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Predicted number of peanut-allergic patients needed to treat with epicutaneous immunotherapy (EPIT) to prevent one allergic reaction: A novel approach to assessing relevance

To the editor:

Peanut allergy is a generally persistent(1), sometimes life-threatening food allergy. With no treatments to date demonstrating the ability to cure peanut allergy, the focus has been on providing a level of protection against accidental exposure reactions through desensitization, defined as an increase in the reaction or eliciting dose (ED) threshold(2–4).In a previously published quantitative risk assessment, modeling demonstrated an approximately 73-78% relative reduction per eating occasion in risk of reaction to peanut-contaminated packaged food products, with no change seen in the placebo group (5).In this study, wesought to model thepredictednumber needed to treat (NNT)in order to prevent an

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allergic reaction when consuming peanut-contaminated food products in the UK, as well as the predicted NNT for the prevention of a moderate/severe allergic reaction (grade 2 or 3) as defined by a task force of the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Initiative (6).

Population-based quantitative risk assessments using Monte Carlo simulations were utilized to model allergic reactions to peanut on a yearly basis (Figure 1, Supplemental Table 1). Four primary inputs for the risk assessment were; 1) the study-population dose distributions at baseline and 12-month double-blind, placebo-controlled food challenges (DBPCFCs) (with 95% confidence intervals), 2) consumption of a food product (frequency of consumption and amount), 3) concentration of peanut if the consumed product is contaminated and 4) the proportion of peanut allergic reactions by each severity group. United Kingdom consumption patterns were estimated for six food product categories (cookies, pastries, ice cream, salty snacks, rice-based meals and chocolate [Supplemental Table 2]) for which data are available and the total number of allergic reactions due to the unintended presence of peanut protein in one of these products was predicted on a yearly basis (365 days of potential exposure to peanut simulated for 1000 peanut-allergic individuals). Clinical data were utilized from a double-blind, placebo-controlled Phase 3 study population of children, aged 4-11 years, treated with epicutaneous immunotherapy (EPIT) for 12 months with either a patch containing 250 µg peanut protein (DBV712 250 µg patch) or a placebo patch (2,5). The concentration of peanut, if the consumed product is contaminated, was estimated from peanut protein concentrations in North American and European food retail surveys as previously summarized (5). The simulation was repeated 50 times per study population to account for variability and uncertainties within input variables (Supplemental Table 1). The NNT in order to prevent one allergic reaction when consuming peanut-contaminated food products in the UK was then calculated.

The NNT to prevent a predicted moderate or severe reaction (as defined above) (6) was also calculated. In order to estimate the proportion of allergic reactions occurring due to accidental peanut consumption, which would result in a moderate and/or severe allergic reaction, a review of the relevant literature was performed. Of a total of 8 published studies identified, which reported episodes of peanut allergic reactions by symptom classification, five studies were able to inform the population estimate of the proportion of all peanut triggered allergic reactions reported that would result in moderate/severe symptoms (grade 2/3). The estimated unweighted mean for moderate and severe reactions was 57.4% (minimum 38.7%, maximum 70.7%). Further details can be found in Supplemental Table 3.

Overall, the predicted risk reductions from treatment with DBV712 250 µg for 12 months gave a NNT of 5.5 for prevention of an objective allergic reaction when consuming peanut-contaminated packaged food

products (Table 1) and a NNT of 9.4 for prevention of a moderate/severe allergic reaction. By modeling using the baseline untreated population, 15.9% of the peanut-allergic individuals (159 of 1000 patients) were predicted to experience a mean total of 235 objective allergic reactions over the course of 1 year, with 136 moderate/severe reactions (Supplemental Table 4). In contrast, the peanut-allergic population treated with the 12 months of DBV712 250 µg demonstrated a significant risk reduction, which resulted in 4.3% of individuals (43 of 1000 patients) predicted to experience a mean total of 53 objective allergic reactions over the course of 1 year, with 30 moderate/severe reactions. The model predicts an average of 182 objective allergic reactions prevented per year for 1000 patients treated and prevention of 106 moderate/severe reactions per 1000 patients treated.

Epicutaneous daily patch treatment with DBV712 250 µg (approximately 1/1000 one peanut) for 12 months has previously been shown to result in a statistically significant increase in desensitization in peanut-allergic children 4-11 years compared with placebo. Increasing the eliciting dose through desensitization should reduce an individual's risk of a reaction to an accidental exposure. It is well known that the severity of an allergic reaction to food ingestion is unpredictable and subject to influence of both known and unknown cofactors. The need for a universal severity grading system has previously been articulated, and while there is general agreement that early adrenaline use is preferred, there is lack of agreement about exactly which signs/symptoms should rise to that level of treatment globally. We used existing consensus EAACI guidelines to identify the moderate and severe allergic reactions where such treatment may be appropriate, acknowledging that this is a decision point that is likely best individualized based on an individual's history and other risk factors. Acknowledging the above caveats and limitations of this literature-based analysis, here we sought to estimate the NNT associated with DBV712 250 µg in order to prevent the most clinically concerning allergic reactions (those rising to the level of moderate/severe and need for adrenaline) based on clinical experience reported from the literature. It is worth noting that the NNTs we have estimated compare favorably with those derived from clinical trials involving other allergic diseases, for example prevention of asthma exacerbations/hospitalizations with omalizumab and mepolizumab (7–9). It should be noted that a potential limitation to the modeling is that it was based upon treatment response to DBV712 in a population with an ED threshold at baseline to 300 mg or less, and may be different for children with significantly higher pre-treatment threshold. Another potential limitation affecting generalizability of the model is that the consumption data do not come from a selected peanut-allergic population, though it has been recently shown in a specific food consumption survey that intake levels of the general population represent those of food allergic patients (10). In

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addition, we rely on modeling data here because of the relatively small sample size and limited time frame of the Phase 3 study, but the findings raise important “real life” questions for further investigation.

In conclusion, the NNTs in this study predict a substantial risk reduction for allergic reactions, for both reactions of any severity as well as for moderate/severe allergic reactions, among peanut-allergic children after 12 months of EPIT with DBV712 250µg. The NNT is important in assessing the benefit/risk profile of a potential therapy and our results support the potential real-world clinical relevance of this investigational immunotherapy.

Tables and figures

Figure 1. Visualization of the quantitative risk assessment model for NNT prediction.

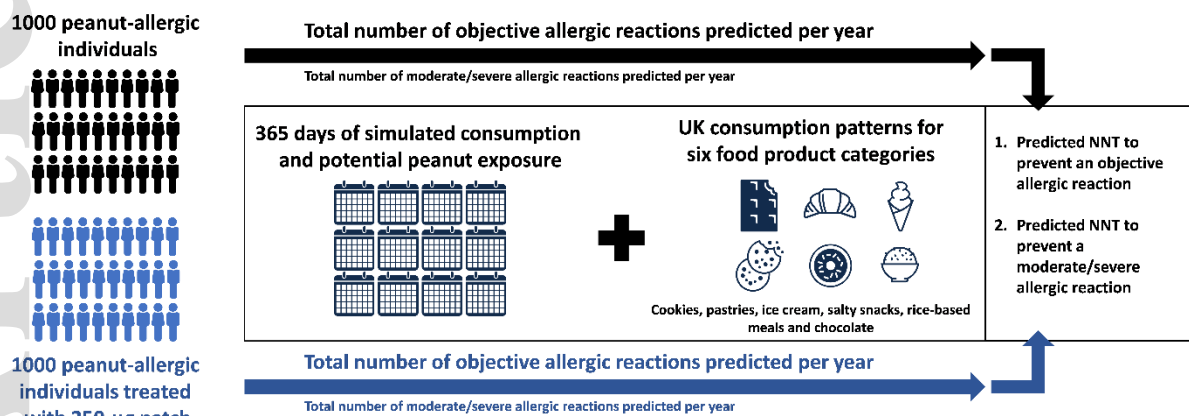


Table 1. Mean estimates of predicted NNT values from 50 repeated model runs.The predicted NNTs (Q25, Q75) for prevention of an objective allergic reaction and prevention of a moderate/severe allergic reaction (grade 2 or 3) as defined by a task force of the European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Initiative are shown. These are calculated within a model using the unweighted averages for the rates of occurrence per allergic reaction (57.4%) presented in Supplemental Table 3, as well as the minimum (38.7%) and maximum (70.7%) rates of occurrence of moderate/severe allergic reactions per allergic reaction in the included studies.

Predicted NNT to prevent an objective allergic reaction	Mean estimate from model (Q25, Q75)		
Using the DBV712250 µg Baseline timepoint (T0) for NNT calculation	5.5 (5.9, 5.1)		
Using the Placebo 12-month timepoint (P12) for NNT calculation	3.9 (4.6, 3.4)		
Predicted NNT to prevent a moderate/severe allergic reaction	Mean estimate using unweighted average frequency of occurrence from literature review (Q25, Q75)	Mean estimate from model if using minimum frequency of occurrence from literature review (Q25, Q75)	Mean estimate from model if using maximum frequency of occurrence from literature review (Q25, Q75)
Using the DBV712250 µg Baseline timepoint (T0) for NNT calculation	9.4 (10.3, 8.9)	14.5 (15.4, 13.3)	7.9 (8.5, 7.2)
Using the Placebo 12-month timepoint (P12) for NNT calculation	6.8 (7.4, 5.9)	10.2 (11.8, 9);	5.4 (6.3, 4.9)

References

1. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014;**69**:992–1007.
2. Fleischer DM, Greenhawt M, Sussman G, Bégin P, Nowak-Wegrzyn A, Petroni D et al. Effect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Ingestion among Children with Peanut Allergy: The PEPITES Randomized Clinical Trial. *JAMA* 2019;**321**:946–955.
3. Kim EH, Yang L, Ye P, Guo R, Li Q, Kulis MD et al. Long-term sublingual immunotherapy for peanut allergy in children: Clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2019;**144**:1320-1326.e1.
4. Vickery BP, PALISADE. AR101 Oral Immunotherapy for Peanut Allergy. *N Engl J Med* 2018;**379**:1991–2001.
5. Remington BC, Krone T, Kim EH, Bird JA, Green TD, Lack G et al. Estimated risk reduction to packaged food reactions by epicutaneous immunotherapy (EPIT) for peanut allergy. *Ann Allergy, Asthma Immunol* 2019;**123**:488-493.e2.
6. Muraro A, Fernandez-Rivas M, Beyer K, Cardona V, Clark A, Eller E et al. The urgent need for a harmonized severity scoring system for acute allergic reactions. *Allergy* 2018;**73**:1792–1800.
7. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;**364**:1005–1015.
8. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;**60**:309–316.
9. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A et al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. *N Engl J Med* 2014;**371**:1198–1207.
10. Blom WM, van Os-Medendorp H, Bijlsma S, van Dijk A, Kruizinga AG, Rubingh C et al. Allergen risk assessment: Food intake levels of the general population represent those of food allergic patients. *Food Chem Toxicol* 2020;**146**:111781.

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Conflict of Interest

Dr. Remington reports grants, personal fees and non-financial support from DBV Technologies, during the conduct of the study; non-financial support from ILSI Europe, outside the submitted work; and is an adjunct faculty member of the University of Nebraska. Dr. Koppelman reports grants, personal fees and other from DBV Technologies, grants from University of Nebraska, during the conduct of the study; personal fees and other from DBV Technologies, outside the submitted work; and is an adjunct faculty

member of the University of Nebraska. Dr. Green reports other from DBV Technologies, during the conduct of the study. Dr. Lack reports grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), other from Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), The Davis Foundation, grants from UK Food Standards Agency (FSA), during the conduct of the study; personal fees and other from DBV Technologies, other from Mighty Mission Me, personal fees from Novartis, Sanofi-Genzyme, Regeneron and ALK-Abello, personal fees and other from Lurie Children's Hospital, outside the submitted work. Dr. Roberts reports acting as a consultant to DBV during the conduct of the study. Dr. Campbell reports personal fees from DBV, during the conduct of the study; grants from National Health and Medical Research Council of Australia, personal fees from Allergenis, other from Nestle Health Science and from Westmead Fertility Centre, outside the submitted work.

Supplementary information

Supplemental Table 1. Population-based quantitative risk assessment model inputs for NNT prediction.

Simulation parameters		Reference
Number of times the simulation is repeated	50	
Number of allergic individuals per simulation	1000	
Number of days per simulation	365	
Clinical study population	Dose-distributions (with 95% confidence intervals) from Phase 3 study population of children treated with epicutaneous immunotherapy (EPIT) for 12 months with either a patch containing 250 µg peanut protein (250 µg patch) or a placebo patch	(2,5)
Consumption estimate		
Food categories, frequency of consumption and amount consumed	Cookies, Pastries, Ice Cream, Salty Snacks, Rice-Based Meals and Chocolate	United Kingdom National Diet and Nutrition Survey (NDNS survey years 1-3), children 3-9 years of age
Percent chance of peanut contamination in consumed product	3%*	
Concentration of peanut in consumed product if contaminated	Log-normal distribution (median 5.9 mg/kg peanut protein, mean 36.6 mg/kg peanut protein)	(5)
If a reaction is predicted...		
Chance of a Moderate/Severe reaction (grade 2/3)	57.4% unweighted mean (minimum 38.7%, maximum 70.7%)	Supplemental Table 3

*- The 12 studies providing concentration data for the current study were previously detailed (6). When looking at those study results, the average contamination frequency across different studies was estimated to be 10% with a reported range of 0.2% to 27.2% frequency of peanut contamination. As means of conservatism when modelling the NNT, the frequency of contamination was estimated to be 3% for the current study.

Supplemental Table 2. Consumption estimates and frequency of consumption for selected food categories from United Kingdom National Diet and Nutrition Survey (NDNS survey years 1-3) for children 3-9 years of age in the EFSA Comprehensive European Food Consumption Database.

Food Category	% Consuming days	Mean (g)	Std Dev (g)	P95 (g)	P99 (g)
Cookies	36.6%	31.8	22.3	75	117
Pastries and cakes	35.1%	68.3	44.3	159.5	212
Ice cream	15.2%	73.6	41.9	142	183
Salty snacks	35.5%	27.4	17.9	55	100
Rice-based meals	2.1%	138.9	56.4	240	300
Chocolate	13.4%	30.0	39.0	98	208

Supplemental Table 3. Literature search results for rates of moderate/severe symptoms (grade 2/3) per allergic reaction as defined by an EAACI Food Allergy and Anaphylaxis Initiative task force. Grade 2 reactions were moderate in nature and consisted of reactions that involve skin away from the site of allergen contact, upper airway, and/or gastrointestinal tract (6). Grade 3 reactions were severe, potentially life-threatening allergic reactions involving cardiovascular, neurological, bronchial, and/or laryngeal symptoms and signs (7).

	Published year	Data collected	Region	n	Study design	AE rate/year*	% of all reactions moderate and severe (as per EAACI guidelines)	Applicability to analysis
Cherkaoui	2015	2004-14	Canada	1941	prospective	12.4%	66.5%	Some mild reactions likely to be considered moderate by Garde 2 and 3. Likely an underestimate
Luu	2011	2004-09	Canada	1411	prospective	12.5%	70.7%	Reasonable alignment with EAACI
Yu	2006	2000-05	Canada	252	retrospective	14.3%	57.1 %	Likely an underestimate as not possible to extract moderate from mild.
Fleischer	2012	Not stated	US	512	prospective	6%	38.7%	Reasonable alignment with EAACI
Niomark	2012	Not stated	UK	969	Prospective recruitment-but data based upon patient recall of prior year	48% (all foods)	Unable to extract	
Neuman-Sunshine	2011	1990-2009	US	782	retrospective	7.3%	Unable to extract	
Clark	2008	Not stated	UK	785	prospective	4%	Unable to extract	
Vander Leek	2000	Not stated	US	83	prospective	33% (1 reaction every 3 years per patient)	54%	Reasonable alignment with EAACI

*- rate of accidental reactions to peanut/year

References for Supplemental Table 3

1. Cherkaoui S, Ben-Shoshan M, Alizadehfar R, et al. Accidental exposures to peanut in a large cohort of Canadian children with peanut allergy. *Clin Transl Allergy*. 2015;5(1):16. doi:10.1186/s13601-015-0055-x
2. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, et al. Inadvertent exposures in children with peanut allergy. *Pediatr Allergy Immunol*. 2012;23(2):134-140. doi:10.1111/j.1399-3038.2011.01235.x
3. Yu JW, Kagan R, Verreault N, et al. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol*. 2006;118(2):466-472. doi:10.1016/j.jaci.2006.04.024
4. Fleischer DM, Perry TT, Atkins D, et al. Allergic Reactions to Foods in Preschool-Aged Children in a Prospective Observational Food Allergy Study. *Pediatrics*. 2012;130(1):e25-e32. doi:10.1542/peds.2011-1762
5. Niemark L, Wales J, Du Toit G, et al. The use of adrenaline autoinjectors by children and teenagers. *Clin Exp Allergy*. 2012;42(2):284-292. doi:10.1111/j.1365-2222.2011.03912.x
6. Neuman-Sunshine DL, Eckman JA, Keet CA, et al. The natural history of persistent peanut allergy. *Ann Allergy, Asthma Immunol*. 2012;108(5):326-331.e3. doi:10.1016/j.anai.2011.11.010
7. Clark AT, Ewan PW. Good prognosis, clinical features, and circumstances of peanut and tree nut reactions in children treated by a specialist allergy center. *J Allergy Clin Immunol*. 2008;122(2):286-289. doi:10.1016/j.jaci.2008.05.015

8. Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SAA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr.* 2000;137(6):749-755.
doi:10.1067/mpd.2000.109376

Supplemental Table 4. Mean estimates of the number of allergic individuals per 1000 predicted to experience 1 or more allergic reactions per year. The table shows mean estimates and the first and third quartile estimates (Q25, Q75) of number of allergic individuals per 1000 predicted to experience 1 or more allergic reactions per year from 50 repeated model runs. The total number of objective allergic reactions predicted per year for 1000 allergic individuals in the simulated population is also presented. The total number of moderate/severe allergic reactions per year for 1000 allergic individuals were calculated within the model using the unweighted average for the rates of occurrence per allergic reaction (57.4%) presented in Supplemental Table 3. Additionally, the minimum (38.7%) and maximum (70.7%) rates of occurrence of moderate/severe allergic reactions per allergic reaction, as reported in Supplemental Table 3, were utilized within the model and presented.

Study population dose distributions fitted to baseline and 12-month DBPCFC data	% of simulated population experiencing 1 or more allergic reactions per year (Q25, Q75)	Mean number of people per 1000 allergic individuals experiencing 1 or more objective reactions per year (Q25, Q75)	Mean total number of objective allergic reactions per 1000 allergic individuals per year (Q25, Q75)	Predicted number of moderate/severe reactions per 1000 peanut-allergic individuals per year		
				Minimum estimate (Q25, Q75)	Mean estimate (Q25, Q75)	Maximum estimate (Q25, Q75)
Placebo 12-month DBPCFC timepoint (P12)	18.2% (16.0%, 20.0%)	182 (160, 200)	310 (264, 351)	119 (101, 135)	178 (160, 203)	221 (190, 248)
DBV712 250 µg Baseline DBPCFC timepoint (T0)	15.9% (14.7%, 17.2%)	159 (147, 172)	235 (215, 258)	90 (81, 99)	136 (122, 146)	163 (148, 182)
DBV712 250 µg 12-month DBPCFC timepoint (T12)	4.3% (3.7%, 4.8%)	43 (37, 48)	53 (46, 60)	21 (16, 24)	30 (25, 34)	37 (31, 43)