children

MDPI

Systematic Review

Incidence, Timing, and Factors Associated with Biphasic Reactions in Children Presenting to the Emergency Department with Anaphylaxis: A Systematic Review and Meta-Analysis

Bing-Shiau Shang [1], Yu-Tzu Li [1], Ko-Huang Lue [1,2], Sai-Wai Ho [2,3,*] and Chia-Ta Wu [2,4,*]

[1] Department of Pediatrics, Institute of Allergy, Immunology, and Rheumatology, Chung Shan Medical University Hospital, Taichung 402, Taiwan; j6ji3@hotmail.com (B.-S.S.); tsz9903028@gmail.com (Y.-T.L.); cshy095@csh.org.tw (K.-H.L.)
[2] School of Medicine, Chung Shan Medical University, Taichung 402, Taiwan
[3] Department of Emergency Medicine, Chung Shan Medical University Hospital, Taichung 402, Taiwan
[4] Department of Emergency Medicine, Changhua Christian Hospital, Changhua 500, Taiwan
* Correspondence: hswwai@gmail.com (S.-W.H.); 133523@cch.org.tw (C.-T.W.)

Highlights

What are the main findings?

- The average incidence of biphasic reactions in children treated in the emergency department for anaphylaxis was approximately 4%, but it varied widely between studies (95% prediction interval 0.7–20.8%).
- In unadjusted analyses, children who needed more than one dose of epinephrine had about three times the odds of a biphasic reaction.

What are the implications of the main findings?

- Observation after pediatric anaphylaxis may be tailored to risk, and longer observation may be warranted for children who needed more than one dose of epinephrine.
- A shorter observation period for low-risk children should be paired with discharge education, a prescription for an epinephrine autoinjector, and clear instructions on when to return. The data do not define a single optimal observation period.

Abstract

Background/Objectives: Observation time after pediatric anaphylaxis depends on the risk of a biphasic reaction. We estimated the incidence, timing, and associated factors of biphasic reactions in children treated in the emergency department. **Methods:** We searched PubMed, Embase, and Web of Science up to 8 October 2026 for cohort studies of biphasic reactions in children (0–18 years) with anaphylaxis. Two reviewers screened studies and verified data extraction, and risk of bias was assessed with the JBI checklist for prevalence studies. Proportions were pooled with a random-intercept logistic generalized linear mixed model, and associated factors with random-effects Mantel–Haenszel odds ratios. The protocol was registered with INPLASY (INPLASY2026100034), and the review received no funding. **Results:** Thirty-five studies were included. In 18 emergency department cohorts (2086 children in 8 patient-based studies and 7651 anaphylaxis episodes in 10 episode-based studies), the pooled incidence was 4.2% (95% confidence interval [CI] 2.6–6.5%), with high heterogeneity (prediction interval 0.7–20.8%). It was 2.9% in patient-based studies and 5.5% in studies requiring complete resolution of the initial reaction. Biphasic anaphylaxis (4 studies) occurred in 2.3% (95% CI 1.2–4.5%). Some reactions occurred 10 h or more after the initial reaction or after discharge. In unadjusted analyses, more than one dose of epinephrine (odds ratio 2.97, 95% CI 1.66–5.32; 3 studies) and a drug trigger (odds ratio 2.70, 95% CI 1.27–5.73; 4 studies) were associated with biphasic reactions. Certainty

Check for updates

Academic Editor: Arianna Dondi

Received: 20 October 2026
Revised: 9 November 2026
Accepted: 12 November 2026
Published: 14 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

of evidence was low for incidence and for both associations. **Conclusions:** On average, about 4% of children treated in the emergency department for anaphylaxis have a biphasic reaction, but rates vary widely across studies and settings. Needing more than one dose of epinephrine is a marker of higher risk that may justify longer observation. The data support risk-stratified observation but do not define a single optimal observation period.

Keywords: anaphylaxis; biphasic reaction; children; emergency department; epinephrine; meta-analysis; observation period; systematic review

1. Introduction

Anaphylaxis is a common pediatric emergency, and emergency department (ED) visits and hospitalizations for anaphylaxis in children have risen steadily over the past two decades [1]. Once symptoms resolve, the most common question facing the ED physician is how long the child should stay. The main concern is a biphasic reaction, in which symptoms return after complete resolution without further exposure to the trigger. This term covers recurrences ranging from mild cutaneous symptoms to a second phase that again meets diagnostic criteria for anaphylaxis (biphasic anaphylaxis), and the two have different clinical implications. Worsening before complete resolution, by contrast, represents persistent or refractory anaphylaxis rather than a biphasic reaction.

Guidance on observation time varies from 1 to 24 h and rests mostly on evidence from adults or mixed-age populations [2–4]. A systematic review of factors influencing ED observation time did not include a meta-analysis [4]. The most widely cited meta-analysis, by Lee and colleagues, pooled 27 studies and 4114 patients, most of them adults, with inconsistent definitions and no separate analysis of children [5]. Since 2015, several pediatric ED studies have been published, including a multicenter study of more than 5000 children from 30 pediatric EDs [6], and a 2020 Delphi consensus has provided a standard definition of biphasic anaphylaxis [7]. These newer data have not been pooled.

We therefore conducted a systematic review and meta-analysis of children presenting to the ED with anaphylaxis to estimate (1) the pooled incidence of biphasic reactions, stratified by how strictly they were defined; (2) the timing of biphasic reactions; and (3) clinical factors associated with biphasic reactions. These estimates are intended to inform decisions on observation time; a review of observational cohorts cannot directly compare the safety of specific observation periods.

2. Materials and Methods

2.1. Registration and Reporting

This review followed the PRISMA 2020 statement [8]. The protocol was registered with INPLASY (registration number INPLASY2026100034) on 8 October 2026 and has been published [9]. There were no amendments to the registered protocol. The subgroup variables and sensitivity analyses were listed in the protocol. The protocol stated that multivariable meta-regression would be used but did not specify its variables, which were chosen on the basis of the subgroup results. Pooling by unit of analysis, pooling by definition with restricted sampling excluded, and stability analyses of the meta-regression were added in response to peer review.

2.2. Ethics

Ethical approval and informed consent were not required because this review used only data from previously published studies.

2.3. Eligibility Criteria

We included prospective or retrospective cohort studies and chart reviews of children aged 0 to 18 years with anaphylaxis (at least 10 cases) that reported the number of children with anaphylaxis and the number with biphasic reactions. Mixed-age studies were eligible if pediatric data could be separated or if children made up at least 80% of the sample. Two studies were included on this basis: one study enrolled patients up to 19 years of age [10], and in the other, 11 of 345 patients were 15 years or older [11]. The influence of each was examined in the leave-one-out analysis (Table S4). The primary analysis was limited to children presenting to the ED, including those admitted through the ED. The secondary analysis also included pediatric cohorts from other settings, such as allergy clinics, inpatient wards, and registries. We excluded case reports, reviews, conference abstracts, and other material not published after peer review because their methods and definitions could not be appraised reliably. We also excluded studies in which all reactions were induced by medical procedures (oral food challenge, immunotherapy, drug provocation testing, or surgery and anesthesia). When two reports fully overlapped, we kept the larger one. Partially overlapping studies were both retained and examined in sensitivity analyses. All partially overlapping studies were in the secondary analysis, so none contributed to the primary pooled estimate. No language restrictions were applied.

2.4. Search Strategy

PubMed, Embase, and Web of Science Core Collection were searched with terms for anaphylaxis, biphasic or delayed reactions and observation time, and children (full strategies in Table S1). Preliminary searches were run on 2 October 2026 to confirm that eligible studies could be retrieved, and the final searches, run on 8 October 2026, when the protocol was registered, retrieved the same records. Broad terms for recurrence and observation time were included in addition to "biphasic" so that studies reporting biphasic reactions as a secondary outcome could be identified. Reference lists of included studies and relevant reviews were checked, and journal websites were searched on 3 October 2026.

2.5. Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts and then full texts, and disagreements were resolved by discussion. No automation tools were used in screening or data extraction. Extracted items included study characteristics, setting, age, unit of analysis (patients or episodes), number and definition of biphasic reactions, follow-up window, timing, and 2 × 2 data for candidate-associated factors. One reviewer extracted the data and a second checked them against the original articles. Study investigators were not contacted for additional data. Information that was missing or unclear was recorded as not reported, and no data were imputed. For published articles whose full text could not be obtained, data were taken from the abstract when it reported the number of children with anaphylaxis and the number with biphasic reactions and the study otherwise met the eligibility criteria; these studies were removed in a sensitivity analysis. In one study, 5 of 8 children with biphasic reactions arrived at the ED during the second phase, so their initial reaction was not observed in the ED. They were excluded from both the numerator and the denominator in the primary analysis (3 of 340) and included in a sensitivity analysis (8 of 345) [11].

2.6. Outcomes

Three outcomes were defined in the protocol. A biphasic reaction (primary outcome) was a recurrence of symptoms after complete resolution of the initial reaction without further exposure to the trigger, as defined by each study. Biphasic anaphylaxis was a second phase that again met diagnostic criteria for anaphylaxis according to the 2020 Delphi

consensus [7]. A clinically important biphasic reaction was one requiring epinephrine or other active treatment (for example, oxygen, vasopressors, intubation, or frequent nebulized bronchodilators). Worsening before complete resolution was regarded as persistent or refractory anaphylaxis and not as a biphasic reaction. A study's definition of a biphasic reaction was classified as explicit when the study stated a definition that required complete resolution of the initial reaction and as not defined otherwise. Studies with an explicit definition were analyzed separately as a core sensitivity analysis. The definitions are summarized in Table S5.

2.7. Risk of Bias

Risk of bias was assessed with the JBI checklist for prevalence studies [12]. This tool was chosen because the primary outcome was a proportion, and its items address the sampling frame, recruitment, sample size, measurement, and coverage that determine the validity of an incidence estimate, whether data were collected prospectively, retrospectively, or through registries. Differences in design were examined in subgroup analyses. One reviewer performed the assessment and a second checked it, and disagreements were resolved by discussion. Studies with 7 or 8 of items 1 to 8 rated "yes" were considered low risk, 5 or 6 moderate risk, and 4 or fewer high risk. These overall categories were defined in advance for summary purposes only, and interpretation relied mainly on item-level judgments. Item 3 (sample size) mainly reflects precision rather than systematic bias. Item 9 (response rate) does not apply to studies based on medical records and was not scored. The sample size threshold for item 3 was set at 203, based on an expected proportion of 5% and a precision of ±3% [13]. Item-level ratings are given in Table S3.

2.8. Statistical Analysis

Study characteristics and results were tabulated (Tables 1–3) and displayed in forest plots. Proportions were pooled with a random-intercept logistic generalized linear mixed model (GLMM) using adaptive Gauss–Hermite quadrature [14], which avoids the bias of the Freeman-Tukey transformation when events are rare [15]. Confidence intervals were obtained by profile likelihood, and we report I^2 [16] and 95% prediction intervals [17]. Exploratory subgroup analyses by definition, follow-up window, region, design, publication period (before or after 2015), and unit of analysis were compared with likelihood ratio tests. Region was assigned by the country in which each study was conducted (Asia: China, Japan, Singapore, and Thailand; Europe and the Middle East: Spain and Türkiye; North America: Canada and the USA; Oceania: Australia; Latin America: Brazil). Because episode-based studies may count repeated episodes in the same child, results were also pooled separately for patient-based and episode-based studies. To explore heterogeneity further, region (Asian vs. non-Asian), unit of analysis, and definition were entered together in a multivariable meta-regression, and the proportion of between-study variance (τ^2) explained was calculated. Because only 18 studies were available, the meta-regression was regarded as exploratory, and its stability was examined with leave-one-out analysis and a permutation test (5000 permutations) of a corresponding random-effects model with the Hartung–Knapp adjustment. Sensitivity analyses excluded loosely defined studies, zero-event studies, studies with restricted sampling (only children who received epinephrine, were hospitalized, or were observed for at least 6 h), the largest study, studies with abstract-only data, partially overlapping studies, and studies including in-hospital onset; a leave-one-out analysis was performed. Outlying studies were identified by studentized residuals with an absolute value above 1.96, and their influence was examined with influence diagnostics [18]. Timing was summarized from studies reporting individual case data, stratified by the reference

point (initial reaction, symptom resolution, or start of treatment), and we calculated the proportion of biphasic reactions occurring after 6 h.

Candidate factors reported by at least three studies were pooled as unadjusted odds ratios (ORs) with a Mantel–Haenszel random-effects model (DerSimonian–Laird). Because DerSimonian–Laird intervals can be too narrow when few studies are available, we repeated the analysis with restricted maximum likelihood and the Hartung–Knapp adjustment [19] and with a fixed-effect model. Multivariable estimates reported by individual studies were summarized alongside the pooled unadjusted ORs. Small-study effects were assessed with funnel plots and Egger's test [20], treated as exploratory and not as evidence of publication bias, because funnel plot methods are unreliable for proportions [21]. Because the standard error of a logit proportion depends largely on the number of events, we also drew a funnel plot against sample size and used a regression test based on the inverse square root of sample size. Proportions were analyzed in R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria) with the metafor package version 4.4.0 [22] and the lme4 package version 1.1-35 [23], and odds ratios in Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, London, UK). Forest plots and risk-of-bias plots were drawn in R version 4.3.3 with the metafor and ggplot2 (version 3.4.4) packages.

2.9. Assessment of Certainty of Evidence

Certainty of evidence was rated with GRADE, following guidance for prognostic estimates [24] and prognostic factors [25]. Evidence from cohort studies started at high certainty and was rated down for risk of bias, inconsistency, indirectness, imprecision, and publication bias, giving a final rating of high, moderate, low, or very low. For associated factors, possible confounding by the severity of the initial reaction was considered under risk of bias.

2.10. Use of Generative Artificial Intelligence

A large language model (Claude Opus 5.5, Anthropic, San Francisco, CA, USA) was used to translate the authors' Chinese draft into English and for English language editing. The tool was not used for literature searching, study selection, data extraction, or risk-of-bias assessment, which were performed by the authors. Only aggregate data from published studies were entered into the tool. The authors reviewed all output and take full responsibility for the content of this article.

Table 1. Characteristics of the studies in the primary analysis (emergency department-based cohorts).

Study	Country	Design	Setting	Age	Unit	N	Biphasic, n (%)	Definition	Window	Risk of Bias
Dribin 2025 [6]	USA	Multicenter retrospective cohort	Pediatric ED	6 mon to <18 y	Episode	5641	322 (5.7%)	Explicit	Not stated	Moderate
Rueter 2026 [26]	Australia	Retrospective cohort	Pediatric ED	0–2 y	Episode	239	11 (4.6%)	Explicit	48 h	Low
Aygün 2026 [27]	Türkiye	Retrospective cohort	Pediatric ED	0–18 y	Patient	166	10 (6.0%)	Explicit	72 h	Low
Bonadio 2025 [10]	USA	Retrospective cohort	Pediatric/ general ED	3 mon–19 y	Episode	357	49 (13.7%)	Not defined	48 h	Moderate
Oliveira 2025 [28]	Brazil	Retrospective cross-sectional	Pediatric ED	0–18 y	Episode	51	8 (15.7%)	Not defined	Not stated	Moderate
Hlady 2024 [29]	USA	Prospective and retrospective cohort	ED	<18 y	Patient	366	21 (5.7%)	Explicit	48 h	Moderate
Short 2024 [30]	USA	Retrospective cohort	ED	<18 y	Patient	292	10 (3.4%)	Not defined	72 h	Moderate
Su 2023 [31]	China	Retrospective	Pediatric ED	0–16 y	Episode	110	2 (1.8%)	Not defined	Not stated	Moderate
Ikegawa 2021 [32]	Japan	Retrospective cohort	Pediatric ED to admission	0 to <16 y	Patient	353	6 (1.7%)	Explicit	72 h	Low
Uppala 2021 [33]	Thailand	Retrospective	Pediatric ED	0–18 y	Patient	76	3 (3.9%)	Not defined	Not stated	Moderate
Olabarri 2020 [34]	Spain	Multicenter prospective	Pediatric ED	<18 y	Patient	453	14 (3.1%) [a]	Explicit	Not stated	Low
Ganapathy 2016 [35]	Singapore	Retrospective	Pediatric ED	<16 y	Episode	485	3 (0.6%)	Not defined	Not stated	Moderate
Alqurashi 2015 [36]	Canada	Retrospective cohort	Pediatric ED	<18 y	Episode	484	71 (14.7%)	Explicit	72 h	Low
Nagano 2013 [11]	Japan	Retrospective	Mainly pediatric ED	Median 36 months	Patient	340	3 (0.9%)	Not defined	Not stated	Moderate
Mehr 2009 [37]	Australia	Retrospective	Pediatric ED, admitted ≥6 h	<18 y	Episode	109	12 (11.0%)	Explicit	Not stated	Moderate

Table 1. *Cont.*

Study	Country	Design	Setting	Age	Unit	N	Biphasic, n (%)	Definition	Window	Risk of Bias
Lee & Greenes 2000 [38]	USA	Retrospective	Inpatient (via ED)	<18 y	Episode	105	6 (5.7%)	Explicit	24-h observation	Moderate
Akcan Yildiz 2022 [39]	Türkiye	Retrospective	Pediatric ED	0–18 y	Patient	40	0 (0%)	Not defined	Not stated	Moderate
Ayar 2026 [40]	Türkiye	Retrospective cohort	Pediatric ED	0–18 y	Episode	70	3 (4.3%)	Explicit	72 h	Low

Definition: "explicit" indicates a stated definition requiring complete resolution of the initial reaction; "not defined" indicates no definition or no requirement for resolution. Unit: "episode" indicates analysis by anaphylaxis episode, "patient" by child. Risk of bias was judged on JBI items 1 to 8. [a] Clinically important biphasic reactions. Nagano 2013: 5 of 8 children with biphasic reactions arrived during the second phase and were excluded from the numerator and denominator; counting them gave 8 of 345 (Table S4). Characteristics of the 17 additional studies in the secondary analysis are given in Table S6. ED, emergency department; N, number of children or episodes analyzed; Window, follow-up window for biphasic reactions; mon, months; y, years.

Table 2. Pooled incidence of biphasic reactions by study characteristics (primary analysis).

Analysis	Studies	N	Events	Pooled Incidence, % (95% CI)	95% PI, %	I^2
All studies (primary analysis)	18	9737	554	4.2 (2.6–6.5)	0.7–20.8	94%
Unit of analysis						
Patient-based studies	8	2086	67	2.9 (1.6–4.6)	1.0–8.2	65%
Episode-based studies	10	7651	487	5.8 (2.9–10.7)	0.9–29.3	96%
Definition						
Explicit, complete resolution required	10	7986	476	5.5 (3.5–8.1)	1.8–15.7	89%
Not defined or resolution not required	8	1751	78	2.7 (0.8–7.1)	0.2–27.1	90%
Explicit and patient-based	4	1338	51	3.7 (1.9–6.7)	1.5–8.8	64%
Sampling						
Restricted sampling excluded [a]	9	2398	125	3.6 (1.6–7.7)	0.4–25.1	91%
Explicit definition and restricted sampling excluded	5	1412	109	5.8 (2.8–10.7)	1.6–18.5	83%
Region						
Non-Asian studies	13	8373	537	6.4 (4.3–9.0)	2.1–18.0	89%
Asian studies	5	1364	17	1.3 (0.7–2.5)	0.7–2.3	7%

Pooled with a random-intercept logistic generalized linear mixed model. N is the number of children (patient-based studies) or anaphylaxis episodes (episode-based studies). [a] Studies that included only children who received epinephrine (Dribin 2025 [6], Bonadio 2025 [10], Hlady 2024 [29], Short 2024 [30]), were hospitalized (Ikegawa 2021 [32], Uppala 2021 [33], Lee & Greenes 2000 [38], Akcan Yildiz 2022 [39]), or were observed for at least 6 h (Mehr 2009 [37]). CI, confidence interval; PI, prediction interval.

Table 3. Timing of biphasic reactions.

Study	Reference Point	Timing of Biphasic Reactions
Primary analysis		
Rueter 2026 [26]	Initial reaction	70–330 min
Bonadio 2025 [10]	Start of treatment	All within 4 h
Short 2024 [30]	Symptom resolution	6 at 30–150 min (mean 96 min); 4 at 10–33 h after discharge
Su 2023 [31]	Initial reaction	4.5 h and 12 h
Ikegawa 2021 [32]	Initial reaction	Median 5.9 h (IQR 3.3–7.6)
Uppala 2021 [33]	Initial reaction	10, 12, and 18 h
Ganapathy 2016 [35]	Initial symptoms	12, 14, and 18 h
Alqurashi 2015 [36]	Initial reaction	Before discharge (n = 53): median 4.7 h (IQR 3.3–6.0); after discharge (n = 18): median 18.5 h (IQR 9.2–25.2)
Nagano 2013 [11]	Initial reaction	5.2, 11, and 18 h
Mehr 2009 [37]	Initial reaction	Median 8.8 h (range 1.3–20.5)
Ayar 2026 [40]	Symptom resolution	All 3 within 3 h

Table 3. *Cont.*

Study	Reference Point	Timing of Biphasic Reactions
Secondary analysis		
Koken 2026 [41]	Symptom resolution	Median 4 h (1–24 h)
Maris 2021 [42]	Not stated	21% after 12 h
Dibek Misirlioglu 2017 [43]	Symptom resolution	Symptom-free interval 30 min–4 h
Vezir 2013 [44]	Symptom resolution	Symptom-free interval 30 min–9 h

IQR, interquartile range; h, hours; min, minutes.

3. Results

3.1. Study Selection

The database searches returned 549 records (PubMed 146, Embase 241, Web of Science 162). After removing duplicates, 325 records were screened by title and abstract. Of 58 reports sought for retrieval, 3 could not be obtained, and 2 of these were included using data from their published abstracts; the abstract of the third did not report biphasic reaction data. Of 55 full texts assessed, 23 were excluded (ineligible population, 16; no biphasic data or mismatched outcome, 6; duplicate population, 1; Table S2), leaving 32. Adding the 2 studies included from published abstracts and 1 further study identified through the updated journal website search gave 35 included studies (Figure 1).

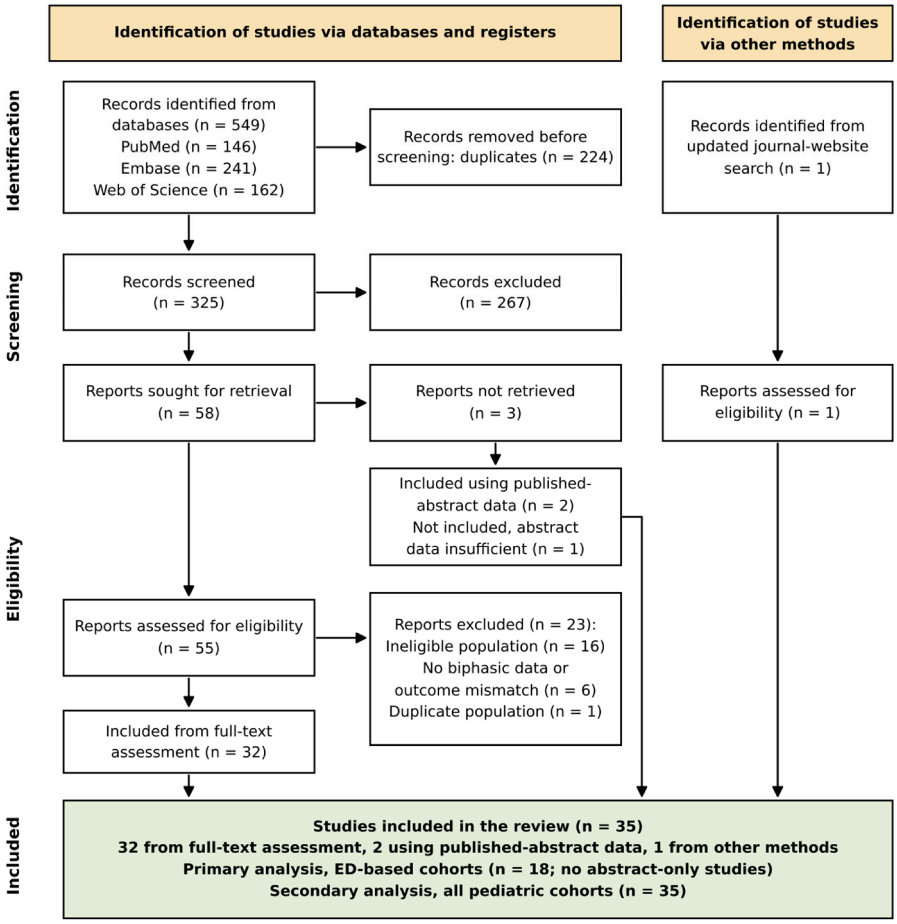

Figure 1. PRISMA 2020 flow diagram of study selection.

3.2. Study Characteristics

The primary analysis included 18 studies [6,10,11,26–40] with 9737 children or anaphylaxis episodes: 8 studies (2086 children) counted patients and 10 studies (7651 episodes) counted episodes. The studies were published between 2000 and 2026, 15 of them in or after 2015. Six were from North America, 5 from Asia, 4 from Europe and the Middle East, 2 from Oceania, and 1 from Latin America. The secondary analysis added 17 studies [41–57], giving a total of 13,765 children or episodes, mostly from allergy clinics, inpatient settings, or registries. Characteristics of the studies in the primary analysis are shown in Table 1, and those of the additional studies in the secondary analysis in Table S6. Nine studies in the primary analysis included only children who received epinephrine, were hospitalized, or were observed for at least 6 h.

3.3. Pooled Incidence

The pooled incidence of biphasic reactions in the primary analysis was 4.2% (95% CI 2.6–6.5%), with individual studies ranging from 0% to 15.7%. Heterogeneity was high (I^2 = 94%), and the 95% prediction interval was 0.7–20.8% (Figure 2), so the incidence expected in each setting could be much lower or higher than the average. Pooled estimates by unit of analysis, definition, sampling, and region are shown in Table 2. The incidence was 2.9% (95% CI 1.6–4.6%) in the 8 patient-based studies (2086 children) and 5.8% (2.9–10.7%) in the 10 episode-based studies (7651 episodes). In the core analysis of the 10 studies with an explicit definition requiring complete resolution, it was 5.5% (3.5–8.1%), and it was 5.8% (2.8–10.7%) when only the 5 that used unrestricted sampling were analyzed. Excluding the nine studies with restricted sampling gave 3.6% (1.6–7.7%). The largest study contributed 5641 episodes [6]; excluding it gave 4.1% (2.4–6.5%). In the secondary analysis of all 35 pediatric cohorts, the pooled incidence was 3.3% (95% CI 2.3–4.6%; Figure S1).

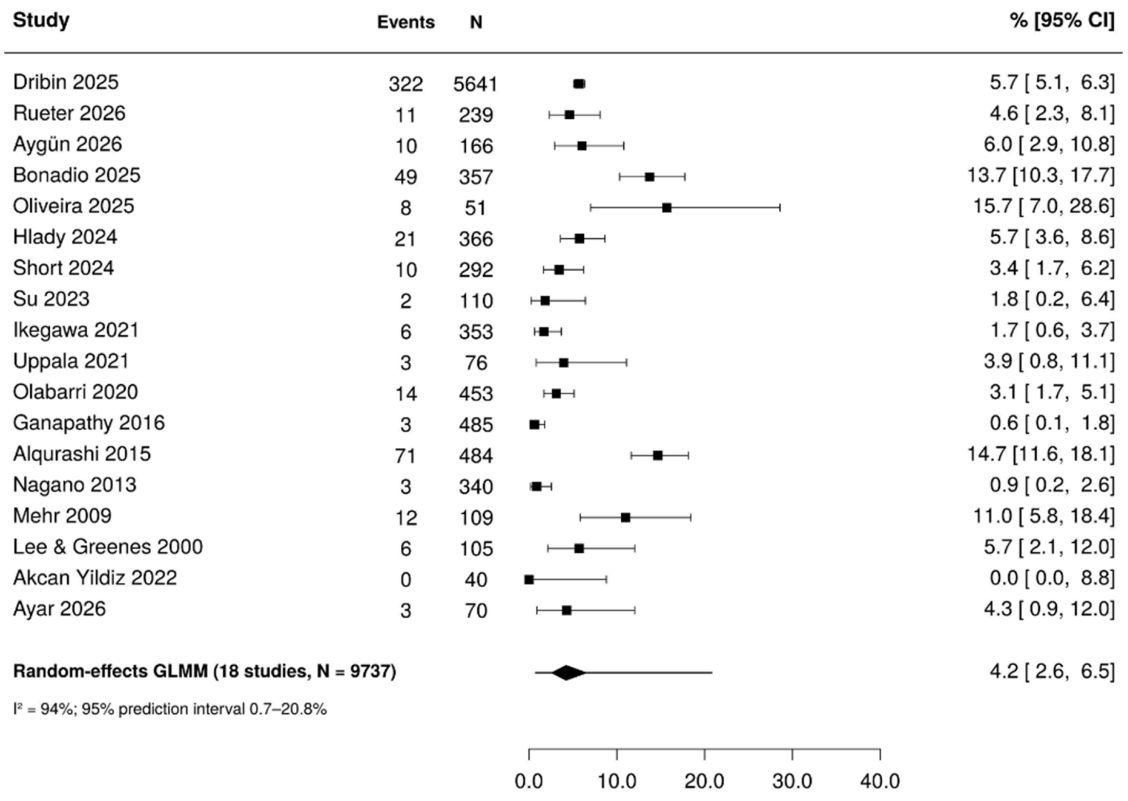

Figure 2. Forest plot of the incidence of biphasic reactions in children presenting to the emergency department with anaphylaxis (primary analysis, 18 studies). Estimates were pooled with a random-

intercept logistic generalized linear mixed model. Study-level 95% confidence intervals are exact (Clopper-Pearson). The diamond shows the pooled estimate and 95% confidence interval, and the line through it shows the 95% prediction interval. N is the number of children or episodes, depending on the unit of analysis (Table 1). Included studies: Dribin 2025 [6], Rueter 2026 [26], Aygün 2026 [27], Bonadio 2025 [10], Oliveira 2025 [28], Hlady 2024 [29], Short 2024 [30], Su 2023 [31], Ikegawa 2021 [32], Uppala 2021 [33], Olabarri 2020 [34], Ganapathy 2016 [35], Alqurashi 2015 [36], Nagano 2013 [11], Mehr 2009 [37], Lee & Greenes 2000 [38], Akcan Yildiz 2022 [39], Ayar 2026 [40].

3.4. Subgroup Analysis and Meta-Regression

In exploratory subgroup analyses, region was the only variable with a significant between-group difference (Figure S2). The pooled incidence was 7.4% (95% CI 4.3–12.0%) in North America, 6.9% (2.3–18.9%) in Oceania, 3.7% (1.8–6.1%) in Europe and the Middle East, and 1.3% (0.7–2.5%) in Asia ($p = 0.001$). Incidence was 5.5% (3.5–8.1%) in studies with an explicit definition and 2.7% (0.8–7.1%) in the remaining studies ($p = 0.19$), and 5.8% (2.9–10.7%) in studies counting episodes compared with 2.9% (1.6–4.6%) in those counting patients ($p = 0.063$). Follow-up window, design, and publication period were not associated with incidence. Asian studies less often used an explicit definition (1 of 5 vs. 9 of 13 non-Asian studies) or reported a follow-up window (1 of 5 vs. 8 of 13) (Table S7). Several subgroups contained few studies (5 from Asia, 2 from Oceania, and 1 from Latin America), so these comparisons had limited power and were sensitive to individual studies.

In the multivariable meta-regression, non-Asian studies still had about five times the odds of biphasic reactions of Asian studies after adjustment for unit of analysis and definition (OR 4.93, 95% CI 2.17–10.85; $p < 0.001$). Patient-based studies tended to report a lower incidence (OR 0.56, 95% CI 0.32–1.03; $p = 0.059$), whereas definition had no independent effect (OR 1.09, 95% CI 0.56–2.03; $p = 0.78$). In the univariable model, studies without an explicit definition had a lower incidence (OR 0.55), as in the subgroup analysis; the direction changed after adjustment because four of the five Asian studies did not use an explicit definition. Together, the three variables explained 75% of the between-study variance (τ^2 fell from 0.77 to 0.19), but residual heterogeneity remained ($I^2 = 75\%$). With 18 studies and three variables, the model should be regarded as exploratory. In leave-one-out analyses, the OR for region ranged from 3.34 to 6.90, and in the permutation test only region remained significant ($p = 0.004$; unit of analysis $p = 0.14$; definition $p = 0.63$; Table S4). These are associations between studies and do not represent the risk of individual children.

3.5. Results by Definition

Biphasic anaphylaxis, in which the second phase again met diagnostic criteria, occurred in 2.3% (95% CI 1.2–4.5%; 4 studies, 6276 children or episodes). Clinically important biphasic reactions occurred in 1.5% (95% CI 0.2–6.7%; 3 studies, 911 children or episodes). Because these estimates are only based on four and three studies, respectively, they are imprecise. Second-phase reactions requiring epinephrine were not reported separately by most studies and could not be pooled.

3.6. Timing

Eleven studies in the primary analysis reported timing, measured from the initial reaction, symptom resolution, or the start of treatment, so the data were summarized descriptively (Table 3). In some studies, reactions clustered early: between 70 and 330 min after the initial reaction [26], within 4 h of starting treatment [10], and within 3 h of resolution [40]. The median time from the initial reaction was 5.9 h in one study [32] and 8.8 h (range 1.3–20.5) in another [37]. Late reactions were not rare. In four small studies, 9 of 11 reactions occurred 10 h or more after the initial reaction, up to 18 h [11,31,33,35].

Alqurashi and colleagues reported that 18 of 71 reactions (25%) occurred after ED discharge, at a median of 18.5 h [36], and Short and colleagues found that 4 of 10 occurred 10 to 33 h after discharge [30]. Eight studies reported individual timing for 84 reactions, and the proportion occurring more than 6 h after the reference point depended on that reference point. When reactions were timed from the initial reaction (5 studies [11,26,31,33,35]), 9 of 22 (41%) occurred after 6 h. When they were timed from symptom resolution (2 studies [30,40]), 4 of 13 (31%) did so, and all 4 occurred after ED discharge [30]. In the one study that timed reactions from the start of treatment and used a loose definition, all 49 occurred within 4 h [10]. All 13 reactions that occurred after 6 h did so 10 h or more after the reference point. The overall proportion was therefore 37% (13 of 35) when that study was excluded and 15% (13 of 84) when it was included. Because reference points differed and most studies did not record the time of symptom resolution, these data describe when reactions occurred but cannot be converted into a safe observation period after symptom resolution.

3.7. Associated Factors

In unadjusted analyses, more than one dose of epinephrine (OR 2.97, 95% CI 1.66–5.32; 3 studies; $I^2 = 0\%$) and a drug trigger (OR 2.70, 95% CI 1.27–5.73; 4 studies; $I^2 = 0\%$) were associated with biphasic reactions (Figure 3). Corticosteroid treatment (OR 1.92, 95% CI 0.87–4.21; $I^2 = 34\%$), an unknown trigger (OR 1.49, 95% CI 0.87–2.57), prior anaphylaxis (OR 1.08, 95% CI 0.66–1.78), and a food trigger (OR 0.73, 95% CI 0.47–1.15) were not significantly associated. Severe initial reactions and asthma were each reported by only two studies and were not pooled. With the Hartung–Knapp adjustment, more than one dose of epinephrine remained significant (OR 2.97, 95% CI 1.19–7.41), and the lower confidence limit for a drug trigger reached 1 (OR 2.70, 95% CI 1.00–7.27). In the fixed-effect model, results were similar, except that corticosteroid treatment became marginally significant (OR 1.70, 95% CI 1.07–2.71).

Only one included study reported a multivariable model for biphasic reactions. After adjustment, more than one dose of epinephrine remained an independent predictor (adjusted OR 2.70, 95% CI 1.12–6.55), consistent with the pooled unadjusted estimate, although initial severity was not adjusted for. Other independent predictors were a delay of more than 90 min in presenting to the ED (adjusted OR 2.58, 95% CI 1.47–4.53), a wide pulse pressure at triage (adjusted OR 2.92, 95% CI 1.69–5.04), age 6 to 9 years (adjusted OR 3.60, 95% CI 1.50–8.58), and inhaled beta-agonist treatment in the ED (adjusted OR 2.39, 95% CI 1.24–4.62) [36]. Another study reported that needing more than one dose of epinephrine or a fluid bolus predicted a biphasic reaction with a sensitivity of 92%, a negative predictive value of 99%, and a positive predictive value of only 32% [37].

3.8. Risk-of-Bias and Sensitivity Analyses

In the primary analysis, 6 studies were at low and 12 at moderate risk of bias. Of the 17 additional studies in the secondary analysis, 7 were at moderate and 10 at high risk (Figures S3 and S4; item-level ratings in Table S3). The most common problems were small samples, inclusion limited to children who received epinephrine or were admitted, and undefined biphasic reactions. Pooled estimates across the sensitivity analyses listed in the protocol ranged from 3.6% to 5.5% and from 3.9% to 4.8% in the leave-one-out analysis (Table S4). Excluding the one study that enrolled a small number of patients aged 15 years or older gave 4.7% (95% CI 2.9–7.0%), and counting all 8 biphasic reactions in that study (8 of 345) gave 4.5% (2.8–6.7%). Influence diagnostics identified one outlying study (studentized residual −2.28) that did not meet criteria for an influential case. Excluding it gave 4.8% (95% CI 3.1–7.1%; $I^2 = 92\%$). Egger's test indicated funnel plot asymmetry, suggesting

small-study effects ($p = 0.002$; Figure S5), but the regression test based on sample size showed no asymmetry ($p = 0.56$), and Egger's test was no longer significant after adjustment for region ($p = 0.14$). These findings were treated as exploratory and not as evidence of publication bias [21].

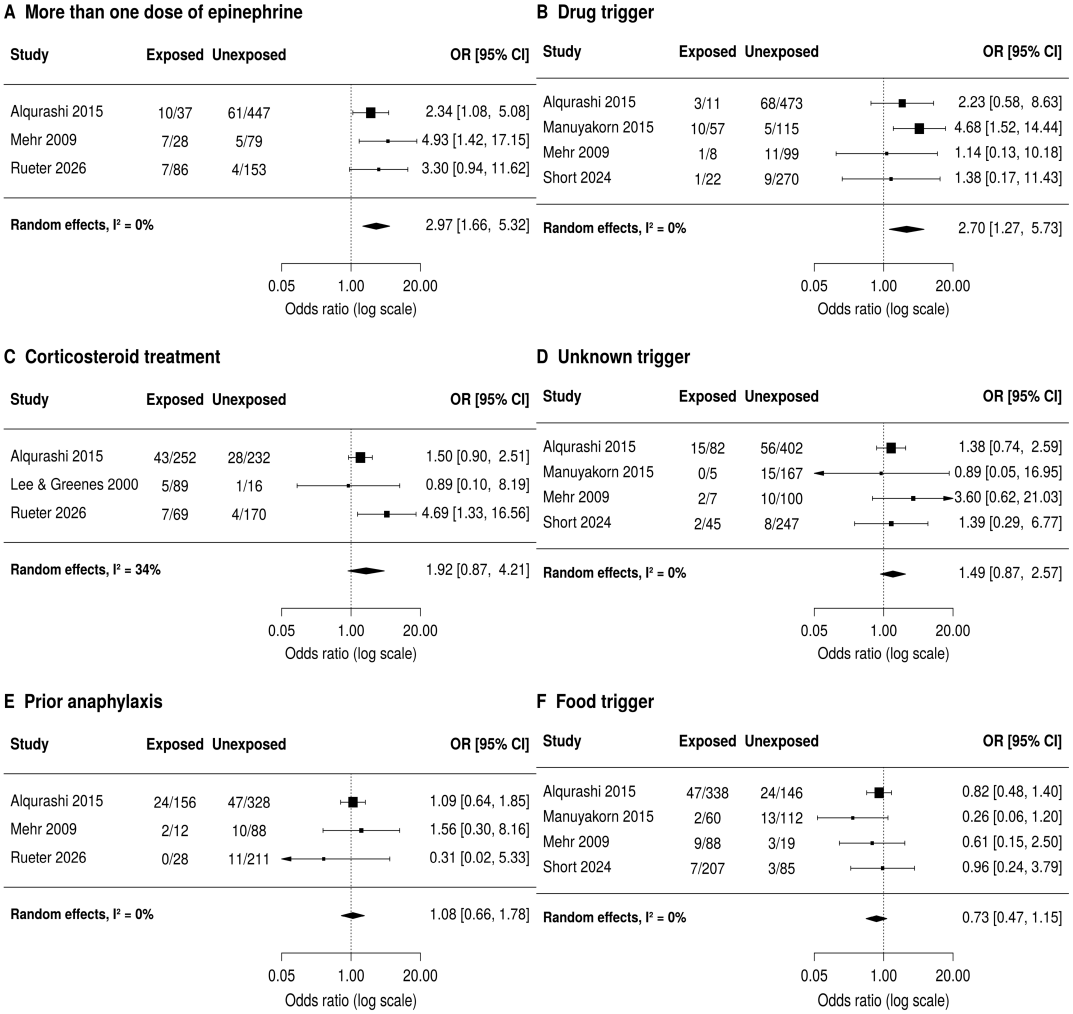

Figure 3. Forest plots of factors associated with biphasic reactions (unadjusted odds ratios, Mantel–Haenszel random-effects model). (**A**) More than one dose of epinephrine; (**B**) drug trigger; (**C**) corticosteroid treatment; (**D**) unknown trigger; (**E**) prior anaphylaxis; (**F**) food trigger. "Exposed" and "Unexposed" show the number of children with a biphasic reaction and the total number of children with and without the factor. An odds ratio above 1 indicates higher odds in children with the factor. Estimates were calculated in RevMan 5.4, and the plots were redrawn in R for readability. CI, confidence interval; OR, odds ratio. Included studies: Rueter 2026 [26], Short 2024 [30], Alqurashi 2015 [36], Mehr 2009 [37], Lee & Greenes 2000 [38], Manuyakorn 2015 [51].

3.9. Certainty of Evidence

Certainty of evidence was low for the overall incidence of biphasic reactions, mainly because of risk of bias and inconsistency. It was also low for more than one dose of epinephrine, which was rated down two levels for risk of bias because the estimate was unadjusted and likely confounded by the severity of the initial reaction. Certainty was low to very low for the other factors (Table 4).

Table 4. Certainty of evidence for the main outcomes (GRADE).

Outcome	Studies (Participants)	Estimate (95% CI)	Certainty	Reasons for Rating Down
Incidence of biphasic reactions (primary analysis)	18 (9737)	4.2% (2.6–6.5)	Low	Risk of bias (−1): mostly retrospective, some with restricted sampling; inconsistency (−1): I^2 = 94%, prediction interval 0.7–20.8%
Incidence of biphasic anaphylaxis	4 (6276)	2.3% (1.2–4.5)	Low	Risk of bias (−1); inconsistency (−1): I^2 = 62%
Clinically important biphasic reactions	3 (911)	1.5% (0.2–6.7)	Very low	Risk of bias (−1); inconsistency (−1): I^2 = 68%; imprecision (−1): wide confidence interval
More than one dose of epinephrine	3 (830)	OR 2.97 (1.66–5.32)	Low	Risk of bias (−2): unadjusted, retrospective, and likely confounded by the severity of the initial reaction; results consistent (I^2 0%) and in line with the only adjusted model (adjusted OR 2.70)
Drug trigger	4 (1055)	OR 2.70 (1.27–5.73)	Low	Risk of bias (−1); imprecision (−1): only 15 events among exposed children
Corticosteroid treatment	3 (828)	OR 1.92 (0.87–4.21)	Very low	Risk of bias (−2): confounding by indication; imprecision (−1): confidence interval includes 1
Unknown trigger	4 (1055)	OR 1.49 (0.87–2.57)	Low	Risk of bias (−1); imprecision (−1)
Prior anaphylaxis	3 (823)	OR 1.08 (0.66–1.78)	Low	Risk of bias (−1); imprecision (−1)
Food trigger	4 (1055)	OR 0.73 (0.47–1.15)	Low	Risk of bias (−1); imprecision (−1)

Evidence on incidence and prognostic factors from cohort studies started at high certainty. Publication bias: Egger's test was significant, but because funnel plot asymmetry is unreliable for proportions, evidence was not rated down for this reason. CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; OR, odds ratio. Participants are children or anaphylaxis episodes, depending on the unit of analysis.

4. Discussion

4.1. Main Findings

Across 18 ED-based pediatric cohorts, the average incidence of biphasic reactions was 4.2%, but heterogeneity was high, and the prediction interval (0.7–20.8%) indicates that the incidence in each setting could be much lower or higher. The estimate was 2.9% in patient-based and 5.8% in episode-based studies, and 5.5% in studies that required complete resolution of the initial reaction. In studies reporting second-phase severity, 2.3% of children had biphasic anaphylaxis and about 1.5% had a clinically important reaction, although these estimates came from only four and three studies, respectively. In unadjusted analyses, needing more than one dose of epinephrine and a drug trigger were each associated with roughly three times the odds of a biphasic reaction. In exploratory analyses, incidence varied considerably by region and was more than five times higher in North American than in Asian studies.

4.2. Comparison with Previous Studies

Lee and colleagues pooled 27 studies with 4114 patients of all ages and found biphasic reactions in 192 (about 4.7%), at a median of 11 h. An unknown trigger and initial hypotension increased the risk, while a food trigger was associated with lower risk [5]. The systematic review behind the 2020 practice parameter identified a severe initial reaction and the need for more than one dose of epinephrine as the strongest risk factors, with a wide pulse pressure, an unknown trigger, cutaneous signs, and delayed epinephrine as additional factors, and a drug trigger in children [2]. Our review focused on children in the ED, included 15 studies published in or after 2015, and stratified results by the strictness of the definition. The overall incidence was similar to that reported by Lee and colleagues. The associations with more than one dose of epinephrine and a drug trigger agree with the practice parameter, and the direction of the estimates for a food trigger (OR 0.73) and an unknown trigger (OR 1.49) matches the earlier meta-analysis, although neither reached significance. Biphasic anaphylaxis (2.3%) and clinically important reactions (1.5%) were uncommon in the studies that reported them, which suggests that many biphasic reactions are mild recurrences. Because these estimates come from different subsets of studies, however, they should not be compared directly with the overall incidence.

4.3. Possible Explanations for the Regional Difference

Region was assigned by country and serves as a proxy for many differences between studies rather than a biological characteristic. Several factors may explain the higher incidence in North America. Large North American studies often counted episodes and used broad definitions in which any recurrence of symptoms qualified. Asian studies more often counted patients, less often used an explicit definition or reported a follow-up window, and some recorded only reactions that occurred during inpatient observation, so recurrences after discharge may have been missed. Access to emergency and specialist care, ED observation and discharge practices, the timing of epinephrine and use of corticosteroids, triggers, caregiver education, and patterns of return visits may also differ between regions. In our meta-regression, the difference between Asian and non-Asian studies persisted after adjustment for unit of analysis and definition. These are study-level associations, however, and meta-regression is prone to ecological bias; only 18 studies, five of them Asian, were available, and other study-level differences could not be measured. The regional difference should therefore be treated as a hypothesis and should not be interpreted as evidence of an intrinsically lower risk in Asian children.

4.4. Clinical Implications

The US practice parameters recommend tailoring observation to risk. Children whose symptoms resolve completely after a single dose of epinephrine and who had no severe initial features may be discharged after a shorter period, whereas those with a severe initial reaction or who needed more than one dose should be observed longer [2,3]. Our findings are consistent with this approach. Children who needed more than one dose of epinephrine had about three times the odds of a biphasic reaction, but this association was unadjusted and probably reflects, at least in part, a more severe initial reaction. It is therefore best regarded as a marker of higher risk rather than as an independent predictor. The association with a drug trigger rests on a few unadjusted studies, with only 15 events among exposed children, and should not on its own determine observation time. Clinically important biphasic reactions occurred in about 1.5% of children in the three studies that reported them. These findings do not support routine prolonged observation for all children, and they do not establish a single optimal observation period. In studies with individual timing data, a substantial proportion of reactions occurred more than 6 h after the reference point (41% when timed from the initial reaction and 31% when timed from symptom resolution), and in one large study a quarter occurred after ED discharge [30,36]. No practical observation period will capture every case, and because reference points varied, these data cannot be used to derive a safe observation period after symptom resolution. Shorter observation therefore needs to be paired with discharge education, a prescription for an epinephrine autoinjector, and clear instructions on when to return.

4.5. The Role of Corticosteroids

Corticosteroid treatment was not significantly associated with biphasic reactions in the random-effects model (OR 1.92, 95% CI 0.87–4.21) and was only marginally significant in the fixed-effect model. Any positive association is most likely explained by confounding by indication, because clinicians tend to give corticosteroids to children with more severe reactions, and severity itself is linked to biphasic reactions. Current evidence neither supports corticosteroids for preventing biphasic reactions nor shows that they cause harm. Prospective studies or analyses adjusted for severity are needed.

4.6. Limitations

This review has several limitations. First, heterogeneity was high ($I^2 = 94\%$), and the prediction interval was wide (0.7–20.8%), so the pooled estimate should be read as an average across heterogeneous settings rather than the value any single center should expect. Second, the number of studies was small for the subgroup analyses and meta-regression. Several subgroups contained only one to five studies, and the meta-regression, with 18 studies and three variables, explained about three quarters of the between-study variance but left substantial residual heterogeneity, so it should be regarded as exploratory. Third, most included studies were retrospective, and they differed in definitions, follow-up windows, reference points for timing, and units of analysis. Episode-based studies may have counted repeated episodes in the same child, which could not be corrected with aggregate data, and nine studies included only children who received epinephrine, were hospitalized, or were observed for at least 6 h. Recurrences treated at other hospitals after discharge may also have been missed. The severity of the initial reaction, the proportion of children treated with epinephrine, the method of post-discharge follow-up, and the length of observation were reported inconsistently and could not be summarized systematically. Fourth, each associated factor was assessed in only three or four studies, mostly as unadjusted ORs, and only one study reported a multivariable model. The severity of the initial reaction and asthma could not be pooled. Fifth, Egger's test suggested small-study effects, although the sample-size-

based test did not, and the asymmetry largely reflected the link between low incidence and few events, together with regional differences. Although funnel plot asymmetry is unreliable for proportions [21], the true incidence may be over- or underestimated. Sixth, data were extracted by one reviewer and checked by a second, which may control errors less well than independent double extraction, although all denominators and event counts were checked against the original articles. Seventh, studies that reported biphasic reactions only as a secondary outcome, without mentioning them in the title or abstract, may have been missed, although the search included broad terms for recurrence and observation time and the reference lists of included studies and reviews were checked. Eighth, the full texts of three studies could not be obtained, and two of them were included using abstract data, although excluding them did not change the results. Finally, we excluded conference abstracts and other unpublished data, which may have left out studies still in the publication process but ensured that all included data had been peer reviewed. Because the review pooled observational cohorts, it could not compare the safety of specific observation periods.

4.7. Future Research

Future studies should use the 2020 Delphi definition [7], count patients rather than episodes, record the time from complete resolution of symptoms and state the reference point for timing, and follow children prospectively for at least 72 h. They should also report clinically important outcomes, including the need for epinephrine after discharge and repeat ED visits. Prospective collection of initial severity, the number of epinephrine doses, and treatment times would allow development of a risk prediction tool for use in the ED.

5. Conclusions

On average, about 4% of children treated in the ED for anaphylaxis have a biphasic reaction, but rates vary widely across studies and settings. In studies reporting second-phase severity, about 2% had biphasic anaphylaxis. Needing more than one dose of epinephrine is a marker of higher risk that may justify longer observation, although the association is unadjusted. A drug trigger may also be associated with higher risk, but the evidence is less certain. For low-risk children, a shorter observation period can be considered if it is accompanied by thorough discharge education, a prescription for an epinephrine autoinjector, and clear instructions on when to return, although the available data do not define a single optimal observation period. Incidence varies widely across regions, probably reflecting differences in study methods and care as much as any true difference in risk, and future studies should adopt a common definition so that results can be compared.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/children13111585/s1, Table S1: Database search strategies; Table S2: Full-text articles excluded, with reasons; Table S3: Item-level JBI risk-of-bias ratings and rationale; Table S4: Sensitivity analyses, leave-one-out analysis, and multivariable meta-regression; Table S5: Definitions of outcomes and classification of study definitions; Table S6: Characteristics of the additional studies in the secondary analysis; Table S7: Characteristics of studies in the primary analysis by region; Figure S1: Forest plot of the incidence of biphasic reactions in all pediatric cohorts (secondary analysis, 35 studies); Figure S2: Subgroup analyses by definition, region, unit of analysis, follow-up window, study design, and publication period; Figure S3: Risk of bias of included studies (JBI checklist for prevalence studies); Figure S4: Proportion of studies by risk-of-bias judgment for each item; Figure S5: Funnel plot for the primary analysis based on sample size. References [58–80] are cited in the Supplementary Materials.

Author Contributions: Conceptualization, B.-S.S., S.-W.H. and C.-T.W.; Methodology, Y.-T.L.; Formal Analysis, Y.-T.L.; Investigation, B.-S.S. and Y.-T.L.; Writing—Original Draft Preparation, B.-S.S.; Writing—Review & Editing, Y.-T.L., K.-H.L., S.-W.H. and C.-T.W.; Supervision, K.-H.L., S.-W.H. and C.-T.W.; Project Administration, C.-T.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The extracted data and analysis code are available from the corresponding author on reasonable request.

Acknowledgments: During the preparation of this manuscript, the authors used Claude Opus 5.5 (Anthropic) for the purposes of translating the authors' Chinese draft into English and English language editing. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CI	confidence interval
ED	emergency department
GLMM	generalized linear mixed model
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
INPLASY	International Platform of Registered Systematic Review and Meta-analysis Protocols
IQR	interquartile range
JBI	Joanna Briggs Institute
OR	odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RevMan	Review Manager

References

1. Motosue, M.S.; Bellolio, M.F.; Van Houten, H.K.; Shah, N.D.; Campbell, R.L. National trends in emergency department visits and hospitalizations for food-induced anaphylaxis in US children. *Pediatr. Allergy Immunol.* **2018**, *29*, 538–544. [CrossRef] [PubMed]
2. Shaker, M.S.; Wallace, D.V.; Golden, D.B.K.; Oppenheimer, J.; Bernstein, J.A.; Campbell, R.L.; Dinakar, C.; Ellis, A.; Greenhawt, M.; Khan, D.A.; et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J. Allergy Clin. Immunol.* **2020**, *145*, 1082–1123. [CrossRef] [PubMed]
3. Golden, D.B.K.; Wang, J.; Waserman, S.; Akin, C.; Campbell, R.L.; Ellis, A.K.; Greenhawt, M.; Lang, D.M.; Ledford, D.K.; Lieberman, J.; et al. Anaphylaxis: A 2023 practice parameter update. *Ann. Allergy Asthma Immunol.* **2024**, *132*, 124–176. [CrossRef] [PubMed]
4. Simard, D.; Bouchard, V.; Plourde, A.; Lefebvre, S.; Herman-Lemelin, A.; Lapointe, S.; Tremblay, L.; Desmeules, C.; Gagné, A.; Bouchard, J. Factors influencing emergency department observation time following anaphylaxis: A systematic review. *Can. J. Emerg. Med.* **2021**, *23*, 480–493. [CrossRef] [PubMed]
5. Lee, S.; Bellolio, M.F.; Hess, E.P.; Erwin, P.; Murad, M.H.; Campbell, R.L. Time of onset and predictors of biphasic anaphylactic reactions: A systematic review and meta-analysis. *J. Allergy Clin. Immunol. Pract.* **2015**, *3*, 408–416.e2. [CrossRef] [PubMed]
6. Dribin, T.E.; Sampson, H.A.; Zhang, Y.; Boyd, S.; Zhang, N.; Michelson, K.A.; Neuman, M.I.; Brousseau, D.C.; Mistry, R.D.; Freedman, S.B.; et al. Timing of repeat epinephrine to inform paediatric anaphylaxis observation periods: A retrospective cohort study. *Lancet Child. Adolesc. Health* **2025**, *9*, 484–496. [CrossRef] [PubMed]
7. Dribin, T.E.; Sampson, H.A.; Camargo, C.A.; Brousseau, D.C.; Spergel, J.M.; Neuman, M.I.; Shaker, M.; Campbell, R.L.; Michelson, K.A.; Rudders, S.A.; et al. Persistent, refractory, and biphasic anaphylaxis: A multidisciplinary Delphi study. *J. Allergy Clin. Immunol.* **2020**, *146*, 1089–1096. [CrossRef] [PubMed]

8. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef] [PubMed]
9. Shang, B.-S.; Li, Y.-T.; Lue, K.-H.; Ho, S.-W.; Wu, C.-T. Incidence, timing, and risk factors of biphasic reactions in children presenting to the emergency department with anaphylaxis: Protocol for a systematic review and meta-analysis. *INPLASY* **2026**, INPLASY2026100034. [CrossRef]
10. Bonadio, W.; Welsh, C.; Pradarelli, B.; Ng, Y. Impact of treatment on rate of biphasic reaction in children with anaphylaxis. *West. J. Emerg. Med.* **2025**, *26*, 171–175. [CrossRef] [PubMed]
11. Nagano, C.; Ishiguro, A.; Yotani, N.; Sakai, H.; Fujiwara, T.; Ohya, Y. Anaphylaxis and biphasic reaction in a children hospital. *Arerugi* **2013**, *62*, 163–170. (In Japanese) [PubMed]
12. Munn, Z.; Moola, S.; Lisy, K.; Riitano, D.; Tufanaru, C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int. J. Evid. Based Healthc.* **2015**, *13*, 147–153. [CrossRef] [PubMed]
13. Naing, L.; Winn, T.; Rusli, B.N. Practical issues in calculating the sample size for prevalence studies. *Arch. Orofac. Sci.* **2006**, *1*, 9–14.
14. Stijnen, T.; Hamza, T.H.; Ozdemir, P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat. Med.* **2010**, *29*, 3046–3067. [CrossRef] [PubMed]
15. Schwarzer, G.; Chemaitelly, H.; Abu-Raddad, L.J.; Rücker, G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Res. Synth. Methods* **2019**, *10*, 476–483. [CrossRef] [PubMed]
16. Higgins, J.P.T.; Thompson, S.G. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* **2002**, *21*, 1539–1558. [CrossRef] [PubMed]
17. IntHout, J.; Ioannidis, J.P.A.; Rovers, M.M.; Goeman, J.J. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* **2016**, *6*, e010247. [CrossRef] [PubMed]
18. Viechtbauer, W.; Cheung, M.W.L. Outlier and influence diagnostics for meta-analysis. *Res. Synth. Methods* **2010**, *1*, 112–125. [CrossRef] [PubMed]
19. IntHout, J.; Ioannidis, J.P.A.; Borm, G.F. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med. Res. Methodol.* **2014**, *14*, 25. [CrossRef] [PubMed]
20. Egger, M.; Davey Smith, G.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* **1997**, *315*, 629–634. [CrossRef] [PubMed]
21. Hunter, J.P.; Saratzis, A.; Sutton, A.J.; Boucher, R.H.; Sayers, R.D.; Bown, M.J. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J. Clin. Epidemiol.* **2014**, *67*, 897–903. [CrossRef] [PubMed]
22. Viechtbauer, W. Conducting meta-analyses in R with the metafor package. *J. Stat. Softw.* **2010**, *36*, 1–48.
23. Bates, D.; Mächler, M.; Bolker, B.; Walker, S. Fitting linear mixed-effects models using lme4. *J. Stat. Softw.* **2015**, *67*, 1–48.
24. Iorio, A.; Spencer, F.A.; Falavigna, M.; Alba, C.; Lang, E.; Burnand, B.; McGinn, T.; Hayden, J.; Williams, K.; Shea, B.; et al. Use of GRADE for assessment of evidence about prognosis: Rating confidence in estimates of event rates in broad categories of patients. *BMJ* **2015**, *350*, h870. [CrossRef] [PubMed]
25. Foroutan, F.; Guyatt, G.; Zuk, V.; Vandvik, P.O.; Alba, A.C.; Mustafa, R.; Vernooij, R.; Arevalo-Rodriguez, I.; Munn, Z.; Roshanov, P.; et al. GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: Rating certainty in identification of groups of patients with different absolute risks. *J. Clin. Epidemiol.* **2020**, *121*, 62–70. [CrossRef] [PubMed]
26. Rueter, K.; Ta, B.; Bear, N.; Lucas, M.; Prescott, S.L. Characteristics of uniphasic and biphasic anaphylaxis in infants and young toddlers: An analysis of clinical signs, predictors and management. *Pediatr. Allergy Immunol.* **2026**, *37*, e70438. [CrossRef] [PubMed]
27. Aygün, E.; Yalçın Güngören, E.; Çırpıcı, İ.; Sipahi Çimen, S. Retrospective evaluation of patients admitted to the emergency department due to anaphylaxis in children: A single-center study from Türkiye. *Children* **2026**, *13*, 203. [CrossRef] [PubMed]
28. Oliveira, F.A.N.; Fernandes, F.R.; Solé, D.; Wandalsen, G.F. Anaphylaxis in pediatric patients: Single-center study in a private hospital. *Allergol. Immunopathol.* **2025**, *53*, 48–54. [CrossRef] [PubMed]
29. Hlady, A.L.; Weinman, A.F.; Zhang, Y.; Mullan, A.F.; Campbell, R.L. Outcomes associated with prehospital epinephrine in adult and pediatric patients with anaphylaxis. *Ann. Allergy Asthma Immunol.* **2024**, *133*, 592–599.e8. [CrossRef] [PubMed]
30. Short, H.B.; Walters, B.; Fabi, M.; Ravida, N.; Boehmer, S.; Reyes, L. Evaluating practice patterns of observation periods following epinephrine administration for anaphylaxis among pediatric patients. *Cureus* **2024**, *16*, e69419. [CrossRef] [PubMed]
31. Su, Y.; Wen, J.; Zhang, H.; Zou, Z.; Cai, Y.; Zhang, C. Clinical characteristics of anaphylaxis in children aged 0-16 years in Xi'an, China. *Int. Arch. Allergy Immunol.* **2023**, *184*, 220–227. [CrossRef] [PubMed]

32. Ikegawa, K.; Morikawa, E.; Nigo, A.; Hataya, H.; Akasawa, A. Epidemiology of anaphylaxis and biphasic reaction in Japanese children. *Acute Med. Surg.* **2021**, *8*, e688. [CrossRef] [PubMed]
33. Uppala, R.; Phungoen, P.; Mairiang, D.; Chaiyarit, J.; Techasatian, L. Pediatric anaphylaxis: Etiology and predictive factors in an emergency setting. *Glob. Pediatr. Health* **2021**, *8*, 2333794X211011301. [CrossRef] [PubMed]
34. Olabarri, M.; Vazquez, P.; Gonzalez-Posada, A.; Sanz, N.; Gonzalez-Peris, S.; Diez, N.; Vinuesa, A.; Martinez-Indart, L.; Benito, J.; Mintegi, S. Risk factors for severe anaphylaxis in children. *J. Pediatr.* **2020**, *225*, 193–197.e5. [CrossRef] [PubMed]
35. Ganapathy, S.; Lwin, Z.; Ting, D.H.; Goh, L.S.; Chong, S.L. Anaphylaxis in children: Experience of 485 episodes in 1,272,482 patient attendances at a tertiary paediatric emergency department from 2007 to 2014. *Ann. Acad. Med. Singap.* **2016**, *45*, 542–548. [CrossRef]
36. Alqurashi, W.; Stiell, I.; Chan, K.; Neto, G.; Alsadoon, A.; Wells, G. Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis. *Ann. Allergy Asthma Immunol.* **2015**, *115*, 217–223.e2. [CrossRef] [PubMed]
37. Mehr, S.; Liew, W.K.; Tey, D.; Tang, M.L. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. *Clin. Exp. Allergy* **2009**, *39*, 1390–1396. [CrossRef] [PubMed]
38. Lee, J.M.; Greenes, D.S. Biphasic anaphylactic reactions in pediatrics. *Pediatrics* **2000**, *106*, 762–766. [CrossRef] [PubMed]
39. Akcan Yildiz, L.; Çetin, M.; Dibek Misirlioğlu, E. Evaluation of clinical and therapeutic characteristics of patients with anaphylaxis at the pediatric emergency department. *Turk. J. Pediatr. Dis.* **2022**, *16*, 476–480. (In Turkish) [CrossRef]
40. Ayar, M.; Demir, Ş.; Şahin, C.; Çağlar, A. Pediatric anaphylaxis in a tertiary pediatric emergency department: Observation duration and biphasic reactions. *Children* **2026**, *13*, 1334. [CrossRef] [PubMed]
41. Koken, G.; Ertoy Karagol, H.I.; Polat Terece, S.; Varer Akpinar, C.; Cetin, K.; Cavdar, Z.; Kara, B.; Baskin, A.K.; Bakirtas, A. Biphasic, refractory, and persistent anaphylaxis in children. *Clin. Transl. Allergy* **2026**, *16*, e70174. [CrossRef] [PubMed]
42. Maris, I.; Dölle-Bierke, S.; Renaudin, J.M.; Lange, L.; Koehli, A.; Spindler, T.; Hourihane, J.; Scherer, K.; Nemat, K.; Kemen, C.; et al. Peanut-induced anaphylaxis in children and adolescents: Data from the European Anaphylaxis Registry. *Allergy* **2021**, *76*, 1517–1527. [CrossRef] [PubMed]
43. Dibek Misirlioglu, E.; Vezir, E.; Toyran, M.; Capanoglu, M.; Guvenir, H.; Civelek, E.; Kocabas, C.N. Clinical diagnosis and management of anaphylaxis in infancy. *Allergy Asthma Proc.* **2017**, *38*, 38–43. [CrossRef] [PubMed]
44. Vezir, E.; Erkoçoğlu, M.; Kaya, A.; Toyran, M.; Özcan, C.; Akan, A.; Azkur, D.; Giniş, T.; Civelek, E.; Kocabaş, C.N. Characteristics of anaphylaxis in children referred to a tertiary care center. *Allergy Asthma Proc.* **2013**, *34*, 239–246. [CrossRef] [PubMed]
45. Schroter, S.; Laubach, S.; Bialostozky, M.; Wang, Y.; Bryl, A. Reducing emergency department observation time for patients with low-risk anaphylaxis. *Pediatrics* **2026**, *158*, e2024066711. [CrossRef] [PubMed]
46. Keser-Ozturk, N.; Maghdeed, Y.; Bozkurt, S.; Yorgun-Altunbas, M.; Can, S.; Amirov, R.; Mahmudov, R.; Colak, B.C.; Eksi-Alp, E.; Bilgic-Eltan, S.; et al. Triggers, clinical spectra and outcomes of pediatric anaphylaxis in a tertiary center: Impact of comorbidities and cofactors on severity. *Allergy Asthma Clin. Immunol.* **2026**, *22*, 47. [CrossRef] [PubMed]
47. Wong-Onta, N.; Sawatchai, A.; Kanchongkittiphon, W.; Manuyakorn, W. Anaphylaxis in children: Effect of age and atopic status. *Asian Pac. J. Allergy Immunol.* **2026**, *44*, 179–185. [CrossRef] [PubMed]
48. Selmanoglu, A.; Haci, I.A.; Koc, F.S.M.; Yildiz, Y.K.; Yilmaz, E.A.; Azkur, D.; Erdem, S.B.; Guvenir, H.; Ozceker, D.; Guc, B.U.; et al. Clinical and treatment evaluation of anaphylaxis in children aged 0-2 years: Multicenter study. *Pediatr. Res.* **2025**, *97*, 1582–1589. [CrossRef] [PubMed]
49. Metbulut, A.P.; Haci, İ.A.; Can, D.; Bekis Bozkurt, H.; Cavkaytar, Ö.; Arga, M.; Özçeker, D.; Yildiz, Y.K.; Vezir, E.; Arikoğlu, T.; et al. Evaluation of drug-related anaphylaxis in children: Multi-center study. *Eur. J. Pediatr.* **2025**, *184*, 230. [CrossRef] [PubMed]
50. Nantanee, R.; Suratannon, N.; Chatchatee, P. Characteristics and laboratory findings of food-induced anaphylaxis in children: Study in an Asian developing country. *Int. Arch. Allergy Immunol.* **2022**, *183*, 59–67. [CrossRef] [PubMed]
51. Manuyakorn, W.; Benjaponpitak, S.; Kamchaisatian, W.; Vilaiyuk, S.; Sasisakulporn, C.; Jotikasthira, W. Pediatric anaphylaxis: Triggers, clinical features, and treatment in a tertiary-care hospital. *Asian Pac. J. Allergy Immunol.* **2015**, *33*, 281–288. [CrossRef] [PubMed]
52. Serbes, M.; Can, D.; Atlihan, F.; Günay, I.; Asilsoy, S.; Altinöz, S. Common features of anaphylaxis in children. *Allergol. Immunopathol.* **2013**, *41*, 255–260. [CrossRef] [PubMed]
53. Topal, E.; Bakirtas, A.; Yilmaz, O.; Ertoy Karagol, I.H.; Arga, M.; Demirsoy, M.S.; Turktas, I. Anaphylaxis in infancy compared with older children. *Allergy Asthma Proc.* **2013**, *34*, 233–238. [CrossRef] [PubMed]
54. Inoue, N.; Yamamoto, A. Clinical evaluation of pediatric anaphylaxis and the necessity for multiple doses of epinephrine. *Asia Pac. Allergy* **2013**, *3*, 106–114. [CrossRef] [PubMed]
55. Liew, W.K.; Chiang, W.C.; Goh, A.E.; Lim, H.H.; Chay, O.M.; Chang, S.; Tan, J.H.; Shih, E.; Kidon, M. Paediatric anaphylaxis in a Singaporean children cohort: Changing food allergy triggers over time. *Asia Pac. Allergy* **2013**, *3*, 29–34. [CrossRef] [PubMed]
56. Orhan, F.; Canitez, Y.; Bakirtas, A.; Yilmaz, O.; Boz, A.B.; Can, D.; Kuyucu, S.; Harmanci, K.; Tahan, F.; Reisli, I.; et al. Anaphylaxis in Turkish children: A multi-centre, retrospective, case study. *Clin. Exp. Allergy* **2011**, *41*, 1767–1776. [CrossRef] [PubMed]

57. Jirapongsananuruk, O.; Bunsawansong, W.; Piyaphanee, N.; Visitsunthorn, N.; Thongngarm, T.; Vichyanond, P. Features of patients with anaphylaxis admitted to a university hospital. *Ann. Allergy Asthma Immunol.* **2007**, *98*, 157–162. [CrossRef] [PubMed]
58. Brazil, E.; MacNamara, A.F. "Not so immediate" hypersensitivity–the danger of biphasic anaphylactic reactions. *J. Accid. Emerg. Med.* **1998**, *15*, 252–253. [CrossRef] [PubMed]
59. Poachanukoon, O.; Paopairochanakorn, C. Incidence of anaphylaxis in the emergency department: A 1-year study in a university hospital. *Asian Pac. J. Allergy Immunol.* **2006**, *24*, 111–116. [PubMed]
60. Yang, M.-S.; Lee, S.-H.; Kim, T.-W.; Kwon, J.-W.; Lee, S.-M.; Kim, S.-H.; Kwon, H.-S.; Park, C.-H.; Park, H.-W.; Kim, S.-S.; et al. Epidemiologic and clinical features of anaphylaxis in Korea. *Ann. Allergy Asthma Immunol.* **2008**, *100*, 31–36. [CrossRef] [PubMed]
61. Brown, S.G.A.; Stone, S.F.; Fatovich, D.M.; Burrows, S.A.; Holdgate, A.; Celenza, A.; Coulson, A.; Hartnett, L.; Nagree, Y.; Cotterell, C.; et al. Anaphylaxis: Clinical patterns, mediator release, and severity. *J. Allergy Clin. Immunol.* **2013**, *132*, 1141–1149.e5. [CrossRef] [PubMed]
62. Lee, S.; Bellolio, M.F.; Hess, E.P.; Campbell, R.L. Predictors of biphasic reactions in the emergency department for patients with anaphylaxis. *J. Allergy Clin. Immunol. Pract.* **2014**, *2*, 281–287. [CrossRef] [PubMed]
63. Rohacek, M.; Edenhofer, H.; Bircher, A.; Bingisser, R. Biphasic anaphylactic reactions: Occurrence and mortality. *Allergy* **2014**, *69*, 791–797. [CrossRef] [PubMed]
64. Civelek, E.; Erkoçoğlu, M.; Akan, A.; Özcan, C.; Kaya, A.; Vezir, E.; Giniş, T.; Azkur, D.; Toyran, M.; Tokaç, M.; et al. The etiology and clinical features of anaphylaxis in a developing country: A nationwide survey in Turkey. *Asian Pac. J. Allergy Immunol.* **2017**, *35*, 212–219. [CrossRef] [PubMed]
65. Lee, S.; Peterson, A.; Lohse, C.M.; Hess, E.P.; Campbell, R.L. Further evaluation of factors that may predict biphasic reactions in emergency department anaphylaxis patients. *J. Allergy Clin. Immunol. Pract.* **2017**, *5*, 1295–1301. [CrossRef] [PubMed]
66. Højlund, S.; Søe-Jensen, P.; Perner, A.; Bestle, M.H.; Carl, P.; Thormar, K.; Viggers, S.; Elberling, S.; Garvey, L.H. Low incidence of biphasic allergic reactions in patients admitted to intensive care after anaphylaxis. *Anesthesiology* **2019**, *130*, 284–291. [CrossRef] [PubMed]
67. Rangkakulnuwat, P.; Sutham, K.; Lao-Araya, M. Anaphylaxis: Ten-year retrospective study from a tertiary-care hospital in Asia. *Asian Pac. J. Allergy Immunol.* **2020**, *38*, 31–39. [CrossRef] [PubMed]
68. Oya, S.; Kinoshita, K.; Daya, M.; Kinoshita, H. Characteristics of anaphylactic reactions: A prospective observational study in Japan. *J. Emerg. Med.* **2020**, *59*, 812–819. [CrossRef] [PubMed]
69. Kraft, M.; Scherer Hofmeier, K.; Ruëff, F.; Pföhler, C.; Renaudin, J.-M.; Bilò, M.B.; Treudler, R.; Lang, R.; Cichocka-Jarosz, E.; Fernandez-Rivas, M.; et al. Risk factors and characteristics of biphasic anaphylaxis. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 3388–3395.e6. [CrossRef] [PubMed]
70. Muñoz, Y.; Rosero, T.; Betancur, S.M.; Arias, J.T.; Arias-Valderrama, O.; Ocampo, J.L.; Serrano, C.D.; Olaya, M. From triggers to treatment: An epidemiological exploration of anaphylaxis in a lower middle-income area in Colombia. *Allergol. Immunopathol.* **2024**, *52*, 89–93. [CrossRef] [PubMed]
71. Ellis, A.K.; Hossenbaccus, L.; Linton, S.; Botting, H.; Badawod, E.; Burrows, A.; Garvey, S. Biphasic anaphylaxis in a Canadian tertiary care centre: An evaluation of incidence and risk factors from electronic health records and telephone interviews. *Allergy Asthma Clin. Immunol.* **2025**, *21*, 7. [CrossRef] [PubMed]
72. Uawattanasakul, W.; Lertvipapath, P.; Krikeerati, T.; Wongsa, C.; Thongngarm, T.; Sompornrattanaphan, M. Incidence, predictors, and treatment outcomes of biphasic anaphylaxis in the emergency department of a tertiary hospital: A 5-year retrospective study. *Asian Pac. J. Allergy Immunol.* **2026**, *44*, 351–361. [CrossRef] [PubMed]
73. Hoppe, J.M.; Böhme, J.; Auer, M.K.; Braunstein, M.; Wörnle, M. Demographic, temporal, and clinical factors of anaphylaxis in an urban emergency department: A retrospective analysis. *Allergo J. Int.* 2026, *online ahead of print*. [CrossRef]
74. Lee, J.; Rodio, B.; Lavelle, J.; Lewis, M.O.; English, R.; Hadley, S.; Molnar, J.; Jacobstein, C.; Cianferoni, A.; Spergel, J.; et al. Improving anaphylaxis care: The impact of a clinical pathway. *Pediatrics* **2018**, *141*, e20171616. [CrossRef] [PubMed]
75. Dribin, T.E.; Michelson, K.A.; Monuteaux, M.C.; Stack, A.M.; Farbman, K.S.; Schneider, L.C.; Neuman, M.I. Identification of children with anaphylaxis at low risk of receiving acute inpatient therapies. *PLoS ONE* **2019**, *14*, e0211949. [CrossRef] [PubMed]
76. Dribin, T.E.; Michelson, K.A.; Zhang, Y.; Schnadower, D.; Neuman, M.I. Are children with a history of asthma more likely to have severe anaphylactic reactions? A retrospective cohort study. *J. Pediatr.* **2020**, *220*, 159–164.e2. [CrossRef] [PubMed]
77. Chaaban, M.R.; Stuart, J.; Watley, D.; Baillargeon, G.; Kuo, Y.F. Recurrent anaphylaxis in the United States: Time of onset and risk factors. *Int. Forum Allergy Rhinol.* **2020**, *10*, 320–327. [CrossRef] [PubMed]
78. Dribin, T.E.; Michelson, K.A.; Monuteaux, M.C.; Schnadower, D.; Neuman, M.I. Timing and predictors of repeat epinephrine administration among children hospitalized for anaphylaxis. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 1400–1402.e2. [CrossRef] [PubMed]

79. Wolpert, K.H.; Kestle, R.; Weaver, N.; Huynh, K.; Yoo, M.; Nelson, R.; Lane, R.D. Reducing admission for anaphylaxis in a pediatric emergency department using a clinical decision support tool. *Pediatr. Qual. Saf.* **2022**, *7*, e590. [CrossRef] [PubMed]
80. Liu, X.; Lee, S.; Lohse, C.M.; Hardy, C.T.; Campbell, R.L. Biphasic reactions in emergency department anaphylaxis patients: A prospective cohort study. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 1230–1238. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.