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## Peanut Allergen Reaction Thresholds during Controlled Food Challenges in 2 Canadian Randomized Studies (Canada-ARM1 and PISCES)

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## **Peanut Allergen Reaction Thresholds during Controlled Food Challenges in 2 Canadian Randomized Studies (Canada-ARM1 and PISCES)**

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### **Clinical Implications**

In 2 randomized studies addressing peanut allergy (Canada-Food Allergy Risk Management 1 [NCT01812798] and Peanut Immunotherapy Starting in Canada, Evaluation and DiSCovery [NCT01601522]), we quantified peanut allergen thresholds to food challenge using Bayesian stacked model averaging to inform policy and clinical practice. About 50% of patients tolerated more than 70 mg (~ ¼ peanut).

Food allergy affects millions worldwide.<sup>1</sup> Vigilance by affected individuals and families is necessary to prevent accidental ingestions, allergic reactions, and anaphylaxis. Understanding the minimum amount of food allergen that elicits a reaction—thresholds—in susceptible individuals is paramount to inform safe practice, food manufacturing, and public health policy.<sup>1</sup> Thresholds can also inform how to optimize food challenge schedules, advise patients about the potential for accidental reactions, and the design of desensitization approaches. Potential differences in populations raise concerns about the generalizability of threshold data generated across countries, and no established thresholds information exists in Canada. We evaluated peanut allergen thresholds in 2 prospective randomized studies using the novel<sup>2</sup> Stacked Model Averaging method of interval-censored survival analysis to account for between-study heterogeneity, limit modeling choice subjectivity, and obtain accurate estimates.

In Canada-Food Allergy Risk Management (ARM) 1 (Canada-ARM1, NCT01812798), a study to quantitate thresholds, eligible patients aged 7 to 65 years with a known or convincing history of peanut allergy (for criteria, see the supplemental information) were challenged over 2 days by double-blind, placebo-controlled food challenge (i.e., blinded patients, providers, assessors, and data collectors; for schedule, see the supplemental information). In Peanut Immunotherapy Starting in Canada, Evaluation and DiSCovery (PISCES, NCT01601522), a randomized trial evaluating peanut oral immunotherapy, patients aged 5 to 10 years were screened (for criteria, see the supplemental information) and included patients who underwent open food challenge (OFC; for schedule, see the supplemental information). We quantified thresholds using R 3.6.1 statistical language and Bayesian stacked model averaging interval-censored survival analysis,<sup>2</sup> which uses 5 parametric distributions that are combined to maximize the accuracy of eliciting dose (ED) values. All ED values refer to cumulative protein. All patients provided written informed consent. Both studies were approved by the Hamilton Integrated Research Ethics Board.

The overall population across the prospective studies (n = 73) had a median age of 9 years (range, 5–21), 42 (58%) were female and had mean (SD) wheal skin prick test of 9.7 ± 3.5 mm and mean (SD) serum peanut IgE level of 63.8 ± 37.5 kU/L (Table I). OFCs were stopped in 53 (73%) because of objective clinical signs; the rest had recurrent and/or persistent subjective symptoms/signs. There were no censored observations.

**Table I.** Summary of findings

Characteristic	Study 1 (n = 22)	Study 2 (n = 51)	Overall (n = 73)
	Canada-ARM1 (NCT01812798)	PISCES (NCT01601522)	
Age (y), median (range)	11.4 (7.0–20.8)	8.0 (5.0–11.0)	9.2 (5.0–20.8)
Gender: male/female, n (%)	11/11 (50/50)	20/31 (39/61)	31/42 (42/58)
Ancestry/panethnicity, n (%)			
European	16 (72)	44 (86)	60 (82)
East Asian	1 (5)	3 (6)	4 (5)
South Asian	0 (0)	1 (2)	1 (1)
Mixed	3 (14)	1 (2)	4 (5)
None of the above	2 (9)	2 (4)	4 (5)
Weight (kg), mean ± SD	45.9 ± 18.0	27.0 ± 6.7	34.3 ± 15.3
BMI (kg/m <sup>2</sup> ), mean ± SD	20.0 ± 5.3	16.5 ± 2.0	17.9 ± 4.0
Peanut SPT (mm mean wheal), mean ± SD	10.0 ± 3.3	9.5 ± 3.6	9.7 ± 3.5
Peanut IgE (kU/L), mean ± SD	25.6 ± 31.8	80.3 ± 26.1	63.8 ± 37.5
History of reaction, n (%)	18 (82)	51 (100)	69 (95)
OFC Objective stopping, n (%)	19 (86)	34 (67)	53 (73)
Population modeling* as amounts of peanut protein <sup>†</sup>			
	n = 22	n = 51	n = 73
ED1, mean (95% CI)	1.24 (0.96–1.86)	1.77 (0.52–8.35)	1.17 (1.01–1.90)
ED5, mean (95% CI)	6.35 (5.05–8.80)	4.34 (1.94–10.24)	5.74 (4.92–9.56)
ED10, mean (95% CI)	13.28 (10.28–18.26)	6.27 (3.24–11.39)	11.82 (10.23–19.69)
ED50, mean (95% CI)	78.44 (58.30–122.26)	12.75 (9.80–16.11)	70.58 (59.40–130.90)

DBPCFC, double-blind placebo-controlled food challenge; SPT, skin prick test

\*Bayesian model averaging can yield 95% CIs that are asymmetric.

<sup>†</sup>ED, eliciting dose, also known as cumulative reactive dose. The amount of peanut protein that causes an allergic reaction in a certain percentage of the population of those with peanut allergy; that is, ED1 denotes that amount of peanut protein that would cause an allergic reaction in 1% of the sampled peanut-allergic population.

In Canada-ARM1 (n = 22), the mean (95% CI) ED for 1% of the population (ED1) in cumulative milligram of protein was 1.24 (0.96–1.86), ED5: 6.35 (5.05–8.80), ED10: 13.28 (10.28–18.26), and ED50: 78.44 (58.30–122.26). In PISCES (n = 51), the ED1 was 1.77 (0.52–8.35), ED5: 4.34 (1.94–10.24), ED10: 6.27 (3.24–11.39), and ED50: 12.75 (9.80–16.11). To increase precision and because the general Canadian peanut-allergic population is likely to comprise individuals sampled from both studies, pooled estimates (n = 73) yielded ED1: 1.17 (1.01–1.90), ED5: 5.74 (4.92–9.56), ED10: 11.82 (10.23–19.69), and ED50: 70.58 (59.40–130.90).

In summary, we prospectively define 2 Canadian cohorts of peanut-allergic patients and quantify food allergen thresholds to inform policy and practice for multiple stakeholders. We also illustrate the utility of novel statistical methods for advanced predictive capability.

Our findings show variability in population thresholds compared with previous studies in Denmark (ED5: 18.9 [13.0–27.6]),<sup>3</sup> Germany (ED5: 2.0 [0.9–4.4]),<sup>4</sup> and a review by the

US Food and Drug Administration (ED10: 0.4 [0.2–0.8])<sup>5</sup> (Table II). Our findings are similar to the multicentre (Ireland/Australia/USA) Peanut Allergen Threshold Study suggesting an ED5 of more than 1.5 mg,<sup>6</sup> and a multicenter study in the United Kingdom (ED5: 3.8 [2.4–5.7]).<sup>7</sup> Although geographic variability in population thresholds is plausible, the magnitude of variability may be modest. Australia and New Zealand’s Allergen Bureau’s Voluntary Incidental Trace Allergen Labelling 2.0 report’s<sup>9</sup> limited geographic comparison across 4 countries found ED5 estimates to mostly fall between 2 and 4 mg. Our findings, in accordance with Voluntary Incidental Trace Allergen Labelling 2.0 and 3.0 recommendations (ED1: 0.2 and ED5: 2.1),<sup>8</sup> contribute the first Canadian data on peanut allergen thresholds. These could inform health risk assessment and efforts to develop medically validated policies or guidance for precautionary allergen labeling, which currently does not reliably correlate with risk.<sup>1</sup> Given the number of countries now analyzed and known variability in thresholds between individuals, we suggest that although the ED5 estimates of 2 to 4 mg could be viewed statistically as variable, this range is clinically narrow.

**Table II.** Research in context\*\*

Study	ED1 (95% CI)	ED5 (95% CI)	ED10 (95% CI)	ED50 (95% CI)
Canada (current report)	1.17 (1.01–1.90)	5.74 (4.92–9.56)	11.82 (10.23–19.69)	70.58 (59.40–130.90)
Denmark <sup>3</sup>	†	18.9 (13.0–27.6)	32.9 (23.6–45.9)	†
PATS (Ireland, Australia, USA) <sup>6</sup>	†	> 1.5	†	†
UK <sup>7</sup>	1.3 (0.8–2)	3.8 (2.4–5.7)	7 (4.5–10.5)	74.7 (51.9–107.3)
Germany <sup>4</sup>	†	2.0 (3.5–17.6)	4.1 (2.0–8.4)	56.3 (33.7–94.1)
US FDA review <sup>5</sup>	†	†	0.4 (0.2–0.8), or 0.7 (0.4–1.3)	†
VITAL 3.0 reference doses <sup>8</sup>	0.2	2.1	†	†

FDA, Food and Drug Administration; PATS, Peanut Allergen Threshold Study; VITAL, Voluntary Incidental Trace Allergen Labelling

\*Values are in milligram of peanut protein.

†ED, eliciting dose, also known as cumulative reactive dose. The amount of peanut protein that causes an allergic reaction in a certain percentage of the population of those with peanut allergy; that is, ED1 denotes that amount of peanut protein that would cause an allergic reaction in 1% of the sampled peanut-allergic population.

‡Values not reported

Our findings accord with the Peanut Allergen Threshold Study whereby OFCs starting at 1 to 2 mg will identify the most sensitive individuals. Conversely, we found that 50% of peanut-allergic individuals may have a relatively higher threshold, approximately 70 mg or (95% CI, 59–131). It should be kept in mind, however, that perturbations (cofactors) including sleep deprivation, exercise, and other factors can decrease thresholds by 45% (95% CI, 22–62).<sup>7</sup>

Geography alone may not fully explain differences seen across publications, because different studies may also include different populations, challenge protocols, and analysis methods.<sup>9</sup> For instance, differences from the US Food and Drug Administration review may be due to the inclusion of subjective symptoms not included in the other studies, and

potential exclusion of individuals with high thresholds, which could bias ED estimates downwards. Our findings suggest that PISCES, an oral immunotherapy trial in which thresholds were measured by open OFC, were more sensitive compared with Canada-ARM1, which was designed for threshold quantitation with a different dosing schedule and evaluated by double-blind, placebo-controlled food challenge. Critically incorporating all information from these studies and others will likely better represent overall patient populations. Therefore, our study supports the need for future food allergen threshold studies with particular attention to potential differences in study populations, challenge protocols (including regimen and blinding), and statistical methods of analysis.

Strengths of this study include the evaluation of peanut-allergic patients in 2 different studies, analyzed using novel Bayesian model averaging methodology, which limits variability and subjectivity in the underlying model choice for data analysis. Stacked model averaging synthesizes 5 parametric survival distributions to yield more accurate ED values. It also accounts for study-to-study heterogeneity, which is absent from previous threshold studies. Potential limitations include the relatively small sample size, lack of ancestry/pan-ethnic diversity, and few included infants and adults.

Altogether, we present peanut allergen reaction thresholds in 2 cohorts of children and young adults in Canada, identifying populations with varying sensitivity to ED while reinforcing the utility of new statistical methods. Further work is required to better characterize the thresholds for peanut and other food allergens, as well as their determinants, for understanding their underlying mechanisms and their clinical use.

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**Conflicts of interest** – Outside the submitted work, A. Marrin was on the advisory board for ALK and aeroallergen immunotherapy. Outside the submitted work, S. Wasserman sits on the Adverse Reactions to Foods Committee; Food Allergy, Anaphylaxis, Dermatology and Drug Allergy; and the American Academy of Allergy and Asthma and Immunology, and is a medical advisor for Food Allergy Canada. The rest of the authors declare that they have no relevant conflicts of interest.

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## Supplemental information

### Canada-ARM1 eligibility criteria

#### Inclusion criteria:

- Children and adults aged between 7 and 65 years.
- Demonstrated history of peanut allergy based on medical history, positive skin prick test result, and peanut-specific IgE CAP-FEIA test. Participants were confirmed to have peanut allergy based on a history of significant clinical symptoms within 60 minutes of the ingestion of peanut, the presence of specific IgE to peanut (a positive skin prick test result to peanut, defined as a wheal 3 mm larger than that of the saline control, and a positive in vitro peanut-specific IgE test value > 0.35 kU/mL).
- Ability to discontinue all prescribed and over-the-counter allergy-related medications for suitable withdrawal periods before starting the challenge.

#### Exclusion criteria:

- Previous desensitization treatment to peanut.
- Allergies to any component of the oral challenge matrix.
- Unstable allergic conditions such as uncontrolled asthma or chronic urticaria.
- Any clinically significant disease/chronic medical condition that may have interfered with study evaluations.

### PISCES eligibility criteria

#### Inclusion criteria:

- Patients must have been aged between 5 and 10 years.
- Patients were confirmed to have peanut allergy based on a history of significant clinical symptoms within 60 minutes after the ingestion of peanut, the presence of specific IgE to peanut (a positive skin prick test result to peanut, defined as a wheal 3 mm larger than that of the saline control, and a positive in vitro peanut-specific-IgE result of > 15 kU/L).
- Patients were also accepted into the study if they had a clinical reaction to peanut ingestion in the preceding past 6 months to enrollment, a positive skin prick test result to peanut as defined previously, and an in vitro peanut IgE result of 7 kU/L or greater.
- Subjects must have been free of any clinically significant disease that may have interfered with study evaluations.

Exclusion criteria:

- Use of antihistamines or decongestant therapy 7 days before the clinic visit (antihistamines, e.g., diphenhydramine and desloratadine).
- Patients who had an acute allergic reaction to food other than peanut, drugs, or stinging insects 1 month before the recruitment clinic visit.
- Patients who have had a respiratory infection 1 month before the recruitment clinic visit.
- Patients with significant or uncontrolled asthma (inhaled corticosteroids [fluticasone > 500 µg/d, ciclesonide > 400 µg/d, or budesonide > 800 µg/d or the corresponding combination inhalers, oral prednisone in the preceding 1 month, and FEV<sub>1</sub> < 80% predicted). Nasal steroids, bronchodilators, and leukotriene inhibitors were permitted. If prednisone was to be taken, it must have also been stopped 1 month before blood being drawn if possible.
- Patients who received allergy injections (immunotherapy) to environmental allergens at any time in the past. Symptomatic atopic dermatitis or chronic urticaria that may have interfered with ability to evaluate outcomes and/or requiring daily medication including antihistamines.
- Patients with difficulty related to compliance or following study procedures.

Canada-ARM1 challenge dose schedule Peanut flour (Light; Golden Peanut Company, Alpharetta, Georgia; 50% protein)		
Dose no.	Discrete (mg peanut protein)	Cumulative (mg peanut protein)
1	0.03	0.03
2	0.11	0.14
3	0.32	0.46
4	1.06	1.51
5	3.17	4.69
6	10.58	15.27
7	31.74	47.01
8	105.8	152.81
9	317.4	470.21
10	529.0	999.21
11	1058.0	2057.21

PISCES challenge dose schedule		
Peanut flour (Light; Byrd Mill Company, Ashland, Virginia; 50% protein)		
Dose no.	Discrete (mg peanut protein)	Cumulative (mg peanut protein)
1	1	1
2	2	3
3	4	7
4	6	13
5	12	25
6	25	50
7	50	100
8	75	175
9	100	275
10	200	475
11	300	775
12	400	1175
13	500	1675
14	575	2250
15	750	3000
16	1000	4000

#### **Additional description of methods**

Skin test reagents were from ALK (ALK-Abelló Pharmaceuticals Inc., Ontario, Canada) and subjects pricked with Duo-tips on the volar forearm with mean wheal size readings at 15 minutes. Serum specific IgE was measured by Phadia ImmunoCAP. In PISCES, participants were equally randomized by pharmacy to being challenged with either peanut (flour weighed for each dose) and then placebo on separate days in identical food matrices, or vice versa according to PRACTALL guidelines.