AFRICAN JOURNAL OF NUTRITION AND DIETETICS

https://doi.org/10.58460/ajnd.v3i1.69

ORIGINAL ARTICLE

Open Access

MJM BIOLABS

Frequency and Severity of Cow's Milk Allergy Reactions in Children: A Prospective Audit

Loise WAMAHIGA WANG'ONDU[1] , **Enock KUYONI TOPISIA**[2]

[1] Department of Sales and Marketing, Avacare Limited

[2] Department of Nutrition and Dietetics, Aga Khan University Hospital

Article History

Submitted:

Accepted:

Published Online: 12th June 2024

To read this paper online, please scan the QR code below:

ABSTRACT

Milk ranks as the second most common allergen, following peanuts. Recent studies from Spain and the USA report an annual frequency of accidental allergic reactions (AAR) ranging from 34% to 40%. AAR severity is influenced by food allergens and the presence of atopic diseases such as asthma, eczema, hay-fever, and recurrent wheezing. The aim of this study was to determine the frequency of accidental allergic reactions in children with cow's milk protein allergy between September 2011 to September 2012. Study design employed is missing. A structured questionnaire was used and the guardians to the patients guided in answering by the research assistants (Students). The questionnaire was conducted on 62 patients (35 males, 27 females) with a median age of 67 months. The inquiries were about the number and locations of accidental reactions, their severity, other food allergies, and risk factors such as asthma, hay-fever, recurrent wheezing, and eczema. Symptoms were classified as mild, moderate, or severe, and previous and current skin prick test results were recorded. Between 2011 and 2012, the frequency of AAR was found to be 57% (inclusive of adults). Among the children, 37 (60%) experienced 51 accidental reactions in the past year, with 43% classified as mild, 19% as moderate, and 38% as severe. The majority of reactions (60%) occurred at home, and treatment primarily involved the use of Chlorphenamine [Piriton©] (79%). Three anaphylactic reactions occurred and were identified leading to hospitalization and administration of epinephrine. Oral exposure was the primary route (89%), with milk-containing products being the most common allergen sources (51%). The main cause of AAR was attributed to mislabeling and misreading of labels, especially in newly implemented recipes and non-packaged cereal products like homemade croissants sold in cafes and restaurants. Other causes included high levels of peanut traces and hazelnuts in cookies and chocolates. In conclusion, accidental allergic reactions are prevalent in children and are often caused by contamination, mislabeling, recipe changes by companies, misinterpretation by caregivers, and direct milk intake. Risk factors for AAR severity include hay-fever, peanut allergy, multiple atopic diseases, and wheal size.

Keywords: accidental allergic reactions; cow's milk; risk factors; mislabeling

INTRODUCTION

Food Allergy is an abnormal or exaggerated immune response to specific food allergens. The immune system mistakes certain proteins in food as harmful invaders and triggers an immune response. The symptoms can range from mild (itching, hives) to severe (anaphylaxis), involving multiple organ systems. Common allergens include peanuts, tree nuts, eggs, milk, soy, wheat, fish, and shellfish (Sasaki et al, 2018). Food Intolerance refers to physiological reactions to food additives or ingested food that are not immunologic but can be metabolic, pharmacological, or toxic in nature. Unlike food allergies, food intolerance does not involve the immune system. Instead, it may result from the body's inability to metabolize certain components of food. An example is lactose intolerance which is a common example of food intolerance. It is caused by a deficiency of the enzyme lactase, leading to the inability to break down lactose, a sugar found in milk and dairy products (Sasaki et al, 2018).

Cow's milk protein allergy (CMPA) is noted as the second major food allergy in children, following peanut allergy (Gupta et al, 2019). Development of CMPA in infants precedes the development of other food allergies in children. Estimated prevalence rates for CMPA in Europe are provided, ranging from 1% to 13.5% in 5–16-year-olds, 1% to 17.5% in preschoolers, and 1% to 4% in adults (Fiocchi et al, 2010). CMPA can manifest as IgE-mediated, non-IgE-mediated, or a combination of both. IgE reactions, classified as immediate type I hypersensitivity, affect 8% of patients with allergies, with cow's milk being a major causative allergen (Du Toit *et al*, 2009). Children with atopic disorders, such as eczema, have an increased risk of developing CMPA. Approximately 6% of children with asthma experience food-induced wheezing related to CMPA (Sicherer, 2006). About 10% of CMPA children may react to beef due to the presence of a small amount of cow's milk protein in beef (Skypala and Ventor, 2009).

Research by Nowak-Wegrzyn et al in 2008 indicates that 75% of children with CMPA can tolerate heated (baked) cow's milk. High temperatures alter the conformation of the protein allergen, making it more tolerable. Patients who could tolerate baked milk at 3 months had a small wheal size but higher IgG4 levels against casein. Confounding factors such as growth and intestinal permeability were statistically insignificant in this context (Nowak – Wegrzyn, 2008). This information underscores the diverse nature of CMPA, its prevalence across different age groups, the importance of considering various immunological responses, and the intriguing aspect of heat-treated milk tolerance. The data presented contributes to a more nuanced understanding of CMPA and its complexities. Elimination diet is the primary mode of treatment for CMPA to achieve remission even though it comes with its own challenges. Traces of milk in various food commodities, such as biscuits, sauce mixes, and processed meats, make the elimination diet challenging. accidental allergic reaction to cow's milk can occur due to contamination, skin contact, misread labels, or new recipes in products and non-packaged foods.

A cross-sectional study in Spain by Boyano-Martinez et al. (2009) reported a high AAR frequency of 40% in the past year. The AAR frequency for cow's milk was higher than the frequency for peanut AAR (14.3%) in Canada (Yu et al, 2006) and egg allergy AAR (21%) in Spain (Boyano-Martinez et al, 2012). Considering differences in products and locations, the suggestion is made to analyze AAR frequency for a similar product in a different country to assess the reproducibility of results depending on geographical distribution.

A study by Pereira et al. (2005), reported that 3% of 11-year-olds and 4% of 15-year-olds had adverse reactions to milk ingestion. Most reactions were immediate, and severity was influenced by a history of asthma and recurrent wheeze. The study had a large sample size of (n=88, 252, 92, n=757, n=775) contributing to increased reproducibility and accuracy of the findings. Studies by Macdougall et al. (2002), and Du Toit et al. (2009), showed an association between coexisting asthma and AAR severity, as well as an association between asthma and egg allergies with CMPA sensitization. Anaphylaxis of CMPA, had a 10% rate for pediatric hospital admissions. In the ten years prior to the Macdougall et al. (2002) study, eight children with CMPA had died, and four of them had CMPA.

Saarinen et al. (2005), demonstrated that children with IgE-mediated CMPA had hayfever, egg allergy, and sensitization to birch and other food allergens. Long-term follow-up provided

evidence for a temporal association between CMPA and other. Rosalie et al. (2002), conducted a cross-sectional study on food allergies' prevalence in young adults (20-45 years). The study found associations between a history of wheeze, asthma, and eczema with an increased risk of peanut and shrimp allergy. This highlights the need for characterizing relationship between atopic diseases and other food allergens with severity of AAR.

A 3-year follow-up study conducted in five USA cities by Fleischer et al. (2012), provides valuable insights into the occurrence and characteristics of AAR in children with documented milk or egg allergy. It involved 512 children aged 3-15 months with documented milk or egg allergy. The annual AAR rate for all allergies (peanut, egg, milk, and others) was reported to be 81%. Milk triggered the majority of reactions (71%), with a high AAR annual frequency of 34%, similar to the frequency found in the Spain CMPA study (Boyano-Martinez et al, 2009). Half of the reactions were attributed to foods provided by parents, while the other half were from caregivers, including grandparents, teachers, and babysitters. 90% of the reactions were accidental, with causes including label errors (16%), cross-contamination (15%), reduced caregiver supervision and forgetfulness (65%), and mistakes in food preparation (4%). Parents had received advice on food avoidance and emergency treatment at the beginning of the study. Despite 10% of the reactions being severe, only a third was treated with adrenaline. The study suggested that fear of using adrenaline injections may be a contributing factor. The study highlighted that 1 in 9 AARs were intentional, possibly conducted to test if the children had outgrown their allergy.

The decision to investigate AAR frequency, place of occurrence, type of food exposure, and mode of treatment is a logical step based on the information provided in the previous discussions. The hypothesis formulated for the investigation indicates a focus on the frequency of AARs in schools and the potential factors influencing their severity. The investigations aimed to explore AAR frequency, place of occurrence, type of food exposure, and mode of treatment. The hypothesis suggested that AARs would occur most frequently in schools. Severity of AARs is hypothesized to be directly dependent on history of atopic diseases, presence of other food allergens and current wheal size (mm). The sample was selected from the Pediatrics Allergy clinic at St. Thomas Hospital in London due to their Allergy and Rhinitis department. This implies that the study is conducted in a clinical setting with access to individuals seeking allergy-related care. This approach indicates a comprehensive effort to understand the circumstances surrounding AARs, with a particular emphasis on the school environment. The use of a systemized questionnaire in a clinical setting adds rigor and structure to the data collection process. The investigation's findings could contribute valuable insights into the prevalence, triggers, and management of AARs, especially in school-aged children. Understanding the factors influencing the severity of reactions can guide better preventive measures and treatment strategies for individuals with food allergies.

The objective of this study is to establish the frequency of accidental allergic reactions in children with cow's milk protein allergy over the past year, while also determining the circumstances, severity, and treatments associated with these reactions. This includes identifying risk factors and patterns to develop targeted interventions for mitigating the risk of severe reactions.

METHODOLOGY

Study design

This was project No: 2807, St. Thomas Hospital, London. This was a cross sectional study carried out on children with cow's milk allergy at St. Thomas Hospital London. The aim was to create awareness to the society on the severities of CMPA and the population they mainly affected.

Study location

The study was carried out at St. Thomas Hospital London United Kingdom due to the extensive research on pediatrics and also the fact that it has one of the largest and busiest allergy centers in the country.

Study population

Subjects included in the survey had to be between 18 months to 20 years. Patients were required to have a clear history of Cow's Milk Protein Allergy (CMPA). This history was determined by explaining the symptoms experienced and the

duration it took for these symptoms to appear. Patients were included if they avoided all forms of cow's milk. Patient selection took place from May 25th to July 14th, 2012.

Box 1: The inclusion and exclusion criteria

Patient inclusion criteria

- Attending Paediatric Allergy clinic
- Over 18 months of age (therefore weaned over 1 year)
- Diagnosis over IgE mediated cow"s milk protein allergy
- Positive SPT (> 3mm wheal size) and/or Positive Specific IgE
- Clear History for cow's milk allergy (correspondence section -clinic letter)
- Avoids all cow's milk and cow's milk containing foods in the diet

Exclusion criteria

- Infants < 18 months of age
- Non IgE mediated cow's milk protein allergy
- Patients without a clear history of cow's milk allergy
- Patients tolerating some cows in their diet e.g. baked milk
- Patients with history of eczema and positive SPT but no other clear history of cow's milk allergy

Sample size determination

There were a total of 73 subjects, who qualified to be in the study, but 10 did not attend their clinical appointments and one did not speak English. Some 13 participants did not fit into the inclusion criteria: 3 could have baked milk, 4 had a wheal size <3mm during follow up, 4 had non IgE CMPA, and 2 were less than 18 months.

The patient selection took place from 25th May till 14th July 2012. The age preferred was >18 months because they had more than one year of weaning and introduction to different kinds of food thus increased risk of allergen intake. The total number (73) of subjects was derived from the documentation present at St. Thomas Hospital London, Allergy clinic. The participants were 49 which was 67% of the total number of patients at the Allergy clinic.

Study instrumentation

A structured questionnaire was used and the guardians to the patients guided in answering by the research assistant during follow up visits.

Data Collection Methods

The questionnaire was filled face-to-face during clinic follow-up visits. This approach facilitated rapport and real-time clarification. Flexibility in questioning allowed for adaptations to participant responses, even though most questions were closed-ended. Closed-ended questions provided specific, quantifiable responses, aiding data analysis. Information from participants' history documents enhanced accuracy and reliability, especially regarding past reactions. Avoidance of leading questions-maintained data integrity**.**

Data analysis

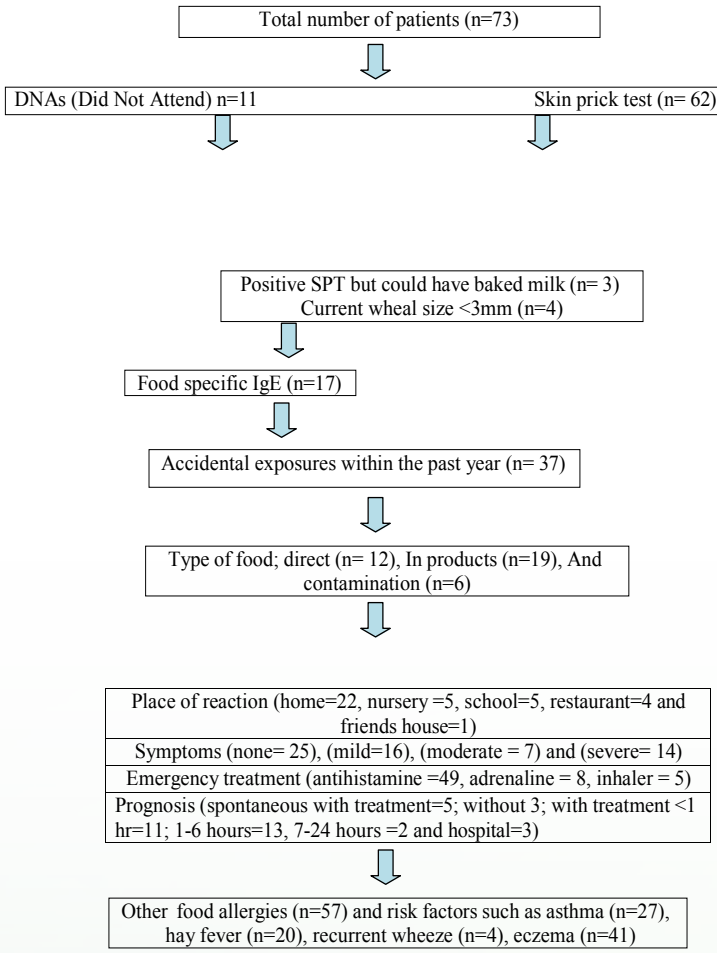
Food types were categorized as milk in products, direct contact, or cross-contamination. Exposure types included skin contact, inhaled exposure, and levels of food ingestion. Reaction locations were classified into home, friend's house, nursery/childcare, school, or restaurant/ cafe. Symptoms encompassed IgE-mediated immediate hypersensitivity reactions. Onset times were divided into intervals (<15 minutes, 15-30 minutes, 30-60 minutes, 60-120 minutes). Treatment options included anti-histamine, adrenaline autoinjector, inhaler, or none. Disease progression was described in terms of spontaneous resolution, treatment outcomes, and resolution time frame. Allergic reaction severity was categorized as mild, moderate, or severe based on reported symptoms.

The statistical analyses conducted in the study involved a range of descriptive and inferential methods, with a focus on exploring relationships between qualitative variables and AAR severity. Data from the questionnaires was recorded in the Excel and exported to SPSS 18.0 for analysis. Variables Analyzed type of food, place of reaction, treatment used and prognosis. The measures taken were frequencies for qualitative variables and mean and standard deviation for continuous variables. Cross tabulations provide a summary of the relationships. Chi-square ($\chi 2$) test was used for independence testing between variables (variable 1 was the food allergen and variable 2 was the size of the skin prick test). Fisher's exact test was employed for smaller sample sizes and when assumptions for the chi-square test was not met. Median values were

used instead of the mean for variables with abnormal distribution. ANOVA is used to assess the variation in treatment used across different levels of AAR severity. The wheal size at the time of diagnosis was not used for analysis; it was mainly used as an inclusion criterion and was not considered a variable that would impact AAR severity.

Data collection procedures

Figure 1:
Chart showing the recruitment and assessment of AAR



Ethical considerations

The Research and Development department at St. Thomas Hospital designated the project as an audit. Given the classification as an audit, the project was deemed not to require a separate ethics application. The project received clearance from the Research and Development department at St. Thomas Hospital (2807). The project strictly adhered to rules and regulations governing the collection and handling of data. Maintaining patient confidentiality was a priority, emphasizing the ethical responsibility to protect the privacy of participants. Patients were identified using numbers and codes, not their actual names. The use of numbers and codes adds a layer of confidentiality and privacy to the participants. The numbering and coding system was implemented to prevent reassessing patients who had more than one appointment within the month of data collection. This approach ensures that each patient is uniquely identified and assessed only once within the specified time frame. The numbering and coding system also serves to prevent data omission, ensuring that each patient's information is accurately captured. Information containing patients' names was kept in the hospital. Access to this information was restricted to only the supervisor and the researcher. This restricted access helps maintain patient confidentiality and data security. After analysis, the questionnaires were discarded.

RESULTS

There was a total of 73 patients, who qualified to be in the study, but 10 did not attend their clinical appointments and 1 had no English. Some 13 patients did not fit into the inclusion criteria: 3 could have baked milk, 4 had a wheal size <3mm during follow up, 4 had non IgE CMPA, and 2 were less than 18 months.

The total number of study participants was 49 who attended St. Thomas, Paediatric allergy clinic from 25th May to 14th July 2012. The males numbered 35 (mean age ± *SD* = 74 ± 44.9 months) and the females 27 (mean age = 69 ± 40.9 months). For the whole group, the range was 18-225 months with a mean age of 71±42.9 and a median of 67 months. All the children had other food allergies. Egg allergy was the most common allergen (79%) and eczema (66%) the most common atopic disease **(Table 1)**.

Table 1

The mean age (months), food allergies, history of atopy, egg, wheat, fish, shellfish, soya, peanuts, tree nuts, Sesame. Asthma, Recurrent wheeze, Hayfever and Eczema for the participants (n=62)

	Participants			Participants	
Total	**62 (100%)**			**62 (100%)**	
Age (months) Mean	71± 42.9		**Peanuts**	43	(69%)
Food allergies	57	(92%)	**Tree nuts**	40	(65%)
History	54	(87%)	**Sesame**	21	(34%)
Egg	49	(79%)	**Asthma**	27	(44%)
Wheat	15	(24%)	**Recurrent wheeze**	4	(6%)
Fish	19	(31%)	**Hayfever**	20	(32%)
Shellfish	11	(18%)	**Eczema**	41	(66%)
Soya	12	(19%)			

A total of 37 (60%) children had 51 accidental reactions in the past year. Further, 57 (92%) participants had other food allergies (egg 49; wheat 15; fish 19; shellfish 11; soya 12; peanuts 43; treenuts 40 and sesame 21). The average number of food allergies per individual was 4±2. 54 (87%) children had clinical histories (asthma 27; recurrent wheeze 4; hayfever 20; and eczema 41).

The average history per individual was 2±1. All the nonparticipants had other food allergies (egg 10; wheat 4; fish 6; shellfish 5; soya 4; peanuts 7; treenuts 7 and sesame 3) and history of atopy (asthma 4; recurrent wheeze 2; hayfever 1; and eczema 6). The average food allergy was 4±2 while for history was 1±1 (**Table 2**). 25 (68%) children had 1 AAR, 10 (27%) had 2 AARs and 2 (5%) had 4 AARs. There was no child with 3 AARs. This led to a total of 51 allergies in the past year.

Table 2

The association of number of accidents to AAR severity

		Symptoms			
		Mild	Moderate	Severe	Total
Number of accidents	Oral	10 (63%)	5 (71%)	10 (71%)	25 (68%)
	Skin	5 (31%)	2 (29%)	3 (21%)	10 (27%)
	Inhalation	1 (6%)	0 (0%)	1 (7%)	2 (5%)
Total		16 (100%)	7 (100%)	14 (100%)	37 (100%)

Type of food and exposure causing AAR

Thirty three (89%) children have AARs caused by oral intake (mouthful 22, trace 8 and full portion 8), 2 (8%) were due to skin contact and 1 (3%) inhalation. 21 children had oral exposure at home, one at a friend's house, 4 in a nursery, 4 in school and 2 in a restaurant. The 2 who had skin contact, one was at home and the other in a nursery. Only one had inhalation exposure in school. **Figure 1** shows the overall patient distribution in relation to food.

Figure 1

Type of food

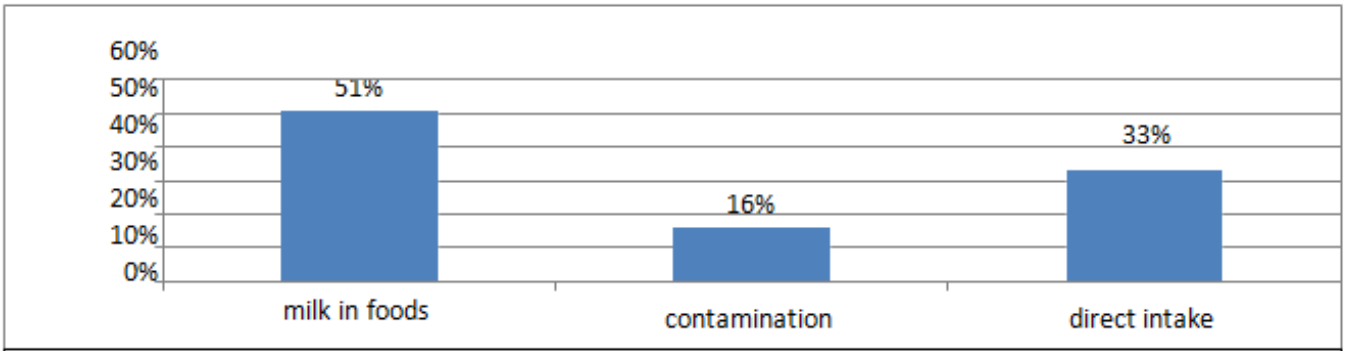


Figure 7: 19 (51%) children had products containing milk as an ingredient were the major causatives of AAR. 12 (33%) had took cow's milk and 6 (16%) had cross-contamination in restaurants and at home

Overall, 3 (50%) children had their milk contamination at home, 2 (33%) in a nursery and one (17%) in a restaurant while 12 (63%) children ingested milk in products at home, 1 (5%) at a friend's house and another (5%) nursery/childcare and 3 (16%) in school There was however, no statistical significance between locations (p-value >0.05) **(Table 3).**

Table 3

The association of type of food causing AAR with location

	Place of reaction					
	Home	**Friend's house**	**Nursery /childcare**	**School**	**Restaurant / cafe**	**Total**
Milk in products	12 (63%)	1 (5%)	1 (5%)	3 (16%)	2 (11%)	19 (100%)
Cross-contamination	` 3 (50%)	0 (0%)	2 (33%)	0 (0%)	1 (17%)	6 (100%)
direct intake	7 (58%)	0 (0%)	2 (17%)	2 (17%)	1 (8%)	12 (100%)

Place of reaction

15 (71%) children below the median age while 7 (44%) children above the median had their AAR at home; 1 under the median in a friend's house, 3 under the median and 2 above the median in a nursery, 5 above the median in school and none at home; 2 below the median and 2 above the median in a restaurant **(Table 4)**. There was no statistical significance between the age and place of reaction showing that the place of reaction was independent of age (χ^2= 7.312, df= 4, p-value= 0.12).

Table 4

The association of place of reaction with median age (months)

		Median age (months)		
		<67	**>67**	**Total**
Place of reaction	Home	15 (71%)	7 (44%)	22 (60%)
	Nursery/ childcare	3 (14%)	2 (13%)	5 (13%)
	School	0 (0%)	5 (31%)	5 (13%)

	Restaurant/ cafe	2	(10%)	2	(13%)	4	(11%)
	Friend's house	1	(5%)	0	(0%)	1	(3%)
Total		21	(100%)	16	(100%)	37	(100%)

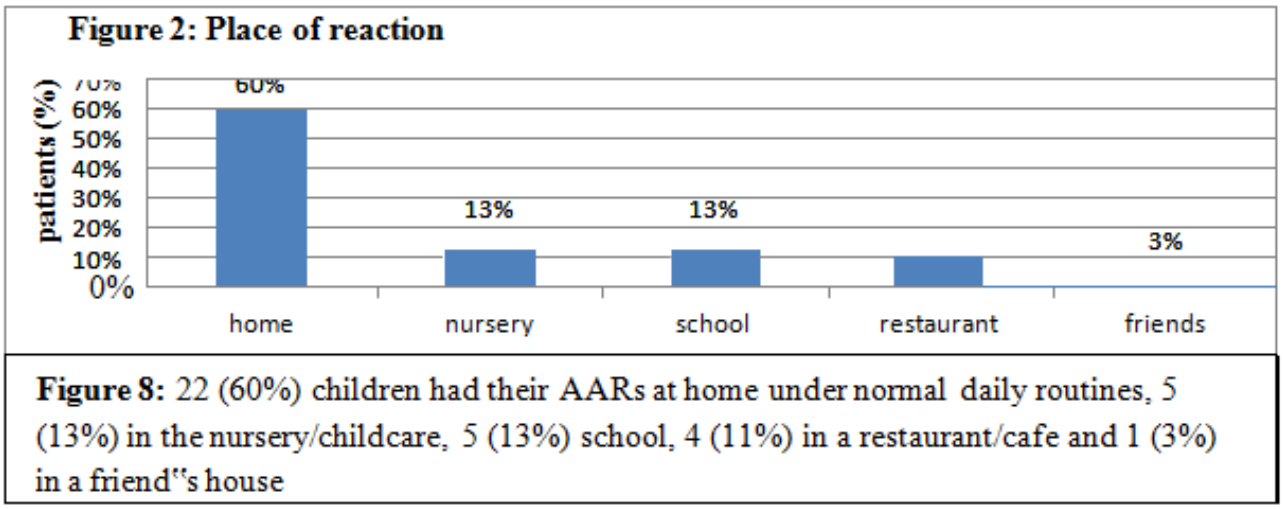


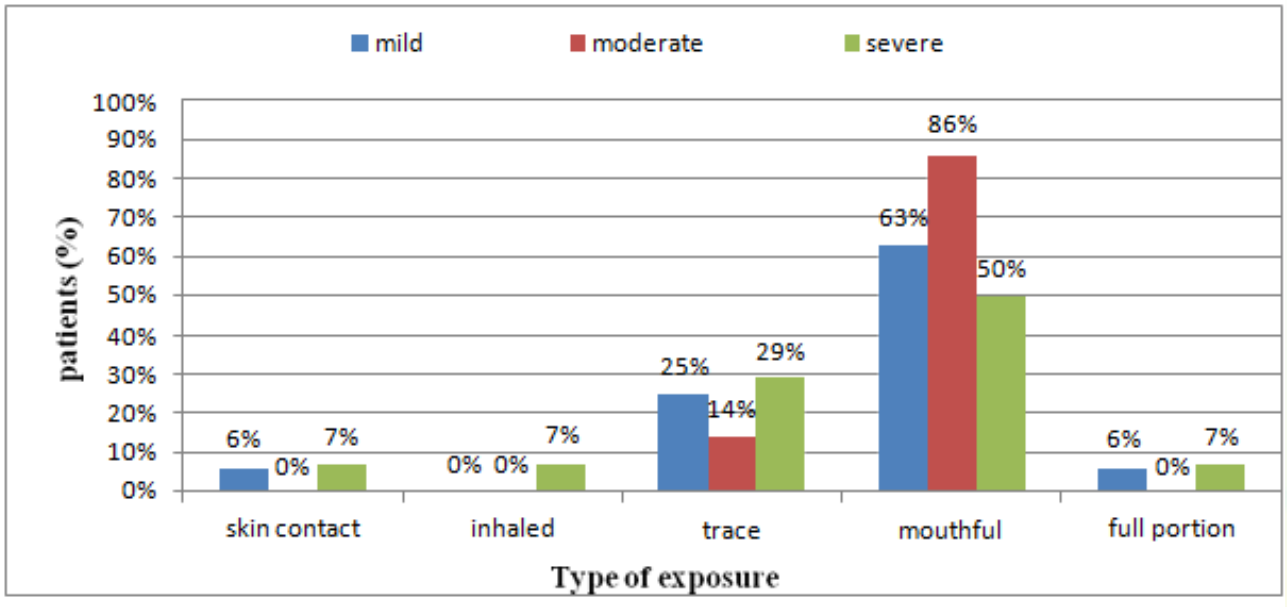
Figure 8: 22 (60%) children had their AARs at home under normal daily routines, 5 (13%) in the nursery/childcare, 5 (13%) school, 4 (11%) in a restaurant/cafe and 1 (3%) in a friend"s house

AAR Symptoms and their time of onset

Symptoms that took more than 4 hours to appear were also excluded since that was a non-IgE mediated response. The cutaneous symptoms observed were 47% (22 hives and rash 5). The respiratory symptoms were 16% (loss of voice 5, cough 3, wheeze 2) while gastrointestinal were 11% (vomiting 4, diarrhea 2, abdominal pain 1). Since most children had more than one symptom it was easier to categorize them into mild moderate and severe. 16 (43%) children had mild symptoms, 7(19%) had moderate and 14 (38%) had severe reactions. There was a statistical significance between those who had <15 minutes' time of onset and those who had >15 minutes (χ^2= 10.316, df= 1, p-value= 0.001). This showed that those who reacted in less than 15 minutes (62%) were more likely to have severe symptoms than those who reacted after 15 minutes (38%).

Figure 3

Severity of symptoms depending on type of exposure



1 child who had skin contact had a mild reaction while the other was severe. 4 patients who ingested traces of food had mild reactions while another 4 had severe reactions and 1 had moderate reactions. 10 had mild, 6 had moderate while 7 had severe symptoms. One who had a full portion had mild while the other had severe symptoms **(Figure 3)**. Only 1 had AAR through inhalation and they had a severe reaction (χ^2= 3.953, df= 8, p-value= 0.861).

Treatment and prognosis

49 (79%) children used antihistamines (Piriton) as their emergency treatment, 8 (13%) used Adrenaline (Epipen) while 5 (8%) used inhaler **(Table 5)**. 21 (34%) patients had severe symptoms.

Table 5

AAR treatment depending on severity

Emergency treatment				**p-value (ANOVA)**
	Mild (A)	**Moderate (B_1)**	**Severe (B_2)**	**(AvsB)**
Antihistamine (n=49)	18 (39%)	13 (24%)	18 (37%)	0.029
Adrenaline (n=8)	2 (14%)	3 (38%)	3 (38%)	
Inhaler (n=5)	5 (100%)	0 (0%)	0 (0%)	

18 (61%) were treated at home using Antihistamine while 3 (50%) were treated with Adrenaline. 3 children who had AARs did not need treatment. 5 subsided spontaneously with treatment, 11 within an hour, 13 in 1-6 hours and 2 within 7-24 hours.

Table 6

AAR treatment and prognosis depending on location

Place of reaction						
	Home	**Friend's house**	**Nursery /childcare**	**School**	**Restaurant/ cafe**	**Total**
Treatment						
Antihistamine	18 (61%)	1 (3%)	3 (13%)	3 (10%)	4 (13%)	29 (100%)
Adrenaline	3 (50%)	0 (0%)	1 (17%)	2 (33%)	0 (0%)	6 (100%)
Prognosis						
Spont. with treatment	4 (80%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	5 (100%)
Spontaneous without	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
Few hours with treat						
<1 hour	7 (64%)	0 (0%)	0 (0%)	2 (18%)	2 (18%)	11 (100%)
1-6 hours	7 (54%)	0 (0%)	3 (23%)	2 (15%)	2 (18%)	13 (100%)
7-24 hours	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
ANE	0 (0%)	0 (0%)	1 (33%)	1 (33%)	1 (33%)	3 (100%)

Relationship between AAR severity and risk factors

For the current wheal size, the frequency of moderate to severe was 48% for those above the median and it was twice those who were below the median (21%). There was statistical significance between those with no AAR and mild to those who had moderate to severe symptoms (χ^2= 5.047, df= 1, p-value= 0.024). This was also the case for Hayfever where there was statistical significance between the no AAR and mild symptoms and; moderate to severe in relation to those who had Hayfever and those who didn"t (χ^2= 5.885, df= 1, p- value= 0.015).

Table 7

The relationship between AAR severity and atopic diseases

AAR severity					*p-value* [a]
	No AAR (A)	**Mild (B_1)**	**Moderate or severe (B_2)**	**Total**	**(A+ B_1vs B_2)**
Gender					
Male	15 (43%)	8 (23%)	12 (34%)	35 (100%)	0.577[b]
Female	12 (44%)	6 (22%)	9 (34%)	27 (100%)	
Age (67 months)					
< 67	10 (33%)	10 (33%)	10 (34%)	30 (100%)	0.572[b]
> 67	17 (53%)	4 (13%)	11(34%)	32 (100%)	
Current wheal size (mm)					
<8	14 (42%)	12 (37%)	7 (21%)	33 (100%)	**0.024**[a]
>8	13 (45%)	2 (7%)	14 (48%)	29 (100%)	
Asthma					
No	18 (51%)	6 (18%)	11 (31%)	35 (100%)	0.423[b]
Yes	9 (34%)	8 (31%)	10 (35%)	27 (100%)	
Recurrent wheeze					
No	26 (45%)	13 (22%)	19 (33%)	58 (100%)	0.417[b]
Yes	1 (25%)	1 (25%)	2 (50%)	4 (100%)	
Hayfever					
No	21 (50%)	11 (26%)	10 (24%)	42 (100%)	**0.015**[a]
Yes	6 (30%)	3 (15%)	11 (55%)	20 (100%)	
Eczema					
No	7 (34%)	7 (33%)	7 (33%)	21 (100%)	0.590[b]
Yes	20 (49%)	7 (17%)	14 (34%)	41 (100%)	
Atopic diseases (total)					
<1	18 (55%)	8 (24%)	7 (21%)	33 (100%)	**0.024**[b]
>1	9 (31%)	6 (21%)	14 (48%)	29 (100%)	

a=χ^2 test b= Fisher exact test

There was however no statistical significance for Gender, Age, Asthma, Recurrent wheeze and Eczema. This showed that there was no difference between the categories in relation to the severity of the symptoms and thus they were not risk factors to AAR severity. **(Table 7)**. There was also no statistical difference between the age at which they got the various atopic diseases and AAR severity (p-value>0.05).

The frequency of moderate to severe was 42% for those who had Peanut allergy while those who didn't was 16% **(Table 8)**. There was statistical significance between those with no AAR and mild to those who had moderate and severe symptoms in relation to those who had peanut allergy and those who didn't (χ^2= 3.999, df= 1, p-value= 0.04).

Table 8

The relationship between AAR severity and other food allergens

AAR severity					*p-value* [a]
	No AAR (A)	**Mild (B_1)**	**Moderate or severe (B_2)**	Total	**(A+ B_1vs B_2)**
Egg					
No (n=13)	6 (46%)	2 (16%)	5 (38%)	13 (100%)	0.466[b]
Yes (n=49)	21 (43%)	12 (24%)	16 (33%)	49 (100%)	
Wheat					
No (n=47)	20 (42%)	13 (28%)	14 (30%)	47 (100%)	0.186[b]
Yes (n=15)	7 (47%)	1 (6%)	7 (47%)	15 (100%)	
Fish					
No (n=43)	19 (44%)	10 (23%)	14 (33%)	43 (100%)	0.480[b]
Yes (n=19)	8 (42%)	4 (21%)	7 (37%)	19 (100%)	
Shellfish					
No (n=51)	22 (44%)	13 (25%)	16 (31%)	51 (100%)	0.288[b]
Yes (n=11)	5 (45%)	1 (10%)	5 (45%)	11 (100%)	
Soya					
No (n=50)	21(42%)	11 (22%)	18 (36%)	50 (100%)	0.359[b]
Yes (n=12)	6 (50%)	3 (25%)	3 (25%)	12 (100%)	
Peanuts					
No (n=19)	9 (47%)	7 (37%)	3 (16%)	19 (100%)	**0.040[b]**
Yes (n=43)	18 (42%)	7 (16%)	18 (42%)	43 (100%)	
Treenuts					
No (n=22)	9 (41%)	8 (36%)	5 (23%)	22 (100%)	0.136[b]
Yes (n=40)	18 (45%)	6 (15%)	16 (40%)	40 (100%)	
Sesame					
No (n=41)	20 (49%)	9 (22%)	12 (29%)	41 (100%)	0.215[b]
Yes (n=21)	7 (33%)	5 (24%)	9 (43%)	21 (100%)	
Food allergies (total)					
<3 (n=35)	17 (48%)	9 (26%)	9 (26%)	35 (100%)	0.101[b]
>3 (n=27)	10 (37%)	5 (19%)	12 (44%)	27 (100%)	

a=χ^2 test b= Fisher exact tes

In contrast, there was however no statistical significance for Egg, Wheat, Fish, Shellfish, Soya, Treenuts, Sesame and total number of food allergies (p-value>0.05). In all the categories, there was no statistical significance between AAR and no AAR. This showed that there was no difference between the categories in relation to the severity of the symptoms and thus they were not risk factors **(Table 17)**. There was also no significance between AAR and no AAR for all categories **(Table 7 and 8)** thus no presentation (p-value>0.05)**.**

Figure 4a

The frequency of AARs with different age groups

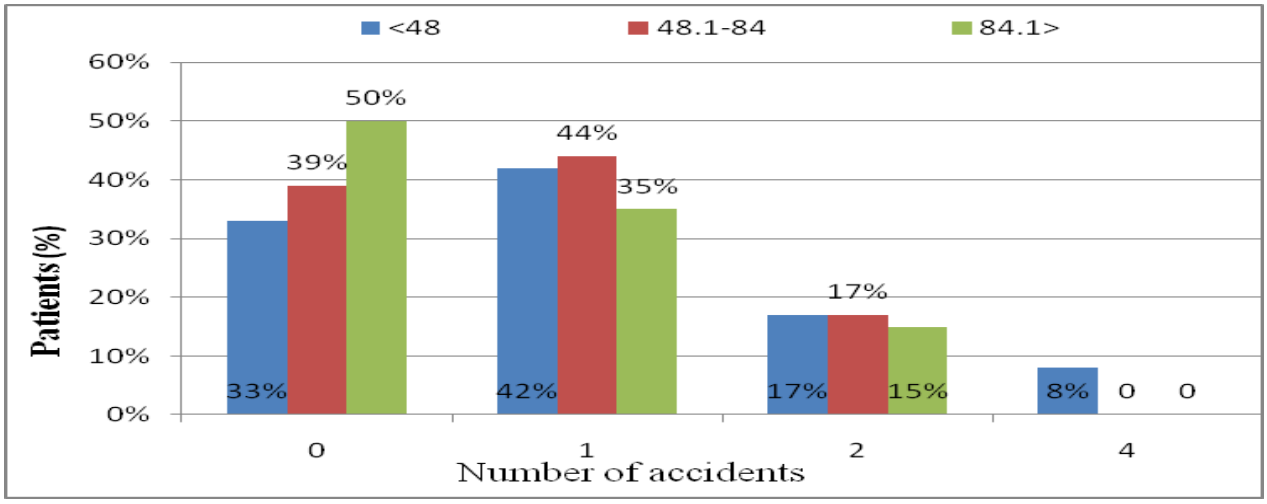


Figure 4b

The number of AARs for the patients above and below the median age

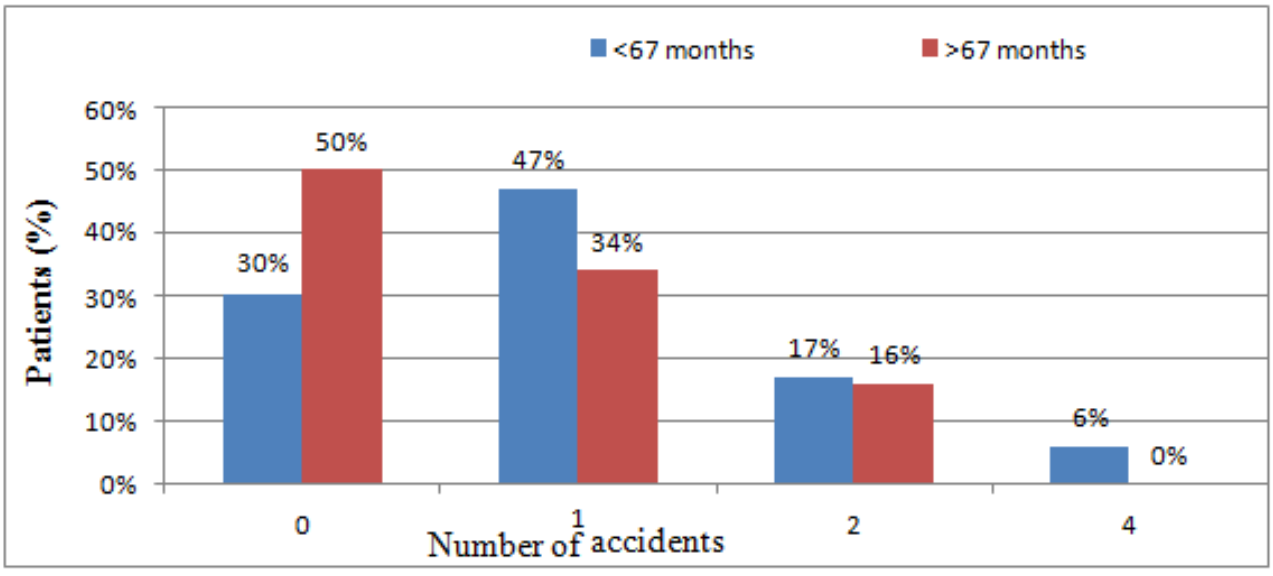


Figure 4: (a) The 1-4 years' age group had the most AARs (51%), 8 children had no AAR, 10 had one, 4 had 2 and 2 had 4 AARs. In the 5-7 years' age group (26%), 7 had no AAR, 8 had one and 3 had 2. And in the 7 and above age group (23%), 10 had no AAR, 7 had only one and 3 had 2 AARs. There was however no statistical significance to number of accidents in relation to age (χ^2= 4.182, df= 6, p-value= 0.652). **(b)** 9 children below the median had no reaction; 14 had one, 5 had 2 and 2 had 4 while those above the median; 16 had no AAR, 11 had one and 5 had 2 AARs. There was no statistical significance between AAR numbers and age, thus no difference between those above and below the median (χ^2= 4.26, df= 3, p-value= 0.235).

DISCUSSION

AAR frequency

The AAR frequency was 57%. This outcome was higher than a similar CMPA AAR cross sectional study carried out in Spain by Boyano-Martinez *et al. (*2009) frequency of 40% and a USA cohort study where the prevalence was 34% {95% CI 0.31-0.37} (Fleischer *et al,* 2012). This may be due to the fact that the sample size for this study was smaller (n= 62) as compared to the studies mentioned (n=88, 512 respectively) hence the high frequency and milk consumption in the UK may be higher than Spain and USA since it is a subsidized food commodity. The difference will however be independent of geographical distribution since the Spain and the USA frequencies were similar.

Other studies showing different food allergies have given lower values than the CMPA studies. Boyano-martinez et al., 2012, showed in an egg allergy study, that the AAR frequency was 21%. Yu *et al.,* 2006 also showed that peanut allergy AAR frequency was 14.3% in the USA and speculated that it was as a result of safer environments, strict food legislation and school awareness campaigns. The sample size (n=252) was large thus the reduced response bias. In North America and Europe, the Peanut allergy AAR prevalence was approximately 50% (Vander leek *et al,* 2000). The high rates were due to high levels of peanut traces and hazelnuts in cookies and chocolates and; lack of proper food labelling (Pele *et al,* 2007). The rates are believed to have gone down in Europe due to the implementation of EU food legislative regulations (Directive 2001/95/EC, 2001; Regulation 2002/178/EC, 2002). The high frequency in this study may have also been due to high milk input into foods, the different types of dairy products and the non-packaged cereal products such as croissants made at home and sold in cafes and restaurants.

Type of food

Majority of the AARs were in the „milk in product" category (51%) and this is due to mislabeling and misreading of labels especially in cases where new recipes had been implemented **(Figure 1)**. Parents are always advised by dietitians to read labels constantly though errors still occur. Studies have shown that in cases of peanut allergy, 54% of parents fail to read or observe the food labels accurately especially in commodities that they are used to purchasing (Joshi *et al,* 2002). Less than 20% had perfect product recognition for milk allergen and this was as a result of the numerous names utilized for milk identification such as casein or whey (Joshi *et al,* 2002). A cross sectional study carried out by Barnett *et al,* 2011 showed that in the recent past, customers were using food labels (allergy box), previous experiences and confidence in manufacturers to make choices on the type of food to purchase though there were requests as observed in this study to have more identifiable specific allergen labelling since some manufacturers are already doing that. A study carried out in Germany, Netherlands and Greece on preferred information strategies for food allergic consumers recommended booklets to provide information on management thus help lower the AAR incidence (Voordouw *et al,* 2011). Peer education on allergens can also help lower risk in homes and school and help children access help during reactions thus lower anaphylaxis (Monk *et al,* 2010).

Cross-contamination in this study had a frequency of 16% **(Figure 1).** A review carried out by Taylor *et al,* 2010 showed that cross-contamination occurs more often than people presume and it can lead to anaphylaxis. The frequency has however not been predetermined and thus difficulty in determining the impact in the population. This was the reason as to why there was no study to compare with in this study. Overall, 3 contaminations occurred at home, 2 in a nursery and one in a restaurant. Direct milk intake was however double the prevalence (33%) of cross contamination and this was as a result of children taking milk on their own without guardian authorization especially at home (58%), forgetfulness from caregivers in nursery/ childcare and teachers in school. Fleisher *et al,* 2012 also showed that 81% of the reactions were accidental reactions due to forgetfulness hence provision of milk products while 1 in 9 of the AARs were intentional with the aim of assessing if the allergy had disappeared.

Route of exposure

The most common route of exposure was oral (89%). Some of the patients, who took traces of the milk allergen, had severe reactions showing that the memory of the immune system was quite high (Fiocchi et al, 2010). Two patients had AAR from skin contact and one by inhalation. Mild AARs were 43%, and this was lower than the Spain CMPA AAR study (53%) due to the fact

that more children with a wheal size above the median had severe symptoms (Boyano-Mattinez *et al,* 2009). An egg allergy study carried out in Spain showed that the mild AARs were 42% while the moderate AARs were more frequent (50%) (Boyano- artinez *et al,* 2012). Yu *et al,* 2006, showed that in Canada the peanut allergy mild AAR prevalence was 31%. The results were similar to the Mehl *et al,* 2005 study carried out in Germany (21%). In both the severe symptoms were high and this may be due to the nature of the allergens. The AAR severity Classification, study design and age of the participants in the studies could also vary bringing about big differences in the findings.

Place of reaction

The main place of reaction was home (60%) **(Figure 2)**. This led to rejecting the hypothesis that most reactions occurred in school and replicated the findings from a nationwide survey carried out in Germany by Mehl *et al,* 2005 that showed that majority of the anaphylactic reactions occurred at home (58%). This was against most reports which stated that the frequency was more in school (Sicherer *et al,* 2001, Fuhlong *et al,* 2001). This may be due to other siblings at home who can have milk and/or the children have easy access to the fridge as compared to school since in this study, 71% of the children who were below the median age (5 years) had their AAR at home and there was none in school. The parents‟ education background, working status and age may also influence AAR frequency though in this study we could not include that due to lack of ethical approval since the study was an audit. Yu *et al,* 2006, showed that majority of the parents were in their 40s, 77% were employed and 60% had completed a university degree. They therefore concluded that it contributed to the low AAR due to better parent understanding of the implications of allergy. Working can also lead to more AAR due to less supervision and this may be the case for the children in the 1-4 years' age group who had the most AARs (51%) **(Figure 4)**. Fleischer *et al,* 2012 showed that a half of the AARs were caused by parents while the other by caregivers such as teachers, babysitters and grandparents. This could also apply in our study given that some patients were brought in by care providers while the parents were rushing to hospital from work though this is an assumption since there is no data to prove this.

Symptoms

A Danish cohort study showed that 60% of children had gastrointestinal symptoms, 50% with skin problems and 20% with respiratory (Fiocchi et al, 2010) while in Norwegian cohort, 48% experienced pain, 32% gastrointestinal, 27% respiratory and 4.5% eczema (Kvenhsangen *et al,* 2008). A Finnish cohort study also showed that 46% had urticaria, 90% had eczema, 52% diarrhea, 31% respiratory and 3% respiratory while in a British study, 33% had eczema, 33% diarrhea and 24% vomiting (Fiocchi et al, 2010). In this study, the cutaneous symptoms observed were (47%) (22 hives and rash 5). The respiratory symptoms were (16%) (loss of voice 5, cough 3, wheeze 2) while gastrointestinal were (11%) (vomiting 4, diarrhea 2, abdominal pain 1). This clearly supported the evidence that CMPA clinical presentation may be dependent on geographical distribution (Fiocchi et al, 2010).

Treatment

Antihistamine (79%) was the main emergency treatment, 13% were treated using Adrenaline and 8% using inhaler. 21 (34%) patients had moderate to severe symptoms. 18 patients were treated using Antihistamine though in anaphylaxis it has been shown not to be effective in improving breathing symptoms (Sicherer, 2006), while 3 who had anaphylaxis were rushed to hospital where Adrenaline was administered **(Table 7 and 8).** 3 out of 16 mild reactions were treated using Adrenaline. This showed wrong drug administration. Fleischer *et al,* 2012 showed in a 3-year cohort study that 11% were severe symptoms and 30% of which, were treated using Adrenaline. They speculated that the reason for the under treatment was fear of administration and lack of severity recognition. This could also be the case in this study. The egg allergy (Boyano-Martinez *et al,* 2012) and the CMPA studies observed that there were no hospitalizations though the overall mode of treatment was not shown except in those exposed to allergen orally. The peanut allergy study showed that 57% had moderate to severe reactions but only 20% were treated using Adrenaline. They also observed that 52% sought medical attention in the participants and 32% in the non-participants (Yu *et al,* 2006). In a Germany study, only 20% received Adrenaline in the 30% who received medical attention and majority received Corticosteroids and antihistamines (Mehl *et al,* 2005). This

collectively shows the urgent need for training on Adrenaline administration and the symptoms severity recognition.

Risk factors

Summers *et al,* 2008 showed in a 12-year study of 1094 patients that coexisting atopic diseases were risk factors to anaphylaxis in peanut and tree nuts allergies. This was accurate for it showed temporal association of anaphylaxis to atopic diseases, the sample size was really large thus increased validity and there was no response bias since there was IgE analysis on every follow up. These results were also replicated in this study whereby having more than one atopic disease was associated with AAR severity (p-value= 0.024) hence we accepted the hypothesis.

The other risk factors were current wheal size (mm), Hayfever and Peanut allergy (p-value=0.024, 0.015, 0.04 respectively) **(Table 7 and 8)**. This supported studies that showed that Hayfever was associated to CMPA sensitization (Saarinen *et al,* 2005, Skripak *et al,* 2007) and replicated the milk (Boyano-Martinez *et al,* 2009) and egg (Boyano-Martinez *et al,* 2012) Spain study which showed that sIgE (kU_A/L) levels were associated to AAR severity. In this study we had only 17 patients who had their sIgE results so we used the current wheal size which is similar to IgE. Clark *et al,* 2003 however showed in a nut allergy of 1000 patients that there was no wheal size and sIgE association to AAR severity and his findings were replicated in Summers *et al,* 2008 peanuts and tree nuts allergy study. This may be attributable to the fact that most of the nuts AARs are usually severe as shown in a single- center study that the clinical thresholds of peanuts and hazelnuts were higher than those of milk and egg while using standardized food challenges (Eller *et al,* 2012), and may therefore lead to the conclusion that their AAR severity is independent of wheal size or sIgE unlike egg and milk. It may also explain the association of Peanut allergy to CMPA severity since other studies have not tested this association.

Asthma in this study was not associated to AAR severity as shown in the other studies mentioned above and this may be due to the fact that very few patients had been diagnosed with asthma and 34% who had asthma had no AARs (**Table 7**). The DRACMA guidelines showed that Hayfever occurs in about 70% of CMPA reactions while asthma 8%. This gave more evidence to this study's results that Hayfever was associated to AAR severity while asthma was not (Fiocchi et al, 2010). Egg allergy was also not associated to AAR severity despite studies showing that it predicts the persistence of CMPA (Saarinen *et al,* 2005). This may be due to the fact that majority (43%) who were egg allergic had no AAR though it was observed that those who were, 16 (76%) had moderate to severe AAR reactions while there were only 5 (24%) who were not egg allergic.

AAR severity depending on age

CMPA has been shown to persist with age only in a minority of patients and this depends on the sIgE levels (Vandeplas *et al,* 2007). This led to the analysis of the severity of symptoms and the number of accidents in accordance to age **(Figure 3 and 4)**. The assumption was that children under the age of 5 had fewer accidents since they are dependent on parents‟ food decision and those more than 5 are in school and hence their diet will be influenced by the friends and school catering services and; Children over 11 years are more prone since they are in high school and thus peer pressure is critical and eating out. There was, however, no significant difference between the age of the patients and the severity of the symptoms or the number of accidents and most accidents occurred at home in the whole study with only 5 in school. This might be a result of the small numbers in each age group. These results replicated the findings of Boyano-Martinez *et al,* (2008) who also showed that there was no statistical significance (p-value=0.115) between age and severity of symptoms in CMPA. Boyano-Martinez *et al,* 2012 showed that there was significant difference between those who had AAR and those who didn't in relation to age (p-value =0.02). This showed that age was a determining factor on the AAR exposure and may be due to the fact that older children may tend to be cautious due to previous AAR experiences. In this study however, there was no statistical difference (p-value>0.05).

Limitations

Sample size was relatively small since the sample collection duration was short though the results may be accurate in comparison to other similar studies carried out.

Self-reported thus prone to response and recall bias though has been shown to be important according to the DRACMA guidelines for public health management.

Language barrier for 1 parent who was not conversant in English thus had to be excluded

Confounding factors -The other type of food allergies could also serve as confounding factors in patients who ate in restaurants though they were only two in this study and those who had unpackaged products such as croissants.

Limited to one hospital and thus need for a large study involving the major hospitals in the UK that would replicate the results of this study and other studies carried out in the past thus show more insight on AAR frequency and risk factors that influence its severity.

CONCLUSION

The severity of AAR frequency for CMPA in this study was high (57%) which was different from the AAR frequency in Spain and USA to UK and this is brought about by the small sample size, high availability and not due to geographical distribution. The risk factors for AAR severity were Hayfever, Peanut allergy, having more than one atopic disease and current wheal size thus acceptance of the hypothesis that the AAR severity was dependent on atopic diseases and other food allergies. Most of the allergies in this study occurred at home (35.5%) thus rejecting the hypothesis that most reactions occur in school. This is despite the increasing public sector awareness on food allergies. Oral was also the main route of exposure (89%) hence the need for emphasis on total oral intake avoidance. 21 (34%) children had moderate to severe reactions and only 3 were treated with Adrenaline while 3 out of 16 mild reactions were treated with Adrenaline.

RECOMMENDATIONS

- Implications on research- Sample size was relatively small since the sample collection duration was short though the results may be accurate in comparison to other similar studies carried out. An intensive study should however be done covering major hospitals in the UK and other countries to ascertain the study's findings.
- Implications on practice- A follow-up study can also be carried out so as to lower response bias and be useful in allergy management for the healthcare professionals and DRACMA public awareness campaigns.
- Implications on practice - carers, siblings and peers education on CMPA and its management can also help lower risk in homes and school and help children access help during reactions thus lower AAR risk.

REFERENCES

Albin, S. (2012). *Food Allergies: Dangers Still Lurk for Food-Allergic Kids.* [ONLINE] Available:http://abcnews.go.com/Health/AllergiesFood/food-allergy-emergencies-accident/story?id=16630948#.UBSDo_VmP21. Last accessed 28th July 2012.

Bahna, S. L. (2002). Cow's milk allergy versus cow milk intolerance. *Annals of Allergy, Asthma and Immunology,* 89(6), 56-60.

Barnett, J., Leftwich, J., Muncer, K., Grimshaw, K., Shepherd R, Raats MM, Gowland MH, Lucas J.S.(2011). How do peanut and nut-allergic consumers use information on the packaging to avoid allergens? *Allergy*, 66 (7), 969-78.

Bauchau, V. and Durham, S. R. (2005). Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy,* 60 (3), 350–353.

Boyano-Martinez, T., Garcia-Ara, C., Pedrosa, M., Diaz-Pena, J. M. (2009). Accidental Allergic Reactions in Children Allergic to Cow"s Milk Proteins. *Journal of Allergy and Clinical Immunology*, 123 (1), 883-8.

Boyano-Martínez, T., Pedrosa, M., Quirce, S., García-Ara, C. (2012). Accidental Allergic Reactions in Children Allergic to Hen"s Egg. *Journal of Investigational Allergology and Clinical Immunology*, 22 (2), 109-115.

Brozek, J. L., Terracciano, L., Compalati, E., Santesso, N. (2012). Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. *Clinical Experimental Allergy,*42(3): 363-374.

Buchanan, A. D., Green, T. D, Jones, S. M., Scurlock, A.M., Christie, L., Althage, K. A., Steele, P. H., Pons, L., Helm, R. M.,

Lee, L. A., Burks, A. W. (2007). Egg oral immunotherapy in nonanaphylactic children with egg allergy. *Journal of Allergy and Clinical Immunology*, 119 (1), 199-205.

Busse, P. J, Jarvinen, K. M., Vila, L., Beyer, K., Sampson, H. A. (2002). Identification of sequential IgE-binding epitopes on bovine alpha(s2)-casein in cow's milk allergic patients. *International Archives of Allergy and Immunology*, 129 (1), 93–96.

Clark, A. T. and Ewan, P. W. (2003). Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. *Clinical and Experimental Allergy*, 33 (8), 1041–1045.

Chehade, M. (2007). IgE and non-IgE-mediated food allergy: treatment in 2007. *Current Opinion in Allergy and Clinical Immunology,* 7 (3): 264-268.

Crespo, J. F., Pascual, C., Dominguez, C., Ojeda, I., Muñoz, F. M, Esteban, M. M.(1995), Allergic reactions associated with airborne fish particles in IgE-mediated fish hypersensitive patients. *Allergy,* 50 (3), 257–261.

Domínguez, C., Ojeda, I., Crespo, J. F, Pascual, C., Ojeda, A., Martín-Esteban, M. (1996). Allergic Reactions Following Skin Contact With Fish. *Allergy and Asthma Proceedings,* 17 (2), 83-87.

Du Toit, G., Santos, A., Roberts, G., Fox, A. T., Smith, P., Lack, G. (2009). The diagnosis of IgE-mediated food allergy in childhood. *Pediatric Allergy and Immunology*, 20 (4), 309–319.

Eller, E. T., Hansen, K., Bindlev-Jensen, C. (2012). Clinical thresholds to egg, hazelnut, milk and peanut: results from a single-center study using standardized challenges. *Annals of Allergy, Asthma and Immunology,* 108(5), 332-336.

FAI (Food Additives and Ingredients Association), (2008). *Food allergy and intolerance.* [ONLINE] Available: http://www.faiusa.org/page.aspx?pid=379 Last accessed 13th July 2012.

Falcao, H., Lunet, N., Lopes, L., Barros, H. (2004). Food hypersensitivity in Portuguese adults. *European Journal of Clinical Nutrition,* 58(12), 1621-1625.

Fiocchi, A., Schünemann, H., Restani, P., Beyer, K., Bozzola, M. (2010). *Diagnosis and rationale for action against cow's milk allergy guidelines.* [ONLINE] Available at: http://www.worldallergy.org/publications/WAO_DRACMA_guidelines.pdf Last accessed 6th August 2012.

Fleischer, D. M., Perry, T. T., Atkins, D., Wood, R. A., Burks, W., Jones, S. M., Henning, A. K.Stablein, D., Sampson, H. A. (2012). Allergic Reactions to Foods in Preschool-Aged Children in a Prospective Observational Food Allergy Study. *Pediatrics*, 130 (1): e25-32

Furlong, T. J, DeSimone, J., Sicherer, S. H. (2001). Peanut and tree nut allergic reactions in restaurants and other food establishments. *Journal of Allergy and Clinical Immunology*, 108 (5), 867– 870.

Garcı´a, A. C., Boyano-Martı´nez, T., Dı´az-Pena, J. M., Martı´n-Muñoz, F., Reche-Frutos, M., Martin-Esteban, M. (2001). Specific IgE levels in the diagnosis of immediate hypersensitivity to cows" milk protein. *Journal of Allergy and Clinical Immunology*, 107 (1), 185-190.

Greer, F. R., Sicherer, S. H., Burks, A. W. (2008). Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*, 121(1), 183-91.

Gupta, R., Sheikh, A., Strachan, D. P., Anderson, H. R. (2007). Time trends in allergic disorders in the UK. *Thorax*, 62 (1), 91–96.

R.S. Gupta, C.M. Warren, B.M. Smith, J. Jiang, J.A. Blumenstock, M.M. Davis, et al. Prevalence and severity of food allergies among US adults. JAMA Netw Open, 2 (2019), Article e185630

Heine, R. G., Elsayed, S., Hosking, C. S., Hill, D. J. (2002). Cow"s milk allergy in infancy. *Current Opinion in Allergy and Clinical Immunology,* 2(3), 217– 225.

Hill, D. J., Murch, S. H., Rafferty, K., Wallis, P., Green, C. J. (2007). The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic

review. *Clinical and Experimental Allergy,* 37(6), 808-822.

Holt, P. G. and Sly, P. D. (2007). Th2 cytokines in the asthma late-phase response. *Lancet,* 370 (9596), 1396–1398.

Host, A., and Halken, S. (2004). Hypoallergenic formulas--when, to whom and how long: after more than 15 years we know the right indication! *Allergy,* 59 Suppl 78, 45-52.

Ihloff, W. (2008). *File: Allergy skin testing. JPG - Wikipedia, the free encyclopedia*. [ONLINE] Available at: http://en.wikipedia.org/wiki/File:Allergy_skin_testing.JPG. Last accessed 26th June 2012.

Joshi, P.S., Mofidi, S. H., Sicherer, S. H. (2002). Interpretation of commercial food ingredient labels by parents of food-allergic children. *Journal of Allergy and Clinical Immunology*, 109 (1), 1019–1021.

Kraneveld, A. D, Sagar, S., Garssen, J., Folkerts, G. (2012). The two faces of mast cells in food allergy and allergic asthma: the possible concept of Yin Yang. *Biochimica et Biophysica Acta*, 1822 (1), 93-9.

Kvenshagen, B., Halvorsen, R., Jacobsen, M. (2008). Adverse reactions to milk in infants. *Acta Paediatrica*, 97 (2), 196–200.

Kwong, K. Y., Eghrari-Sabet, J. S., Mendoza, G. R., Platts-Mills, T., Horn, R. (2011). The benefits of specific immunoglobulin E testing in the primary care setting review. *Americal Journal of Managed Care,* 17:S447-59.

Lucas, J. S., Lewis, S. A., and Hourihane, J. O. (2003). Kiwi fruit allergy: A review. *Pediatric Allergy and Immunology*, 14 (6), 420–428.

Macdougall, C. F., Cant, A. J., Colver, A. F. (2002). How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Archives of Disease in Childhood,* 86 (4), 2236-9.

Mehl, A., Wahn, U., Niggemann, B. (2005). Anaphylactic reactions in children – a questionnaire based survey in Germany. *Allergy,* 60 (3), 1440–1445.

Monks, H., Gowland, M. H., MacKenzie, H., (2010). How do teenagers manage their food allergies? *Clinical and Experimental Allergy,* 40(10), 1533–40.

Noimark, L. and Cox, H. E. (2008). Nutritional problems related to food allergy in childhood. *Pediatric Allergy and Immunology*,19 (2), 188–195.

Nowak-Wegrzyn, A., Bloom, A. K., Sicherer, S. H., Shreffler, W. G., Noone, S., Niya, R.N. (2008). Tolerance to extensively heated milk in children with cow's milk allergy. *Journal of Allergy and Clinical Immunology*, 122 (2), 342-347.

Passalacqua, G., Landi, M., Pajno, G. B. (2012). Oral immunotherapy for cow's milk allergy. *Journal of Allergy and Clinical Immunology*, 12 (3) , 271-277.

Pele, M., Brohée, M., Anklam, E., Arjon, V. H. (2007). Peanut and hazelnut traces in cookies and chocolates: Relationship between analytical results and declaration of food allergens on product labels. *Food Additives and Contaminants,* 24 (12), 1334- 1344.

Pereira, B. C., Venter, J., Grundy, B., Clayton, S. H., Arshad, T. (2005). Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. *Journal of Allergy and Clinical Immunology*, 116 (4), 884– 892.

Pessler, F.and Nejat, M. (2004). Anaphylactic reaction to goat's milk in a cow's milk- allergic infant. *Pediatric Allergy and Immunology,* 15(2), 183-185.

Restani, P., Beretta, B., Fiocchi, A. (2002). Cross-reactivity between mammalian proteins. *Annals of Allergy, Asthma and Immunology,* 89(6), 11-15.

Saarinen, K. M., Pelkonen, A. S., Mäkelä, M. J., Savilahti, E. (2005). Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *Journal of Allergy and Clinical Immunology*, 116 (4), 869-75.

M. Sasaki, J.J. Koplin, S.C. Dharmage, M.J. Field, S.M. Sawyer, V. McWilliam, et al. Prevalence of clinic-defined food allergy in early adolescence: the SchoolNuts study J Allergy Clin Immunol, 141 (2018)

Skypala, I. and Ventor, C. (2009). *Food hypersensitivity*. United Kingdom: John Wiley and Sons Ltd. p120-264.

Sicherer, S. H., Furlong, T. J., DeSimone, J.,

Sampson, H. A. (2001). The US peanut and tree nut allergy registry: characteristics of reactions in schools and day care. *Journal of Pediatrics,* 138 (4), 560–565.

Sicherer, S. H. (2006). *Understanding and Managing Your Child's Food Allergies*. 1st ed. Baltimore: Johns Hopkins University Press.

Skripak, J. M., Matsui, E. C., Mudd, K., Wood, R. A. (2007). The natural history of IgE-mediated cow's milk allergy. *Journal of Allergy and Clinical Immunology*, 120 (5), 1172-7.

Steinke, M., Fiocchi, A., Kirchlechner, V., Ballmer-Weber, B., Brockow, K., Hischenhuber C (2007). Perceived food allergy in children. A report on a representative telephone survey in 10 European countries. *International Archives of Allergy and Immunology*, 143 (4), 290-5.

Strobel, S. (2011). Immune function, food allergies and intolerance. In: Geissler, C; Powers, H. *Human nutrition*. 12th ed. London: H.M.S.O. p509-532.

Summers, C. W., Pumphrey, R. S., Woods, C. N, McDowell, G. (2008). Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *Journal of Allergy and Clinical Immunology*, 121(3), 632-638.e632.

Tariq, S. M., Matthews, S. M., Hakim, E. A. and Arshad, S. H. (2000). Egg allergy in infancy predicts respiratory allergic disease by 4 years of age. *Pediatric Allergy and Immunology,* 11 (3), 162–167.

Taylor, S., and Baumert, J. (2010). Cross-Contamination of Foods and Implications for Food Allergic Patients. *Current Allergy and Asthma Reports*, 10(4): 265-270.

Vandenplas, Y., Koletzko, S., Isolauri, E., Hill, D., Oranje, A. P., Brueton, M., Staiano, A., Dupont, C. (2007). Guidelines for the diagnosis and management of cow's milk protein allergy in infants. *Archives of Disease in Childhood*, 92 (10), 902-8.

Vander Leek, T. K., Liu, A. H., Stefanski, K., Blacker, B., Bock, S. A. (2000). The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *Journal of Pediatrics*, 137(6), 749– 755

Vanto, T., Helppila, S., Juntunen-Backman, K., Kalimo, K., Klemola, T., Korpela, R., (2004). Prediction of the development of tolerance to milk in children with cow's milk hypersensitivity. *Journal of Pediatrics*, 144 (2), 218–222.

Vassilopoulou, E., Konstantinou, G., Kassimos, D., (2008). Reintroduction of cow's milk in milk-allergic children: safety and risk factors. *International Archives of Allergy and Immunology,* 146(2), 156–61.

Voordouw, J., Cornelisse-Vermaat, J.R., Pfaff, S., Antonides ,G., Niemietz, D., Linardakis, M., Kehagia, O., Frewer, L.J. (2011). Preferred information strategies for food allergic consumers. A study in Germany, Greece, and The Netherlands. *Food Quality and preference,* 22 (4), 384-390.

William, S. (2008). *File:Epipen.jpg - Wikipedia, the free encyclopedia*. [ONLINE] Available at: http://en.wikipedia.org/wiki/File:Epipen.jpg Last accessed 27th June 2012.

Woods, R. K., Thien, F., Raven, J., Walters, D. M. (2002). Prevalence of food allergies in young adults and their relationship to asthma, nasal allergies, and eczema. *Annals of Allergy, Asthma and Immunology,* 88(2), 183-189.

Yamada, C., Izumi, H., Hirano, J., Mizukuchi, A., Kise, M., Matsuda, T., Kato, Y. (2005). Degradation of soluble proteins including some allergens in brown rice grains by endogenous proteolytic activity during germination and heat-processing. *Bioscience, Biotechnology, and Biochemistry*. 69 (10), 1877-83.

Young, E., Stoneham, M. D., Petruckevitch, A., Barton, J., Rona, R. (1994). A population study of food intolerance. *Lancet*, 343(8906), 1127–1130.

Yu, J. W., Kagan, R., Verreault, N., Nicolas, N., Joseph, L., Pierre, Y., Clarke, A. (2006). Accidental ingestions in children with peanut allergy. *Journal of Allergy and Clinical Immunology,* 118 (2), 466-472.