Appendix E Evidence tables

Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?

Table 1

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
Brown et al (2004)	Cross-sectional (prospective) Diagnostic test accuracy study as part of a RCT to evaluate the effect	64	17% (11/64) had severe systemic allergic reactions to sting challenge	Participants with a history of anaphylactic reactions to the jack jumper ant (*Myrmecia pilosula*) who had an anaphylactic reaction to a sting challenge (see 'definition	Serum mast tryptase (UniCAP Tryptase) measured at baseline (prior to the sting challenge) then 15 min and 60 min after the challenge. Manufactu	Clinical diagnosis of anaphylaxis (severe systemic reaction involving respiratory or CV compromise [dyspnoea, wheeze, stridor, O_2 saturations <92%, or SPB<90mm Hg])	Cut-off: peak tryptase 12.0µg/l (manufacturer's level) sens: 36% (11% to 69%) spec: 89% (77% to 96%) Cut-off: peak tryptase 9.0µg/l (derived from the	(calculated by analyst) Cut-off: peak tryptase 12.0µg/l (manufacturer's level) PPV 40% (12% to 74%) NPV 87% (75% to 95%)	Information on timing was only reported in chart form and it was difficult to extract data from this chart.	Royal Hobart Research Foundation Dick Buttfield Memorial Scholarship NSL	Patients in this study present with anaphylaxis after a sting challenge; it is possible that patients presenting with experimentally induced anaphylactic reactions are different from those presenting with anaphylaxis naturally. It is not clear if this difference is likely to affect the measurement of MCT. Patients with mild reactions were excluded.

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
	of venom immunotherapy (using a sting challenge)			of anaphylaxis in 'reference standard' column). Age and gender not reported.	rer's normal range<12 µg/l; detection limit 1.0µg/l		ROC curve) sens: 55% (23% to 83%) spec: 87% (75% to 95%) Cut-off: delta tryptase 2.0µg/l (change from baseline) sens: 73% (35% to 93%) spec: 91% (79% to 97%)	Cut-off: peak tryptase 9.0µg/l (derived from the ROC curve) PPV 46% (19% to 75%) NPV 90% (79% to 97%) Cut-off: delta tryptase 2.0µg/l (change from baseline) PPV 62% (32% to 86%)		Health Ltd Cosy Cabins Tasmania	Histamine levels were not reported in this study.

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
								NPV 94% (84% to 99%)			
Enrique et al (1999)	Cross-sectional (probably prospective) Aim to assess usefulness of UniCAP Tryptase to identify episodes of anaph	30	57%	Patients presenting at emergency room within clinical symptoms of allergic reaction of less than 6 h duration. Of 17 with anaphylaxis: mean age 41 y (range: 18 to 79), 53% female. Causes	UniCAP Tryptase which permits measurement of active and inactive forms of both α and β tryptase (serum samples taken and stored at -20°C) Serum levels ≥ 13.50 ng/ml were	Clinical data taken within 2 weeks (including detailed clinical history, measurement of complement proteins and activity antinuclear antibodies, skin tests to aeroallergen foods and drugs) 'Anaphylaxis' if sudden onset of symptoms	With 13.50 ng/ml threshold: sens: 35.29% (CI 15.73 – 59.51%) spec: 92.31% (CI 67.52 – 99.62%) With 8.23 ng/ml threshold (ROC cut-off level): sens: 94.12% (CI 74.25 – 99.71%)	(calculated by analyst) With 13.50 ng/ml threshold: PPV: 86% (95% CI 42 – 100%) NPV: 52% (95% CI 31 – 73%) With 8.23 ng/ml threshold (ROC cut-off level): PPV: 93% (95% CI 66 –	Study reported that there was no relationship between the time elapsed from the beginning of the reaction to the time of sampling and serum tryptase levels (but exact	Not reported	Serum samples taken when patients arrived at hospital but exact timing after onset of symptoms not clear. If it was taken at an inappropriate time, this could explain the low sensitivity of the test. Serum samples stored at -20°C before the index test was performed. Timing between index test and reference standard was not clear and results from one may have had an effect on the interpretation of the other giving an

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
	ylaxis			were idiopathic (4), walnut (2), dipirone (2), immunotherapy (2), and snail, atriacurium, tomato, honey, fish, amoxicillin, cefuroxime (1 each). Of the 13 with no anaphylaxis: mean age 34 y (range: 7 to 85), 46%	considered positive	AND 2 or more of areas involved: - bronchial tree - oropharynx - subcutaneous tissue/skin - GI tract - CV system	spec: 92.31% (CI 67.52 – 99.62%)	100%) NPV: 75% (95% CI 48 – 93%)	timing of sampling after reaction was not reported so it was not clear how the authors came to this conclusion).		overestimation of the accuracy of the test (incorporation or review bias). Only 21 had second blood test 1-2 months later to determine baseline tryptase level. Ratio of reaction to baseline serum tryptase was 2.85 in the 17 with anaphylaxis and 1.29 in those without anaphylaxis. This study only includes one paediatric patient (aged 7) who was one of the 13 patients without anaphylaxis.

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
				female. Causes were idiopathic (6), scombroidosis (2), dipirone (1), chronic urticaria (1), sulphites (1), anxiety (1), and unknown (1)							
Malinovsky et al (2008)	Cross-sectional (prospective) Aim to evalua	31	71%	Patients with suspected hypersensitivity reaction to anaesthetics (29	Tryptase measurements from radioimmunoassays (RIA, Immunotech,	Hypersensitivity reaction diagnosed based on clinical history, mediator	(confidence intervals calculated by analyst) With 12 µg/l threshold: sens: 63.6% (95%	(confidence intervals calculated by analyst) With 12 µg/l threshold:	Of the ratio between T_0 to T_{24h}: sensitivity: 63% specificit	Not reported	Unclear if the definition of hypersensitivity reaction in the study was anaphylaxis. Patients with just urticaria and/or angioedema alone

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
	te incidence of hypersensitivity reactions during anaesthesia by using histamine and tryptase measurements and allergological investigations to			general, 2 regional) at University Hospital Nantes from May 2001 to April 2003 (hypersensitivity reaction determined if presented with cutaneous symptoms *i.e. urticaria and//or angioedema) isolated or in associatio	Beckman-Coulter, Marseille) 30 min when not life threatening and between 30 and 60 min when life threatening Serum levels > 11 nmol/l were considered positive; thresholds of both 12 and 25 µg/l were	concentration in blood and skin tests (both prick and intradermal tests performed 4 weeks later)	CI 40.7 – 82.8%) spec: 100% (when calculated by analyst specificity was 88.9% with 95% CI 51.8 – 99.7%) With 25 µg/l threshold: sens: 40.9% (95% CI 20.7 – 63.6%) spec: 100% (95% CI 66.4 – 100%)	PPV: 100% NPV: 53% (when calculated by analyst these values were PPV: 93.3% [95% CI 68.1 – 99.8%] NPV: 50% [95% CI 24.7 – 75.3%] With 25 µg/l threshold: PPV: 100% (95% CI 66.4 – 100%)	y: 83% PPV: 92% NPV: 42%		were included and these patients are not likely to be considered to have anaphylaxis. 8 patients excluded from analysis because they did not undergo skin prick tests Tryptase (and histamine) tests formed part of the reference standard leading to possible incorporation bias (which could lead to inflated agreement between index and reference tests and an inflated measure of diagnostic accuracy).

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
	investigate suspected or unexplained reactions			n with other clinical symptoms like bronchospasm, hypotension, or cardiovascular collapse or if circulatory inefficacy in close relation with anaesthetic drug injection in absence of other explanation	tested			NPV: 41% (95% CI 20.7 – 63.6%)			

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
				Patients with IgE-mediated hypersensitivity reactions: Median age: 43 y (range: 8-80) 45% (10/22) male, 55% (12/22) female Patients without IgE-mediated hypersensitivity reactions: Median age: 45 y (range:							

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
				19-78) 56% (5/9) male, 44% (4/9) female							
Mertes et al (2003)	Cross-sectional (retrospective) Aim to survey of allergic and non immunity-mediated reaction during anaest	789 with adverse reaction during anaesthesia in France between Jan 1999 and Decemb	68% (of the 259 tested for tryptase)	Of the 518 diagnosed with anaphylaxis, 70% were female and in those 15.5% had atopy, 10.7% asthma, 18.1% drug intolerance. Of the 271 with anaphylactoid	UniCAP Tryptase (serum samples taken and test performed 'during adverse reaction' in 259 patients only) Serum levels ≥ 25 µg/l were considere	Anaphylaxis (immune-mediated reaction) diagnosed with clinical history, skin tests (prick and intradermal), and / or IgE assay results	(confidence intervals calculated by analyst) With 25 µg/l threshold: sens: 64% (95% CI 56.4 – 71.1%) spec: 89.3% (95% CI 80.6 – 95.0%)	(confidence intervals calculated by analyst) With 25 µg/l threshold: PPV: 92.6% (95% CI 86.3 – 96.5%) NPV: 54.3% (95% CI 45.7 – 62.8%)	Not reported	From institutional and/or departmental sources (not specified)	Retrospective nature of study may preclude ability to blind assessors to results of index test when performing reference standard. Also, timing of reference standard was not clear. Serum samples taken 'during reaction' but exact timing after onset of symptoms not clear. The timing of the test could have an impact on its sensitivity. Authors include only 32.8% (259/789) of patients in whom

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
	hesia, description of clinical characteristics, and identification of possible factors and responsible drugs	er 2000		reaction, 66% were female, 12.7% had atopy, 9.8% had asthma and 19.8% drug intolerance. There was no difference in atopy, asthma and drug intolerance except in anaphylaxis group Age not reported.	d positive						tryptase concentrations were determined at the time of the reaction. Details of other patients and reasons why tryptase tests were not performed at the time of reaction not reported; this may lead to selection bias. The accuracy of histamine was also reported.
Abbreviations: CI, confidence interval; h, hour; IgE, immunoglobulin E; MCT, mast cell tryptase; min, minutes; NPV, negative predictive value;											

Evidence Table 1 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	**Study type and objective**	**# of patients**	**Prevalence**	**Patient characteristics**	**Type of test**	**Reference standard**	**Sensitivity & specificity**	**Positive & negative predictive value**	**Timing**	**Source of funding**	**Additional comments**
PPV, positive predictive value; RIA, radioimmunoassay; sens, sensitivity; spec, specificity; SD, standard deviation; $t_{1/2}$, half-life; y, years											

Table 2

Studies included for information on timing only:

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
Kanthawatana et al (1999)	Case series Aim to retrospectively analyse the clinical value of an elevated level of α-protryptase (≥20 ng/mL) with normal or slightly elevated (≤5 ng/mL) level of β-tryptase	19	Samples received in a diagnostic immunology laboratory over a 3.5-y period from patients with suspected anaphylaxis that had elevated total tryptase levels (≥20 ng/mL) and normal β-tryptase levels (< 1 ng/mL) or modestly elevated (≤ 5 ng/mL) Mean age 39 y (range: 19 to 55), 52.6%	B12 mAb used to measure total tryptase and biotinylated G4 and G3 mAbs used,; β-tryptase also measured to calculate a ratio of total to β-tryptase (ELISA)	Timing of sample collection after onset of signs and symptoms was from 20 min to 12 h. The study reported that there is not apparent correlation between timing of blood collection and either total tryptase values, β-tryptase values or total tryptase/β-tryptase ratios.	Partly supported by National Institutes for Health grant	There were 30 cases of suspected anaphylaxis but 11 of these had died (and specimens were post-mortem). The results from these deceased patients has not been reported here. The study also analysed 22 patients with suspected mastocytosis to look at tryptase values to help diagnose mastocytosis.

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
			(10/19) male.				
Laroche et al (1991)	Case control Aim to determine if tryptase is a consistent and reliable marker for anaphylaxis	19 cases, 19 controls	Patients with adverse reaction to drugs compared with 35 anaesthetised patients. Of those with the drug reactions, - 12 occurred immediately after induction with anaesthesia [all but one with muscle relaxant] - 4 appeared unrelated to the anaesthetic drug injection [2 after gelatine infusion, 1 after Peruvian balsam, 1 after 1 h],	MCT measured by plasma or serum by immunoradiometric assay (Tryptase RIACT kit, Pharmacia, Uppsala, Sweden; lower limit of detection is 0.5 U/l).	In 3 cases, the half life was 90 min and in one it was 5 h. In one patient with a reaction to injection of tetanus vaccine, tryptase levels were higher 2 h after the reaction than 1 h before.	Tryptase kits were supplied by the manufacturer	There was also a comparator group of non-anaesthetised controls but they have not been included here because they did not have exposure to anaesthetics. Not clear if patients had anaphylaxis.

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
			- 3 were not related to anaesthetics but occurred immediately after a single drug injection (penicillin, tetanus vaccine and contrast medium) Cases: mean 55.1 y (range: 24 to 81; SD 14.6) Controls: mean 51 y (range: 18 to 79; SD 17) Gender not reported.				
Laroche et al (1992b)	Case series Aim to compare the diagnostic	33	Patients referred following adverse reactions to drugs, mostly general	MCT measured with immunoradiometric assay (tryptase RIACT kit,	Tryptase was high in 15 and normal in 18. In all subjects with elevated levels of tryptase, this persisted 2 h after reaction but usually disappeared by 24 h except in one patient who	Pharmacia France supplied tryptase kits	Not clear if patients had anaphylaxis.

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
	value of plasma histamine and mast cell tryptase *in vivo* histamine-release during anaphylactoid reactions.		anaesthesia with cutaneous, cardiovascular or bronchopulmonary clinical signs (associated or not) Age and gender not reported.	Pharmacia, Uppsala, Sweden) Values > 2 µg/l appears to have been considered elevated	deceased after being in a prolonged coma. Tryptase half-life, measured in 3 patients, was 90 min.		

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
Laroche (1998)	Case-control Aim to investigate mechanisms of immediate reactions	20 (and 20 controls)	Participants if experienced allergic-type reactions (immediate anaphylactoid reactions) after the administration of contract media 20 (15 male; 5 female) Mean age 51 yrs (range: 17 to 79; SD 17)	Serum mast tryptase (Tryptase RIACT) Levels considered elevated if ≥3 µg/l Samples taken as soon as possible after the reaction or when resuscitation had been started; then at 30 min, 2 and 24 h.	Values of tryptase remained at pathologic levels (not defined) for 2, 3, or 4 h depending on severity grade of the reaction (no details). All patients had normal concentrations the day after the reaction.	None acknowledged	The definition of anaphylactoid reactions was not clear. Since the patients in this study had reactions after the injection of contrast media, it is not clear how applicable these test results of MCT timing are to an unselected population presenting with suspected anaphylaxis
Ordoqui et al (1997)	Case series Aim to find a tool for	64 to clinic of which 27 were confirme	Patients with adverse drug reactions (including cutaneous or	Tryptase levels measured with radioimmuno	Peak value of serum tryptase was in the first 30 min in 2 cases of anaphylactic shock from oral erythromycin and oral cotrimoxazole (post-reaction maximum level 53 U/l	Not reported	Study reports that blood was taken 2 h after onset of symptoms but

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
	the diagnosis of drug allergy	d to have drug allergy: - 7 with anaphylactic shock (cutaneous, digestive and/or respiratory symptoms with hypotension with or without consciousness) - 13 anaphylactic reactions (similar as above	systemic symptoms) presenting at the allergology section and from the emergency unit at one hospital. Age and gender not reported.	assay (Tryptase RIACT™ Pharmacia, Uppsala, Sweden) taken from blood obtained 2 h after onset of symptoms and 7 days later (in the 7 with anaphylactic shock or anaphylaxis, sera was separated and stored at -20°C for later use) Not clear what level was considered elevated.	and 4.09 U/l) and in 2 cases of anaphylaxis caused by intravenous fluorescein and oral dipirone (post-reaction maximum 66.2 U/l and 9.05 U/l). The highest level was detected after 2 h in a patient who developed anaphylactic shock with oral amoxicillin (5.87 U/l). Tryptase peaked 3-4 h after onset of symptoms in anaphylactic shock induced by oral amoxicillin (27.54-27.38 U/l) and at 6 h in another anaphylactic shock caused from oral amoxicillin (20.7 U/l). Serum tryptase decreased to baseline by 24 h in all patients. Timing of occurrence of serum tryptase was said not to be related to the severity of symptoms or the amount of protease released.		then the peak value of serum tryptase was reported to have been in the first 30 min. It is not clear how this is possible. Includes patients who have symptoms that do not appear to be anaphylaxis.

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
		but normal arterial pressure) - 17 with urticaria-angioedema					
Schwartz et al (1987)	Case series Aim to describe use of particular assay to detect mast-cell involvement (both active and inactive tryptase) in patients with anaphylactic events	6	Patients with presenting with clinical evidence of anaphylaxis from penicillin, aspirin, melon ingestion, wasp sting, exercise (later found to be allergic to mountain cedar pollen or horse antilymphocyte globulin (to suppress rejection of kidney transplant).	Tryptase measured with sandwich ELISA from serum samples taken retrospectively from serum samples collected at the time of admission (and stored at stored at -20°C) or at the time of	In four patients in who follow-up was obtained, the time course of the disappearance of tryptase was analysed. In 3 patients with reactions from penicillin, wasp venom and exercise, tryptase levels had decreased to under 5 ng/ml in samples obtained after 24 h. In one patient with acute systemic anaphylaxis after eating honeydew melon, tryptase had decreased from 39 to 18 ng/ml after 6 h (exact timing of initial test not reported).	Supported by grant from National Institutes of Health	Study included measurements of tryptase in patients with myocardial disease (n = 9), sepsis (n = 6, 3 with shock), systemic mastocytosis (n = 17) and 16 hospital controls

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
	or systemic mastocytosis		Age and gender not reported.	admission Levels from 9 to 75 ng/ml were considered elevated			
Schwartz et al (1989)	Case series (laboratory examination of stability of tests) Aim to analyse the levels of tryptase in circulation over time and to investigate the stability of serum	5	A: After bee sting challenge: 2 presenting with 'profound hypotension associated with pruritis' and 1 with 'pruritis and moderate inspiration and wheezing without a change in BP' All treated with injectable epinephrine with good response. B: 2 more	Serum mast tryptase (sandwich ELISA) Levels considered elevated if ≥10 ng/l, and marginally elevated if 5-10 Samples taken as soon as possible after the reaction and up to 19 h post reaction	A: Histamine levels increased over baseline, reached a peak by 5-10 min after challenge, and declined to approx baseline by 30-40 min. Respective levels in two of these patients were not detectably elevated until 15 and 30 min after the challenge, reached a maximum at 1 and 2 h, and then declined with a $t_{1/2}$ of 1.5 and 2 h. In each case the clinical condition returned to normal at the time of the peak level of tryptase. The third patient had a biphasic pattern with an initial peak at 15 min and a second peak at 2 h; tryptase levels then declined with a $t_{1/2}$ of 1.5 h.	National Institutes of Health grant Virginia Center for Innovative Technology Pharmacia	Not clear if all cases were true anaphylaxis. It is possible that the three patients presenting with experimentally induced anaphylactic reactions (from bee sting challenge) are different from those presenting with anaphylaxis naturally. It is not clear if this

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
	samples		presented with 'systematic anaphylaxis' (one 60-90 min after bee sting another rafter indomethacin ingestion)		B: One patient (with bee sting) had an initial tryptase level that was markedly elevated upon admission (60-90 min after bee sting) and declined with a $t_{1/2}$ of 2 h. The other showed initial tryptase levels that were clearly elevated and declined with at $t_{1/2}$ of 1.5 h.		difference is likely to affect the measurement of MCT or the timing of its presence.

<table>
<tr><th colspan="8">Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?</th></tr>
<tr><th>Bibliographic reference</th><th>Study type and objective</th><th># of patients</th><th>Patient characteristics</th><th>Type of test</th><th>Timing</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Schwartz et al (1994)</td>
<td>Case control

Aim to describe the production of a new monoclonal antitryptase antibody and its use as a capture antibody in an immunoassay capable of detecting tryptase in normal serum and plasma</td>
<td>9 with history of severe reaction, 20 with history of mild reaction</td>
<td>Patients given a sting challenge divided into 4 groups:
1) normal controls with no history of anaphylactic reaction;
and patients with a history of venom hypersensitivity
2) with no reaction
3) mild to moderate reactions (skin, gastrointestinal or airway)
4) severe reactions (at least 15 mmHg fall in arterial pressure)

(only those in</td>
<td>Samples from a previously reported study which conducted insect sting-induced anaphylaxis were re-assayed with the new tryptase immunoassay (ELISA) up to 75 min after the sting challenge in the first 2 groups with no history of a reaction to venom and up to 60 min after the onset of</td>
<td>Samples taken at different time periods to give the time course for tryptase release was only available in a 9 of the 17 patients with a history of severe reactions to venom (reported as ‘hypotensive’) and 20 of the 22 patients with a history of mild reactions to tryptase. These samples were collected at baseline and 1, 5, 15 and 60 min after onset of symptoms.

Peak tryptase levels after onset of symptoms after venom challenge:
<table>
<tr><th>Time period</th><th>Patients with severe reaction</th><th>Patients with mild reaction</th></tr>
<tr><td>1 min</td><td>1</td><td>2</td></tr>
<tr><td>5 min</td><td>1</td><td>5</td></tr>
<tr><td>15 min</td><td>4</td><td>4</td></tr>
<tr><td>60 min</td><td>3</td><td>5</td></tr>
<tr><td>Total</td><td>9</td><td>20</td></tr>
</table>
</td>
<td>Supported by grant from National Institutes of Health</td>
<td>The study also reported that baseline tryptase levels were higher in those with a more severe reaction.

Patients in this study present with anaphylaxis after a sting challenge; it is possible that patients presenting with experimentally induced anaphylactic reactions are different from those presenting with anaphylaxis naturally. It is</td>
</tr>
</table>

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
			the later two groups are included in this table) Age and gender not reported.	symptoms in those in the two groups with a history of a reaction to venom (1 to 40 min after sting).	In both groups, elevations above baseline levels were usually detected 1 to 5 min after onset of symptoms (despite the peak usually appearing later). The authors concluded that the maximal level of tryptase occurs from 15 to 60 min after the onset of symptoms. Tryptase levels increased at least two-fold from baseline to the 60-min time point after the challenge in 10/22 patients with a mild reaction and 16/17patients with severe reactions (referred to as 'hypotensive subjects') with levels from baseline to 60 min significantly higher in both groups ($p = 0.005$ and $p = 0.0003$). No patients in the first two groups had a twofold increase and the tryptase levels from baseline to 60 min were not significant.		not clear if this difference is likely to affect the measurement of MCT or the timing of its presence.
Stone et al (2009)	Case series Aim to identify	36 (severe), 40 (moderate)	Patients presenting to emergency departments with acute-onset	MCT concentrations analysed with Phadia ImmunoCAP	Peak levels appeared both at time of enrolment (T_0), or approximately 1 h after enrolment (T_1, target time, or from 40 to 80 min), and occasionally before discharge from the	Supported by grants from Food Allergy and	Reactions were considered 'moderate' if they had features

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
	cytokines and chemokines whose concentrations increase during anaphylaxis and see how they correlate with severity		illness with typical skin features (hives, pruritus or flushing, swollen lips and/or tongue), with or without involvement or other organ systems or any acute onset of hypotension or bronchospasm where anaphylaxis was possible even if no skin features OR reactions occurring in response to treatment in the emergency department for other conditions. Median age 36	system Median time from enrolment to first sample was 60 min and to last sample was 288 min A deviation from 2.0 µg/L (ng/mL) between high and low values for each case was considered 'positive' (so that those with baseline MCT levels above normal and that do not change	emergency department (T_2). [see Lowess best fit curve after table to show relationship between interval from reaction onset and tryptase concentration]	Anaphylaxis network and 2 hospital research foundations.	suggesting respiratory, cardiovascular or gastrointestinal involvement. They were considered 'severe' if hypoxemia, hypotension or neurologic compromise was present.

Evidence Table 2 for Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	**Study type and objective**	**# of patients**	**Patient characteristics**	**Type of test**	**Timing**	**Source of funding**	**Additional comments**
			y (range 9 to 99)	during event are considered negative)			
Abbreviations: ELISA, enzyme-linked immunosorbent assay; h, hour; MCT, mast cell tryptase; min, minutes; SD, standard deviation; $t_{1/2}$, half-life; y, years							

Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Table 3

<table>
<tr><td colspan="11">Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?</td></tr>
<tr><th>Bibliographic reference</th><th>Study type and objective</th><th>n</th><th>Patient characteristics</th><th>Definitions</th><th>Characteristics of initial reaction</th><th>Anaphylaxis treatment protocol and observation</th><th>Rate of biphasic reactions</th><th>Timing of biphasic reaction and characteristics</th><th>Comparison of patients with biphasic to those with uniphasic reactions</th><th>Funding source</th><th>Additional comments</th></tr>
<tr>
<td>Brady (1996)

USA</td>
<td>Retrospective case series

Purpose to determine the rate of clinical significant recurrence of symptoms in patients treated for</td>
<td>67 cases of anaphylaxis (5.3% of 1261 allergic reactions</td>
<td>Patients with anaphylaxis out-of-hospital, ED, hospital records over a 4.5 year period (1991–5).

Identified from ICD-9 codes for allergic reaction, anaphylaxis and related phenomena.

Mean age: 30.2 years

Gender:</td>
<td>Anaphylaxis–immediate, life-threatening, multi-system allergic reaction, representing a true medical emergency.

Those with allergic reactions were</td>
<td>Causes (of the 70% with identified causes):
<table><tr><th></th><th>% of patie</th></tr><tr><td>Food</td><td>40 %</td></tr><tr><td>Animal or insect venom*</td><td>35 %</td></tr><tr><td>Medication</td><td>18 %</td></tr><tr><td>Other</td><td>7%</td></tr></table>*both with biphasic reactions had</td>
<td>Treatment protocol and observation period not described.

However, the 14 patients with uniphasic reactions which who were</td>
<td>3% (2/67) presented with urticaria and were subsequently seen again at the ED</td>
<td>26 hours (22-year old female) and 40 hours (19-year old male) after initial ED visit.

Both were treated with subcutaneous epinephrine, IV steroid and IV antihistamine.

Both were</td>
<td>No comparison made.</td>
<td>Not reported</td>
<td>Not clear how long all patients who were not admitted and did not have biphasic reactions were followed-up. Records were taken from surrounding</td>
</tr>
</table>

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
	anaphylaxis in the emergency department (ED)	and 0.5% of total ED census)	51% (34) male 49% (33) female	considered to have anaphylaxis if they experienced a multi-system reaction involving ≥ 2 of the following organ systems: skin (urticaria and angioedema), cardiovascular system (distributive shock),	anaphylaxis from Hymenoptera envenomation Treatments received: Antihistamine (H-1, IV) 79% Antihistamine (H-2, IV) 57% Steroid (IV) 69% Steroid (PO) 16% Epinephrine (SQ 63% β- 25%	admitted were observed for mean 63 hours. Both patients with biphasic reactions were observed for 4-7 hours.		observed for 4-7 hours after symptom resolution of the index reaction. Ongoing antihistamine and steroids was given to the male and antihistamine to the female. The first reaction was more serious			institutions within 75-mile radius but it is possible that some could have developed a biphasic reaction and presented elsewhere, beyond the 75-mile radius.

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
				and respiratory system (bronchospasm and airway angioedema). (GI symptoms noted but not used to define anaphylaxis) Complete response– if reaction resolved within 30 minutes of treatment	agonist (nebulized) IV fluid (bolus) 63% Vasopressor 20% Intubation 1%			(hypotension and upper airway angioedema) than the biphasic reaction (urticaria).			The authors state that those with biphasic reactions had an earlier onset of the initial reaction after antigen exposure than those reported in other studies and that the

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
				Biphasic anaphylaxis–not defined							'recurrence' was relatively minor. Serum markers not obtained in patients to distinguish between IgE and non-IgE reactions.
Brazil (1998)	Retrospective case series	34	Patients admitted to short-stay ward of	Anaphylaxis: occurrence of one or	Causes:	Adrenaline (intramuscular or	18% (6/34)	Interval until development of the biphasic	Patients with biphasic reactions required significantly more adrenaline	Not reported	Anaphylaxis definition only

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
UK	Objective: assess how common clinically significant biphasic anaphylaxis occurs after apparently successful treatment after		medium sized accident and emergency (A&E) department over 8 months with diagnosis of anaphylaxis requiring adrenaline. Gender: 56% (19) male 44% (15) female Age: 16 to 81 years	more of generalised urticaria, upper or lower airway respiratory symptoms, gastrointestinal, central nervous system, or cardiovascular symptoms that occurred after antigen exposure.	<table><tr><th></th><th>Bipha</th><th>Uniph asic</th></tr><tr><td>Insect bite/sting</td><td>3</td><td>9</td></tr><tr><td>Nuts</td><td>1</td><td>5</td></tr><tr><td>Penicillin</td><td>1</td><td>2</td></tr><tr><td>Cephalosporin</td><td>-</td><td>1</td></tr><tr><td>Non-steroid</td><td>1</td><td>1</td></tr></table>	subcutaneous) at conventional doses until symptom resolution. Observation period not described.		reaction: 4.5 to 29.5 hours (all but one occurred within 24 hours). Symptoms were similar to initial presentation.	than those with uniphasic reactions (mean 1.2 mg [0.5 to 2 mg] compared with 0.6 mg [0.3 to 1 mg]; p = 0.03). No other comparisons made (though authors stated that no other presenting clinical features predicted a biphasic response).		required one system to be affected; biphasic reaction needed to require adrenaline (biphasic was only rash + dyspnoea in one and rash + dysphagia in another)

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
	an anaphylactic reaction			Biphasic reaction– when patient had completely improved after initial treatment only to develop further symptoms requiring adrenaline (without repeated exposure to causal agent).	al anti-inflammatory drugs (NSAIDs) | | Shellfish | - | 1 Unknown | - | 9 There were no deaths.						Clinical features of anaphylaxis of individual patients reported in study but not here because of space (and definitions of what was considered anaphylaxis was felt sufficient

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
											; this applies to other studies in this table). Not clear how long patients were followed-up and if some could have developed a biphasic reaction and presented at

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
											another A&E department or elsewhere.

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
De Swert (2008) **Belgium**	Prospective cohort Purpose to investigate frequency of anaphylaxis in paediatric population at tertiary or secondary referral level, demogr	64 cases in 48 children	Consecutive paediatric patients seen for investigation of anaphylaxis at a paediatric department's outpatient allergy clinic, in a private practice for paediatric allergy, or in a private paediatric practice. Gender: 65% (31/48) male 35% (17/48) female	Anaphylaxis–a serious allergic reaction with rapid onset of symptoms occurring on a site that is remote from the contact site of the trigger and/or in at least two organ systems. Biphasic anaphylaxi	Causes: Food*,** 75% (48) Medication 9% (5) Insect sting 7% (4) Latex 6% (3) Birch pollen 2% (1) Unidentified causes** 86% (55/64) *12 peanut, 7	Treatment protocol and observation period not described.	3% (2/64) of cases	After a 30-minute and 4-hour asymptomatic period	No comparison made.	Funded with grant from UCB, Belgium (global biopharma company)	Purpose was to look at frequency of anaphylaxis and rate of biphasic reactions was also reported but there was no comparison with uniphasic reactions. Not clear how long

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
	aphic characteristics of these patients, clinical course and triggers, its therapeutic approach and the coexistence of allergic symptoms and asthma		Age: 6 months to 14.8 years (mean and median: 6.9 years) 66.7% (32/48) with history of atopic disease 45.8% (22/48) were known to have asthma	s–not defined	egg, 7 nut, 4 cow's milk, 3 kiwi, 2 apple, 1 in each of wheat, lupine, fish, shellfish, 3 food additives **of those with no identified trigger, 6 had onset within minutes after ingestion of food but ingredients could not be fully identified (these have been included in 'food' category) All causes had been confirmed with skin prick						patients were followed-up and if some could have developed a biphasic reaction and presented elsewhere. Authors suggested low rate of biphasic reactions

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
	. (not explicitly about biphasic anaphylaxis)				test, CAP-system test or provocation test. Total duration of symptoms until complete recovery from 20 minutes to 120 hours Treatments received: Antihistamine 72% (41) Corticosteroids 46% (26) Beta-2 mimetic 25%						compared to other studies could be because it may be lower in children or because of the use of corticosteroids in these patients but were unable to make conclusions.

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
					s (14) Adrenaline 19% (11) Paracetamol 1 None 3						
Douglas (1994) **USA**	Retrospective case series Purpose to determine incidence of systemic	94 Outpatient: 35 (44 reactions) (of 80	Outpatient: patients who, during the 30-minute waiting period in the clinic, had experienced symptoms and signs consistent with anaphylaxis (between 1988 and 1991)	Anaphylaxis–occurrence of one or more of the following: generalised urticaria or rash, laryngeal oedema with	Outpatient causes: Pollen/dust/moulds/mites: Biphasic 2, Uniphasic 28 Cat: Biphasic -, Uniphasic 2	Outpatient treatment–either adrenergic receptor agonist (subcutaneous epinephrine or inhaled	Outpatient: 5% (2/44) of reactions Inpatient: 7% (4/59) of patients	Outpatient: 22-24 hours and 6-8 hours Inpatient: 1, 24, 24 and 72 hours Of the 4 in the inpatient study group, 2	Authors state that there were no distinguishing features between those with or without biphasic reactions. This includes the presence of hypotension or any other single sign of symptoms in the initial phase, such as urticaria.	Not reported	Anaphylaxis definition only required one system to be affected. Authors noted that

<table>
<tr><td colspan="11">Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?</td></tr>
<tr><th>Bibliographic reference</th><th>Study type and objective</th><th>n</th><th>Patient characteristics</th><th>Definitions</th><th>Characteristics of initial reaction</th><th>Anaphylaxis treatment protocol and observation</th><th>Rate of biphasic reactions</th><th>Timing of biphasic reaction and characteristics</th><th>Comparison of patients with biphasic to those with uniphasic reactions</th><th>Funding source</th><th>Additional comments</th></tr>
<tr>
<td></td>
<td>biphasic anaphylactic reactions in both out and inpatients</td>
<td>0 treated with 81,000 allergy injections over 3 years)

Inpati</td>
<td>Gender: 34% (12/35) male, 66% (23/35) female
Mean age: 36 y (7 to 69)

Inpatient: patients admitted to medical ward or intensive care unit (Madigan Army Medical Centre) with diagnosis of systematic anaphylaxis (1986 to 1992)
Gender: 71% (42/59)</td>
<td>symptoms referable to this area such as throat tightness, hoarseness, dysphagia, dysarthria, wheezing, tightness, shortness of breath, sensation of impending doom, hypotension or cardiac or respiratory</td>
<td>
<table>
<tr><td>Venom*</td><td>-</td><td>3</td></tr>
</table>
*1 yellow jacket, 1 white face hornet, 1 wasp or mixed vespid

Inpatient causes:
<table>
<tr><th></th><th>Bipha</th><th>Uniph</th></tr>
<tr><td>Amoxicillin</td><td>2</td><td>1</td></tr>
<tr><td>Penicillin</td><td>-</td><td>2</td></tr>
<tr><td>Ampicillin</td><td>-</td><td>1</td></tr>
<tr><td>Other</td><td>-</td><td>14</td></tr>
</table>
</td>
<td>Alupent or Proventil via nebulizer), H_1 receptor antagonist (oral diphenhydramine, terfenadine or hydroxyzine) or both as indicated (none had glucocorticosteroids either during or</td>
<td></td>
<td>had biphasic reactions of greater severity than in the initial phase (the other 2 were of similar or less severity – only urticaria).

Of the 2 in the outpatient group, the biphasic symptoms were similar to the index</td>
<td>In the inpatient study, the absence of hypotension or severe upper or lower respiratory tract obstruction did seem to distinguish those who did not have a late-phase reaction or biphasic pattern.

See also ‘characteristics of reaction’.

Age:
<table>
<tr><th>Setting</th><th>Biphasic</th><th>Uniphasic</th></tr>
<tr><td>Out</td><td>39</td><td>7 to</td></tr>
</table>
</td>
<td></td>
<td>reported rate of biphasic reactions is lower than in other publications. They could not determine why but suggested that, in the inpatient group, early intervention with glucocort</td>
</tr>
</table>

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?												
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
		ents: 59 inpatient	male 29% (17/59) female Mean age:35 y (6 months to 81 y)	arrest after antigen exposure of any type (except in cases that were determined to be idiopathic). Biphasic reactions–occurred without repeat exposure to inciting antigen (not	drugs[1] Vaccine - 2 Peanuts/peanut butter - 3 Shrimp/crab 2 4[2] Fish - 2 Chicken - 2[2] Egg - 1 Radiocontrast media - 1	after the initial episode). Outpatient observation– all were discharged after resolution of signs and symptoms but were instructed to return to either the clinic or		reaction (urticaria for both in one patient and urticaria/angioedema followed by angioedema and rhinitis in the other)	patient and 7 years 69 years Inpatient 20, 52, 64, 77 years 6 months to 81 years		icosteroids may have played a role (but noted the opposing findings by Stark et al [1986]). Outpatient observation period (12 or 24 hours) may not be long enough to detect biphasic

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
				otherwise defined).	Skin test - 1 Hymenoptera sting - 3 Exercise - 5 Idiopathic - 12 [1]Codeine, aspirin, ibuprofen, tolmetin, captopril, lisinopril, or septra [2]in one patient, the agent was either shrimp or chicken There were no	hospital emergency room if symptoms recurred. Repeat history and physical examination by an allergist or telephone contact by the clinic registered nurse occurred within 12					reactions (in patient observation period not described).

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
					deaths.	to 24 hours & detailed status was taken for the period 12 to 24 hours after initial episode. Inpatient treatment– adrenergic receptor agonist (subcutaneous					

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
						epinephrine or inhaled β-receptor agent), H_1 and/or H_2 receptor antagonist, intravenous fluids, or glucocorticosteroids at the discretion of the patient. (observation					

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
						period for inpatient group not described)					

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
Ellis (2007) **Canada**	Prospective cohort The objective was to determine the incidence, predictors and characteristics of biphasic anaphylactic reactions.	134 (FU only obtained for 103)	All patients with emergency department visits and all inpatients with a diagnosis of 'allergic reaction' or 'anaphylaxis' during 3 year period at a tertiary centre (1999–2001). Patients were contacted within 72 hours to establish symptoms and determine if they had biphasic	Anaphylaxis (as per Canadian Pediatric Surveillance Program)– "severe allergic reaction to any stimulus, having sudden onset and generally lasting less than 24 hours; a disorder involving at least two body	Causes: % Number: Biphasic (n=20); Uniphasic (n=83) Hymenoptera: 22% (18); 22% (30) Food: Peanut: 11% (9); 8% (11) Other nuts: 8% (7); 8% (11) Seafo: 7% (6); 9% (12	Patients were contacted after 72 hours after the ED visit to see if biphasic reaction occurred. Average duration of ED observation time was 3.8 hours. (Treatment protocol	19.4% (20/103) of those available for follow-up (FU) had biphasic activity. 55% were clinically similar to the initial reaction, 35% were milder, 40% involved life-threateni	Average 10 hours after initial reaction, range: 2 to 38 hours, but 40% (8) occurred more than 10 hours later. 20% (4) occurred after 20 h (most within 22 h, but one at 38h) All cases were carefully checked to ensure no	Comparisons: (for difference in causes see 'characteristics of reaction') Biphasic (n=20); Uniphasic (n=83); P value Median age: 25; 33; 0.09 Paediatric (<13 years): 15% (3); 8% (7); 0.40 Femal: 45%; 47%; 0.81	Not reported	In those with late biphasic reactions (after 9 hours), a longer time to resolution of initial symptoms was the only predictor of a late reaction (193 minutes compared with 112 minutes

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?												
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			activity. Median age: 33 y (11 months to 79 years) Gender: 54% (56/103) male 47% (48/103) female	systems, with multiple symptoms such as hives, flushing, angioedema, stridor, wheezing, shortness of breath, vomiting, diarrhoea or shock". Biphasic reaction– the reaction had to meet the	od) / Milk 2% (2) 2% (3) / Other 4% (3) 6% (8) / Total 35% (29) 38% (51) / Medication: / Penicillin derivatives 1% (1) 2% (3) / Other antibiotics 5% (4) 3% (4) / NS 5% 4%	not reported)	ng manifestations (i.e.. hypotension, throat or tongue swelling; usually these were also present in the initial reaction), 20% required more aggressive therapy	further antigen exposure caused 2nd reaction (ex. food cases with 2nd reaction occurring > 20 hours later to exclude secondary antigen absorption). However, for the reaction that occurred at 38h, it was not possible to	es (9) (39) / Prior anaphylaxis 35% (7) 47% (39) 0.56 / Prior asthma 40% (8) 36% (30) 0.90 / Median time to symptom onset 15 15 0.90		for uniphasic reactions, p = 0.006). No biphasic reactions occurred in patients who responded completely to treatment in less than half hour.

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
				same definition as above without further antigen exposure (recurrence of urticaria or another rash alone were excluded)	AIDs (4) (5) Immunotherapy 1% (1) 3% (4) Other 6% (5) 5% (6) Total 18% (15) 16% (22) Unknown/idiopathic: Unknown 15% (12) 14% (19) Idiopathic 7% (6) 5% (7)		to resolve symptoms. Urticaria occurred in all biphasic reactions but was not always present in the initial reaction.	determine cause and rule out repeated exposure.	B-agonist use 10% (2) 28% (23) 0.15 Epinephrine use 55% (11) 82% (68) 0.13 Total/median epinephrine 0.30 mg/0.21mg 0.39 mg/0.32 mg 0.048 Corticosteroid use 35% (7) 55% (46) 0.07		All 14 patients with symptom resolution within 30 minutes were treated with epinephrine (100% vs 73%, p = 0.03). They were also more likely to have had a history

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
					Total: 21% (18) vs 19% (26). (occurrence rates between different antigens not significantly different between uniphasic and biphasic reactions, p > 0.25)				Mean prednisone dose: 31 mg vs 63 mg, 0.06 H_1-antagonist use: 95% (19) vs 95% (7), > 0.99 H_2 antagonist use: 20% (4) vs 30% (25), 0.42 Time to resolution: 133 min vs 112 min, 0.03		of anaphylaxis than biphasic reactors (57% vs 26%), and were slightly younger (median 22 vs 25 years) but these were not statistically significantly different. They were significan

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
									of initial symptoms (medical records of those lost to FU did not reveal any ostensible differences in age).		tly younger than the others with uniphasic reactions (median 22 vs 35 years, p = 0.03). Higher rate of biphasic reactions could be due to prospective nature (with retrospec

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
											tive designs not capturing all reactions); timing suggests previously recommender 1-8 hours is not sufficient.
Järvinen (2009) **USA**	Retrospective case series Objective: to	50	Children with positive oral food challenges to diagnose allergy who had reactions	Anaphylaxis–serious allergic reaction that is rapid in onset	Causes: No. of Egg 15 Milk 14	Patients observed for 4 hours after reaction.	2% (1/50)	1 hour	No comparison made.	One author is a consultant and	Patients only followed up for 4 hours and they could

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
	determine the prevalence and risk factors of reactions requiring epinephrine and the rate of biphasic reactions during oral food challen		requiring epinephrine. 34% (436/1273) of oral food challenges resulted in a reaction with 11% (50/436) requiring epinephrine Reactions requiring epinephrine occurred in older children (median 7.9 vs 5.8 years, p < 0.001) and were most often caused	(within minutes to several hours after food ingestion) and affecting at least 2 major organ systems; all required epinephrine Biphasic–recurrence of symptoms after resolution	Peanut 10 Tree nuts 4 Soy 3 Wheat 3 Fish 1 Median time of onset of reaction from last dose of food challenge: 5 minutes (range 1-60) None were life-threatening respiratory or cardiovascular compromise. Treatment: 2 doses of	Patients were treated with epinephrine if signs of a reaction.				shareholder for Allertein Pharmaceuticals and is 45% owner of Herbal Springs, LLC.	have developed a biphasic reaction beyond this period (so the rate may be an underestimate).

<table>
<tr><td colspan="11">Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?</td></tr>
<tr><th>Bibliographic reference</th><th>Study type and objective</th><th>n</th><th>Patient characteristics</th><th>Definitions</th><th>Characteristics of initial reaction</th><th>Anaphylaxis treatment protocol and observation</th><th>Rate of biphasic reactions</th><th>Timing of biphasic reaction and characteristics</th><th>Comparison of patients with biphasic to those with uniphasic reactions</th><th>Funding source</th><th>Additional comments</th></tr>
<tr><td></td><td>ges in children</td><td></td><td>by peanuts (p = 0.006)

Children with positive challenges ranged from 1.25 to 18 years (median 6 years)

Gender: 60% (30) male, 40% (20) female</td><td>of the initial event in 1 to 78 hours</td><td>epinephrine were required in 3 patients reacting to wheat, cow’s milk, and pistachio.
<table><tr><td></td><td>Epinephrine (n = 50)</td><td>No epinephrine (n= 386)</td></tr><tr><td>Antihistamine</td><td>98% (49)</td><td>80% (309)</td></tr><tr><td>Steroids</td><td>58% (29)</td><td>5% (21)</td></tr></table></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
					Albuterol nebulization: 14% (7); <1% (3) IV fluids: 8% (4); <3% (10) Oxygen: 4% (2); 0%						
Jirapongsananuruk (2007) **Thai**	Retrospective case series Objective: to describe the	101	All inpatient department admissions for 5 years (1999–2004). ICD-10 codes: T78.0 (anaphylactic shock due to	Anaphylaxis–severe, life-threatening generalised or systemic hypersens	Causes: Unidentified causes: 15 Drugs	Treatment protocol and observation period not described.	7% (4) of children and 2% (1) of adults	No more details provided	No comparison made.	Not reported	Not clear how long patients were followed-up and if some could have

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
land	clinical characteristics of patient with anaphylaxis admitted to Siriraj Hospital		adverse food reaction), T78.2 (anaphylactic shock, unspecified), T78.3 (angioneurotic oedema, laryngeal oedema, Quincke oedema, urticaria-larynx), T80.5 (anaphylactic shock due to serum), T88.6 (anaphylactic shock due to adverse effect of correct drug of medicament	itivity reaction as suggested by the World Allergy Organisation. In order to be considered anaphylaxis, one of the symptom of generalised mediator release such as flushing,	Antibiotics 21 Radiocontrast media 7 Allergen immunotherapy 7 Chemotherapy 5 NSAIDs 4 IV immunoglobulin /hydrochlorothiazide/10% Cocaine/Iron-sucrose 1 each						developed a biphasic reaction and presented elsewhere. ICD codes identified 228 records; 2 authors selected 101 that met definition of anaphylaxis.

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			properly administered), T63.2 (venom of scorpion), T63.4 (venom of other arthropods, insect bit or sting, venomous), T38.3 (angioedema), L50.0 (allergic urticaria), L50.9 (urticaria unspecified), J38.4 (oedema of larynx exclude laryngitis, croup), J46 and R11 (asthma and	pruritis or paraesthesia of the lips, axilla, hands, or feet; general pruritis, urticaria or angioedema, lip tingling or paraesthesia, and conjunctivitis or chemosis AND at least one of: 1) oral and gastrointestinal	/amifostine, unidentified drugs Total: 51 Food Seafood 11 Wheat 2 Wheat-dependent exercise 1 Milk 1 Fried insects/ freshwater prawn/freshwat 1 each						Significantly more male paediatric patients experienced anaphylaxis than female paediatric patients; while significantly more female adults experienced anaphyla

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			vomiting), J46 and R55 (asthma and syncope), R06.2 and R11 (wheezing and vomiting), R06.2 and T38.3 (wheezing and angioedema), J46 and T38.3 (asthma and angioedema) Mean age: 23.7 years (SD 21.8, range:2.8 months to 81.3 years) 54 were paediatric (≤ 16 years), 47	system (oral mucosal pruritus; intraoral angioedema or buccal mucosa, tongue, palate, or oropharynx; nausea, emesis, dysphagia, abdominal cramps, or diarrhoea, 2) respiratory system: rhinitis,	er fished bread/freshwater fish maw Unidentified food: 5 Total: 24 Insect sting/bite Fire ant: 6 Wasp: 3 Centipede/rasp: 1 each Treatments received: Antihistamine: 93					xis than male adult patients.

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			were adult Gender: 5% (53) male, 48% (48) female Gender of paediatric patients: 37 male, 17 female Gender of adults: 16 male, 31 female	stridor, cough, hoarseness, aphonia, tightness in the throat, dyspnoea, wheezing, hypopharyngeal or pharyngeal oedema, or cyanosis or 3) cardiovascular system: chest pain,	Corticosteroids 83 IV fluid 81 Epinephrine 78 Inhaled β_2-agonist 39 Dopamine 9 O_2 therapy 5 Sodium bicarbonate 1						

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
				arrhythmia, hypotension, presyncope, syncope, tachycardia, bradycardia, orthostasis, seizures or shock Biphasic anaphylaxis–not defined							
Lee (2000)	Retrospective case series	108 episo	All children admitted to children's hospital	Anaphylaxis–acute allergic reaction	Causes:	Patients were observed if they	6% (6/105) (95% confiden	Resolution of symptoms to onset of	Comparison: Biphasic / Uniphasic	Not reported	Only patients hospitalised for

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
USA	Objective: 1 – determine incidence of biphasic reaction in children with anaphylaxis, 2 – establish risk factors, 3 – assess utility of inpatien	des in 106 patients but only 77% (83) considered serious (se	**inpatient service** between 1985 and 1999 with acute anaphylaxis. Medical records searched by ICD-9 classifications: 1) 995.0-995.3 (anaphylactic shock, angioneurotic oedema, unspecified adverse effect of drug, medicinal, biological substance, or	with involvement of at least 2 body systems: dermatologic, neurologic, gastrointestinal, respiratory, cardiovascular (chronic idiopathic cases and anaphylaxis that developed during	Bipha / Uniphasic Food: 2[1] / 49[1] Medications: 2[2] / 22 Insect bite: 2 / 10 Immunotherapy: - / 3 Immunization: - / 1	had significant biphasic reaction within 24 hours of admission. Of all patients, mean length of hospitalisation was 24 hours (median 19).	ce interval [CI]: 2, 12) 3% (3/105) were considered significant (95% CI 0.6, 8).	biphasic reaction: from 1.3 hours to 28.4 hours (all but one had occurred within 12 hours). The same organ systems were involved. One patient experienced more serious respiratory symptoms in the	(n=6) / (n=99) Male gender: 50% (3) / 64% (63) Mean age (y): 8.0 / 8.6 Oral ingestion of trigger: 67% (4) / 60% (59) Epinephrine given initially: 100% / 91% (90) Median time to initial: 190 / 48		anaphylaxis so may not be representative of all those with anaphylaxis or biphasic reactions compared to those presenting to an ED. 24 hours may not be sufficient

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
	ts observation for patients with appear to have resolved anaphylaxis	e definitions column)	allergy unspecified) 2) 995.6-995.69 (due to adverse food reaction) 3) 999.4 (due to serum) 62% (66) male 40% (42) female Median age: 8 years (range 6 months to 21 years) 64% (69) had positive atopic history for asthma, eczema, or	hospitalisation for another condition excluded). Biphasic reactions–worsening of symptoms requiring new therapy after resolution of anaphylaxis (defined as cessation of all symptoms	Contrast dye - 1 Unknown - 16 [1] 14 tree nut, 12 peanuts, 8 seafood, 3 fruit, 2 eggs, 2 seeds, (biphasic: nut and fish), [3] dicloxacillin, trimethoprim-sulfamethoxazole (of those with identified trigger, 33% [30/92] with prior history of allergy to the same trigger).			second reaction and also experienced new onset stridor.	dose of epinephrine (min)* Steroids given initially 84% (5) 85% (84) *p = 0.03 (Mann-Whitney *U* test) No difference in serious respiratory or cardiovascular symptoms in initial reaction and no significant differences in the type of allergenic trigger.		period to detect a biphasic reaction. One patient had a reaction beyond the 24 hours they were observed. Unclear how long patients without a significant reaction were

<table>
<tr><td colspan="11">Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?</td></tr>
<tr><th>Bibliographic reference</th><th>Study type and objective</th><th>n</th><th>Patient characteristics</th><th>Definitions</th><th>Characteristics of initial reaction</th><th>Anaphylaxis treatment protocol and observation</th><th>Rate of biphasic reactions</th><th>Timing of biphasic reaction and characteristics</th><th>Comparison of patients with biphasic to those with uniphasic reactions</th><th>Funding source</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>allergic rhinitis</td><td>requiring no therapy for at least 1 hour).

Significant biphasic reactions– requiring oxygen, vasopressors, intubation, subcutaneous epinephrine, unscheduled bronchodilator treatments</td><td>Route:<table><tr><th></th><th>Total</th></tr><tr><td>Oral</td><td>65</td></tr><tr><td>Subcutaneous</td><td>18</td></tr><tr><td>Intravenous</td><td>8</td></tr><tr><td>Inhaled</td><td>2</td></tr><tr><td>Unknown</td><td>15</td></tr></table>2% (2/108) were fatal

Time from exposure to allergen to onset of symptoms (available in 76</td><td></td><td></td><td></td><td></td><td></td><td>observed so unable to tell if observed sufficiently to detect a biphasic reaction.</td></tr>
</table>

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
					patients): mean 31 ± 71 minutes (from < 1 minute to 9.7 hours), median 10 minutes. Time from onset of symptoms to first administration of subcutaneous epinephrine: mean 113 ± 176 minutes (from < 1 minute to 17.4 hours), median 50 minutes.						
Mehr (2009)	Retrospective case series	145 episode	Children presenting with anaphylaxis to a major paediatric	Anaphylaxis–multi-system allergic reaction	Causes:	Treatment protocol not describe	11% (12/109) Of these only 5 (4.6% of	Median time from onset of original reaction to onset of	*Comparison of patient characteristics:* Bip has / Unip hasi	None declared	Not clear how long patients were followed-

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
Australia	Objective was to determine predictive factors for biphasic reactions in children presenting with anaphylaxis	s in 138 children but 104 after exclusion criteria applied (see 'ad	emergency department and admitted for greater than 6 hours over 5 years (1998– 2003). Medical records searched using International Classification of Disease (ICD) version 10 with Australian Modification codes: anaphylactic shock due to adverse food	characterised by one or more clinical features involving the respiratory and/or cardiovascular system (CVS) associated with one or more clinical features involving the skin and/or gastrointe	Biphasic (n=12) vs Uniphasic (n=95): Food: 75% (9) vs 83% (79) Drug: 8% (1) vs 7% (7) Insect bite: 0% (0) vs 4% (4) Unknown: 17% (2) vs 5% (5) (none of these differences were statistically significant)	d. Patients included if they were admitted for at least 6 hours but time period they were observed after this was not described.	all) were 'anaphylactic' and 7 (6.4% of all) they were 'non-anaphylactic'. The biphasic reaction was milder in 58% (7/12), of similar severity in 33% (4/12) and	biphasic reaction: 8.8 hours (range: 1.3 to 20.5)	ic n=12 vs c n=90: Male gender: 67% (8) vs 59% (53) Median age at presentation (y): 9.6 (0.2-16.7) vs 2.4 (0.2-18.8) Presence of atopic disease: 58% (7) vs 58% (52) Asthma: 25% (3) vs 31% (28) Prior anaph: 17% vs 11% (10)		up and if some could have developed a biphasic reaction and presented elsewhere. Exclusions: 23 episodes of patients observed for < 6 hours (0.9 to

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
		ditional comments' column)	reaction (T78.0), unspecified (T78.2), serum (T80.5), properly administered drugs (T88.6), allergy unspecified (T78.4) and other adverse food reactions not elsewhere classified (T78.1). Median age: 2.5 years (range 0.2 to 18.8) Gender: 60% (62) male,	stinal tract (GIT) as described by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network consensus definitions. Biphasic – second reaction after initial recovery	Route: Biphasic (n=12) / Uniphasic (n=95) Oral: 75% (9) / 86% (82) Subcutaneous: 0% (0) / 4% (4) Intravenous/intramu		more severe in one case (9%). One had hypotension requiring adrenaline infusion.		ylaxis (2) Median time from exposure to anaphylaxis (min): 10 (2-210) / 10 (1-450) (none of these differences were statistically significant) *Comparison of adrenaline use at initial reaction:* Biphasic n=12 / Uniphasic n=95		4.4 hours) and discharged directly from the emergency department, 13 episodes because of daily use of chemotherapeutic or biological agents (n = 10), corticosteroids (n

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			40% (42) female	for at least 1 hour during which there were no new treatments or symptoms or re-exposure. Protracted – no initial recovery period Non-anaphylactic allergic reaction– characterised by	scular Topical: 0% (0); 1% (1) Unknown: 17% (2); 4% (4) (none of these differences were statistically significant) There was one death in a patient with a protracted reaction.				% administered: 75% (9); 84% (80) Median time to first dose (min): 28 (3-130); 40 (1-300) >1 dose[1]: 58% (7); 22% (21) Route of administration: Parenteral: 44% (4; 75% (60) Nebulized: 11% (1); 6% (5) Parenteral: 44%; 15% (12)		= 2), or antihistamines (n = 1) Need for > 1 adrenaline dose and / or fluid bolus during the initial reaction were calculated to be sensitive and moderately specific

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
				one or more symptoms or signs involving the skin and/or GIT without involvement of either the CVS or respiratory systems (CVS-hypotension, loss of impairment of conscious state, pale and floppy presentati					and nebulized[2] (4) Unknown 0% (0) 4% (3) Administration site: Royal Children's Hospital Emergency Department 56% (5) 48% (38) Local emergency department 33% (3) 16% (13) General 11% 20% (16)		predictors of a biphasic reaction (sensitivity 92%, 95% CI 62-100%, specificity 76%, 95% CI 66-84%). Absence of either risk factor was strongly predictive of the absence of a

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
				on in an infant; respiratory - difficulty or noisy breathing, swelling of the tongue, swelling or tightness of the throat, difficulty talking, hoarse voice, stridor, wheeze, persistent cough, tachypnoea; GIT-					practitioners (1) Parents 0% (0) 8% (6) Ambulance 0% (0) 9% (7) [1] p=0.01, [2] p = 0.05 (all others not significantly different) *Comparison of other therapies at initial reaction:* IV fluid bolus* 83% (10) Biphasic n=12 79% (75) Uniphasic n=95		biphasic reaction (negative predictive value: 99%, 95% CI 93-100%) while presence of either factor was poorly predictive of a biphasic reaction (positive predictive value: 32%,

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
				abdominal pain, vomiting, diarrhoea; skin-angioedema, hives, urticaria, generalised pruritis, erythema).					Median volume of fluid bolus (ml/kg) 20 (8-56) 15 (2-33) Oxygen required 50% (6) 31% (29) Intubated 8% (1) 79% (75) *p = 0.01 (others not significant) There were also no significant differences in corticosteroid or antihistamine use or in the time to use of these drugs between		95% CI 17-51%).

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
									groups.		

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
Poachanukoon (2006) **Thailand**	Retrospective case series Objective: estimate incidence of anaphylaxis in an emergency department	64 patients with 65 anaphylactic episodes (223/100000 anap	Patients who attended emergency department at one hospital in Thailand during a one year period (2003–4) (based on ICD-9 and ICD-10 terms). 53% (34) male 47% (30) female Median 26 years old (range: 1 month to 65 years)	Anaphylaxis: presence of one symptom of generalised mediator release such as flushing; pruritis or paraesthesia of lips, axilla, hands, or feet; general pruritis; urticaria or angioedema; lip tingling;	Causes: Food[1] 40% (26) Drugs 36% (23) *Hymenoptera* 5% (3) Radiocontrast agent 2% (1) Unknown 17% (11) [1] 22 seafood, 3	Treatment protocol and observation period not described.	15% (8/52) of those with resolved initial anaphylactic symptoms	Timing not reported.	*Comparison:* Biphasic n=8 / Uniphasic n=44 Age 22, 6y / 28y Male sex 50% (4) / 55% (24) Atopy 50% (4) / 50% (22) Shock in initial phase 38% (3) / 23% (10) Mean time after allerg 48 min / 39 min	Thammasat University research fund.	Not clear how long patients were followed-up and if some could have developed a biphasic reaction and presented elsewhere. Rate of those with biphasic

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
		hylaxis occurrence rate)	55% (35) had atopy of allergic rhinitis, atopic dermatitis, asthma, urticaria or drug/food allergy.	and conjunctivitis or chemosis INCLUDING at least one symptom involving the oral and gastrointestinal, respiratory, or cardiovascular systems. Biphasic anaphylaxis–not defined	cow milk, 1 wheat [2] 8 NSAID, 9 penicillin and others like anti-tuberculosis drugs and muscle relaxants 1 patient with history of cardiovascular disease died (1.6% death rate) 89% (57) received epinephrine (40 intramuscular, 16 subcutaneous, 1				en exposure Epinephrine use: 100% (8) vs 91% (40) Steroid use: 88% (7) vs 80% (35) Mean time to initial dose of epinephrine: 263 min vs 82 min All p > 0.05.		reactions is in patients with resolved symptoms from the initial episode. The reason why these patients' symptoms were unresolved was not stated (i.e.. if protracted

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
					IV), 100% H_1-antagonists, 61% (39) H_2-antagonists, 77% (49) corticosteroids, 23% (15) beta-agonists.						symptoms).

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
Sampson (1992) **USA**	Cross-sectional study To identify reports of fatal or near-fatal anaphylactic reactions to food by children	13	Children or adolescents with fatal or near-fatal anaphylactic reactions to foods identified from a review of emergency medical case reports, medical records, depositions by witnesses to the events, interviews with parents (and some patients). (in 3 metropolitan areas over a period of 14	Near-fatal reaction–episode of anaphylaxis requiring admission to an intensive care unit for intubation, mechanical ventilation, and vasopressor support. Severe symptoms–obvious respiratory distress,	Causes: Peanuts 4 Nuts 6 Eggs 1 Milk 2 (all had known allergies) 6 had symptoms within 3 to 30 minutes but only two received epinephrine in the first hour. 6 died Of those that	Treatment protocol and observation period not described.	3 patients included had biphasic reactions (because of cross-sectional design, this study does not give information about the frequency)	1 to 2 hours symptom-free period	No comparison made.	Not reported	Since the design of this study is cross-sectional, it does not give information on the frequency of biphasic reactions (the authors acknowledge this). Patients included have had very

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			months) Gender: 76% (10/13) female; 23% (3/13) male Mean age: 12y (2 to 17)	retractions, wheezing, and in some cases, cyanosis or loss of consciousness Biphasic reaction–not defined	survived, all had symptoms within 5 minutes of allergen ingestion and all but one received epinephrine within 30 minutes.						severe reactions (near-fatal or fatal) so are a very specific subgroup of patients and do not represent all patients presenting with anaphylaxis.
Scranton (200	Prospective cohort	60 (55 pat	Patients treated with epinephrine for	Anaphylaxis–life-threatenin	25% (15) occurred in children less	Observation for 1 to 2	23% (14/60) of	Median time 5.5 hours (range 2 to	*Comparison of patient and immunotherapy*	Not reported	Precise definition of

<table>
<tr><td colspan="11">Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?</td></tr>
<tr><th>Bibliographic reference</th><th>Study type and objective</th><th>n</th><th>Patient characteristics</th><th>Definitions</th><th>Characteristics of initial reaction</th><th>Anaphylaxis treatment protocol and observation</th><th>Rate of biphasic reactions</th><th>Timing of biphasic reaction and characteristics</th><th>Comparison of patients with biphasic to those with uniphasic reactions</th><th>Funding source</th><th>Additional comments</th></tr>
<tr><td>9)

USA</td><td>Objective: to determine the incidence, clinical characteristics, and risk factors for biphasic reactions after allergen-specific immunotherapy</td><td>ients)

(of 10,932 immunotherapy injections in 330 patients</td><td>systemic reactions after allergen immunotherapy (with aqueous extracts; either Hymenoptera or aeroallergens) at 2 hospitals in 14 month period (2006–07).

Mean age: 33 years (range: 6 to 76)

Gender: 35% (19) male, 65% (36) female</td><td>g allergic reaction (symptoms assessed with a 31-symptom scoring system with 5 main categories: general, skin, gastrointestinal, respiratory, cardiovascular/neurologic).

Biphasic</td><td>than 18 years old.

63% (38) occurred during the build-up phase of immunotherapy.

Time from allergen immunotherapy to initial systemic reaction was 25 minutes (range: 1-180)</td><td>hours after last dose of epinephrine. Subjects then instructed to observe and record any clinical symptoms during the next 24 hours when they were telephoned and</td><td>reactions

(none occurred in children)</td><td>24)

Subjective severity of biphasic reaction was 10% or less in 64% (9) patients. 93% (13/14) considered the severity to be 25% or less of their initial reaction. Total symptom score was significantly less during the biphasic reaction</td><td>characteristics:
<table><tr><td></td><td>Biphasic n=14</td><td>Uniphasic n=46</td></tr><tr><td>Age[1]</td><td>41 y ±13</td><td>30 y ±16</td></tr><tr><td>Male sex[2]</td><td>1</td><td>18</td></tr><tr><td>Build-up phase</td><td>9</td><td>29</td></tr><tr><td>Immunotherapy duration</td><td>2.3 y ±6.0</td><td>0.9 y ±1.6</td></tr><tr><td>Aeroallergen</td><td></td><td>33</td></tr></table></td><td></td><td>anaphylaxis not reported (though all required epinephrine).

24 hours may not be long enough to detect biphasic reactions.

At one site 1, 5 were excluded because</td></tr>
</table>

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?												
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**			**Funding source**	**Additional comments**
		at one site and 12.796 in 366 patients at the other site)	*Immunotherapy characteristics:* 62% were receiving 1:1 vol/vol vial and 13% 1:10 vol/vol vial (average duration of immunotherapy was 1.2 ± 3.2 years) 70% aeroallergen vs 30% venom Of all that received immunotherap	reaction– any reaction occurring after discharge from the clinic up to 24 hours after their initial symptoms		results on the 31-symptom scoring system were recorded. Treatment protocol not reported.		compared with initial symptom scores (1.3 ± 0.5 and 4.1 ± 1.8, p < 0.001). Median duration of biphasic symptoms: 53 minute (from 1-480) and 57% lasted ≤1 hour. None of the biphasic reactions required epinephrine	immunotherapy				they did not require epinephrine and 10 because the site investigator was not present when they were being treated. Site 2 excluded 4 patients who did not
									Current asthma		23		
									Daily antihistamine	11	30		
									Prior systematic reaction to immunotherapy	4	14		
									Less than 18	0	15		

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			y at both sites, the rate of patients requiring epinephrine: Site 1 – 0.78% Hymenoptera, 0.38% aeroallergens (p = 0.32) Site 2 – 0.91% Hymenoptera, 0.23% aeroallergen (p < 0.0001).					or required a trip to the emergency department. 21% (3/14) took an additional oral antihistamine at the onset of biphasic symptoms, 21% (3/14) used their β_2-agonist rescue inhaler.	years old[3] [1] p = 0.01, [2]p = 0.03, [3]p = 0.01 *Comparison of reaction and therapy:* Biphasic n=14 / Uniphasic n=46 Symptom onset (min): 17 ±14 / 28 ±22 Time to epinephrine (min): 8.2 ± 12.8 / 8.5 ± 13.8 > 1: 9 / 8		require epinephrine. Symptoms in the biphasic reaction were not as severe and none required epinephrine.

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?												
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**			**Funding source**	**Additional comments**
									dose epinephrine *				
									Oral antihistamine	11	37		
									Oral corticosteroid	1	6		
									Albuterol nebulization	2	10		

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
									Time to >90% improvement (min) 20 ± 10 33 ± 37 *p = 0.001		

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
Smit (2005) **Hong Kong**	Retrospective case series Objective to describe the epidemiology, clinical characteristics, and management of acute anaphylaxis in a populati	282 (9 were excluded – see 'additional comments')	Patients presenting consecutively to the resuscitation room of a large Hong Kong emergency department with a diagnosis of anaphylaxis from 1999 to 2003. Only those with hypotension, severe cutaneous manifestation, respiratory or airway	Anaphylaxis– included both anaphylactic (IgE-mediated systematic immune response) and anaphylactoid reaction (non-IgE-mediated systemic immune response). Biphasic reaction- any	Causes: Biphasic (n=15) / Uniphasic (n=267) Seafood: 33% (5) / 31% (84) Other food: 0% (0) / 13% (36) Drugs*: 26% (4) / 37% (98) Insect: 7% (1) / 6% (17	Median time spent in the observation ward was 10.6 hours (observation protocol: patients were admitted into the ED observation ward if the specialist emergency physician	5.3% (15/282)	Mean time from treatment to onset of biphasic reaction: 8 hours (range 1 to 23) (9 occurred more than 8h after initial presentation and 6 of these 8h after initial treatment). 3 were paediatric patients (< 15 years)	*Comparison of patient characteristics & of first reaction:* Biphasic (n=15) / Uniphasic (n=267) Age: 33y (IQR 19-41.3) / 28y (IQR 19-44) Male sex: 67% (10) / 59% (157) Time from onset to: 3 h (IQR 2.0- / 1.0 h (IQR 0.7-3.0)	Not reported	Authors confirmed (with Hong Kong ID #) that no patients presented to other hospitals with a biphasic reaction within 5 days. Definition of anaphylaxis includes

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?												
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
	on in Hong Kong to determine the incidence and nature of biphasic reactions and possibly predict progression to a biphasic reaction		compromise, cardiovascular compromise, cardiovascular compromise (such as hypotension or dysrhythmias, syncope or loss of consciousness), or any suspicious by the triage nurse of likely respiratory or circulatory compromise were triaged to resuscitation room. All those	reaction occurring after initial treatment and complete resolution of symptoms.	bite/sting:) Plants and hair dye: 0% (0); 1% (4) Gas inhalation: 0% (0); 0.4% (1) Unknown: 13% (2); 0% (0) Not documented: 20% (3); 0% (0) *including	believed the patient was likely to be discharged within 12 and 24 hours but follow-up protocol length not described). Treatment protocol not describe		Most reactions were mild with the same clinical features as the same reaction. Mean time to presentation at the ED onset of biphasic reaction was 8.22 hours (SD 5.46, range 1.4-23); time from	presentation*: 6.3) Time in ED*: 1.42 (IQR 0.74-2.2); 0.72 (IQR 0.5-1.0) Time in hospital (observation and general ward)*: 1.33d (IQR 0.67-2.58); 0.53 (IQR 0.34-1.09) Asthmatic: 33%; 67% (53)		non-IgE mediated reactions. 9 patients excluded (5 charts were unavailable and 4 had a final diagnosis was not anaphylaxis – 3 asthma and 1 Steven Johnson'

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			logged as 'allergy, allergic reaction, anaphylactic reaction or shock, anaphylaxis, anaphylactoid reaction, bee stings or other insect bits, drug reactions, angioedema/angioneurotic oedema, or urticaria' were included but those without final diagnosis of anaphylaxis were excluded.		analgesia in 26 cases, antibiotics in 24 and 52 of other drugs (including 22 from Chinese medicine); this was the only comparison that was significantly different (p = 0.032) Median time from onset of symptoms to presentation at the department was: 1.3 hours (IQR 0.79-3.0). 6% (17) had antihistamines	d.		receiving treatment from onset of biphasic reaction: 7.57 hours (SD 5.46, range: 1.22-22.5)	history (1) Allergy history 39% (5) 47% (111) *p < 0.01 (all others not significant) *Comparison of therapy:* Biphasic (n=15) Uniphasic (n=267) IV fluids 20% (3) 32% (85) Epinephrine 73% (11 66% (177)		s syndrome) 10.6 hours not likely to be long enough to detect biphasic reactions. Causes of anaphylaxis were as reported by patient (i.e..

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			Median age: 28 years (range: 1-91, interquartile range [IQR] 19-43) Gender: 59% (167) male, 41% (115) female Previous history of asthma: 19% (54)		before arrival but only 6 received steroids and 2 epinephrine before arrival. None died. 1.4% (4) were discharged from ED, 3.2% (9) discharged themselves against medical advice, 40.8% (115) were admitted to hospital, 82% (93/115) to general ward, 19% 22/115) to ICU.				) H1 antagonist: 100% (15) vs 95% (254) H2 antagonist: 0% (0) vs 1.5% (4) Steroids: 87% (13) vs 92% (245 Salbutamol*: 7% (1) vs 35% (94) *p = 0.023 (only significant difference) There was also no significant difference in ipratroprium bromide use or		which food eaten) and not based on allergy testing.

<table>
<tr><td colspan="11">Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?</td></tr>
<tr><th>Bibliographic reference</th><th>Study type and objective</th><th>n</th><th>Patient characteristics</th><th>Definitions</th><th>Characteristics of initial reaction</th><th>Anaphylaxis treatment protocol and observation</th><th>Rate of biphasic reactions</th><th>Timing of biphasic reaction and characteristics</th><th>Comparison of patients with biphasic to those with uniphasic reactions</th><th>Funding source</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Median time spent as an inpatient was 1.45 days (range: 0.33-21.57).</td><td></td><td></td><td></td><td>intubation.</td><td></td><td></td></tr>
<tr><td>Stark (1986)

USA</td><td>Prospective cohort

Objective to analyse causes, presenting characteristics, and subsequent courses</td><td>25</td><td>Consecutive patients presenting in a 2-year period (1982–84) with anaphylaxis (IgE and non-IgE mediated) to one hospital.

Adults: mean 41.8 years (range 17 to 71)</td><td>Anaphylaxis–based on 2 criteria: 1) presence of acute, otherwise unexplained syndrome that included hypotension, laryngeal oedema,</td><td>Causes:<table><tr><td></td><td>Biphasic (n=5)</td><td>Uniphasic (n=20)</td></tr><tr><td>Drugs</td><td>5*</td><td>7**</td></tr><tr><td>Antivenom</td><td>0</td><td>1</td></tr><tr><td>Insulin</td><td>0</td><td>1</td></tr><tr><td>Foo</td><td>0</td><td>3</td></tr></table></td><td>Cardiac monitoring, airway management, oxygen, epinephrine, diphenhydramine, cimetidine, theophylline, infused sympthat</td><td>20% (5/25)</td><td>Asymptomatic intervals between 1 and 8 hours.

3 of the 5 had initial treatment with glucocorticoids</td><td>Comparison of patient characteristics and treatments:<table><tr><td></td><td>Biphasic (n=5)</td><td>Uniphasic (n=20)</td></tr><tr><td>Age</td><td>35y (21–67)</td><td>43y (17–71)</td></tr><tr><td>Male sex</td><td>40% (2)</td><td>25% (5)</td></tr></table></td><td>Not reporter</td><td>‘Anaphylaxis’ included non-IgE-mediated reactions (13 had evidence IgE mechanism).

12 hours may not be long enough</td></tr>
</table>

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
	of patients with anaphylaxis to determine the incidence of recurrent or prolonged anaphylaxis and identify factors that might predict or diminis		Gender: 28% (7/25) males, 72% (18/25) female	or lower respiratory obstruction and 2) clinical or immunologic phenomena supporting the diagnosis (concurrent presence of other symptoms or signs of mast cell-mediator release such as flushing,	d Unknown 0 1 * these included penicillin (2), cephalexin (2) and radiocontrast media (1); ** these included these included penicillin (4), cephazolin (1) and radiocontrast media (2) 13 were shown to have had IgE mechanism involved	omimetrics and normal saline were administered in most instances according to published guidelines. Patients were observed for 12 hours, until the			Epinephrine 80% (4) 95% (19) H1 antagonist 100% (5) 90% (18) H2 antagonist 60% (3) 65% (13) Steroids 80% (4) 80% (16) (percentages calculated by analyst from raw data)		to observe patients to detect biphasic reaction (and those with prolonged symptoms were not observed beyond resolution of symptoms which may also be inadequa

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
	h their occurrence.			urticaria, angioedema, or intense pruritis or evidence of the presence of IgE to the substance considered likely to have caused the reaction. Biphasic anaphylaxis–not defined	Skin tests positive in 10 of 11 with penicillin and cephalosporin causes (1 had persistent antihistamine and α-adrenergic agonist therapy), both with insulin and antivenom, and one food-allergic patient (soy bean extract). The other 2 food-allergic patients did not have IgE-mediated reactions.	reaction ceased, if symptoms persisted longer than 12 hours, or until death. When probably IgE-mediated, specific IgE by immediate wheal-and-flare skin testing					te to detect biphasic reaction). 10 patients excluded from analysis because: course and treatment could not be verified (6), recurrent idiopathic anaphylaxis and

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
						was used and patients were tested for sensitivity to penicillin, cephalosporin, insulin, equine antiserum and selected foods.					self-treated at home (2), and believed not to have been anaphylaxis (2: one with hypotension and the other with bronchospasm and urticaria and chronic asthma)

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
Yang (2008) **Korea**	Retrospective case series Objective was to study the incidence and mortality rate of anaphylaxis at a Korean hospital	138	Inpatients and outpatients (visiting the allergy clinic or emergency department) with anaphylaxis over a 6-year and 7-month period (2000–6). ICD-10 codes: T78.0 (anaphylactic shock due to adverse food reaction), T78.2 (anaphylactic shock, unspecified),	Anaphylaxis–any 1 of the following 3 criteria: 1) abrupt skin reaction plus either cardiovascular or respiratory system involvement, 2) at least 2 cutaneous, respiratory, gastrointestinal, or cardiovasc	Causes: Drugs: Radiocontrast media 20; NSAIDs 11; Antibiotics 8; Other 9; Total: 34% (48) Foods: Wheat flour 6; Buckwheat 4; Seafoo 4	Treatment protocol and observation period not reported.	1.6% (3/138) Causes: food (wild grape), NSAID, and exercise.	Not reported.	It was reported that no apparent sign or symptom could help predict a biphasic reaction but no explicit comparisons were made.	Not reported	Definition of anaphylaxis included patients with reduced blood pressure after exposure to known allergen. Not clear how long patients were followed-up and if some could

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			T80.5 (anaphylactic shock due to serum), T88.6 (anaphylactic shock due to adverse effect of correct drug of medicament properly administered). Food dependent exercise-induced anaphylaxis and anaphylactic transfusion records were mapped to these 4 codes in the hospitals	ular symptoms shortly after exposure to a likely allergen for that patient, 3) reduced blood pressure after exposure to known allergen for that patient. Biphasic anaphylaxis–not defined	d: Other: 9 Total: 21 % (29) Idiopathic: 13 % (18) Food-dependent exercise-induced: Wheat: 14 Apple: 1 Shrimp: 1 Unknown: 2 Total: 13 % (18						have developed a biphasic reaction and presented elsewhere. Authors state that low rate of biphasic reactions may be due to lack of prolonged observation of the

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
			electronic Order Communication System and other forms of anaphylaxis not associated with clinical feature of shock are included in the study. Gender: 54% (74/138) male, 46% (64/138) female Mean age: 40y (5 to 76) 0-9y: 0.7% (1) 10-: 9%		) Insect stings Bee: 13 Ant: 1 Mosquito: 1 Unknown: 1 Total: 12% (16) Exercise-induced: 2.9% (4) Transfusion-related (platelet concentrates): 3% (4) Latex: 0.7						patient after recovery. Patients with other forms of anaphylaxis not associated with clinical feature of shock are included.

Evidence Table 3 for Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	**Study type and objective**	**n**	**Patient characteristics**	**Definitions**	**Characteristics of initial reaction**	**Anaphylaxis treatment protocol and observation**	**Rate of biphasic reactions**	**Timing of biphasic reaction and characteristics**	**Comparison of patients with biphasic to those with uniphasic reactions**	**Funding source**	**Additional comments**
			<table><tr><td>19y</td><td>(12)</td></tr><tr><td>20-29y</td><td>28% (38)</td></tr><tr><td>30-39y</td><td>17% (23)</td></tr><tr><td>40-49y</td><td>10% (14)</td></tr><tr><td>50-59y</td><td>19% (26)</td></tr><tr><td>≥ 60 y</td><td>16% (22)</td></tr></table> Atopy: 70% (52) History of: food allergy (15), asthma (11), allergic rhinitis (9), skin allergy (7), drug allergy (5)		<table><tr><td></td><td>% (1)</td></tr></table> Causes were determined from clinical history of exposure to possible causative agents within 8 hours of reaction onset (used provocation and skin tests).						

Review question 3: What should be part of the review after a reaction to confirm a diagnosis of anaphylaxis and to guide referral?

No evidence

Review question 4: What information do people need after an anaphylactic reaction, and before referral?

Table 4

Evidence Table 4 for Review question 4: What information do people need after an anaphylactic reaction, and before referral?						
Bibliography (Ref ID)	**Research question/ study design**	**Population**	**Intervention**	**Outcomes**	**Comments**	**Author's conclusions**
Kastner, M. et all(2010)	Systematic Review to investigate the gaps in anaphylaxis management at the level of physicians, patients and the community	Physicians, patients and community settings	[Studies assessing the gaps in knowledge of anaphylaxis management]	**Gaps at Physician Level,** ***Theme 1 – Lack of Knowledge*** signs and symptoms to correctly diagnose anaphylaxis Auto – Injector provision, use and dose. ***Theme 2 – Anaphylaxis Management*** treatment with adrenaline and timing of administration ***Theme 3 – Follow-up Care*** Referral of patients to allergy service Prescribing auto injectors **Gaps at Patient & Community Level** ***Theme 1 – Lack of Knowledge*** Trigger avoidance, availability of educational tools instructions for use of auto injectors ***Theme 2 – Anaphylaxis Management*** use of auto injectors following anaphylaxis management plans ***Theme 3 – Follow-up Care*** Fear for restrictions of social activities and anxiety of subsequent reactions		Identified a total of 200 gaps in anaphylaxis management. Key themes that were common to all groups are insufficient knowledge of anaphylaxis and its management and how to use adrenaline injectors.

Evidence Table 4 for Review question 4: What information do people need after an anaphylactic reaction, and before referral?						
Bibliography (Ref ID)	**Research question/ study design**	**Population**	**Intervention**	**Outcomes**	**Comments**	**Author's conclusions**
Estelle, F. et al (2011)	World allergy organisation guideline summary – organised into 3 main sections: Assessment of patients with anaphylaxis Management of anaphylaxis in a health care setting Management of anaphylaxis at the time of discharge	Patients with anaphylaxis	n/a	**Management of anaphylaxis at time of discharge from a health care setting** Preparation of self treatment for anaphylaxis recurrence in the community • Patients should be discharged with epinephrine or a prescription for epinephrine • Should be taught why, when and how to inject epinephrine • Equip patients with a personalised written anaphylaxis emergency action plan that helps them to recognise anaphylaxis symptoms and instructs them to inject epinephrine promptly and seek emergency assistance **Anaphylaxis education before discharge** • Advise that patients have experienced a potentially life threatening medical emergency • Advise on biphasic reactions within 72 hours and use of the Epipen and call emergency services • Advise that they are at increased risk for future episodes of anaphylaxis • Advise patients they require a follow up by an allergy/immunology specialist • Medical identification should be given e.g. bracelet or wallet card stating their diagnosis of anaphylaxis and any concomitant diseases and concurrent medications		At the time of their discharge from the healthcare setting equip patients with epinephrine for self administration an anaphylaxis emergency plan and medical identification to facilitate prompt recognition and treatment of anaphylaxis recurrence

Evidence Table 4 for Review question 4: What information do people need after an anaphylactic reaction, and before referral?						
Bibliography (Ref ID)	**Research question/ study design**	**Population**	**Intervention**	**Outcomes**	**Comments**	**Author's conclusions**
Danica, B (2008)	Opinion Piece	n/a	n/a	**<u>Hospital Discharge and follow up after anaphylaxis</u>** Before discharge every patient successfully treated for an anaphylactic reaction should be given specific instructions on: • Prevention strategies • identification of symptoms of anaphylaxis • adrenaline administration	Continuing medical education activity	Before discharge all patients should receive patient education about anaphylaxis, a prescription for self injectable adrenaline
Lieberman, P. (2007)	Opinion Piece to provide an overview of the scientific literature documenting the inconsistencies and limitations in the managem	n/a	n/a	**Use of SAFE system in treating and managing anaphylaxis**: **<u>S</u>**<u>eek Support</u> Advise patients there is a risk of recurrence **<u>A</u>**<u>llergen identification and Avoidance</u> Advise on avoiding trigger **<u>F</u>**<u>ollow-up for Speciality Care</u> Advise the patient they require a follow up with a allergy specialist	Designed by expert panel of allergy specialists	It was noted that emergency department physicians who interact with patients in the immediate aftermath of an anaphylactic event are in a unique

Evidence Table 4 for Review question 4: What information do people need after an anaphylactic reaction, and before referral?						
Bibliography (Ref ID)	**Research question/ study design**	**Population**	**Intervention**	**Outcomes**	**Comments**	**Author's conclusions**
	ent of anaphylaxis			**E**pinephrine for emergencies Instructions on use of adrenaline injectors and when to use them		position to facilitate patient education about the importance of follow up and ongoing disease management to prevent future allergic emergencies

Review question 5: Who should be referred, when and to where or whom?

Table 5

Evidence table for review question: 5 Who should be referred, when and to where or whom??

Bibliographic reference	Study type	Study quality	Number of patients	Patient Characteristics	Prognostic factor(s)	Length of follow-up[1]	Outcome measures	Results	Source of funding	Additional comments
Cianferoni A, Novembre E, Pucci N, et al. 2004 Anaphylaxis: a 7 year follow—up survey of 46 children. Ann Allergy Asthma Immunol; 92:464-468 Italy	Observational retrospective	Low risk of bias but unclear how patients were selected	46 (of 76 from a previous cohort study, re-evaluated after a mean of 7 years) Inclusion for previous study: Patients with anaphylaxis referred to an allergy unit (Florence, Italy) who had at least 2 of the main indicators of anaphylactic	Diagnosed anaphylaxis. Mean age 14 yrs (SD 4.92 yrs, range 7-26 yrs). Age at first episode: 5.8 yrs (SD 4.9, 1-18 yrs). 61 % male. No details on weight and ethnicity. Aetiology, food 19.5% (9/46), exercise 4.4% (2/46), drug 2.2% (1/46), idiopathic 4.4% (2/46).	Age, Gender, Age at first episode, allergen, other medical conditions.	7 yrs (SD 1 yr, range 5-8.6 yrs)	Recurrence defined as the presence of another anaphylaxis episode: at least 2 of the main indicators of anaphylactic reaction (hypotension, inspiratory dyspnea, and urticaria-angioedema) within 2 hours after exposure to one of the most probable causative agents. Defined risk factors for	Risk of recurrence: 30 % (14/46)	N/R	

[1] For those studies which were retrospective follow up is defined as the length of time that was retrospectively considered.

Evidence table for review question: 5 Who should be referred, when and to where or whom??										
Bibliographic reference	**Study type**	**Study quality**	**Number of patients**	**Patient Characteristics**	**Prognostic factor(s)**	**Length of follow-up[1]**	**Outcome measures**	**Results**	**Source of funding**	**Additional comments**
			reaction (hypotension, inspiratory dyspnea, and urticaria-angioedema) within 2 hours after exposure to one of the most probable causative agents.				recurrence: history of atopic dermatitis, current urticaria/ angioedema, history to sensitivity to 1 food allergen.			
Decker WW, Bellolio MF, Campbell RE, et al 2008 Recurrent Anaphylaxis in patients presenting to the Emergency Department over a 10 year period. Annals of Emergency Medicine; 51 (4): 536	Observational prospective	Low risk of bias but no definition of recurrence given.	211 (visiting an ED). Diagnosed anaphylaxis criteria from the National Institutes of Health/Food and Allergy	Mean age: 29.3 years (SD 18.2). 44.1 % male. No further details.	Gender, Age, Race, Allergens (no details provided on how these were ascertained)	Mean 1.1 yrs (range 7 days to 13 yrs)	No details provided	2nd event in 45/211 (21.3 %). Median time of presentation: 395 days (range 7d-13yrs). 3rd event in 11/211 (5.2 %). Risk of	N/R	

Evidence table for review question: 5 Who should be referred, when and to where or whom??										
Bibliographic reference	**Study type**	**Study quality**	**Number of patients**	**Patient Characteristics**	**Prognostic factor(s)**	**Length of follow-up[1]**	**Outcome measures**	**Results**	**Source of funding**	**Additional comments**
Abstract only USA			and Anaphylaxis network.					recurrence for women higher (RR 2.14, 95 %-CI 1.17 to 3.9). No difference in age (p=0.535) or race (p=0.743) for a subsequent event.		
Mehl A, Wahn U, Niggemann 2005 Anaphylactic reactions in children - a questionnaire based survey in Germany Allergy 2005: 60: 1445 Germany	Observational retrospective	Medium risk of bias as no definition of recurrence was given. Role of funding source unclear.	103 children (<12 yrs) Inclusion: reported accidental anaphylactic reactions occurring during 12 months in infants and children below 12 years of	Median age 5 yrs (range 3mths-12 yrs). 58 % male. No details on weight and ethnicity. Causative allergen was known or strongly suspected in 95/103 (92 %) of all patients. Overall: Food 57 % (59/103), Insect sting	Allergens investigated: Food (peanut, tree nut, cow's milk, fish, hen's egg, other); Insect sting; SIT; Medication; Other; Unknown. Allergy testing performed in	1 yr (patients identified over a period of 12 mths retrospectively)	Questionnaire covering demographic data, symptoms and physical findings of the episode, place of occurrence, suspected allergen, diagnostic tests, treatment	'No significant difference was found for allergens looking only at severe reactions (grades III and IV)' (no data reported). Age differences:	Industry: InfectoPharm Arzneimittel und Consilium GmbH, Heppenheim, Germany ('financial support')	

Evidence table for review question: 5 Who should be referred, when and to where or whom??										
Bibliographic reference	**Study type**	**Study quality**	**Number of patients**	**Patient Characteristics**	**Prognostic factor(s)**	**Length of follow-up[1]**	**Outcome measures**	**Results**	**Source of funding**	**Additional comments**
			age. Reports reviewed individually by two paediatric allergologists. Exclusion: reported cases excluded if the reported episode was not accidental (e.g. occurred after diagnostic provocation) or if the patient was not under the age of 12.	13 % (13/103), SIT 12 % (12/103), Medication 6% (6/103), Other* 4 % (4/103), Unknown 8 % (9/103). Foods only: 57 % (59/103): Peanut 20 % (12/59), Tree nut 20 % (12/59), Cow's milk 14 % (8/59), Fish 14 % (8/59), Hen's egg 7 % (4/59), Other* 25 % (15/59)	70 (68%) cases, not performed in 26 (25%) of cases, no information provided for 7 (7%) cases. Specific IgE serum concentrations determined in 63 children and/or skin prick tests performed in 28 cases. 10 children went through an allergen provocation and 4 underwent atopy patch testing.		modalities such as use of drugs, route of application, and drug administering person, hospitalization and prescribed emergency set after the episode	Food, 'patients significantly younger than the overall group' (mean 3.9 yrs, SD 3). SIT, ' significantly older' (mean 9.8 yrs, SD 1.9) Venom, 'patients significantly older' (mean 7.6 yrs, SD 3.2) Recurrence: Overall 27 % (28/103). Food-related 71 % (20/28). Insect sting		

Evidence table for review question: 5 Who should be referred, when and to where or whom??										
Bibliographic reference	**Study type**	**Study quality**	**Number of patients**	**Patient Characteristics**	**Prognostic factor(s)**	**Length of follow-up[1]**	**Outcome measures**	**Results**	**Source of funding**	**Additional comments**
								7 % (2/28). SIT 7 % (2/28). Unknown 14.3 % (4/28). Same allergen as episode(s) in medical history 50 % (14/28)		
Mugica Garcia M, Tejedor Alonso M, RojasPerez Ezquerra P, et al 2010 A study of the recurrence of anaphylaxis Allergy 65 (Suppl 92): 587 Abstract only Spain	Observational retrospective	Medium risk of bias as only 58.7 % of previous cohort were included and no details on age, gender, weight and ethnicity were reported.	933 (original cohort of 1590). Presented anaphylaxis and were followed in allergy unit (no further details).	Diagnosed anaphylaxis. Mainly urban community. No details on age, gender, weight and ethnicity.	Various allergens investigated: Latex, food, drug, anisakis, exercise, idiopathic, hymenoptera venom	N/R	Recurrence defined as any new episode of anaphylaxis, irrespective of the cause of the first episode and whether the recurrence was the same or different. The recurrence	Overall risk 325/933 (34.8 %). Same type as first episode. Latex: 72.7 % Food: 38.8 % Unknown 32.9 % Hymenoptera venom 33.3 %	N/R	

Evidence table for review question: 5 Who should be referred, when and to where or whom??										
Bibliographic reference	**Study type**	**Study quality**	**Number of patients**	**Patient Characteristics**	**Prognostic factor(s)**	**Length of follow-up[1]**	**Outcome measures**	**Results**	**Source of funding**	**Additional comments**
							of the same subtype of anaphylaxis was considered when the same subtype of anaphylaxis (e.g. food, drugs, exercise) was responsible for both the first episode and for the recurrence.			
Mullins RJ 2003 Anaphylaxis; risk factors for recurrence Australia	Observational prospective	Low risk of bias but no definition of recurrence given.	432 patients referred for evaluation of possible anaphylaxis to community-based specialist medical	Mean age 27.4 yrs (SD 19.5, range: 1-82). 48 % male. No details on weight and ethnicity. 1st episode during study course/ before study: 71 %/ 29 %	Gender, allergen, co—morbidity.	2.2 yrs	Recurrence presented as proportion of patients relapsing. Rate of recurrence/ 100 patient-years of observation: calculated by dividing	130/304 (42.8 %) have experienced 386 episodes of recurrent symptoms (median 2, range 0-18). Risk of	N/R	

Evidence table for review question: 5 Who should be referred, when and to where or whom??										
Bibliographic reference	**Study type**	**Study quality**	**Number of patients**	**Patient Characteristics**	**Prognostic factor(s)**	**Length of follow-up[1]**	**Outcome measures**	**Results**	**Source of funding**	**Additional comments**
			practice between Feb 1995 and July 2000..				the cumulative length of observation by the number of recurrences involving that trigger.	overall recurrence: 57/100 pat-years; Risk of severe recurrence: 10/100 pat-years. Risk factors for recurrence: exercise and idiopathic cause, female gender. Risk of overall recurrence: 57/patient-years Risk of severe recurrence: 10/patient-years No deaths Serious recurrences: 10.4%		

Evidence table for review question: 5 Who should be referred, when and to where or whom??										
Bibliographic reference	**Study type**	**Study quality**	**Number of patients**	**Patient Characteristics**	**Prognostic factor(s)**	**Length of follow-up[1]**	**Outcome measures**	**Results**	**Source of funding**	**Additional comments**
								(45/432); had adrenaline: 40% (18/45) No serious recurrences: 19.7 (85/432); had adrenaline: 1.2% (1/85)		

Review question 6: Who should be given an emergency treatment plan and when should that include an adrenaline injector?

No evidence

Review question 7: What model or organisation of care should be adopted to improve the diagnosis of anaphylaxis post reaction?

Bibliographic reference	Review type and objective	Study inc/exc criteria	Databases searched	Study quality assessment	Results	Author conclusions or recommendations	Source of funding	Additional comments
Kastner et al. (2010)	Systematic review To summarise studies that examined gaps in anaphylaxis management	Included if quantitative or qualitative studies that investigated gaps in management and could be addressed in the context of quality of life of patients at risk or their carers Excluded if basic science, animal studies, case reports, or narrative reviews.	Medline (1966 to 2008) Embase (1980 to 2008) Cinahl (1982 to 2008) Cochrane Database of Systematic Reviews, ACP Journal Club, Dare (no dates) Grey literature (websites and digital dissertations) Handsearching of named journals	Assessed using various methods by study type Not clear how this was used in the results	59 studies included [Results on organisation of care only presented here] Referral to an allergy specialist was infrequently or not done after an acute reaction was identified as a gap (6 references). One study found that allergy testing and follow-up	No specific recommendations on referral, but general call for the development of interventional strategies and practice tools to address the knowledge and practice gaps in order to improve care.	King Pharmaceuticals Canada	Limited detail on methods Quality of studies not accounted for

Bibliographic reference	Review type and objective	Study inc/exc criteria	Databases searched	Study quality assessment	Results	Author conclusions or recommendations	Source of funding	Additional comments
			Reference lists Contacted experts		were more frequent in children attending hospital clinics. Settings included emergency departments (2), schools (1), community paediatric services (1), army hospital (1), and a local authority (1). Countries included France (1), UK (3), and the US (2).			
Abbreviations:								

Table 1 Evidence tables for primary studies on the model or organisation of care for the diagnosis of anaphylaxis

Bibliographic reference	Study type and objective	Number of participants	Description of study	Patient characteristics	Follow-up	Results	Source of funding	Additional comments
Krøigaard et al. (2005)	Retrospective record review To investigate	107 patients (assumed adults) with 111 allergic	Case notes of all patients with completed investigations at a single specialist allergy centre (Denmark; anaesthesia)	Not reported	Not relevant	36/48 (75%) grade III and III+ reactions had a 'suggested' potential allergen;	None reported	Single allergen Retrospective Single centre

Bibliographic reference	Study type and objective	Number of participants	Description of study	Patient characteristics	Follow-up	Results	Source of funding	Additional comments
	whether the cause of reaction as identified by the anaesthetist was the same as that confirmed on subsequent investigation	reactions 1999 to 2003	Allergen confirmed with specific IgE analysis (Pharmacia UniCAP for latex [all patients], and succinylcholine, thiopental, fentanyl, morphine, and various antibiotics [if exposed before reaction]) and skin testing (prick testing and if negative, intradermal [except latex]) for all substances exposed to before reaction.			25% had no suggested allergen. Overall, for all grades of reaction, 49/67 (73%) where a suggestion was made had no allergy confirmed (31/67; 46%) or had other allergens found (18/67; 27%). 5/67 (7%) had a complete match between the suggested allergen and the investigation result. 13/67 (19%) had a partial match (because of additional allergens either suggested and not confirmed or confirmed but not suggested).		Investigated results may be susceptible to false positives/negatives.
Abbreviations: IgE, immunoglobulin E								

Table 2 Evidence tables for referral guidelines on the model or organisation of care for the diagnosis of anaphylaxis

Bibliographic reference	Scope and purpose	Stakeholder involvement	Development process	Presentation	Applicability	Source of funding	Recommendations	Additional comments
Sweetman et al. (2006)	American Academy of Allergy Asthma and Immunology	AAAAI	Limited detail provided on evidence base	Clear recommendations with cited	Adults and children with suspected	None reported Declarations of	The following patients should be referred to a	None

Bibliographic reference	Scope and purpose	Stakeholder involvement	Development process	Presentation	Applicability	Source of funding	Recommendations	Additional comments
	(AAAAI) Aims to assist patients and HCPs in determining when referral to an allergist-immunologist could be helpful		or consensus process	references Recommendations graded	anaphylaxis	interest reported	allergist-immunologist: - Individuals with a severe allergic reaction (anaphylaxis) without an obvious or previously defined trigger (After a severe allergic reaction without a known cause, a trigger should be identified if at all possible. An allergist-immunologist is the most appropriate medical professional to perform this evaluation, which might include skin testing, in vitro tests, and challenges when indicated (including with exercise, see below). Major triggers for anaphylaxis are foods and food constituents, medications and biologic agents, latex, and insect stings. Future avoidance of the identified triggers should prevent subsequent anaphylactic episodes. Management of idiopathic anaphylaxis by an allergist-immunologist is associated with a reduction in hospitalizations and emergency department visits.) - Persons with anaphylaxis attributed to	

Bibliographic reference	Scope and purpose	Stakeholder involvement	Development process	Presentation	Applicability	Source of funding	Recommendations	Additional comments
							food (Food allergy is the most common cause of anaphylaxis outside of the hospital setting. Allergist-immunologists use diagnostic modalities to confirm the trigger and use their specific training and clinical experience to educate patients regarding avoidance and immediate management to prevent potentially deadly outcomes.) - Exercise-induced anaphylaxis and food-dependent exercise-induced anaphylaxis (After an anaphylactic reaction that appears to have a significant relationship to exercise, it is crucial to be certain whether exercise is the cause and to determine whether a food might be involved.) - Drug-induced anaphylaxis (Allergist-immunologists use diagnostic agents to confirm the drug responsible for the reaction, if these agents are available.)	

Bibliographic reference	Scope and purpose	Stakeholder involvement	Development process	Presentation	Applicability	Source of funding	Recommendations	Additional comments
							Based on non-randomised controlled intervention studies, observational, cohort or case controlled studies, and review articles or expert opinion.	
Waserman et al. (2010)	Various groups represented (Canada) To develop evidence based recommendations for gaps in anaphylaxis management in primary care	8 clinical experts in anaphylaxis (recruitment not described; not clear if patient/lay members or other relevant HCPs)	Based on systematic review (see Kastner 2010 above) and NGT consensus process	Clear recommendations Recommendations graded	Adults and children with suspected anaphylaxis	Funded by King Pharmaceuticals Canada Declarations of interest not reported.	Referral to an allergist - After acute anaphylaxis patients should be assessed for future risk of anaphylaxis + Anybody who has any rapid onset systemic allergic reaction (GI, respiratory cardiac) or diffuse hives to any food or stings + Anybody who has any rapid onset (i.e. minutes to hours) reaction of any severity to higher risk food such as peanuts, tree nuts, shellfish sesame - If uncertain, refer patient to allergist for evaluation Based on expert committee reports or opinions or clinical experience of respected authorities or both; or extrapolated from higher categories of evidence.	None
Abbreviations: HCP, healthcare professional; NGT, nominal group technique.								

Question 7 Evidence tables for narrative reviews on the model or organisation of care for the diagnosis of anaphylaxis

Bibliographic reference	Conclusions or recommendations	Source of funding	Additional comments
Zeiger and Schatz (2000)	Defined the allergist as 'the specialist called on to identify eth cause of an episode of anaphylaxis, to determine potential preventive measures, and to evaluate the patient who may need to receive a substance to which he or she has reacted previously.'	Novartis Pharmaceutical Corp	None
Abbreviations:			