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Use of multiple epinephrine doses in anaphylaxis: A systematic review and meta-analysis

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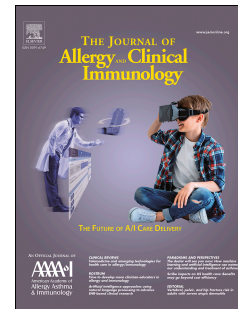
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Title:**Use of multiple epinephrine doses in anaphylaxis: A systematic review and meta-analysis****Short Title:** Multiple epinephrine doses to treat anaphylaxis

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Author Contributions:

PJT conceived the study. NP, RBJ, PJT and JB designed the protocol. Data extraction was undertaken by JB, AYG, KWC, NP and PJT, and analysed by NP, DI, KWC and PJT. The manuscript was drafted by NP and PJT, and then reviewed and the final version approved by all authors.

Conflicts of Interest:

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Abstract:

Background: Regulatory bodies recommend all patients at risk of anaphylaxis are prescribed two epinephrine auto-injectors, which they should carry at all times. This is in contrast to some guidelines. The proportion of anaphylaxis reactions which are treated with multiple doses of epinephrine has not been systematically evaluated.

Objective: To undertake a systematic review and meta-analysis of published studies reporting epinephrine treatment for anaphylaxis, where data relating to the number of doses administered was available.

Methods: We searched Medline, Embase and Cochrane databases for relevant studies reporting at least 10 anaphylaxis events (due to food or venom), from 1946 until January 2020. Data were extracted in duplicate for meta-analysis, and risk of bias assessed. Study registration: PROSPERO CRD42017069109.

Results: 86 studies (36,557 anaphylaxis events) met the inclusion criteria (20 (23%) prospective studies; 64 (74%) reported reactions in the community, 22 (26%) food challenge data). Risk of bias was assessed as low in 50 studies. Overall, 7.7% (95% confidence interval 6.4-9.1) of anaphylaxis events (from any cause) were treated with multiple doses of epinephrine. Considering only epinephrine-treated reactions where subsequent doses were administered by a healthcare professional, 11.1% (95%CI 9.4-13.2) of food-induced and 17.1% (95%CI 11.3-25.0) of venom-induced reactions were treated with >1 epinephrine dose. Heterogeneity was moderate-high in the meta-analyses, but at sensitivity analysis this was not affected by study design or anaphylaxis definition.

Conclusion: Around 1 in 10 anaphylaxis reactions are treated with >1 dose of epinephrine.

Keywords: epinephrine, allergic reaction, anaphylaxis, auto-injector device, refractory anaphylaxis

Abbreviations:

CI Confidence Interval

EAI Epinephrine autoinjector

FAAN Food Allergy and Anaphylaxis Network

IPD Individual patient data

NIAID National Institutes of Allergy and Infectious Diseases

85 CAPSULE SUMMARY

86 In this systematic review and meta-analysis of the literature, we found that around 1 in 10
87 anaphylaxis reactions are treated with >1 dose of epinephrine.

88

89 KEY MESSAGES

90 Around 10% of anaphylaxis reactions are treated with more than 1 dose of epinephrine,
91 including when the decision as to administer a further dose was made by a healthcare
92 professional.

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Introduction

Epinephrine is established as the first line treatment for anaphylaxis.¹ The majority of allergic reactions occur in the community.² Delayed administration of epinephrine has been associated with poor outcomes in anaphylaxis.^{3,4} To mitigate against this, patients at risk of anaphylaxis to food and insect stings are often prescribed epinephrine autoinjectors (EAI) for self-administration.

National and international regulatory agencies, including the United States Food and Drug Administration (FDA), the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom and the European Medicines Agency (EMA), recommend individuals at risk of anaphylaxis carry at least two EAI at all times.⁵ This is in contrast to guidelines from some specialist societies, which make this recommendation for only selected 'at-risk' patients.⁶⁻⁹ This divergence in advice is potentially problematic for clinicians, who might be faced with medicolegal consequences if they go against official recommendations from regulatory authorities and only prescribe a single EAI device.

There are a number of observational studies which have assessed the frequency of anaphylaxis reactions which fail to adequately respond to a single dose of epinephrine.^{2,6,10-15} However, these data are limited by small sample sizes, differences in local practice in defining and treating anaphylaxis and heterogeneity in study design. As a result, estimates for the rate of allergic reactions treated with more than a single dose of epinephrine range widely, from 0%¹⁶ to 32%.⁶ We therefore undertook a systematic review and meta-analysis to assess the proportion of anaphylaxis reactions reported in the literature treated with at least 2 doses of epinephrine.

Methods

This systematic review was registered at inception with PROSPERO (CRD42017069109) and the study is reported in accordance with PRISMA Statement 2009 and MOOSE recommendations.¹⁷⁻¹⁸

Search Strategy and Eligibility/Inclusion Criteria

We searched MEDLINE, EMBASE and the Cochrane Register of Controlled Trials, including all primary records from 1946 to July 2019 referring to anaphylaxis to food or venom triggers, which included data with respect to the use of epinephrine (see Table S1-3 for search strategies and terms). The search was updated in January 2021 using the same methodology to include those relevant studies published between July 2019 and December 2020. Eligible studies included those reporting more than 10 cases of anaphylaxis (by any definition) in individuals of all ages and in any country; the requirement for at least 10 cases was to minimise selection bias. We included both prospective and retrospective data, including data from food challenges conducted under medical supervision and patient surveys where the categorisation of anaphylaxis was evaluated by a healthcare professional (see online supplement for further details). No language restrictions were made, and we planned to include non-English papers if they met our inclusion criteria. We excluded data relating to adverse events following immunotherapy, as well as datasets which exclusively reported fatal anaphylaxis. Abstracts were independently screened by two researchers, and disagreements resolved by discussion with a third team member. We also reviewed reference lists of included studies and review articles to identify other relevant studies. Where potentially eligible studies did not report the number of epinephrine doses given, authors were contacted to see if these additional data could be provided.

Data Extraction and Additional Data

Data were extracted in duplicate (JB, KWC, NP, AY) and any discrepancies identified were resolved by discussion and consensus with a third reviewer (PJT). Authors were contacted for clarifications, where needed. The screening process was undertaken using Endnote X8. For all studies, we extracted data relating to the proportion of study-defined anaphylaxis treated with more than a single dose of epinephrine, and noted whether the definition used was that published by the National Institutes of Allergy and Infectious Diseases/Food Allergy

and Anaphylaxis Network (NIAID/FAAN).¹⁹ Authors were asked to provide further data to determine the proportion of reactions which involved objective cardiovascular and/or lower respiratory signs (which we termed “cardiorespiratory anaphylaxis”). We also extracted data with respect to the number of epinephrine-treated reactions as the denominator, given that anaphylaxis is frequently not treated with epinephrine and, conversely, some non-anaphylaxis reactions are treated with epinephrine.⁶ We also noted whether epinephrine doses were administered by a healthcare professional in order to facilitate sensitivity analyses. Risk of bias was assessed in duplicate (NP, KWC) using the approach of Hoy et al.²⁰

Data Analysis and Statistical Methods

Meta-analysis of proportions (Meta Package, R project, version 4.0.3) was undertaken using an inverse variance method for summary estimates of logit transformed data, in a random-effects model, with a continuity correction of 0.5 for studies with zero events (Clopper-Pearson for confidence intervals and restricted maximum-likelihood estimator for heterogeneity estimates). Where substantial heterogeneity existed, meta-regression of categorical and continuous variables was performed to assess for potential moderators (e.g. publication year). For meta-analyses where there were at least 10 studies, tests for small study effects were performed using Funnel plots to assess asymmetry and Egger tests (using weighted linear regression of the outcome on its standard error).

We undertook the following pre-specified sub-group analyses: by trigger (community reactions to food, supervised food challenge, venom); patient age (adult, child under 18 years, or both). Sensitivity analyses were undertaken to assess how estimates varied by the use of different anaphylaxis definitions (study defined anaphylaxis, reactions with “cardiorespiratory” signs, or reactions with any use of injected epinephrine); inclusion of studies at low risk of bias only; full-text publications only; publication after 2006 (when the NIAID/FAAN clinical criteria for anaphylaxis were published);¹⁹ studies where subsequent epinephrine doses were given by a healthcare professional (presumably on the basis of a sub-optimal response to the initial epinephrine dose).

Results

Included Studies and Study/Reaction Characteristics

The PRISMA diagram for this systematic review is shown in Figure 1. Eighty-six studies were eligible for inclusion (76 from the original search, and a further 10 when the search was updated in 2021),^{2,3,10-16,22-99} representing 88 datasets (2 studies reported both retrospective and prospective datasets in the same publication)^{14,16} and a total of 36,557 anaphylaxis events. Thirty-five studies reported only food-induced reactions, while one study reported venom-induced reactions only. For the remaining 50 studies, trigger-specific data was available for 23. Risk of bias and individual study characteristics are reported in Table S6 and S15 respectively (online supplement) and summarised in Table 1. Forty-seven of 86 studies (55%) used the NIAID/FAAN criteria for anaphylaxis. Overall, epinephrine was administered in 50.4% of reactions (range 11.1-100% across studies).

Rate of anaphylaxis reactions treated with >1 dose of epinephrine

Overall, at meta-analysis, 7.7% (95% CI 6.4-9.1) of anaphylaxis reactions (all triggers) were treated with more than a single dose of epinephrine (Figure 2). We undertook sensitivity analyses to further refine this pooled estimate by limiting the definition of anaphylaxis to those reactions with objective cardiovascular or lower respiratory symptoms only ("cardiorespiratory" anaphylaxis), and those reactions where epinephrine was administered. These estimates are reported in Table 2 (corresponding forest plots are shown in Figures 2 & 3, and Figures S1-S18 (online supplement)). A slightly higher proportion of reactions (9.8%, 95% CI 7.8-12.2) were treated with >1 dose of epinephrine when considering only "cardiorespiratory" anaphylaxis. We also performed a separate analysis limiting the numerator to include only those reactions where any subsequent doses were given by a healthcare professional (on the basis that such doses would only be given if there was a suboptimal response to the first dose of epinephrine). In this analysis, the pooled estimate of anaphylaxis reactions given further doses of epinephrine by a healthcare professional was 7.0% (95% CI 5.5-8.9%) for food-induced reactions, and 10.0% (95% CI 5.1-18.8%) for venom-induced reactions. For food reactions, the rate of subsequent administration of epinephrine was higher in those reactions due to allergen exposure in the community, compared to anaphylaxis at food challenge performed under medical supervision, but this difference was not statistically significant.

We also undertook sensitivity analyses assessing the impact of study design, risk of bias, publication after 2006 or full-text publications only (see Tables S9-12 online supplement). The only significant difference ($p < 0.001$) identified was for the comparison of prospective versus retrospective studies, when subsequent doses were administered by a healthcare professional (estimated rate of 5.1% (95%CI 2.9-8.9%) of anaphylaxis reactions treated with >1 dose of epinephrine by a healthcare professional for prospective versus 7.9% (95%CI 6.5-9.7%) for retrospective studies (Table S9).

Heterogeneity and moderator assessment

Heterogeneity (as represented by I^2) was moderate-high for all meta-analyses (range: 51.7-99.5%). Assessment of the contribution of potential moderators to the overall heterogeneity for all-trigger and food-trigger datasets were undertaken using pre-specified variables including age group, study design (prospective/retrospective), publication year. No evidence of a moderator effect was noted. We also explored the impact of study size on the pooled estimates. Funnel plots for all meta-analyses are provided in Figure S19 (online supplement). Mild asymmetry was noted for smaller studies with a relative absence of small studies demonstrating higher proportions of multiple epinephrine use. Egger tests for all meta-analyses were performed (Table S8, online supplement); we did not identify any statistical evidence of small-study effects in the various meta-analyses undertaken, with the exception of venom and food-induced reactions irrespective of who administered the second epinephrine dose (when limited to second doses given by a healthcare professional, the small-study effect was not apparent). Risk of bias was low in 56%, 52% and 65% of studies contributing to all-trigger, food-trigger and venom-trigger meta-analyses, respectively.

Administration of 3+ doses of epinephrine

Eleven studies reported the precise number of epinephrine doses administered. Overall, 3+ doses were administered in 2.2% (95% CI 1.1-4.1%) of anaphylaxis reactions, or 3.4% of reactions treated with epinephrine (Table 3).

Discussion

This is the first systematic review in the literature using meta-analysis to evaluate the rate of anaphylaxis reactions treated with more than one dose of epinephrine. We found that approximately 1 in 10 reactions are treated with at least one additional epinephrine dose. This estimate did not significantly change in sensitivity analyses, including limiting data to those reactions where subsequent doses were administered by a healthcare professional (which arguably might reflect a higher degree of confidence in the persistence of anaphylaxis symptoms despite initial treatment with epinephrine). This estimate was robust, despite a high degree of heterogeneity between the included datasets, reflecting differences in cohort characteristics, study design and setting, and anaphylaxis definition used. The majority of the datasets assessed anaphylaxis occurring in the community; it is therefore likely that these data are representative of the broader allergic population.

One potential limitation is that we were unable to distinguish between the administration route or dose of epinephrine given, as these data were not available for most datasets. However, the majority of data included related to initial doses given in the community using EAls. Excluding datasets published prior to 2006 (when the Joint Task Force on Practice Parameters published their recommendation for epinephrine to be administered by the intramuscular route²¹) did not demonstrate any significant impact on the pooled estimates. Furthermore, we did not find that year of publication was a significant moderator in heterogeneity across studies. Several datasets reported biphasic reactions; unfortunately, we were unable to clarify with study authors whether the data provided with respect to epinephrine administration was for the first or delayed phase of these reactions. Thus, we were unable to assess the need for more than one dose of epinephrine to treat late-phase reactions.

A strength of this meta-analysis is the high response rate from authors who were contacted to provide further clarifications. Many authors shared anonymised raw data, which facilitated the analyses. However, meta-analyses were undertaken using aggregate data from individual studies rather than individual patient data (IPD); while this allowed for the inclusion of a greater number of studies, we were unable to further assess potential risk factors for the use of multiple epinephrine doses which would have been possible with an

IPD meta-analysis. Given the inconsistencies in reported risk factors for multiple epinephrine usage,^{10,11,13-15,22-24} an IPD-meta-analysis would help address this evidence gap.

Recommendations vary with respect to the number of EAls that patients at risk of anaphylaxis should be prescribed – both between countries, but also within a single country, where guidelines from specialist societies may contradict official government advice.⁵⁻⁹ Many anaphylaxis reactions resolve spontaneously without treatment,^{2,78} and in this analysis, we found that only 50.4% of anaphylaxis reactions were treated with *any* epinephrine, a rate consistent with the literature. It is clearly inappropriate to *not* treat anaphylaxis with epinephrine, which is rightly the universal recommendation in all international guidelines. A single dose of epinephrine may be insufficient to terminate a reaction for multiple reasons: reaction progression; underdosing (international guidelines recommend teenagers and adults receive 0.5mg epinephrine, but for most EAI devices, the highest dose available is 0.3mg epinephrine); incorrect administration; subcutaneous administration which is associated with a prolonged onset of action; delayed administration; biphasic course of reaction. Our analysis, based on over 25,000 anaphylaxis events, provides an important estimate of the frequency of multiple epinephrine doses given to treat anaphylaxis. Whether patients could be risk-stratified to assess the need for repeat doses of epinephrine requires further analysis, as discussed in a recent publication by Shaker et al.¹⁰⁰

Conclusions

Around 10% of patients receiving epinephrine for anaphylaxis have a suboptimal response to a single dose of epinephrine, as assessed by a healthcare professional. These data are important in informing guidance on the provision of EAI for patients at risk of anaphylaxis in the community.

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594 **TABLES**

	Any trigger	Food only	Venom only
<i>Datasets available for Meta-analysis</i>			
Number of studies included	86	58	20
Number of available datasets	88	60	20
Data reports accidental reactions in the community	66	38	20
<i>Study Design</i>			
• Prospective	20/88	18/60	6/20
• Retrospective	66/88	42/60	14/20
• Both	2/88	0/60	0/20
<i>Continent of Study</i>			
• Europe	27	21	8
• USA/Canada	38	24	8
• Australia	12	8	3
• Asia	11	7	1
<i>Patient Characteristics</i>			
• Children <18 years only	51	37	6
• Adults only	3	2	0
• Includes children and adults	34	21	14
<i>Risk of Bias</i>			
• Low	50	31	13
• Moderate	36	27	7
• High	2	2	0

Table 1: Summary of included studies

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%reactions treated with >1 dose epinephrine	Trigger					
	ALL		FOOD			VENOM
	Any Setting N=36,557	Community N=34,121	Any Setting N=12,615	Community N=10,179	Food Challenge N=2,436	Any Setting N=3,194
A) Study-defined anaphylaxis	7.7% (6.4-9.1%)	7.9% (6.5-9.7%)	7.3% (5.8-9.1%)	7.7% (6.5-10.0%)	6.5% (4.2-9.8%)	10.5% (6.2-17.1%)
B) "Cardiorespiratory" anaphylaxis	9.8% (7.8-12.2%)	9.6% (7.6-12.1%)	9.7% (7.0-13.4%)	9.1% (6.2-13.1%)	10.8% (6.0-18.8%)	11.1% (4.3-26.0%)
C) Reaction treated with at least one dose of epinephrine	12.9% (11.2-14.9%)	13.5% (11.5-15.9%)	11.7% (9.9-13.9%)	12.3% (9.9-15.2%)	10.6% (7.9-14.1%)	17.9% (13.2-24.0%)
D) Reaction where further epinephrine administered by a healthcare professional	7.1% (5.8-8.7%)	7.2% (5.7-9.0%)	7.0% (5.5-8.9%)	7.1% (5.3-9.5%)	6.8% (4.4-10.4%)	10.0% (5.1-18.8%)
E) Epinephrine-treated reaction where with further epinephrine administered by a healthcare professional	12.2% (10.4-14.3%)	12.8% (10.6-15.4%)	11.1% (9.4-13.2%)	11.4% (9.1-14.0%)	10.8% (8.0-14.4%)	17.1% (11.3-25.0%)

598 **Table 2:** Summary of pooled estimates for all meta-analyses undertaken, by definition of
599 anaphylaxis used. Further subgrouping of meta-analyses by reaction trigger (any trigger,
600 food, venom) and setting (community reactions, food challenges under medical supervision,
601 or 'any setting') are listed. Data are presented as percentage pooled estimate (95% CI).

602

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Reference	% food trigger	(i) Proportion of anaphylaxis reactions treated with epinephrine				(ii) Proportion of epinephrine-treated reactions given multiple doses of epinephrine		
		1 dose (%)	2 doses (%)	3 doses (%)	≥4 doses (%)	2 doses (%)	3 doses (%)	≥4doses (%)
Jarvinen et al, 2008	100%	77/95 81%	12/95 13%	6/95 6.3%	0/95 0%	12/95 13%	6/95 6.3%	0/95 0%
Manivannan et al, 2009	33%	77/208 37%	25/208 12%	2/208 1.0%	0/208 0%	25/104 24%	2/104 1.9%	0/104 0%
Noimark et al, 2012	91%	28/245 11%	12/245 4.9%	1/245 0.4%	0/245 0%	12/41 29%	1/41 2.4%	0/41 0%
Brown et al, 2013	36%	130/315 54%	59/315 19%	39/315 12%	17/315 5.4%	59/245 24%	39/245 16%	17/245 6.9%
Campbell et al, 2015	36%	281/582 48%	36/582 6.2%	6/582 1.0%	3/582 0.5%	36/326 11%	6/326 1.8%	3/326 0.9%
Nogic et al, 2016	75%	38/52 73%	10/52 19%	1/52 1.9%	0/52 0%	10/49 20%	1/49 2.0%	0/49 0%
Yanagida et al, 2017	100%	70/190 37%	18/190 9.5%	2/190 1.1%	0/190 0%	18/90 20%	2/90 2.2%	0/90 0
Tsuang et al, 2018	100%	197/221 89%	19/221 8.6%	4/221 1.8%	1/221 0.5%	19/221 8.6%	4/221 1.8%	1/221 0.5%
Anvari S et al, 2019	48%	218/275 79%	20/275 7.3%	5/275* 1.8%	-	20/243 8.2%	5/243* 2.1%	-
Gabrielli et al, 2019	79%	2276/3498 65%	234/3498 6.7%	36/3498 1.0%	12/3498 0.3%	234/2558 9.1	36/2558 1.4	12/2558 0.5
Liu et al, 2019	38%	255/430 59%	34/430 7.9%	16/430* 3.7%	-	34/305 11%	16/305* 5.2%	-
Pooled estimate at meta-analysis (95% CI)		57% (41-72%)	9.2% (7.2-12%)	2.2% (1.1-4.1%)		14% (11-19%)	3.4% (1.9-5.9%)	
				1.9% (1.0-3.5%)	0.3% (0.1-1.3%)		2.9% (1.7-5.0%)	0.5% (0.1-1.9%)

604 *Data available only for 3 or more doses.

605

606 **Table 3:** Total number of epinephrine doses given to individual patients receiving multiple
607 doses of epinephrine. These data were available in 11 studies. The pooled estimate for each
608 dosing bracket is provided as a percentage of either the total number of (i) study defined
609 anaphylaxis reactions or (ii) epinephrine-treated reactions (95% CI).

610

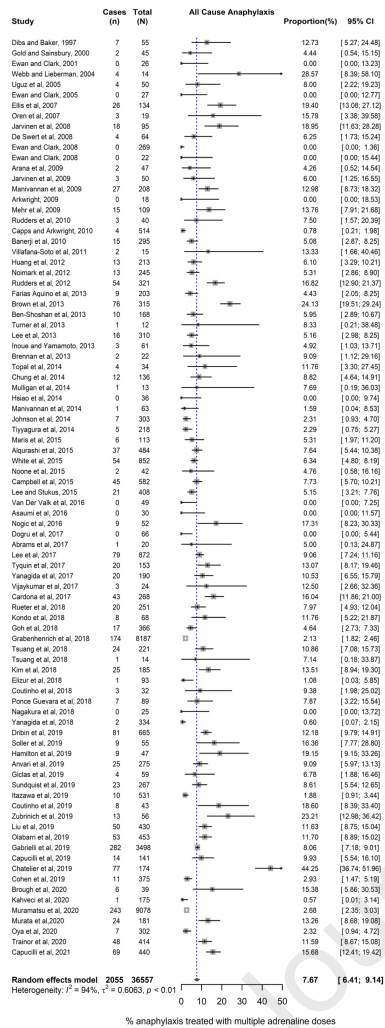
FIGURE LEGENDS

Figure 1: PRISMA Flow Diagram.

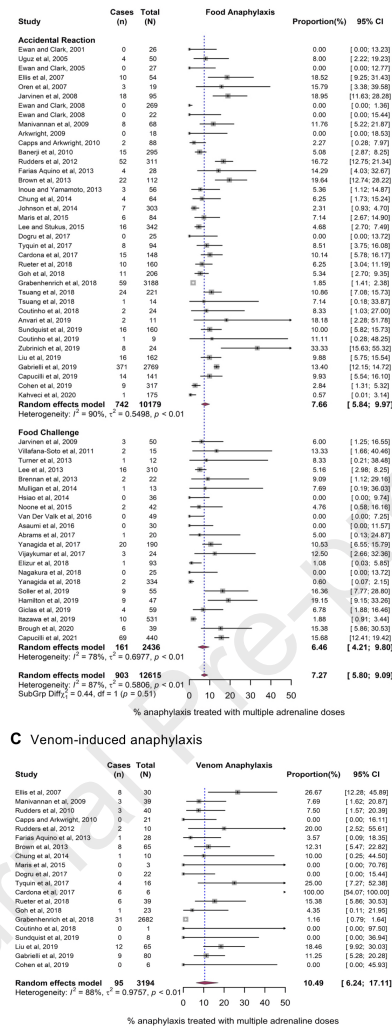
Figure 2: Forest plots for the use of 2 (or more) doses of epinephrine to treat allergic reactions. **A**, all triggers; **B**, food-induced reactions; **C**, venom-induced reactions.

Figure 3: Forest plots for the use of 2 (or more) doses of epinephrine to treat food-related anaphylaxis occurring in the community due to accidental exposure. Study-defined anaphylaxis (**A**) and epinephrine-treated reactions only (**B**), irrespective of who administered the 2nd (and subsequent) dose of epinephrine; study-defined anaphylaxis (**C**) and epinephrine-treated reactions only (**D**), where a subsequent dose of epinephrine was administered by a healthcare professional (HCP).

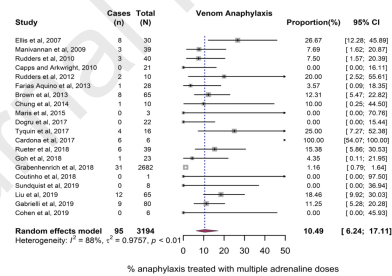
A Anaphylaxis reactions, all triggers



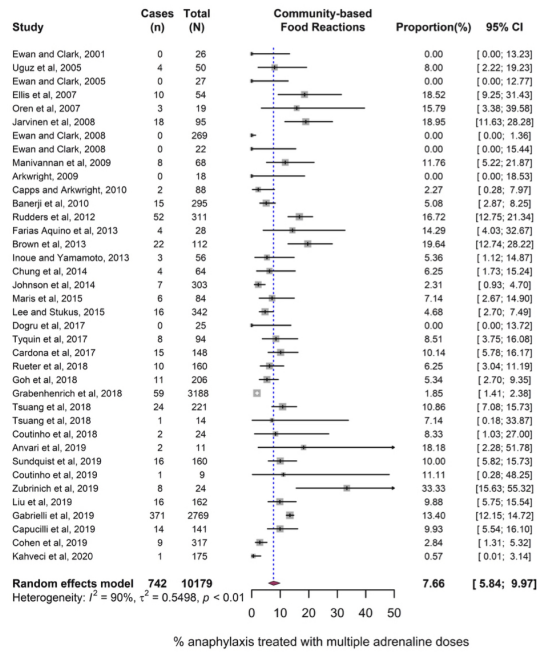
B Food-induced anaphylaxis



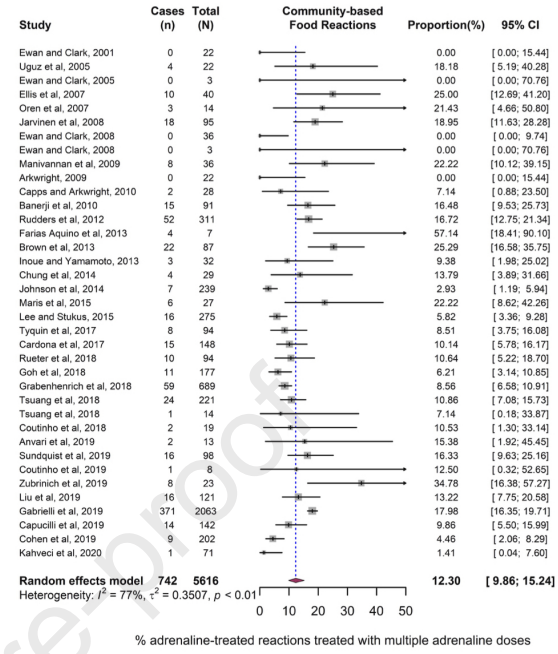
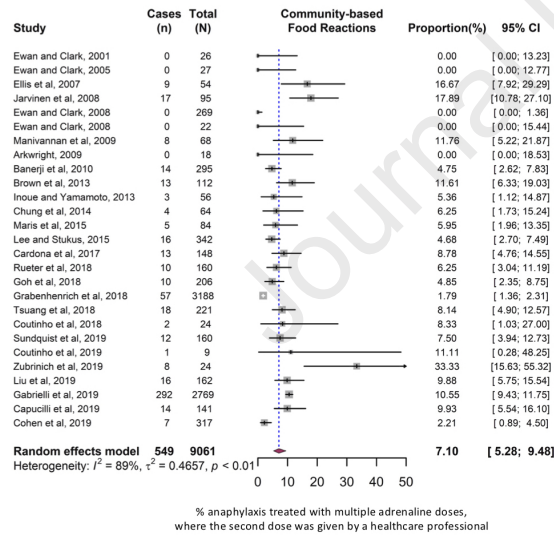
C Venom-induced anaphylaxis



A Study-defined food-anaphylaxis



B Food-anaphylaxis, treated with adrenaline

C Study-defined food-anaphylaxis, 2nd dose given by HCPD Food-anaphylaxis, treated with adrenaline, 2nd dose by HCP