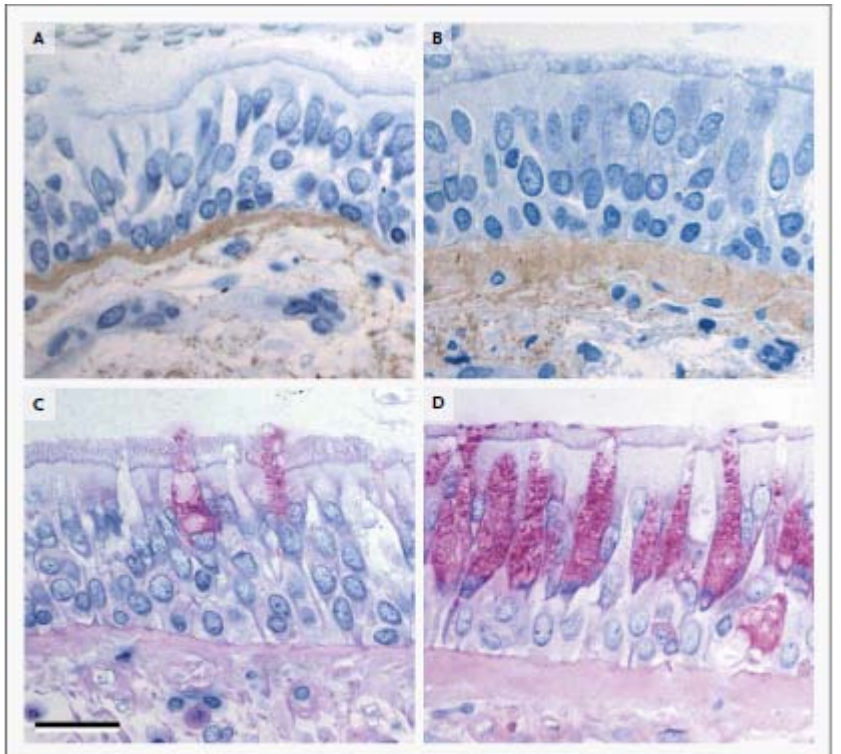
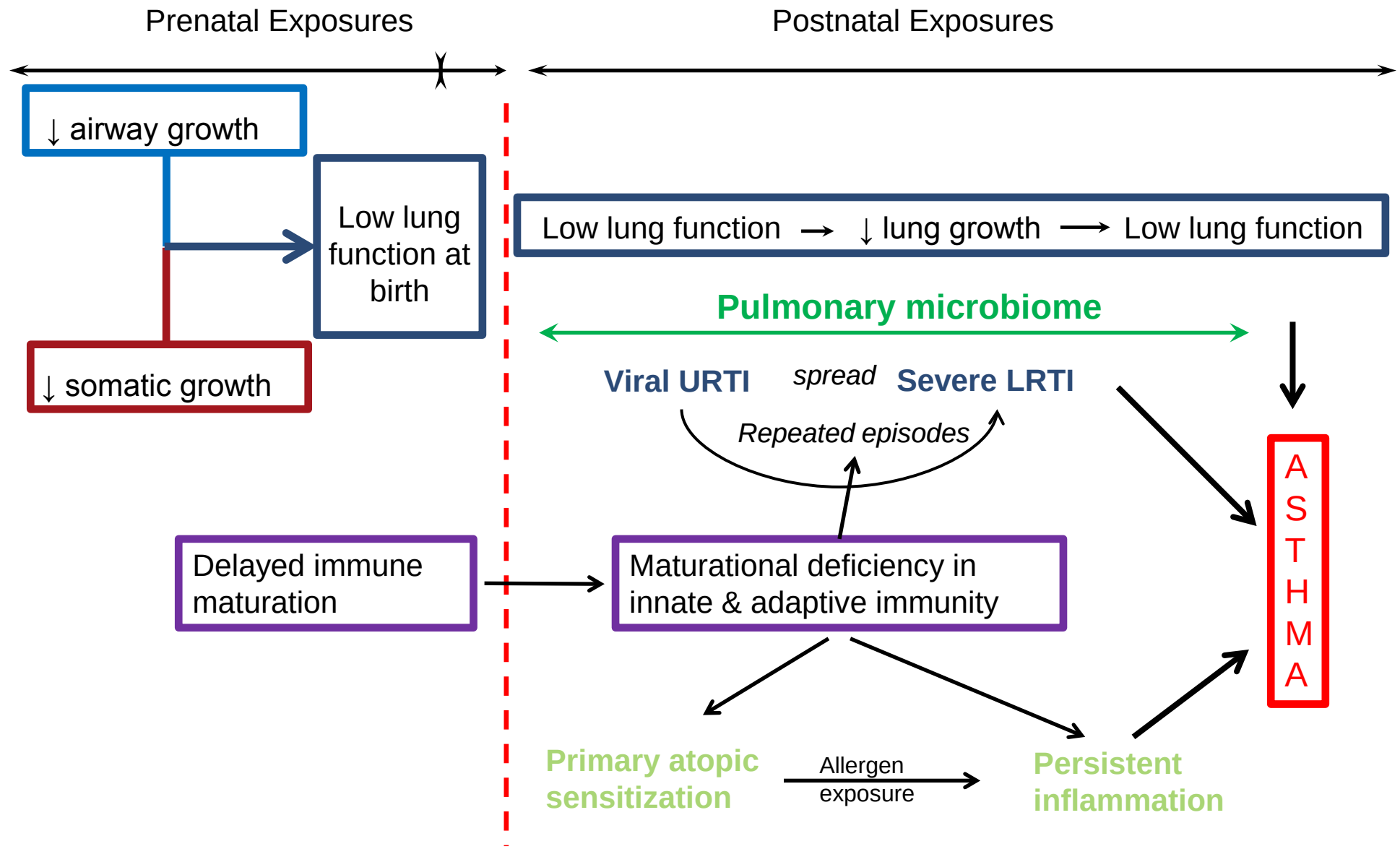


Figure 3. Representative Photomicrographs of Respiratory Epithelium from Bronchial-Biopsy Specimens before and after Repeated Inhaled Methacholine Challenge.

Panels A and C show the respiratory epithelium before the challenges, and Panels B and D show the epithelium after the challenges. Biopsy specimens were immunostained with an antibody to collagen type III (in Panels A and B) and with periodic acid–Schiff (in Panels C and D). The horizontal bar represents 30 μm.


Prenatal Exposures
Postnatal Exposures
↓ airway growth
Low lung function at birth
↓ somatic growth
Low lung function → ↓ lung growth → Low lung function
Pulmonary microbiome
Viral URTI
spread
Severe LRTI
Repeated episodes
Delayed immune maturation
Maturational deficiency in innate & adaptive immunity
ASTHMA
Primary atopic sensitization
Allergen exposure
Persistent inflammation
Genetic Predispositions
Genetic Predispositions

Wheeze in infants and young children

- Who warrants treatment?
  - Strong family history
  - Personal history of atopy
  - Severe symptoms
    - Interfering with sleep, feeding or growth
- What are the aims of treatment?
  - Satisfy parents
  - Symptomatic relief
  - Prevent disease progression

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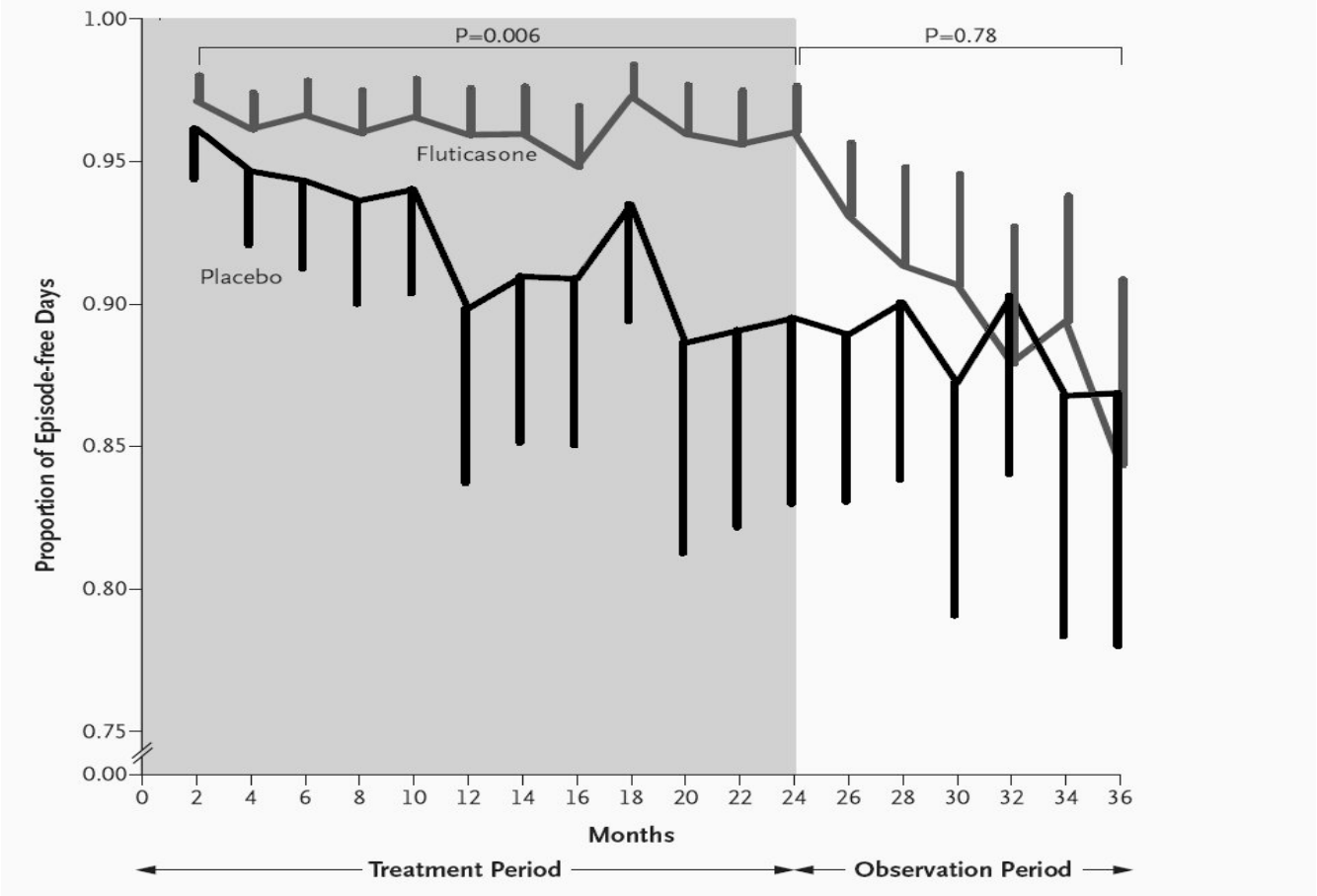
Treatment of recurrent wheeze



Early treatment does not prevent persistent asthma

(PEAK study: Guilbert NEJM 2006;354:1985-1997)

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TREATMENT OF RECURRENT WHEEZE

Use of age-appropriate delivery device critical

	< 2y	2-4 y	5-7 y
MDI + small spacer (mask)	Yes	Yes	
MDI + small spacer (mouthpiece)		Yes	
MDI + large spacer		Maybe	Yes
DPI			Maybe

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TREATMENT OF RECURRENT WHEEZE

- Deciding who to treat?
  - Based on assessment of symptoms frequency and severity
  - GINA 5y and under guidelines

Levels of asthma control in children 5y and under			
	Controlled	Partly controlled	Uncontrolled
Day symptoms	None	≥ twice/week (short, rapidly relieved)	≥ twice/week (min/hours)
Activity limitation	None	Any	Any
Night symptoms	None	Any	Any
Reliever treatment	≤ 2d/week	>2d/week	>2d/week

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Preventer treatment

- **LTRAs**
  - Effective in frequent intermittent/mild persistent
  - **Less effective than ICS for persistent asthma**
  - Modest effect at preventing need for oral steroid in preschoolers with intermittent use
  - May prevent “return to school” exacerbations
  - **Effective at preventing EIA**
  - Good safety profile

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LTRA: MAINTENANCE TREATMENT

Outcomes	Comparative risk (per 1000)		OR (95%CI)	n (studies)	GRADE
	Placebo*	LRTA			
OCS	173	201 (128-302)	1.20 (0.70-2.06)	347 (1)	mod
ED visits	179	126 (75-208)	0.66 (0.37-1.20)	347 (1)	mod
Admission	52	34 (12-93)	0.66 (0.23-1.87)	347 (1)	mod
Withdrawal	154	137 (107-171)	0.87 (0.66-1.13)	1729 (2)	mod
*placebo group pooled across studies					

Brodie M Cochrane Database Syst Rev 2015

LTRA: Intermittent treatment

Outcomes	Comparative risk (per 1000)		OR (95%CI)	n (studies)	GRADE
	Placebo*	LRTA			
OCS	336	285 (215-382)	0.85 (0.64-1.14)	343 (2)	mod
ED visits	553	553 (378-714)	1.00 (0.49-2.02)	141 (1)	mod
Admission	85	64 (18-203)	0.73 (0.20-2.73)	141 (1)	mod
Withdrawal	183	188	1.03 (0.79-1.35)		mod
*placebo group pooled across studies					

Brodie M Cochrane Database Syst Rev 2015

Preventer treatment

- **ICS**
  - 1st line preventer for persistent asthma
    - Twice daily FP or BUD
    - Once daily ciclesonide effective
    - Dose received depends on delivery device
  - No effect in intermittent viral wheeze
    - Does not prevent exacerbations
  - Improves exercise capacity by improving asthma control

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ICS DOSES

Drug	Initial dose (µg/day)	High dose (µg/day)	
		< 5y	> 5y
BUD	400	> 400	> 800
FP or HFA-BDP	200-250	> 200-250	>400-500
CIV	160	*	>320

* Not licensed <6y

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PREVENTER TREATMENT

- **ICS + LABA**
  - **Should not be used <5y**
  - Limited paediatric data >5y
    - Effective for persistent asthma not controlled by low dose ICS
  - Should not be used as 1st line therapy
  - Little evidence for SMART in children
- **Combination therapy overused in children**

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Designer molecules in childhood asthma

- Omalizumab: anti-IgE
- Mepolizumab: anti-IL5
- Dupilumab: anti-IL4/13

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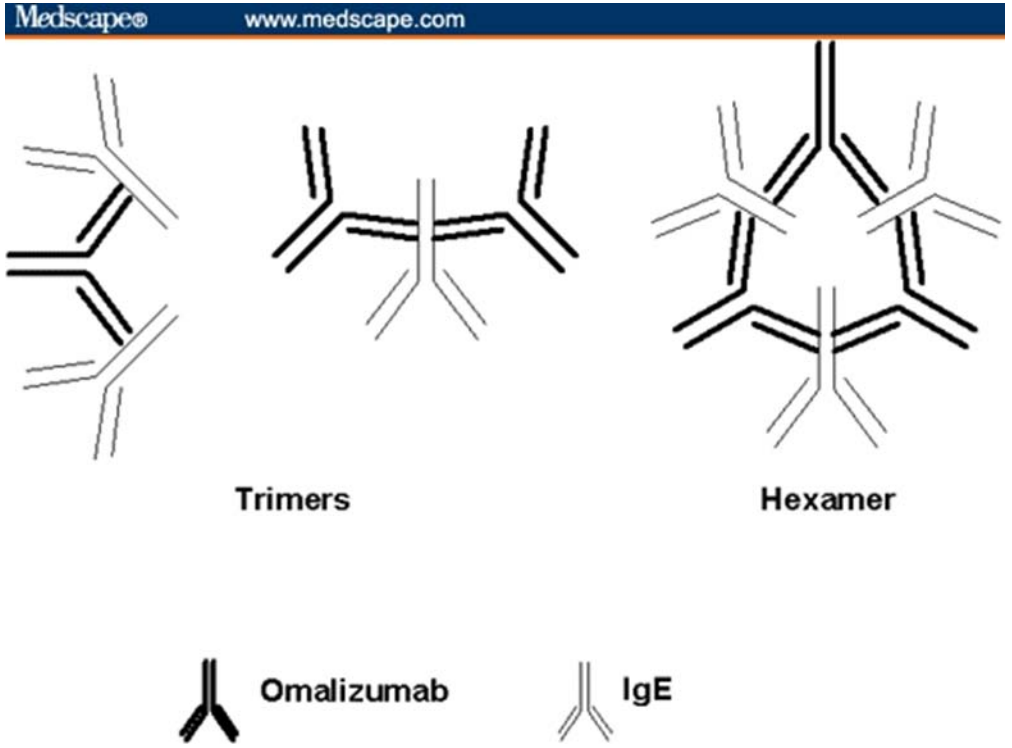
OMALIZUMAB

- Humanized monoclonal antibody targeting high-affinity receptor binding site on IgE
- Bound IgE is not available to bind to receptors
- Serum IgE reduces over time
- Clinical efficacy not closely related to reduction in IgE



Omalizumab

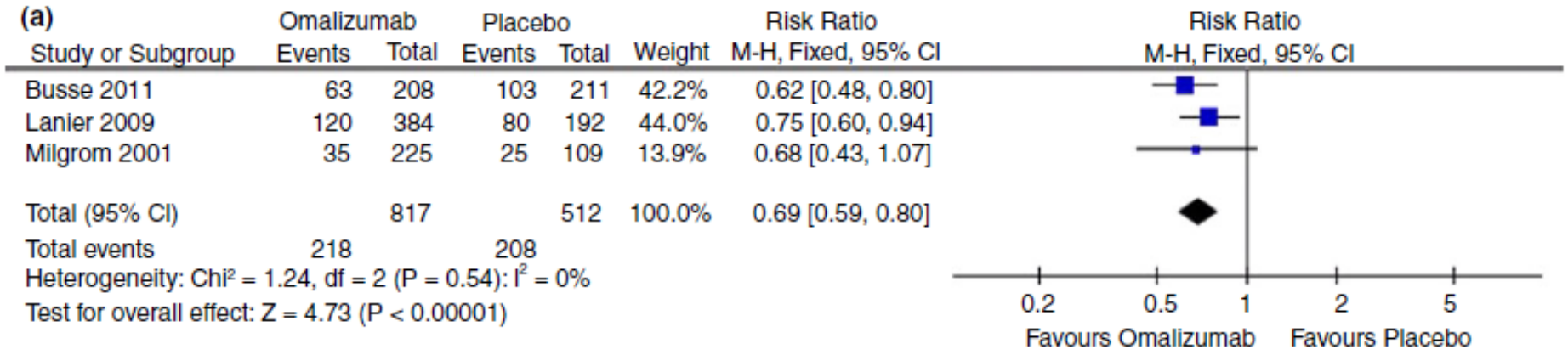
- Used in children
- Deep sub-cut injection 2-4 weekly
- Dose related to serum IgE and weight
- Used as add-on therapy to those on maximal therapy
- Clinical benefits
  - Reducing acute exacerbations
    - Fall exacerbations in USA
  - Steroid sparing
- Anaphylaxis risk
  - Often delayed – 2 hour observation period in RCTs
  - Less frequent in clinical practice than anticipated

Systematic review of Omalizumab in children

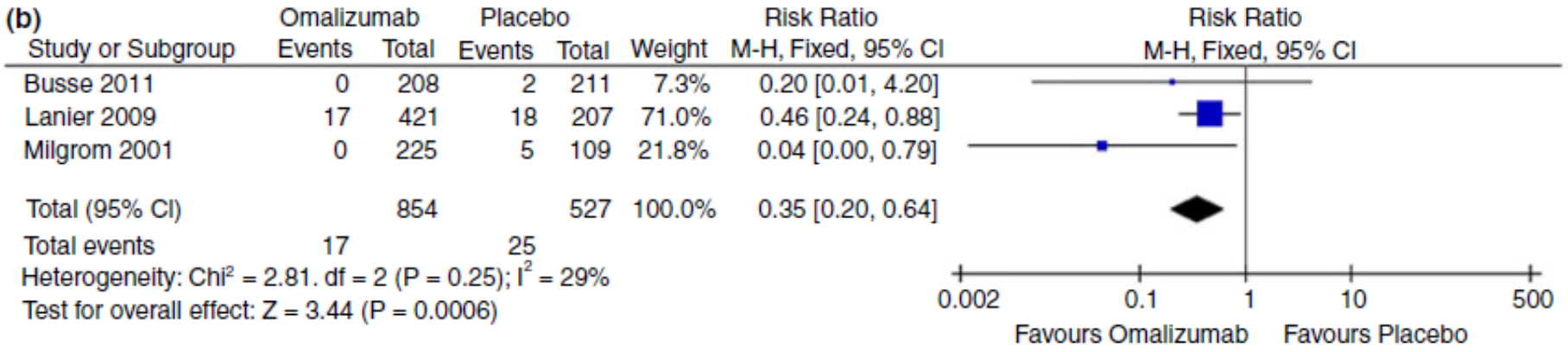
- 3 RCTS, 1381 participants
- Stable treatment as add-on
- Steroid reduction phase

Rodreigo GJ, Pediatric Allergy Immunology 2015

Reduced number with at least one acute asthma exacerbation



Reduction of severe exacerbations requiring hospitalization



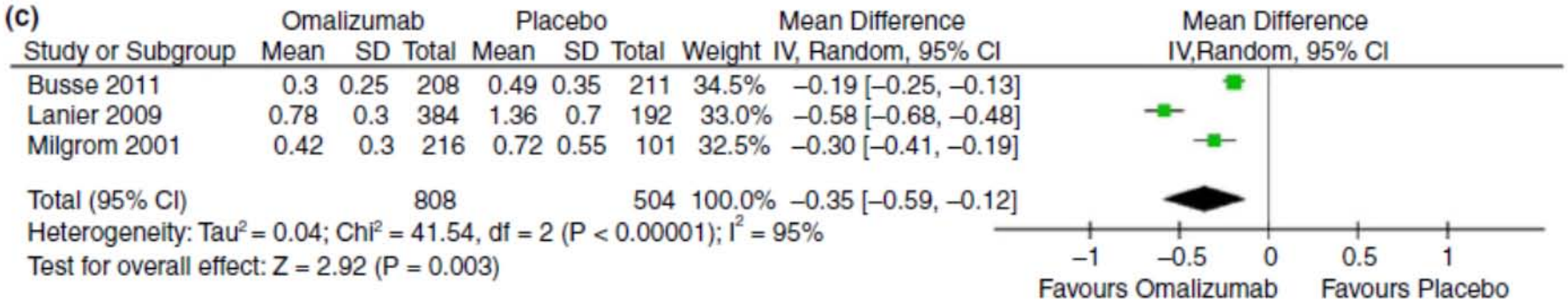
(b)

Study or Subgroup	Omalizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Busse 2011	0	208	2	211	7.3%	0.20 [0.01, 4.20]
Lanier 2009	17	421	18	207	71.0%	0.46 [0.24, 0.88]
Milgrom 2001	0	225	5	109	21.8%	0.04 [0.00, 0.79]
Total (95% CI)		854		527	100.0%	0.35 [0.20, 0.64]
Total events	17		25			

Heterogeneity: $Chi^2 = 2.81$. df = 2 (P = 0.25); $I^2 = 29\%$

Test for overall effect: Z = 3.44 (P = 0.0006)

Reduction in mean number of exacerbations per patient



(c)

Study or Subgroup	Omalizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Busse 2011	0.3	0.25	208	0.49	0.35	211	34.5%	–0.19 [–0.25, –0.13]
Lanier 2009	0.78	0.3	384	1.36	0.7	192	33.0%	–0.58 [–0.68, –0.48]
Milgrom 2001	0.42	0.3	216	0.72	0.55	101	32.5%	–0.30 [–0.41, –0.19]
Total (95% CI)			808			504	100.0%	–0.35 [–0.59, –0.12]

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 41.54$, df = 2 (P < 0.00001); $I^2 = 95\%$

Test for overall effect: Z = 2.92 (P = 0.003)

OMALIZUMAB

- More effective for severe than moderate exacerbations
- No carry-over effect once treatment stops

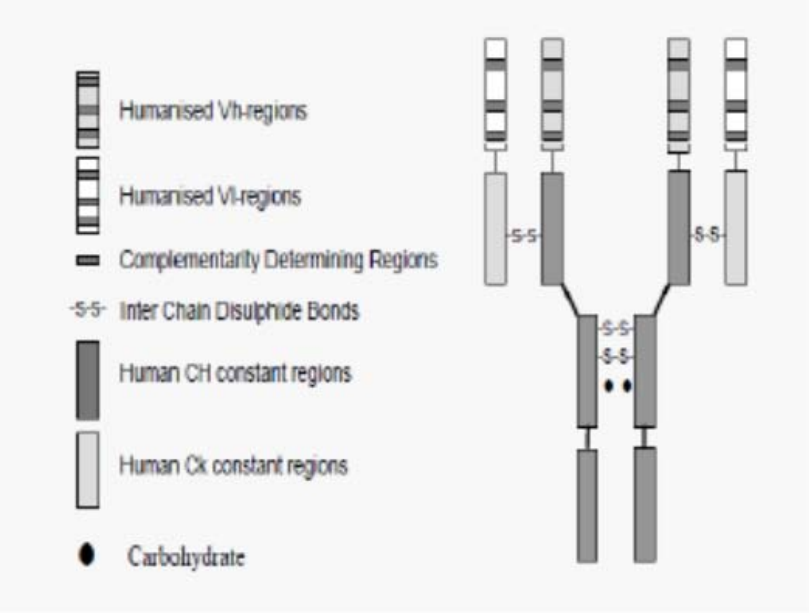
	Omalizumab	**Placebo**
Severe exacerbations incident rate time to exacerbation (days)	 1 240.5 (87.9)	 10.8 107.0 (115.9)
Moderate exacerbations incident rate time to exacerbation (days)	 1 177.3 (140.6)	 1.52 87.3 (89.6)

Sly PD, JACI 206

MEPOLIZUMAB

- Humanized IgG1 monoclonal antibody
- Initial studies disappointing until patients with high eosinophils targeted
- DREAM Study
  - i.v. infusion 4 weekly, 1 year
  - Dose-dependent reduction in exacerbation
  - 2.40/pt (placebo); 1.46/pt (250mg); 1.15/pt (750mg)

Pavord Lancet 2012

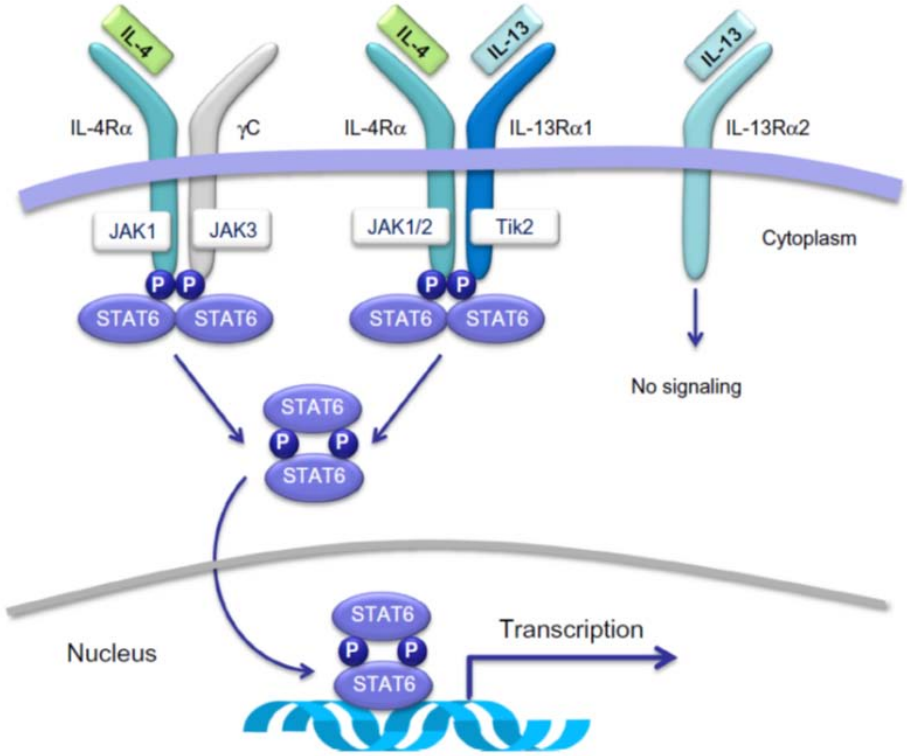


Mepolizumab

- Registered >12 y with severe asthma on maximal therapy
- Eosinophil number and function both IL-5 dependent and independent
  - Segmental allergen challenge: Mepolizumab ↓ eos number but not activation status [Kelly AJRCCM 2017]
  - EBI2 gene and EBI2 episterol ligands increase after segmental challenge independent of IL-5 [Shen AJRCCM 2017]

DUPILUMAB

- Fully human antibody against IL-4Rα
- Inhibits signally of IL-4 and IL-13
- Inhibits inflammatory signalling
- Effective in AD and severe asthma



Vatrella A, J Asthma Allergy 2014

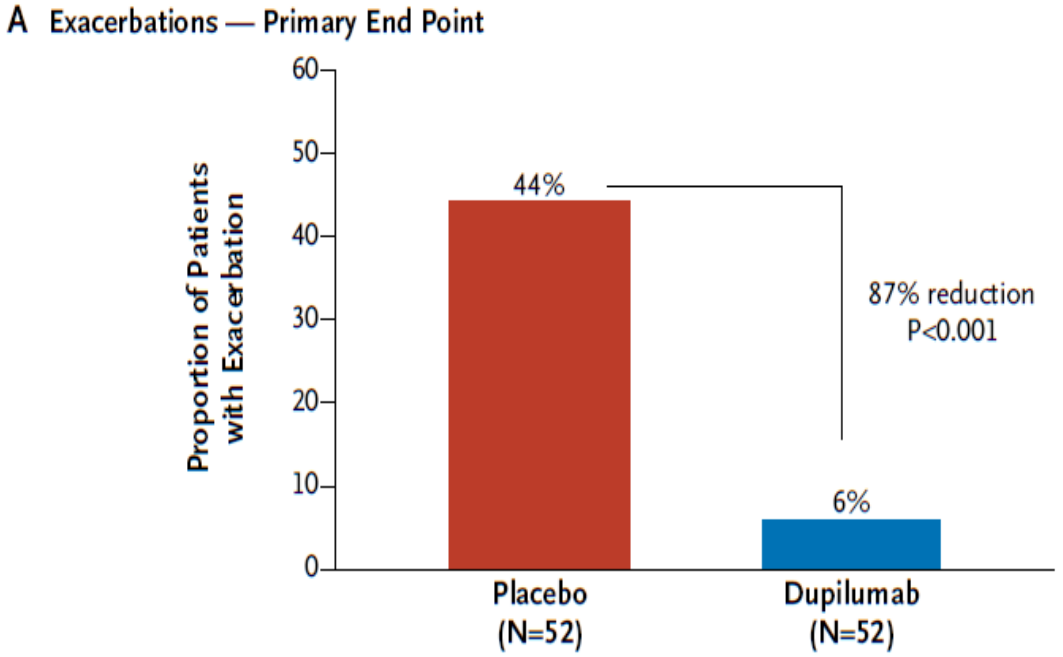
The NEW ENGLAND JOURNAL of MEDICINE

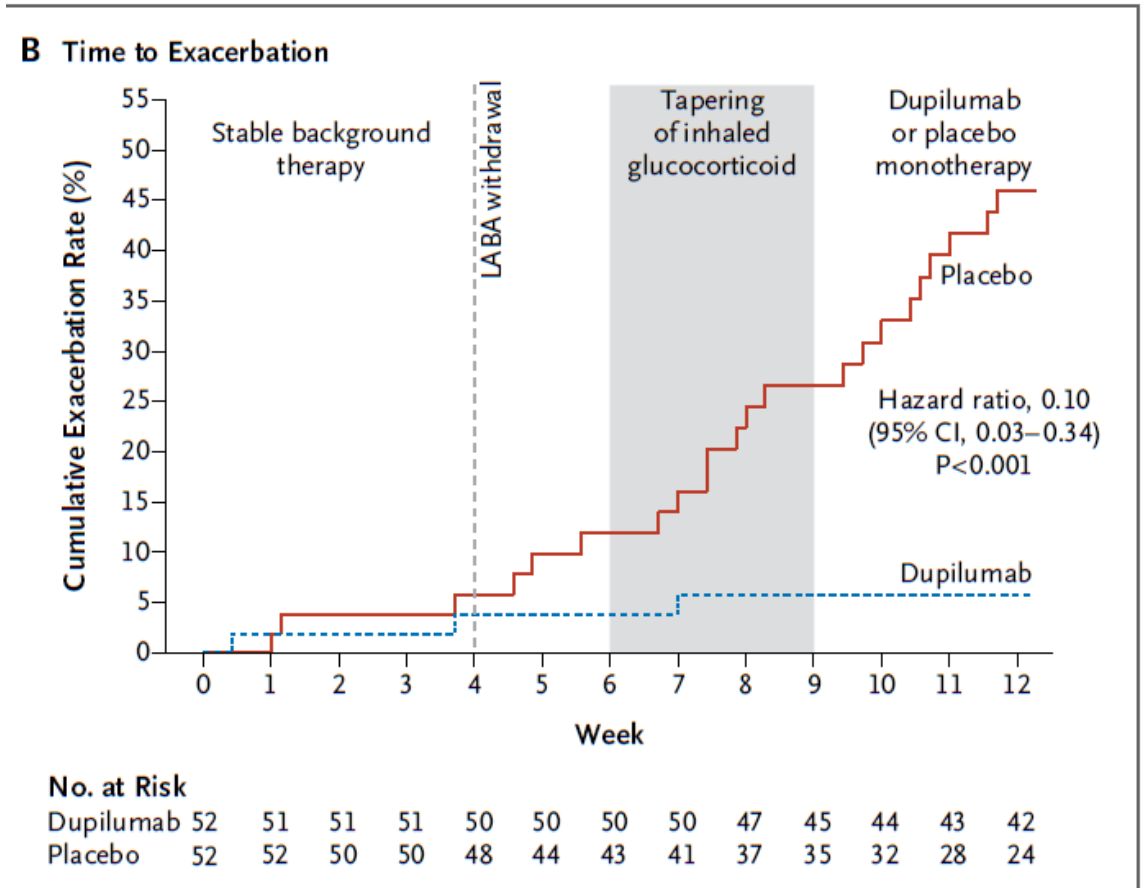
ESTABLISHED IN 1812 JUNE 27, 2013 VOL. 368 NO. 26

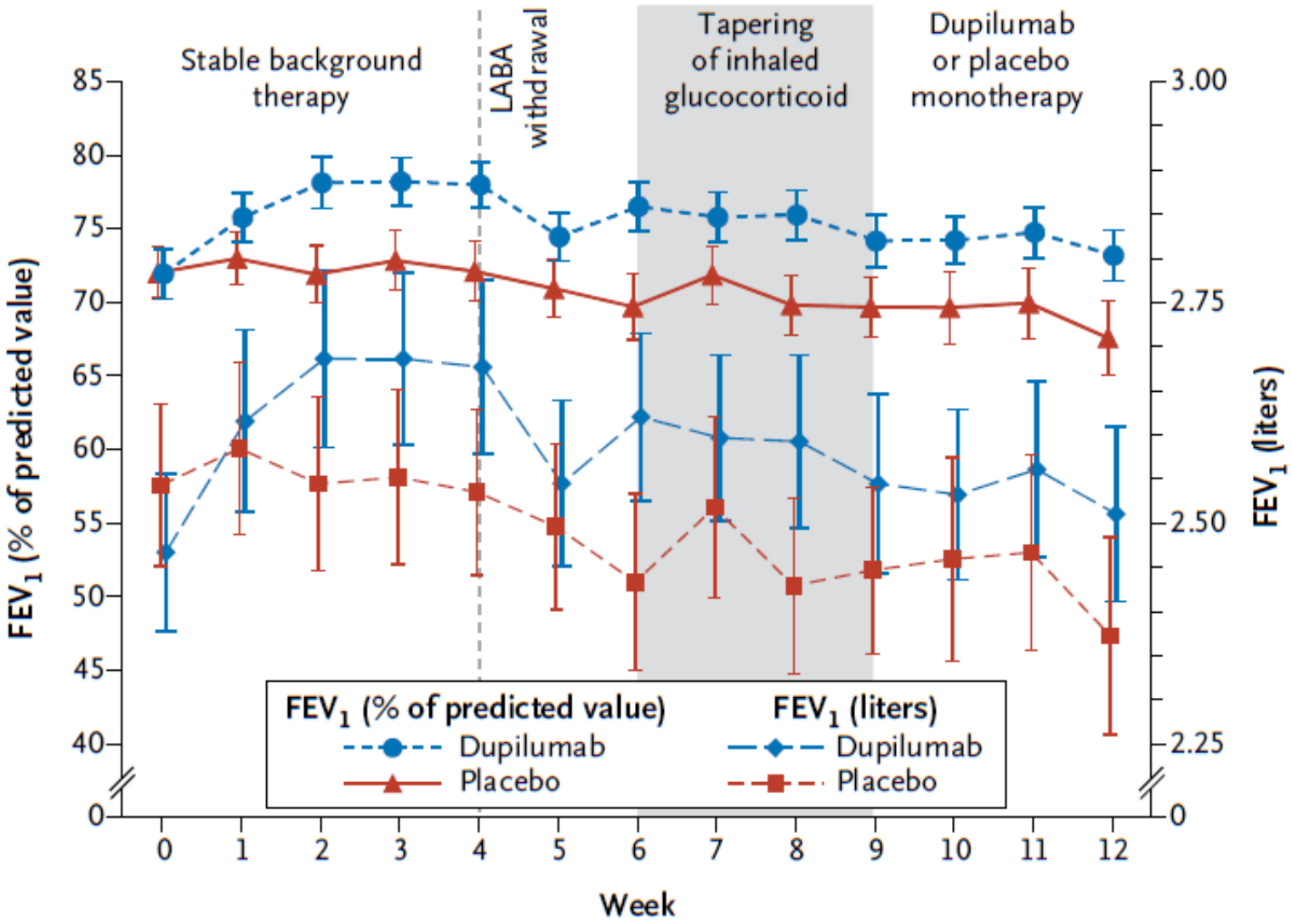
Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.

Adults with moderate to severe asthma, high serum or sputum eos, taking ICS+LABA
Dupilumab 300mg (n-52) or placebo (n=52) sc weekly 13 weeks, LABA stopped after 4w, ICS tapered weeks 6-9

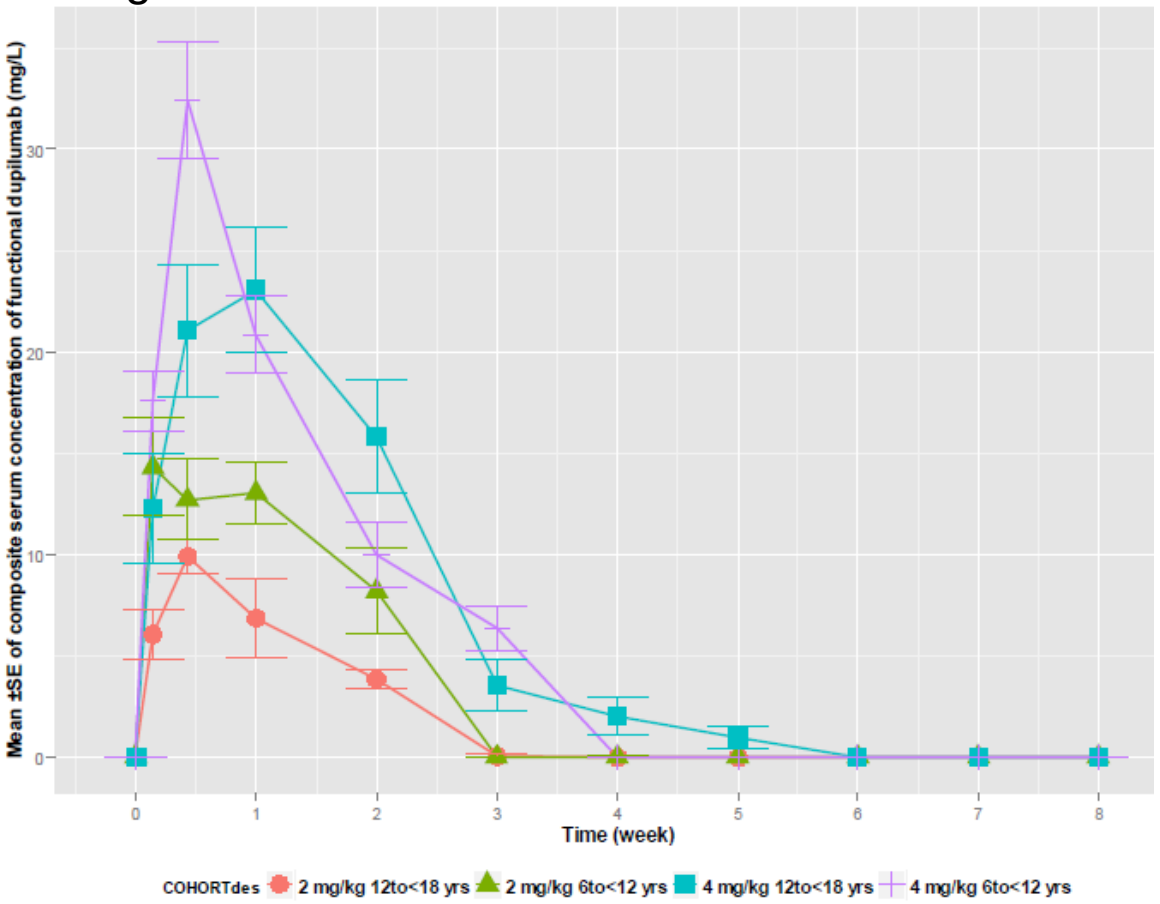

A Exacerbations — Primary End Point
Proportion of Patients with Exacerbation
60
50
40
30
20
10
0
44%
6%
87% reduction
P<0.001
Placebo
(N=52)
Dupilumab
(N=52)


B Time to Exacerbation
Cumulative Exacerbation Rate (%)
55
50
45
40
35
30
25
20
15
10
5
0
Stable background therapy
LABA withdrawal
Tapering of inhaled glucocorticoid
Dupilumab or placebo monotherapy
Placebo
Hazard ratio, 0.10
(95% CI, 0.03–0.34)
P<0.001
Dupilumab
0 1 2 3 4 5 6 7 8 9 10 11 12
Week
No. at Risk
Dupilumab 52 51 51 51 50 50 50 50 47 45 44 43 42
Placebo 52 52 50 50 48 44 43 41 37 35 32 28 24

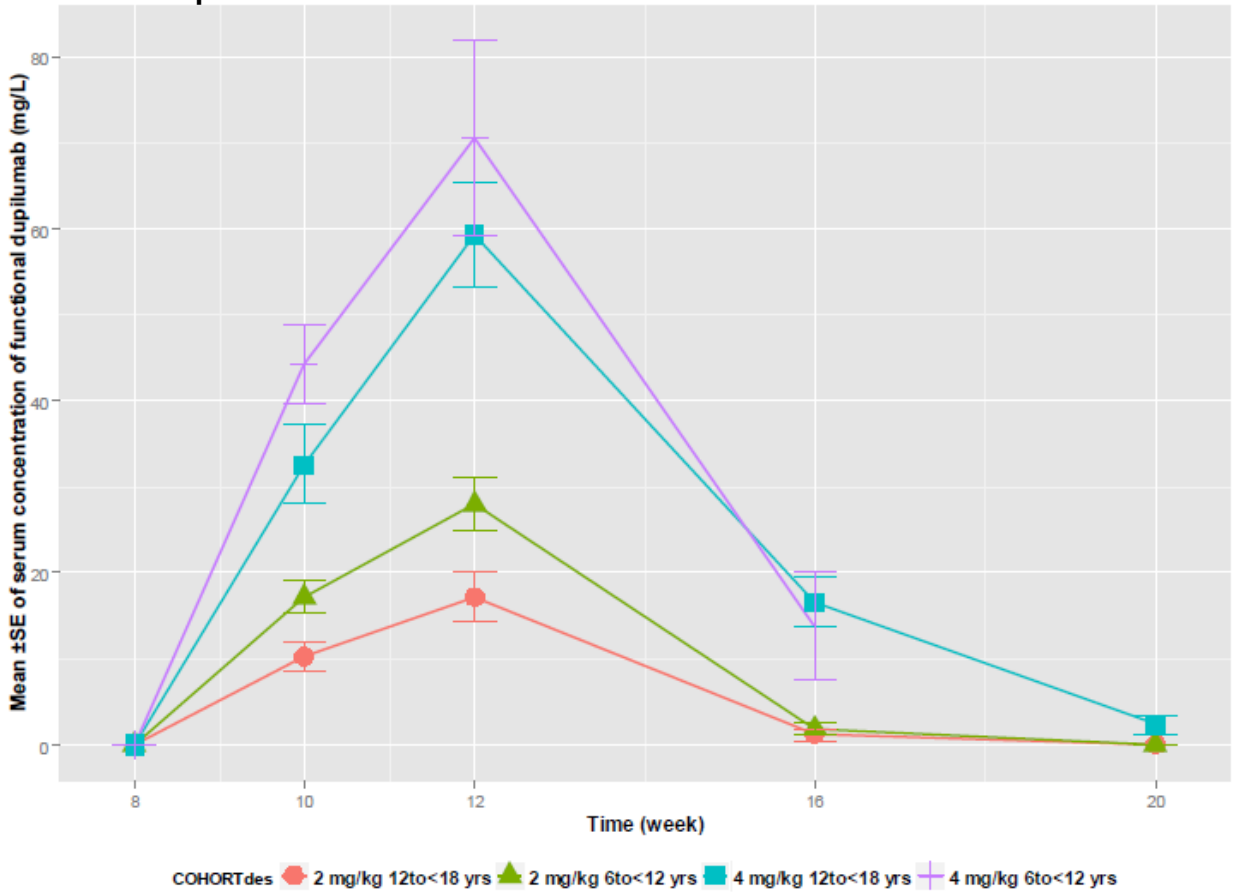

Stable background therapy
LABA withdrawal
Tapering of inhaled glucocorticoid
Dupilumab or placebo monotherapy
FEV1 (% of predicted value)
FEV1 (liters)
Week
FEV1 (% of predicted value)
Dupilumab
Placebo
FEV1 (liters)
Dupilumab
Placebo

Dupilumab pharmacokinetics in children

Single dose



Multiple doses



Current and new treatments

- Many wheezy pre-schoolers treated unnecessarily
- Ensure effective delivery device and use before increasing doses
- Don’t use LABA or ICS+LABA under 5y
- Monoclonals may help children with severe asthma
  - Optimize other treatments first
  - Difficulty in determining who will benefit
  - Children don’t like injections!