PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Canadian Anaphylaxis Network- Predicting Recurrence after Emergency Presentation for Allergic REaction (CAN-PREPARE): A Prospective, Cohort Study Protocol
AUTHORS	Alqurashi, Waleed; Shaker, Marcus; Wells, George; Collins, Gary; Greenhawt, Matthew; Curran, Janet; Zemek, Roger; Schuh, Suzanne; Ellis, Anne; Gerdts, Jennifer; Kreviazuk, Cheryl; Dixon, Andrew; Eltorki, Mohamed; Freedman, Stephen; Gravel, Jocelyn; Poonai, Naveen; Worm, Margitta; Plint, Amy

VERSION 1 – REVIEW

REVIEWER	Lee, Bee Natl Univ Hlth Syst
REVIEW RETURNED	20-Apr-2022

GENERAL COMMENTS	This is a multicentre prospective study evaluating the risk factors for biphasic anaphylaxis as its primary objective. As the authors pointed out, it addresses an important aspect of pediatric anaphylaxis, which until now is an unmet need. The proposed data collection is comprehensive. I am however unable to comment on the statistical methods as it is not within my expertise. I have a few minor comments. Comments: 1. Is there a fixed time period for monitoring of the patient in ED? What is the criteria for discharge from ED. 2. There is a typo on page 36 line 53. R2=0.10 or 0.50 (0.50 should be 0.15). 3. What is the statistical software package that would be use for data analysis and modelling?

REVIEWER	Lejeune, Stéphanie CHU Lille
REVIEW RETURNED	07-May-2022

GENERAL COMMENTS	The authors have designed a study to address an important question in the field. The outcome is well-defined but probably overestimated. Thus, my main remark concerns the estimated rate of biphasic anaphylaxis (BA). The authors state that “based on their earlier research and estimates from well-designed adult and pediatric studies,[28,35]” 10% is a conservative of the population-wide event rate for BA. I am afraid this is overestimated. The authors state that they will focus on

	"clinically important or major biphasic reactions" and that "mild symptoms that involve only the skin (e.g., urticarial rash) will be captured and classified as minor biphasic responses, but they do not meet our case definition for BA". The estimated percentage of the event is based on only 2 studies. 1/ In the pediatric study by Alqurashi W, et al (ref 35), which was conducted 7 years ago, BA occurred in 14.6% of cases in children admitted in the ER for anaphylaxis, but not all BR were anaphylaxis (69% involved respiratory and/or cardiovascular manifestations and 49% were treated with epinephrine). 2/ In the other study by Brown S, et al (ref 28), patients were mostly adults at inclusions (25 patients out of 443 cases aged < 17 years), we do not know precisely how many children experienced delayed deterioration, but based on one supplementary table, only one experienced a reaction treated with epinephrine, for a moderate reaction (urticaria, generalized itch). However, as illustrated by the authors and these 2 studies, data on BA in children is scarce and the study will provide new estimation of its rate and risk factors. Including more patients based on a lower estimated rate (5% for instance) may allow the investigators to develop a more accurate prediction model. My other remark concerns the methods and the bias induced by this prospective non-interventional study. If I understood currently, patients will be included in the ER after an anaphylaxis event, but before any BA event. They will then be discharged (or not) and the event will be later monitored by phone calls and or emails. The design may change the behavior of clinicians involved in the ER care of the patients, in particular: use of epinephrine, length of surveillance, disposition time. Thus, those data may not reflect the standard of care practice in the 7 centers participating in the study. It would induce less bias to be more precise on the inclusion criteria (e.g. anaphylaxis treated with epinephrine) and to recommend a minimal length of surveillance in the ER in all centers / cases. Finaly, I am not a specialist statistical reviewer and the described model needs to be assessed by a specialist.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a multicentre prospective study evaluating the risk factors for biphasic anaphylaxis as its primary objective. As the authors pointed out, it addresses an important aspect of pediatric anaphylaxis, which until now is an unmet need. The proposed data collection is comprehensive. I am however unable to comment on the statistical methods as it is not within my expertise. I have a few minor comments.

1. Is there a fixed time period for monitoring of the patient in ED? What is the criteria for discharge from ED.

Since this is a non-interventional prospective study**,** our protocol does not influence the ED management of participants. More specifically, the decisions for and how long to monitor a participant in ED and when to discharge from ED are left entirely to the discretion and clinical judgment of the treating physician. Based on our published survey (2020, PMID: 33448918) of emergency physicians in our Pediatric Emergency Research Canada (PERC) network, the monitoring period is an area of a wide practice variation.

2. There is a typo on page 36 line 53. R2=0.10 or 0.50 (0.50 should be 0.15).

Thank you. We have fixed this typo. The revised line now is "R^2cs=0.10 or 0.15 - proportion of overall variation explained."

3. What is the statistical software package that would be use for data analysis and modelling? The statistical analysis will be performed using R statistical software version 4.0.5 (R Core Team, Vienna, Austria). We added this statement to the revised manuscript.

Reviewer: 2

The outcome is well-defined but probably overestimated. Thus, my main remark concerns the estimated rate of biphasic anaphylaxis (BA). The authors state that "based on their earlier research and estimates from well-designed adult and pediatric studies,[28,35]" 10% is a conservative of the population-wide event rate for BA. I am afraid this is overestimated. The authors state that they will focus on "clinically important or major biphasic reactions" and that "mild symptoms that involve only the skin (e.g., urticarial rash) will be captured and classified as minor biphasic responses, but they do not meet our case definition for BA". The estimated percentage of the event is based on only 2 studies.

1/ In the pediatric study by Alqurashi W, et al (ref 35), which was conducted 7 years ago, BA occurred in 14.6% of cases in children admitted in the ER for anaphylaxis, but not all BR were anaphylaxis (69% involved respiratory and/or cardiovascular manifestations and 49% were treated with epinephrine).

2/ In the other study by Brown S, et al (ref 28), patients were mostly adults at inclusions (25 patients out of 443 cases aged < 17 years), we do not know precisely how many children experienced delayed deterioration, but based on one supplementary table, only one experienced a reaction treated with epinephrine, for a moderate reaction (urticaria, generalized itch). However, as illustrated by the authors and these 2 studies, data on BA in

children is scarce and the study will provide new estimation of its rate and risk factors. Including more patients based on a lower estimated rate (5% for instance) may allow the investigators to develop a more accurate prediction model.

Thank you. You raise a valid point. While we agree that there is a wide range in the reported incidence of BA, we believe our sample size calculation is based on a critical review of the literature. Overall, the published studies to date vary considerably in their design (prospective vs retrospective), enrolled population (adults vs children or mixed), settings (emergency departments vs outpatient allergy clinics), and definition and severity of anaphylaxis and biphasic reaction. The 2014 meta-analysis (ref 83), our 2017 systematic review (ref 77), and the meta-analysis from the 2020 anaphylaxis practice parameter (ref 84) underline these epidemiological factors that explain the significant clinical heterogeneity between previous observational studies. For example, three prospective adult ED studies to date (Brown et al, Ellis and Day, and Scranton et al,) respectively reported an incidence of 13%, 19.4%, and 23%, compared to <5.6% reported in eleven adult ED retrospective studies. From the perspective of population settings, studies that enrolled ED or hospitalized patients reported a higher proportion of BA than those from allergy clinics. This likely reflects the severity of the initial anaphylactic reactions and the variability of the risk of BA, as a result. Furthermore, approximately 15% of children who presented to ED with anaphylaxis developed BA (ref 35), compared to 1.5% in children who experienced allergic reactions during controlled oral food challenges in an allergy clinic (ref 23). Confirming this issue further, data from recent large cohort studies also reported a high incidence of BA. Nagata and colleagues from Japan reviewed national databases of hospitalized patients with anaphylaxis who were treated with adrenaline on admission to hospitals between July 2010 and March 2018(2022, PMID: 35526528). Out of 31,570 patients, 11.2% developed BA (defined as re-administration of two or more ampules of epinephrine within seven days of the admission date). Similarly, nearly 13% of 2258 parents reported a biphasic reaction during their children's most recent food-allergic reaction (2021, PMID: 34033980). Therefore, based on our research, estimates from prospective ED studies, and published data from large adult and pediatric studies, we believe 10% is a reasonable assumption to use in our sample size calculation of the population-wide event rate of BA.

My other remark concerns the methods and the bias induced by this prospective non-interventional study. If I understood currently, patients will be included in the ER after an anaphylaxis event, but before any BA event. They will then be discharged (or not) and the event will be later monitored by phone calls and or emails. The design may change the behavior of clinicians involved in the ER care of the patients, in particular: use of epinephrine, length of surveillance, disposition time. Thus, those data may not reflect the standard of care practice in the 7 centers participating in the study. It would induce less bias to be more precise on the inclusion criteria (e.g. anaphylaxis treated with epinephrine) and to recommend a minimal length of surveillance in the ER in all centers / cases.

To clarify the recruitment procedure, upon presentation to ED with anaphylaxis, the research team will verbally administer a participant survey to participants or caregivers. The survey collects demographics, medical history, risk factors for biphasic anaphylaxis, reaction characteristics, symptoms checklist, and treatment before and after ED arrival. The research team will also capture BA events during the monitoring period in ED. To accurately capture all BA events while participants are in the ED, the research team will follow closely with the participant/caregiver and medical team during the ED visit and again prior to discharge from the ED to ascertain any symptom recurrence. We will contact participants by phone/email 2-5 days

after enrollment into the study to complete a standardized follow-up questionnaire to query details of nature and timing for new and recurrent symptoms or signs that occurred after ED/hospital discharge. Any BA events that were revealed to having taken place in-hospital but were not previously captured by the study team (e.g., outside of study team hours or return visits to the ED for BA within the 48-hour window after study enrollment) will be confirmed by verifying the participant's medical chart.

We believe our strategy for ascertaining the occurrence of BA is robust. This strategy was used successfully in a pilot study. Over 3 months, 50 patients with anaphylaxis were enrolled. Twelve of 50 participants (24%) developed BA, and 8/12 (67%) had BA within 4h of ED presentation. Six of the 50 patients (12%) had severe BA that needed treatment with epinephrine. Given the lack of a robust evidence-based guideline for the minimal length of surveillance in ED, we do not believe mandating a specific ED monitoring period is appropriate.

With regards to introducing bias by not using requirement of treatment with epinephrine, we believe our pragmatic approach is appropriate. Anaphylaxis will be diagnosed based on the 2019 World Allergy Organization criteria. Several previous large epidemiological studies in Canada and globally demonstrated that not all pateints with anaphylaxis are treated with epinephrine, including severe anaphylaxis. Furthermore, lack of treatment with epi has been found to increase the risk of BA. Therefore, it is particularly important to include all participants with anaphylaxis regardless of treatment received.

VERSION 2 – REVIEW

REVIEWER	Lee, Bee Natl Univ Hlth Syst
REVIEW RETURNED	14-Aug-2022

GENERAL COMMENTS	Thank you for your revision. I have no further comments.

REVIEWER	Lejeune, Stéphanie CHU Lille
REVIEW RETURNED	20-Sep-2022

GENERAL COMMENTS	I thank the authors for this reviewed version and for their responses to my previous comments. In particular, I thank them for the thorough literrature search conducted to estimate the rate of BA. I would suggest adding a few sentences to summarize those points in the introduction of this paper, and in particular to distinguish pediatric and adult studies on the matter, as all references are currently mixed together (16-47). I am unable to comment on the statistical methods as it is not within my expertise and I would suggest a specialist statistical review.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. Bee Lee, Natl Univ Hlth Syst
Comments to the Author:
Thank you for your revision. I have no further comments.
Thank you for accepting the revision. We appreciate your thorough review.

Reviewer: 2
Dr. Stéphanie Lejeune, CHU Lille
Comments to the Author:
I thank the authors for this reviewed version and for their responses to my previous comments. In particular, I thank them for the thorough literrature search conducted to estimate the rate of BA. I would suggest adding a few sentences to summarize those points in the introduction of this paper, and in particular to distinguish pediatric and adult studies on the matter, as all references are currently mixed together (16-47).
I am unable to comment on the statistical methods as it is not within my expertise and I would suggest a specialist statistical review.
Thank you. We appreciated your insightful comment. As requested, we have revised the Introduction and Sample Size sections. We added the following sentences to the Introduction: "However, these studies vary considerably in their design (prospective vs retrospective), enrolled population (adults vs children or mixed), settings (emergency departments vs outpatient allergy clinics), and definition and severity of anaphylaxis and biphasic reaction. Recent systematic review and meta-analyses [48,49] underline these epidemiological factors that explain the significant clinical heterogeneity between previous observational studies. This inconsistency of the literature creates dilemma for ED physicians in deciding which patients should be observed and the optimum duration of observation.[50]"
We also included the following sentence to the Sample Size section: "Based on our research[35,48,49], estimates from prospective ED studies [28,44,45,96] and published data from large adult and pediatric studies,[79,80] 10% is a conservative estimate of the population-wide event rate of BA." And we have added the revised citations of this section to the References.