

Journal Pre-proof

Inconsistences in prescribing epinephrine autoinjectors

Paul J. Turner, FRCPCH PhD, Nandinee Patel, MBBS PhD, Karla Adams, MD,
Vishaka Hatcher, MD, Patricia Bigas, MD, David Golden, MD



PII: S2213-2198(25)00756-1

DOI: <https://doi.org/10.1016/j.jaip.2025.07.045>

Reference: JAIP 6157

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 9 June 2025

Revised Date: 7 July 2025

Accepted Date: 23 July 2025

Please cite this article as: Turner PJ, Patel N, Adams K, Hatcher V, Bigas P, Golden D, Inconsistences in prescribing epinephrine autoinjectors, *The Journal of Allergy and Clinical Immunology: In Practice* (2025), doi: <https://doi.org/10.1016/j.jaip.2025.07.045>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2025 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

ROSTRUM**Inconsistences in prescribing epinephrine autoinjectors**

Paul J. Turner FRCPCH PhD,¹ Nandinee Patel MBBS PhD,¹ Karla Adams MD,² Vishaka Hatcher MD,² Patricia Bigas MD,³ David Golden MD⁴

1. National Heart & Lung Institute, Imperial College London, London, UK.
2. Wilford Hall Ambulatory Surgical Center, Lackland AFB, San Antonio, TX.
3. Allergy Department, Hospital Clinic de Barcelona, Barcelona, Spain.
4. Johns Hopkins School of Medicine, Baltimore, Maryland, USA

Corresponding author:

Dr Paul Turner

National Heart & Lung Institute,
Imperial College London,
Norfolk Place
London, W2 1PG, UK

Email: p.turner@imperial.ac.uk

ORCID ID 0000-0001-9862-5161

Disclosures:

PJT declares grants from UK Medical Research Council, the UK Food Standards Agency, The Jon Moulton Charity Trust, NIHR/Imperial Biomedical Research Centre, outside the submitted work; personal fees from UK Food Standards Agency, UpToDate, Elsevier, ALK, and Allergenis outside the submitted work. NP declares grants from UK National Institute for Health and Care Research (NIHR), outside the submitted work. DG has received payment as a consultant to Aquestive, Novartis, ARS, Blueprint, Kokua, Celldex, Thermofisher, outside the submitted work. The other authors have no conflicts of interest to declare.

Funding

PJT is supported by the UK Medical Research Council (reference MR/W018616/1).

Abstract

A key strategy in supporting patients at risk of anaphylaxis is the provision of self-administered epinephrine (“self-epi”). However, there seems to be a lower threshold for prescribing self-epi in food allergy than for venom. Self-epi is often recommended to someone where the risk of food-anaphylaxis is relatively low (under 5%) yet a similar level of risk in a venom-allergic patient is considered not to justify self-epi. We can only speculate as to the reasons for this: it may be harder to avoid food allergens (which can be hidden and undisclosed) compared to a bee or wasp, and the effort needed to avoid food allergens is greater. Evidence suggests that self-epi does not reduce rates of hospitalization or fatal anaphylaxis. Therefore, the rationale for self-epi should be based on supporting patients and empowering them to lead a more normal life. Surprisingly, studies suggest that self-epi has an adverse impact on quality-of-life, perhaps because it creates a perception that those with self-epi are more at risk of a life-threatening reaction. We must be cognizant of the fact that when the risk of anaphylaxis is relatively low, the prescription of self-epi can be associated with harms as well as potential benefits.

Key words:

Anaphylaxis; autoinjector; epinephrine; food; insect venom.

Abbreviations used

QoL	Quality of life
LLR	large local reactions
PFAS	Pollen-food allergy syndrome
Self-epi	Self-administered epinephrine
SR	Systemic reaction

A key strategy in supporting patients at risk of anaphylaxis is the provision of self-administered epinephrine (“self-epi”) for use as rescue treatment in the event of a reaction. Guidance has been published to support clinicians in determining when to prescribe self-epi (and, conversely, when it may not be warranted based on the level of risk),¹⁻⁴ which we have recently reviewed.⁵ In doing so, we became aware of a number of inconsistencies which challenge the traditional paradigms of risk evaluation for patients at risk of anaphylaxis.

For venom allergy, guidelines typically consider someone with a >30–50% risk of future systemic reaction (SR) to a sting as “high risk”, and therefore recommend self-epi for these individuals.¹ Patients with a history of only cutaneous SR or large local reactions (LLR) have an estimated <5% of future SR with a further sting (i.e. an order of magnitude lower), and are generally not recommended for self-epi.^{1,6} Self-epi may also be considered in those with a history of milder reactions (e.g. cutaneous SR (but not anaphylaxis) or LLR) but have known risk factors for severe reaction to a future sting: such examples include where exposure is frequent or unavoidable (e.g. beekeepers, forestry workers, refuse collectors, firefighters), or there is an underlying mast cell disorder or cardiovascular disease. The frequency of exposure is important because the risk associated with a sting is only relevant if the patient is stung. The average frequency of getting stung has been estimated in the US at once every 10 years (or 10% per year) for flying Hymenoptera⁶ and almost 50% in areas of the US infested with imported fire ants. However, some people clearly get stung more often than others.

How do these scenarios compare to food allergy? Studies show that the rate of accidental reactions in nut-allergic children is around 10-15% per annum,^{7,8} i.e. similar to the frequency of Hymenoptera sting. The vast majority of food reactions are not severe.^{8,9} Support from a specialist allergy clinic can reduce the risk of future anaphylaxis in nut-allergic children to around 0.6 per 100 person years.⁸ This figure is consistent with a 2013 meta-analysis, which estimated the annual risk of medically-coded food anaphylaxis to be 0.2% (95%CI 0.09, 0.43) in a young person (aged 0-19 years) with a diagnosis of food allergy.¹⁰ Rates may be higher in some cohorts: in a prospective study of 157 food-allergic adults in the Netherlands, 46% reported at least one reaction over a 1 year period; 26% of reactions were categorized as “severe” (equivalent to anaphylaxis), suggesting an approximate annual risk of future *anaphylaxis* of 10%.¹¹

Comparing venom to food, therefore, there seems to be a lower threshold for prescribing self-epi in food allergy than for venom. Self-epi is often recommended to someone where the risk of food-anaphylaxis is relatively low (under 5% for a nut-allergic teenager with asthma under specialist care), whereas a similar level of risk in a venom-allergic patient (history of mild truncal urticaria to a sting) is considered not to justify self-epi (Figure 1). We can only speculate as to the reasons for this, which are likely to include the perception that food allergen-related risks may be hidden within other foods, that risk of exposure is greater and affect a much larger “at-risk” population.

These are not the only inconsistencies: guidelines in the USA recommend self-epi for patients receiving omalizumab for asthma – a scenario that carries a risk of anaphylaxis of 0.1–0.2%,¹² and only for a short-term (3-6 months).¹³ Perhaps the rationale for this is to mitigate against a much smaller risk of anaphylaxis that nonetheless would only occur due to the physician prescribing a medicine. In a similar vein, in the USA, the FDA mandates self-epi (but not necessarily 2 devices) for patients receiving sublingual immunotherapy,¹ even though the rate of anaphylaxis in clinical trials has been reported to be just as low.¹⁴ At the same time, around 0.1-1% of the general population report allergic reactions to non-steroidal anti-inflammatory drugs (NSAIDs) and around 25-35% of these will be anaphylaxis, yet self-epi is not considered to be required when prescribing an NSAID.¹⁵

The risk of death is actually so small that this cannot be the justification for self-epi (see Figure 2).¹⁶ Perhaps the goal of self-epi is to reduce morbidity and hospitalization. Self-epi is not available globally – most countries in the South America, Africa/Middle-East and Asian-Pacific regions do not have EAs widely available.¹⁷ Using published data, we compared rates of hospitalization and fatalities due to food-anaphylaxis in the UK (where self-epi is widely available and provided either for free or at minimal cost) to Brazil (where self-epi is not widely available and usually not reimbursed) (Figure 3).¹⁸⁻²⁰ Interestingly, the latter situation does not seem to be associated with more hospitalizations or a higher rate of fatal reactions – something consistent with the observation that while prescription of epinephrine autoinjectors has increased in many countries, rates of hospitalization or fatal anaphylaxis have not fallen.²¹

There are clearly some differences between self-epi indication for food allergy compared to insect sting. It is likely that the majority of food-allergic individuals with primary food sensitisation (rather than pollen food allergy syndrome) do not present with a history of anaphylaxis because they have not been exposed to a sufficient dose in the past.²² Evidence suggests that up to 75% of peanut-allergic children would have anaphylaxis at a typical food challenge if dosing was allowed to continue after onset of non-anaphylaxis symptoms and signs.²³ Therefore, a previous history of non-anaphylaxis cannot provide reassurance unless the mild reaction occurred to a significant amount of food allergen. There may also be a perception that it is harder to avoid food allergens (which may be hidden and undisclosed) compared to a bee or wasp, for most people – and that the effort needed to avoid food allergens is greater.

Interestingly, while guidelines suggest that patients with a diagnosis of asthma (as opposed to those with poorly controlled asthma) are at greater risk of anaphylaxis,¹⁻⁴ there is little evidence to support this.²² The impact of these factors on risk can be misunderstood. There is a tendency to equate the presence of these factors with an increased risk and therefore an indication for self-epi. However, a relative increase in the chance of anaphylaxis is less significant when the absolute risk of reaction is low to begin with (Figure 4). Even if a risk factor doubles the risk of anaphylaxis, the absolute risk remains low if it was low to begin with.

The rationale for prescribing self-epi should ideally be based on an assessment of the future risk of (i) *any* anaphylaxis (when access to self-epi is likely to hasten recovery and an individual's ability to return to normal activities) and (ii) *life-threatening* anaphylaxis (where self-epi may act as a partial bridging measure until definitive treatment can be delivered). A third consideration is to support patients and empower them to lead a more normal life. These considerations are summarised in Table 1.

However, in this respect, there are further data that should make one pause for thought. We are aware of only two studies that have assessed the impact of self-epi on quality-of-life (QoL) measures, one in food-allergic children/young people²⁴ and the other in venom-allergic adults.²⁵ Both – surprisingly – report a negative impact on QoL with self-epi, perhaps because prescription may confer a “badge” of their allergy being worse – resulting in the perception that they are more at risk of a life-threatening reaction. This probably explains the further impairment in QoL that has been reported in patients with insect sting anaphylaxis who were randomized to receive self-epi instead of immunotherapy, while in those patients who chose to have self-epi, QoL actually improved (i.e. these individuals chose self-epi because they felt reassured by it).²⁵ This reinforces the need for patient engagement when recommending self-epi, and the importance of discussing risk of re-exposure as well as the patient's values and preferences.^{1,26}

We must be cognizant of the fact that when the risk of anaphylaxis is relatively low, the prescription of self-epi can be associated with harms as well as potential benefits. Potential harms include not only the fear and impairment of QoL described above, but the financial and social burden that has been reported in association with self-epi.

By raising these issues, we hope we can support better shared-decision making which must underpin any recommendation for self-epi, and perhaps challenge some of the inconsistencies which currently exist, for example with respect to sublingual immunotherapy. To quote the singer James Keelaghan, “the things we never challenge are the things that never change.” (Turn of the Wheel; 1995).

REFERENCES

1. Golden DBK, Wang J, Wasserman S, Akin C, Campbell RL, Ellis AK, et al. Anaphylaxis: A 2023 practice parameter update. *Ann Allergy Asthma Immunol*. 2024 Feb;132(2):124-176. doi: 10.1016/j.anai.2023.09.015.
2. Angier E, Choudhury D, Luyt D, Baker S, Warner A, Clark A, et al. Adrenaline auto-injector prescription for patients at risk of anaphylaxis: BSACI guidance for primary care. *Clin Exp Allergy*. 2023 Sep;53(9):951-954. doi: 10.1111/cea.14325. Epub 2023 May 29. PMID: 37246592.
3. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al; European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: Anaphylaxis (2021 update). *Allergy*. 2022 Feb;77(2):357-377. doi: 10.1111/all.15032.
4. Australasian Society of Clinical Immunology and Allergy. ASCIA Guidelines - Adrenaline (Epinephrine) Device Prescription. 2025. Available at: <https://www.allergy.org.au/hp/anaphylaxis/adrenaline-device-prescription>.
5. Adams K, Patel N, Hatcher V, Bigas P, Golden DBK, Turner PJ. Deprescribing self-administered epinephrine: why, who, and when? *J. Allergy Clin Immunol. Pract.* 2025; (under review).
6. Golden DBK. Large Local Reactions to Insect Stings. *J Allergy Clin Immunol Pract* 2015;3:331-334.
7. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, Allen M, et al. Inadvertent exposures in children with peanut allergy. *Pediatr Allergy Immunol*. 2012 Mar;23(2):133-9. doi: 10.1111/j.1399-3038.2011.01235.x.
8. Ewan PW, Clark AT. Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. *Clin Exp Allergy*. 2005 Jun;35(6):751-6. doi: 10.1111/j.1365-2222.2005.02266.x.
9. Muraro A, Sublett JW, Haselkorn T, Nilsson C, Casale TB. Incidence of anaphylaxis and accidental peanut exposure: A systematic review. *Clin Transl Allergy*. 2021 Oct;11(8):e12064. doi: 10.1002/clt2.12064.
10. Umasunthar T, Leonardi-Bee J, Turner PJ, Hodes M, Gore C, Warner JO, et al. Incidence of food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin Exp Allergy*. 2015 Nov;45(11):1621-36. doi: 10.1111/cea.12477.
11. Versluis A, van Os-Medendorp H, Blom WM, Michelsen-Huisman AD, Castenmiller JJM, Noteborn HPJM, et al. Potential cofactors in accidental food allergic reactions are frequently present but may not influence severity and occurrence. *Clin Exp Allergy*. 2019 Feb;49(2):207-215. doi: 10.1111/cea.13282.
12. Cox L, Platts-Mills TAE, Finegold I, Schwartz LB, Simons FER and Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007;120:1373-1377.

13. Cox L, Lieberman P, Wallace D, Simons FER, Finegold I, Platts-Mills T, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. *J Allergy Clin Immunol* 2011;128:210-212.
14. Janz TA, Jimoh RO, Nguyen SA, Haroun KB, McKinnon B, Siddiqui FN. Exploring Side Effects of Sublingual Immunotherapy: A Systemic Review and Meta-Analysis. *Ear Nose Throat J*. 2024 Jun 5;1455613241257827. doi: 10.1177/01455613241257827.
15. National Institute for Health and Care Excellence. Drug allergy: diagnosis and management - Clinical guideline. 2014. Available at www.nice.org.uk/guidance/cg183
16. Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal Anaphylaxis: Mortality Rate and Risk Factors. *J Allergy Clin Immunol Pract*. 2017 Sep-Oct;5(5):1169-1178. doi: 10.1016/j.jaip.2017.06.031.
17. Tanno LK, Worm M, Ebisawa M, Ansotegui IJ, Senna G, Fineman S, et al; WAO Anaphylaxis Committee and the WAO Junior Members Steering Group. Global disparities in availability of epinephrine auto-injectors. *World Allergy Organ J*. 2023 Oct 20;16(10):100821. doi: 10.1016/j.waojou.2023.100821.
18. Baseggio Conrado A, Ierodiakonou D, Gowland MH, Boyle RJ, Turner PJ. Food anaphylaxis in the United Kingdom: analysis of national data, 1998-2018. *BMJ*. 2021 Feb 17;372:n251. doi: 10.1136/bmj.n251.
19. Tanno LK, Molinari N, Annesi-Maesano I, Demoly P, Bierrenbach AL. Anaphylaxis in Brazil between 2011 and 2019. *Clin Exp Allergy*. 2022 Sep;52(9):1071-1078. doi: 10.1111/cea.14193.
20. 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 Jun;67(6):783-9. doi: 10.1111/j.1398-9995.2012.02829.x.
21. Sim M, Sharma V, Li K, Gowland MH, Garcez T, Shilladay C, et al. Adrenaline Auto-Injectors for Preventing Fatal Anaphylaxis. *Clin Exp Allergy*. 2025 Jan;55(1):19-35. doi: 10.1111/cea.14565.
22. Turner PJ, Arasi S, Ballmer-Weber B, Baseggio Conrado A, Deschildre A, Gerdts J, et al; Global Allergy, Asthma European Network (GA2LEN) Food Allergy Guideline Group. Risk factors for severe reactions in food allergy: Rapid evidence review with meta-analysis. *Allergy*. 2022 Sep;77(9):2634-2652. doi: 10.1111/all.15318.
23. Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Pediatr Allergy Immunol*. 2010 Jun;21(4 Pt 1):603-11. doi: 10.1111/j.1399-3038.2010.01063.x.
24. Pinczower GD, Bertalli NA, Bussmann N, Hamidon M, Allen KJ, DunnGalvin A, et al. The effect of provision of an adrenaline autoinjector on quality of life in children with food allergy. *J Allergy Clin Immunol*. 2013 Jan;131(1):238-40.e1. doi: 10.1016/j.jaci.2012.09.038.
25. Oude Elberink JN, De Monchy JG, Van Der Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in patients allergic to yellow

- 248 jacket venom. J Allergy Clin Immunol. 2002 Jul;110(1):174-82. doi:
249 10.1067/mai.2002.125827.
250 26. Greenhawt M. Shared decision-making in the care of a patient with food allergy. Ann
251 Allergy Asthma Immunol. 2020 Sep;125(3):262-267. doi: 10.1016/j.anai.2020.05.031.
252

253 **Table 1:** Factors impacting on the decision to recommend self-epi in food allergy

	Judged by medical team		Considered in conjunction (consultation) with family	
	Clinical 'Risk'	Clinical 'considerations'	Patient perspectives	Lifestyle/life changes
Increases likelihood of recommending self-epi	• "Primary" food allergy rather than pollen food allergy syndrome (PFAS) • Reacts to low doses of allergen (high sensitivity) • Previous anaphylaxis • Multiple food allergies • Poor asthma control • Allergen difficult to avoid • Risk-taking behaviours • Communication difficulties affecting comprehension of risks • Starting immunotherapy	• Language restrictions • Significant anxiety impacting upon life (e.g. fear of travel) • Required by school or work	• Would availability of self-epi reduce stress/anxiety? • Can help mitigate against severe reactions • Required by school or childcare Change in patient/carer preference	• During OIT • Occupation – joining army • Travel e.g. extended time abroad in a country with limited supply of self-epi • Recurrence of allergy post-immunotherapy
Decreases likelihood of recommending self-epi	• Food exposure controlled by parents (e.g. in infant) • Rare allergen • PFAS • High reaction threshold and maintaining strict avoidance • Evidence of spontaneous resolution	• Self-epi won't be carried by patient or unlikely to be used e.g. due to needle phobia	• Increased anxiety • Increase burden / perception of being at greater risk of severe reactions • Financial cost	• Following immunotherapy? •

254

255

Journal Pre-proof

FIGURE LEGENDS

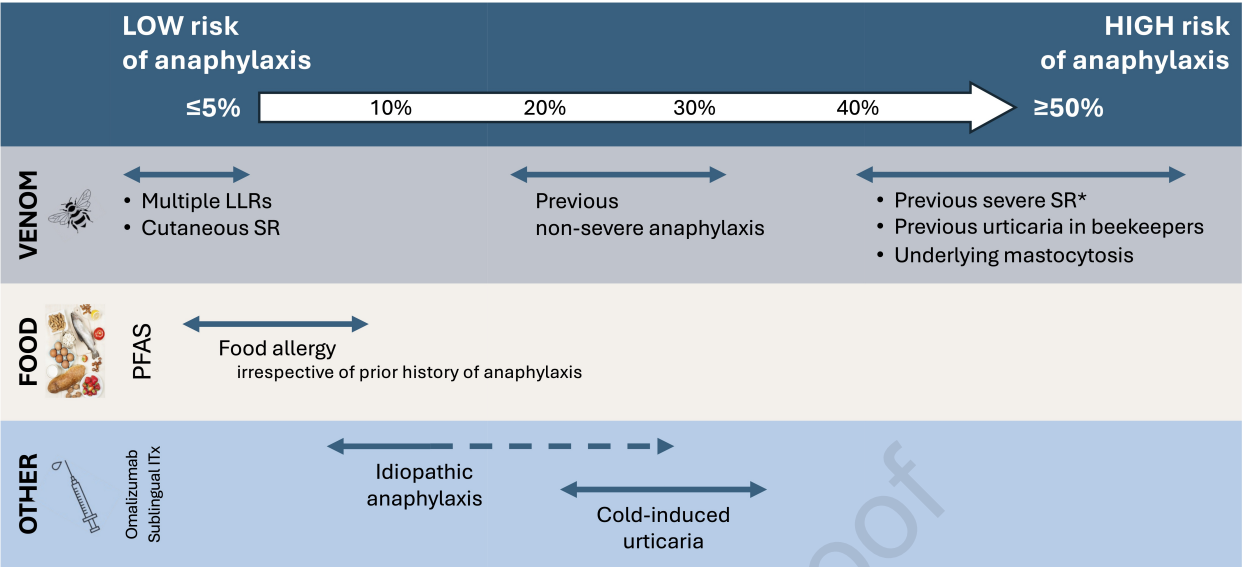
Figure 1: Risk of future anaphylaxis to the triggering allergen for food, insect venom, omalizumab and sublingual immunotherapy. For idiopathic anaphylaxis and cold-induced urticaria, the risk of anaphylaxis over a 1-year period has been included for comparison.

*severe SR = dyspnoea ($\pm$ drop in peak flow of $>30\%$) or documented hypotension $\pm$ syncope.

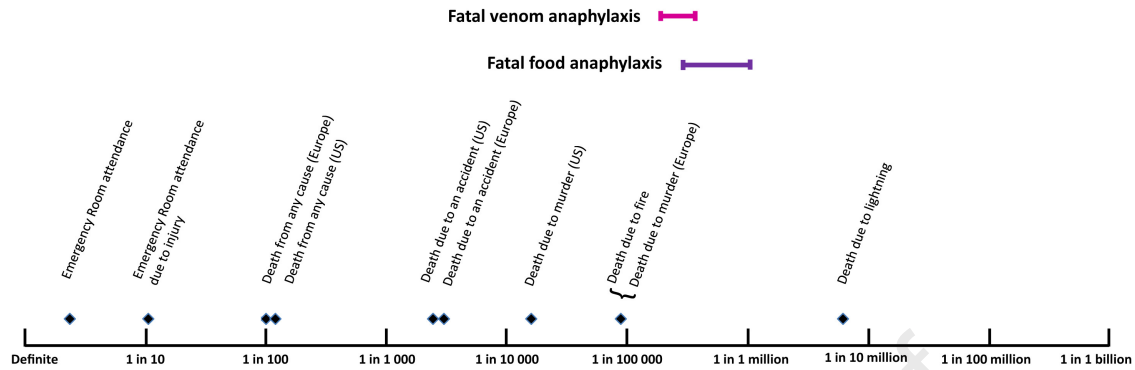
Figure 2: Estimated rates of fatal food and venom anaphylaxis for people with known food allergy or insect venom allergy. Reference risks are for the US population, unless otherwise stated. Figure reproduced from Turner et al, 2017.¹⁶

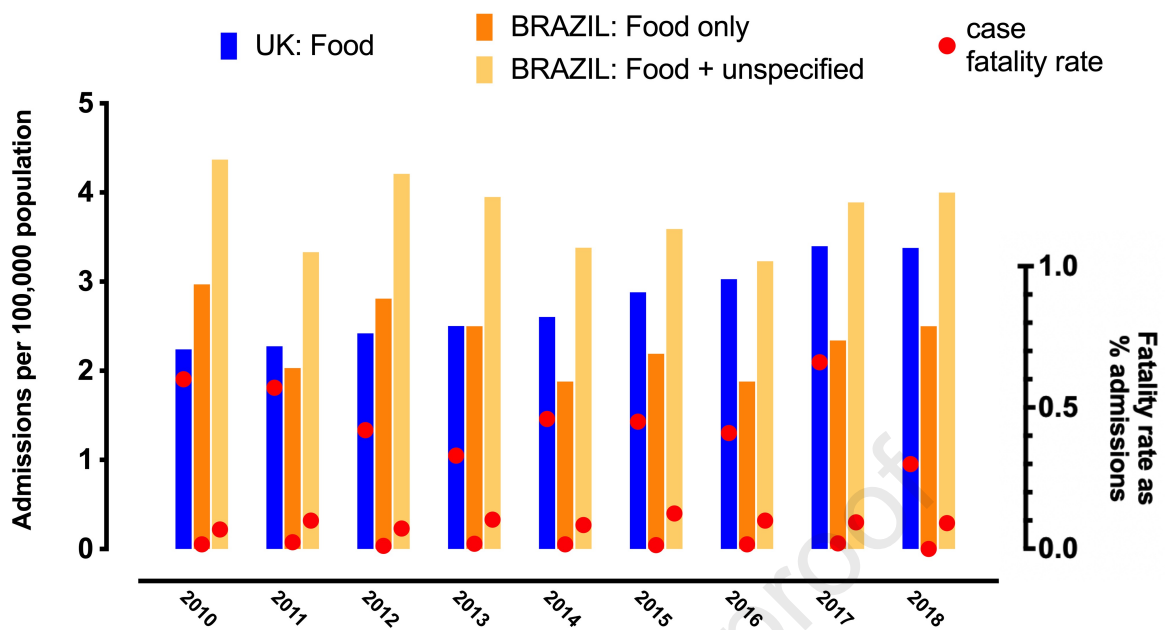
Figure 3: Hospital admissions for food-anaphylaxis between 2010 and 2018 (bars), together with case fatality rate (red dots), in Brazil compared to United Kingdom.^{18,19} Fatality data from Brazil are likely to reflect a degree of underreporting,²⁰ although not to the extent that would result in significantly higher rates than that reported in the UK. Data also presented for the inclusion of “unspecified trigger” in Brazil, since the age-distribution for this matches that for food-anaphylaxis and therefore suggests a significant proportion of food-anaphylaxis cases.¹⁹

Figure 4: Hazard, exposure and risk considerations



Annual incidence of fatal anaphylaxis in food or venom allergic individuals

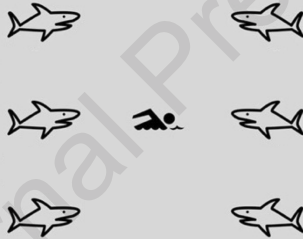




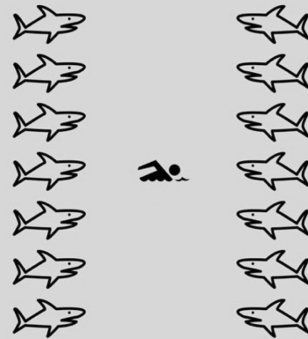
**Previous SR
to venom:**



When sharks are everywhere
Swimmers can't avoid them
Risk is high to meet one

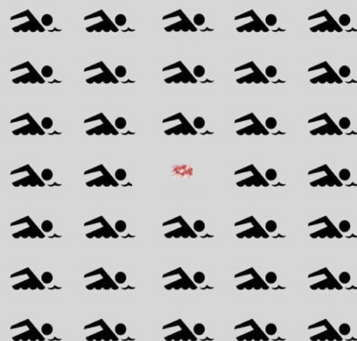


In beekeepers, the risk
of a sting is higher...



**Nut-allergic
individual:**

When the exposure is
smaller and the risk lower:



Risk can double but the
absolute risk remains low:

