Title

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Journal

BMJ Open, 14(1)

Authors

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Publication Date

2024-01-12

DOI

10.1136/bmjopen-2023-077471

Peer reviewed

BMJ Open

Sepsis epidemiology in Australian and New Zealand children (SENTINEL): protocol for a multicountry prospective observational study

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To cite: Long E, Borland ML, George S, *et al*. Sepsis epidemiology in Australian and New Zealand children (SENTINEL): protocol for a multicountry prospective observational study. *BMJ Open* 2024;**14**:e077471. doi:10.1136/bmjopen-2023-077471

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-077471).

Received 06 July 2023
Accepted 20 December 2023

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ABSTRACT

Introduction Sepsis affects 25.2 million children per year globally and causes 3.4 million deaths, with an annual cost of hospitalisation in the USA of US$7.3 billion. Despite being common, severe and expensive, therapies and outcomes from sepsis have not substantially changed in decades. Variable case definitions, lack of a reference standard for diagnosis and broad spectrum of disease hamper efforts to evaluate therapies that may improve sepsis outcomes. This landscape analysis of community-acquired childhood sepsis in Australia and New Zealand will characterise the burden of disease, including incidence, severity, outcomes and cost. Sepsis diagnostic criteria and risk stratification tools will be prospectively evaluated. Sepsis therapies, quality of care, parental awareness and understanding of sepsis and parent-reported outcome measures will be described. Understanding these aspects of sepsis care is fundamental for the design and conduct of interventional trials to improve childhood sepsis outcomes.

Methods and analysis This prospective observational study will include children up to 18 years of age presenting to 12 emergency departments with suspected sepsis within the Paediatric Research in Emergency Departments International Collaborative network in Australia and New Zealand. Presenting characteristics, management and outcomes will be collected. These will include vital signs, serum biomarkers, clinician assessment of severity of disease, intravenous fluid administration for the first 24 hours of hospitalisation, organ support therapies delivered, antimicrobial use, microbiological diagnoses, hospital and intensive care unit length-of-stay, mortality censored at hospital discharge or 30 days from enrolment (whichever comes first) and parent-reported outcomes 90 days from enrolment. We will use these data to determine sepsis epidemiology based on existing and novel diagnostic criteria. We will also validate existing and novel sepsis risk stratification criteria, characterise antimicrobial stewardship, guideline adherence, cost and report parental awareness and understanding of sepsis and parent-reported outcome measures.

Ethics and dissemination Ethics approval was received from the Royal Children's Hospital of Melbourne, Australia Human Research Ethics Committee (HREC/69948/RCHM-2021). This included incorporated informed consent for follow-up. The findings will be disseminated in a peer-reviewed journal and at academic conferences.

Trial registration number ACTRN12621000920897; Pre-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ As the first prospective sepsis landscape analysis undertaken in Australia and New Zealand, this study will improve our understanding of the burden of disease in children presenting to emergency departments (EDs) in major urban centres with community-acquired sepsis.
⇒ This study will allow prospective evaluation of existing and novel sepsis diagnostic criteria and risk stratification tools, antimicrobial use and stewardship, and quality of care.
⇒ This study will provide insight into parent-reported outcome measures, as well as parental awareness and understanding of sepsis.
⇒ This study is being conducted across 12 EDs in Australia and New Zealand. While multiple EDs are included in this study, most are tertiary referral centres and may not reflect the population seen in rural and regional centres.

INTRODUCTION

Sepsis is an important global health issue. Over 25.2 million children per year worldwide develop sepsis, resulting in 3.4 million deaths with most in children younger than 5 years of age.[1] The hospitalisation cost per child with

sepsis in the USA is estimated at US$26 592, resulting in an annual expenditure of US$7.31 billion that represented 18.1% of nationwide paediatric hospitalisation costs in the USA in 2019.[2] Reducing childhood deaths from sepsis is essential if the United Nations Millennium Development Goals are to be achieved.[3]

Despite advances in public health, prevention and treatment of many infectious diseases, invasive infections and sepsis remain leading causes of preventable childhood death worldwide.[4] Mortality from sepsis remains substantial, even in high-income counties.[5] Any reduction in sepsis mortality mirrors that of children hospitalised for non-infectious causes, suggesting improved survival is, in part, due to improved routine hospital-based care rather than attributable to improved sepsis-related therapies.[6] This may in be partly due to an increasing number of patients with high-risk conditions that predispose to sepsis, such as extreme prematurity, acquired or innate immunodeficiency, or the presence of indwelling vascular catheters.[7] To this point, trials evaluating novel sepsis-related therapies, such as activated protein C, have not improved sepsis outcomes.[8] Trials evaluating existing therapies, such as volume and timing of fluid resuscitation, have had variable and sometimes conflicting effects on sepsis outcomes.[9–11] Trials evaluating other existing therapies, such as corticosteroids, are limited by small sample sizes, inconsistent findings and methodological concerns.[12] As a result, guidelines for the management of sepsis in children have been largely limited to weak treatment recommendations based on low-quality evidence for many sepsis therapies in children.[13]

Many challenges contribute to the lack of high-quality evidence for sepsis epidemiology, diagnosis and therapies in children:

1. The current case definition for sepsis, established in 2005,[14] is difficult to apply and often leads to variable estimates of sepsis prevalence, severity, outcomes, cost, difficulty benchmarking care and inconsistent enrolment strategies for clinical trials. Originally sepsis was defined as systemic inflammation due to suspected or proven infection,[14] operationalised using the systemic inflammatory response syndrome (SIRS) diagnostic criteria. A major challenge has been that the SIRS criteria are neither sensitive nor specific for sepsis; 80% of febrile children in the emergency department (ED) meet SIRS criteria for sepsis, most of whom are discharged without antibiotics and <2% actually have sepsis.[15] Conversely, SIRS criteria achieve only moderate correlation with clinician-diagnosed severe sepsis requiring admission to the intensive care unit (ICU).[16] In recognition of the limitations of defining sepsis using systemic inflammation, and in the absence of a criterion standard, the Adult Sepsis Definition Taskforce has identified organ dysfunction as the key differentiator between uncomplicated infection and sepsis.[17] In adults, sepsis is currently defined as life-threatening organ dysfunction due to a dysregulated host response to infection (Sepsis-3).[18] Operationalising an organ-dysfunction-based Sepsis-3 definition in children will require consideration of age-based pathophysiological and clinical manifestations, evaluation of predictive versus descriptive performance of scoring systems, and validation outside of the ICU setting.[19] Several issues remain unclear, including: (a) how organ dysfunction should best be captured (eg, which organs, what thresholds for determining dysfunction and whether dysfunctional organs should receive weighted scores), (b) the relationship between sepsis diagnosis, severity of disease and timing in disease course (where diagnostic scores should be applicable early to an undifferentiated population and identify patients at risk of progression to severe disease) and (c) how to account for uncertainty of infection (such as in culture-negative sepsis, pretreated infections and non-infectious aetiologies mimicking sepsis).[20]
2. Diagnostic criteria operationalising SIRS criteria perform poorly, yet the optimal criteria to diagnose sepsis based on organ dysfunction criteria remain unclear. Diagnostic criteria should prioritise a combination of sensitivity and specificity as measured using the area under the receiver operating characteristic curve (AUROC).[21] Three diagnostic components have been proposed[22]: (1) The presence of infection. This is usually indicated by fever in children, but infection may also manifest as hypothermia, particularly in young infants and neonates, and children with certain comorbid medical conditions.[23] However, fever in children may also be due to non-infectious auto-immune or inflammatory process.[24] (2) The presence of organ dysfunction. This is commonly diagnosed based on abnormal vital signs or biomarkers. However, the criteria to determine sepsis-related organ dysfunction, which organs to include, cut-off values for diagnosis (particularly in children with pre-existing organ dysfunction and those receiving organ support therapy) and timing of development are not clear.[25] (3) Sepsis diagnostic criteria. These should identify children at high risk of disease progression and mortality. Although an increasing number of dysfunctional organs are associated in with increased mortality in children,[26–28] existing scores use different criteria,[29] are designed for use during different phases of treatment (ED vs intensive care)[30] and do not have suitable test characteristics in terms of sensitivity and specificity for widespread application.[25]
3. Risk stratification tools available early in the ED treatment of children with sepsis are of limited value for predicting mortality. Risk stratification tools prioritise predictive value rather than AUROC, with worsening Sequential Organ Failure Assessment (SOFA) score in adults being predictive of mortality.[17] In children, risk stratification scores have been evaluated in several populations. In the general ICU population, the Paediatric Index of Mortality-3 and Paediatric Risk of Mortality scores have been validated for prediction of death.[31 32] In the ICU population with suspected infection, the SIRS organ dysfunction criteria, paediatric

SOFA score and Paediatric Logistic Organ Dysfunction score (PELOD-2) have been validated for prediction of death.[30 33 34] In the general paediatric ED population, the paediatric SOFA score has been validated for prediction of death.[28] In the ED population with suspected infection, the quick SOFA and quick PELOD scores have been validated as predictors of ICU admission and death.[35] In general, scores derived for application in the paediatric ICU include more organ dysfunction criteria, weight the severity of organ dysfunction and have better performance for predicting mortality than those derived for application in the ED setting. Validated risk stratification tools available early in the treatment of children with sepsis are crucial for targeting therapies to those with modifiable risk of severe disease and poor outcomes.

4. Effective early antimicrobial therapy is an important predictor of survival from paediatric sepsis,[36 37] yet empirical treatment for sepsis is one of the most common reasons for antibiotic prescribing in children in Australia[38] and linked to antibiotic resistant bacteria and adverse long-term outcomes in children.[39 40] Australia and New Zealand (NZ)-specific data are needed on the microbiology, resistance patterns and antibiotic prescribing practice in paediatric sepsis to better target guidelines and policy.
5. Finally, the role of parents in early sepsis recognition is unclear. Parents are at the front line of early sepsis recognition, yet only 27% think they could recognise the signs of sepsis in their own children.[41] Coroner investigations repeatedly highlight the failure of healthcare providers to heed parental concerns, contributing to delays in sepsis recognition and timely treatment.[42]

In a collaboration between emergency physicians, paediatricians and critical care physicians, this study will provide a landscape analysis of community-acquired childhood sepsis in Australia and NZ through the PREDICT network. We will characterise sepsis prevalence, severity, outcomes and cost. We will validate existing and novel diagnostic and risk stratification criteria, explore novel biomarkers, report antimicrobial use and stewardship, guideline compliance, and parent-reported sepsis awareness and understanding, and parent-reported outcome measures. This study will provide a comprehensive epidemiological assessment of sepsis in children in the ED setting of major urban centres in Australia and NZ as a basis for future interventional trials and guideline development.

METHODS

Design

This is a multicentre prospective observational study. The study will follow the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for the reporting of observational studies and the Standards for the Reporting of Diagnostic Accuracy studies (STARD) guidelines for the validation of sepsis organ dysfunction criteria.[43 44]

Patient and public involvement

The research team includes a parent consumer lead with lived experience caring for a child with infection-related conditions including sepsis. This parent consumer and a hospital family advisory council reviewed all patient/parent facing study materials and provided feedback on their acceptability, content, timing and mode of delivery. Once study results are available, feedback from this parent consumer and family advisory council will be included in publications and presentations. Study data and outcomes collected include those deemed of high importance to parents and clinicians.[45 46]

Setting and participants

The study will take place at 12 EDs, 9 tertiary paediatric EDs and 3 large mixed paediatric/adult EDs. All are located in Australia and New Zealand and individually see at least 20 000 children per year. These centres are members of the PREDICT network[47]: in Australia: Monash Medical Centre, Clayton, VIC, Children's Hospital at Westmead and Sydney Children's Hospital, Sydney, NSW, The Royal Children's Hospital, Melbourne, VIC, Queensland Children's Hospital, Brisbane, QLD, Perth Children's Hospital, Perth, WA, Women's & Children's Hospital, Adelaide, SA, The Royal Darwin Hospital, Darwin, NT, Gold Coast University Hospital, Gold Coast, QLD and Townsville Hospital, Townsville, QLD; in New Zealand: Kidz First Middlemore Hospital and Starship Children's Hospital, Auckland. The annual volume of the 12 participating EDs is >450 000 presentations. The central site for the study is the Murdoch Children's Research Institute (MCRI), which is affiliated with The Royal Children's Hospital Melbourne.

Inclusion and exclusion criteria

Patients up to 18 years of age who present to a participating ED with suspected sepsis will be included. Suspected sepsis will be defined as children admitted to hospital for parenteral antibiotics and either: (1) a provisional (admission) diagnosis of sepsis, septicaemia or septic shock or (2) treatment for sepsis, operationalised as treatment with one or more fluid boluses (defined as a fixed volume of fluid administered over <30 min to treat impaired perfusion, not dehydration) (table 1). ICU admission logs will be screened to ensure all patients with sepsis, including those not initially treated for nor diagnosed with sepsis, are captured.

Patients who are not admitted through the ED (such as direct interhospital ICU transfers) and patients who are admitted to another hospital ward prior to ED transfer will be excluded due to difficulty obtaining initial vital signs and biomarkers. Patients presenting with trauma will be excluded.

Outcome

Primary and secondary outcomes are listed in box 1.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Emergency department presentation	Patients not admitted through the emergency department
Up to 18 years of age	Interhospital transfers from a hospital ward to the emergency department
Admission to hospital	Patients with trauma
Treatment with parenteral antibiotics	
Provisional diagnosis of sepsis or treatment for sepsis*	

*Treatment for sepsis: administration of one or more fluid bolus (fixed volume of fluid administered over <30 min to treat impaired perfusion, not dehydration).

Patient recruitment, study procedures and data collection

All patients will be screened in the ED by their treating clinicians for eligibility. Prospective enrolment may occur at any time during an ED presentation through the completion of a paper-based Clinical Report Form by the treating clinician (CRF, online supplemental file). This will include perceived severity of disease and level of suspicion for sepsis using a Likert scale. Verbal or written consent (depending on jurisdiction) will be sought and documented at the time of enrolment for permission to contact families 90 days after the ED visit for follow-up. Should prospective consent not be obtained, the study team will seek consent either during the in-patient stay, or at the time of follow-up. Clinical management will not be delayed and will proceed independent of study participation.

Box 1 Primary and secondary outcome measures

Primary outcome

Proportion of paediatric emergency department attendances with community-acquired sepsis, proportion delivered intensive care unit-level care, proportion who die; functional outcome at day 90 in sepsis survivors and median hospitalisation cost.

Secondary outcomes

Validation of existing (systemic inflammatory response syndrome (SIRS), quick Paediatric Logistic Organ Dysfunction (qPELOD-2), quick Sequential Organ Failure Assessment (qSOFA), pSOFA) and novel (through inclusion of sepsis specific biomarkers) diagnostic criteria.

Validation of existing (SIRS, qPELOD-2, qSOFA, pSOFA) and novel (through inclusion of sepsis-specific biomarkers) risk stratification tools.

Pathogens and resistance patterns in children with community-acquired sepsis.

Median duration of parenteral and enteral antimicrobial treatment and median time to antibiotic rationalisation.

Proportion of children with community-acquired sepsis who achieve local guideline time targets for antimicrobial administration.

Proportion of parents of children with community-acquired sepsis who are aware of and understand the characteristics of sepsis.

Nature and frequency of parent-reported outcomes for children with community-acquired sepsis.

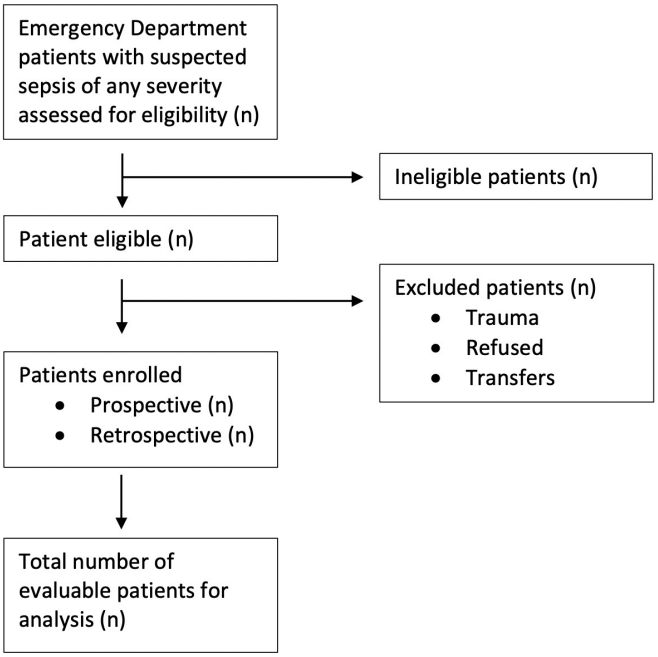

Figure 1 Participant enrolment flow chart.

For prospectively enrolled patients, a parental sepsis awareness survey will be administered via quick response (QR) code at the time of enrolment (online supplemental file). Parents/guardians will provide implied consent by completing the survey.

Identification of missed eligible patients will be undertaken by the research team in each participating centre by a review of the daily ED attendance and ICU admission record for patients meeting inclusion criteria (figure 1). Retrospectively identified eligible participants will be enrolled by the research team and approached on the hospital wards or by telephone for verbal consent for follow-up. The CRF will not be completed on this patient group.

We will extract certain deidentified data from medical records on patients enrolled both prospectively and retrospectively and enter the data into an electronic database. Data to be extracted is outlined in box 2. The data will be stored in a web-based Research Electronic Data Capture (REDCap) database securely housed at MCRI.[48] Comorbidities recorded will include immunodeficiency or immunosuppression, presence of central venous access device, long-term steroid treatment, diabetes, congenital heart disease, congenital syndrome, ex-prematurity, chronic respiratory disorder, home ventilation, chronic renal failure, neurodevelopmental condition and recent surgery or burns.

Follow-up at 90 days (90–120 days) post-ED presentation will be undertaken by telephone, text message, email or REDCap survey link depending on the patients'/caregivers' preference. Three contact attempts will be made. If more than 120 days have elapsed since presentation to

Box 2 Data to be collected by all participating emergency departments (EDs) by time point

Initial ED attendance
Clinician-reported severity of illness and likelihood of sepsis (Likert scale) and clinical variables (eg, *GCS score, CRT, presence of non-blanching rash/severe unexplained pain/blue or grey colour/grunting).
Detailed patient demographic information (age, sex, Indigenous status and comorbidities).
Vital signs (†HR, MBP, SBP, RR, SpO2, RR, GCS score and CRT).
Pathology tests (‡VBG, FBC, UEC, LFT, coagulation profile and troponin).
Therapies administered (antibiotics, oxygen, fluids—bolus/maintenance/drug administration line, steroids and organ support).

Admission diagnosis
Parental sepsis awareness and understanding survey.
During hospital stay.
Disposition (hospital ward and ICU).
Vital signs (4, 8, 12 and 24 hours from ED arrival).
Pathology tests (4, 8, 12 and 24 hours from ED arrival).
Therapies administered (duration of hospitalisation censored at 30 days).
Intensive care unit and hospital length of stay (censored at 30 days).

Discharge diagnosis
Results of all microbiological tests.
In-hospital mortality (censored at 30 days).
Follow-up contact 90 days after hospitalisation.
Paediatric Overall Performance Category score.
Parent-reported outcome measures.
Days off work and out-of-pocket expenses for parents.
Repeat hospitalisations.
90-day mortality.

*GCS, Glasgow Coma Scale; CRT, capillary refill time.
†HR, heart rate; MBP, mean blood pressure; SBP, systolic blood pressure; RR, respiratory rate.
‡VBG, venous blood gas; FBC, full blood count; UEC, urea electrolytes creatinine; LFT, liver function test.

ED or if there have been three failed contact attempts, the patient follow-up will be considered unsuccessful, and the patient will be considered lost to follow-up. Medical record review will be conducted on all patients lost to follow-up to ensure capture of return visits.

Paper-based CRFs will be deidentified after all data points have been extracted and entered, and all data queries have been addressed.

All research assistants (RAs) will receive formal training in the completion of the study CRFs and REDCap database prior to commencing enrolment. Identical materials and procedures will be used across all sites. The study CRF was piloted on 20 patients prior to use. Data will be regularly audited by the central coordinating team.

Data management

Data collected on the paper CRFs and from the medical records will be entered into a password-protected database enabled through the REDCap (Research electronic Data Capture) web-based application hosted by the MCRI.[48] This database will only be accessible to trained research staff. All data entered into this database will be deidentified. The identifiable paper-based CRFs and satisfaction surveys will be kept in a locked office, accessible only to the researchers at the local site. All sites will maintain a separate password-protected logbook on a secure online database containing reidentifying information for data queries.

Oversight of data collection and auditing of data entry compliance will be undertaken both remotely and through regular site visits in line with the clinical monitoring plan for the study. If there is a need to reidentify data for clarification, this will be done by the principal investigator (PI) at the site level.

All data will be retained in line with the ethics and governance requirements of the local site.

This trial steering committee consisting of the chief PI, trial coordinator, site PIs and trial statistician will meet quarterly to discuss the progress of the trial and review recruitment.

STATISTICAL METHODS

Sample size and power calculation

We aim to enrol more than 2500 children over 18 months. This will provide a large sample for describing the sepsis landscape in Australia and NZ.

We conducted a precision-based sample size calculation for derivation of Sepsis-3 diagnostic criteria using death and long-term disability as outcomes. Based on pilot data and a retrospective study of 6500 children presenting to the ED with febrile illnesses at the central study site,[49] death in the proposed paediatric study population is ~2.1% and long-term disability ~14%. A sample size of 2500 eligible children with sepsis or being treated for suspected sepsis will yield approximately 52 patient deaths and 350 patients with long-term disabilities. For a 100% sensitivity, this sample size would yield upper and lower limits of the 95% CIs of 93% to 100%, respectively, for death and 99% to 100% for long-term disability. We expect a loss to follow-up rate of 10% (similar to a prior large observational study in PREDICT with 20 000 patients[50]).

Descriptive statistics will be calculated for key epidemiological variables, using means and SD for normally distributed data, and medians and IQR for skewed data. To evaluate sepsis diagnostic criteria, we will assess the accuracy of existing and novel organ dysfunction criteria following the STARD and clinical decision rule guidelines.[44 51] Existing organ dysfunction criteria will be based on the organs and cut-off points used in pSOFA, PELOD-2, qSOFA and qPELOD-2(25). Novel organ dysfunction criteria will include the addition of sepsis biomarkers such as lactate, coagulation profile and troponin. To evaluate risk-stratification tools, we will evaluate the performance of existing and novel organ dysfunction criteria (as outlined above) for identifying multiple outcomes based on severity of disease and outcome (hospital and ICU length of stay, duration of organ support therapies,

and mortality). Diagnostic accuracy and risk stratification criteria will be assessed via sensitivity, specificity, negative and positive predictive values, and the area under the receiver-operating characteristic curve (AUROC) with 95% CIs. The association between increasing number of dysfunctional organs and multiple outcomes will be evaluated using the Cochrane-Armitage trend test.[28] Diagnostic statistics will include multiple logistic regression models and sensitivity analyses. Missing predictor variables will be presumed to be normal (negative). Sensitivity analyses will be performed to compare negatively imputed results to those where missing data were excluded. The level of significance will be set at $p<0.05$. The economic evaluation of this study will take a societal perspective, with both acute-care and long-term time horizons. Direct healthcare costs associated with ED presentation and hospitalisation will be estimated using activity-based funding estimates provided by the Independent Health and Aged Care Pricing Authority.[52] The National Efficient Price for the Australian Refined Diagnosis Related Groups codes for sepsis (T60A-C) will be adjusted by the national weighted activity units for paediatrics, care in specialised children's hospitals, residential remoteness, COVID-19 and sepsis-related complications. Similarly, the costs for NZ study sites will be estimated using price weights based on NZ's casemix framework for publicly funded hospitals. The costs in NZ dollars will be converted to Australian dollars based on the average exchange rates. Indirect costs of parent's time off work and out-of-pocket healthcare costs will be collected at the follow-up contact for the study cohort using a standardised questionnaire. The economic burden of ongoing health impacts of sepsis care on survivors will be estimated at 3 months, from which we will extrapolate the long-term economic consequences of sepsis in children.

Ethical issues, consent and dissemination

Parents who voluntarily complete the sepsis awareness and understanding survey do so under implied consent. Parents who do not wish to participate in the study may decline follow-up or may have their child withdrawn from the study at any stage, in which case no patient-level identifiable data will be retained. The study protocol will follow successful processes used for other large multicentre observational studies performed by the PREDICT network.[50]

Risk management, adverse events and patient safety

As an observational study, there are no anticipated adverse events related to the research, except a minor risk of loss of confidentiality.

Time plan

The 1-year pilot for the study started enrolling patients in April 2021 at the central site (The Royal Children's Hospital Melbourne). Four-hundred and fifty patients have been recruited. With funding secured, the study will be rolled out at the remaining 11 sites with a 2-year recruitment period, with a planned completion date of January 2024.

DISCUSSION

Our study is the first landscape analysis of childhood sepsis in Australia and NZ. It will improve the understanding of sepsis incidence, severity and outcomes, and provide baseline data for the conduct of interventional trials.

This study has several limitations. We will rely on a high recruitment rate to achieve the desired sample size, and a rate of primary outcome (death or long-term disability) of 2.1% and 14%, respectively, in the study population. Characteristics of organ dysfunction criteria for defining paediatric sepsis may differ in populations with different incidence of the primary outcome, and standard practice will be decided by the treating clinician. Where no test for organ dysfunction was obtained at baseline in the ED, the result will be assumed to be normal, although this may not be the case. While multiple EDs are included in this study, most are tertiary referral centres and may not reflect the population seen in rural and regional centres. The study focuses on community-acquired sepsis, while hospital-acquired sepsis is a significant contributor to sepsis morbidity and mortality. Though we include participants up to the age of 18 years, study sites may have different age thresholds for treating older adolescents, which may skew study age demographics.

This study will have an impact on clinical practice, antimicrobial stewardship, public policy and sepsis research conduct in major urban centres in Australia, NZ and beyond.

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Acknowledgements This study is being conducted on behalf of the PREDICT network. The authors would like to thank our parent consumer Ms Kate Rawnsley for her involvement in study design.

Contributors EL, AW and FEB were integral in conceiving the study. EL, MLB, SG, SJ, ET, JN, NP, AK, SC, AL, AR, SD, EO, SH, SS, BG, SM, FB, SW, NK, AW and FEB made substantial contributions to the study design and development of the study protocol. SH provided statistical oversight of the study protocol. EL wrote the first draft of the study protocol paper, and MLB, SG, SJ, ET, JN, NP, AK, SC, AL, AR, SD, EO, SH, SS, BG, SM, FB, SW, NK, AW and FEB provided feedback. EL, MLB, SG, SJ, ET, JN, NP, AK, SC, AL, AR, SD, EO, SH, SS, BG, SM, FB, SW, NK, AW and FEB have read and approved the final version to be published and agree to be accountable for all aspects of the work.

Funding This study is funded in part by a National Health and Medical Research Council (NHMRC) Medical Research Futures Fund grant (GNT1190814). EL is funded by a Royal Children's Hospital Clinician-Scientist Fellowship (N/A). FEB is funded by a grant from the Royal Children's Hospital Foundation and an NHMRC Practitioner Fellowship (GNT1127542). This study is supported by the Melbourne Children's Trials Centre at MCRI. The Royal Children's Hospital and MCRI are supported by the Victorian Government's Operational Infrastructure Support, Australia (N/A).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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