

Applying prevention concepts to anaphylaxis: A call for worldwide availability of adrenaline auto-injectors

1 | WE URGENTLY NEED TO APPLY PREVENTION CONCEPTS TO ANAPHYLAXIS

1.1 | Anaphylaxis: a public health issue

Anaphylaxis is currently recognized as a severe, immediate systemic allergic or hypersensitivity reaction characterized by rapid onset and the potential to endanger life through respiratory and cardiovascular compromise.¹ Anaphylaxis can be considered a syndrome with a constellation of features and signs, not pathognomonic of only one disease. This multi-faceted condition can manifest at any age, and all healthcare professionals may be faced with it. All anaphylaxis guidelines²⁻⁵ consistently highlight the possibility of death during an anaphylactic episode.

The estimated annual direct cost of anaphylaxis is \$1.2 billion in the United States of America⁶ and 4.8 million € in France.⁷ The estimated annual number of anaphylaxis deaths ranges from 0.12 to 1.12 per million population per year and differs from country to country.⁸⁻¹⁰ However, healthcare providers frequently underreport anaphylaxis because of the unexpected nature of the event, lack of accurate diagnosis, multi-faceted presentations involving various organ systems resulting in inappropriate coding and a lack of accurate diagnostic coding of anaphylaxis itself also contributes to underdiagnosis of non-fatal cases and underestimation of fatalities.⁹ More precise classification and coding have proved to enable the accumulation of accurate mortality data¹⁰; therefore, the allergy and hypersensitivity subsection of the forthcoming 11th version of the International Classification of Disease (ICD-11) will support the determination of more accurate costs of life-threatening anaphylaxis vs the costs related to preventive measures.

Due to the multi-dimensional clinical presentations, risk of fatality and the possibility of occurring in any setting, the allergy community has designated anaphylaxis as a high priority public health issue. From a public health point of view, preventing the disease (or injury) by finding the underlying cause of fatality through death certificates results in the greatest health gain. 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. Although anaphylaxis appears to be increasing in frequency, it has never been considered as an underlying cause of death. Due to under-diagnosis and under-reporting, published data likely represent "the tip of the iceberg."

1.2 | Prevention in the context of public health

Conceptually, from the World Health Organization (WHO) perspective, public health is defined as "the science and art of science of preventing disease, prolonging life and promoting health through the organized efforts of society".¹¹ Although nowadays public health encompasses a wide range of areas including chronic diseases, science of ageing and the influence of epigenetics, public health actions generally become necessary when increased morbidity and mortality and lack of appropriate epidemiologic data are associated with a specific disorder. In these situations, strategic preventive interventions at national and international levels are launched.

For anaphylaxis, although the allergy community has made substantial efforts to develop documents that advocate increased awareness and optimal management,¹⁻⁵ there has been no tangible progress. Up until recently, there had never been a consensus about the universal language and coding required for use in diagnosis of anaphylaxis in many different healthcare settings. This was a roadblock to obtaining the accurate morbidity¹² and mortality⁹ epidemiological data required for decision-making about preventive actions and adequate allocation of resources. Most anaphylaxis research data have addressed specific populations or triggers, which does not facilitate a global view from the public health perspective.

The repercussions are clear in clinical practice. In contrast to chronic respiratory diseases, assigned as non-communicable conditions by the WHO, and therefore considered a high investment priority in all healthcare settings, anaphylaxis is still not universally recognized at the same level. The improved recognition of anaphylaxis in the ICD-11^{10,13,14} is a major step forward, but this will not be in place before 2018 and new data will not be generated before 2020. Regardless of national regulations, one of the main

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

consequences is the lack of global availability of adrenaline auto-injectors (AAIs) as the first-line treatment for this condition (Figure 1).

As public health's core mission is prevention of injury or disease, there are many potential strategic interventions (Table 1). In concept, the levels of prevention follow the natural history of disorders (Figure 2), and for this reason, the application of the prevention aims differs in each disease or group of diseases. Here we review prevention concepts and apply them to anaphylaxis in order to support awareness, to reach a consensus regarding the best management of this condition and to strengthen the need for global availability of AAIs as an essential treatment for anaphylaxis (Figure 1). Indeed, fewer than 35% of the world population have access to AAIs (Figure 1).

1.3 | Prevention concepts applied to anaphylaxis

Taking the concept of prevention levels and applying it to anaphylaxis (Table 1), facilitates understanding that the measures proposed as primary and secondary preventions are addressed mostly to asymptomatic conditions, in which the main concerns are identifying individuals who are at risk and sensitized, or populations at risk and sensitized. The concepts considered here may depend on the perspectives of each specialty. As an example, screening for asthma in patients with diagnosed allergic rhinitis is secondary prevention measure for the allergy community, although a primary prevention measure for other specialties.

The context of primary and secondary preventions addresses additional questions: How should *individuals or populations at risk* be defined? In general, most anaphylaxis guidelines or consensus statements typically uses the term *risk factors* in cases for which patients experienced anaphylaxis to better understand underlying pathophysiology and avoid new reactions. Therefore, in the clinical context, it is applied as a tertiary prevention measure, in contrast to the concepts used in primary prevention. Most of the risk factors described, such

as age (infancy, adolescence, advanced age), physiologic state (pregnancy), concomitant diseases including asthma, cardiovascular diseases and mast cell disorders with or without mastocytosis, and/or concurrent medications such as beta-blockers and angiotensin-converting enzyme inhibitors² are considered under tertiary prevention context. However, each of these risk factors could support individual specific recommendations, exemplified by the early introduction of peanut in the diet of children at risk for peanut allergy¹⁵ or banning of powdered latex gloves in hospitals to prevent occupational respiratory allergies and anaphylaxis.¹⁶ Therefore, considering the concept of primary prevention applied to anaphylaxis, *individuals or populations at risk* are those presenting with specific risk factor(s) that increase the susceptibility of sensitization (eg bee keepers have potential risk of sensitization due to frequency of exposure to *Hymenoptera* venom allergens).¹⁷

Secondary prevention actions in the context of anaphylaxis aim to identify sensitized individuals in order to prevent the development of allergic disorders. Although validated scientific data are lacking to support the screening the whole population for sensitization, it might be appropriate to do so in individuals with known risk factors. An example of secondary prevention to avoid development of anaphylaxis is the use of latex-free gloves and latex-free medical settings for patients with neural tube defects and known latex sensitization.¹⁸

Tertiary prevention actions are the most familiar for allergists, indeed for all physicians, world-wide who are involved in clinical medicine. A main concern of the allergy community is related to tertiary prevention as it is addressed to existing allergic or hypersensitivity diseases and focuses on their accurate diagnosis and management in order to avoid new exacerbations or reactions. In the context of anaphylaxis, whether immunologic or non-immunologic in aetiology, episodes involve multi-system presentation and can be potentially fatal. All healthcare professionals should be prepared to recognize anaphylaxis promptly, manage it properly and provide recommendations for prevention of the next episode. Patients, too, should be prepared to recognize and self-treat anaphylaxis promptly.

GLOBAL AVAILABILITY OF AUTO-INJECTABLE ADRENALINE

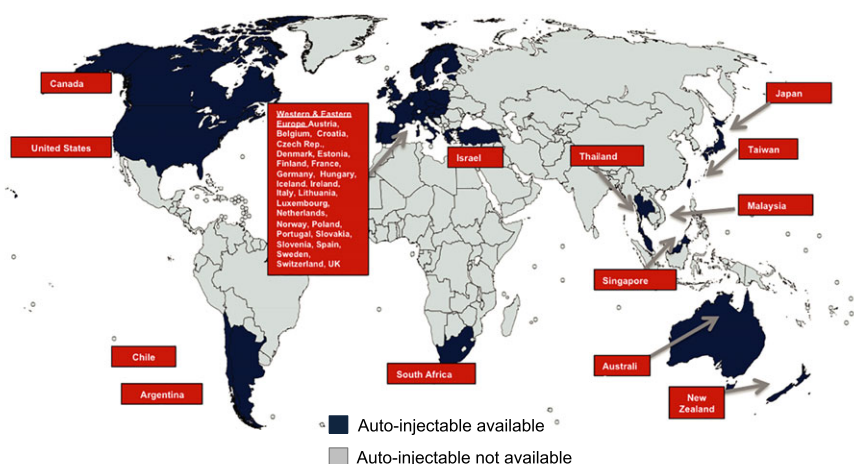


FIGURE 1 Global availability of adrenaline auto-injectors (adapted from 34, 38)

TABLE 1 Prevention concepts from a public health perspective, applied to anaphylaxis and intervention actions

Levels of prevention	Public health concepts regarding prevention	Applying prevention concepts to anaphylaxis	Interventions and actions applied to anaphylaxis	Need for adrenaline auto-injectors
Primary prevention	Primary prevention seeks to prevent the onset of specific diseases via risk reduction: by altering behaviours or exposures that can lead to disease, or by enhancing resistance to the effects of exposure to a disease agent. Generally, targets specific causes and risk factors for specific diseases.	Primary prevention addressed to anaphylaxis would imply the identification of individuals or populations at risk in order to avoid sensitization. For this, specific risk factors should be identified in unsensitized individuals with no history of an anaphylactic reaction	Increase health professionals' awareness through education and continuing education programs (eg breastfeeding, latex avoidance, early food diversification for infants). Support dissemination of accurate information to the public (eg EAACI Anaphylaxis campaign, WAO Allergy week). Specific interventions with early introduction of specific foods in the infant diets (eg peanut). Remove strong sensitizers from public places and workplace environments (eg remove powdered latex gloves to prevent occupational latex allergy/anaphylaxis, remove OTC use of pholcodine to prevent neuromuscular blocking agent anaphylaxis). Strengthen standard international definitions, notification, classification and coding (eg International Classification of Diseases) to support monitoring morbidity and mortality	No
Secondary prevention	Secondary prevention includes procedures that detect and treat pre-clinical pathological changes and thereby control disease progression. Screening procedures are often the first step, leading to early interventions that are more cost-effective than intervening once symptoms appear	Secondary prevention in the context of anaphylaxis includes sensitized individuals with no history of an anaphylactic reaction. The aim is to prevent the development of an allergic disorder in patients previously sensitized. Screening of the general population for sensitization is not recommended. Sensitization is common and does not imply the diagnosis of an allergic disease. Screening should be applied to individuals with known risk factors	Individualized screening to identify sensitized individuals and support specific measures (eg those with occupational latex sensitization). Increase health professionals' awareness through education and regular information programs. Specific interventions with early introduction of specific foods in the infant diets (eg peanut). Strengthen standard international definitions, notification, classification and coding (eg International Classification of Diseases) to support monitoring morbidity and mortality	Individualized indication
Tertiary prevention	Tertiary prevention seeks to soften the impact caused by the disease on the patient's function, longevity and quality of life. It can include modifying risk factors or, when the condition is not reversible, tertiary prevention focuses on rehabilitation, assisting the patient to accommodate to his/her disability	Tertiary prevention: This concept should be focused on patients who have experienced an anaphylactic reaction. After initial clinical presentation, it is intended to reduce the risk of another reaction and/or manage it appropriately and avoid negative outcomes	Complete allergological work-up to confirm triggers (inducers) and support specific immunomodulation (eg allergen immunotherapy for Hymenoptera venom anaphylaxis, peanut allergy or full drug allergy work-up as indicated) and provide a written documentation of the diagnosis and the confirmed triggers/agents. Individualize patient's education and provide specific information: environmental or behaviour modifications to reduce patient's exposure to allergens, provide a written anaphylaxis emergency action plan. Support accurate food allergen labelling to protect consumers. Support the emergency training of health professionals to rapidly identify and manage anaphylaxis. Correct notification of new cases (eg as new allergens arise, support large cohort analysis). Increase health professionals' awareness through education and continuous information programs. Strengthen standard international definitions, notification, classification and coding (eg International Classification of Diseases) to support monitoring morbidity and mortality	Yes, mostly (individualized indication)

OTC, over-the-counter.

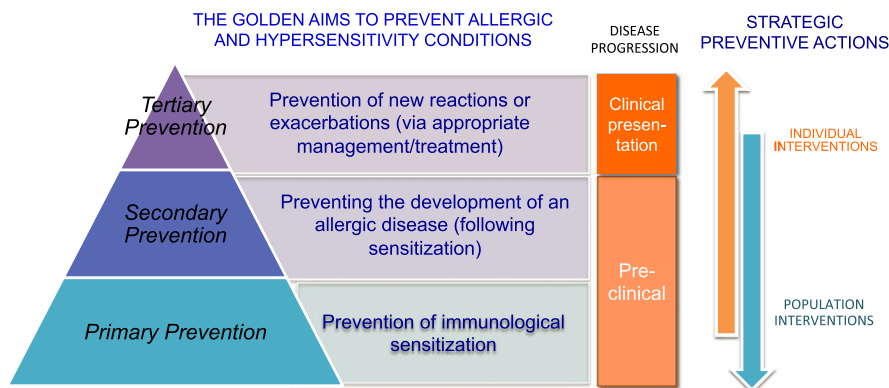


FIGURE 2 General application of prevention concepts to allergic and hypersensitivity conditions

Therefore, AAls as the first-line treatment should be globally available in both private and public (eg school) settings and health networks to be used for any individual who develops anaphylaxis.

Essential is aligning international and national efforts for increasing awareness and availability of generic devices of AAls. As an example, in 2013, President Obama signed the School Access to Emergency Epinephrine Act into law. This federal legislation provides a financial incentive for states to enact their own laws requiring schools to keep student non-specific epinephrine auto-injectors in case of an emergency.¹⁹ Nearly every state has passed legislation regarding stocking undesignated epinephrine auto-injectors in K-12 schools. As another example, the state of Florida passed a law to allow public facilities such as amusement parks, sports leagues, camps, city parks, restaurants and other businesses to maintain a large number of epinephrine auto-injectors for emergency treatment of anaphylaxis.²⁰

2 | STRATEGIC INTERVENTIONS TO PREVENT ANAPHYLAXIS: ACHIEVEMENTS AND UNMET NEEDS

2.1 | Preventive measures for anaphylaxis: past/current initiatives

Conceptually, appropriate preventive actions should occur at both individual and population levels (Figure 2) and most of them are given (or taken) concurrently. Most population interventions have historically focused on primary and secondary prevention measures (Table 1). The allergy community has been promoting anaphylaxis awareness to both health professionals¹⁻⁵ and the general public. Meanwhile, actions to strengthen standard international definitions, notification tools, classification and coding to support obtaining more accurate morbidity and mortality¹⁰ anaphylaxis data are ongoing. This is exemplified by the efforts taken to have an improved classification of allergic and hypersensitivity conditions in ICD-11 revision,^{9,10,12,13,21-31} which resulted in the construction of a pioneer section entitled "Allergic and hypersensitivity conditions," in which anaphylaxis is one of the main headings.^{13,14} The construction of the

new section dealing with anaphylaxis means that the latter will now be recognized as a clinical condition requiring specific documentation and management.

The goals of tertiary prevention include reducing the negative impact or progression of an already-established condition and reducing complications and the risk of new reactions. In higher income countries, great achievements have been reported in many countries at individual and population levels (Table 1) in the past by improving awareness, diagnostic work-up and management methods. As an example, allergen immunotherapy (eg peanut immunotherapy for patients allergic to peanut), which aims specific immune modulation to modify the natural history of the disorder, is therefore considered a tertiary prevention measure. However, we still observe discrepancies in lower income and lower-middle income countries, where some supplementary diagnostic tools, such as the tryptase measurements, and high priority medications are not available.³²⁻³⁴

2.2 | The role of adrenaline (epinephrine) as a preventive measure

Adrenaline (epinephrine) is listed as an essential medication for the treatment of anaphylaxis by the WHO.³⁵ It is a life-saving non-selective adrenergic agonist. Its α 1-adrenergic vasoconstrictor activity prevents and relieves laryngeal oedema, hypotension and shock. Its β 1-adrenergic activity produces inotropic and chronotropic effects,²⁹ increasing the force and rate of cardiac contractions. Its β 2-activity includes bronchodilation and decreased release of mediators of inflammation. Its effects are time-dependent, mandating a recommendation for prompt administration.

Criticism related the availability of AAls as public health measure can be considered as it only benefits individuals who can also access a correct diagnosis, afford and maintain a safe unexpired supply of the devices. Nevertheless, according to the United States Internal Revenue Service, from the prevention perspective, medications are preventive care when taken by a person who has developed risk factors for a disease that has not yet manifested itself or not yet become clinically apparent, or to prevent the recurrence of a disease from which a person has recovered.³⁶ Therefore, the indication of

adrenaline (epinephrine) would be as both a secondary and a tertiary preventive measure (Table 1).

As adrenaline (epinephrine) is the only medication documented to prevent hospitalization and fatalities in anaphylaxis, as a clear, critically important tertiary prevention measure, its availability in some countries is taken for granted and it is widely available in the community for first-aid treatment. However, it is *not* readily available in the majority of countries (Figure 1) in which best management of patients with anaphylaxis is therefore impossible. Lack of availability of this first-aid medication for immediate injection in an anaphylactic reaction increases the risk of progression to a severe episode and death.

Adrenaline is the key measure to prevent fatal anaphylaxis. Although considered rare, the under-notification of anaphylaxis deaths is a well-recognized challenge. A relevant reason for this is the difficulty of coding anaphylaxis fatalities under the previous WHO ICD editions.⁹ Recent publication demonstrated considerable increase in sensitivity and accuracy of anaphylaxis vital statistics data when ICD-11 was used,³¹ opening perspectives to reach quality anaphylaxis mortality statistics to support argumentation for the need of world-wide AAls availability.

Information about the natural history of anaphylaxis is greatest in relationship to specific triggers or populations. Lack of uniform data regarding the natural history of anaphylaxis hampers our understanding of which sensitized and exposed individuals will eventually develop anaphylaxis and does not permit identification of patients who are most likely to present with severe reactions in initial or subsequent episodes. For this reason, adrenaline is considered to be both a secondary and a tertiary preventive measures (Table 1). Most of the adrenaline indications are based on clinical criteria taking in account concepts related to previous history of reaction or sensitization, severity of the reaction, allergy work-up and possibility of avoiding allergen/trigger exposure, among others.

2.3 | Adrenaline auto-injector availability: a matter of life or death

AAls are commercially available in many devices in doses suitable for most, but not all, adults and children. The availability of AAls for use in the first-aid treatment of anaphylaxis is limited to only 32% of all 195 world countries (Figure 1). In some countries in which AAls are not available through official distribution networks, they are available through distribution by special licence arrangements, through distribution on a "named-patient" basis, or through the so-called suitcase trade. This latter, unofficial, source is unreliable because of the possibility of interruptions in the supply, and shipping and storing AAls under conditions outside the recommended temperature range, leading to increased possibility of degradation of the adrenaline (epinephrine) content. Although not ideal, in specific situations, where AAls are not available through official distribution networks, some patients and families can afford to order them online from an international pharmacy or travel to another country to purchase them.³³

A recognized limitation as a public health measure is the lack of direct evidence to show that AAls improve quality of life. Indeed, although it has been shown that the burden of treatment with AAls does not impair quality of life,³⁷ there is little evidence of adrenaline improving quality of life presumably because most clinical consultations provide diagnostic reassurance at the same time as the prescription.

In high-resource countries, there is an increased focus on post-discharge management after successful treatment of anaphylaxis.² Where resources are limited, post-discharge management is severely compromised by lack of availability and affordability of AAls.² The key issues leading to the lack of availability include cost but also national regulations, lack of regional evidence about the value of epinephrine and the limited accurate data about the epidemiology of anaphylaxis morbidity and mortality data. For these reasons, regional and international allergy academies support the initiatives to narrow these gaps. It is important that physicians play a role in educating patients and other clinicians about anaphylaxis and the need for AAls. The availability of generic AAls can become a reality due to combined actions with patients, parents and lawmakers. As a successful example, there was a congressional inquiry in United States as to why the steep increase in epinephrine in a short amount of time, from \$100 in 2007 to over \$600 in 2016. This congressional inquiry led to the availability of generic AAI soon afterwards.

More than reviewing and applying prevention concepts to anaphylaxis, in this manuscript, we have tried to increase awareness and call for the global availability of AAls for best management of anaphylaxis to prevent undue morbidity and mortality. Objective and accurate data related to anaphylaxis fatalities, impact in quality of life and cost are essential requirements to start the discussions with regulators for the availability of AAls in affordable prices in different settings of the health system. Physicians must collaborate with lawmakers, patients and pharmaceutical companies to make this possible. We here flag a strong public health, societal and academic need for prevention and optimal care of allergic patients and best practice of allergology.

ACKNOWLEDGEMENTS

We are extremely grateful to all the representatives of the ICD-11 Revision Project with whom we have been carrying on fruitful discussions, helping us to refine the classification presented here: Robert Jakob, Linda Best, Nenad Kostanjsek, Robert J G Chalmers, Jeffrey Linzer, Linda Edwards, Ségolène Ayme, Bertrand Bellet, Rodney Franklin, Matthew Helbert, August Colenbrander, Satoshi Kashii, Paulo E. C. Dantas, Christine Graham, Ashley Behrens, Julie Rust, Megan Cumerlato, Tsutomu Suzuki, Mitsuko Kondo, Hajime Takizawa, Nobuoki Kohno, Soichiro Miura, Nan Tajima and Toshio Ogawa.

CONFLICT OF INTEREST

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

FUNDING INFORMATION

This research was conducted with support from AstraZeneca

Montpellier Cedex 5, France.

Email: luciana.tanno@gmail.com

AUTHOR CONTRIBUTIONS

Luciana Kase Tanno and Pascal Demoly contributed to the construction of the document (designed the study, analysed and interpreted the data, and wrote the manuscript). F. Estelle R. Simons, Thomas Casale, Mario Sanchez-Borges, Victoria Cardona, Hee-Bom Moon, Moises Calderon, Juan Carlos Sisul and Antonella Muraro contributed to tuning the document and revision of the manuscript.

L. K. Tanno^{1,2,3}

F. E. R. Simons⁴

M. Sanchez-Borges⁵

V. Cardona⁶

H.-B. Moon⁷

M. A. Calderon⁸

J. C. Sisul^{9,10}

A. Muraro^{11,12}

T. Casale^{13,14}

P. Demoly^{2,3}

on behalf of the Joint Allergy Academies*

¹Hospital Sírio Libanês, São Paulo, Brazil

²University Hospital of Montpellier, Montpellier, France

³Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPLESP, Equipe EPAR, Paris, France

⁴Section of Allergy & Clinical Immunology, Department of Pediatrics & Child Health, University of Manitoba, Winnipeg, Canada

⁵Allergy and Clinical Immunology Department, Centro Medico Docente La Trinidad, Caracas, Venezuela

⁶Allergy Section, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain

⁷Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan, Seoul, Korea

⁸Section of Allergy and Clinical Immunology, Imperial College London, National Heart and Lung Institute, Royal Brompton Hospital, London, UK

⁹Latinalerican Society of Allergy, Asthma and Immunology, Villarica, Paraguay

¹⁰American College of Allergy, Asthma and Immunology, Villarica, Paraguay

¹¹European Academy of Allergy and Clinical Immunology, Padua, Italy

¹²Department of Women and Child Health, Food Allergy Referral Centre Veneto Region, Padua General University Hospital, Padua, Italy

¹³American Academy of Allergy Asthma and Immunology, Tampa, FL, USA

¹⁴Morsani College of Medicine, University of South Florida, Tampa, FL, USA

Correspondence

Luciana Kase Tanno, Division of Allergy, Department of Pulmonology, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier,

REFERENCES

1. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol*. 2006;117:391-397.
2. Simons FER, Arduzzo LR, Bilò MB, et al. International consensus on (ICON) Anaphylaxis. *World Allergy Organ J*. 2014;30:9.
3. Panesar SS, Javad S, de Silva D, et al. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy* 2013;68:1353-1361.
4. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis-a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115:341-384.
5. Simons FER, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. *World Allergy Organ J*. 2015;8:32.
6. Patel DA, Holdford DA, Edwards E, Carroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. *J Allergy Clin Immunol* 2011;128:110-115.e5.
7. Flabbee J, Petit N, Jay N, et al. The economic costs of severe anaphylaxis in France: an inquiry carried out by the Allergy Vigilance Network. *Allergy*. 2008;63:360-365.
8. Tejedor-Alonso MA, Moro-Moro M, Múgica-García MV. Epidemiology of Anaphylaxis: contributions From the Last 10 Years. *J Investig Allergol Clin Immunol*. 2015;25:163-175.
9. Tanno LK, Ganem F, Demoly P, Toscano CM, Bierrenbach AL. Undernotification of anaphylaxis deaths in Brazil due to difficult coding under the ICD-10. *Allergy*. 2012;67:783-789.
10. Tanno LK, Bierrenbach AL, Calderon MA, Sheikh A, Simons FE, Demoly P; Joint Allergy Academies. Decreasing the undernotification of anaphylaxis deaths in Brazil through the International Classification of Diseases (ICD)-11 revision. *Allergy*. 2017;72:120-125. <https://doi.org/10.1111/all.13006>.
11. Asheson D. Independent Inquiry into Inequalities in Health Report. Department of Health report, 1998. <https://www.gov.uk/government/publications/independent-inquiry-into-inequalities-in-health-report>. Accessed September 2016.
12. Tanno LK, Calderon MA, Goldberg BJ, Akdis CA, Papadopoulos NG, Demoly P. Categorization of allergic disorders in the new world health organization international classification of diseases. *Clin Transl Allergy*. 2014;4:42.
13. Tanno LK, Calderon MA, Demoly P; on behalf the Joint Allergy Academies. New allergic and hypersensitivity conditions section in the international classification of diseases-11. *Allergy Asthma Immunol Res*. 2016;8:383-388.
14. World Health Organization, ICD-11 Beta Draft website. <http://apps.who.int/classifications/icd11/browse/l-m/en>. Accessed September 2016.
15. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med*. 2016;374:1435-1443.
16. Tarlo SM, Easty A, Eubanks K, et al. Outcomes of a natural rubber latex control program in an Ontario teaching hospital. *J Allergy Clin Immunol*. 2001;108:628-633.
17. Bilò MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. *Clin Exp Allergy*. 2009;39:1467-1476.
18. Blumchen K, Bayer P, Buck D, et al. Effects of latex avoidance on latex sensitization, atopy and allergic diseases in patients with spina bifida. *Allergy*. 2010;65:1585-1593.

19. The United States legislation report, November 13th 2013. <https://www.whitehouse.gov/blog/2013/11/13/president-obama-signs-new-epipen-law-protect-children-asthma-and-severe-allergies-an> <https://www.congress.gov/bill/113th-congress/senate-bill/1503>. Accessed September 2016
20. The United States legislation report, June 13th 2014. <http://knowledgecenter.csg.org/kc/system/files/Emergency%20Allergy%20Treatment.pdf>. Accessed September 2016.
21. Demoly P, Tanno LK, Akdis CA, et al. Global classification and coding of hypersensitivity diseases – An EAACI – WAO survey, strategic paper and review. *Allergy*. 2014;69:559-570.
22. Tanno LK, Calderon MA, Goldberg BJ, et al. Constructing a classification of hypersensitivity/allergic diseases for ICD-11 by crowdsourcing the allergist community. *Allergy*. 2015;70:609-615.
23. Tanno LK, Calderon M, Papadopoulos NG, Demoly P. Mapping hypersensitivity/allergic diseases in the International Classification of Diseases (ICD)-11: cross-linking terms and unmet needs. *Clin Transl Allergy*. 2015;5:20.
24. Tanno LK, Calderon MA, Demoly P; on behalf the Joint Allergy Academies. Making allergic and hypersensitivity conditions visible in the International Classification of Diseases-11. *Asian Pac Allergy*. 2015;5:193-196.
25. Tanno LK, Calderon MA, Demoly P; on behalf the Joint Allergy Academies. Optimization and simplification of the allergic and hypersensitivity conditions classification for the ICD-11. *Allergy*. 2016;71:671-676.
26. Tanno LK, Calderon MA, Papadopoulos NG, et al. Revisiting desensitization and allergen immunotherapy concepts for the international classification of diseases (ICD)-11. *J Allergy Clin Immunol Pract*. 2016;4:643-649.
27. Tanno LK, Calderon MA, Li J, Casale T, Demoly P. Updating allergy/hypersensitivity diagnostic procedures in the WHO ICD-11 revision. *J Allergy Clin Immunol Pract*. 2016;4:650-657.
28. Tanno LK, Calderon MA, Papadopoulos NG, et al. Surveying the new allergic and hypersensitivity conditions chapter of the International classification of diseases (ICD)-11. *Allergy* 2016;71:1235-1240. <https://doi.org/10.1111/all.12945>.
29. Tanno LK, Calderon M, Demoly P; Joint Allergy Academies. Supporting the validation of the new allergic and hypersensitivity conditions section of the World Health Organization International Classification of Diseases-11. *Asia Pac Allergy*. 2016;6:149-156.
30. Tanno LK, Calderon M, Sublett JL, Casale T, Demoly P; Joint Allergy Academies. Smoothing the transition from International Classification of Diseases, Tenth Revision, Clinical Modification to International Classification of Diseases, Eleventh Revision. *J Allergy Clin Immunol Pract* 2016;4:1265-1267. <https://doi.org/10.1016/j.jaip.2016.06.024>.
31. Tanno LK, Bierrenbach AL, Calderon MA, Sheikh A, Simons FE, Demoly P; Joint Allergy Academies. Decreasing the undernotification of anaphylaxis deaths in Brazil through the International Classification of Diseases (ICD)-11 revision. *Allergy*. 2017;72:120-125.
32. Simons FER. Lack of worldwide availability of epinephrine auto-injectors for outpatients at risk of anaphylaxis. *Ann Allergy Asthma Immunol*. 2005;94:534-538.
33. Simons FER; for WAO. Epinephrine auto-injectors: first-aid treatment still out of reach for many at risk of anaphylaxis in the community. *Ann Allergy Asthma Immunol* 2009;102:403-409.
34. Simons FER; for WAO. World Allergy Organization survey on global availability of essentials for the assessment and management of anaphylaxis by allergy-immunology specialists in healthcare settings. *Ann Allergy Asthma Immunol* 2010;104:405-412.
35. WHO Model List of Essential Medicines, 19th ed, April 2015. http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1. Accessed September, 2016.
36. US Internal Revenue Service. Internal Revenue Bulletin: 2004-33. Notice 2004-50. https://www.irs.gov/irb/2004-33_IRB/ar08.html#d0e1823. Accessed 20 March 2016.
37. Saleh-Langenberg J, Flokstra-de Blok BMJ, Goossens NJ, Kemna JC, van der Velde JL, Dubois AEJ. The compliance and burden of treatment with the epinephrine auto-injector in food-allergic adolescents. *Pediatr Allergy Immunol*. 2016;27:28-34.
38. Song TT, Worm M, Lieberman P. Anaphylaxis treatment: current barriers to adrenaline auto-injector use. *Allergy*. 2014;69:983-991.