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Fatal anaphylaxis in France: analysis of national anaphylaxis data, 1979-2011

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Capsule summary

The anaphylaxis mortality rate has fallen about 2% per year in France over the past 3 decades. Increased awareness of anaphylaxis treatment guidelines will hopefully continue this trend.

Key words: anaphylaxis, mortality rate, fatalities, drug allergy, food allergy, venom insect allergy, iatrogenic.

Abbreviations

AMR: anaphylaxis mortality rate; ICD: International classification of diseases; CI: confidence interval.

Word count: 1018

To the Editor:

Anaphylaxis-related mortality (AMR) has been estimated at less than 1 per million population from the United States and the United Kingdom [1-3]. In these countries, the AMR remained stable during the last decade [1-3]. In contrast, the incidence of anaphylaxis fatalities increased in Australia from 1997 to 2013 [4]. The most common triggers of fatal anaphylaxis cases are drugs, insect venoms, and foods, with drugs accounting for most of the fatalities [1-4]. In France, comprehensive data from anaphylaxis-related deaths is collected by the National Mortality Center. The aim of our study was to determine the AMR in France and analyze time trends, specificities according to triggers, age groups, sex and regional differences.

All deaths in France are recorded by a physician and death certificates are collected and analyzed by the CEPIDC Unit of the National Institute of Health and Medical Research. We included all reported deaths recorded under International Classification of Diseases (ICD)-9 and ICD-10 codes related to anaphylaxis, from 1979 to 2011. As previously described, trigger of fatal anaphylaxis were placed in four groups, foods, iatrogenic (drugs and contrast media), venoms, and unspecified [1-3]. Data about the characteristics of the French population were collected from the databases of the French National Institute for Economical and Statistical Studies. The geographical regions North and South were defined using the official French mapping. The AMR were calculated

by standardizing to the age distribution (by 5-year periods) of the overall census population of 2011 as a standard population. AMR are expressed as per million population per year. We used a log-linear Poisson regression model to assess the impact of time period, age, sex and geographic region on anaphylactic deaths. All regression analyses were adjusted for age-effect and a multivariable log-linear Poisson regression model was further performed. Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.3 (SAS Institute, Cary, NC). The study was approved by the National Research Ethics Committee of the French Pediatric Society.

From 1979 to 2011, 1603 fatal anaphylaxis cases were identified: 1564 (97.6%) occurred in adults and 39 (2.4%) in children. AMR was higher in the adult population [0.84 (95%CI, 0.79 to 0.88)] compared to the pediatric population [0.08 (95%CI, 0.05 to 0.10)] ($p < 10^{-4}$). From 2005 to 2011, overall AMR was 0.60 [95%CI, 0.52 to 0.68]). The highest AMR was observed in the ≥ 70 year age group [3.50 (95%CI, 3.25 to 3.76)]. The AMR was higher in men [1.08 (95%CI, 1.00 to 1.16)] than in women [0.86; (95%CI, 0.80 to 0.92)] ($p < 10^{-4}$) and it was similar comparing the southern and the northern regions for all causes ($p = 0.15$) (see Figure E1 in this article's Online Repository at www.jacionline.org). In the whole population, annual percentage change for case fatality rate was -2.1% (95%CI: -2.6 to -1.6) indicating a significant decrease during the study period ($p < 10^{-4}$) (Fig 1).

Triggers of anaphylaxis were iatrogenic ($n = 1011$, 63%), unspecified ($n = 364$, 23%), venoms ($n = 220$, 14%), and food ($n = 8$, 0.6%) (see Table E1 in this article's Online Repository at www.jacionline.org). The overall iatrogenic-related AMR was 0.53 (95%CI, 0.50 to 0.56) and this rate decreased over the study period ($p < 10^{-4}$) (Fig 1). Among the iatrogenic causes, drugs ($n = 930$, 92%) were primarily implicated, with antibiotics ($n = 725$, 78%) mainly involved. Venom-induced AMR was stable during the time period at 0.12 (95%CI, 0.10 to 0.13) (Fig 1). Most of these cases were recorded in adults ≥ 40 years, especially in the ≥ 70 years group (55 cases). It was higher in men than in women ($p < 10^{-4}$), in the South than the North ($p = 0.003$). Food-induced anaphylaxis was

the least common cause of fatal anaphylaxis and food-induced AMR was under 0.01. Most of unspecified-related anaphylaxis fatalities (n=160, 44%) occurred in persons ≥ 70 years (Fig 2) with a stable AMR of 0.19 (95%CI, 0.17 to 0.21) in the whole population (Fig 1). The highest unspecified-related AMR was observed in persons aged ≥ 70 years [0.77 (95%CI, 0.65 to 0.89)] and in men as compared to women (p=0.02).

In the multivariate analysis, older age and male sex were associated with an increased risk for anaphylaxis death of any cause of 32% (95%CI, 30 to 33) for each 5 years from birth, and a 29% (95%CI, 17-42) increased risk for male sex.

The AMR (expressed as per million population per year) that we observed during the time period is quite similar as those observed in the United States (1999-2009; 0.69), Australia (2013; 0.99), Finland (1996-2013; 0.59) and higher than reported in United Kingdom (1992-2012; 0.47) [1-5]. While AMR remains stable in the United States and United Kingdom, an increase of anaphylaxis fatalities of 6%/year is reported in Australia (1997-2013) [1, 2, 4]. In contrast, our data demonstrate a 2%/year decrease from 1979 to 2011, especially of iatrogenic cause. In our study, male sex was a risk factor for fatal anaphylaxis as previously described [2, 3]. To date, no clear explanation has been presented to explain this finding. Advancing age is known to be another risk factor for fatal anaphylaxis [1-3]. This is likely explained by underlying comorbidities, such as cardiovascular or cerebrovascular diseases and also by an increased medication use [1]. Fatal anaphylaxis is mostly due to medications, mainly antibiotics, as described in Australia and the United States [2-4]. Our data showed a decrease in antibiotic-related fatal cases, especially during the last decade, in line with the decrease of 10.7% in antibiotic consumption reported in France (ANSM report 2013). We are also in agreement with other studies in finding that venom-induced fatal anaphylaxis is rare before the fifth decade of life and associated with male sex [1-6]. Venom-induced mortality rate is higher in the South of France which may be explained by the geographical location of hives and greater/longer exposure to venomous insects in that area. Unspecified cause accounts for a sizeable proportion (23%) of fatalities in our study which might explain the small

number of food-induced anaphylaxis.

In conclusion, our work is the longest time period study reporting AMR. Overall, AMR is on the decrease and our study highlights some previous messages: the role played by medications, and risk factors including age and geographic region.

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ACCEPTED MANUSCRIPT

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Figure Legends:

FIG 1. Time trends in anaphylaxis mortality rate (AMR) by triggering agent (iatrogenic, insect stings and unspecified), between 1979 and 2011. Food-related AMR is not represented on this figure.

FIG 2. Trends in anaphylaxis mortality rate (AMR) among triggering agent by age group (food-related anaphylaxis mortality is not represented due to small sample size).

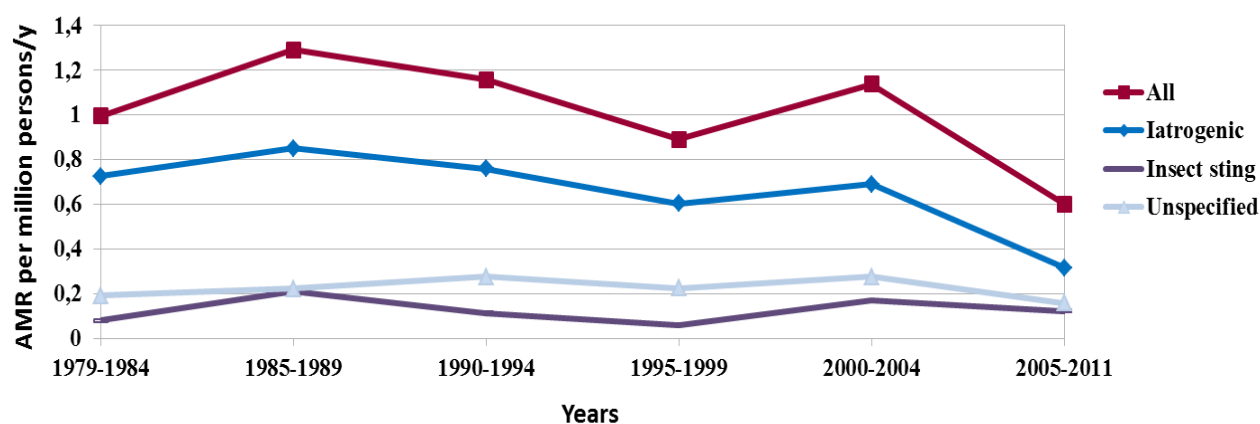


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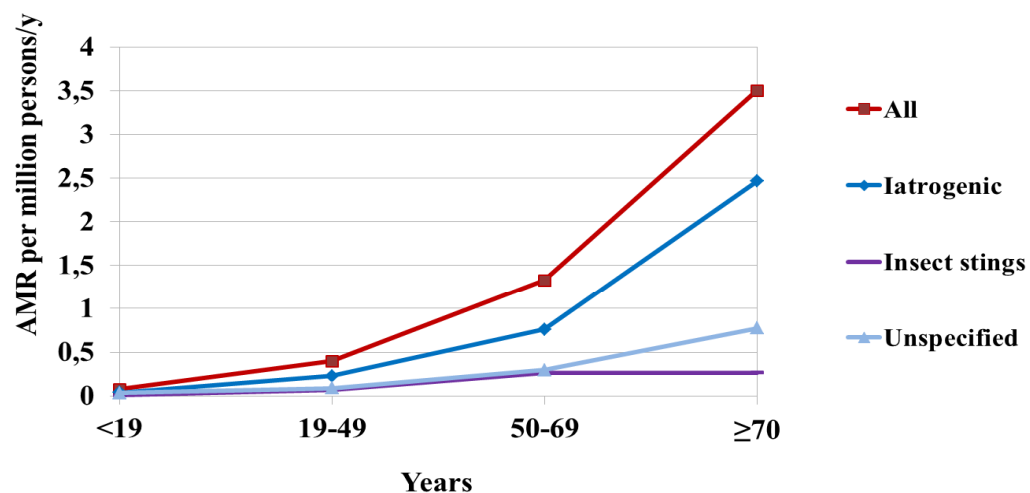


FIG 2. Trends in anaphylaxis mortality rate (AMR) among triggering agent by age group (food-related anaphylaxis mortality is not represented due to small sample size).

FIG E1. Anaphylaxis mortality rate (AMR) for the whole population and by sex for each age group (1979 -2011).

TABLE E1. Characteristics of anaphylaxis fatalities by specific cause.

	Anaphylaxis				
	Iatrogenic n=1011(63%)	Insect stings n=220 (13.7%)	Food n=8 (0.5%)	Unspecified n=364 (22.7%)	All n=1603 (100%)
Sex					
Men	439 (56.0%)	159 (20.3%)	6 (0.8%)	180 (23.0%)	784 (100%)
Women	572 (69.8%)	61 (7.4%)	2 (0.2%)	184 (22.5%)	819 (100%)
Population					
Adult	993 (63.5%)	217 (13.9%)	6 (0.4%)	348 (22.3%)	1564 (100%)
Pediatric	18 (46.2%)	3 (7.8%)	2 (5.1%)	16 (41%)	39 (100%)
Geographic region					
North	599 (64.6%)	111 (12%)	4 (0.4%)	213 (23%)	927 (100%)
South	412 (60.9%)	109 (16.1%)	4 (0.6%)	151 (22.3%)	676 (100%)
Median age (year)					
Men	63	58	28	64	62
Women	77	60	17.5	67.5	73

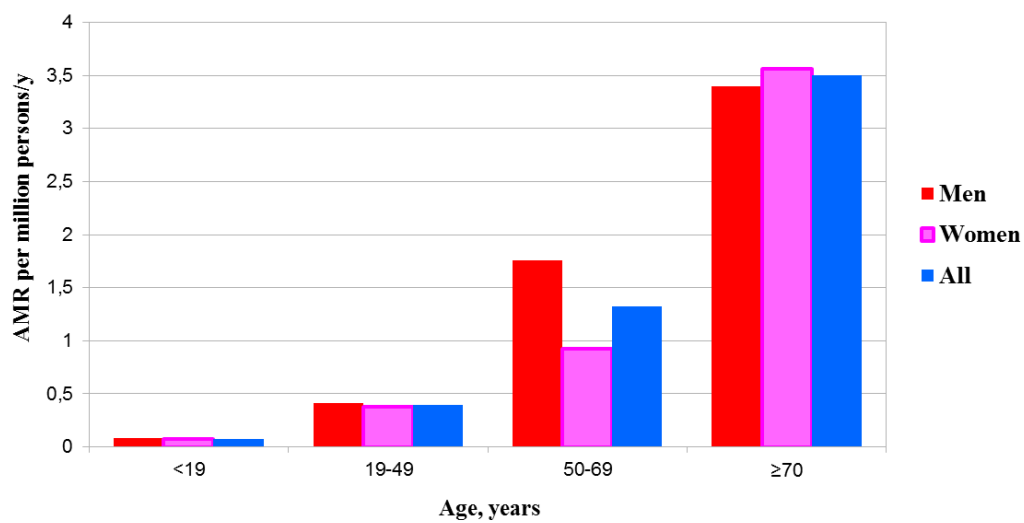


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