Epinephrine in Severe Allergic Reactions

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Abstract: Background. Current guidelines recommend intramuscular administration of epinephrine as the first-line drug for the emergency treatment of severe allergic reactions (anaphylaxis), but no randomized trial evidence supports this consensus.
Objective. We aimed to assess anaphylaxis treatment practices over ten years, covering several European regions, all allergen sources, and all age groups.

Methods. The European Anaphylaxis Register tracks elicitors, symptoms, emergency treatment, diagnostic workups and long-term counselling for anaphylaxis incidents through web-based data entry from tertiary allergy specialists, covering information from the emergency respondent, patient, tertiary referral, and laboratory/clinical test results.

Results. We analyzed 10,184 anaphylaxis incidents. In total, 27.1% of patients treated by a health professional received epinephrine and, in total, 10.5% received a second dose. Successful administration was less frequent in German-speaking countries (min. 19.6%) than in Greece, France, and Spain (max. 66.7%). Over the last decade, epinephrine administration from a health professional almost doubled to reach 30.6% in 2015-17, half of which was applied intramuscularly.
14.7% of lay- or self-treated cases were treated with an auto-injector (AAI). Of those w/o treatment, 22.4% carried a device for administration.

No change in successful administration by lay emergency respondents was found over the last ten years.
Of the reaction and patient characteristics analyzed, only clinical severity considerably influenced the likelihood of receiving epinephrine, with 66.9% of successful administrations in near-fatal (grade IV) reactions.

Conclusion. Despite clear recommendations, only a small proportion of anaphylaxis incidents are treated with epinephrine. We demonstrated a slight increase in treated patients when handled by professionals, but stagnation in lay- or self-treated anaphylaxis. The reaction circumstances, the respondent's professional background, and patient characteristics did not explain which reactions were treated.

Title

Epinephrine in severe allergic reactions - the European Anaphylaxis Register

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Abstract

Background. Current guidelines recommend intramuscular administration of epinephrine as the first-line drug for the emergency treatment of severe allergic reactions (anaphylaxis), but no randomized trial evidence supports this consensus.

Objective. We aimed to assess anaphylaxis treatment practices over ten years, covering several European regions, all allergen sources, and all age groups.

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14.7% of lay- or self-treated cases were treated with an auto-injector (AAI). Of those w/o treatment, 22.4% carried a device for administration. No change in successful administration by lay emergency respondents was found over the last ten years.

Of the reaction and patient characteristics analyzed, only clinical severity considerably influenced the likelihood of receiving epinephrine, with 66.9% of successful administrations in near-fatal (grade IV) reactions.

Conclusion. Despite clear recommendations, only a small proportion of anaphylaxis incidents are treated with epinephrine. We demonstrated a slight increase in treated patients when handled by professionals, but stagnation in lay- or self-treated anaphylaxis. The reaction circumstances, the respondent's professional background, and patient characteristics did not explain which reactions were treated.

Highlight Box

1. What is already known about this topic?

There is international agreement that epinephrine is the first-line emergency treatment for anaphylaxis. The current (2014) EAACI guidelines and the Cochrane database could not identify a randomized interventional trial to support the administration of epinephrine.

2. What does this article add to our knowledge?

Despite clear recommendations, only one in four anaphylaxis patients treated by a health professional receive epinephrine, and there was no increase to receive epinephrine in lay- and self-treated anaphylaxis over the last decade.

3. How does this study impact current management guidelines?

The discrepancy between recommendations and actual treatment habits suggests that there is need for strong evidence to support the guidelines, pushing their implementation.

Conflict of Interest statements

LG declares that he has no conflict of interest to declare. All other COI statements will be completed upon reception of the Journal's COI forms, as completed and signed by each coauthor separately.

Funding

The European Anaphylaxis Register was supported by the Network for Online Registration of Anaphylaxis NORA e. V. Irish data collection from 2013-2015 was supported by a grant from the National Children's Research Centre.

Key words

Anaphylaxis
Emergency Treatment
Epinephrine
Hypersensitivity
Registries

Abbreviations

AAI – Adrenaline Auto-Injector
AIT – Allergen Immuno-Therapy
CI – Confidence Interval
DAG – Directed Acyclic Graph
EAACI – European Academy of Allergy and Clinical Immunology
EAR – European Anaphylaxis Register
EMA – European Medicines Agency
GI – Gastrointestinal
GP – General Practitioner
ICON – International Consensus
ICU – Intensive Care Unit
OR – Odds Ratio

Introduction

Most allergic reactions take a mild course and only rarely evolve into life-threatening anaphylaxis. However, these incidents, which are inherently diverse in terms of their clinical appearance and progression, require the quickest possible emergency treatment, either by the patient him or herself, a lay helper, or by the nearest health professional, who in many cases is not an expert in allergy or emergency medicine. There is no point-of-care test to assist with the clinical diagnosis.

In addition to non-specific emergency measures, such as fluids and oxygen, a number of pharmaceutical agents have been introduced for the first-line management of anaphylaxis, most notably intramuscular or intravenous epinephrine (adrenaline) as the first-line treamtent, and corticosteroids, antihistamines and beta-agonists as adjunctive therapies. Because these incidents are very rare and can occur in almost any setting, valid interventional assessments of the efficacy of these drugs and their effectiveness for the treatment of severe allergic reactions have never been conducted (1, 2), especially investigations of the even rarer outcome of case fatality (3-6). At present, the current rationale behind the use of epinephrine as the key intervention to manage anaphylaxis besides its pharmacologic activity and the known physiology of anaphylaxis is evidence from other emergency conditions (which may be weak), retrospective clinical observations (7), and individual experience (e.g., EMA assessment 478468/2015).

Regardless of the almost complete absence of robust evidence (evidence level IV (8)), there is widespread expert agreement that epinephrine should be applied (intramuscularly (9)) with no delay in all cases of anaphylaxis. This recommendation is reflected in the current guidelines; the guidelines considered most current include those developed by European allergy specialists and published for the EAACI in 2014 (10), the ICON statement (11), and the World Allergy Organization guideline (12, 13). Notably, these quasi-standards substantially limit the scope for randomization in interventional assessments of epinephrine's impact in future research.

The discrepancy between scientific evidence and guideline-based recommendations has implications reaching far beyond an individual's health in terms of efficacy and safety, including professional liability, personal and societal financial issues, and manufacturers' economic and market interests (14). Therefore, a detailed record of what actually happens in real-life anaphylaxis emergencies must be created.

The aim of the European Anaphylaxis Register (EAR) is to document data from patients who have experienced severe allergic reactions (15-19). Available for the first time, the current analysis focusses to report all details on the use of epinephrine as the recommended first-line drug by all stakeholders, including health professionals, lay helpers, and self-administrators, and thus includes all reaction types, elicitors and covering all age groups. The multinational scope of this platform covering data collected for more than a decade aims to estimate the proportion of anaphylactic reactions treated with epinephrine throughout Europe to allow comparisons between countries and investigation of time trends. Here, we explore the link between the clinical reaction and patient characteristics and the likelihood of receiving epinephrine (**figure 1**) to pave the way for targeted interventions with the potential to improve guideline adherence and health outcomes research and to provide evidence for public health decision making.

Methods

Study design

The EAR is a multicenter, disease-specific online platform that is used to document incidents of anaphylaxis, including all confirmed, suspected or unknown elicitors and any reaction circumstances in terms of location, emergency respondent, and previous reactions (15, 17-19). Data are entered locally in tertiary allergy and dermatology referral centers through a web-based interface by trained health professionals based on information collected during face-to-face visits scheduled for a post-reaction diagnosis and/or counselling and from medical records (e.g., emergency protocols, intensive care unit (ICU) records, and lab or clinical test results). The Ethics Committee at Charité - Universitätsmedizin Berlin approved the project as the coordinating center and was accredited by the local ethics committees in all participating countries.

Data collection and Variables

The multi-language online questionnaire is available in German for Germany, Austria, and Switzerland, in French for France and Switzerland (cooperation with the Allergy Vigilance Network (20)), and in English for all other participating countries. The questionnaire was developed and piloted in the German Anaphylaxis Register and translated/back-translated for its international continuation (16, 21). The

questionnaire underwent yearly updates that introduced new topics and items suggested by an international group of allergy experts. Interrater reliability was demonstrated by repeated data entry through two independent health professionals. The questionnaire captures information on elicitors, symptoms, emergency treatment, diagnostic procedures and long-term counselling and is accessible at www.anaphylaxie.net (22).

The current analysis separately reports two core strata of the complete sample: incidents where emergency treatment was conducted by a health professional and incidents where a lay-person or the patient him-/herself took care of the treatment. The small fraction of patients who were initially lay-/self-treated and later supported by a professional are reported within both groups.

The above-participant-level data used in this analysis include the (single) study center and country, year of reaction (categorized in two-year intervals), location of the reaction and the emergency respondent's professional background (medical specialization).

The reported participant-level characteristics include the age (unrestricted report in four categories) and gender of the patient, co-morbidities, elicitors and their confirmation status (confirmed, suspected, or unknown), short-acting co-factors (e.g., psychological stress, medical and social drugs, alcohol, or exercise), previous reactions and previous diagnostic procedures, and the symptom pattern (exposure-symptom interval, specific symptoms and organ systems). The severity of the reaction was derived manually from the symptoms in four levels as proposed by Ring and Messmer (23): grade II with at least two organ systems, grade III including signs of circulatory and/or respiratory failure (shock), and grade IV with circulatory and/or respiratory arrest.

Patients

Individuals referred to a collaborating tertiary referral center after a (first or recurrent) anaphylactic reaction were asked to provide written informed consent to have their medical data entered under a pseudonym into the register after completion of the diagnostic workup or the data collected during routine care were entered anonymously without individual consent depending on the countries' data protection regulations. As there is no international standard for an unambiguous distinction between severe and non-severe anaphylaxis, the decision to enroll a patient (ie, the case definition) had to be

given to the local allergy expert. From the register, only non-fatal cases with a documented date of reaction and information about the person who conducted the emergency treatment were used for this analysis. The stratum of professionally treated cases was limited to cases with information about epinephrine administration, including the route of administration, and the stratum of lay-treated individuals to cases with a known AAI status.

Because the register continuously records data, the sample for the current analysis was drawn from the project server in March 2017 and covered all reactions from the initiation of the register in 2006 onwards. To allow robust comparisons between countries, the cases were limited to countries reporting at least 100 incidents. To further increase the comparability, two narrowed case definitions were additionally assessed; these cases were limited to grade II and grade III reactions caused by food allergens or insect venom and excluded preschoolers (<6 years) and the elderly (>64 years) to yield more homogeneous sub-samples (23, 24).

Statistical analysis

The data were cleaned and analyzed using the SAS 9.4 software system (SAS Institute, Cary, NC). Individual queries were pursued to improve the completeness of the original data. Free text answers were manually assigned to default categories when appropriate. Data missing by item were accepted for all variables except emergency respondent, epinephrine administration and year of reaction. Information documented as unknown was handled as missing. Assuming that local documentation habits differed at random, all proportional measures were reported using all valid answers by item as the denominator. Confidence intervals for frequencies were calculated based on the beta distribution and were reported at a symmetric 95%.

To account for the time-varying proportion of cases contributed by each country, weighted frequency estimates for the strata of year-of-reaction were calculated by multiplying stratum-specific estimates for each country by the country's overall proportion of cases in the register.

A mutually adjusted logistic approach was used to model the predictive information of the patient-level characteristics. Using a DAG-like (directed acyclic graph), content-based selection process, the model was further conditioned on the study center (individual center, assuming referral differences arise on a

regional/center level not confined by country), location of the reaction (medical setting, home, work/school, restaurant, or outdoors), and person treating (emergency doctor, GP, allergy specialist, self, family member, and teacher) as nuisance parameters. Year-of-reaction was not controlled for because we assumed similar referral patterns within a given center over time.

Role of the funding source

The European Anaphylaxis Register was supported by the Network for Online Registration of Anaphylaxis NORA e. V. Irish data collection from 2013-2015 was supported by a grant from the National Children's Research Centre. The funders had role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

In the EAR, ten countries (Austria, Bulgaria, France, Germany, Greece, Ireland, Italy, Poland, Spain, and Switzerland) reported more than 100 incidents of anaphylaxis. Of the 10,184 registered cases, 7,694 (75.5%) provided details of emergency treatment, including the administration of epinephrine.

Epinephrine

Of these 7,694 complete cases, 1,782 (23.2%) were treated with epinephrine.

A total of 5,352 (69.6%) individuals were treated by a health professional, 1,094 (14.2%) received emergency treatment through a lay person (including self-administration), and 444 (5.8%) were first treated by a lay person followed by a health professional. A total of 804 (10.5%) individuals received no emergency treatment.

Detailed treatment information was available for 5,796 professionally treated cases, of which 1,570 (27.1%) were treated with epinephrine. The epinephrine was administered intramuscularly in 649 cases (11.2%), intravenously in 758 cases (13.1%), and per inhalation in 226 cases (3.9%). A total of 10.5% of the cases received a second dose of epinephrine (123/1,175 cases had information on the second dose).

Emergency management was documented for 1,538 lay- or self-treated individuals, of which 226 (14.7%) received epinephrine using an autoinjector (AAI). The reasons for not receiving epinephrine were as

follows: AAI available but not used (22.4%); AAI prescribed but not available (4.7%); and AAI not prescribed (72.8%, percentage of 655 individuals with information on failed administration).

Other Treatment

In the emergency situation, 4,967 (85.7%) professionally treated patients received corticosteroids, 4,492 (77.5%) received antihistamines, 647 (11.2%) received beta-2-agonists, and 1,761 (30.4%) received i.v. fluids and/or oxygen. Of the lay-/self-treated patients, 741 (48.2%) received corticosteroids, 1,194 (77.6%) received antihistamines, and 276 (18.0%) received beta-2-agonists. In total, 46.1% of the reactions occurring outside of medical settings resulted in admission to a hospital following the incident, and 7.2% required ICU handling. Of the anaphylaxis cases that occurred within a hospital or medical practice, 27.0% required ICU treatment.

Setting and Emergency Responder

Of the 5,281 reactions that occurred outside of medical settings, 2,541 occurred in private homes, 1,885 occurred outdoors (inner city or countryside), 477 occurred in the working environment or school, and 378 occurred in restaurants. By location, 17.1% to 22.3% of these cases received epinephrine. Conversely, 39.6% of the anaphylaxis cases that occurred in medical settings (940 cases) were treated with epinephrine.

Most of the professionally treated cases were handled by an emergency doctor (2,605), of which 29.7% received epinephrine, followed by GPs (716) and allergy specialists (377), of which 18.0% and 38.5%, respectively, were given epinephrine. Administration of an AAI by lay persons was reported similarly often for the 706 patients who treated themselves compared to the 712 patients who were treated by a family member (13.9% and 15.9%, respectively). Four of the 40 patients (10.0%) treated by a nursery or school teacher received epinephrine.

Country

The proportion of patients receiving epinephrine from health professionals varied between countries, with the lowest numbers in Germany (19.6%) and Switzerland (24.2%) and the highest numbers in Greece (66.7%) and France (46.7%, **figure 2**). With six referral centers, Germany was the only country with more than one site contributing 100+ cases, which allowed robust comparisons between different catchment

areas within a given country. Within these six centers, the percentage of patients administered epinephrine by a professional ranged from 13.7% to 23.9%.

To account for potential country-specific referral patterns in terms of oversampling age groups, certain elicitors or disease severity, two commonly reported case definitions were selected to improve comparability between countries. In total, 347/1,543 (22.5%) of insect venom reactions - excluding the least severe reactions (grade I), near-fatal reactions (grade IV), preschoolers, and the elderly - were treated with epinephrine when handled by a professional, with a low extreme in Germany (17.5%) and a high extreme in France (63.6%). Similarly, 313/1,131 (27.7%) of patients who experienced food-induced reactions with the same age and severity restrictions received epinephrine, with the outliers in Germany (19.1%) and Ireland (43.2%, **figure 3**).

Administration of AAI in lay-treated anaphylaxis varied between European countries, with the lowest numbers in Bulgaria (7.7%) and France (9.1%) and the highest in Greece (25.3%) and Ireland (24.6%). The inter-country differences were even higher when only patients with recurrent reactions were compared, with 7.7% receiving an AAI in Italy and 34.6% in Ireland (**e-table 1**).

Time

With the introduction of the Register in 2006-2008, only 16.1% of the cases (weighted for the country's contribution) received epinephrine when treated by a professional; this percentage steadily increased to 30.6% from 2015-2017. Of those treated, 17.2% received the treatment intramuscularly from 2006-2008, and this percentage increased steadily to 50.8% from 2015-2017. The percentage of patients who were treated with an AAI by a lay helper was relatively stable at 15.4% from 2006-2008 and 12.9% from 2015-2017 (weighted estimates, **figure 4**).

Patient and reaction characteristics

When treated by professionals, the proportion of patients receiving epinephrine was very similar between men and women, age groups, and individuals with or without co-morbidities. Patients with known mastocytosis were treated with epinephrine more often (39.4%). Administration of AAI devices by the patients themselves or by lay helpers was less frequent in preschoolers (11.9%) and more frequent in the elderly (19.2%, **table 1**).

When elicitors were compared, only drug-induced anaphylaxis treated by health professionals was treated with epinephrine more often (31.7%), with the highest percentages for reactions to antibiotics and AIT treatment (35.5% and 41.7%, respectively). In contrast, patients with lay- or self-treated insect venom reactions received emergency epinephrine (AAI) more often than patients with drug-induced reactions (20.9% and 4.8%, respectively).

Patients who had reacted to the same allergen several times previously and those in whom the elicitor was confirmed by a diagnostic test previous to the reaction received epinephrine more often, with 25.3%/27.0% for lay and 32.2%/34.3% for professionally treated individuals. As co-factors, only psychological stress was associated with a higher proportion of receiving epinephrine by a professional (36.5%, **table 1**).

Professionals administered epinephrine more often in reactions with a very short (<10 min) interval between allergen exposure and the first symptoms (31.4%), but the organ system involved and the number of different organ systems was not strongly associated with epinephrine treatment. Only a few specific symptoms led to considerably higher numbers of professionals applying epinephrine (e.g., cardiac arrest (71.2%), respiratory arrest (64.3%), and loss of consciousness (37.1%)), which was reflected by the strong association with the overall severity rating, ranging from 10.1% for the mildest reactions (grade I) to 66.9% for near-fatal reactions (grade IV, **table 1**).

Irrespective of the person performing the treatment, other indirect indicators of the reaction severity were associated with receiving epinephrine, including factors unknown during the emergency (e.g., elevated tryptase levels, 44.7%) or parameters of post-emergency management (hospital admission, 38.8% and ICU, 51.2%).

Independent predictors

When the patient-level characteristics (mutual adjustment) and the setting (conditioned/stratified modelling) were controlled, few factors remained as independent predictors for receiving epinephrine for the emergency treatment of anaphylaxis. Medical professionals tended to withhold epinephrine in women (OR [95%-CI] 0.83 [0.77;0.97], p=0.016) and only applied epinephrine more often in very immediate reactions (OR 1.22 [1.05;1.42], p=0.010), with cardiovascular symptoms (OR 1.74 [1.43;2.11],

p<0.001) and near-fatal (grade IV) reactions vs grade II reactions (OR 6.38 [3.91;10.39], p<0.001). Age, the type of elicitor, and previous reactions to the same allergen were not independently associated with epinephrine treatment (**table 2**, left columns).

Conversely, lay persons treating anaphylaxis were appropriately prompted towards applying an AAI by existing cardiovascular co-morbidities or the presence of cardiovascular symptoms (OR 2.01 [1.05;3.85], p=0.036 and OR 1.70 [1.07;2.71], p=0.026, respectively). Previous reactions to the same allergen seemed to increase the availability of an AAI on site, as reflected by the higher proportion of administrations (OR 2.50 [1.70;3.66], p<0.001). Other characteristics of the patient and the reaction circumstances were not independently associated with AAI administration, including the severity of the reaction (**table 2**, right columns).

Discussion

Key results

This is the first report of epinephrine use in children and adults alike, covering a whole decade and several European countries, demonstrating that only one in four patients experiencing an anaphylactic reaction received epinephrine, which remained the current first-line recommendation throughout that time period (10, 11). Most incidents were treated by health professionals, who frequently administered corticosteroids and antihistamines (approximately three times out of four) but did not adhere to the European guideline to administer epinephrine first (10). Comparing countries, health professionals in German-speaking countries withheld epinephrine more often than their counterparts in other countries, including Greece, Spain, and France. The last ten years have seen a doubling of epinephrine treatment completion in Europe, especially by health professionals, which may reflect improved guideline distribution and awareness. The steep increase in the use of intramuscular administrations from one in six to more than half of epinephrine receivers supports this interpretation. Still, only about half of all documented cases who received epinephrine received it via the recommend route, that is intramuscularly.

The likelihood of the use of AAIs in self- or lay-treated anaphylaxis is even lower (one in seven) and may be explained by those who have reactions for the first time not being aware of the potential for an allergic reaction to occur, in which case they would clearly not be carrying the device. However, the likelihood was only slightly higher for the severest (anaphylaxis grade III and IV) recurrent reactions treated by lay emergency respondents. This is the first report of a decade-long stagnation of the use of AAIs in lay- or self-treated incidents, despite all efforts directed towards patient education, target group training programs (e.g., school or nursery school teachers), or in some countries the availability of AAIs to the public (e.g., in schools, malls, stations, and airports (24)).

To target professional training and identify areas for further investigation, factors potentially influencing the chance to receive epinephrine have not yet been examined. Strikingly, our data suggest that almost none of the characteristics of the actual reaction (e.g., place and elicitor) or the patient (e.g., age and co-morbidities) influenced guideline adherence. Even in the setting where AITs take place, less than half of anaphylaxis incidents caused by immune therapy were treated with epinephrine. Only the overall symptom severity was linked positively to the likelihood of receiving epinephrine in the community. This finding limits the identification of targets for new strategies to improve successful administration.

Because the wealth of data available in this project on severe allergic reactions was only able to explain a small proportion of the cases treated according to the guideline recommendations, this pattern could be in part a random process (i.e., unknown and/or unmeasurable factors) or could be ruled by aspects not yet covered by this approach. These aspects may differ between individuals (i.e., some professionals tend to give epinephrine and some tend to refrain from doing so). Moreover, the individual appraisal of the situation may be shifted towards or away from giving epinephrine by personal experiences and guideline interpretation, especially in light of the lack of high level evidence for these recommendations.

Strengths and Limitations

With more than ten thousand incidents documented over more than a decade, the EAR involves countries that together constitute close to half of the European population. The EAR contains details about all major aspects of incidents of anaphylaxis, including allergen exposure, symptoms, emergency treatment, diagnostic workup, and long-term counselling.

Notably, our approach is limited to the upper end of the severity spectrum, with an aim to oversample the most threatening reactions. At the same time, we only sporadically captured fatal incidents, which were not accounted for in the current analysis. Because these incidents are very rare occurrences (25-27), our design gives robust estimates for the worst survived episodes, leading to conservative estimates for successful administration linked to severity. However, our design does not support generalization to unstratified whole populations, especially with the selective choice made for participating tertiary care centers and their individual referral patterns, documentation habits, and voluntary data entry (28). Selecting well-defined clinical entities for sensitivity analyses substantially improved the inter-national comparability.

Comparisons between treated and untreated patients in terms of health outcomes (e.g., symptom development, hospital/ICU admission, lab diagnostics, or mortality) does not lead to valid efficacy estimates from these data because this study is retrospective and observational. These comparisons are urgently needed. The treated subjects paradoxically appear to have the worst outcomes, because treatment with epinephrine appears to be most strongly related to the assessed clinical severity. In particular, the confounding effect of disease severity in anaphylaxis is neither well defined nor well assessed and thus cannot be fully accounted for statistically (e.g., through stratification).

Conclusion

A better understanding of what happens at the point-of-care may shape future research and support the targeting of interventions to improve guidelines and guideline adherence and can direct focused medical and public education efforts (29, 30). Unbiased input from the person responding to the emergency about their decision making, training background, drug availability and individual professional (or personal, if lay- or self-treated) appraisal would aid in better understanding the gap between current practice and the recommendations. Specifically, future studies should collect data on what if any factors did or did not convince a person (be it professional or lay) to give epinephrine. To fill this knowledge gap, the EAR is currently being advanced to capture important aspects from the emergency respondent's perspective and at the same time also the patient's own experience and views.

Perhaps even more importantly, this report accentuates the need for community-based and individual interventional data on epinephrine's health and side effects under both ideal and real-life circumstances. Despite the logistical challenges behind such ventures, ethical considerations should also be discussed in light of the economic impact of current and future resource spending. For instance, designs based on randomization may first compare groups of different dosing schemes or drug orders in pragmatic samples to avoid some of the ethical objections. Even telephone support may improve treatment plan compliance by both increasing appropriate use and discouraging the inappropriate or unnecessary use of epinephrine (31).

Our findings suggest that despite the clear medical consensus on epinephrine as the first-line drug for anaphylaxis, health professionals do not follow this recommendation in the majority of even the most severe incidents, and lay people appear to be using this drug less often. We encourage an open and multi-disciplinary debate about the reasons for this striking discrepancy.

Tables

Table 1: Proportion of patients receiving epinephrine treatment by characteristics of the patient and reaction. * less than 30 cases in the stratum.

	Professionally treated received epinephrine		**Lay-/self-treated** received epinephrine	
	n	%	n	%
All	**5,796**	**(27.1)**	**1,538**	**(14.7)**
Patient characteristics				
Female	2,979	(24.3)	769	(13.8)
Age				
Preschoolers (0-5 years)	728	(30.2)	387	(11.9)
School-age children (6-17 years)	976	(31.7)	402	(16.2)
Adults (18-64 years)	3,423	(24.8)	671	(14.9)
Elderly (65+ years)	669	(28.6)	78	(19.2)
Co-morbidities (current and/or earlier)				
Asthma	903	(28.5)	424	(14.4)
Allergic rhinitis	1,349	(24.7)	528	(13.1)
Eczema	657	(30.0)	414	(15.9)
Cardiovascular disease	982	(28.4)	129	(22.5)
Diabetes	161	(28.0)	*	
Malignant disease	185	(30.8)	*	
Mastocytosis	93	(36.6)	*	
Elicitors				
Known or reasonably suspected				
Insect	2,041	(22.8)	350	(20.9)
Food	1,911	(27.9)	955	(13.5)
Drugs	1,219	(31.7)	84	(4.8)
AIT	127	(41.7)	*	
Unknown	362	(24.9)	101	(12.9)
Reacted before to the same allergen	1,568	(27.3)	738	(20.9)
≥2 previous reactions	404	(32.2)	265	(25.3)
Confirmed by an earlier test	353	(34.3)	241	(27.0)
Cofactors				
Exercise (vigorous)	427	(27.2)	126	(15.9)
Stress (psychological)	375	(36.5)	75	(12.0)
Alcohol	245	(28.2)	73	(13.7)
Symptoms				
Interval exposure to symptoms				
<10 min	2,260	(31.4)	674	(16.2)
10-30 min	1,213	(26.5)	306	(11.8)
>30 min	934	(23.6)	223	(12.1)
Biphasic reaction	241	(27.8)	77	(11.7)
Organ system involved				
Skin	5,165	(26.3)	1,393	(13.6)
Gastrointestinal tract	2,482	(28.7)	768	(14.3)
Respiratory tract	4,174	(28.2)	1,214	(14.4)
Cardiovascular system	3,793	(30.8)	786	(18.1)
More than 2 systems involved	3,091	(29.5)	833	(15.4)
Severity (Ring)				
I	326	(10.1)	97	(7.2)
II	2,944	(21.4)	730	(14.8)
III	2,347	(34.1)	687	(15.4)
IV	142	(66.9)	*	

Table 2: Patient-level predictors for the use of epinephrine. Predictive multivariate logistic model (mutual adjustment), conditioned on study center (individual center), location of reaction (medical setting, home, work/school, restaurant, or outdoors), and person treating (emergency doctor, GP, allergy specialist, self, family member, or teacher).

*less than 30 cases in the stratum. p-value for contribution to model, <0.05 highlighted bold. OR, Odds ratio, CI, confidence interval.

#in reference to those with no signs/symptoms in this organ system

		Professionally treated			Lay-/self-treated		
		OR	**95%-CI**	**p-value**	**OR**	**95%-CI**	**p-value**
Female gender		0.83	[0.72;0.97]	**0.016**	1.01	[0.69;1.46]	0.976
Age (vs 18-64 years)	children	0.86	[0.64;1.14]	0.130	1.37	[0.60;3.12]	0.691
	elderly	1.17	[0.92;1.49]	0.094	1.31	[0.60;2.88]	0.795
Cardiovascular co-morbidity		1.10	[0.89;1.36]	0.387	**2.01**	**[1.05;3.85]**	**0.036**
Elicitor (vs unknown)	Insect	0.87	[0.60;1.26]	0.356	1.03	[0.44;2.41]	0.980
	Food	0.82	[0.59;1.15]	0.108	0.80	[0.38;1.69]	0.983
	Drugs	0.94	[0.65;1.36]	0.782	0.63	[0.17;2.34]	0.985
	AIT	1.19	[0.56;2.51]	0.497	*		
Reacted before to the same allergen		1.00	[0.84;1.18]	0.973	**2.50**	**[1.70;3.66]**	**<.001**
Stress (as co-factor)		1.20	[0.88;1.64]	0.241	1.08	[0.45;2.63]	0.860
Immediate-type reaction (<10 min)		**1.22**	**[1.05;1.42]**	**0.010**	1.05	[0.72;1.55]	0.791
Organ system involved#	Skin	0.91	[0.73;1.15]	0.441	**0.58**	**[0.34;0.96]**	**0.036**
	GI	0.90	[0.77;1.05]	0.178	0.86	[0.58;1.28]	0.463
	Respiratory	1.15	[0.96;1.38]	0.120	1.07	[0.65;1.76]	0.793
	Cardiovascular	**1.74**	**[1.43;2.11]**	**<0.001**	**1.70**	**[1.07;2.71]**	**0.026**
Severity (vs grade II)	Grade I	**0.59**	**[0.36;0.96]**	**<0.001**	0.56	[0.17;1.86]	0.163
	Grade III	1.57	[1.33;1.85]	0.918	1.02	[0.68;1.55]	0.728
	Grade IV	**6.38**	**[3.91;10.39]**	**<0.001**	*		

Figure legends

Figure 1: Factors potentially influencing the administration of epinephrine after anaphylactic reactions (conceptual).

Figure 2: Proportion of professionally treated anaphylactic cases (n=5,352) that received epinephrine via any administration/route. The 95% confidence intervals are provided in square brackets. No cases were registered in the countries w/o numbers.

Figure 3: Proportion of professionally treated cases of insect venom (n=1,543) and food-induced anaphylaxis (n=1,131) that received epinephrine by country. Pre-schoolers, the elderly and the least severe (grade I) and near-fatal (grade IV) reactions were excluded. Horizontal lines represent the total in the register (including countries not shown). Error bars indicate 95% confidence intervals.

*less than 15 cases (applied for both case definitions in Greece and Irish referral center pediatric cases only)

Figure 4: Proportion of patients receiving epinephrine by year of reaction. *country-specific estimates weighted by the country's overall proportion of cases.

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Response to Reviewers' comments

INPRACTICE-D-17-00817
Adrenaline in severe allergic reactions - the European Anaphylaxis Register

COMMENTS FROM REVIEWER #1:
None.

COMMENTS FROM REVIEWER #2:
This manuscript describes a study analyzing data from a European registry on anaphylaxis and use of epinephrine. The following comments can be made:

1. While adrenaline and epinephrine are often used interchangeably, the term epinephrine is more commonly used when discussing pharmacologic therapy and should be used throughout the title and the manuscript.
RESPONSE: We changed the terminology now using "epinephrine" throughout the manuscript, including the title and tables (changes NOT highlighted).

2. The Abstract conclusion is too long and the last line in abstract too strong. This data does not really indicate whether trials are necessary or not as no important epinephrine-related outcomes are really discussed. While I agree with this premise, this is better stated in the manuscript conclusion and does not belong in the Abstract.
RESPONSE: We shortened the whole abstract to fit the Journal's formal requirements, at the same time we limited the abstract conclusion to statements based on our findings.

3. Line 120: patients themselves are often the 1st that can and should use epinephrine if available.
RESPONSE: Absolutely – we added this aspect.

4. Line 129: This statement is not accurate. The rationale for use of epinephrine in anaphylaxis is not based on its use in shock per se but on the pharmacologic activity of epinephrine and the known physiology of anaphylaxis.
RESPONSE: Yes, there are several aspects supporting the use of epinephrine – we now explained these in more detail.

5. While not robust evidence, the case control study by Sampson (NEJM 1992) in fatal and near fatal anaphylaxis did suggest delayed use of epinephrine as a risk factor for fatal food reactions and this should be mentioned.
RESPONSE: Given that the report included only six fatal and seven near fatal cases, no comparison/control group, and very limited information on treatment (receiving any type of epinephrine at various/uncontrolled time intervals after allergen exposure: two of six, and four of seven, respectively), this case series provides virtually no evidence for the effect of epinephrine.

6. It is not clear in the Methods what the criteria for defining anaphylaxis was? This should be detailed.
RESPONSE: The decision whether to document a patient as an incident of "severe anaphylaxis" was given to the supervising allergy specialist in each participating center (first paragraph in Methods/Patients, highlighted). The definition for different severities was based on the documented symptoms (final sentence in Methods/Data collection and Variables, highlighted).

7. How were patients who self-administered epinephrine but never sought medical care captured in the system?
RESPONSE: The Register relies on tertiary referral centers as their main sampling setting, assuming that patients with severe reactions eventually be referred from GPs and other primary caretakers for diagnostic workup and counselling. Although it does not aim to yield a representative sample of all anaphylaxis incidents, it is ideal to describe clinical details and management of various types of reactions. That said, the proportion of patients who self-administered epinephrine but never sought professional care in a tertiary center might well be lower compared to actual cases.

8. Are there any estimates or actual data to indicate how often patients who are diagnosed with anaphylaxis at a given center are actually entered into this database? Information on an estimate of what percentage of cases is believed to be captured by this manual entry of data would be of interest.
RESPONSE: As the Register runs on a voluntary basis, there is no formal tracking of the "completeness" in regard to all patients handled by the centers. As explained in the above comment, representativeness is not the key aim of the Register, but a detailed description the clinical variance and handling strategies.
Besides systematically assessing completeness indicators, we know from individual quality approval site visits that most centers aim to document all severe anaphylaxis cases. On the other hand, data entry occurs relatively stable for most centers, only sometimes interrupted by intervals w/o any activity, probably indicating a shortage of personnel or other administrative hurdles. We assume these patterns to occur irrespective of characteristics of the anaphylactic reactions and thus not to skew the distribution/patterns of cases entered.

9. Line 371: "almost absent scientific base" is too strong. Lack of high level evidence would be better.
RESPONSE: changed

10. The finding that IV use was higher than IM use is quite interesting and deserves further discussion and should be highlighted and compared to the literature.
RESPONSE: We now highlight this aspect in the Key Results section of the discussion.

11. Tryptase is mentioned only once in the text but this data would be of interest to expand upon and be placed in the table or additional information in the text.
RESPONSE: As this analysis focusses on aspects of treatment, and within that almost only on epinephrine, all other characteristics including diagnostic test results were only analyzed as indicators of guideline adherence, for example, more severe cases were treated more often with epinephrine. We provided some Register data on Tryptase in the previous publication, and are currently preparing an in-depths analysis of diagnostic aspects covered in the Register.

12. The admission rate of 46% is quite high and deserves further discussion and comparison with the literature.
RESPONSE: As mentioned above, the proportions reported from the Register do not represent estimates for a whole population. The cited admission rate only refers to the incidents which occurred primarily outside of medical settings, and can be seen as the successful sampling of severe anaphylaxis only.

13. It is interesting that only 35-41% of AIT anaphylaxis cases received epinephrine. This seems quite low as in an allergist office, there is a very low threshold for use of epinephrine, especially for anaphylaxis. Further discussion and comparison to the literature would be useful.
RESPONSE: Yes, we fully agree – we were surprised to see that even in this setting, the proportion to receive epinephrine was very similar. Even with the availability and professional training (which can be both assumed in these settings), there seem to be other hurdles to apply epinephrine in all cases. We added a statement in the discussion (highlighted).

14. The discussion is devoid of any discussions with existing literature, which is a significant deficiency as there are numerous papers on large populations of anaphylaxis patients and their management.
RESPONSE: We are happy to refer to publications at the reviewer's and/or editor's discretion.

15. Discussion on difference in epinephrine uses between countries would be helpful. Why is Germany so low, Greece so high?
RESPONSE: We are currently establishing a new online platform for the Register, which will allow collection of details from other sources, such as first-hand data from the emergency respondent. This will enable us to tailor the data collection tool to incorporate items e.g. on guideline adherence, and thus answer questions on country differences. As of now, the data does not provide insight about the reasons behind treatment decisions.

16. Figure 1 is not very illustrative and very simple. An improved design figure would be better incorporating more elements, number of countries, centers, etc. Perhaps a consolidation of a revised Figure 1 and details of Figure 2 would be useful.
RESPONSE: The figure is meant to serve as a general outline of which factors from which domains might impact the treatment decision. We are happy to have the figure transferred to the online appendix at the reviewer's and/or editor's discretion.

17. The highlights boxes are far too wordy and the highlights are lost in the excess verbiage. These should be just 2 sentences, not a paragraph each.
RESPONSE: We followed the editorial office's recommendation to drop the capsule summary and key facts but include a three-item list of highlights.

Figure No. 1

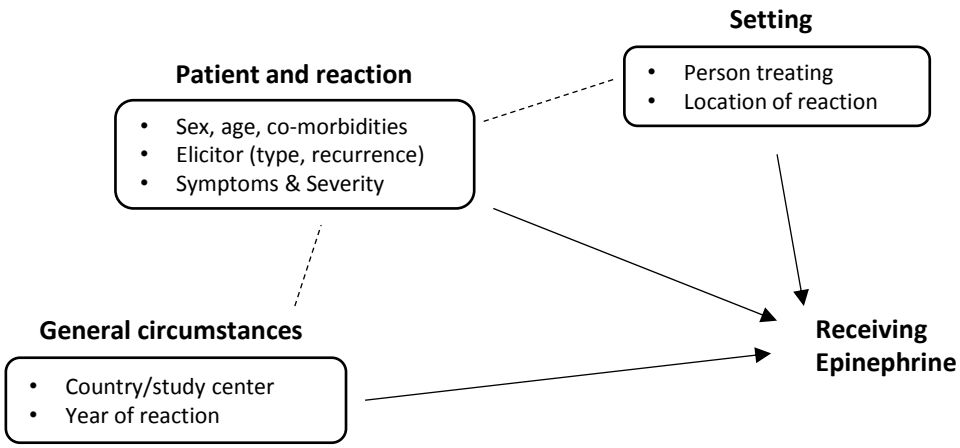
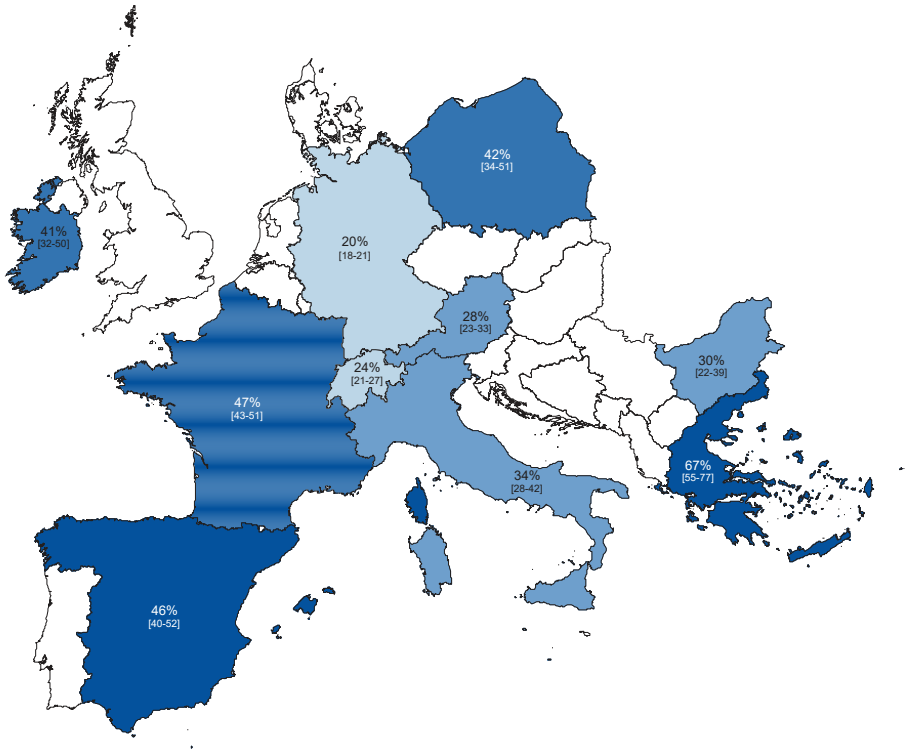

Setting
Person treating
Location of reaction
Patient and reaction
Sex, age, co-morbidities
Elicitor (type, recurrence)
Symptoms & Severity
General circumstances
Country/study center
Year of reaction
Receiving Epinephrine

Figure No. 2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[34-51]
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Figure No. 3

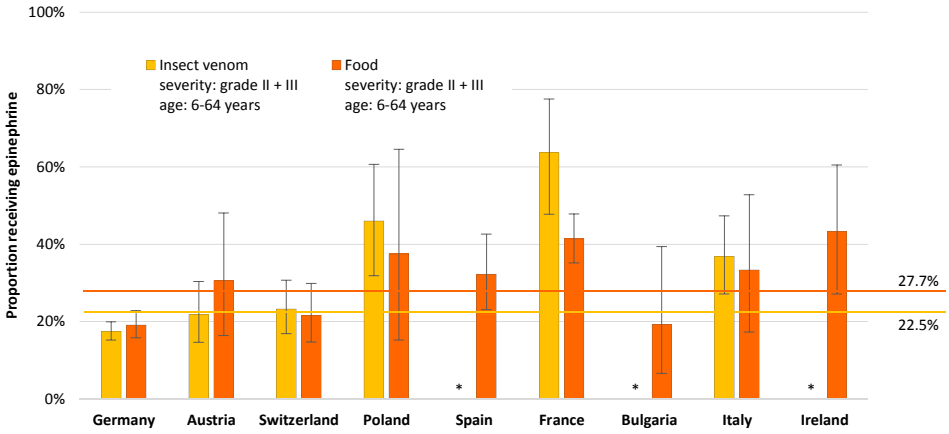
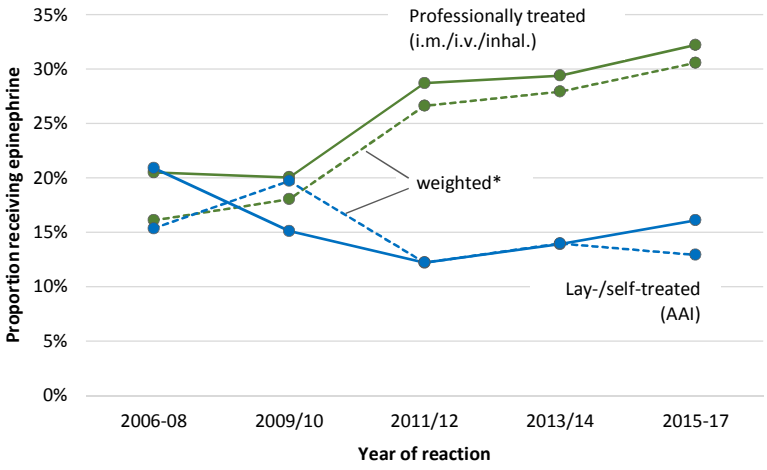

100%
80%
60%
40%
20%
0%
Proportion receiving epinephrine
Insect venom
severity: grade II + III
age: 6-64 years
Food
severity: grade II + III
age: 6-64 years
27.7%
22.5%
*
*
*
Germany
Austria
Switzerland
Poland
Spain
France
Bulgaria
Italy
Ireland

Figure No. 4


35%
30%
25%
20%
15%
10%
5%
0%
Proportion receiving epinephrine
Professionally treated
(i.m./i.v./inhal.)
weighted*
Lay-/self-treated
(AAI)
2006-08
2009/10
2011/12
2013/14
2015-17
Year of reaction

Online Appendix

e-table 1: Proportion of lay-/self-treated anaphylaxis cases treated with an AAI, including all registered reactions and the strata of recurrent and severest reactions.

	All reactions AAI applied		**Recurrent reactions** AAI applied		**Recurrent grade III + IV** AAI applied	
	n	%	n	%	n	%
All	**1312**	**(14.7)**	**584**	**(20.9)**	**348**	**(21.0)**
Germany	558	(16.3)	265	(23.2)	162	(22.2)
Austria	44	(13.7)	17	(26.1)	11	(18.2)
Switzerland	241	(10.4)	111	(13.3)	48	(12.5)
Greece	56	(25.3)	29	(31.0)	11	(27.3)
Poland	37	(15.9)	12	(29.4)	10	(30.0)
Spain	42	(14.3)	13	(27.8)	10	(20.0)
France	241	(10.7)	99	(14.7)	64	(20.3)
Bulgaria	24	(7.7)	9	(10.0)	6	(16.7)
Italy	20	(9.1)	12	(7.7)	6	(16.7)
Ireland	49	(24.6)	17	(34.6)	20	(30.0)

Title

Epinephrine in severe allergic reactions - the European Anaphylaxis Register

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Abstract

Background. Current guidelines recommend intramuscular administration of epinephrine as the first-line drug for the emergency treatment of severe allergic reactions (anaphylaxis), but no randomized trial evidence supports this consensus.

Objective. We aimed to assess anaphylaxis treatment practices over ten years, covering several European regions, all allergen sources, and all age groups.

Methods. The European Anaphylaxis Register tracks elicitors, symptoms, emergency treatment, diagnostic workups and long-term counselling for anaphylaxis incidents through web-based data entry from tertiary allergy specialists, covering information from the emergency respondent, patient, tertiary referral, and laboratory/clinical test results.

Results. We analyzed 10,184 anaphylaxis incidents. In total, 27.1% of patients treated by a health professional received epinephrine and, in total, 10.5% received a second dose. Successful administration was less frequent in German-speaking countries (min. 19.6%) than in Greece, France, and Spain (max. 66.7%). Over the last decade, epinephrine administration from a health professional almost doubled to reach 30.6% in 2015-17, half of which was applied intramuscularly.

14.7% of lay- or self-treated cases were treated with an auto-injector (AAI). Of those w/o treatment, 22.4% carried a device for administration. No change in successful administration by lay emergency respondents was found over the last ten years.

Of the reaction and patient characteristics analyzed, only clinical severity considerably influenced the likelihood of receiving epinephrine, with 66.9% of successful administrations in near-fatal (grade IV) reactions.

Conclusion. Despite clear recommendations, only a small proportion of anaphylaxis incidents are treated with epinephrine. We demonstrated a slight increase in treated patients when handled by professionals, but stagnation in lay- or self-treated anaphylaxis. The reaction circumstances, the respondent's professional background, and patient characteristics did not explain which reactions were treated.

Highlight Box

1. What is already known about this topic?

There is international agreement that epinephrine is the first-line emergency treatment for anaphylaxis. The current (2014) EAACI guidelines and the Cochrane database could not identify a randomized interventional trial to support the administration of epinephrine.

2. What does this article add to our knowledge?

Despite clear recommendations, only one in four anaphylaxis patients treated by a health professional receive epinephrine, and there was no increase to receive epinephrine in lay- and self-treated anaphylaxis over the last decade.

3. How does this study impact current management guidelines?

The discrepancy between recommendations and actual treatment habits suggests that there is need for strong evidence to support the guidelines, pushing their implementation.

Conflict of Interest statements

LG declares that he has no conflict of interest to declare. All other COI statements will be completed upon reception of the Journal's COI forms, as completed and signed by each coauthor separately.

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Key words

Anaphylaxis
Emergency Treatment
Epinephrine
Hypersensitivity
Registries

Abbreviations

AAI – Adrenaline Auto-Injector
AIT – Allergen Immuno-Therapy
CI – Confidence Interval
DAG – Directed Acyclic Graph
EAACI – European Academy of Allergy and Clinical Immunology
EAR – European Anaphylaxis Register
EMA – European Medicines Agency
GI – Gastrointestinal
GP – General Practitioner
ICON – International Consensus
ICU – Intensive Care Unit
OR – Odds Ratio

Introduction

Most allergic reactions take a mild course and only rarely evolve into life-threatening anaphylaxis. However, these incidents, which are inherently diverse in terms of their clinical appearance and progression, require the quickest possible emergency treatment, either by the patient him or herself, a lay helper, or by the nearest health professional, who in many cases is not an expert in allergy or emergency medicine. There is no point-of-care test to assist with the clinical diagnosis.

In addition to non-specific emergency measures, such as fluids and oxygen, a number of pharmaceutical agents have been introduced for the first-line management of anaphylaxis, most notably intramuscular or intravenous epinephrine (adrenaline) as the first-line treamtent, and corticosteroids, antihistamines and beta-agonists as adjunctive therapies. Because these incidents are very rare and can occur in almost any setting, valid interventional assessments of the efficacy of these drugs and their effectiveness for the treatment of severe allergic reactions have never been conducted (1, 2), especially investigations of the even rarer outcome of case fatality (3-6). At present, the current rationale behind the use of epinephrine as the key intervention to manage anaphylaxis besides its pharmacologic activity and the known physiology of anaphylaxis is evidence from other emergency conditions (which may be weak), retrospective clinical observations (7), and individual experience (e.g., EMA assessment 478468/2015).

Regardless of the almost complete absence of robust evidence (evidence level IV (8)), there is widespread expert agreement that epinephrine should be applied (intramuscularly (9)) with no delay in all cases of anaphylaxis. This recommendation is reflected in the current guidelines; the guidelines considered most current include those developed by European allergy specialists and published for the EAACI in 2014 (10), the ICON statement (11), and the World Allergy Organization guideline (12, 13). Notably, these quasi-standards substantially limit the scope for randomization in interventional assessments of epinephrine's impact in future research.

The discrepancy between scientific evidence and guideline-based recommendations has implications reaching far beyond an individual's health in terms of efficacy and safety, including professional liability, personal and societal financial issues, and manufacturers' economic and market interests (14). Therefore, a detailed record of what actually happens in real-life anaphylaxis emergencies must be created.

The aim of the European Anaphylaxis Register (EAR) is to document data from patients who have experienced severe allergic reactions (15-19). Available for the first time, the current analysis focusses to report all details on the use of epinephrine as the recommended first-line drug by all stakeholders, including health professionals, lay helpers, and self-administrators, and thus includes all reaction types, elicitors and covering all age groups. The multinational scope of this platform covering data collected for more than a decade aims to estimate the proportion of anaphylactic reactions treated with epinephrine throughout Europe to allow comparisons between countries and investigation of time trends. Here, we explore the link between the clinical reaction and patient characteristics and the likelihood of receiving epinephrine (**figure 1**) to pave the way for targeted interventions with the potential to improve guideline adherence and health outcomes research and to provide evidence for public health decision making.

Methods

Study design

The EAR is a multicenter, disease-specific online platform that is used to document incidents of anaphylaxis, including all confirmed, suspected or unknown elicitors and any reaction circumstances in terms of location, emergency respondent, and previous reactions (15, 17-19). Data are entered locally in tertiary allergy and dermatology referral centers through a web-based interface by trained health professionals based on information collected during face-to-face visits scheduled for a post-reaction diagnosis and/or counselling and from medical records (e.g., emergency protocols, intensive care unit (ICU) records, and lab or clinical test results). The Ethics Committee at Charité - Universitätsmedizin Berlin approved the project as the coordinating center and was accredited by the local ethics committees in all participating countries.

Data collection and Variables

The multi-language online questionnaire is available in German for Germany, Austria, and Switzerland, in French for France and Switzerland (cooperation with the Allergy Vigilance Network (20)), and in English for all other participating countries. The questionnaire was developed and piloted in the German Anaphylaxis Register and translated/back-translated for its international continuation (16, 21). The

questionnaire underwent yearly updates that introduced new topics and items suggested by an international group of allergy experts. Interrater reliability was demonstrated by repeated data entry through two independent health professionals. The questionnaire captures information on elicitors, symptoms, emergency treatment, diagnostic procedures and long-term counselling and is accessible at www.anaphylaxie.net (22).

The current analysis separately reports two core strata of the complete sample: incidents where emergency treatment was conducted by a health professional and incidents where a lay-person or the patient him-/herself took care of the treatment. The small fraction of patients who were initially lay-/self-treated and later supported by a professional are reported within both groups.

The above-participant-level data used in this analysis include the (single) study center and country, year of reaction (categorized in two-year intervals), location of the reaction and the emergency respondent's professional background (medical specialization).

The reported participant-level characteristics include the age (unrestricted report in four categories) and gender of the patient, co-morbidities, elicitors and their confirmation status (confirmed, suspected, or unknown), short-acting co-factors (e.g., psychological stress, medical and social drugs, alcohol, or exercise), previous reactions and previous diagnostic procedures, and the symptom pattern (exposure-symptom interval, specific symptoms and organ systems). The severity of the reaction was derived manually from the symptoms in four levels as proposed by Ring and Messmer (23): grade II with at least two organ systems, grade III including signs of circulatory and/or respiratory failure (shock), and grade IV with circulatory and/or respiratory arrest.

Patients

Individuals referred to a collaborating tertiary referral center after a (first or recurrent) anaphylactic reaction were asked to provide written informed consent to have their medical data entered under a pseudonym into the register after completion of the diagnostic workup or the data collected during routine care were entered anonymously without individual consent depending on the countries' data protection regulations. As there is no international standard for an unambiguous distinction between severe and non-severe anaphylaxis, the decision to enroll a patient (ie, the case definition) had to be

given to the local allergy expert. From the register, only non-fatal cases with a documented date of reaction and information about the person who conducted the emergency treatment were used for this analysis. The stratum of professionally treated cases was limited to cases with information about epinephrine administration, including the route of administration, and the stratum of lay-treated individuals to cases with a known AAI status.

Because the register continuously records data, the sample for the current analysis was drawn from the project server in March 2017 and covered all reactions from the initiation of the register in 2006 onwards. To allow robust comparisons between countries, the cases were limited to countries reporting at least 100 incidents. To further increase the comparability, two narrowed case definitions were additionally assessed; these cases were limited to grade II and grade III reactions caused by food allergens or insect venom and excluded preschoolers (<6 years) and the elderly (>64 years) to yield more homogeneous sub-samples (23, 24).

Statistical analysis

The data were cleaned and analyzed using the SAS 9.4 software system (SAS Institute, Cary, NC). Individual queries were pursued to improve the completeness of the original data. Free text answers were manually assigned to default categories when appropriate. Data missing by item were accepted for all variables except emergency respondent, epinephrine administration and year of reaction. Information documented as unknown was handled as missing. Assuming that local documentation habits differed at random, all proportional measures were reported using all valid answers by item as the denominator. Confidence intervals for frequencies were calculated based on the beta distribution and were reported at a symmetric 95%.

To account for the time-varying proportion of cases contributed by each country, weighted frequency estimates for the strata of year-of-reaction were calculated by multiplying stratum-specific estimates for each country by the country's overall proportion of cases in the register.

A mutually adjusted logistic approach was used to model the predictive information of the patient-level characteristics. Using a DAG-like (directed acyclic graph), content-based selection process, the model was further conditioned on the study center (individual center, assuming referral differences arise on a

regional/center level not confined by country), location of the reaction (medical setting, home, work/school, restaurant, or outdoors), and person treating (emergency doctor, GP, allergy specialist, self, family member, and teacher) as nuisance parameters. Year-of-reaction was not controlled for because we assumed similar referral patterns within a given center over time.

Role of the funding source

The European Anaphylaxis Register was supported by the Network for Online Registration of Anaphylaxis NORA e. V. Irish data collection from 2013-2015 was supported by a grant from the National Children's Research Centre. The funders had role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

In the EAR, ten countries (Austria, Bulgaria, France, Germany, Greece, Ireland, Italy, Poland, Spain, and Switzerland) reported more than 100 incidents of anaphylaxis. Of the 10,184 registered cases, 7,694 (75.5%) provided details of emergency treatment, including the administration of epinephrine.

Epinephrine

Of these 7,694 complete cases, 1,782 (23.2%) were treated with epinephrine.

A total of 5,352 (69.6%) individuals were treated by a health professional, 1,094 (14.2%) received emergency treatment through a lay person (including self-administration), and 444 (5.8%) were first treated by a lay person followed by a health professional. A total of 804 (10.5%) individuals received no emergency treatment.

Detailed treatment information was available for 5,796 professionally treated cases, of which 1,570 (27.1%) were treated with epinephrine. The epinephrine was administered intramuscularly in 649 cases (11.2%), intravenously in 758 cases (13.1%), and per inhalation in 226 cases (3.9%). A total of 10.5% of the cases received a second dose of epinephrine (123/1,175 cases had information on the second dose).

Emergency management was documented for 1,538 lay- or self-treated individuals, of which 226 (14.7%) received epinephrine using an autoinjector (AAI). The reasons for not receiving epinephrine were as

follows: AAI available but not used (22.4%); AAI prescribed but not available (4.7%); and AAI not prescribed (72.8%, percentage of 655 individuals with information on failed administration).

Other Treatment

In the emergency situation, 4,967 (85.7%) professionally treated patients received corticosteroids, 4,492 (77.5%) received antihistamines, 647 (11.2%) received beta-2-agonists, and 1,761 (30.4%) received i.v. fluids and/or oxygen. Of the lay-/self-treated patients, 741 (48.2%) received corticosteroids, 1,194 (77.6%) received antihistamines, and 276 (18.0%) received beta-2-agonists. In total, 46.1% of the reactions occurring outside of medical settings resulted in admission to a hospital following the incident, and 7.2% required ICU handling. Of the anaphylaxis cases that occurred within a hospital or medical practice, 27.0% required ICU treatment.

Setting and Emergency Responder

Of the 5,281 reactions that occurred outside of medical settings, 2,541 occurred in private homes, 1,885 occurred outdoors (inner city or countryside), 477 occurred in the working environment or school, and 378 occurred in restaurants. By location, 17.1% to 22.3% of these cases received epinephrine. Conversely, 39.6% of the anaphylaxis cases that occurred in medical settings (940 cases) were treated with epinephrine.

Most of the professionally treated cases were handled by an emergency doctor (2,605), of which 29.7% received epinephrine, followed by GPs (716) and allergy specialists (377), of which 18.0% and 38.5%, respectively, were given epinephrine. Administration of an AAI by lay persons was reported similarly often for the 706 patients who treated themselves compared to the 712 patients who were treated by a family member (13.9% and 15.9%, respectively). Four of the 40 patients (10.0%) treated by a nursery or school teacher received epinephrine.

Country

The proportion of patients receiving epinephrine from health professionals varied between countries, with the lowest numbers in Germany (19.6%) and Switzerland (24.2%) and the highest numbers in Greece (66.7%) and France (46.7%, **figure 2**). With six referral centers, Germany was the only country with more than one site contributing 100+ cases, which allowed robust comparisons between different catchment

areas within a given country. Within these six centers, the percentage of patients administered epinephrine by a professional ranged from 13.7% to 23.9%.

To account for potential country-specific referral patterns in terms of oversampling age groups, certain elicitors or disease severity, two commonly reported case definitions were selected to improve comparability between countries. In total, 347/1,543 (22.5%) of insect venom reactions - excluding the least severe reactions (grade I), near-fatal reactions (grade IV), preschoolers, and the elderly - were treated with epinephrine when handled by a professional, with a low extreme in Germany (17.5%) and a high extreme in France (63.6%). Similarly, 313/1,131 (27.7%) of patients who experienced food-induced reactions with the same age and severity restrictions received epinephrine, with the outliers in Germany (19.1%) and Ireland (43.2%, **figure 3**).

Administration of AAI in lay-treated anaphylaxis varied between European countries, with the lowest numbers in Bulgaria (7.7%) and France (9.1%) and the highest in Greece (25.3%) and Ireland (24.6%). The inter-country differences were even higher when only patients with recurrent reactions were compared, with 7.7% receiving an AAI in Italy and 34.6% in Ireland (**e-table 1**).

Time

With the introduction of the Register in 2006-2008, only 16.1% of the cases (weighted for the country's contribution) received epinephrine when treated by a professional; this percentage steadily increased to 30.6% from 2015-2017. Of those treated, 17.2% received the treatment intramuscularly from 2006-2008, and this percentage increased steadily to 50.8% from 2015-2017. The percentage of patients who were treated with an AAI by a lay helper was relatively stable at 15.4% from 2006-2008 and 12.9% from 2015-2017 (weighted estimates, **figure 4**).

Patient and reaction characteristics

When treated by professionals, the proportion of patients receiving epinephrine was very similar between men and women, age groups, and individuals with or without co-morbidities. Patients with known mastocytosis were treated with epinephrine more often (39.4%). Administration of AAI devices by the patients themselves or by lay helpers was less frequent in preschoolers (11.9%) and more frequent in the elderly (19.2%, **table 1**).

When elicitors were compared, only drug-induced anaphylaxis treated by health professionals was treated with epinephrine more often (31.7%), with the highest percentages for reactions to antibiotics and AIT treatment (35.5% and 41.7%, respectively). In contrast, patients with lay- or self-treated insect venom reactions received emergency epinephrine (AAI) more often than patients with drug-induced reactions (20.9% and 4.8%, respectively).

Patients who had reacted to the same allergen several times previously and those in whom the elicitor was confirmed by a diagnostic test previous to the reaction received epinephrine more often, with 25.3%/27.0% for lay and 32.2%/34.3% for professionally treated individuals. As co-factors, only psychological stress was associated with a higher proportion of receiving epinephrine by a professional (36.5%, **table 1**).

Professionals administered epinephrine more often in reactions with a very short (<10 min) interval between allergen exposure and the first symptoms (31.4%), but the organ system involved and the number of different organ systems was not strongly associated with epinephrine treatment. Only a few specific symptoms led to considerably higher numbers of professionals applying epinephrine (e.g., cardiac arrest (71.2%), respiratory arrest (64.3%), and loss of consciousness (37.1%)), which was reflected by the strong association with the overall severity rating, ranging from 10.1% for the mildest reactions (grade I) to 66.9% for near-fatal reactions (grade IV, **table 1**).

Irrespective of the person performing the treatment, other indirect indicators of the reaction severity were associated with receiving epinephrine, including factors unknown during the emergency (e.g., elevated tryptase levels, 44.7%) or parameters of post-emergency management (hospital admission, 38.8% and ICU, 51.2%).

Independent predictors

When the patient-level characteristics (mutual adjustment) and the setting (conditioned/stratified modelling) were controlled, few factors remained as independent predictors for receiving epinephrine for the emergency treatment of anaphylaxis. Medical professionals tended to withhold epinephrine in women (OR [95%-CI] 0.83 [0.77;0.97], p=0.016) and only applied epinephrine more often in very immediate reactions (OR 1.22 [1.05;1.42], p=0.010), with cardiovascular symptoms (OR 1.74 [1.43;2.11],

p<0.001) and near-fatal (grade IV) reactions vs grade II reactions (OR 6.38 [3.91;10.39], p<0.001). Age, the type of elicitor, and previous reactions to the same allergen were not independently associated with epinephrine treatment (**table 2**, left columns).

Conversely, lay persons treating anaphylaxis were appropriately prompted towards applying an AAI by existing cardiovascular co-morbidities or the presence of cardiovascular symptoms (OR 2.01 [1.05;3.85], p=0.036 and OR 1.70 [1.07;2.71], p=0.026, respectively). Previous reactions to the same allergen seemed to increase the availability of an AAI on site, as reflected by the higher proportion of administrations (OR 2.50 [1.70;3.66], p<0.001). Other characteristics of the patient and the reaction circumstances were not independently associated with AAI administration, including the severity of the reaction (**table 2**, right columns).

Discussion

Key results

This is the first report of epinephrine use in children and adults alike, covering a whole decade and several European countries, demonstrating that only one in four patients experiencing an anaphylactic reaction received epinephrine, which remained the current first-line recommendation throughout that time period (10, 11). Most incidents were treated by health professionals, who frequently administered corticosteroids and antihistamines (approximately three times out of four) but did not adhere to the European guideline to administer epinephrine first (10). Comparing countries, health professionals in German-speaking countries withheld epinephrine more often than their counterparts in other countries, including Greece, Spain, and France. The last ten years have seen a doubling of epinephrine treatment completion in Europe, especially by health professionals, which may reflect improved guideline distribution and awareness. The steep increase in the use of intramuscular administrations from one in six to more than half of epinephrine receivers supports this interpretation. Still, only about half of all documented cases who received epinephrine received it via the recommend route, that is intramuscularly.

The likelihood of the use of AAIs in self- or lay-treated anaphylaxis is even lower (one in seven) and may be explained by those who have reactions for the first time not being aware of the potential for an allergic reaction to occur, in which case they would clearly not be carrying the device. However, the likelihood was only slightly higher for the severest (anaphylaxis grade III and IV) recurrent reactions treated by lay emergency respondents. This is the first report of a decade-long stagnation of the use of AAIs in lay- or self-treated incidents, despite all efforts directed towards patient education, target group training programs (e.g., school or nursery school teachers), or in some countries the availability of AAIs to the public (e.g., in schools, malls, stations, and airports (24)).

To target professional training and identify areas for further investigation, factors potentially influencing the chance to receive epinephrine have not yet been examined. Strikingly, our data suggest that almost none of the characteristics of the actual reaction (e.g., place and elicitor) or the patient (e.g., age and co-morbidities) influenced guideline adherence. Even in the setting where AITs take place, less than half of anaphylaxis incidents caused by immune therapy were treated with epinephrine. Only the overall symptom severity was linked positively to the likelihood of receiving epinephrine in the community. This finding limits the identification of targets for new strategies to improve successful administration.

Because the wealth of data available in this project on severe allergic reactions was only able to explain a small proportion of the cases treated according to the guideline recommendations, this pattern could be in part a random process (i.e., unknown and/or unmeasurable factors) or could be ruled by aspects not yet covered by this approach. These aspects may differ between individuals (i.e., some professionals tend to give epinephrine and some tend to refrain from doing so). Moreover, the individual appraisal of the situation may be shifted towards or away from giving epinephrine by personal experiences and guideline interpretation, especially in light of the lack of high level evidence for these recommendations.

Strengths and Limitations

With more than ten thousand incidents documented over more than a decade, the EAR involves countries that together constitute close to half of the European population. The EAR contains details about all major aspects of incidents of anaphylaxis, including allergen exposure, symptoms, emergency treatment, diagnostic workup, and long-term counselling.

Notably, our approach is limited to the upper end of the severity spectrum, with an aim to oversample the most threatening reactions. At the same time, we only sporadically captured fatal incidents, which were not accounted for in the current analysis. Because these incidents are very rare occurrences (25-27), our design gives robust estimates for the worst survived episodes, leading to conservative estimates for successful administration linked to severity. However, our design does not support generalization to unstratified whole populations, especially with the selective choice made for participating tertiary care centers and their individual referral patterns, documentation habits, and voluntary data entry (28). Selecting well-defined clinical entities for sensitivity analyses substantially improved the inter-national comparability.

Comparisons between treated and untreated patients in terms of health outcomes (e.g., symptom development, hospital/ICU admission, lab diagnostics, or mortality) does not lead to valid efficacy estimates from these data because this study is retrospective and observational. These comparisons are urgently needed. The treated subjects paradoxically appear to have the worst outcomes, because treatment with epinephrine appears to be most strongly related to the assessed clinical severity. In particular, the confounding effect of disease severity in anaphylaxis is neither well defined nor well assessed and thus cannot be fully accounted for statistically (e.g., through stratification).

Conclusion

A better understanding of what happens at the point-of-care may shape future research and support the targeting of interventions to improve guidelines and guideline adherence and can direct focused medical and public education efforts (29, 30). Unbiased input from the person responding to the emergency about their decision making, training background, drug availability and individual professional (or personal, if lay- or self-treated) appraisal would aid in better understanding the gap between current practice and the recommendations. Specifically, future studies should collect data on what if any factors did or did not convince a person (be it professional or lay) to give epinephrine. To fill this knowledge gap, the EAR is currently being advanced to capture important aspects from the emergency respondent's perspective and at the same time also the patient's own experience and views.

Perhaps even more importantly, this report accentuates the need for community-based and individual interventional data on epinephrine's health and side effects under both ideal and real-life circumstances. Despite the logistical challenges behind such ventures, ethical considerations should also be discussed in light of the economic impact of current and future resource spending. For instance, designs based on randomization may first compare groups of different dosing schemes or drug orders in pragmatic samples to avoid some of the ethical objections. Even telephone support may improve treatment plan compliance by both increasing appropriate use and discouraging the inappropriate or unnecessary use of epinephrine (31).

Our findings suggest that despite the clear medical consensus on epinephrine as the first-line drug for anaphylaxis, health professionals do not follow this recommendation in the majority of even the most severe incidents, and lay people appear to be using this drug less often. We encourage an open and multi-disciplinary debate about the reasons for this striking discrepancy.

Tables

Table 1: Proportion of patients receiving epinephrine treatment by characteristics of the patient and reaction. * less than 30 cases in the stratum.

	Professionally treated received epinephrine		**Lay-/self-treated** received epinephrine	
	n	%	n	%
All	**5,796**	**(27.1)**	**1,538**	**(14.7)**
Patient characteristics				
Female	2,979	(24.3)	769	(13.8)
Age				
Preschoolers (0-5 years)	728	(30.2)	387	(11.9)
School-age children (6-17 years)	976	(31.7)	402	(16.2)
Adults (18-64 years)	3,423	(24.8)	671	(14.9)
Elderly (65+ years)	669	(28.6)	78	(19.2)
Co-morbidities (current and/or earlier)				
Asthma	903	(28.5)	424	(14.4)
Allergic rhinitis	1,349	(24.7)	528	(13.1)
Eczema	657	(30.0)	414	(15.9)
Cardiovascular disease	982	(28.4)	129	(22.5)
Diabetes	161	(28.0)	*	
Malignant disease	185	(30.8)	*	
Mastocytosis	93	(36.6)	*	
Elicitors				
Known or reasonably suspected				
Insect	2,041	(22.8)	350	(20.9)
Food	1,911	(27.9)	955	(13.5)
Drugs	1,219	(31.7)	84	(4.8)
AIT	127	(41.7)	*	
Unknown	362	(24.9)	101	(12.9)
Reacted before to the same allergen	1,568	(27.3)	738	(20.9)
≥2 previous reactions	404	(32.2)	265	(25.3)
Confirmed by an earlier test	353	(34.3)	241	(27.0)
Cofactors				
Exercise (vigorous)	427	(27.2)	126	(15.9)
Stress (psychological)	375	(36.5)	75	(12.0)
Alcohol	245	(28.2)	73	(13.7)
Symptoms				
Interval exposure to symptoms				
<10 min	2,260	(31.4)	674	(16.2)
10-30 min	1,213	(26.5)	306	(11.8)
>30 min	934	(23.6)	223	(12.1)
Biphasic reaction	241	(27.8)	77	(11.7)
Organ system involved				
Skin	5,165	(26.3)	1,393	(13.6)
Gastrointestinal tract	2,482	(28.7)	768	(14.3)
Respiratory tract	4,174	(28.2)	1,214	(14.4)
Cardiovascular system	3,793	(30.8)	786	(18.1)
More than 2 systems involved	3,091	(29.5)	833	(15.4)
Severity (Ring)				
I	326	(10.1)	97	(7.2)
II	2,944	(21.4)	730	(14.8)
III	2,347	(34.1)	687	(15.4)
IV	142	(66.9)	*	

Table 2: Patient-level predictors for the use of epinephrine. Predictive multivariate logistic model (mutual adjustment), conditioned on study center (individual center), location of reaction (medical setting, home, work/school, restaurant, or outdoors), and person treating (emergency doctor, GP, allergy specialist, self, family member, or teacher).

*less than 30 cases in the stratum. p-value for contribution to model, <0.05 highlighted bold. OR, Odds ratio, CI, confidence interval.

#in reference to those with no signs/symptoms in this organ system

		Professionally treated			Lay-/self-treated		
		OR	**95%-CI**	**p-value**	**OR**	**95%-CI**	**p-value**
Female gender		0.83	[0.72;0.97]	**0.016**	1.01	[0.69;1.46]	0.976
Age (vs 18-64 years)	children	0.86	[0.64;1.14]	0.130	1.37	[0.60;3.12]	0.691
	elderly	1.17	[0.92;1.49]	0.094	1.31	[0.60;2.88]	0.795
Cardiovascular co-morbidity		1.10	[0.89;1.36]	0.387	**2.01**	**[1.05;3.85]**	**0.036**
Elicitor (vs unknown)	Insect	0.87	[0.60;1.26]	0.356	1.03	[0.44;2.41]	0.980
	Food	0.82	[0.59;1.15]	0.108	0.80	[0.38;1.69]	0.983
	Drugs	0.94	[0.65;1.36]	0.782	0.63	[0.17;2.34]	0.985
	AIT	1.19	[0.56;2.51]	0.497	*		
Reacted before to the same allergen		1.00	[0.84;1.18]	0.973	**2.50**	**[1.70;3.66]**	**<.001**
Stress (as co-factor)		1.20	[0.88;1.64]	0.241	1.08	[0.45;2.63]	0.860
Immediate-type reaction (<10 min)		**1.22**	**[1.05;1.42]**	**0.010**	1.05	[0.72;1.55]	0.791
Organ system involved#	Skin	0.91	[0.73;1.15]	0.441	**0.58**	**[0.34;0.96]**	**0.036**
	GI	0.90	[0.77;1.05]	0.178	0.86	[0.58;1.28]	0.463
	Respiratory	1.15	[0.96;1.38]	0.120	1.07	[0.65;1.76]	0.793
	Cardiovascular	**1.74**	**[1.43;2.11]**	**<0.001**	**1.70**	**[1.07;2.71]**	**0.026**
Severity (vs grade II)	Grade I	**0.59**	**[0.36;0.96]**	**<0.001**	0.56	[0.17;1.86]	0.163
	Grade III	1.57	[1.33;1.85]	0.918	1.02	[0.68;1.55]	0.728
	Grade IV	**6.38**	**[3.91;10.39]**	**<0.001**	*		

Figure legends

Figure 1: Factors potentially influencing the administration of epinephrine after anaphylactic reactions (conceptual).

Figure 2: Proportion of professionally treated anaphylactic cases (n=5,352) that received epinephrine via any administration/route. The 95% confidence intervals are provided in square brackets. No cases were registered in the countries w/o numbers.

Figure 3: Proportion of professionally treated cases of insect venom (n=1,543) and food-induced anaphylaxis (n=1,131) that received epinephrine by country. Pre-schoolers, the elderly and the least severe (grade I) and near-fatal (grade IV) reactions were excluded. Horizontal lines represent the total in the register (including countries not shown). Error bars indicate 95% confidence intervals.

*less than 15 cases (applied for both case definitions in Greece and Irish referral center pediatric cases only)

Figure 4: Proportion of patients receiving epinephrine by year of reaction. *country-specific estimates weighted by the country's overall proportion of cases.

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