PEER REVIEW HISTORY

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ARTICLE DETAILS

Title (Provisional)

Duration, Course, and Caregiver Burden of Croup in Children: Two Observational Cohorts

Authors

Bjornson, Candice Leigh; Nettel-Aguirre, Alberto; Williamson, Janielee; Johnson, David

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Chen, Jingguo**
Affiliation	**Xi'an Jiaotong University Second Affiliated Hospital**
Date	**05-Nov-2023**
COI	**None.**

The study objective hasn't been clearly defined, the abstract was not attractive for reader, and lack of novolty.

Reviewer	**2**
Name	**Seddon, Paul**
Affiliation	**Brighton and Sussex Medical School**
Date	**25-Feb-2024**
COI	**None**

General comments

This is a descriptive paper aimed at documenting aspects of the natural history of viral croup. The authors describe it as a “secondary analysis of two prospective cohorts of children with croup enrolled from EDs in Alberta, Canada as part of other studies”. A strength of the paper that it includes data from a large number of children. The main weaknesses are:

- The data are already over 20 years old – it is unclear why they are being submitted for publication only now. We know that the epidemiology of other infectious diseases (eg pneumococcal disease and empyema) changes over time, and management in ED is also likely to have changed since then.

- The paper is lumping together data from 2 separate studies conducted years apart with what appear to be different methodologies – one recruiting from a single tertiary paediatric centre, one from multiple secondary, general centre. It is unclear whether some of the children in the tertiary cohort were referred from other hospitals.

- The cohorts did not include all children presenting with croup over the study periods – this weakness is acknowledged by the authors and is at least partially addressed by collecting data retrospectively on the children coded as croup, but not included in the prospective cohorts.

The paper does present important new data about the natural history of croup, but the combination of data from tertiary and general cohorts, and of prospective and retrospective cohorts, is extremely confusing. My advice would be that it would be much preferable to report the general ED cohort (with its parallel retrospective cohort) only because this sample is much larger, is more recent, and would include only children presenting directly to the hospital – and therefore more representative.

Specific comments:

Methods

P6 L10: “tertiary level ED” - but were children seen here referred from other hospitals or did they present directly?

P6 L52: What is the justification for excluding children with a history of asthma? This is a common childhood disease, and commonly associated with recurrent croup.

P7 L3: “For the general ED cohort, ED staff documented at presentation” – no description of what data were collected for the pediatric ED cohort, or when.

Results

P10 L36: What is the point of presenting seasonal data from the prospective cohorts if they did not collect data for the whole year?

It seems from the data presented that the children enrolled in the 2 prospective studies were a more severe subgroup – presumably because they had to meet eligibility criteria..

P12 L3 onwards: It is unclear whether these differences are significant . What is meant by “predicted median”

P12 L33: 20% had worse symptoms on follow-up day 1 – this is not insignificant – and a third had as severe. This is at variance with the conclusion that parents can be advised that (P14

L38) “only a small percentage that will experience symptoms as bad or worse than those witnessed in the first ED visit”

P13 L45; but were they self-referring or were they referred?

Discussion

Generally a balanced discussion, but

a) The additional limitations listed above need to be acknowledged

b) The statement of rapid resolution of symptoms (p14 L38) needs to reflect the actual data – see above

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VERSION 1 - AUTHOR RESPONSE

Response to Reviewers

Thank you for the opportunity to respond to reviewers’ comments and re-submit a revised manuscript. Please see below for a point-by-point response.

(Please note that the new line numbers and comments referred to in our response correspond to the revised manuscript denoted as Main Document – marked copy with ‘track changes’ for easier visualisation of the edits made.)

REVIEWER 1 (Comments Italicized)

“The study objective hasn't been clearly defined, the abstract was not attractive for reader, and lack of novelty.”
We respectfully disagree with Reviewer 1’s assessment. First, we believe our study objectives are clearly defined, which are copied below in red. Second, we also believe that our manuscript provides novel information about the clinical course of croup that will be valuable for educating clinicians-in-training and families of children with croup.

The primary objective of this study was to describe the peak and duration of symptoms in children presenting to an emergency department (ED) with croup. Secondary objectives were: to determine if age, sex, season of presentation, or severity of croup at presentation were associated with duration of symptoms; and to describe associated caregiver stress, loss of sleep and time from work during the child’s croup illness.

REVIEWER 2 (Comments Italicized)

General comments. A strength of the paper that it includes data from a large number of children.

We thank the reviewer for noting this strength of our study.

The main weaknesses are:
- The data are already over 20 years old – it is unclear why they are being submitted for publication only now. We know that the epidemiology of other infectious diseases (eg

pneumococcal disease and empyema) changes over time, and management in ED is also likely to have changed since then.

We acknowledge that our cohorts are dated. First, to answer why we are submitting this manuscript now, the impetus for it stemmed from a conversation with colleagues about 'what are the gaps in the literature for croup'. We realized that one of the identified gaps for croup - symptom progression, caregiver burden, and whether age, sex, or season and initial severity of disease are associated with symptom duration – could be addressed using our previously conducted patient cohorts gathered for other purposes.

Second, to answer why we believe the course of illness for croup is unlikely to have changed since these cohorts were created, please see Appendix below showing annual ED visits per capita for croup determined using standardized Canadian emergency department data sets utilizing ICD10 coding for the province of Alberta from 2003 to 2023. The per capita rates of ED visits shown in both graphic and tabular form highlight a distinct biannual pattern without any significant trend or deviation, except since the COVID pandemic. The biannual pattern has been well described in the literature dating back to the 1980's.[1] During COVID, the rates of croup substantially dropped (see Alberta data below), but now appear to be normalizing.

Also, the recommended management of croup has remained the same since the late 1990's which consists of corticosteroids (most commonly dexamethasone) for mild, moderate, and severe respiratory distress, and nebulized epinephrine for severe distress.[2,3,4] Further, as noted in the *Results*, very high percentages of children in both the pediatric and general ED prospective cohorts were treated with corticosteroids, 81 and 90%, respectively. Last, unlike pediatric pneumonia, where the occurrence of empyema has been well documented to have changed,[5] the one recognized complication of croup – the occurrence of bacterial tracheitis – has remained unchanged and rare.[6,7]

- The paper is lumping together data from 2 separate studies conducted years apart with what appear to be different methodologies – one recruiting from a single tertiary paediatric centre, one from multiple secondary, general centre. It is unclear whether some of the children in the tertiary cohort were referred from other hospitals.

Yes, we do report our findings from two distinct cohort studies; one recruited from the Alberta Children's Hospital (ACH) emergency department (ED) between November 1999 and March 2000, and the other recruited between September 2002 and April 2006 from 26 different general emergency departments distributed across the province of Alberta that included those located in general metropolitan cities (Calgary or Edmonton), regional cities, and rural towns. None of the children recruited into the prospective ACH ED cohort were referred from another hospital; all parents brought their child directly to the ACH ED when their child became symptomatic. Ninety-seven per cent (298/307) of these children were discharged home, while only 3% (9/307) were admitted and none to the Pediatric Intensive Care Unit. We have highlighted this in the manuscript (lines 249-250)

As explained below in detail, we believe it critically important to report the results from both the pediatric and general ED cohorts separately, in order to provide a fuller and ultimately more accurate understanding of croup's clinical course.

- The cohorts did not include all children presenting with croup over the study periods – this weakness is acknowledged by the authors and is at least partially addressed by collecting data retrospectively on the children coded as croup, but not included in the prospective cohorts.

We thank the reviewer for noting that we have addressed an important limitation of our prospective cohorts – that they do not include all children presenting with croup – as best we could through presenting data from retrospective cohorts which compares demographic and clinical characteristics of those enrolled versus those not enrolled.

The paper does present important new data about the natural history of croup, but the combination of data from tertiary and general cohorts, and of prospective and retrospective cohorts, is extremely confusing. My advice would be that it would be much preferable to report the general ED cohort (with its parallel retrospective cohort) only because this sample is much larger, is more recent, and would include only children presenting directly to the hospital – and therefore more representative.

We acknowledge that our study design presenting data separately from the ACH ED and Alberta general EDs prospective and retrospective cohorts is complicated and makes it difficult for the reader to easily understand. However, the ACH and general ED cohorts yielded some important differences in their findings that we believe are important to report. The most notable difference between the cohorts is that, in the general ED cohort, children less than 12 months remained symptomatic significantly longer (median 61.5 hours) than children older than 12 months (median 48 hours), whereas in the ACH ED cohort those under 12 months (median 33 hours) had shorter time to symptom resolution than those over12 months (median 39 hours). We are uncertain what factors account for the opposing results. Arguments can be made for both ED cohorts as being more representative and hence more accurate than the other cohort. Given this, we think it important to be even handed and report both results.

To minimize the risk of confusion on the part of the reader, we have clarified, starting with the abstract (lines 20 and 21) that the two cohorts are reported separately, and the reasons for this (lines 217 to 220).

Specific comments:
Methods: P6 L10: "tertiary level ED" - but were children seen here referred from other hospitals or did they present directly?

As noted above, all children enrolled into the pediatric ED prospective cohort presented directly and were not referred. This has been clarified in the manuscript.

Methods: P6 L52: What is the justification for excluding children with a history of asthma? This is a common childhood disease, and commonly associated with recurrent croup.

In retrospect, we agree with the reviewer and would do it differently, had we the opportunity to do it over. However, we believe this exclusion criteria did not result in a significant number of children being excluded since the diagnosis of asthma is not reliably made in pre-school children and 66% and 60% of children enrolled in the prospective ACH and general ED cohorts were three years or less, and 89% and 88% were six years or less. Hence, we

think exclusion of children with a firm diagnosis of asthma from enrollment in our prospective cohorts is very unlikely to result in significant bias.

Methods: P7 L3: "For the general ED cohort, ED staff documented at presentation" – no description of what data were collected for the pediatric ED cohort, or when.

We clarified in the manuscript that croup severity at presentation for the pediatric ED cohort was determined using review of physician, nurse and respiratory therapist documentation (lines 177 to 179).

Results P10 L36: What is the point of presenting seasonal data from the prospective cohorts if they did not collect data for the whole year? It seems from the data presented that the children enrolled in the 2 prospective studies were a more severe subgroup – presumably because they had to meet eligibility criteria.

With regard to the reviewer's question regarding seasonality, we consciously did not recruit children with croup during late spring and summer (June, July and August) because relatively few cases of croup occur during this time. We focused on the beginning of September through to the end of May, because epidemiological and virological studies, have shown that, historically, croup presenting in autumn and early winter (September to December) versus winter and early spring (January to May) have shown different disease patterns and been associated with different viruses.[1] Our retrospective general ED cohort is consistent with this; of the 4,739 children in the cohort, 492 (10.4%) presented June to August, 1,907 (40.2%) presented September to December, and 2340 (49.4%) presented January to May. Because of these different seasonal patterns, we thought it important to explore if the two seasons showed differences in symptom duration. And, in fact, both cohorts showed that children presenting September to December (pediatric ED median 26 hours, and general ED median 43 hours) were symptomatic longer than January to May (pediatric ED median 36 hours, and general ED median 53 hours).

Regarding the reviewer's comment about children with more severe symptoms being enrolled into both prospective cohorts, it's more accurate to say, on average, children in the prospective cohorts were somewhat more severe. However, while a smaller proportion of children with mild croup were enrolled than not enrolled, the children with the greatest severity, e.g. the seven children admitted to PICU, were also not enrolled. This information has been added to the manuscript (lines 282 to 284).

Results P12 L3 onwards: It is unclear whether these differences are significant. What is meant by "predicted median"

The term 'predicted median' alluded to our adjustment of the median for the following co-variates: age, sex, severity of croup at presentation, and season of presentation. To make this clearer, we have re-written this sentence to be explicit that the median was adjusted for co-variates (Lines 306 to 308).

Results P12 L33: 20% had worse symptoms on follow-up day 1 – this is not insignificant – and a third had as severe. This is at variance with the conclusion that parents can be advised that (P14 L38) "only a small percentage that will experience symptoms as bad or worse than those witnessed in the first ED visit"

The proportion of children with worse symptoms on follow-up day 1 than at presentation is a second example of a significant difference between the pediatric and general ED cohorts (2.3% vs 20.6%, respectively). After reflection, we realized our interpretation that *"only a small percentage"* experienced worse symptoms reflected our unjustified bias that the pediatric cohort was more accurate than the general ED cohort. We re-wrote this sentence to better reflect both cohort's findings [lines 376 to 377 - "most children's symptoms did not worsen following discharge with a minority experiencing worse symptoms in the days following ED discharge."]

Results P13 L45; but were they self-referring or were they referred?

As noted above, all children enrolled in the ACH ED prospective cohort were self-referred.

Generally a balanced discussion, but
a) The additional limitations listed above need to be acknowledged

We have added limitations to the manuscript regarding the exclusion of children with asthma, and how old the data is (Lines 386 to 392)
b) The statement of rapid resolution of symptoms (p14 L38) needs to reflect the actual data – see above
As noted above, this change has been made.

REFERENCES

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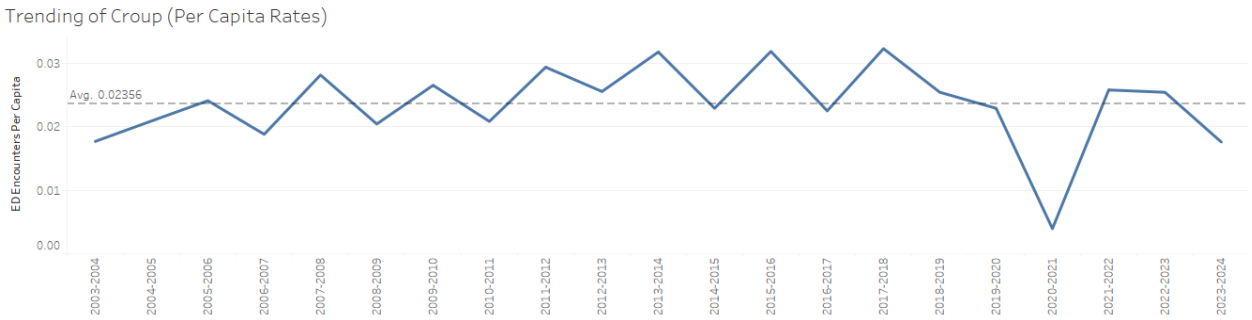
6. Burton LV, Lofgren DH, Silberman M. Bacterial Tracheitis. 2023 Jun 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29262085
7. Kuo CY, Parikh SR. Bacterial tracheitis. Pediatr Rev. 2014 Nov;35(11):497-9. doi: 10.1542/pir.35-11-497. PMID: 25361911

Appendix – Annual ED visits per capita for croup in the province of Alberta from July 1, 2003 to June 30th, 2003 [determined using ICD10 codes J04 and J05 for children 0-6 years of age]



CROUP_YEAR	ED_ENCOUNTER_CNT	YEARLY_U6_POP_CNT	ED_ENCOUNTERS_PER_CAPITA
2003-2004	4847	273990	0.01769043
2004-2005	5807	277656	0.02091437
2005-2006	6842	283873	0.02410233
2006-2007	5494	292061	0.01881114
2007-2008	8465	300700	0.02815098
2008-2009	6395	312948	0.02043470
2009-2010	8577	323263	0.02653258
2010-2011	6936	332823	0.02083991
2011-2012	10022	341103	0.02938115
2012-2013	9000	352263	0.02554909
2013-2014	11485	361512	0.03176935
2014-2015	8509	371531	0.02290253
2015-2016	12008	376828	0.03186600
2016-2017	8596	382062	0.02249897
2017-2018	12400	383866	0.03230294
2018-2019	9755	383593	0.02543060
2019-2020	8758	382320	0.02290751
2020-2021	1499	379810	0.00394671
2021-2022	9734	377362	0.02579486
2022-2023	9523	374509	0.02542796