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1 CHANGING THE HISTORY OF ANAPHYLAXIS MORTALITY STATISTICS 2 THROUGH THE WORLD HEALTH ORGANIZATION'S 3 INTERNATIONAL CLASSIFICATION OF DISEASES (ICD)-11 4

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60

61 **ABSTRACT**

62 We review the history of the classification and coding changes for anaphylaxis and provide
63 current and perspective information in the field. In 2012, an analysis of Brazilian data
64 demonstrated under-notification of anaphylaxis deaths due to the difficulties of coding using
65 the International Classification of Diseases, ICD-10. This work triggered strategic
66 international actions supported by the Joint Allergy Academies and the ICD World Health
67 Organization (WHO) leadership to update the classification of allergic disorders for the ICD-
68 11 revision, which resulted in the construction of the pioneer “Allergic and hypersensitivity
69 conditions” chapter. The usability of the new framework has been tested by evaluating the
70 same data published in 2012 from the ICD-11 perspective. Coding accuracy was much
71 improved, reaching 95% for definite anaphylaxis.

72 As the results provided to the WHO Mortality Reference Group, coding rules have been
73 changed allowing anaphylaxis to be recorded as underlying cause of death in official
74 mortality statistics. The mandatory use of ICD-11 from January 2022 for documenting cause
75 of death may likely have two immediate consequences: (i) the reported number of
76 anaphylaxis deaths may increase due to more appropriate coding and (ii) the cross-sectional
77 and longitudinal mortality data generated may ultimately lead to better understanding of
78 anaphylaxis epidemiology and improved health policies directed at reducing anaphylaxis-
79 related mortality.

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

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96 **MORTALITY STATISTICS: HISTORY, IMPORTANCE AND RECORD STANDARD METHODS**

97 *Historical background of vital statistics*

98 Rational disease classification dates back to Hippocrates, but the first modern medical
99 classification considering true ontology of diseases was developed in 1735 by Carl Linnaeus,
100 who divided diseases into 11 classes, 37 orders, and 325 species (1). Although this
101 classification contained some errors from a modern perspective, this framework laid the
102 foundation for work that eventually led to the first edition of the International Classification
103 of Diseases (ICD), published in 1893 (2). It had been preceded in 1885 by the first
104 International List of Causes of Death, which had been drafted by Jacques Bertillon and
105 colleagues and it distinguished between systemic diseases and those localized to a particular
106 organ or anatomical site and was officially adopted for use in mortality registries in 1893 (3).
107 This classification, which was accepted by many countries, constituted the basis of ICD.
108 Anaphylaxis was not included in the original list of diseases because it was not formally
109 described until 1902 (3). Currently, most of countries have been using the ICD-10 (or
110 adaptations) version for morbidity and mortality statistics. Although the ICD is generally
111 reviewed by the World Health Organization (WHO) periodically, anaphylaxis has never been
112 well captured in this international system.

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

119

120 *What Can Mortality Data Tell Us*

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

126

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

128 Adrenaline/epinephrine is the first-line treatment for anaphylaxis and, therefore,
129 listed by the WHO as an essential medication for the treatment of anaphylaxis. However, the
130 availability of adrenaline auto-injectors (AAI) for use in the first-aid treatment is limited to
131 just 32% of the world's 195 nations, the majority of them high-income countries (7). The key
132 issues leading to the lack of availability of AAIs include high cost but also national

133 regulations, lack of regional evidence about the value of epinephrine and a paucity of
134 accurate data on anaphylaxis epidemiology. Lack of accurate mortality information hinders
135 understanding of the public health impact of anaphylaxis and of the need for appropriate
136 therapeutic interventions and investments, for instance in AAls, to reduce that impact.

137

138 *How worldwide mortality data are recorded and harmonized*

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

143 Analysis of mortality data typically involves comparisons of data sets. However, unless
144 the data have been compiled using the same methods and according to the same standards,
145 such comparisons have the potential to yield misleading results. For these reasons, the WHO
146 has issued international instructions on data collection, coding and classification, and
147 statistical presentation of causes of death. In most countries, mortality statistics are
148 routinely compiled according to regulations and recommendations adopted by the World
149 Health Assembly (WHA). The international mortality coding instructions presuppose that
150 data have been collected with a death certificate conforming to the *International Form of*
151 *Medical Certificate of Cause of Death* (8). It is the responsibility of the medical practitioner
152 or other qualified certifier signing the death certificate to indicate which morbid conditions
153 led directly to death and to state any antecedent conditions giving rise or contributing to
154 this cause.

155 The WHO's mortality data reflect deaths registered by national civil death registration
156 systems, with the underlying cause of death coded by the national authority (8). If a
157 condition or a disease is not considered an "underlying cause of death", national registration
158 systems are not able to capture related accurate data on cause of death.

159

160 ANAPHYLAXIS: THE UNDER-NOTIFICATION OF A KILLING HYPERSENSITIVITY

161 *Anaphylaxis: the killing hypersensitivity*

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

167 Good epidemiological data are essential components for a nation's health service
168 planning, including identifying priorities for reducing morbidity and mortality. In the case of
169 anaphylaxis, however, there are only a limited number of population-based epidemiologic
170 studies of mortality, particularly in the case of low- and middle-income countries (15-25).
171 Under-recognition and under-notification of anaphylaxis lead to sparse data and contribute
172 to lack of recognition of the importance of anaphylaxis and the consequent neglect of health
173 care strategies for improving diagnosis, treatment and prevention at many levels of the
174 health care system.

175

176 *Evidence-based data call for changes of anaphylaxis mortality records*

177 In 2012, we estimated the magnitude of under-notification and under-reporting of
178 anaphylaxis deaths using the information derived from both the underlying and the
179 contributing causes of death data from the Brazilian Mortality Information System (*Sistema*
180 *de Informação sobre Mortalidade - SIM*). In this study, we analyzed all 3,296,247 death
181 records from 2008 to 2010 using ICD-10 and found a total of 498 anaphylaxis deaths based
182 on secondary data, with an average anaphylaxis death rate of 0.87/million/year, categorized
183 as "definitive" or "possible" cases (5). We considered as "possible anaphylaxis deaths",
184 cases that had an isolated allergic or hypersensitivity clinical condition listed as a
185 contributing cause of death (*e.g.*, angioedema or urticaria). We decided that such
186 conditions, unless presented together with other more specific anaphylaxis codes, could
187 only rarely be considered an underlying cause of death. All records described as anaphylaxis
188 or having an allergic or hypersensitivity condition as the underlying cause of death
189 associated with the possible trigger as contributing mortality data were classified as
190 "definitive anaphylaxis deaths". The remaining and unspecified cases (*e.g.*, missing
191 immediate cause of death in the death certificates) were considered "death unrelated to
192 anaphylaxis", for example, cases of sepsis shock. Two coders were responsible for the
193 analysis and there was a high agreement on the classification procedures between the two
194 coders (Cohen-kappa value 0.91) (5).

195 The most striking observation derived from this study was that none of these deaths
196 would have been attributed to anaphylaxis had we exclusively considered information from
197 the underlying cause-of-death field (5). The study called attention to the need for better
198 coding not only for anaphylaxis deaths, but also for all allergic and hypersensitivity
199 conditions, which would otherwise be misclassified in ICD-10 and early ICD-11 versions (May

200 2014 version) (26). The timing of the study was opportune as the ICD-11 revision process
201 was underway.

202 An important reason for this misclassification is the difficulty of coding anaphylaxis
203 fatalities under the WHO ICD system. In the ICD-10 (2016 version) platform (26), anaphylaxis
204 is classified under the “XIX Injury, poisoning and certain other consequences of external
205 causes” chapter, specifically the “T78 Adverse effects, not elsewhere classified” section.
206 Striking is that under the same category, are listed only severe cases of anaphylaxis (T78.2
207 Anaphylactic shock) and it is classified at the same level of “Anaphylactic shock due to
208 adverse food reaction”, “Angioneurotic oedema” and “Allergy, unspecified”. Causes of
209 deaths are classified and grouped according to the ICD edition in use at the time and the
210 information on death certificates is collected using the international form recommended by
211 the WHO. However, a limited number of ICD-10 codes are considered to be valid for
212 representing underlying causes of death on the current death certificates, and with regard
213 to anaphylaxis as such, there are simply no valid codes (Figure 1).

214

215

216 IMPROVING THE ACCURACY OF ANAPHYLAXIS MORTALITY STATISTICS THROUGH THE 217 INTERNATIONAL CLASSIFICATION OF DISEASES (ICD)-11

218 *The ALLERGY in ICD-11 initiative and the pioneer “Allergic and hypersensitivity conditions”* 219 *section*

220 Under development since 2007, ICD-11 is intended not only to rectify deficiencies in
221 ICD-10 and to incorporate changes driven by scientific advances, but also to take advantage
222 of the revolution in electronic data handling since the publication of ICD-10 a quarter of a
223 century ago (8). ICD-11 may be regarded as a suite of classifications which is based on a
224 detailed and comprehensive polyhierarchical web-like Foundation (Figure 2) in which any
225 single disease entity may be represented in more than one location (28).

226 Considering the ICD-11 revision as a key window of opportunity, a detailed action plan
227 was coordinated under the *ALLERGY in ICD-11* initiative (led by LKT and PD) with the aim of
228 creating a more appropriate classification for allergic and hypersensitivity conditions in this
229 new edition of ICD-11. Subsequently, we have produced technical and scientific evidence
230 demonstrating the need for classification and coding changes and we have participated in an
231 ongoing dialogue with the WHO ICD-11 revision governance team. All these efforts have
232 been documented in peer-reviewed publications (5,7,15-16,25,28-45), and are being
233 acknowledged and supported by the Joint Allergy Academies comprising the American

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

239 The main outcome of this process has been the construction of the section titled
240 “Allergic and hypersensitivity conditions” under the new “Immune system disorders”
241 chapter of ICD-11 (27,30). By consolidating all allergic conditions into a single ICD-11 section,
242 rather than distributing them over many chapters as in ICD-10 and by allowing all the
243 relevant codes to be used for mortality and morbidity outcomes, we aimed to make it
244 simpler for clinicians, epidemiologists, statisticians, data custodians and other relevant
245 personnel to locate and document allergic disorders (Figure 1).

246 As part of the validation process of this new framework, we analyzed the capacity of
247 ICD-11 to capture anaphylaxis deaths by coding the original Brazilian data set of deaths
248 attributed to anaphylaxis during the period 2008 to 2010 using ICD-11 (5). In 2016, a manual
249 review of each of the records was performed. As a result, we identified 639 anaphylaxis
250 deaths, of which 95% were classified as “definite anaphylaxis deaths” (43). In contrast to the
251 2012 published data, we found a higher number of cases; moreover, all 606 definite
252 anaphylaxis deaths would be considered as underlying causes of death utilizing ICD-11. Even
253 more striking was the effect on the accuracy, reaching 95% for definite anaphylaxis when
254 ICD11 was used. This study was the first example of how the new “Allergic and
255 hypersensitivity conditions” section of the forthcoming ICD-11 can improve the quality and
256 accuracy of official vital statistics data and the visibility of an important public health
257 concern (43) (Figure 3).

258

259 *Changing the WHO ICD Mortality Coding rules for anaphylaxis*

260 Changes have been made in order to give allergic and hypersensitivity disorders
261 greater representation in ICD-11. During the revision process we have been in close contact
262 with the WHO Mortality Reference Group, because of our concerns that neither anaphylaxis
263 nor other specified allergies could be officially considered underlying causes of death in the
264 death certificate. A systematic review confirmed that countries other than Brazil have faced
265 the same problem with recording anaphylaxis mortality methods (15). The result of our
266 deliberations with the Mortality Reference Group is that coding rules have been changed by

267 the addition of allergic conditions, including anaphylaxis, as underlying causes of deaths in
268 official mortality statistics.

269

270 ANAPHYLAXIS IN ICD-11: CURRENT STATUS AND PERSPECTIVES

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

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

286 As knowledge derived from populations is key information for more realistic decision-
287 making, the construction of the new section of ICD-11 addressing to allergic and
288 hypersensitivity conditions will facilitate the collection of more accurate epidemiological
289 data. Ultimately, this will result in better health care planning to implement public health
290 measures for prevention and reduction of the morbidity and mortality attributable to these
291 conditions reflecting in a higher quality management of patients. As continuation of the
292 achievements in ICD-11, the heads of the WHO CC representing allergy (PD and LKT) are
293 working in an evidence-based process, together with the allergy academies, experts and
294 stakeholders, in order to reach global availability of adrenaline auto-injectors (7).

295 The timely introduction of the new classification of allergic and hypersensitivity
296 disorders in ICD-11 can be considered a much needed milestone in the history of the allergy
297 specialty. More reliable, accurate, comprehensive and comparable anaphylaxis
298 epidemiological data are expected in the forthcoming years. This technical, economical and
299 political move may provide a more representative global picture of these conditions and is
300 expected to support improvements to the management of allergic disorders worldwide.

301

302 **ABREVIATIONS**

303 AAI: adrenaline auto-injector

304 AAAAI: American Academy of Allergy Asthma and Immunology

305 ACAAI: American College of Allergy Asthma and Immunology

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

307 EAACI: European Academy of Allergy and Clinical Immunology

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

309 ICD: International Classification of Diseases

310 SIM: Brazilian Mortality Information System

311 SLAAI: Latin American Society of Allergy, Asthma and Immunology

312 WAO: World Allergy Organization

313 WHA: World Health Assembly

314 WHO: World Health Organization

315 WHO CC: World Health Organization Collaborating Centre

316

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466 **LEGEND OF FIGURES**

467

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

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

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

476

ICD-10 Version:2016

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ICD-10 | Versions - Languages | Info

- ▼ 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 or 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 (A05.-) 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

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

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Foundation Id : <http://id.who.int/icd/entity/1868068711>

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
For detail to **Anaphylaxis**

Severity (use additional code, if desired)

XS5W	Mild
XS0T	Moderate
XS25	Severe

▼ Anaphylaxis

- ▶ Anaphylaxis due to allergic reaction to food
- ▼ Drug-induced anaphylaxis
 - ▶ Anaphylaxis due to radiocontrast 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

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

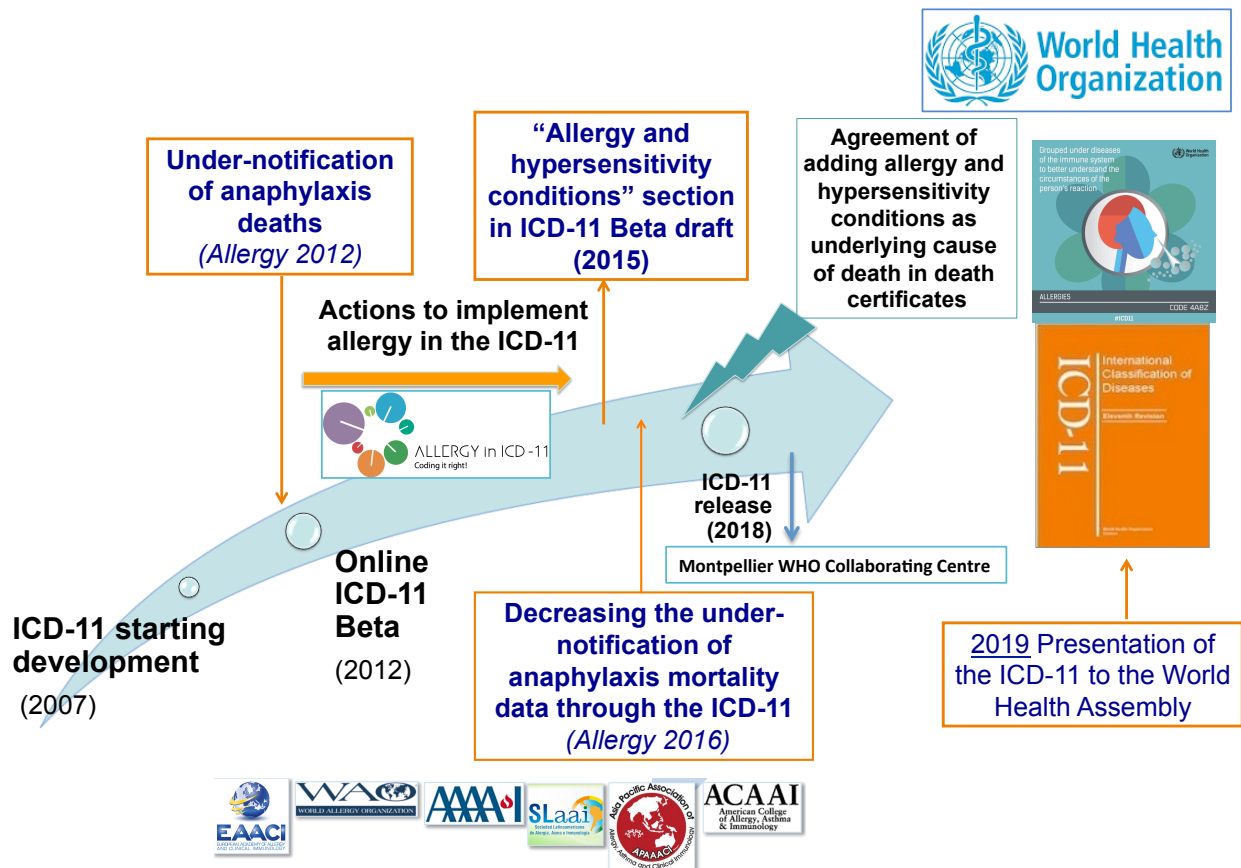


Figure 2: Timeline of ICD-11 revision and implementation, and historic-prospective actions of the ALLERGY in ICD-11 initiative

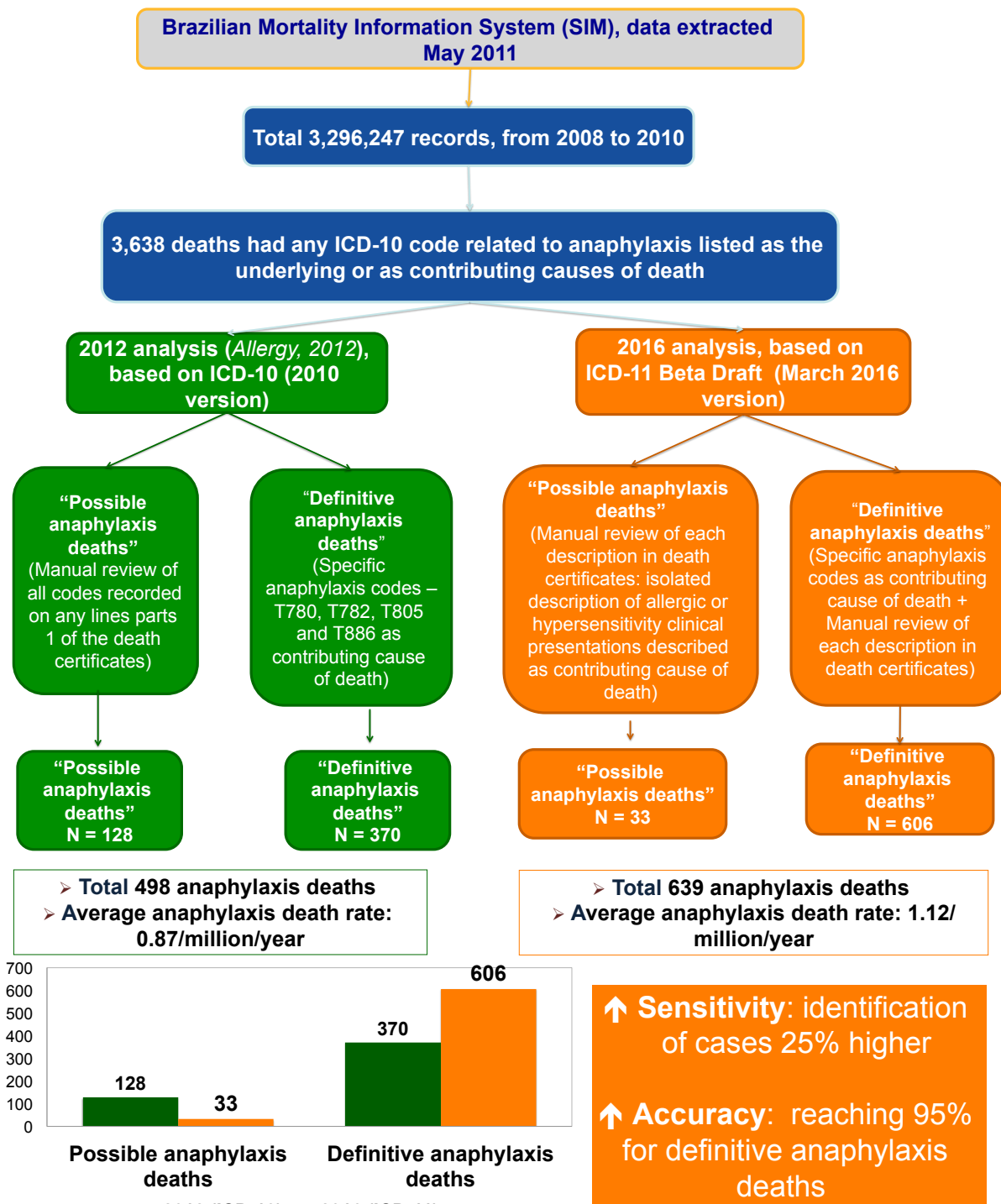


Figure 3: Evidence-based data demonstrates the increase of accuracy and sensitivity of ICD-11 for anaphylaxis vital statistics in Brazil, adapted references 5 and 43. Coding accuracy and sensitivity was much improved over ICD-10 when ICD-11 was used.