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Who is at-risk for severe anaphylaxis in France?

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ABSTRACT

Background: The understanding of risk factors related to severe anaphylaxis is key to implementing prevention strategies. We present the first French population-based nine-year anaphylaxis hospitalization study evaluating specific trends and factors related to severe anaphylaxis (SA), to support identification of phenotypes at-risk.

Methods: This study used descriptive data from the French hospitalization database for the years 2012–2021, and included all patients hospitalized with anaphylaxis using International Classification of Diseases (ICD)-10 codes listed as a primary diagnosis. SA were cases that either required a hospitalization in intensive care units or resulted in death. Potential risk factors were identified according to corresponding ICD codes, available as secondary data during the patient's hospitalization.

Results: The average hospitalization rate of all cases of anaphylaxis (SA and non-SA) was 1.34/100,000/year, and rate of admissions for SA was 0.08/100,000/year. Among the 5463 SA, 37.7% had unspecified coding label, when trigger was not identified. For SA cases in which trigger was identified, most were related to drugs (45.6%), followed by food (9.3%) and insect sting (7.2%). Overall, admissions due to anaphylaxis (SA and non-SA) were more frequent in males (57%). However, when the trigger was drugs, the proportion was significantly higher in females. For children aged 5–9 years, the most common trigger for SA was food. Patients for which SA was triggered by insect stings were identified exclusively in the 10–14 years age group. Chronic spontaneous urticaria was associated with insect sting-induced anaphylaxis, regardless of the severity. Angioedema was associated with all causes of SA. Cases of anaphylaxis presenting with urticaria and angioedema included cases with identified and unidentified triggers. Asthma and a personal history of allergy were associated with drug- and food-induced anaphylaxis.

Conclusion: This is the first study to provide data on severe phenotypes of anaphylaxis in France. Data presented is key to the implementation of public health actions and preventive strategies to improve quality care.

Keywords: Anaphylaxis, Classification, Coding, Epidemiology, Hospitalization, Mortality, Trends, Risk factors, Severity

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BACKGROUND

Epidemiology of diseases is considered a key instrument in public health to evaluate trends, burden of disease, and impact of interventions.[1,2] There is no doubt that the evaluation of epidemiology data is able to improve our understanding of the impact of diseases, identify potential populations at-risk, and relevant environmental factors.[3,4]

Anaphylaxis is known as a serious, generalized, allergic or hypersensitivity condition that can be life-threatening and even fatal. It is most commonly triggered by drugs, food, and insect stings.[5] Since the severity of anaphylaxis is not predictable, the identification of risk factors related to severe reactions remains a knowledge gap.[6] A better understanding of these factors can help identify phenotypes at-risk of severe anaphylaxis in order to implement prevention strategies.

Different methods have been applied in an attempt to obtain reliable epidemiological data on anaphylaxis, but most of the studies have focused on specific triggers or populations. Currently, most robust data are derived from hospitalization datasets and national mortality databases, but they probably do not reflect the true rate of anaphylaxis since most of cases occur in the community and not all cases are brought to hospital settings.[4,7,8] Until now, there has not been a mechanism for identification of community anaphylaxis, particularly when rescue services are not summoned and/or the patient does not go to the emergency department (ED) or another medical facility. This is a true deficiency of reporting in all countries.

The overall anaphylaxis mortality rate was estimated to be 0.60 per million of population per year.[9] However, hospitalization data are lacking worldwide, in particular in low-income countries.

We here present the first French population-based study based on 9 years of anaphylaxis hospitalization data, with the evaluation of specific trends of severe and non-severe cases and factors related to severe anaphylaxis, aiming to support identification of at-risk phenotypes. We believe this study provides crucial evidence-based data to French health-care managers and governmental bodies that can help to prevent anaphylaxis and to better manage patients with anaphylaxis.

METHODS

Type of study, data source and collection

This is a descriptive study using routinely reported data to the French hospital discharge database (PMSI) for the years 2012–2021, extracted on February 8, 2021. This system is electronic, stores information on hospital admissions that occur in the public and private health systems, is mandatory, and thus accounts for 100% of hospitalizations in France.[10] No personal identification is available in this database. Information available is coded based on the ICD-10 and covers main cause of hospitalization (primary cause).

From all 4,021,488 records collected during this period, we identified all patients hospitalized with anaphylaxis using the anaphylaxis-related ICD-10 codes listed as primary diagnosis (T78, T78.0, T78.2, T78–3, T80.5, T88.2, and T88.6).[11] We considered as severe cases of anaphylaxis the cases that evolved to death or those hospitalized in intensive care units. Non-severe cases were those who did not fit the previous criteria. Potential risk factors have been selected according to published data and assigned according to the corresponding ICD codes (Table S1), available as secondary data of hospitalization.

Data analysis

Rates of anaphylaxis hospitalization per 100,000 population and 95% confidence intervals were calculated for each year. Population estimates were obtained from the *French National Institute of Statistics and Economic Studies* (*INSEE*).[12] Age-standardized rates for hospital admissions were calculated by standardizing for the age distribution of the population in mid-2010, the year of the last census. A Kendall test has been applied to assess the trend of the rates per 100,000 of anaphylaxis hospitalizations. Qualitative analysis included data on gender, age, possible aetiology to both severe and non-severe cases of anaphylaxis (Table 1). Poisson regressions were run to model each type of anaphylaxis events according to the age taking into account temporal tendency. Data related to

French anaphylaxis data (2012 - 2021)	DRUG				FOOD				INSECT				UNSPECIFIED			
Characteristic	Non severe N = 18,969	Severe N = 2,494	N	P value	Non severe N = 8,548	Severe N = 509	N	P value	Non severe N = 4,659	Severe N = 398	N	P value	Non severe N = 49,015	Severe N = 2,062	N	P value
Sex			21,463	**<0.001**			9,057	**0.006**			5,057	0.3			51,077	**0.026**
Female	10,396 **(55%)**	1,272 **(51%)**			3,646 **(43%)**	249 **(49%)**			1,372 (29%)	107 (27%)			24,383 **(50%)**	974 **(47%)**		
Male	8,573 **(45%)**	1,222 **(49%)**			4,902 **(57%)**	260 **(51%)**			3,287 (71%)	291 (73%)			24,632 **(50%)**	1,088 **(53%)**		
Age	**57** (42 - 68)	**59** (47 - 70)	21,463	**<0.001**	**13** (4 - 30)	**34** (20 - 55)	9,057	**<0.001**	**54** (40 - 65)	**57** (46 - 66)	5,057	**<0.001**	**46** (24 - 63)	**55** (39 - 67)	51,077	**<0.001**
Age group			21,463	**<0.001**			9,057	**<0.001**			5,057				51,077	**<0.001**
0-4	239 (1.3%)	4 (0.2%)			2,169 (25%)	32 (6.3%)			63 (1.4%)	0 (0%)			2,614 (5.3%)	14 (0.7%)		
5-9	230 (1.2%)	6 (0.2%)			1,244 (15%)	16 (3.1%)			107 (2.3%)	0 (0%)			2,135 (4.4%)	7 (0.3%)		
10-14	425 (2.2%)	18 (0.7%)			1,537 (18%)	34 (6.7%)			123 (2.6%)	1 (0.3%)			3,111 (6.3%)	44 (2.1%)		
15-19	454 (2.4%)	40 (1.6%)			641 (7.5%)	45 (8.8%)			84 (1.8%)	9 (2.3%)			2,354 (4.8%)	64 (3.1%)		
20-29	1,093 (5.8%)	128 (5.1%)			758 (8.9%)	96 (19%)			267 (5.7%)	21 (5.3%)			4,760 (9.7%)	213 (10%)		
30-39	1,726 (9.1%)	207 (8.3%)			509 (6.0%)	62 (12%)			483 (10%)	34 (8.5%)			5,364 (11%)	191 (9.3%)		
40-49	2,703 (14%)	317 (13%)			496 (5.8%)	62 (12%)			750 (16%)	63 (16%)			6,545 (13%)	294 (14%)		
50-59	3,845 (20%)	544 (22%)			506 (5.9%)	73 (14%)			1,063 (23%)	91 (23%)			7,378 (15%)	403 (20%)		
60-69	3,985 (21%)	590 (24%)			396 (4.6%)	49 (9.6%)			1,008 (22%)	109 (27%)			7,281 (15%)	418 (20%)		
70-79	2,604 (14%)	404 (16%)			195 (2.3%)	31 (6.1%)			537 (12%)	44 (11%)			4,522 (9.2%)	273 (13%)		
> 80	1,665 (8.8%)	236 (9.5%)			97 (1.1%)	9 (1.8%)			174 (3.7%)	26 (6.5%)			2,951 (6.0%)	141 (6.8%)		
Pearson's Chi-squared test; Wilcoxon rank sum test																

Table 1. Demographic data of cases of severe and non-severe anaphylaxis in France, PMSI (2012–2021)

potential risk factors were evaluated according to the triggers (Table 2) and anaphylaxis severity using Poisson regression model. *P*-values of <0.05 were considered significant.

RESULTS

Anaphylaxis admissions rates

Over 9 years, we could identify 44,638 patients, who had 124,780 admissions due to anaphylaxis for all-causes, with a mean number of 1.34 per 100,000 population per year. The average hospitalization rate related to anaphylaxis for 9 years was 0.31 per 100,000 population per year, and the rate of admissions for severe anaphylaxis during the same period was 0.08 per 100,000 population per year. These results show that in 25% of hospitalized patients with anaphylaxis, the outcome was ICU admission or death.

Characteristics of the population

For all admissions for anaphylaxis, main triggers were drugs (25.4%), food (10.5%), and insect sting (6.2%), but most were classified as unspecified

		FOOD				DRUG/IATROGENIC				INSECT				UNSPECIFIED		
Characteristic	**N**	**non_sévère**, N = 8,548[1]	**sévère**, N = 509[1]	**p-value**[2]	**N**	**non_sévère**, N = 18,969[1]	**sévère**, N = 2,494[1]	**p-value**[2]	**N**	**non_sévère**, N = 4,659[1]	**sévère**, N = 398[1]	**p-value**[3]	**N**	**non_sévère**, N = 49,015[1]	**sévère**, N = 2,062[1]	**p-value**[2]
Asthma	9,057			**<0.001**	21,463			**<0.001**	5,057			0.054	51,077			<0.001
NO		7,845 (92%)	431 (85%)			18,445 (97%)	2,372 (95%)			4,607 (99%)	389 (98%)			47,778 (97%)	1,969 (95%)	
YES		703 (8.2%)	78 (15%)			524 (2.8%)	122 (4.9%)			52 (1.1%)	9 (2.3%)			1,237 (2.5%)	93 (4.5%)	
Atopic dermatitis	9,057			0.5	21,463			>0.9	5,057				51,077			0.13
NO		8,411 (98%)	503 (99%)			18,954 (100%)	2,492 (100%)			4,659 (100%)	398 (100%)			48,914 (100%)	2,061 (100%)	
YES		137 (1.6%)	6 (1.2%)			15 (<0.1%)	2 (<0.1%)							101 (0.2%)	1 (<0.1%)	
Allergic rhinitis	9,057			0.7	21,463			0.7	5,057				51,077			0.7
NO		8,512 (100%)	508 (100%)			18,956 (100%)	2,492 (100%)			4,659 (100%)	398 (100%)			48,971 (100%)	2,060 (100%)	
YES		36 (0.4%)	1 (0.2%)			13 (<0.1%)	2 (<0.1%)							44 (<0.1%)	2 (<0.1%)	
Chronic spontaneous urticaria	9,057			0.4	21,463			0.2	5,057			**<0.001**	**51,077**			0.2
NO		7,648 (89%)	449 (88%)			18,057 (95%)	2,390 (96%)			4,323 (93%)	347 (87%)			46,810 (96%)	1,958 (95%)	
YES		900 (11%)	60 (12%)			912 (4.8%)	104 (4.2%)			336 (7.2%)	51 (13%)			2,205 (4.5%)	104 (5.0%)	
Mastocytosis	9,057			>0.9	21,463			>0.9	5,057				51,077			<0.001
NO		8,547 (100%)	509 (100%)			18,964 (100%)	2,494 (100%)			4,659 (100%)	398 (100%)			49,012 (100%)	2,055 (100%)	
YES		1 (<0.1%)	0 (0%)			5 (<0.1%)	0 (0%)							3 (<0.1%)	7 (0.3%)	
Angioedema	9,057			**<0.001**	21,463			**<0.001**	5,057			**<0.001**	51,077			<0.001
NO		8,081 (95%)	442 (87%)			12,673 (67%)	2,016 (81%)			3,117 (67%)	343 (86%)			15,652 (32%)	1,134 (55%)	
YES		467 (5.5%)	67 (13%)			6,296 (33%)	478 (19%)			1,542 (33%)	55 (14%)			33,363 (68%)	928 (45%)	
Personal history of drug allergy	9,057			**0.037**	21,463			0.3	5,057				51,077			0.001
NO		8,482 (99%)	500 (98%)			17,545 (92%)	2,321 (93%)			4,659 (100%)	398 (100%)			48,820 (100%)	2,044 (99%)	
YES		66 (0.8%)	9 (1.8%)			1,424 (7.5%)	173 (6.9%)							195 (0.4%)	18 (0.9%)	
Personal history of allergy (other than drug allergy)	9,057			**<0.001**	21,463			**<0.001**	5,057			0.089	51,077			0.046
NO		8,328 (97%)	481 (94%)			18,880 (100%)	2,468 (99%)			4,641 (100%)	394 (99%)			48,676 (99%)	2,040 (99%)	
YES		220 (2.6%)	28 (5.5%)			89 (0.5%)	26 (1.0%)			18 (0.4%)	4 (1.0%)			339 (0.7%)	22 (1.1%)	

[1]n (%)

[2]Pearson's Chi-squared test; Fisher's exact test

[3]Fisher's exact test; Pearson's Chi-squared test

Table 2. Comorbidities of severe and non-severe anaphylaxis in France, PMSI (2012–2021)

(57.9%). For all 44,638 patients, 5463 (12.2%) experienced severe anaphylaxis, 37.7% were considered unspecified, most triggered by drugs (45.6% of all severe cases), followed by cases related to food (9.3%) and insect sting (7.2%) (Fig. 1). Severe cases of anaphylaxis had 1.2-fold chance of new hospitalization when compared to non-severe anaphylaxis *($P < 0.002$)*, mostly related to drug-induced and unspecified anaphylaxis. Although not significant, the proportion of recurrences per patient occurred mostly in unspecified and food-induced anaphylaxis. Each anaphylaxis presentation was equal to a hospitalization, we did not observe more than 1 episode of anaphylaxis per hospitalization.

Admissions were more frequent in males (57%), but females experienced the most drug-induced anaphylaxis, both severe and non-severe presentations (Table 1). Age range of the studied population was from 0 to 103 years, 23.8% were elderly, aged more than 65 years-old. Mean age of the population studied was 44.8 years, 44.3 years for NSA and 52.5 years for SA. Table 1 also shows that the majority of admissions occurred in adulthood, from 30 to 59 years, and elderly, 7.1% of admissions were in children ages 0–9 years. Severe anaphylaxis occurred most frequently in patients aged more than 55 years, and were associated with drugs, insect sting and unspecified cases.

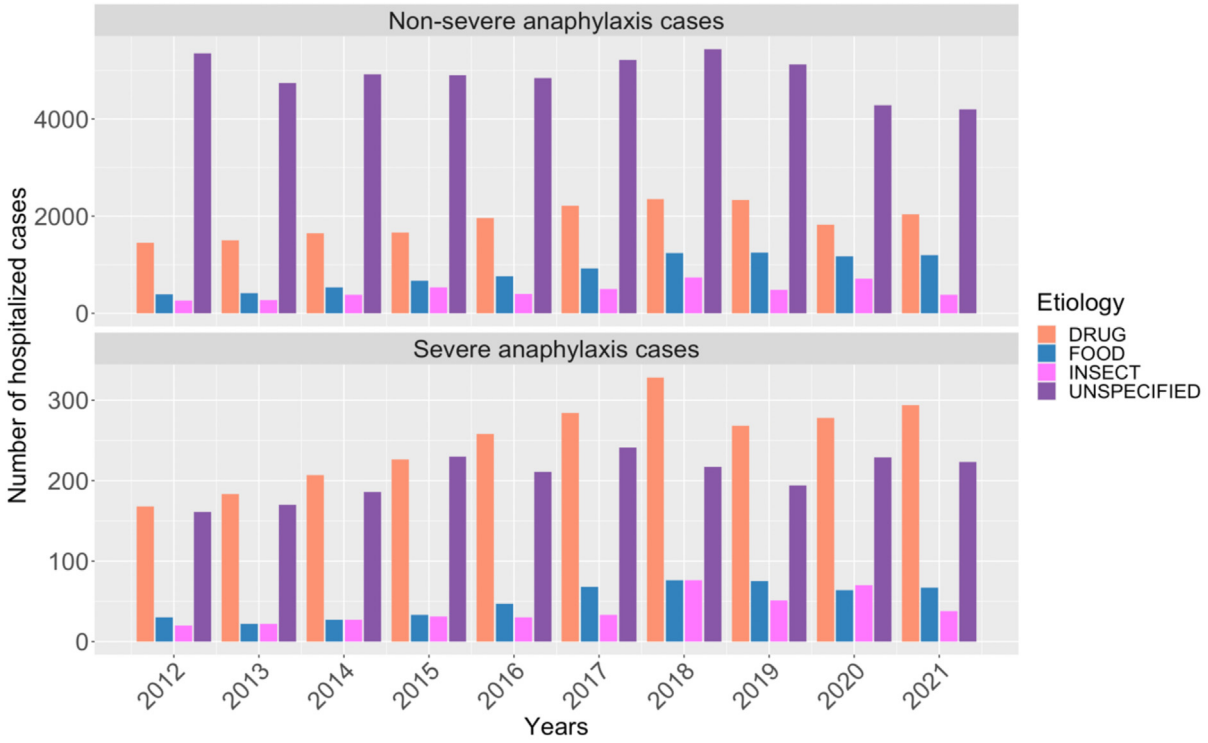

Fig. 1 Distribution of anaphylaxis per year, severity, and aetiology in France, PMSI (2012–2021).

Although food-induced anaphylaxis is more frequent in childhood, the most of cases occurred in adolescence (15–19 years) and in early adulthood (20–29 years) (Table 1). Food was highly related to severe cases of anaphylaxis at the ages of 5–9 years, but rates of severe anaphylaxis decreased dramatically after this age (Fig. 2). Non-severe cases of insect sting-induced anaphylaxis occurred in all age groups, but severe cases were observed only from 10 to 14 years of age (Fig. 2). Drugs were the main causes of anaphylaxis (Table 1), and the main cause of severe cases of anaphylaxis in all years of the study (Fig. 1). Rate of admissions for severe and non-severe drug-induced anaphylaxis

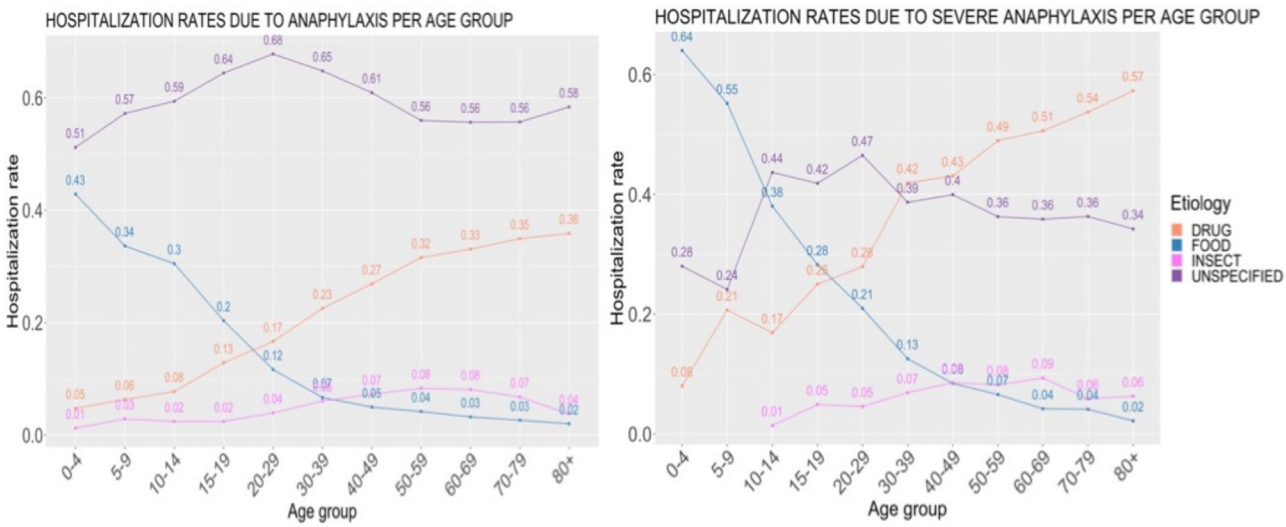

Fig. 2 Rates of hospitalization for anaphylaxis per age group in France, PMSI (2012–2021).

increased with age, but severe cases increased remarkably starting from the age of 40 years (mean trend = +1.06%/year [0.9%, 1.2%], $P < 0.001$) (Fig. 2). Unspecified cases of anaphylaxis were the main cause of admissions at all years of the study, and responsible for an increased incidence of severe anaphylaxis from the age of 10–29 years (Figs. 1 and 2). We considered each presentation equal to an admission.

Anaphylaxis trends and comorbidities

The Kendall model showed a strong positive correlation between the number of hospitalizations for severe anaphylaxis and year of hospitalization (magnitude of 0.78, $P < 0.001$), but non-significant association for non-severe cases (magnitude of 0.55, $P = 0.028$).

Using Poisson regression, we observed a significant effect of year on the total cases of anaphylaxis (mean trend = + 2.2%/year [1.9-%, 2.7%], $P < 0.0001$) and on each specific anaphylaxis cause, including iatrogenic/drugs (mean trend = +14.6%/year [4.0%, 5.0%], $P < 0.001$), insect (mean trend = +7.6%/year [6.6%, 8.7%], $P < 0.001$) and food (mean trend = +13,9%/year [+13.1%, 14.8%], $P < 0.0001$). Decreased temporal tendency was observed for unspecified cases of anaphylaxis (mean trend −1.14%/year [−1.43%, −0.84%], $P < 0.001$). For anaphylaxis in general and for almost all causes there was a trend to increase the incidence of anaphylaxis, with the exception of unspecified-related anaphylaxis.

There was a significant increase of severe cases ratio admissions over the years for all causes of anaphylaxis (mean trend = +5.9%/year [5%, 6.9%], $P < 0.001$) and on specific causes, including iatrogenic/drugs (mean trend = +6.4%/year [4.7%, 7.6.0%], $P < 0.001$), insect (mean trend = +12.5%/year [8.6%, 16.5%], $P < 0.001$), food (mean trend = +13,2%/year [+9.7%, 16.8%], $P < 0.0001$) and unspecified causes (mean trend = +2,9%/year [+1.4%, 4.5%], $P < 0.0001$). We observed a significant association between increased age and severe anaphylaxis related to drugs (mean trend = +1.0%/9 years [0.9%, 1.2%], $P < 0.0001$) and unspecified causes (mean trend = +0.4%/9 years [0.3%, 0.6%], $P < 0.0001$). There was a significant decrease in the number of admissions for severe anaphylaxis related to food over lifetime (mean trend = −1.0%/9 years [−1.4% -0.6%], $P < 0.0001$). There was not a significant association between the number of admissions due to severe anaphylaxis related to insect sting or age.

Table 2 shows the association of pre-existing chronic spontaneous urticaria with non-severe insect sting-induced anaphylaxis ($P < 0.001$), while pre-existing angioedema was associated with severe anaphylaxis for all-causes. Chronic spontaneous urticaria and angioedema refer to historical diagnosis, based on the codes described as secondary diagnosis of hospitalization. Asthma and personal history of allergy were positively associated with non-severe cases of drug- and food-induced anaphylaxis ($P < 0.001$). No significant association has been observed with mastocytosis and severe and non-severe anaphylaxis.

DISCUSSION

In this study, based on the French hospitalization data, we were able to provide detailed epidemiological data regarding hospital admissions due to anaphylaxis, with focus on severe cases, and identify potential risk factors, which may be the basis of the implementation of preventive strategies and public health interventions.

In France, which had a population of 68,035,000 in 2021,[12] most citizens have the right of access to public health settings for receiving care. The national Program for the Medicalization of Information Systems (PMSI) is a platform of the French health system aimed to collect hospitalizations data in order to reduce inequalities in resources among health establishments.[13] All hospitalization data, whether in public or private sectors, is systematically recorded in the PMSI and codified with the International Classification of Diseases (ICD),[10] currently the ICD-10.[13,11] Introduced in France in the mid-1980s, the PMSI database was first presented as an epidemiological tool before becoming a budget allocation tool. It is mandatory for public hospitals since 1991 and private hospitals since 1996.

Qualitative and quantitative data derived from PMSI are key measures of the activities and resources of establishments, and the basis of local, regional and national decision-making.[13]

There are significant differences in global anaphylaxis admission rates, with the highest rates in Australia and lowest rates reported in the United States, Spain and Taiwan.[14–17] Our data demonstrated that, in France, the rate of hospitalizations for all causes of anaphylaxis was 1.34 per 100,000 population per year and for SA was 0.08 per 100,000 population per year.

Although both non-severe and severe cases increased over time for all causes, this was not true for non-severe cases of unspecified cause. We are aware that anaphylaxis data can vary widely and may be impacted by a number of factors, such as misdiagnosis, miscoding and undernotification.[7] Difficulties on collecting accurate data should be acknowledged and anaphylaxis data can vary widely.[7] However, data from national administrative databases are the strongest tool to provide official statistics from a country or region to provide comparable data.[4,5]

Drugs are the main cause of hospitalizations due to anaphylaxis in France, after cases coded as unspecified anaphylaxis. According to our previous study, drug-indued anaphylaxis is increasing overtime and is the main cause of severe anaphylaxis admissions in adults and in elderly population.[18–21] Drug-induced anaphylaxis occurs mostly in females and higher rates are observed in adults of more than 55 years, possibly due to the increased number of drugs consumed with aging.[18–21]

Although data driven from national databases do not allow specifications, our data corroborates with previous publication in which It was shown that most of cases of severe drug-induced anaphylaxis happen at health care settings, which may contribute to the increased rates attributed to drugs. Additional data related to drug-induced anaphylaxis are that most of cases are triggered by medications administered though the intravenous route, and most patients who evolved to drug induced-anaphylaxis fatalities presented with a prior history of severe anaphylaxis (to anything) or of allergy to the same drug or same pharmacological drug class. Overall, antibiotics, anaesthesia drugs and radio contrast media are the main implicated drugs in these reactions.[20,21]

The highest rates of non-fatal food-induced anaphylaxis occur in young children, but the greatest risk appears to be in older children and adolescents. Older children and adolescent patients are at higher risk of severe food-induced anaphylaxis due to specific challenges associated with this age group where transition to adulthood requires an added multidisciplinary involvement for training, enhancing knowledge and skills to guide and empower them to self-manage their health condition.[22] Other studies have reported that the risk for severe anaphylaxis is higher in older (50–75 years) than middle aged (35–50 years) individuals.[23]

In contrast to drug-induced anaphylaxis, most episodes of food-induced anaphylaxis occur outside the healthcare settings and by accidental food allergen exposure.[2,24] Until now, it was not possible to know the rate of hospitalization of those patients who had food-induced anaphylaxis for accidental exposure outside healthcare facilities.

The number of admissions to the hospital can be reduced due to the possible spontaneous remission of anaphylaxis. More than half of all anaphylaxis cases resolve spontaneously without treatment. Only a minority of anaphylaxis cases require hospitalization. The reported data on hospitalizations for anaphylaxis varies with the observation time stipulated by the hospital emergency department and whether the visit were coded as a hospital admission or an emergent consultation.[8]

Although asthma has been reported as an identified risk factor for food-induced anaphylaxis fatalities,[24,25] our study was not able to confirm this association with severe non-fatal cases of food-induced anaphylaxis.

Insect sting-induced anaphylaxis is one of the leading causes of anaphylaxis in western countries,[26] in the adult population. In the adolescent and adult population, severe insect sting-induced anaphylaxis is also a cause for frequent admissions to the hospital.

A history of chronic spontaneous urticaria and/or angioedema, unspecified, are risk factors for hospital admissions with patients who had insect sting induced anaphylaxis, as demonstrated in our results. Although chronic spontaneous urticaria and angioedema refer to historical diagnosis, this association may be a signal of an underlying mast

cell condition even when the history is negative for mastocytosis. Data presented can be in part influenced by the process of diagnosis and coding.[7] Identifying and coding isolated manifestations, such as urticaria and angioedema, is easier than diagnosing complex conditions, such as mastocytosis.[25–27] Another possible cause of the association between chronic spontaneous urticaria and/or angioedema unrelated to any trigger with a higher risk of admissions due to insect sting-induced anaphylaxis is the hereditary alpha tryptasemia. Patients with insect sting-induced anaphylaxis may also have underlying undiagnosed hereditary alpha tryptasemia.[28] Unfortunately, ICD-10 does not have a code for hereditary alpha tryptasemia.[11] Hereditary alpha tryptasemia is present in up to 6% of the general population, which dramatically increases the risk of anaphylaxis and severe anaphylaxis, and that is not assessed routinely. The association with angioedema and/or urticaria and higher risk of admissions due to insect sting-induced anaphylaxis also raises the questions whether these mucocutaneous manifestations were underdiagnosed mild manifestations of anaphylaxis.

A personal history of allergy is associated with hospitalization due to both drug and food-induced anaphylaxis. It flags the need of detailed clinical history from health professionals, referral to the specialist and need of the implementation of personalized emergency recommendations for patients who experienced a previous episode. Another hypothesis is that anaphylaxis can be over-diagnosed in patients who have underlying atopic conditions with symptoms that can be misconstrued as part of an anaphylactic response, especially when other symptoms are entirely subjective (eg, globus).[5]

Although unspecified cases represent almost 40% of all cases, the majority are non-severe, but relapse more. This group possibly consists of patients with no or incomplete allergy work-up. Different from other phenotypes, there is no significant association with comorbidities. Biomarkers may help in the future to further dissect and understand this phenotype. We may have to keep a warning position in these cases. In the early studies of idiopathic anaphylaxis by Greenberger et al in Chicago, it was said to be uniformly non-fatal. Only after many years of study, they identified patients who became progressively worse as well as fatal cases. It has also been noted in several reports that biphasic anaphylaxis (and therefore severe or fatal anaphylaxis) is more common in cases with unspecified cause.[29] Therefore, these cases should be followed in order to improve the diagnosis and prevent new episodes.

DRUG-INDUCED ANAPHYLAXIS	FOOD-INDUCED ANAPHYLAXIS	INSECT STING-INDUCED ANAPHYLAXIS	UNESPECIFIED ANAPHYLAXIS
• Gender: female • Age: >54 years • Increased number of drug intake • Personal history of drug allergy/hypersensitivity with no or incomplete allergy work-up • Comorbidities: cardiovascular disease, uncontrolled/underdiagnosed asthma • Need of recurrent hospitalization and/or frequent health care assistance • Need frequent use of intravenous antibiotics and/or undergoing surgery or image investigation with radiocontrast media	• Gender: male • Age: older children and adolescents • Personal history of allergy/hypersensitivity (including angioedema unrelated to any trigger), personal history of anaphylaxis • Comorbidities: uncontrolled or underdiagnosed asthma, multiple food allergies • Difficult accessibility to or delayed use of epinephrine auto-injectors • Accidental exposure to the trigger	• Gender: male • Age: middle age • Personal history of allergy/hypersensitivity (including chronic spontaneous urticaria and angioedema) • Comorbidities: cardiovascular disease, mast cell disease • Difficult accessibility to epinephrine auto-injectors. • Outdoor exposure due to professional or leisure reasons, during spring and summer	• Gender: female • Age: middle-age (40-50 years) • No or incomplete allergy work-up • Comorbidities: angioedema, allergic contact dermatitis, and chronic urticaria

Table 3. Summary of high-risk factors associated with each trigger for severe anaphylaxis

Most cases of anaphylaxis in all ages were considered unspecified, but the majority were non-severe and decreased over time. The allergy community has been making efforts to correctly label allergic patients, and issues on correct recording anaphylaxis in electronic health records has been pointed as one of the main obstacles.[4,23] Many health care workers who document the cases have minimal formal knowledge in the field, which limits the accuracy of the reports. Reaching consensus on the definition, classification and coding of anaphylaxis may contribute to better quality morbidity and mortality data. Hopefully more accurate coding of anaphylaxis will occur with the worldwide implementation of ICD-11, which includes a more detailed section on anaphylaxis.[30–34]

Our findings together with published data[1,2,4,8,9,14–21,24–27,35–38] may be able to help identify phenotypes of allergic patients who are at-risk for severe anaphylaxis, based upon specific triggers. A summary of high-risk factors associated with each trigger for severe anaphylaxis is presented (Table 3).

This study presents some limitations. As with any health-care reported data, there is a number of caveats including the accuracy of coding, clinical diagnosis of anaphylaxis, and the proportion of cases either treated in the community without hospital admission or treated in outpatient accident and emergency departments without admission. However, these caveats should be stable over the 9 years of our study analysis. Data of ED have not been included in this study due to the fact that it is not available in the PMSI, but it will be available in a forthcoming study. As expected in all population-based studies, it was not possible to identify detailed clinical data or details of biphasic cases of anaphylaxis. Although the classification of severity used in this study was not consistent with any of the common grading systems for anaphylaxis, hospitalization setting has been used as a parameter due to the fact that the PMSI, based on ICD-10, is not able to provide markers of severity related to the manifestation of complex conditions. Mild reactions are usually not captured in these studies, mostly because the ICD-10 is not able to capture mild degrees of anaphylaxis.[33] Many versions of the ICD-10 were used over the period of analysis, but anaphylaxis related codes have always been stable and badly classified in all versions of ICD-10.[32,34,39,40] However, the ICD-11 may provide new perspective by allowing accurate diagnosis of anaphylaxis and by combining with severity scores and/or aetiology.[27,33] Findings should be validated in other countries and nationally prospectively.

CONCLUSION

More than providing epidemiological data on anaphylaxis, this study based on the French national hospitalization database provided data related to severe phenotypes of anaphylaxis. Information presented are key to implement public health actions and preventive strategies to provide quality care of patients suffering from anaphylaxis.

Abbreviations

ICD, International Classification of Diseases; INSEE, French National Institute of Statistics and Economic Studies; PMSI, Program for the Medicalization of Information Systems.

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Availability of data and materials

Raw data may be available after acceptance of the article and per request.

Authors' contributions

The first and last authors contributed to the construction of the document (designed the study, designed the questionnaire, analysed and interpreted the data, and wrote the manuscript). All the authors critically revised and approved the final version of the manuscript and agree to be accountable for all the aspects of the work.

Authors' consent for publication

All the authors consent for publication.

Declaration of competing interest

The authors declare that they do not have any conflict of interests related to the contents of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100951.

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