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Epidemiology of community acquired sepsis in children in Australia and New Zealand: a multicentre prospective cohort study

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Summary

Background Paediatric sepsis epidemiology is unclear due to variability in case ascertainment. We describe the epidemiology of community acquired sepsis in Australian and New Zealand children using the Phoenix sepsis criteria.

Methods Prospective observational study conducted in 11 hospitals through the Paediatric Research in Emergency Departments International Collaborative (PREDICT) Network from April 2021 to December 2023. Children aged 0–<18 years with suspected sepsis were included. Demographic information, therapies administered, and outcomes were collected, and the Phoenix sepsis criteria were applied.

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Findings Of 822,072 children assessed, 6232 (0.8%) children had suspected sepsis and 306 (<0.1%) met the Phoenix sepsis criteria. Children who met the Phoenix sepsis criteria had higher rates of intensive care unit admission (245/306; 80.1% vs 1080/6232; 17.3%), vasoactive infusion (144/306; 47.1% vs 179/6232; 2.9%) mechanical ventilation (146/306; 47.7% vs 251/6232; 4.0%), and extracorporeal life support (12/306; 3.9% vs 13/6232; 0.2%) compared to the overall cohort. Intensive care unit and hospital length of stay were longer for those meeting Phoenix sepsis criteria than for the overall cohort (median 48.4 h vs 79.8 h and 69.7 h vs 189.8 h, respectively). Overall, 87/6232 (1.4%) patients died within 90 days, 42/306 (13.7%) of whom met Phoenix sepsis criteria.

Interpretation Hospitalisation for suspected sepsis was relatively infrequent. The Phoenix sepsis criteria identified children with more severe illness and worse outcomes, but underestimated the overall burden of sepsis.

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Keywords: Sepsis; Child; Organ dysfunction; Epidemiology

Research in context

Evidence before this study

There are global data to show that severe infection and sepsis are major causes of childhood death with particularly high rates of morbidity and mortality in low- and middle-income countries. Yet, even in high income countries like Australia and New Zealand there are limited data on the epidemiology of community acquired sepsis in the emergency department setting where children with sepsis need to be identified and treatment initiated. Recently the Society of Critical Care Medicine has derived and validated the international data driven Phoenix criteria (based on measures of dysfunction of four organs) to diagnose and report sepsis epidemiology in children. We searched PubMed, without date restriction, using the terms: (sepsis) AND (Phoenix) AND (Australia OR New Zealand). There are no original studies exploring the Phoenix sepsis criteria in Australia and New Zealand. Available studies on sepsis in children from Australia and New Zealand focus on the intensive care unit setting.

Added value of this study

Our study is a large prospective study at 11 hospitals in Australia and New Zealand which included children <18 years with suspected community acquired sepsis identified in the emergency department, defined as diagnosed with sepsis and/or receiving treatment for sepsis (intravenous antibiotics and intravenous fluid bolus/es) and those who fulfilled Phoenix sepsis criteria (a Phoenix sepsis score ≥2). Of 6232 children with suspected sepsis 306 fulfilled Phoenix sepsis criteria. While children who fulfilled Phoenix criteria had elevated rates of intensive care unit admission compared to the overall cohort (80.1% vs 17.3%), children who fulfilled Phoenix criteria had very high rates of vasoactive infusions (47.1% vs 2.9%) and mechanical ventilation (47.7% vs 4.0%) compared to the overall cohort. 12 of the 13 children who received extracorporeal life support and 7 of the 10 children who received new haemo/peritoneal dialysis fulfilled Phoenix criteria. The proportion of children meeting Phoenix sepsis criteria who died within 90 days was 13.7% (42/306), while only 1.4% (87/6232) of those in the overall cohort died within 90 days.

Implications of all the available evidence

Within a cohort of children with suspected sepsis in the emergency department, the Phoenix criteria identified a group of children with high rates of intensive care unit admissions and a requirement for organ support. Yet, most children in this cohort who ultimately died did not fulfil Phoenix sepsis criteria. These baseline epidemiological data will be critical to improve sepsis pathways and for future interventional studies in community acquired sepsis. They will also be useful to understand the role of the Phoenix criteria in children admitted from the emergency setting.

Introduction

Invasive infections and sepsis are thought to be leading causes of preventable childhood death worldwide.[1] However, the global burden of sepsis in terms of incidence, severity, and outcomes, is surprisingly unclear. From a global perspective, sepsis incidence in children has been difficult to determine due to the lack of recognition of sepsis as a separate disease by the Global Burden of Disease statistics, the lack of inclusion of children in some mortality estimates, and the lack of data from low and middle-income countries where sepsis incidence and mortality are thought to be highest.[2,3] Country-specific sepsis incidence has been infrequently and inconsistently reported. This is largely

driven by variability in case definition and a lack of a clear reference standard for diagnosis. International Classification of Disease codes have been used to retrospectively identify children with sepsis or infection-related organ dysfunction, with a seven-fold difference in incidence found between these two case ascertainment methods.[4] Case ascertainment using International Sepsis Consensus Conference criteria has been found to be discordant with clinician ascertainment of sepsis, with an inter-rater agreement (kappa) of 0.57.[5] There are no standardised criteria for reporting sepsis severity or routinely collected core outcome sets for patients with sepsis. As a result, the burden of sepsis on healthcare systems is largely unknown.

To address the lack of consensus criteria for sepsis case ascertainment in children, the paediatric sepsis definition task force, convened by the Society of Critical Care Medicine, has performed an international survey and systematic review and meta-analysis to develop a new score (the Phoenix sepsis score) to identify children hospitalised with infection who are at high risk of death.[6,7] A four-organ model was developed that combined derangements in the cardiovascular, neurological, respiratory, and coagulation systems. Using a large dataset, this score has been validated, and new criteria for diagnosing and reporting sepsis proposed as the Phoenix sepsis criteria (a Phoenix sepsis score $\geq$2).[8,9]

In Australia and New Zealand, there are no data on the epidemiology of sepsis outside of the ICU setting[10] and there are very limited data from high and low and middle income countries using the Phoenix criteria.[8] We report the incidence, severity, and outcomes of children with community acquired suspected sepsis and in those with sepsis meeting the Phoenix sepsis criteria in prospectively identified hospitalised children as the basis for improving sepsis care pathways and to prepare for interventional studies.

Methods

Design

In this multi-centre multi-country prospective observational study, data were collected from 11 emergency departments (EDs); 8 tertiary paediatric EDs and 3 large mixed paediatric/adult EDs. All participating sites were in Australia and New Zealand, had annual ED censuses of >20,000 children, and were members of the Paediatric Research in Emergency Departments (PREDICT network).[11] The annual census of the 11 participating EDs in total was >450,000 childhood and adolescent presentations, and these sites collectively represent all major paediatric centres in Australia and New Zealand. Each site had its own sepsis guideline/pathway, which were similar in most treatment recommendations.[12] All sites were capable of initiating vasoactives and mechanical ventilation. Five study sites provided extracorporeal life support (ECLS) on site. Three study sites initiated ECLS and transferred patients to an ECLS centre within 1-h transport. Three sites transferred all children requiring ECLS to a centre that was greater than 1-h transport. The study was conducted between April 2021 and December 2023, with staggered start dates at some sites due to COVID-19-related delays in obtaining ethics and governance approval.[13] Consent was obtained according to local jurisdictional requirements with details set out in the protocol paper.[13] The trial was registered through the Australian and New Zealand Clinical Trials Registry prior to commencement of recruitment (ACTRN12621000920897).

Participants

Children aged 0–<18 years were included if they were: admitted to hospital for parenteral antibiotics (duration unspecified, initiated by ED staff) with either a) a provisional diagnosis of sepsis, as determined by the treating clinician AND/OR b) received treatment for sepsis (defined as one or more fluid boluses to treat impaired perfusion, not dehydration, initiated in the ED by ED staff). The presence of fever was not required. These inclusion criteria were thought to be broadly representative of the patient group hospitalised with suspected sepsis, as prior studies had indicated that a substantial proportion of patients with infection requiring ICU-level care did not have an admission diagnosis of sepsis.[14] This was operationalized using the administration of a fluid bolus as this was the initial treatment for sepsis recommended in all guidelines and pathways at participating sites in addition to the use of intravenous antibiotics.[12]

Patients not admitted through the ED (such as direct inter-hospital ICU transfers) and patients who were admitted to another hospital ward prior to ED transfer were excluded due to difficulty obtaining initial data on organ dysfunction. Patients presenting with trauma were excluded.

Recruitment, study procedures, and data collection

Patients were screened by their treating clinicians for eligibility. Enrolment of eligible patients included verbal or written informed consent (jurisdiction dependent) for permission to contact families for follow-up 90 days from enrolment. Missed eligible patients were identified by the research team at each participating site through real-time reviews of all ED attendances and ICU admission records. Consent was obtained in-person for hospitalized patients. In the rare instance where the patient was discharged home prior to consent, telephone consent was obtained as soon as possible. De-identified routinely collected data from the medical records of included patients were extracted and entered into a secure web-based Research Electronic Data Capture (REDCap) database housed at Murdoch Children's Research Institute (MCRI), Parkville, Australia according to the study protocol.[13] The

requirement for organ support therapy or ICU admission was evaluated over the entire course of hospitalisation. Ninety-day mortality follow-up was performed by research staff by screening the medical record for in-hospital death or death following discharge. Children not recorded as deceased received routine study follow-up, including Pediatric Overall Performance Category score, parent-reported outcome measures, days off work and out-of-pocket expenses, and repeat hospitalisations.[13]

Definitions

The Phoenix sepsis criteria were defined as a Phoenix sepsis score ≥2 over the first 24 h of hospitalization.[8] Sepsis incidence was defined as number of cases per overall number of ED presentations. Sepsis severity was defined as requirement for organ support therapies (vasoactive infusion, mechanical ventilation, renal replacement therapy, extracorporeal life support). Sepsis outcomes were defined as ICU and hospital length of stay and 90-day mortality.

Statistical methods

Descriptive statistics were calculated for key epidemiological variables, using means and standard deviations for normally distributed data, and medians and interquartile ranges (IQR) for continuous data. Unadjusted relative risk was calculated using log-binomial regression. Quantile regression models were used to compare medians of length of stay outcomes (ICU and hospital).

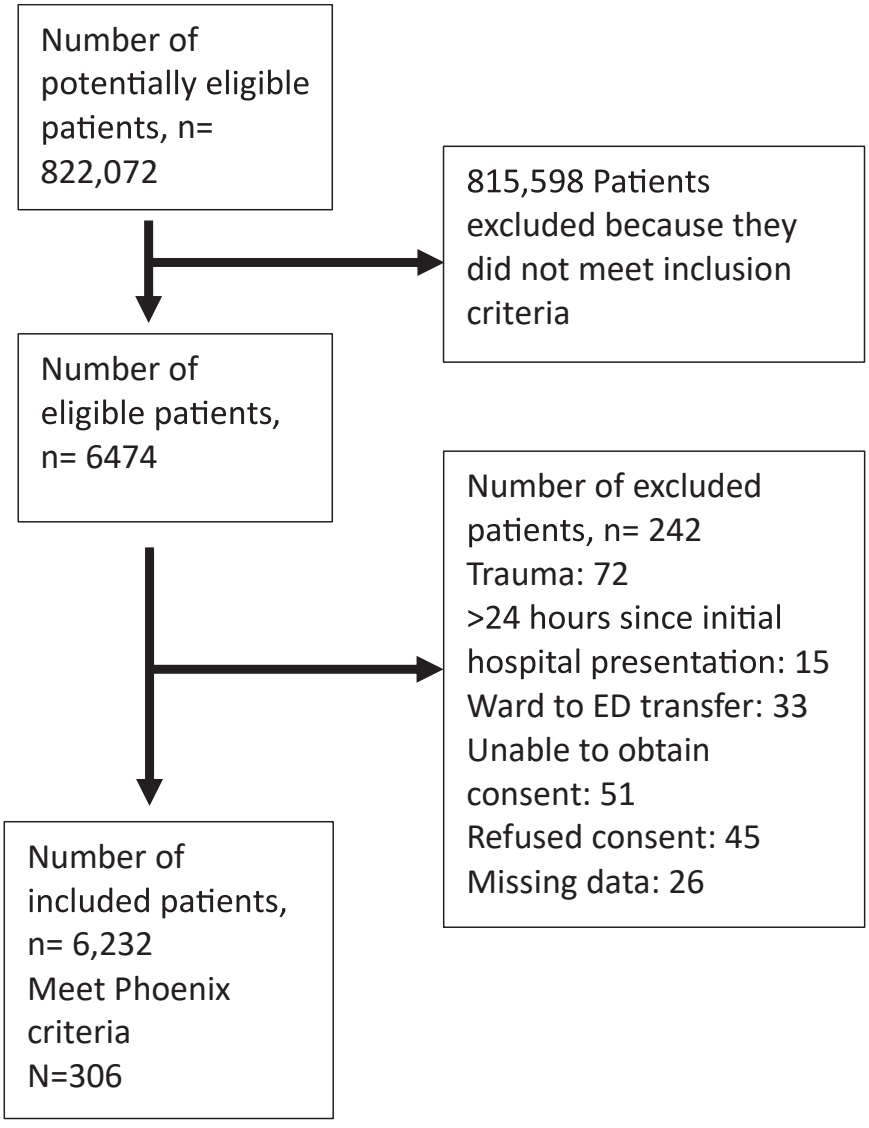

Fig. 1: **SENTINEL flow diagram.**

As defined by the original paper, data from the first 24 h of patient hospitalization were used to determine the Phoenix sepsis score, with the most abnormal overall score during this time used for analysis.[8] For asynchronously collected data points used in the calculation of the Phoenix sepsis score, we used a 'last observation carried forward' approach within physiologically appropriate time windows.[8] Completely missing values were treated as non-additive to organ dysfunction scoring, as reported, and in keeping with the original Phoenix derivation and validation study.[8,9] The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for the reporting of observational studies.[15] Statistical analysis was performed using Stata (18.5, StataCorp LLC, College Station, TX).

Ethics approval

Ethics approval was obtained through The Royal Children's Hospital Human Research Ethics Committee (HREC/69948/RCHM-2021), Parkville, Australia.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, interpretation, writing of the report.

Results

Over a three-year period, 11 EDs screened 822,072 participants, and identified 6474 as eligible for inclusion. Of these, 6232 were included in the analysis, and 306 met the Phoenix sepsis criteria (Fig. 1). The incidence of suspected sepsis in this population was 7.5/1000 hospital emergency presentations, and the incidence of sepsis identified using the Phoenix sepsis criteria was 0.4/1000 hospital emergency presentations.

Demographics of enrolled patients with suspected sepsis and those meeting the Phoenix sepsis criteria are shown in Table 1. The median Phoenix sepsis score in the overall cohort was 0.0 (IQR 0.0–0.0), for those meeting the Phoenix sepsis criteria was 2.0 (IQR 2.0–4.0), and for those not meeting the Phoenix sepsis criteria was 0.0 (IQR 0.0–0.0). The most common dysfunctional organ in those meeting Phoenix sepsis criteria was cardiovascular. The median age for those meeting the Phoenix sepsis criteria was older than in the overall cohort, while similar proportions of children were female and from Aboriginal, Torres Strait Islander, or Māori families. Some co-morbidities were over-represented in children meeting the Phoenix sepsis criteria, including immune deficiency or immunosuppression, congenital heart disease, syndromic conditions, ex-prematurity, chronic respiratory disorder, and home ventilation.

Children meeting Phoenix criteria for sepsis were more unwell than those in the overall suspected sepsis cohort, with a much higher proportion admitted to ICU and requiring organ support therapies (vasoactive infusion, mechanical ventilation, or renal replacement therapy) (Table 2). The majority (12/13; 92.3%) of children receiving extra-corporeal life support met Phoenix sepsis criteria.

	Overall	Meet Phoenix sepsis criteria	Do not meet Phoenix sepsis criteria
	(N = 6232)	(N = 306)	(N = 5926)
Age at presentation; median (IQR)	2.1 (0.3, 7.1)	4.3 (1.0, 9.7)	2.0 (0.2, 6.9)
Age category; n (%)			
<1 month	821 (13.2)	23 (7.5)	798 (13.5)
1 month–<1 year	1475 (23.7)	50 (16.3)	1425 (24.1)
1 year–<2 years	778 (12.5)	31 (10.1)	747 (12.6)
2 years–<5 years	1026 (16.5)	59 (19.3)	967 (16.3)
5 years–<12 years	1366 (21.9)	84 (27.5)	1282 (21.6)
12 years–<18 years	747 (12.0)	59 (19.3)	688 (11.6)
Missing	19 (0.3)	0 (0.0)	19 (0.3)
Sex; n (%)			
Female	2830 (45.4)	139 (45.4)	2691 (45.4)
Male	3386 (54.3)	167 (54.6)	3219 (54.3)
Other	2 (0.0)	0 (0.0)	2 (0.0)
Missing	14 (0.2)	0 (0.0)	14 (0.2)
Ethnicity groups; n (%)			
Non-Aboriginal or Torres Strait Islander/Non-Māori	5619 (90.2)	274 (89.5)	5345 (90.2)
Aboriginal or Torres Strait Islander/Māori	599 (9.6)	32 (10.5)	567 (9.6)
Missing	14 (0.2)	0 (0.0)	14 (0.2)
Comorbidities; n (%)			
Any	2513 (40.3)	183 (59.8)	2330 (39.3)
Immunodeficiency or immune suppressed	593 (9.5)	28 (9.2)	565 (9.5)
Indwelling central line (including PICC)	436 (7.0)	28 (9.2)	408 (6.9)
Long term steroids	174 (2.8)	13 (4.3)	161 (2.7)
Diabetes	32 (0.5)	7 (2.3)	25 (0.4)
Congenital heart disease	215 (3.5)	33 (10.8)	182 (3.1)
Syndromic condition	378 (6.1)	39 (12.8)	339 (5.7)
Ex premature	478 (7.7)	33 (10.8)	445 (7.5)
Chronic respiratory disorder	325 (5.2)	34 (11.1)	291 (4.9)
Chronic renal failure	68 (1.1)	4 (1.3)	64 (1.1)
Neurological developmental condition	596 (9.6)	81 (26.5)	515 (8.7)
Home ventilation	101 (1.6)	16 (5.2)	85 (1.4)
Primary pathogen; n (%)			
None	2752 (44.2)	120 (39.2)	2632 (44.4)
Bacterial	1237 (19.9)	96 (31.4)	1141 (19.3)
Viral	2132 (34.2)	85 (27.8)	2047 (34.5)
Fungal	10 (0.2)	1 (0.3)	9 (0.2)
Parasitic	2 (0.0)	1 (0.3)	1 (0.0)
Other	2 (0.0)	0 (0.0)	2 (0.0)
Missing	97 (1.6)	3 (1.0)	94 (1.6)
Organ dysfunction; n (%)			
Respiratory	190 (3.1)	87 (28.4)	103 (1.7)
Cardiovascular	459 (7.4)	217 (70.9)	242 (4.1)
Coagulation	513 (8.2)	129 (42.2)	384 (6.5)
Neurological	371 (6.0)	166 (54.2)	205 (3.5)

PICC, peripherally inserted central cannula; IQR, inter-quartile range.

Table 1: **Overall demographics of eligible patients and those meeting the Phoenix sepsis criteria.**

	Overall cohort (N = 6232)	Phoenix sepsis cohort (N = 306)	Relative risk (95% CI)
ICU/NICU admission; n (%)	1080 (17.3)	245 (80.1)	5.68 (5.2, 6.2)
Vasoactive infusion; n (%)	179 (2.9)	144 (47.1)	79.68 (56.1, 113.2)
Mechanical ventilation; n (%)	251 (4.0)	146 (47.7)	26.93 (21.6, 33.7)
Extracorporeal life support; n (%)	13 (0.2)	12 (3.9)	232.39 (30.3, 1781.5)
New haemo/peritoneal dialysis; n (%)	10 (0.2)	7 (2.3)	45.19 (11.7, 173.9)
Vasoactive infusion and mechanical ventilation; n (%)	120 (1.9)	107 (35.0)	159.40 (90.7, 280.2)

ICU, intensive care unit; NICU, neonatal intensive care unit; CI, confidence interval.

Table 2: **Severity of illness overall and for children meeting the Phoenix sepsis criteria.**

Median ICU and hospital length of stay was longer for children who met vs who did not meet the Phoenix sepsis criteria, and the proportion who died within 90-days was higher (Table 3). The relative risk of death within 90 days was 18.1 times higher (95% CI 12.1–27.1) for children meeting the Phoenix sepsis criteria than for those who did not.

Discussion

In this large prospective cohort of children from Australia and New Zealand, hospitalisation for suspected sepsis was relatively uncommon as a proportion of all ED visits. Most of the children hospitalised with suspected sepsis were less than 5 years of age, boys, and children with comorbidities. These findings are in-keeping with the demographic characteristics found in prior sepsis epidemiology studies, conducted before the Phoenix sepsis criteria became available, though the study by Balamuth et al. from the US demonstrated a higher proportion of children with sepsis having comorbidities (70%).[4,10,16] Globally, the peak incidence of sepsis is seen in a similar age group, with more than half of all sepsis cases worldwide occurring in children <5 years of age, with a higher incidence in girls than in boys (co-morbidities are not reported).[17]

Nearly one fifth of children with suspected community acquired sepsis in our study were admitted to ICU, though only a small proportion required organ support therapies. These children may have required enhanced/more frequent monitoring or may have been admitted to ICU based on local guidelines (for example, children having received large volume fluid resuscitation but not requiring a vasoactive infusion, children with persistent hyperlactaemia, or children with empyema).[18] Mechanical ventilation was the most common ICU-level therapy administered, followed by vasoactive infusion. Prior epidemiological studies of community acquired sepsis from the US report substantially higher ICU admission rates (70–90%).[4] As expected, ICU-based epidemiological studies of childhood sepsis report much higher proportion of patients treated with organ support therapies, with mechanical ventilation and vasoactive infusion being the most commonly administered.[10,16]

Only a small proportion of children with community acquired sepsis died within 90 days, and median ICU and hospital length of stay (LOS) were 2 and 3 days, respectively. Prior epidemiological studies from the US demonstrated similar median ICU LOS, but substantially longer median hospital LOS (15 days) and mortality (8–21% depending on case ascertainment method used).[4] Median ICU LOS reported in ICU-based epidemiological studies is longer (5 days) and mortality higher (25%) than in our study.[16] This difference may be due to different study locations (ICU vs ED patients), different inclusion criteria ('severe sepsis' using consensus criteria[19] vs pragmatic criteria), and time (enrolment in prior epidemiological studies between 2013 and 2014).[16]

Application of the Phoenix criteria to the cohort with suspected sepsis identified a critically unwell cohort of children. Children meeting Phoenix sepsis criteria had a similar sex distribution to the overall cohort but were

	Overall (N = 6232)	Meet Phoenix criteria (N = 306)	Relative risk (95% CI)	Median difference (95% CI)
ICU length of stay (hours); median (IQR)	48.4 (24.2, 103.2)	79.83 (35.85, 152.23)	N/A	35.2 (24.4, 46.1)
Hospital length of stay (hours); median (IQR)	69.7 (45.4, 138.2)	189.8 (80.0, 364.2)	N/A	121.7 (115.1, 128.3)
Patient died within 90 days; n (%)	87 (1.4)	42 (13.7)	18.1 (12.1, 27.1)	N/A

ICU, intensive care unit; IQR, interquartile range.

Table 3: **Outcomes for children meeting Phoenix sepsis criteria.**

older and more likely to have comorbidities. The demographics of children meeting the Phoenix sepsis criteria more closely resembled those of children in prior ICU-based epidemiological studies.[10,16] The severity of illness in children meeting the Phoenix sepsis criteria was worse than the overall cohort, with the majority being admitted to the ICU and one half requiring mechanical ventilation or vasoactive infusion. These findings were similar to prior ICU-based epidemiological studies.[10,16] Outcomes in the cohort meeting Phoenix sepsis criteria were substantially worse than the overall cohort, with longer ICU and hospital LOS, and higher proportion of 90-day mortality. Prior ICU-based epidemiological studies report both lower[10] and higher[16] mortality than that seen in the cohort meeting the Phoenix sepsis criteria.

Our study contributes to the ongoing discussion about the optimal criteria for clinical case definition and reference standard for diagnosis of sepsis in children for use in reporting sepsis epidemiology.[4,5] In our study, less than 5% of children admitted to hospital with suspected sepsis met the Phoenix sepsis criteria. Though the Phoenix sepsis criteria identified most of the children requiring acute circulatory support (vasoactive infusion or extracorporeal life support), they did not identify a substantial proportion of children admitted to the ICU or who required mechanical ventilation. In addition, the Phoenix sepsis criteria did not identify over half of the children who died within 90-days of hospitalisation. Death in some children may not have been attributable to sepsis, particularly late deaths occurring in children with complex underlying conditions.[20] Although the Phoenix criteria provide a standardised set of parameters for reporting sepsis epidemiology and benchmarking care, the healthcare and societal burden of sepsis is much greater than might be inferred when the Phoenix criteria alone are used for case ascertainment.

Studies on the epidemiology of community acquired sepsis such as this one are fundamental to understand and improve sepsis management pathways and policy. The initial impetus for the study was a lack of detailed epidemiological data to undertake a 39 centre randomised controlled trial on fluid management in sepsis.[21] The data will be critical for planned interventional studies across the PERN (Pediatric Emergency Research Networks).[22]

The findings of our study should be considered in the context of some limitations. First, our study was confined to tertiary care centres participating in the PREDICT network, which may limit generalisability to non-tertiary hospitals or other healthcare settings. Australia and New Zealand are both high income countries with government funded health care systems. However, we observed a similar overall mortality rate to the high-income country data of the original Phoenix derivation and validation study, indicating similarities between populations. A study using similar enrolment criteria should be conducted across high-, middle- and low-income countries to elucidate differences in the epidemiology of community acquired sepsis. Such a study is under way. In keeping with all sepsis epidemiological studies, mortality in the study population may not have been attributable to sepsis.

In conclusion, this study highlights differences in incidence, severity, and outcomes of paediatric sepsis based on the case ascertainment criteria used. The Phoenix criteria identify a cohort with substantially worse clinical outcomes, but do not identify many patients who require ICU-level care or who die within 90 days, underscoring the importance alternative methods for case ascertainment.

Contributors

EL, AW and FEB were integral in conceiving the study. All authors made substantial contributions to the study design and development of the study protocol. SH provided statistical oversight of the study. EL wrote the first draft of the study paper, and all authors provided feedback. EL, FB, AW and SH have accessed and verified the raw data. All authors have read and approved the final version to be published and agree to be accountable for all aspects of the work.

Data sharing statement

Anonymised participant data will be available upon request from the corresponding author within the constraints of ethics and regulatory requirements.

Declaration of interests

The authors have no declared conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2025.101608.

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