

Article type : Letter to the Editor

Fatal anaphylaxis in children in France: analysis of national data.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12828

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Key words: anaphylaxis, child, fatalities, mortality, mortality rate.

To the Editor:

Anaphylaxis is a recognized cause of death for all ages. A better understanding of mortality data could help identify patients at risk and implement prevention measures. However, accurate epidemiological mortality data can differ widely due to a number of variables. Currently, the anaphylaxis-related mortality rate (AMR) is less than 1 per million population per year in most countries. In France, it was 0.83 per million population per year (95%CI, 0.80-0.88) for the period 1979 to 2011 (1-6). However, data regarding anaphylaxis fatalities in children are scarce and vary from country to country. For example, the most common triggers of pediatric anaphylaxis fatalities the United Kingdom and Australia are food allergens, whereas drugs account for most of the pediatric anaphylaxis fatalities in the United States (1-4).

In France, an official system recording vital statistics – the National Mortality Center (CEPIDC) (www.cepide.inserm.fr/site4/) – was created in 1967 and works closely with the World Health Organization (WHO). Mortality data are thus collected through death declarations following the WHO statements for vital statistics and coded based on the International Classification of Diseases (ICD). An allergy vigilance network (www.allergyvigilance.org) has also been available for French-speaking countries (mainly France) since 2002. This network is a professional registry of more than

300 allergists and collects anaphylaxis cases including fatalities, but does not allow epidemiological analysis as it is based on voluntary declarations. To date, therefore, there is no specific national registry for anaphylaxis fatalities.

The aim of our study was to determine the pediatric anaphylaxis mortality rate (PAMR) in France from 1979 to 2014 and analyze demographic data, trends, and specific patterns according to triggers (iatrogenic, venom, food, unknown), age groups, sex and geographical regions (North and South).

This was a descriptive national-based study using mortality data routinely reported to the CEPIDC Unit of the National Institute of Health and Medical Research (INSERM) for the years 1979-2014 and extracted on 31st January 2017. Each death certificate records primary and secondary causes of death, demographic data including sex, age, date of birth, and geographic region of death. These data are anonymized and do not include information such as race, medical history or comorbidities or, in the case of anaphylaxis death, details on the triggering food or where the anaphylaxis occurred. CEPIDC vital statistics are coded based on the ICD: using the ninth edition (ICD-9) from 1979 to 1999 and the tenth (ICD-10) since 2000. We included all reported deaths recorded under ICD-9 and ICD-10 codes related to anaphylaxis (Table 1). Selected codes and clinical validation were based on the current accepted international diagnostic criteria for anaphylaxis (1-3, 5-7).

Data about the characteristics of the French population by region, year, sex and age were collected from the databases of the French National Institute for Economical and Statistical Studies (INSEE) (www.insee.fr). The geographical regions North and South were defined using the official French mapping from 2014.

The study was approved by the National Research Ethics Committee of the French Pediatric Society (CER_SFP 2015-004).

PAMRs were calculated using the French census population and results were expressed per million children (< 19 years) and per year. In univariate log-linear Poisson regression model (using the logarithm of French population as the offset variable and the number of fatal anaphylaxis cases for any cause as the dependent variable), we assessed the impact of the time period, age, sex and geographic region on PAMR. Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

Of the 294 312 death certificates registered in children from 1979 to 2014, 43 ICD codes were related to anaphylaxis given a PAMR of 0.077 per million children per year (95%CI, 0.053 to 0.101). Thirty-eight of these codes were selected as being directly related to anaphylaxis and five as being associated to anaphylaxis. Based on clinical validation, four groups were defined based on the main triggers of fatal anaphylaxis: food, iatrogenic (medication, serum, vaccine....), venom, and unspecified (1-3, 5, 6). The number of fatal anaphylaxis cases across the 5-year periods ranged from one (2001-2005) to 12 cases (1979-1985) (Fig1), with an estimated 5-year change over the study period of -7.8% (95%CI, -20.2 to 6.5, $P=0.27$). Median age at death was 11 years (interquartile range: 2-15).

There was no difference in PAMR between the four 5-year age groups (Fig2, $P=0.59$). In terms of school age categories, anaphylaxis cases occurred in 15 preschool children (< 7 years), 14 in school children (7-12 years), and 14 in adolescents (> 12 years). Over the study period, the incidence of cases of fatal anaphylaxis (number, PAMR [95%CI]) were similar in boys ($n=24$; 0.084 [0.050 to 0.118]) and girls ($n=19$, 0.069 [0.038 to 0.101]) ($P=0.54$). Similarly, no difference in PAMR [95%CI] of any cause was observed between the South ($n=17$, 0.086 [0.045 to 0.128]) and North of France ($n=26$, 0.072 [0.044 to 0.100]) ($P=0.55$).

As shown in Figure 2, the main trigger for pediatric fatal anaphylaxis was iatrogenic (n=21, 48.8%), mainly drugs, but was specified in only five cases (antibiotics, n=3). In the overall population, iatrogenic-related PAMR was 0.038 (95%CI, 0.021 to 0.054). Other triggers were less reported with food and insect venom accounting each for 7% of anaphylaxis fatalities (n=3, for each). Fatalities of unspecified causes were observed in 16 cases (37.2% of cases), giving a PAMR for the study period of 0.029 (95%CI, 0.014 to 0.043).

In this first document focusing on fatal anaphylaxis in children performed in France by collecting data from the national database from 1979 to 2014, we demonstrate a small number of anaphylaxis fatalities (< 19 years) with a PAMR of around 1 per 10 million children per year. This is 10 times lower than for anaphylaxis mortality in adults in France (6). For purpose of comparison, the rate of drowning-related deaths in children (< 15 years) is reported as 20 per million children per year in France (www.invs.santepubliquefrance). Furthermore, our data demonstrate a decrease of around 8% per 5-year period in PAMR over the last three decades. As in adults, iatrogenic cause was the main identified trigger of anaphylaxis fatalities, with venom insect and food being even more rarely reported. However, anaphylaxis of unspecified cause accounted for up to 37% of all fatalities.

To date, few studies have described pediatric anaphylaxis fatalities and those that do report inconsistent data about the triggers involved in anaphylaxis deaths. Most of them report only a small number of pediatric anaphylaxis fatalities: for example, 12 deaths in Ontario between 1986 and 2011, and nine in Australia from 1997 to 2013 (4, 8). Of the nine cases reported in Australia, eight were food-related fatalities, mainly due to peanut/tree nut. Turner et al. reported data extracted from national databases of fatal anaphylaxis cases recorded in England and Wales from 1992 to 2012 (1). Thirty-nine pediatric (< 16 years) anaphylaxis fatalities were collected with food allergens as the dominant trigger. These results differ from those reported in our study and in the United States (3). In the United States, death certificates from the National Mortality Database were analyzed between 1999 and 2010: 119 pediatric anaphylaxis fatalities were identified with the most common

cause being drug related (n=49, 41%), followed by food allergens (n=37, 31%) (3). There were also six (5%) insect-related deaths and 27 (23%) fatalities of unspecified cause. Global PAMR expressed as per million persons ≤ 19 years for drug, food, insect and of unspecified cause were the following: 0.05 (95%CI 0.04-0.07), 0.04 (95%CI 0.03-0.05), 0.03 (95%CI 0.02-0.04) and 0.01 (95%CI 0.00-0.01), respectively. These PAMRs are similar to those observed in our study.

In the European Anaphylaxis Registry, half of pediatric anaphylaxis cases occurred in children < 6 years of age (9). This was not observed in our study with an equal distribution of anaphylaxis fatalities among the age groups. It is striking to note the discrepancy between the small number of anaphylaxis fatalities in preschool children and the large number of anaphylaxis cases in this age group. The relatively large number of cases of unspecified anaphylaxis might explain the small number of reported food-induced anaphylaxis which might currently be miscoded and thus under-reported in the French database. Regardless of the possible etiology, the total number of anaphylaxis deaths decreased markedly from 2001 to 2005. This may be due to the transition from ICD-9 to ICD-10 which occurred during this period.

The considerable number of unspecified cases may also reflect difficulties in completing the death certificate and/or quality assessment of clinical diagnosis of anaphylaxis. Strengthening awareness through academic actions such as national and international guidelines could serve to decrease this number of unspecified causes.

The major limitations of the present study, as well as other studies examining anaphylaxis mortality, are linked to the ICD coding system, coding errors, clinical misdiagnosis and the possibility of under- or misreporting anaphylaxis fatalities on death certificates. In 2012, an analysis of the Brazilian mortality database demonstrated under-reporting of anaphylaxis deaths due, at least in part, to difficult coding under the ICD-10 (10). This work gave rise to a cascade of international action plans supported by six major international academies and the WHO, and resulted in a new section specifically addressing allergic and related conditions in the ICD-11 framework (10, 11). In an

attempt to validate this new section of the ICD-11 version pertaining to allergic and hypersensitivity conditions to capture anaphylaxis deaths, the Brazilian group finally reported a decrease in reporting of anaphylaxis deaths due to improvements in anaphylaxis classification and coding (11).

In conclusion, our work is the first to focus on pediatric anaphylaxis mortality. We identify the role played by medications even if the impact of food allergens as a trigger of anaphylaxis fatalities might be under-estimated. Although the PAMR appears to be low and on the decrease, we believe that the data presented here flags the need to introduce preventable measures to decrease anaphylaxis fatalities in children and tools to identify avoidable fatal cases. Improvements in the reporting of anaphylaxis cases along with appropriate coding using the ICD-11 and its adoption in national and international registries will allow better mapping and monitoring of anaphylaxis.

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Table 1: ICD-9 and ICD-10 codes used as selection criteria.

Description	ICD 9 alphanumeric code of anaphylaxis	ICD 9 alphanumeric code associated	ICD 10 alphanumeric code of anaphylaxis	ICD 10 alphanumeric code associated	Anaphylaxis cause
Unspecified anaphylaxis	995.0		T78.2		Unspecified
Upper respiratory tract hypersensitivity reaction, site unspecified	478.8		J39.3		Unspecified
Toxic effect of contact with venom or other arthropods	995.0	905.3 905.5 906.4	T78.2	X23 / X25	Venom
Anaphylactic shock caused by serum	999.4		T80.5		Iatrogenic
Anaphylactic shock due to an adverse effect of correct drug or medicament properly administered			T88.6		Iatrogenic
Drug, medical and biological substances causing adverse effects in therapeutic use	995.0	930-949			Iatrogenic
Misadventures to patient during surgical and medical care	995.0	870-876			Iatrogenic

Surgical and medical procedures as the cause of abnormal reaction of patient or later complication, without mention of misadventure at the time of procedure	995.0	878-879			iatrogenic
Accidental poisoning by drug, medicaments and biologicals	995.0	850-858			iatrogenic
Complications of medical and surgical care			T78.2	Y40-Y84	iatrogenic
Food-induced anaphylaxis	995.6		T80.5		Food
Accidental poisoning by foodstuffs and poisonous plants	995.0	865			Food

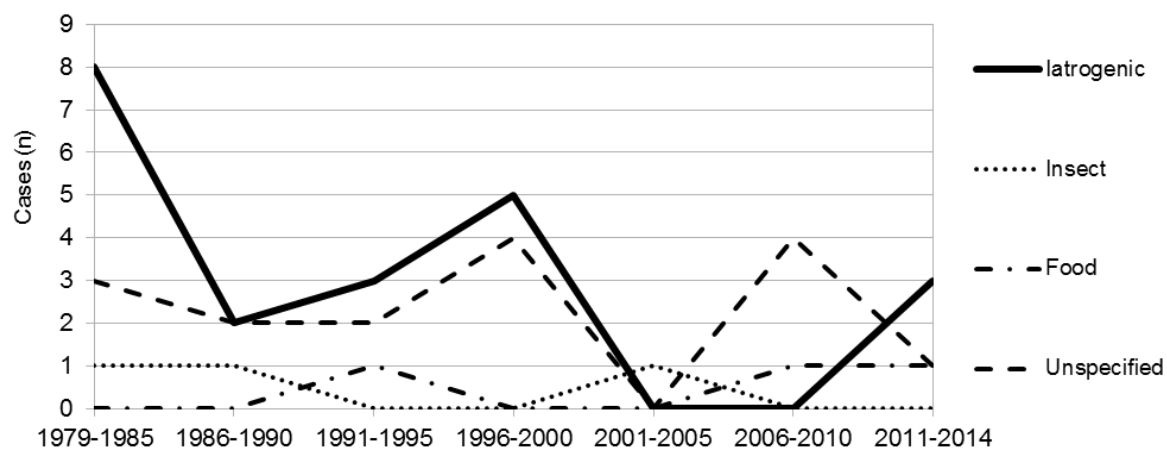


Figure 1. Number of fatal anaphylaxis cases in children (< 19 years) by triggering cause in France (1979-2014).

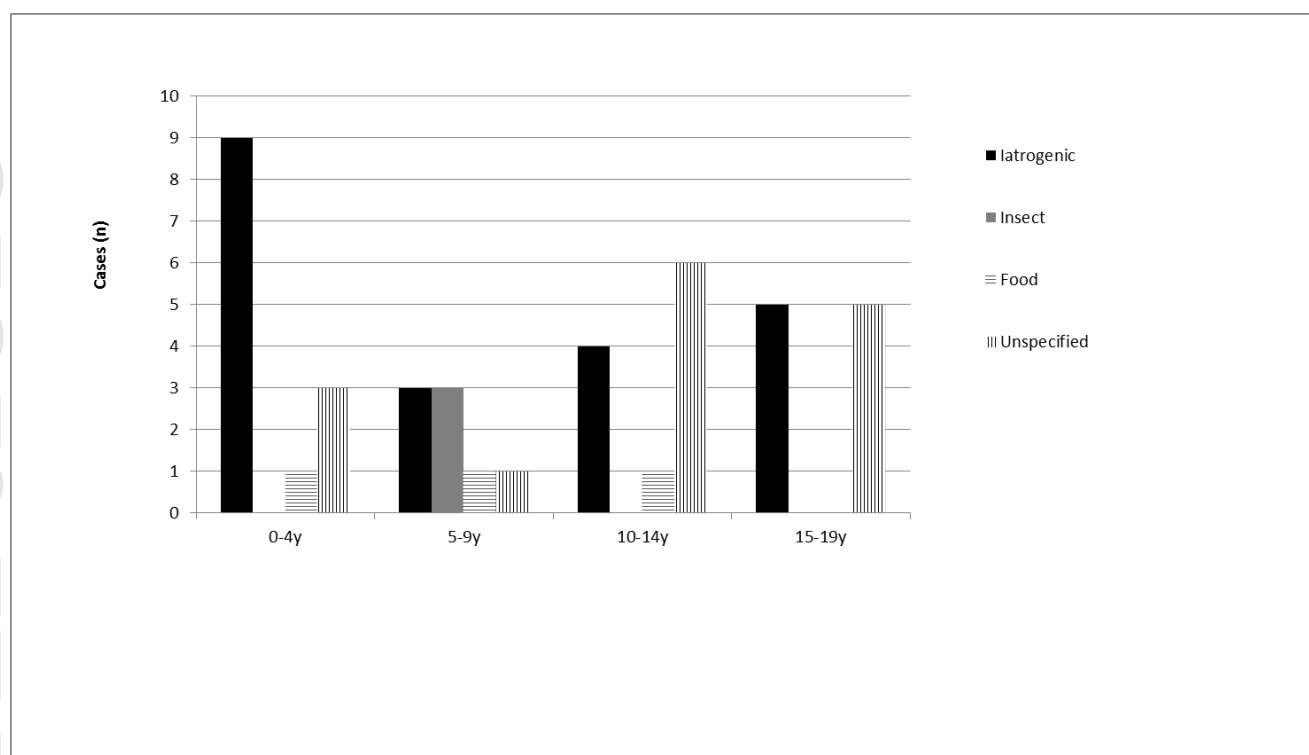


Figure 2. Number of fatal anaphylaxis cases in children (< 19 years) per 5-year period of life and by triggering cause in France (1979-2014).