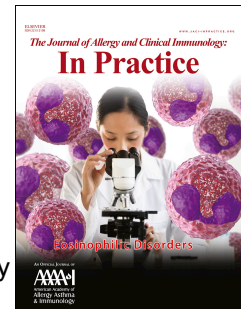


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Real-world peanut OIT in infants may be safer than non-infant preschool OIT, and equally effective

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Title: Real-world peanut OIT in infants may be safer than non-infant preschool OIT, and equally effective

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Conflicts of Interest:

LS participates in research sponsored by DBV Technologies.

SC has received speaking honorarium from Aralez and Sanofi

SK has received speaking honorarium from Pediapharm and has been a member of advisory boards for Bausch Health, Pediapharm, and Pfizer.

MM has received a speaking honorarium from Merck and has been on an advisory committee for Novartis.

VC has been a member of advisory boards for Sanofi Genzyme, Bausch Health, and ALK, and has received speaking honoraria from Aralez Pharmaceuticals and CSL Behring.

TW has received speaking honoraria from Stallergenes Greer, Novartis, Pfizer and is a sub investigator in research sponsored by DBV Technologies.

TVL has served on advisory boards for Aralez and Pediapharm, and has served on speaker bureaus for and received honoraria from Aralez, Pediapharm and Pfizer.

TVG has received a grant/research support from Merck and speaker honoraria from Pfizer and Mylan.

JY has received unrestricted educational grants from Bausch Health, AstraZeneca, Stallergenes Greer, Novartis, Sanofi, Pediapharm, and Covis Pharma and has been on the following advisory committees: Pfizer, Health Link BC, Stallergenes Greer, Sanofi, and LEO Pharma.

RM has received speaker fee from Novartis, Pediapharm, and Astra Zeneca and advisory board honoraria for Sanofi.

KJH has received a speaker fee from Novartis, is a consultant to Health Link BC Allergy Nutrition services, and was paid travel expenses by AllerGen as allergy expert for management of food allergy in schools systematic review.

SBC has been a member of advisory boards for Bausch Health, and Pfizer, and was a committee member of the CSACI oral immunotherapy guidelines.

ESC has received research support from DBV Technologies, has been a member of advisory boards for Pfizer, Pediapharm, Leo Pharma, Kaleo, DBV, AllerGenis, Sanofi Genzyme, Bausch Health, Avir Pharma, is a member of the healthcare advisory board for Food Allergy Canada, was an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Guidelines for Peanut Allergy Prevention, and is co-lead of the CSACI oral immunotherapy guidelines.

The other authors have no conflicts to declare.

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Clinical Implications (Max 40 words): Real-world preschool peanut OIT may be safer in infants than non-infant preschoolers with no infants having severe reactions. It is equally effective, with 81% of patients tolerating 4000mg protein (and all patients tolerating ≥ 1000 mg) at their 1-year food challenge.

Early introduction of peanut reduces risk of peanut allergy as noted in the landmark LEAP study;¹ however, some infants fail primary prevention and still develop peanut allergy.² There is evidence that preschoolers tend to have milder, more modifiable food allergy,³ which may make them excellent candidates for immunotherapy.⁴ Real-world data from our group has shown peanut oral immunotherapy (P-OIT) to be particularly safe and effective in preschoolers (< 70 months of age),^{5,6} but there was not a specific focus on infants (< 12 months of age). This paper presents the results of a subgroup analysis of infants, in which we calculate real-world safety and effectiveness of P-OIT, and compare these outcomes with non-infant preschoolers (hereafter referred to as NI-preschoolers) 12-70 months of age.

Preschool patients (0-70 months) were enrolled in P-OIT at community and academic allergy clinics across Canada according to our previously published stringent inclusion criteria which required a convincing clinical history and skin prick test (SPT) ≥ 3 mm or peanut-specific IgE (ps-IgE) ≥ 0.35 kU/L, or no history and ps-IgE > 5 kU/L, and a reaction during baseline oral food challenge (OFC) or build-up.⁶ Updosing was performed in clinic every two weeks over 8-11 visits, with daily doses given at home, up to 300mg protein maintenance. Allergists recorded

symptoms using a modified WAO scale graded 1 (mild) to 4 (severe) (<https://ars.els-cdn.com/content/image/1-s2.0-S2213219819303836-gr1.jpg>).⁵ Treatment for reactions occurring during baseline or follow-up OFC, or updosing visits, was also recorded. SPT and ps-IgE were performed at baseline, and selectively at maintenance and/or OFC. After approximately one year on maintenance, patients were invited to an open peanut follow-up OFC to 4000mg protein. This paper includes only patients on maintenance for ≥ 1 year, regardless of whether they had received follow-up OFC or not.

Safety outcomes included: allergic reaction of grade 2 or more (hereafter referred to as grade 2+), and proportion requiring epinephrine, during baseline OFC or P-OIT build-up, maintenance, or follow-up OFC. Effectiveness outcomes included: proportion of patients tolerating 4000mg peanut protein, or 1000mg peanut protein, at follow-up OFC after ≥ 1 year maintenance. For the data analysis, descriptive statistics were compiled, with mean and 95% confidence interval (CI) used for all continuous variables where statistical tests were performed. Two-sample t-tests were used for statistical comparisons between infants and NI-preschoolers, and paired t-tests were used to compare baseline and follow-up OFC measurements. Statistical significance was set at $p < 0.05$. Per-protocol, and intention-to-treat, analyses were performed to determine effectiveness of desensitization. Data were analyzed using Stata 15. Ethics approval was granted from University of British Columbia/BC Children's Hospital.

Between 2017-2020, 452 preschoolers (69 infants and 383 NI-preschoolers) started P-OIT. Of these, 403 preschoolers (62 infants and 341 NI-preschoolers) completed P-OIT, and 49 (7 infants and 42 NI-preschoolers) dropped out (10.8%). See Figure E1 for a flow diagram. In terms of

safety, infants who completed P-OIT buildup had fewer grade 2+ reactions during baseline OFC or P-OIT build-up than NI-preschoolers (33.9% vs. 53.7%; $p=0.002$; Table 1). One (1.60%) infant received epinephrine, compared to 5.90% NI-preschoolers, although this difference was not statistically significant. During maintenance, there were no statistical differences in safety outcomes between infants and NI-preschoolers.

NI-preschoolers who dropped out (Table E1) had less favourable safety outcomes than NI-preschoolers who completed P-OIT (Table 1), with significantly more severe reactions (14.2% vs. 0.9%; $p<0.0001$) and epinephrine use (19.0% vs. 5.90%; $p<0.0001$). This stark reduction in safety among P-OIT dropouts was not observed in infants; none of the 7 infant dropouts experienced severe reactions or needed epinephrine. Additionally, grade 2+ reactions during baseline OFC or build-up were significantly more common for NI-preschooler dropouts compared to infant dropouts (90.5% vs 57.1%, $p<0.05$) (Table E1).

Forty-two of 62 infants underwent follow-up OFC after ≥ 1 year maintenance (Figure E1). For effectiveness, according to our per-protocol analysis, 81.0% (34/42) of infants tolerated 4000mg peanut protein, and 100% tolerated 1000mg which was comparable to NI-preschoolers (75.6% and 96.2%, respectively). Infants had no grade 2+ reactions during follow-up OFC whereas 7.70% of NI-preschoolers did ($p=0.03$; Table 1). There were 27 infants who did not receive a follow-up OFC. 20 of these infants remained on treatment but did not receive a follow-up OFC, and 7 dropped out. Assuming that all 27 would have reacted, our intention-to-treat analysis would have resulted in 49.3% effectiveness (34/69).

SPT and ps-IgE decreased significantly from baseline to follow-up for NI-preschoolers with negative and positive OFC. SPT decreased significantly from baseline to follow-up for infants with negative and positive OFC, but this was not the case for ps-IgE. There were no significant differences between infants and NI-preschoolers in terms of baseline SPT or ps-IgE, follow-up SPT or ps-IgE, or change in SPT or ps-IgE from baseline to follow-up OFC. (Figure 1).

This is the first study to analyze real-world data on safety and effectiveness of P-OIT in infants < 12 months of age, and expands upon our previously published data of 270 preschoolers.⁵ We demonstrate that P-OIT may be safer in infants than NI-preschoolers, and equally effective after one year of maintenance.

Recent studies suggest infant anaphylaxis is less severe than in older children, which could greatly assist with implementation of food immunotherapy.⁷ Our data supports this assertion, with infants experiencing fewer grade 2+ reactions than NI-preschoolers during P-OIT, and no infants having severe grade 4 reactions. The difference in safety between infants and NI-preschoolers was also seen with dropouts, with NI-preschooler dropouts having more grade 2+ reactions during baseline OFC or buildup than infant dropouts. As noted in a systematic review, P-OIT build-up in older children is associated with higher rates of anaphylaxis requiring epinephrine (7.6%),⁸ rendering the risk-benefit profile less favourable. Our previously published data on preschoolers,⁵ and the current subgroup analysis, supports the findings of that systematic review.

Effectiveness of P-OIT was similar in infants and NI-preschoolers, with about 80% of patients tolerating 4000mg after one year 300mg daily maintenance, in contrast to the 68.9% passing the exit OFC in the meta-analysis of older children by Grzeskowiak et al.⁸ Infants in our study who reacted during the follow-up OFC had fewer grade 2+ reactions than NI-preschoolers none required epinephrine.

Limitations of this study include a small sample of infants, and an even smaller sample of infants with ps-IgE measurements, both of which could partly explain the lack of significant differences in effectiveness, and/or SPT and ps-IgE, between infants and NI-preschoolers. Moreover, because of the rarity of severe reactions and epinephrine use in both infants and NI-preschoolers, our study was underpowered to detect differences in these safety outcomes. Our patients did not undergo baseline OFC to confirm peanut allergy as is commonly done in prospective controlled OIT studies. This reflects the real-world nature of our retrospective analysis. We have attempted to mitigate this limitation through use of stricter inclusion criteria.⁶

Given evidence that the immune system is more pliable in infancy,⁹ it is critical to make every effort to prevent food allergy through early introduction, and to consider offering infant OIT for those who fail primary prevention. Our data, showing that peanut OIT may be safer in infants than in NI-preschoolers, with similar effectiveness, should be weighed with some of the limitations of offering OIT to infants, such as inability to provide assent and report subjective symptoms. For interested and appropriate families and patients, healthcare system capacity should be increased to ensure that infant OIT can commence as soon as primary prevention fails.

206

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235 Table 1. Comparison of baseline characteristics, and safety and effectiveness outcomes for infants and non-infant (NI)-preschoolers
 236

	All patients	Infants	NI-Preschoolers	p-value
Baseline data	N=403	N=62	N=341	
Age (in months) at entry into OIT, mean (95% CI)	27.6 (26.0, 29.2)	9.61 (9.27, 9.96)	30.9 (29.2, 32.6)	<0.001
Male, n (%)	245 (60.8)	43 (69.4)	202 (59.2)	0.06
Eczema, n (%)	291 (72.2)	46 (74.2)	245 (71.8)	0.71
Grade of initial reaction prior to entry into OIT, n (%)				
Never exposed, n (%)	14 (3.5)	0	14 (4.10)	0.05
Grade 1*	265 (65.8)	49 (79.0)	216 (63.3)	0.008
Grade 2**	110 (27.3)	13 (21.0)	97 (28.4)	0.03
Grade 3	1 (0.2)	0	1 (0.30)	
Grade 4	13 (3.2)	0	13 (3.90)	
Baseline OFC and buildup data	N=403	N=62	N=341	
Highest grade of reaction during baseline OFC/build-up, n (%)				
Grade 1*	199 (49.4)	41 (66.1)	158 (46.3)	0.002
Grade 2**	200 (49.6)	21 (33.9)	179 (52.5)	0.002
Grade 3	1 (0.3)	0	1 (0.30)	
Grade 4	3 (0.7)	0	3 (0.90)	
Epinephrine administered during build-up, n (%)	21 (5.21)	1 (1.60)	20 (5.90)	0.08
Maintenance data	N=403	N=62	N=341	
Highest grade of reaction during maintenance, n (%)				
No reaction during maintenance	367 (91.1)	58 (93.5)	309 (90.6)	0.23
Grade 1	24 (6.00)	4 (6.50)	20 (5.90)	0.43

Grade 2 [‡]	11 (2.70)	0	11 (3.20)	0.07
Grade 3	0	0	0	
Grade 4	1 (0.20)	0	1 (0.30)	
Epinephrine administered during maintenance, n (%)	6 (1.49)	0	6 (1.80)	0.14
<i>Follow-up OFC Data</i>	N=251	N=42	N=209	
Grade of reaction during follow-up OFC, n (%)				
No reaction during follow-up OFC	192 (77.5)	34 (81.0)	158 (75.6)	0.23
Grade 1	43 (17.1)	8 (19.0)	35 (16.7)	0.36
Grade 2 ^{*‡}	15 (5.00)	0	15 (7.2)	0.03
Grade 3	1 (0.40)	0	1 (0.50)	
Grade 4	0	0	0	
Epinephrine administered during follow-up OFC, n (%)	5 (2.00)	0	5 (2.40)	0.16

*Statistically significant ($p < 0.05$) difference between infants and non-infant preschoolers. All other differences between these two groups were not significant.

[‡]For statistical comparisons, grade 2, 3 and 4 reactions were combined into an aggregate category called 'grade 2 plus reactions'.

Figure Legends:

Figure 1: Comparison of immunologic changes from baseline to follow-up OFC in infants and non-infant preschoolers, according to negative or positive follow-up OFC result. Squares represent patients with a negative OFC; circles represent patients with a positive OFC. Each patient is shown in a separate line. * denotes a statistically significant difference ($p < 0.05$) using a t-test. No significant differences noted between infants and NI-preschoolers in terms of baseline SPT, IgE, follow-up SPT, IgE, or change in SPT or IgE from baseline to follow-up OFC.

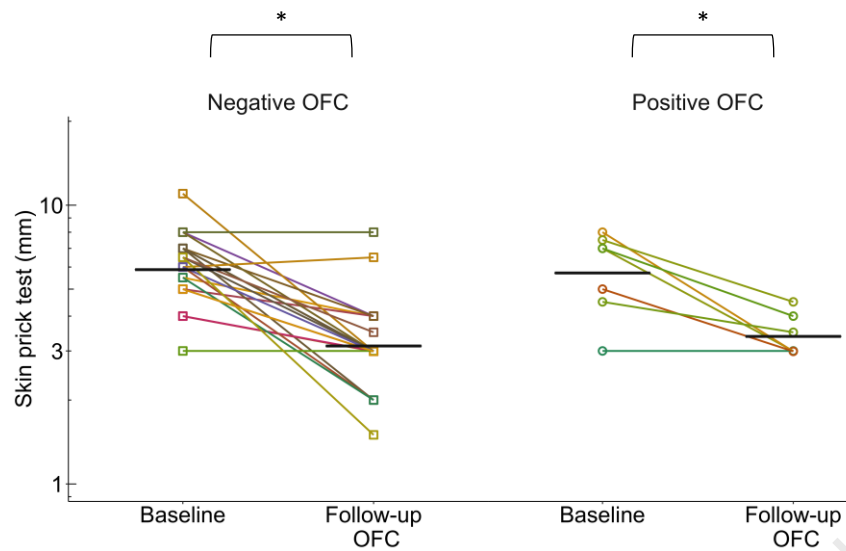
Table E1: Safety of P-OIT among dropouts

	All patients N=49	Infants N=7	NI-Preschoolers N=42
Highest grade of reaction during baseline OFC or build-up, n (%)			
Grade 1*	7 (14.3)	3 (42.9)	4 (9.50)
Grade 2* [‡]	36 (73.5)	4 (57.1)	32 (76.3)
Grade 3	0	0	0
Grade 4	6 (12.2)	0	6 (14.2)
Epinephrine administered during build-up, n (%)	8 (16.3)	0	8 (19.0)

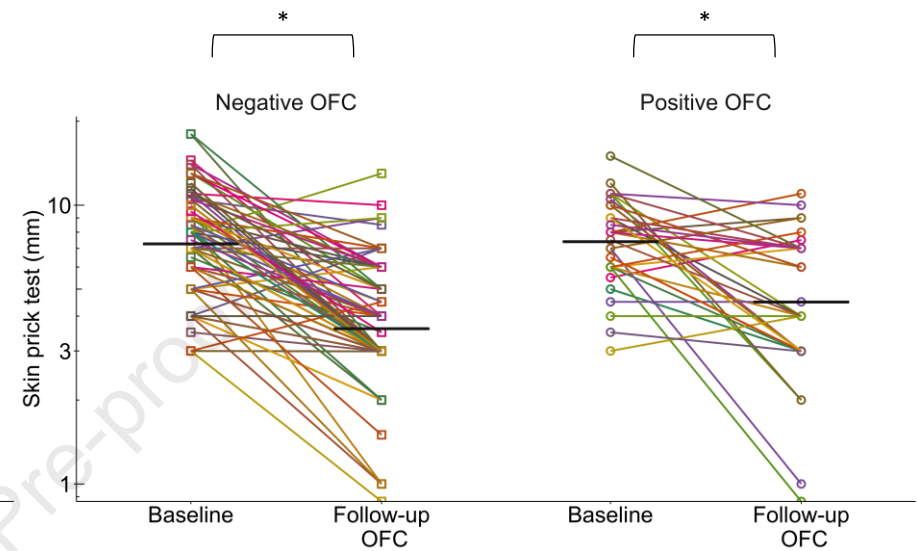
*Statistically significant ($p < 0.05$) difference between infants and non-infant preschoolers. All other differences between these two groups were not significant.

[‡]For statistical comparisons, grade 2, 3 and 4 reactions were combined into an aggregate category called 'grade 2 plus reactions'.

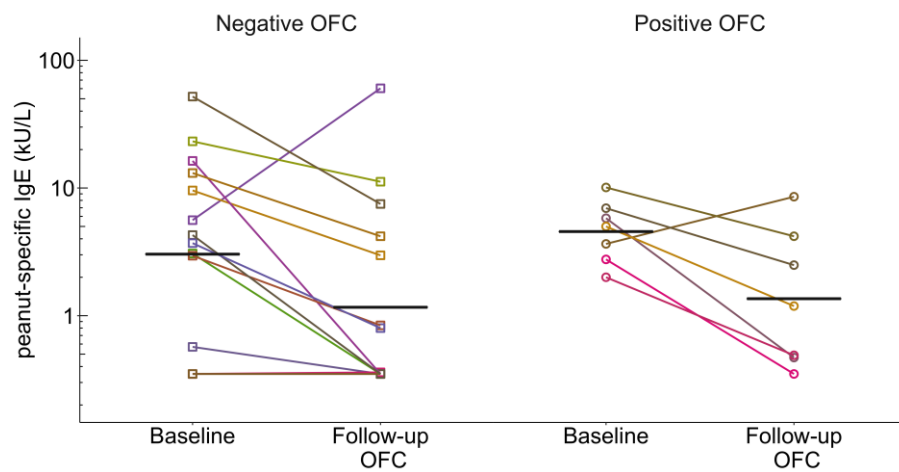
A: Skin prick test in Infants



B: Skin prick test in NI-preschoolers



C: Peanut-specific IgE in Infants



D: Peanut-specific IgE in NI-preschoolers

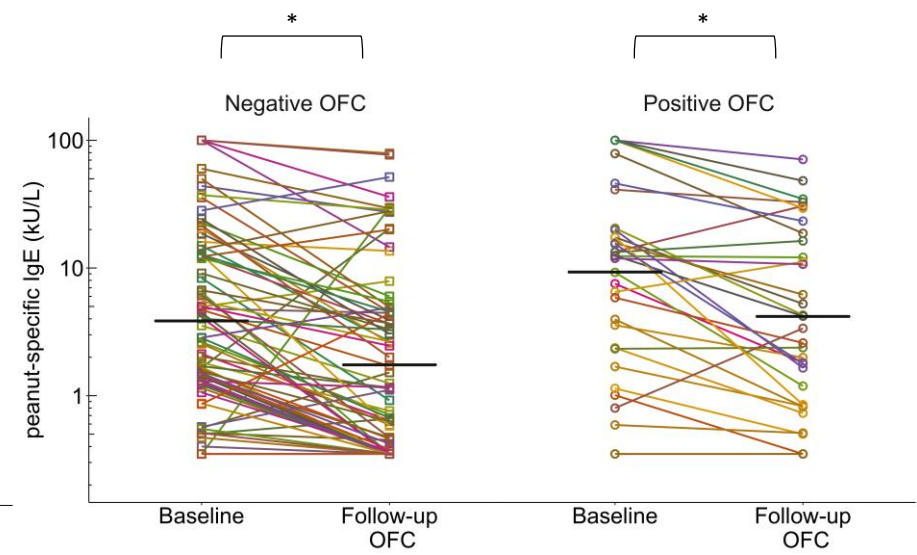


Figure E1: Flow Diagram of Infants participating in P-OIT

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