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FOOD-INDUCED FATAL ANAPHYLAXIS:

FROM EPIDEMIOLOGICAL DATA TO GENERAL PREVENTION STRATEGIES

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Abstract:

Background. Anaphylaxis hospitalisations are increasing in many countries, in particular for medication and food triggers in young children. Food-related anaphylaxis remains an uncommon cause of death, but a significant proportion of these are preventable.

Aim. To review published epidemiological data relating to food-induced anaphylaxis and potential risk factors of fatal and/or near-fatal anaphylaxis cases, in order to provide strategies to reduce the risk of severe adverse outcomes in food anaphylaxis.

Methods. We identified 32 published studies available in MEDLINE (1966–2017), EMBASE (1980–2017), CINAHL (1982–2017), using known terms and synonyms suggested by librarians and allergy specialists.

Results. Young adults with a history of asthma, previously known food allergy particularly to peanut/tree nuts are at higher risk of fatal anaphylaxis reactions. In some countries, cow's milk and seafood/fish are also becoming common triggers of fatal reactions. Delayed adrenaline injection is associated with fatal outcomes, but timely adrenaline alone may be insufficient. There is still a lack of evidence regarding the real impact of these risk factors and co-factors (medications and/or alcohol consumption, physical activities, and mast cell disorders).

Conclusions. General strategies should include optimization of the classification and coding for anaphylaxis (new ICD 11 anaphylaxis codes), dissemination of international recommendations on the treatment of anaphylaxis, improvement of the prevention in food and catering areas and, dissemination of specific policies for allergic children in schools. Implementation of these strategies will involve national and international support for ongoing local efforts in relationship with networks of centres of excellence to provide personalized management (which might include immunotherapy) for the most at-risk patients.

Key words: anaphylaxis, fatality, fatal anaphylaxis, food-induced anaphylaxis, mortality, mortality rate

Introduction

Trends in anaphylaxis epidemiology are often assessed using health-data relating to anaphylaxis admissions. Estimates can differ widely depending on a number of variables. For instance, in Europe, the lifetime prevalence of anaphylaxis is estimated to be 0.3% (95% CI 0.1-0.5) (1), but higher in the United States of America at 1.6 to 5.1% (2,3). Hospitalisations due to anaphylaxis are also increasing in many countries (4-6), in particular in young children; these increases are noted particularly for medication and food triggers (5-6). These reported increases probably reflect a true increase in the prevalence of allergic disease, but are also confounded by cumulative incidence of anaphylaxis, better awareness and recognition of anaphylaxis, and changes in anaphylaxis coding, in part due to modifications in the international classification of diseases (5,7-9).

Anaphylaxis is an uncommon cause of death (10-12), particularly for food, and is difficult to study because it is typically a community event, occurring outside the hospital environment. Severe anaphylaxis is unpredictable, which contributes to the high adverse impact of the diagnosis on health-related quality of life of individuals at risk of anaphylaxis. Estimates of anaphylaxis mortality epidemiology are generally based on retrospective case series, post-mortem studies or population-based studies based on national or institutional administrative databases (5,8,13-19). Using these methods, the case fatality rate is estimated to be 0.65% to 2% (5,8,13-19). Data from National Vital Statistics Systems can be used to facilitate comparisons between different geographical zones and time periods, so long as the data have been compiled using the same methods and according to the same standards. The World Health Organization (WHO) has issued international guidance on data collection, coding and classification, and statistical presentation of causes of death. In most countries, mortality statistics are routinely compiled through the International Classification of Diseases (ICD) and follows the regulations and recommendations adopted by the World Health Assembly (WHA).

The aim of this article is to review published epidemiological data relating to food-induced anaphylaxis and potential risk factors of fatal and/or near-fatal food-related anaphylaxis cases, in order to provide strategies to reduce the risk of severe adverse outcomes in food anaphylaxis.

Methods

We identified published studies available in MEDLINE (1966–2017), EMBASE (1980–2017), CINAHL (1982–2017). Search terms were generated using known terms and synonyms suggested by librarians and allergy specialists to capture all text words and Medical Subject Heading (MeSH) terms. We included 32 reports describing epidemiological data and risk factors on fatal food-related anaphylaxis cases and/or mortality and strategies to reduce food-related anaphylaxis mortality.

Studies were included if they provided epidemiological data or risk factors on fatal food-related anaphylaxis cases and/or anaphylaxis mortality, or strategies to reduce food-related anaphylaxis mortality. Studies were reviewed by two authors (GP, LKT), who screened full-text articles; the final version was finally approved by all co-authors and counted with 32 documents. Two authors (GP,

LKT) extracted data on the study design, population characteristics, rates of anaphylaxis mortality, food triggers, location of occurrence of the fatal event, treatment.

Results

Scope of the problem: Foods as a cause for fatal anaphylaxis

The mortality rate for all-cause anaphylaxis is less than 1 death per million inhabitants per year over the last 20 years (5,8,13-19) (Table 1). However, this estimate is likely to be lower than the true rate of fatal anaphylaxis, due to under-diagnosis and under-notification (7-9).

In the majority of countries, the most common causes for fatal anaphylaxis are medication/iatrogenic triggers and foods; foods are the most common elicitors in children and young adults. Fatal food-induced anaphylaxis rates range from 0.03 to 0.3 deaths per million inhabitants per year (5,8-13-19), (Table 1). However, these data are impacted by a significant proportion of fatalities in which the allergic trigger cannot be determined.

Reassuringly, trends in anaphylaxis mortality are stable in the majority of studies, although recent Australian data reported that incidence of fatal anaphylaxis has doubled from 1997 to 2013 (17,19). Conversely, mortality is reported to have decreased in France, by an average of 2% per annum (13). Given the increase in occurrence of non-fatal anaphylaxis, the lack of increase in fatal outcomes may be due to improved recognition and treatment, in part driven by the dissemination of anaphylaxis guidelines and greater availability of adrenaline auto-injectors (AAI) which might increase public awareness (5).

Understanding the specifics of mortality data can support the identification of patients at highest risk of fatal and near-fatal events, facilitating the implementation of prevention measures.

Risk-factors associated with food anaphylaxis mortality

The available data from published registries of fatal food anaphylaxis has provided some further insights into risk factors for severe, fatal outcomes (Table 2) (14,15,17,20-25). Similarities between all the studies as well as differences in epidemiological patterns helped us to described these risk factors (Tables 1 and 2).

Food-induced anaphylaxis deaths are most frequent in adolescents and younger adults

The highest rates of non-fatal food-related anaphylaxis occur in young children (26), but fatal outcomes are rare in this age group (5,13). The greatest risk appears to be in adolescence and young adulthood (5). It has been proposed that this reflects increased risk taking in this age group, however at least in the United Kingdom (UK), the increased risk persists into the fourth decade of life where arguably, risk-taking is less common: thus, there may be an age-dependent physiological predisposition to fatal food anaphylaxis in this age group (5,27). Non-food allergens are more common as a cause of fatal anaphylaxis in mid-late adulthood; this is probably due to associated comorbidities (especially cardiovascular and neurological diseases) and polypharmacy.

Most cases of fatal food anaphylaxis occur in individuals with a history of asthma with a previously diagnosis of food allergy

The majority of fatal food anaphylaxis occurs in individuals known to be food-allergic; less than half have received before a prescription of an AAI (17,20,22-25) (Table 2). A history of asthma is present in more than two-thirds of cases and may explain the tendency of fatal food-related anaphylaxis to primarily be due to bronchospasm and laryngeal angioedema, with cardiovascular collapse generally occurring secondary to hypoxia and respiratory arrest (21-24). This is in contrast to non-food causes, where primary cardiovascular arrest is more common (23,24).

Peanuts and tree nuts are the most common causes of fatal food anaphylaxis, but seafood and cow's milk are also common triggers

The most frequent food allergens involved in lethal anaphylaxis at any age are peanut and tree nuts, accounting for 55% to 87% of deaths (14,15,17,20-25) (Table 2). However, other allergens are also implicated. In the UK fatal anaphylaxis registry, cow's milk was the most common cause of

fatal anaphylaxis in children (5) (Table 2), and seafood accounts for 50% of Australian fatalities due to food (17). In the European registry of paediatric anaphylaxis cases, peanut was identified in 16% of cases, nuts in 15% and cow's milk in 8% (28). Food triggers also vary with country-specific consumption patterns. For instance, goat and sheep milk are responsible for 13% of anaphylaxis deaths in France (25) (Table 2).

Delayed adrenaline injection is often reported in fatal food anaphylaxis cases.

A delay in adrenaline injection has been identified as a feature in several reports of fatal food anaphylaxis (20-24). Nevertheless, fatal reactions can occur despite timely administration of adrenaline – in the UK Fatal Anaphylaxis registry, up to one third of fatalities occurred despite timely adrenaline (23,24). This may be related to the incorrect administration of adrenaline (e.g. insufficient dose or inappropriate route), or more likely, by the need for additional ongoing interventions (further adrenaline, fluid resuscitation) in severe cases.

Discussion of knowledge gaps and general prevention strategies

Knowledge gaps relating to impact of co-morbidities and "co-factors".

Although personal history of asthma is reported in the majority of anaphylaxis fatalities, the association between these conditions is still not clear. Individuals with food allergy are more likely to have a history of asthma than the general population (29). In the European registry of 1970 paediatric anaphylaxis cases, 23% of children had a history of asthma (28). Among 1094 patients with an allergy to peanut or nuts, severe bronchospasm during food-induced anaphylaxis was all the most frequent when the patient had a history of severe asthma (OR 6.8; 95% CI: 4.1-11.3) but also a history of a mild asthma (OR 2.7; 95% CI: 1.7-4.0) (30). Of note, in the UK Fatal Anaphylaxis Registry, the majority of cases did not have evidence of poorly controlled asthma (R. Pumphrey, personal communication). There is a need to better clarify the real impact of asthma as a risk factor for fatal anaphylaxis. A history of asthma alone is a very poor predictive factor for severe outcomes, as asthma is so common amongst food-allergic individuals: the vast majority of food-allergic patients will never have a severe anaphylaxis reaction. There is insufficient data to assess whether poorly controlled asthma is the most important risk factor. The impact of other atopic comorbidities (atopic dermatitis and allergic rhinitis) have also been proposed as a risk factor (30), although this probably reflects underlying atopy.

Physical activity and the consumption of alcohol or illicit substances consumption are identified in about 20% of studies (17,25) (Table 2) but these co-factors are also reported for non-lethal anaphylaxis (31,32), and their contribution towards fatal outcomes remains unclear. Although mast cell disorders are known risk factors for anaphylaxis, they have not been addressed by the majority of epidemiological studies and their specific role in fatal food anaphylaxis is unclear. A higher risk of severe all-causes anaphylaxis (death, cardiac arrest, need for invasive mechanical ventilation or vasopressor drugs, admission to the intensive care unit, and length of stay) was also associated with age >50 years or having experienced cardiac arrhythmia, coagulation disorder, associated fluid-electrolyte imbalance, chronic pulmonary disease in more than 5000 patients hospitalized for anaphylaxis in Spain (33). In a cohort study of 38000 patients hospitalized for anaphylaxis in the United-States, 11.6% of patients had severe all-causes anaphylaxis (0.45% a near-fatal anaphylaxis); age > 65 years, medication as a trigger, and presence of comorbid conditions (specifically cardiac and lung disease) were also associated with significantly higher odds of severe reaction (hospital admission, intensive care unit admission, or intubation or being a near-fatal reaction) (34).

As compared with severe asthmatic patients, we need to better phenotype food-allergic patients would support: (I) specific strategies of management, (II) identification of risk factors associated with recurrent anaphylaxis reactions or occurrence of near-fatal and fatal reactions during the follow-up and (III) determine who are those at a particular risk of fatal reactions.

General strategies to reduce near-fatal and fatal food-induced anaphylaxis

Kastner et al. identified and classified more than 200 gaps at the level of physicians, patients, and the community: knowledge and anaphylaxis management (physician and patients), follow-up care (physicians), and quality of life of patients and caregivers (35). Findings from our review on epidemiological data and risk-factors of fatal anaphylaxis cases could be used to provide a basis for developing multiple strategies to improve knowledge of life-threatening anaphylaxis reactions at both national and international public health levels, and improve patient access to care and prevention (Table 3). Importantly, this will also result in improvements to patient/public education, reducing the burden of disease on affected individuals, their families and those responsible for caring for food-allergic individuals.

Novelty: the ongoing new International Classification of Disease 11 will optimize epidemiological data collection.

Public health plays a critical role maintaining and improving the health of our communities. Analyses of health trends in a population are the basis of public health interventions, and can identify changes in trends (for example, reactions due to new allergens or impact of public health safety campaigns). In the context of anaphylaxis mortality, different models have been used to capture these data as accurately as possible (Table 4). A recognized limitation in using national administrative databases is the lack of specificity of coding for anaphylaxis and World Health Organization (WHO) rules on notification in death certificates which have tended to underestimate the true rate of fatal anaphylaxis (8). The upcoming implementation of the new ICD-11 classification of allergic and hypersensitivity conditions will be an opportunity to improve the anaphylaxis coding to hopefully obtain more accurate data relating to the number of anaphylaxis deaths and also their cause (36).

However, improvements in coding will have little impact on other known difficulties in evaluating anaphylaxis population-based studies, namely: (i) mis-coding of anaphylaxis as other diagnoses, in particular the difficulties in distinguishing between severe asthma and food-induced anaphylaxis; (ii) under-recognition of atypical manifestations of anaphylaxis, especially in infants and elderly patients; (iii) the limited quality of data derived by certificate of deaths which is dependent on the experience of the physician notifying the event; (iv) the need for clinical validation if the analysis is based on secondary data (7,8).

The analysis of institutional registries allows the identification of key local or regional problems, such as risk factors, management issues, emerging allergens, and alerts for the need of specific improvements (regular food allergens information in labels and in different establishments such as schools and restaurants), but it turn assumes the comprehensive nature of case collection (whereas in reality, case identification may not always be complete). Case-collection can be improved through education or requiring notification of potential cases.

National and international collaborations may allow the creation of standard shared databases, exemplified by the European Anaphylaxis Registry, which has analysed risk factors for severe anaphylaxis irrespective of cause, to support better identification of patients at-risk and factors related to severe reactions in order to personalise the health care (28,32,37,38). However, relatively few cases of fatal anaphylaxis have been included to date, which probably reflects under-reporting by non-allergy specialists (e.g. emergency physicians and anaesthetists) which limits the utility of the data in assessing risk factors for fatal anaphylaxis.

Involving general public, public authorities, patients' associations.

Although few studies have confirmed that adrenaline injection reduces mortality in anaphylaxis, all recommendations place intramuscular adrenaline as the first line treatment for anaphylaxis (39-43). Despite this, intramuscular adrenaline continues to be underused to treat anaphylaxis (38). The dissemination of national and international guidelines on the treatment of anaphylaxis should be shared with all those involved in the emergency care of anaphylaxis, including first-response paramedics and emergency physicians. Furthermore, patients should receive an AAI prescription before leaving the emergency room, with adequate education on their use as an interim measure and referral to an allergist within an optimal period of 4 to 6 weeks for further education (39-43). The quality of care provided in emergency departments can be improved by the dissemination of recommendations, the use of primary care protocols, and a full collaboration between emergency professionals and allergists (44,45).

In the various reports to date, most patients who died due to food anaphylaxis were known to be allergic, but generally not prescribed AAI. Although it is not possible to predict severe anaphylaxis, it is likely that many of these deaths might have been associated with preventable factors. Work to improve our ability to identify patients at greatest risk of serious reactions, collaboration among healthcare professionals, the quality of education provided to patients and carers and advice on allergen avoidance are therefore vital.

Information to the general public is essential to raise public awareness and public authorities. Scholarly societies and patient associations have a fundamental role to alert and inform the general public through awareness campaigns in the media and social networks, in partnership each other and in connection with health and education programs (46-48).

Management of comorbidities, cofactors and triggers to reduce severe food-induced anaphylaxis

Although there is a consensus that it is difficult to predict those most at risk of severe reactions, certain features can be used to help target education to those more likely to have significant reactions. Asthma is a common comorbidity in food-allergic individuals and has been associated with severe outcomes (15,17,20-25). Nonetheless adequate control of asthma is seen as an important strategy to reduce the risk of severe reaction in those at risk of anaphylaxis (30).

Most fatal food reactions are caused by peanut, tree nuts, and seafood; in children, persistent cow's milk allergy is also described in a significant proportion of severe and fatal anaphylaxis reactions (25,49). There is increasing interest in oral immunotherapy to treat food allergy, which may be considered in children aged more than 4-5 years with a persistent allergy to peanut, cow's milk or egg, according to the recommendations of the European Academy of Allergy and Clinical Immunology (Evidence level I, grade of recommendation A or B according to allergens) (50). Food allergy desensitisation, such as oral immunotherapy (OIT), must only be performed in specialized centres by experienced allergists and many argue that OIT is not yet ready for routine clinical use. Desensitisation may, in the future, be one approach in the management of those most at-risk of severe anaphylaxis, although up to 20% of patients do not tolerate OIT: importantly, data suggests this group includes those most at risk of anaphylaxis (51).

Biological markers are not helpful in predicting severity (39-43), although it has been proposed that the basophil activation test might provide information for the clinician at least in terms of risk of anaphylaxis of any severity (52). Due to the lack of severe anaphylaxis in this study, no conclusion can be drawn on whether the basophil activation test might predict severe anaphylaxis.

Limiting exposure to known food allergens: the potential impact of new European legislation on the provision of food information to consumers.

The majority of fatal reactions to food are due to unintended exposure to a known trigger (Table 2) (14,15,17,20-25). These circumstances may arise from a lack of vigilance from patients and carers with respect to food labels, a failure in communication when eating out e.g. in a restaurant or at a catered event, poor food-handling procedures resulting in allergen cross-contamination, or eating in an unfamiliar environment. Recent changes in European legislation (enshrined in European Food Information to Consumers Regulation 1169/2011) now requires allergen information to be made available with respect to 14 food allergens on all foods irrespective of whether the food is pre-packed or sold from a catering establishment (53). These allergens include the most common ones implicated in fatal anaphylaxis (peanuts, nuts, milks, fish and shellfish). However, while allergen disclosure is regulated under the legislation in terms of font size and language, more flexibility is allowed in catering establishments and for “loose” non-prepacked foods. Unfortunately, this has also allowed for wide variations in the provision of allergen information to consumers across the EU. The Regulation also requires that “may contain” or "precautionary" warnings are only used where justified. Unfortunately, the use of such warnings as a measure to counter risk due to allergen cross-contamination is voluntary, unregulated and not consistently applied across food businesses in everyday life. There is an urgent need to address this by the public authorities, through education and training of catering staff.

Communication is a crucial element of allergen avoidance allowing the provision of safe food to allergic consumers, particularly in restaurants and schools where a disproportionate number of fatalities occur (Table 2) (14,15,17,20-25).

Strategies to avoid severe to fatal anaphylaxis reactions in the school setting: dissemination of specific policies for allergic children and new legislations to stock adrenaline auto-injectors at school.

In some countries, such as France, UK, USA and Canada, Individual Healthcare Plans should be used in the school setting to communicate food allergies and their emergency to staff (54). Some schools advocate a peanut-free ban with respect to both on-site catering and products brought home, however there is a lack of evidence that this is an effective strategy (55,56). In particular,

there is a concern that such peanut-bans are unenforceable and may result in a false sense of security which can place food-allergic children at greater risk. Indeed, instead of focusing on allergen-free policies, perhaps efforts should focus on increasing awareness and education of school personnel and creation of mandatory standardized reporting mechanisms to better manage food allergies in the school setting.

A number of countries now require schools to have specific policies and procedures to help keep food-allergic children safe. In addition, the USA, UK and Australia now have legislation which allows for schools to source their own AAI devices (rather than an individual patient's) for emergency use. Up to 1 in 5 fatal anaphylaxis reactions in school-aged children occur in school and the occurrence of anaphylaxis at school is not uncommon as the first manifestation of the allergic disease (Table 2) (14,15,17,20-25). Important data has been generated by a pilot study in Chicago (USA) where all public and charter schools were provided with AAI in 2012 (with commercial funding) (57). Over the following school year, AAIs were administered to 38 children, with 55% experiencing a reaction for the first time (57). The supply of AAI to schools is not without cost and may only be cost-effective where a school's own supply can be used instead of a child having to provide their own devices (58); this may not be disadvantage, as limiting the number of AAI in schools may improve staff-familiarity with emergency procedures and avoid the issues with school children failing to remember to bring their own AAI to school on a daily basis.

Importantly, schools need adequate support and training in order to maintain a safe environment, something exemplified by the government-funded drive in New South Wales, Australia to mandate anaphylaxis training in state schools (59). Unfortunately, not all regions have provided funding to support schools in this aim, and changes in legislation to encourage training and local availability of AAI need to be backed-up with resources to implement recommendations. The availability of care plans, policies and emergency protocols for families and in schools – approved by academies and available to all physicians and healthcare professionals – should allow harmonized procedures and support ongoing dialog with governmental regulators.

Conclusions

Mortality from food anaphylaxis is low and stable, but this still has a profound adverse impact on health-related quality of life and a significant proportion of deaths may be preventable. Improving the quality of epidemiological data relating to anaphylaxis should clarify some areas of uncertainty about risk factors, leading to better targeting of strategies to protect those most at risk. We have described general national and international strategies, which we hope can be implemented in the future. This will involve national and international support for ongoing local efforts to improve prevention, optimize care and implement national and international networks of centres of excellence to provide personalized medicine for those most at risk of severe outcomes (60).

ABBREVIATIONS:

AAI: adrenaline auto-injectors

ICD: International Classification of Diseases

WHA: World Health Assembly

WHO: World Health Organization

DECLARATIONS:

CONFLICT OF INTEREST:

The authors declare no conflict interest.

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CONTRIBUTIONS

GP and LKT contributed to the construction of the document (designed the study, analyzed and interpreted the data, and wrote the manuscript). PJT has co-led a working group resulting in changes in UK legislation and the development of national guidelines to schools on the management of food allergies. PJT interpreted the data, wrote and reviewed the manuscript. VC, MW, AD, JMR, EB, PD contributed on tuning and reviewing the manuscript.

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Table 1. Published anaphylaxis mortality epidemiological data in different countries (mortality data presented as cases per million population per year).

	United Kingdom (5)	**United States** (14,16)	**Australia** (17,19)	**France** (13)	**Finland** (18)	**Brazil** (8)	**Canada** (15)
Period of study	1992-2012	1999-2009 and 1999-2009	1997-2013	1979-2011	1996-2013	2008-2010	1986-2011
Type of mortality record	National registry	Death certificates	Death certificates	Death certificates	Death certificates	Death certificates	Coroner's reports
Rate of fatal anaphylaxis (all triggers)* **(95%CI)**	0.47	0.69	0.99	0.83 (0.80-0.88)	0.59	0.65 (0.54-0.78) (2010)	0.15 (2011)
Food-induced-anaphylaxis mortality* **(95%CI)**	0.10 (1992) 0.12 (2012)	0.04 (2009)	0.09 (2014)	ND	ND	0.03 (2012)	) 0.08 (2011)
Trends of anaphylaxis mortality rates of all causes per one-year period (%) (95%CI)	Stable +1.00 (0.98 to 1.01)	Stable -0.3 (-1.5 to 0.9)	Increase +6.2 (3.8 to 8.6)	Decrease -2 (-2.5 to -1.5)	Increase ND	Stable (ND)	Decrease (p=0.02)
Sex ratio M/F	1.7 (< 15 years) 1/1.4 (> 15 years)	1.2	>1	1.04	1.6	1.37	1.3
Age at death (globally or by cause)	**Average age (range)**	**Median age (quartiles)**	**Median age (quartiles)**	**Median age (quartiles)**	**Average age (range)**	**Median age (quartiles)**	**Average age (range)**
Food	**25 (22-28)**	**40 (20-60)**	**28 (4-66)**	**24 (17-28)**		**32 (3-52)**	**32 (9-78)**
Iatrogenic	58 (56-61)		65 (26-94)	69 (52-74)		52 (6-77)	
Insects	59 (56-63)		50 (19-79)	59 (56-63)		56 (9-71)	

Total					59 (17-83)		47 (9-86)
Number of fatal paediatric cases (mortality rate)	39 (caused by food only)	84 (0.1)	< 10 (< 20 years)	39 (< 18 years) (0.08 ; IC95% : 0.05-0.10)	0 (< 16 years)	43 (< 15 years) (0.09 ; IC95% : 0.05-0.11)	12 (< 18 years)
Distribution of fatal anaphylaxis cases by trigger (%)							
Food	**26**	**7**	**8**	**1**	**9**	**2**	**33**
Iatrogenic	55	59	16	63	39	42	17
Insects	19	15	11	14	41	35	33
Non specified	-	17	64	23	7	21	0

ND: not defined

Table 2. Detailed analysis of food-induced anaphylaxis deaths data.

	United States (20-22)	United Kingdom (14,23,24)	Australia (17)	France (25)	Canada (15)
DATABASE	Registry	National fatal anaphylaxis registry	National Coronial Information System	Allergy Vigilance Network	Ontario Coroner's database
PERIOD	1994-1999 and 2001-2006	1992-2016	1997-2013	2002-2017	1986-2011
NUMBER OF SUBJECTS (children)	63 (28)	124 (39)	22	16 (11)	40
SEX RATIO	1.3	~1	1.4	1.7	ND
AGE	Average: 19.9 years (DS 9.1), Median age: 18 years (range : 3-50)	ND	Median age: 28 years (range: 4–66).	Average: 23.5 years (DS : 5.2)	ND
FOOD TRIGGERS	Peanut and nuts (87%), cow's milk (8%), seafood (5%)	Peanut and nuts (73%) cow's milk (21% in children)	Seafood (50%), peanut and nuts (18%)	Peanut and nuts (56%) goat/sheep's milk (13%)	goat/sheep's milk (55%), seafood (10%)
HISTORY OF ASTHMA (%)	73	78	68	56	ND
HISTORY OF FOOD ALLERGY (%) (anaphylaxis in %)	83	69 (21)	91 (32)	69 (25)	85
PREVIOUS PRESCRIPTION OF AAI (%)	ND	ND	27	56	38
LOCAL OF THE REACTION	Home (21%), restaurant (19%), school (17%)	Home (27%), restaurant (20%), school (17% of children)	Home (23%), school (14%)	School (n=3), hospital during oral provocation test (n=1)	Home (n=14), school (n=4)
CO-FACTORS	ND	ND	Alcohol/drugs (27%)	Effort (19%), alcohol (13%)	ND
REACTION	ND	ND	Respiratory impairment (n=14), cardiovascular arrest (n=11)	Respiratory impairment (n=10); with bronchospasm (n=8) and laryngeal oedema (n=2), cardiovascular arrest (n=5)	ND
ADMINISTRATION OF ADRENALINE	17 (10 late administration)	ND	2 AAI, 9 in ambulances, 4 at emergency departments, 2 other health care	8 (4 late administration)	ND

ND: not defined ; AAI: adrenaline auto-injectors

Table 3. Strategies to reduce food-induced anaphylaxis deaths

IMPROVE KNOWLEDGE IN ANAPHYLAXIS MORTALLITY EPIDEMIOLOGY	OPTIMIZE DOCTORS' KNOWLEDGE	IMPROVING PATIENT AWARENESS	IMPROVE ACCESS TO CARE AND PREVENTION
Optimize classification and coding for allergic diseases and anaphylaxis (ICD11).	Improve knowledge of allergy, especially food, doctors not specialized in allergology, including emergency healthcare workers.	Promote therapeutic patient education with safety objectives: recognition of allergies and foods at risk, recognition of signs of anaphylaxis, adequate attitude during an allergic reaction (including the use of AAI).	Promote the availability of AAI in more countries around the world for patients and caregivers.
Promote networking and the establishment of large-scale registries on anaphylaxis (food and non-food causes) allowing a detailed analysis of reactions (allergen exposure modalities, risk factors, cofactors, treatment ...).	Disseminate international recommendations on the treatment of anaphylaxis and indications of prescriptions of AAI, especially in emergency medicine.	Anticipate higher risk situations (meals outside the home, school trips…) and applying an appropriate risk assessment.	Improve prevention in schools: extend the use of the Individual healthcare plans, train teachers and school meals staff, evaluate the impact of "peanut free" vs “allergy-aware” policies and the provision of AAI in schools.
Extend the epidemiological analysis to reactions occurring in hospitals, especially for peri-anesthetic reactions or during hospital provocation tests.	Promote the provision of AAI in ambulances and first aid services.	Keep your emergency kit (with AAI) on you at the all time and check the expiry and storage conditions.	Improve prevention in food and catering areas: adequate and informative labelling of pre-packaged and non-packaged foods from a list of notifiable ingredients, implementation of European legislation in force (FIC-INCO).
Continue the analysis of risk factors and the interest of biomarkers which might help predict severity	Refer the patient with allergy to an allergist specialist for comprehensive diagnosis and management by managing comorbidities (asthma).		
	Identify with the expertise of the allergist the patients most at risk (history of asthma and anaphylaxis, comorbidities, allergens ...) and propose a personalized treatment (oral food immunotherapy).		Continue public information campaigns on this topic and carry on discussions with national regulators, agency and governance.

AAI: adrenaline auto-injectors

Table 4. Advantages and limitations of different ways of performing anaphylaxis deaths studies.

National epidemiological databases		Institutional or regional databases	
Advantages	**Limitations**	**Advantages**	**Limitations**
Broader population (country)	Diagnostic and coding issues due to the under representation of anaphylaxis in ICD-9 and ICD-10	Evaluation and notification by allergy specialists	Limited number of cases (under-estimation) Possible selection bias
Temporal trends evaluation	Limited refined and detailed evaluation of cases	Detailed evaluation of cases (triggers, personal history of allergy, comorbidities, description of the allergic reaction…)	Limited epidemiological value *stricto sensu*
Allows comparison with other countries data.	Under or over-estimation	Allows better evaluation of risk factors.	Underestimation for some causes, poorly taking into account of reactions in a hospital environment (non-food especially)
Allow comparison among data from different regions of the same country	No validation from allergy specialists		

ICD: international classification of diseases