

Translational: Early Life Events in Asthma Expression

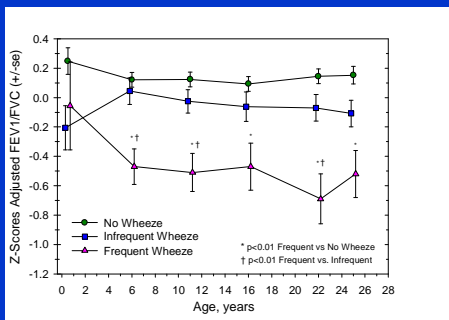
Fernando D. Martinez, M.D.

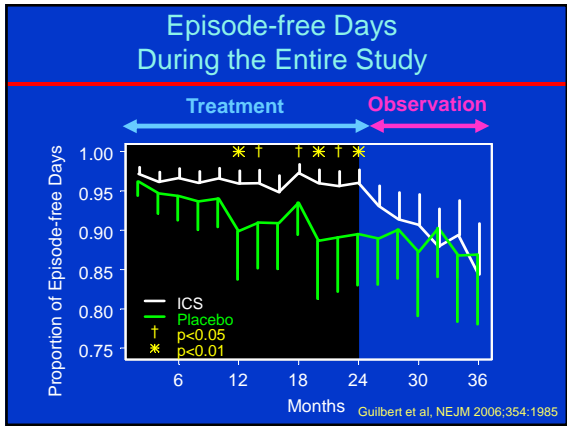
Asthma and Airway Disease Research Center
The University of Arizona

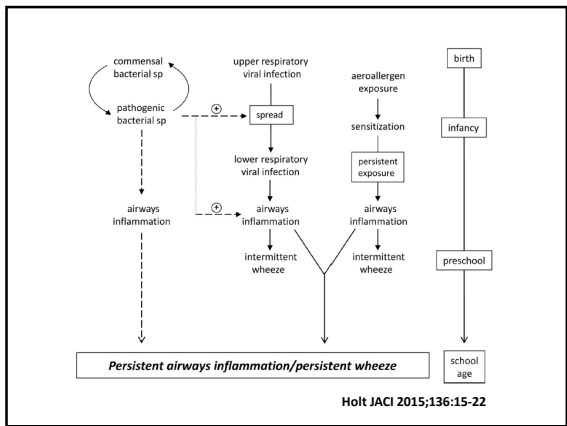
Disclosures

- Recipient of a contract with Johnson and Johnson to assess asthma preventive compounds in farm dust

Lung Function from Birth by Wheezing at Age 24-26 Yrs









Microbial Diversity, Living on a Farm, and Asthma

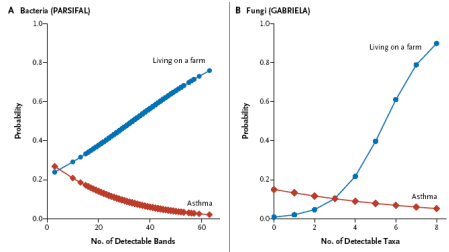
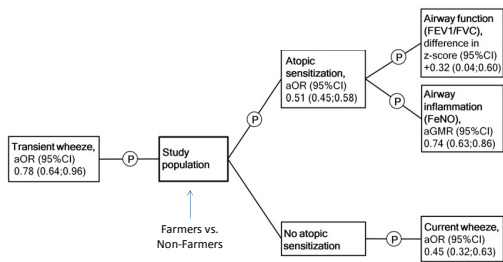


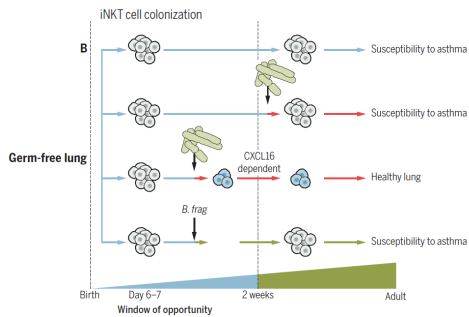
Figure 3. Relationship between Microbial Exposure and the Probability of Asthma.
In both the PARSIFAL study and GABRIELA, the range of microbial exposure was inversely associated with the probability of asthma.

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

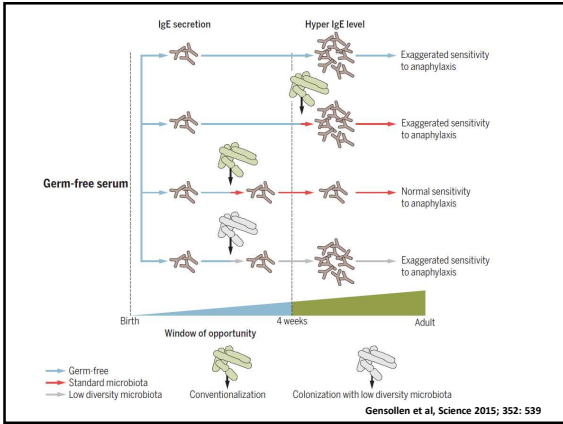
Farming Environment Protects Against All Forms of Early Wheeze

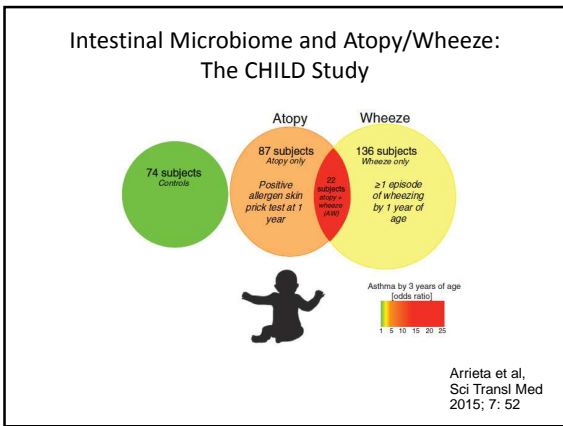


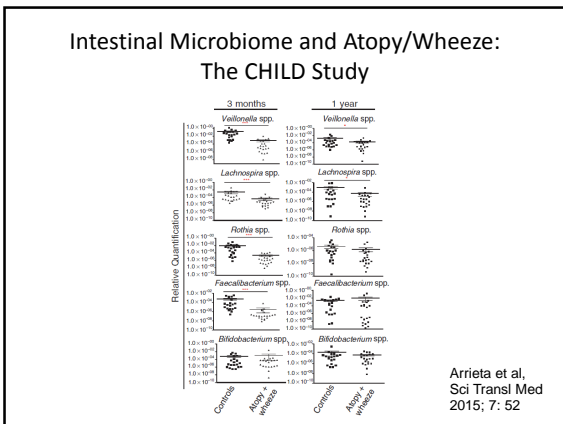
Fuchs et al, JACI 2012;130:382-8.



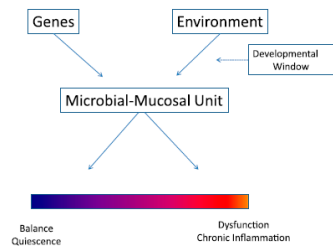
Gensollen et al, Science 2015; 352: 539







The Microbial-Mucosal Unit



Ann Am Thorac Soc. 2014;11 Suppl 1:S7-S12

Intestinal Microbes and Allergic Asthma

- Several investigators have used live oral probiotics to treat and prevent many diseases including eczema and asthma
- Results of a recent review: "We found no evidence to support a protective association between perinatal use of probiotics and doctor diagnosed asthma or childhood wheeze" (Azad et al, BMJ 2014; 347:f6471).
- Biochemical complexity of live probiotics poses great challenges re: drug regulation/standardization
- Investigators have thus explored the possibility that bacterial extracts could be used as a surrogate

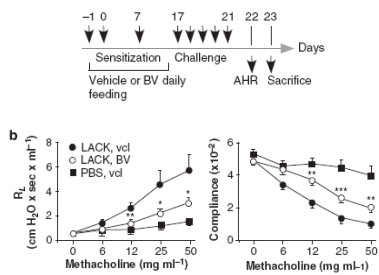
Bacterial Extracts

- Bacterial extracts (OM-85BV) are lyophilized fractionated alkaline extracts of *H. influenzae*, *D. pneumoniae*, *K. ozaenae*, *K. pneumoniae*, *S. aureus*, *S. pyogenes*, *S. viridans*, and *N. catarrhalis*
- It is a mixture of acidic proteins, peptides and amino acids, with minor components of detoxified LPS and lipoteichoic acids

Clinical Use of Bacterial Extracts

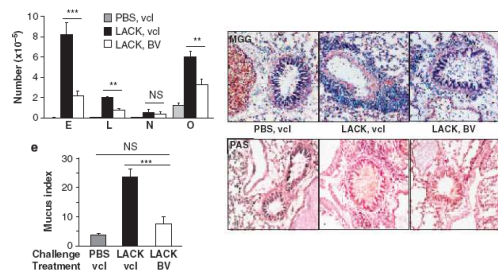
- Bacterial extracts have been widely used in Europe for the last 2-3 decades in children and adults as oral medicines to reduce the frequency and duration of URIs
- They have also been used in the prevention of exacerbations in CF and COPD

Prevention of BHR by Oral Administration of Bacterial Extracts



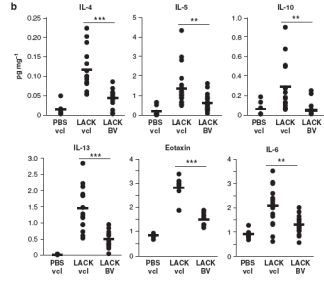
Navarro et al, Mucosal Immunol 2011; 4:43

Decreased Airway Inflammation by Oral Administration of Bacterial Extracts



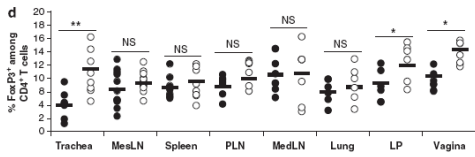
Navarro et al, Mucosal Immunol 2011; 4:43

Decreased BAL Cytokines by Oral Administration of Bacterial Extracts



Navarro et al, Mucosal Immunol 2011; 4:43

Increased Tracheal Treg Cells by Oral Administration of Bacterial Extracts



Navarro et al, Mucosal Immunol 2011; 4:43

Activation of Treg in Airway Mucosa by Oral OM-85BV in Rats

- Oral pretreatment of sensitized rats with OM-85BV strikingly accelerated the resolution of AHR that is triggered by aeroallergen exposure.
- The kinetics of the AHR response in treated animals closely mirrored associated CD86 expression on airway mucosal dendritic cells
- The principal feature distinguishing OM-85BV treated rats from controls was their markedly increased (2 ×) baseline numbers of airway mucosal Tregs.

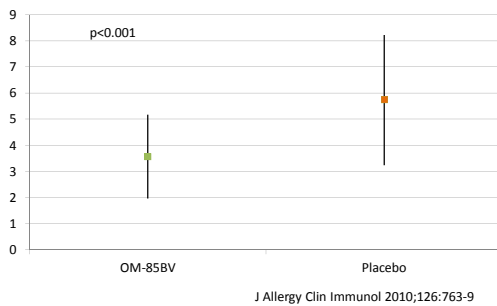
Strickland and Holt, Mucosal Immunol, 2011; 4:43-52

The Study by Razi et al

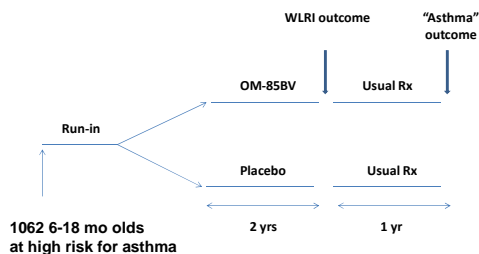
- This study was a randomized, double-blind, placebo-controlled, parallel group study with OM-85 BV in patients with recurrent wheezing in Ankara, Turkey
- 75 (40 OM-85BV, 35 placebo) 1-6 yr old children with recurrent wheezing
- Participants were randomly assigned to groups given either OM-85 BV or placebo (1 capsule per day for 10 days each month for 3 consecutive months) at the start of the trial.

J Allergy Clin Immunol 2010;126:763-9

Cumulative Yearly Number of Wheezing Episodes per Participant



ORBEX Trial Schemata



Participants in ORBEX

DCC: Dave Mauger, Penn State Hershey
CCC: Fernando Martinez, University of Arizona

Clinical Centers

- Wanda Phipatanakul, Boston Children's
- Dan Jackson, UW Madison
- Meyer Kattan, Columbia University NYC
- Anne Fitzpatrick, Emory University Atlanta
- Len Bacharier, Washington University S. Louis
- Steve Teach, Children's National DC
- Wayne Morgan, University of Arizona
