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CHANGING THE HISTORY OF ANAPHYLAXIS MORTALITY STATISTICS THROUGH THE WORLD HEALTH ORGANIZATION'S INTERNATIONAL CLASSIFICATION OF DISEASES (ICD)-11

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ABSTRACT

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 under-notification of anaphylaxis deaths due to the difficulties of coding using the International Classification of Diseases, ICD-10. This work triggered strategic international actions supported by the Joint Allergy Academies and the ICD World Health Organization (WHO) leadership to update the classification of allergic disorders for the ICD-11 revision, which resulted in the 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 provided to the WHO Mortality Reference Group, coding rules have been changed allowing anaphylaxis to be recorded as underlying cause of death in official mortality statistics. The mandatory use of ICD-11 from January 2022 for documenting cause of death my likely have two immediate consequences: (i) the reported number of anaphylaxis deaths may increase due to more appropriate coding and (ii) the cross-sectional and longitudinal mortality data generated may ultimately lead to better understanding of anaphylaxis epidemiology and improved health policies directed at reducing anaphylaxis-related mortality.

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

MORTALITY STATISTICS: HISTORY, IMPORTANCE AND RECORD STANDARD 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 (1). 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), published in 1893 (2). 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 it distinguished between systemic diseases and those localized to a particular organ or anatomical site and was officially adopted for use in mortality registries in 1893 (3). This classification, which was accepted by many countries, constituted the basis of ICD. Anaphylaxis was not included in the original list of diseases because it was not formally described until 1902 (3). Currently, most of countries have been using the ICD-10 (or adaptations) version 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 which initiated the train of morbid events leading directly to death (4). 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, most recently confirmed in research performed in Brazil (5).

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 (4). Mortality data provide valuable benchmarks for evaluating progress in increasing years of healthy life (6).

An example of negative outcome due to the lack of accurate anaphylaxis mortality

Adrenaline/epinephrine is the first-line treatment for anaphylaxis and, therefore, listed by the WHO as an essential medication for the treatment of anaphylaxis. However, the availability of adrenaline auto-injectors (AAI) for use in the first-aid treatment is limited to just 32% of the world's 195 nations, the majority of them high-income countries (7). The 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 impact of anaphylaxis and of the need for appropriate therapeutic interventions and investments, for instance in AAIs, to reduce that impact.

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 periodically 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* (8). 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 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 (8). 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: THE UNDER-NOTIFICATION OF A KILLING HYPERSENSITIVITY

Anaphylaxis: the killing hypersensitivity

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

Good epidemiological 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 (15-25). Under-recognition and under-notification of anaphylaxis lead to sparse data and contribute 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 of anaphylaxis mortality records

In 2012, we estimated the magnitude of under-notification and under-reporting 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 based on secondary data, with an average anaphylaxis death rate of 0.87/million/year, categorized as "definitive" or "possible" cases (5). 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. Two coders were responsible for the analysis and there was a high agreement on the classification procedures between the two coders (Cohen-kappa value 0.91) (5).

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 (5). 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 early ICD-11 versions (May

2014 version) (26). The timing of the study was opportune as 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 (26), 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. Striking is that under the same category, are listed only severe cases of anaphylaxis (T78.2 Anaphylactic shock) and it is classified at the same level of "Anaphylactic shock due to adverse food reaction", "Angioneurotic oedema" 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 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 (Figure 1).

IMPROVING THE ACCURACY OF ANAPHYLAXIS MORTALITY STATISTICS THROUGH THE INTERNATIONAL CLASSIFICATION OF DISEASES (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 (8). ICD-11 may be regarded as a suite of classifications which is based on a detailed and comprehensive polyhierarchical web-like Foundation (Figure 2) in which any single disease entity may be represented in more than one location (28).

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 LKT and PD) with the aim of creating a more appropriate classification for allergic and hypersensitivity conditions in this new edition of 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 (5,7,15-16,25,28-45), and are being acknowledged and supported by the Joint Allergy Academies comprising the American

Academy of Allergy Asthma and Immunology (AAAAI), the European Academy of Allergy and Clinical Immunology (EAACI), the World Allergy Organization (WAO), the American College of Allergy Asthma and Immunology (ACAAI), the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI), and the Latin American Society of Allergy, Asthma and Immunology (SLAAI) (45).

The main outcome of this process has been the construction of the section titled "Allergic and hypersensitivity conditions" under the new "Immune system disorders" chapter of ICD-11 (27,30). By consolidating all allergic conditions into a single ICD-11 section, 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 (Figure 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 (5). In 2016, a manual review of each of the records was performed. As a result, we identified 639 anaphylaxis deaths, of which 95% were classified as "definite anaphylaxis deaths" (43). In contrast to the 2012 published data, we found a higher number of cases; moreover, all 606 definite anaphylaxis deaths would be considered as underlying causes of death utilizing ICD-11. Even more striking was the effect on the accuracy, reaching 95% for definite anaphylaxis when ICD11 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 (43) (Figure 3).

Changing the WHO ICD Mortality Coding rules for anaphylaxis

Changes have been made in order 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 mortality methods (15). 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

The ICD-11 was released in June 2018 in preparation for presentation to the World Health Assembly (WHA) in May 2019 (7). In June 2018, the WHO designated the University of Montpellier an official WHO Collaborating Centre (WHO CC) for Classification Scientific Support, with LKT and PD as heads. This designation as the only WHO CC addressed to allergic and hypersensitivity conditions' classification is the result of recognition by WHO of the work done by *ALLERGY in ICD-11* in providing academic, research and scientific support the WHO in the areas of our expertise in the implementation, refinement and maintenance of the WHO Family of International Classifications (FIC) (46) (Figure 2).

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, the use of ICD-11 is scheduled to January 2022. Once implemented, there will likely to have two immediate consequences of the use of the new classification based on the logic of the ICD-11: (i) the number of reported anaphylaxis deaths may increase and (ii) inclusion of cases in official mortality statistics will provide a global standard for comparability and, therefore, for decision-making and prevention.

As knowledge derived from populations is key information for more realistic decision-making, the construction of the new section of ICD-11 addressing to allergic and hypersensitivity conditions will facilitate the collection of more accurate epidemiological 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 in a higher quality management of patients. As continuation of the achievements in ICD-11, the heads of the WHO CC representing allergy (PD and LKT) are working in an evidence-based process, together with the allergy academies, experts and streakholders, in order to reach global availability of adrenaline auto-injectors (7).

The 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 epidemiological data are expected in the forthcoming years. This technical, economical and political move may provide a more representative global picture of these conditions and is expected to support improvements to the management of allergic disorders worldwide.

ABREVIATIONS

AAI: adrenaline auto-injector

AAAAI: American Academy of Allergy Asthma and Immunology

ACAAI: American College of Allergy Asthma and Immunology

APAAACI: Asia Pacific Association of Allergy, Asthma and Clinical Immunology

EAACI: European Academy of Allergy and Clinical Immunology

WHO-FIC: World Health Organization - Family of International Classifications

ICD: International Classification of Diseases

SIM: Brazilian Mortality Information System

SLAAI: Latin American Society of Allergy, Asthma and Immunology

WAO: World Allergy Organization

WHA: World Healh Assembly

WHO: World Health Organization

WHO CC: World Health Organization Collaborating Centre

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

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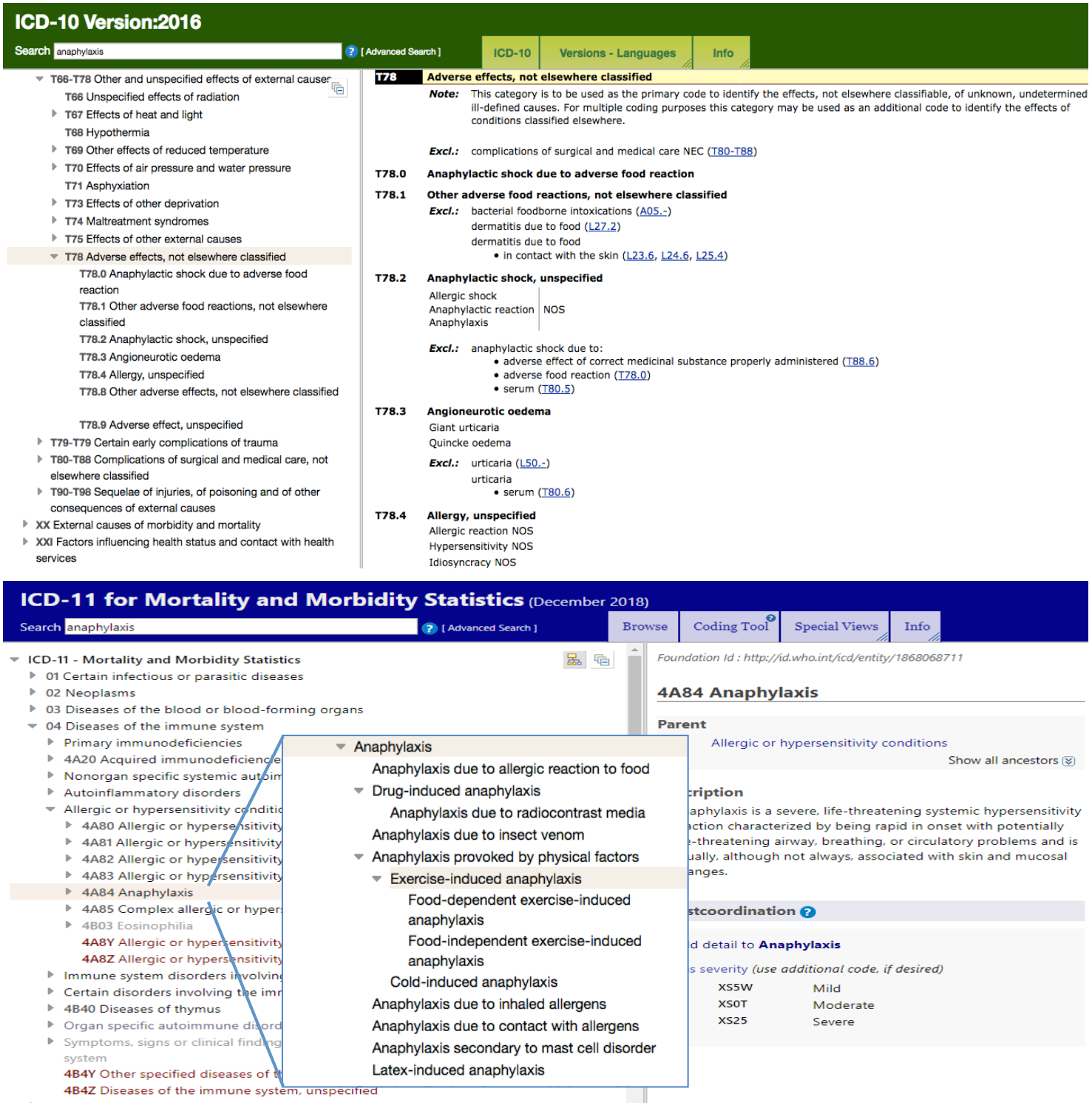
LEGEND OF FIGURES

Figure 1: Changes of anaphylaxis classification in the International Classification of Diseases (ICD)-10 and in the ICD-11

Figure 2: Timeline of ICD-11 revision and implementation, and historic-prospective actions of the ALLERGY in ICD-11 initiative

Figure 3: Evidence-based data demonstrates the increase of accuracy and sensisitity of ICD-11 for anaphylaxis vital statistics in Brazil, adapted references 5 and 43. Coding accuracy and sensitivity was much improved over ICD-10 when ICD-11 was used.



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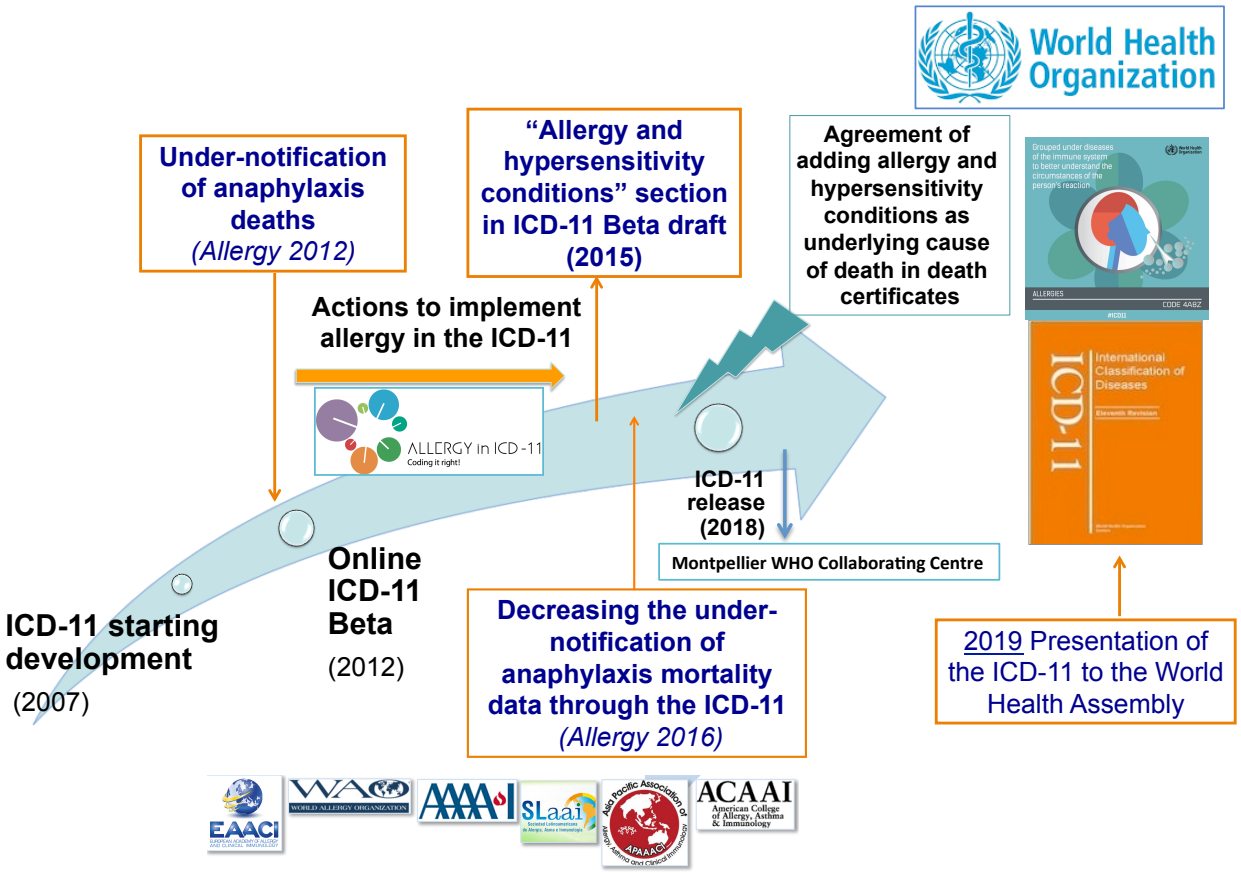

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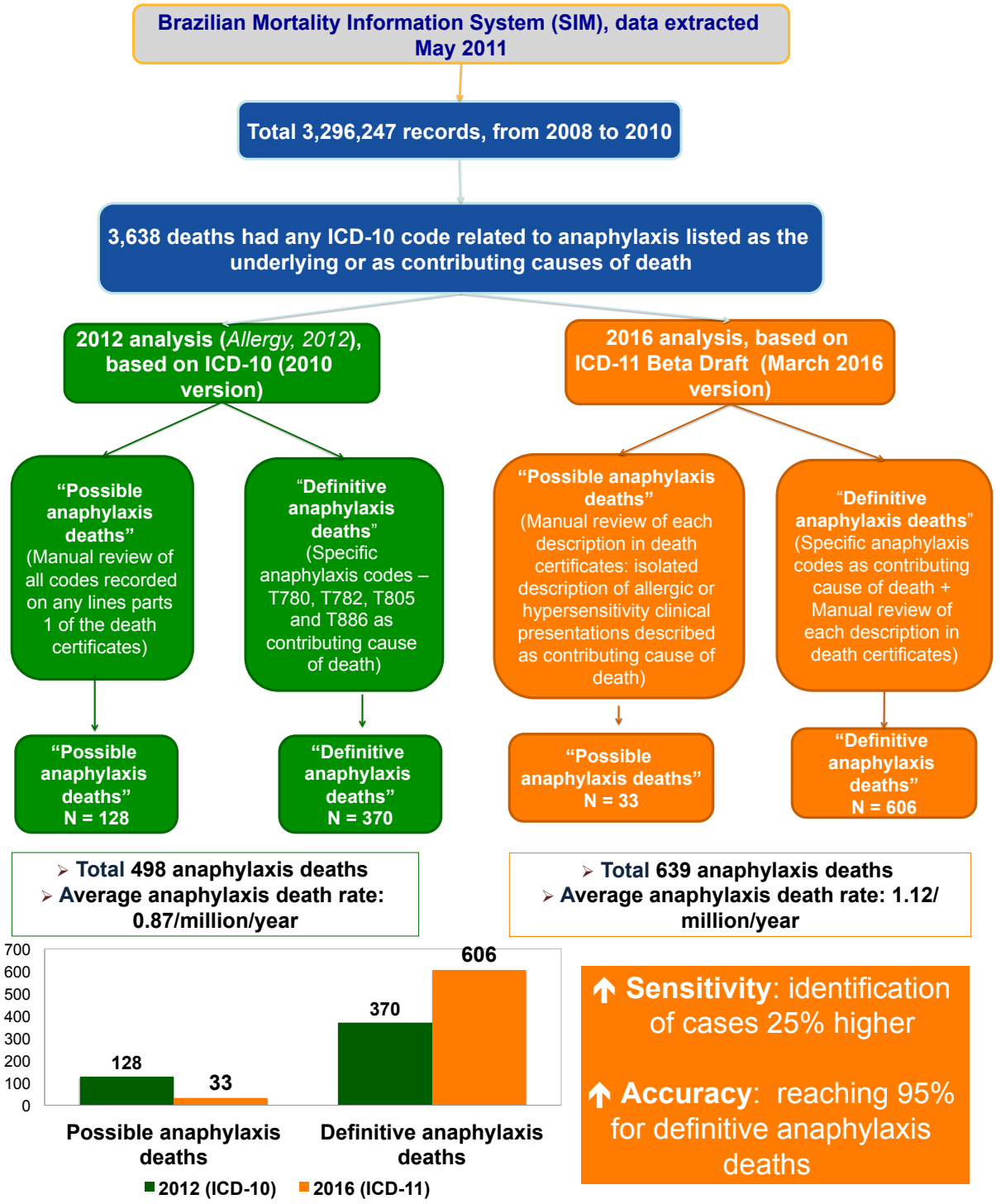

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