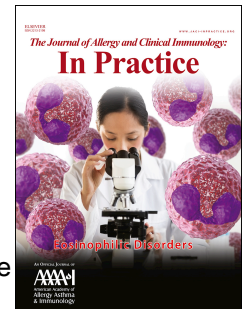


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Title

Peanut allergen reaction thresholds during controlled food challenges in two Canadian randomized studies (Canada-ARM1 and PISCES)

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34 Declarations

35 Chu: Nothing to declare.

36 Baumert: Nothing to declare.

37 Taylor: Nothing to declare.

38 Nordlee: Nothing to declare.

39 Nham: Nothing to declare.

40 Bramson: Nothing to declare.

41 La Vieille: Nothing to declare

42 Abbott: Nothing to declare

43 Spill: Nothing to declare

44 Marrin: Outside the submitted work, was on Advisory board for ALK and aeroallergen immunotherapy.

45 Jordana: Nothing to declare.

46 Wasserman: Outside the submitted work, sits on the Adverse Reactions to Foods Committee FADDA the
47 American Academy of Allergy and Asthma and Immunology, and is a medical advisor for Food Allergy
48 Canada.

49 Clinical Implications (40 of 40 word limit)

50 In two randomized studies addressing peanut allergy (Canada-ARM1 [NCT01812798]; PISCES
51 [NCT01601522]), we quantified peanut allergen thresholds to food challenge using Bayesian Stacked
52 Model Averaging to inform policy and clinical practice. About 50% of patients tolerated >70 mg
53 (approximately ¼ peanut).

Main Text (988 of 1000 word limit)

Food allergy affects millions worldwide¹. 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 policy¹. 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 two prospective randomized studies using the novel² Stacked Model Averaging method of interval-censored survival analysis to account for between-study heterogeneity, limit modelling 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 7-65 years with a known or convincing history of peanut allergy (Online-Repository for criteria) were challenged over 2 days by double-blind, placebo-controlled food challenge (DBPCFC; ie. blinded patients, providers, assessors, data collectors; Online-Repository for schedule). In Peanut Immunotherapy Starting in Canada, Evaluation and DiSCovery (PISCES, NCT01601522), a randomized trial evaluating peanut oral immunotherapy (OIT), patients 5-10 years old were screened (Online-Repository for criteria) and included patients underwent open food challenge (OFC; Online-Repository for schedule). We quantified thresholds using R 3.6.1 statistical language and Bayesian stacked model averaging interval-censored survival analysis², which uses five parametric distributions that are combined in order to maximize the accuracy of eliciting dose (ED) values. All ED values refer to cumulative protein. All patients provided written informed consent.

The overall population across the prospective studies (n=73) was median age 9 years (range 5-21), 42 (58%) female, mean (SD) wheal skin prick test in mm 9.7 (3.5) mm and mean (SD) serum peanut IgE 63.8 (37.5) kU/L (Table 1). OFCs were stopped in 53 (73%) due to objective clinical signs; the rest recurrent and/or persistent subjective symptoms/signs. There were no censored observations.

In Canada-ARM1 (n=22), the mean (95% CI) ED for 1% of the population (ED1) in cumulative mg 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 as 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) and ED10: 11.82 (10.23-19.69), ED50: 70.58 (59.40-130.90).

In summary, we prospectively define two 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 to previous studies in Denmark (ED5: 18.9 [13.0-27.6])³, Germany (ED5: 2.0 [0.9-4.4])⁴, and a review by the US FDA (ED10 0.4 [0.2-0.8])⁵ (Table 2). Our findings are similar to the multicentre (Ireland/Australia/USA) PATS study suggesting an ED5 >1.5 mg⁶, and a multicentre study in the UK (ED5 3.8 [2.4-5.7])⁷. While geographic variability of population thresholds is plausible, the magnitude of variability may be modest. Australia and New Zealand's Allergen Bureau's Voluntary Incidental Trace Allergen Labelling (VITAL) 2.0 report's⁸ limited geographic comparison across 4 countries found ED5 estimates to mostly fall between 2-4 mg. Our findings, in accordance with VITAL 2.0 and 3.0 recommendations (ED1 0.2, ED5 2.1)⁹, 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 labelling, which currently

does not reliably correlate with risk¹. Given the number of countries now analyzed and known variability in thresholds between individuals, we suggest that although the ED5 estimates of 2-4 mg could be viewed statistically as variable, this range is clinically narrow..

Our findings accord with PATS whereby OFCs starting at 1-2 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 more. 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)⁷.

Geography alone may not fully explain differences seen across publications, as different studies may also include different populations, challenge protocols, and analysis methods⁸. For instance, differences from the US FDA 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 OIT trial where thresholds were measured by open OFC, were more sensitive compared to Canada-ARM1, which was designed for threshold quantitation with a different dosing schedule and evaluated by DBPCFC. Critically incorporating all information from these studies and others will likely better represent overall patient populations. Therefore, our study further 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 two different studies, and analyzed using novel Bayesian model averaging methodology, which limits variability and subjectivity in the underlying model choice for data analysis. Stacked model averaging synthesizes five parametric survival distributions to yield more accurate ED values. It also accounts for study-to-study

123 heterogeneity, which is absent from previous threshold studies. Potential limitations include the
124 relatively small sample size, lack of ancestry/panethnic diversity, and few included infants and adults.

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

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References (9 out of a limit of 9)

1. National Academies of Sciences E, and Medicine. Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management, and Public Policy. Washington, DC, 2017.
2. Remington BC, Westerhout J, Meima MY, Blom WM, Kruizinga AG, Wheeler MW, et al. Updated population minimal eliciting dose distributions for use in risk assessment of 14 priority food allergens. *Food and Chemical Toxicology* 2020; 139:111259.
3. Eller E, Hansen TK, Bindslev-Jensen C. Clinical thresholds to egg, hazelnut, milk and peanut: results from a single-center study using standardized challenges. *Annals of Allergy, Asthma & Immunology* 2012; 108:332-6.
4. Blumchen K, Beder A, Beschorner J, Ahrens F, Gruebl A, Hamelmann E, et al. Modified oral food challenge used with sensitization biomarkers provides more real-life clinical thresholds for peanut allergy. *J Allergy Clin Immunol* 2014; 134:390-8.
5. Zhu J, Pouillot R, Kwegyir-Afful EK, Luccioli S, Gendel SM. A retrospective analysis of allergic reaction severities and minimal eliciting doses for peanut, milk, egg, and soy oral food challenges. *Food Chem Toxicol* 2015; 80:92-100.
6. Hourihane JOB, Allen KJ, Shreffler WG, Dunngalvin G, Nordlee JA, Zurzolo GA, et al. Peanut Allergen Threshold Study (PATS): Novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy. *Journal of Allergy and Clinical Immunology* 2017; 139:1583-90.
7. Dua S, Ruiz-Garcia M, Bond S, Durham SR, Kimber I, Mills C, et al. Effect of sleep deprivation and exercise on reaction threshold in adults with peanut allergy: A randomized controlled study. *Journal of Allergy and Clinical Immunology* 2019; 144:1584-94.e2.
8. Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol* 2014; 133:156-64.
9. Bureau TA. Food Industry Guide to the Voluntary Incidental Trace Allergen Labelling (VITAL®) Program Version 3.0. Australia, 2019.

Tables (2 out of a limit of 2 display items)

Table I. Summary of Findings

	Study 1 (n=22) Canada-ARM1 [NCT01812798]	Study 2 (n=51) PISCES [NCT01601522]	Overall (n=73)
Age (years), median (range)	11.4 (7.0-20.8)	8.0 (5.0-11.0)	9.2 (5.0-20.8)
Gender, n male/female (%)	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, 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 of 73 (95%)
OFC Objective stopping	19 (86%)	34 (67%)	53 (73%)
Population modeling* as amounts of peanut protein**			
	n=22	n=51	n=73
ED ₁ , mean (95% CI)	1.24 (0.96-1.86)	1.77 (0.52-8.35)	1.17 (1.01-1.90)
ED ₅ , mean (95% CI)	6.35 (5.05-8.80)	4.34 (1.94-10.24)	5.74 (4.92-9.56)
ED ₁₀ , mean (95% CI)	13.28 (10.28-18.26)	6.27 (3.24-11.39)	11.82 (10.23-19.69)
ED ₅₀ , mean (95% CI)	78.44 (58.30-122.26)	12.75 (9.80-16.11)	70.58 (59.40-130.90)

*Bayesian model averaging can yield 95%CI's that are asymmetric

**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. ie. ED₁ denotes that amount of peanut protein that would cause an allergic reaction in 1% of the sampled peanut allergic population.

DBPCFC, double blind placebo-controlled food challenge; OFC, oral food challenge

176 Table II. Research in context

	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)
Denmark³	\	18.9 (13.0-27.6)	32.9 (23.6-45.9)	\
PATS study (Ireland, Australia, USA)⁶	\	>1.5	\	\
UK⁷	1.3 (0.8-2)	3.8 (2.4-5.7)	7 (4.5-10.5)	74.7 (51.9-107.3)
Germany⁴	\	2.0 (3.5-17.6)	4.1 (2.0-8.4)	56.3 (33.7-94.1)
US FDA review⁵	\	\	0.4 (0.2-0.8), or 0.7 (0.4-1.3)	\
VITAL 3.0 reference doses⁹	0.2	2.1	\	\

177 * Values are in mg of peanut protein

178 ** ED, eliciting dose also known as cumulative reactive dose. The amount of peanut protein that causes
 179 an allergic reaction in a certain percentage of the population of those with peanut allergy. I.e. ED1
 180 denotes that amount of peanut protein that would cause an allergic reaction in 1% of the sampled
 181 peanut allergic population.

182 \ Values not reported

Online-Repository Text

Canada-ARM1 eligibility criteria

Inclusion Criteria:

- Children and adults between 7-65 years of age.
- Demonstrated history of peanut allergy based on medical history, positive skin prick test, 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 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 which may have interfered with study evaluations

PISCES eligibility criteria

Inclusion Criteria:

- Patients must have been between 5 and 10 years of age.
- 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 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 enrolment, a positive skin prick test 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 which may have interfere with study evaluations.

Exclusion Criteria:

- Use of antihistamines or decongestant therapy 7 days prior to the clinic visit. (antihistamines eg. diphenhydramine, desloratadine etc).
- Patients who had an acute allergic reaction to food other than peanut, drugs, or stinging insects one month prior to the recruitment clinic visit.
- Patients who have had a respiratory infection one month prior to the recruitment clinic visit.

- Patients with significant or uncontrolled asthma, (inhaled corticosteroids (fluticasone >500 mcg per day, ciclesonide >400 mcg per day or budesonide >800 mcg per day or the corresponding combination inhalers, oral prednisone in the preceding 1 month and FEV1 < 80% predicted). Nasal steroids, bronchodilators and leukotriene inhibitors were permitted. If Prednisone was to be taken, it must have also been stopped 1 month prior to 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 which 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, GA; 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, VA; 50% protein)

Dose No.	Dose (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 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.