Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable: Pediatric Sepsis Definition Task Force

Task force selection process: The Society of Critical Care Medicine (SCCM) appointed two Co-Chairs and two Co-Vice-Chairs to lead the project who met with leaders of the 2016 adult Sepsis Definition task force (Sepsis-3) to gain insights into the lessons learned from the Sepsis-3 approach. A diverse panel in terms of discipline, gender, and healthcare setting was considered essential by the Pediatric Sepsis Definition Task Force leadership group. To ensure global representation and relevance, the task force included 35 nurse and physician experts with clinical and content expertise in intensive care (pediatric and neonatal), pediatric emergency medicine, infectious diseases, and public health, as well as expertise in quality improvement, clinical trials, epidemiology, and informatics who treat acute and critically ill children across a range of resource settings.

Name	Institution	Discipline
Luregn J. Schlapbach, MD, PhD *(Co-Chair)*	Department of Intensive Care and Neonatology, and Children's Research Center, University Children's Hospital Zurich, University of Zurich, Zurich, Switzerland; and Child Health Research Centre, The University of Queensland, Brisbane, QLD, Australia	Pediatric Critical Care
R. Scott Watson, MD, MPH *(Co-Chair)*	Center for Child Health, Behavior and Development, Seattle Children's Research Institute; Division of Pediatric Critical Care Medicine, Seattle Children's Hospital and University of Washington, Seattle, WA, USA	Pediatric Critical Care
Andrew C. Argent, MD, MBBCh, MMed *(Co-Vice-Chair)*	Department of Pediatrics and Adolescent Health, Red Cross War Memorial Children's Hospital and University of Cape Town, Cape Town, South Africa	Pediatric Critical Care
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Paolo Biban, MD	Verona University Hospital, Verona, Italy	Pediatric Critical Care
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Kathleen Chiotos, MD	Children's Hospital of Philadelphia, Philadelphia, PA, USA	Pediatric Infectious Diseases
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Name	Institution	Discipline
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Mark W. Hall, MD *(Survey co-lead)*	Nationwide Children's Hospital, Columbus, OH, USA	Pediatric Critical Care
David Inwald, MB, MB BChir PhD	Addenbrooke's Hospital, Cambridge University Hospital NHS Trust, Cambridge, United Kingdom	Pediatric Critical Care
Paul Ishimine, MD, FACEP, FAAP	University of California, San Diego School of Medicine, La Jolla, CA, USA	Pediatric Emergency Medicine
Niranjan Kissoon, MD, MCCM	British Columbia Women and Children's Hospital and the University of British Columbia, Vancouver, BC, Canada	Pediatric Critical Care
Michael Levin, MD, PhD	Imperial College London, London, United Kingdom	Pediatric Infectious Diseases
Rakesh Lodha, MD	All India Institute of Medical Sciences, New Delhi, India	Pediatric Critical Care
Kusum Menon, MD, MSc *(Methodologist)*	Department of Pediatrics, Children's Hospital of Eastern Ontario, Ontario, Canada and University of Ottawa, Ontario, Canada	Pediatric Critical Care
Simon Nadel, MBBS, MRCP, FRCP	St. Mary's Hospital, London, United Kingdom	Pediatric Critical Care
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Adrienne G. Randolph, MD, MS, FCCM	Boston Children's Hospital, Boston, MA, USA	Pediatric Critical Care
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eMethods 1: Task force project plan.

PEDIATRIC SEPSIS DEFINITION TASKFORCE – PROJECT PLAN approved by the Society of Critical Care Medicine
Version 1.0, date: January 2019

Objectives of this project plan:

1) To provide the rationale, aims, and methodology of the Pediatric Sepsis Definition Taskforce for Taskforce members
2) To develop a project and analysis plan that will be submitted for publication prior to the main part of analyses performed
3) To propose and justify expansion of scope in comparison to the SCCM/ESPNIC-approved initiative

Key words: childhood; mortality; infection; sepsis; SIRS; sepsis-3, septic shock, organ dysfunction

Abbreviations:

EHR	Electronic Health Record
HIC	High-income countries
LMIC	Low- and middle-income countries
MODS	Multi-Organ Dysfunction Syndrome
OR	Odds ratio
PELOD	Pediatric Logistic Organ Dysfunction score
PICU	Pediatric Intensive Care Unit
PIM	Pediatric Index of Mortality
qSOFA	quick Sequential (Sepsis-related) Organ Failure Assessment
SSC	Surviving Sepsis Campaign
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential (Sepsis-related) Organ Failure Assessment

1. CURRENT PEDIATRIC SEPSIS DEFINITIONS, AND GAPS IN THE ERA OF SEPSIS-3

Sepsis accounts for a large proportion of the estimated over 3 million annual childhood deaths due to infection, and sepsis-associated long-term mortality and morbidity lead to a disproportionate impact on disability-adjusted life years for the society[1-5]. The World Health Organization (WHO) resolution on sepsis urges member states to dedicate efforts to improve diagnosis, prevention, and management of sepsis[6]. The Surviving Sepsis Campaign, and the American College of Critical Care Medicine (ACCCM) guidelines advocate for the implementation of institutional sepsis screening tools and sepsis management bundles as a best practice[7-11]. The experience from New York State demonstrated that a mandate for sepsis care can reduce sepsis-associated mortality in children[12], and similar initiatives have been implemented in many settings, in particular in the United Kingdom and the United States. At the same time, recent reports in adult patients demonstrate that the coding for sepsis has increased in certain countries[13], which may reflect changes in either epidemiology or in coding practices[13-15]. Improving sepsis-related clinical care and research is dependent on valid, generalizable definitions of sepsis, as accurate definitions are required for benchmarking and performance review and to enhance the optimal use of ICU resources[16,17], and to design and perform research on sepsis.

While the term "sepsis" has been used to identify patients presenting with infection at higher risk of mortality, the absence of a gold standard for the condition leads to substantial challenges[18]. Over the past 20 years, different strategies were used to operationalize the “essence” of sepsis, which is considered to be the result of dysregulated host response to a infection, while acknowledging challenges to characterize dysregulated across phenotypes, age groups, and patients[19-22],. Historically, definitions put variable weight on the need for sensitive clinical criteria to facilitate rapid recognition, versus the need for robust criteria to enable a specific diagnosis. Following the 1992 and 2001 consensus statements of the American College of Chest Physicians and the Society of Critical Care Medicine, pediatric sepsis was defined as infection in presence of at least two out of four criteria of systemic inflammatory response syndrome (SIRS), including temperature, heart rate, respiratory rate, and white blood cell count, also called as Sepsis-2[23,24]. The Sepsis-2 concept assumed a progression of infection towards infection with excessive inflammation (SIRS) defined as sepsis, which may then progress towards severe sepsis (characterized by organ dysfunction) and septic shock. The current pediatric sepsis definitions are based on the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) [24]. In view of the high mortality seen with sepsis, the goal of this expert consensus conference was to identify a high-risk of group of patients with mortality around 15-20% who were not responding to initial therapy for the purpose of enrolment in a interventional trial. The IPSCC definitions were largely aligned with the adult Sepsis-2 definitions, with the specifications of age-specific cut-offs for SIRS criteria, the requirement that at least 1 of the SIRS criteria must be abnormal white cell count or temperature, and pediatric-specific definitions of organ failure for cardiovascular (shock), respiratory, central nervous system, hepatic, renal, and haematological organ dysfunction. More recently, the challenges in applying these definitions have been highlighted, which include poor performance in validation studies, inaccurate application in clinical practice, lack of specificity of SIRS to discriminate children with higher infection-related severity, and limitations in the operationalization of organ dysfunction for severe sepsis[19,25-27 28,29].

The recent Sepsis-3 consensus definition in adults differentiated sepsis from uncomplicated infection by the presence of life-threatening organ dysfunction as a result of a dysregulated host response to infection[30]. These revised adult sepsis definitions used data from large scale development and validation cohorts in highly resourced countries to identify clinical criteria that allow robust assessment of sepsis, with mortality and/or mortality and/or ICU length of stay of 3 days or longer, as outcomes[31,32]. A two-point increase in the Sequential Organ Failure Assessment (SOFA) score emerged as best criterion to identify patients with new or worse infection-associated organ dysfunction. Septic shock was defined as the triad of arterial hypotension, vasopressor treatment, and hyperlactataemia[31]. Of note, the work by the Taskforce did not attempt to define “infection” nor “dysregulated host response”, and focused on clinical criteria to identify patients with infections at higher mortality.

The criteria were derived and validated on datasets from North America and Germany and were based on the worst physiological alteration for a time window ranging from 48 hours before to 24 hours after the onset of infection[32]. The consensus committee members placed emphasis on the need for accurate and specific sepsis characterization and operationalization in the electronic health record (EHR). At the same time, a parsimonious tool was developed, the quick SOFA (qSOFA) score, composed of abnormal mentation, tachypnea, and arterial hypotension to facilitate rapid screening for sepsis.

The consensus statement proposes a two-step approach utilizing first the qSOFA score for rapid screening of patients with suspected infection, followed by performing the full SOFA score to assess for evidence of organ

dysfunction. If despite adequate fluid resuscitation vasopressors are required to maintain blood pressure and an increased lactate is present, then the diagnosis of septic shock is made. qSOFA was validated using the same dataset, outcomes, and methodology as used for SOFA.

Subsequent to the publication of the Sepsis-3 definitions, a number of publications have highlighted advantages and potential disadvantages of the definitions[18,29,33-37], specifically related to the applicability of the SOFA score outside the ICU, the validation having been restricted to high-income settings, choice of lactate cut-offs, and moderate performance of qSOFA. In addition, the time windows used during which SOFA and qSOFA "worst" scores were developed and validated imply that some of the performance is descriptive rather than predictive. The advantages of Sepsis-3 providing robust, operationalization-enabled endpoints to robustly categorize sepsis have been widely recognized. At the same time, the focus on specificity risks disconnection from quality improvement programs which emphasize early recognition[33]. Early recognition is not only important in low and middle-income countries (LMICs), which may have no or limited PICU capacity, but similarly in high income countries (HICs) where delays in treatment can have disastrous consequences. The Sepsis-3 definitions of shock include vasopressor treatment implying that a patient can not be in shock prior to vasopressor commencement, yet presence of shock is what prompts clinicians to start vasopressors. Interestingly, while lactate is used to make a diagnosis of shock in Sepsis-3, but is not part of criteria that operationalize sepsis.

Sepsis screening, awareness, and early intervention campaigns have been focusing on sensitive early clinical signs/markers in patients with suspected sepsis given the rapid increase in worse outcomes associated with delays in initiation of treatment[12].

2. PEDIATRIC SPECIFIC ASPECTS OF SEPSIS AND SEPSIS SEVERITY RELEVANT FOR FUTURE DEFINITIONS

The Sepsis-3 consensus statement specifically mentioned "*the need to develop similar updated definitions for pediatric populations*"[30]. While presence of progressive multi-organ failure was shown to increase sepsis mortality in children[38], the SOFA score is not validated in children. Thus, testing of the validity of criteria for sepsis-related organ-dysfunction, and septic shock to recognize, and characterize children with infections is urgently needed. Specific aspects of this effort pertinent to pediatric age groups have to be considered[39]:

1. *Age-specific measures of organ dysfunction*: SOFA was neither designed nor adapted for the pediatric age group, although several studies have demonstrated that the approach can be in principle applied to children[25,40-42]. The Pediatric Logistic Organ Dysfunction Score-2 (PELOD-2)[43] represents the closest scoring system to SOFA and has shown promise to be applied in sepsis[42]. However, it has not yet been validated prospectively in children with sepsis outside ICU. In comparison to large databases which are becoming rapidly available through EHRs[31,32,44], currently used pediatric organ dysfunction scores are based on relatively small cohorts. In addition, the neonatal group brings additional challenges due to physiologic adaptive processes which affect measures of organ function[45-48].
2. *Age-specific variation in response to infection*: Severe increases in heart rate and respiratory rate are commonly observed in non-septic conditions, such as bronchiolitis[49]. Myocardial dysfunction is a common feature of pediatric septic shock, with implications for treatment[50,51]. Importantly, arterial hypotension represents a late sign of Pediatric septic shock[11,23,52]. The triad of hyperlactataemia, hypotension, and vasopressor requirement characteristic for adult septic shock is only seen in a minority of pediatric sepsis deaths at time of ICU admission[53].
3. *Age-specific patterns of severity and outcomes:* Pediatric sepsis is a fulminant disease: many presentations occur with very rapid deterioration, often subsequent to an unspecific mild illness. Sepsis-related MODS onset[38,54,55] and sepsis-related deaths in many children occur within 24 to 48 hours of presentation[53,56-58]. In LMICs up to 75% of children with sepsis have MODS resulting in very high mortality[59]. Hence predictive modeling based on first observation data is likely to yield substantially different results from modeling based on worst-within-24-hour data due to the confounding effect of time on severe outcomes[60,61]. Similarly, accurate prediction of mortality in an ICU setting of patients with high severity disease is considerably different than predicting adverse outcomes at an earlier disease stage when children present to Emergency Department.
4. *Age-specific patterns pertinent to epidemiology, host, and pathogens:* The epidemiology of pediatric sepsis is strongly age-dependent, with the highest incidence across all age groups seen in neonates and young children under five years of age, before incidence approaches young adult rates by the age of early adolescence[62,63]. Distinct patterns of pathogens characterize the younger age groups. Unique

aspects of pediatric host susceptibility to infection account for these findings, such as innate and adaptive immunity[64-68], and pediatric-specific comorbidities due to malnutrition and congenital disease.

5. *Challenges in early recognition of sepsis:* Febrile infections of viral origin and mild infections such as urinary tract infection and pneumonia (without organ dysfunction) represent globally the leading reasons for children to present to Emergency Departments and hospitals. However, the majority of these will not progress to organ dysfunction and shock. Thus, the recognition of sepsis is further challenged given that sepsis is a relatively rare event in most pediatric facilities outside of ICUs[69,70] and given that the average acuity of pediatric ED presentations in high income countries is substantially lower than that of adults. Most evidence for screening tools to aid in the recognition of children with severe bacterial infections presenting to emergency departments[71-74] is not sepsis specific but includes many bacterial infections that do not progress to organ dysfunction if properly treated. As institutions are implementing quality improvement initiatives in sepsis, accurate diagnosis of sepsis is a key requirement to monitor the impact of such initiatives and benchmark institutional performance.

In summary, there is an urgent need for pediatric-specific sepsis and septic shock definitions: While this process should be aligned as much as possible with methodology used to establish adult Sepsis-3 definitions, it is important to ensure the pediatric translation of Sepsis-3 will sufficiently address unique characteristic of children.

3. SCOPE, AIMS AND GOALS OF THE TASKFORCE

The scope is to assess, develop, and validate clinical criteria for sepsis in children, aged birth to under 18 years. This will include clinical criteria to identify an infection phenotype likely to benefit from specific treatment (predictive recognition), and clinical criteria to identify a infection phenotype with sepsis-related organ dysfunction (definitive diagnosis).

There is a fundamental tension between developing criteria to identify patients that may need therapy (e.g., antibiotics) for suspected sepsis vs. criteria that definitely identify a patient as having a diagnosis of sepsis (which often takes time for cultures and aspects of the clinical course to evolve). The Taskforce will aim to identify two sets of robust criteria to meet each of these goals. Therefore, the first set of criteria should help to capture patients at high risk of mortality as soon as possible after presentation to medical care. These particular criteria should rely on information that is easily accessible (simple, commonly used, rapidly available at low cost) in a wide variety of medical settings. Criteria to establish a definitive diagnosis of sepsis will be more specific and less time-sensitive. The criteria should fulfill the requirements of reliability, content validity, construct validity, criterion validity, measurement burden and timeliness[32].
The specific aims are to develop criteria which allow

1) To discriminate patients suffering from an infection from patients with a response to infection that places them at substantially greater mortality risk for the purposes of treatment (prediction who is likely to benefit from treatment) and accurate burden of sepsis assessment (is/was the disease present)
2) To facilitate timely enrolment of appropriate patients into sepsis trials, using reliable and robust definitions.
3) To allow accurate phenotyping of pediatric sepsis patients, required for comparison of pediatric sepsis epidemiology, interventions, and outcomes (including comparisons with adult age groups, comparisons across different settings, and comparisons between units for benchmarking).

Key steps in the process include:

1. To setup a Taskforce of international experts across disciplines, backgrounds, and healthcare settings.
2. To evaluate suitability of existing databases on children with infection (including sepsis) for the project. Ideally the project will have access to several databases from a variety of settings, including ICU, Emergency, and ward settings from HIC and LMIC. The databases, where accessible, will be used for development and validation of sepsis criteria.
3. To use a modified Delphi-type approach (which may be enhanced by an international survey of practices and perceptions pertinent to sepsis definition, see below) to define key components of the approach, and unpack the priorities/perspectives between clinicians, researchers, administrators and fund managers in different settings.
4. To systematically review the literature on criteria for early, and for accurate assessment of sepsis, and septic shock in children.
5. To develop clinical criteria for early, and for accurate assessment of sepsis, and septic shock in children.

6. To derive simple/parsimonious tools for early, and for accurate assessment of sepsis, and septic shock in children.
7. To contextualize these criteria for HIC and LMIC settings.

4. PROJECT PLAN

4.1. Governance, Organization, and Publications

The Pediatric Sepsis Definition Taskforce is an approved, budgeted, in-progress initiative of the Society of Critical Care Medicine (SCCM). Two Co-Chairs and two vice-chairs have been nominated and confirmed by SCCM/ESPNIC/WFPICCS. The chairs are selected for the duration of the Taskforce. The chairs are accountable towards the Societies to report on progress and to give timely updates if obstacles potentially leading to delays occur. The chairs and vice-chairs are supported by a SCCM manager assisting with meeting organization, minutes and administrative aspects. SCCM is providing methodologist and librarian support.
The chairs, vice-chairs, the society leads, and representatives from the adult Sepsis Definition Taskforce (Prof. Derek Angus) have selected members for the Taskforce. The members were selected according to their scientific expertise in sepsis, epidemiology, clinical trials, and basic or translational research. Selection criteria included the need to have representatives from pediatric critical care, pediatric infectious disease, pediatric emergency care, neonatology, basic science, and public health; and diversity in relation to gender, age, region, and background[75].

Any publications resulting from the Pediatric Sepsis Definition Taskforce will list "The Pediatric Sepsis Definition Taskforce" as a Group authorship with all contributors listed. Authorship and publication process will be based on contributions and handled according to scientific journal standards and as defined by SCCM publication policies.

4.2. Overview

The methodology will be aligned with the adult Sepsis Definition Taskforce, as detailed by Seymour et al and Shankar-Hari et al in JAMA 2016[30-32]. Content validity, construct validity, predictive validity, and ecologic validity will be assessed using a similar step-wise process.

4.3 Considerations for systematic reviews, data selection, and data analyses

It is anticipated that the following factors will be taken into consideration during design and analyses:
Cohort population

- High-, versus middle- versus low income setting
- PICU/ICU, Emergency Department, Pediatric General Ward, Remote/Outpatient setting
- Timing of the clinical criteria collection in relation to disease presentation
- Inclusion criteria: suspected infection (diagnostic code for infection, and/or treatment with antibiotics and sampling of cultures within 72h prior to 24h after initiation of antibiotics)

Patient factors

- previously healthy versus comorbidity including malnutrition
- community-acquired versus hospital-acquired sepsis (>48hrs after admission to hospital as per CDC criteria[76]).
- If available: pathogens (such as N. meningitidis, S. aureus, S. pneumoniae, GAS, GBS, E.coli, others)
- underlying organ dysfunction prior to sepsis: for community-acquired sepsis this will be assumed as zero. For hospital-acquired sepsis a baseline of severity obtained prior to sepsis will be required.

Predictors/Descriptors of organ dysfunction

- Cardiac: heart rate, blood pressure (systolic, diastolic, mean, pulse pressure), central capillary refill, cool peripheries, mottling; *support*: inotrope (types, dose; Vasopressor-Inotrope Score[50], ECMO)
- Respiratory: respiratory rate, PaO_2/FiO_2 ratio, SpO_2/FiO_2 ratio[77], oxygen saturation, work of breathing *support*: oxygen, non-invasive and invasive ventilation, ECMO
- Neurology: Glasgow coma scale, pupillary dilatation, AVPU, irritability/lethargy, Blantyre Coma Score
- Metabolic: lactate[50,53,78-82], base excess, pH
- Hepatic: bilirubin, AST/ALT,
- Coagulation: INR, fibrinogen, aPTT, platelets
- Hematologic/immunologic: platelet count, white cell count (including absolute neutrophil and absolute lymphocyte counts)
- Renal: creatinine, urine output; *support*: renal replacement therapy

- Inflammation: C-reactive protein, procalcitonin, white cell count, other biomarkers

Scores:
- PELOD-2
- PIM-2/3
- PRISM
- NPMODS
- Pediatric adaptations of SOFA[40]
- qSOFA
- Note: we anticipate that during the course of the work led by the Pediatric Sepsis Definition Taskforce, the in-progress PODIUM project by SCCM may proposed updated criteria for organ dysfunction.

4.4. Proposed International survey on application of pediatric sepsis definitions
It is planned that an international survey will be conducted to explore how clinicians, researchers, and public health experts across the globe assess patients for presence of sepsis in their daily practice, what the implications for treatment are, and how they perceive the use and usefulness of sepsis definitions in their daily practice. The results will feed into the Delphi process.

4.5. Modified Delphi process:
A three staged Delphi process will be performed to provide expert opinion input towards reaching consensus on revising definitions. Specific consideration for LMIC settings will be discussed.
Phase 1: Definition of variables of interest. Review of clinical questions/scenarios and ranking of importance of variables.
Phase 2: Integration of systematic review information.
Phase 3: Review of development and validation cohort results.
The Delphi process will be open to all Taskforce members, and will be based on the Delphi process from the adult Taskforce, the surveys, and systematic reviews.

4.6. Systematic reviews:
Systematic reviews and meta-analysis of observational studies in patients aged birth to under 18 years published between January 1, 1992, and December 31, 2018, will be performed to determine clinical criteria currently reported to identify sepsis, and septic shock, and to perform a meta-analysis of the association of these clinical criteria with the defined outcomes. Full term neonates older than three days of life will be included in search processes. This will inform the Delphi process. In addition to age, Medline MeSH search terms will include “sepsis”, “septic shock”, “mortality”, and “epidemiology”. Only English literature and original studies will be considered.

4.7. Databases for development and validation
Taskforce members will be sent a questionnaire regarding access to potential databases. Databases across several countries and institutions will be evaluated for suitability for inclusion through the help of the Taskforce members. These should include ED, ICU, and ward settings in HIC and LMICs.

5. SIGNIFICANCE AND IMPACT
The recent UN World Health Assembly resolution on sepsis urges members to take specific measures aiming at reduction of the burden of sepsis, through prevention, diagnosis and management. At present, there is a major gap between pediatric sepsis definitions (largely based on Sepsis-3) and adult Sepsis-3 definitions[19]. There is thus an urgent need to translate Sepsis-3 into definitions adapted for the specific disease characteristics, susceptibilities and patterns of pediatric sepsis. Failure to embark on revision of pediatric sepsis definitions will represent an ongoing risk for future pediatric research and practice due to lack of robust, validated definitions, and incompatibility with adult research and hospital coding practice. In particular, timely translation of Sepsis-3 in to pediatrics will be key to support ongoing and new quality improvement initiatives[33].The present proposal embraces a methodology for the Pediatric Sepsis Definition Taskforce strongly aligned with the adult process, to ensure revised definitions will be robust, evidence-based, and more likely to be widely accepted and implemented.

The Pediatric Sepsis Definition Taskforce can benefit from the controversies and experiences resulting from the adult definition revision process. It will be the first time that a global combination of databases in the field of severe pediatric infections and sepsis will be undertaken by a large group of diverse experts in the field. The project has a unique opportunity to yield meaningful robust clinical criteria for sepsis in children.

eMethods 2: Key materials guiding the SCCM Pediatric Sepsis Definition Task Force (opening meeting).

Pediatric Sepsis Definition Taskforce: Salzburg June 21/22, 2019 Meeting
Key objectives, controversies, and deliverables for each session

Friday, June 21, 2019 - DAY 1

Welcome, introductions, agenda overview, and meeting ground rules (Luregn, Scott, Lauren, Lori, Jerry), 20 minutes

Scope as per project plan: ***The scope is to assess, develop, and validate clinical criteria for sepsis in children, aged birth to under 18 years. This will include clinical criteria to identify an infection phenotype likely to benefit from specific treatment (predictive recognition), and clinical criteria to identify a infection phenotype with sepsis-related organ dysfunction (definitive diagnosis).***

Project overview - Overall objective and components (Systematic review, Delphi, data-driven validation) (Lauren), 10 minutes

Updated timeline:

- Preparation for Salzburg meeting, Jan-June 2019
- 1st Face-to-face meeting at ESPNIC 2019 June 21/22, Salzburg, Austria
- August 2019
    - Project Plan finalization →submission for publication
    - WFPICCS survey finalization
    - Systematic review plan finalization
    - Candidate Database list finalization
- Workgroups conduct regularly-scheduled conference calls (e.g., once or twice per month)
- WFPICCS survey (September to November 2019)
- Systematic Review (August 2019 to June 2020)
- Database/analysis plan creation (August to October 2019)
- Development and validation studies (September 2019 – June 2020),
- Informal (unfunded) face-to-face meeting at 49th SCCM Congress in Orlando, February 16-19, 2020
- Informal (unfunded) face-to-face meeting at WFPICCS, Mexico City, June 13-17, 2020
- Finalization of analyses and recommendations (July to September 2020)
- Journal submission and review (August 2020 to January 2021)
- Dissemination (February 2021 SCCM)

Elephants in the room, part 1 - Controversies for discussion (moderated by Andrew), 75 minutes

Red font denotes topics that require a decision to move forward with aspects of the work (and will be discussed more on day 2)

1) Is any infection-associated organ dysfunction = sepsis (e.g., respiratory failure in bronchiolitis)? Is death the ultimate organ dysfunction (are all infection-associated deaths death from sepsis, e.g., deaths due to infectious diarrhea)? Does it matter what type of infection (bacterial, viral, parasitic)? (Kusum) - 15 minutes

Controversy: How to operationalize infection? **Sepsis-3: Confirmed or suspected infections require either a diagnostic code of infection, and/or the combination of a physician decision to treat with antibiotics with sampling of body fluid cultures (blood, urine, or CSF cultures), with cultures obtained within 24 hours after or no more than 72 hours prior to initiation of antibiotic therapy**

Treat all types of infection equally (bacterial, viral, fungal, parasitic) or do we need to generate infection type-specific approaches? Is respiratory failure in bronchiolitis, shock due to dehydration in gastroenteritis, cerebral malaria, etc. = sepsis?

What do we do with the majority of patients with suspected but microbiologically not confirmed infection?

How do we define a "sepsis syndrome" that is applicable to viruses (for example, enteroviruses)?

Should one consider all infection-associated deaths as sepsis deaths? --- Can one die of infection without being septic?

POTENTIAL SOLUTIONS:

- Similar to adults, consider all organ dysfunction equally
- "Ignore" the infected organ system
- Come up with infection- and organ system-specific rules
- Only consider infections that create a systemic respone
- All infection-related deaths are sepsis deaths

2) How to define shock - sensitive (2005) versus specific (Sepsis-3) criteria? (Jerry) - 15 minutes

Controversy: Sepsis-3: Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Septic Shock 3.0 is met if hypotension AND vasopressors AND elevated lactate despite adequate volume resuscitation. 2005 septic shock can be simplified to hypotension AN/OR vasopressors AND/OR signs of impaired perfusion such as high lactate.

- How do we assess shock? Rapid clinical signs (perfusion, altered mentation) →2005 and WHO definitions emphasize early clinical recognition
- What is the role of hypotension?
- Should laboratory markers be part of the shock definition?
- Can a definition for a disease state (shock) rely on presence of a treatment (inotropes) which is given as a result of identifying the disease state?
- Lactate was already controversial in adults (should it be used, if yes, what cut-offs?), alignment with initiatives (e.g., NICE, which uses lactate of 2, and of 4 as cut-offs), applicability to LMIC settings which often don`t have lactate
- Problems arise when treatment for a condition becomes a requirement for the diagnosis of the condition. For example, inotropes may not be available in many settings, suggesting such death would not be able to be classified as septic shock.
- "Despite adequate volume resuscitation" - requirement of having received a defined amount of fluids as an eligibility criterion (40ml/kg in Goldstein) – as a result of the controversy around fluids in sepsis, clinicians may increasingly treat children as shock/with inotropes even after lesser amounts of fluids
- Do we need criteria for Refractory Shock?

POTENTIAL SOLUTION:

- Base shock definition entirely of physiologic measures and add biomarkers when available

3) How to account for different sepsis phenotypes and response to intervention? (Andrew) - 15 minutes

Controversy: Are there different phenotypes/clusters, similar to those found in respiratory diseases (e.g., asthma)?

See work on Septic shock endotypes (Hector Wong) and clinical phenotypes (Chris Seymour JAMA 2019, Mike Levin Lancet Resp Med 2019). Subtypes may have different response to treatment.

Should this group use more innovative approaches (machine learning, cluster analyses etc) to derive/develop new phenotypes? Can we develop criteria to characterize subtypes or is this too high a goal? Need to balance granularity with the need to be pragmatic.

POTENTIAL SOLUTION:

- Explore phenotypes in secondary data analyses

4) What age range should we include - term newborns, post-pubertal adolescents? (Lauren) - 15 minutes

Controversy: Upper age limit: <16, 18, <20 years? Lower age limit: Anyone from birth, term born only, after perinatal adaptation (>72hours, >1 week), >28d post-term (corrected)? Impact of maturational changes in physiological response and immune response; difficulties in measuring (and validating) organ dysfunction in neonates).

Neonatal immune response may more likely be hypoactive; organ dysfunction is hard to measure in neonates; deleterious effects on immature brain have been demonstrated by invasive infections without organ dysfunction (PVL)

POTENTIAL SOLUTIONS:

- Exclude preterm infants
- Include term infants starting at 72 hours or 1 week of age
- Include teenagers up to age 16

5) Should we accept the Sepsis-3 "concept" (definition) of sepsis: Dysregulated host response to infection leading to organ dysfunction? (Pierre) – 15 minutes

Controversy: Sepsis 3: Sepsis = dysregulated host response to infection leading to organ dysfunction.

Is sepsis "universal"? Is it only about the host? Can we live with the concept as proposed from adults if we simply add age-specific (and maybe context-specific) criteria? Does it make sense to have a definition which incorporates a key element (dysregulated host response), which is currently not operationalizable (or is that ambiguity an advantage)? We don`t know what dysregulated host response is and to what extent it is applicable to various age groups (e.g., neonates), and there is no simple measure of dysregulated host response. It is not all on the host – may mislead to the assumption that fixing host response will fix sepsis; however, without antibiotics, a substantial proportion of patients exposed to significant bacteremia will ultimately develop organ dysfunction and die.

A fundamental question is whether sepsis is conceptually different in children than in adults.

POTENTIAL SOLUTIONS:

- Create a new “definition” – Keeping in mind that if we propose changing the definition, we are contending that the underlying concept is different by age, which risks creating confusion (and major push back from the adult CCM community)
- Conversely, we could agree that there is a syndrome that affects all ages and focus only how to identify/operationalize that definition in different age groups.
- Or “accept” the current definition but articulate its limitations as it relates to children

Elephants in the room, part 2 - Controversies for discussion (moderated by Andrew), 60 minutes

6) Tension between need to identify patients at high risk of sepsis early to guide prompt treatment (highly sensitive criteria) and need for most accurate diagnosis of sepsis for research and other purposes (highly specific criteria) (Luregn) - 20 minutes

Controversy:

- How can we integrate definition work with the need for quality improvement initiatives?
- Do we need to create a "At RISK" group?
- If early treatment prevents deterioration - are those patients not septic?
- Predictive capacity (prior): identify phenotype of patients with infection that are likely to progress/deteriorate without intervention who may benefit from intervention (What intervention? A sepsis bundle?)
- Descriptive capacity (post-hoc): reliably characterize severity manifestations to accurately measure presence/absence of the disease
- qSOFA was intended to address this, but is qSOFA good enough?
- Having all the data available would allow creation of two temporal approaches to analyses →consider two time frames: early presentation for early recognition versus worst-within-24-hrs for specific diagnosis
- Which criteria identify a phenotype likely to benefit from treatment with a sepsis bundle? I.e., is this child septic or on a trajectory towards sepsis and ***at risk*** for poor outcomes unless treated (sepsis bundle). Some children may not yet have measurable organ dysfunction or advanced shock. The aim of this question is to find criteria discriminating children likely to respond to a sepsis bundle (or to deteriorate if not treated), from children with uncomplicated infection that may or may not require antibiotics or other treatment. Such criteria ideally should be rapidly available (i.e., not reliant on detailed laboratory investigations) and inexpensive; and models should favor sensitivity over specificity. Contextualization to special health care settings (such as those

that are resource-limited) may be required. The response to the question is intended to guide clinicians whether to initiate treatment in a patient. Criteria are intended for predictive use.
POTENTIAL SOLUTIONS:

- Create two sets of criteria, one for screening, one for definitive diagnosis
- Focus entirely on definitive diagnosis

7) What outcomes should we use to validate criteria? (Scott Watson) - 20 minutes

Controversy: Sepsis-3: The primary outcome is defined as death during hospital stay?
The secondary outcome is defined as death and/or ICU length of stay of three days or longer.

- Consideration of using PICU and hospital length of stay, multi-organ failure, proportion of patients with multi-organ failure, ventilator-free days, inotrope free days, severely impacted functional outcomes (Pediatric Overall Performance Score or similar)?
- Variability in PICU admission thresholds
- What about settings without ICUs? Is death the only marker?

POTENTIAL SOLUTIONS:

- Death is primary outcome
- Study secondary outcomes of progressive/new organ dysfunction, need for higher level of care, and lengths of stay

8) How to account for variation in availability of markers/criteria in differently resourced settings? (Tex) - 20 minutes

Controversy: Will we propose "main criteria" and "context-specific" criteria/one-size-fits-all versus context-specific criteria?
- Most components in SOFA scores are not easily/not at all applicable to ED, ward, and many LMIC settings
- Time needed to obtain full score
- Even lactate is restricted in terms of availability
- How to categorize settings by resource availability, which varies even within regions/countries. World Bank list is controversial.
- How to operationalize "resource setting" for the Taskforce work (in terms of systematic review, databases, and potentially targeted recommendations)

POTENTIAL SOLUTIONS:

- Use WHO resource/income classifications
- Create context-specific criteria

Workgroup discussions/working session, 45 minutes**:** 1) Systematic review *(Kusum, Lauren)*, 2) Consensus/Delphi *(Tex, Pierre)*, 3) Data validation *(Tell, Scott Weiss)*

45 minutes of small group discussion followed by brief report back to full group
Task:

1. Each Group to appoint
   a. person taking notes
   b. a presenter who will report back to the full group
2. Review "Major Discussion Points" (next pages) and modify as needed.
3. Consider how the Elephants in the room relate to your group.

This may not involve solution-making – most essential in this session is to ensure that important controversies are captured and exchange opinions around them.

Brief Reports - 35 minutes

Summary of Taskforce Survey Round 1 *(Luregn - 5 min)* - Key findings from the Taskforce respondents
Workgroups report back to larger group (10 minutes each x 3)

Saturday June 22, 2019 - DAY 2

Variation in available resources and healthcare settings - how to approach (Andrew and Tex) - 20 minutes
How will we account for variation in availability of markers/criteria in differently resourced settings? (building on controversy 8 from Day 1)

Deliverables:

- Decide on approach to develop "main criteria" and "context-specific" criteria
- Operationalize "resource setting" for the Task force work (in terms of systematic review, databases, and potentially targeted recommendations)

Essential considerations based on practice setting, 80 minutes**:** What are the needs from the perspective of 1) Resource-limited settings (Andrew, Tex), 2) ED (Enitan, Fran), 3) PICU/NICU (Scott, Mark Hall)

35 minute small group discussions, followed from 45 min (3x15min) reporting back/discussion in full group

→ Divide into 3 groups

→ Each Group to appoint

a. person taking notes
b. a presenter who will report back to the whole Taskforce

Deliverables:

1. Identify key requirements relevant your group that the new Pediatric Sepsis Definitions should meet
2. Identify approaches/strategies to achieve this
3. Highlight remaining areas of major uncertainty/disagreement

Putting key elephants to bed, 120 minutes: To develop proposals to move forward for urgent controversies -- 1) Age range (James Wynn, Lauren); 2) Types of infections to include (Suchitra, Mark Peters); 3) Sensitive (screening) criteria or/and specific (definitive) criteria (Halden, Matt); 4) Outcomes to consider for systematic review and data validation (Pierre, Jerry)

40 minute small group discussions, followed by 80 minutes (4 x 20 min) reporting back/discussion in full group

→ Divide into 4 groups. Each group to come up with solution for the below.

→ Each Group to appoint

c. person taking notes
d. a presenter who will report back to the whole Taskforce

Deliverables:

Operationalize approach relevant for systematic review and database project work in relation to

1) Age range
2) Types of infections to include
3) Sensitive (screening) criteria or/and specific (definitive) criteria
4) Outcomes to consider for systematic review and data validation

Workgroups discussions/working session: Ongoing work and to refine next steps/timeline - 1) Systematic review (Kusum, Lauren), 2) Consensus/Delphi (Tex, Pierre), 3) Data validation (Tell, Scott Weiss)

60 minute small group discussions, followed by 90 minutes (3 x 30min) reporting back/discussion in full group

Task:

1. Each group generates plans to address group-specific deliverables (Appendix and revision from Day 1)
2. Assign action-items, roles and create timeline
3. Highlight remaining areas of major uncertainty/disagreement

This is solution-making stage – ensure that important controversies are captured and exchange views around these.

Salzburg meeting: Specific instructions for each of the workgroups (Review; Survey/Delphi; Data)

Systematic Review Group

Major discussion points for systematic review protocol development:

1. Do we want to develop criteria for early recognition of sepsis, identification of septic patients who develop significant organ dysfunction or both? Should ED literature on early recognition (of what? severity, severe bacterial infection, organ dysfunction, death?) be included?

Goal	Pros	Cons
Recognition	• Comprehensive • Can develop a continuum approach • High sensitivity • Primary use is in patient care	• Time consuming • Being looked at by other groups like PERFORM • More ER rather than ICU based • Low specificity
Definition	• Focuses on sickest patients • High specificity • Primary uses in research and benchmarking	• ICU focused • Low sensitivity • Likely less clinical applicability
Prediction	• Primary uses in research and treatment of severe sepsis patients • Overall with definition	• Need a high specificity

2. Should the primary outcome be mortality or hospital/PICU/monitored area length of stay?
3. Do we want our definition to include criteria that will only include bacterial infections or could include other infectious agents (viruses, malaria etc.)?
4. Should we include/exclude pre-term infants who are now at term or greater corrected?

Pros	Cons
• Comprehensive	• The search strategy will yield a large number of extra studies to screen

5. Should we include or exclude articles limited to specific sub-populations of the ICU cohort? For example, TBI, oncology patients, etc.
6. Should we use a staged approach to the definition, broken down by illness severity, resource setting or both?
7. Should we include all study designs or just observational studies like the adults?
8. The listed definition is: "*Confirmed or suspected infections require either a diagnostic code of infection, and/or the combination of a physician decision to treat with antibiotics with sampling of body fluid cultures (e.g. blood, urine, or CSF cultures, and other cultures), with cultures obtained within 24 hours after or no more than 72 hours prior to initiation of antibiotic therapy."* Should we make this less specific?
   Suggestion: Suspected sepsis – "shock with no other diagnosis and history suggestive of infection".
9. Rather than use PICU, could we use a more diverse term to reflect the lack of availability of PICUs in all settings (e.g. HDU, critical care area, monitored setting etc.)?
10. Patients can die of infection and not have sepsis (e.g. bronchiolitis with isolated lung failure). Need to be aware of this in our definition.
11. Methodological issues
    a. Should we dichotomize the secondary outcome of PICU LOS at 3 days or longer?
    b. Different versions of PIM and PRISM in the literature
    c. Can we calculate the risk of mortality as a way to normalize all illness severity tools?

Deliverables systematic review group:

1. Define approach to the 11 points as above.
2. Define interaction with PODIUM – how can this project leverage of the PODIUM reviews and full-text database which identified manuscripts referring to infection/sepsis leverage?

3. Define actions required Systematic Review Plan finalization (due August 2019)
4. Timeline and organization for systematic review work.
5. Database used (COVIDENCE)? RedCap?
6. Allocate roles – who will do what, identify group lead/co-leaders

Delphi/Survey Group

Major discussion points for Delphi/Survey Group:

Overview:
A three staged Delphi process will be performed to provide expert opinion input towards reaching consensus on revising definitions. Specific consideration for limited-resource settings will be discussed.
Phase 1: Definition of variables of interest. Review of clinical questions/scenarios and ranking of importance of variables.
Phase 2: Integration of systematic review information.
Phase 3: Review of development cohort results.
The Delphi process will be open to all Taskforce members, and will be based on the Delphi process from the adult Taskforce, the surveys, and systematic reviews. Voting will be based on 5-point Likert scales (strong agreement to strong disagreement).
The Delphi process will run in parallel to Survey, Systematic Review, and Database work. We need to design how these interact, and when/how to vote.
Qualitative versus quantitative responses.
Documentation of voting

- When do we vote: Should we vote formally on the elephants discussed in this meeting?
- What is the minimum % of respondents required (panelists, consultants, all taskforce members?)
- What is the minimum % to constitute consensus?

Should we use SCCM's guidelines, or generate different, Taskforce-specific guidelines?
How do we develop the questions to be asked to the group - Who will lead? What is the timeline?
Example of Delphi process: Sepsis-3 JAMA Shankar-Hari Supplement eTable 2
WFPICCS Survey: the Survey will complement the Taskforce work. The aim is to improve the survey piloted by Taskforce members now in June 2019 before disseminating widely.
Consider involvement of families/patient representatives in the process of identifying important outcomes

Deliverables Survey/Delphi group:

1. Define approach to the points as above.
2. Identify areas in the WPFICCS survey that need changing
3. Define actions required for WFPICCS survey finalization (due August 2019)
4. Timeline and organization for WFPICCS survey, including planning of translation (which languages, by whom), and dissemination
5. Define steps in Delphi process, and interaction with Survey, Systematic Reviews, and data analysis results
6. Define timeline for Delphi process
7. Define governance of Delphi process (voting, data capture)
8. Allocate roles – who will do what, identify group lead/co-leaders

Data Group

Major discussion points for Data Group:

1. Setup and governance:
    a. How can we access data from various owners across the world? Governance issues? Costs?
    b. How do we acknowledge data owners?
    c. Attempt to merge datasets vs. Central analysis generation with local data analyses
    d. Workforce - this is the biggest piece of work. Who will clean original data, who will merge/combine (if a data merging approach is taken), who will analyze?
    e. Interaction with Delphi and Systematic review group
2. Database selection
    a. Overview of suitable databases - anything key missing? How will we decide which ones to use? Review list of databases; prioritize database candidates to pursue (based on survey and discussion)
    b. Which data do we want? Study data, EHR data, etc.?
3. Cleaning
    a. Feasibility (meeting time requirements) versus getting perfect data

    b. Avoiding generating poor results by using poor data
    c. Heterogeneity in terms of patients, population, interventions
    d. How to harmonize data (relevant if data are merged or if data are analyzed locally by dataset owners)
    e. Do we need to predefine data groups for subgroup analyses? For example low-resource settings, where laboratory features may be missing?
4. Analysis plan
    a. How to operationalize infection?
        i. Should data from patients with malaria, diarrhea, dengue, bronchiolitis etc be included?
    b. How to operationalize organ dysfunction (which score, novel scores?)
        i. How do we set age-specific criteria? Z-scores? Use cut-offs of published scores (PELOD etc)? Derive new cut-offs?
    c. Consider methodology: cluster analysis, machine learning etc
    d. Development vs validation
    e. Time windows: initial presentation/at time of suspected infection (blood culture?); versus worst-within-24-hours
        i. Define time factor in data (early upon presentation - worst within 24hours); consider pitching analyses to higher sensitivity for the purpose of screening, followed by higher specificity for the purpose of correct identification
    f. Top-performing versus parsimonious models (qSOFA equivalent)

Deliverables Data group:

1. Draft DUA (SCCM, ?other examples, as potential templates), specifically
    a. how to acknowledge data owners, group authorship
    b. how to overcome governance/access issues
    c. publication policy (if data owners are pursuing own publication)
    d. open data access plan
2. Draft Data SOP
3. Define Minimal Dataset for harmonization of data
4. Define actions required for Data analysis plan finalization (due August 2019)
5. Timeline and organization for further data work
6. Allocate roles – who will do what, identify group lead/co-leaders

eMethods 3: Systematic review protocol and pooled results for criteria for sepsis in children.

Please refer to the published systematic review protocol by Menon et al in 2020[83] and the published systematic review results.[84] In the meta-analysis of data from 16 studies on 9,629 patients, we found sepsis among children with suspected infection was associated with decreased level of consciousness (OR 9.8 [95% CI 5.8, 16.7]) and higher Pediatric Risk of Mortality (PRISM) scores (mean difference 6.0 [95% CI 4.0, 8.0]). Among children with sepsis, factors associated with mortality were assessed from 69 studies of 145,461 patients. Pooled estimates found increased mortality based on multiple patient baseline characteristics, clinical characteristics, laboratory values, and organ dysfunction/illness severity scores (see table).

	Pooled estimate (95% CI)
Patient characteristics	
Severe acute malnutrition	4.7 (1.4, 16.3)
Chronic conditions	2.4 (1.4, 4.1)
Oncologic conditions	2.3 (1.7, 3.1)
Clinical characteristics	
Hypotension	2.3 (1.8, 2.9)
Vasoactive agents	6.5 (4.2, 10.0)
VIS	23.5 (3.4, 43.6)
Stroke index	0.2 (0.1, 0.4)
Mechanical ventilation	11.0 (7.4, 16.3)
Decreased LOC	4.1 (2.9, 5.9)
GCS	-4.0 (-6.2, -1.8)
Laboratory values	
pH	-0.10 (-0.14, -0.05)
Lactate (mmol/L)	1.9 (1.2, 2.6)
Base deficit	-3.2 (-5.8, -0.6)
Urea (mg/dL)	1.5 (0.7, 2.3)
Creatinine (μmol/L)	13.0 (4.6, 21.5)
Potassium (meq/L)	0.2 (0.02, 0.44)
Platelet count (10^9/L)	-87 (-107, -67)
Fibrinogen (g/L)	-1.5 (-2.5, -0.6)
Albumin (g/L)	-4.3 (-8.4, -0.2)
Procalcitonin (ng/ml)	4.0 (2.0, 6.0)
ALT (units/L)	10.1 (4.0, 16.2)
Severity of illness/organ dysfunction scores	
No. of organ dysfunctions	0.9 (0.3, 1.5)
Renal dysfunction	4.0 (1.0, 18.4)
MODS	7.8 (3.9, 15.6)
PELOD	6.1 (2.5, 9.8)
PELOD-2	8.7 (5.7, 11.6)
SOFA	3.8 (2.7, 4.9)
pSOFA	4.8 (3.7, 5.8)
PRISM	11.0 (5.6-16.5)
PIM-2	12.1 (9.3-14.9)
PIM-3	7.8 (2.5-13.1)

[b]Pooled estimate is for the odds ratio for categorical variables and the mean difference for continuous variables.

ALT = alanine aminotransferase; GCS = Glasgow Coma Scale; LOC = level of consciousness; MODS = multiorgan dysfunction syndrome; PELOD = pediatric logistic organ dysfunction; PIM = pediatric index of mortality; PRISM = pediatric risk of mortality; SOFA = sequential organ failure assessment; VIS = vasoactive inotropic score.

Table modified from Table 3 in Menon K, Schlapbach LJ, Akech S, et al. Pediatric Sepsis Definition-A Systematic Review Protocol by the Pediatric Sepsis Definition Taskforce. Crit Care Explor. 2020 Jun 11;2(6):e0123. doi: 10.1097/CCE.0000000000000123. PMID: 32695992; PMCID: PMC7314341.

eMethods 4: Results of voting.

Delphi Round 1 Results

31/36 respondents (86%, above >80% threshold)

Selection of subscores:

- Preferred or Preferred + Acceptable >80%
- If two subscores for same organ >80%, then highest preferred % selected.

Score components voting:

Setting	Organ	Subscores	Components	Preferable	Prefer. + Acceptable
High Resource	Renal	Proulx	Cr, BUN, Dialysis	13%	52%
High Resource	Renal	**pSOFA**	age-based Cr	87%	100%
Low Resource	Renal	Proulx	Cr, BUN, Dialysis	13%	68%
Low Resource	Renal	**pSOFA**	age-based Cr	48%	93%
Low Resource	Renal	IPSCC	Cr change from baseline	23%	84%
High Resource	Respiratory	PELOD-2	MV, PaCO2, PF	10%	58%
High Resource	Respiratory	PODIUM	SF, PF, OI, OSI, ECMO	19%	73%
High Resource	Respiratory	**pSOFA**	SF, PF	48%	96%
High Resource	Respiratory	PELOD-2+PODIUM	see above	13%	48%
High Resource	Respiratory	PELOD-2+pSOFA	see above	23%	65%
High Resource	Respiratory	PODIUM+pSOFA	see above	26%	74%
High Resource	Respiratory	PELOD-2+PODIUM +pSOFA	see above	0%	52%
Low Resource	Respiratory	PELOD-2	MV, PaCO2, PF	13%	55%
Low Resource	Respiratory	PODIUM	SF, PF, OI, OSI, ECMO	19%	86%
Low Resource	Respiratory	**pSOFA**	SF, PF	81%	94%
Low Resource	Cardiovascular	VIS proxy	Vasoactives	13%	61%
Low Resource	Cardiovascular	pSOFA	Mean BP, Vasoactives	10%	81%
Low Resource	Cardiovascular	Proulx	SBP, HR, pH, Vasoactives	16%	61%

Setting	Organ	Subscores	Components	Preferable	Prefer. + Acceptable
Low Resource	Cardiovascular	PELOD-2	Mean BP, lactate	19%	87%
Low Resource	Cardiovascular	**VIS + PELOD-2**	See above	58%	81%
Low Resource	Neurological	**PELOD-2**	GCS, pupils	71%	90%
Low Resource	Neurological	Proulx	GCS, pupils	13%	78%
Low Resource	Neurological	PODIUM	GCS, GCS motor	26%	94%
Low Resource	Hematological/ coagulation	IPSCC	Platelets, INR	23%	81%
Low Resource	Hematological/ coagulation	**pSOFA**	Platelets	35%	96%
Low Resource	Hematological/ coagulation	PELOD-2	Platelets, WBC	32%	93%
Low Resource	Hepatic	**IPSCC**	bilirubin, ALT	65%	100%
Low Resource	Hepatic	pSOFA	bilirubin	13%	90%
Low Resource	Hepatic	PODIUM	bilirubin, ALT, AST, or GGT, INR, GCS	13%	74%

Delphi Round 2 Results

28/35 respondents (80%, meets >=80% threshold)

Selection of subscores:

- Preferred + Acceptable >80%
- If two subscores for same organ >80%, then highest preferred %

Score components voting:

Setting	Organ	Subscores	Components	Preferable	Prefer. + Acceptable
Low Resource	Cardiovascular	pSOFA	Mean BP, Vasoactives	11%	75%
Low Resource	Cardiovascular	PELOD-2	Mean BP, lactate	39%	96%
Low Resource	Cardiovascular	VIS + PELOD-2	See above	46%	89%
Low Resource	Haematological/ coagulation	**pSOFA**	Platelets	71%	99%
Low Resource	Haematological/ coagulation	PELOD-2	Platelets, WBC	25%	89%
Low Resource	Hepatic	**IPSCC**	bilirubin, ALT	68%	100%
Low Resource	Hepatic	pSOFA	bilirubin	25%	93%

Delphi Round 3 Results

30/35 respondents (86%, meets >=80% threshold)

Selection of subscores and criteria:

- Preferred + Acceptable >80%
- If two options >80%, then highest preferred %

Score components voting:

Setting	Organ	Subscores	Components	Preferable	Prefer. + Acceptable
Low Resource	Cardiovascular	PELOD-2	Mean BP, lactate	20%	90%
Low Resource	Cardiovascular	VIS + PELOD-2	Mean BP, lactate, vasoactives	67%	87%

Setting	Criteria version	Components	Preferable	Prefer. + Acceptable
High Resource	Ridge	All 8 organ systems	23%	100%
High Resource	LASSO	Resp, CV, Coag, Neuro	70%	100%
High Resource	Not sure yet/need more info		17%	44%

Desired versions	Components	Yes	No
Septic shock	Sepsis + CV	93%	7%
Sepsis-associated coagulopathy	Sepsis + Coag	40%	57%
Same criteria, higher threshold	Sepsis + tuning	63%	30%
Other		13%	30%

Delphi Round 4 Results

29/34 respondents (85%, meets >=80% threshold)

Selection of subscores and criteria:

- Preferred + Acceptable >80%
- If two options >80%, then highest preferred %

Sepsis criteria voting:

Criteria version	Components	Preferable	Prefer. + Acceptable
Ridge	All 8 organ systems	21%	90%
LASSO	Resp, CV, Coag, Neuro	72%	93%

High Risk Sepsis criteria voting:

Desired versions	Components	Preferred	Acceptable
LASSO higher threshold	Sepsis (4) + tuning	59%	90%
Ridge higher threshold	Sepsis (8) + tuning	34%	89%
Other		7%	24%

Delphi Round 5 Results

31/34 respondents (91%, meets >=80% threshold)

Selection of subscores and criteria:

- Preferred + Acceptable >80%
- If two options >80%, then highest preferred %

High Resource - Sepsis criteria voting:

Criteria version	Components	Preferable	Prefer. + Acceptable	Not Acceptable
LASSO 2 point	4 organ systems	39%	87%	13%
LASSO 2 pt "remote"	4 organ systems/no single organ resp or neuro	58%	90%	10%

Aligment of sepsis criteria between high and low resource settings:

Question	Yes	No
Should Low and High Resource Sepsis criteria be the same?	97%	3%

Delphi Round 6 Results

32/35 complete responses (91%, meets >=80% threshold)

Selection of subscores and criteria:

- Preferred + Acceptable >80%
- If two options >80%, then highest preferred %

Sepsis criteria voting:

Criteria version	Components	#1 choice	#1 choice or Acceptable	Not Acceptable
Option A	La2pt	13%	84%	16%
Option B	La2rem	13%	66%	34%
Option C	La2pt plus "synthesis"	72%	94%	6%

Delphi Round 7 Results

Qualitative discussion – no voting

Delphi Round 8 Results

33/35 responses (94%, meets >=80% threshold)

Selection of subscores and criteria:

- Preferred + Acceptable >80%
- If two options >80%, then highest preferred %

Inclusion of screening criteria voting:

Option	Components	Preferable	Prefer. + Acceptable	Not Acceptable
A	Screening criteria in main manuscripts	12%	60%	36%
B	ED/screening manuscript, no screening criteria	**79%**	**91%**	9%

High risk sepsis and septic shock criteria voting:

Option	Components	Preferable	Prefer. + Acceptable	Not Acceptable
A	Both septic shock and high-risk criteria	9%	70%	27%
B	Only septic shock, show range of LASSO	**85%**	**94%**	0%

Delphi Round 9 Results

31/35 responses (89%, meets >=80% threshold)

Selection of subscores and criteria:

- Preferred + Acceptable >80%
- If two options >80%, then highest preferred %

Septic Shock Criteria voting:

Option	Criteria	Preferable	Prefer. + Acceptable	Not Acceptable
A	**LA2CV1**	**84%**	**100%**	0%
B	LA2CV2	6%	77%	3%
C	Other	6%	10%	39%

Delphi Round 10 Results

30/35 responses (86%, meets >=80% threshold)

Question	Yes	No
Should the new pediatric sepsis criteria and score be referred to as the "Phoenix criteria/score"?	**87%**	13%
Should we use the phrase "Sepsis with organ dysfunction remote to the site of infection" to refer to instances where at least one dysfunctional organ is not the organ that is infected?	**83%**	17%

eTable 2. Comparison of the Phoenix Sepsis criteria with the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) criteria.
Criteria which differ in IPSCC compared to the Phoenix Sepsis Criteria are highlighted in RED.

In comparison with the IPSCC criteria, the Phoenix Sepsis criteria

- Do not require SIRS
- Do not use "severe sepsis" as a term
- Do not require administration of intravenous fluid boluses to meet cardiovascular dysfunction criteria
- Do not use elevated carbon dioxide for respiratory dysfunction
- Do not use base excess, urine output, capillary refill, or temperature gradient for cardiovascular dysfunction
- Do not include presence of renal or hepatic dysfunction
- Apply different thresholds for severity of specific organ failures (P/F or S/F ratio; MAP versus SBP; platelets; GCS)
- Include D-dimers, fibrinogen, and dilated pupils

Variable/Organ	**Phoenix Sepsis Score**				**IPSCC[85,86]**	
SIRS	Not necessary				At least 2 of 4 criteria (abnormal heart rate, respiratory rate, white cell count or temperature), of which one must be white cell count or temperature	
Sepsis	Phoenix Sepsis Score ≥2 points in a child with suspected/confirmed infection				Presence of SIRS in a child with suspected/confirmed infection	
Severe sepsis	Not applicable				Sepsis in presence of organ dysfunction, specifically defined as either respiratory or cardiovascular dysfunction, or at least 2 other organ dysfunctions	
Septic shock	Sepsis in presence of cardiovascular dysfunction (cardiovascular Phoenix Sepsis Score component ≥1 points)				Sepsis in presence of cardiovascular dysfunction (as defined below)	
Score construction	***0 points***	***1 point***	***2 points***	***3 points***	***IPSCC: No points allocated***	***IPSCC Comments***
Respiratory	P/F ≥400 or S/F ≥292	P/F <400 on any respiratory support or S/F <292 on any respiratory support	P/F 100-200 and IMV or S/F 148-220 and IMV	P/F <100 and IMV or S/F <148 and IMV	P/F <300 and/or IMV or NIV or PaCO2 >65mmHg or S/F <182	Did not use S/F ratio explicitly (FiO_2 >50% for Sats >92%)

Cardiovascular	• No vasoactive medications • Lactate <5 mmol/L • MAP (mmHg) <1 week - <1 month >30 1 to 11 months >38 1 to <2 years >43 2 to <5 years >44 5 to <12 years >48 12 to 18 years >51	1 point each (up to 3) for: • 1 vasoactive medication • Lactate 5-10.9 mmol/L • MAP (mmHg) - 17-30 25-38 31-43 32-44 36-48 38-51	2 points each (up to 6) for: • ≥2 vasoactive medications • Lactate ≥11 mmol/L • MAP (mmHg) - <17 <25 <31 <32 <36 <38		Despite administration of fluid bolus 40 mL/kg in 1 hr • ≥1 vasoactive medication • ≥2 of base deficit, lactate 2x upper limit, oliguria, core to peripheral temperature gap, prolonged capillary refill • SBP (mmHg) <59 <79 <75 <74 <74 <83 <90	IPSCC SBP (mmHg) age groups <1 week 1 week to 1 month 1 mo to 12 mo 1 yr to 5 years 1 yr to 5 years >5 to 12 years >12 to 18 years
Coagulation	• Platelets ≥100 K/μL • INR ≤1.3 • D-Dimer ≤2 mg/L FEU • Fibrinogen ≥100 mg/dL	1 point each (max. 2 points) for: • Platelets <100 K/μL • INR >1.3 • D-Dimer >2 mg/L FEU • Fibrinogen <100 mg/dL			• Platelets <80 K/μL or 50% decline • INR >2.0	
Neurologic	• GCS >10 • Pupils reactive	GCS ≤10	Fixed pupils		GCS ≤11 or acute decrease by ≥3 points	
Renal	Not available	-	-		Serum creatinine 2 times upper limit of normal for age or ≥2-fold increase	
Hepatic	Not available	-	-		Total bilirubin ≥4mg/dL or ALT ≥2 times upper limit of normal for age	

eTable 3. Comparison of the Phoenix Sepsis criteria with the 2016 Sepsis-3 criteria.
Criteria which differ in Sepsis-3 compared to the Phoenix Sepsis Criteria are highlighted in RED.

In comparison with the Sepsis-3 criteria, the Phoenix Sepsis criteria

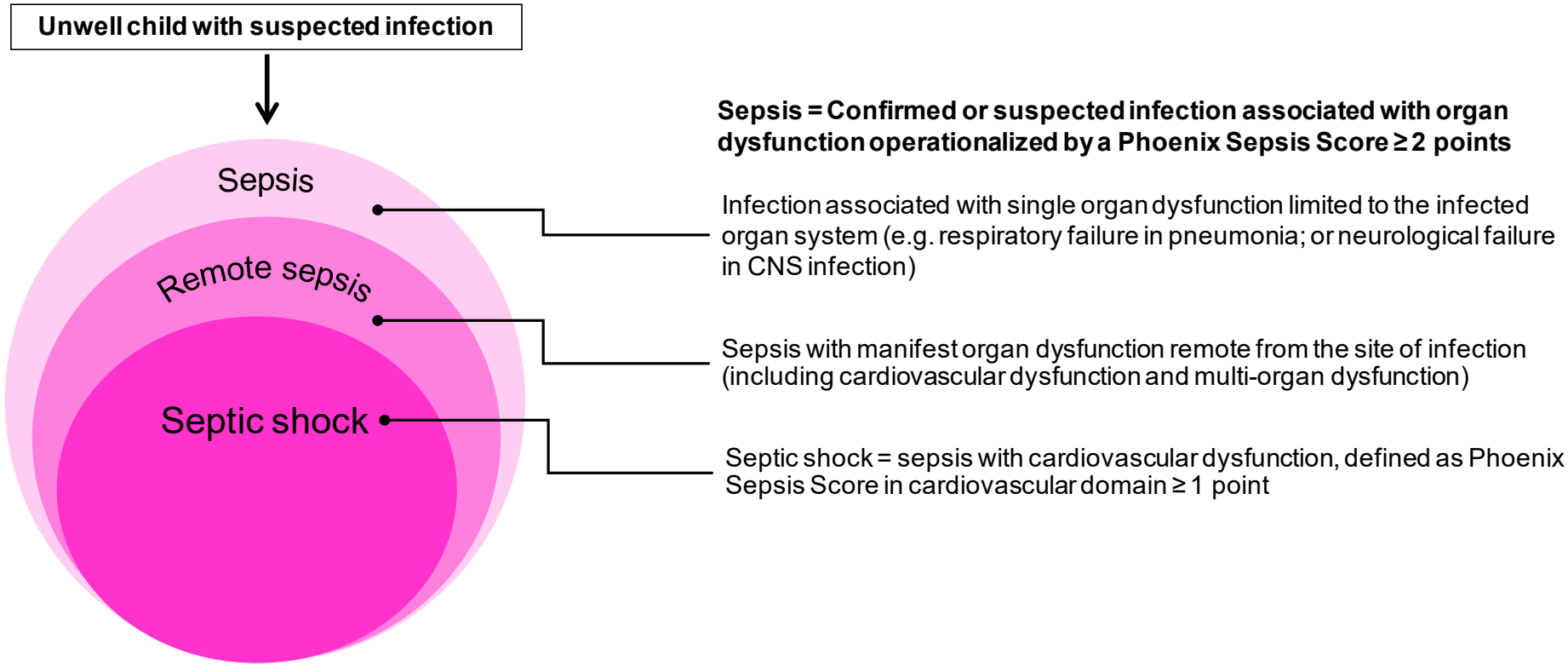
- Have a definition of septic shock which is based on the score used to adjudicate presence of organ dysfunction (rather than separate criteria as in Sepsis-3).
- Allocate a maximum of 3 points for some organs (contrary to maximum of 4 points for each organ in the adult SOFA score)
- Use S/F ratios as a proxy of P/F ratios
- Include INR, D-Dimers, and fibrinogen as variables for coagulation dysfunction
- Do not include presence of renal or hepatic dysfunction
- Apply age-specific thresholds for arterial hypotension

Variable/Organ	**Phoenix Sepsis Score**				**Sepsis-3[30]**	
SIRS	Not necessary				Not necessary	
Sepsis	Phoenix Sepsis Score ≥2 points in a child with suspected/confirmed infection				SOFA Score ≥2 points in an adult with suspected/confirmed infection	
Severe sepsis	Not applicable				Not applicable	
Septic shock	Sepsis in presence of cardiovascular dysfunction (cardiovascular Phoenix Sepsis Score component ≥1 points)				Sepsis in presence of arterial hypotension AND lactate >2mmol/l AND treatment with vasopressors	
Score development	Derived and validated using best composite score construction				Use of existing SOFA score	
Score construction	***0 points***	***1 point***	***2 points***	***3 points***	***Sepsis-3: up to 4 points allocated***	***Sepsis-3 comments***
Respiratory	P/F ≥400 or S/F ≥292	P/F <400 on any respiratory support or S/F <292 on any respiratory support	P/F 100-200 and IMV or S/F 148-220 and IMV	P/F <100 and IMV or S/F <148 and IMV	Allocates up to 4 points based on P/F ratio and any respiratory support (additional cut-off at P/F <300) No use of S/F	Did not use S/F ratio explicitly (FiO_2 >50% for SaO_2 >92%)
Cardiovascular	• No vasoactive medications	1 point each (up to 3) for: • 1 vasoactive medication	2 points each (up to 6) for: • ≥2 vasoactive medications		• ≥1 vasoactive medication in incremental doses with specified vasoactives	

	• Lactate <5 mmol/L • Age-specific MAP (mmHg)	• Lactate 5-10.9 mmol/L • Age-specific MAP (mmHg)	• Lactate ≥11 mmol/L • Age-specific MAP (mmHg)		• Lactate not used in score • MAP (mmHg) single cut-off <70mmHg	
Coagulation	• Platelets ≥100 K/µL • INR ≤1.3 • D-Dimer ≤2 mg/L FEU • Fibrinogen ≥100 mg/dL	1 point each (max. 2 points) for: • Platelets <100 K/µL • INR >1.3 • D-Dimer >2 mg/L FEU • Fibrinogen <100 mg/dL			• Allocates up to 4 points based on Platelets <150, <100, <50, <20 K/µL	
Neurologic	• GCS >10 • Pupils reactive	GCS ≤10	Fixed pupils		Allocates up to 4 points based on GCS 13-14, 10-12, 6-9, <6	
Renal	**Not available**	-	-		Allocates up to 4 points based on creatinine 1.2-1.9, 2.0-3.4, 3.5-4.9, >5.0 mg/dL or urine output	
Hepatic	**Not available**	-	-		Allocates up to 4 points based on bilirubin 1.2-1.9, 2.0-5.9, 6.0-11.9, >12.0 mg/dL	

eFigure 1: Relationship of the criteria.

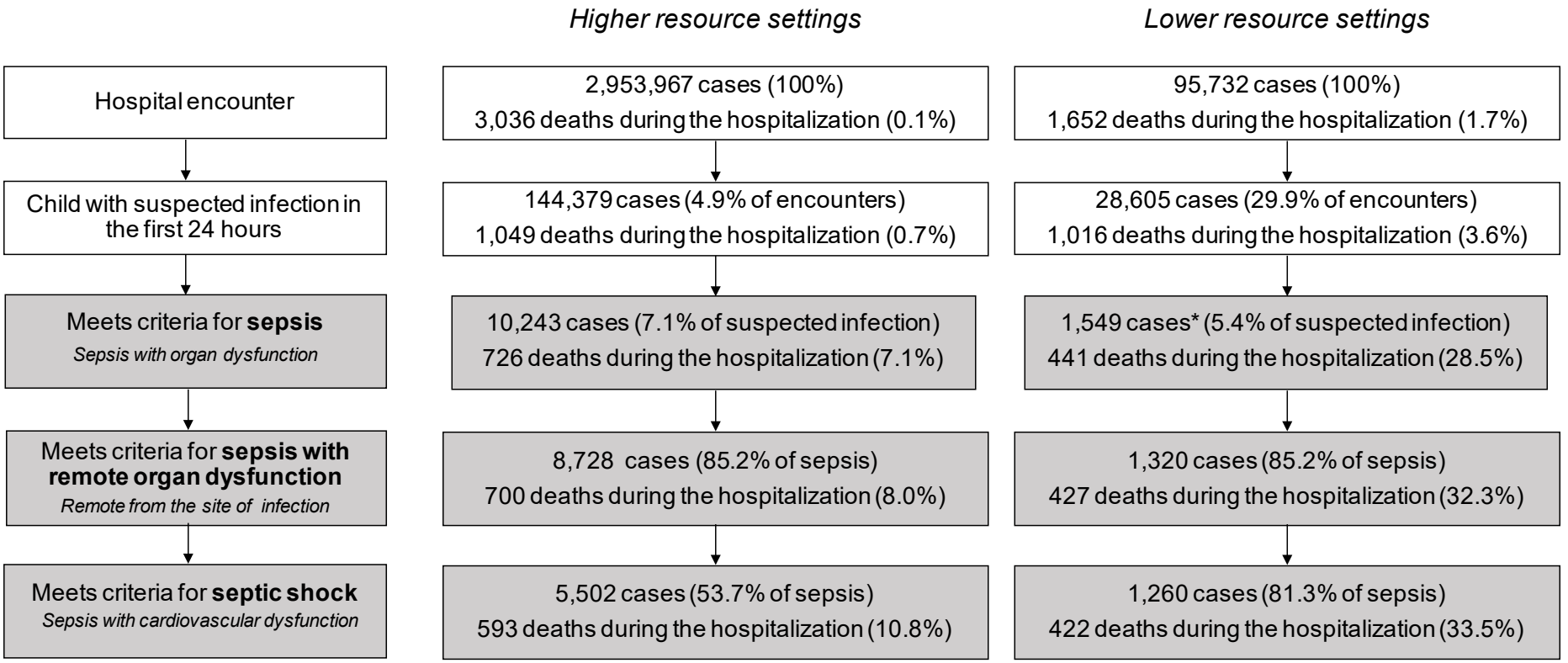
Sepsis diagnosis is operationalized as 2 points or more on the Phoenix Sepsis Score, and septic shock as sepsis with cardiovascular dysfunction. Sepsis with organ dysfunction remote from the primary site of infection is a subgroup of children who have an even higher mortality, and captures children with septic shock and/or multi-organ dysfunction.. There is a need for early sepsis criteria to screen children at risk of future development of sepsis.



eFigure 2: Prevalence and mortality of children with sepsis, remote sepsis, and septic shock in the first 24 hours, compared to all encounters, and all encounters with suspected infection in the first 24 hours.

Absolute (percentage) prevalence and in-hospital mortality are shown for each disease group, separately for higher and lower resourced settings. Numbers relate to encounters in the development set (derivation and internal validation).

*Of note, one of the two lower resource sites in the development set had incomplete data for respiratory and neurologic dysfunction. The lower resource site with complete data represents a more accurate estimate of sepsis in the first 24 hours amongst children with suspected infection in a lower resource setting, with a prevalence of 15.1% (1,298/8,595) and an in-hospital mortality of 22.2% (289/1,298).



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