

INPLASY

INPLASY2026100034

doi: 10.37766/inplasy2026.10.0034

Received: 8 October 2026

Published: 8 October 2026

Corresponding author:

Chia-Ta Wu

allenpig1102@gmail.com

Author Affiliation:

Chung Shan Medical University.

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

Shang, BS; Li, YT; Lue, KH; Ho, SW; Wu, CT.

ADMINISTRATIVE INFORMATION**Support** - This study received no specific funding.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100034**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 October 2026 and was last updated on 8 October 2026.**INTRODUCTION**

Review question / Objective In children aged 0 to 18 years presenting to the emergency department (ED) with anaphylaxis, what is (1) the pooled incidence of biphasic reactions, overall and by strictness of definition; (2) the timing of biphasic reactions; and (3) which clinical factors are associated with biphasic reactions?

Rationale Recommended observation times after anaphylaxis range from 1 to 24 hours and are based mainly on adult or mixed-age data. The most widely cited meta-analysis of biphasic reactions pooled mostly adult studies with inconsistent definitions and did not analyze children separately. Several large pediatric ED studies have since been published, and a 2020 Delphi consensus now provides a standard definition of biphasic anaphylaxis. A pooled estimate of incidence, timing, and risk factors specific to children in the ED would help clinicians

decide how long to observe a child after anaphylaxis.

Condition being studied Biphasic reactions after anaphylaxis in children. A biphasic reaction is a recurrence of symptoms after complete resolution of the initial reaction without further exposure to the trigger. Biphasic anaphylaxis is a second phase that meets diagnostic criteria for anaphylaxis, as defined by the 2020 Delphi consensus.

METHODS

Search strategy PubMed: (("Anaphylaxis"[Mesh] OR anaphyla[tiab]) AND (biphasic[tiab] OR "bi-phasic"[tiab] OR multiphasic[tiab] OR "second phase"[tiab] OR "second-phase"[tiab] OR "late phase reaction"[tiab] OR "late-phase reaction"[tiab] OR "delayed reaction"[tiab] OR "secondary reaction"[tiab] OR "recurrent reaction"[tiab] OR "symptom recurrence"[tiab] OR "recurrence of symptoms"[tiab] OR rebound[tiab] OR protracted[tiab] OR "observation period"[tiab] OR

“observation time”[tiab]) AND (“Child”[Mesh] OR “Infant”[Mesh] OR “Adolescent”[Mesh] OR “Pediatrics”[Mesh] OR child[tiab] OR pediatric[tiab] OR paediatric[tiab] OR infan[tiab] OR adolescen[tiab] OR toddler[tiab] OR teen[tiab] OR youth*[tiab] OR “school age”[tiab] OR preschool[tiab])) NOT (“Case Reports”[pt] OR “Editorial”[pt] OR “Letter”[pt] OR “Comment”[pt]) NOT (“Animals”[Mesh] NOT “Humans”[Mesh])

Embase: (‘anaphylaxis’/exp OR anaphyla*:ti,ab,kw) AND (biphasic:ti,ab,kw OR ‘bi-phasic’:ti,ab,kw OR multiphasic:ti,ab,kw OR ‘second phase’:ti,ab,kw OR ‘late phase reaction’:ti,ab,kw OR ‘delayed reaction’:ti,ab,kw OR ‘secondary reaction’:ti,ab,kw OR ‘recurrent reaction’:ti,ab,kw OR ‘symptom recurrence’:ti,ab,kw OR ‘recurrence of symptoms’:ti,ab,kw OR rebound:ti,ab,kw OR protracted:ti,ab,kw OR ‘observation period’:ti,ab,kw OR ‘observation time’:ti,ab,kw) AND (‘child’/exp OR ‘infant’/exp OR ‘adolescent’/exp OR ‘pediatrics’/exp OR child:ti,ab,kw OR pediatric:ti,ab,kw OR paediatric:ti,ab,kw OR infan:ti,ab,kw OR adolescen:ti,ab,kw OR toddler:ti,ab,kw OR teen:ti,ab,kw OR youth:ti,ab,kw OR preschool:ti,ab,kw) AND [humans]/lim NOT (‘case report’/de OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [conference abstract]/lim)

Web of Science Core Collection (Topic field): #1 anaphyla; #2 biphasic OR “bi-phasic” OR multiphasic OR “second phase” OR “late phase reaction” OR “delayed reaction” OR “secondary reaction” OR “recurrent reaction” OR “symptom recurrence” OR “recurrence of symptoms” OR rebound OR protracted OR “observation period” OR “observation time”; #3 child* OR pediatric* OR paediatric* OR infan* OR adolescen* OR toddler* OR teen* OR youth* OR preschool*; #1 AND #2 AND #3; Document type: Article.

Participant or population Children aged 0 to 18 years with anaphylaxis. Mixed-age studies are eligible if pediatric data can be separated or if children make up at least 80% of the sample. The primary analysis is limited to children presenting to the ED, including those admitted through the ED. The secondary analysis also includes pediatric cohorts from other settings, such as allergy clinics, inpatient wards, and registries.

Intervention Anaphylaxis from any community trigger. For the risk factor analysis, candidate exposures include more than one dose of epinephrine, drug trigger, food trigger, unknown trigger, corticosteroid treatment, prior anaphylaxis, severity of the initial reaction, and asthma.

Comparator For incidence, no comparator. For risk factors, children without the factor of interest.

Study designs to be included Prospective and retrospective cohort studies and chart reviews with at least 10 children with anaphylaxis.

Eligibility criteria Inclusion: cohort studies or chart reviews of children aged 0 to 18 years with anaphylaxis that report the number of children with anaphylaxis and the number with biphasic reactions. Exclusion: case reports, reviews, conference abstracts, and other material not published after peer review; 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 overlap, the larger one is kept. No language restrictions.

Information sources PubMed, Embase, and Web of Science Core Collection, from inception. Reference lists of included studies and relevant reviews, and websites of relevant journals.

Main outcome(s) Incidence of biphasic reactions as defined by each study, in children presenting to the ED with anaphylaxis.

Additional outcome(s) (1) Biphasic anaphylaxis (second phase again meeting anaphylaxis criteria per the 2020 Delphi consensus); (2) clinically important biphasic reactions (requiring epinephrine or other active treatment, for example oxygen, vasopressors, intubation, or frequent nebulized bronchodilators); (3) timing of biphasic reactions, including the proportion occurring after 6 hours; (4) odds ratios for clinical factors associated with biphasic reactions; (5) incidence in all pediatric cohorts regardless of setting.

Data management Records are imported into reference management software and duplicates removed. Two reviewers independently screen titles and abstracts and then full texts, and disagreements are resolved by discussion. One reviewer extracts data using a standardized form and a second checks them against the original articles. Extracted items include 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 risk factors.

Quality assessment / Risk of bias analysis Risk of bias is assessed with the JBI critical appraisal checklist for prevalence studies by two reviewers. Studies with 7 or 8 of items 1 to 8 rated “yes” are

considered low risk, 5 or 6 moderate, and 4 or fewer high. Item 9 (response rate) does not apply to record-based studies. Certainty of evidence is rated with GRADE, following guidance for prognostic estimates and prognostic factors.

Strategy of data synthesis Proportions are pooled with a random-intercept logistic generalized linear mixed model, with profile likelihood confidence intervals, I^2 , and 95% prediction intervals. Risk factors reported by at least three studies are pooled as unadjusted odds ratios with a Mantel-Haenszel random-effects model. Timing data are summarized descriptively. Small-study effects are assessed with funnel plots and Egger's test, together with a funnel plot and regression test based on sample size, because the standard error of a logit proportion depends largely on the number of events. Results are treated as exploratory and not as evidence of publication bias.

Subgroup analysis Exploratory subgroup analyses by definition (explicit vs not defined), follow-up window, geographic region, study design, publication period (before vs after 2015), and unit of analysis (patients vs episodes). Multivariable meta-regression is used to explore sources of heterogeneity.

Sensitivity analysis Exclusion of studies with loose definitions, zero events, restricted sampling, abstract-only data, partial population overlap, or in-hospital onset; exclusion of the largest study; leave-one-out analysis; influence diagnostics; Hartung-Knapp adjustment and fixed-effect models for risk factor analyses.

Language restriction No language restrictions.

Country(ies) involved Taiwan (primary institution).

Other relevant information None

Keywords anaphylaxis; biphasic reaction; children; emergency department; meta-analysis; observation time; risk factors.

Dissemination plans Publication in a peer-reviewed journal.

Contributions of each author

Author 1 - Bing-Shiau Shang - Conceptualization; study selection (title, abstract, and full-text screening); data extraction; risk-of-bias assessment; writing of the original draft.
Email: j6ji3@hotmail.com

Author 2 - Yu-Tzu Li - Methodology; literature search; study selection; verification of extracted data; risk-of-bias assessment; statistical analysis; writing, review, and editing.

Email: tsz9903028@gmail.com

Author 3 - Ko-Huang Lue - Clinical interpretation of the findings; supervision; writing, review, and editing.

Email: cshy095@csh.org.tw

Author 4 - Sai-Wai Ho - Conceptualization; supervision; resolution of disagreements during study selection and data extraction; writing, review, and editing.

Email: hswwai@gmail.com

Author 5 - Chia-Ta Wu - Conceptualization; supervision; project administration; writing, review, and editing.

Email: allenpig1102@gmail.com