Pediatric Critical Care Medicine

Operationalizing appropriate sepsis definitions in children worldwide: Considerations for the Pediatric Sepsis Definition Taskforce

--Manuscript Draft--

Manuscript Number:	
Full Title:	Operationalizing appropriate sepsis definitions in children worldwide: Considerations for the Pediatric Sepsis Definition Taskforce
Article Type:	Clinical Investigation
Keywords:	infection; pediatric; sepsis; criteria; globally; organ dysfunction; operationalize
Corresponding Author:	Enitan D. Carrol, MBChB, MD, FRCPCH University of Liverpool UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Liverpool
Corresponding Author's Secondary Institution:	
First Author:	Enitan D. Carrol, MBChB, MD, FRCPCH
First Author Secondary Information:	
Order of Authors:	Enitan D. Carrol, MBChB, MD, FRCPCH
	Suchitra Ranjit, MD, FCCM
	Kusum Menon, MD, MSc
	Tellen D Bennett, MD, MS
	L. Nelson Sanchez-Pinto, MD, MBI, FAMIA
	Jerry J Zimmerman, MD, PhD, MCCM
	Daniela C Souza, MD, PhD
	Lauren R Sorce, PhD, RN, CPNP-AC/PC, FCCM, FAAN
	Adrienne G Randolph, MD
	Paul Ishimine, MD
	Claudio Flauzino de Oliveira, MD, PhD
	Rakesh Lodha, MBBS, MD
	Lori Harmon, RRT, MBA
	Lynn Retford, BA
	R. Scott Watson, MD, MPH
	Luregn J Schlapbach, MD, PhD
	Niranjan Kissoon, MBBS
	Andrew C Argent, MBBCh, MMed, MD, FCPaeds, FRCPCH
Order of Authors Secondary Information:	
Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	Sepsis is a leading cause of global mortality in children, yet definitions for pediatric sepsis are outdated and lack global applicability and validity. In adults, the Sepsis-3 Definition Taskforce queried databases from high-income countries to develop and validate the criteria. The merit of this definition has been widely acknowledged,

	however, important considerations about less resourced and more diverse settings pose challenges towards its use globally. To improve applicability and relevance globally, the Pediatric Sepsis Definition Taskforce sought to develop a conceptual framework and rationale of the critical aspects and context-specific factors that must be considered for the optimal operationalization of future pediatric sepsis definitions. It is important to address challenges in developing a set of pediatric sepsis criteria which capture manifestations of illnesses with vastly different etiologies and underlying mechanisms. Ideal criteria need to be unambiguous, and capable of adapting to the different contexts in which children with suspected infection present around the globe. Additionally, criteria need to facilitate early recognition and timely escalation of treatment to prevent progression, and to limit life-threatening organ dysfunction. To address these challenges, locally adaptable solutions are required, which permit individualized care based on available resources and the pre-test probability of sepsis. This should facilitate affordable diagnostics which support risk stratification and prediction of likely treatment response, and solutions for locally relevant outcome measures. For this purpose, global collaborative databases need to be established, using minimum variable datasets from routinely collected data. In summary, a “Think globally, act locally” approach is required.
Additional Information:	
Question	**Response**
Enter Twitter handles of authors separated by semicolons, if available. List in order of authorship, i.e., @author1; @author2; @author3	@CarrolEnitan
RETAINED RIGHTS: Except for copyright, other proprietary rights related to the Work (e.g., patent or other rights to any process or procedure) shall be retained by the author. To reproduce any text, figures, tables, or illustrations from this Work in future works of their own, the author must obtain written permission from Wolters Kluwer Health, Inc. ("WKH"). ORIGINALITY: Each author warrants that his or her submission to the Work is original, does not infringe upon, violate, or misappropriate any copyright or other intellectual property rights, or any other proprietary right, contract or other right or interest of any third party, and that he or she has full power to enter into this agreement. Neither this Work nor a similar work has been published nor shall be submitted for publication elsewhere while under consideration by this Publication.	I agree

AUTHORSHIP RESPONSIBILITY: Each author warrants that he or she has participated sufficiently in the intellectual content, the analysis of data, if applicable, and the writing of the Work to take public responsibility for it. Each has reviewed the final version of the Work, believes it represents valid work, and approves it for publication. Moreover, should the editors of the Publication request the data upon which the work is based, they shall produce it. PREPRINTS: Upon acceptance of the article for publication, each author warrants that he/she will promptly remove any prior versions of this Work (normally a preprint) that may have been posted to an electronic server. DISCLAIMER: Each author warrants that this Work contains no libelous or unlawful statements and does not infringe or violate the publicity or privacy rights of any third party, libel or slander any third party, contain any scandalous, obscene, or negligently prepared information, or infringe or violate any other personal or proprietary right of others. Each author warrants that the Work does not contain any fraudulent, plagiarized or incorrectly attributed material. Each author warrants that all statements contained in the Work purporting to be facts are true, and any formula or instruction contained in the Work will not, if followed accurately, cause any injury, illness, or damage to the user. If excerpts (e.g., text, figures, tables, illustrations, or audio/video files) from copyrighted works are included, a written release will be secured by the author prior to submission, and credit to the original publication will be properly acknowledged. Each author further warrants that he or she has obtained, prior to submission, written releases from patients whose names or likenesses are submitted as	

part of the Work. Should the Editor or WKH request copies of such written releases, the author shall provide them in a timely manner. **DISCLOSURES/CONFLICT OF INTEREST** **Each author must identify any financial interests or affiliations with institutions, organizations, or companies relevant to the manuscript by completing the form below. Additionally, any financial associations involving a spouse, partner or children must be disclosed as well**. Note: Some sections below come from the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest at http://www.icmje.org/downloads/coi_disclosure.pdf (dated July 2010).	
Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, consulting fee or honorarium, support for travel to meetings for the study or other purposes, fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like, payment for writing or reviewing the manuscript, provision of writing assistance, medicines, equipment, or administrative support, etc...)?	No
Other: Did you or your institution at any time receive additional payments or support in kind for any aspect of the submitted work?	No
Please indicate whether you have financial relationships (regardless of amount of compensation) with entities. You should report relationships that were present during the 36 months prior to submission including board membership, consultancy, employment, expert testimony, grants/grants pending, payment for lectures including service on	No

speakers bureaus, payment for manuscript preparation, patents (planned, pending or issued), royalties, payment for development of educational presentations, stock/stock options, travel/accommodations/meeting expenses unrelated to activities listed (for example, if you report a consultancy above there is no need to report travel related to that consultancy), etc.	
Other (err on the side of full disclosure): Please indicate whether you have any additional financial relationships (regardless of amount of compensation) with entities. You should report relationships that were present during the 36 months prior to submission.	
Other Relationships Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No other relationships/conditions/circumstances that present potential conflict of interest
AUTHOR'S OWN WORK: In consideration of WKH and the Society of Critical Care Medicine's (SCCM) and World Federation of Pediatric Intensive and Critical Care Societies' (WFPICCS) publication of the Work, the author hereby transfers, assigns, and otherwise conveys all his/her copyright ownership worldwide, in all languages, and in all forms of media now or hereafter known, including electronic media such as CD-ROM, Internet, and Intranet, to SCCM and WFPICCS. If SCCM and WFPICCS should decide for any reason not to publish the Work, SCCM and WFPICCS shall give prompt notice of its decision to the corresponding author, this agreement shall terminate, and neither the author, WKH, nor SCCM and WFPICCS shall be under any further liability or obligation. Each author grants WKH and SCCM and WFPICCS the rights to use his or her name and biographical data (including professional affiliation) in the Work and in its or the journal's promotion. Notwithstanding the foregoing, this paragraph shall not apply, and any	I agree

transfer made pursuant to this paragraph shall be null and void if (i) the Work has been accepted by WKH for publication, and (ii) the author chooses to have the Work published by WKH as an open access publication. WORK MADE FOR HIRE: If this Work or any element thereof has been commissioned by another person or organization, or if it has been written as part of the duties of an employee, an authorized representative of the commissioning organization or employer must also sign this form stating his or her title in the organization. GOVERNMENT EMPLOYEES: If the Work or a portion of it has been created in the course of any author's employment by the United States Government, check the "Government" box at the end of this form. A work prepared by a government employee as part of his or her official duties is called a "work of the U.S. Government" and is not subject to copyright. If it is not prepared as part of the employee's official duties, it may be subject to copyright. INSTITUTIONAL REVIEW BOARD/ANIMAL CARE COMMITTEE APPROVAL: Each author warrants that his or her institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research. WARRANTIES: Each author warranty made in this form is for the benefit of WKH, SCCM and WFPICCS, and the Editor; each author agrees to defend, indemnify, and hold harmless those parties for any breach of such warranties.	
Pediatric Critical Care Medicine will permit	I agree

the author(s) to deposit for display a "final peer-reviewed manuscript" (the final manuscript after peer-review and acceptance for publication but prior to the publisher's copyediting, design, formatting, and other services) 12 months after publication of the final article on the author's personal web site, university's institutional repository or employer's intranet, subject to the following: * You may only deposit the final peer-reviewed manuscript. * You may not update the final peer-reviewed manuscript text or replace it with a proof or with the final published version. * You may not include the final peer-reviewed manuscript or any other version of the article on any commercial site or in any repository owned or operated by any third party. For authors of articles based on research funded by the National Institutes of Health ("NIH"), Wellcome Trust, Howard Hughes Medical Institute ("HHMI"), or other funding agency, see below for the services that WKH will provide on your behalf to comply with "Public Access Policy" guidelines. * You may not display the final peer-reviewed manuscript until twelve months after publication of the final article. * You must attach the following notice to the final peer-reviewed manuscript: "This is a non-final version of an article published in final form in (provide complete journal citation)". * You shall provide a link in the final peer-reviewed manuscript to the Pediatric	

Critical Care Medicine website.	
"Public Access Policy" Funding Disclosure Please disclose below if you have received funding for research on which your article is based from any of the following organizations:	Other - Please list in the following comments box
Other (Please list): as follow-up to ""Public Access Policy" Funding Disclosure Please disclose below if you have received funding for research on which your article is based from any of the following organizations:"	UK National Institute for Health and Care Research
Please select:	Author's Own Work
Any additional comments?	
Compliance with RCUK and Wellcome Trust Open Access Policies Both the Research Councils UK (RCUK) and the Wellcome Trust have adopted policies regarding Open Access to articles that have been funded by grants from the RCUK or the Wellcome Trust. If either “Wellcome Trust” or “Research Councils UK (RCUK)” has been selected above, and the authors of the applicable article choose to have the article published as an open access publication, the following policies will apply: * If the article is to be published pursuant to the “Gold” route of Open Access, both the RCUK and the Wellcome Trust require that WKH make the article freely available immediately pursuant to the Attribution 4.0 Creative Commons License, currently found at http://creativecommons.org/licenses/by/4.0/legalcode (the “CC BY License”). The CC BY License is the most accommodating of the Creative Commons licenses and allows others to distribute, remix, tweak, and build upon the article, even commercially, as long as they credit the authors for the original creation.	I agree

* If the article is to be published pursuant to the “Green” route of Open Access, both the RCUK and the Wellcome Trust require that WKH make the article freely available within six months pursuant to the Attribution-NonCommerical 4.0 Creative Commons License, currently found at http://creativecommons.org/licenses/by-nc/4.0/legalcode (the “CC BY-NC License”). The CC BY-NC License allows others to remix, tweak, and build upon the article non-commercially, and although their new works must also acknowledge the authors for the original creation and be non-commercial, they don't have to license their derivative works on the same terms.

As a service to our authors, WKH will identify the National Library of Medicine (NLM) articles that require deposit pursuant to the RCUK and Wellcome Trust policies described in this section. This Copyright Transfer Agreement provides the mechanism for identifying such articles.

WKH will transmit the final peer-reviewed manuscript of an article based on research funded in whole or in part by either RCUK or the Wellcome Trust to Pub Med Central.

Upon NIH request, it remains the legal responsibility of the author to confirm with NIH the provenance of his/her manuscript for purposes of deposit. Author will not deposit articles him/herself. Author will not alter the final peer-reviewed manuscript already transmitted to NIH.

With respect to the “Green” route of Open Access, author will not authorize the

display of the final peer-reviewed manuscript prior to 6 months following publication of the final article. Authors of articles that have been funded from grants from the RCUK or the Wellcome Trust are required to sign the WKH Open Access License Agreement prior to publication of the applicable article. Please contact the Editorial Office of the applicable journal to receive the Open Access License Agreement that is to be signed in connection with the publication of the article.	
I am the person in question for this submission or otherwise have approval to complete this agreement.	I agree
CME/CE Disclosure Each author must identify and disclose any financial associations involving a spouse, partner or children by completing the Family Disclosure question below, and whether any off-label uses or unapproved drugs or devices are discussed in his/her manuscript by completing the Off-Label Use/Unapproved Drugs or Products question below. In the event that the Work is published as a continuing education or continuing medical education article, this information will be provided to the accrediting body and may be included in the published article. When applicable, articles accepted for publication may need to comply with additional standards related to CME or CE accreditation. Please refer to guidelines for authors for details. WKH and its affiliates reserve the right to publish the manuscript as a continuing education article.	I agree
Family Disclosure Do your children or your spouse or partner have financial relationships with entities that have an interest in the	No other relationships/conditions/circumstances that present potential conflict of interest

content of the submitted work?	
Off-Label Use/Unapproved Drugs or Products If your manuscript discusses an unlabeled use of a commercial product or device or an investigational use of a product or device not yet approved by the FDA for any purpose, you must specifically disclose in the manuscript that the product is not labeled for the use under discussion or that the product is still investigational. Please check the item below that applies to you	I will not discuss unlabeled/investigational uses of any commercial product or device
Suggested Reviewers:	
Opposed Reviewers:	

Professor Enitan Carrol
Dept of Clinical Infection, Microbiology and Immunology,
Institute of Infection, Veterinary and Ecological Sciences,
Ronald Ross Building,
8 West Derby Street,
Liverpool,
L69 7BE
Email: edcarrol@liverpool.ac.uk

14 February 2023

Dear Editor

We wish to submit a revised version of our Concise Clinical Science Review entitled "**Operationalizing appropriate sepsis definitions in children worldwide: Considerations for the Pediatric Sepsis Definition Taskforce "**for consideration by *Pediatric Critical Care Medicine*. We have addressed all your previous comments, which have served to improve the manuscript.

In this paper, we present a conceptual framework and a rationale of the critical aspects and context-specific factors that must be considered for the operationalization of sepsis definitions applicable to children around the world. Sepsis is a leading cause of global mortality, with almost half of cases affecting children, yet definitions for pediatric sepsis remain outdated, despite their known limitations in terms of global applicability, validity, and relevance. In adults, the new Sepsis-3 definition was developed in 2016, using databases from high resource countries, to develop and validate the criteria, which were then claimed to be globally applicable. While the merit of this definition has been widely acknowledged, it has created controversy because it fails to account for less resourced and more diverse settings, posing great challenges towards the implementation of these criteria in sepsis quality improvement initiatives around the world.

There are inherent challenges in developing a set of paediatric sepsis criteria that address similar presentations of illness, but with vastly different aetiologies and underlying mechanisms. The criteria need to be unambiguous yet flexible, capable of adapting to the widely different contexts in which children with suspected infection present around the globe, so they can be implemented locally. These criteria need to facilitate early recognition and timely escalation of treatment to prevent progression, and support life-threatening organ dysfunction in children with sepsis. At the same time, in order to improve outcomes of all children with suspected infection, it is imperative too that the criteria are able to identify children with infections other than sepsis early, for whom management with specific interventions other than intravenous antibiotics and vasoactive drugs will be life-saving. In this review, we discuss the challenges and opportunities in operationalizing sepsis in the global and diverse settings in which children present, and highlight that any criteria developed must be applicable locally in order to identify, manage and study children with sepsis.

We present locally adaptable solutions are required, which permit individualized care based on available resources and the pre-test probability of sepsis. This should facilitate affordable diagnostics which support risk stratification and prediction of likely treatment response, and solutions for locally relevant outcome measures.

We have no conflicts of interest to disclose. Please address all correspondence concerning this manuscript to Professor Enitan Carrol at edcarrol@liverpool.ac.uk

Thank you for your consideration of this manuscript.

Sincerely,

Professor Enitan Carrol
Corresponding Author

on behalf of the Pediatric Sepsis Definition Taskforce.

280-Character Summary

A brief summary, not to exceed 280 characters and suitable for a social medium communication, must be included in the submission. This summary will be used for publicity and promotion if the manuscript is accepted and published.

To facilitate rapid identification, optimal management and rigorous study of children with sepsis, future criteria defining pediatric sepsis must capture manifestations of illnesses across varying pathogen and patient subgroups, and be applicable both locally and globally.

Operationalizing appropriate sepsis definitions in children worldwide: Considerations for the Pediatric Sepsis Definition Taskforce

Enitan D. Carrol MBChB, MD, FRCPCH[1], Suchitra Ranjit, MD, FCCM[2], Kusum Menon, MD, MSc[3], Tellen D. Bennett, MD, MS[4], L. Nelson Sanchez-Pinto, MD, MBI, FAMIA[5], Jerry J. Zimmerman, MD, PhD, MCCM[6], Daniela C. Souza, MD, PhD[7], Lauren R. Sorce PhD, RN, CPNP-AC/PC, FCCM, FAAN[5], Adrienne G. Randolph, MD[8], Paul Ishimine, MD[9], Claudio Flauzino de Oliveira, MD, PhD[10], Rakesh Lodha, MBBS, MD[11], Lori Harmon, RRT, MBA[12], R. Scott Watson MD, MPH[6], Luregn J. Schlapbach MD, PhD[13,14], Niranjan Kissoon MBBS*[15], Andrew C Argent MBBCh, MMed(Paeds), MD(Paeds), FCPaeds(SA), FRCPCH(UK)*[16]

on behalf of the Society of Critical Care Medicine's Pediatric Sepsis Definition Taskforce.

*contributed equally

[1] Department of Clinical Infection, Microbiology and Immunology, University of Liverpool Institute of Infection, Veterinary and Ecological Sciences, Liverpool, United Kingdom

[2] Apollo Children's Hospital, Chennai, India

[3] Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Canada

[4] Departments of Biomedical Informatics and Pediatrics (Critical Care Medicine), University of Colorado School of Medicine, and Children's Hospital Colorado, Aurora, CO

[5] Ann & Robert H. Lurie Children's Hospital of Chicago and Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL

[6] Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA

[7] Hospital Universitário da Universidade de São Paulo and Hospital Sírio Libanês, São Paulo, Brazil

[8] Department of Anesthesiology, Critical Care Medicine and Pain Medicine, Boston Children's Hospital, and Department of Anesthesia and Pediatrics, Harvard Medical School, Boston, MA

[9] Departments of Emergency Medicine and Pediatrics, University of California, San Diego School of Medicine, La Jolla, CA

[10] Associação de Medicina Intensiva Brasileira, São Paulo, Brazil

[11] All India Institute of Medical Sciences, New Delhi, India

[12] Society of Critical Care Medicine, Chicago, IL

[13] Department of Intensive Care and Neonatology, and Children`s Research Center, University Children`s Hospital Zurich, Zurich, Switzerland

[14] Child Health Research Centre, The University of Queensland, Brisbane, Australia

[15] Global Child Health Department of Pediatrics and Emergency Medicine, British Columbia Women and Children's Hospital and the University of British Columbia, Vancouver, Canada

[16] Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa

Correspondence:

Prof. Enitan D Carrol

Department of Clinical Infection, Microbiology and Immunology

University of Liverpool Institute of Infection, Veterinary and Ecological Sciences

Ronald Ross Building

8 West Derby Street

Liverpool, L69 7BE

Email : edcarrol@liverpool.ac.uk

FUNDING: This project was sponsored by the Society of Critical Care Medicine (SCCM). No specific funding was required to perform this sub-study. EDC is a United Kingdom National Institute for Health and Care Research (NIHR) Senior Investigator. TDB and LNSP were supported by NIH/NICHD Grant # R01HD105939.

DECLARATION OF CONFLICT OF INTEREST: The authors' work on the Pediatric Sepsis Definition Taskforce has been commissioned by the Society of Critical Care Medicine (SCCM).

Key words: pediatric, sepsis, criteria, global, biology

Word count: 2926

Tables: 1

Figures: 1

Abstract

Sepsis is a leading cause of global mortality in children, yet definitions for pediatric sepsis are outdated and lack global applicability and validity. In adults, the Sepsis-3 Definition Taskforce queried databases from high-income countries to develop and validate the criteria. The merit of this definition has been widely acknowledged, however, important considerations about less resourced and more diverse settings pose challenges towards its use globally. To improve applicability and relevance globally, the Pediatric Sepsis Definition Taskforce sought to develop a conceptual framework and rationale of the critical aspects and context-specific factors that must be considered for the optimal operationalization of future pediatric sepsis definitions.

It is important to address challenges in developing a set of pediatric sepsis criteria which capture manifestations of illnesses with vastly different etiologies and underlying mechanisms. Ideal criteria need to be unambiguous, and capable of adapting to the different contexts in which children with suspected infection present around the globe. Additionally, criteria need to facilitate early recognition and timely escalation of treatment to prevent progression, and to limit life-threatening organ dysfunction.

To address these challenges, locally adaptable solutions are required, which permit individualized care based on available resources and the pre-test probability of sepsis. This should facilitate affordable diagnostics which support risk stratification and prediction of likely treatment response, and solutions for locally relevant outcome measures. For this purpose, global collaborative databases need to be established, using minimum variable datasets from routinely collected data. In summary, a "Think globally, act locally" approach is required.

(248 words)

Introduction

Across the world substantial morbidity, mortality, expense and adverse impacts on healthcare systems are attributed to pediatric sepsis [1]. Unfortunately, variability in the operationalization of pediatric sepsis definitions leads to difficulties in measuring the burden of sepsis and optimising management, and may compromise quality improvement initiatives. In many settings, "sepsis" has been used synonymously with "severe infection" resulting in substantial challenges and variability in recognition and coding for sepsis [2]. Although Sepsis-3 definitions [3] were intended to unify the various definitions and terminologies, they have some limitations when applied to the global healthcare community, limitations which are even more pronounced when considering pediatric age groups. There are significant differences in the epidemiology, biology, susceptibility, and approach to sepsis management between adults and children, which are magnified between high income (HIC) and upper middle-income country (UMIC) settings compared to low and low middle-income country (LMIC) settings, where the majority of pediatric sepsis occurs.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, but there are no validated measures that determine when a child transitions from having an "infection" to having "sepsis" [4]. The purpose of establishing criteria for pediatric sepsis is to support a structured process for the early diagnosis of sepsis, development of appropriate interventions for that diagnosis, and to facilitate post-hoc assessment of the accuracy of management decisions. It is particularly important to recognise children on a trajectory towards infection-induced organ dysfunction early, rather than when the signs are florid, especially in resource-limited settings where advanced organ support may be lacking. A recent international survey with over 2,500 respondents highlighted that the currently available diagnostic frameworks for sepsis in children fall short of the desirable requirements in terms of benchmarking, correct disease classification, clinical recognition, and outcome

prognostication [5]. Operationalizing criteria for pediatric sepsis may require a more context-specific approach (e.g. considering time from onset, resources available, geography, prevalent pathogens etc.). There is therefore an urgent need for a data- and evidence-driven, approach to derive and validate criteria for sepsis in children, applicable across global settings and reflective of different clinical situations (from first contact in primary care through to intensive care) [5].

Sepsis varies in its clinical manifestations over time, which necessitates different requirements for identification of sepsis across the various stages of its progression. In the early phases, clinicians may have limited information available, but require criteria to make a *presumptive* diagnosis which is sufficient to implement effective therapeutic approaches. At later stages, clinicians usually have access to substantive information, including results of diagnostic testing, clinical progression, and response to therapy, to allow a *definitive* diagnosis. This concept enables clinicians to consider parameters for early initiation of antibiotic therapy, while allowing early termination of antibiotic therapy, once additional information allows re-evaluation of the diagnosis and risk. To ensure widespread adoption and patient benefit, criteria for sepsis should correlate with clinically relevant intervention points (e.g. invasive bacterial infection = antibiotic therapy, organ dysfunction = organ support therapy), as well as the risk of mortality in each situation.

Sepsis represents a broad umbrella term covering a condition that may be caused by a wide range of pathogens (bacterial, viral, fungal, and parasitic). There are no simple and unambiguous clinical, biological, imaging, or laboratory features that uniquely identify a patient with sepsis. The lack of rapid and reliable sepsis tests hampers the ability to make an definitive diagnosis of life-threatening organ dysfunction caused by a dysregulated host response to infection, [3], [2] at time of presentation.

Dysregulation of host response includes imbalances in pro- and anti-inflammatory states driven by the innate and adaptive immune systems and contributing to new or worsening organ injury and death. The adult Sepsis-3 criteria emphasize the importance of identification of organ dysfunction in patients with infection and have led to research that improves our mechanistic understanding of the pathobiology of sepsis, including infection-specific biology and responses to specific interventions [6], [7]. In this context, phenotyping utilizing biological and clinical characteristics, and specific pathophysiology, has great potential to be employed as an enrichment strategy in the evaluation of treatment responses [8].

The 2005 International Pediatric Sepsis Consensus Conference (IPSCC) [9] provided criteria for categories of increasing disease severity (infection, sepsis, severe sepsis, septic shock), and definitions of organ dysfunction in children. Since then, our understanding of organ dysfunction and practice of pediatric critical care have changed considerably. In 2022, the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) proposed 43 criteria to characterize children with single or multiple organ dysfunction, to identify phenotypes associated with poor outcome, and to serve as entry criteria for clinical trials [10]. The number of concurrent PODIUM organ dysfunction has been shown to have good-to-excellent discrimination for in-hospital mortality at two U.S. centers, and compared favorably to the IPSCC criteria [11]. However, although the PODIUM criteria were designed to be feasible, minimally invasive, generalizable and easily operationalizable [12], their application to LMIC settings could be challenging. Moreover, these criteria have never been validated across the world and may not be applicable to children of different age-groups; countries; nutritional and genetic backgrounds; and in the context of conditions rarely found in HIC settings.

More recently, a multicentre study of children with sepsis and organ dysfunction, demonstrated that mortality risk increased in children with high CRP or ferritin alone, with greater mortality risk when CRP and ferritin were both elevated [13]. Additionally, the biomarker combination

stratified groups of children with differing systemic inflammation cytokine profiles. As both these markers are easily measurable and affordable, the study results open up the possibility of stratification in randomised controlled trials of novel therapies in pediatric sepsis, including in LMICs.

Ideally, future criteria for pediatric sepsis should be:

1) Sensitive enough to enable clinicians to recognise the condition early, but specific enough to not waste potentially limited resources [14], and avoid harming patients as a consequence of over- or inappropriate treatment.

2) Flexible enough to allow clinicians to consider other possibilities with the resolution/progression of signs [14].

3) Applicable globally, and adaptable locally.

4) Correlated with biologically relevant phenotypes of sepsis to ensure correct selection of patients that will benefit from specific therapies and organ support.

In this Special Article from the Pediatric Sepsis Definition Taskforce of the *Society of Critical Care Medicine* (SCCM), we present a conceptual framework and a rationale of the critical aspects and context-specific factors that must be considered for the operationalisation of sepsis definitions in children around the world **(Figure 1).** These include biological factors, epidemiology, differences in the pathways to care, pre-test probabilities of sepsis at different levels of care, and the resources that are available to provide care.

Biological factors impacting sepsis

Pathogen-related biology

The pathogens responsible for severe infections and illnesses in children are often different from those in adults. Even responses to the same viral infections may be different, as

highlighted by the manifestations of SARS-CoV-2 infections in adults and children [15]. The pathogens responsible for severe pediatric infections in LMIC settings, where most deaths from infection occur, are different than those in HIC settings.

The Fluid Expansion As Supportive Therapy (FEAST) trial included many patients with malaria and anemia and no access to intensive care [16], and demonstrated that fluid boluses significantly increased 48-hour mortality in critically ill children. Scepticism by many clinicians in HIC settings to findings of the FEAST trial may have been based on their perception that the spectrum of disease differed to what they considered to be "sepsis", and specifically, bacterial sepsis. This conclusion has major implications for future criteria of pediatric sepsis, as a large proportion of the world's children are in countries where infections like malaria and dengue are common. In children, there are many conditions caused by non-bacterial pathogens such as viruses (e.g., enterovirus shock, dengue haemorrhagic fever/dengue shock syndrome, severe bronchiolitis, gastroenteritis with severe dehydration), and parasites (e.g., severe malarial anaemia), which result in organ dysfunction causing severe morbidity and mortality, yet clinicians may not consider these to be "sepsis". Host response profiles and endotypes may be influenced by co-infection with organisms such as HIV, malaria and helminths, by severe acute malnutrition, and immunisation against vaccine-preventable invasive bacterial infections [17, 18]. As per the pediatric Surviving Sepsis Campaign, patients with shock due to bacterial sepsis require broad-spectrum antibiotics within an hour [4]. Children with non-bacterial sepsis may require specific antimicrobials/immunosuppressives or only supportive care. Difficulties in differentiation, especially during the early stages, often lead to the prescription of broad-spectrum antimicrobials to all patients with a presumed infection and shock/organ dysfunction and could have far-reaching consequences in terms of antimicrobial resistance [19]. For example, based on endemicity (e.g., monsoon season) and the typical pattern of illness, clinicians in certain geographic regions may correctly suspect dengue in patients

with shock following defervescence, hemoconcentration and thrombocytopenia, as opposed to malaria in patients with fever with mental status changes, pallor and metabolic acidosis.

Patient-related biology

Primary or secondary immunodeficiencies, and genetic conditions such as sickle cell disease, influence predisposition to infection and host responses to infection and disease severity [20], [21], [22] and are fundamentally differently in children. Malnutrition, invasive bacterial disease and HIV co-infection are risk factors for death among children with moderate-to-severe diarrhea. The presence of malarial anemia and/or malnutrition may profoundly affect the response to therapy such as bolus fluid administration. Finally, there is growing awareness of the significance of specific genetic common (polymorphisms) and rare variation in the manifestations and treatment of infection-associated critical illness [23],[24].

Age-related biology

The term "pediatric" encompasses a range of age-groups, from neonates through to young adults, which are characterised by sometimes profound variations in physiology, immune maturation and specific responses to infection. The fine balance between pro- and anti-inflammation and the interconnectedness between inflammation and other host responses (neuroendocrine, metabolic, coagulation, endothelial, and immunosuppression) have been shown to vary substantially across age groups. Prematurity, low birth weight and younger age remain major risk factors for sepsis and poor outcome [25].

Due to their ability to initially maintain blood pressure in septic shock, overall, infants and young children have lesser reserves to compensate for serious illness compared to adults; thus shortening the window of opportunity for clinicians to recognise signs, respond quickly, and avoid the progression of organ deterioration. However, in the early phases of infection, children

who progress to life-threatening illness may be virtually indistinguishable clinically from those who will not progress [26].

Previous and current therapies

Vaccine-preventable infections have substantially decreased in high income (HIC) and upper middle-income (UMIC) country settings but may still present in some LMIC settings. Morbidity and mortality from childhood pneumonia has decreased in LMIC settings due to more widespread availability of conjugate vaccines, but a considerable burden remains from viruses, *Staphylococcus aureus, Escherichia coli* and other bacteria for which vaccines are not available [27]. Antimicrobial resistant infections remain highly prevalent in many LMIC settings, due to underlying complex and multifactorial problems. In the Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) neonatal sepsis study, only a third of Gram-negative isolates were susceptible to the WHO recommended first-line regimen [28]. Poor sanitation and hygiene, malnutrition and overcrowding also contribute to increased transmission of multi-resistant pathogens [29].

Epidemiology

Pneumonia, malaria, HIV, TB, dengue, meningitis, and neonatal infection represent a large proportion of emergency presentations in LMIC settings, whereas self-limiting (mainly viral) infections are common presentations in pediatric Emergency Departments (EDs) in HIC/UMIC settings. In South-East Asia, common causes of childhood sepsis include dengue, rickettsia, typhoid, non-typhoidal Salmonella, *Streptococcus suis*, and *Burkholderia pseudomallei*, all of which are rarely seen in North America and Europe, and most of which do not respond to standard antimicrobial interventions. Mixed infections are also common in LMICs and may be difficult to diagnose because of rudimentary laboratory support.

The highest burden of bacterial meningitis occurs in the "Meningitis belt" in Africa, with increased incidence and epidemics in the dry season (October to March) [30]. Colder weather also promotes higher transmission due to individuals spending more time indoors, or in close proximity outdoors, with exposure to smoke from wood fires [31]. The co-occurrence of viral respiratory infections further facilitates invasive disease. Climate change has a significant influence on incidence and severity of infections through environmental effects of floods, heat, drought, and freshwater decline [32]. For example, the incidence of dengue, a mosquito-borne viral disease which may present as septic shock, has increased due to global warming, and increasing wetland areas facilitating transmission (**Figure 1).**

Processes and pathways influencing timing of presentation

In HIC settings, many presentations to primary and emergency care settings are for those who are "worried well" (requiring reassurance), or early presentations who may require a period of observation. In LMIC settings, health facilities may be in remote locations with inaccessible emergency and specialised critical care transport services, and consequently are often faced with mostly late presentations. In early presentations, symptoms and signs may relate to direct effects of the pathogen, but in late presentations, they may be related to organ dysfunction as consequences and progression of infection and the host response.

The experience and specialization of health care professionals assessing children with suspected infection influences how sepsis criteria are operationalized. In primary care, there are fewer specialist assessments, fewer investigations, and potentially more antibiotics prescribed [33]. Some EDs have co-located primary care physicians, which allows for sicker children to be referred to more specialised ED physicians onsite. In a LMIC setting, children

might first present to a village health centre before referral to a district/tertiary hospital, and there may be delay in securing intravenous access and administering antibiotics, or intravenous fluids and vasoactive-inotropic drugs if available at all. In the latter setting, florid multi-organ dysfunction may be established by the time the child receives advanced care.

Resources and access

A classification of countries or regions into high, middle or low-income setting has significant limitations: the resources available to a particular child who presents to a health care facility with suspected infection may vary significantly. In certain HIC/UMIC settings, some disadvantaged populations may show features otherwise seen in LMIC, and yet some LMIC settings have highly resourced tertiary ICU facilities depending on the location. Differential resources and access thus relate to: a) within institution differences (ED, ward, PICU), b) within country differences (urban, rural, academic, general/district), and c) within high, middle or low-income country differences[34]. Literature on the epidemiology of presentations to the ED in LMIC is scant. Many PICUs in LMICs do not have specialised transport teams, so many children will die of sepsis outside PICUs. Under-reporting of sepsis incidence, and limited research funding for sepsis in LMIC countries further limits the impact of any quality improvement initiatives [35]. In many LMIC settings, facilities are challenged by patient load and inadequate human resources, as well as limited availability of oxygen saturation and blood pressure monitoring, oxygen, balanced IV fluids, vasoactive-inotropic drugs, and staff with expertise in skilled intravenous/arterial access and intubation/ventilation. Conversely, in many HIC/UMIC settings, a variety of fluid types, antibiotics, vasoactive-inotropic drugs, renal replacement therapy, electronic data capture, and even sepsis algorithms embedded into the electronic patient record, are routinely available.

New considerations

While concepts such as sepsis and pediatric acute respiratory distress syndrome have enabled the development of management strategies, standardized research cohorts and research protocols, our understanding of sepsis is evolving thanks to more detailed phenotyping, providing opportunities for enrichment of cohorts towards precision medicine [8]. As we focus on criteria for sepsis across the world, we need to develop global databases which are granular enough in content to examine the details of specific communities, and broad enough to contain information on multiple additional factors. Databases ideally will capture the full "narrative" of illness (not just presentation), and incorporate concepts of probability rather than definitive "certainty of diagnosis". While the Pediatric Sepsis Definition Taskforce has included primary care and emergency practitioners into the "definition" process, during the implementation of new criteria it will be necessary to reach out to other practitioners such as those who provide long-term care; laboratory teams; and those with expertise in implementation science. Social determinants of health (SDOH) in pediatric sepsis studies are not commonly reported, with marked variability in categorizations and definitions of SDOH variables. Standardized reporting of SDOH in pediatric sepsis studies is needed to understand the role these factors play in the development, progression, and recovery of sepsis, in order to implement policies aimed at addressing socioeconomic conditions related to sepsis [36] .

Actionable solutions to the considerations above are described in **Table 1**, and include individualized approaches dependent on setting, affordable diagnostics for accurate risk stratification, optimisation of data capture from routinely collected datasets to support collaborative registries, and development of locally relevant outcome measures.

Conclusions

Subsequent to the wide uptake of adult data-driven Sepsis-3 criteria, it is important to address the practical challenges in developing pediatric sepsis criteria which capture manifestations of illness in a range of settings and with vastly different aetiologies and underlying mechanisms. The criteria will need to be unambiguous yet flexible, capable of adapting to the widely different contexts in which children with suspected infection present around the globe. These criteria should facilitate early recognition of patients at risk, improved diagnosis and risk stratification to enable timely escalation of treatment to prevent progression. At the same time, we must endeavour to avoid the problems associated with over-diagnosis and treatment.

In summary, there are challenges and opportunities in operationalising sepsis in the global and diverse settings in which children present, but we present potential actionable solutions that can be applied locally in order to identify, manage and study children with sepsis.

ACKNOWLEGEMENTS

The authors would like to thank the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS), the Society of Critical Care Medicine (SCCM), and the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) for their support in facilitating this project. We thank Lori Harmon and Lynn Retford from the SCCM for their support with SCCM's Pediatric Sepsis Definitions Task Force.

On behalf of SCCM's **Pediatric Sepsis Definition Taskforce**: Luregn J. Schlapbach (Co-Chair), Department of Intensive Care and Neonatology, and Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland, and Child Health Research Centre, The University of Queensland, Brisbane, Australia; R. Scott Watson (Co-Chair), Center for Child Health, Behavior and Development, Seattle Children's Research Institute,

Seattle Children's Hospital, Seattle, WA; Andrew Argent (Vice-Chair), Department of Pediatrics and Adolescent Health, Red Cross War Memorial Children's Hospital and University of Cape Town, Cape Town, South Africa; Lauren R. Sorce (Vice-Chair), Ann & Robert H. Lurie Children's Hospital of Chicago and Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL; Samuel Akech, KEMRI Wellcome Trust Research Programme, Kenya; Elizabeth R. Alpern, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; Fran Balamuth, Children's Hospital of Philadelphia, Philadelphia, PA; Tellen D. Bennett, University of Colorado and Children's Hospital of Colorado, Aurora, CO; Paolo Biban, Verona University Hospital, Verona, Italy; Joe Carcillo, Department of Critical Care Medicine, UPMC Children's Hospital, Pittsburg, PA; Enitan D Carrol, University of Liverpool, Liverpool, United Kingdom; Kathleen Chiotos, Children's Hospital of Philadelphia, Philadelphia, PA; Mohammod Jobayer Chisti, International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh; Idris Evans, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; Lu Guoping, Children's Hospital of Fudan University, Shanghai, China; Mark W. Hall, Nationwide Children's Hospital, Columbus, OH; David Inwald, Addenbrooke's Hospital, Cambridge University Hospital NHS Trust, Cambridge, United Kingdom; Paul Ishimine, University of California, San Diego School of Medicine, La Jolla, CA; Michael Levin, Imperial College London, London, United Kingdom; Niranjan Tex Kissoon, British Columbia Women and Children's Hospital and the University of British Columbia, Vancouver, Canada; Rakesh Lodha, All India Institute of Medical Sciences, New Delhi, India; Kathryn Maitland, Imperial College, London, United Kingdom; Simon Nadel, St. Mary's Hospital, London, United Kingdom; Satoshi Nakagawa, National Center for Child Health & Development, Tokyo, Japan; Claudio Flauzino Oliveira, Associação de Medicina Intensiva Brasileira, São Paulo, Brazil; Mark Peters, University College London Great Ormond Street Institute of Child Health, London, United Kingdom; Adrienne G. Randolph,

Boston Children's Hospital, Boston, MA; Suchitra Ranjit, Apollo Children's Hospital, Chennai, India; L. Nelson Sanchez-Pinto, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; Halden F. Scott, Children's Hospital of Colorado, Denver, CO; Daniela C. Souza, University Hospital of The University of São Paulo, Sao Paulo, Brazil; Pierre Tissieres, Hospital de Bicetre, Paris, France; Juliane Bubeck Wardenburg, Department of Pediatrics Washington School of Medicine St. Louis, MO; Scott L. Weiss, Children's Hospital of Philadelphia, Philadelphia, PA; Wilson Milton Were, Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland; Matthew O. Wiens, University of British Columbia, Vancouver, Canada; James L. Wynn, University of Florida, Gainesville, FL; Jerry J. Zimmerman, Seattle Children's Hospital, Seattle, WA.

Figure 1: Operationalizing Sepsis Definitions in Children

REFERENCES

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet.* Jan 18 2020;395(10219):200-211.
2. Tidswell R, Parker T, Brealey D, Singer M. Sepsis - the broken code how accurately is sepsis being diagnosed? *J Infect.* Dec 2020;81(6):e31-e32.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* Feb 23 2016;315(8):801-810.
4. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatr Crit Care Med.* Feb 2020;21(2):e52-e106.
5. Morin L, Hall M, de Souza D, et al. The Current and Future State of Pediatric Sepsis Definitions: An International Survey. *Pediatrics.* Jun 1 2022;149(6).
6. Zhang Z, Zhang G, Goyal H, Mo L, Hong Y. Identification of subclasses of sepsis that showed different clinical outcomes and responses to amount of fluid resuscitation: a latent profile analysis. *Crit Care.* Dec 18 2018;22(1):347.
7. Seymour CW, Kennedy JN, Wang S, et al. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. *JAMA.* May 28 2019;321(20):2003-2017.
8. Maslove D, Tang B, Shankar-Hari M, et al. Redefining critical illness. *Nat Med. .* 2022;28:1141-1148.
9. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* Jan 2005;6(1):2-8.
10. Schlapbach LJ, Weiss SL, Bembea MM, et al. Scoring Systems for Organ Dysfunction and Multiple Organ Dysfunction: The PODIUM Consensus Conference. *Pediatrics.* Jan 1 2022;149(Supplement_1):S23-S31.
11. Sanchez-Pinto LN, Bembea MM, Farris RW, et al. Patterns of Organ Dysfunction in Critically Ill Children Based on PODIUM Criteria. *Pediatrics.* Jan 1 2022;149(1 Suppl 1):S103-S110.
12. Bembea MM, Agus M, Akcan-Arikan A, et al. Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Contemporary Organ Dysfunction Criteria: Executive Summary. *Pediatrics.* Jan 1 2022;149(Supplement_1):S1-S12.
13. Horvat CM, Fabio A, Nagin DS, et al. Mortality Risk in Pediatric Sepsis Based on C-reactive Protein and Ferritin Levels. *Pediatr Crit Care Med.* Dec 1 2022;23(12):968-979.
14. Klompas M, Calandra T, Singer M. Antibiotics for Sepsis-Finding the Equilibrium. *JAMA.* Oct 9 2018;320(14):1433-1434.
15. Vella LA, Giles JR, Baxter AE, et al. Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. *Sci Immunol.* Mar 2 2021;6(57).
16. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med.* Jun 30 2011;364(26):2483-2495.
17. Madhi SA, Klugman KP, Kuwanda L, Cutland C, Kayhty H, Adrian P. Quantitative and qualitative anamnestic immune responses to pneumococcal conjugate vaccine in HIV-infected and HIV-uninfected children 5 years after vaccination. *J Infect Dis.* Apr 15 2009;199(8):1168-1176.
18. Schachter J, Alvarinho de Oliveira D, da Silva CM, et al. Whipworm Infection Promotes Bacterial Invasion, Intestinal Microbiota Imbalance, and Cellular Immunomodulation. *Infect Immun.* Feb 20 2020;88(3).
19. Schlapbach LJ, Weiss SL, Wolf J. Reducing Collateral Damage From Mandates for Time to Antibiotics in Pediatric Sepsis-Primum Non Nocere. *JAMA Pediatr.* May 1 2019;173(5):409-410.

20. Borghesi A, Truck J, Asgari S, et al. Whole-exome Sequencing for the Identification of Rare Variants in Primary Immunodeficiency Genes in Children With Sepsis: A Prospective, Population-based Cohort Study. *Clin Infect Dis.* Dec 17 2020;71(10):e614-e623.
21. Battersby AJ, Knox-Macaulay HH, Carrol ED. Susceptibility to invasive bacterial infections in children with sickle cell disease. *Pediatr Blood Cancer.* Sep;55(3):401-406.
22. Payne AB, Link-Gelles R, Azonobi I, et al. Invasive pneumococcal disease among children with and without sickle cell disease in the United States, 1998 to 2009. *Pediatr Infect Dis J.* Dec 2013;32(12):1308-1312.
23. Kumpf O, Gurtler K, Sur S, et al. A Genetic Variation of Lipopolysaccharide Binding Protein Affects the Inflammatory Response and Is Associated with Improved Outcome during Sepsis. *Immunohorizons.* Dec 17 2021;5(12):972-982.
24. Cvijanovich NZ, Anas N, Allen GL, et al. Glucocorticoid Receptor Polymorphisms and Outcomes in Pediatric Septic Shock. *Pediatr Crit Care Med.* Apr 2017;18(4):299-303.
25. Tan B, Wong JJ, Sultana R, et al. Global Case-Fatality Rates in Pediatric Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis. *JAMA Pediatr.* Apr 1 2019;173(4):352-362.
26. Van den Bruel A, Thompson M, Buntinx F, Mant D. Clinicians' gut feeling about serious infections in children: observational study. *BMJ.* Sep 25 2012;345:e6144.
27. Marangu D, Zar HJ. Childhood pneumonia in low-and-middle-income countries: An update. *Paediatr Respir Rev.* Nov 2019;32:3-9.
28. Schlapbach LJ, van Rossum A, Carrol ED. Antibiotics for neonatal sepsis in low-income and middle-income countries-where to go from here? *Lancet Infect Dis.* Dec 2021;21(12):1617-1618.
29. Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. *Antimicrob Resist Infect Control.* 2017;6:47.
30. Agier L, Deroubaix A, Martiny N, Yaka P, Djibo A, Broutin H. Seasonality of meningitis in Africa and climate forcing: aerosols stand out. *J R Soc Interface.* Feb 2013;10(79):20120814.
31. Cooper LV, Robson A, Trotter CL, et al. Risk factors for acquisition of meningococcal carriage in the African meningitis belt. *Trop Med Int Health.* Apr 2019;24(4):392-400.
32. Mirsaeidi M, Motahari H, Taghizadeh Khamesi M, Sharifi A, Campos M, Schraufnagel DE. Climate Change and Respiratory Infections. *Ann Am Thorac Soc.* Aug 2016;13(8):1223-1230.
33. Leigh S, Mehta B, Dummer L, et al. Management of non-urgent paediatric emergency department attendances by GPs: a retrospective observational study. *Br J Gen Pract.* Jan 2021;71(702):e22-e30.
34. Burstein R, Henry NJ, Collison ML, et al. Mapping 123 million neonatal, infant and child deaths between 2000 and 2017. *Nature.* Oct 2019;574(7778):353-358.
35. Souza DC, Jaramillo-Bustamante JC, Cespedes-Lesczinsky M, et al. Challenges and health-care priorities for reducing the burden of paediatric sepsis in Latin America: a call to action. *Lancet Child Adolesc Health.* Feb 2022;6(2):129-136.
36. Menon K, Sorce LR, Argent A, et al. Reporting of Social Determinants of Health in Pediatric Sepsis Studies. *Pediatr Crit Care Med.* Jan 25 2023.

Your image file "Figure 1.tif" cannot be opened and processed. Please see the common list of problems, and suggested resolutions below.

Reason: The image file is corrupt or invalid. Please check and resubmit.

Other Common Problems When Creating a PDF from an image file

You will need to convert your image file to another format or fix the current image, then re-submit it.

Table 1: Actionable solutions to support operationalization of pediatric sepsis criteria

Tailored approaches for different settings	Consider pre-test probability of sepsis, available resources and prevalence of other diseases with "sepsis-like" presentations
Sepsis bundle components individualized for specific settings	Impact of individual components on improving outcomes, should be evaluated
Develop minimum variable datasets using routinely collected data	Minimum variable datasets and a common dictionary for data labelling can allow merging of data for collaborative development and assessment of data-driven criteria and patient-relevant outcomes
Develop datasets from multiple settings around the world	The datasets should include information on patients through the continuum of care (primary care, emergency department, ward and PICU). Ideally the datasets should originate from diverse settings (geographical, sociodemographic, resource availability etc)
Determine locally relevant time zero	Depending on setting, first presentations of sepsis may be to local health centre, primary or secondary care
Determine locally relevant clinical decision support systems	Clinical decision support systems can be incorporated into electronic patient records in HIC/UMIC settings, and mobile phone apps in LMICs
Address antimicrobial stewardship	Structured clinical assessments and investigations can help determine treatment urgency of antimicrobials, to balance patient safety and antimicrobial stewardship
Develop locally relevant outcome measures	Outcome measures may include mortality, disability, critical care admission or organ dysfunction depending on setting
Develop affordable and accurate diagnostics	Affordable host response and/or pathogen diagnostics can support risk stratification, and stratification of likely response to novel therapies