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DECREASING THE UNDER-NOTIFICATION OF ANAPHYLAXIS DEATHS IN BRAZIL THROUGH THE INTERNATIONAL CLASSIFICATION OF DISEASES (ICD)-11 REVISION

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ABSTRACT:

Background: In 2012, an analysis of the Brazilian mortality database demonstrated under-notification of anaphylaxis deaths due, at least in part, to difficult coding under the International Classification of Diseases (ICD)-10. This work triggered a cascade of strategic international actions supported by the Joint Allergy Academies and the ICD World Health Organization (WHO) representatives to update the classifications of allergic disorders for the ICD-11 revision. These efforts have resulted in the construction of the new “Allergic and hypersensitivity conditions” section under the “Disorders of the Immune system” chapter.

Objective: To analyze the capacity of the new ICD-11 revision to capture anaphylaxis deaths.

Methods: We re-estimated the anaphylaxis deaths that occurred in Brazil during the period 2008 to 2010, utilizing this new framework and the database of the Brazilian mortality information system that had initially been extracted in May 2011. However, in 2016, a manual review of each of the 3,638 records was performed.

Results: We identified 639 anaphylaxis deaths, of which 95% were classified as “definitive anaphylaxis deaths”. In contrast to the 2012 published data, we found a higher number of cases; moreover, all 606 definitive anaphylaxis deaths would be considered as underlying causes of death utilizing the ICD-11 revision.

Conclusion: This study is the first example of how the new “Allergic and hypersensitivity conditions” section of the forthcoming ICD-11 can improve the quality of official vital statistics data and the visibility of an important public health concern. This research will facilitate comprehensive, comparable population-based epidemiologic data collection on anaphylaxis.

KEY WORDS: anaphylaxis, classification, International Classification of Diseases, mortality, World Health Organization

BACKGROUND

Anaphylaxis is defined as a severe life-threatening generalized or systemic hypersensitivity reaction (1). All anaphylaxis guidelines (1-4) consistently highlight the possibility of death during an anaphylactic episode. That said, there are only a limited number of population-based epidemiologic studies of anaphylaxis mortality, particularly in low- and middle-income countries (5-8). Under-

notification can potentially lead to paucity of data and contribute to lack of recognition of the importance of anaphylaxis, which in turn can impact health care planning, including diagnosis, treatment and prevention, and hamper decision-making at many levels of the health care system.

Under-notification of anaphylaxis deaths is a well-recognized challenge. An important reason for this is the difficulty of coding anaphylaxis fatalities under the World Health Organization (WHO) International Classification of Diseases (ICD) system. In most countries, mortality statistics are routinely compiled according to regulations and recommendations adopted by the World Health Assembly (WHA). Causes of deaths are classified and grouped according to the ICD edition in use at the time and the information on death certificates is collected using the international form recommended by the WHO. However, a limited number of ICD-10 codes are considered to be valid for representing underlying causes of death on the current death certificates, and with regard to anaphylaxis as such, there are simply no valid codes (8, 9).

In 2012, we estimated the magnitude of under-notification of anaphylaxis deaths using the information derived from both the underlying and the contributing causes of death data from the Brazilian Mortality Information System (*Sistema de Informação sobre Mortalidade - SIM*). In this study, we analyzed all 3,296,247 death records from 2008 to 2010 using ICD-10 and found a total of 498 anaphylaxis deaths (Figure 1), with an average anaphylaxis death rate of 0.87/million/year, categorized as “definitive” or “possible” cases.

The most striking observation from this study was that none of these deaths would have been attributed to anaphylaxis had we exclusively considered information from the underlying cause-of-death field (8). The study called attention to the need for better coding not only for anaphylaxis deaths, but also for all allergic and hypersensitivity conditions, which would otherwise be misclassified in ICD-10 and ICD-11 (May 2014 version) (10). The timing of the study was opportune (2) as the ICD-11 revision process was underway.

In order to create a more appropriate classification for allergic and hypersensitivity conditions in the ICD-11, a detailed action plan was coordinated based on scientific evidences for the necessity of changes (8, 10-19). Collaboration with the WHO ICD-11 revision governance is ongoing so far and all the efforts are being acknowledged by the Joint Allergy Academies. The main outcome of this process was the construction of the “Allergic and hypersensitivity conditions” section in the ICD-11 Beta draft (16, 20). By consolidating all allergic conditions into one ICD-11 single section, as opposed to spreading them out over many ICD-10 chapters (Table 1) and by allowing all the relevant codes to be used to represent mortality and morbidity outcomes, our aim was to increase data accuracy and

facilitate the use of such codes by clinicians, epidemiologists, and statisticians, as well as all data custodians and other relevant personnel.

To further inform these deliberations and to follow the ICD-11 revision agenda, we report here on a re-analysis of anaphylaxis deaths in the Brazilian SIM evaluated in the 2012 publication (8) using the online ICD-11 Beta draft (March 2016 version) as the basis.

METHODS

In order to re-estimate the anaphylaxis deaths that occurred in Brazil during the period 2008 to 2010 under the new framework of the ICD-11, we re-analyzed the database of the Brazilian SIM, which had been extracted on May 2011 using ICD-10. As in our previous study, out of the total 3,296,247 records of all-causes mortality, we selected an initial sample of 3,638 records that listed any ICD-10 code related to anaphylaxis as the underlying or as contributing causes of death (Figure 1).

In contrast to the methodology used in our previous paper (8), we performed a manual review of all 3,638 records in order to reclassify them based on the online ICD-11 Beta draft (March 2016 version). In order to do this, we carefully looked at the ICD-10 codes listed as the underlying or as contributing causes of death of each of the records and categorized them as “possible anaphylaxis deaths”, “definitive anaphylaxis deaths” or “deaths unrelated to anaphylaxis” using the logic of the ICD-11 framework (online ICD-11 Beta draft - March 2016 version). The methods have been reviewed by the co-authors. All records were independently evaluated by the first and last authors. Disagreements were resolved through open discussion and external review. The degree of inter-rater agreement was assessed using Cohen’s kappa. Annual anaphylaxis mortality rate per 1 000 000 population was calculated based on estimated population obtained from the Brazilian Institute of Geography and Statistics.

We considered as “possible anaphylaxis deaths”, cases that had an isolated allergic or hypersensitivity clinical condition listed as a contributing cause of death (*e.g.*, angioedema or urticaria). We decided that such conditions, unless presented together with other more specific anaphylaxis codes, could only rarely be considered an underlying cause of death.

All records described as anaphylaxis or having an allergic or hypersensitivity condition as the underlying cause of death associated with the possible trigger as contributing mortality data were classified as “definitive anaphylaxis deaths”. The remaining and unspecified cases (*e.g.*, missing

immediate cause of death in the death certificates) were considered “death unrelated to anaphylaxis”, for example, cases of sepsis shock.

RESULTS

In the 2012 publication (8), we identified 498 cases of anaphylaxis deaths, 370 (75%) of which were categorized as “definitive anaphylaxis death”. In 2016, after the manual review of all 3,638 records and re-analysis based on ICD-11, we identified 639 anaphylaxis deaths, of which 606 (95%) were classified as “definitive anaphylaxis deaths” (Figure 1). There was a high agreement on the classification procedures between the two coders (Cohen-kappa value 0.91). This higher number of cases includes all the 498 cases identified in our previous paper based on the ICD-10 classification system. We found an average rate of 1.12 (95% CI: 0.8–0.95) anaphylaxis deaths per million population per year, which is higher than the one from the previous publication estimated of 0.87 deaths per million per year.

When comparing cases found by using the ICD-11 and the ICD-10 classification systems, we found a similar demographic pattern (Table 2). Overall, most individuals who died from anaphylaxis were male (59%) and many were elderly (41%). Deaths typically took place in hospitals, which includes the Emergency Department and patients dead on arrival. Drugs were the leading cause.

In contrast to our previous study in which 25.7% of records were categorized as “possible anaphylaxis death”, in the 2016 analysis, we had only 33 cases (5.2%) in this category.

In stark contrast to the results presented in 2012, in which none of the identified deaths had “anaphylaxis” listed as the underlying cause, in the current analysis, following the logic of the new ICD-11 framework, anaphylaxis would be considered as the underlying cause of all 639 deaths.

DISCUSSION

This study represents the first attempt to prove that utilization of the new section titled “Allergic and hypersensitivity conditions” in ICD-11 can improve the quality of official vital statistics data and the visibility of an uncommon disease of public health concern. As in most countries, the information on death certificates is collected using the international form recommended by the WHO. The conditions and the sequence of events described on this form highlight some diseases and conditions as underlying causes of death, but not others (8, 9).

The WHO defines the underlying cause of death as: (i) the disease or injury which initiated the sequence of morbid events leading directly to death or (ii) the circumstances of the accident or violence which produced the fatal injury. Based on the ICD-10 codes, some external stimuli are considered as underlying causes-of-death, but anaphylaxis as such has never been prioritized as the underlying cause-of-death. In fact, having allergic and hypersensitivity conditions classified in a more detailed scheme in the ICD-11 (Table 1) and not as in ICD-10 into a specific chapter in the “External causes of morbidity and mortality” or in the “Injury, poisoning and certain other consequences of external causes” chapters allows for capture of more realistic anaphylaxis mortality data from now on.

From a public health point of view, preventing the disease or injury identified as the underlying cause of fatality on death certificates results in the greatest health gain. Underlying cause of deaths statistics are widely used to determine priorities for health service and public health programs and for resource allocation. This study emphasizes the previous findings by providing objective public health data to substantiate mortality rules and health care decision-making changes. In addition to supporting the validation of the new structure, this study emphasizes the previous findings by providing objective public health data to substantiate health care changes and decision-making. As an example, although we found 68% of cases recorded as occurring in hospital, 19% occurred outside health care establishments, reinforcing the need of making adrenaline auto-injector devices available in all countries (1, 21, 22), including Brazil.

We have found a higher proportion of “definitive anaphylaxis deaths” when compared to that of our previous publication (8), probably due to the use of a more detailed classification and a manual review of all 3,638 records. As a result, some cases previously classified as “deaths unrelated to anaphylaxis” have now been classified as “definite anaphylaxis deaths”. Importantly, there still may be additional anaphylaxis deaths in Brazil, as we only reviewed a proportion of cases that had any codes possibly related to anaphylaxis.

There are two immediate consequences of the use of the new classification based on the logic of the ICD11: (i) the reported number of anaphylaxis deaths increased and (ii) all cases would be included in official mortality statistics. However, it is important to keep in mind that in order to apply the new classification, we still depend on the cause of death information available on death certificates. In other words, we are facing the same problems of data quality due to the inadequate completion of the death certificates by the end-users. This issue reflects lack of comprehension about the proper recording and interpretation of events, reinforcing the need for education interventions. For this reason, the core ALLERGY in ICD-11 operational team (LKT, MC, PD) intends to

implement educational tools to cover this gap, following the ICD-11 logic. Educational efforts will also help to address the decrease of under-recognition of anaphylaxis by patients, caregivers, and health professionals.

In our analysis the death rate with the diagnosis anaphylaxis is approximately 25% higher, without overlooking a single death from the 2012 publication. Clearer is the effect on the accuracy reaching 95% for definite anaphylaxis when ICD11 was used. In a higher perspective, besides increasing the accuracy of vitals statistics data, unifying the allergic and hypersensitivity conditions into a single section of the ICD, endorsed by the WHO ICD governance bodies, can be considered a strong epidemiological, economical and political move that advocates in favor of the best diagnosis and management of allergic patients worldwide.

As main limitations: (i) There is a risk of having the classification tuned up until the end of the revision process due to regular ICD-11 beta draft platform updates. (ii) Possibility that we cannot foresee on the manual classification, although we tried to minimize it by performing classification by independent investigators with third-party evaluation in cases of discordance.

CONCLUSION

This study represents the first attempt to prove that utilization of the new “Allergic and hypersensitivity conditions” section of the ICD-11 can improve the quality of official vital statistics data. The model presented can be considered as a springboard to facilitate comprehensive, comparable population-based epidemiologic data collection on anaphylaxis from a global perspective.

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Table 1: Differences in the classification of the main allergic and hypersensitivity conditions in the ICD-10 and ICD-11

MAIN HYPERSENSITIVITY DISORDERS (according to the EAACI-WAO revised nomenclature)		ICD-10 VERSION 2016 CORRESPONDING CHAPTER(S)	ICD-11 BETA DRAFT "ALLERGIC AND HYPERSENSITIVITY CONDITIONS" (March 2016 version) SECTION
Asthma		Chapter X: Diseases of the respiratory system	"Allergic or hypersensitivity disorders involving the respiratory tract"
Rhinitis		Chapter X: Diseases of the respiratory system	"Allergic or hypersensitivity disorders involving the respiratory tract"
Conjunctivitis		Chapter VII Diseases of the eye and adnexa	"Allergic or hypersensitivity disorders involving the eye"
Skin diseases	Dermatitis	Chapter XII Diseases of the skin and subcutaneous tissue	"Allergic or hypersensitivity disorders involving skin and mucous membranes"
	Urticaria	Chapter XII Diseases of the skin and subcutaneous tissue	
	Angioedema	Chapter XIX Injury, poisoning and certain other consequences of external causes	
Chapter III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism			
Food hypersensitivity		Chapter XIX Injury, poisoning and certain other consequences of external causes	"Food hypersensitivity" section of the "Complex allergic or hypersensitivity conditions"
		Chapter XII Diseases of the skin and subcutaneous tissue	
		Chapter XI Diseases of the digestive system	
		Chapter XXI Factors influencing health status and contact with health services	
Drug hypersensitivity		Chapter XIX Injury, poisoning and certain other consequences of external causes	"Drug hypersensitivity" section of the "Complex allergic or hypersensitivity conditions"
		Chapter XX External causes of morbidity and mortality	
		Chapter XII Diseases of the skin and subcutaneous tissue	
		Chapter XXI Factors influencing health status and contact with health services	

Venom hypersensitivity	Chapter XX External causes of morbidity and mortality	“Allergic or hypersensitivity reactions to arthropods” section of the “Complex allergic or hypersensitivity conditions”
Anaphylaxis	Chapter XIX Injury, poisoning and certain other consequences of external causes	“Anaphylaxis” section subheadings: <ul style="list-style-type: none"> – Drug-induced anaphylaxis – Anaphylaxis due to insect venom – Anaphylaxis provoked by physical factors – Anaphylaxis due to inhaled allergens – Anaphylaxis due to contact with allergens – Anaphylaxis secondary to mast cell disorders

Table 2: Demographic characterization of anaphylaxis deaths recorded from 2008 to 2010 in the Brazilian Mortality Information System

DEMOGRAPHIC DATA	ANAPHYLAXIS DEATHS ACCORDING TO THE 2012 PUBLICATION, USING THE ICD-10			ANAPHYLAXIS DEATHS REVIEWED BASED ON THE LOGIC OF THE ICD-11 BETA DRAFT (MARCH 2016 VERSION)		
	Possible anaphylaxis deaths N = 128 (%)	Definitive anaphylaxis deaths N = 370 (%)	Total N = 498 (%)	Possible anaphylaxis deaths N = 33 (%)	Definitive anaphylaxis deaths N = 606 (%)	Total N = 639 (%)
Gender						
Male	90 (70)	198 (53.5)	288 (58)	13 (40)	363 (60)	376 (59)
Female	38 (30)	172 (46.5)	210 (42)	20 (60)	243 (40)	263 (41)
Age groups (years)						
Children (0-15)	8(6)	35 (9)	43 (9)	2 (6)	49 (8)	51 (8)
Young adults (15-40)	19 (15)	83 (23)	102 (20)	4 (12)	144 (24)	148 (23)
Adults (40-60)	33 (26)	105 (29)	138 (28)	10 (30)	167 (28)	177 (28)
Elderly (60+)	68 (53)	144 (39)	212 (43)	17 (52)	246 (40)	263 (41)
Place of occurrence						
Hospital	70 (55)	277 (75)	347 (70)	17 (52)	422 (70)	439 (68)
Other health establishment	4 (3)	20 (5)	24 (5)	1 (3)	23 (4)	24 (4)
Home	18 (14)	34 (9)	52 (10)	5 (15)	82 (13)	87 (14)
Street	8 (6)	17 (5)	25 (5)	1 (3)	31 (5)	32 (5)
Other	28 (22)	22 (6)	52 (10)	9 (27)	48 (8)	57 (9)
External stimulus						
Insect bite	87 (68)	85 (23)	172 (35)	16 (49)	163 (27)	179 (28)
Drug	19 (15)	189 (51)	208 (42)	7 (21)	317 (52)	324 (51)
Food	2 (1)	11 (3)	12 (2)	0 (0)	12 (2)	12 (2)
Unspecified	20 (16)	85 (23)	106 (21)	10 (30)	114 (19)	124 (19)

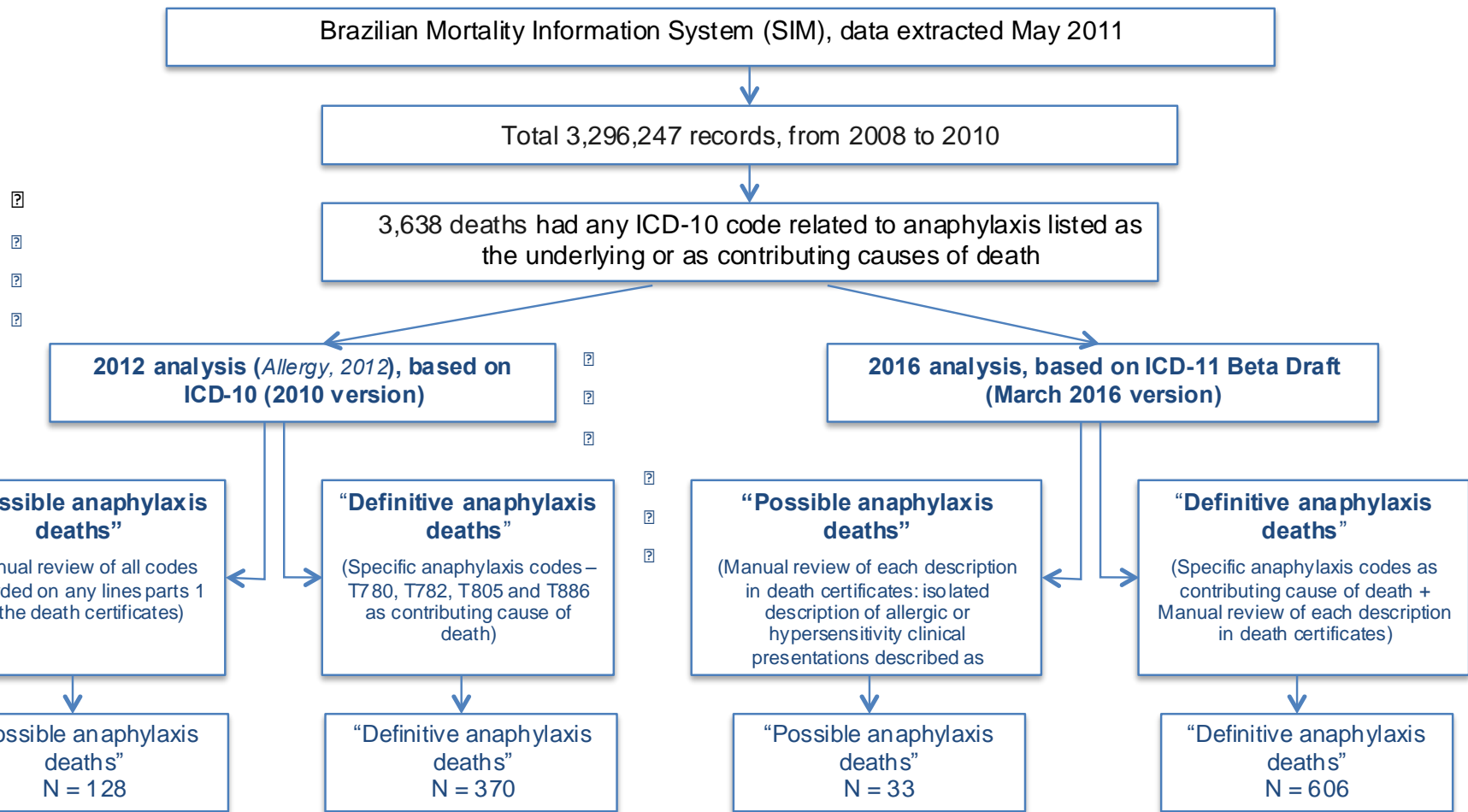


Figure 1: Methodological flow-chart used to evaluate Brazilian anaphylaxis deaths based on ICD-10 (2010 version) and ICD-11 Beta draft (March 2016 version)

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AUTHOR CONTRIBUTIONS:

Luciana Kase Tanno and Pascal Demoly contributed to the construction of the document (designed the study, analyzed and interpreted the data, and wrote the manuscript). Ana Luiza Bierrenbach contributed to analyze and interpret data, tuning and reviewing the document. Moises A Calderon and F. Estelle R. Simons contributed to tuning the document and revision of the manuscript. Aziz Sheikh commented critically on an earlier draft of this manuscript.

CONFLICT OF INTERESTS:

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

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