A National Approach to Pediatric Sepsis Surveillance

Heather E. Hsu, MD, MPH,[a] Francisca Abanyie, MD, MPH,[b] Michael S.D. Agus, MD,[c] Fran Balamuth, MD, PhD, MSCE,[d] Patrick W. Brady, MD, MSc,[h] Richard J. Brilli, MD, FAAP, MCCM,[i] Joseph A. Carcillo, MD,[j] Raymund Dantes, MD,[b,k] Lauren Epstein, MD, MSc,[b] Anthony E. Fiore, MD, MPH,[b] Jeffrey S. Gerber, MD, PhD,[e] Runa H. Gokhale, MD, MPH,[b] Benny L. Joyner, Jr, MD, MPH,[l] Niranjan Kissoon, MD, FRCP(C), FAAP, MCCM,[m] Michael Klompas, MD, MPH,[n,o] Grace M. Lee, MD, MPH,[p] Charles G. Macias, MD, MPH,[q] Karen M. Puopolo, MD, PhD,[f] Carmen D. Sulton, MD,[r] Scott L. Weiss, MD, MSCE,[g] Chanu Rhee, MD, MPH[n,o]

Pediatric sepsis is a major public health concern, and robust surveillance tools are needed to characterize its incidence, outcomes, and trends. The increasing use of electronic health records (EHRs) in the United States creates an opportunity to conduct reliable, pragmatic, and generalizable population-level surveillance using routinely collected clinical data rather than administrative claims or resource-intensive chart review. In 2015, the US Centers for Disease Control and Prevention recruited sepsis investigators and representatives of key professional societies to develop an approach to adult sepsis surveillance using clinical data recorded in EHRs. This led to the creation of the adult sepsis event definition, which was used to estimate the national burden of sepsis in adults and has been adapted into a tool kit to facilitate widespread implementation by hospitals. In July 2018, the Centers for Disease Control and Prevention convened a new multidisciplinary pediatric working group to tailor an EHR-based national sepsis surveillance approach to infants and children. Here, we describe the challenges specific to pediatric sepsis surveillance, including evolving clinical definitions of sepsis, accommodation of age-dependent physiologic differences, identifying appropriate EHR markers of infection and organ dysfunction among infants and children, and the need to account for children with medical complexity and the growing regionalization of pediatric care. We propose a preliminary pediatric sepsis event surveillance definition and outline next steps for refining and validating these criteria so that they may be used to estimate the national burden of pediatric sepsis and support site-specific surveillance to complement ongoing initiatives to improve sepsis prevention, recognition, and treatment.

Sepsis is a major cause of death and disability in patients across the age spectrum. In May 2017, the United Nations World Health Assembly and the World Health Organization adopted as a global health priority the need to improve sepsis recognition, management, and prevention, and, among other key points, recognized the substantial toll of sepsis on child health.[1,2] Globally, medical professional societies and sepsis advocacy organizations have played an important role in developing innovative approaches to improve sepsis care for adults and children.[3] In the United States, local, state, and national agencies have targeted sepsis for quality improvement initiatives. New York and Illinois, for example,

abstract

[a]Department of Pediatrics, School of Medicine, Boston University and Boston Medical Center, Boston, Massachusetts; [b]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; [c]Division of Medical Critical Care, Department of Pediatrics, Harvard Medical School and Boston Children's Hospital, Boston, Massachusetts; [d]Divisions of Emergency Medicine, [e]Infectious Diseases, and [f]Neonatology, and Center for Pediatric Clinical Effectiveness, Departments of Pediatrics and [g]Anesthesiology and Critical Care, University of Pennsylvania Perelman School of Medicine and Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [h]Division of Hospital Medicine, Department of Pediatrics, College of Medicine, University of Cincinnati Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [i]Division of Critical Care Medicine, Department of Pediatrics, College of Medicine, The Ohio State University and Nationwide Children's Hospital, Columbus, Ohio; [j]Department of Critical Care Medicine, School of Medicine, University of Pittsburgh and Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; [k]Division of Hospital Medicine, School of Medicine, Emory University, Atlanta, Georgia; [l]Department of Pediatrics, Division of Critical Care Medicine, School of Medicine, University of North Carolina, Chapel Hill, North Carolina; [m]Departments of Pediatrics and Emergency Medicine, University of British Columbia, Vancouver and British Columbia's Children's Hospital, British Columbia, Canada; [n]Department of Population Medicine, Harvard Medical School, Harvard University and Harvard Pilgrim Health Care Institute, Boston, Massachusetts; [o]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; [p]Department of Pediatrics, School of Medicine, Stanford University and Lucille Packard Children's Hospital, Palo Alto, California; [q]Division of Pediatric Emergency Medicine, Department of Pediatrics, Case Western Reserve University and Rainbow Babies and Children's Hospital, Cleveland, Ohio; and [r]Departments of Pediatrics and Emergency Medicine, School of Medicine, Emory University and Children's Healthcare of Atlanta at Egleston, Atlanta, Georgia;

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established regulations for all hospitals to implement sepsis protocols and track compliance in response to tragic cases of unrecognized sepsis in children.[4,5] More recently, >50 US children's hospitals joined the Improving Pediatric Sepsis Outcomes collaborative, which aims to reduce pediatric sepsis mortality by 75%.[6]

However, as noted by the World Health Organization sepsis resolution, there remains a lack of reliable data and tools to measure pediatric sepsis incidence, therefore limiting hospitals' and regulators' efforts to better understand sepsis risk factors, resource needs, and the impact of performance-improvement initiatives. In the United States, researchers of most epidemiological studies have used administrative data, which suggest a substantial rise in sepsis incidence and a decrease in patient fatalities over time in both adults and children.[7–11] However, recent studies in adults reveal that administratively derived sepsis rates are likely biased by increased vigilance in sepsis diagnosis and coding over time.[12–14] As clinicians and hospitals screen, diagnose, and code for sepsis more aggressively, a larger number of patients with less-severe illness and lower mortality are being identified. However, the impact of such ascertainment bias on sepsis epidemiology in children has yet to be examined. Large-scale studies in PICUs in which manually abstracted clinical data are used likely offer more reliable point prevalence estimates[15,16] but are resource-intensive, exclude sepsis patients cared for in non-ICU locations, are subject to changes in ICU admission thresholds over time, and are not practical for longitudinal epidemiological surveillance.

The increasing national uptake of electronic health record (EHR) systems creates an opportunity to conduct population-level disease surveillance by using routinely collected clinical data rather than administrative data or a manual chart review. In 2015, the US Centers for Disease Control and Prevention (CDC) recruited sepsis experts and representatives of key professional societies to develop an approach to adult sepsis surveillance by using clinical EHR data. This led to the establishment of the adult sepsis event (ASE) surveillance definition, which was adapted from consensus clinical criteria and was used to estimate the national burden of sepsis in adults.[17] The CDC additionally created a tool kit for hospitals to employ this surveillance methodology to monitor the effectiveness of local sepsis prevention, early recognition, and treatment programs.[18] These efforts excluded patients <20 years old given the important differences in defining sepsis in infants and children versus adults.

To address this gap, the CDC convened a separate working group in July 2018 that included pediatric sepsis experts and representatives from pediatric critical care, emergency medicine, hospital medicine, infectious diseases, and neonatology (Appendix) as well as the investigators and CDC officials who developed the ASE surveillance definition. The working group's goal was to propose an agenda for the development of a reliable, pragmatic, and generalizable method for pediatric sepsis surveillance in the United States, including establishing a preliminary pediatric sepsis surveillance case definition and a plan for its testing and refinement.

From July to October 2018, the CDC convened working group members for a series of conference calls in preparation for an in-person meeting in Atlanta, Georgia, on November 1, 2018. At the meeting, an initial proposed approach to pediatric sepsis surveillance and review of pediatric organ-dysfunction scoring systems was presented (H.E.H. and C.R.) as well as preliminary results from a single pediatric institution's experience with adapting the ASE methodology to their patient population (F.B. and S.L.W.). Working group members were assigned to small groups and CDC officials facilitated discussions of each potential component of a pediatric sepsis surveillance definition to identify criteria with clinical face validity that would be feasible to incorporate into widespread surveillance. Here, we summarize the working group's considerations, outline a pediatric sepsis event (PSE) case definition proposed by working group members, and describe a road map for future work needed to refine, validate, and apply the proposed criteria.

CHALLENGES FOR SEPSIS SURVEILLANCE: EVOLVING CLINICAL DEFINITIONS

Efforts to standardize sepsis surveillance in both children and adults are challenged by ongoing controversy regarding what constitutes sepsis and the lack of gold standard diagnostic criteria. The 1992 and 2001 international consensus criteria for adults (Sepsis-1 and Sepsis-2) characterized "sepsis" as a systemic inflammatory response syndrome (SIRS) secondary to infection, with SIRS defined as ≥2 abnormalities in temperature, heart rate, respiratory rate, or white blood cell count, and characterized "severe sepsis" as sepsis with organ dysfunction.[19,20] These criteria provided a useful conceptual framework but yielded low specificity,[21] created semantic confusion between the terms "sepsis" and "severe sepsis," and had limited applicability to pediatrics given the age-dependence of normal laboratory and vital signs values among infants and young children.[22]

Acknowledging that children and adults have different physiology, immune responses to infection, and comorbidities, an international panel

convened in 2005 to modify Sepsis-2 criteria for children. The International Pediatric Sepsis Consensus Criteria (IPSCC) adopted the Sepsis-2 framework for specified pediatric age groups and, through expert consensus, defined sepsis-associated organ-dysfunction thresholds.[22] The IPSCC provided a consistent framework for research studies, but it has not been validated, can be complex and labor intensive to apply, and has limited overlap with sepsis diagnosed at the bedside.[23]

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) redefined sepsis in adults as "life-threatening organ dysfunction due to a dysregulated host response to infection."[24,25] This new paradigm eliminated SIRS because of insufficient sensitivity and low specificity for severe infections and emphasized organ dysfunction as an essential feature of sepsis. "Septic shock" was defined as a subset of sepsis with particularly profound circulatory, cellular, and metabolic abnormalities, whereas "severe sepsis" was considered redundant and eliminated. Sepsis-3 operationalized measurement of organ dysfunction as an increase in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points over baseline. Analyses of >1.3 million adult hospitalizations and external validation in separate data sets revealed that SOFA scores of ≥2 points over baseline had high predictive validity for death and/or prolonged ICU stay in patients with suspected infection.[26]

Authors of recently published studies and commentaries support applying Sepsis-3 to pediatrics but note the importance of considering the unique physiology of infants and children.[27–37] As in adults, new or progressive organ failure is associated with higher mortality in children with suspected infections.[31] Likewise, SIRS is common in febrile children who are otherwise well and correlates poorly with the presence of infection or sepsis.[29,38,39] A recent study of nearly 2600 children admitted to PICUs in Australia and New Zealand revealed that organ-dysfunction scoring systems outperformed SIRS criteria for identifying children at risk for death or prolonged ICU stay.[29] A similar study in China yielded comparable results.[36]

TABLE 1 Performance Domains for Sepsis Criteria and Their Priority for Clinical Care Versus Surveillance

Domain	Definition	Priority for Different Applications	
		Clinical Care	Surveillance
Reliability[a]	The extent to which a given classification scheme yields stable and reproducible results	Moderate to high	High
Timeliness[a]	The speed with which criteria are generated with respect to the course of disease	High	Low
Minimizing measurement burden[b]	Assessment of the relative cost, safety, and complexity of collecting data incorporated into a set of criteria	Moderate to high	High
Validity[c]			
Content	The extent to which criteria fit with current understanding and knowledge	High	High
Construct	The degree to which criteria measure what they are reported to measure	High	High
Criterion	The degree to which comparison of the criteria in question agrees with a related outcome assessed at the same time or in the future	High	High

[a] In sepsis criteria for clinical care, a high priority should be placed on timeliness and ability to influence real-time clinical decision-making. Sensitivity is generally emphasized over specificity to avoid missing patients with potential sepsis. In contrast, the priority for surveillance is objectivity, reproducibility, and suitability for widespread implementation. For surveillance, specificity is also generally prioritized over sensitivity.

[b] Measurement burden for clinical care refers to the cost and safety of obtaining diagnostic tests for patients and the complexity of data interpretation for health care providers. For surveillance, measurement burden reflects the time and resources required to abstract data and apply case definitions on a population level.

[c] Criteria for clinical care and surveillance should have at least a moderate overlap but need not match perfectly. The prognostic value of sepsis criteria for mortality is a major component of criterion validity that is important for both clinical care and surveillance.

DEFINING SEPSIS FOR SURVEILLANCE

There are multiple purposes for which sepsis must be defined, including clinical care, basic science, clinical research, quality improvement, benchmarking, advocacy, public discourse, surveillance, and epidemiology.[40,41] Given the complexity of defining sepsis, it is unlikely that a single set of criteria will be able to satisfy all parameters desired by interested stakeholders. Stakeholders from each arena have different priorities and values that inform their perception of which evaluation domains should be prioritized and where along the spectrum of severity the line should be drawn to define sepsis (Table 1). For example, clinicians require a sepsis definition optimized for sensitivity, rapid diagnosis, and ease of real-time application at the bedside because their goals are early identification, avoiding missed cases, and timely treatment. In contrast, the purpose of public health surveillance is to reliably track sepsis incidence and outcomes across settings and over time to frame public health policy and research, prioritize resource allocation, and identify opportunities to improve prevention and treatment. Although surveillance efforts must be clinically credible, they generally place less emphasis on timeliness and early identification and more emphasis on specificity, objectivity, and reproducibility. This often means excluding ambiguous or less-severe cases. Measurement burden for surveillance should also

be low to facilitate widespread implementation. Given the wide-ranging connotations of the term "sepsis," we will use "sepsis event" to refer to a case identified explicitly for surveillance.

ASE SURVEILLANCE

The ASE concept was developed by a multicenter team of investigators to estimate the national burden of adult sepsis by using EHR data.[17,42,43] The investigators adapted Sepsis-3 criteria to facilitate wide-scale, retrospective surveillance, focusing on clinical indicators of presumed serious infection and organ dysfunction that are objective, routinely measured or used to treat sepsis, easily ascertainable from diverse EHRs, and suitable for consistent and uniform application across different hospitals.[42,43]

The ASE case definition defines presumed serious infection as ≥1 blood culture draw and concurrent administration of ≥4 consecutive days of antimicrobial agents (fewer if patients die or are transferred to hospice or another acute care hospital) and identifies organ dysfunction through a modified version of the SOFA score that dichotomizes organ dysfunction as present or absent for each organ system.[17,42] A minimum of 4 antimicrobial days was chosen as a threshold for presumed infection to minimize false-positives from patients who had empirical treatment stopped when an initially suspected infection was not confirmed. ASE thresholds for organ-dysfunction presence generally correspond to a SOFA score increase of ≥2 points and simplify or eliminate SOFA components that may be inconsistently measured, documented, and stored in EHRs, such as the Glasgow Coma Scale,[44] vital signs,[45–47] vasopressor doses, urine output,[48] arterial blood gases,[49,50] and fraction of inspired oxygen (FIO_2) at the time blood gases are drawn. These changes make the ASE feasible to reliably measure by using retrospective data and applicable across hospitals with different EHRs that use a common data specification.[43]

Validation by using medical record reviews suggested 70% sensitivity and a 70% positive predictive value for the ASE in identifying patients meeting Sepsis-3 criteria.[17] The positive predictive value reached 88% when sepsis was defined as organ dysfunction concurrent with clinically suspected (rather than confirmed) infection. These performance characteristics also compared favorably to administrative data; explicit diagnosis codes for severe sepsis or septic shock were less sensitive (33%) than the ASE but had a similar positive predictive value (76%), whereas implicit codes for infection and organ dysfunction had comparable sensitivity (66%) but a lower positive predictive value (31%). Chart reviews also suggested that the Sepsis-3 patients missed by ASE had mild organ dysfunction (such as mild hypoxemia not requiring mechanical ventilation) and favorable prognoses.[17] Furthermore, analyses of large data sets revealed good concordance between patients flagged by ASE and Sepsis-3 criteria and revealed that the ASE organ-dysfunction criteria had equivalent or better prognostic accuracy for mortality than the full SOFA score.[51]

Applying the ASE definition to EHR data from a nationally representative cohort of 409 academic, community, and federal hospitals from 7 independent data sets indicated that sepsis was present in 6% of US adult hospitalizations in 2014 and in one-third of all hospitalizations culminating in death.[17] Sepsis incidence and short-term all-cause mortality (in-hospital death or discharge to hospice) did not significantly change between 2009 and 2014, whereas diagnosis codes from the same hospitals revealed steady increases in sepsis incidence and decreases in mortality. In addition to establishing these national estimates, the CDC also released a tool kit to help hospitals implement the ASE to improve monitoring of local sepsis epidemiology and evaluation of the impact of quality improvement efforts.[18]

ADAPTING SEPSIS EVENT SURVEILLANCE TO PEDIATRICS AND ESTIMATING NATIONAL PEDIATRIC SEPSIS BURDEN

The pediatric working group convened by the CDC agreed that although the general ASE framework could be used for pediatric sepsis surveillance, adapting the adult approach to infants and children presented a number of challenges. In proposing a preliminary PSE definition, we outline these challenges as well as our proposed plan to address them (Table 2). We also discuss plans for exploring alternative criteria to optimize case ascertainment, validating the proposed definition with chart review, and applying it to hospitals across the United States to estimate the national burden of pediatric sepsis. We emphasize, however, that the criteria described are preliminary and are subject to modification on the basis of continued refinement during testing in pediatric data sets. It is also important to note that the ASE surveillance scheme was developed for use in the United States and may not be generalizable to other locations with more-limited resources. This known limitation will also apply to proposed pediatric efforts.[52]

The Sepsis-3 Conceptual Model in Pediatrics

In anticipation that forthcoming updated clinical definitions for sepsis in children will be based on Sepsis-3 criteria, we propose using the

TABLE 2 Proposed PSE Criteria With Planned Analyses to Optimize Case Ascertainment

	Adaptation of Sepsis-3 to Pediatric Population[33]	Proposed PSE Case Definition	Proposed Sensitivity Analyses to Optimize Case Ascertainment
Age range	Birth to age 21 y	Inclusion of ages 30 d to 21 y, excluding infants continuously hospitalized since birth	Include infants <30 d old with corrected gestational age >37 wk Include infants continuously hospitalized since birth if age ≥30 d and corrected gestational age >37 wk
Infection	Patient with confirmed or suspected infection	Blood culture obtained (regardless of result) New antimicrobial started within ±2 d of blood culture and continued for ≥4 consecutive d (or until ≤1 d before death, discharge to hospice or acute care hospital, or transition to comfort care); antimicrobials include any nonprophylactic antibiotic, antifungal, or antiviral; ≥1 antimicrobial must be parenteral[a]	Allow for no blood culture to be obtained if patient was transferred from another acute care hospital and antimicrobial criteria were met Allow for ≥3 consecutive antimicrobial d Allow for culture of any body fluid Incorporate antibiotics prescribed at hospital discharge
Organ dysfunction	Increase in SOFA score by ≥2 points from preinfection baseline with age-dependent adaptations	≥1of the below organ-dysfunction criteria met within ±2 d of blood culture	
System, Points and Criterion			
Cardiovascular	Inclusion of age-based MAP thresholds for pSOFA 1. age-based MAP thresholds 2. dopamine ≤5 μg/kg per min or any dobutamine 3. dopamine >5 μg/kg per min or epinephrine ≤0.1 μg/kg per min or norepinephrine ≤0.1 μg/kg per min 4. dopamine >15 μg/kg per min or epinephrine >0.1 μg/kg per min or norepinephrine >0.1 μg/kg per min	Vasopressor initiation (dopamine, epinephrine, norepinephrine, phenylephrine, or vasopressin)[b]	Include receipt of ≥60 mL/kg fluid bolus within ±1 d of initiation of antimicrobial
Pulmonary	Addition of $Sp_{O_2}/F_{I_{O_2}}$ as an alternative surrogate measure of lung injury 1. $Pa_{O_2}/F_{I_{O_2}}$ of 300–399 or $Sp_{O_2}/F_{I_{O_2}}$ of 256–291 2. $Pa_{O_2}/F_{I_{O_2}}$ of 200–299 or $Sp_{O_2}/F_{I_{O_2}}$ of 221–264 3. $Pa_{O_2}/F_{I_{O_2}}$ of 100–199 or $Sp_{O_2}/F_{I_{O_2}}$ of 148–220 with respiratory support 4. $Pa_{O_2}/F_{I_{O_2}}$ of <100 or $Sp_{O_2}/F_{I_{O_2}}$ of <148 with respiratory support	Mechanical ventilation initiation (>1 calendar d required between ventilation episodes)[c]	Include initiation of new noninvasive positive pressure ventilation Include new high-flow nasal cannula
Renal	Incorporation of age-based creatinine ranges, exclusion of urine output measurements 1. aged-based creatinine ranges[e] 2. aged-based creatinine ranges 3. aged-based creatinine ranges 4. aged-based creatinine ranges	2 times increase of creatinine levels or ≥50% decrease of the eGFR relative to baseline[d] (excluding patients with end-stage renal disease)	Assume normal age-based creatinine values as baseline values Analyze a subset of patients with available previous creatinine values
Hepatic	No changes from adult SOFA 1. bilirubin level of 1.2–1.9 mg/dL 2. bilirubin level of 2.0–5.9 mg/dL 3. bilirubin level of 6.0–11.9 mg/dL 4. bilirubin level >12 mg/dL	Bilirubin level ≥2.0 mg/dL and 2 times increase from baseline[d]	Exclude hepatic criteria

TABLE 2 Continued

	Adaptation of Sepsis-3 to Pediatric Population[33]	Proposed PSE Case Definition	Proposed Sensitivity Analyses to Optimize Case Ascertainment
Coagulation	No changes from adult SOFA 1. platelet count of 100–149 $\times$ 10^9 cells per L 2. platelet count of 50–99 $\times$ 10^9 cells per L 3. platelet count of 20–49 $\times$ 10^9 cells per L 4. platelet count <20 $\times$ 10^9 cells per L	Platelet count <100 $\times$ 10^9 cells per L and ≥50% decrease relative to baseline[d] (baseline count must be >100 $\times$ 10^9 cells per L to meet this criterion)	Exclude coagulation criteria if patient received chemotherapy during hospitalization or has an identified oncologic diagnosis
Neurologic	Incorporation of pediatric Glasgow Coma Scale score 1. score of 13–14 2. score of 10–12 3. score of 6–9 4. score <6	Not applied because of variability in measurement, subjectivity, and difficulty assessing in patients who are sedated	None planned
Perfusion	Not included in pSOFA score	Lactate level ≥2.0 mmol/L	Exclude lactate from score calculation Adjust lactate threshold to ≥3.0 or 4.0 mmol/L

eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; —, not applicable.

[a] A new antimicrobial refers to one not given in the previous 2 calendar d.

[b] A particular vasopressor must not have been administered in the previous calendar day to count as a new vasopressor. Vasopressors given by bolus injection or in the operating room (or other procedural areas where anesthesia is administered) are excluded.

[c] More than 1 calendar d between mechanical ventilation events is required to avoid false-positives due to extubation failure, routine use of nighttime ventilator support, or capture of patients already mechanically ventilated who have blood cultures drawn and are started on antibiotics but otherwise have no new organ dysfunction.

[d] In the case of infection present on admission (ie, when the blood culture day or first antimicrobial administration occurs on hospital d 1 or 2), baseline laboratory values are defined as the best values during the hospitalization. For hospital-onset infection (blood culture day occurring on hospital d ≥3), baseline laboratory values are defined as the best values during the ±2-d period surrounding the day of the blood culture draw.

[e] pSOFA score points (No.) are awarded by age for different creatinine values: for 1–11 mo: (1) 0.3–0.4 mg/dL, (2) 0.5–0.7 mg/dL, (3) 0.8–1.1 mg/dL, and (4) ≥1.1 mg/dL; for 12–23 mo: (1) 0.4–0.5 mg/dL, (2) 0.6–1.0 mg/dL, (3) 1.1–1.4 mg/dL, and (4) ≥1.5; for 24–59 mo: (1) 0.6–0.8 mg/dL, (2) 0.9–1.5 mg/dL, (3) 1.6–2.2 mg/dL, and (4) ≥2.3 mg/dL; for 60–143 mo: (1) 0.7–1.0 mg/dL, (2) 1.1–1.7 mg/dL, (3) 1.8–2.5 mg/dL, and (4) ≥2.6 mg/dL; for 144–216 mo: (1) 1.0–1.6 mg/dL, (2) 1.7–2.8 mg/dL, (3) 2.9–4.1 mg/dL, and (4) ≥4.2 mg/dL; and for >216 mo: (1) 1.2–1.9 mg/dL, (2) 2.0–3.4 mg/dL, (3) 3.5–4.9 mg/dL, and (4) ≥5 mg/dL.

framework of infection with organ dysfunction for PSE surveillance and capturing sepsis events by using EHR data in a manner similar to the ASE approach. This consistency will help minimize confusion that could otherwise arise from use of different surveillance frameworks for sepsis events in children versus adults. Focusing on severe infections with concurrent organ dysfunction also means that tracking PSE incidence can be helpful for understanding the impact of upstream sepsis initiatives that aim to prevent progression to organ dysfunction, ICU admission, or death. In the absence of an externally validated Sepsis-3-aligned pediatric case definition at this point in time, we plan to begin with a definition published by Matics and Sanchez-Pinto[33] as a reference standard for assessments of the performance of the PSE definition by using chart review. An alternative analysis, using the IPSCC as a reference standard, may also be pursued,[22] and we will also consider and incorporate other updated pediatric sepsis definitions and criteria as they become available. As described below, we plan to conduct sensitivity analyses to further refine the PSE definition to ensure adequate case ascertainment, compared with chart review (Table 2).

Establishing an Appropriate Age Range for PSE Surveillance

The American Academy of Pediatrics considers the pediatric population to range from birth to 21 years of age but acknowledges that the age cutoff between pediatric and adult patients is arbitrary.[53] To explore the transition between adolescence and adulthood, we plan to assess the performance of the PSE in comparison with the ASE for patients aged 15 to 30 years. In addition, sepsis surveillance for patients at the lowest end of the age range requires special considerations because clinical practices and conceptual models of sepsis are different in

neonatology compared with pediatrics.[54] Specifically, 2 issues unique to newborns make it difficult to adapt the ASE criteria to this population. First, for infants <30 days old, a blood culture order does not signify the same level of concern for infection as for older pediatric patients because blood cultures are routinely obtained from well-appearing term and preterm newborns on the basis of infection risk factors. Second, organ dysfunction due to developmental immaturity is common among preterm newborns and cannot be readily distinguished from organ dysfunction due to infection. As a result, preterm infants often receive prolonged antimicrobial treatment in the absence of clear clinical or microbiologic evidence of infection. We therefore propose focusing PSE surveillance on children aged 30 days to 21 years, additionally excluding all infants continuously hospitalized since birth.

Appropriate EHR Capture of Presumed Serious Infection in Children

In the ASE surveillance scheme, a blood culture order, along with administration of ≥4 days of antimicrobial agents, identifies presumed serious infection.[43] We reached an agreement that blood culture ordering as a marker of concern for serious infection applied similarly to children ≥30 days old as to adults because this is also standard practice for suspected pediatric sepsis. Likewise, we agreed that ≥4 days of antimicrobial agents represented a reasonable threshold to start with for distinguishing empirical treatment of suspected infection from definitive treatment in children, with fewer days allowed in the case of death or transfer to hospice or another acute care facility. However, we identified alternative scenarios that should be explored to optimize case ascertainment. For example, we plan to conduct sensitivity analyses to allow a culture of any body fluid rather than just blood and to examine a range of requirements for the number of antimicrobial days and the timing of the culture (Table 2). These scenarios are important to explore because clinicians may be more reluctant to draw repeat or multiple blood cultures in children compared with adults because of their more-limited blood volume. This difference in practice would primarily impact detection of PSE cases in scenarios in which a blood culture is obtained in a community setting and then the child is transferred to a tertiary care center for continued management or in scenarios in which repeat blood cultures may not be ordered when new or worsening organ dysfunction is identified. Therefore, we propose exploring the impact of removing the blood culture requirement for patients transferred from outside health care facilities who otherwise meet all other PSE criteria at the receiving institution. Acknowledging that some sepsis syndromes in children may resolve quickly with appropriate treatment, we also propose testing the definition with fewer qualifying antimicrobial days (ie, ≥3 days). We also plan to explore the feasibility of capturing oral antimicrobial agents prescribed on discharge, reflecting the scenario in which children hospitalized with sepsis rapidly improve with treatment and are discharged from the hospital to complete a course of oral therapy after <4 days in the hospital.

Appropriate EHR Capture of Organ Dysfunction in Children

The IPSCC adaptation of Sepsis-2 to pediatric populations appropriately recognized the need for age-dependent ranges for SIRS criteria. Likewise, applying the Sepsis-3 framework to pediatrics would require incorporating age-specific organ-dysfunction thresholds. There are a number of candidate organ-dysfunction scoring systems that could be incorporated into pediatric Sepsis-3 criteria, including an age-adapted variant of SOFA (pediatric Sequential Organ Failure Assessment [pSOFA]),[33] the Pediatric Logistic Organ Dysfunction (PELOD-2) score,[55] or the Pediatric Multiple Organ Dysfunction Score (P-MODS).[56] All of these scoring systems were developed to predict in-hospital mortality in critically ill children and account for age-related variation and were internally validated. The closest system to the adult SOFA score is the pSOFA score, which was modified from the adult SOFA score by using cutoffs from the PELOD-2 scoring system and tested by using data from >6000 critically ill children aged ≤21 years old. Pediatric adaptations within pSOFA include validated age-dependent cutoffs for the cardiovascular and renal systems from PELOD-2, expanded respiratory criteria that include noninvasive surrogates of lung injury (ie, use of pulse oxygen saturation [Sp_{O_2}]/$F_{I_{O_2}}$ in addition to $Pa_{O_2}/F_{I_{O_2}}$),[57] and the pediatric version of the Glasgow Coma Scale.

Whereas Sepsis-3 uses a SOFA score of ≥2 points over baseline to identify organ dysfunction, the ASE simplifies this scoring system by dichotomizing new organ dysfunction as present versus absent using thresholds that roughly correspond to ≥2 SOFA points. The ASE developers found this simplified EHR-based implementation increased feasibility without affecting prognostic accuracy.[51] Following this paradigm, we propose beginning by modifying the pSOFA score to dichotomize new organ dysfunction and test different scenarios to determine the optimal threshold based on associations with outcomes, correlation with medical record reviews, and feasibility of extraction in diverse EHRs. For example, we will explore definitions with and without noninvasive positive pressure ventilation and high-flow oxygen as surrogates for respiratory failure and

definitions that incorporate fluid-resuscitation volume as a marker of persistent hypotension. Adding these respiratory support modalities and fluid parameters may increase the clinical relevance of a surveillance definition but may come at the cost of added complexity or diminished generalizability across EHRs.[58] In addition, given that pSOFA has not been independently validated, we will explore the impact of a number of changes that would allow the PSE criteria to more closely mirror the PELOD-2 or P-MODS scoring systems rather than pSOFA. For example, hepatic dysfunction did not reach the threshold for inclusion in the PELOD-2 score,[55] did not predict death in the P-MODS,[56] and may rarely be the sole manifestation of sepsis in pediatrics.[16] Therefore, it may be less useful as a surveillance criterion. Hyperlactatemia, however, is included in both the PELOD-2 score and the P-MODS. As such, we will explore the impact of eliminating hepatic dysfunction or adding lactate as case-ascertainment criteria.

Accounting for Heterogeneity in Pediatric Populations and Locations of Care

Any approach to pediatric sepsis surveillance in the United States should account for the heterogeneity of pediatric populations with respect to age, race and/or ethnicity, comorbidities, and level and locations of care. When comparing PSE case ascertainment to chart review, we will identify each patient's age, sex, race and/or ethnicity, comorbidities, and other relevant clinical characteristics (location of care, sepsis present on admission versus hospital onset, ICU admission, hospital length of stay, and discharge disposition). This will allow us to assess the ability of the PSE approach to appropriately capture pediatric patients with different characteristics. In particular, it is vital to recognize the rising prevalence of children with medical complexity,[59–61] defined as infants, children and young adults with serious chronic conditions, substantial functional limitations, and/or increased health and other service needs.[60] To ensure that the PSE definition appropriately identifies sepsis both in children who were previously healthy and those with medical complexity, we plan to use the pediatric complex chronic conditions classification system[62] to identify patients with baseline technology dependence or organ dysfunction. We will then conduct targeted chart reviews of patients with $\geq$1 and $\geq$2 complex chronic conditions to ensure adequate capture of new or worsening organ dysfunction and sepsis in these patients with medical complexity.

In addition, a national approach to pediatric sepsis surveillance should also account for the increasing regionalization of health care (ie, the growing concentration of care at larger referral centers), which affects infants and children to an even greater extent than adults.[63–65] As such, the development and validation process for the PSE and the proposed subsequent study to estimate the national burden of pediatric sepsis must incorporate data from children's hospitals, larger general academic medical centers, and community hospitals, where both previously well children and children with medical complexity may initially present before transfer or stay to receive definitive care. We plan to conduct targeted chart reviews to ensure adequate capture of sepsis cases in children transferred to and from these facilities.

Road Map for Future Work

The scope of future directions proposed by our working group is ambitious and broad. It includes (1) refining and validating a PSE case definition that can accommodate diverse EHRs; (2) conducting a multicenter, national study to estimate the burden of pediatric sepsis in the United States by using EHR data; and (3) developing a tool kit that can be used by hospitals to implement PSE surveillance. This work will require time, funding, and effort. Once a tool kit is developed, the incorporation of PSE surveillance into routine hospital operations will then require buy-in from local clinicians and administrators as well as substantial effort from informatics teams. However, the experience of using shared code and a common data specification to apply the ASE to 409 hospitals from 7 separate data sets derived from different EHRs suggests that it is feasible and can yield valuable information on sepsis incidence and outcomes.[66]

CONCLUSIONS

Pediatric sepsis is a major public health concern, and robust surveillance tools are needed to characterize its burden, outcomes, and trends. The increasing uptake of EHRs throughout the United States allows for the possibility of surveillance that uses objective clinical data rather than administrative claims or a manual chart review. A pediatric surveillance definition based on EHR data could use the framework of the ASE definition but requires adaptation to address specific differences and challenges in the pediatric population. A nationally representative study of pediatric sepsis incidence, outcomes, and trends in which EHR data are used would shed light on the impact of recent initiatives to improve sepsis recognition and management and would help identify additional priorities for intervention. A PSE tool kit could also support site-specific surveillance that would complement ongoing pediatric sepsis quality improvement efforts. Ultimately, our vision would be for local and national PSE surveillance data to be used

by clinicians, quality officers, policy-makers, and public health officials to further drive innovation and improvements in the prevention, detection, and management of pediatric sepsis.

APPENDIX

The professional society and government affiliations for Pediatric Sepsis Surveillance Working Group participants are as follows:

American Academy of Pediatrics Committee on Fetus and Newborn: Karen Puopolo, MD, PhD;

American Academy of Pediatrics Committee on Infectious Diseases: Jeffrey Gerber, MD, PhD;

American Academy of Pediatrics Section on Critical Care: Michael S.D. Agus, MD;

American Academy of Pediatrics Section on Emergency Medicine: Charles Macias, MD, MPH;

Academy of Pediatrics Section on Hospital Medicine: Patrick W. Brady, MD, MSc;

American Academy of Pediatrics Section on Neonatal-Perinatal Medicine: Karen Puopolo, MD, PhD;

American College of Emergency Physicians Section of Pediatric Emergency Medicine: Carmen D. Sulton, MD;

American Thoracic Society Scientific Assembly of Pediatrics: Benny L. Joyner Jr, MD, MPH;

California Perinatal Quality Care Collaborative: Grace Lee, MD, MPH;

Centers for Disease Control and Prevention: Francisca Abanyie, MD, MPH, Raymund Dantes, MD, Lauren Epstein, MD, MSc, Anthony Fiore, MD, MPH, and Runa Gokhale, MD, MPH;

Children's Hospital Association: Fran Balamuth, MD, PhD and Richard Brilli, MD, FAAP, MCCM;

Society for Critical Care Medicine: Joseph A. Carcillo, MD and Scott Weiss, MD, MSCE;

Surviving Sepsis Campaign: Niranjan Kissoon, MD, FRCP(C), FAAP, MCCM; and

Vermont Oxford Network: Karen Puopolo, MD, PhD.

ABBREVIATIONS

ASE: adult sepsis event
CDC: Centers for Disease Control and Prevention
EHR: electronic health record
FIO_2: fraction of inspired oxygen
IPSCC: International Pediatric Sepsis Consensus Criteria
PELOD-2: Pediatric Logistic Organ Dysfunction
P-MODS: Pediatric Multiple Organ Dysfunction Score
PSE: pediatric sepsis event
pSOFA: pediatric Sequential Organ Failure Assessment
Sepsis-3: Third International Consensus Definitions for Sepsis and Septic Shock
SIRS: systemic inflammatory response syndrome
SOFA: Sequential Organ Failure Assessment
SpO_2: pulse oxygen saturation

Drs Hsu and Rhee created the initial proposed approach to pediatric sepsis surveillance presented at the November 1, 2018, working group meeting, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Abanyie, Dantes, Epstein, Fiore, and Gokhale coordinated and facilitated the Centers for Disease Control and Prevention Pediatric Sepsis Surveillance Working Group and reviewed and revised the manuscript; Drs Balamuth and Weiss presented local data on pediatric sepsis surveillance at the November 1, 2018, working group meeting and reviewed and revised the manuscript; Drs Klompas and Puopolo reviewed and revised the manuscript; Drs Agus, Brady, Brilli, Carcillo, Gerber, Joyner Jr, Kissoon, Lee, Macias, and Sulton critically reviewed the manuscript for important intellectual content; and all authors attended the Centers for Disease Control and Prevention Pediatric Sepsis Surveillance Working Group meeting on November 1, 2018, made substantial contributions to the conception and design of the proposed national approach to pediatric sepsis surveillance through their participation in working group calls and meetings, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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Address correspondence to Heather E. Hsu, MD, MPH, Department of Pediatrics, School of Medicine, Boston University and Boston Medical Center, 801 Albany Street, Boston, MA 02119. E-mail: heather.hsu@bmc.org

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