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Anaphylaxis in Brazil between 2011 and 2019

Luciana Kase Tanno^{1,2,3,4}  | Nicolas Molinari^{2,3} | Isabella Annesi-Maesano³ |
Pascal Demoly^{2,3,4}  | Ana Luiza Bierrenbach^{1,5}

¹Hospital Sírio-Libanês Sao Paulo, São Paulo, Brazil

²University Hospital of Montpellier, Montpellier, France

³Desbrest Institute of Epidemiology and Public Health, UMR UA-11, INSERM University of Montpellier – INSERM, Paris, France

⁴WHO Collaborating Centre on Scientific Classification Support, Montpellier, France

⁵Sanas Epidemiology and Research, São Paulo, Brazil

Correspondence

Luciana Kase Tanno, Division of Allergy, Department of Pulmonology, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, 371, av. du Doyen Gaston Giraud - 34295, Montpellier cedex 5, France.

Email: luciana.tanno@gmail.com

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Abstract

Background: There is a lack of population-based studies of anaphylaxis from low- and middle-income countries. This hampers public health planning and investments and may influence availability of adrenaline auto-injectors.

Objective: We conducted the first national population-based study of anaphylaxis hospitalization in Brazil.

Methods: Descriptive study using routinely reported data to the Brazilian Hospital Information System for the years 2011–2019. Information available is coded based on the International Classification of Diseases (ICD)-10 and covers main cause of hospitalization (primary cause) and any conditions contributing to it (secondary cause).

Results: Over 9 years, we identified 5716 admissions due to anaphylaxis for all causes. The average hospitalization rate related to anaphylaxis was 0.71/100,000 population per year, with a 2.4% (95% CI 1.9%, 2.9%) increase per annum over the study period. Admissions were more frequent among females (52.8%), except for cases due to insect sting. Most admissions occurred in adulthood, from 30 to 59 years (36.3%) but 13.8% in preschool children (0–4 years). There were more young children admitted for food-related anaphylaxis, and more adults admitted for drug/iatrogenic-related anaphylaxis. There were 334 cases (5.8% of admissions) of fatal anaphylaxis over the study period, with increased case fatality rate over time.

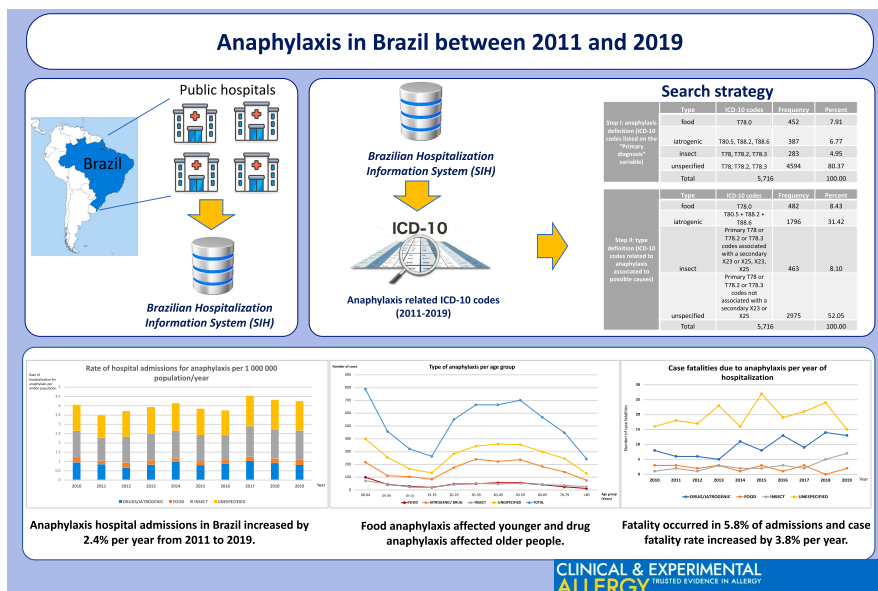
Conclusions and Clinical Relevance: This is the first study of anaphylaxis hospital admissions using nation-wide data from a low- or middle-income country. Hospital admissions and fatalities from anaphylaxis in Brazil appear to be increasing.

KEYWORDS

anaphylaxis, classification, epidemiology, international classification of diseases, management, prevention; adrenaline/epinephrine auto-injector, treatment

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GRAPHICAL ABSTRACT

Data from the Brazilian Hospital Information System, which accounts for approximately 75%–80% of hospitalizations in Brazil, were analysed for 2011–2019. A stepwise approach was used to identify hospitalizations for anaphylaxis, using ICD-10 codes. This first study on anaphylaxis hospital admissions using Brazilian national data showed an average rate of 0.71 admissions per 100,000 population per year, with a 2.4% increase per annum between 2011 and 2019. More young children were admitted for food-related anaphylaxis and more adults for drug-related anaphylaxis. Fatal anaphylaxis occurred in 5.8% of admissions, and fatalities appeared to increase over time.

[Correction added on 10 August 2022, after first online publication: The Graphical Abstract text was incorrect and has been updated in this version.]

1 | BACKGROUND

The frequency of hospital admissions for anaphylaxis is increasing in many countries, although most countries report no parallel change in fatal anaphylaxis rates.^{1–9} However, a regular and systematic data collection and dissemination of statistics on diagnoses-based morbidity does not exist, and epidemiological data differ from country to country depending on a number of variables. The lack of accurate anaphylaxis morbidity and mortality information impacts on public health policy development and investments such as public reimbursement of adrenaline auto-injectors and relevant environmental changes. Recent publications show a global incidence of anaphylaxis between 50 and 112 episodes per 100,000 person-years while the estimated lifetime prevalence is 0.3%–5.1%, variations depending on the definitions used, study methodology and geographical areas.^{2,5}

Improving the quality of epidemiological data related to anaphylaxis should clarify some areas of uncertainty about risk factors, leading to better targeting of strategies to protect those patients at risk and support decision making to facilitate healthcare planning and implementation of public health measures to prevent anaphylaxis. Hospital admissions data sets represent the largest and most robust data available to understand trends in anaphylaxis. However, most of publications utilizing this source come from high-income countries.^{2,10} There are limited population-based anaphylaxis studies from low- and middle-income countries. The lack of anaphylaxis epidemiological data hampers public health planning and investments, exemplified by the limited availability of adrenaline auto-injectors as first-line treatment of anaphylaxis in many of these countries, such as in Brazil.^{10,11}

Key Messages

- Anaphylaxis hospital admissions in Brazil increased by 2.4% per year from 2011 to 2019.
- Fatality occurred in 5.8% of admissions and case fatality rate increased by 3.8% per year.
- Food anaphylaxis affected younger and drug anaphylaxis affected older people.

Brazil had a population of 212,558,417 in 2020. In 1988, the Brazilian Constitution defined health as a universal right and a state responsibility. Progress towards universal health coverage in Brazil was achieved through the Unified Health System (SUS), with universal access to healthcare services for the population. All the public institutions' hospitalization data derived from the SUS are automatically recorded in the Brazilian Hospital Information System (SIH) and coded using the International Classification of Diseases (ICD).¹²

We here present the first Brazilian population-based study based on 8 years anaphylaxis hospitalization data. We believe the study to be of international importance as the first population-based anaphylaxis data for a low- or middle-income country; and to be of national importance to provide evidence-based data for healthcare managers and governmental bodies in order to support actions for better care of anaphylactic patients. For this, we used the information derived not only from the main cause of hospitalization but also from the causes of the SIH to estimate the number and trends of anaphylaxis hospital admissions.

2 | METHODS

2.1 | Type of study, data source and collection

This is a descriptive study using routinely reported data to the Brazilian SIH for the years 2011–2019, extracted on 8 June 2020. This system is electronic, stores information on hospital admissions that occur in the public health system, which accounts for approximately 75%–80% of hospitalizations in Brazil.¹² 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) and any conditions contributing to it (secondary causes).

From all 117,090,886 records identified during this period, the following strategy was applied: Step I: Firstly, 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, T88.6); Step II: We further classified the common causes of anaphylaxis (food, insect, iatrogenic/drug and unspecified) for all anaphylaxis patients using a combination of ICD-10 codes from the primary or secondary causes. The 3- and 4-digits ICD-10 codes applied in both stages have been validated by two independent professionals. The need for step II was due to the proven limitations of the ICD-10 coding to directly capture the aetiology of anaphylaxis cases (Table 1). If we had only considered Step I, additional information related to aetiologies would be lost and most cases would have been considered as unspecified. Strategy has been validated by two independent coders and the agreement has been analysed using by the Cohen kappa.

2.2 | Data analysis

Annual anaphylaxis hospital admission and mortality rates per 100,000 population and 95% confidence intervals were calculated for each year. Population estimates were obtained from the Brazilian Institute

of Geography and Statistics (IBGE).¹³ For this analysis, we tested the hypothesis that the proportion of anaphylaxis cases identified in both steps was equivalent at each category of the qualitative analysis, which included data on gender, age, possible aetiology and outcome (death or not). *p* values of <.05 were considered significant. Age-standardized rates for hospital admissions were calculated by standardizing to the age distribution of the population in mid-2010, the year of the last census. Poisson regressions were run to evaluate changes over time for anaphylaxis admissions and case fatality rates, both overall and by specific cause.

3 | RESULTS

Over 9 years, we identified 5716 admissions due to anaphylaxis for all causes. The average hospitalization rate related to anaphylaxis over the 8 years was 0.71 per 100,000 population per year (Figure 1).

We confirmed the under-notification of anaphylaxis morbidity data by comparing the number of anaphylaxis cases identified in Steps I and II. The ICD-10 code *T72 Anaphylactic shock, unspecified* was used in 73% of cases (Table 2). With the application of Step II codes, 28.32% of cases classified as unspecified in Step I could reach implemented precision (Table 1). As final evaluation, 52% were classified as unspecified, 31.4% as iatrogenic, 8.4% as food-related and 8.1% insect-related anaphylaxis (Table 3, Figure 1). Internal validation by evaluation the agreement between coders was high (Cohen kappa = 0.74). We were able to observe that a quarter of anaphylaxis was captured among children under 5 years of age who had suffered from iatrogenic anaphylaxis. There was no clear trend towards an increase or decrease of specific aetiology ratio over the years (Figure 1). Using Poisson regression, we observed a significant increase in the total cases of anaphylaxis (mean trend = + 2.4%/year [1.9%, 2.9%, *p*-value <.0001) and for some specific anaphylaxis causes, including iatrogenic/drugs (mean trend = +1.6%/year [0.2%, 3.3%], *p*-value = .046), insect (mean trend = +5.05%/year [1.75%,

TABLE 1 Strategy applied to gather implemented etiological details in Brazilian SIH (2011–2019), frequency of use of ICD-10 codes (Step I) and outcomes after applying strategy to gather implemented etiological details (Step II)

Type	ICD-10 codes	Frequency	Percent
Step I: Anaphylaxis definition (ICD-10 codes listed on the "Primary diagnosis" variable)			
Food	T78.0	452	7.91
Iatrogenic	T80.5, T88.2, T88.6	387	6.77
Insect	T78, T78.2, T78.3	283	4.95
Unspecified	T78, T78.2, T78.3	4594	80.37
Total		5716	100.00
Step II: Type definition (ICD-10 codes related to anaphylaxis associated to possible causes)			
Food	T78.0	482	8.43
Iatrogenic	T80.5 + T88.2 + T88.6	1796	31.42
Insect	Primary T78 or T78.2 or T78.3 codes associated with a secondary X23 or X25, X23, X25	463	8.10
Unspecified	Primary T78 or T78.2 or T78.3 codes not associated with a secondary X23 or X25	2975	52.05
Total		5716	100.00

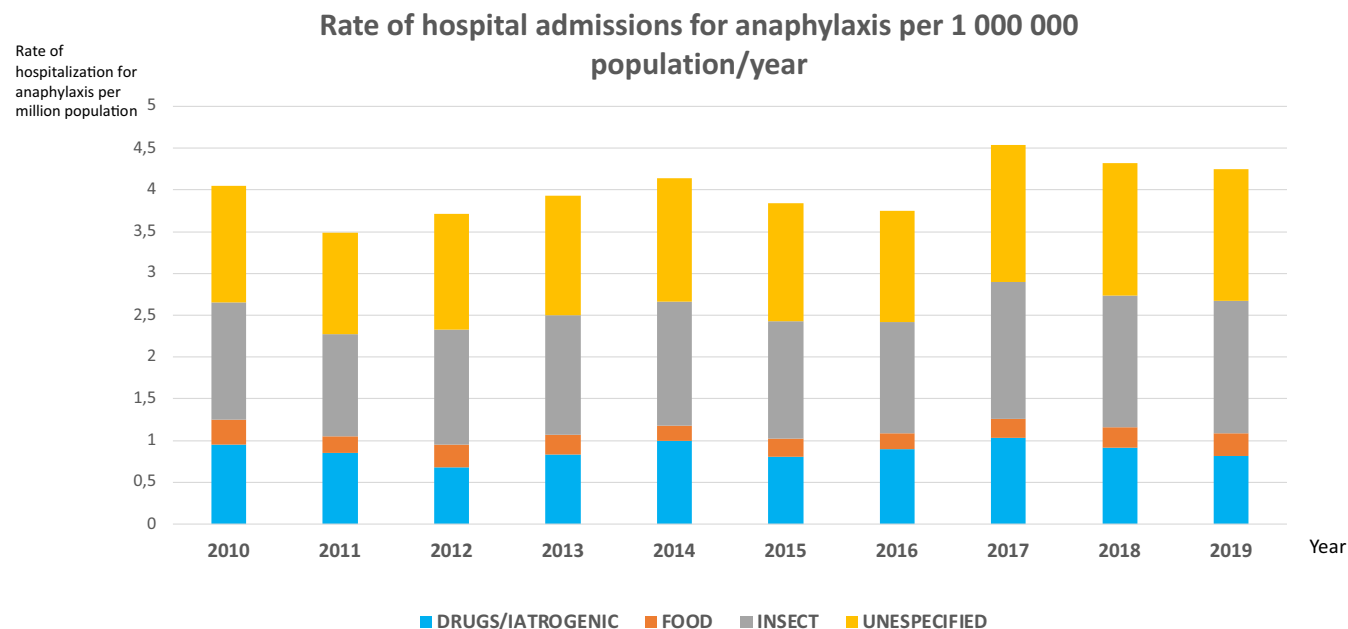


FIGURE 1 Anaphylaxis hospitalization trends and aetiology distribution, as recorded on Brazilian SIH, 2011–2019. There was a significant increase in anaphylaxis rates over the years, with mean increase 2.4% per year (95% CI 1.9%, 2.9%, p -value < .0001)

TABLE 2 Frequency of anaphylaxis ICD-10 codes used as principal diagnosis in Brazilian SIH (2011–2019)

Main diagnoses	ICD-10 labels	Number of cases	Percent	Cumulative
T78	Anaphylaxis, Adverse effects, not elsewhere classified	4	0.07	0.07
T780	Anaphylaxis, Anaphylactic shock due to food allergy	452	7.91	7.98
T782	Anaphylactic shock, unspecified	4183	73.18	81.16
T783	Angioneurotic edema	690	12.07	93.23
T805	Anaphylactic shock due to serum	69	1.21	94.44
T882	Shock due to anaesthesia	107	1.87	96.31
T886	Anaphylactic shock due to adverse effect of correct and properly administered drug or medication	211	3.69	100.00
Total		5716	100.00	

8.46%, p -value = .024) and unspecified (mean trend = +2.88%/year [1.6%, 4.18%], p -value < .0001). There was no significant change in rate of food-related anaphylaxis over time (mean trend 0.05%/year [−3.0%, 3.2%], p -value = .975).

Table 3 demonstrates hospital admissions due to anaphylaxis for all causes vary according to patients' demographic characteristics. Admissions were more frequent among females (52.8%), except for those cases due to insect sting. The majority of admissions occur in adulthood, from 30 to 59 years (36.3%). However, 13.8% of all admissions have been reported in early ages (0–4 years). All age groups are affected, but there are more young children admitted for food-related anaphylaxis and more adults admitted for medications/iatrogenic-related anaphylaxis (Figure 2). Race/colour data were missing in 24.4% of cases. Patterns across race/colour are mostly similar, except for white individuals admitted more often for insect sting-related anaphylaxis.

From overall 5716 admissions due to anaphylaxis for all causes over 8 years, 334 cases (5.8%) resulted in fatal outcome, with case fatality rate varying from 4.9% to 7.5% over time. There was a significant increase of case fatality rates over the years (mean trend = +3.8%/year [2.1%, 6.1%], p -value = .037). Case fatality ratio varied with the cause, 59% of fatal anaphylaxis cases were due to unspecified anaphylaxis (no significant change over time 1.02 [0.97–1.07], p = 0.52), 26% were attributed to iatrogenic anaphylaxis (increase over time 1.09 [1.02–1.18], p = .014), 8% to insects (increase over time 1.20 [1.04–1.38], p = 0.01) and 6% to food triggers (no change over time 0.91 [0.79–1.07], p = .27) (Figure 3 and Table S1). From all 344 anaphylaxis deaths 44% occurred in patients aged more than 60 years. In Poisson regression, we observed a significant association between increased age and risk of fatal anaphylaxis (mean trend = +2.5%/10 years [2.0%, 2.9%], p -value < .0001).

TABLE 3 Demographic characteristics of anaphylaxis hospital admissions, as recorded on Brazilian SIH, 2011–2019

	Latrogenic N (%)	Food N (%)	Insect N (%)	Unspecified N (%)	Total N (%)	p-Value
Sex						
Female	1024 (57)	251 (52.1)	141 (30.4)	1602 (53.8)	3018 (52.8)	<.0001
Male	772 (43)	231 (47.9)	322 (69.6)	1373 (46.2)	2698 (47.2)	
Age, median (IQR)	38.4 (15.8–57.1)	30.4 (8–52.4)	35.3 (9.7–57.5)	37.3 (12.2–58.1)	36.8 (12.4–57.2)	.001
Age group						
0–4	217 (12.1)	100 (20.8)	72 (15.6)	400 (13.4)	789 (13.8)	.003
5–9	112 (6.2)	43 (8.9)	48 (10.4)	255 (8.6)	458 (8)	
10–14	104 (5.8)	29 (6)	23 (4.9)	165 (5.5)	321 (5.6)	
15–19	84 (4.7)	20 (4.2)	20 (4.3)	139 (4.7)	263 (4.6)	
20–29	176 (9.8)	47 (9.7)	44 (9.5)	284 (9.6)	551 (9.6)	
30–39	241 (13.4)	50 (10.4)	52 (11.2)	343 (11.5)	686 (12)	
40–49	223 (12.4)	57 (11.8)	47 (10.2)	359 (12.1)	686 (12)	
50–59	238 (13.3)	57 (10.8)	52 (11.2)	355 (11.9)	702 (12.3)	
60–69	184 (10.2)	42 (8.7)	43 (9.3)	300 (10.1)	569 (10)	
70–79	141 (7.9)	25 (5.2)	36 (7.8)	246 (8.3)	448 (7.8)	
80+	76 (4.2)	12 (2.5)	26 (5.6)	129 (4.3)	243 (4.3)	
Race/colour						
White	785 (43.7)	196 (40.7)	246 (53.1)	1253 (42.1)	2480 (43.4)	<.001
Black	79 (4.4)	15 (3.1)	12 (2.6)	108 (3.6)	214 (3.7)	
Brown	525 (29.2)	154 (32)	120 (26)	773 (26)	1572 (27.5)	
Yellow	14 (0.8)	3 (0.6)	3 (0.6)	31 (1)	51 (0.9)	
Indigenous	0 (0)	0 (0)	0 (0)	2 (0.1)	2 (0.1)	
Not available	393 (21.9)	114 (23.6)	82 (17.7)	808 (27.2)	1397 (24.4)	
Total	1796	482	463	2975	5716	

4 | DISCUSSION

This study based on national hospitalization database was able to provide for the first time detailed epidemiological data regarding hospital admissions due to anaphylaxis and outcomes in Brazil. The SIH stores information on hospital admissions that occur in the public health system, which accounts for approximately 75%–80% of hospitalizations in Brazil. All the data are coded using the ICD, and currently the ICD-10.¹²

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.^{1,3,6,7,8,9,14,15} Our data demonstrated that anaphylaxis accounts for up to 0.26% of overall hospital admissions, less than most reports from other countries. It can be related to the different definitions of anaphylaxis used, diagnosis of anaphylaxis in clinical practice and under notification of anaphylaxis due to the ICD codes. Severe episodes of anaphylaxis or deaths from anaphylaxis often have multiple risk factors present. Recent studies by Yao et al.¹⁴ and Robinson et al.¹⁵ showed similar results from ours, but they showed that total presentations increased but hospital admissions were stable, largely because of higher rates of presentation and treatment in outpatient emergency departments. We can also hypothesize that most severe acute cases evolve to death before arriving at

the hospital, perhaps partly due to the lack of availability of AAls in Brazil, although there is no evidence availability/provision of AAI reduces deaths. There is little doubt that epidemiological data alone are not enough to move public policies or measures, but the data presented is intended to be a starting point to trigger discussions with regulators and governmental bodies regarding public health actions, such as the national availability of AAls.¹¹

In concordance with the population data from other countries, we have demonstrated increases in hospitalizations for anaphylaxis, both with respect to all-cause anaphylaxis and by triggers,^{1,3,6,7,8,9,14,15} with the exception of food-related anaphylaxis. In contrast with most other population-based studies, where food anaphylaxis shows the greatest temporal increase, our data demonstrated that food-induced anaphylaxis did not increase. Possible reasons for the variations include differences in recognition, particularly when food-induced anaphylaxis occurs outside the healthcare settings, limited access and quality of medical care and methods for data retrieval and analysis. Due to the fact that adrenaline autoinjectors (AAI) are lacking in Brazil,¹⁶ available only by importation, patients with high risk of fatal anaphylaxis may have increased out of hospital death rates in Brazil. However, it should be noted that increased AAI prescriptions were not associated with any change in numbers of fatal anaphylaxis cases in the United Kingdom.¹

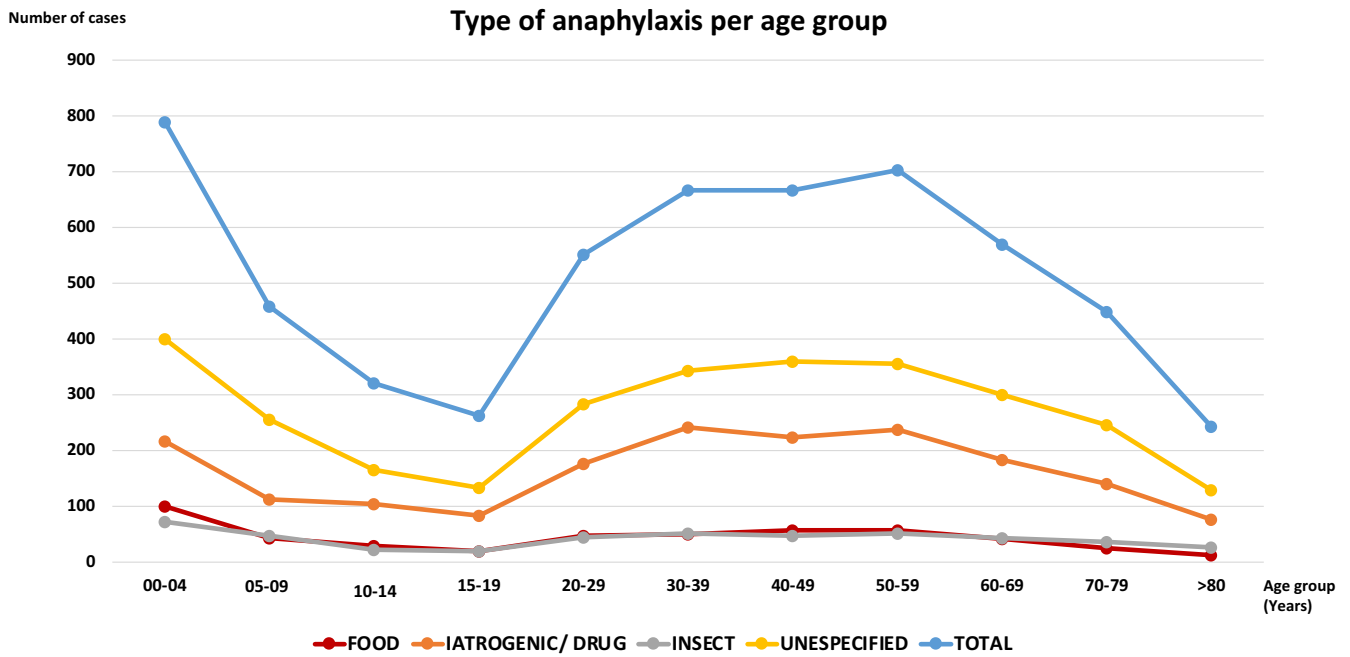


FIGURE 2 Type of anaphylaxis per age group based on hospitalization data reported in the Brazilian SIH (2011–2019)

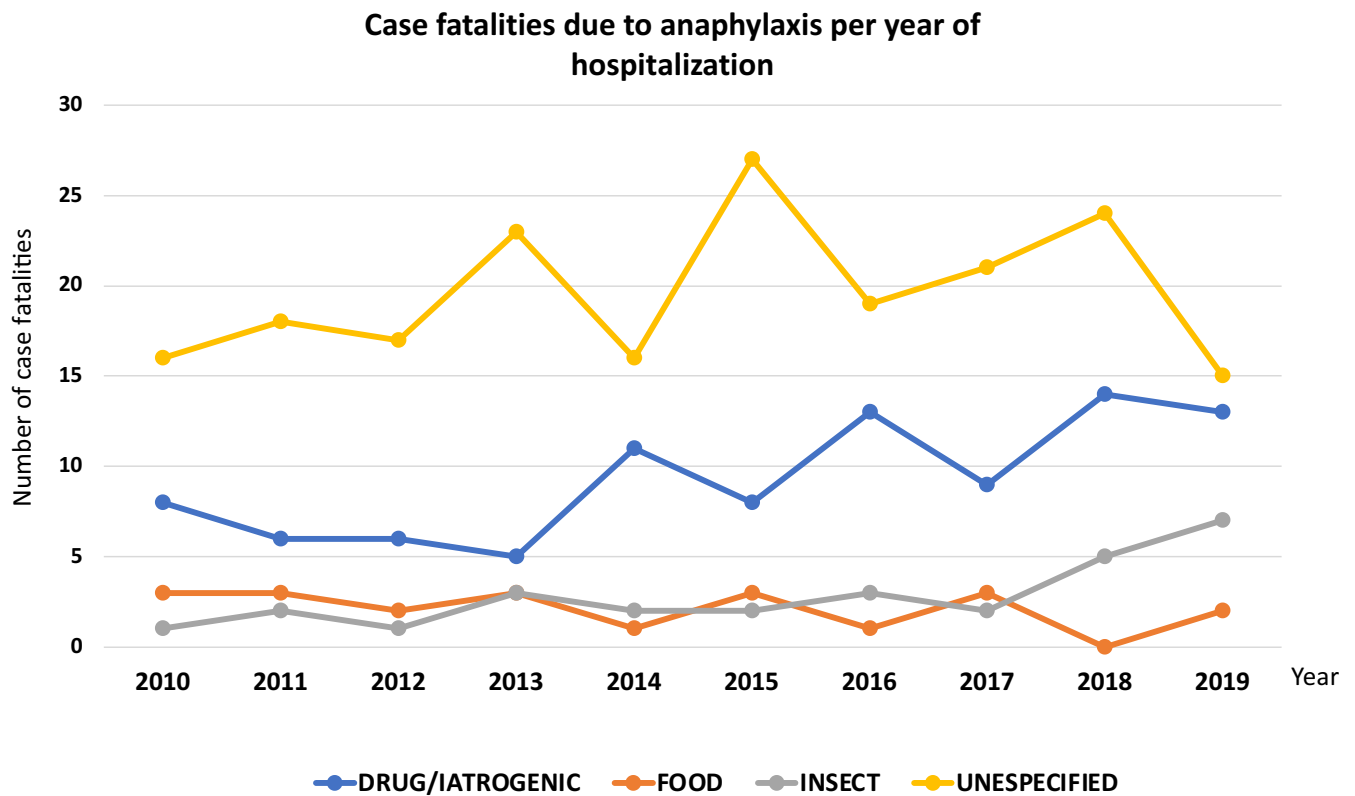


FIGURE 3 Number of anaphylaxis deaths and aetiology distribution, as recorded on Brazilian SIH, 2011–2019. There was a significant increase in case fatality rates over the years, with mean increase 3.8% per year (95% CI 2.1%, 6.1%, p -value = .037)

Age and aetiology distribution of our study was quite similar from the reports from other countries.^{1,3,6,7,8,9,14,15} Iatrogenic/medications represented the most common trigger for anaphylaxis admissions to hospital and was the main cause of anaphylaxis-related fatalities.¹⁷

Unexpected finding of iatrogenic causes is that one quarter was observed in the 0–14 years age group, which is contrary to what we know about the rarity of drug allergies in childhood. Hospitalization due to food-related anaphylaxis peaks in the paediatric age range

(<4 years) but contributes significantly to adult admissions, where typically anaphylaxis admissions due to medication exceed those due to food by the fifth decade onwards. Insect-related anaphylaxis rates increased over the years, and were more frequent in adults from 30 to 59 years probably due to the risk of exposure.

Our age-related pattern of food anaphylaxis admissions is different to that seen in the UK data set, where there is a peak in younger age group and a peak for fatal food anaphylaxis in adolescence/early adulthood.^{2,7} Although we have no specific data of anaphylaxis fatalities outside the period of hospitalization or ED admissions in Brazil, anaphylaxis can occur virtually in any setting. We hypothesize that patients in Brazil may incur a higher risk of death before accessing healthcare facilities, as the limited facilities to access healthcare settings and the absence of AAls may increase the risk of fatal outcome.

Reports have been mentioning adolescence as a risk factor for anaphylaxis due to the characteristics of this transition period and difficulties in the self-management of the condition.¹⁸ We did not observe higher rate of hospitalization at this age group (Figure 2). It may be due to age-related unacceptance of the diagnosis and limited access to healthcare services as a consequence. We have no data of anaphylaxis fatalities outside the period of hospitalization or ED admissions.

Case fatality rates are estimated at 0.5%–1% of fatal outcomes for hospitalization.² In our study, fatal outcome occurred in 5.8% of anaphylaxis admissions, with significant increasing number of deaths over time, mostly related to iatrogenic/medications triggers and insect-related cases. Interestingly, we observed that although food was the second cause of admissions to hospital due to anaphylaxis, it was a less frequent cause of death in our population and we did not observe any change in food anaphylaxis admission or case fatality rates. Likely explanation for high mortality rate in Brazil is perhaps the fact that in Brazil more severe cases are admitted.

Current population in Brazil is 213,993,437 according to the IBGE, which is the agency responsible for official collection of statistical, geographic, cartographic, geodetic and environmental information in Brazil. Although the Brazilian population is known as its mixed ethnicity, according to data provided by the IBGE, most of the population self-reported as being white (Caucasian).¹³ Brazil is also known for significant social-economic disparities and due to the history of slavery, the white population (45% of all population) is in general more privileged, having easier access to healthcare settings. These factors may have influenced our results (Table 3).

Recognized difficulties in obtaining accurate anaphylaxis data are the variations in definitions of anaphylaxis across different world regions, classification and coding issues related to collection of large health data sets, and the difficulties in collecting data for a disease state that frequently occurs in the community, not within a hospital, captive region or health resources.^{2,10} Recently, the definition of anaphylaxis by the World Allergy Organization (WAO) was reviewed, in order to capture not only severe cases,¹⁹ but also align this effort with the anaphylaxis definition proposed in the World Health Organization (WHO) ICD-11: "Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening

airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes".^{19–21} The ICD-11 is under implementation worldwide and will provide the tools for a better classification and coding of anaphylaxis, and, probably, the strategy used in this paper to capture anaphylaxis will not be required.^{22,23}

Population-based studies that make use of secondary data source such as SIH are very much contingent on the quality and methods used to classify the data. Given the considerable number of anaphylaxis cases considered unspecified at the initial evaluation (Step I), the strategy applied was successful in gathering 28.3% of conditions and give them implemented detail, with incremental number of cases identified as iatrogenic as the final analysis. If we only considered Step I, additional information related to aetiologies would be lost and most cases would be considered as unspecified.

Most of anaphylaxis hospitalization reports in our study were classified as unspecified, followed by ICD code related to more severe cases of anaphylaxis. The ICD-10 has proven deficiencies to capture anaphylaxis to both mortality and morbidity data.^{24,25} However, anaphylaxis epidemiological data may gain incremental accuracy and refinements thanks to the implementation of the ICD-11.^{26,27}

This study however presents some limitations. As with any study reliant on government derived data, there is a number of caveats including accuracy of coding, access to medical care (potentially influenced by location of residence or socio-economic status), availability of adrenaline auto-injectors (which might reduce the need for hospital treatment), 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. As expected in all population-based studies, it was not possible to identify recurrences nor biphasic cases of anaphylaxis. The SIH does not capture emergency departments admissions data, which could enrich the study, but the quality of the data presented has not been affected. Mild reactions are usually not captured in these studies, mostly because the ICD-10 is not able to capture mild degrees of anaphylaxis. 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. No detailed etiological ICD-10 codes have been used due to the data unavailability in the SIH. However, the ICD-11 may provide new perspective by allowing to add the severity of the reactions.

5 | CONCLUSION

This is the first study on anaphylaxis hospital admissions using nationwide data from a lower or middle-income country. There are increasing anaphylaxis admissions for all causes in Brazil and increasing case fatality rates. Anaphylaxis in Brazil is an important public health issue due to the number of hospitalizations and potential risk of death. Data presented here will be used to support national public health actions to improve emergency care for people with anaphylaxis.

AUTHOR CONTRIBUTIONS

The first and last authors contributed to the construction of the document (designed the study, including 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.

CONFLICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in dataSUS website at [<https://datasus.saude.gov.br/aceso-a-infor-macao/morbidade-hospitalar-do-sus-sih-sus/>], reference number.¹²

ORCID

Luciana Kase Tanno  <https://orcid.org/0000-0003-3236-1225>

Pascal Demoly  <https://orcid.org/0000-0001-7827-7964>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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