Presidential Forum:
Preventing Asthma and the Atopic March

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HARVARD MEDICAL SCHOOL

Disclosures/Objectives

- Funding NIH
- Advisory Genentech, Novartis, Teva, Regeneron, GSK
- Goal: To Discuss Strategies for Prevention and Logical Next Steps

Typical Patient Seen in Our Allergy Clinic

- JB is a 2 year old male with history of eczema and milk allergy
- He was just evaluated in the ER with a bad case of wheezing
- Family History:
  - Father and brother with moderate persistent asthma and allergies
  - Mom has bad "hay fever"
- Mom is very concerned– "Dr. P, will my child develop asthma like my husband and my older son? Can I do anything to stop this process??"

Is this child at risk for persistent asthma?

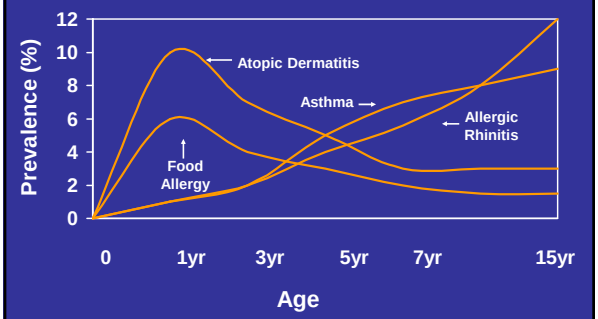
Is there anything we can do about it?

What are some logical approaches and considerations?

- Targeting allergies and atopy?
- Modification of exposures?
- Infection-directed approaches?
- Medications and Antibiotics?
- Microbial Modifications?
- Vitamins and Supplements?
- Early identification of at-risk individuals?
- Timing, Effectiveness, Feasible?

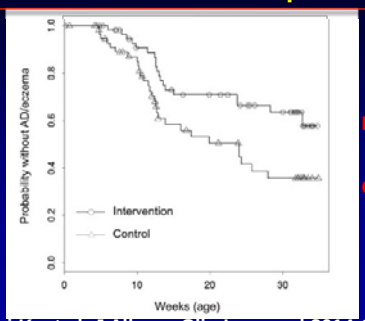
Let's Review the Natural History of the Allergic/Asthma March

Relative Prevalence of Allergic Diseases by Age and the Atopic March



Eczema Interventions

Application of Moisturizer to High Risk Neonates Prevents Development of AD

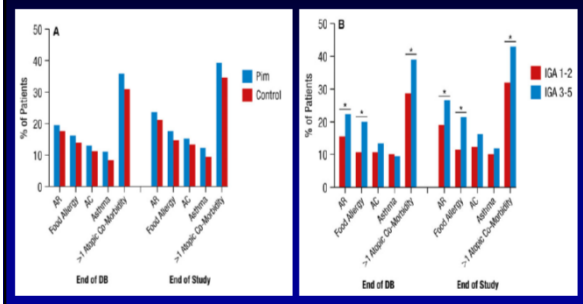


Moisturizer

Control

Horimukai K, et al. J Allergy Clin Immunol 2014;134:824-30

Study of the Atopic March- Prevention Study Tacrolimus versus Control DIDN'T WORK



Schneider LC, et al – Pediatric Dermatology 2016

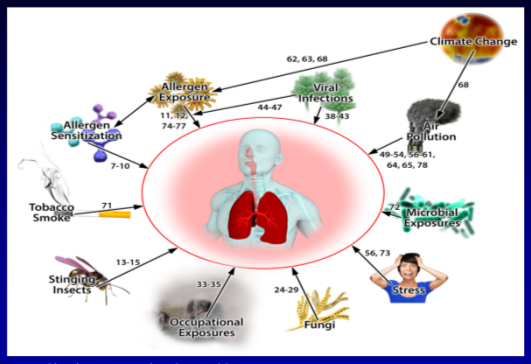
Environment

Randomized Primary Prevention Environmental HMD Studies- Mixed Bag

Studies	Intervxn	N	Years Follow UP	Major findings
Isle of Wright-England	Dust mite/food avoidance	120	1-18	↓ Asthma and atopy all ages
Manchester Asthma and Allergy Prevention	Stringent Dust Mite Control Infancy	291	1-16 (published only age 1 and 3)	↓ Severe wheezing (infancy) ↑ lung function (age 3 years) ↑ mite sensitization (age 3 years)
Canadian Asthma Primary Prevention	Dust mite, diet	545	1- 15	↓ asthma (up to age 7) ↓ age 15 in females only
Prevention of Incidence of Asthma and Mite Allergy Netherlands	Mattress Covers	810	1- 8	↓ Asthma at age 2. ↔ NO effect at other ages.
Australia: Childhood Asthma Prevent	HDM Covers, Diet	616	18 months-5	↔ asthma, wheeze, or atopy. ↑ Eczema

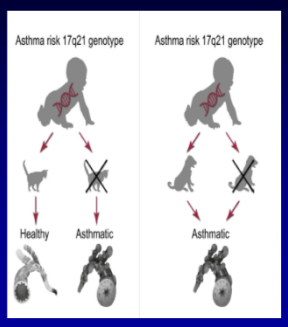
Table. NIH/ environment workshop. Gold DR et al. JACI 2017

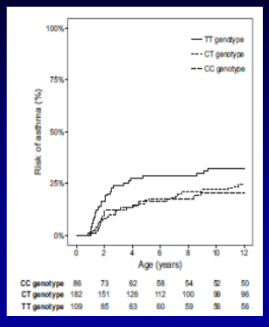
Complexities in the Environment



Sheehan WJ, et al JACI Dec 2017

Cat Exposure in Early Life Decreases Asthma Risk by 17q21 high risk variant

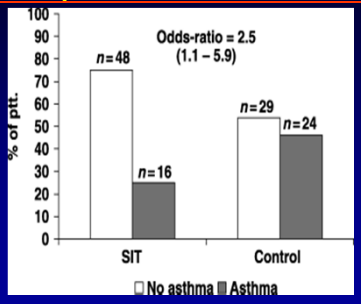




Stockholm J,Bisgaard H, JACI May 2018

Allergen Immunotherapy

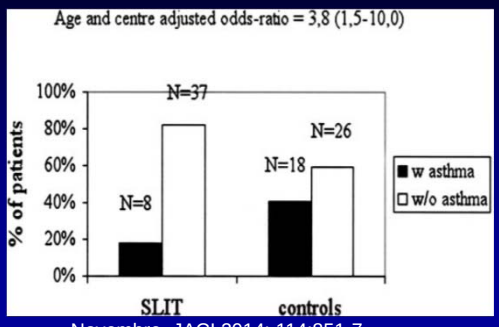
Open Label Allergy Shots in School age Kids, Reduces Allergen Specific IgE Response and Asthma Risk



•Jacobsen L *Ann Allergy Asthma Immunol* 2001; 87: 43-46
•Jacobson L. Allergy 2007; 62: 943-8.

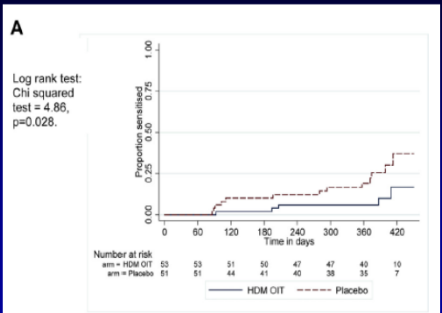
7 years off Therapy

Coseasonal Grass Sublingual IT In Elementary Kids Reduces Reported Asthma



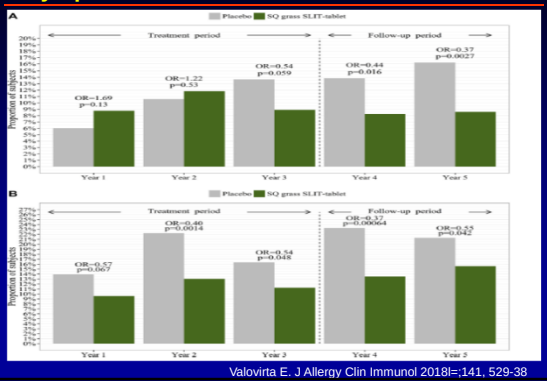
Novembre, JACI 2014; 114:851-7.

Consideration of Primary Prevention of Allergy with Dust Mite OIT in Babies



Zolkipli Z. J Allergy Clin Immunol 2015;136:1541-7.

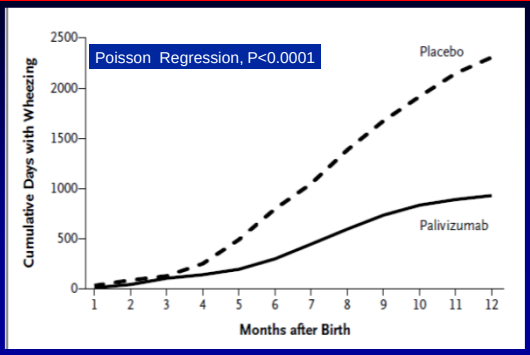
DBPC Grass SLIT Prevention Study Helped Symptoms in the Winter but Failed Prevention



Valovirta E. J Allergy Clin Immunol 2018l=;141, 529-38

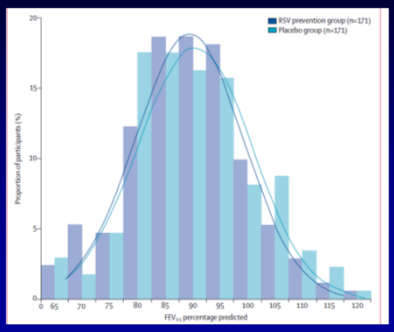
Infection Approaches
RSV

Palvizumab Prophylaxis and Recurrent Wheeze in Healthy Preterm Infants at age 1



Blanken MO, N Engl J Med 2013;368:1791-9.

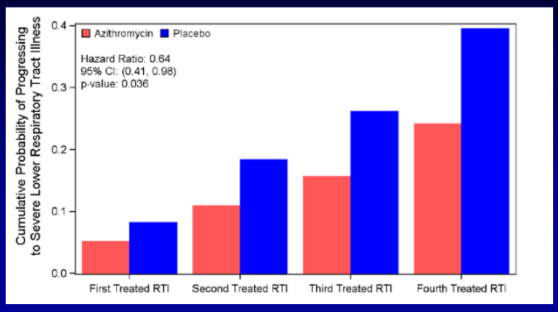
Palvizumab Prophylaxis Outcomes at Age 6: No Prevention



Scheltema NM. Lancet Resp Med March 2018

Antibiotics and Antipyretics

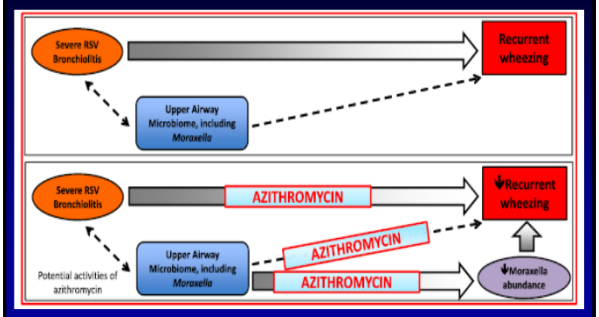
Azithromycin Prevents LRI in Preschool Wheezers



Bacharier LB, et al, AsthmaNet JAMA, Nov 2015

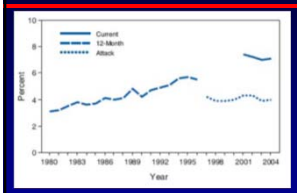
Early Azithromycin Alters Airway Microbiome– Possible Prevention?

NCT02911935 **APW-RSV-II,** Beigelman A PI



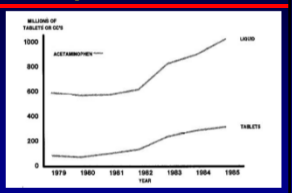
Zhou Y, et al. JACI Oct 2016

Rise in Asthma Has Coincided with the Rise in Acetaminophen Use



•Prevalence of Asthma in US

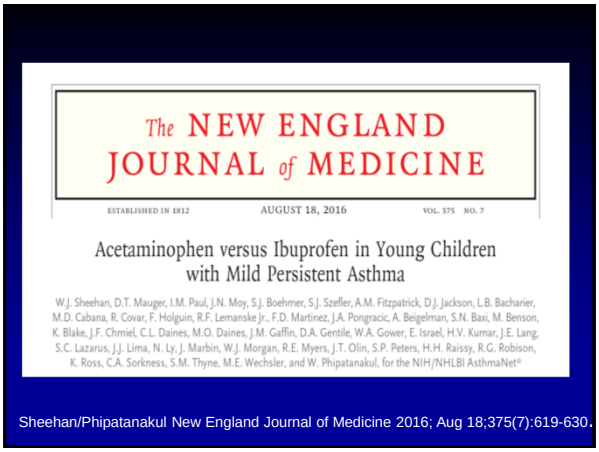
•MMWR Surveill Summ. 2007; 56(8):1-54



•Purchases of Acetaminophen in US

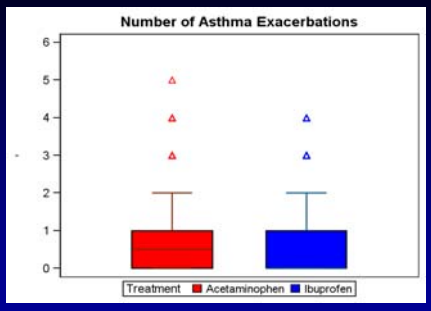
•Arrowsmith et al. *Pediatrics* 1987; 79:858-63

•By 1990, Acetaminophen was the most common medication in the US



Sheehan/Phipatanakul New England Journal of Medicine 2016; Aug 18;375(7):619-630.

Primary Outcome



Sheehan WJ, et al NEJM August 2016

Paracetamol or Ibuprofen in the Primary Prevention of Asthma in Tamariki (PIPPA Tamariki).

- Randomised controlled trail of Paracetamol or Ibuprofen, as required for fever and pain in the first year of life, for prevention of asthma at age six years.
- **Universal Trial Number (UTN)** U1111-1203-1961
- Enrolling nearly 4000 infants with primary outcome of wheeze last year at age 6

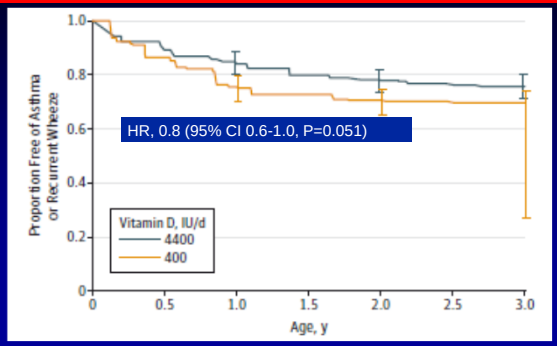
When to Feasibly and Effective Intervene? Pregnancy or Early Childhood?

Interventions During Pregnancy

Vit-D-Kids

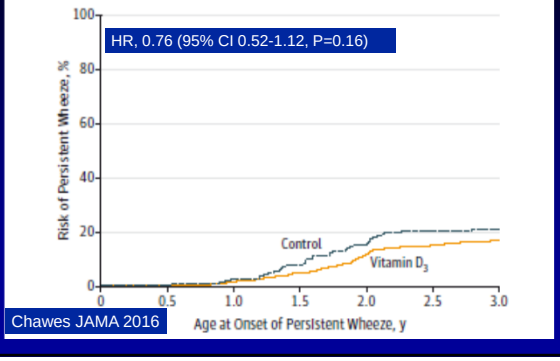
asthma study

Asthma or Recurrent Wheeze-Free Proportion by Vitamin D Treatment- US



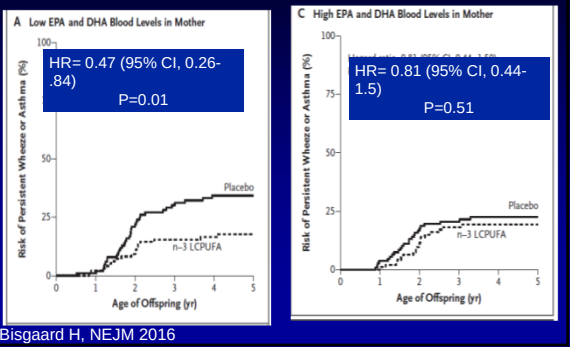
Litonjua JAMA 2016

Copenhagen Study: 700 Pregnant Women 2400 IU/D vs. STD 400 IU



Chawes JAMA 2016

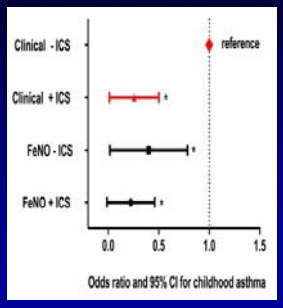
Strongest Fish Oil Effect in Moms with low EPA and DHA Pre Intervention



Bisgaard H, NEJM 2016

Managing Asthma in Pregnancy by F_ENO and ICS use

- 179 pregnant moms
- 140 children followed to age 4-6
- Intervention: F_ENO guided ICS use during Pregnancy
- Results mediated in F_ENO guided group by increased ICS use during pregnancy



Collison A, et al JACI 2018 In Press https://doi.org/10.1016/j.jaci.2018.02.039

Why do we keep striking out on prevention?

Weaknesses in the Studies so far…

- Environment: Impossible to fully intervene/microbiome-complicates
- Sublingual or SCIT: only open label trials- Immunology ? Only targets specific allergens, early on child still developing allergies
- SLIT FDA approved only single allergens even mixes, immunologic efficacy questionable- didn't meet primary outcome-
- RSV specific time window certain kids- Rhinovirus associated more with asthma- no effective treatment
- Vitamins- too weak/ Antibiotics/Antipyretics conflicting effects/benefit
- Timing: Pregnancy Management-Hard to implement-
- Do we start genotyping everyone? 17q21?
- Fish Oil conflicting and high doses- Long term effects? No effect on allergic outcomes

Two NIH Funded Approaches/Interventions

Microbial Diversity, Living on a Farm and Lower Rates of Asthma

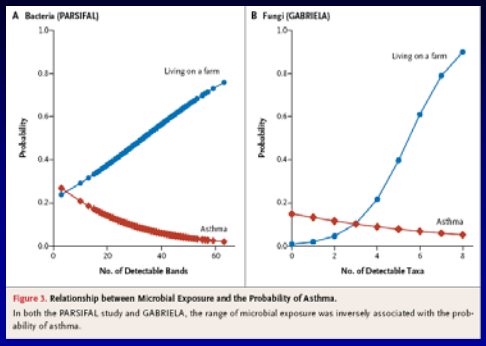
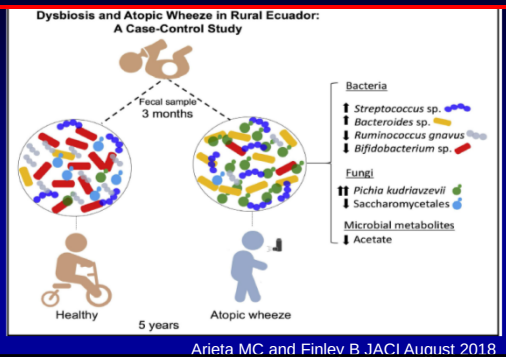


Figure 3. Relationship between Microbial Exposure and the Probability of Asthma.
In both the PARSIFAL study and GABRIELA, the range of microbial exposure was inversely associated with the probability of asthma.

Ege et al, N Engl J Med 2011;364:701-9.

Fungal and Bacterial Dysbyosis and Risk of Atopic Asthma



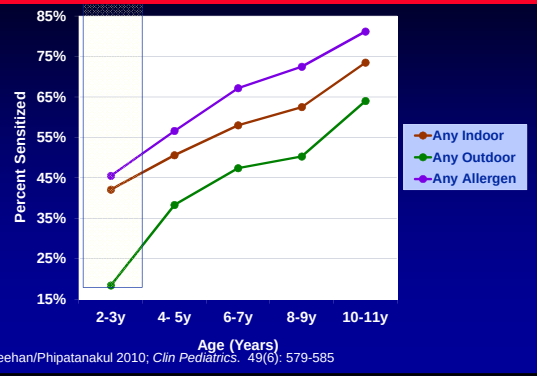
Arieta MC and Finlay B JACI August 2018

BronchoVaxom®

- BronchoVaxome® is made up of lyophilized fractionated alkaline extracts of H. influenzae, D. pneumonia, K. ozaenae, K. pneumoniae, S. aureus, S. pyogenes, S. viridans, and N. catarrhalis grown on vegetal substrate
- It is a powder mixture of acidic proteins, peptides and amino acids, with minor components of detoxified LPS and lipoteichoic acids
- No live bacteria
- Marketed in the EU for the prevention of respiratory illness for over 25 years

What about allergy?? Could we block the atopic march to persistant asthma?

Allergen Sensitization (IgE) Begins in Early Childhood and then Takes Off

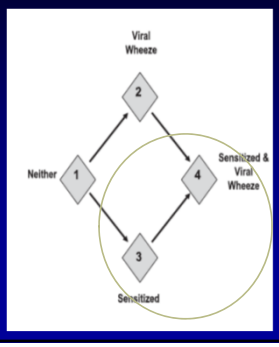


Sheehan/Phipatanakul 2010; *Clin Pediatrics*. 49(6): 579-585

Which Came First-- the Chicken or the Egg in the Asthma Pathway?

Virus Allergy

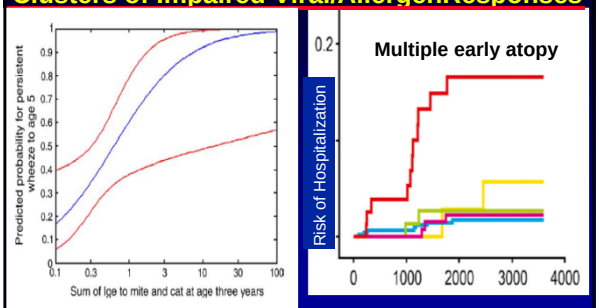
Allergen-specific IgE Production Precedes Viral Wheeze in Pivotal Causal Pathway for Asthma



	ATOPY FIRST	VIRUS FIRST
ANY VIRUS	1.7 (0.98-2.9)	0.77 (0.45-1.30)
HRV*	**2.4 (1.3-4.3)**	**0.66 (0.38-1.1)**
RSV	1.8 (0.9-3.6)	0.78 (0.48-1.1)

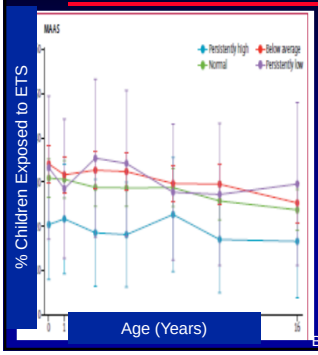
Jackson/Lemanske 2012; AJRCCM 185:281-85

Timing and Degree of Atopy Markedly Increases Risk of Asthma by School Age with Clusters of Impaired Viral/AllergenResponses



Simpson A, et al, JACI 2005 116(4): 744-9 ; Simpson A, et al AJRCCM. 2010;181(11):1200-6; Custovic A, et al. AJRCCM May 2018

Predictors of Lung Function Trajectories in 3 Population Cohorts in UK and Australia

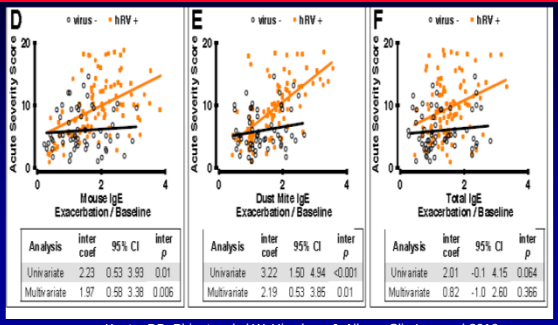


Predominant Risk:

- Recurrent wheeze/ severe exacerbations by age 3
- At least one positive skin test by age 3
- Exposure to environmental tobacco smoke

Belgrave D, Lancet Resp Med July 2018

Rhinovirus Interacts with Mouse/Dust IgE in Severity and Rise in IgE levels



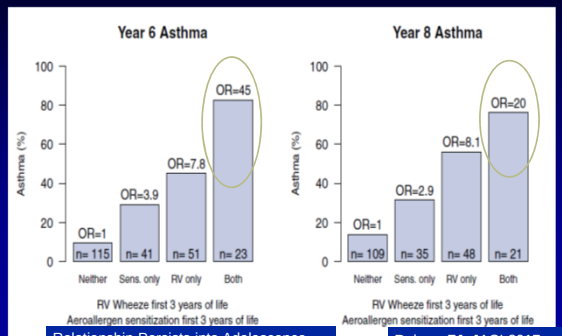
Analysis	inter coef	95% CI		inter p
Univariate	2.23	0.53	3.93	0.01
Multivariate	1.97	0.58	3.38	0.006

Analysis	inter coef	95% CI		inter p
Univariate	3.22	1.50	4.94	<0.001
Multivariate	2.19	0.53	3.85	0.01

Analysis	inter coef	95% CI		inter p
Univariate	2.01	-0.1	4.15	0.064
Multivariate	0.82	-1.0	2.60	0.366

Kantor DB, Phipatanakul W, Hirschorn J. Allergy Clin Immunol 2016

Early Allergy and Viral Wheeze Markedly Increases Risk of Asthma

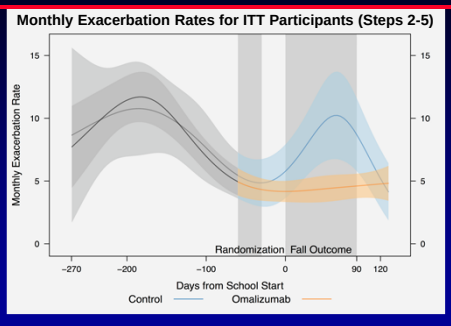


Relationship Persists into Adolescence

Rubner FJ, JACI 2017

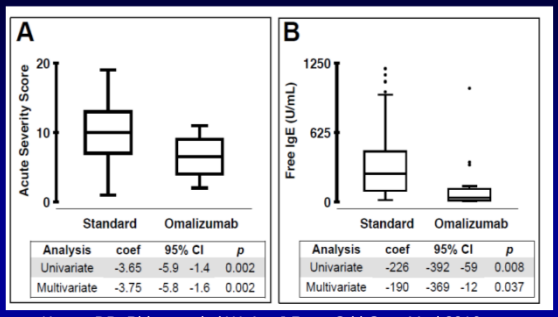
What is a feasible agent that could be used in young children that blocks IgE/allergic processes related to exposures and may be the logical next step in targeting atopy in the prevention of asthma?

Preseasonal Treatment with Anti-IgE reduces seasonal exacerbations



Teach, SJ et al. J Allergy Clin Immunol 2015; 136:1476-1485

Omalizumab is Associated with a Reduction in Acute Severity of RV+ Asthma Exacerbation

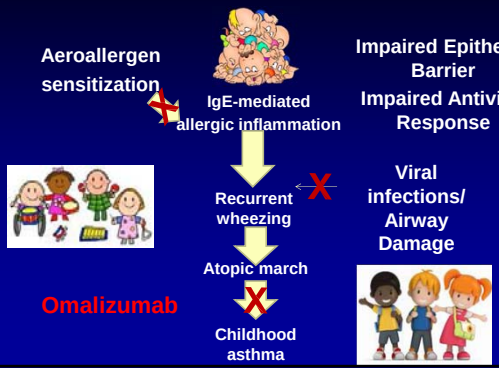


Analysis	coef	95% CI		p
Univariate	-3.65	-5.9	-1.4	0.002
Multivariate	-3.75	-5.8	-1.6	0.002

Analysis	coef	95% CI		p
Univariate	-226	-392	-59	0.008
Multivariate	-190	-369	-12	0.037

Kantor DB, Phipatanakul W. Am J Resp Criti Care Med 2016

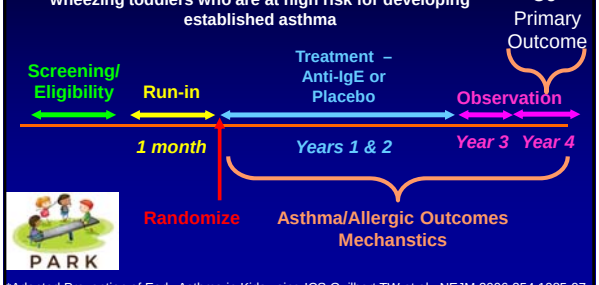
Could Early IgE Blockade Prevent or Modify the Course of Asthma?



Preventing Asthma in High Risk Kids- PARK

U01AI126614- Principal Investigator Phipatanakul- NCT02570984

Randomized, multicenter, DBPC Trial in 250 allergic wheezing toddlers who are at high risk for developing established asthma



*Adapted Prevention of Early Asthma in Kids using ICS Guilbert TW et al. NEJM 2006;354:1985-97

Strategies and Approaches

- Targeting allergies and atopy?
- Modification of exposures?
- Infection-directed approaches?
- Medications and Antibiotics?
- Microbial Modifications?
- Vitamins and Supplements?
- Early identification of at-risk individuals?
- Timing, Effectiveness, Feasible?

Prevention: the Holy Grail: What will work if anything?

- Complete Blockade of Atopy?
- Killed Bacterial Lysate?
- Future?
- We should have major advancements in our understanding of what may really work in prevention and modifying asthma/allergies the next decade

Preventing Asthma in High Risk Kids (PARK)

PI: Phipatanakul U01AI126614

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- DCC-Penn State University- Dave Mauger, PhD

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- St. Louis – Leonard Bacharier, MD
- Tucson/Phoenix – Fernando Martinez, MD and Cindy Bauer, MD
- Sacramento-Bradley Chipps, MD
- Seattle- Frank Virant, MD
- Hans Oettgen, MD, PhD, Mechanistic Lead
- NIH/NIAID, FDA, Genentech/Novartis, Alk Abello, Glaxo Smith-Kline, Kaleo, Monaghan