Paediatric Sepsis 1

The burden and contemporary epidemiology of sepsis in children

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This is the first in a **Series** of four papers on paediatric sepsis (Paper 4 appears in *The Lancet Digital Health*). All papers in the Series are available at thelancet.com/series/paediatric-sepsis

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Sepsis is a dysregulated host response to infection that leads to life-threatening organ dysfunction. Half of the 50 million people affected by sepsis globally every year are neonates and children younger than 19 years. This burden on the paediatric population translates into a disproportionate impact on global child health in terms of years of life lost, morbidity, and lost opportunities for children to reach their developmental potential. This Series on paediatric sepsis presents the current state of diagnosis and treatment of sepsis in children, and maps the challenges in alleviating the burden on children, their families, and society. Drawing on diverse experience and multidisciplinary expertise, we offer a roadmap to improving outcomes for children with sepsis. This first paper of the Series is a narrative review of the burden of paediatric sepsis from low-income to high-income settings. Advances towards improved operationalisation of paediatric sepsis across all age groups have facilitated more standardised assessment of the Global Burden of Disease estimates of the impact of sepsis on child health, and these estimates are expected to gain further precision with the roll out of the new Phoenix criteria for sepsis. Sepsis remains one of the leading causes of childhood morbidity and mortality, with immense direct and indirect societal costs. Although substantial regional differences persist in relation to incidence, microbiological epidemiology, and outcomes, these cannot be explained by differences in income level alone. Recent insights into post-discharge sequelae after paediatric sepsis, ranging from late mortality and persistent neurodevelopmental impairment to reduced health-related quality of life, show how common post-sepsis syndrome is in children. Targeting sepsis as a key contributor to poor health outcomes in children is therefore an essential component of efforts to meet the Sustainable Development Goals.

Introduction

Sepsis affects about 50 million people globally every year, half of whom are children younger than 19 years.[1] This enormous burden translates into a disproportionate impact on global child health, in terms of years of life lost, morbidity (including life-long disability), and lost opportunities for children to reach their developmental potential. The extraordinary cost to children, families, and society stands in stark contrast to the comparatively small amount of effort dedicated to improving the prevention, recognition, and treatment of paediatric sepsis and ensuring follow-up support for children with sepsis. Disparities in global health equity particularly disadvantage children, exacerbating their susceptibility to infectious diseases. Furthermore, many aspects of paediatric sepsis management are not supported by enough paediatric-specific evidence, potentially exposing thousands of children to suboptimal diagnosis and therapy.

This Series on paediatric sepsis presents the current state of paediatric sepsis care. As a diverse, international, and multidisciplinary group of paediatricians, we face complex challenges of clinical care in our daily work across a range of settings and have, collectively, unique insight of the barriers to alleviating the burden of paediatric sepsis. With this Series, we emphasise the need for holistic care and offer a roadmap to improving sepsis care for children everywhere. Neonatal sepsis, given the different epidemiology, host susceptibility, and therapeutic implications, is beyond the scope of this Series and has been reviewed elsewhere.[2]

In this first paper of the Series, we start with a global perspective on the burden of paediatric sepsis and present contemporary epidemiology in light of evolving diagnostic criteria. Our understanding of short-term and long-term outcomes of sepsis is improving, and we review the emerging evidence. We discuss the intersection between improving paediatric sepsis outcomes and meeting the Sustainable Developmental Goals (SDGs).

In the second paper of this Series,[3] we focus on the susceptibility of the paediatric host to sepsis and discuss current and future approaches to recognising and treating sepsis in children. The third paper[4] delivers a critical appraisal of the evidence base and ongoing initiatives to support systematic quality improvement for paediatric sepsis. Finally, the fourth paper in this Series[5] maps out digital approaches in paediatric sepsis, highlighting both opportunities and barriers for advancing paediatric care and explaining the risks pertinent to digital sepsis solutions for children.

The evolving concept of paediatric sepsis

Sepsis appears in medical literature that dates back to the era of Hippocrates. Derived from ancient Greek for putrefaction (σηψις), sepsis was initially used in reference to tissue decay and death associated with fever.[6] Infections have been a leading cause of childhood mortality throughout history. For centuries, the triad of high exposure, paediatric host susceptibility, and perceptions of fate (which can sometimes stand for suboptimal care) exerted an immense death toll. With the emergence of

the scientific method and microbiology, awareness of pathogenicity and virulence, and discovery of antimicrobials came the era of treating and surviving infections that had once been fatal.

Although sepsis, septicaemia, and blood poisoning have been diffusely used in lay terms, the design of intensive care with technological capacity for organ support fostered attempts to formulate scientific criteria for sepsis (table).[7] In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine published Sepsis-1 (or Bone criteria).[8] The Sepsis-1 criteria were intended to define a syndrome characterised by a systemic inflammatory process resulting from infection that leads, in its most severe form, to infection-associated organ dysfunction. These eminence-based criteria were shaped to address the need for early bedside detection, effective intervention, and a reproducible framework for research on sepsis. According to Sepsis-1, sepsis required the presence of systemic inflammatory response syndrome (SIRS), defined by abnormal heart rate, respiratory rate, and white cell count, and fever or hypothermia, which would remain part of sepsis criteria for almost a quarter of a century. The concept underlying Sepsis-1 postulated a stepwise progression from infection to SIRS and organ dysfunction (termed severe sepsis), septic shock (a hypotensive state despite adequate fluid resuscitation, with markers of abnormal perfusion), multiorgan failure, and death. The terms were intentionally generic, and no reference to paediatric sepsis or adjustments were proposed. In 2001, Sepsis-2 provided further specification of sepsis criteria applicable to adults, but included the first paediatric-specific criteria.[9] Sepsis-2 emphasised the clinical primacy of considering the gestalt of sepsis at the bedside over robust but potentially too simplistic objective criteria.

To design standardised enrolment criteria for paediatric clinical trials, an expert panel convened to define age-specific criteria for SIRS and for organ dysfunction.[10,11] The resulting criteria, published in 2005, and widely known as the International Pediatric Sepsis Definition Consensus Conference (IPSCC) criteria, were variably used and have been minimally validated.[12] Since the release of the IPSCC criteria, the notion that SIRS was a sensitive and discriminative feature of sepsis (rather than an adaptive response to noxious stimuli such as infection, trauma, or burns) has been challenged, whereas data consistently confirm organ dysfunction as the hallmark of increased risk of mortality associated with infection.[13,14]

In adults, SIRS criteria were eventually abandoned in 2016, with the release of the Sepsis-3 criteria. Importantly, the process of deriving Sepsis-3 was data-driven, coupling systematic reviews and expert opinion with electronic health record data from hundreds of thousands of patient encounters.[15] Sepsis-3 explicitly excluded paediatric age groups, and defined sepsis as an unspecified dysregulated host response to infection resulting in life-threatening organ dysfunction, which was operationalised by an increase of at least 2 points in the Sequential Organ Failure Assessment (SOFA) score. These landmark criteria triggered a wealth of validation studies (and controversies) and have improved standardisation of sepsis in adults. The emphasis on dysregulated host response established new interest in sepsis immunity and host response, which is the focus of the second paper of this Series.[3]

The Society of Critical Care Medicine subsequently convened the Pediatric Sepsis Definition Taskforce. With experts in paediatric intensive care, infectious diseases, emergency medicine, general paediatrics, neonatology, data science, and public health from across six continents, the Taskforce completed a systematic review of criteria for sepsis and identified consistent associations of markers of organ dysfunction with poor outcomes.[16] Its global survey of the diversity in available criteria and tools to diagnose and manage sepsis confirmed widespread support for the concept of sepsis as infection with associated organ dysfunction.[17] With a central focus on the disproportionate burden related to sepsis in low-income and middle-income countries (LMICs), this work led to a conceptual framework for paediatric sepsis criteria that are globally applicable.[18] Drawing on harmonised data from ten sites in the USA, Colombia, Bangladesh, China, and Kenya, the Taskforce derived the Phoenix Sepsis Score for cardiovascular, respiratory, neurological, and coagulation

Key messages

- Sepsis in children is defined as life-threatening organ dysfunction operationalised by a Phoenix Sepsis Score of at least 2 points in the presence of suspected or confirmed infection; septic shock is defined as sepsis in the presence of cardiovascular dysfunction, requiring a cardiovascular subscore of at least 1 point of the Phoenix Sepsis Score
- Estimates for paediatric sepsis burden vary as a result of inconsistent application of previous sepsis definitions and methods; the Global Burden of Disease assessment for sepsis estimated that 25 million sepsis cases affected paediatric and neonatal age groups in 2017, resulting in approximately 3 million deaths
- In addition to early mortality associated with sepsis in children, sepsis accounts for increased late mortality, and survivors often have new morbidities that affect their health-related quality of life, sometimes for decades to come
- An increasing body of observational evidence points towards various sequelae associated with sepsis in paediatric survivors, identified as a post-sepsis syndrome that affects physical, emotional, behavioural, and neurocognitive domains, and which, in addition, negatively affects parents and parental functioning
- Studies based on direct health-care costs in high-income countries indicate a major economic burden resulting from paediatric sepsis for society in terms of costs for patients, families, and health-care systems, but these estimates generally do not include indirect and long-term costs unique to paediatric patients
- To address sepsis as a threat to child health more specifically, there is a need for coordinated initiatives at local, national, and international levels, tailored for paediatric age groups; such initiatives should be designed to jointly address needs for infection prevention and control, pandemic preparedness, and improved recognition and management of life-threatening infections in children

	1992: Sepsis-1	2001: Sepsis-2	2005: IPSCC	2016: Sepsis-3	2024: Phoenix Sepsis Score
Society	American College of Chest Physicians, Society of Critical Care Medicine	Society of Critical Care Medicine, European Society of Intensive Care Medicine, American College of Chest Physicians, American Thoracic Society, Surgical Infection Society	IPSCC	Society of Critical Care Medicine, European Society of Intensive Care Medicine	Society of Critical Care Medicine
Methodology	Consensus	Consensus	Consensus	Delphi; review; development and validation	Global survey; review; development and validation; Delphi
What is new	SIRS	PIRO staging	Age-specific criteria to permit enrolment in interventional trial	Abandons SIRS and severe sepsis; operationalises definition with SOFA	Abandons SIRS and severe sepsis; new Phoenix Sepsis Score
Infection	Pathological process caused by invasion of normally sterile tissue, fluid, or body cavity by pathogenic micro-organisms	Pathological process caused by invasion of normally sterile tissue, fluid, or body cavity by pathogenic micro-organisms	Proven (pathogen identification) infection or a clinical syndrome associated with a high probability of infection	Not defined; operationalised in development or validation study as microbiological sampling of body fluids and treatment with antibiotics	Not defined; operationalised in development or validation study as microbiological test and treatment with antimicrobials
Sepsis	Systemic inflammatory response to infection; operationalised as SIRS associated with a confirmed infectious process	SIRS and infection and some additional variables	SIRS must include abnormal temperature or white cell count	Infection and organ dysfunction with SOFA score increase ≥2	Suspected or confirmed infection and organ dysfunction with Phoenix Sepsis Score ≥2
Severity and organ dysfunction	Sepsis-associated organ dysfunction; MODS	Sepsis-associated organ dysfunction (mention of existing scores, such as SOFA, PELOD, and P-MODS)	Age-specific criteria for cardiovascular, respiratory, neurological, haematological, hepatic, and renal dysfunction; for severe sepsis, organ dysfunction must be cardiovascular or respiratory, or be present in at least two organs	Organ dysfunction assessed with SOFA score	Organ dysfunction assessed with the new Phoenix Sepsis Score, including cardiovascular, respiratory, neurological, and coagulation criteria
Septic shock	Hypotension despite adequate fluid resuscitation with signs of hypoperfusion (eg, lactic acidosis, oliguria, or altered mentation)	Hypotension despite adequate fluid resuscitation with signs of hypoperfusion (eg, lactic acidosis, oliguria, or altered mentation)	Hypotension, need for inotrope or vasoactive, or clinical signs for hypoperfusion (eg, increased temperature gap, base excess, lactate, prolonged capillary refill, or oliguria) despite administration of ≥40 mL/kg of fluid in the first hour	Hypotension and treatment with inotrope or vasoactive in the presence of lactate >2 mmol/L	Sepsis with at least 1 cardiovascular point in the Phoenix Sepsis Score (ie, any of hypotension, inotrope or vasoactive use, or lactate ≥5 mmol/L)
Paediatric sepsis and septic shock	Not discussed	SIRS plus at least one sign of dysfunctional organ function: altered mental status, hypoxaemia, elevated serum lactate concentration, or bounding pulses; specific mention that hypotension occurs late in paediatric septic shock (decompensated shock); tachycardia, bounding pulses, flash or prolonged capillary refill >2 s, mottled or cool peripheries, altered mentation, and decreased urine output	Specifically addressed with paediatric expert panel and age-specific criteria designed for paediatric age groups	Not discussed	Specifically addressed with derivation and validation based on over 3·5 million paediatric encounters in all socioeconomic settings across ten sites in the USA, Colombia, Bangladesh, China, and Kenya

IPSCC=International Pediatric Sepsis Definition Consensus Conference. MODS=multiple organ dysfunction syndrome. P-MODS=paediatric multiple organ dysfunction syndrome. PELOD=Pediatric Logistic Organ Dysfunction. PIRO=predisposition, infection or insult, response, and organ dysfunction. SIRS=systemic inflammatory response syndrome. SOFA=Sequential Organ Failure Assessment.

Table: **Evolution of sepsis criteria and paediatric-specific application**

dysfunctions. With a derivation dataset of more than 3 million paediatric encounters and a validation dataset of around 580 000 encounters, the Phoenix Sepsis Score proved superior to any existing organ dysfunction scores in predicting mortality in children with infection.[19] Following a process of iterative voting based on data-driven results, with an emphasis on globally applicable and specific criteria, the Phoenix criteria for sepsis and septic shock in children were thus defined: sepsis, as life-threatening organ dysfunction, operationalised by a Phoenix Sepsis Score of at least 2 points in children with suspected or confirmed infection; and septic shock, as sepsis in the presence of cardiovascular dysfunction, operationalised by a cardiovascular subscore of at least 1 point.[20] Importantly, whereas the Phoenix criteria serve to standardise the approach to capturing sepsis for the purposes of benchmarking, quality improvement, and research, they are not intended as screening tools or guidance for treatment decisions. Further work is in progress to design early recognition tools for children with sepsis that can inform early treatment choices.

Throughout this Series, we refer to sepsis as infection-associated organ dysfunction, and septic shock as sepsis-associated cardiovascular dysfunction.[21]

The global burden of paediatric sepsis

In 2017, the Global Burden of Disease study group presented the first estimates of worldwide sepsis incidence and mortality specific to age, sex, and location.[1] The group also modelled sepsis-related case-fatality data from hospital administrative data to the mortality estimates.[1] These analyses revealed that worldwide, 20·3 million incident cases of sepsis were in children younger than 5 years, whereas 4·9 million incident cases were in children and adolescents aged 5–19 years, and 23·7 million incident cases were in adults aged 20 years and older.[1] The most common causes of sepsis among children younger than 5 years were diarrhoeal diseases, neonatal disorders, and lower respiratory tract infections (figure 1).

Sepsis incidence peaks in early childhood, with a second smaller peak in incidence among older adults. A systematic review and meta-analysis of population-based reports suggested an aggregate incidence of sepsis in paediatric populations (aged between 4 weeks and 20 years) of 22 per 100 000 person-years.[23] However, the review also highlighted the paucity of age-specific data from LMICs and major heterogeneity in how sepsis has been recorded, largely due to difficulties in applying sepsis criteria,[24] coding practices not mentioning sepsis explicitly,[25] and challenges in coding organ dysfunction.[26] Most studies have thus substantially underestimated the true burden of sepsis in children and, accordingly, under-reported true sepsis mortality. For example, in an international point prevalence study, only 301 (69%) of 438 physicians' diagnoses of severe sepsis in children were in agreement with the 2005 IPSCC criteria.[24] A WHO global report on the epidemiology and burden of sepsis also noted that comparisons of sepsis incidence over time are hampered by methodological heterogeneity.[27] Although population-based epidemiological studies covering sufficiently long time periods are rare, sepsis incidence is generally assumed to have dropped over time as a result of vaccinations and improved health care.[28] However, findings from a large, paediatric intensive care unit (PICU)-based study indicated increased admissions, which could reflect changing admission thresholds, increasingly complex patient cohorts, or a true increase in sepsis incidence.[29]

Further justification to prioritise paediatric sepsis stems from the enormous costs to society. In the USA, direct hospitalisation costs for paediatric severe sepsis increased from about US$4·8 billion in 2005, to $7·3 billion in 2016 (an inflation-adjusted increase of 25%), accounting for 18% of total paediatric hospitalisation costs.[30–32] The median cost per hospitalisation in 2016 was $26 592, which is 12 times the median cost of all-cause paediatric hospitalisations. For comparison, mean paediatric sepsis hospitalisation costs were $77 446 in children's hospitals in the USA and AU$62 062 in Australia and New Zealand.[29] However, the true financial cost of paediatric sepsis to society is unclear. Extraction of age-specific costs can be difficult as cost data from neonatal and paediatric populations are often combined, health economic studies are largely done in HIC settings and mostly analyse direct health-care costs, and sepsis-attributable costs can be hard to ascertain when children are admitted to hospital for reasons other than suspected sepsis. Thus in terms of loss of life-years due to death or disability, increased long-term health-care requirements, and intergenerational effects, the costs associated with sepsis in children are likely to exceed these hospitalisation costs by several folds (figure 2).[33]

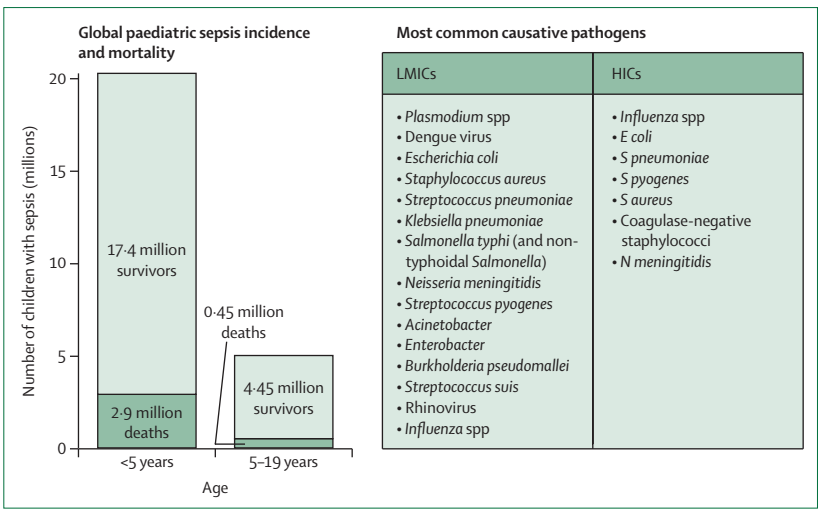

Figure 1: **Global burden and leading causative pathogens of paediatric sepsis**
Global sepsis incidence and mortality data are from 1990 to 2017, based on the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 estimates.[1] Leading causative pathogens of paediatric sepsis were extracted from the GBD 2019 Antimicrobial Resistance Collaborators' systematic analysis.[22] HICs=high-income countries. LMICs=low-income and middle-income countries.

Epidemiology of paediatric sepsis

Epidemiological studies of sepsis and disease severity in children predominantly use PICU cohorts. Detailed information on pathogens, particularly in LMIC settings, is obtained primarily from infectious disease studies, many of which do not specifically refer to sepsis. In 2015, the results of a point prevalence study involving 128 PICUs in 26 countries across six continents showed a prevalence of severe sepsis of 8·2% (95% CI 7·6–8·9) and median age of 3·0 years (IQR 0·7–11·0).[34] The most common sites of infection were respiratory (40%) and bloodstream (19%). By comparison, the prevalence of severe sepsis in PICUs across South America was 25·9% (the prevalence of septic shock at admission being 19·8%).[35,36] In the USA, an electronic surveillance algorithm of emergency department and hospital encounters from a single academic centre showed a hospital-wide incidence of paediatric sepsis of 0·69% (95% CI 0·67–0·71) and inpatient incidence of 2·8% (2·7–2·9).[37]

Severe infections

In the European childhood life-threatening infectious disease study (EUCLIDS), a third of children with

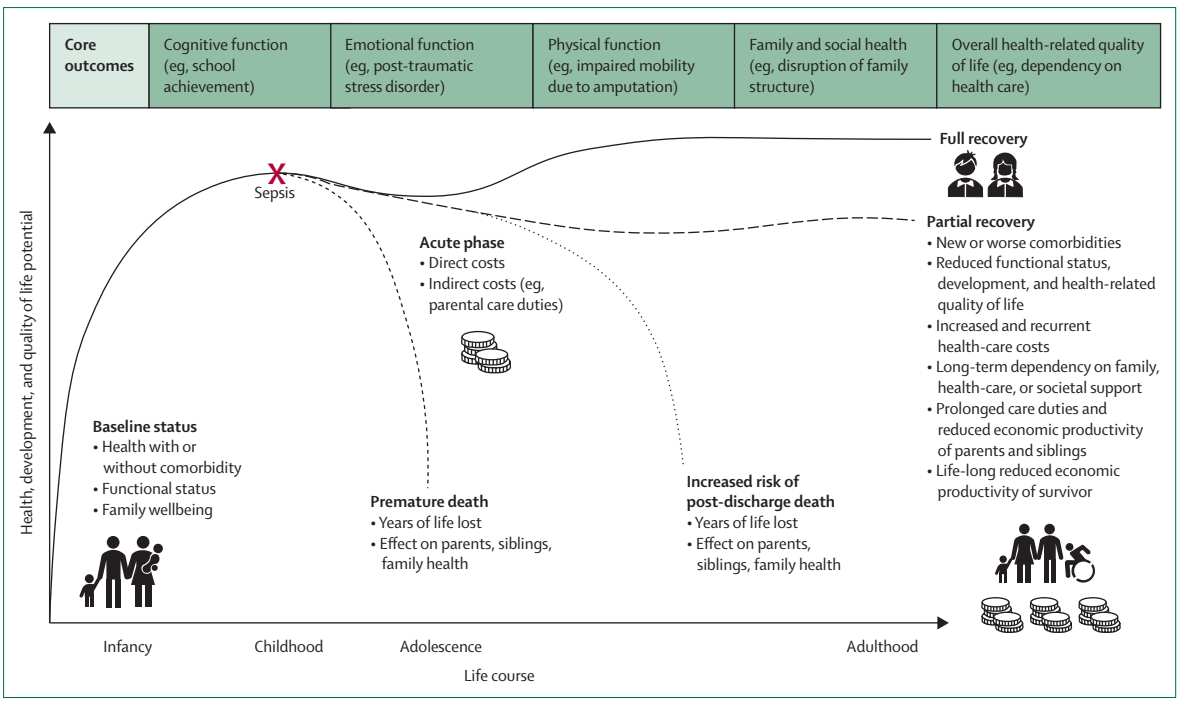

Figure 2: **Trajectories of paediatric sepsis and their impact on burden along the life course**
Sepsis most commonly affects children at an age of rapid development and can—transiently or permanently—affect their ability to reach their full developmental potential due to mortality and morbidity across several core outcome domains, with associated indirect and intergenerational costs for society.

life-threatening infections were admitted to a PICU.[38,39] The cohort was mainly recruited before pneumococcal conjugate vaccine and meningococcal B vaccine implementation, and the causal microorganism of community-acquired sepsis was identified in about half of the children. In a study of blood culture-proven bacterial sepsis in Switzerland, *Escherichia coli*, *Staphylococcus aureus*, coagulase-negative staphylococci, and *Streptococcus pneumoniae* were the most prevalent causative pathogens.[40] Pathogens and site of infection tended to differ between previously healthy children and children with chronic health conditions. Unlike previously healthy children, in whom group A and group B streptococcal, pneumococcal, and community-acquired staphylococcal infections predominated in addition to urinary tract infections with common Gram-negative pathogens, a predominance of staphylococcal and Gram-negative health-care-associated pathogens was observed among children with chronic health conditions. A population-based observational study of children in England over five decades showed very clearly that hospital admission rates for childhood invasive bacterial disease decreased after the introduction of conjugate vaccines against *Haemophilus influenzae*, *Neisseria meningitidis*, and *S pneumoniae*, corroborating trends in other countries.[41]

In a systematic analysis of deaths associated with 33 bacteria,[22] the Global Burden of Diseases Study Group found that *Salmonella typhi* was associated with the most deaths in children aged 5–14 years, and that *S pneumoniae* was associated with the most deaths among young children, followed by *S aureus*, non-typhoidal *Salmonella*, *E coli*, *Klebsiella pneumoniae*, and *N meningitidis*. Similarly, gram-negative bacteria (*E coli*, *K pneumoniae*, *Acinetobacter* spp, *Enterobacter* spp, and *Burkholderia pseudomallei*) and Gram-positive bacteria (*S aureus*, *S pneumoniae*, *Streptococcus suis*, and β-haemolytic *Streptococcus* spp) were primarily associated with sepsis in adults and children in a study in southeast Asia.[42] In a rural hospital in sub-Saharan Africa, malaria was the leading cause of acute severe infection in children.[43] In South Africa, rates of Gram-negative infections have increased markedly, replacing Gram-positive and fungal pathogens as the leading cause of paediatric blood and cerebrospinal fluid infections.[44]

Antimicrobial resistance

A systematic review of antimicrobial resistance in children in sub-Saharan Africa reported a high prevalence of extended-spectrum, β-lactamase-producing organisms and Gram-positive bacteria in infections among children beyond the neonatal period.[45] Concerningly, there was a high prevalence of non-susceptibility to empirical treatment recommended by WHO therapeutic guidelines. In a systematic review describing pathogen distribution and antimicrobial resistance patterns in paediatric bacteraemia, Gram-negative bacteria accounted for

63·9% of all episodes,[46] with *Salmonella* spp as the most commonly reported pathogen in Asia, and *S aureus* and *S pneumoniae* in Africa. The systematic review also showed a high and geographically variable overall antimicrobial resistance rate to the first-line drugs (ampicillin and gentamicin) and second-line drugs (third-generation cephalosporins and amikacin).

Viral sepsis

In children, many conditions are associated with organ dysfunction as a result of infection by viruses[47] (eg, enterovirus shock, dengue haemorrhagic shock, severe bronchiolitis, and gastroenteritis with severe dehydration), parasites (eg, severe malarial anaemia), or inflammatory post-infectious conditions (eg, COVID-19-associated multisystem inflammatory syndrome in children).[48] Viral sepsis was recognised long before the COVID-19 pandemic.[49] A prospective study in southeast Asia showed that viruses accounted for 76% of the documented sepsis cases in children.[50] The most common viruses identified in this study were dengue virus (27%), followed by rhinovirus (23%), influenza viruses (14%), and respiratory syncytial virus (12%). Globally, herpes simplex virus and enteroviruses are the most common viral causes of neonatal sepsis, and enteroviruses, human parechoviruses, and influenza viruses are the leading causes of viral sepsis in young children. When detected, these viruses could be disease-causing as the single infective pathogen, predispose children to secondary bacterial infection, represent co-infections, or indicate persistent shedding from previous infection or latent virus.[51]

Mortality

Sepsis is a leading cause of death worldwide, with an estimated 2·9 million sepsis-related deaths in children younger than 5 years, and 454 000 deaths in children and adolescents aged 5–19 years.[1] A point prevalence study of severe sepsis, involving 6925 patients (median age 3·0 years [IQR 0·7–11·0]) from 128 PICUs in 26 countries across six continents throughout 2013–14, reported a 25% hospital mortality.[34] A meta-analysis identified geographical location (ie, studies done in HICs had lower mortality than those in LMICs), younger age, septic shock, and early medical era as independently associated with mortality.[52] Whether sepsis-related mortality in LMIC settings has been decreasing is unclear. In Brazil, nationwide case-fatality rates for children hospitalised with bacterial sepsis from 1992 to 2006 changed little over time (20·5% in 1992–96 *vs* 19·7% in 2002–06).[28] In a study of 144 PICUs in Brazil in 2019,[36] the case-fatality rate was 19·8% and associated with high paediatric SOFA (pSOFA) scores, unknown or incomplete vaccination status, and health-care-associated infections. However, these data might not be directly comparable to settings where intensive care unit (ICU) services are scarce.[43]

Sepsis patient studies in HICs are often biased towards the PICU setting and indicate that overall sepsis case mortality has decreased somewhat over previous decades, but this decline was similar to the overall improvement in PICU survival among patients without sepsis.[29] In a multicentre, retrospective cohort study in Australia and New Zealand, in-PICU mortality was 5·6% among children with sepsis and 17·0% among children with septic shock. In the prospective cohort study from the EUCLIDS consortium, sepsis mortality was 2·2% overall but increased to 6% among children admitted to a PICU, and 10% among children with septic shock.[38,39] In a population-based study of blood culture-proven bacterial sepsis with SIRS in Switzerland, the case-fatality ratio was 7%, increasing from 1% for children without organ dysfunction to 17% for children with organ dysfunction.[40,53] In the USA, a single-centre study of patients (median age 6 years [IQR 1–13]) that used an electronic surveillance algorithm showed a 6·7% hospital-wide sepsis case-fatality rate.[37] In comparison, an analysis from 43 children's hospitals in the USA, from 2004 to 2012, showed a 14·4% hospital mortality among children with severe sepsis, with increased mortality among infants and among children with underlying cardiovascular conditions or multiple organ dysfunction.[32] According to a pSOFA validation study across emergency departments in the USA, mortality was 0·9% among children meeting pSOFA-based sepsis criteria and 8·0% in children meeting pSOFA-based sepsis criteria in addition to increased lactate and need for vasopressors (indicating shock).[54] Much higher mortality rates in the context of sepsis-associated multiple organ failure have been reported from nine PICUs within the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Collaborative Pediatric Critical Care Research Network, for example, in phenotypes associated with macrophage activation syndrome.[55]

A substantial proportion of sepsis fatalities occur soon after hospital admission due to refractory septic shock and fulminant organ failure such as disseminated intravascular coagulation, myocardial failure, and acute respiratory distress syndrome. Often unaccounted for in studies, some early sepsis deaths happen during transport to hospital and in settings that do not have the technical facilities and expertise of major children's hospitals in metropolitan areas. In high-resource health-care settings, most deaths thus typically occur within the first days of admission among children without comorbidities, whereas mortality among children with chronic health-care conditions usually peaks after 7 days in hospital.[56–58] Later deaths are mostly attributable to multiple organ dysfunction syndrome or neurological injury and usually occur in the context of persistent, rather than worsening, organ dysfunction, with eventual withdrawal of life-sustaining therapies.[56] For patients with multiple comorbidities, reports commonly do not distinguish if they died because of sepsis, or if they

developed sepsis as a complication during preterminal or terminal illness (ie, die with sepsis rather than because of sepsis).

For LMICs, less is known about time to death, but selection and survival bias in relation to transport and admission to hospital and ICU facilities need to be considered when interpreting unadjusted mortality figures. In Brazil, several public health interventions related to immunisation, water, and sanitation were associated with a decrease in sepsis hospitalisations but with little change in hospital mortality rates in children.[28] Although out-of-hospital deaths were not assessed, these findings suggest that improved public health correlated with an overall decrease in the number of sepsis-associated deaths in children.

Long-term outcomes beyond hospital discharge

Children who survive sepsis are, like adults,[59,60] at heightened risk of ongoing sequelae (figure 2), but it remains unclear to what extent the aftermath of sepsis has unique manifestations in children versus adults, given the developmental trajectory of children and the role of their families in recovery. Impairments that persist after a child's discharge from PICU are commonly conceptualised by the post-intensive care syndrome framework,[61] which considers overall health and physical, cognitive, mental health, and social domains in the context of the interdependent aspects of a child's family, growth, and development.[62,63] In addition to the adverse impact of critical illness generally (eg, hypoxaemia, metabolic stress, and the need for relative immobility and sedation), the hyperinflammatory state resulting from sepsis during a vulnerable phase of active brain development might predispose children to poor neurocognitive outcomes.[64,65]

In resource-poor health-care settings, post-discharge mortality after hospitalisation for malaria, diarrhoea, or pneumonia has been reported as 1–15%.[66,67] In studies of hospitals in Uganda with high follow-up rates, post-discharge mortality among children younger than 5 years with suspected sepsis was 5·5% within 6 months (median 1 month).[66,68] Similarly, late post-discharge (>28 days after discharge) mortality was 6·5% in a population-based study of children hospitalised for severe sepsis between 1990 and 2004 in Washington state, USA.[69] Although oncological comorbidities were most strongly associated with post-discharge deaths, many children died from injuries (including by suicide and overdose). Thus, although late death might relate to the patient with sepsis' medical history (eg, poor nutrition or underlying severe disease) and sequelae of hospitalisation (eg, depression), underlying predisposing factors and sequelae of sepsis might increase the risk of death long after the acute sepsis episode has ended.

Early studies of post-discharge outcomes of paediatric sepsis were dominated by patients recovering from meningococcal infections, many of whom had limb ischaemia—clinical circumstances that are extremely rare in PICU care nowadays. The Life After Pediatric Sepsis Evaluation (LAPSE) study,[70,71] by contrast, offers a more contemporary picture of survivorship. In this large longitudinal study of morbidity of children with community-acquired septic shock across 12 academic PICUs in the USA, 354 (91%) of 389 enrolled children were discharged from PICU. 16 (5%) of 354 children who were discharged died within 12 months of discharge. Of the 338 survivors, 308 (91%) completed a baseline survey, and at least one post-discharge survey. Of these 308 children, 128 (42%) were readmitted to hospital, 145 (47%) had an emergency department visit, 156 (51%) had started a new class of medication, and 102 (33%) were using a new device class.[72] In EUCLIDS, 31% of children admitted to ICUs with life-threatening bacterial infection were discharged with disability. Of the children who had previously been healthy (with no underlying condition at admission), 24% were discharged with some disability.[38,39] In a study of a US national insurance claims database, outpatient visits increased by 60% the year after a paediatric severe sepsis hospitalisation, with 16% of these children having a new subspecialist visit within 90 days of hospitalisation.[73] In a further study in the USA, 19% of paediatric sepsis survivors had a new or progressive respiratory failure, seizure disorder, supplemental nutritional dependence, or chronic kidney disease within 6 months of hospital discharge.[74]

Children surviving sepsis are also at risk of impaired physical and cognitive function and diminished health-related quality of life (HRQL) for months to years after discharge. In the LAPSE study, 35% of survivors showed deteriorated HRQL 1 year after PICU admission relative to baseline.[71] Strong risk factors for new morbidity and poor HRQL were acute kidney injury[75] and disease severity (measured by paediatric logistic organ dysfunction-2 scores).[76] The largest improvement in HRQL occurred by 3 months after admission, with little improvement over the subsequent 9 months. Accordingly, 3 months after discharge from hospital might be the optimal time to screen for post-intensive care syndrome in these settings.[71] Similar findings were observed in a single-centre study of 790 children admitted to a hospital in the USA with community-acquired sepsis,[77] 24% of whom did not return to their baseline level of HRQL within 12 weeks of discharge.

Most post-discharge outcome data originate from HICs, but children in LMICs appear at similar risk of long-term sequelae, albeit with less access to care that could facilitate recovery. In a single-centre study at a tertiary PICU in India,[78] 45 (51%) of 89 children with severe sepsis had worsened physical function at discharge, and 25 (28%) had worsened cognitive function, compared with before admission. At 1 year of follow-up, 41 (95%) of 43 children with new physical disability at hospital discharge had recovered to their overall baseline physical functioning, and 18 (86%) of 21 children with impaired cognitive function at discharge

had improved to baseline. Higher pSOFA scores and cardiopulmonary resuscitation were independently associated with worse outcomes (eg, decreased physical function, decreased cognitive function, or death).

The evidence available to date stems largely from questionnaire-by-proxy assessment of HRQL and functional status; however, a few small studies offer more granular assessments of cognitive performance. In a single-centre study in the Netherlands, 22 (44%) of 50 children surviving septic shock had cognitive scores below 25% of normal values for their age.[79] In a study of neuropsychological function associated with PICU admission in 16 children in the UK, eight children with sepsis had poor pattern recognition memory at a mean 4·8 months (SD 1·4) of follow-up, and lower pattern-recognition memory scores were associated with post-traumatic stress.[80] In the USA, bacteraemic sepsis in children being treated for acute lymphoblastic leukaemia was associated with poorer neurocognitive function long term, including in executive functioning, attention, visual processing speed, spatial visualisation, and vocabulary.[81] These deficits might also affect academic performance, as shown in a small study in the UK with high rates of difficulties in attention and completion of school work among 22 children with sepsis from 2007 to 2010.[82] In a large population-based linkage study in Australia and New Zealand, the rates of failure to meet minimal requirements at primary school age were higher among children who survived septic shock than other children who had survived other treatments in the PICU, and matched peers from the same school.[83] Machine learning-based tools to predict educational outcomes revealed severity of disease, comorbidities, and socioeconomic status as key prediction features, but overall, the models performed less well in sepsis survivors than in other patient groups.[84]

Families are often profoundly affected by a child's sepsis hospitalisation, and a prolonged period of moderate-to-high amount of distress after discharge is common among caregivers.[85] Parental post-traumatic stress disorder and other mental health conditions can negatively affect parents' emotional or cognitive ability to support their children through post-sepsis recovery.

The public health context

Paediatric sepsis is strongly associated with socioeconomic factors and primarily affects people living in poverty, with 85% of cases and deaths affecting children in LMICs. The link between poverty and health inequity is exacerbated by political corruption, financial mismanagement, and inadequate public health systems. Delays in recognising sepsis, the seeking of appropriate care, and provision of care are common. Few caregivers are sufficiently informed to be able to recognise sepsis symptoms, and typical travel distances between homes and the nearest health-care facility can be a cost and time barrier.[86,87] Especially in LMICs, PICU facilities are rare and tend to be overcrowded, resulting in scenarios whereby a child with sepsis receives care by health-care professionals without formal critical care training (or even paediatric training) in non-intensive care settings. As noted by Cheng and colleagues,[88] health-care workers in LMIC settings should receive integrated training on the prevention, recognition, and management of sepsis in children. WHO's Paediatric Emergency Triage Assessment and Treatment guidelines[89] form a central part of its Integrated Management of Childhood Illness strategy[90] and can be applied to pre-hospital and acute care services in resource-constrained systems. Such approaches are a good starting point for the development of LMIC-specific guidelines for sepsis that use simple diagnostic criteria based on physical examination.

The WHO–UNICEF–*Lancet* Commission on the future for the world's children[91] flagged major gaps in addressing SDGs from a child health perspective, highlighting the immense societal losses as a result of impaired child health, given the impact of health across the lifespan and across generations. Although SDG goal 3 (good health and well-being) and its targets refer specifically to ensuring healthy lives and reducing mortality, decreasing sepsis burden and improving care and outcomes are also relevant to other SDGs: goal 1 (no poverty), goal 2 (addressing all causes of malnutrition), goal 4 (supporting high quality education), goal 5 (fighting gender inequities), goal 6 (preventing disease through safe water and sanitation), goal 9 (promoting national bed capacity and manufacturing of essential medicines), goal 10 (equitable access to health services), and goal 12 (promoting responsible consumption of medicines to combat antimicrobial resistance). Alleviating the paediatric sepsis burden and ending health inequity thus intersect across multiple SDGs, which emphasises the need for holistic approaches to sepsis care (figure 3). Work by the Child Health and Mortality Prevention Surveillance (CHAMPS) network underlines the need for such a holistic approach. In 2021, reporting on postmortem investigations of causes of child deaths in Bangladesh, Ethiopia, Kenya, Mali, Mozambique, Sierra Leone, and South Africa, CHAMPS showed that when considering conditions anywhere in the causal chain (ie, underlying, antecedent, and immediate causes of death), infant mortality attributable to sepsis was 11-fold higher than if only considering underlying conditions.[92]

For more on **CHAMPS** see https://champshealth.org/

The Global Sepsis Alliance has been advocating for the need to advance the prevention, recognition, and treatment of sepsis worldwide. These efforts led to the 2017 World Health Assembly resolution on sepsis.[93,94] Although the heightened global awareness of the burden of paediatric sepsis has provided an opportunity for change, progress so far has been slow, especially in resource-poor health-care settings.

For more on the **Global Sepsis Alliance** see https://www.global-sepsis-alliance.org/

Given children's high potential for recovery, sepsis in children must be appropriately prioritised as a major national and international public health problem. Context-specific strategies specifically designed to reduce the burden of sepsis in LMICs are urgently needed, and must

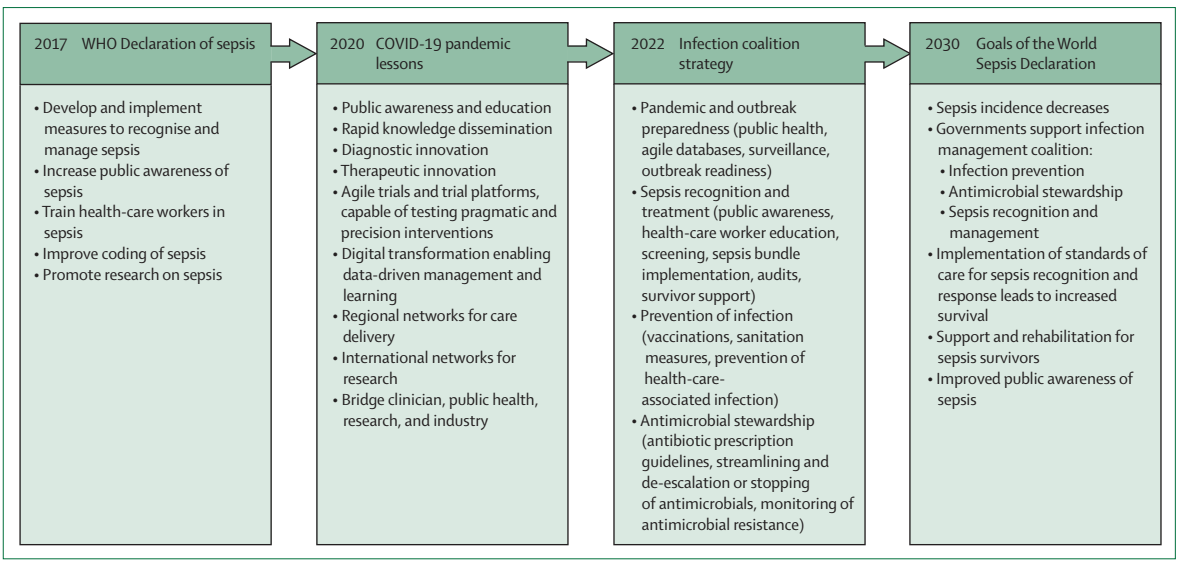

Figure 3: **Achieving the targets of the 2030 World Sepsis Declaration**
Lessons learnt during the COVID-19 pandemic are shaping joint strategies that address sepsis together with pandemic preparedness, infection prevention, and antimicrobial resistance, as outlined by the UK Infection Management Coalition, to reach the targets of the 2030 World Sepsis Declaration, as laid out by the Global Sepsis Alliance.

Search strategy and selection criteria

We searched PubMed using the MeSH terms ("sepsis" OR "severe sepsis" OR "septic shock" OR "trial") AND ("child" OR "paediatric") for reports published between Jan 1, 2000, and March 30, 2024. We only considered publications with abstracts in English, French, or German. In specific subsearches we added the terms ("criteria" OR "scores"), ("epidemiology" OR "microbiology" OR "incidence"), ("sustainable developmental goals"), ("surviving sepsis campaign"), and ("mortality" OR "long-term outcome" OR "health-related quality of life" OR "functional outcome"). Reference lists from key articles of interest were searched for additional related important publications. Publications included were those that had relevance to the manuscript topic.

consider important differences in the populations at risk, infecting pathogens, and health-care capacity to manage sepsis across all settings. Solutions must be simple, easily applicable, reliant on frugal and ubiquitous technology, and cost-effective. In this context, the WHO Infection Prevention and Control[95] approach and the UK's Infection Management Coalition conceptualise the benefits of strategic coordination between pandemic preparedness, sepsis recognition and treatment, infection prevention, and antimicrobial stewardship to prevent antimicrobial resistance (figure 3). Preparedness for emerging threats[96] thus goes hand in hand with measures to tackle sepsis in the population. The COVID-19 pandemic made it abundantly clear how crucial data-informed coordination between high-level governmental policies, health-care providers, and research groups is to ensuring effective management of infection threats to child health worldwide. Such collective insight, if harnessed, should spur on synergisms and drive progress towards meeting the targets of the 2030 World Sepsis Declaration.[97]

For more on the **Infection Management Coalition** see https://theimc.org/

Conclusions

Thanks to increasing attention to the global burden of paediatric sepsis and greater insights into the associated long-term sequelae, the understanding of what an enormous impact sepsis has on child health and society as a whole, worldwide, has fundamentally improved. The disproportionate burden imposed by sepsis on child health relates to the unique susceptibility of children to sepsis.[3] More investment in deciphering the host immune response to paediatric sepsis is needed to allow development of targeted therapies and begin to fulfil the promise of personalised medicine for children with sepsis. The new Phoenix criteria for paediatric sepsis will facilitate internationally harmonised delineation of the burden of paediatric sepsis and the development of tools for early recognition and treatment. In addition, the criteria will facilitate quality improvement efforts and benchmarking to improve outcomes for children with sepsis.[4] Finally, increasing digitalisation harbours enormous potential for tackling the burden of sepsis on child health.[5] Specifically, technological innovation in machine learning, electronic medical records, and handheld applications could dismatle pervasive barriers to improving outcomes of paediatric sepsis, from identifying more precise risk factors and phenotypes to disseminating tools that can optimise care.

Contributors

LJS and RSW initiated the writing process and wrote the first draft. All authors contributed to iterative meetings during manuscript development and individual sections of the manuscript, and revised the manuscript and approved the final version.

Declaration of interests

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