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The Aetiology and Global Impact of Paediatric Sepsis

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Abstract

Purpose of Review This review provides an overview of paediatric sepsis, focusing on sepsis definitions in children, global aetiology of sepsis, application of biomarkers in clinical practice, and challenges of global application of current evidence.

Recent Findings Clinical definitions for paediatric sepsis vary, and a validated measurement is lacking. Aetiology varies by age and geography, with differences in healthcare, vaccination, and pathogens. Biomarkers show promise but have limited translation to clinical practice, especially in children.

Summary Paediatric sepsis has a significant global impact, with high mortality and long-term morbidity, particularly in low- and middle-income countries (LMICs). Adapting definitions and validating biomarkers are crucial, especially in LMICs. Global efforts are needed to improve identification and management of paediatric sepsis, along with the evolving challenges of antimicrobial resistance (AMR). A global approach is essential to address complexities and enhance outcomes for affected children worldwide.

Keywords Paediatric sepsis · Sepsis definition · Sepsis biomarkers · Sepsis aetiology. Sepsis impact · Global sepsis

Introduction

Sepsis remains a leading cause of morbidity and mortality in children across the globe, with data from the Global Burden of Disease study estimating a total number of 25.2 million cases of paediatric and neonatal sepsis in 2017 [1••]. Clinical definitions remain varied, and a validated measurement identifying the transition point from a child with severe infection to sepsis has yet to be identified [2•]. In addition, significant differences in aetiology, organism pattern, treatment options, and resource allocation make it difficult to fully appreciate the burden of paediatric sepsis across the world, especially in low- and middle-income countries (LMIC). Early diagnosis and treatment are key to improving outcomes in children with sepsis [3]. However, due to the lack of a unified consensus on a gold standard definition for sepsis diagnosis and the continued reliance on organism identification through culture, early diagnosis remains a challenge. In recent years, research efforts have therefore focused on exploring the role of biomarkers in sepsis diagnosis, classification of organ dysfunction, and prognosis prediction.

Defining Paediatric Sepsis

The first consensus definition of sepsis was developed from the American College of Chest Physicians and Society of Critical Care Medicine in 1991, based on the perception that sepsis was caused by development of a systemic inflammatory response syndrome (SIRS) in response to an infection [4].

SIRS can be defined in the adult population as the presence of two or more of the following:

- Temperature > 38 °C or < 36 °C
- Heart rate > 90/min
- Respiratory rate > 20/min or $PaCO_2$ > 32 mmHg
- Leukocyte count > 12,000/mm^3 or < 4000/mm^3 or > 10% immature bands

The development of organ dysfunction in a patient with sepsis was defined as ‘severe sepsis’. If these patients

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developed hypotension resistant to adequate fluid resuscitation, this was termed 'septic shock' [4, 5].

In paediatrics, this definition was amended to include at least one of temperature or leukocyte count as a mandatory requirement to acknowledge that tachycardia and tachypnoea are more common in unwell children [6, 7], along with the development of age-appropriate parameters for heart rate and respiratory rate. This allowed acknowledgement that bradycardia can be a sign of SIRS in the newborn period but, in older children, would represent significant decompensation. Paediatric age-specific definitions for sepsis and severe sepsis were revised in 2005 at the International Paediatric Sepsis Consensus Conference (IPSCC) [7]. Severe sepsis was defined as sepsis (suspected or proven infection with SIRS) plus one of the cardiovascular dysfunctions or acute respiratory distress syndrome, or two or more organ dysfunctions (respiratory, renal, neurological, haematological, or hepatic). A key limitation of the septic shock definition was identified: as children are able to maintain blood pressure until significant decompensation occurs, hypotension is a late marker of decompensated shock in a paediatric population. Therefore, septic shock was re-defined as severe sepsis with cardiovascular dysfunction [7, 8].

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (known as the Sepsis-3 definitions) were published, defining sepsis as 'a life-threatening organ dysfunction caused by a dysregulated host response to infection'. Clinically, organ dysfunction was quantified as an increase in the Sequential Organ Failure Assessment (SOFA) score by 2 points or more, associated with an increase in in-hospital mortality by over 10% in adult patients [5]. The Sepsis-3 definition removed 'severe sepsis' from the nomenclature and gave acknowledgement to the limitations of criteria based on the systemic inflammatory response syndrome (SIRS) definitions, due to their poor discriminant and convergent validity in the adult population [5, 9, 10]. Septic shock was re-defined as sepsis with 'profound circulatory, cellular, and metabolic abnormalities, associated with a greater risk of mortality than with sepsis alone', with a partner clinical definition of non-hypovolaemic patients with a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg and serum lactate > 2 mmol/L [5].

However, the Sepsis-3 definitions again focused on the adult population and did not consider paediatric patients in their development. Matics et al. developed the paediatric Sequential Organ Failure Assessment (pSOFA) which allowed attempts of the Sepsis-3 guidelines to a paediatric cohort [11, 12], and the surviving sepsis guidelines were developed in response to the need for evidence-based recommendations for the care of children with sepsis-associated organ dysfunction [13].

Recognising a limitation that many criteria for paediatric organ dysfunction were derived from expert opinion, the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) collaborative considered the performance characteristics of the existing clinical support tools built to identify organ dysfunction in critically unwell children and has published a set of 43 criteria for single and multiple organ dysfunctions in the critically unwell child (Table 1) [14]. An evaluation of these criteria in two hospitals in the USA has shown good-to-excellent discrimination for in-hospital mortality following all-cause admission to paediatric intensive care (with the exclusion of patients with congenital heart disease) [15]. However, these criteria have not been validated across the world, and there is some concern regarding their applicability in LMIC areas [2•].

There remains an ongoing lack of globally valid and applicable definitions for paediatric sepsis. The Sepsis-3 definitions were derived from interrogation of datasets from HIC countries, with a subsequent lack of consideration for their implication in LMICs and the challenges faced in these settings [2•]. As summarised by the Paediatric Sepsis Definition Taskforce, there is both a research and clinical need for unambiguous definitions of sepsis which can adapt to the different presentations of children around the world [2•].

Risk Stratification of Paediatric and Neonatal Sepsis

The development of screening algorithms to recognise deterioration has also been identified as a research opportunity by the Surviving Sepsis Campaign [13]. Current risk stratification tools lack substantial data validity. For example, the UK National Institute for Health and Care Excellence (NICE) 'Fever in the Under 5s' guideline is designed to be used by non-paediatricians (such as in general practice or the emergency department) to identify children at risk of serious infective illness [16]. It categorises symptoms and clinical features into red, amber, and green criteria. A child with green criteria is felt to be safe to be managed at home with safety netting advice, one with amber should be assessed in a face to face setting, and if red criteria are present, the child should be referred for assessment by a specialist paediatrician. Recent analysis of admission data for children with febrile illnesses highlighted that, when applied alone, the red criteria demonstrated sensitivity of 58.8% and specificity of 68.5% [17]. This indicated that it will fail to identify over 40% of children who went on to require an unplanned hospital admission [17].

Early-onset neonatal sepsis (EONS) is managed as a separate clinical condition due to specific physiology within the intrapartum and postpartum periods and presence of unique risk factors (such as group B *Streptococcus* colonisation of the vagina and prolonged rupture of membranes) [18] and is defined as sepsis occurring within the first 72 h of

Table 1 Comparison of components of pSOFA [12] and PODIUM [14] organ dysfunction scores, categorised by organ system

pSOFA categories	PODIUM categories
Respiratory -PaO 2 :FiO 2 or SpO 2 :FiO 2	Respiratory - PaO_2/FiO_2 - SpO_2/FiO_2 - Ventilatory failure - Invasive ventilation - Oxygenation index - Oxygenation saturation index, extracorporeal life support for respiratory failure
Coagulation -Platelet count	Coagulation (in absence of liver dysfunction and requires at least 1 additional coagulation dysfunction criteria) - Platelet count - INR - Fibrinogen - D-dimer
Hepatic -Total bilirubin	Hepatic - AST - ALT - GGT - Total bilirubin - Direct bilirubin - Liver-based coagulopathy with hepatic encephalopathy
Cardiovascular -Mean arterial pressure or vasoactive infusion	Cardiovascular - Venoarterial extracorporeal life support; temporary/durable left/right ventricular assist device - Cardiac arrest - Heart rate - Systolic blood pressure - Vasoactive-inotropic score - Serum lactate - Serum troponin - Central venous oxygen saturation - Left ventricle ejection fraction estimate by echocardiogram
Neurologic -Glasgow Coma Score	Neurology - Glasgow Coma Score - Glasgow Coma Score: motor response - Cornell Assessment of Paediatric Delirium - Electrographic seizure activity
Renal - creatinine	Renal - Urine output - Serum creatinine increase - eGFR - Renal replacement therapy - Fluid overload following ICU admission
	Gastrointestinal - Bowel ischaemia
	Haematology - Platelets - Leukocytes - Haemoglobin
	Endocrine - Blood glucose - Serum thyroxine - Serum cortisol following Synacthen test
	Immune - Absolute neutrophil count - Absolute lymphocyte count - CD4 + T-lymphocyte count - CD4 + T-lymphocyte percentage of total lymphocytes - Monocyte HLA-DR expression - Ex vivo LPS-induced TNF-alpha production capacity

life. Kaiser Permanente developed a risk calculator in the USA validated for infants from 34 weeks corrected gestational age. It applies a regression model to these risk factors, alongside integration of prophylactic antimicrobial therapy and the clinical condition of the newborn [19]. A prospective study comparing Kaiser Permanente to national guidelines across neonatal units in London, UK, found no significant difference in the incidence of early-onset sepsis identified > 24 h after birth, with 50% fewer infants requiring antibiotics in the first 24 h of life [20]. However, the data for this model was taken from Northern California and may not be directly applicable to LMICs.

Aetiology of Paediatric Sepsis

Aetiology

The aetiology of sepsis in children varies significantly by age ('neonatal sepsis' vs. 'paediatric sepsis') and geography. Important geographical factors include differences in healthcare infrastructure, sanitation, vaccination, and pathogen prevalence in different climates. Whilst most clinicians in HIC settings predominantly associate bacterial infection with sepsis, viruses, fungi, and parasites can all cause dysregulated host responses leading to significant organ dysfunction. Understanding the variation in aetiology is important in addressing challenges and barriers for sepsis, as differing pathogen syndromes require different resources for prevention, diagnosis, and management.

Neonatal Sepsis

Neonatal sepsis is usually defined as sepsis within the first 28 days of life. Generally, in the HIC setting, the implicated pathogens are those vertically transmitted from the vaginal tract and/or hospital-acquired infections. Common isolated bacterial pathogens in this setting are *Streptococcus agalactiae* (group B streptococcus) or less commonly *Escherichia coli* [21].

Viruses that have been implicated in this setting are herpes simplex virus (HSV), usually due to vertical transmission, and enterovirus and parechovirus [21, 22].

In LMIC settings with more limited access to prenatal and peri-natal healthcare and frequent out-of-hospital births, community-acquired infection is more often implicated, as well as vertical transmission. The most commonly associated bacterial pathogens are *Klebsiella* species, *Staphylococcus aureus,* Enterobacterales, and non-typhoidal *Salmonella* based on data from studies conducted at hospital sites [23, 24]. However, accurate and comprehensive epidemiological data on causative bacteria is likely to be lacking, due to the extent of cases that occur outside of a healthcare setting [25••]. Similarly, robust epidemiological data on viruses implicated in neonatal sepsis in LMICs is also lacking. However, there is an acknowledgement of the contribution of diarrhoeal disease such as *Rotavirus* [26].

Paediatric Sepsis

The aetiology of paediatric sepsis varies globally. A highly cited comprehensive international epidemiological study by Weiss et al. identified respiratory tract and bloodstream infections as the most prevalent sources of sepsis in children [27]. *Staphylococcus aureus*, *Pseudomonas*, and *Klebsiella* were most frequently isolated from cultures, and fungi such as *Candida* species were also identified. Nearly a third of patients had evidence of viral aetiology, with respiratory syncytial virus (RSV), rhinovirus, and adenovirus frequently isolated. In particular, RSV is a leading cause of viral sepsis with especially poor outcomes for children with a history of prematurity and cardiorespiratory co-morbidities in LMICs [22].

The findings of Weiss et al. may not fully reflect the overall picture of sepsis aetiology in LMICs and regions with limited healthcare infrastructure. The data were predominantly captured from academic PICUs in HIC settings, potentially leading to an over-representation of healthcare-associated pathogens or biases related to healthcare access and diagnostic capabilities and under-representation of infection in community-based settings.

The Global Burden of Disease study identified the most common aetiology of sepsis in children as lower respiratory infections and diarrheal diseases [1••]. Whilst previously *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* were the leading causes of severe infection in children, this has vastly reduced in HIC settings, due to the widespread availability of conjugate vaccines; however, vaccine-preventable illness from these pathogens remains a problem worldwide [28, 29].

In Asia, drug-resistant bacteria such as *Pseudomonas*, *Acinetobacter* species, and *Burkholderia* species are important causes of bloodstream infections, providing significant treatment challenges due to their association with antimicrobial resistance [25••]. Dengue virus is a common cause of paediatric sepsis, presenting with varied and challenging clinical manifestations such as dengue haemorrhagic fever and dengue shock syndrome. In sub-Saharan Africa, *Plasmodium falciparum* malaria is another major cause of paediatric sepsis [28].

The effect of HIV co-infection in endemic settings also increases the risk of sepsis for children from opportunistic pathogens such as *Pneumocystis jirovecii*, mycobacteria, and cytomegalovirus [30].

Emergence of Antimicrobial-Resistant Pathogens

The emergence of increasingly antimicrobial-resistant (AMR) bacteria as the cause of sepsis in neonates and children provides a growing challenge in the management of neonatal and paediatric sepsis.

The BARNARDS study (Burden of Antimicrobial Resistance in Neonates from Developing Societies) analysed data from neonates with culture-confirmed sepsis across 7 LMICs in Africa and Asia [25••]. The study reported significant resistance rates of Gram-negative isolates, of particular note 95% resistance to ampicillin, 83% to cefotaxime, and 80% to ceftriaxone. Further study, incorporating data on antibiotic use, demonstrated less than 80% probability of drug target attainment for two thirds of patients treated with the current WHO recommended first-line combination of ampicillin and gentamicin [31].

There is a recognised need to collate AMR data, especially in the LMIC setting. The ACORN project (A Clinically Oriented Antimicrobial Resistance Surveillance Network) aims to develop an AMR surveillance system which can be implemented alongside clinical care in LMICs to understand the impact of drug-resistant infections (DRI) [32].

The Role of Biomarkers

In patients with suspected sepsis, the ideal biomarker would answer the following clinically actionable questions: firstly, does this patient require urgent antibiotics; secondly, what further diagnostic tests should be performed to make the diagnosis; and thirdly, is this patient likely to require organ support in a critical care setting? It would provide an answer with high accuracy and within a short time frame to guide treatment, ideally within an hour of presentation to the emergency department [33]. Validation in diverse economic and geographic settings would be essential to ensure that sensitivity and specificity are consistent across different settings and aetiologies of sepsis.

As highlighted in Fig. 1, development of such tests would facilitate both appropriate escalation and de-escalation of treatment in potentially septic patients presenting to the emergency department. In terms of treatment escalation, a diagnostic test to 'rule-in' bacterial infection would facilitate early escalation to antimicrobial therapy, whilst avoiding unnecessary treatment in children suspected to have viral or non-infectious inflammatory disease. For the latter group, a 'rule-out' diagnostic test for bacterial infection would also be beneficial for de-escalation of treatment and admission avoidance. Biomarkers of organ dysfunction would also be of benefit, with biomarkers predicting organ dysfunction and impending decompensation facilitating escalation of care with closer monitoring and possible intensive care unit transfer, whilst supporting decision-making in low-risk patients to enable admission and treatment avoidance [34•]. The latter group is particularly significant in resource-limited settings, where there may be restricted capacity for escalation of treatment [35].

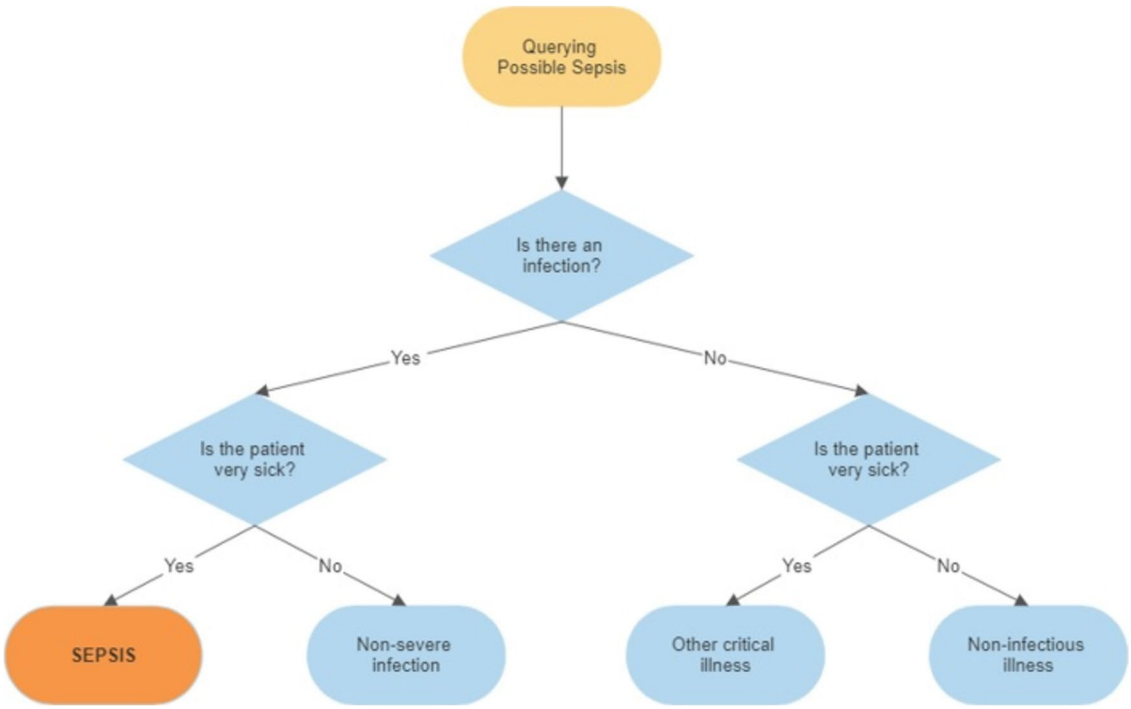

Fig. 1 The characteristics of a diagnostic test which would allow identification of sepsis in an accurate and rapid manner [34•]

Over 250 biomarkers have been evaluated in diagnosis of sepsis since 2009; however, translation to clinical practice remains limited and exclusion of patients under 18 from study cohorts is common [36, 37]. This is due in part to a lack of framework for effective evaluation of novel biomarkers, particularly in children (Table 2). Nijman et al. endeavoured to address this, with the use of C-reactive protein (CRP), neutrophil count, and pathogen isolates in conjunction with clinical features to categorise febrile children into broader diagnostic groups ranging from 'definite bacterial' to 'definite viral' infection [38•]. This framework considers the diagnostic uncertainty when dealing with an undifferentiated group of patients presenting with infection, whilst providing a means to distinguish patient groups that are appropriate for assessing the effectiveness of novel biomarkers.

The development of novel diagnostic testing for infection has also seen integration of multiple biomarkers to define aetiology. An example of this is the MeMed BV test immunoassay. The BV (bacterial viral) score integrates CRP, IP-10, and TRAIL to classify patients into viral or non-bacterial aetiology, equivocal, bacterial, or co-infection and has shown promising diagnostic accuracy in a number of validation studies [39–44], with some evidence in increasing appropriate antibiotic use [45].

The PERFORM framework developed by Nijman et al. [38•] has since been used to assess the performance of biomarkers and severity scores, such as the use of procalcitonin (PCT) and Paediatric Early Warning Scores (PEWS) alongside MR-proADM, to assess risk stratification in febrile children presenting to the ED [51]. This study demonstrates how the use of existing clinical parameters and biomarkers already established in clinical practice alongside novel biomarkers improves clinical utility of novel tests.

The term 'precision medicine' refers to the use of '-omics' disciplines, such as transcriptomics, to stratify risk and tailor treatment strategies to specific patient groups. Over the last 20 years, the cost of genome and whole blood RNA sequencing has declined exponentially, making RNA molecular signatures increasingly viable as a diagnostic tool in paediatric sepsis [56]. A study reporting febrile children presenting to participating hospitals in the UK, Spain, the Netherlands, and the USA between 2009 and 2013 demonstrated that a 2-transcript host RNA signature was able to distinguish between bacterial and viral infections with a sensitivity in the validation group of 100% (95% CI, 85–100%) and specificity of 96.4% (95% CI, 89.3–100%) [57]. PERSEVERE (paediatric sepsis biomarker risk model) utilised a combination of transcriptomics and machine learning to isolate gene expression patterns associated with septic shock, identifying five biomarkers: C–C chemokine ligand 3 (CCL3), interleukin-8 (IL-8), heat shock protein 70 kDa 1B (HSPA1B), granzyme B (FZMB), and matrix metallopeptidase 8 (MMP8) [58] integrated with patient age. The PERSEVERE-II model saw the introduction platelet count on admission with the aim to predict development of various phenotypes of septic shock (thrombocytopenia-associated multiple organ failure, multiple organ failure without new onset thrombocytopenia, and prognosticate risk of 28-day mortality with good performance (AUC 0.87, 95% CI 0.84–0.90) [59, 60].

Most exploratory work on novel biomarkers still takes place in HIC countries, but there is a need for the performance of these biomarkers to be assessed in different settings, where income and aetiology of sepsis will vary, such as the work by Rao et al. in identifying host response gene signatures in cohorts from Nepal and Laos [61] and Ishaque et al. validating the PERSEVERE-II model in Pakistan [62]. In addition to assessing the performance, specific health economic assessments for individual biomarkers would be necessary, including the necessary infrastructure required for biomarker test provision, such as cold chain, electricity, and Wi-Fi for transfer of results.

The Impact of Paediatric Sepsis

The global impact of sepsis in children and neonates is considerable in terms of mortality, morbidity, and cost. In 2017, there were an estimated 2.9 million deaths related to sepsis worldwide among children younger than 5 years and approximately 454,000 deaths among children and adolescents aged

Table 2 Commonly evaluated biomarkers in paediatric sepsis and organ dysfunction

Biomarker	Physiological Role
C-Reactive protein (CRP)	Acute phase protein, identified in infective, inflammatory, and tissue-damaging processes [7, 46, 47]
Interleukin-6 (IL-6)	A pleitropic cytokine, acting in inflammatory and anti-inflammatory processes [7, 48]
Procalcitonin (PCT)	Precursor to calcitonin hormone, expressed in patients with bacterial infection [49–51]
Mid-regional proadrenomedullin (MR-proADM)	Derived from adrenomedullin, a vasodilator utilised in endothelial function in patients with sepsis [51–53]
Interferon γ-induced protein 10 (IP-10)	Cytokine, involved in chemotaxis and inhibition of cell growth [39, 54, 55]
TNF-related apoptosis-inducing ligand (TRAIL)	Tumour necrosis factor protein, role in programmed cell death. Upregulated in viral infection [39, 54]

5–19 years. The 2006 Confidential Enquiry into Maternal and Child Health report 'Why children die: a pilot study' found that infection was the largest single cause of death following an acute physical illness in children in the UK, implicated in 20% of deaths overall [63]. However, this study utilises the Australia and New Zealand Paediatric Intensive Care (ANZPIC) coding system [64], which does not allow infection to be coded as a primary diagnosis.

Estimations of sepsis mortality completed by the Global Burden of Illness Study were more than double those previously identified by Fleischmann-Struzek et al. [65], attributed by the authors to inclusion of more data from previously under-represented LMICs where cases are known to be disproportionately high [66]. They go onto estimate that over half of all sepsis cases worldwide in 2017 occurred in the paediatric population, with a considerable proportion in the neonatal period [1••]. Geographically, LMICs, especially in sub-Saharan Africa, are disproportionately affected [1••].

It has been estimated that up to a third of paediatric sepsis survivors develop at least mild cognitive or physical disability, and considerable impact of paediatric sepsis on childhood morbidity is evident [27]. Whilst there is some literature on neurodevelopmental delay for specific infections [22], comprehensive long-term morbidity data for survivors of neonatal and paediatric severe infections is generally lacking, especially in the LMIC setting [67]. A recent systematic review highlighted the scarcity of knowledge in this area, identifying 9 studies which explored long-term outcomes for survivors of paediatric sepsis within the post-intensive care syndrome-paediatrics framework (PICS-p) domains of physical, cognitive, emotional, and social health outcomes [68]. In the identified studies, there was evidence of ongoing physical, cognitive, and emotional impairments up to 12 months of survivorship; however, no studies conducted follow-up beyond this time point, and no studies explored social health outcomes. Crucially, the majority of studies included data from HICs, with LMICs under-represented. As such, accurate estimations of the true global impact of paediatric sepsis remain difficult.

Paediatric sepsis exerts a significant cost on healthcare systems [1••] and hospitalisation because paediatric sepsis was estimated to account for $7.31 billion dollars of expense in the USA in 2016 [69]. Most estimates of hospitalisation cost are derived from HIC settings such as this, but the impact of such costs is likely to be greatest in the context of resource-constrained health systems in LMICs.

In addition to the economic impact on healthcare systems, paediatric sepsis has a huge economic impact at an individual and societal level for families and communities. There are substantial costs associated with post-sepsis morbidity and long-term sequelae. One study estimating the economic burden of neonatal sepsis in sub-Saharan Africa suggested that annually, 5.29–8.73 million disability-adjusted life years are lost, equating to an economic burden of $10 billion–$469 billion [70]. 'Out-of-pocket' (OOP) costs are another key aspect when considering the impact of paediatric sepsis. These include costs associated with seeking care for children, hospitalisation, and time cost of caregiving. In addition, there can be significant impact on the physical and mental health of caregivers themselves [71]. When considering the global impact of paediatric sepsis, such OOP costs are of critical importance, where such costs for families can be catastrophic, as well as acting as barriers to timely care seeking for serious illness, especially in the LMIC setting [72].

Conclusion

Paediatric sepsis is a condition with significant global impact, complicated by varieties in aetiology, the ongoing development of AMR, and inextricable links to social and geographical determinants for health, particularly in LMICs. A global definition of sepsis requires global research to ensure that children from all populations are represented. As summarised by the Paediatric Sepsis Definition Taskforce, a 'think local, act global' approach is required to optimise defining, identifying, and treating sepsis for all children [2•]. Given the challenges outlined above in formulating clinical criteria for definition of sepsis in children, the use of biomarkers in the emergency room may be important for early recognition and prognostication. However, despite ample scientific literature published on the subject of diagnosis of sepsis over the last 15 years, translation to clinical practice remains limited.

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Data Availability Not applicable.

Declarations

Competing interests The authors declare no competing interests.

Ethics Approval Not applicable.

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- • Of importance
- •• Of major importance

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