

ORIGINAL ARTICLE

Inadvertent exposures in children with peanut allergyNha Uyen Nguyen-Luu¹, Moshe Ben-Shoshan², Reza Alizadehfar², Lawrence Joseph^{1,3}, Laurie Harada⁴, Mary Allen⁵, Yvan St-Pierre³ & Ann Clarke^{3,6}

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Keywords

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Abstract

Objectives: To determine the annual incidence, characterize the severity and management, and identify predictors of accidental exposure among a cohort of children with peanut allergy.

Methods: From 2004 to November 2009, parents of Canadian children with a physician-confirmed peanut allergy completed entry and follow-up questionnaires about accidental exposures over the preceding year. Logistic regression analyses were used to examine potential predictors.

Results: A total of 1411 children [61.3% boys, mean age 7.1 yr (SD, 3.9)] participated. When all children were included, regardless of length of observation, 266 accidental exposures occurred over 2227 patient-years, yielding an annual incidence rate of 11.9% (95% CI, 10.6–13.5). When all accidental exposures occurring after study entry and patients providing <1 yr of observation were excluded, 147 exposures occurred over a period of 1175 patient-years, yielding a rate of 12.5% (95% CI, 10.7–14.5). Only 21% of moderate and severe reactions were treated with epinephrine. Age ≥ 13 yr at study entry (OR, 2.33; 95% CI, 1.20–4.53) and a severe previous reaction to peanut (OR, 2.04; 95% CI, 1.44–2.91) were associated with an increased risk of accidental exposure, and increasing disease duration (OR, 0.88; 95% CI, 0.83–0.92) with a decreased risk.

Conclusion: The annual incidence rate of accidental exposure for children with peanut allergy is 12.5%. Children with a recent diagnosis and adolescents are at higher risk. Hence, education of allergic children and their families is crucial immediately after diagnosis and during adolescence. As many reactions were treated inappropriately, healthcare professionals require better education on anaphylaxis management.

Peanut allergy is a potentially fatal condition affecting 1.2–1.8% of children in North America and the United Kingdom (1–4), and it has been implicated in 55% of food allergy-related deaths in the United States (5). The amount of peanut triggering a reaction is often minimal (6, 7), and resolution rates range from 18.3% to 21.5% (8, 9). Therefore, for the majority, peanut allergy is lifelong and a source of consider-

able anxiety (10). Unfortunately, there is no well-established curative treatment, and management relies on avoidance (11). Patients and their caregivers must exercise extreme dietary vigilance by reading food labels and inquiring about ingredients. However, strict peanut avoidance is difficult, and accidental exposure remains a substantial concern.

Studies have shown that the incidence of inadvertent exposure to peanut and nuts ranges from 3% to 75% in the United States and the United Kingdom (12–15). In 2006, we reported an annual incidence rate of accidental exposure to peanut of 14.3% among children in Quebec, Canada (15).

Abbreviations

CI, confidence interval; MCH, Montreal Children's Hospital; SD, standard deviation; SPT, skin prick test.

However, there has been no nationwide study evaluating the rate of accidental exposure in a large cohort of peanut allergic children over time, and predictors of accidental exposure have never been clearly identified. Therefore, we extended our original study to include children across Canada and collected longitudinal data on inadvertent reactions and, in this manuscript, report on the annual incidence of accidental exposures, characterize the severity and management of inadvertent reactions, and identify predictors of accidental exposure.

Methods

Patient selection

Children with peanut allergy across Canada were identified from three sources: (i) the Allergy Clinics at the Montreal Children's Hospital (MCH), (ii) provincial and national advocacy organizations for food allergic patients (Anaphylaxis Canada, *Association Québécoise des Allergies Alimentaires*, and the Allergy/Asthma Information Association), and (iii) organizations providing products to allergic individuals (MedicAlert Foundation, an emergency medical information service, and Paladin, the distributor of Twinject, an epinephrine autoinjector device).

Starting in 2004, all children (under 18 yr old) diagnosed at the MCH with peanut allergy between 2000 and 2004 were retrospectively identified and invited to participate through a letter from their treating physician. Their medical charts were reviewed to confirm eligibility (eligibility criteria listed later). The parents of eligible participants were invited to complete an initial questionnaire on demographics, atopic history, and initial and past inadvertent reactions to peanut. Details collected on inadvertent exposures included the food ingested and the location, signs, symptoms, duration, and treatment. Follow-up questionnaires were sent to parents biennially inquiring on accidental exposures over the preceding year. Reminders were sent to families who did not return their questionnaire within 2 wk of the mailing.

From 2004 through to November 2009, all children diagnosed with peanut allergy at the MCH were also identified prospectively at the time of their visit, and their parents were invited to complete an initial questionnaire and follow-up questionnaires biennially.

Recruitment from the advocacy associations, the MedicAlert Foundation, and Paladin began in 2006. Potential participants were identified through advertisements placed in newsletters, websites, and at the annual meetings of the advocacy associations. Interested individuals were asked to contact the investigative team and to consent to a release of medical information from their treating physician to confirm the diagnosis of peanut allergy. Upon confirmation of the diagnosis, the parents of allergic children completed an initial questionnaire and then biennial questionnaires on accidental exposures to peanut.

Informed consent was obtained with the initial questionnaire and was renewed biennially. The study was approved by the McGill University Health Center Ethics Board.

Criteria for the diagnosis of peanut allergy

Children were considered to be allergic to peanut if either of the following criteria were fulfilled:

- 1 A convincing clinical history of an allergic reaction to peanut and a positive skin prick test (SPT) to peanut or a peanut-specific IgE level ≥ 0.35 kU/l or
- 2 No clinical history or uncertain history of an allergic reaction to peanut and either a positive SPT to peanut and a peanut-specific IgE level ≥ 15 kU/l or a positive food challenge to peanut.

A convincing clinical history of peanut allergy was defined as a minimum of two mild signs or symptoms or either one moderate or one severe sign or symptom that was likely IgE mediated and occurred within 120 min after peanut ingestion or contact. Reactions were considered mild if they involved only pruritus, urticaria, flushing, or rhinoconjunctivitis; moderate if angioedema, throat tightness, gastrointestinal complaints, or breathing difficulties (other than wheeze); and severe if wheeze, cyanosis, or circulatory collapse (16). An uncertain history was any reaction that did not include the preceding features.

A SPT to peanut was defined as positive if the greatest diameter of the wheal was at least 3 mm > the negative control (saline or diluent). A peanut-specific IgE level ≥ 15 kU/l using the CAP system fluoroenzyme immunoassay (Phadia AB Diagnostics, Uppsala, Sweden) has been shown to be 95% predictive of clinical reactivity to peanut (17). Therefore, patients who had no or an uncertain history of peanut exposure were considered allergic if their SPT was positive and their peanut-specific IgE level was ≥ 15 kU/l without requiring a food challenge. However, for participants with a convincing history, a peanut-specific IgE level of ≥ 0.35 kU/l was considered sufficient to diagnose peanut allergy as this level is regarded highly predictive of clinical reactivity in the context of a convincing clinical history (18). Oral food challenges to peanut were open, single blinded, or double blinded, at the discretion of the treating physician.

The age of diagnosis of peanut allergy was either the age at which the child had his/her first reaction to peanut or, in the case of a child who had never been exposed to peanut, the age at which the diagnosis was made by a physician after confirmatory diagnostic testing. An accidental exposure was defined as an allergic reaction to peanut occurring any time after the child was diagnosed with peanut allergy. Only accidental exposures occurring within the year preceding a questionnaire were included for the calculation of accidental exposure rate.

Statistical analysis

Descriptive statistics were compiled for all variables. The annual incidence rate of accidental exposure was expressed as the number of events divided by the sum of the patient-years at risk. We calculated the annual incidence rate including all children regardless of whether they provided one full year of observation at study entry and including all the observation data obtained through follow-up questionnaires. Because we suspected that the annual incidence rate of accidental

exposure may vary with the length of observation for each individual, we also calculated an annual incidence rate of accidental exposure excluding any accidental exposures occurring after the completion of the initial questionnaire and excluding children who provided <1 full year of observation at study entry (i.e., those recently diagnosed). By doing so, each individual contributed exactly 1 yr of observation, and any potential bias resulting from varying lengths of observation on the estimate of the rate of accidental exposure is then minimized.

Univariate and multivariate logistic regression analyses were used to examine potential predictors of accidental exposure including sex, race, age at study entry, source of recruitment (i.e., MCH or other sources), other atopic conditions, presence of a previous reaction to peanut, severity of most severe reaction to peanut, initial level of IgE to peanut, disease duration, whether the children attended a school prohibiting peanut, and parental factors (i.e., age, level of education, employment, and marital status). Comparing univariate to multivariate results allowed us to investigate possible confounding factors. Model selection was based on Bayes factors as approximated by the Bayesian information criteria.

Results

Patient characteristics

At study entry, 1411 participants completed a questionnaire: 1309 of these individuals had completed at least 1 yr of follow-up after study entry and were eligible for a follow-up questionnaire; 772 (59.0%) completed one follow-up questionnaire. Three hundred and ninety-seven participants were eligible for a second follow-up questionnaire; 177 (44.6%) completed it. Among all the eligible participants, 854 were recruited from the MCH. The participants were predominantly boys (61.3%) and Caucasian (91.5%), with a mean age [standard deviation (SD)] of 7.1 (3.9) yr at the initial questionnaire and a mean age (SD) of 2.2 (1.8) yr at diagnosis. Most participants had at least one other atopic condition, and 52.9% had another food allergy (Table 1). Overall, 54 participants were defined as having a peanut allergy based on a positive oral food challenge. In the non-food-challenged group, 1126 individuals were found to have a convincing clinical history of an allergic reaction to peanut and a SPT to peanut ≥ 3 mm and/or a peanut-specific IgE ≥ 0.35 kU/l; 231 participants had no clinical reaction or an uncertain history of peanut reaction and a SPT to peanut ≥ 3 mm and a peanut-specific IgE ≥ 15 kU/l. Finally, the range of length of follow-up was 1 day–3 yr. The median length of follow-up was 1.8 yr. For the patients followed for <1 yr at study entry, the range of length of follow-up was 1–364 days with a median of 0.4 yr. For the remainder of the cohort, the range of length of follow-up was 1–3 yr with a median of 2 yr.

Individuals recruited from the MCH were similar to those recruited through organizations (Table 1) for most variables, including parental demographics. However, children recruited from the MCH were slightly younger (6.9 vs. 7.6 yr) at study

Table 1 Characteristics of participants

	All respondents (n = 1411)	MCH patients (n = 854)	Organizations* (n = 557)
Age at initial questionnaire (yr)			
Mean (SD)	7.1 (3.9)	6.9 (4.0)	7.6 (3.7)
Range	0–17	0–17	1–17
Age at diagnosis, yr (SD)	2.2 (1.8)	2.4 (2.0)	1.9 (1.4)
Disease duration, yr (SD)	4.9 (4.0)	4.5 (3.9)	5.7 (3.9)
Sex, % boys	61.3	62.9	58.9
Ethnic background of child, % Caucasian	91.5	87.5	97.6
Personal atopic history (%)			
Atopic dermatitis	51.3	51.4	51.2
Asthma	52.1	50.7	54.2
Allergic rhinitis	38.5	33.6	46.0
Other food allergies	52.9	49.9	57.6
At least one atopic comorbidity	88.5	87.7	89.8
Initial reaction to peanut (%)			
No reaction	13.5	17.3	7.7
Mild reaction	22.2	21.4	23.3
Moderate reaction	49.8	49.9	49.7
Severe reaction	14.5	11.4	19.2
Age of parents			
Mother, yr (SD)	38.1 (5.7)	37.8 (5.9)	38.6 (5.3)
Father, yr (SD)	40.3 (6.2)	40.2 (6.3)	40.5 (6.1)
Mother's education and work status (%)			
Completed high school	11.4	14.0	7.4
Completed college education	28.4	26.1	31.8
Completed university education	58.6	57.2	60.8
Currently employed	68.5	68.3	68.8
Father's education and work status (%)			
Completed high school	16.8	18.4	14.5
Completed college education	25.6	23.3	28.9
Completed university education	52.8	52.5	53.3
Currently employed	90.9	89.7	92.8

MCH, Montreal Children's Hospital; SD, standard deviation; CI, confidence interval.

*Anaphylaxis Canada, *Association Québécoise des Allergies Alimentaires*, Allergy/Asthma Information Association, MedicAlert Foundation, Paladin.

entry and were diagnosed later (at 2.4 vs. 1.9 yr). The initial reaction to peanut tended to be more severe in children recruited from the organizations.

Rate, location, and management of accidental exposures

When all children are included, regardless of length of observation, 266 accidental exposures occurred in 221 children

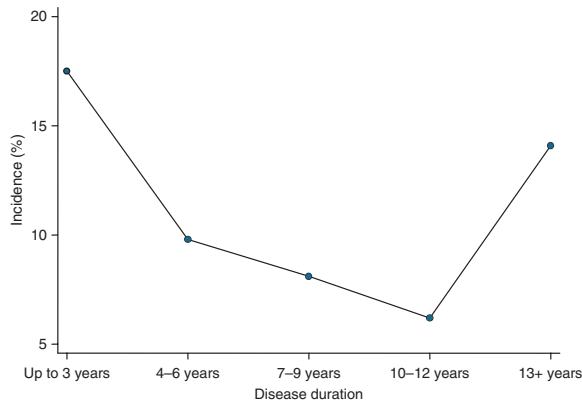


Figure 1 Annual incidence rate of accidental exposure stratified by disease duration.

over 2227 patient-years, yielding an annual incidence rate of accidental exposure of 11.9% (95% confidence interval (CI), 10.6–13.5). When all accidental exposures occurring after study entry and recently diagnosed cases are excluded, there were 147 exposures in 137 children over 1175 patient-years, for an annual rate of 12.5% (95% CI, 10.7–14.5). Figure 1 summarizes the annual rate of accidental exposure stratified according to disease duration.

Many inadvertent exposures (39.5%) occurred at the participant’s home; 16.5% occurred at the home of a relative or friend, 10.9% in restaurants, 6.4% at school, including 4.5% in schools prohibiting peanut, 3.8% in day care, and 22.9% at other or unknown places. Although the proportion of reactions occurring in schools prohibiting peanuts exceeds that occurring in schools permitting peanuts, most children (87.2%) attended schools prohibiting peanuts. Hence, the proportion of children experiencing reactions at school is slightly lower in schools prohibiting vs. permitting peanuts (0.9% vs. 2.8%).

According to caregivers’ answers, 174 reactions occurred through oral ingestions, 65 through skin contact, and 13 through inhalation. The route of exposure for the remaining 14 was either undetermined or missing. No treatment was given for 32.1% of the 78 mild reactions, 19.3% of the 145 moderate reactions, and 4.7% of the 43 severe reactions. In addition, 49.6% of the reactions, including 46.5% of severe reactions, were treated at home. Epinephrine was used in only 21.3% of moderate and severe reactions; 62.8% of severe reactions were not treated with epinephrine (Fig. 2).

Severity of initial reaction vs. accidental exposure

Among accidental exposures, 26.7% of the corresponding initial reactions were mild (i.e., 71 of 266), 44.0% moderate,

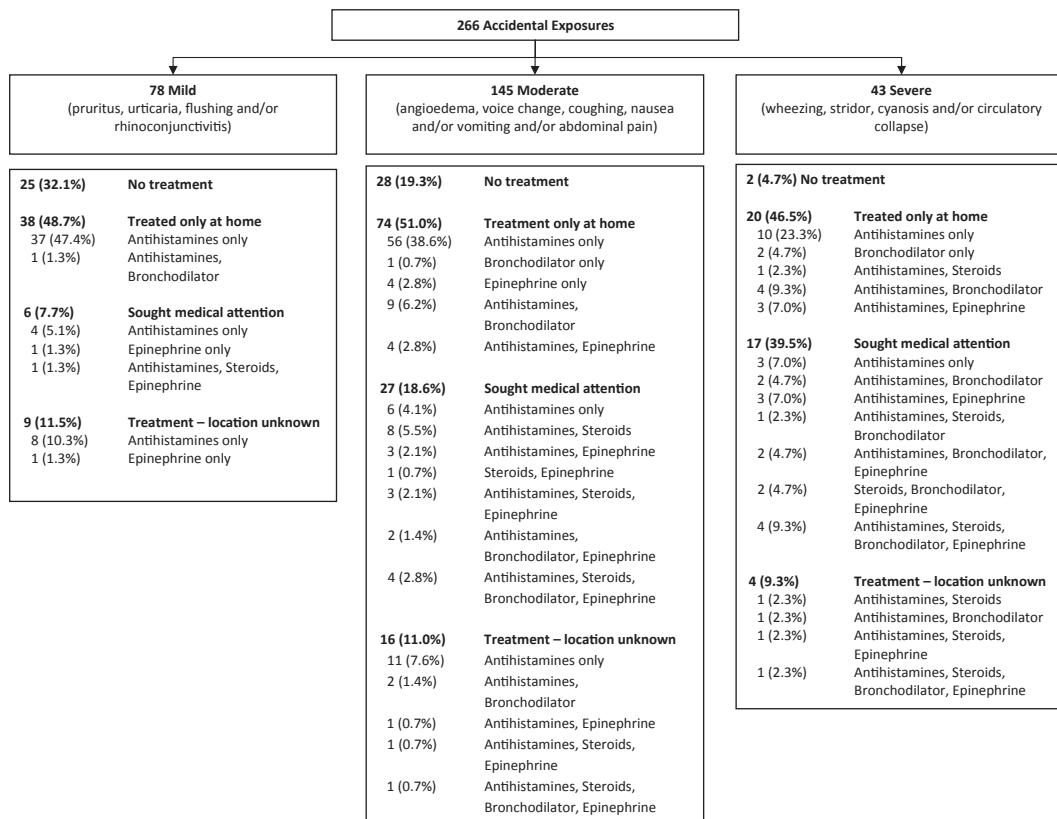


Figure 2 Severity and management of accidental exposures.

Table 2 Severity of initial reactions and accidental exposures

	Accidental exposures		
	Mild	Moderate	Severe
Initial reaction			
Mild	32	35	4
Moderate	24	77	16
Severe	9	21	16
None	13	12	7
Total	78	145	43

and 17.3% severe (Table 2). For 32 accidental reactions (12.0%), there was no previous peanut exposure, and the participants were diagnosed according to confirmatory test results as elaborated previously. Among 234 accidental exposures preceded by an initial reaction, 23.5% were more severe than the initial reaction to peanut (i.e., 39 moderate or severe accidental reactions while the initial one was mild + 16 severe accidental reactions while the initial one was moderate), 23.1% were less severe, and 53.4% were of comparable severity (Table 2).

Predictors of accidental exposure

Age ≥13 yr at study entry [odds ratio (OR) 2.33, 95% CI, 1.20–4.53] and a severe previous reaction to peanut (OR 2.04, 95% CI, 1.44–2.91) were associated with an increased risk of accidental exposures. Longer disease duration (time elapsed since diagnosis) decreased the risk of accidental exposure (OR for each additional year 0.88, 95% CI, 0.83–0.92).

Discussion

Ours is the largest longitudinal study on the rate and predictors of accidental exposure among children with peanut allergy. The Canadian children included in our survey with peanut allergy have an annual incidence rate of accidental exposure of 11.9% (95% CI, 10.6–13.5). When accidental exposures after study entry and recently diagnosed cases are excluded, the rate increases slightly to 12.5% (95% CI, 10.7–14.5). Because the probability of having an inadvertent exposure decreases with disease duration, exclusion of data after study entry actually increases the rate and exclusion of recently diagnosed cases reduces the rate. Hence, the overall effect is to slightly increase the accidental exposure rate. The decline in accidental exposure with disease duration is likely attributable to increasing awareness and development of allergen avoidance strategies. As the rate of accidental exposure is highest immediately following diagnosis, education of patients and caregivers during this interval is particularly crucial.

Although the rate of accidental exposure declines with disease duration, participants who were ≥13 yr at study entry are at higher risk than younger participants, given equal disease duration. Combining the independent effect of age with

disease duration can thus explain the shape of the curve in Fig. 1, with the rate decreasing initially and then increasing when subjects with the longest disease durations become teenagers. This is consistent with prior reports of teenagers being at increased risk for fatal food reactions presumably because of their risk-taking behaviors (19, 20). Educational interventions targeting this group might help reduce accidental exposure.

Our rate of inadvertent exposures is comparable to that reported in our much smaller single-site study in 2006 [annual incidence rate excluding recently diagnosed cases of 11.0% (95% CI, 7.2–16.1)] (15). However, it is much lower than that reported by others. In 1989, Bock reported that 50% of 32 children had experienced an allergic reaction in the year preceding contact, and 75% had had an allergic reaction in the preceding 5 yr (13). In 2000, Vander Leek reported that 60% of 83 children had an accidental exposure to peanut, yielding an annual incidence rate of 33% (14). Although methodological differences between the studies may contribute to the differing rates, our substantially lower estimate is likely partially attributable to an increased societal awareness of food allergy. Our results are nonetheless higher than the 3.1% accidental exposure rate to peanut and nuts reported by Clark in 2008 after subjects participated in a comprehensive management plan (12).

We found that a surprising 39.5% of accidental exposures occurred at the participant’s home, a presumably controlled environment. Given that previous reports have also shown that many reactions occurred at sites considered safe (21), our findings reinforce the importance of educating families. In addition, 6.4% of reactions occurred in schools, 71% of these in schools prohibiting peanut. As most participants attended schools prohibiting peanut, the proportion of children experiencing an accidental exposure in school is actually slightly lower in schools prohibiting vs. permitting peanut. In a previous study, our group found that lunches of children attending schools prohibiting peanut can contain peanut product (22). Yet, even in ‘peanut-free’ schools, accidental exposures occur and children and school personnel should remain cautious.

Although previous work by our group on a subgroup of the current cohort suggests that 98.5% are prescribed an epinephrine autoinjector (23), many moderate and severe reactions in our study were managed inappropriately: 78.7% of moderate and severe reactions were not treated with epinephrine, including 45.5% of reactions treated at a medical facility. Delay may result from failure to recognize allergic symptoms, reluctance to use epinephrine because of fear of adverse effects, or inability to administer the autoinjector (24–26). As delay in epinephrine administration increases the risk of fatality (5, 27), it is crucial that patients, their caregivers, and healthcare providers be better educated on anaphylaxis management.

Although we tried to optimize the number of completed questionnaires by sending reminders, we obtained response rates of 59% and 45%, respectively, for our 1st and 2nd follow-up questionnaires. These rates are comparable to response rates reported in other studies using mailed ques-

tionnaires (28). It is possible that the accidental exposure rate differs between those who provided and those who did not provide follow-up data. Although we cannot exclude such non-response bias, we found that the two groups had very similar rates of accidental exposure in the year preceding study entry: 12.3% (95% CI, 9.8–15.2) vs. 12.8% (95% CI, 9.9–16.4).

Our study may have underestimated the rate of accidental exposure for several reasons. Had some of the children we included been only sensitized without true clinical allergy, then we may have underestimated the annual rate of accidental exposure; those who are only sensitized are not actually at risk of accidental exposure, and including their years of observation in the denominator is actually artificially inflating it and diluting our accidental exposure estimates. Hence, we decided to perform a sensitivity analysis and use stricter inclusion criteria [i.e., a positive oral food challenge or a clinical history of anaphylaxis and peanut-specific IgE ≥ 15 kU/l or SPT to peanut ≥ 8 mm ($n = 485$)]. The history of anaphylaxis was based on the consensus definition from the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (29). For this group of patients included based on these strict criteria, we found an annual incidence rate of inadvertent exposure of 12.7% (95% CI, 10.3–15.5), which is not significantly different from the rate found with our larger sample. When all accidental exposures occurring after study entry and recently diagnosed cases are excluded, we found a rate of 14.3% (95% CI, 10.9–18.4), which again is not significantly different from the rate found with our larger sample.

It is also possible that the annual incidence rate of accidental exposure may have been underestimated because children who may have undetected resolved peanut allergy and thus are no longer at risk may have been included. If it is estimated that resolution occurs in 20% of children (8, 9), the annual incidence rate would increase from 12.5% to 15.2% (95% CI, 13.0–17.7). Our study population may have been more informed about allergy, and therefore, at lower risk of experiencing an accidental exposure as all had been diagnosed by an allergist, about 40% were members of advocacy associations, most of the parents (92.7%) had completed at least a college degree, and ethnic minorities were underrepresented (8.5%). Although it would have been ideal to include a population-based sample of children with food allergy, it is infeasible. We recruited from several sources and required that patients be seen by an allergist to ensure that only clinically allergic children were included. Our data collection was retrospective, potentially resulting in inaccurate recall. Ideally, our study would have been prospective with participants contacting the research team at the time of their accidental exposure. However, this would be extremely demanding on participants and likely unsuccessful. An additional limitation of our study was our inability to examine the independent effects of disease duration and calendar year

on accidental exposure rates. To do so, larger samples with similar disease duration followed during different calendar years are needed.

Although oral immunotherapy and other potentially curative therapies are currently being investigated (30), preventive measures remain the cornerstone of anaphylaxis management. However, our study has demonstrated that accidental exposure rates remain unacceptably high and many reactions are managed inappropriately. Patients, their caregivers, and healthcare professionals require better education on allergen avoidance and anaphylaxis management. Moreover, as the risk of accidental exposure is higher early after diagnosis, education may be most efficient if implemented during this period. Teenagers are a vulnerable group requiring particular attention. Further, policies and regulations addressing allergy management in public settings, as well as stricter labeling requirements for food allergens, may help create safer environments and further reduce risks.

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Author's contribution

All of the following authors contributed to this study and have approved the final manuscript. Nha Uyen Nguyen Luu, MD: Participation in the study design, data development, data revision and analysis, data interpretation, preparation and revision of the manuscript. Moshe Ben-Shoshan, MD: Participation in the study design, data revision, data interpretation, and revision of the manuscript. Reza Alizadehfar, MD: Participation in the study design, data development, recruitment process, data interpretation, and revision of the manuscript. Lawrence Joseph, PhD: Participation in the study design, data analysis (expert for complex statistical analysis), data interpretation, revision of the manuscript. Laurie Harada, Mary Allen: Data development and recruitment process, data interpretation, revision of the manuscript. Yvan St. Pierre, MSc: Data analysis (main person in charge for the statistical analysis), data interpretation, revision of the manuscript. Ann Clarke MD, MSc: Participation in the study design, data development, data analysis, data interpretation, revision of the manuscript. Main supervisor of the project.

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