Food Allergy Prevention
(Peanuts)
Gideon Lack
Conflict of Interest

- Scientific advisory board to DBV Technologies and shareholder
- National Peanut Board support for other studies
Overview

1. Background & Study Design
2. Clinical Outcomes
3. Immunological Outcomes
4. Public Health Implications
5. Conclusions
**Background**

**Prevalence of Peanut Allergy in Children 4 - 18yrs**

- **United Kingdom**: 1.85% (p < 0.001)
- **Israel**: 0.17%

**Peanut Protein Consumption 8 - 14 months**

- **United Kingdom**: 0 g/week (p < 0.0001)
- **Israel**: 7.1 g/month

---

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

ABSTRACT

BACKGROUND
The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia. We evaluated strategies of peanut consumption and avoidance to determine which strategy is most effective in preventing the development of peanut allergy in infants at high risk for the allergy.

From the Department of Pediatric Allergy, Division of Asthma, Allergy and Lung Biology, King’s College London and Guy’s and St. Thomas’ National Health Service Foundation Trust, London (G.D.T., S.R., A.F.S., H.A.B., M.B., M.F., V.T., G.L.),
LEAP Study Design

Recruitment: 2006 -- 2009

n = 640 infants with severe eczema and/or egg allergy

Age at clinic visits: 4-11 months, 12 months, 30 months, 60 months

Intervention group; SPT-Positive Stratum (n=47)

Control Group; SPT-Positive Stratum (n=51)

Intervention group; SPT-Negative Stratum (n=272)

Control Group; SPT-Negative Stratum (n=270)

n=319

n=321
Peanut-specific IgE levels at Baseline by group

Recommended Dietary Interventions

- **Consumption**: 2 g of peanut protein 3 times per week for duration of study.
- **Avoidance**: Avoid peanut consumption

Bamba or peanut butter from infancy, whole peanuts could be added after 3 years of age.
Clinical Outcomes

- Peanut Allergy Prevalence
  - Primary and Secondary Prevention
  - Primary Outcome by Race
Intention-to-Treat Analysis

86% Relative Reduction

70% Relative Reduction

81% Relative Reduction
Primary and Secondary Prevention for Different Levels of Sensitisation (SPT and/or Specific-IgE)

<table>
<thead>
<tr>
<th></th>
<th>SPT-Negative &amp; IgE Negative</th>
<th>SPT-Negative &amp; IgE Positive</th>
<th>SPT-Positive &amp; IgE Negative</th>
<th>SPT-Positive &amp; IgE Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention Group</td>
<td>n=378 p-value = 0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Prevention Groups</td>
<td></td>
<td>31.6% n=149 p-value &lt; 0.001</td>
<td>21.4% n=22 p-value = 0.16</td>
<td>40.5% n=76 p-value = 0.006</td>
</tr>
<tr>
<td>Avoidance Group</td>
<td>6.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consumption Group</td>
<td>1.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidance Group</td>
<td></td>
<td>4.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consumption Group</td>
<td></td>
<td></td>
<td></td>
<td>12.8%</td>
</tr>
</tbody>
</table>
## Primary Outcome by Race

<table>
<thead>
<tr>
<th>Race</th>
<th>Avoidance Group</th>
<th>Consumption Group</th>
<th>Avoidance Group</th>
<th>Consumption Group</th>
<th>Avoidance Group</th>
<th>Consumption Group</th>
<th>Avoidance Group</th>
<th>Consumption Group</th>
<th>Avoidance Group</th>
<th>Consumption Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>13.0%</td>
<td>3.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td></td>
<td>30.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>44.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0%</td>
<td></td>
<td></td>
<td>23.1%</td>
</tr>
</tbody>
</table>

- **White**: n=460, p-value < 0.001
- **Mixed**: n=87, p-value < 0.001
- **Asian**: n=24, p-value = 0.012
- **Black**: n=48, p-value = 0.025
Anthropometry
Anthropometry: Height
Immunological Outcomes
Per-protocol Analyses
Peanut Skin Prick Test Wheal Sizes

Peanut Avoidance

Peanut Consumption

Peanut Wheal (mm)

Age at Visit (mo)

Trajectories of Participants with Peanut Allergy at 60 mo

Group Mean

Density of Distribution

Participants with Peanut Allergy at 60 mo

Participants without Peanut Allergy at 60 mo
LEAP Study Conclusions

- **Peanut consumption** beginning in the first year of life prevents **peanut allergy** in a high-risk population.
  - 86% reduction in the **SPT-negative stratum**
  - 70% reduction in the **SPT-positive stratum**
  - Both primary and secondary prevention effective
  - Prevention is **effective in all races**
  - Peanut consumption in high-risk children is **safe**
  - Prevention of allergy is associated with an **early and sustained rise in IgG and IgG4** and a later and progressive suppression of **high levels of peanut-specific IgE production**.
Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants

- American Academy of Asthma Allergy and Immunology
- American Academy of Pediatrics,
- American College of Allergy, Asthma & Immunology
- Australasian Society of Clinical Immunology and Allergy, Canadian Society of Allergy & Clinical Immunology
- European Academy of Allergy and Clinical Immunology
- Israel Association of Allergy and Clinical Immunology
- Japanese Society for Allergology
- Society for Pediatric Research
- World Allergy Organization
‘healthcare providers should recommend introducing peanut-containing products into the diet of “high-risk” infants early on in life (between 4 – 11 months of age) in countries where peanut allergy is prevalent, since delaying the introduction of peanut may be associated with an increased risk of developing peanut allergy’

‘Infants with early-onset atopic disease, such as severe eczema, or egg allergy in the first months of life (see Text Box 1 for example LEAP criteria), may benefit from evaluation by an allergist or physician trained in management of allergic diseases in this age group to diagnose any food allergy and assist in implementing these suggestions regarding the appropriateness of early peanut introduction’

‘Evaluation of such patients may consist of performing peanut skin testing and/or in-office observed peanut ingestion, as deemed appropriate following discussion with the family. The clinician may perform an observed peanut challenge for those with evidence of a positive peanut skin test to determine if they are clinically reactive, before initiating at-home peanut introduction. Both such strategies were used in the LEAP study protocol’
Intention-to-Treat Analysis

SPT-Negative Cohort (N=530)
- P<0.001

SPT-Positive Cohort (N=98)
- P=0.004

Both Cohorts (N=628)
- P<0.001

86% Relative Reduction
70% Relative Reduction
81% Relative Reduction
The Effect of the LEAP Intervention on the Screening Cohort was 53.1% Reduction in PA

<table>
<thead>
<tr>
<th>Allergy Rates Given:</th>
<th>Screening Study Sample Size</th>
<th>Avoidance Group Allergy Rate</th>
<th>Consumption Group Allergy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>118</td>
<td>2.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Group II</td>
<td>542</td>
<td>13.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Group III</td>
<td>98</td>
<td>35.3%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Group IV</td>
<td>76</td>
<td>77.6%</td>
<td>77.6%</td>
</tr>
<tr>
<td>Totals</td>
<td>834</td>
<td>20.4%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>

ESTIMATED PERCENT REDUCTION OF PEANUT ALLERGY IN THE SCREENING SAMPLE 53.1%
Peanut Wheal Size by Age

Age p-value <0.001

Unpublished data
Increasing Wheal Size with Age and SCORAD

- SCORAD p-value <0.001
- Age p-value <0.001
Both duration and severity of eczema are significantly associated with allergy at 60 months in a multivariate logistic regression model.
Applying LEAP Intervention to a “Normal Population” where 15% has eczema in first 11 months of life

<table>
<thead>
<tr>
<th>SCORAD GROUPS</th>
<th>DISTRIBUTION OF THE POPULATION</th>
<th>CALCULATED PA PROPORTION FROM LEAP AND PAS</th>
<th>WEIGHTED PREVALENCE IN POPULATION</th>
<th>PREVALENCE AFTER INTERVENTION (81%)</th>
<th>DIFFERENCE IN PREVALENCE</th>
<th>PREVALENCE AFTER INTERVENTION IN SUCCESSIVE STRATA</th>
<th>RELATIVE REDUCTION IN PREVALENCE FOR EACH STRATUM</th>
<th>RELATIVE REDUCTION IN PREVALENCE IN SUCCESSIVE STRATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40</td>
<td>2.0%</td>
<td>30%</td>
<td>0.60%</td>
<td>0.11%</td>
<td>0.49%</td>
<td>2.53%</td>
<td>16.12%</td>
<td>16.12%</td>
</tr>
<tr>
<td>15 to 40</td>
<td>3.0%</td>
<td>22%</td>
<td>0.66%</td>
<td>0.13%</td>
<td>0.53%</td>
<td>1.99%</td>
<td>17.73%</td>
<td>33.85%</td>
</tr>
<tr>
<td>1 to 15</td>
<td>10.0%</td>
<td>15%</td>
<td>1.50%</td>
<td>0.29%</td>
<td>1.22%</td>
<td>0.78%</td>
<td>40.30%</td>
<td>74.15%</td>
</tr>
<tr>
<td>0</td>
<td>85.0%</td>
<td>0.30%</td>
<td>0.26%</td>
<td>0.05%</td>
<td>0.21%</td>
<td>0.57%</td>
<td>6.85%</td>
<td>81.00%</td>
</tr>
<tr>
<td>TOTAL PREVALENCE</td>
<td></td>
<td></td>
<td>3.02%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PREVALENCE AFTER INTERVENTION (81%)*
Factors that Could Increase Treatment Efficacy at a Population Level

- Apply intervention before SPT grows above 4mm; there is a narrow window of opportunity
- Early intervention: (Ideally before 5 months)
  - For infants with no eczema
    - Introduce peanut without screening as of 4 months of age and once weaning has been established
  - For all infants with eczema
    - Screen using SPT
    - Introduce peanut under supervision if SPT <5mm
    - Incremental challenge
**LEAP Study Conclusions**

- **Peanut consumption** beginning in the first year of life **prevents peanut allergy** in a high-risk population.
  - 86% reduction in the SPT-negative stratum
  - 70% reduction in the SPT-positive stratum
  - Both primary and secondary prevention effective
  - Prevention is **effective in all races**
  - Peanut consumption in high-risk children is **safe**
LEAP-On Study

**Primary Endpoint** - proportion of participants with peanut allergy at 72 months of age

- **N=319** enrolled on LEAP Study
- **87% (n=558)** enrolled on LEAP-On Study
- **N=321** avoided consumption

Comparison at 72 months of the observed rates within Group A - **transient desensitisation**

Comparison at 72 months of the observed rates between Groups A and B - **persistent tolerance**

As of Jan 2015: 92% have completed LEAP-On final visit
Pregnant women 20/40 scan

1302 subjects

Early weaning onto allergenic foods

Randomization (3 months)

Current weaning recommendations

3 year assessment
- Food allergy
- Eczema
- Atopic wheeze
- Cumulative allergy

www.eatstudy.co.uk
Breastfeeding in the EAT cohort

Infant Feeding Survey 2010 Data. All comparisons between EIG or SIG and Infant Feeding Survey data at varying ages significantly different, p<0.001

Perkin M, et al. J Allergy Clin Immunol 2015; (Submitted)
Consumption of allergenic foods by the EIG in the four weeks prior to their four, five and six monthly birthdays

Perkin M, et al. J Allergy Clin Immunol 2015; (Submitted)
Differences in frequency of allergenic food consumption in SIG and EIG groups by 4, 5 and 6 months of age

Perkin M, et al. J Allergy Clin Immunol 2015; (Submitted)
<table>
<thead>
<tr>
<th>Week 1</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thurs</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baby Rice</td>
<td>Cow's Milk Yoghurt</td>
<td>Baby Rice</td>
<td>Cow's Milk Yoghurt</td>
<td>Baby Rice</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 2</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thurs</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Star 1</td>
<td>Cow's Milk Yoghurt</td>
<td>Star 1</td>
<td>Cow's Milk Yoghurt</td>
<td>Star 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 3</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thurs</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Star 1</td>
<td>Cow's Milk Yoghurt</td>
<td>Star 1</td>
<td>Cow's Milk Yoghurt</td>
<td>Star 2</td>
<td>Star 4</td>
<td>Star 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 4</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thurs</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Star 1</td>
<td>Cow's Milk Yoghurt</td>
<td>Star 1</td>
<td>Cow's Milk Yoghurt</td>
<td>Star 2</td>
<td>Star 4</td>
<td>Star 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 5 and Onwards</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thurs</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Star 1</td>
<td>Cow's Milk Yoghurt</td>
<td>Wheat*</td>
<td>Cow's Milk Yoghurt</td>
<td>Wheat*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Food 1: PEANUT  
Food 2: SESAME  
Food 3: EGG  
Food 4: FISH

Perkin M, et al. J Allergy Clin Immunol 2015; (Submitted)
Influence of number of foods consumed, quantity and frequency of consumption on compliance in the EIG

<table>
<thead>
<tr>
<th></th>
<th>≥4 FOODS</th>
<th></th>
<th>≥5 FOODS</th>
<th></th>
<th>≥6 FOODS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥50%</td>
<td>≥75%</td>
<td>100%</td>
<td>≥50%</td>
<td>≥75%</td>
</tr>
<tr>
<td>≥4 weeks</td>
<td>81%</td>
<td>70%</td>
<td>54%</td>
<td>≥4 weeks</td>
<td>74%</td>
</tr>
<tr>
<td>≥5 weeks</td>
<td>67%</td>
<td>53%</td>
<td>34%</td>
<td>≥5 weeks</td>
<td>58%</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>56%</td>
<td>41%</td>
<td>24%</td>
<td>≥6 weeks</td>
<td>44%</td>
</tr>
</tbody>
</table>

Perkin M, et al. J Allergy Clin Immunol 2015; (Submitted)
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

Senior Co-investigator: George Du Toit

Co-authors:
- Graham Roberts
- Peter H. Sayre
- Henry T. Bahnson
- Suzana Radulovic
- Alexandra F. Santos
- Helen A. Brough
- Deborah Phippard
- Monica Basting
- Mary Feeney
- Victor Turcanu
- Michelle L. Sever
- Margarita Gomez Lorenzo
- Marshall Plaut
The LEAP Study Team

- **Clinical support**: Rosa Caballero, Susan Chan, Adam Fox.
- **Dietitians**: Tammy Amarra, Kathryn Cockerell, Sarah Lacey, Gail Harland, Charlotte Stedman, Ruth Towell.
- **Study management and administration**: Catherine Clarke, Richard Cleaver, Gemma Deutsch, Erica Harris, Lori Nirenstein, Alicia Parr.
- **Laboratory projects**: Natalia Becares, Matthew Crossley, Natalia do Couto Francisco, Kerry Richards, Deeviya Patel, Ewa Pietraszewicz, Alick Stephens, Asha Sudra, Rianne Wester, Alastair Wilson, Celine Wu.
- **Play Specialists**: Jenna Heath, Kathryn Hersee.
- **Phlebotomist**: Devi Patkunam.
- **ITN Staff**: Michael Adamkiewicz, Adam Asare, Eduard Chani, Judith Evind, Kristina Harris, Noha Lim, Nariman Nasser, Audrey Plough, Jennifer Romaine, Michael Stahly.
- **NIAID Staff**: Joy Laurienzo Panza.

The EAT Study Team

- Michael Perkin, Kirsty England, Tom Marrs.
Research Support

- Immune Tolerance Network
- National Institute of Allergy and Infectious Disease
- Food Allergy Research & Education
- The MRC & Asthma UK Centre; The UK Department of Health through the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy’s & St. Thomas’ NHS Foundation Trust in partnership with King’s College London and King’s College Hospital NHS Foundation Trust.
- Food Standards Agency UK
- Rho Federal Systems Division
Acknowledgements – Participants & Families

- Families helped us achieve:
  - 98.4% retention over 5 years,
  - 92% compliance with intervention,
  - OFC in 96%,
  - Near complete blood draws at all time points