Food allergy in children:

Accidental exposure and management in school

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1. ACCIDENTAL EXPOSURES IN CHILDREN WITH PEANUT ALLERGY

LIST OF ABBREVIATIONS

CI: Confidence Interval

MCH: Montreal Children's Hospital

SD: Standard Deviation

SPT: Skin Prick Test

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2. MANAGEMENT OF ANAPHYLAXIS IN SCHOOL: EVALUATION OF EPIPEN® USE BY SCHOOL PERSONNEL AND COMPARISON OF TWO APPROACHES OF SOLICITING PARTICIPATION

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ABSTRACT (English)

Background

Food allergy management relies mainly on avoidance and appropriate treatment of severe reactions (anaphylaxis) with epinephrine. Accidental exposure remains a concern, and may occur in school, where allergic children must rely on school personnel to recognize and treat their reaction with an epinephrine auto-injector such as the EpiPen®. Methods used to solicit participation in a study to assess the ability of school personnel to use the EpiPen® may introduce selection bias.

Objectives

1) To determine the annual incidence, characterize the severity and management, and identify predictors of accidental exposure among a cohort of children with peanut allergy. 2) To determine if the consent process introduces selection bias by comparing 2 methods of soliciting the participation of Quebec school personnel in a study evaluating their ability to use the EpiPen® and identify anaphylaxis.

Methods

1) Parents of Canadian children with peanut allergy completed questionnaires about accidental exposures over the preceding year. 2) School personnel from randomly selected schools in Quebec were approached using 1) a *partial disclosure* or 2) a *full disclosure* approach, and were assessed on their ability to use the EpiPen® and to identify anaphylaxis.

Results

1) 1411 children participated in the 1st study: an annual incidence rate of accidental exposure of 12.5% was found. Age ≥13 years at study entry and a severe previous reaction to peanut were associated with an increased risk of accidental exposure, and increasing disease duration with a decreased risk. 2) 343 school personnel participated in the 2nd study. The participation rate was higher in schools with a *partial disclosure* approach. Participants from the *full disclosure* group were more likely to have a perfect score, and were more able to identify 3 signs of anaphylaxis.

Discussion

The annual incidence rate of accidental exposure for children with peanut allergy is 12.5%. Children with a recent diagnosis and adolescents being at higher risk, education of allergic children and their families is crucial immediately after diagnosis and during adolescence. Accidental exposures occur in school; adequate treatment of anaphylactic reactions by school personnel is important. Despite training, school personnel perform poorly when asked to demonstrate the EpiPen® technique. The quality and frequency of anaphylaxis training programs have to be re-examined. As the process of consent can influence participation and bias outcomes, researchers and Ethics Boards may need to consider conditions under which studies can proceed without full consent.

ABRÉGÉ (Français)

Contexte

La gestion des allergies alimentaires repose principalement sur l'évitement et le traitement des réactions sévères (anaphylaxie) aves l'épinéphrine. Les expositions accidentelles surviennent, entre autres à l'école. Les enfants allergiques doivent ainsi se fier sur la capacité du personnel scolaire à reconnaître et traiter leurs réactions avec un auto-injecteur d'épinéphrine tel que l'EpiPen®. Les méthodes utilisées pour solliciter la participation à une étude sur l'usage de l'EpiPen® par le personnel scolaire peuvent introduire des biais de sélection.

Objectifs

1) Déterminer l'incidence annuelle, caractériser la sévérité et le traitement, et identifier les facteurs de risque d'exposition accidentelle chez une cohorte d'enfants allergiques aux arachides. 2) Déterminer si le processus de consentement introduit un biais de sélection en comparant 2 méthodes pour solliciter la participation du personnel scolaire dans une étude évaluant sa capacité à utiliser un auto-injecteur d'épinéphrine et à identifier l'anaphylaxie.

Méthodologie

1) Des parents d'enfants canadiens allergiques aux arachides ont complété des questionnaires sur les expositions accidentelles survenues au cours de l'année précédente. 2) Le personnel scolaire provenant d'écoles québécoises sélectionnées au hasard a été approché avec une approche : 1) à *divulgation*

partielle ou 2) à *divulgation complète*, et a été évalué sur son habileté à utiliser l'EpiPen® et sur sa connaissance de l'anaphylaxie.

Résultats

1) 1411 enfants ont participé à la 1ère étude : une incidence annuelle d'exposition accidentelle de 12.5% est trouvée. Un âge ≥13 ans au recrutement et la présence d'une réaction sévère aux arachides dans le passé sont associés avec un risque plus élevé d'exposition accidentelle; une durée de la maladie plus longue est associée avec un risque diminué. 2) 343 membres du personnel scolaire ont participé à la 2e étude. Le taux de participation était plus élevé dans les écoles avec une approche à *divulgation partielle*. Les participants provenant du groupe à *divulgation complète* sont plus nombreux à obtenir un score parfait et à identifier 3 signes d'anaphylaxie.

Discussion

L'incidence annuelle d'exposition accidentelle chez les enfants avec allergie aux arachides est de 12.5%. Les enfants avec un diagnostic récent et les adolescents ayant un risque plus élevé, l'éducation des enfants allergiques et de leurs familles est cruciale immédiatement après le diagnostic et pendant l'adolescence. Les expositions accidentelles peuvent survenir à l'école et un traitement adéquat par le personnel scolaire est important. Malgré la formation, le personnel scolaire démontre une piètre performance lorsqu'il doit montrer comment utiliser l'EpiPen®. La qualité et la fréquence des programmes de formation doivent être revues. Comme le processus de consentement peut

influencer le taux de participation et biaiser les résultats, les chercheurs et les comités d'éthique devraient considérer les situations où une étude peut se faire sans consentement complet.

I. INTRODUCTION

Rationale

Food allergies are adverse immune responses toward food proteins.[1] Studies have suggested that the prevalence of food allergy, known to be higher in children,[2] has been increasing over the past 10 years.[3] Food allergy management relies mainly on avoidance, which is difficult. Hence, accidental exposure remains a substantial concern, and needs to be characterized. Accidental exposures may occur in school, where allergic children must rely on school personnel to recognize and treat their food allergic reaction. Epinephrine administration using an auto-injector such as the EpiPen® is often necessary when the reaction becomes systemic or anaphylactic. Therefore, school personnel's ability to use the EpiPen® needs to be examined. Methods used to approach school personnel are variable and may introduce selection bias and influence the final outcomes: such bias in allergy studies needs to be acknowledged and discussed.

Objectives

In this thesis, I aim to provide background information and a literature review on: food allergy, focusing particularly on peanut allergy; accidental exposure to food in allergic children; management of food allergy in school settings; and selection bias such as volunteer bias and consent bias. Moreover, I present 2 studies: in the 1st one, my objectives are to determine the annual incidence of

accidental exposures to peanut in a cohort of peanut-allergic children, to characterize the severity and management of inadvertent reactions, and identify predictors of accidental exposure; in the 2nd study, my objective is to compare 2 methodological approaches to determine if a volunteer or a consent bias is present while evaluating Quebec school personnel's ability to demonstrate the EpiPen® technique and identify anaphylaxis.

Thesis content

As mentioned earlier, this thesis focuses on food allergy in children. The rationale and objectives for studying this topic were presented in the introduction above. A literature review is provided in Chapter II. In Chapter III, a specific food allergy, peanut allergy, is examined in a study on accidental exposures occurring in Canadian allergic children. Chapter IV explains why it is critical that accidental exposures, particularly in the school setting, are managed appropriately. As food allergy can cause anaphylaxis, the management of anaphylaxis, especially in the school environment, is studied by looking at the ability of school personnel to use an epinephrine auto-injector device: the EpiPen®. The results, as well as a comparison of 2 different approaches used in the study to recruit participants, are presented in Chapter V. In Chapter VI, a discussion summarizes the findings, explores the significance of the results, and explains the necessity for future studies.

II. LITERATURE REVIEW

Introduction to food allergy in children

Definition and classification

Adverse reactions to food can be categorized as involving the immune system or not. Non-immune mediated reactions may involve metabolic (e.g. lactose intolerance), toxic (e.g. scombroid poisoning), pharmacologic (e.g. effects of caffeine), or neurological (auriculotemporal syndrome) mechanisms.[4] A food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.[4] Food allergy includes reactions caused by specific IgE antibody to a food (IgE-mediated reactions) and reactions mediated by immunologic but non-IgE mechanisms such as food protein-induced enteropathy, eosinophilic gastrointestinal disorders, and atopic dermatitis.[5] For the purpose of this thesis, the expression "food allergy" will designate only IgE-mediated reactions. Food-induced allergies are usually caused by 8 main allergens: milk, egg, peanut, tree nut, soy, wheat, fish, shellfish.[6,7]

Prevalence of food allergy

Many studies have estimated the prevalence of food allergy. However, results vary because of difference in study design and definition of food allergy. The

prevalence of food allergy based solely on self-report is higher than when based on classic IgE-mediated symptoms and specific testing for the allergen. The meta-analysis by Rona et al, published in 2007 and focusing on milk, egg, peanut, fish and crustacean allergy, reported a prevalence of self-reported food allergy varying between 3% and 35%.[8] Although this heterogeneity in prevalence among included studies may indicate a real difference among the various populations studied, it may also be attributable to the different definitions of food allergy. Some participants may indeed report non-immunological adverse food reactions as food allergy. When self-reported symptoms were combined with specific testing, the prevalence rate dropped to 2% to 5%. In a recent study using data from the 2005-6 National Health and Nutrition Examination Survey in the United States, it was estimated that 2.5% of Americans have food allergies based on the detection of specific IgE to food allergens in blood; children, males, and black subjects are at increased risk for food allergy.[2] For the pediatric population, the prevalence of food allergy based on suggestive symptoms and detection of specific IgE is estimated to be about 4-8%,[3,7,9,10] making it an important health issue.

For peanut allergy, the prevalence varies worldwide. The prevalence is highest in the United Kingdom, the United States and Canada. In a follow-up study based on a random telephone survey in the United States published in 2010, Sicherer et al. reported a prevalence of self-reported peanut allergy of 1.4% in children,

significantly higher than the prevalence of 0.4% reported in 1997.[11] In Canada in 2010, Ben-Shoshan et al. used the same survey methodology and reported a prevalence of perceived peanut allergy of 1.8%.[12] In the United Kingdom, reported prevalence rates varied between 1.2% and 1.8%.[13,14] An increase in peanut allergy prevalence was observed in the United States between 1997 and 2010, but more recent data from the United Kingdom showed that the rate seems to have stabilized.[14] Data from Canada also reported that the prevalence of peanut allergy has not increased between 2002 and 2007.[15] The prevalence is estimated to be about 0.3%-0.75% in France,[16] 0.04% in Israel;[17] peanut allergy is rare in Asia.[18]

Development and natural history of food allergy

Risk factors for the development of food allergy include a family or personal history of allergic disease.[19,20] Other factors such as maternal diet during pregnancy and lactation, breastfeeding, and timing of food introduction to infants have been studied, but no definite conclusion could be drawn in terms of their influence on the development of food allergy.[4] For peanut allergy, many potentially triggering factors have been studied. First, a family history of peanut allergy is a risk factor for developing the condition as the prevalence of peanut allergy in siblings of a peanut-allergic child is 7%.[19] Other factors, such as timing of first exposure to peanut, high environmental (without ingestion) exposure to peanut, soy consumption, and use of skin products with peanut oil have been

studied, but no definitive conclusion can be drawn regarding their effect on the development of peanut allergy.[21-24]

The natural history of food allergy varies depending on the food. For milk allergy, about 75% of children developed clinical tolerance by age 3-5;[25,26] for egg allergy, tolerance is estimated to be achieved in 66% of children who had their 1st reaction at ≤ 2 years of age after 5 years of follow-up.[27] More recent studies including highly atopic patients suggested that the rate of resolution may be lower for milk and egg, but tolerance is still often acquired during childhood or the teenage years.[28,29] Hence, these allergies are rarely seen in adults. For soy allergy, tolerance is acquired in 45% of children by age 6;[30] and for wheat allergy, it is acquired in 56% of children by age 8.[31] For peanut, children usually have their 1st reaction to peanut between 1 and 2 years of age upon their 1st known exposure.[32] For most children, peanut allergy lasts lifelong, but about 20% of children outgrow their condition.[33] Fleischer et al. followed 80 children with peanut allergy and demonstrated that 63% of children with peanut IgE levels ≤ 2kU/L (measured by the Phadia ImmunoCAP system) passed their challenge to peanut, indicating they were no longer allergic.[34] However, the same group showed that about 8% of those with resolved peanut allergy experienced a recurrence.[35] For tree nuts, a study by Fleischer et al. showed that 9% of 101 patients with a history of tree nut reaction outgrew their allergy.[36] Although few

studies have assessed the natural history of fish and shellfish allergy, it is known that these allergies are usually acquired in adulthood, and are often lifelong.[4]

Clinical manifestations of food allergy and anaphylaxis

Signs and symptoms of food allergy are caused by the release of mediators from mast cells and basophils after a food allergen cross-links with specific IgE.[37] A food allergic reaction can involve several body systems: skin and mucosal tissue (flushing, pruritus, urticaria, angioedema), the gastro-intestinal tract (abdominal pain, nausea, vomiting, diarrhea), the respiratory system (sneezing, nasal congestion, rhinorrhea, throat pruritus, laryngeal edema, stridor, wheezing, cough, dyspnea), and the cardiovascular system (dizziness, tachycardia, hypotension).[4]

Anaphylaxis is defined as a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance.[38] Anaphylaxis is usually diagnosed based on clinical presentation, and laboratory tests are rarely contributory. Criteria have been published for the diagnosis of anaphylaxis: anaphylaxis is highly suspected in an individual with 1) An acute onset of an illness involving skin and/or mucosal tissue associated with respiratory compromise or reduced blood pressure or 2) Symptoms involving 2 or more systems (skin/mucosa, respiratory, cardiovascular, gastro-intestinal)

after exposure to a likely allergen or 3) Hypotension after exposure to a known allergen.[38] Food-induced anaphylaxis involves rapid onset of symptoms within several hours of food exposure. It accounts for about 1/3 to 1/2 of all anaphylaxis treated in the emergency department,[39] and is the most common cause of anaphylaxis in children in the community.[40] It is most often attributable to peanut, nut, fish and shellfish.[39] Peanut is a common cause of food-induced anaphylaxis. In a series of patients with fatal or near-fatal food-induced anaphylaxis, peanut was often involved: 4 out of 13 children in one series were allergic to peanut,[41] and 20 of 32 individuals in another series.[42] The threshold dose for eliciting an objective response to peanut in many allergic individuals is equivalent to 1-3 peanut kernels (about 300-1000 mg of peanut protein).[43] However, some individuals, especially those with more severe reactions, have lower threshold doses: some may report subjective symptoms at doses as low as 0.1 mg of peanut protein when submitted to double-blind placebo controlled food challenges.[44,45] In a case-series of near-fatal and fatal food-induced anaphylaxis in children, symptoms develop within 1 to 30 minutes following exposure to the culprit food.[41] Individuals with higher risk for severe or fatal anaphylaxis are teenagers and young adults, asthmatics, especially if it is poorly controlled, and individuals with a prior history of food-induced anaphylaxis.[41,42,46] Delay in epinephrine administration also contributes to fatalities.[41,42,46,47] Hence, prompt and adequate administration of epinephrine is critical. The ability to recognize anaphylaxis and administer epinephrine is examined in Chapter V.

Establishing the diagnosis of food allergy

The diagnosis of food allergy is based on 1) a detailed clinical history of symptoms occurring after ingestion of the suspected food and 2) specific testing for IgE antibodies to the food or 3) a food challenge.[4,48] IgE can be identified through a 1) skin prick test, or 2) blood test. Although there are no standard reagents nor international standards for performing a skin prick test (also called a puncture or epicutaneous test), it is still the most commonly performed procedure for the diagnosis of food allergy, and results are available within about 15 minutes.[49] In this procedure, a source of food allergen such as a commercially available food extract is applied on the forearm as well as negative (saline or diluents) and positive controls (histamine). A sharp device is then used to prick the skin through the allergen and the mean diameter of the induration (also termed a wheal) resulting at the prick site is measured. A positive skin prick test is often defined as a wheal with a mean diameter ≥ 3 mm than the negative control.[48,49] The sensitivity of the skin prick test is about 90%, but its specificity can be as low as 50%.[6] Hence, the positive predictive value of skin prick test depends on clinical suspicion based on clinical history, but its negative predictive value is high at about 90-95%.[48] Correct interpretation of the predictive values of skin prick test in the context of the clinical history is essential to classify children

as allergic or not, as illustrated in Chapter III in a cohort of Canadian children with peanut allergy.

Serum IgE tests detect the presence of specific food IgE antibodies in the blood. They are often performed when skin prick tests cannot be performed because of severe dermatitis or dermatographism, or failure to discontinue antihistamines which interfere with the interpretation of the skin test.[4] They are also done when there are inconsistencies between clinical history and skin prick tests. Specific IgE levels used to be obtained with a radioallergosorbent method, a method where radiolabeled anti-human antibodies are used to bind a specific IgE and the degree of radioactivity is measured, and the test was often called "RAST" test. However, nowadays, levels of specific IgE are quantifed using fluorescence enzyme labelled assays; these assays involve antibodies that are linked to an enzyme, can bind specific IgE, and emit a detectable signal through a fluorochrome. There are several assay systems available (e.g. Phadia ImmunoCAP system), and the results obtained from different systems may differ.[50] It is therefore important to know which system is used when results are interpreted. Many studies have used the Phadia ImmunoCAP system, and estimated 95% predictive values have been published.[51,52] Sampson et al. obtained positive predictive values ≥ 95% with specific IgE levels of 7kU/L for egg, 15 kU/L for milk, 15kU/L for peanut, and 20kU/L for fish using this system in

a population of highly atopic children older than 2 years of age.[52] The cut-off level of 15kU/L for peanut was used to define peanut allergy in Chapter III.

Food challenges are procedures in which patients ingest the food suspected of causing the allergic reaction according to a supervised protocol.[53] During a food challenge, the patient is frequently assessed for symptoms suggestive of an allergic reaction. A double-blind placebo-controlled food challenge is the gold standard for the diagnosis of food allergy.[4] However, it is time-consuming and impractical. In general practice, single-blind or open challenges are usually acceptable.[48] Although challenges are sensitive and specific, they put patients at risk for a potentially severe reaction, and are not always necessary, especially when the history and skin prick tests or measurement of serum specific IgE are supportive of the diagnosis (as discussed further in Chapter III).

The diagnosis of peanut allergy, as for other food allergies, relies on clinical history, presence of specific IgE to peanut as demonstrated by skin prick test and serum IgE test, and occasionally on peanut challenges. Several studies in atopic children using the Phadia ImmunoCAP system have shown that an IgE level of 13-15kU/L to peanut has ≥ 92% positive predictive value.[51,52,54,55] A wheal obtained by a skin prick test ≥ 8 mm using a peanut extract has a ≥ 95% positive predictive value.[55-57] However, as mentioned previously, these tests are difficult to interpret on their own and careful selection of tests guided by the clinical history

are necessary to make the diagnosis of peanut allergy. It has been suggested that a positive test for specific IgE to peanut is sufficient to establish the diagnosis if the history is unequivocal.[43]

Management of food allergy and anaphylaxis

The mainstay of food allergy management relies on avoidance of the culprit food.[6] Good avoidance strategies are obtained through education of patients and families. They include careful reading of ingredients and interpretation of food labels. In the United States, the Food Allergen Labeling and Consumer Protection Act, passed in 2004, requires that the 8 major food allergens be listed in simple English on food packages that contain them.[58] In Canada, in 2008, Health Canada has proposed changes to the *Food and Drug Regulations* and will require that the 10 main food "allergens" (milk, egg, soy, gluten, peanut, tree nut, sesame, crustacean, shellfish, fish) be declared on food labels if they or some of their protein derivatives are included in the ingredients. Once the final regulations are published, manufacturers and importers will have 18 months to comply with the new labelling requirements.[59]

Avoidance strategies also include prevention of cross-contact through cleaning of surfaces where food allergens are prepared, and discouragement of sharing of meals and utensils.[6,60] All these strategies are challenging, especially for children

and caregivers who have to supervise them. Because it has been suggested that children with food allergy are at risk for nutritional deficiency, growth monitoring and nutritional counseling are recommended.[61] Food avoidance involves many aspects of daily life activities[62] and is a source of anxiety for patients and caregivers.[63] Bollinger et al. reported that food allergy affects meal preparation, family social activities and school attendance: 10% of the caregivers surveyed chose to home-school their children because of food allergy.[62] Studies have indeed shown that children with food allergy as well as their family experience a lower quality of life.[63-66]

There is currently no well-established curative treatment for food allergy. Even with strict avoidance measures, accidental exposure to food allergens and acute allergic reactions occur as demonstrated in a cohort of Canadian children with peanut allergy in Chapter III. Early recognition of an allergic reaction and adequate management are therefore essential. Rapid intramuscular administration of epinephrine remains the first-line therapy for food-induced anaphylaxis.[4,67] Delay in epinephrine injection may result in fatality.[41,42,46] An epinephrine auto-injector (a device which enables the user to inject epinephrine before seeking medical attention) should therefore be readily available. In addition, patients and/or their caregivers should be trained to use the auto-injector rapidly and adequately. The ability of school personnel to properly use the auto-injector is assessed in Chapter V. Epinephrine's biological actions

include increased vasoconstriction, increased heart rate and force of heart contraction, and bronchodilation.[68] There is no absolute contraindication to the administration of epinephrine if anaphylaxis is suspected.[69] Although serious effects are rare, epinephrine may cause minor and transient adverse effects in some patients such as tremor, dizziness, palpitations, anxiety, and headache.[68] Epinephrine's onset of action is rapid (within minutes), but its effect is short-lived. Hence, repeated doses are necessary in 12 to 19% of individuals with food-induced anaphylaxis.[70-72] It is usually recommended to give epinephrine intramuscularly in the anterolateral thigh because studies have shown that this route and this site provide more rapid absorption.[73,74] Administration of epinephrine should be followed by transfer to a medical facility where the patient is observed for at least 4 to 6 hours.[69] Prolonged observation is often recommended, especially in severe cases, and also to manage biphasic reactions which occur in up to 20% of patients.[75]

Simons et al. showed that unintentional injections of epinephrine into a digit or other parts of the body occur.[76] Hence, education regarding appropriate and safe use of an epinephrine auto-injector is warranted and is discussed further in Chapter V. There are 2 autoinjectors widely available in Canada: the EpiPen® and the Twinject®. The latter one was introduced only in 2005. For both devices, there are an "adult" or "regular" form delivering 0.3 mg of epinephrine and a "junior" form delivering 0.15 mg of epinephrine. For adults and children

weighing ≥ 25kg, an injector containing 0.3 mg of epinephrine is recommended; for children between 10 and 25 kg, it is recommended to prescribe an autoinjector containing 0.15 mg of epinephrine.[77]

Other adjunctive treatments for anaphylaxis include bronchodilators, H1 antihistamines such as diphenhydramine and H2 antihistamines such as ranitidine as well as corticosteroids, oxygen therapy, and intravenous fluids.[69] These treatments are supplemental and should not replace epinephrine.

Accidental Exposure

Because strict avoidance is difficult, accidental exposure to food allergens occurs. There are only a few studies on accidental exposure. Most studies on accidental exposure included patients with peanut or nut allergy, but involved only a small number of participants. In 2006, Yu et al. reported an annual incidence rate of accidental exposure to peanut of 14.3% among children in Quebec, Canada.[78] The data from these children are included in the nationwide analysis described in the next chapter. In 1989, Bock et al. contacted 32 children who had a positive double-blind placebo-controlled food challenge to peanut 2 to 14 years after their challenge. He reported that 50% had experienced an allergic reaction in the year preceding contact, and 75% had had an allergic reaction in the preceding 5 years.[79] In 1998, Sicherer et al. found that 55% of 102 peanut-allergic children

(diagnosed based on history and detection of serum specific IgE) had an accidental exposure over a median period of 5.4 years and 30% of 54 nut-allergic children had an accidental reactions over a median period of 5.5 years.[80] Accidental ingestions occurred in school, home and restaurants. Causes of accidental exposure were food sharing, hidden ingredients in processed foods, cross-contamination, and skin contact with peanut butter in school projects. In 2000, Vander Leek et al. followed 83 children with peanut allergy on a yearly basis. Among these children, 60% had a total of 115 accidental exposures to peanut during follow-up, yielding an annual incidence rate of 33%.[81] It was also reported that the nature of symptoms experienced during subsequent adverse reactions were not consistent with symptoms experienced during initial reactions. More recently, in 2008, Clark et al. reported only a 3.1% annual accidental exposure rate to peanut and nuts after 785 children participated in a comprehensive management plan.[82] Most reactions (53%) occurred at home, and 5% in school. In 2010, Chiang et al. reported that half of their cohort of 31 Asian children allergic to peanut living in Singapore had an accidental reaction. Although the annual incidence rate of accidental exposure was not calculated, the authors indicated that the median time from diagnosis to 1st accidental exposure was 4 months.[83] The high number of accidental exposures was attributed to the ubiquitous presence of peanut within Asian cuisine, inappropriate food labelling, and deficiency in public awareness.

For milk, Boyano-Martinez surveyed 88 milk-allergic children and found 53 reactions to milk in 35 children over a 1-year period.[84] Reactions took place at home in 47% of cases, at a neighbour's home in 19%, at daycare in 19%, at school in 6%, and at other places in 6%. Factors associated with severe accidental reactions were high serum IgE to cow's milk and asthma although the Odds Ratio (OR) found for this latter factor (OR 10.19) had a wide 95% Confidence Interval (CI) (95% CI, 1.13-91.54), probably because of the small number of severe reactions. The high frequency of accidental exposures was attributed by the authors to the frequent consumption of milk and dairy products as well as their ubiquitous presence in commonly consumed foods.

Eigenmann et al. used an internet-based survey to inquire about circumstances of severe accidental reactions in a cohort of food-allergic patients identified based on suggestive history.[85] Among the 51 responders, 24 were allergic to peanut, 12 to milk, 6 to nuts, and 5 to fish and shellfish. Reactions occurred at home in 25.5% of the cases, in restaurants in 17.6%, at school or daycare in 15.7%, at a relative or friend's home in 13.7%.

Food allergy in school settings

As children with food allergy spend a lot of time in school, management of food allergy in school settings has become a concern and a challenge for the

educational system. However, only a few studies have looked at the impact of food allergy and its management in school settings and none have examined the Canadian environment. Weiss et al. surveyed 400 school nurses in the United States: 44% of them reported an increase in children with food allergies in their schools and 37% of them had ≥ 10 students with food allergies.[86] Allergic reactions in school are not rare but not always well documented. In a study by Nowak-Wegrzyn et al. in the United States, it was shown that 39% of schools reported ≥ 1 allergic reaction and 58% of 132 food-allergic children experienced a reaction at school during the prior 2 years.[87] In addition, about 25% of children had their 1st food-induced allergic reaction at school.[88,89] Milk was the most common cause of reaction among preschool-aged children and peanut among school-aged children.[87] The study presented in Chapter III is the first to document accidental exposures to peanut in Canadian schools. Food is ubiquitous in school: in addition to lunches brought by children and the meals served in school cafeterias, food items can be present in craft projects or brought in during special events such as birthday celebrations. In a study on peanut and nut allergy in the United States, it was reported that 79% of reactions in school occurred in the classroom, and 12% in lunchrooms.[89] A significant number of reactions were caused by food brought in for projects or celebrations.

Schools may not be adequately prepared to handle allergic reactions. Sicherer et al. showed that for reactions occurring in school, medications were given for 90%

of the reactions: 86% of children received antihistamines and 28% epinephrine; 53% of the medications were given in the school building.[89] However, among 36 cases who required medicine and did not receive it, various reasons were given for not administering it: the reaction was not noticed by school personnel, the parents were called to pick-up the child, or the teacher was unable to use the epinephrine auto-injector. In 60% of cases, the 1st action taken was to call the parents to find out what to do. This report suggested that school personnel may not be able to recognize anaphylaxis, nor administer a life-saving medication. Hence, the ability of school personnel to recognize anaphylaxis and administer epinephrine is evaluated and the results are presented in Chapter V. Although epinephrine is the drug of choice for an acute allergic reaction, it is not always readily accessible. In a study by Rhim et al., epinephrine was readily accessible in only a minority of schools: it was either in the classroom, carried by the student or passed from teacher to teacher.[90] In many schools, epinephrine is kept in the health office or the main office. More recently, Ben-Shoshan et al. showed that 48% of 271 peanut-allergic children in Quebec do not carry their epinephrine auto-injector with them at school although older children tend to carry their auto-injector more often.[91] For 78% of them, the auto-injector was located in the nurse's office or another school office and not easily accessible.

Over the past few years, the importance of allergic reactions occurring in the school environment has been acknowledged. In 1998, the American Academy of

Allergy Asthma and Immunology published a position statement on anaphylaxis in schools and other childcare settings.[92] Since then, many authors from various countries and regions, including Australia, Europe, Japan, and the United States have published guidelines to help manage allergies in school settings.[93-96] These guidelines usually recommend the establishment of general policies and individualized updated allergy management plans. They also emphasize the importance of preventive measures (meal supervision, hand washing, no food sharing) and education of school personnel to recognize and treat anaphylaxis using an epinephrine auto-injector. Finally, they underline the responsibilities of schools, children, parents and clinicians. Although a preliminary study by Moneret-Vautrin showed that personalized management plans may be beneficial,[97] more studies are needed to evaluate the implementation and efficacy of such policies. Ethical principles guiding the implementation of management plans for allergy in school have also been discussed by Behrmann: the necessity to ensure confidentiality, guarantee fairness, avoid stigmatization, provide education to personnel and other students, and allow allergic children to gain further control over their health is important, while trying to create a safe environment for the allergic children.[98] To help allergists guide their patients and their community to find the best strategies to help allergic children in school settings, Young et al. have recently published a review on management of food allergies in school.[99] With the proliferation of such guidelines, more studies are

needed to evaluate the impact of these recommendations on the occurrence and management of accidental exposures in school.

Management of allergy in school in Canada and Quebec

Despite the critical importance of proper management of anaphylaxis in school settings, little is known about local regulations as well as the competence of school personnel to recognize and manage anaphylaxis in Canada and in Quebec. In Canada, starting in the 1990s, there was a growing concern regarding food allergy, especially in school-aged children, possibly related to increasing research on food allergy and anaphylaxis, and better dissemination of information through the internet.[99,100] In 1995, the Canadian Society of Allergy and Clinical Immunology published a consensus statement *Anaphylaxis in Schools and Other Child Care Settings* to call attention to the need for education on avoidance strategies and management of anaphylaxis in school.[101] A handbook based on this statement was published in 2005.[102] Initiatives to control peanut exposure in school were also recommended, and many elementary schools started to restrict peanut-containing products in schools.[100] Increased awareness lead the Canadian School Board Association to publish the 1st Edition of *Anaphylaxis: a Handbook for School Boards*.[103] Provincial policies regarding allergy and anaphylaxis management in school were developed in the following years.[100] In 2006, following the death of a child due to an allergic reaction in school, Ontario

legislated the management of anaphylaxis in public schools by implementing Bill 3 - *Sabrina's Law*.[104] Sabrina's Law requires Ontario public school boards to establish an anaphylaxis policy to reduce allergen exposure, provide regular education and anaphylaxis management training for school personnel, maintain a file and establish individual management plans for each student at risk. In 2008, Manitoba passed Bill 232 - *The Public Schools Amendment Act (Anaphylaxis Policy)* to protect students at risk for anaphylaxis.[105]

In 1988 in Quebec, a letter was sent by the *Ordre des infirmiers et infirmières du Quebec* (Quebec Nurses' Association) to all Quebec nurses working with children asking them to provide training to school personnel on the management of anaphylaxis.[106] In 1990, following the death of a girl from peanut allergy in Quebec, the coroner's report recommended identification of all children at risk at the beginning of the school year; education of patients, parents, school personnel, and health care providers on allergy prevention and treatment; and preparation of epinephrine administration protocols.[107] The same year, the *Association québécoise des allergies alimentaires – AQAA* (Quebec Food Allergy Association) was founded. It aims to provide answers and support to people affected by food allergies. In 2003, this association published a document entitled "*La prévention des allergies alimentaires dans les centres de la petite enfance, les services de garde et à l'école"* to promote the standardization of

allergy management in educational centres for children.[108] In 2006, the *Agence de la santé et des services sociaux de Montréal* (Montreal Health Care and Social Services Agency) issued a "*Guide d'intervention pour les élèves à risque de réaction anaphylactique en milieu scolaire"* to outline the steps to be taken when an allergic reaction occurs in a school setting.[109] This document is the reference used by school nurses in the Montreal area. It has also been adapted and used by school nurses in other Quebec areas.

Despite a long standing public interest in Quebec in providing a safe environment for children with food allergy, there had been no systematic attempt to determine if policies addressing allergy existed in each school board. In 2007, all Quebec school board policies that discuss allergies/anaphylaxis (i.e., anaphylaxis/allergy policy, food policy, health/first aid policy, medication administration policy) were reviewed using a checklist based on Sabrina's Law.[110] School board policies were retrieved mainly from board websites and supplemented with information from the Ministry of Education and the Federation of Quebec School Boards websites. Among the 72 public school boards in Quebec, 52 boards had no allergy/anaphylaxis policy and only 3 boards (2 French-speaking and 1 English-speaking) had a specific policy regarding allergy/anaphylaxis management. These 3 boards are located in different regions: 2 included large urban areas although none covers the Island of Montreal. The policies were created between 1998 and 2005. Although the 3

boards require regular training on anaphylaxis for employees in direct contact with students, none explicitly describes the modality of training. In addition, 17 boards had policies addressing some aspects of allergy avoidance/ anaphylaxis management (5 with food policy, 11 with first aid / health or medication administration policy, 1 with both). Food policies were similar: they forbid the use of peanut oil in cooking at school and recommend clear identification of foods containing peanut, nuts, milk, egg, soy, fish, shellfish, sesame and wheat. It was not known why only a small number of Quebec boards have specific policies regarding allergy/anaphylaxis. Schools in Quebec are staffed, at least part-time, by a nurse. It is hypothesized that school boards rely on these nurses for developing an approach to life-threatening allergies and ensuring all school personnel are properly educated. Given the absence of anaphylaxis management policies in many Quebec school boards, it is important to determine if, in the current environment, school personnel are able to recognize and properly manage anaphylaxis. The study examining this question is detailed in Chapter V.

Selection bias: volunteer bias and consent bias

As an additional aim in my research on anaphylaxis management in schools, I was interested in examining the influence of the consent process on selection bias. In chapter V, 2 approaches of consenting school personnel to participate in a study on anaphylaxis knowledge are compared to evaluate the presence of a

selection bias. Selection bias is a systematic error in a study that comes from the procedures used to select subjects and from factors that influence participation.[111] Many types of selection bias exist. A volunteer bias, sometimes also called self-selection bias, is a selection bias that occurs when individuals who volunteer for a study differ in relevant clinical characteristics from those who do not.[112] Depending on the type and the field of studies, volunteers may have specific characteristics that distinguish them from non-volunteers and that may affect outcomes. Hence, the presence of a volunteer bias may compromise both the internal validity (relationships among variables) and the external validity (generalizability of the results of a study).[113]

Consent bias, also called authorisation bias, is also a selection bias. It is sometimes considered similar to volunteer bias. However, it introduces the notion of consent, which is the voluntary agreement of a subject to participate in research after information on potential risks and benefits is obtained.[114] Consent bias refers to the error that appears when those who consent to participate in a study differ from those who do not or cannot.[115] Hewison et al. noted that consent requirements for recruiting participants in medical research might lead to incorrect estimation of an outcome.[116] Although studies on the impact of consent requirements, especially in the field of allergy, are still rare, a growing body of evidence shows that ethical requirements regarding the consent process can bias medical research, in particular in the area of cardiovascular disease.[117-

[119] To help readers detect consent bias, Junghans et al. have published a checklist to look for effects of consent bias.[115] For example, it is suggested to carefully examine consent method, response rate, and data provided by authors to ensure that their results are valid and generalizable. Most studies on consent bias explored the difference between consenters and non-consenters. The consent process itself has not been well studied. In a school-based study on obesity, Crosbie et al. used 2 different consent procedures: 1) an active parental consent procedure which required a signed authorization from parents to weight and measure students and 2) a passive parental consent procedure which included weight and height measurements under a general heading on the health form given to parents.[120] This study did not reveal major differences between groups, but it suggested 2 different approaches to the consent procedure: an active and a passive one. However, the influence of the methods of approaching subjects and the timing of the consent process still have to be better characterized.

III. ACCIDENTAL EXPOSURES IN CHILDREN WITH PEANUT ALLERGY

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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

1411 children (61.3% male, mean age 7.1 years (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 year 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 years 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, health care professionals require better education on anaphylaxis management.

Introduction

Peanut allergy is a potentially fatal condition affecting 1.2% to 1.8% of children in North America and the United Kingdom[11-14,121] and it has been implicated in over 55% of food allergy-related deaths in the United States.[42,46] The amount of peanut triggering a reaction is often minimal[44,45] and resolution rates range from 18.3% to 21.5%.[33,122] Therefore, for the majority, peanut allergy is lifelong and a source of considerable anxiety.[63,65] Unfortunately, there is no well-established curative treatment and management relies on avoidance.[123] 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.[78-82] In 2006, we reported an annual incidence rate of accidental exposure to peanut of 14.3% among children in Quebec, Canada.[78] 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.

Patients and methods

Patient selection

Children with peanut allergy across Canada were identified from 3 sources: 1) the Allergy Clinics at the Montreal Children's Hospital (MCH), 2) provincial and national advocacy organizations for food allergic patients (Anaphylaxis Canada, *Association Québécoise des Allergies Alimentaires*, and the Allergy/Asthma Information Association), and 3) 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 years 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 below). 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 weeks 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 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 history of peanut ingestion or an uncertain clinical history of peanut allergy 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 2 mild signs or symptoms or either 1 moderate or 1 severe sign or symptom that was likely IgE-mediated and occurred within 120 minutes 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.[124] An uncertain history was any reaction after ingestion or contact which 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 ≥ 15kU/L using the CAP system fluoroenzyme immunoassay (Phadia AB Diagnostics, Uppsala, Sweden) has been shown to be 95% predictive of clinical reactivity to peanut.[51,52] 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 ≥ 15kU/L without requiring a food challenge. However, for participants with a convincing history, a peanut specific IgE level of ≥ 0.35kU/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.[125] 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 calculation of the 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 1 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 less than 1 full year of observation (i.e. those recently diagnosed). By doing so, each individual contributed exactly 1 year 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, 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.[126] We used the Bayesian Information Criteria algorithm in order to explore the most plausible predictive models, and to select among these a model which included as many predictors as possible which were either significantly associated with the outcome and/or confounding the association between the outcome and our main predictors of interest (i.e. age, other atopic conditions, severity of previous reactions, and disease duration).

Results

Patient characteristics

At study entry, 1411 participants completed a questionnaire: 1309 of these individuals had completed at least 1 year of follow-up and were eligible for a

follow-up questionnaire; 772 (59.0%) completed 1 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) years at the initial questionnaire and a mean age (SD) of 2.2 (1.8) years at diagnosis. Most participants had at least 1 other atopic condition, and 52.9% had another food allergy. Overall, 86.5% of the participants had an initial clinical reaction to peanut (Table 1).

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 years versus 7.6 years) at study entry and were diagnosed later (at 2.4 years versus 1.9 years). The initial reaction to peanut tended to be more severe in children recruited from the organizations.

Table 1 – Characteristics of participants

	All respondents (n = 1411)	MCH patients (n = 854)	Organizations [1] (n = 557)
Age at initial questionnaire, years			
Mean (SD)	7.1 (3.9)	6.9 (4.0)	7.6 (3.7)
Range	0 - 17	0 - 17	1 - 17
Age at diagnosis, years (SD)	2.2 (1.8)	2.4 (2.0)	1.9 (1.4)
Disease duration, years (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 1 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
Province of residence, %			
Alberta	2.7	0.1	6.8
British Columbia	2.1	0.1	5.3

Manitoba	1.4	0.1	3.3
New-Brunswick	0.4	0.0	1.1
Newfoundland	0.4	0.0	1.1
Nova Scotia	1.0	0.0	2.6
Ontario	19.5	0.2	49.5
Prince Edward Island	0.2	0.0	0.5
Quebec	71.8	99.4	28.8
Saskatchewan	0.4	0.0	1.1
Age of parents			
Mother, years (SD)	38.1 (5.7)	37.8 (5.9)	38.6 (5.3)
Father, years (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

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

Rate, location, and management of accidental exposures

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

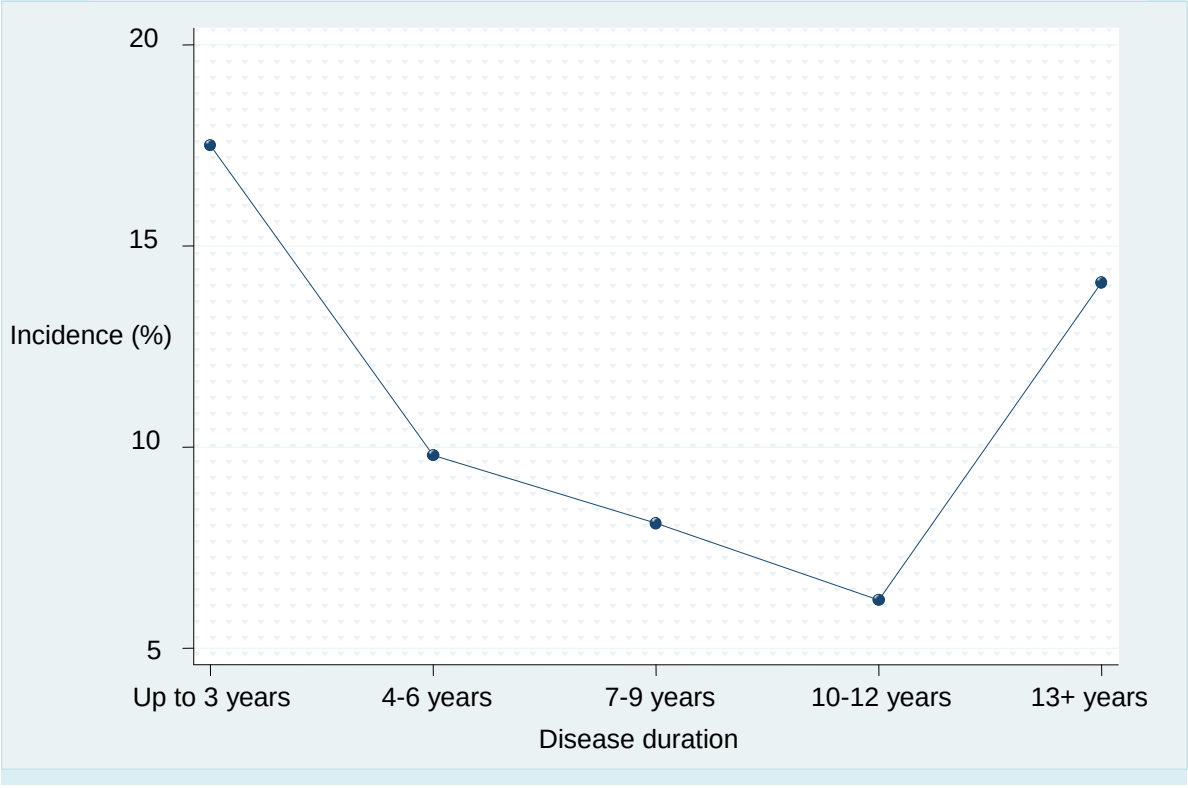

Figure 1 Annual incidence rate of accidental exposure stratified by disease duration

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 daycare, 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 versus permitting peanuts (0.9% versus 2.8%).

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 (Figure 2).

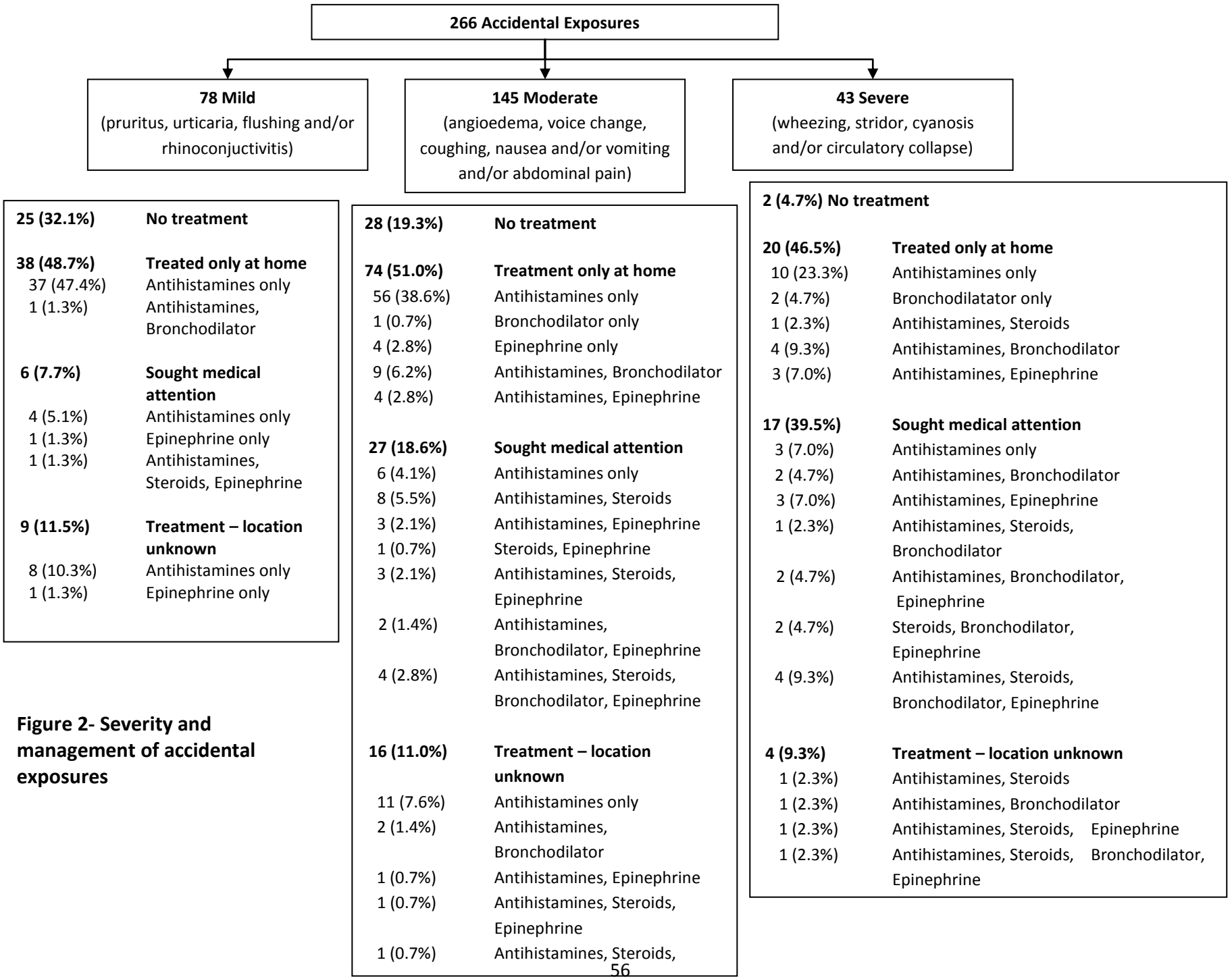

Figure 2- Severity and management of accidental exposures

Severity of initial reaction versus accidental exposure

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

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

Predictors of accidental exposure

In the multivariate logistic regression analyses, age ≥ 13 years old 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. Since 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 years 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 Figure 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 due to their risk-taking behaviors.[127,128] 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%)).[78] However, it is much lower than that reported by others. In 1989, Bock reported 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 years.[79] In 2000, Vander Leek reported that 60% of 83 children had an accidental exposure to peanut, yielding an annual incidence rate of 33%.[81] 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.[82]

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,[80,85] our findings reinforce the importance of educating families. In addition, 6.4% of reactions occurred in schools, 71% of these in schools prohibiting peanut. Since most participants attended schools prohibiting peanut, the proportion of children experiencing an accidental exposure in school is actually slightly lower in schools prohibiting versus permitting peanut. 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,[91] 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.[89,129-131] Since delay in epinephrine administration increases the risk of fatality,[46,47] it is crucial that patients, their caregivers, and health care 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 questionnaires.[132,133] 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 2 groups had very similar rates of accidental exposure in the year preceding study entry: 12.3% (95% CI, 9.8%-15.2%) versus 12.8% (95% CI, 9.9%-16.4%).

Our study may have underestimated the rate of accidental exposure for several reasons. 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,[(10;11)] 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 under-represented (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.

Conclusion

Although oral immunotherapy and other potentially curative therapies are currently being investigated,[134-136] 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 health care 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.

IV. ACCIDENTAL EXPOSURES IN SCHOOL: THE IMPORTANCE OF STUDYING THE MANAGEMENT OF ALLERGY IN THE SCHOOL ENVIRONMENT

In the previous chapter, it was shown that accidental exposure rates remain high and many reactions are managed inappropriately. Among all the accidental exposures reported, 6.4% occurred at school, including 4.5% in schools prohibiting peanut. It is not known if schools are adequately prepared to handle allergic reactions. As mentioned earlier, early recognition of an allergic reaction and adequate management including rapid administration of epinephrine remain the first-line therapy for food-induced anaphylaxis as delay in epinephrine injection may result in fatality. A report by Sicherer et al. in 2001 in the United States focusing mainly on peanut and tree nut allergy suggested that school personnel may not be able to recognize anaphylaxis, nor to administer a life-saving medication such as epinephrine.[89] Hence, it is important to evaluate the competence of Canadian school personnel regarding the identification and management of anaphylaxis, which is the focus of the next chapter. Finally, the process of consenting personnel to participate in such a study on anaphylaxis knowledge provided an opportunity to study selection bias, a concept that has not been well studied in the field of allergy.

V. MANAGEMENT OF ANAPHYLAXIS IN SCHOOL: EVALUATION OF EPIPEN® USE BY SCHOOL PERSONNEL AND COMPARISON OF TWO APPROACHES OF SOLICITING PARTICIPATION

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ABSTRACT

Objectives

To determine if the consent process introduces selection bias by comparing 2 methods of soliciting participation of Quebec school personnel in a study evaluating their ability to demonstrate the epinephrine auto-injector (EpiPen®) and identify anaphylaxis.

Methods

School personnel from randomly selected schools in Quebec were approached using 1) a *partial disclosure* or 2) a *full disclosure* approach. They were assessed on their ability to use the EpiPen® using a 4-item scoring tool and their knowledge regarding anaphylaxis.

Results

343 school personnel participated. The participation rate was higher in schools with a *partial disclosure* approach: 40.7% (95% CI, 36.1%-45.3%) versus 21.9% (95% CI, 19.0%-25.2%). A higher percentage of participants from the *full disclosure* group achieved a perfect score of 4: 26.3% (95% CI, 19.6%-33.9%) versus 15.8% (95% CI, 10.8%-21.8%), and correctly identified 3 signs of anaphylaxis: 71.8% (95% CI, 64.0%-78.7%) versus 55.6% (95% CI, 48.2%-62.9%).

Discussion

Selection bias is suspected as school personnel who were fully informed of the purpose of the assessment were less likely to participate; those who participated among the fully informed were more likely to earn perfect scores and identify

anaphylaxis. As the process of consent can influence participation and bias outcomes, researchers and Ethics Boards may need to consider conditions under which studies can proceed without full consent. Finally, despite training, school personnel perform poorly when asked to demonstrate the EpiPen® technique. The quality and frequency of anaphylaxis training programs have to be re-examined.

Introduction

Food allergy is a serious condition affecting 3.9% of children in the United States,[3] and can lead to systemic life-threatening symptoms or anaphylaxis.[67] There is currently no well-established curative treatment for food allergy and management relies on avoidance and rescue therapy of accidental exposures with epinephrine.[6] We and others have shown that despite increasing societal awareness of the potentially fatal consequences of food allergy, accidental exposures continue to occur[78,79,81,82,87] and about 10% of fatal food-associated anaphylactic reactions take place in school.[42,46] As school represents a situation where parents must rely on other caregivers to respond to a severe allergic reaction, school personnel must be able to recognize anaphylaxis and know how to administer epinephrine using an auto-injector device such as the EpiPen®.[89] A delay in epinephrine administration substantially increases the risk for fatality.[41,46,47]

Previous research has shown that school personnel are not well prepared to recognize and treat food-induced allergic reactions and anaphylaxis.[90,137] However, there has not been any large study focusing on the ability of school personnel to administer the EpiPen®. In 2005, a brief report showed that only 12% of 100 elementary school teachers in Ontario, Canada correctly demonstrated the use of the EpiPen®.[138] As part of a Canadian-wide study examining the influence of different provincial policies on the recognition and management of anaphylaxis in schools, our research team assessed the ability of

school personnel in Quebec to demonstrate the EpiPen® technique and identify symptoms of anaphylaxis. In the other Canadian provinces, school personnel were fully informed of the purpose of the assessment (i.e., *full disclosure*). However, it was anticipated that such *full disclosure* may result in volunteer or consent bias, a form of selection bias where those who volunteer or consent to participate differ from those who do not, leading to an incorrect assessment of performance capacity.[115,118,139] In Quebec, we explored the potential role of volunteer or consent bias by approaching school personnel in 2 different ways: 1. A *partial disclosure* approach in which school personnel were not notified in advance of the EpiPen® demonstration and 2. A *full disclosure* approach in which school personnel were informed in advance that they would have to demonstrate the use of the EpiPen®. In this manuscript, the participation rates and outcomes of these 2 groups were compared to determine if a volunteer or a consent bias was present.

Methods

Selection of participants

In 2008, 2 school boards out of 10 within 1 hour of traveling time from downtown Montreal, Quebec were randomly selected. Initially, 20 schools, including elementary (kindergarten – grade 6) and secondary schools (grade 7 – 11), were randomly identified within each selected school board in a 4:1 ratio, representing the ratio of elementary to secondary schools in Quebec.[140]

Following the approval by school boards and the principals of the selected schools, the school secretary was contacted to arrange a time for the assessors to visit the school. Once a time was arranged, the research team provided invitations (detailing date, time, location) to the school secretary for distribution to all school staff. If a school board or a school refused to participate or did not provide an answer within 6 months after multiple contacts, another one was randomly selected to replace it. All school personnel, including teachers, lunch monitors, administrative staff, school nurses, and janitors, were invited to participate.

Methods of approaching school personnel

In the other Canadian provinces where the ability of school personnel to recognize anaphylaxis and administer the EpiPen® was also assessed, the investigators were required by their Research Ethics Boards to fully disclose the purpose of the assessor's visit in advance to participating school personnel. However, because we suspected that such an approach might introduce bias, in Quebec, the *partial and full disclosure* approaches were compared. In 1 of the selected school boards, school personnel and school contacts were approached using a *partial disclosure* approach. They were not informed in advance of the EpiPen® demonstration and were told in the study invitation that the investigators were studying school personnel's knowledge "regarding allergies and how schools are prepared for children with allergies." In the 2nd school board, a *full disclosure* approach was used. School personnel were informed in

the study invitation of the exact purpose of the assessor's visit, i.e., they would be asked to "show how they use an EpiPen® to help students with life-threatening allergies (anaphylaxis)." Both groups were told in the invitation that they would be provided "feedback, education, and materials on helping students with allergies in school." For both groups, on the day of the visit, prior to the assessment, all school personnel who were interested presented themselves to the assessor and were requested to sign an informed consent which informed them that they would be asked to demonstrate the use of the EpiPen®. It should be noted that no participants in the *partial disclosure* group refused to participate at this stage.

EpiPen® assessment

Although there are 2 epinephrine auto-administration devices on the market in Canada, the Twinject® was only introduced in the fall of 2005 and has had relatively limited uptake. In addition, the Quebec Ministry of Health and Social Services stipulated that school personnel that are not trained health care workers are not allowed to administer the 2nd dose of the Twinject®,[141] making this device less favored in the school environment. Therefore, it was decided to only assess the EpiPen® technique.

The assessors visited schools between October 2008 and May 2009. The assessment visit for each school was concluded within one day; there were no repeat visit to schools. A location in the school was secured to allow for privacy

and a one-to-one interface with the assessor. Assessors were trained nurses or allergists, and their technique was assessed and ensured for accuracy.

EpiPen® technique was assessed based on accurate completion of 4 steps[99,142] using an auto-injector demonstrator:

1. Removal of the grey safety cap;

2. Placement of the black tip against the mid-outer thigh;

3. Application of firm pressure until the device activates ("click" heard);

4. Holding of the device in place for 10 seconds.

To calculate a score for each participant, one point was assigned for successful completion of each step (maximum 4 points).

Participants were also asked to verbally provide 3 symptoms or signs of anaphylaxis. The answers were evaluated using previously published work on the definition of anaphylaxis.[38] After the assessor evaluated the participant's EpiPen® technique and the participant answered questions regarding previous training and indications for administration of an EpiPen®, the assessor provided feedback on the participant's technique and coaching until accurate technique was achieved.

Statistical analysis

Descriptive statistics were compiled for all variables. The participation rate was defined as the number of school personnel who participated divided by the estimated number of school personnel as provided by school secretaries. Data were analyzed according to each step of the EpiPen® technique regarding

whether or not the step was performed accurately and an overall accuracy score was calculated. School personnel with a *partial disclosure* approach were compared to those with a *full disclosure* approach in terms of participation rate, scores and capacity to provide indications for EpiPen® administration, and confidence intervals (CI) are reported. Multivariate logistic regression analyses were used to determine if the method of approach (i.e., *partial* versus *full* disclosure) was associated with accurate demonstration of the EpiPen® technique after adjustment for potential confounders. These included type of school (elementary or secondary), prior training of the school personnel in the use of the EpiPen®, prior training by a nurse, and prior training using an EpiPen® trainer. These analyses were adjusted for clustering of participants within schools.

This study was approved by the Research Ethics Board of the McGill University Health Center.

Results

In the *partial disclosure* group*,* 33 schools were approached and 9 schools participated (7 elementary, 2 secondary); 460 personnel were approached and 187 participated (40.7%, 95% CI, 36.1%-45.3%). In the *full disclosure* group*,* 34 schools were approached and 11 participated (9 elementary, 2 secondary); 711 personnel were approached and 156 participated (21.9%, 95% CI, 19.0%-25.2%) (Table 3). The majority of participants in both groups were teachers: 64.2% in

the *partial disclosure* group and 66.7% in the *full disclosure* group (Table 4). The vast majority of participants in both groups (89.2%) reported previous training, most of them having been trained by school nurses (93.8%). The training involved practice with an EpiPen® demonstrator for 76.1% in the *partial disclosure* and 54.9% in the *full disclosure* group.

Table 3 Participation rates

	Partial and Full Disclosure Groups	Partial Disclosure Group	Full Disclosure Group	Difference % (95% CI)
Participants	343	187	156	
School personnel approached	1171	460	711	
Participation rate %	29.3	40.7	21.9	18.7 (13.3, 24.1)
Participants from elementary schools	258	130	128	
School personnel approached in elementary schools	805	334	471	
Participation rate in elementary schools %	32.0	38.9	27.2	11.7 (5.2, 18.3)
Participants from secondary schools	85	57	28	
School personnel approached in secondary schools	366	126	240	
Participation Rate in secondary schools %	23.2	45.2	11.7	33.6 (24.0, 43.2)

CI – Confidence Interval

Table 4 Characteristics of school personnel and training

Characteristics	All participants %	Partial Disclosure Group %	Full Disclosure Group %
Teachers	65.3	64.2	66.7
Personnel from elementary schools	75.2	69.5	82.1
Prior Training			
Training	89.2	87.2	91.7
Training among elementary school personnel	91.5	91.5	91.4
Training among secondary school personnel	82.4	77.2	92.9
Training by Nurse	93.8	95.1	92.3
Training using an EpiPen® demonstrator	66.2	76.1	54.9

The mean scores for the EpiPen® assessment were 2.52 (95% CI, 2.39-2.65) in the *partial disclosure* group versus 2.64 (95% CI, 2.46-2.83) in the *full disclosure* group (Table 5). Overall, only 20.6% of participants had a perfect 4 point score. Participants from the *full disclosure* group were more likely to have a perfect score: 26.3% (95% CI, 19.6%-33.9%) versus 15.8% (95% CI, 10.8%-21.8%). Mean scores were also higher in elementary schools: 2.67 (95% CI, 2.55-2.80) versus 2.28 (95% CI, 2.04-2.51) in secondary schools, and school personnel from elementary schools were more likely to earn a perfect score: 23.7% (95% CI, 18.7%-29.4%) versus 10.8% (95% CI, 5.1%-19.6%) in secondary schools.

Table 5 School personnel scores for EpiPen® assessment

Score	All participants %	Partial Disclosure Group % (95% CI)	Full Disclosure Group % (95% CI)	Difference % (95% CI)
0	3.5	1.6 (0.3, 4.7)	5.8 (2.7, 10.7)	-4.1 (-8.2, 0.0)
1	10.0	7.6 (4.2, 12.4)	12.8 (8.0, 19.1)	-5.2 (-11.7, 1.3)
2	32.4	43.5 (36.2, 51.0)	19.2 (13.4, 26.3)	24.2 (14.8, 33.7)
3	33.5	31.5 (24.9, 38.8)	35.9 (28.4, 44.0)	-4.4 (-14.5, 5.7)
4	20.6	15.8 (10.8, 21.8)	26.3 (19.6, 33.9)	-10.5 (-19.2, -1.8)
Mean Score (95% CI)	2.58	2.52 (2.39, 2.65)	2.64 (2.46 , 2.83)	-0.12 (-0.34, 0.11)

CI – Confidence Interval

The multivariate logistic regression analysis showed that a *full disclosure* approach remained associated with a perfect score after adjustment for potential confounders: Odds Ratio (OR) 2.6 (95% CI, 1.5-4.6). Prior training with an EpiPen® demonstrator was also associated with accurate demonstration of the EpiPen® technique: OR 5.3 (95% CI, 2.6-10.7)

When considering the percentage of participants correctly demonstrating each step of the EpiPen® technique (Table 6), there was no between group difference for steps 1 (removal of the safety cap) and 4 (holding the device in place for 10 seconds). However, those in the *full disclosure* group were slightly more likely to perform step 2 (placement of the black tip against the mid-outer thigh) correctly: 59.6% (95% CI, 51.5%-67.4%) versus 45.1% (95% CI, 37.8%-52.6%). In contrast, those in the *partial disclosure* group were slightly more likely to perform step 3

(application of firm pressure until the device activates) correctly: 91.3% (95% CI, 86.3%-94.9%) versus 82.1% (95% CI, 75.1%-87.7%). However, because it is not known if keeping the EpiPen® device against the thigh for 10 seconds (step 4) is really necessary to ensure efficacy, we also calculated participants' scores based on accurate completion of the first 3 steps described above. When this last step is omitted, those in the *full disclosure* group were more likely to complete steps 1 through 3 correctly: 51.3% (95% CI, 43.3%-59.4%) versus 31.0% (95% CI, 24.4%-38.2%).

Table 6 School personnel's ability to complete each step of the EpiPen® assessment

	All participants %	Partial Disclosure Group % (95% CI)	Full Disclosure Group % (95% CI)	Difference % (95% CI)
Step 1	81,5	81.0 (74.6, 86.4)	82.1 (75.1, 87.7)	-1.1 (-9.3, 7.2)
Step 2	51,8	45.1 (37.8, 52.6)	59.6 (51.5, 67.4)	-14.5 (-25.0, -4.0)
Step 3	87,1	91.3 (86.3, 94.9)	82.1 (75.1, 87.7)	9.3 (2.0, 16.5)
Step 4	37,2	34.6 (27.8, 41.9)	40.4 (32.6, 48.5)	-5.8 (-16.1, 4.5)

CI – Confidence Interval

Step 1 - Removal of the grey safety cap
Step 2 - Placement of the black tip against mid-outer thigh
Step 3 - Application of firm pressure until the devices activates ("click" heard)
Step 4 - Holding of the device in place for 10 seconds

Overall, 63% of participants were able to identify 3 signs or symptoms of anaphylaxis that should prompt the administration of epinephrine, more in

schools with *full disclosure:* 71.8% (95% CI, 64.0%-78.7%) versus 55.6% (95% CI, 48.2%-62.9%).

Discussion

In this study, we explored the existence of volunteer or consent bias by using 2 different methods to solicit the participation of school personnel in research evaluating competency in EpiPen® use: *partial disclosure* and *full disclosure*. The participation rate was higher in the *partial disclosure* group (between group difference 18.7%, 95% CI, 13.3%-24.1%) and participants from the *full disclosure* group were more likely to earn a perfect score (between group difference 10.5%, 95% CI, 1.8%-19.2%), demonstrate the 3 critical steps correctly (between group difference 20.3%, 95% CI, 10.0%-30.6%), and identify signs of anaphylaxis (between group difference 16.2%, 95% CI, 6.2%-26.2%). These results suggest the existence of a volunteer or consent bias, a form of selection bias where individuals who volunteer for a study may have specific characteristics that distinguish them from non-volunteers and that may affect outcomes; for example, participants may be more likely to find the topic interesting and usually expect to be evaluated positively.[143] In our study, school personnel from the *partial disclosure* group were not given all the information about the purpose of the study and the EpiPen® assessment prior to the assessors' visit. Consequently, they were unlikely to be reluctant to participate because of concerns regarding their knowledge and competence, but their performance was

generally poorer. In contrast, those in the *full disclosure* group were completely aware of the purpose of the assessment and those with a greater interest and possibly knowledge in the topic were more willing to participate, leading to an overestimation of competence relative to the general population. It is also possible that those who chose to participate also practiced or prepared prior to the evaluation, enhancing their performance. This suggests that the timing and the process of informed consent can affect the participation rate and the interpretation of the results. Although this threat to the validity of a study that arises from the consent process has been described previously,[115,117,118,144] we are the first to explore its influence in allergy research.

In comparing the 2 approaches, we tried to ensure that the school boards were as similar as possible other than in the detailing of the consent by randomly selecting school boards of similar size in the same urban area. In addition, in Quebec, as school nurses responsible for school personnel training are employed by the Ministry of Health and Social Services and not by individual school boards, the EpiPen® training is less likely to be influenced by school board environments and likely to be reasonably similar throughout the province. Further, we adjusted for possible differences between the *partial* and *full disclosure* groups through regression analyses and demonstrated that the *full disclosure* group continues to perform more favourably. However, it is possible that the school boards differed in ways we did not consider or were unable to measure and these differences influenced the performance of school personnel. It is also possible that there was

contamination within and between groups. As it was not feasible to conduct all school assessments on the same day, assessments were staggered over an 8-month period. Hence, it is possible that school personnel within the *partial* or *full disclosure* group assessed early in the process communicated with those in the *partial disclosure* group who were assessed later, informing them of the purpose of the assessment. Such contamination would likely minimize our between group difference and make our assessment of selection bias conservative. In addition, our analyses were adjusted to take into account the grouping of participants by school, and we found that the effects of within-school versus between-school variations were not significant. Although it was not the purpose of this small study, it would have been interesting to compare participants and non-participants in terms of their anaphylaxis interest and knowledge to better characterize the bias illustrated in this study.

Our results reporting that only 26.3% (95% CI, 19.6%-33.9%) among the *full disclosure* group are able to accurately demonstrate the use of the EpiPen® are disturbing as they likely overestimate the competence of school personnel. The 15.8% (95% CI, 10.8%-21.8%) demonstrating correct usage in the *partial disclosure* group is likely more representative, but it, too, is probably an overestimate as the most informed were still more likely to participate even in this group. Although personnel in elementary schools performed more favourably, possibly because they feel younger children are more reliant on them, only 23.7% (95% CI, 18.7%-29.4%) were able to correctly use the EpiPen®.

These results are worrisome because it has been shown that inability to use an epinephrine auto-injector may contribute to a delay in the treatment of anaphylaxis[89,129] which can increase the risk for fatality.[46,47]

Given the poor performance observed despite 89.2% of all participants reporting training, the quality and frequency of school personnel training needs to be examined. In Quebec, school personnel are trained in allergy and anaphylaxis management and EpiPen® use on a regular basis.[145] However, the content and frequency of training programs may vary as there are no provincial guidelines. In our study, training involving an EpiPen® demonstrator was associated with better performance. Others have also recommended use of the auto-injector training device and frequent review to increase knowledge retention.[89,90] A training model using an audio-visual presentation and written material on anaphylaxis and epinephrine administration followed by a meeting with allergic children was developed for school personnel in San Francisco in 2004, and significantly increased knowledge and perceived self-efficacy in 53 participants.[146] Such a training model could be adapted and studied in Canada.

In conclusion, although Research Ethics Boards usually ask investigators to fully disclose the intended purpose of their research to potential participants, we have shown that the process of consent can influence participation and bias outcomes. Investigators need to appreciate and acknowledge the potential bias that may be introduced by the consent process and attempt to fulfill ethical requirements while minimizing bias. While respecting participants' rights, ethical

issues regarding the consent process have to be discussed with Research Ethics Boards whenever the scientific validity of results may be compromised. Researchers and Ethics Boards may need to be educated on circumstances under which studies can proceed without full prior disclosure. Further, we have shown that despite being trained to recognize anaphylaxis and to administer epinephrine, school personnel perform poorly when asked to demonstrate how to use the EpiPen®. The content, quality and frequency of allergy and anaphylaxis training programs for school personnel have to be re-examined. As recommended by numerous guidelines[92,96,102] and required by legislation in at least one Canadian province,[104] management plans targeting allergies and anaphylaxis should be introduced in schools to create a safer environment for children with life-threatening allergies. Further studies on the process of implementation and the impact of such plans are also needed.

V. CONCLUDING DISCUSSION AND SUMMARY

A food allergy is an adverse immune response that occurs reproducibly on exposure to a food. Its prevalence in the pediatric population is estimated to be about 4-8% and it has possibly increased over the past 10 years. Peanut is a common allergen, especially in North America and the United Kingdom, where its prevalence is estimated to be about 1-2%. The diagnosis of food allergy relies on clinical history, skin prick test, measurement of serum levels of specific IgE to food, and/or food challenge. Food allergy can induce anaphylaxis, which involves rapid onset of severe systemic symptoms within minutes to hours after contact with an allergy-causing substance. Often attributable to peanut, nut, fish, and shellfish, food-induced anaphylaxis is the most common cause of anaphylaxis in children. There is currently no well-established curative treatment for food allergy. Its management relies mainly on avoidance of the culprit food, which is difficult and stressful for patients and their caregivers. Despite avoidance measures, accidental exposures occur.

In Chapter III of this thesis, I report the results of the largest longitudinal nationwide study on the rate and predictors of accidental exposure among children with peanut allergy. This is the 1st study to my knowledge to explore such predictors. Canadian children with peanut allergy have an annual incidence rate of accidental exposure of 11.9%. This rate increases slightly to 12.5% when

adjustments are made to incorporate the length of observation. Indeed it was found that the rate of accidental exposure declines with disease duration, and is highest immediately after diagnosis. Teenagers were also at higher risk for accidental exposure. Educational measures are therefore of particular importance immediately after diagnosis and for the adolescent population. It was shown that many reactions occur at home, and 6.4% of them occur in school, even in schools prohibiting peanut. Although epinephrine can be life-saving and a delay in its administration can result in fatality, 78.7% of moderate and severe reactions were not treated with epinephrine. This is possibly associated with failure to recognize allergic symptoms, fear of epinephrine adverse effects, or inability to use the epinephrine auto-injector. A study focusing on patients' and caregivers' beliefs and knowledge regarding allergy, anaphylaxis and epinephrine may help improve allergy management and design better training programs for patients, families, and health care practitioners.

Although many issues were addressed in the study described in Chapter III, the study also has limitations. As mentioned previously, the study population may have been more informed about allergy and therefore at lower risk of experiencing an accidental exposure. Considering that all participants had been diagnosed by an allergist, many were members of advocacy associations, most of the parents were well-educated, and ethnic minorities were under-represented, it is possible that the true population rate of accidental exposure may be higher,

which is even more worrisome. In order to minimize selection bias and recall bias, it would have been ideal to include a population-based sample of Canadian children with peanut allergy and record accidental exposures prospectively as they occur. However, such study would be difficult to conduct and very demanding on participants. Finally, most participants were from Quebec and Ontario. Although it is unlikely that the rate of accidental exposure is significantly different in other provinces, a future study with more participants from other Canadian regions and including more participants from different ethnic background is desirable.

Management of food allergy in school settings has become a concern and in Chapter V of the thesis, the ability of school personnel to recognize and manage anaphylaxis is explored, with a particular focus on their competency with the EpiPen®, an epinephrine auto-injector. Despite increasing societal awareness regarding anaphylaxis and enhanced efforts to create safer environments for allergic children, schools are often not well prepared to handle allergic reactions and anaphylaxis; management plans for allergic children are variable and a medication such as epinephrine is not always easily accessible. In addition, school personnel may not be able to administer epinephrine adequately. In Quebec, only a handful of school boards have specific policies regarding food allergies and anaphylaxis, but school nurses, under the authority of the Ministry of Health, are responsible for developing management plans for allergic children

and educating school personnel. Despite most personnel having received training from a nurse, the findings reported in Chapter V revealed that only 20.6% were able to adequately demonstrate the EpiPen® technique. Hence, training procedures, as well as frequency of training sessions need to be re-examined. Standardized education programs, using an EpiPen® demonstrator, warrant consideration. Currently available epinephrine auto-injectors have to be examined, as new devices with vocal instructions, which may be easier to use, will soon be available on the market. Moreover, the impact of various regulations, policies, and legislations needs to be studied to determine the best strategies to ensure safe environments for allergic children. Education of patients, parents, physicians, school personnel, and administrators is necessary; each group needs to share responsibility for the well-being of the affected individual. Education strategies are important to better manage food-allergic reactions in school settings and in other settings, but they are also required to increase awareness in order to improve preventive measures. Accurate labelling of food products that contain major allergens is crucial to ensure safety for allergic children. Measures to decrease cross-contamination, especially in public places such as cafeterias and restaurants, also need to be explored and studied. Finally, individualized management plans targeting at-risk population and empowering patients and their community may help further decrease rates of accidental exposure.

The study on school personnel's ability to use the EpiPen® provided the opportunity to explore volunteer bias and consent bias, two types of selection bias where those volunteering or consenting to participate differ in relevant clinical characteristics from those who do not. In the study, 2 different methodological approaches were used to recruit school personnel to participate in a study on their ability to use the EpiPen®: a *full disclosure* approach where school personnel knew in advance that they would have to demonstrate the use of the EpiPen® and a *partial disclosure* approach where they were only informed in advance that they would be questioned on their knowledge regarding allergy management. It was found that the participation rate in the *partial disclosure* approach group was higher. However, participants from the *full disclosure* group were also more likely to earn perfect scores and to identify correctly 3 signs of anaphylaxis. The findings suggest the presence of a volunteer bias and a consent bias. It has been shown that ethical requirements regarding the consent process can bias medical research. As most studies on consent bias explored the difference between consenters and non-consenters, the impact of different recruitment approaches has not been well studied. Hence, further research is warranted especially in the field of allergy.

As selection bias can affect the validity of a study, it is important to remind researchers and readers to examine methods and data carefully in order to detect biases and interpret findings adequately. After examining selection bias

associated with informed consent in a systematic review of prospective observational studies, Kho et al. offered strategies to minimize consent bias: increase awareness by clinicians and researchers of the impact of selection bias introduced by the consent process; educate clinicians, researchers and ethics boards on conditions under which studies can proceed without individual consent; standardize reporting methods used to seek informed consent; report and discuss participations rates.[147] Moreover, the consent process itself has to be better studied to fully characterize its impact on study results. While respecting participants' right, ethical issues regarding the consent process have to be discussed with research ethics boards whenever the scientific validity of results may be compromised.

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