

# Changing the history of anaphylaxis mortality statistics through the World Health Organization's International Classification of Diseases–11

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We review the history of the classification and coding changes for anaphylaxis and provide current and perspective information in the field. In 2012, an analysis of Brazilian data demonstrated undernotification of anaphylaxis-related deaths because of the difficulties of coding using the International Classification of Diseases, 10th Revision. This work triggered strategic international actions supported by the Joint Allergy Academies and the International Classification of Diseases World Health Organization (WHO) leadership to update the classification of allergic disorders for the International Classification of Diseases, 11th Revision (ICD-11), which

resulted in construction of the pioneer “Allergic and hypersensitivity conditions” chapter. The usability of the new framework has been tested by evaluating the same data published in 2012 from the ICD-11 perspective. Coding accuracy was much improved, reaching 95% for definite anaphylaxis. As the results were provided to the WHO Mortality Reference Group, coding rules have been changed, allowing anaphylaxis to be recorded as an underlying cause of death in official mortality statistics. The mandatory use of ICD-11 from January 2022 for documenting cause of death could have 2 immediate consequences: (1) the reported number of

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**anaphylaxis-related deaths might increase because of more appropriate coding and (2) the cross-sectional and longitudinal mortality data generated might ultimately lead to a better understanding of anaphylaxis epidemiology and improved health policies directed at reducing anaphylaxis-related mortality. (J Allergy Clin Immunol 2019;■■■:■■■-■■■.)**

**Key words:** *Anaphylaxis, big data, classification, International Classification of Diseases, mortality, World Health Organization*

## MORTALITY STATISTICS: HISTORY, IMPORTANCE, AND STANDARD RECORDING METHODS

### Historical background of vital statistics

Rational disease classification dates back to Hippocrates, but the first modern medical classification considering true ontology of diseases was developed in 1735 by Carl Linnaeus, who divided diseases into 11 classes, 37 orders, and 325 species.<sup>1</sup> Although this classification contained some errors from a modern perspective, this framework laid the foundation for work that eventually led to the first edition of the International Classification of Diseases (ICD), which was published in 1893.<sup>2</sup> It had been preceded in 1885 by the first “International List of Causes of Death,” which had been drafted by Jacques Bertillon and colleagues, and distinguished between systemic diseases and those localized to a particular organ or anatomic site; it was officially adopted for use in mortality registries in 1893.<sup>3</sup> This classification, which was accepted by many countries, constituted the basis of the ICD.

Anaphylaxis was not included in the original list of diseases because it was not formally described until 1902.<sup>3</sup> Currently, most countries have been using the International Classification of Diseases, 10th Revision (ICD-10; or adaptations), for morbidity and mortality statistics. Although the ICD is generally reviewed by the World Health Organization (WHO) periodically, anaphylaxis has never been well captured in this international system.

According to the WHO ICD rules, the underlying cause of death is defined as the disease or injury that initiated the train of morbid events leading directly to death.<sup>4</sup> Although a well-known cause of death, particularly in the fields of allergy and emergency medicine, anaphylaxis has never been appropriately classified in the different versions of the ICD and has never been considered an underlying cause of death on death certificates, as demonstrated repeatedly and most recently confirmed in research performed in Brazil.<sup>5</sup>

### What can mortality data tell us?

Mortality data provide a snapshot of current health problems, can point to persistent patterns of risk in specific communities, and show trends in specific causes of death over time. Many of the latter are preventable or treatable and therefore warrant the attention of public health officials.<sup>4</sup> Mortality data provide valuable benchmarks for evaluating progress in increasing years of healthy life.<sup>6</sup>

### An example of negative outcomes caused by the lack of accurate anaphylaxis-related mortality

Adrenaline/epinephrine is the first-line treatment for anaphylaxis and therefore is listed by the WHO as an essential medication for the treatment of anaphylaxis. However, the availability of adrenaline autoinjectors (AAIs) for use in first-aid treatment is limited to just 32% of the world's 195 nations, the majority of them high-income countries.<sup>7</sup> Key issues leading to the lack of availability of AAIs include high cost but also national regulations, lack of regional evidence about the value of epinephrine, and a paucity of accurate data on anaphylaxis epidemiology. Lack of accurate mortality information hinders understanding of the public health effect of anaphylaxis and of the need for appropriate therapeutic interventions and investments, such as AAIs, to reduce that effect.

#### Abbreviations used

AAI: Adrenaline autoinjector  
 ICD: International Classification of Diseases  
 ICD-10: International Classification of Diseases, 10th Revision  
 ICD-11: International Classification of Diseases, 11th Revision  
 WHA: World Health Assembly  
 WHO: World Health Organization  
 WHO CC: World Health Organization Collaborating Centre

## How worldwide mortality data are recorded and harmonized

Because mortality monitoring is of such value to public health authorities, mortality registration is mandatory in almost all countries. Vital statistics systems record certain information on each death and periodically sum the number of deaths to calculate rates and trends.

Analysis of mortality data typically involves comparisons of data sets. However, unless the data have been compiled using the same methods and according to the same standards, such comparisons have the potential to yield misleading results. For these reasons, the WHO has issued international instructions on data collection, coding, and classification and statistical presentation of causes of death. In most countries, mortality statistics are routinely compiled according to regulations and recommendations adopted by the World Health Assembly (WHA). The international mortality coding instructions presuppose that data have been collected with a death certificate conforming to the “International form of medical certificate of cause of death.”<sup>8</sup> It is the responsibility of the medical practitioner or other qualified certifier signing the death certificate to indicate which morbid conditions led directly to death and to state any antecedent conditions giving rise to or contributing to this cause.

The WHO's mortality data reflect deaths registered by national civil death registration systems, with the underlying cause of death coded by the national authority.<sup>8</sup> If a condition or a disease is not considered an “underlying cause of death,” national registration systems are not able to capture related accurate data on cause of death.

## ANAPHYLAXIS: UNDERNOTIFICATION OF A KILLING HYPERSENSITIVITY

### Anaphylaxis: the killing hypersensitivity

All definitions of anaphylaxis for clinical use by health care professionals incorporate the concept of a serious, generalized, allergic or hypersensitivity reaction that can be life-threatening and even fatal.<sup>9</sup> All anaphylaxis guidelines<sup>9-14</sup> consistently highlight the possibility of death during an anaphylactic episode. Anaphylaxis lethality has been estimated to be 17%.<sup>15</sup>

Good epidemiologic data are essential components for a nation's health service planning, including identifying priorities for reducing morbidity and mortality. In the case of anaphylaxis, however, there are only a limited number of population-based epidemiologic studies of mortality, particularly in the case of low- and middle-income countries.<sup>15-25</sup> Underrecognition and undernotification of anaphylaxis led to sparse data and contributed to lack of recognition of the importance of anaphylaxis and the consequent neglect of health care strategies for improving diagnosis, treatment, and prevention at many levels of the health care system.

## Evidence-based data call for changes in anaphylaxis mortality records

In 2012, we estimated the magnitude of undernotification and underreporting of anaphylaxis-related deaths using information

**ICD-10 Version:2016**

Search: anaphylaxis [Advanced Search]

- T66-T78 Other and unspecified effects of external cause
  - T66 Unspecified effects of radiation
  - T67 Effects of heat and light
  - T68 Hypothermia
  - T69 Other effects of reduced temperature
  - T70 Effects of air pressure and water pressure
  - T71 Asphyxiation
  - T73 Effects of other deprivation
  - T74 Maltreatment syndromes
  - T75 Effects of other external causes
  - T78 Adverse effects, not elsewhere classified**
    - T78.0 Anaphylactic shock due to adverse food reaction
    - T78.1 Other adverse food reactions, not elsewhere classified
    - T78.2 Anaphylactic shock, unspecified
    - T78.3 Angioneurotic oedema
    - T78.4 Allergy, unspecified
    - T78.8 Other adverse effects, not elsewhere classified
    - T78.9 Adverse effect, unspecified
  - T79-T79 Certain early complications of trauma
  - T80-T88 Complications of surgical and medical care, not elsewhere classified
  - T90-T98 Sequelae of injuries, of poisoning and of other consequences of external causes
  - XX External causes of morbidity and mortality
  - XXI Factors influencing health status and contact with health services

**T78 Adverse effects, not elsewhere classified**

**Note:** This category is to be used as the primary code to identify the effects, not elsewhere classifiable, of unknown, undetermined ill-defined causes. For multiple coding purposes this category may be used as an additional code to identify the effects of conditions classified elsewhere.

**Excl.:** complications of surgical and medical care NEC (T80-T88)

**T78.0 Anaphylactic shock due to adverse food reaction**

**T78.1 Other adverse food reactions, not elsewhere classified**

**Excl.:** bacterial foodborne intoxications (A03.-)  
dermatitis due to food (L27.2)  
dermatitis due to food  
• in contact with the skin (L23.6, L24.6, L25.4)

**T78.2 Anaphylactic shock, unspecified**

Allergic shock  
Anaphylactic reaction NOS  
Anaphylaxis

**Excl.:** anaphylactic shock due to:  
• adverse effect of correct medicinal substance properly administered (T88.6)  
• adverse food reaction (T78.0)  
• serum (T80.5)

**T78.3 Angioneurotic oedema**

Giant urticaria  
Quincke oedema

**Excl.:** urticaria (L50.-)  
urticaria  
• serum (T80.6)

**T78.4 Allergy, unspecified**

Allergic reaction NOS  
Hypersensitivity NOS  
Idiosyncrasy NOS

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**ICD-11 for Mortality and Morbidity Statistics (December 2018)**

Search: anaphylaxis [Advanced Search]

- ICD-11 - Mortality and Morbidity Statistics
  - 01 Certain infectious or parasitic diseases
  - 02 Neoplasms
  - 03 Diseases of the blood or blood-forming organs
  - 04 Diseases of the immune system
    - Primary immunodeficiencies
    - 4A20 Acquired immunodeficiency
    - Nonorgan specific systemic autoimmune
    - Autoinflammatory disorders
    - Allergic or hypersensitivity conditions
      - 4A80 Allergic or hypersensitivity
      - 4A81 Allergic or hypersensitivity
      - 4A82 Allergic or hypersensitivity
      - 4A83 Allergic or hypersensitivity
      - 4A84 Anaphylaxis
      - 4A85 Complex allergic or hypersensitivity
      - 4B03 Eosinophilia
      - 4A8Y Allergic or hypersensitivity
      - 4A8Z Allergic or hypersensitivity
    - Immune system disorders involving
    - Certain disorders involving the immune
    - 4B40 Diseases of thymus
    - Organ specific autoimmune disorders
    - Symptoms, signs or clinical findings
    - 4B4Y Other specified diseases of the immune system
    - 4B4Z Diseases of the immune system, unspecified

**Anaphylaxis**

- Anaphylaxis due to allergic reaction to food
  - Drug-induced anaphylaxis
  - Anaphylaxis due to radiopaque contrast media
  - Anaphylaxis due to insect venom
- Anaphylaxis provoked by physical factors
  - Exercise-induced anaphylaxis
    - Food-dependent exercise-induced anaphylaxis
    - Food-independent exercise-induced anaphylaxis
    - Cold-induced anaphylaxis
  - Anaphylaxis due to inhaled allergens
  - Anaphylaxis due to contact with allergens
  - Anaphylaxis secondary to mast cell disorder
  - Latex-induced anaphylaxis

**4A84 Anaphylaxis**

Parent: Allergic or hypersensitivity conditions

**Description**

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.

**Coordination**

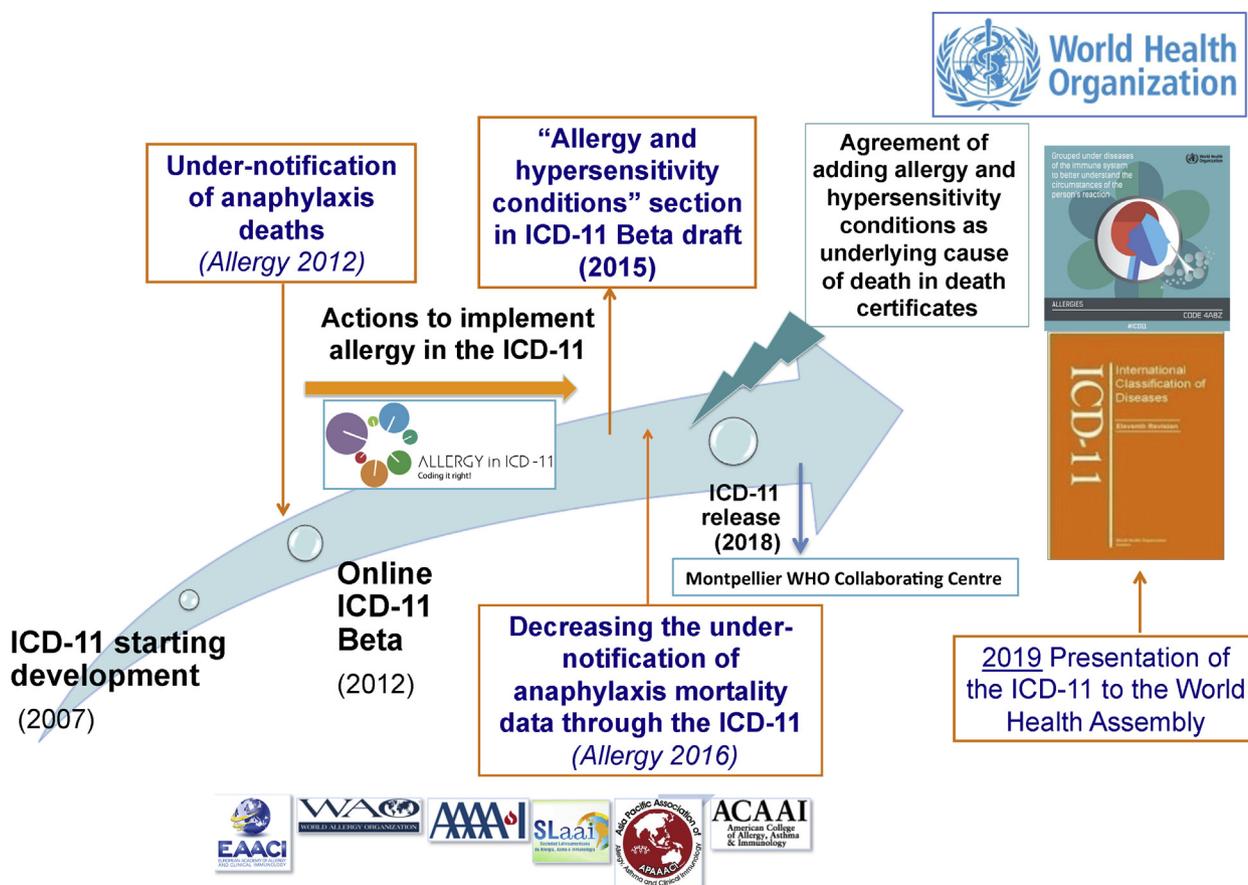
Code	Severity
XS25	Mild
XS24	Moderate
XS23	Severe

FIG 1. Changes of anaphylaxis classification in ICD-10 and ICD-11.

derived from both the underlying and contributing causes of death data from the Brazilian Mortality Information System (Sistema de Informação sobre Mortalidade). 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-related deaths based on secondary data, with an average anaphylaxis-related death rate of 0.87/million/y categorized as “definitive” or “possible” cases.<sup>5</sup> We considered as “possible anaphylaxis-related deaths” cases that had an isolated allergic or hypersensitivity clinical condition listed as a contributing cause of death (eg, 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-related deaths.” The remaining and unspecified cases (eg, missing immediate cause of death in the death certificates) were considered “death unrelated to anaphylaxis,” such as cases of septic shock. Two coders were responsible for the analysis, and there was a high agreement on classification procedures between them (Cohen  $\kappa$  value = 0.91).<sup>5</sup>

The most striking observation derived 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.<sup>5</sup> The study called attention to the need for better coding not only for anaphylaxis-related deaths but also for all allergic and hypersensitivity conditions, which would otherwise be misclassified in ICD-10 and early International Classification of Diseases, 11th Revision (ICD-11; May 2014



**FIG 2.** Timeline of ICD-11 revision and implementation and historic-prospective actions of the ALLERGY in ICD-11 Initiative.

version).<sup>26</sup> The timing of the study was opportune because the ICD-11 revision process was underway.

An important reason for this misclassification is the difficulty of coding anaphylaxis fatalities under the WHO ICD system. In the ICD-10 (2016 version) platform,<sup>26</sup> anaphylaxis is classified under the “XIX Injury, poisoning and certain other consequences of external causes” chapter, specifically the “T78 Adverse effects, not elsewhere classified” section. It is striking that only severe cases of anaphylaxis are listed under the same category (“T78.2 Anaphylactic shock”) and that it is classified at the same level of “anaphylactic shock due to adverse food reaction,” “angioneurotic edema,” and “allergy, unspecified.” 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 by 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 current death certificates, and with regard to anaphylaxis as such, there are simply no valid codes (Fig 1).

### IMPROVING THE ACCURACY OF ANAPHYLAXIS MORTALITY STATISTICS THROUGH THE ICD-11

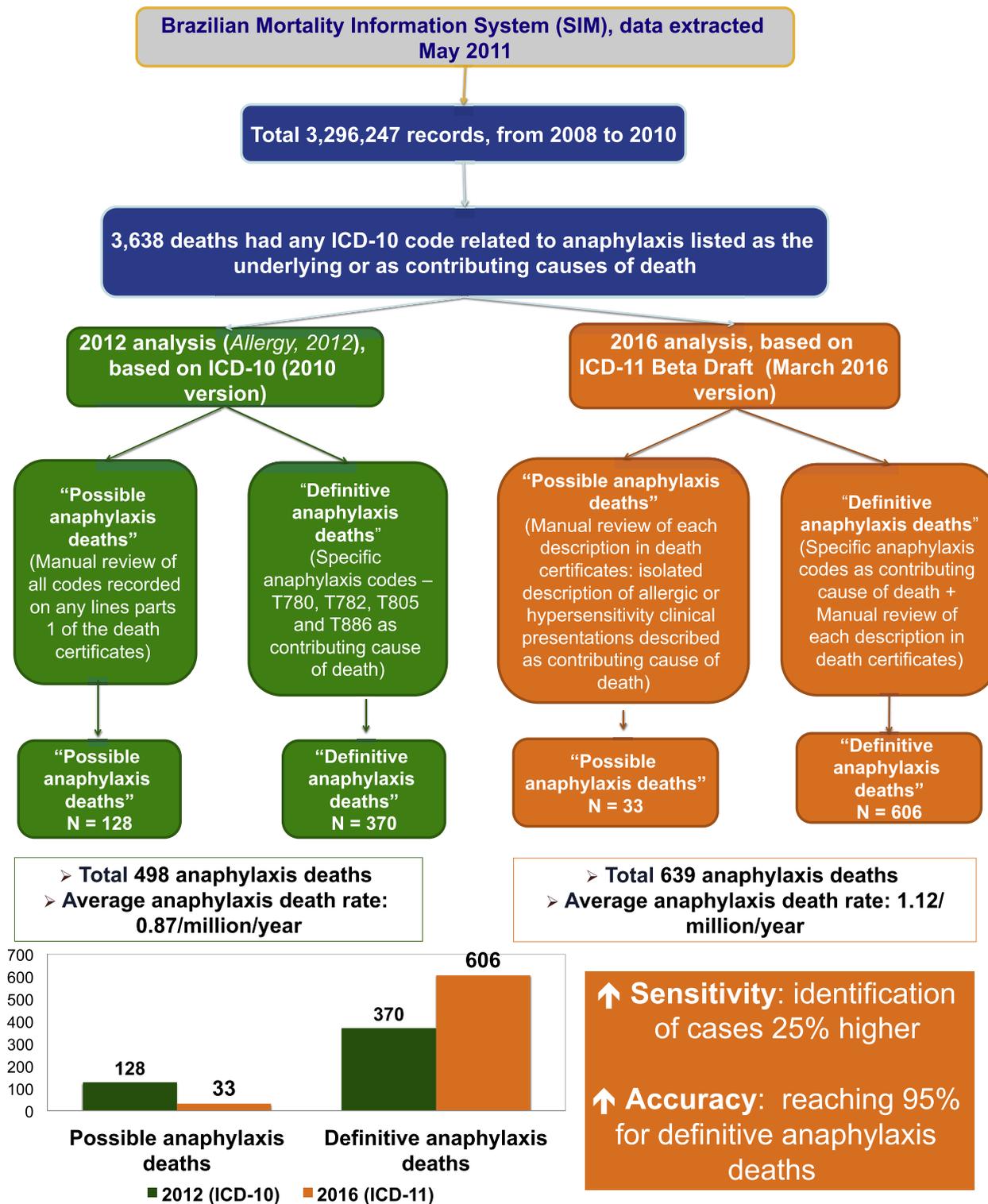
#### The ALLERGY in ICD-11 Initiative and the pioneer “Allergic and hypersensitivity conditions” section

Under development since 2007, ICD-11 is intended not only to rectify deficiencies in ICD-10 and to incorporate changes driven

by scientific advances but also to take advantage of the revolution in electronic data handling since the publication of ICD-10 a quarter of a century ago.<sup>8</sup> ICD-11 can be regarded as a suite of classifications based on a detailed and comprehensive polyhierarchical Web-like Foundation (Fig 2) in which any single disease entity can be represented in more than 1 location.<sup>27</sup>

Considering the ICD-11 revision as a key window of opportunity, a detailed action plan was coordinated under the ALLERGY in ICD-11 Initiative (led by L.K.T. and P.D.), with the aim of creating a more appropriate classification for allergic and hypersensitivity conditions in this new edition of the ICD-11. Subsequently, we have produced technical and scientific evidence demonstrating the need for classification and coding changes, and we have participated in an ongoing dialogue with the WHO ICD-11 revision governance team. All these efforts have been documented in peer-reviewed publications<sup>5,7,15,16,25,27-43</sup> and are being acknowledged and supported by the Joint Allergy Academies comprising the American Academy of Allergy, Asthma & Immunology; the European Academy of Allergy and Clinical Immunology; the World Allergy Organization; the American College of Allergy, Asthma & Immunology; the Asia Pacific Association of Allergy, Asthma and Clinical Immunology; and the Latin American Society of Allergy, Asthma and Immunology.<sup>43</sup>

The main outcome of this process has been construction of the section titled “Allergic and hypersensitivity conditions” under the new “Immune system disorders” chapter of ICD-11.<sup>16,44</sup> By consolidating all allergic conditions into a single ICD-11 section



**FIG 3.** Evidence-based data demonstrate the increase in accuracy and sensitivity of ICD-11 for anaphylaxis vital statistics in Brazil. Coding accuracy and sensitivity was much improved over ICD-10 when ICD-11 was used. Adapted from Tanno et al.<sup>5,42</sup>

rather than distributing them over many chapters, as in ICD-10, and by allowing all the relevant codes to be used for mortality and morbidity outcomes, we aimed to make it simpler for clinicians, epidemiologists, statisticians, data custodians, and other

relevant personnel to locate and document allergic disorders (Fig 1).

As part of the validation process of this new framework, we analyzed the capacity of ICD-11 to capture anaphylaxis deaths by

coding the original Brazilian data set of deaths attributed to anaphylaxis during the period 2008 to 2010 using ICD-11.<sup>5</sup> In 2016, a manual review of each of the records was performed. As a result, we identified 639 anaphylaxis-related deaths, of which 95% were classified as “definite anaphylaxis-related deaths.”<sup>41</sup> In contrast to the 2012 published data, we found a greater number of cases; moreover, all 606 definite anaphylaxis-related deaths would be considered as underlying causes of death using ICD-11. Even more striking was the effect on accuracy, reaching 95% for definite anaphylaxis-related deaths when ICD-11 was used. This study was the first example of how the new “Allergic and hypersensitivity conditions” section of the forthcoming ICD-11 can improve the quality and accuracy of official vital statistics data and the visibility of an important public health concern (Fig 3).<sup>5,41</sup>

### Changing the WHO ICD mortality coding rules for anaphylaxis

Changes have been made to give allergic and hypersensitivity disorders greater representation in ICD-11. During the revision process, we have been in close contact with the WHO Mortality Reference Group because of our concerns that neither anaphylaxis nor other specified allergies could be officially considered underlying causes of death in the death certificate. A systematic review confirmed that countries other than Brazil have faced the same problem with recording anaphylaxis-related mortality methods.<sup>15</sup> The result of our deliberations with the Mortality Reference Group is that coding rules have been changed by the addition of allergic conditions, including anaphylaxis, as underlying causes of deaths in official mortality statistics.

### ANAPHYLAXIS IN ICD-11: CURRENT STATUS AND PERSPECTIVES

ICD-11 was released in June 2018 in preparation for presentation to the WHA in May 2019.<sup>7</sup> In June 2018, the WHO designated the University of Montpellier an official World Health Organization Collaborating Centre (WHO CC) for Classification Scientific Support, with Drs Tanno and Demoly as heads. This designation as the only WHO CC addressed to classification of allergic and hypersensitivity conditions is the result of recognition by the WHO of the work done by the ALLERGY in ICD-11 Initiative in providing academic, research, and scientific support to the WHO in the areas of our expertise in the implementation, refinement, and maintenance of the WHO Family of International Classifications (Fig 2).<sup>45</sup>

Once ICD-11 has been approved by the WHA, the process of implementation of ICD-11 into each country's health information systems will be formally started, and the use of ICD-11 is scheduled to January 2022. Once implemented, there will likely be 2 immediate consequences of the use of the new classification based on the logic of ICD-11: (1) the number of reported anaphylaxis-related deaths might increase and (2) inclusion of cases in official mortality statistics will provide a global standard for comparability and therefore for decision making and prevention.

Because knowledge derived from populations is key information for more realistic decision making, the construction of the new section of ICD-11 addressing allergic and hypersensitivity conditions will facilitate collection of more accurate

epidemiologic data. Ultimately, this will result in better health care planning to implement public health measures for prevention and reduction of the morbidity and mortality attributable to these conditions reflecting higher-quality patient management. As a continuation of the achievements in ICD-11, the heads of the WHO CC representing allergy (L.K.T. and P.D.) are working in an evidence-based process, together with allergy academies, experts, and stakeholders, to reach global availability of AAI.<sup>7</sup>

Timely introduction of the new classification of allergic and hypersensitivity disorders in ICD-11 can be considered a much-needed milestone in the history of the allergy specialty. More reliable, accurate, comprehensive, and comparable anaphylaxis epidemiologic data are expected in the forthcoming years. This technical, economic, and political move might provide a more representative global picture of these conditions and is expected to support improvements in the management of allergic disorders worldwide.

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