Can we control the “Atopic March”: How do we design and assess relevant intervention studies?

Thomas AE Platts-Mills FRS
Oscar Swineford Jr Professor of Medicine

We are grateful to the NIH for continued generous support including AI-20565-31 (TPM) & K-O8 AI-085190 and R-56 AI113095 (SPC). these studies have also been supported by Phadia Thermo/Fisher in the form of unrestricted support for IgE and IgG4 assays.
Potential Strategies for Intervention in Atopic March (1)

- **Timing**: Initiate 3 months – 2 years
  - Continue for 3 years – 5 years
  - But maximum evidence of the role of allergy in asthma comes at age 9-14

- **Intervention**: i) Avoidance
  - ii) Oral or other allergen exposure
  - iii) Other!!

- **Target**: Random population
  - At risk (primarily family history)
  - Some allergic disease already established: ie Atopic Dermatitis
Developmental Profiles of Eczema, Wheeze, and Rhinitis: Two Population-Based Birth Cohort Studies

Danielle C. M. Belgrave\textsuperscript{1,2,*}, Raquel Granell\textsuperscript{3,9}, Angela Simpson\textsuperscript{1,9}, John Guiver\textsuperscript{4,9}, Christopher Bishop\textsuperscript{4,9}, Iain Buchan\textsuperscript{2,9}, A. John Henderson\textsuperscript{3,9}, Adnan Custovic\textsuperscript{1,9}

October 2014 | Volume 11 | Issue 10 | e1001748
What is “Atopic March”, and is it a normal sequence.

- Many or most patients do not proceed consistently: AD, rhinitis, asthma; In some studies only 7% of allergic children have a consistent pattern.
- March may be seen as progression from one allergen or epitope to another or as progression of clinical disease.
- Some evidence that immunotherapy for grass can prevent sensitization to mite.
Dr John Snow (1813-1858)

Challenged the prevailing theory of miasmas (smells and bad air from putrefying matter) as the cause of diseases such as cholera, typhoid and bubonic plague.

Traced the 1854 Broad street cholera outbreak in Soho to a water pump.

Monitored the great experiment which demonstrated that water provided by a company which took their water from above London sewage was much safer.

Administered chloroform analgesia to Queen Victoria for the birth of her eighth child.
A. London water supplies in 1854 used by John Snow as evidence that typhoid and Cholera were spread through the water.

B. Typhoid fever deaths in Chicago 1892, which were controlled by extending the water intake into the lake and pumping 407 million gallons per day from the Chicago River into the Mississippi.
Bretton Woods resort

Ragweed Free areas 1880

Hay Fever: 1870-1900

The Allergy Epidemics 1870-2010
JACI 2015
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1900</td>
<td>Shoes universal; water clean.</td>
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<tr>
<td>1920</td>
<td>Helminths and malaria eradicated on Staten Island.</td>
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<tr>
<td>1924</td>
<td>Last abattoir closed; horses becoming rare.</td>
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<tr>
<td>1932-50</td>
<td>Ratner &amp; Silverman: Allergic Disease 10-13%.</td>
</tr>
<tr>
<td>1946</td>
<td>City initiated ragweed eradication campaign because of the severity of hay fever.*</td>
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<tr>
<td>1982</td>
<td>Mayor Koch: Asthma rated #1 medical problem of the city.#</td>
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<tr>
<td>1996</td>
<td>Emerging epidemic of asthma in NYC schools.</td>
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<tr>
<td>1997</td>
<td>Mayor Giuliani declares war on rats.</td>
</tr>
</tbody>
</table>

*Waltzer and Siegel, J Allergy 1956;27:113.  #Cancelled because of HIV.  
Hygiene in action: IgE antibodies to dust mite in sera from wheezing (○) and non-wheezing (●) children attending two schools one mile apart in the city of Kumasi, Ghana.

Both the prevalence and titer of IgE antibodies to mite were strongly associated with asthma in the affluent school, but not in the poor school.

Atopy, Mite Sensitization and Exposure to Dust Mites in Early Childhood as Risk Factors for Asthma at Age 11

<table>
<thead>
<tr>
<th>Current Asthma</th>
<th>Early* wheezing only</th>
<th>Never* wheezed</th>
<th>Relative risk</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Atopy at age 11</td>
<td>16/17</td>
<td>19/50</td>
<td>9/25</td>
</tr>
<tr>
<td>Mite sensitization at age 11</td>
<td>16/17</td>
<td>12/50</td>
<td>4/25</td>
</tr>
<tr>
<td>Exposure to $\geq 10\mu g$ Der p 1 at age 2</td>
<td>12/13</td>
<td>30/46</td>
<td>16/23</td>
</tr>
</tbody>
</table>

Current asthma = wheeze in the last year & bronchial reactivity to histamine
* Subgroups of no current asthma.

Sporik et al, NEJM 1990 ; 323: 502
Potential Immunological Effects of Biologically Active Components in Mite Fecal Particles

- Der p 1
- Endotoxin
- Der p 2
- Chitin
- Mite DNA
  - Bacterial DNA (unmethylated)

* MyD88 independent: type I IFNs, IL-10 and IFN-inducible genes

* GM-CSF, IL-1β, IL-6, IL-12, IL-18, IL-25, IL-33, TNF-α, TSLP

* IL-5, IL-6, IL-13, IL-15, IL-23, TNF-α, type I IFNs

* Cysteine protease can open tight junctions and cleave CD23 and CD25

Adapted from Yang and Seki, 2012.
Isotype Diversity in the Response to Low (A) or High (B) Allergen Exposure: Aalberse and Platts-Mills JACI 2004

A. \( \mu \)
   - TH2
   - IL-4
   - CD25+ TReg
   - Lymph Node or Bone Marrow
   - \( \varepsilon \) → IgE

B. \( \mu \)
   - Germinal Center
   - \( \gamma_1 \) → \( \gamma_1 \) → IgG\(_1\)
   - \( \gamma_4 \) → \( \gamma_4 \) → IgG\(_4\)
   - IL-10
   - Tr1
   - Apoptosis of IgE-Switched B Cells
   - Circulating Memory Cells

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The enigma of IgE B-cell memory in human subjects:
J.Davies, T.Platts-Mills and R.Aalberse, JACI 2013
Sequential class switching is required for the generation of high affinity IgE antibodies.

Huizhong Xiong, Maria de Lafaille, and Juan Lafaille.
Journal of Experimental Medicine: Jan 16th 2012

i. IgE B cells are rare in germinal centers (GC).

ii. IgE plasma cells can be derived by direct switch from IgM or via IgG B cells which have undergone maturation in germinal centers.

iii. They suggest that only IgE antibodies made via the germinal center route are relevant to allergic disease and even that low affinity antibodies are protective.

NB Deficiency of Bcl6 impairs GC but allows normal IgE in patients with DOCK8 mutations and immunodeficiency. See Zhang et al NEJMEd 2009
What is Hygiene and when did it happen?

The essence of Hygiene is some simple changes in how we live

i) Complete separation of untreated sewage from drinking water and food

ii) Control of helminth infection by:
    - eradication of sources of worm exposure,
    - shoes
    - regular anti-helminth treatment.

iii) Houses worth living in..

=In the UK and USA the major changes were complete by 1920.
=In Kenya, Ecuador, Ghana etc changes are occurring today.

=Costa Rica is already post-hygiene and already has a fully western form of asthma.
Potential Interventions

• Allergen Specific:
  – Oral allergens: Food (LEAP study, NEJM 2015) or Dust Mite (I.O.W. study, JACI 2015)
  – Sublingual drops or tablets
  – Transdermal patch.
  – Intradermal immunotherapy with peptides.

• Other:
  – Live on a farm -- Anti-histamines
  – Dog fecal bacteria -- Mab; anti-IgE, anti-IL-5, etc..
  – Probiotics -- IL-10, etc..
  – CPG
Impact of Dog in the Home:

Dog in the home can alter microbiome of the infant in first few months of life: increased *Lactobacilli* in stool

**Man’s best friend? The effect of pet ownership on house dust microbial communities**

Kei E. Fujimura, Ph.D.¹, Christine C. Johnson, Ph.D.², Dennis R. Ownby, M.D.³, ...

A. Boushey, M.D.⁶, and Susan V. Lynch, Ph.D.¹,*  
*J Allergy Clin Immunol. 2010 August; 126(2)*

House dust exposure mediates gut microbiome *Lactobacillus* enrichment and airway immune defense against allergens and virus infection

Kei E. Fujimura¹, Tine Demoor²,¹, Marcus Rauch³, Ali A. Faruqi¹, Sihyug Jang⁴, Christine C. Johnson⁵, Homer A. Boushey⁶, Edward Zoratti⁷, Dennis Ownby⁴, Nicholas W. Lukacs²,³, and Susan V. Lynch⁶,¹  

*PNAS 2014; 111*

**But see…**

The intestinal microflora in allergic Estonian and Swedish 2-year-old children

*Clinical and Experimental Allergy, 1999, Volume 29, pages 342–346*

B. BJÖRKSTÉN*†, P. NAABER‡, E. SEPP‡ and M. MIKELSAAR‡
New Zealand: very high exposure to both mite and cat allergens.

- Wheezing ~20%; mite sensitization dominates risk for asthma*.

- Sera from 224 children enrolled in an ISAAC based study on 1,500.$

Cat ownership (50%) was associated with decreased sensitization to cat, but had no effect on mite IgE ab

- Of the 55 with asthma living in a home with a cat, 34 were sensitized to mite, but not cat.

* Sears et al., Clin. Exp. All. 1989: 19:419;  *Peat, Li & Woolcock, JACI 1999: 103:1;  $Erwin, Crane, Wickens, Barry et al., JACI ’05: 115:74
Spontaneous deep inspiration is the first line of defense against bronchospasm (more potent than isoprenaline).
Fredberg JJ et al AJRCCM 159:959 ‘99

Sigh rates fall among students watching a screen compared to reading.
Hark et al, Annals of Allergy :’05, 94:247

Shim et al Physical deconditioning as the cause of breathlessness among Obese teenagers with a diagnosis of asthma. PLOS ONE 2013
Physical activity and bronchial hyperresponsiveness: European Community Respiratory Health Survey II

- 5,158 subjects age 28-56 in the ECRHS underwent Methacholine challenge for BHR; and detailed questionnaire on exercise.
- Both frequency and duration of physical activity were inversely related to BHR. Exercising 4 times weekly had an odds ratio for BHR of 0.69 (0.5-0.94).
- Conclusion: BHR is strongly and independently associated with decreased physical activity

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- See also, Hark et al., Spontaneous sigh rates during sedentary activity, Ann Allergy Asthma Immunol, 2005;94:247–50.
San Jose, Costa Rica: Manuel Soto-Quiros, Lydiana Avila, and Peter Heymann

Esmeraldas, Ecuador: Phil Cooper
Costa Rica: Titers of allergen-specific IgE antibody (wheezing children 7-12 years; n=96)

*GM values (in blue) include only children whose titers were ≥ 0.35 IU/ml
Pre-hygiene housing Esmereldas province Ecuador
.....courtesy Dr Philip Cooper.
IgE to Ascaris is the most significant association with Wheezing in Esmereldas Villages: Odds ratio, 2.7 (1.5-4.8).

Moncayo ....& Cooper PJ; Clin Exp All  2013.

Childs stool on day two of anti-helminth treatment
## Risk Factors for Wheezing in Esmeraldas Province, Ecuador (n=290)

<table>
<thead>
<tr>
<th>Specificity of IgE</th>
<th>IgE Positive</th>
<th>IgE Negative</th>
<th>Odds Ratios</th>
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<tbody>
<tr>
<td></td>
<td>Wheeze/No Wheeze#</td>
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<tr>
<td>Mite &gt; 0.35 IU/ml</td>
<td>52/41</td>
<td>89/108</td>
<td>1.5 (0.9-2.5)</td>
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<tr>
<td>Mite ≥ 3.5 IU/ml*</td>
<td>20/4</td>
<td>121/145</td>
<td>6.0 (2.0-18.0)**</td>
</tr>
<tr>
<td>Alpha-Gal &gt; 0.35 IU/ml</td>
<td>55/55</td>
<td>89/96</td>
<td>1.1 (0.7-1.7)</td>
</tr>
<tr>
<td>Ascaris &gt; 0.35 IU/ml</td>
<td>121/101</td>
<td>22/50</td>
<td>2.7 (1.5-4.8)**</td>
</tr>
</tbody>
</table>

*Values <3.5 IU/ml classified as negative

#Histories of wheezing 2013
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>19–23 mos</th>
<th>2–3 yrs</th>
<th>4–6 yrs</th>
<th>7–10 yrs</th>
<th>11–12 yrs</th>
<th>13–15 yrs</th>
<th>16–18 yrs</th>
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<tr>
<td>Hepatitis B</td>
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<td>Rotavirus</td>
<td>1st</td>
<td>2nd</td>
<td>See footnote 2</td>
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<td>DTaP</td>
<td>1st</td>
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<tr>
<td>Hib</td>
<td>1st</td>
<td>2nd</td>
<td>See footnote 5</td>
<td>3rd or 4th dose</td>
<td>See footnote 5</td>
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<tr>
<td>Pneumo. Conj.</td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
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<td>Pneumo. Polys.</td>
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<tr>
<td>Polio</td>
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<td>Influenza</td>
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<td>Annual vaccination (IIV only) 1 or 2 doses</td>
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<td>MMR</td>
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<td>Annual vaccination (LAIV or IIV) 1 dose only</td>
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<tr>
<td>Varicella</td>
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<td>1st</td>
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<tr>
<td>Hepatitis A</td>
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<td>1st</td>
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<td>2-dose series, See footnote 11</td>
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<tr>
<td>HPV</td>
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<td>(3-dose series)</td>
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<td>Meningococcal</td>
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<td></td>
<td>1st</td>
<td>Booster</td>
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</tr>
</tbody>
</table>

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

Range of recommended ages during which catch-up is encouraged and for certain high-risk groups

Not routinely recommended

Footnotes:
1. 2-dose series
2. Annual vaccination
3. LAIV
4. IIV
5. See footnote 5
6. See footnote 9
7. See footnote 13
8. Booster
Randomized controlled trial of primary prevention of atopy using house dust mite allergen oral immunotherapy in early childhood

Sensitization to Any Common Allergens

Log rank test:
Chi squared test = 4.86, p=0.028.

Sensitization to House Dust Mite

Log rank test:
Chi squared test = 0.26, p=0.6124.
Approaches to Preventing Allergy: 2016

• Avoidance of Allergens

• Oral Feeding of Allergens: Immunotherapy (i.e., peanut or dust mite)

• Altering the “microbiome”
  – Dog in the house during the first year
  – Bacterial
  – Worms, etc.
  – Living on a farm / exposure to diverse

• New products

• Can we prevent allergy?

[Gore C and Custovic A. Allergy 2004; 59:151]
IgE Antibodies to Mammalian or Other Allergens in Relation to Persistent Asthma (i.e., since age 6 years), Late Onset Asthma (only at age 18 years) and No Asthma

Perzanowski et al 2016: JACI revision under review!
Approaches to Preventing Allergy: 2016

- Avoidance of Allergens
- Oral Feeding of Allergens: Immunotherapy (i.e., peanut or dust mite)
- Altering the “microbiome”
  - Dog in the house during the first year
  - Bacterial
  - Worms, etc.
  - Living on a farm / exposure to diverse
- New products
- Can we prevent allergy?

[Gore C and Custovic A. Allergy 2004; 59:151]
“By the 1880s hay fever (also called June Cold, Rose Cold, hay asthma, hay cold, or autumnal catarrh) had become the pride of America’s leisure class.”
Overview, routes of sensitization

**Inhaled:** pollen, mite fecal particles, cockroach frass & animal dander.

**Lungs:** Either by colonization or inhaled.
   eg. *Aspergillus, C.albicans* or mite, cat etc,

**Oral:** Lips, mouth, esophagus, small intestine: local or absorbed.
   eg nuts, shell fish, wheat, cows milk etc.

**Skin:** bites, stings, contact, with or without eczema or filagrin defects.
   eg peanut, wheat, schistosomules and tick bites
And the many other colleagues who have enrolled or referred adult and pediatric cases with the alpha-gal syndrome.
Age, sex, and the association between skin test responses and IgE titres with asthma

Mohammad HR, Belgrave D, Kopec Harding K, Murray CS, Simpson A, Custovic A

(A 2016; In Press)
Age, sex, and the association between skin test responses and IgE titres with asthma
Mohammad HR, Belgrave D, Kopec Harding K, Murray CS, Simpson A, Custovic A

(Age 3)

(A) Predicted probability of asthma vs. Sum of SPT MWD to mite, cat and dog (mm)
- Boys n=467, Girls n=383
- Key: Male (Blue), Female (Green)
- p<0.001

(B) Predicted probability of asthma vs. Sum of serum sIgE levels to mite, cat and dog (kUA/L)
- Boys n=106, Girls n=72
- Key: Male (Blue), Female (Green)

(C) Predicted probability of asthma vs. Sum of SPT MWD to mite, cat and dog (mm)
- Boys n=460, Girls n=374
- Key: Male (Blue), Female (Green)

(D) Predicted probability of asthma vs. Sum of serum sIgE levels to mite, cat and dog (kUA/L)
- Boys n=285, Girls n=224
- Key: Male (Blue), Female (Green)
Developmental Profiles of Eczema, Wheeze, and Rhinitis: Two Population-Based Birth Cohort Studies

Danielle C. M. Belgrave¹,²,*, Raquel Granell³, Angela Simpson¹, John Guiver⁴, Christopher Bishop⁴, Iain Buchan², A. John Henderson³, Adnan Custovic¹

October 2014 | Volume 11 | Issue 10 | e1001748
IgE to Alpha-gal, inhalant, food and venom allergens in patients with a history of anaphylaxis

Delayed Anaphylaxis, Atopic (n=130)

Delayed Anaphylaxis, Non-atopic (n=115) : IgE neg to mite, grass and ragweed

IgE to galactose alpha-1,3 galactose (alpha-gal) induced by bites of the lone star tick.
Interventions

• Allergen Specific:
  – Oral allergens: Food (LEAP study, NEJM 2015) or Dust Mite (I.O.W. study, JACI 2015)
  – Sublingual drops or tablets
  – Intradermal immunotherapy with peptides

• Other:
  – Probiotics
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  – Live on a farm
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Age, sex, and the association between skin test responses and IgE titres with asthma

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