Prevalence of Food Allergy

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Declaration of interests

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Genon Laboratories
Campden BRI
Spin-out company
ReactaBiotech
Thirty years ago no one had ever heard of food allergies.

Now we have allergen labelling legislation and complex risk assessment of new foods to protect allergic consumers.
But managing food allergies needs data which have been lacking.

- How many people suffer from food allergy in Europe?
- Which are the major foods?
- What is the relationship with severity/minimum eliciting doses?
- What are the risk factors/causes?
- What is the impact of quality of life?
- How much does food allergy cost society?
How many people suffer from food allergy in Europe? ........self-reported symptoms

Overall allergy prevalence varied 3-35%!

Studies using challenge procedures for diagnosis had a prevalence of 1-4%
General Conclusions

The rates of food allergy determined in previous studies are HIGHLY HETEROGENEOUS

This is probably due to
• Variations in response rates
• Variations in diagnostic procedures

Only a cohesive study such as EuroPrevall can define the reasons for this heterogeneity

In 1989 1.3% of children on the Isle of Wight had IgE to peanut and 0.5% actual allergy.

In 1994-96 this INCREASED. 3.3% of children had IgE to peanut and 1.4% actual allergy.

In 2001-2002 this FELL BACK; 2% of children had IgE to peanut and 1.2% actual allergy.

Manchester Asthma and Allergy Study

• Of 933 children aged ~12 years, 110 (11.8%) were peanut-sensitized.
• Of the 110 children, 12 had a convincing history of peanut allergy and of 79 challenged 7 had objective reactions
• The prevalence of clinical peanut allergy is ~2% in this population

The Prevalence, Cost and Basis of Food Allergy Across Europe

(IP, 4 years 7 months; €14.3M)

• Investigating environmental, dietary & genetic influences on food allergy.
• Delivering information (patterns & prevalence, socioeconomic cost) & new tools to improve management

63 Partners from 23 countries including Europe (UK, NL, D, B, S, F, I, IRL, E, GR, PL, CZ, HU, IT, CH, A, DK, IS, BG, RU) Africa (Ghana) and Asia (India, China) with collaborating centres from USA, Canada, NZ and Australia
EuroPrevall Cohorts – seeking to define how many people suffer from food allergy

Birth Cohort
(Kirsten Beyer, Berlin)

Community Surveys
(Peter Burney, London)

Outpatient Clinic Study
(Montserrat Fernandez-Rivas, Madrid)
......and across the world in
• Russia (Tomsk)
• China (Hong Kong, Beijing)
• India (Mysore, Bangalore)

(Led by Gary Wong, Hong Kong)
Foods studied include those from EU allergen Labelling Directive (Eggs, milk, fish, shrimp, peanut, soy, hazelnut, walnut, wheat, celery, sesame, mustard)

And selected additional foods:

- Known geographic distribution
  - e.g. peach and lentil S Europe,
- Emerging allergenic foods, e.g. kiwi fruit
- Potential allergenic foods in new member states
  - e.g. buckwheat, poppy seeds
- Those linked to environmental allergies to
  - ✔ pollen e.g. apple
  - ✔ latex e.g. banana
DBPCFC: Common protocols and materials for older children and adults
Clinical leader: Barbara Ballmer-Weber; Food Materials leader: Alan Mackie

Priority 1 foods blinded in

(1) Chocolate desert (stored at room temp, just add water)
(2) Chocolate (peanut, hazelnut only)
(3) Puree desert peach and apple (freshly prepared; no threshold)
(4) Burgers and tomato sauce (shrimp)
Dose 1: designed to give the no observed adverse effect level (NOEL) and: lowest observed adverse effect level (LOAEL)

Dose 9: Equivalent to a daily serving

<table>
<thead>
<tr>
<th>Dose no</th>
<th>Mass</th>
<th>Protein</th>
<th>Matrix dose (%)</th>
<th>Cumulative Dose (mass)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6µg</td>
<td>3µg</td>
<td>0.0006</td>
<td>6µg</td>
</tr>
<tr>
<td>2</td>
<td>60µg</td>
<td>30µg</td>
<td>0.0006</td>
<td>66µg</td>
</tr>
<tr>
<td>3</td>
<td>600µg</td>
<td>300µg</td>
<td>0.06</td>
<td>666µg</td>
</tr>
<tr>
<td>4</td>
<td>6mg</td>
<td>3mg</td>
<td>0.06</td>
<td>6.67mg</td>
</tr>
<tr>
<td>5</td>
<td>60mg</td>
<td>30mg</td>
<td>3</td>
<td>66.67mg</td>
</tr>
<tr>
<td>6</td>
<td>0.12g</td>
<td>600mg</td>
<td>3</td>
<td>0.186g</td>
</tr>
<tr>
<td>7</td>
<td>0.6g</td>
<td>0.3g</td>
<td>3</td>
<td>0.786g</td>
</tr>
<tr>
<td>8</td>
<td>4.5g</td>
<td>2.2g</td>
<td>3</td>
<td>5.286g</td>
</tr>
<tr>
<td>9</td>
<td>6g</td>
<td>3g</td>
<td>3</td>
<td>11.286g</td>
</tr>
</tbody>
</table>
Birth cohort (Kirsten Beyer, Berlin) – final size ~ 12,000

Child
with signs of allergic diseases

- Patient history
- Specific IgE
- SPT

DBPCFC
Community Surveys (Peter Burney, London)

3000 Subjects

x Cases

(500-x) Controls

Extended Questionnaire Serology (IgE)

IgE determined to:
- food mixes
- individual foods
1: Egg, milk, peanut, soy, wheat, fish
2: Sesame seed, wheat, buckwheat, corn, rice
3: Hazelnut, tomato, walnut, carrot, celery
4: Shrimp, poppy seed, lentil, mustard, sunflower
5: Apple, kiwi, melon, banana, peach

History+/IgE+ History+/IgE-

History-/IgE+ History-/IgE-

All

Only if workload permits

Clinical evaluation (with DBPCFC) as outpatient clinic study

Outcome:
- Prevalence
- Thresholds
- Serum bank
Outpatient Clinic Survey (Montserrat Fernandez-Rivas, Madrid) ~ 2,200 patients recruited

Selection of patients

Adverse Reaction to any food < 2 hr

Medical history

SPT: foods/inhalants/latex

CAP: foods/inhalants/latex

DBPCFC: Priority 1 foods

Milk      Egg      Peanut
Hazelnut  Celery  Apple
Peach     Fish     Shrimp

EuroPrevall Serum Bank (Stefan Vieths, PEI)
EuroPrevall – definitions applied in the cohorts

**Screening Questionnaires**

- "**Perceived [possible] food allergy**" to any foodstuff: reported reactivity collected with the questionnaire.

**Serum IgE +/- SPT, History**

- "**Probable food allergy**" to the 24 selected foods: reported immediate reactions to a food item and specific IgE (positive SPT and/or CAP) to the same food.

**Food Challenge**

- "**Confirmed food allergy**" to the 9 foods selected for DBPCFC: reported immediate reactions together with specific IgE and a positive DBPCFC (or a positive open food challenge after a negative DBPCFC).
Symptoms and sensitisation to foods in infants (Birth cohort, 9,700 children 30 months old)

• Perceived [possible] food allergy: ~20% reported symptoms

• Probable food allergy:
  • Important sensitising foods were hens’ egg, cows’ milk.
  • Peanut sensitisation was significant but less prevalent.
  • Wheat, soy and fish were minor sensitisers

• Confirmed food allergy:
  • In some countries (UK, NL) a significant proportion of cows milk allergic infants were not sensitised but in many other countries almost all allergic infants were sensitised.
Symptoms and sensitisation to foods in adults (community survey, 17,366 subjects age 20-54)

• **Perceived [possible] food allergy:** ~20% reported symptoms

• **Probable food allergy:**
  • Rates varied greatly across Europe.
  • Important sensitising foods were fresh fruits and vegetables, tree nuts and seeds and shrimp.
  • Fish was a minor sensitiser.

• **Confirmed food allergy:** only a small number of those eligible for challenge accepted. Rates of confirmed allergy were similar to those in the outpatient clinic study
DBPCFC: Comparison between outpatient and community studies

### Outcomes
- **Placebo reactor**: Community study: 11.9%, Outpatient study: 14.9%
- **Reactive**: Community study: 56.0%, Outpatient study: 64.4%
- **Tolerant**: Community study: 32.1%, Outpatient study: 20.7%

**P-values**:
- Placebo reactor: Community study vs. Outpatient study: p = 0.54
- Reactive: Community study vs. Outpatient study: p = 0.18
- Tolerant: Community study vs. Outpatient study: p = 0.05

**Sample sizes**:
- Community study: n = 461
- Outpatient study: n = 87

### Symptoms
- **Placebo reactor**: Community study: 11.9%, Outpatient study: 14.9%
- **Reactive**: Community study: 56.0%, Outpatient study: 63.6%
- **Tolerant**: Community study: 32.1%, Outpatient study: 36.4%

**Sample sizes**:
- Community study: n = 258
- Outpatient study: n = 56

**p-values**:
- Placebo reactor: Community study vs. Outpatient study: p = 0.54
- Reactive: Community study vs. Outpatient study: p = 0.18
- Tolerant: Community study vs. Outpatient study: p = 0.05
## EuroPrevall Threshold Database

<table>
<thead>
<tr>
<th>Food</th>
<th>Total</th>
<th>Reactive</th>
<th>Tolerant</th>
<th>Placebo reactors</th>
<th>% Reactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>135</td>
<td>61</td>
<td>61</td>
<td>13</td>
<td>45.2%</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>132</td>
<td>91</td>
<td>24</td>
<td>17</td>
<td>68.9%</td>
</tr>
<tr>
<td>Fish</td>
<td>50</td>
<td>34</td>
<td>12</td>
<td>4</td>
<td>68%</td>
</tr>
<tr>
<td>Shrimp</td>
<td>55</td>
<td>31</td>
<td>19</td>
<td>5</td>
<td>56.4%</td>
</tr>
<tr>
<td>Celery</td>
<td>64</td>
<td>41</td>
<td>19</td>
<td>4</td>
<td>64.1%</td>
</tr>
<tr>
<td>Apple</td>
<td>71</td>
<td>41</td>
<td>17</td>
<td>13</td>
<td>57.7%</td>
</tr>
<tr>
<td>Peach</td>
<td>54</td>
<td>32</td>
<td>13</td>
<td>9</td>
<td>59.3%</td>
</tr>
<tr>
<td>Milk</td>
<td>418</td>
<td>146</td>
<td>239</td>
<td>33</td>
<td>34.9%</td>
</tr>
<tr>
<td>Egg</td>
<td>314</td>
<td>178</td>
<td>122</td>
<td>14</td>
<td>56.7%</td>
</tr>
</tbody>
</table>
Visualising symptoms during an challenge using fish (Icelandic patient) with freeze-dried cod in chocolate dessert

Challenge stopped at dose 8

Urticaria appears transiently during a challenge (3mg, 0.3g)

At 1g multiple symptoms appear and the challenge is stopped
Dose-response modelling using Lowest Observed Adverse Effect Levels (LOAELs) and interval censoring survival analysis

Total of 135 peanut challenges undertaken in EuroPrevall
• Birth cohort: 60 challenges, 47% reactive, median age 2 years;
• Outpatient clinic study: 75 challenges, 43% reactive, median age 30 years
• Of the reactive population, 9 individuals experienced delayed and other types of reaction and were excluded from the reference population

68% of the reference population (n=51) reacted with objective symptoms

Defernez, Ballmer-Weber, Beyer, Fernandez-Rivas, Hourihane, Mackie, Mills et al
• Dose-response modelling using LOAEILs from the combined population (median age 15.6) gave a ED10 value of ~3 mg peanut protein depending (log-normal model). This equates to ~12 mg of peanut seed.

• 95% Confidence intervals are wide (0.2, 36)

• This value is similar to the 12.3 (9.0, 16.8 95% confidence intervals) mg of peanut (median age 7) reported previously (Taylor et al Food Chem 2010)

These data indicate that sufficient evidence is becoming available to allow action levels to be set for allergens in foods in the coming years.
There are still gaps in our knowledge to allow effective evidence-based allergenic risk assessment

We still lack

• Effective methods for determining allergens in foods, naturally-incurred reference materials and reference methods

• Data on levels of cross-contact allergens in foods and their distribution

• Information on factors such as the food matrix, exercise, stress, infections and alcohol consumption which may alter thresholds

Any risk assessment/management method will also need validation and verification!
Integrated Approaches to Food Allergen and Allergy Management (iFAAM)

Coordinated by Professor Clare Mills, University of Manchester

- Developing evidence-based approaches and tools for MANAGEMENT of ALLERGENS in FOOD
- Integrating knowledge derived from their application into FOOD ALLERGY MANAGEMENT plans and dietary advice.
- The resulting holistic strategies will reduce the burden of food allergies in Europe and beyond whilst enabling the European food industry to compete in the global market place.

36 Partners from 15 countries including Europe (UK, AU, BE, DK, CH, CR, DE, FR, IE, IS, IT, ES, GR, LT, NL, PL, ), Turkey and the USA
Objective 1: Nutrition and allergy throughout life (Module 1)
- Early life nutrition and allergy
- Dietary interventions for allergy prevention

Objective 2: Risk factors and severity (Module 2)
- Biomarkers for severe reactions to food
- Intrinsic and extrinsic risk factors

Objective 3: Validated Risk Models (Module 3)
- Modelling allergenic risk
- Clinical evidence and validation of models

Objective 4: Tools for Allergen Management (Module 4)
- Multi-analyte allergen analysis
- Clinically-relevant analysis

Objective 5: Delivery of evidence-based integrated tools for food allergen and allergy management across the food chain to key stakeholders groups (Module 5)

Allerg-e-Lab, STAKEHOLDERS (Consumers, risk assessors/managers, Industry, Health professionals)

INNOVATION, INDUSTRIAL COMPETITIVENESS AND SMEs
iFAAM Stakeholder Engagement

**Patient Groups and Clinicians**
- Championed by DAAB with UK, NL and IE patient groups as partners and the European Academy of Allergy and Clinical Immunology (EAACI) facilitating dissemination to the clinical community (through Food Allergy Interest Group and the Dieticians)

**Risk Assessors and Managers**
- Championed by DTU to which regulators are being invited including UK FSA, Health Canada, USFDA, FSANZ, EFSA

**Industry**
- Championed by Unilever with SME partners and Nestle
- Industrial platform run by Manchester including all major manufacturers of allergen test kits, analytical service providers, reference laboratories, food manufacturers and retailers.

Delivering harmonised integrated approaches to manage population risk, ensure consumer protection, food allergy management plans and dietary advice.
Developing transparent, knowledge-based validated risk assessment strategies will help reduce the use of precautionary statements.

This will help consumers and the health professionals who advise them, to make safe food choices!
All only possible through the 63 EuroPrevall partners and collaborating centres AND those individuals who have participated in the studies!