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Undernotification of anaphylaxis deaths in Brazil due to difficult coding under the ICD-10

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Abstract

Background: Undernotification is well recognized as a key challenge to the study of anaphylaxis mortality, but it is seldom mentioned that one of its reasons is the difficult coding of the condition under the tenth revision of the international classification of diseases (ICD-10), given that there are no anaphylaxis-specific ICD-10, which are considered valid for coding underlying causes-of-death, and that official mortality statistics consider exclusively the underlying and disregard the contributing causes-of-death data recorded on death certificates. Brazilian mortality data were used as a case study to call attention to the inadequacy of the ICD-10 for the measurement of anaphylaxis deaths.

Methods: Underlying and contributing causes-of-death data were used to estimate the rates of anaphylaxis deaths in the country over the years 2008–2010.

Results: Of 498 anaphylaxis deaths were found, of which 75% were classified as 'definite' and 25% as 'possible anaphylaxis deaths'. The average national rate for these years was 0.87 per million per year. None of these deaths would have been found had we exclusively considered information from the underlying cause-of-death field.

Conclusion/Recommendations: The study of anaphylaxis mortality using secondary data requires the use of information derived from the underlying as well as from the contributing causes-of-death fields. Coding definitions should be standardized with a view of enabling trend analyses and international comparisons. The ICD-11 revision is a unique opportunity to improve the coding system so as to facilitate epidemiological studies of anaphylaxis mortality. Educational interventions targeted at improving the quality of death certificate completion are urgently needed.

There are sparse studies of anaphylaxis epidemiology, and its burden is in all probability underestimated (1, 2). These studies are hampered by the limited recognition of this condition among health professionals, the lack of universally accepted clinical definitions, and the undernotification of anaphylactic events (3).

Even though undernotification is well recognized as a key challenge to the study of anaphylaxis, it is seldom mentioned that one of its reasons is the difficult coding of the condition under the International Classification of Diseases (ICD) system. Mortality studies based on vital registration data are particularly affected, given that there are no specific ICD-10 codes for anaphylaxis, which are valid for coding underlying causes-of-death, and that official mortality statistics consider exclusively the underlying and disregard the contributing causes-of-death.

In this study, we used the information derived not only from the underlying but also from the contributing causes-of-death data from the Brazilian Mortality Information System (SIM) to estimate the number and the amount of undernotification of anaphylaxis deaths in this country. Our objective is to call attention to the inadequacy of the ICD-10 for the measurement of this condition and to contribute to improvements to be made in the forthcoming revision. We believe the study to be opportune given that the work of the WHO Revision Groups for the 11th revision has already started

and is expected to arrive at a new generation of classification by 2015.

Methods

Type of study, data source, and study period

This is a descriptive study using data routinely reported to the Brazilian SIM for the years 2008–2010, extracted on May 2011. This system is electronic, case based, has had significant improvements in coverage and overall data quality over the last two decades (4), and derives its information almost entirely from death certificates (5). Information available on death certificates includes the following: Part 1: the underlying cause-of-death, the immediate cause-of-death, and the sequence of causes from the underlying to the immediate cause and Part 2: any conditions not directly leading to death but contributing to it. The certificate also includes the duration of all the reported conditions.

Data retrieval and classification

Step 1 – an analysis procedure was developed that identified all records with the following codes listed on Parts 1 and 2 of the death certificate, as being possibly related to anaphylaxis deaths (Table 1).

Of the 3638 records identified, two blocks of records were formed which were submitted to different classification proce-

Table 1 ICD-10 codes identified in the first step of the mortality records classification

ICD-10 codes*	Description
J38.4	Edema of larynx
L50	Urticaria
T61	Toxic effect of noxious substances eaten as seafood
T62	Toxic effect of other noxious substances eaten as food
T63	Toxic effect of contact with venomous animals
T78.0	Anaphylactic shock owing to adverse food reaction
T78.1	Other adverse food reactions, not elsewhere classified
T78.2	Anaphylactic shock, unspecified
T78.3	Angioneurotic edema
T78.4	Allergy, unspecified
T78.8	Other adverse effects, not elsewhere classified
T78.9	Adverse effect, unspecified
T80.5	Anaphylactic shock owing to serum
T88.6	Anaphylactic shock owing to adverse effect of correct drug or medicament properly administered
T88.7	Unspecified adverse effect of drug or medicament
X23	Contact with hornets, wasps, and bees
X25	Contact with other venomous arthropods
Y40.0, Y40.1, Y40.3, Y40.5, Y40.7–Y40.9	Adverse effects in therapeutic use of systemic antibiotics
Y41.1, Y41.5	Adverse effects in therapeutic use of other systemic anti-infectives and antiparasitics
Y42	Adverse effects in therapeutic use of hormones and their synthetic substitutes and antagonists, not elsewhere classified
Y43.1–Y43.3, Y43.6, Y43.8–Y43.9	Adverse effects in therapeutic use of primarily systemic agents
Y44.2, Y44.5–Y44.9	Adverse effects in therapeutic use of agents primarily affecting blood constituents
Y46.0–Y46.4	Adverse effects in therapeutic use of antiepileptics and antiparkinsonism drugs
Y50.1–Y50.2, Y50.8–Y50.9	Adverse effects in therapeutic use of central nervous system stimulants, not elsewhere classified
Y51.0–Y51.5, Y51.3–Y51.5	Adverse effects in therapeutic use of drugs primarily affecting the autonomic nervous system
Y52.4, Y52.7–Y52.9	Adverse effects in therapeutic use of agents primarily affecting the cardiovascular system
Y55	Adverse effects in therapeutic use of agents primarily acting on smooth and skeletal muscles and the respiratory system
Y58	Adverse effects in therapeutic use of bacterial vaccines
Y59	Adverse effects in therapeutic use of other and unspecified vaccines and biological substances
W57	Bitten or stung by nonvenomous insect and arthropods
Z88	Personal allergy status to drugs and biological substances
Z91	Personal allergy status, other than drugs and biological substances

*All 4-digit codes comprised within the 3-digit categories were included.

dures: Block A, comprised of 2646 records that had adverse effects codes (Y40–Y59) in any of the cause-of-death variables and did not mention any of the other codes on Table 1, and Block B, comprised of 992 records that, irrespective of having a mention to an adverse effect code, had one or more of the other codes on Table 1.

Step 2 – Block A records were discarded if their underlying cause-of-death had the following codes (chapters not listed here are not valid for coding underlying causes-of-deaths): (i) Chapters I to VIII; (ii) Chapter IX, excluding codes I46.1, I46.9, I95.2, and I95.9; (iii) Chapter X, excluding J38.4, J38.7, J39.2, J39.3, J39.9, J45, J46, J96.0, J96.9, J98.8, and J98.9; (iv) Chapters XI to XVII; and (v) Chapter XX, excluding X20–X29, X40–X49, X58–X59, and Y49–Y55.

The logic behind this classification was that in the absence of any specific codes relating to anaphylaxis, it would have been impossible to classify these records as being possible cases, just on the basis of them having a code of an adverse effect to medication as a contributing cause-of-death.

Step 3 – For Block B records, whenever the four specific anaphylaxis codes – T78.0 (anaphylactic shock owing to adverse food reaction), T78.2 (anaphylactic shock, unspecified), T80.5 (anaphylactic shock owing to serum), and T88.6 (anaphylactic shock owing to adverse effect of correct drug or medicament properly administered) – were listed on the Part 1 causes-of-death variables, records were classified as 'definite anaphylaxis deaths'.

Step 4 – All remaining 874 records (252 left unclassified from Block A and 622 from Block B) were manually reviewed and classified into two classes: 'possible anaphylaxis death' and 'death unrelated to anaphylaxis'.

'Possible anaphylaxis death' are therefore deaths that were classified in our study as being possibly due to anaphylaxis, even though they did not have any of the four ICD-10 codes that are directly dedicated to this condition – T78.0, T78.2, T80.5, and T88.6, for example, a record with codes relating to an *Hymenoptera* species insect bite, laryngeal edema, and acute respiratory failure.

Data analysis

For 10% of the 874 records, the manual review was performed by two raters. The degree of inter-rater agreement was assessed using Cohen's kappa.

Records classified as 'definite' or 'possible' were further separated into four subtypes representing the stimuli that triggered the reaction: (i) food: L27.2, T61, T62, and T78.0; (ii) drugs: L27.0, L27.1, T63, T80.5, T88.6, X40–X46, X48–X49, Y10–Y19, Y40–Y59, and Y83–Y84; (iii) insect bites: X21–X25 and W57; and (iv) unspecified: other codes.

Annual anaphylaxis mortality rates per 1 000 000 population and 95% Poisson confidence intervals were calculated for each year. Population estimates were obtained from the Brazilian Institute of Geography and Statistics. We tested the hypothesis that the proportion of 'definite' and 'possible anaphylaxis deaths' was equivalent at each category of sex, age, place of death, and presence of an external stimulus using appropriate tests of equality of proportions. *P*-values of <0.05 were considered significant.

Undernotification of anaphylaxis deaths was calculated by comparing the number of deaths obtained using our methodology with the number of deaths obtained exclusively considering information from the underlying cause-of-death field, as is done in official mortality statistics.

Results

Over the 3-year study period, there were 498 anaphylaxis deaths, of which 75% were classified as definite anaphylaxis deaths. The average anaphylaxis death rate for these years was 0.87 per million per year (Table 2). Annual rates varied across the studied years, but with no obvious trend.

None of the 498 deaths would have been found in our study had we exclusively considered information from the underlying cause-of-death field, and not a combination of the underlying as well as the contributing causes. In other words, 100% of anaphylaxis deaths would have been undernotified if the methodology that is usually employed in official country mortality statistics had been used.

Of the total 498 deaths, 58% were males, 43% were elderly individuals, 70% occurred at hospitals, and 79% had an attributable external stimuli (Table 3). Drugs (42%) and insect bites (35%) were the most frequent stimuli, while only 2% of deaths had a reference to food being the external stimuli. When comparing deaths classified as definite or possible, the former had significantly smaller proportions of males (53.5% against 70%) and of deaths attributable to insect bites (23% against 68%), and significantly larger proportions of deaths that occurred in the hospital (75% against 55%) and that were attributable to drugs (51% against 15%).

With a kappa value of 0.84, there was a high agreement on the classification procedures between the two raters.

Table 2 Number of deaths and mortality rates for anaphylaxis in Brazil for the years 2008, 2009, and 2010

	2008	2009	2010	Total
Possible anaphylaxis deaths				
N	29	52	47	128
Rate per 1 000 000	0.15	0.27	0.25	0.22
95% CI	0.1–0.22	0.2–0.36	0.18–0.33	0.18–0.27
Definite anaphylaxis deaths				
N	113	132	125	370
Rate per 1 000 000	0.6	0.69	0.65	0.65
95% CI	0.49–0.72	0.58–0.82	0.54–0.78	0.58–0.72
Total				
N	142	184	172	498
Rate per 1 000 000	0.75	0.96	0.9	0.87
95% CI	0.63–0.88	0.83–1.11	0.77–1	0.8–0.95

Table 3 Characteristics of anaphylaxis deaths, as recorded on SIM. Brazil, 2008–2010

	Possible anaphylaxis deaths *N* = 128 (%)	Definite anaphylaxis deaths *N* = 370 (%)	Total *N* = 498 (%)	*P*-value*
Gender				
Male	90 (70%)	198 (53.5%)	288 (58%)	0.008
Female	38 (30%)	172 (46.5%)	210 (42%)	0.063
Age groups (years)				
Children (0–15)	8 (6%)	35 (9%)	43 (9%)	0.793
Young adults (15–40)	19 (15%)	83 (23%)	102 (20%)	0.444
Adults (40–60)	33 (26%)	105 (29%)	138 (28%)	0.738
Elderly (60+)	68 (53%)	144 (39%)	212 (43%)	0.055
Place of occurrence				
Hospital	70 (55%)	277 (75%)	347 (70%)	0.001
Other health establishment	4 (3%)	20 (5%)	24 (5%)	0.863
Home	18 (14%)	34 (9%)	52/10%)	0.579
Street	8 (6%)	17 (5%)	25 (5%)	0.917
Other	28 (22%)	22 (6%)	50 (10%)	0.115
External stimulus				
Insect bite	87 (68%)	85 (23%)	172 (35%)	<0.001
Drug	19 (15%)	189 (51%)	208 (42%)	0.003
Food	2 (1%)	11 (3%)	12 (2%)	0.872
Unspecified	20 (16%)	85 (23%)	106 (21%)	0.494

**P*-value for test of equality of proportions.

Discussion

This is the first study on anaphylaxis deaths using vital registration data from a developing country. Compared with the two studies that derived overall mortality rates from nationally representative databases, ours is the one with the highest rates (6, 7). We found an average rate of 0.87 (95% CI: 0.8–0.95) deaths per million population per year, which is higher than the one from the United Kingdom estimate of 0.33 (data for 1992–1998) (6) and the Australian estimate of 0.64 (data for 1997–2005) (7). Population-based studies limited to subnational areas have shown lower (Florida/USA/1996–2005: estimate of 0.5) (8), higher (Olmsted county/USA/1983–1987: estimate of 2) (9), or more comparable rates (Berne/Switzerland/1996–1998: estimate of 1) (10).

Possible reasons for the variations include differences in exposure to risk factors, access and quality of medical care, and methods for data retrieval and analysis. The UK study obtained data from a dedicated registry, which depended on passive reporting and might thus be less inclusive, but probably more accurate. Similar to our study, the Australian data came from a mandatory national database, allowing for a lower probability of missing data, at the expense of heavily depending on the quality of the information. However, codes used to define anaphylaxis deaths in the Australian study were restricted to the four anaphylaxis-specific codes and three allergy-associated codes – T78.1, T78.3, and T78.4. Interestingly, our results would have been very similar to those found by the Australian study (0.65 against 0.64, respectively) if we had exclusively considered records classified as 'definite anaphylaxis deaths' in our case definition. Compared with the UK and Australian studies, fatal anaphylactic reactions in our study were caused less often by food and more often by insect bites.

Some knowledge about the correct recording and interpretation of the events and conditions leading to death using the international certificate of cause-of-death is important in order to fully appreciate our findings. As for most countries, death certificates in Brazil are collected on the international form recommended by the World Health Organization (WHO) (11). In Part 1 of the section of the death certificates dedicated to the causes-of-death statement, the immediate cause-of-death is the first one to be stated, which should be followed back by the logic sequence of intermediate causes up to the disease or condition that started the process. The lowest completed line should be the main disease or injury that initiated the chain of morbid events leading directly to death, that is, the underlying cause-of-death. In Part 2, any other significant condition should be stated.

An external stimulus of some kind is needed to trigger the massive degranulation of mast cells and basophils of the anaphylactic reaction, which may be an insect bite, ingestion of particular foods, or being administered particular medications or substances. Following the ICD coding logic, such stimuli are the more distal events that lead to the more immediate event of the anaphylactic reaction, and therefore, they should be considered the underlying cause-of-death.

Some of these external stimuli do have ICD-10 codes, which are considered valid underlying causes-of-death. However, it is impossible to verify whether deaths coded as having such external stimuli as their underlying causes are truly due to anaphylaxis, in the absence of information on more immediate causes-of-death. Therefore, measurement of the anaphylaxis burden using the underlying cause-of-death as an

exclusive source of data is always likely to lead to an underestimation of this condition, a fact that has yet not been widely acknowledged in studies of anaphylaxis mortality (3, 12, 13).

While the physician responsible for filling in the death certificate should always indicate an underlying cause-of-death, his/her diagnosis is not always kept by governmental authorities. The underlying cause-of-death that will eventually be considered for official purposes may be selected by specialized coders using a complicated set of rules developed by the WHO, which allegedly takes into account the most useful information from a public health standpoint (11). In practice, however, one of the reasons why it is necessary for the coders to modify many of the originally stated underlying causes-of-death is unfortunately the lack of training of physicians on the correct completion of the certificates, and the errors that result because of this (14).

A full explanation of the ICD-10 coding rules is beyond the scope of this study, but in order to understand the logic of the system, the different standards it uses for different diseases, and the difficulties in interpreting such data, let us consider three examples of records from the Brazilian SIM, which were classified in this study as anaphylaxis deaths, but which would have been missed had we exclusively considered the information from the underlying cause-of-death field (Table 4).

There is little scope for arguing that patient 1 died of anaphylaxis after being administered penicillin. Code Y40.0 from chapter XX (external causes) was chosen as the underlying cause, because T36.0, the lowest listed code, is from chapter XIX (injury, poisoning, and certain other consequences of external causes), and this chapter does not have codes considered valid for underlying causes-of-death.

Patient 2 very likely died of anaphylaxis, even though no specific codes were mentioned. Code X23 from chapter XX (contact with hornets, wasps, and bees) was chosen as the underlying cause-of-death, which is a typical example of the logic of the ICD coding system that highlights the trigger but not the anaphylactic reaction for itself.

Patient 3 could have a coding error. Being assaulted by a firearm discharge and having an anaphylaxis reaction seem quite disconnected events. While it is possible that an anaphylaxis reaction may have been caused by the medical procedures used for the treatment of the assaulted victim (e.g., use of antibiotics), it seems more likely that shock without further specifications was listed on the death certificate as the condition directly leading to death, which was mistakenly coded as anaphylactic shock. Source document verification would be needed to discriminate these hypotheses. What is clear is that both the information on this patient being a victim of violence and of anaphylaxis are important.

There are two important points to be taken:

1 ICD-10 coding rules highlight some diseases and conditions as underlying causes-of-death to the detriment of others and
2 Anaphylaxis is *never* considered an underlying cause-of-death because
   - The only four ICD-10 codes that are directly dedicated to this condition – T78.0, T78.2, T80.5, and T88.6 – are under chapter XIX, whose codes are never considered valid for coding underlying causes-of-death and
   - Following the ICD-10 coding rules, when ICD-10 codes representing the external stimuli that triggered the anaphylactic reaction are written on the death certificate, they are usually chosen as the underlying cause of death. However, it may be impossible to discriminate whether a death coded as an 'adverse effect to antibiotic use', for example, was due to the toxic effect of the drug *per se* or to the fact that it triggered an anaphylactic reaction, in the absence of further information.

Just as a further example of how the ICD-10 coding lacks standardization, urticaria (L50/Chapter XII), a skin rash that is mostly due to a far less serious allergic reaction than anaphylaxis, is a valid underlying cause-of-death.

Table 4 Example of records from the Brazilian Mortality Information System

	Patient 1	Patient 2	Patient 3
Causes-of-death as listed on death certificates			
Disease or condition directly leading to death	J96.0 – Acute respiratory failure	J38.5 – Laryngeal spasm	T78.2 – Anaphylactic shock, unspecified
Antecedent cause	J38.4 – Edema of larynx	J39.3 – Upper respiratory tract hypersensitivity reaction	X95.1 – Assault by other unspecified firearm discharge
Antecedent cause	T78.2 – Anaphylactic shock, unspecified	X23.0 – Contact with hornets, wasps, and bees at home	
Antecedent cause	Y40.0 – Adverse effects in therapeutic use of systemic antibiotics – penicillin		
Antecedent cause	T36.0 – Poisoning by systemic antibiotics – penicillin		
Underlying causes-of-death selected based on ICD-10 coding rules			
	Y40.0 – Adverse effects in therapeutic use of systemic antibiotics – penicillin	X23.0 – Contact with hornets, wasps, and bees at home	X95.1 – Assault by other unspecified firearm discharge

Population-based studies that make use of secondary data sources such SIM are therefore very much contingent on the quality and methods used to classify the data (3). Given our inability to verify the stated cause-of-death diagnoses, it is possible that we may have overestimated anaphylaxis deaths by wrongly classifying records that had no specific mention to the four anaphylaxis-specific codes as 'possible anaphylaxis death', and even by considering all records that had one of these codes as 'definite anaphylaxis deaths'. 'Possible anaphylaxis deaths' in our study may represent misclassifications of cause-of-death, although we are quite confident that they do not. These records were mostly of adult and elderly males who had an insect sting. The fact that almost half of them died outside hospitals probably indicates that the condition happened quite suddenly. With such characteristics, it is hard to think of other diseases that could have caused such deaths, and this reinforced our decision to include them in the estimation of the total death rates.

Alternatively – and in our opinion more likely – we may still have underestimated anaphylaxis deaths, both by not identifying deaths that did have such clinical diagnosis but that did not fit into our classification procedures (e.g., deaths incorrectly attributed to asthma) (15), and because a number of anaphylaxis deaths must have been left undiagnosed. Of note, because the existing anaphylaxis-specific codes are not valid for coding underlying causes-of-death (11), none of the 498 anaphylaxis deaths would have been identified as being due to anaphylaxis, had it not been for our careful analysis of the contributing causes-of-death. In other words, all 498 anaphylaxis deaths would have been undernotified.

Apart from mortality studies, a number of morbidity studies have been performed on hospitalization and other dedicated registries that use ICD codes to identify patients whose principal discharge diagnosis is anaphylaxis (16–19). Morbidity investigations are also likely to be affected by the difficult ICD coding of this condition, albeit in a lesser degree (because anaphylaxis-specific codes can be used for morbidity).

Recognizing the importance of epidemiological studies that use ICD data, we recommend that allergist and other researchers interested in this field attempt to develop standardized coding procedures, with a view of enabling trend analyses and international comparisons.

In addition, we recommend that representatives of allergy and clinical immunology societies seek to actively participate in the technical work associated with the ICD-11 revision. WHO has organized groups of experts designated to deal with issues in each field, and some of them, like the one for mental and behavioral disorders, are quite advanced in their task (20). To our knowledge, no explicit advisory group has been launched for the field of allergy. The current ongoing ICD revision represents an unique opportunity to improve the coding system, and the particularities of anaphylaxis as well as other allergic conditions should be adequately looked after (21).

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Authors' contribution

Luciana K. Tanno and Ana L. Bierrenbach designed the study, analyzed and interpreted the data, and wrote the manuscript. Fernando Ganem, Cristiana Toscano, and Pascal Demoly helped in the interpretation of the data and with the revision of the manuscript.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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