



# PEDIATRIC CRITICAL CARE IN RESOURCE-LIMITED SETTINGS

EDITED BY: Krishan Chugh, Srinivas Murthy, Ndidi Musa, Yves Ouellette  
and Phuc Huu Phan

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# PEDIATRIC CRITICAL CARE IN RESOURCE-LIMITED SETTINGS

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Millions of children are dying each year with preventable and reversible critical illness, including circulatory shock and respiratory failure. According to the World Health Organization, in 2015, the under-five mortality rate in low-income countries was 76 deaths per 1000 live births – about 11 times the average rate in high-income countries (7 deaths per 1000 live births). There is limited data about the nature of the delivery of critical care in resource-limited regions.

The care of critically ill children in low-resource settings is challenging, contributing factors include limitations in the existing infrastructure, lack of resources, and low numbers of appropriately trained healthcare workers. Meeting these challenges requires clinical evidence pertinent to the local settings, adequate number of well-trained personnel, quality improvement activities, and the ongoing development of preventative measures. In addition, approaches to prevent worsening critical illness in at-risk hospitalized patients are needed.

We are presenting 15 state-of-the art manuscripts from international experts, from all settings, involved in the care of critically ill children in resource-limited settings. This collection of manuscripts covers topics including education, research, clinical experience and infectious diseases. We hope that we are providing a window into the future of critical care delivery for all children around the world.

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# Editorial: Pediatric Critical Care in Resource-Limited Settings

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**Keywords:** critical care, pediatrics, global health, health equity, research agenda-setting, health workforce

## Editorial on the Research Topic

### Pediatric Critical Care in Resource-Limited Settings

The young field of pediatric critical care has reached an inflection point in its growth. Over its first few decades, practice was driven from a select few intensive care units in rich countries that produced the bulk of our fields' research and served as the training ground for its practitioners (1). The past 10 years, however, have revolutionized our field. There are pediatric critical care units in nearly every country in the world that provide life-saving care to more children than at any point in history (2).

Alongside that growth, we have realized that the research we perform needs to reflect the needs of those children. Given the hugely discrepant global burden of pediatric mortality, this means ensuring that children in lower-income regions of the world are kept at the forefront of any research agenda. As Paul Farmer of Partners in Health has stated, achieving excellence without achieving equity is the main human rights dilemma of healthcare in the twenty-first century, and no field is more emblematic of that challenge than pediatric critical care.

In this issue of *Frontiers in Pediatrics*, we have collected a diverse array of manuscripts examining a variety of issues pertaining to the critically ill child in lower-income countries. The recent growth in the field brings with it new challenges that deserve thoughtful consideration if our field is to grow in an evidence-driven, cost-effective, and ethical way.

## A WELL-TRAINED WORKFORCE

As many have stated, maintaining a well-trained health workforce is likely the biggest challenge in achieving a higher standard of care for those around the world (3). A lack of training opportunities and the ongoing brain-drain leads to a vacuum of skilled clinicians to provide advanced pediatric care in many regions of the world.

Collaboration for education is described, focusing on ensuring that materials are relevant to local practitioners. Primarily, focusing any educational opportunities on what communities want through needs assessments allows teachers to incorporate the varied learning styles and needs around the world with what is practical to implement. As care is often provided by those with limited training in critical care, teaching the fundamental principles to non-intensive care physicians can be achieved by adapting standardized short term pediatric critical care training courses to fill in the gaps. Ultimately, establishing formal training programs that are locally-organized with locally-driven rules and local accountability will be the path to ensuring a sustainable workforce. Practitioners from high-income countries must support these programs at all possible opportunities, facilitating local control of training opportunities to foster sustainability.

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## UNDERSTANDING THE BURDEN OF PEDIATRIC CRITICAL ILLNESS

A major part of targeting research to need is in defining an agenda. Fundamental to that is ensuring that research performance has the appropriate infrastructure in place to be done well. Establishing regional registries has been incredibly valuable in many high-income regions, and similar experiences are being rolled out in lower-income countries, such as India and Sri Lanka. Yet, challenges remain in performing well-designed research in much of the world, especially in designing and performing well-crafted implementation programs that are vital to translate research knowledge into practice.

Specific research will be highlighted to demonstrate how region- and population-specific epidemiology can be targeted to improve our understanding of disease and impacting outcomes. The burden and impact of specific viral infections vary by geography and socio-economic status. The management of fungal infections is unique in some regions, compared to others. Trauma management in resource-limited systems requires a drastically different approach from what many in high-income countries are familiar. Sepsis management, as always, will be context and resources-dependent. Most crucially, palliative care, which is an often under-appreciated component of critical care practice, deserves much more attention in the global literature. As demonstrated from well-known studies such as FEAST (4), for research to be relevant it must involve participants that are from the affected communities and reflect local practice and disease patterns.

## THE ETHICS OF COST-INTENSIVE CARE

From a practical standpoint, the ethics and economics of providing resource-intensive care when resources are constrained needs to be adequately explored. Simply because we *can* provide interventions does not necessarily mean that

we *should* provide those interventions, both at the individual and the health system level. Balancing effective public health interventions such as vaccination and ensuring access to primary care with the resource-intensity of critical care requires a focused understanding of the principles of distributive justice and resource allocation. Assessing the appropriateness of this high-cost care should be an integral part of the growth of our field, not just in low-income regions, but in all regions around the world as the technological complexity of the care we provide continues to increase.

The history of pediatric critical care is a short one, and researchers in lower-income countries have begun to ensure that they will be at the forefront of future advances. Innovations and research from lower-income regions are informing practice globally, with a number of high-impact randomized trials changing how the world manages sick children (4–7). We are slowly beginning to match the burden and distribution of disease with research to improve outcomes from those diseases, and are breaking out of the antiquated top-down approach of knowledge dissemination. This issue of *Frontiers in Pediatrics* is hopefully another step in that direction.

As high-income countries learn from their low-income country colleagues, working toward improving the resources available and the determinants of pediatric critical illness must be a collective ambition. As pediatric critical care providers in both higher- and lower-income regions, we call on our field to unite behind this common goal of improving the still-too-high rates of child mortality around the world. Through high-quality, patient-focused research dedicated on improving outcomes in populations most at-risk, we can achieve both excellence and equity.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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# Challenges and Priorities for Pediatric Critical Care Clinician-Researchers in Low- and Middle-Income Countries

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**Introduction:** There is need for more data on critical care outcomes and interventions from low- and middle-income countries (LMIC). Global research collaborations could help improve health-care delivery for critically ill children in LMIC where child mortality rates remain high.

**Materials and methods:** To inform the role of collaborative research in health-care delivery for critically ill children in LMIC, an anonymous online survey of pediatric critical care (PCC) physicians from LMIC was conducted to assess priorities, major challenges, and potential solutions to PCC research. A convenience sample of 56 clinician-researchers taking care of critically ill children in LMIC was targeted. In addition, the survey was made available on a Latin American PCC website. Descriptive statistics were used for data analysis.

**Results:** The majority of the 47 survey respondents worked at urban, public teaching hospitals in LMIC. Respondents stated their primary PCC research motivations were to improve clinical care and establish guidelines to standardize care. Top challenges to conducting research were lack of funding, high clinical workload, and limited research support staff. Respondent-proposed solutions to these challenges included increasing research funding options for LMIC, better access to mentors from high-income countries, research training and networks, and higher quality medical record documentation.

**Conclusion:** LMIC clinician-researchers must be better empowered and resourced to lead and influence the local and global health research agenda for critically ill children. Increased funding options, access to training and mentorship in research methodology, and improved data collection systems for LMIC PCC researchers were recognized as key needs for success.

**Keywords:** low- and middle-income countries, low resource settings, researchers, pediatric critical care, support of research, surveys and questionnaires, intensive care unit



## INTRODUCTION

The United Nations established Millennium Development Goal 4 aimed to reduce the under-five mortality rate by 2/3 between 1990 and 2015 based on the United Nations Millennium Declaration (1). Although overall progress was realized, only 58 of 138 countries achieved these targets with highest rates of childhood deaths concentrated primarily in low- and middle-income countries (LMIC) (2–4). For example, despite a 67% decrease in under 5 mortality rates (U5MR) in Latin America (LA) over the last 25 years, U5MR on average are still 10% higher in LA than in high-income countries (HIC) (5). Investment in resuscitation and critical care improves patient outcomes in LMIC (6–9). However, this health disparity is exacerbated by the “10–90 gap”: only 10% of health-care research expenditures worldwide address diseases that primarily affect the poorest 90% of the world's population (10).

The high burden of child mortality in LMIC is egregious considering that many lives could be saved by proven, simple resuscitative, and critical care interventions despite austere environments and fewer pediatric critical care (PCC) resources compared with HIC (11–15). There is need for LMIC institutions and researchers to conduct critical care research according to local resources and disease spectra, to disseminate results in-country, and influence policymakers, program managers and medical/public health practice (15, 16). Recent data from LMIC showed very clearly that we cannot translate critical care guidelines from HIC to LMIC, and in fact this practice, especially for sepsis, can be harmful (17–19). As such, the World Health Report 2013 called for LMIC to be not only users, but also producers of health research (16). Such health research requires study of leading regional causes of death and disability, which will provide data necessary to inform allocation, determine health-care delivery strategy, and assess quality standards required for effective critical care (15, 20, 21). Therefore, we conducted a survey with the following objectives: (1) to assess major challenges and potential solutions to PCC research in LMIC; (2) to foster worldwide research collaborations; and (3) to begin building a global research network to promote high quality research focused on improving outcomes for critically ill children.

## MATERIALS AND METHODS

The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Global Health (GH) subgroup (<http://www.palisiglobalhealth.org>), which includes PCC investigators from Canada and the United States (US), developed an online survey with input from leaders in PCC research in LMIC (Table S1 in Supplementary Material). Survey data were collected and managed using Research Electronic Data Capture (REDCap), an electronic data capture tool, hosted at the University of Washington in Seattle, United States (22). The survey was determined exempt by the Seattle Children's Institutional Review Board (IRB). The anonymous survey was emailed four times between January and June 2016 to a convenience sample of 56 clinician scientists in LMICs. These clinician scientists were identified by leading PCC researchers from LMIC, and through the PALISI GH subgroup's network. In addition, survey recipients were asked to forward the survey to

LMIC colleagues in the field, and a survey recipient from LA placed this survey on the PCC website “Sociedad Latino Americana de Cuidados Intensivos Pediatricos.” Given that responses were anonymous, we cannot determine between responders from the original convenience sample and responses to the survey posted on the above website. A response rate can therefore not be determined. Descriptive statistics were used for data analysis with subgrouping into respondents' geographic areas using STATA12.

## RESULTS

### Survey Respondent Characteristics

Forty-seven clinician-researchers from LMIC responded to the survey, the majority from LA (62%) (Table 1). Sixty-six percent of respondents were trained pediatric intensivists, and 23%

**TABLE 1 |** Survey respondents' demographics, research background, and involvement.

Survey respondents' information	Total <i>n</i> = 47 (%)	SE Asia <i>n</i> = 5 (%)	Africa <i>n</i> = 12 (%)	Latin America <i>n</i> = 29 (%)	Eastern Europe <i>n</i> = 1 (%)
<b>Credentials</b>					
Pediatric intensivist	31 (66)	4 (80)	4 (33)	22 (76)	1 (100)
Pediatrician with ICU experience	11 (23)	1 (20)	5 (42)	5 (17)	0 (0)
Other	5 (11)	0 (0)	3 (25)	2 (7)	0 (0)
<b>ICU beds</b>					
Less than 7	12 (25)	0 (0)	5 (41)	7 (24)	0 (0)
7–12	16 (34)	3 (60)	4 (33)	8 (28)	1 (100)
More than 12	19 (40)	2 (40)	3 (25)	14 (48)	0 (0)
<b>Protected research time<sup>a</sup></b>					
None	18 (53)	3 (60)	4 (50)	11 (55)	0 (0)
<10 h/week	10 (29)	1 (20)	0 (0)	8 (40)	1 (100)
>10 h/week	5 (15)	1 (20)	3 (38)	1 (5)	0 (0)
<b>Research training</b>					
Research degree	5 (15)	0 (0)	0 (0)	4 (20)	1 (100)
University-level coursework	14 (41)	2 (40)	1 (13)	11 (55)	0 (0)
Research seminar	15 (44)	4 (80)	3 (38)	8 (40)	0 (0)
Research project	25 (74)	5 (100)	4 (50)	16 (80)	0 (0)
<b>Potential research funding sources</b>					
International collaboration	9 (19)	0 (0)	5 (42)	4 (14)	0 (0)
Local hospital/foundation	19 (40)	3 (60)	2 (17)	14 (48)	0 (0)
Government	2 (4)	1 (20)	1 (8)	0 (0)	0 (0)
International grant	6 (13)	1 (20)	5 (42)	0 (0)	0 (0)
None	18 (38)	2 (40)	3 (25)	12 (41)	1 (100)
Currently funded research	7 (21)	1 (20)	3 (40)	3 (15)	0 (0)
Current research involvement	34 (72)	5 (100)	8 (67)	20 (69)	1 (100)
Clinical observational	27 (79)	5 (100)	6 (75)	15 (75)	1 (100)
Randomized controlled trial	14 (41)	2 (40)	3 (38)	9 (45)	0 (0)
Quality improvement	15 (44)	3 (60)	4 (50)	8 (40)	0 (0)
Research publication	18 (53)	3 (60)	5 (63)	10 (50)	0 (0)
<b>Research role</b>					
Principal investigator	20 (59)	4 (80)	6 (75)	9 (45)	1 (100)
Coinvestigator	10 (29)	1 (20)	2 (25)	7 (35)	0 (0)
Data collector	2 (6)	0 (0)	0 (0)	2 (10)	0 (0)
Local research network	12 (26)	2 (40)	4 (33)	6 (21)	0 (0)

SE, South East; ICU, intensive care unit.

<sup>a</sup>Nine respondents were not actively involved in a research project at the time of survey participation and did not respond to this question.

were intensivists by experience gained through practice. The proportion of trained pediatric intensivists was lowest in Africa (33%). Most respondents worked in combined adult–pediatric intensive care units at urban, public teaching hospitals.

## Respondents' Research Involvement and Resources

Active research involvement was reported by 34 (72%) respondents, all of whom had completed variable amounts of training in research methodology (Table 1). Fifty-eight percent were principal investigators (PIs) and 29% Co-PIs. Most respondents classified their research focus as clinical (82%), as compared with basic science (2%) and quality improvement (QI) (3%). Forty-seven percent had protected research time, and of those, 29% reported no more than 10 h of dedicated research time per week (Table 1). Twenty-one percent of active researchers, mostly from Africa, had research funding, and 53% reported publishing their results in a peer-reviewed journal.

## Current Research Priorities, Challenges, and Potential Solutions

Most respondents considered research of high importance (Table 2). Generating data that improved clinical care (51%) and establishing guidelines to standardize care (28%) were the most important reasons to perform research involving critically ill children. The main personal benefits cited were opportunities for research collaboration (70%), peer recognition (62%), and career advancement (40%).

Sepsis was the most common research area (38%), followed by invasive/non-invasive mechanical ventilation management (30%), trauma/traumatic brain injury (26%), and QI/patient safety (23%). Key research topics varied by region, with African respondents emphasizing cost-effectiveness, while South East (SE) Asian and LA respondents favored sepsis.

The highest-rated challenges to performing PCC research in LMIC were lack of funding (60%), few research support staff (47%), and high clinical workload (47%). A higher proportion of African researchers found it challenging to find mentors (42%); whereas LA researchers lacked statistical support (31%). The highest-rated solutions to these challenges were increasing research funding options for LMIC (70%), better access to mentors from HIC (51%), improved access to research training (45%), and better medical record keeping (34%).

Research networks were available to 26% of responders, to which LA researchers had the least access. Over half of the respondents collaborated with HIC researchers. These relationships were critically important for 9%, very important or important for 26 and 13% of LMIC clinician-researchers, respectively. The benefits of HIC collaborations included obtaining formal research training and experience (45%); gaining experience in manuscript preparation and publication (40%); and using established guidelines, protocols, and pathways to guide protocol development (34%). The top-rated benefits varied slightly by geographic region (Table 2). The primary challenges of HIC research collaboration were a lack of understanding of local settings (38%), communication limitations (26%), and the inability to sustain benefits over time (26%). Overall, 62% of researchers

**TABLE 2 |** Importance of challenges and solutions to pediatric critical care (PCC) research in LMIC.

Research description, challenges and solutions	Total <i>n</i> = 47 (%)	SE Asia <i>n</i> = 5 (%)	Africa <i>n</i> = 12 (%)	Latin America <i>n</i> = 29 (%)	Eastern Europe <i>n</i> = 1 (%)
<b>Importance of PCC research in LMIC</b>					
Critical	18 (38)	3 (60)	5 (42)	9 (31)	1 (100)
Very important	20 (43)	1 (20)	4 (33)	15 (52)	0 (0)
Important	9 (19)	1 (20)	3 (25)	5 (17)	0 (0)
<b>Most important reason to do research</b>					
Affect positive change in clinical care	24 (51)	3 (60)	6 (50)	14 (48)	1 (100)
Establish guidelines/protocols	13 (28)	2 (40)	3 (25)	8 (28)	0 (0)
Greater understanding of disease	2 (4)	0 (0)	0 (0)	1 (3)	0 (0)
Increase resource availability	3 (6)	0 (0)	2 (17)	1 (3)	0 (0)
Quality and safety	4 (9)	0 (0)	1 (8)	3 (10)	0 (0)
<b>Key areas of research in LMIC</b>					
Sepsis	18 (38)	2 (40)	3 (25)	12 (41)	1 (100)
Trauma	12 (26)	0 (0)	1 (8)	10 (34)	1 (100)
Invasive and non-invasive positive pressure ventilation	14 (30)	0 (0)	3 (25)	11 (38)	0 (0)
Quality improvement and patient safety	11 (23)	2 (40)	2 (17)	7 (24)	0 (0)
Health-care associated infections	9 (19)	3 (60)	2 (17)	4 (14)	0 (0)
ARDS/ALI	7 (15)	1 (20)	0 (0)	6 (21)	0 (0)
Cost-effectiveness	7 (15)	1 (20)	5 (42)	1 (3)	0 (0)
Education/capacity building	6 (13)	1 (20)	2 (17)	3 (10)	0 (0)
Nutrition	6 (13)	2 (40)	0 (0)	4 (14)	0 (0)
Mortality risk/severity of illness scores	5 (11)	1 (20)	0 (0)	4 (14)	0 (0)
Ethics and palliative care	5 (11)	0 (0)	1 (8)	4 (14)	0 (0)
<b>Personal benefits of research</b>					
Research collaboration	33 (70)	3 (60)	6 (50)	23 (79)	1 (100)
Peer recognition	29 (62)	3 (60)	7 (58)	18 (62)	1 (100)
Career advancement	19 (40)	3 (60)	6 (50)	9 (31)	1 (100)
Salary	6 (13)	0 (0)	4 (44)	2 (7)	0 (0)
Other	4 (9)	2 (40)	1 (8)	1 (3)	0 (0)
<b>Research challenges</b>					
Lack of funding	28 (60)	4 (80)	8 (67)	16 (55)	0 (0)
High clinical burden	22 (47)	3 (60)	3 (25)	15 (52)	1 (100)
Limited research support staff	22 (47)	3 (60)	3 (25)	16 (55)	0 (0)
IRB issues	12 (26)	0 (0)	4 (33)	7 (24)	1 (100)
Lack of statistical support	12 (26)	2 (40)	0 (0)	9 (31)	1 (100)
Limited research training opportunities	10 (21)	1 (20)	3 (25)	6 (21)	0 (0)
Finding research mentor(s)	7 (15)	0 (0)	5 (42)	2 (7)	0 (0)
Difficulty with publications	8 (17)	1 (20)	2 (17)	5 (17)	0 (0)
Lack of reliable medical records	4 (9)	0 (0)	3 (25)	1 (3)	0 (0)
Study subject recruitment	4 (9)	0 (0)	1 (8)	3 (10)	0 (0)
<b>Research solutions</b>					
More funding for low resource settings	33 (70)	5 (100)	8 (67)	19 (66)	1 (100)
Access to mentors in HIC	24 (51)	3 (60)	8 (67)	13 (45)	0 (0)
Access to research training	21 (45)	0 (0)	4 (33)	16 (55)	1 (100)
Access to research network	18 (38)	2 (40)	3 (25)	13 (45)	0 (0)
Improved medical records	16 (34)	2 (40)	3 (25)	10 (34)	1 (100)
Opportunities to present	9 (19)	1 (20)	3 (25)	5 (17)	0 (0)
Streamlined IRB review	6 (13)	0 (0)	3 (25)	3 (10)	0 (0)
Protected research time	4 (9)	2 (40)	0 (0)	2 (7)	0 (0)
HIC research collaborations	27 (57)	4 (80)	8 (67)	14 (48)	1 (100)
<b>Importance of collaboration</b>					
Critical	4 (9)	0 (0)	3 (25)	0 (0)	1 (100)
Very	12 (26)	3 (60)	3 (25)	6 (21)	0 (0)

(Continued)

TABLE 2 | Continued

Research description, challenges and solutions	Total <i>n</i> = 47 (%)	SE Asia <i>n</i> = 5 (%)	Africa <i>n</i> = 12 (%)	Latin America <i>n</i> = 29 (%)	Eastern Europe <i>n</i> = 1 (%)
Important	6 (13)	0 (0)	1 (8)	5 (17)	0 (0)
Less	3 (6)	1 (20)	0 (0)	2 (7)	0 (0)
Not	1 (2)	0 (0)	0 (0)	1 (3)	0 (0)
<b>Benefits of collaboration</b>					
Research training	21 (45)	0 (0)	6 (50)	14 (48)	1 (100)
Experience in manuscript preparation	19 (40)	2 (40)	4 (33)	12 (41)	1 (100)
Established guidelines	16 (34)	3 (60)	3 (25)	9 (31)	1 (100)
Financial support	13 (28)	0 (0)	5 (42)	8 (28)	0 (0)
Medical supplies	9 (19)	0 (0)	6 (50)	3 (10)	0 (0)
Other	5 (11)	1 (20)	2 (17)	2 (7)	0 (0)
<b>Problems with collaboration</b>					
Lack of understanding of local setting	18 (38)	1 (20)	6 (50)	11 (38)	0 (0)
Lack of sustainable benefit	12 (26)	0 (0)	6 (50)	6 (21)	0 (0)
Communication limitations	12 (26)	0 (0)	3 (25)	1 (3)	0 (0)
Lack of data sharing	9 (19)	1 (20)	1 (8)	6 (21)	1 (100)
Lack of local research administration	7 (15)	2 (40)	3 (25)	2 (7)	0 (0)
Lack of proper acknowledgment	7 (15)	1 (20)	1 (8)	4 (14)	1 (100)
Dissimilar vision and goals	7 (15)	0 (0)	1 (8)	6 (21)	0 (0)
Ethical conflict	4 (9)	1 (20)	0 (0)	3 (10)	0 (0)
Political barriers	4 (9)	0 (0)	3 (25)	1 (3)	0 (0)
Lack of high tech equipment	1 (2)	0 (0)	1 (8)	0 (0)	0 (0)
Benefits of collaboration outweigh problems	29 (62)	4 (80)	8 (67)	16 (55)	1 (100)

LMIC, low- and middle-income countries; HIC, high-income countries; SE, South East; ARDS/ALI, acute respiratory distress syndrome/acute lung injury; IRB, Institutional Review Board.

in LMICs thought the benefits of collaboration outweighed the difficulties.

## DISCUSSION

This study provides information on the vast needs and enormous challenges facing PCC clinician-researchers in LMIC. Most respondents rated the importance of research in PCC to improving health outcomes very highly, but cited lack of funding, heavy clinical workload, and limited research staff as major disincentives. Highest-rated solutions included increased funding opportunities and access to HIC mentors and research training.

Currently, no LMIC invests >1% of its gross domestic product on research and development, as compared with 2–4% in Korea, Japan, the US, and the United Kingdom (17, 23). HIC funders may insist that principal recipients of grants are based in donor countries, thus excluding LMIC institutions from receiving overhead support. It is not surprising then that only 21% of respondents were able to obtain funding and 60% lacked the financial support to conduct research. Lack of trained personnel is also a barrier; however, some solutions exist, such as the US National Institute of Health Fogarty Emerging Global Leader Award program, the NHLBI-UnitedHealth Global Health Centers of Excellence Program, and the World Health Organization/Special

Programme for Research and Training in Tropical Diseases Career Development Fellowship, which support scientists from LMIC (24). These programs are promising and are partly facilitated in LMIC, but successful applicants need established mentorship and if locally not available, mentors will come from HIC. Global networking should not be daunting because frugal technology is ubiquitous, hence building research communities, and linking like-minded scientists is relatively easy and highly beneficial. Improving record keeping was also rated as one of the main solutions to research challenges. In low-income settings, there is considerable pressure to contain the cost of data acquisition and still implement effective data management frameworks that produce quality data while research staff and physician time are limited. Introduction of the data capture tool REDCap, a non-commercial software solution designed for rapid development and deployment of electronic data, to a multi-site clinical information and research network in Kenya is now delivering quality pediatric data for clinical improvement and research use (25). This low-cost, sustainable and scalable program could be a solution for other resource-limited settings.

Physician-investigators in HIC face similar challenges as faculty in LMIC, which include securing funding for research programs; promotion or tenure systems not being responsive to the different needs of faculty working in both research and clinical care; and the increasing burdens of clinical care (26, 27). Problems with workload and burnout have been described for intensivists in HIC (28). Equivalent literature is lacking from LMIC, but given that most of sub-Saharan Africa has less than 0.5 doctors, and a large portion of LA less than 1.5 doctors per 1,000 population, compared with 2.5 and 3–4 per 1,000 in North America and Western Europe, respectively (29), clinician-researchers in LMIC are likely more stretched than in HIC. The contrast for numbers of PCC providers between LMIC and HIC is even more stark and likely plays into a PCC clinician-researchers workload dilemma: in LA the number of PCC physicians ranges between 2 in Honduras and 318 in Mexico, respectively; Kenya has a total of 3 PCC physicians serving more than 21 million people less than 18 years of age; compared with 1,805 PCC doctors in the US for 78 million children and adolescents (30–32).

The vast majority of LMIC researchers involved in collaborations with HIC rated these relationships as important for their research, emphasizing the value of nurturing and sustaining these partnerships. The main benefit of collaborations was the opportunity to be trained and gain experience in research, protocol, and guideline development. Mentoring was important, as well as the need for equal, mutually beneficial partnerships. Recent qualitative studies from LMIC highlight common themes of poorly distributed benefits from research involvement, and poor translation of research into local settings (21, 23).

Researchers in LMIC should have opportunities to obtain research funding to provide protected time for research. Research partnerships are often unequal; LMIC researchers should be included in research protocol development, grant applications, and investigation leadership. Funding often depends on successful research track records; if LMIC researchers are not given the opportunity to be PIs or gain acknowledgment for their work, they will continue to be disenfranchised. Mentorship should be



complementary of expertise, experience, and understanding, and foster symbiotic relationships. Previous high-impact studies have proven that HIC–LMIC collaboration can successfully improve clinical care, directly benefit the participating communities and give career opportunities to local researchers (17, 33, 34). This should be the paradigm for PCC research study design in LMIC.

Association with experienced PALISI researchers and mentorship in grant writing could help address the funding problems of LMIC PCC researchers. To help address barriers to research in LMIC identified in this survey, the PALISI GH subgroup has begun outreach to PCC researchers in LMIC. Specifically, some PCC researchers have presented research proposals (in-person and *via* webinar) for purposes of feedback and/or recruitment of sites, while others have identified mentors and collaborators. The PALISI-GH subgroup supports the development of PALISI-like groups in LMIC to increase growth of research collaborations and research investigator development. PALISI provides annual research training opportunities for North American PCC fellows, which could be modeled by LMIC countries or potentially be offered to LMIC researchers *via* remote participation or subsidized for in-person attendance by grants.

Although this survey generated interesting data regarding PCC research in LMIC, it had several limitations. The low total number of survey responses limits the generalizability of the results, especially for SE Asia and Eastern Europe. Responses from LA were higher likely due to better local survey publicizing. A response rate cannot be determined given that respondents *via* original invitation versus website survey cannot be distinguished. Given some of the survey recipients were acquired through the PALISI GH subgroup's network, responses may be biased. The term "local research network" was not specifically defined in the survey and could have been interpreted differently by responders, such as hospital, regional, country or continent-wide networks.

## CONCLUSION

Since over 95% of the global under-five mortality still occurs in LMIC, researchers from these regions must play a role in setting research priorities, developing clinical guidelines for their settings, informing national policy and improving care for their communities. Increased funding options; access to training and mentorship in research methodology, to research networks, and improved data collection systems are paramount for the success of LMIC PCC researchers. Even in the absence of independent

funding mechanisms, HIC–LMIC collaborations as well as regional and international research networks such as PALISI GH can provide important support to colleagues around the world.

## ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Seattle Children's Institutional Review Board, which determined the study to be exempt from IRB approval, since the human subject research involved the use of survey procedures; and the survey did not record information in such a manner that human subjects could be identified, directly or through identifiers linked to the subjects; and any disclosure of the human subjects' responses outside the research could not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

## AUTHOR CONTRIBUTIONS

AA was involved in survey design, obtained IRB approval, distributed the survey, and participated in data analysis and manuscript writing. EF was involved in survey design, assisted in survey distribution, and participated in data interpretation and in manuscript writing. JA, NK, and EM were involved in survey design, data interpretation, and manuscript writing. NM was involved in manuscript writing. KN completed the data analysis and was involved data interpretation and manuscript writing. TK was involved in data interpretation and manuscript writing.

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## SUPPLEMENTARY MATERIAL

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# Commentary: Challenges and Priorities for Pediatric Critical Care Clinician–Researchers in Low- and Middle-Income Countries

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**Keywords:** low- and middle-income countries, low resource settings, researchers, pediatric critical care, support of research, surveys and questionnaires, intensive care unit

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Von Saint Andre-Von Arnim and colleagues noted that LMIC clinicians should be empowered to influence local and global research agendas for critically unwell children (1). We too can report that clinicians trained in LMIC acknowledge the need for systematic gathering of outcome data in improving services and endorse the role that non-LMIC collaborators can play in contributing to training, surveillance, and research (2). Interestingly, these perceptions were more strongly held when compared to High Income Country (HIC) counterparts with experience in LMIC settings. These findings perhaps point to untapped opportunities to upskill LMIC clinicians to build equitable research and training partnerships with their non-LMIC counterparts.

Network for Improving Critical Care Systems and Training (NICST) is an LMIC-based organization working collaboratively, since 2012, with clinical teams to build capacity for research, training, and continuous audit to improve patient outcomes (3). A collaboration between clinicians, researchers, and educational experts based in HICs and LMIC, the network, funded in part by a UK grassroots charity of the same name, links over 110 state and private sector hospitals and has trained over 4,500 nurses and doctors in acute and critical care skills.

The NICST platform, a clinician-led mobile electronic health information initiative, is an example of a setting-adapted national registry for critically unwell adults, children, and neonates in Sri Lanka and beyond. Output from the registry supports a critical care bed availability system that facilitates access to and utilization of resources and provides information on post-hospital outcomes (4). Mobile applications linked to the platform improve the availability of information essential for the care of individual patients and enable practical training for nurses and doctors (5). Partnered with institutions based in HIC (UK and the Netherlands), it is creating educational opportunities (MSc, PhD pathways) (6, 7) and undertaking frontline quality improvement projects in Sub-Saharan Africa and South Asia.

Creating sustainable partnerships that harness the power of the existing LMIC-based network enables equitable exchange of expertise and fosters greater understanding of setting-specific research priorities. We anticipate that these successful collaborations coupled with rising awareness of the importance of high-quality surveillance systems in LMIC will somewhat help address the challenges

currently experienced by LMIC-based researchers approaching traditional funding streams. We believe our model provides a template for promoting setting-relevant research, which can enable successful south-to-south (and perhaps south-to-north!) collaborations.

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## AUTHOR CONTRIBUTIONS

RH and AB wrote the first draft of the manuscript. AD and PA approved and improved the manuscript. All the authors approved the contents.

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# Advances in Pediatric Critical Care Research in India

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Over last 2 decades, there has been a significant progress made in the field of pediatric critical care in India. There has been complementary and parallel growth in the pediatric critical care services in India and the number of pediatric critical care providers who are either formally trained in India or who have returned to India after their formal training abroad. The pediatric critical care community in India has recognized obvious differences in profiles of critical illnesses and patients between Indian subcontinent and the West. Therefore there is a growing interest in generating scientific evidence through local research which would be applicable to critically ill children in Indian subcontinent. This article focuses on advances in pediatric critical care research in India and its future directions.

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## INTRODUCTION

Pediatric Critical Care Medicine (PCCM) is a relatively new but a rapidly growing pediatric specialty in resource-limited countries. Pediatric Intensive Care Units (PICUs) were introduced into the lower- and middle-income countries (LMICs) somewhere in late 1980's or early 1990's. Few countries in Africa and south-east Asia still do not have a dedicated PICU. Though pediatric intensive care practices were introduced into India in the 1980's, early units were simply located in a special "treatment room" and lacked the constant monitoring of vital sign, respiratory or hemodynamic support characteristic of a PICU. One author (KC) recalls his first exposure to a PICU at Kalawati Saran Children's Hospital, Lady Hardinge Medical College in 1983 in New Delhi, although the first organized PICU was reportedly established in 1991 at Kanchi Kamakoti Childs Trust Hospital in Chennai, India with seven beds, a separate team of doctors and nurses, and with a pediatric anaesthesiologist as the director of the unit (1). Currently, there are more than 100 dedicated PICUs in the private and public sectors in India. With growth in pediatric critical care services in India, there has been a parallel growth in academic medicine in pediatric critical care in India. This article describes advances in critical care research in the west and in India, particularly in PCCM and future of pediatric critical care research in India.

## Advances in Pediatric Critical Care Research in the West

For any specialty in medicine, research is key to understanding the epidemiology and pathophysiology of disease processes, exploring potential new therapies and measuring response to therapies. With rapidly growing specialty of pediatric critical care, there have been parallel advances in research in pediatric critical care in the West. The first collaborative pediatric critical care study group (PCCSG) was founded by Gregory Stidham and associates in the early 1990s. Approximately 60 pediatric ICUs, mostly from the United States worked together to generate a number of studies related to PICU outcomes (2–7). The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI)

Network, was founded by Adrienne Randolph at Children's Hospital of Boston in the late 1990s. Around 48 pediatric ICUs throughout North America participated to study therapies for acute lung injury, sepsis and multi-organ failure (8–11). Randall Wetzel at Children's Hospital Los Angeles founded the first electronic database, the Virtual PICU (vPICU) in 2000, to create a shared patient database for outcomes analysis and improve critical care practices (12). In 2004, National Institutes of Health, founded the Collaborative Pediatric Critical Care Research Network (CPCCRN) to study the pathophysiological bases of critical illness and safety and efficacy of treatment of critically ill children (12). The pediatric interest group of Canadian Critical Care Trial Group (CCCTG) has conducted large, multicenter trials such as TRIPICU and HypHIT (13). Similarly, European Society of Pediatric and Neonatal Intensive Care (ESPNIC) has been active in multi-center evaluation of respiratory distress syndrome (14) and in collaboration with European Extracorporeal Life Support (EuroELSO), it has created a working group to evaluate actual and future trends about neonatal and pediatric ECMO in Europe (15). The ANZICS (Australian and New Zealand Intensive Care Society) Pediatric Group has fostered and promoted meaningful research within the Australian and New Zealand pediatric intensive care communities (16).

There are now innumerable, ongoing single-site and multi-site clinical trials and large database studies in America and Europe which are substantially contributing to our understanding of science of PCCM. Some examples of recent key studies are—therapeutic hypothermia after pediatric cardiac arrest (THAPCA), heart and lung failure—pediatric insulin titration (HALF-PINT) and randomized evaluation of sedation titration for respiratory failure (RESTORE) trials (17–19).

## Advances in Adult Critical Care Medicine Research in India

Before the turn of the century, critical care medicine in India was practiced in a few hospitals, either by those interested in the field and learning on the job, or by physicians returning to India after training overseas. Establishment of the Indian Society of Critical Care Medicine (ISCCM) in 1993 was a turning point in the history of critical care medicine in India. ISCCM has grown to become one of the largest professional organizations and serves as the premier organization supporting the training and research in critical care medicine in India (20). In 2012, the Medical Council of India (MCI) recognized critical care medicine as an independent speciality, enabling 3-year training programmes, which have facilitated the development of academic departments of intensive care medicine with greater emphasis on research (21). Adult critical care community in India has made significant contributions to large multicenter randomized controlled trials such as the PROWESS-SHOCK (22) and OSCILLATE studies (23) and to a number of international, multicenter observational studies (24–28). Over last decade, several multicenter, adult critical care studies conducted in ICUs in India have contributed to a body of literature relevant to the Indian population (21). Though, Divatia and co-authors reported a 35% increase in

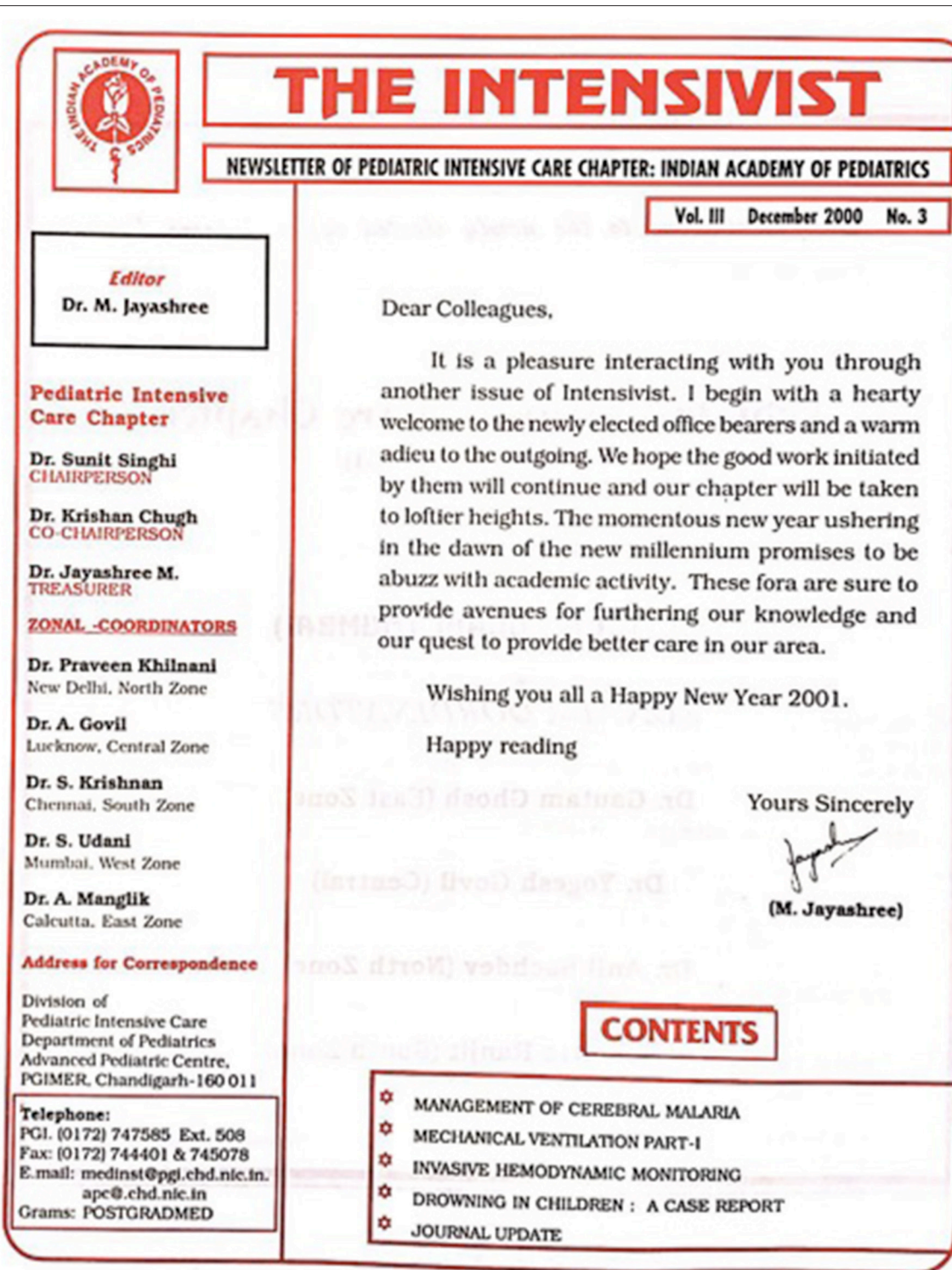
the number of abstracts submitted to the annual conference of the ISCCM in 2013 as compared to the 2012 conference, their publication rate in international journals has been low (21, 29). Time constraints and lack of motivation to publish could be important contributing factors to the low publication rate. Overall, the advances in adult critical care medicine research in India have encouraged the pediatric critical care community to make forward steps toward pediatric critical research relevant to the unique diseases and child populations in India.

## Advances in Pediatric Critical Care Research in India

The initiative to upgrade neonatal and pediatric critical care facilities has come primarily from major teaching institutions (30). India has shown tremendous growth in the practice of pediatric critical care. From a single PICU in 1991 to a young dynamic speciality in 2017, it has come a long way. India, foremost amongst the resource-limited countries has been a leader in that. The intensive care chapter of the Indian Academy of Pediatrics (IAP) started a formal fellowship training program in 2002 and they now have 22 accredited centers that are running this program successfully. More than 250 students have been trained through this program (31).

Similarly, research in neonatal and pediatric critical care has also picked up in India. The early published reports on outcomes of intensive care units in India were related to neonatal intensive care unit (NICU) graduates (32). Subsequently, Singhi and co-authors published the first report on electrolyte abnormalities in pediatric pneumonia in 1992 (33). As listed in PubMed, pediatric critical care research has grown from only 31 published clinical trials, 19 randomized controlled trials (RCTs) and 2 multicenter studies in 1990 to an impressive 198 RCTs and 92 multicenter studies in 2016. This progress shows that the growth of research in Pediatric Critical Care in India has come a long way. As the interest in research grew, the Government of India also tried to streamline it by setting up the Clinical Trial Registry of India (CTRI) in 2007. Registration of trial in CTRI is now mandatory and is also an important factor for publication in various journals. As on 30th June 2017, 8950 trials are registered with the CTRI (34).

Retrospective and prospective pediatric critical care studies conducted in India and their subsequent publication in regional and international journals have grown steadily in the past two decades (35–41). A handful of studies conducted by pediatric critical care researchers in India have impacted PICU care not only in the region but also outside the region—for example, original studies published from India on monitoring of intracranial and cerebral perfusion pressures in patients with acute meningoencephalitis have reinvigorated the field of neurocritical care (42–44). Recently, newer developments in collaborative, multicenter research initiatives in pediatric critical care have occurred in India. The Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh, India has initiated the first, national, multi-institutional database for pediatric cardiac arrest and cardiopulmonary resuscitation. Currently, large, government-run, teaching institutions are



**FIGURE 1** | The picture of the periodical "The Intensivist" which was started by Indian Academy of Pediatrics Intensive Care Chapter, which ultimately culminated into launching of the official journal of pediatric critical care of the intensive care chapter of the Indian Academy of Pediatrics.



putting collaborative efforts to launch similar multicenter collaborative studies.

Under the auspices of ISCCM, several pediatric critical care leaders in India have started a multicenter PICU data registry called INSPIRED (personal communication). Also, several institutions in India are now contributing to multicenter, international, pediatric critical care studies such as point prevalence studies, or quality improvement studies led by western institutions (45, 46). The Intensive Care Chapter of IAP started the quarterly periodical called “The Intensivist” (**Figure 1**), which grew in popularity over time and culminated into launching the Journal of Pediatric Critical Care in 2014, which is the official journal of the chapter (**Figure 2**) (47).

## Factors Influencing Advancement of Pediatric Critical Care Research in India

India is a large country and continues to be second most populated country in the world. The healthcare in India has been constantly challenged with issues of manpower, resources, infrastructure and financial support. Though the number of pediatric intensivists trained either within or outside India has

grown significantly in India over last 15 years, current manpower is not sufficient to cope with the number of critically ill children in India. Due to heavy clinical commitments and burn-out issues, pediatric critical care professionals in India lack sufficient protected time for research. Also, unlike western countries, India has very limited government funds allocated to research. This further restricts the support needed for research data gathering, statistical analyses, research coordination and dissemination of research findings. Several research institutes, research task forces, and grants-in-aid developed by Indian Council of Medical Research (ICMR) have led to improved research support in India (48). The pediatric critical care faculty at large, government-run, teaching institutes have tapped into these resources for investigator-initiated clinical trials in PCCM. Also, some of the industry funds have also become available for PCCM research in India (49).

The initiation of PCCM fellowship training programs by the Intensive Care Chapter of IAP have not only promoted clinical training in pediatric critical care but also fueled research enthusiasm among young and budding pediatric intensivists in India (31). A formal 3-year post-doctoral training program



**FIGURE 2 |** The picture of journal of pediatric critical care—the official journal of the intensive care chapter of the Indian Academy of Pediatrics.

in PCCM, started by the PGIMER in Chandigarh, India and subsequently adopted by two other premier institutes in India has paved the pathway for protected research time and formal research training of PICU fellows.

The national conference of pediatric critical care (NCPCC) organized annually by IAP intensive care chapter has provided tremendous opportunities to PCCM community in India to showcase and discuss their research findings and collaborate on research (50). Similarly, the annual conferences organized by World Federation of Pediatric Intensive and Critical Care Societies and Society of Critical Care Medicine have allowed networking of pediatric intensivists from India with those from other countries and improved research collaborations (51). Several global health institutions of leading universities and hospitals in the West have collaborated with institutes in India and conducted research related to neonatal and pediatric critical care (52).

## Future of Pediatric Critical Care Medicine Research in India

India is a country with the world's second largest population, a relatively low median age, and a demographic trend that is very different from developed countries. Also India is a fast growing emerging market, especially in the field of information technology. This signifies a great potential for research especially in pediatrics given the young population and disease burden. It is likely that with a transition from a developing nation to a developed nation, India will witness a wide spectrum of healthcare issues of children common to both developing and developed nations. It is likely that there will be a growing population of longer-term survivors of prematurity, congenital heart disease and genetic syndromes, which used to be otherwise deemed fatal in the past. These future trends will affect PICU research in India.

As the PCCM specialty continues to grow, more research is likely to occur at both government-run, teaching institutions as well as corporate hospitals. Due to several obvious differences in disease profiles, host characteristics (e.g., malnutrition), access to medical care, or resource availability and allocation, the pediatric

critical care community understands that scientific evidence generated through studies done in the West cannot always be extrapolated to patients in the Indian context. Among the pediatric intensivists, there is a growing awareness of the need of generating scientific evidence locally through studies within India. This is likely to culminate into an increase in investigator-initiated, single-center studies and also improved collaboration among a larger number of PCCM programs to create data registries and multicenter clinical trials in India.

The strengths of critical care medicine community in India include a huge knowledge-base for tropical and infectious diseases (53, 54), large patient burden, cost-effective strategies and the development of low-cost technology solutions through frugal innovation (55). As the investigator-initiated single-center and multicenter studies in PCCM grow in India, parallel efforts need to be made by government and corporate healthcare systems to improve the research infrastructure. Also, It will be equally important for institutions and professional organizations such as the ISCCM and IAP to establish structured research training for PCCM in India. A quality improvement research project and/or research thesis done during fellowship and an opportunity to present research work at a national and international conferences might encourage the pediatric critical care fellows to pursue academic careers. Finally, the contributions of national organizations such as ISCCM in supporting research through research resources, funding and research collaborations will define the future of the pediatric critical care research in India.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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# Pediatric Critical Care Medicine Training in India: Past, Present, and Future

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Pediatric critical care services in India have grown with leaps and bounds. There has been a growing need of physicians specially trained in pediatric critical care medicine (PCCM) in India. Physicians returning to India after their formal training in PCCM abroad have partly supported this growing need. Development of formal PCCM training programs in India has been a huge step toward supporting the growing clinical needs. This article focuses on advances in pediatric critical care training in India and its future directions.

**Keywords:** pediatric critical care, training, fellowship, simulation, India, resource-limited settings

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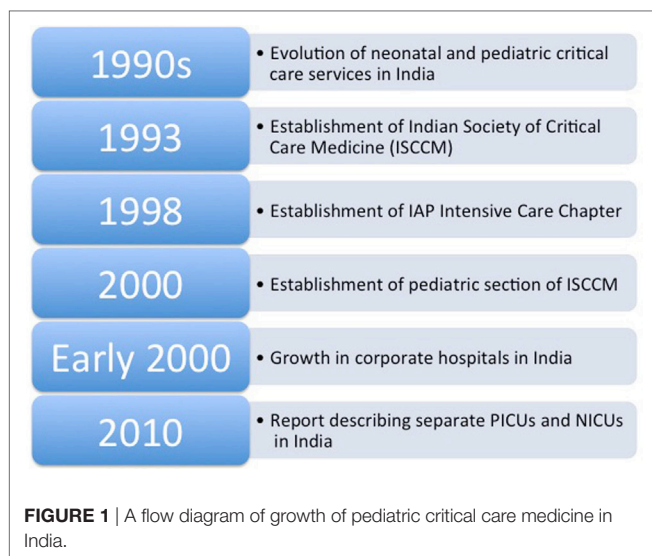
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## INTRODUCTION

Until 2002, formal fellowship training in pediatric critical care medicine (PCCM), accredited by a national governing body did not exist in India. Therefore, pediatricians interested in such training, explored options outside of India for formal PCCM fellowship. Over the subsequent 15 years, the scenario of PCCM changed dramatically in India. Quite a few physicians after completing a formal PCCM fellowship and gaining some experience working as senior house officers or faculty abroad returned to India to lead the PCCM programs in major metropolitan areas of India. Also, a very good number of hospitals established formal fellowship training in PCCM. This article focuses on formal, curriculum-based PCCM training as well as recent advances in simulation-based PCCM training in India.

## GROWTH OF PEDIATRIC CRITICAL CARE SPECIALTY IN INDIA (FIGURE 1)

In 1997, Vidyasagar and co-authors summarized the evolution of neonatal and pediatric critical care in India (1) (Figure 1). The initiative to upgrade neonatal and pediatric critical care came primarily from major teaching hospitals, especially government sponsored institutions (1). Around the turn of the century, India witnessed a boom in the field of healthcare (2, 3). There was a significant growth in number of corporate hospitals capable of providing state-of-the-art services to patients in metropolitan areas of India (3). These corporate hospitals took the lead in establishing units based on Western standards of equipment and personnel, thereby moving the PCCM specialty in a favorable direction in India (1, 4). The establishment of these hospitals created newer opportunities and attracted well-trained and experienced physicians and surgeons to either return to India or move from government hospitals to corporate hospitals to establish specialty and subspecialty divisions. In 2010, Lodha and co-authors reported a few centers in government and private hospitals in India with separate pediatric intensive care units (PICUs) (5). Now there are multiple, small-to-medium size PICUs all over India, which are run by pediatric intensivists formally trained either abroad or within India. In fact, Dr. Khilnani under auspices of Indian Academy of Pediatrics (IAPs) published consensus guidelines for design and operation of PICUs in India (6). Needless to say, large proportions



of children in rural and remote parts of India are still deprived of timely critical care services and succumb to the illness.

## CONTRIBUTIONS OF NATIONAL SOCIETIES IN SUPPORTING THE PEDIATRIC CRITICAL CARE TRAINING IN INDIA

Indian Society of Critical Care Medicine (ISCCM) was established in Mumbai, India in 1993. It is the largest non-profit association of Indian physicians, nurses, physiotherapists, and other allied health care professionals involved in the care of the critically ill. ISCCM, which started with a small group of intensivists, from Mumbai, has grown to membership of 7,440, comprising of 67 city branches all across the India with headquarter in Mumbai (7). The pediatric section of ISCCM was established in 2000. It has more than 200 members. Indian College of Critical Care Medicine was established by ISCCM to implement and carry out all the educational activities, including Indian fellowship in critical care medicine and Indian diploma in critical care medicine (7). The intensive care chapter of IAPs was established in 1998 (8). Since then, IAP Intensive Care Chapter has been successful in promoting the field of pediatric critical care. It has more than 500 members. The chapter has established guidelines for PICUs and education programs (8). ISCCM in coordination with the IAP intensive care chapter has developed PCCM fellowship with an established curriculum and training at the approved PICUs all over the country (9). The pediatric section of ISCCM and IAP has been active in beginning Diplomate in National Board certification in PCCM (7, 10). The national bodies have been active in organizing critical care conferences, workshops, and courses such as basic pediatric intensive care in India (8). This has not only improved networking opportunities connecting the potential PCCM fellows to the appropriate fellowship programs but also reinforced their clinical and academic training.

## PCCM TRAINING IN INDIA

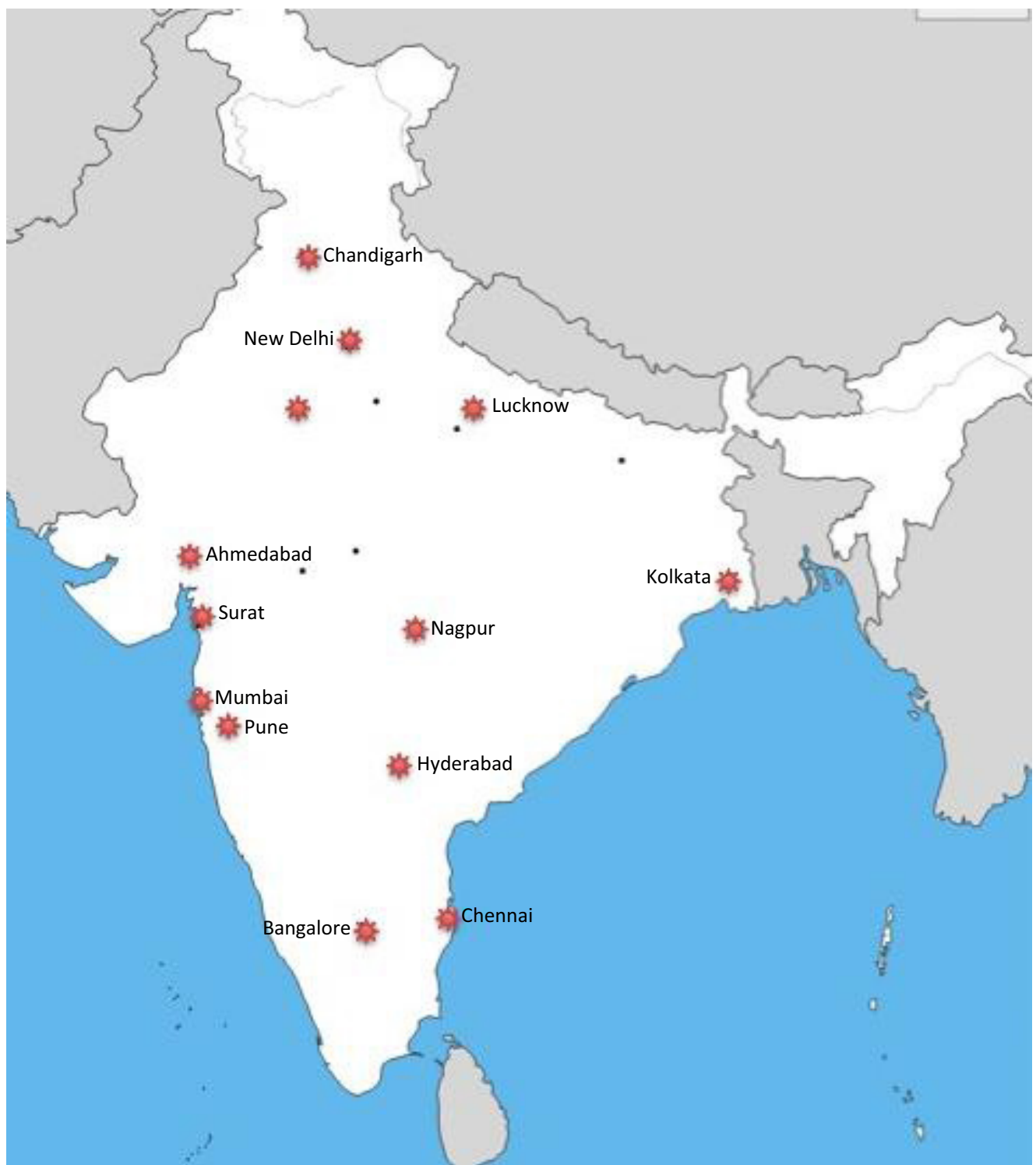
There are now 22 official PCCM fellowship programs listed on the college of pediatric critical care website and the number is growing every year (8) (**Figure 2**). There are different curriculum-based PCCM fellowships—a 1-year fellowship and a 2-year fellowship, each heavily clinically focused. There are only a handful of institutions in India, which have started a 3-year PCCM fellowship with curriculum similar to that of PCCM training in the West. The 3-year fellowship provides sufficient time for accomplishing a meaningful research project. The 3-year fellowship programs, which offer Doctor of Medicine degree upon successful completion of the fellowship, have been restricted to large, esteemed, government-run teaching institutions (10).

During fellowship, the fellows work closely with pediatric critical care consultants, pediatric cardiologists, surgeons, and other specialists. In India, traditional bedside teaching is still far more prevalent than classroom teaching. Apart from fundamental critical care training, the fellows also get exposed to counseling families, delivering difficult news, quality, and safety in PICU and end of life care. The fellows also get trained in designing a PICU, understanding a need for PICU in rural setting, creating, managing and maintaining a new PICU, and working on a budget for building a new PICU, implementing PICU protocols and a teaching program. Critical care ultrasound has been increasingly utilized in India (10–12). A significant number of PICUs in India have started using bedside ultrasound for assessment of critically ill children and monitoring of the therapies (13, 14). But the training of the PCCM fellows in India occurs largely based on the traditional “see one, do one and teach one” model. A handful of PCCM fellows attend critical care ultrasound workshop or course (15) but there is no formal curriculum or credentialing process for critical care ultrasound (16).

For PCCM fellows in India, majority of clinical learning, including procedural skills occur on the job. In the USA, a large number of PCCM fellowship training programs have adopted a formal fellow orientation process, which often includes hands-on airway skills in the operating room under supervision of a pediatric anesthesiologist and simulation-based training before they actually begin to work in the PICU. Similar to the West, majority of PCCM fellowship programs in India offer hands-on airway skills training in the operating room in the first year of fellowship. Recently, there is an increase in awareness and use of simulation-based teaching and training methodologies in pediatric emergency and critical care medicine.

## SIMULATION-BASED PCCM TRAINING IN INDIA

Over last 5 years, there is a significant growth in simulation-based PCCM training. Pediatric Simulation Training and Research Society (pediSTARS) has played vital role in introducing and spreading the simulation-based pediatric training in India (17). Back in 2011, the society introduced the first simulation workshop focused on pediatric emergencies as a pre-congress workshop prior to National Conference of Pediatric Critical



**FIGURE 2** | Map of major cities of India with pediatric critical care medicine fellowship training centers.

Care (NCPCC) (17). But the simulation-based training in PCCM remained largely dormant in India for a couple of years beyond the initial attempt at introducing the concept of simulation. Our first regional pediatric critical care simulation workshop

organized and conducted by us in Mumbai in 2013 (18) drew a significant interest and enthusiasm in simulation-based PCCM training in rest of the India. Ever since then, the IAP intensive care chapter adopted it as a standing pre-congress workshop for

the NCPCC. Also, following this, pediSTARS launched the first national conference in pediatric simulation, SIMULUS along with the first pediatric simulation training of trainers' workshop in 2014 in India (17). PediSTARS India has played a prominent role in organizing SUCCESS—Simulation Course for Critical care Emergencies for pediatric intensive care trainees (17). Moving forward, simulation-based PCCM training must focus on basic and advanced PCCM training in keeping with the challenges of critical care delivery unique to the developing world, such as limitation of resources (19), fulminant infections unique to the developing world (20) and transportation of critically ill children (21).

Simulation training of PICU fellows should also focus on training them on multidisciplinary care, prevention, and management of team conflicts, dealing with difficult situation, delivering bad news, dealing with hostile and uncooperative family.

## FUTURE OF PCCM TRAINING IN INDIA

A rapid growth of PCCM training programs in India has paralleled and complemented the rapid growth of healthcare sector in India. Two national societies—ISCCM and IAPs have played pivotal role in growing and supporting PCCM fellowship programs all over India and in future they will continue to advance the field. In future, it is likely that a larger number of teaching institutions in India will adopt a 3-year fellowship curriculum with balanced clinical and academic PCCM training. Critical care ultrasound

training, simulation-based training, training in advanced therapies, such as renal replacement and extracorporeal life support, training in quality and safety, and research methodologies are likely to become integral part of the PCCM fellowship in India in future. Western influence is likely to bring less hierarchy in healthcare. Therefore, a formal, 360° evaluation system within PCCM fellowship is likely to be introduced in India in future. Similar to what western countries witnessed in the last decade, PCCM subspecialty services in India, such as pediatric cardiac critical care and pediatric neurocritical care, are likely to grow and branch out from the general pediatric critical care. Separate pediatric cardiac intensive care units already exist in a good number of private and government hospitals since last few years. It is likely that special critical care training programs focused on pediatric cardiac critical care and pediatric neurocritical care will begin in India in the near future. In short, since the beginning of the new century, the PCCM training in India has grown with leaps and bounds and it is still growing. The contributions of national societies and quality of standards of PCCM fellowship programs maintained by national societies and governing bodies, such as ISCCM, IAP intensive care chapter, Medical Council of India, and National Board of Examinations, will define the future of pediatric critical care training in India.

## AUTHOR CONTRIBUTIONS

Each author contributed equally to this manuscript.

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# A Standardized Needs Assessment Tool to Inform the Curriculum Development Process for Pediatric Resuscitation Simulation-Based Education in Resource-Limited Settings

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**Introduction:** Under five mortality rates (UFMR) remain high for children in low- and middle-income countries (LMICs) in the developing world. Education for practitioners in these environments is a key factor to improve outcomes that will address United Nations Sustainable Development Goals 3 and 10 (good health and well being and reduced inequalities). In order to appropriately contextualize a curriculum using simulation, it is necessary to first conduct a needs assessment of the target learner population. The World Health Organization (WHO) has published a tool to assess capacity for emergency and surgical care in LMICs that is adaptable to this goal.

**Materials and methods:** The WHO Tool for Situational Analysis to Assess Emergency and Essential Surgical Care was modified to assess pediatric resuscitation capacity in clinical settings in two LMICs: Uganda and Myanmar. Modifications included assessment of self-identified learning needs, current practices, and perceived epidemiology of disease burden in each clinical setting, in addition to assessment of pediatric resuscitation capacity in regard to infrastructure, procedures, equipment, and supplies. The modified tool was administered to 94 respondents from the two settings who were target learners of a proposed simulation-based curriculum in pediatric and neonatal resuscitation.

**Results:** Infectious diseases (respiratory illnesses and diarrheal disease) were cited as the most common causes of pediatric deaths in both countries. Self-identified learning needs included knowledge and skill development in pediatric airway/breathing topics, as well as general resuscitation topics such as CPR and fluid resuscitation in shock. Equipment and supply availability varied substantially between settings, and critical

shortages were identified in each setting. Current practices and procedures were often limited by equipment availability or infrastructural considerations.

**Discussion and conclusion:** Epidemiology of disease burden reported by respondents was relatively consistent with WHO country-specific UFRM statistics in each setting. Results of the needs assessment survey were subsequently used to refine goals and objectives for the simulation curriculum and to ensure delivery of pragmatic educational content with recommendations that were contextualized for local capacity and resource availability. Effective use of the tool in two different settings increases its potential generalizability.

**Keywords:** pediatric resuscitation, simulation-based training, limited-resource settings, pediatric critical care, needs assessment, neonatal resuscitation, developing countries, PIPES tool

## INTRODUCTION

Globally, 5.6 million children under the age of 5 years died in 2016 (1). Since 1990, early childhood mortality has decreased substantially around the world, from 98 to 41 of every 1,000 live births. However, this rate remains much higher than the United Nations Sustainable Development Goal target of 25/1,000, and significant progress is needed to achieve this objective (2, 3). For the past two decades, it has been recognized that a multitude of factors contribute to potentially preventable child deaths in low- and middle-income countries (LMICs) (4). One thing that has not changed among these factors is the lack of high quality and contextually appropriate educational curricula to teach provision of care to critically ill children in these settings.

The World Health Organization (WHO) has developed the integrated management of childhood illness (IMCI) strategy and the emergency triage assessment and treatment (ETAT) guidelines for use in resource-limited settings (5, 6). Despite the demonstrated feasibility and success of some of these initiatives in LMICs (7), adherence to these guidelines by medical providers is highly variable (8, 9). Provider education has been shown to improve quality of care, but even among trained providers, performance remains suboptimal, suggesting the need for additional educational reinforcement (10).

For this reason, effective resuscitation education programs are needed in LMICs. Some training programs have been designed specifically for use in resource-limited settings, such as the Helping Babies Breathe (HBB) and Helping Mothers Survive (HMS) Bleeding after Birth initiatives (11–16). However, other resuscitation courses, such as the American Heart Association (AHA) Pediatric Advanced Life Support (PALS) and Pediatric Emergency Assessment Recognition and Stabilization (PEARS), have not been fully adapted for use in resource-limited settings. This has led many investigators to undertake these adaptations on an individual basis, often without a clear process to guide their efforts (17). However, “contextualized training,” defined as “local adaptation of training, utilizing existing and sustainable resources for both care and training,” has been associated with increases in provider confidence and short-term knowledge retention (18).

Contextualization of training requires rigorous understanding of the target learners and local clinical environment. In the

curriculum development process, this understanding is gained through a needs assessment, which allows educators to ensure that curricula are appropriate and relevant to the target learner group (19). Needs assessment is particularly critical in international education, where epidemiology, resource availability, and practice standards vary widely (20). While several needs assessment surveys addressing critical care capacity have been described in the literature (21–25), there is presently no validated and comprehensive tool that is specific to pediatric resuscitation education in LMICs.

The WHO developed a tool in 2008 to measure surgical capacity (the Tool for Situational Analysis to Assess Emergency and Essential Surgical Care) (26), which has been validated and used in more than 10 LMICs (27–37). It was subsequently modified to develop a survey for specific facilities based on personnel, infrastructure, procedures, equipment, and supplies (PIPES) (38). PIPES has been used with further modifications to assess pediatric surgical capacity in 37 hospitals in West Africa (PediPIPES) (39).

In order to garner information needed to develop an appropriately contextualized pediatric resuscitation curriculum for use in two LMIC settings, we adapted the PIPES and PediPIPES to construct a novel needs assessment tool. Our immediate goal in developing this new tool was to evaluate local pediatric emergency care capacity, resources, and practices (PIPES), as well as perceived causes of pediatric morbidity and mortality, and self-assessed educational needs of target learners. Our ultimate goal, however, was to identify curricular adaptations needed to ensure relevance, feasibility, and appropriateness of educational content to the target setting in which pediatric resuscitation education is to be conducted. This process enabled us to implement fully contextualized curricula in two very different international venues.

## MATERIALS AND METHODS

### Tool Development

The original PIPES tool has 105 data items divided into five sections and functions as a scoring tool to compare the surgical capacity of different health-care facilities by calculating the PIPES Index (26, 38). The index can be calculated by tallying the total scores obtained in the survey. The Personnel section queries the total number of key practitioners (e.g., surgeons). The

infrastructure, procedures, equipment and supplies sections have a binary response system of either “Always Available” versus “Not Always Available” or “Done” versus “Not Done.”

We modified the PIPES tool in order to assess the pediatric medical resuscitation capacity of health-care facilities in resource-limited settings. As our tool was to be used for contextualization of a curriculum as opposed to rating facility capacity, we omitted the scoring component of the tool and replaced it with qualitative open-ended questions in order to garner more details about the hospital environments. We omitted items that were specific to surgical capacity and added items relevant to pediatric medical resuscitation. We also replaced the binary response system with a three-option response system (i.e., always available, usually available or seldom/never available) in order to account for potential variability in the availability of resources at different sites. Finally, we omitted the “Personnel” section, as this was specific to measuring overall hospital operational capacity and was less relevant for the curriculum development process.

In order to ensure that our curriculum addressed clinical topics of importance to our learners, we added a Section “Epidemiology.” In this section, we queried the most common causes of potentially preventable death among children in the local practice setting. We also queried survey respondents to elucidate their perceived learning needs and prior pediatric resuscitation training and experience. We also added a Section “Current Practices/Skills,” which used a five-point Likert scale to measure the confidence of survey respondents in managing emergency clinical scenarios and performing emergency procedures (see Appendix S1 in Supplementary Material for final iteration of tool used in the study—the PIPES Tool for Assessment of Pediatric Resuscitation Capacity in LMIC).

## Tool Implementation

### Study Settings

We implemented our needs assessment tool at two locations: Yangon Children's Hospital (YCH) in Yangon, Myanmar and Makerere University College of Health Sciences (MUCHS) in Kampala, Uganda. The study proposal was reviewed by the Institutional Review Board (IRB) of Johns Hopkins University School of Medicine and was considered to be exempt. In addition, local site approval to conduct the study was obtained from the ethics board and/or training committee leadership at both YCH and MUCHS. The two study sites were selected for convenience reasons, due to existing institutional partnerships.

### Study Participants

At YCH in Myanmar, intended study participants consisted of first, second, and third year postgraduate trainees in Pediatrics, as well as a group of general practitioners pursuing a 1-year Diploma in Child Health course. At MUCHS, intended study participants consisted of second and third year postgraduate trainees in Pediatrics.

### Data Collection

The needs assessment survey was administered to all participants immediately prior to the start of a resuscitation course. The paper-based survey was administered in person at both sites.

## Data Analysis and Use of Results

Results were analyzed using simple descriptive statistics in Microsoft Excel. Results were used to make modifications to the planned curriculum as needed in order to appropriately contextualize the content in each setting. Of note, the investigators completed multiple phone meetings with local stakeholders as well as in-person visits to both sites prior to administration of the survey. This process allowed development of the majority of the curriculum in advance of the needs assessment survey. Survey results were then used in an iterative fashion to “fine-tune” and modify the curriculum at subsequent sites in order to optimize feasibility of recommendations and relevance to the local clinical context.

## RESULTS

A total of 94 participants completed the pre-course needs assessment survey, 62 in Myanmar and 32 in Uganda (100% response rate). Age range of respondents was 25–40 years. 74% of respondents were in their second or third postgraduate year of pediatric specialty training. Further results are presented below by category.

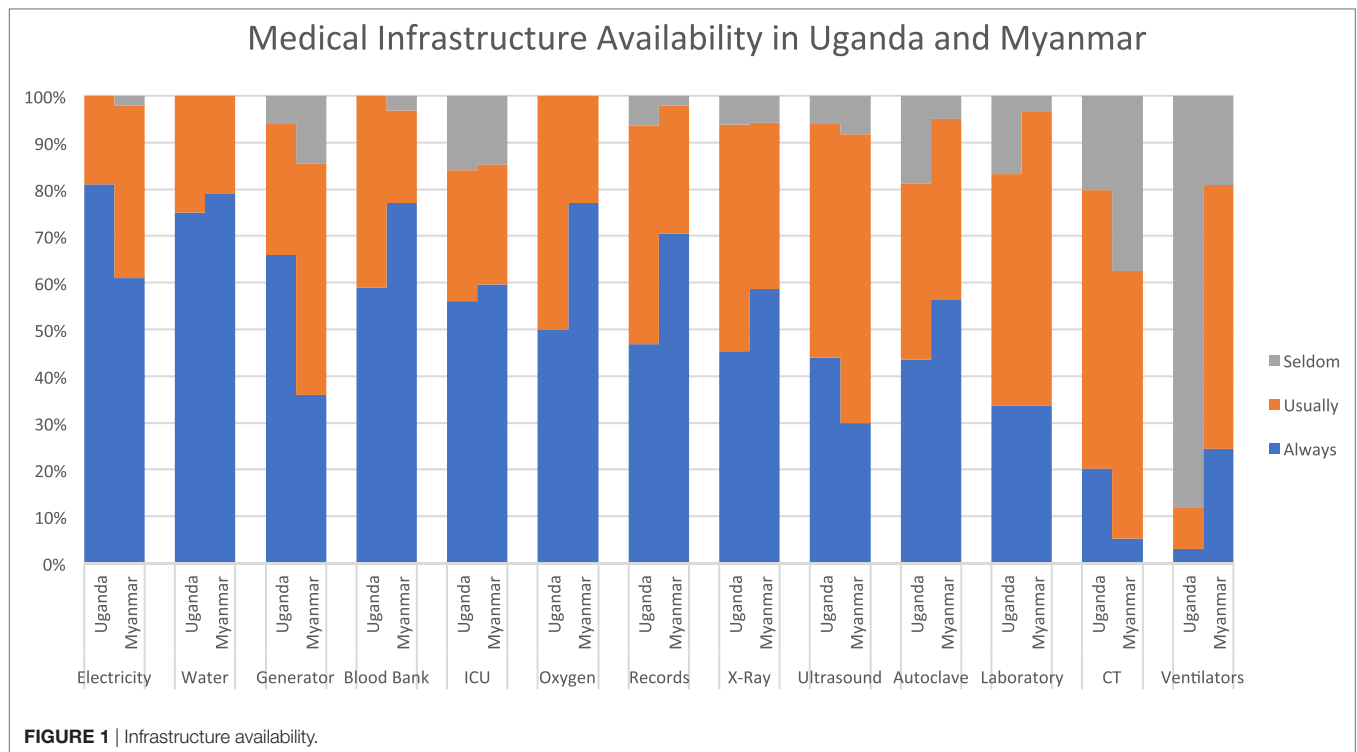
### Infrastructure

At both sites, most infrastructure items were described as being “always” or “usually” available by the majority of respondents. The one exception was ventilators at the Uganda site, which were described as “seldom/never” available by 88%. Compared to Uganda, respondents in Myanmar reported more variability in availability of electricity. The vast majority at both sites reported they “always” or “usually” had access to specialized services including blood bank, intensive care, and medical records. While no respondents described oxygen as “seldom/never” available, it is notable that only 50% in Uganda and 77% in Myanmar described it as “always” available. Access to diagnostic testing was limited at both sites. X-ray was the most commonly available imaging modality, cited as “always available” by 44% in Uganda and 61% in Myanmar. Laboratory services and advanced imaging were described as “usually” or “seldom” available by a majority at both sites. Ventilators were much more available in Myanmar compared to Uganda (see **Figure 1**).

### Procedures

Peripheral intravenous access was the only procedure described as being performed “routinely” at both sites. In Uganda, 70% of respondents reported that intraosseous access was performed “routinely,” compared to Myanmar where 83% indicated that this procedure was performed “rarely.” Over half of respondents at both sites described administering epinephrine “routinely.” In Myanmar, a similar number reported “routinely” administering vasopressor infusions, while this proportion was much smaller in Uganda. At both sites, a sizeable minority of respondents described use of atropine and antiarrhythmics as routine. Chest tube placement was the most commonly performed invasive procedure, with a majority at both sites describing it as routine. Intubation was much more common in Myanmar than in Uganda, with 40% of respondents indicating that they perform





this procedure “routinely” in Myanmar compared to only 3% in Uganda. Central venous access, arterial line placement and electrical therapies for the heart were rare in both settings (see **Figure 2**).

## Equipment

Most respondents at both sites reported that noninvasive respiratory support equipment was “always” or “usually” available, including oxygen delivery devices, bag-valve-mask ventilation devices, and continuous positive airway pressure systems. Diagnostic equipment like pulse oximeters, blood pressure cuffs, electrocardiogram machines, and glucometers were much more readily available in Myanmar than Uganda, where access to these items was extremely limited. Respondents from both sites reported limited access to cardiac monitors, with only 19% in Uganda and 37% in Myanmar reporting them as “always available.” Respondents in Myanmar reported better availability of advanced airway adjuncts compared to those in Uganda, although access to these items was suboptimal in both settings. Both sites reported very limited availability of quality CPR equipment like backboards and stepstools (see **Figure 3**).

## Supplies

All respondents at both sites indicated that basic supplies like syringes, gloves, and intravenous catheters were “always” or “usually” available. While this was also true for intravenous fluids, a significant proportion at each site (34% in Uganda and 15% in Myanmar) indicated that this essential supply is not always available. Similarly, infant suction bulbs were not uniformly available at either site. Both sites reported a lack of access to intraosseous

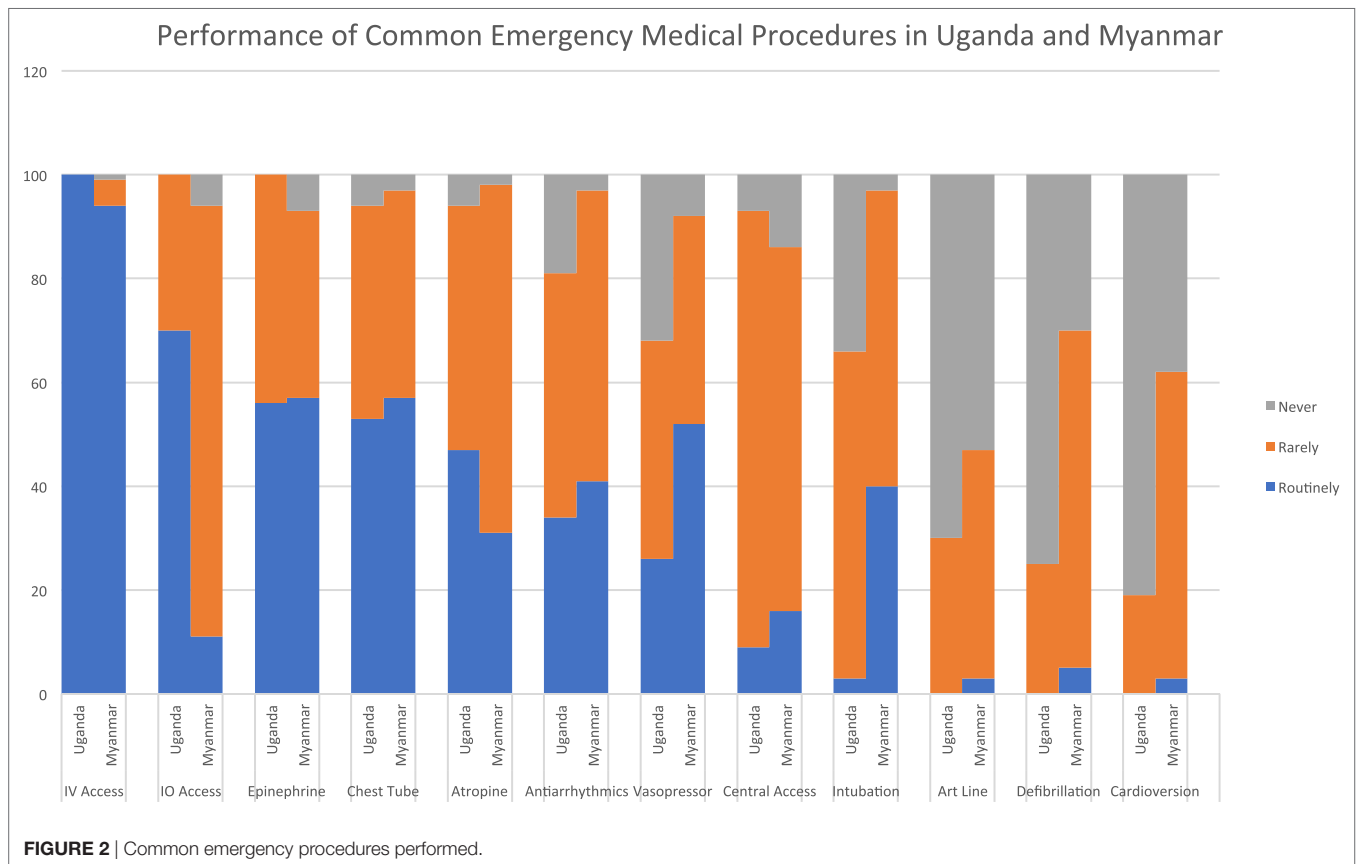
needles, with 66% in Uganda and 27% in Myanmar reporting that these are “seldom/never” available. Higher-level procedural equipment was relatively unavailable in both settings, with endotracheal tubes more readily available than invasive vascular access devices and chest tubes (see **Figure 4**).

## Epidemiology

Infectious diseases were listed as the predominant cause of preventable death in children at both the Myanmar and Uganda sites (see **Figure 5**). Specifically, respiratory infections occupied the top position at both sites, and gastrointestinal diseases were also common. Differences in local epidemiology were seen between the two sites, as malaria was frequently cited as a major cause of preventable death in Uganda but was rarely noted in Myanmar. Sepsis, on the other hand, was frequently cited in Myanmar but not in Uganda.

## Self-Identified Learning Needs

At the Myanmar site, the three most commonly cited learning needs were in the categories of airway/breathing management (28% of respondents), circulation/fluid resuscitation (22%), and cardiac arrest management (16%). Within each of these categories, the most frequently cited learning needs were intubation (54%), intraosseous needle (IO) placement (65%), and defibrillation/cardioversion (38%). At the Uganda site, the three most commonly cited learning needs were in the categories of general resuscitation principles (27%), cardiac arrest management (22%), and circulation/fluid resuscitation (19%). Within each of these categories, the most frequently cited learning needs were basic neonatal/pediatric resuscitation topics (65%),



defibrillation/cardioversion (33%), and central venous cannulation (17%).

## Pediatric Resuscitation Experience

At the Uganda site, 87.5% of participants stated that they had prior formal training in pediatric resuscitation, 75% of whom stated that the course involved either simulation or hands-on skills practice. At the Myanmar site, only 63% of participants stated that they had prior training, only 50% of whom reported simulation or hands-on skills practice as part of this training. 97% of participants in Uganda indicated that they managed critically ill children either “daily” or “regularly,” compared to only 48% in Myanmar (see **Table 1**).

## Current Practices/Skills

The clinical scenarios that participants reported the greatest confidence in managing were similar at both sites: respiratory distress and shock. The clinical scenarios that the participants were “least confident” managing were also similar: cardiac arrest and pneumothorax. See **Table 2** for detailed results. Participants in Uganda reported higher confidence overall compared to those in Myanmar.

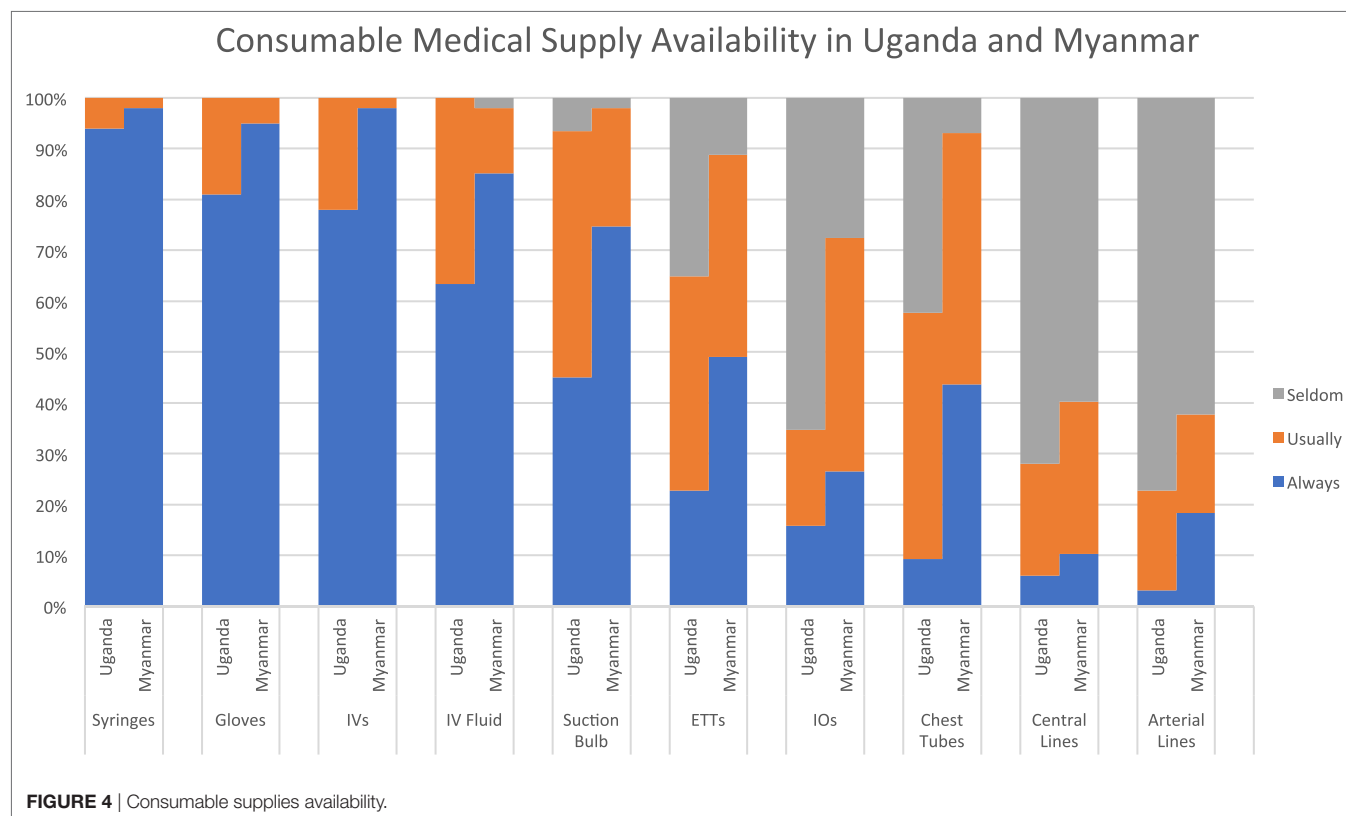
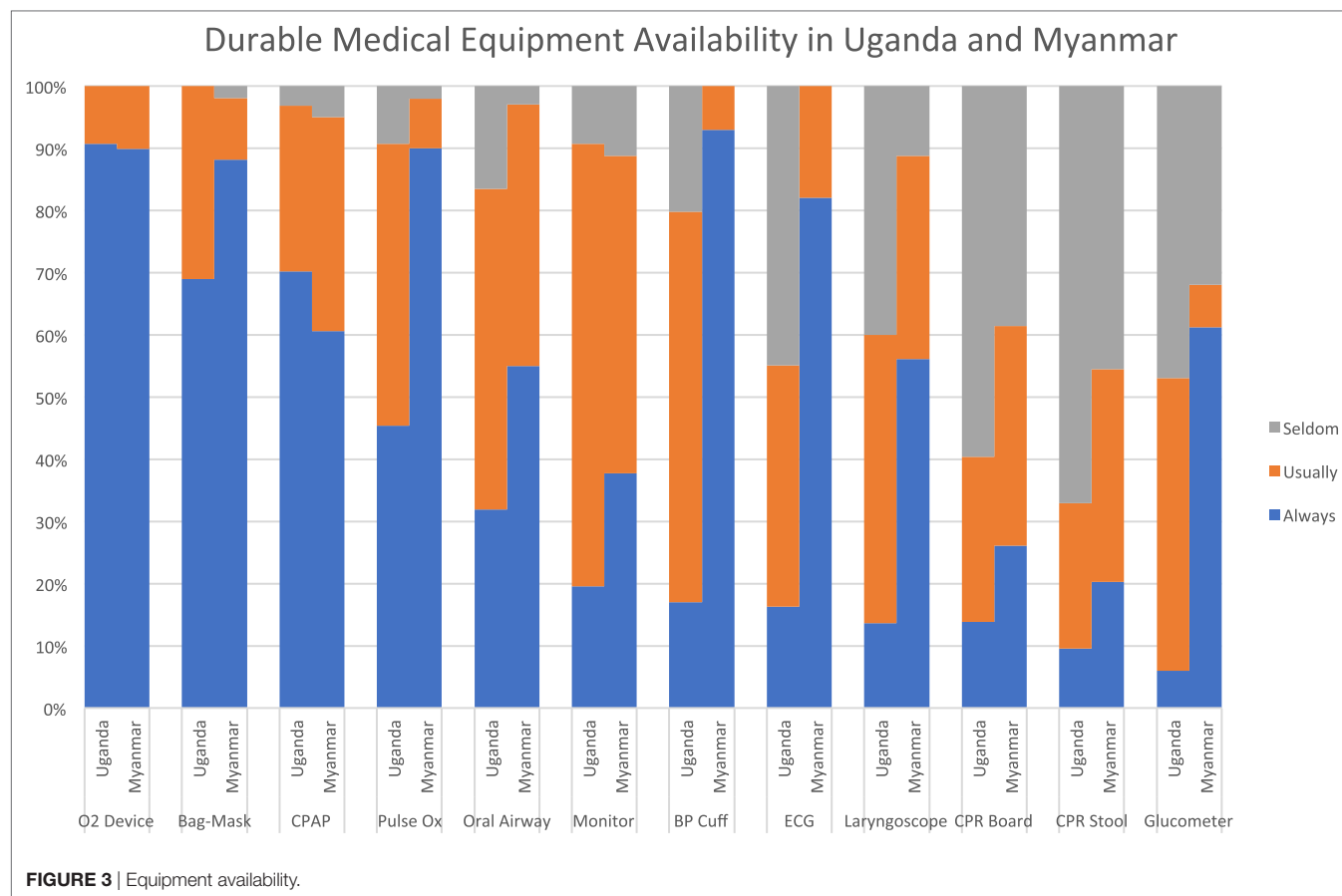
The procedures that the participants reported highest confidence in performing were the same at both sites, with differences only in rank order: airway assessment, breathing assessment, circulation assessment, and IV placement. The procedures that the participants were least confident performing also had some

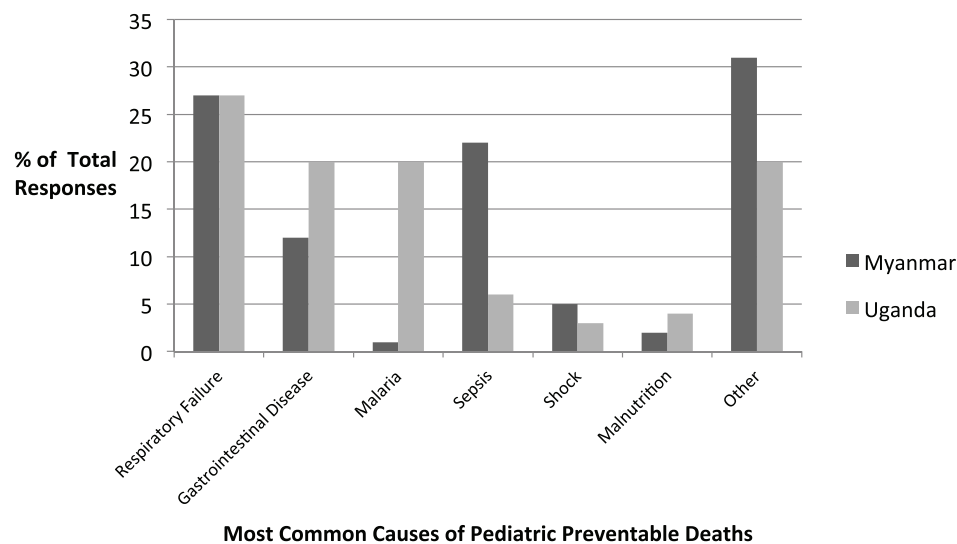
similarities between the sites. Participants at both sites were not confident performing central line placement, defibrillation/cardioversion, and intubation. See **Table 3** for detailed results.

## DISCUSSION

Our modified PIPES tool was administered to a group of physician learners in Myanmar and Uganda as part of a needs assessment process for the design and implementation of a contextualized curriculum in pediatric resuscitation using simulation-based pedagogy. We were able to achieve a 100% response rate to the needs assessment survey, which was achievable due to in-person administration of the survey immediately prior to the start of the course. As the purpose of collecting these data was to inform the curriculum development process, we reviewed the results with the goal of optimally contextualizing our training program to each setting. While it would be impossible to exhaustively describe every curricular adaptation made in each setting, **Table 4** offers several key examples of how these data were used to optimize applicability of our educational content for the target learner groups.

In applying our results from the needs assessment to refine the curriculum, we took into account a prior systematic review of resuscitation training in developing countries, which demonstrated that important educational outcomes are inconsistently defined and that training courses are often modified to available training resources, rather than to the needs and resources of





**FIGURE 5 |** Most commonly cited causes of pediatric preventable death in survey participants' clinical settings.

**TABLE 1 |** Frequency of exposure to critically ill children in clinical settings.

	Myanmar, % respondents	Uganda, % respondents
Daily (4 or more times per week)	8	75
Regularly (1–2 times per week)	40	22
Occasionally (1–2 times per month)	40	0
Rarely (1–2 times per year)	3	0
No response	9	3

**TABLE 2 |** Clinical scenario management confidence scores.

	Uganda, mean Likert Score (SD)	Myanmar, mean Likert Score (SD)
Bradycardia	3.7 (0.9)	3.4 (1.2)
Cardiac arrest	3.2 (1.0)	2.3 (1.2)
Decreased level of consciousness	4.2 (0.8)	3.4 (1.0)
Hypoxia	4.0 (0.7)	3.6 (0.9)
Respiratory distress	4.3 (0.7)	3.6 (0.9)
Seizures	4.4 (0.6)	3.7 (1.0)
Shock	4.3 (0.6)	3.8 (0.9)
Tachycardia	3.6 (1.0)	3.4 (1.2)

Likert scale consisted of numeric options ranging from 1 to 5: 1 = "Not at all confident" 3 = "Somewhat confident" and 5 = "Very confident."

the local health-care setting and patients (40). Training that is not tailored to local needs perpetuates a "common misconception that emergency medical care is inherently expensive and requires high-technology interventions as opposed to simple and effective strategies" (41). This needs assessment was an effort to facilitate essential contextualization of the curriculum in both settings. The process by which the needs assessment was used to tailor simulation scenarios and skills stations to the local settings and resource availability was analogous to the process used in similar studies in Africa that utilized a shorter assessment tool known as the facilities readiness assessment (18). The modified tool used in our study allowed for a more

**TABLE 3 |** Procedural confidence scores.

	Uganda, mean (SD)	Myanmar, mean (SD)
Airway assessment	4.2 (0.7)	4.0 (0.9)
Breathing assessment	4.3 (0.7)	4.0 (0.9)
BVM ventilation	4.0 (0.8)	3.8 (0.9)
Central line placement	1.9 (1.3)	1.3 (0.8)
Circulation assessment	4.3 (0.8)	4.0 (0.9)
CPR	3.9 (0.7)	3.7 (0.9)
Defibrillation/cardioversion	1.4 (0.7)	1.4 (0.8)
EKG or cardiac rhythm interpretation	2.1 (1.1)	2.9 (0.8)
Intraosseous line placement	4.2 (1.0)	2.4 (1.3)
Intubation	2.1 (1.1)	2.1 (1.0)
IV placement	4.6 (0.6)	3.9 (1.0)

Likert scale consisted of numeric options ranging from 1 to 5: 1 = "Not at all confident" 3 = "Somewhat confident" and 5 = "Very confident."

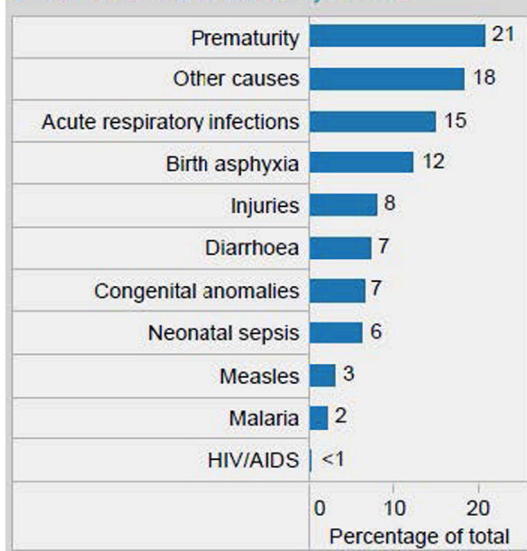
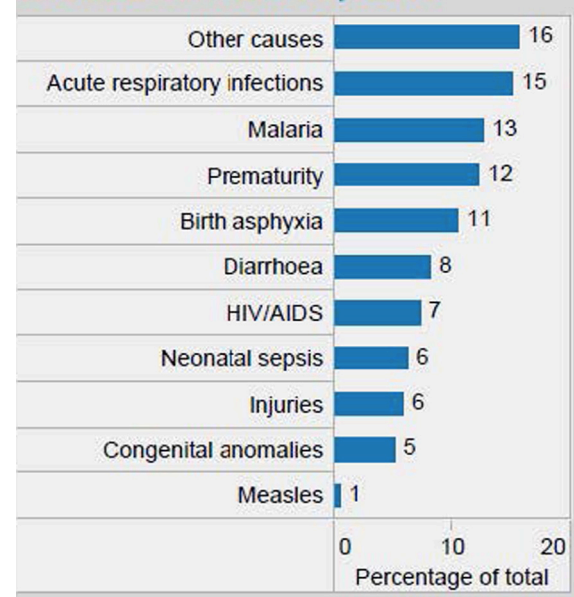
extensive evaluation of the local health-care resources specifically applicable to pediatric resuscitation and proved effective in understanding the local landscape of our target learners in both Uganda and Myanmar. Below, we highlight notable findings from the results and how they compare with what is already known in the literature.

## Epidemiology—Local Disease Burden

The epidemiology section of the survey allowed us to determine if the national morbidity and mortality statistics provided by the WHO were reflected in the local pediatric population served by our target learners. In Myanmar, the majority of the causes of under five mortality rates (UFMR) listed in WHO national statistics were mentioned by survey respondents, although the ranking of diseases differed somewhat. One of the major differences was that in the 2013 WHO statistics, neonatal sepsis was listed as the seventh leading cause of death in Myanmar, whereas in our survey, it was the second most common response for preventable causes of mortality (see **Figure 6**). In Uganda, many of the causes

**TABLE 4** | Examples of key findings and their use in curriculum development.

Finding	Action
Absence of ventilators and laryngoscopes in Uganda	Focused on effective noninvasive ventilation and omitted advanced airway skills from curriculum at this site
Limited access to cardiac monitors at both sites	Emphasized frequent clinical reassessment to determine response to treatment and trajectory of condition
Variable access to diagnostic support tools, including pulse oximetry, blood pressure cuffs, glucometers, and laboratory services (particularly in Uganda)	Emphasized established clinical criteria for empiric administration of oxygen, IV fluid, glucose, and blood products (major focus of training in Uganda)
Rare performance of cardioversion or defibrillation at either site (related to lack of defibrillators)	Despite participants' self-identified learning needs, chose to omit these skills from curriculum at both sites
Lack of availability of intraosseous needles at both sites	Addressed improvisation of equipment for intraosseous access when needed
Relatively lower confidence in intraosseous needle placement in Myanmar	Spent additional time on this skill at this site
Relatively lower confidence in CPR performance at both sites	Allotted significant time to this skill at both sites, and incorporated CPR quality feedback tools to optimize learner performance
Frequent mortality associated with malaria in Uganda	Added entire module about life-threatening complications of malaria for this site
Frequent use of epinephrine at both sites	Emphasized alternate appropriate treatments, particularly respiratory support for bradycardia, and volume expansion for shock

**Distribution of causes of deaths in children under-5, 2013****FIGURE 6** | World Health Organization (WHO) distribution of causes of death in children under five in Myanmar (Source: country statistics and global health estimates by WHO and UN partners <http://www.who.int/gho/countries/mmr.pdf>).**Distribution of causes of deaths in children under-5, 2013****FIGURE 7** | World Health Organization (WHO) distribution of causes of death in children under five in Uganda (Source: country statistics and global health estimates by WHO and UN partners <http://www.who.int/gho/countries/uga.pdf>).

of death listed in the WHO national statistics were also mentioned by the survey respondents, with rankings also differing somewhat (see **Figure 7**). Some important causes of death listed by WHO were not mentioned by survey respondents, including prematurity, HIV/AIDS, and injuries. Of note, our survey asked for causes of *preventable* death. Our Ugandan learners, working in a severely resource-constrained environment, may encounter these causes of death routinely, but simply not perceive them as preventable. Our curriculum ultimately incorporated both locally identified and WHO-cited causes of pediatric mortality. Our educational team felt strongly that it was important to design simulation scenarios targeting causes of UFMR identified through an emic or local perspective in order to enhance face validity of the curriculum with target learners.

## Pediatric Resuscitation Training and Prior Clinical Exposure

The majority of participants at both local sites had some form of prior pediatric resuscitation training. Interestingly, this is in contrast with many other studies that have reported on baseline knowledge prior to training courses (40), perhaps because our survey was conducted at facilities that had formal residency training programs in pediatrics. Prior exposure to hands-on skills practice and/or simulation was more variable and differed between the two sites. In Myanmar, only one-third of participants had prior simulation-based resuscitation training, despite the fact that they resuscitate children on a fairly regular basis.



The percentage of survey participants who indicated that they managed critically ill children on a daily basis was significantly higher in Uganda compared to Myanmar, and this was reflected in the higher confidence scores reported by Ugandan participants. Participants at both sites reported frequent exposure to critically ill children, reinforcing the importance of formal training and frequent refreshers in pediatric and neonatal resuscitation skills for both cohorts of clinicians.

## Self-Identified Learning Needs

Airway management was listed as a learning need for a significant percentage of participants in both the Uganda and Myanmar cohorts. This is not surprising given that respiratory illnesses and respiratory failure were the most frequently listed causes of preventable death at both sites. The self-identified learning needs of airway and cardiac arrest management were reflected in the low mean confidence scores for these scenarios at both sites, as well as for related skills such as intubation and defibrillation/cardioversion. However, it was noted in the PIPES survey that the necessary equipment and supplies for these procedures were often not available, raising the question of whether these skills are truly contextually relevant, but also likely leading to minimal practical use of these skills and, hence, lower confidence scores.

Although this study was conducted in resource-limited settings, the major learning needs we identified were consistent with self-identified knowledge gaps in a recent large scale survey of over 700 emergency medical care providers for children in rural settings in the United States, where resource limitations are often also present (42). These gaps included pediatric airway management and procedural skills in neonatal resuscitation and intraosseous access. This concordance with the literature even in a developed setting highlights the importance of addressing specific educational needs for health-care providers to care for neonatal and pediatric populations.

## Impact on Curriculum Design

The sections of the needs assessment survey that had the greatest impact on the curriculum instructional design were the local epidemiology, followed by the available equipment and infrastructure in each setting. These data allowed us to focus the curriculum in each location on high-yield material that was relevant to the learners and the population they serve. For example, in Uganda, one learning station focused on management of malaria according to local guidelines. In Myanmar, this was not needed, but a learning station did focus on resuscitation in dengue shock, a common cause of morbidity and mortality in the Southeast Asian region (see **Table 4** for examples).

Participants' self-identified learning needs were also taken into account, but coverage of these topics emphasized techniques and procedures that could be performed with available equipment based on the PIPES survey. For example, due to the lack of defibrillators, central venous catheters, arterial line catheters, and the inconsistent availability of ventilators at both sites, the procedural skills of defibrillation/cardioversion, central line placement, arterial line placement, and intubation/advanced airway management were de-emphasized. Greater emphasis was placed on clinical assessment skills, effective noninvasive airway

management (e.g., high quality BVM ventilation), and management of shock using available local equipment.

In order to ensure relevance and feasibility, we taught procedures using locally available equipment. For example, emergency intraosseous (IO) access was taught using bone marrow needles or other large-bore devices rather than with the commercially available IO needles used in the United States. When certain equipment was not available in the local setting, the educational team worked with the local team to design workable alternatives. When equipment for certain procedures is not available, it is also essential for trainers to understand if and how clinicians improvise in order to perform these procedures. For example, our respondents reported very limited access to chest tubes, yet a majority indicated that chest tube placement is a "routinely" performed procedure. Had chest tube placement been an objective of our curriculum, it would have been essential to explore how clinicians perform this procedure in the absence of purpose-specific equipment and to incorporate locally available supplies and techniques in the teaching of this skill.

When designing simulation scenarios, we took care to mimic resource constraints in the actual clinical environment and to require learners to address these issues in their management. For example, glucometers were scarce in Uganda, while they were more readily available in Myanmar. In our hypoglycemia scenarios, we provided a finger-stick glucose reading for participants in Myanmar, but required participants in Uganda to rely on clinical assessment to determine the need for glucose administration. Similarly, the 10% dextrose (D10) solutions used for hypoglycemia in young children are not commercially available in Uganda, necessitating that clinicians mix their own solutions using sterile water and higher concentration dextrose. In order to ensure mastery of this skill, our hypoglycemia simulation included mixing of D10 from locally available products as a critical action. Subtle alterations such as these ensured contextual relevance of our scenarios and reinforced essential skills required of health-care providers in their actual clinical settings.

Overall, the data acquired through our survey allowed for the curriculum to be tailored to local needs and resources to increase its feasibility, applicability, and impact. This practice is consistent with recommendations in the literature to appropriately calibrate and contextualize resuscitation courses from developed countries in order to ensure feasibility in resource-limited settings, thereby strengthening the chain of survival from within the local health-care system (17, 20, 41).

## Limitations and Next Steps

The needs assessment survey in this study was implemented at only two sites in East Africa and Southeast Asia, and therefore its generalizability may be limited to sites with similar learning needs and epidemiology. Furthermore, our participants were subspecialty trainees based at referral centers, so our tool may be less applicable for first-line providers and facilities. Although the needs assessment is based on a WHO tool that has been validated in multiple resource-limited settings, our modified tool has not yet undergone validity testing. This will be a goal of future studies. In addition to tool validation, our next steps will include the further revision of existing simulation-based curricula in pediatric resuscitation to be more appropriately contextualized to local epidemiology, learning needs, and available resources.

## CONCLUSION

The WHO Tool for Situational Analysis to Assess Emergency and Essential Surgical Care and the PIPES tools were successfully adapted to assess pediatric resuscitation capacity and learning needs in two different clinical settings. The implementation of the tool in two different countries in Asia and Africa helps to improve its generalizability for LMIC settings in the developing world. Results from the needs assessment at each site provided the basis for design of a pragmatic and appropriately contextualized curriculum in neonatal and pediatric resuscitation at each site, as well as a process for iterative revision of the curriculum for subsequent courses. These results informed curriculum development and instructional design, enabling the team to address self-identified learning needs, while emphasizing high-yield procedural skills that were of practical value, given the local resource limitations. The results also improved engagement of local stakeholders and participants in the curriculum, as they perceived that they had input into successive iterations of the curriculum through their responses to the needs assessment survey. The approach of partnering with local educational stakeholders in the curriculum design process through a formal needs assessment is consistent with recommendations by the Lancet Commission in 2010 in their publication *Health professionals for a new century: transforming education to strengthen health systems in an interdependent world* (43). These recommendations include reformation of local competencies through global flows of knowledge and cultivation of ownership through local clinician leadership in shaping educational processes. This concept provided a foundation for the ultimate design of our curriculum based on our needs assessment survey. Future studies will focus on validation of the PIPES tool in its modified form and dissemination of the tool to other resource-limited settings, in addition to implementation and evaluation of subsequent curricular interventions.

## ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Johns Hopkins University School of Medicine Institutional Review Board (JHUSOM IRB). The study protocol was determined to be exempt research by the JHUSOM IRB under the DHHS regulations (i.e., research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods). In addition, local

site approval and consent for conduct of the study in Uganda and Myanmar were obtained from the Head of the Department of Paediatrics and the Director of Training and Education at Children's Hospital of Yangon, Myanmar, as well as from the ethics board of Mulago Hospital and Makerere University College of Health Science in Kampala, Uganda.

## AUTHOR CONTRIBUTIONS

NS, AC, JR, and JJ conceived of the needs assessment survey, implemented the survey in each setting, performed data analysis, and contributed to the writing of the manuscript. TM, YK, and SG assisted in implementation of the survey at each site and assisted in data collection. LC assisted in data analysis and writing of the manuscript. All authors approved the final version of the manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at <http://www.frontiersin.org/articles/10.3389/fped.2018.00037/full#supplementary-material>.

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# Teaching the Principles of Pediatric Critical Care to Non-Intensivists in Resource Limited Settings: Challenges and Opportunities

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## INTRODUCTION

It is a dismal reality of global health that the vast majority of critically ill or injured children are found in regions of the world least equipped to care for them. Most of these severely ill or injured children are cared for in clinics, hospital wards, or, when available, adult intensive care units (ICUs) by providers with variable amounts of training. This lack of training may, in fact, play a significant role in the premature demise of children <5 years old, since millions of these deaths are felt to be preventable with the resources available (1). Evidence shows that even in a setting with constrained resources, early recognition, and prompt, decisive intervention may reduce mortality (2–4). It seems intuitive, therefore, that training of non-intensivists that focuses on these principles might improve the outcomes in critically ill children. How can this instruction be best achieved in areas where it is most needed? In this article, we review the benefits and challenges of implementing short-term curricula to teach the basic principles and practice of critical care medicine in resource limited settings (RLS).

## CURRENT STATE OF THE CARE OF THE CRITICALLY ILL CHILD

The essential role of community and preventative healthcare in promoting the well-being of children in RLS is well established and assumed here. Yet, improvements in primary and preventive care do not eliminate need for hospital-based care. A high percentage of children (an estimated 12–34%) seen in ambulatory settings, for example, are felt to require hospital assessment and/or admission (5). Multiple studies have shown mortality inversely related to distance from a hospital and that prehospital/emergent or advanced care resources are most limited where the majority of children die (6–8). In addition, we know that a growing percentage of preventable deaths result from the “neglected burden” of trauma; approximately 90% global trauma deaths occur in low- and middle-income countries (LMICs) and road deaths alone kill more than 200,000 children per year in RLS (9–11). All these ill or injured children require some (and perhaps an increasing) degree of medical care and demise is, in many cases, related to an inability to deliver timely or appropriate care (12).

Yet for those patients who require and receive hospital-level care, mortality remains high, with infection and sepsis often the common final pathway (13). A study from Guinea-Bissau observed that 25% of childhood deaths occurred after admission to a regional hospital (14). In general, the sparse available data cite a pediatric inpatient mortality rate between 12 and 50% in RLS, with a high percentage of those occurring during the first 24 h following admission (9, 15). This latter observation underscores the belief that treatment is often delayed in these settings for children arriving at care facilities after the onset of critical illness. It is not a foregone conclusion, however, that mortality for these hospitalized patients has improved over time. For instance, a large, retrospective study on pediatric sepsis admissions to Brazilian

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hospitals from 1992 to 2006 showed an overall reduction in cases of sepsis, but no improvement in the mortality rate of 19% (16, 17).

What is clear is that most critically ill children who survive to inpatient care facilities are treated in clinics, hospital wards, and infrequently in mixed ICUs by caregivers with variable amount of pediatric or advanced care training. In Nigeria, for example, there are only 380 ICU trained nurses in a country of 140 million people (17). In reality, critical care is just the continuum of care provided to any child with a life-threatening illness or injury beginning with the time of presentation to a health care facility (18). Where and by whom care is provided may go a long way in determining outcome.

## THE ROLE OF CRITICAL CARE TRAINING

There is evidence that the presence of pediatric intensive care units (PICUs) and trained critical care physicians (intensivists) improves patient care and saves lives in both high resource and RLS (19–22). It is likely that the mortality benefit from intensive care is attributable to an integration of multiple elements including basic infrastructure, essential supplies, and equipment, training, and staffing. In practical terms, however, “intensive care” can only be provided where these substantial resources and trained, multidisciplinary personnel are in place. The mere presence of an “intensive care unit” does not guarantee the presence of intensive, integrated care, or good outcomes, as the mortality rates in mixed and exclusively pediatric ICUs in LMICs can be as high as 50–58% (22, 23). In any case, ICUs are uncommon in many parts of the world and, with rare exception, most of the world’s sickest children are cared for outside of conventional ICUs (pediatric or mixed) by caregivers without pediatric or critical care training.

How can the critical care of these children be improved? To begin, in RLS, critical care capacity is “developed” not “created” (24–26). This is not just a matter of semantics, but underlines the importance of a gradual cultivation and blending of training and technical capacity over time, rather than the creation of a physical space. Ultimately, there are two intertwining aspects of this undertaking: training and educational enrichment, and developing physical/technological ICU capacity to facilitate care. This is a delicate balance because most would agree that the introduction of material assets without concomitant thoughtful, systemic training is a futile endeavor. In fact, the lack of trained personnel in sufficient numbers is routinely cited as a weakness of healthcare delivery—often even more than inadequate supplies and equipment (26–28). Accordingly, training programs/courses that include a range of health care providers and focus on principles of early recognition and management of severe illness could play an important role in combatting healthcare-associated mortality.

## STANDARDIZED CRITICAL CARE COURSE: WHY? WHAT, AND WHERE ARE THEY?

Standardized emergency and pediatric critical care curricula such as emergency, triage, assessment and treatment (ETAT), pediatric basic assessment and support intensive care (BASIC),

and pediatric fundamentals of critical care study (PFCCS) are among of the educational initiatives used for supporting training in RLS (29). These courses provide a number of advantages even if they require some degree of “recalibration” to be effective in RLS (30). Standardized teaching modules are readily deployable, consistent, and comprehensive. They can also be shared and implemented for various training levels in a range of settings, reducing needless, and wasteful redundancy (31, 32). Tools such as the pediatric, emergency, assessment, recognition and stabilization (PEARS), and pediatric advanced life support (PALS) have even been bundled and used on system-wide levels to improve the care of sick children in Botswana and India (33).

Pediatric BASIC and PFCCS, both modeled on adult courses, have been specifically designed to teach non-intensivists the essential principles of care for the critically ill (32). The aim of these courses is to serve as a resource for those interested in learning to recognize critical illness and initiate care in the absence of an intensivist. As such, the courses focus on early identification of the critically ill child, initial steps in timely resuscitation, and organ support, and includes the rudiments of mechanical ventilation. Typically 2–3 days in duration, the sessions mix formal didactics, lectures, simulations, and practical sessions. Pretests are administered and the formal assessments at the end of the courses determine whether certificates are awarded to participants.

Pediatric fundamentals of critical care study is licensed by Society of Critical Care Medicine (SCCM). It can be administered either through a traditional live, instructor-led course, directed by a certified PFCCS director, or online. There is a well-defined process and oversight for certification of instructors and directors and periodic revision of content by an appointed task force. Although the course material covered can vary (based on the setting or participants’ needs), the contents of particular lectures are not modifiable. There has been a significant increase in international PFCCS courses recently, and between 2013 and 2016, more than 30 courses per year have been conducted around the world. There are currently 32 countries that have international PFCCS sites. SCCM has made significant effort to make the course affordable by having an option for tiered pricing based on a country’s gross domestic product at Purchasing Power Parity Per Capita but still the minimum cost is \$630. However, in the absence of consistent external funding, even this subsidized rate can make access in RLS prohibitive.

Pediatric BASIC is another standardized critical care course created by pediatric critical care educational leaders during the 2011 World Congress of Pediatric Intensive and Critical Care Societies (WFPICCS). Its creators sought to design a course to teach the fundamentals of critical care in a format that was flexible and affordable and thus suitable for both high-income countries and RLS. This course, endorsed by WFPICCS, is run by volunteer pediatric critical care faculty from around the world in select places with strong local support. Target audience include mainly non-intensivist physicians and pediatric trainees (many with limited PICU experience), emergency medicine physicians, and senior PICU nurses. The development of Pediatric BASIC is overseen by a steering committee with expertise in pediatric critical care. No member of the steering committee, the original writers of the course, the instructors, or their families receive any



financial benefit from the use of the course material and no individual owns intellectual property. Since there are no proprietary fees associated with the course, it is always offered free of charge.

In addition, to meet local needs, the BASIC course allows flexibility to adapt not only the shape and content of the overall course but also individual lectures. Within the course, there is also an effort to do needs assessment at the training facility, soliciting input, and feedback from local faculty. While BASIC also has separate foundation courses for training nurses, in some institutions, nurses can also be trained in the standard course. Since its inception in 2011, this course has been conducted in 63 different sites across 17 countries on 5 continents and a total of 1,617 providers have been trained. Pediatric BASIC has also shown success in building sustainable local critical care capacity through a “train the trainer” model in select institutions in countries such as India, Trinidad and Tobago, and Barbados. The first course in India was conducted in January 2014 and over next 4 years several local trainers (mostly Pediatricians with ICU experience) were trained as trainers using the model.

## STANDARDIZED COURSE: EVIDENCE AND CHALLENGES

There is little research on the utility of short-term training programs, a deficiency not unique to RLS. Such programs, even in high-income countries, have a thin evidentiary underpinning, trying to answer three fundamental questions: Are the courses an effective way to transfer knowledge? Is this knowledge retained for any meaningful period? Finally, does this retained knowledge, in the end, translate into clinical benefit (34). Often data on “softer” or surrogate measures or outcomes are all that are available. Data on a decade of PALS courses in Israel, for example, revealed only participant satisfaction with the course and satisfactory completion by a high percentage of participants (35). Residents in Canada performed well on the PALS posttest, but not on the technical skills assessment, and showed poor retention at 12 months (36).

The lack of data bases in RLS makes it difficult to assess training programs of any kind. However, several studies have looked at various parameters in short-term courses. For instance, there is evidence that short training courses improve short-term knowledge in emergency and critical care (37, 38). Short courses teaching trauma care have been shown to identify deficiencies, increase provider skills, and improve trauma outcomes—including mortality—in developing countries like Trinidad, India, Ecuador, and Tanzania (30, 39–42). In fields such as pediatric surgery and obstetrics, short-term, specialized training courses have shown some success in knowledge retention (43, 44).

Standardized adult critical care programs have also been evaluated, both as educational instruments and as a means of transmitting knowledge (32). Training of Kenyan physicians using the Fundamental Critical Care Study (FCCS) course has been shown to increase the knowledge and confidence of new critical care skills (45). FCCS course participants in Zambia and Kenya felt that the material was site-appropriate and demonstrated an increase in clinical knowledge and confidence with procedures

(46). There is less experience and evidence for pediatric standardized critical care curricula in RLS. However, a recent evaluation of Pediatric BASIC program in Northern Haiti showed post-course improvement in participants’ ability to manage patients in all topics covered by the course. The topics which showed the greatest improvement were related to support for respiratory failure using noninvasive and invasive ventilator support as well as the interpretation of blood gases (Silverman AMP, Napolitano et al., unpublished data, 2017).

The issue of course evaluation begs the very important question of the appropriateness of these tools in RLS. Given the range of disease and variable shortages of material encountered in RLS, training programs developed and taught by physicians from higher resourced countries may lack relevance (47). Consider, for instance, the teaching of PALS in places without defibrillators, or only a fraction of the recommended medications. It is, therefore, essential that courses should be tailored to local needs and, to assure ongoing relevance, have feedback mechanisms allowing for new data to inform future course modifications (30, 48).

Cost-effectiveness analysis is another important consideration, since optimizing the effects of expenditures takes on greater significance in regions where such funds are scarce. This type of evaluation, however, is complicated by a general dearth of data as well as uncertainty over relevant outcomes. Although the BASIC course itself is free, accurately measuring the actual cost of the “inputs” (i.e., concrete and opportunity costs of volunteer staff, cost to the facilities, etc.) would be difficult. In fact, the significance of the burden borne by the host institution could be hard to contextualize. In any case, without funding for educational programs, organizing courses may be overly burdensome to partners in RLS, threatening the feasibility and sustainability of these initiatives.

Another challenge to teaching these courses is the task of simulating the core critical care concepts of teamwork and collaborative learning in settings where these are not commonly practiced (49). In some cases, these difficulties may be due to cultural and hierarchical attitudes, but, nevertheless, could hinder training in optimal resuscitation and ongoing care. Nurses and ancillary personnel have variable levels of education and training and little experience with programs that train and integrate personnel at different levels concurrently (50).

Language can present a further practical barrier, limiting the effectiveness of these courses (51). Recent data from Haiti suggest that even with variable levels of skill in English and the use of translators, language problems were seen to limit course effectiveness (Silverman AMP, Napolitano et al., unpublished data, 2017). PFCCS course materials have been translated into Japanese, Spanish, and Chinese. BASIC is currently only available in English, but plans are underway to translate the teaching material into French and Spanish, allowing greater applicability.

In the end, assumptions on the benefits of training may have to suffice pending further evidence. Achieving a sustainable teaching model, however, through a “train the trainer” approach could assure long-term educational gains (48). Over time, steadfast application and consistent reinforcement may show the greatest benefits (33, 52). Yet this strategy will only be possible in settings with strong local interest and support.

## CONCLUSION

Training in the recognition and initial management of critical illness and injury may be an effective way to save the lives of countless children in RLS. Standardized courses in the fundamentals of critical care could be an effective component of this overall effort, helping to fill in gaps of trained personnel. Such courses should be adapted to local needs and resources. Also, while maintaining a consistent and readily reproducible, comprehensive curriculum, these courses should incorporate the feedback necessary to keep them locally relevant. In spite of the many challenges, standardized

courses provide an opportunity to train large numbers of diverse personnel and achieve sustainability by instructing local trainers. Identifying relevant outcomes and gathering data will be an essential aspect of assuring future effectiveness and relevance.

## AUTHOR CONTRIBUTIONS

AS and MC wrote the draft together and revised the contents. MC is primarily responsible for parts 1–3 and AS wrote the rest of the manuscript. Both authors revised the manuscript several times based on the feedback received from the coauthor.

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# A “Fundamentals” Train-the-Trainer Approach to Building Pediatric Critical Care Expertise in the Developing World

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Pediatric Fundamental Critical Care Support (PFCCS) is an educational tool for training non-intensivists, nurses, and critical care practitioners in diverse health-care settings to deal with the acute deterioration of pediatric patients. Our objective was to evaluate the PFCCS course as a tool for developing a uniform, reproducible, and sustainable model for educating local health-care workers in the optimal management of critically ill children in the Republic of Georgia. Over a period of 18 months and four visits to the country, we worked with Georgian pediatric critical care leadership to complete the following tasks: (1) survey health-care needs within the Republic of Georgia, (2) present representative PFCCS lectures and simulation scenarios to evaluate interest and obtain “buy-in” from key stakeholders throughout the Georgian educational infrastructure, and (3) identify PFCCS instructor candidates. Georgian PFCCS instructor training included the following steps: (1) US PFCCS consultant and content experts presented PFCCS course to Georgian instructor candidates. (2) Simulation learning principles were taught and basic equipment was acquired. (3) Instructor candidates presented PFCCS to Georgian learners, mentored by PFCCS course consultants. Objective evaluation and debriefing with instructor candidates concluded each visit. Between training visits Georgian instructors translated PFCCS slides to the Georgian language. Six candidates were identified and completed PFCCS instructor training. These Georgian instructors independently presented the PFCCS course to 15 Georgian medical students. Student test scores improved significantly from pretest results ( $n = 14$ ) (pretest:  $38.7 \pm 7$  vs. posttest  $62.7 \pm 6$ ,  $p < 0.05$ ). A Likert-type scale of 1 to 5 (1 = not useful or effective, 5 = extremely useful or effective) was used to evaluate each student's perception regarding (1) relevance of course content to clinical work students rated as median (IQR): (a) relevance of PFCCS content to clinical work, 5 (4–5); (b) effectiveness of lecture delivery, 4 (3–4); and (c) value of skill stations for clinical practice, 5 (4–5). Additionally, the mean ( $\pm$ SD) responses were  $4.6 (\pm 0.5)$ ,  $3.7 (\pm 0.6)$ , and  $4.5 (\pm 0.6)$ , respectively. Training local PFCCS instructors within an international environment is an effective method for establishing a uniform, reproducible, and sustainable approach to educating health-care providers in the fundamentals of pediatric critical care. Future collaborations will evaluate the clinical impact of PFCCS throughout the Georgian health-care system.

**Keywords:** education, train-the-trainer, pediatric critical care, training, pediatric fundamental critical care support

## INTRODUCTION

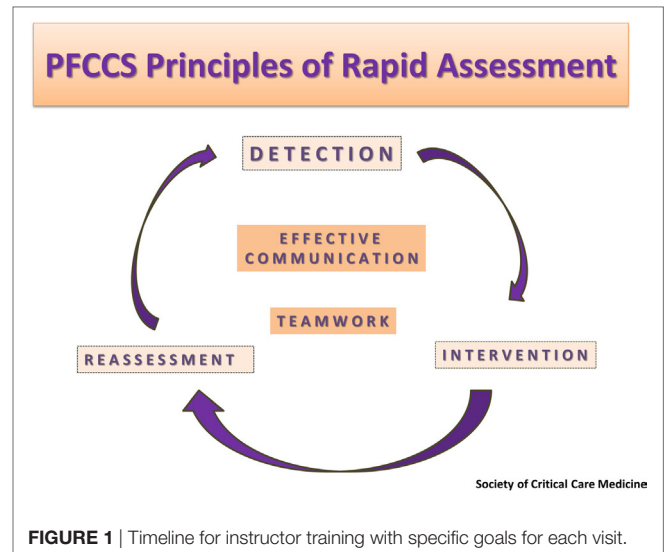
The failure to recognize and appropriately intervene in the early presentation of critical illness results in significant morbidity and mortality worldwide (1, 2). Patient outcomes could be dramatically improved through the application of basic resuscitation and stabilization principles (3, 4). Initiatives seeking to successfully spread this high impact medical knowledge to resource-limited health-care settings face significant challenges that are difficult to overcome during short-term visits (5). Overcoming language barriers, relationship building with key local stakeholders, and understanding the intricacies of the cultural environment are critical pre-requisites for implementing and sustaining any educational initiative (6). Recognizing that local providers and leaders are best suited to overcome these challenges (7), we sought an effective tool for teaching acute care management principles to both community and critical care providers within the Republic of Georgia.

Health-care leaders in the Republic of Georgia and the Ministry of Health approached physicians at our institution to explore opportunities for improving Georgian maternal and child health outcomes through education. The Republic of Georgia, through a colleague who completed her professional training at our institution, sought assistance in developing a uniform sustainable approach to educating health-care workers in the acute care management of children throughout the Republic of Georgia.

In 1991, the country's independence from the Soviet Union provided an unprecedented opportunity to transform Georgian health care from the Soviet model (Semashko model) to a new health-care system. The original transition period trialed both free health care to all citizens and privatized medicine, before establishing the current system in 2013 of government funded health care that is distributed through a state agency. Under this model the state finances health care, but the delivery is largely reliant on private medical facilities and personnel. Simultaneous changes in the Georgian political climate, which now permitted unprecedented access to Western medicine, generated growing interest in restructuring the country's health-care education to align with current evidence based practices (8, 9).

The Society of Critical Care Medicine (SCCM) has developed and standardized adult and pediatric courses that teach the fundamentals of critical care management through didactic lectures and hands-on simulation scenarios. The Pediatric Fundamental Critical Care Support (PFCCS) is intended to train non-intensivists, nurses, and critical care providers. The main objective is to provide an educational framework to address recognition and initial management of the clinically unstable pediatric patient and to accurately identify the need for expert consultation and/or transfer to a higher level of care (**Figure 1**) (10). These goals make the PFCCS course an ideal educational tool for advancing critical care expertise in resource-rich and limited areas where training in critical care management is needed (11–13). The course management principles are applicable to all patients, regardless of the resources available within the health-care setting to which they present.

In collaboration with Georgian health-care leaders, a group of multidisciplinary intensivists from the Mayo Clinic utilized a



“train the trainer” approach to establish a PFCCS course through a series of short-term visits to the Republic of Georgia (14, 15). The main objective was to train Georgian health-care providers as PFCCS instructors to promote the development of a consistent, uniform, and sustainable approach to the management of critically ill children throughout the country.

## MATERIALS AND METHODS

Over 18 months and four visits, Mayo Clinic and the Georgian health-care providers collaborated to achieve the following goals: (1) survey the health-care needs within the Republic of Georgia, (2) preview PFCCS lectures and simulation scenarios throughout the Georgian health-care infrastructure to obtain “buy-in” from key stakeholders, and (3) train Georgian health-care workers as PFCCS instructors. Leadership organizations supporting the Georgian PFCCS Development included the Georgian Ministry of Health, United Nations Children's Fund (UNICEF), United Nations Population Fund (UNFPA), United States Agency for International Development (USAID), Centers for Disease Control and Prevention (CDC), and Mayo Clinic Global Health.

The initial needs assessment visit to Georgia included tours of tertiary hospitals providing pediatric critical care and maternal birthing centers. Tours included on-site assessment of equipment resources along with demonstrations of local resuscitation protocols. At each location, Mayo team members presented samples of PFCCS course material to determine interest and relevance of the material to the Georgian health-care system. Meetings were held with the Minister of Health and representatives from UNICEF, UNFPA, and USAID to understand the maternal and child health challenges and the existing efforts to address them.

At the conclusion of the needs assessment visit, through discussions with Georgian health-care leadership the following objective was established: Train local health-care providers as PFCCS instructors to promote the development of a uniform, reproducible, and sustainable approach to the management of

acutely ill children throughout Georgia. Once trained, Georgian PFCCS instructors would educate clinicians at every point of care within the health-care system (regional hospitals and clinics, transport teams, and tertiary centers). This approach would have the added benefit of strengthening relationships between health-care providers in tertiary and regional settings thereby enhancing access to critical care expertise across the country.

## Instructor Selection and Training

To optimize the success of Georgian PFCCS course development, the initial instructor candidates were selected based on specific criteria. Candidates chosen were established, influential providers within local health-care communities with experience providing critical care. There were no training programs specific to critical care in Georgia, so instructor candidates were physicians practicing in the disciplines of pediatric, neonatal, and emergency medicine. English fluency was required to assure optimal didactic understanding and translation of the PFCCS course materials (textbooks and slide sets) which we could only offer in English.

Training of PFCCS instructor candidates is outlined in **Figure 2** and was accomplished through the following steps consistent with SCCM guidelines for achieving instructor certification (10): (1) US PFCCS consultants presented the PFCCS course in its entirety to the Georgian instructor candidates, (2) US PFCCS consultants and Georgian instructor candidates spent 1 day focused on adult learning principles, practicing hands-on simulated case scenarios, and rehearsing lectures, (3) instructor candidates presented the PFCCS course to Georgian students while mentored by US PFCCS consultants. (4) US consultants provided individual feedback to each instructor candidate based on PFCCS course evaluation forms completed by the students and US PFCCS consultants. (5) Georgian candidates translated the PFCCS slides for their lectures into the Georgian language so

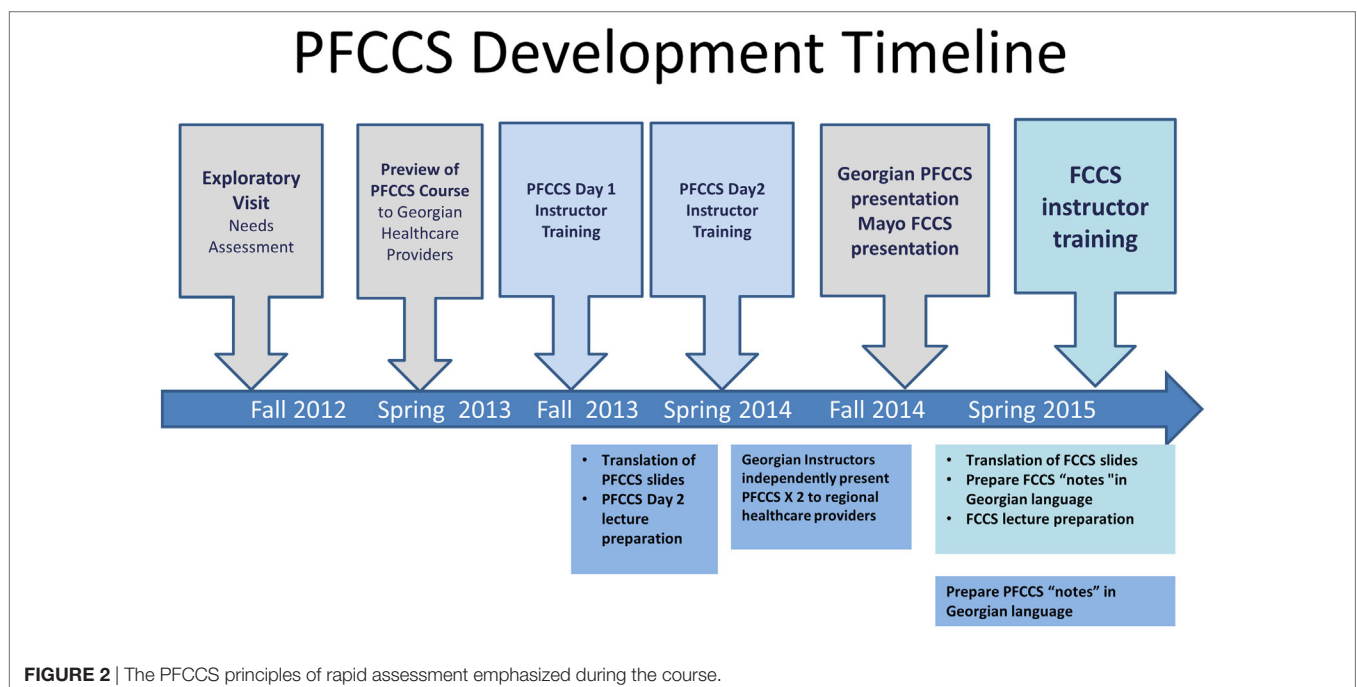
that future course presentations could be provided to learners in their native tongue.

At the conclusion of Georgian instructor training, a course director and administrator were identified from the candidate pool. The job description and responsibilities for these positions were outlined and the next steps and expectations were established in collaboration with the Georgian and US leadership. The process for obtaining a Georgian PFCCS course license was reviewed with the newly identified course administrator and director. Prior to this, all training related PFCCS presentations and materials were provided free of charge through the multi-course license purchased by the US consultants home institution. Finally, the appropriate paperwork was completed and submitted to SCCM to obtain official instructor certificates for each Georgian instructor candidate meeting all usual SCCM requirements (10).

## Developing Sustainability and Transitioning to Independence

In order to build confidence, optimize instructor retention, and promote dissemination of the course throughout Georgia, US instructors returned to Georgia at 6 month intervals. With each visit, US team members proctored Georgian led PFCCS courses, and dedicated a day during each visit to discuss successes and challenges encountered by Georgian instructors between visits. Additional skill training in simulated learning and educational methods, such as debriefing, were taught and practiced together. Finally, administrative processes were reviewed and goals established for ongoing course maintenance and expansion throughout Georgia.

Nurturing independence and maintaining momentum and enthusiasm for the Georgian PFCCS course between the US provider visits was critical to establishing sustainable infrastructure that would function independently of US collaborators.





The PFCCS course case-based, interactive, and hands-on approach were novel concepts to the Georgian medical education culture. Therefore, it was important for the Georgian instructors to practice these new presentation and teaching skills. Toward the goal of fostering independence, Georgian instructors were expected to teach a minimum of two courses between US visits, and videotape one presentation to permit remote viewing and feedback.

## Regional Dissemination

With the first generation of Georgian instructors established, the collaboration turned to expanding the instructor pool within the country. Regional health-care workers became the next target in order to exponentially increase opportunities for course dissemination and foster adoption of the fundamental principles of patient management across the country. In this phase, at each US visit, Georgian and US instructors presented samples of the PFCCS course within each regional health-care setting. Following each presentation, Georgian leadership identified and invited health-care providers within those regions to pursue instructor training and provided travel and accommodations for candidates to convene at a centralized training site. The Georgian PFCCS instructors then independently trained these new candidates by repeating the steps used in their own training process, under the mentorship of the US consultants. US consultants were paired with an interpreter to observe every aspect of the training process. Specifically, they evaluated the integrity of the course material presented and provided feedback and encouragement to the Georgian instructors as they trained in the new candidates. The interpreters facilitating this process were Georgian physicians educated within both Georgian and United States training programs. The same interpreters were employed for every US visit to assure continuity in the assessment of program development and accuracy in translation of the course material and concepts.

## Statistical Analysis

For the test scores in both the pretest and in the posttest data, a mean with SD was calculated. The Likert-type scale included nominal data collected and was evaluated using a mean  $\pm$  SD statistical. We chose median (IQR) as the set of survey data analysis to describe the value because of the small sample size of the learners. To highlight the clarity, mean ( $\pm$ SD) values are added as well.

## RESULTS

Seven Georgian health-care providers were identified and completed the first PFCCS instructor training course in Georgia. Six candidates became SCCM certified PFCCS instructors and the seventh participant was selected as the course administrator. These instructor candidates presented the PFCCS course to 15 Georgian medical students with no prior training in critical care and limited clinical experience. The success of the Georgian instructors in teaching the PFCCS principles of management was demonstrated by significant improvement in the learner's test scores ( $n = 14$ ) (pretest:  $38.7 \pm 7$  vs. posttest  $62.7 \pm 6$ ,  $p < 0.05$ ).

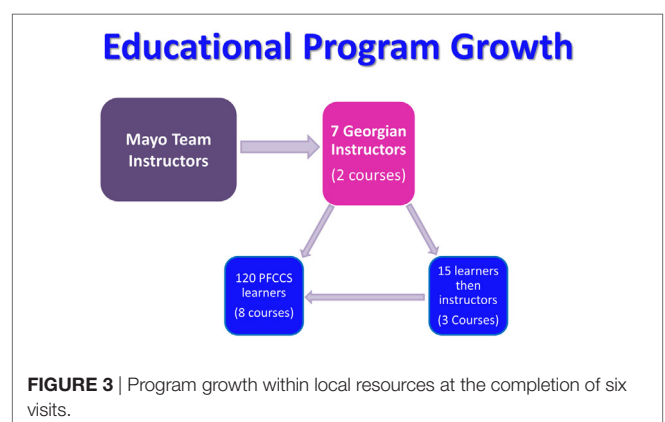
This first class of PFCCS students was surveyed following the course presentation. Responses were based on a Likert-type scale

of 1–5 (1 = not useful; 5 = extremely useful). These 14 students rated as median (IQR): (a) relevance of PFCCS content to clinical work, 5 (4–5); (b) effectiveness of lecture delivery, 4 (3–4); and (c) value of skill stations for clinical practice, 5 (4–5). Additionally, the mean ( $\pm$ SD) responses were 4.6 ( $\pm 0.5$ ), 3.7 ( $\pm 0.6$ ), and 4.5 ( $\pm 0.6$ ), respectively, denoting that relevance of content and value of skills stations were highly rated.

At the completion of their training, the Georgian instructors reported enhanced communication and teamwork surrounding resuscitation events and improved consistency in the application of evidence based principles to clinical management. Furthermore, the instructors believed the course had positively impacted their approach to education within their health-care communities. Specifically, the PFCCS format had improved their presentation skills, ability to increase audience engagement, and introduced them to simulation-based learning methods that were now being utilized for teaching within each instructor's local health-care setting. Finally, instructors reported that PFCCS textbooks were a highly utilized and sought after clinical reference book.

As PFCCS training continued, Georgian instructors began seeking opportunities to establish measurable criteria for hospital performance that would objectively demonstrate the benefit of PFCCS training on patient outcomes. These requests highlighted the need to parallel the PFCCS medical education with an introduction to quality improvement (QI) methods. Thereafter, visits included instruction in QI methodology and identifying relevant applications for QI models such as the Plan-Do-Study-Act cycles. Together, we explored goals and walked through a plan (P) to test the initial goal, introduce the change (D), observe and collect results (S), and identify modifications necessary to achieve the initial goal (A). Specific projects discussed focused on infection prevention, interdisciplinary communication, and protocol compliance.

The original six Georgian PFCCS instructors have now trained an additional nine instructors. These 15 individuals, representing diverse regions and health-care systems throughout Georgia, have independently presented PFCCS 8 times to more than 120 health-care workers (Figure 3). Establishing a Georgian PFCCS instructor network has positively impacted other educational programs within the Georgian health-care system. Local efforts





to develop Pediatric Advance Life Support courses within Georgia were already underway when PFCCS was first introduced.

## DISCUSSION

There are many advantages to leveraging an educational platform such as PFCCS to support international collaborations. In our experience, PFCCS promoted rapid relationship building between US and Georgian health-care providers. The SCCM sponsorship and oversight of the course provides information deemed important by an internationally recognized organization rather than any one individual or specific institution. The interactive lecture format and case scenarios provide a non-threatening framework for rapidly understanding existing practice patterns, resource limitations, and potential barriers to change within a foreign health-care environment. PFCCS material is presented to learners as being relevant to all health-care settings (resource abundant and resource limited) and therefore unifies international and local collaborators around a common cause.

PFCCS teaches principles that may not only be considered best practices within US systems, but may also represent novel ideas and concepts within certain health-care environments. The course framework facilitates non-threatening discussion of these ideas while respectfully highlighting the cultural diversity between the instructor and student's health-care environments. Case discussions unite instructor and student around universal clinical challenges, thereby accelerating relationship building and improving receptiveness to the course objectives. For example, PFCCS development in Georgia introduced interosseous (I/O) needles as a method for gaining rapid intravenous access during resuscitation. The suggestion of an I/O needle during our initial PFCCS presentations was met with shock and dismissed by the Georgian health-care providers in attendance. On future trips, we brought the intraosseous equipment to demonstrate the ease of use and the lifesaving potential of this equipment. The PFCCS instructors were the first Georgians to adopt the idea. Their acceptance of the I/O as a valuable medical tool was the gradual result of continuing to teach about I/O application within the context of the PFCCS case scenarios. Ultimately, one of the PFCCS instructors, the director of Pediatric Emergency Medicine training in Georgia, has decided to implement I/O needles as part of her PhD thesis. The research for her thesis involves the pilot introduction of I/O use in the emergency department and pediatric intensive care unit of a major children's hospital in Georgia.

The PFCCS course approach to addressing common pediatric emergencies creates a platform to promote interdisciplinary communication and team dynamics (**Figure 1**). The simulation-based medical scenarios provide an excellent venue for promoting and practicing positive culture changes to improve collective decision making and ultimately patient care. Health-care delivery in these hands-on sessions is presented as an interdisciplinary team collaboration rather than an individual performance, highlighting the critical role played by both physician and non-physician team members. In Georgia, gradual cultural shifts stemming from these PFCCS teamwork principles, have translated to inviting nurses to join physicians in becoming PFCCS instructor candidates. Inclusion of nursing leadership in the PFCCS instructor network

has accelerated adoption of PFCCS principles at the bedside, improved interdisciplinary communication, and led to lifesaving changes in health-care delivery throughout the Georgian health-care system.

Fundamental concepts for enhancing team dynamics include mutual respect and creating a shared mental model. These concepts are explicitly taught and promoted in the debriefing sessions that follow PFCCS simulation scenarios. These discussions play an essential role in establishing a psychologically safe framework where learners can reflect on their actions, identify performance gaps, and discuss areas for personal and process improvements. The opportunity for transparent discussion of patient management was unprecedented in the Georgian medical culture. Following the first introduction to debriefing, Georgian PFCCS instructor candidates expressed immense gratitude for the opportunity to safely ask questions regarding medical decisions the team made during the case scenario, while receiving constructive feedback specific to their management. Eclipsing all this was the opportunity to recognize they were not alone in their feelings of uncertainty or the emotional turmoil that surrounds the care of a critically ill child. The impact of these sessions on our Georgian colleagues impressed upon us the importance of continuing to pursue debriefing opportunities within our own US health-care environment as an effective method for supporting team members and enhancing team dynamics.

Although PFCCS proved to be effective in achieving our educational objectives there are several inherent limitations to this approach that must be addressed. First, it must be acknowledged that PFCCS is one of many courses to utilize the "train the trainer" approach. The American Red Cross and American Heart Association, to name a few, have a long history of educating the world in optimal resuscitation techniques. These forerunners lent support to our idea that this educational model would also be effective for enhancing critical care knowledge in diverse settings. Unfortunately, the most important barrier to developing any of these standardized courses in a developing country is that the cost for training materials and licensing are often prohibitive. These financial barriers limit the feasibility of sustaining the courses over the long run in economically challenged settings. Finally, although trainees found the course useful, we have yet to establish that PFCCS training of health-care providers increases the survival of critically ill children in Georgia. However, the training process led to the country's adoption of QI methodology and implementation of the interosseous needle. The potential for these changes to positively impact patient outcome are well documented in the medical literature.

In addition to the course limitations listed above, we encountered a number of logistic challenges that had to be overcome to successfully achieve our collaborative goals. The language barrier was perhaps the most difficult challenge encountered in the training process. At the time of our first visit, we encountered limited English fluency throughout Georgia. The PFCCS textbook and slides are written in English and time and cost made initial translation of the materials to Georgian infeasible. Instead, we selected PFCCS instructor candidates fluent in English. After gaining permission from the SCCM PFCCS leadership, each instructor translated their lecture into the

Georgian language. This step was an essential work around as English fluency was even less common in the regional areas that have the greatest need for critical care education. Unfortunately, although the course slides have now been translated to Georgian and the course is taught in Georgian, the textbooks are still written in English, thereby limiting this reference as a tool in clinical management for a large percentage of the Georgian health workforce. Efforts are underway to translate the textbook into Georgian. In the interim, English fluency within the Georgian population continues to increase.

The PFCCS course utilizes a combination of case-based lectures and hands-on simulated sessions to reinforce course objectives. The first Georgian instructor candidates had limited experience with simulated case-based learning prior to their PFCCS training. To develop this skill set, extended simulation practice sessions were part of every US visit, and included real-time debrief and training in simulation teaching methods and principles of adult learning. Between visits, instructors were required to lead a minimum of two simulated teaching sessions within their individual place of work. These “practice sessions” raised instructor confidence in simulated teaching and inadvertently changed their approach to training the local medical teams they supervised.

Financing educational programs within low-income countries is always a challenge and often places significant limitations on successful achievement of project goals. Training PFCCS instructors in a foreign health-care system is labor intensive for both the local work force and the international collaborators. The perceived financial cost to developing internationally recognized courses such as PFCCS is often seen as prohibitive for resource-limited locations. PFCCS is not a free educational resource. A license purchased through SCCM is required to access and present the course lectures and training materials. The license cost for a country is determined by a tiered structure and is therefore available at a markedly reduced rate for resource-limited countries (10). However, successful international collaborations that lead to sustainable changes in health-care environments are rare. Recognizing the uncertainty in the feasibility of achieving our objective we sought to minimize the financial cost of this project to our hosts. We asked our Georgian stakeholders and instructor candidates to invest their time and effort in course development without financial risk or obligation. Institutions can purchase a multi-course licenses through SCCM to permit unlimited course presentations in any location they choose. The US PFCCS team under the Mayo Clinic institutional license was able to present the PFCCS course to Georgian instructor candidates free of charge. US instructors covered their own travel costs and donated PFCCS textbooks to reduce the financial cost for development even further. Once the Georgian instructors were certified by SCCM and independently teaching PFCCS in Georgia, they purchased their own multi-course license. At this stage of development, the success of the initiative and value of the program to Georgian health care was well recognized by the Georgian Ministry of Health and the non-government organizational sectors. As a result, Georgian PFCCS leadership was able to secure financial support from local sources and UNICEF, CDC, and UNFPA. Regular meetings with these entities during each US visit to

Georgia was critical to maintaining enthusiasm for the project and ultimately financial support. Furthermore, as recognition of the course value grew, opportunities for offering PFCCS to surrounding countries is creating new opportunities for generating revenue to sustain the course and promote the international visibility of the Georgian health-care developments.

Perhaps, the most significant outcome of PFCCS development in Georgia were the relationships developed between US and Georgian health-care teams. Successful certification of Georgian PFCCS instructors increased enthusiasm for considering additional educational courses such as the adult Fundamental of Critical Care Support (FCCS) course and Advanced Trauma and Life Support. Recognizing that the majority of providers in Georgia are treating primarily adults, the efforts to establish FCCS in Georgia proceeded rapidly. The number of clinicians seeking to become FCCS instructors more than doubled that of the original seven PFCCS instructor candidates. FCCS candidates were required to complete the PFCCS course, taught by their pediatric colleagues, who were now certified PFCCS instructors. The PFCCS instructors approached this process with great trepidation. These instructors disclosed to the US consultants that the FCCS instructor candidates were actually their former teachers, each a highly respected anesthesiologist or internist within the Georgian health-care community. Despite their initial concerns, the PFCCS instructors delivered the course seamlessly. At the conclusion, FCCS candidates were overcome with pride in their former students and marveled at the effectiveness of the course format for teaching critical care management and developing instructors into highly competent teachers. To date, there are more than 50 FCCS instructors in Georgia representing every medical discipline and region. The PFCCS and FCCS courses are the first Georgian educational programs to qualify for continuing medical education (CME) credit. The Georgian FCCS director, Dr. Marika Toidze, plans to train an additional 80 FCCS instructors in 2018 to accommodate the new CME requirements in Georgia.

In summary, our experience confirms those reported elsewhere that high impact, sustainable changes in patient management can be accomplished through education that occurs independent of expensive investments in material resources (12, 13). An established and internationally recognized educational program such as PFCCS is a successful method for developing international collaborations with long term benefit through a series of short-term visits. The PFCCS interactive format permits efficient exchange of information to pursue focused needs assessment and understanding of the local infrastructure strengths and challenges. The learning objectives are relevant to all health-care settings (resource abundant and resource limited) and therefore unify international and local collaborators around a common cause. The original request of the US consultants was to help improve maternal and child health-care delivery. We have found PFCCS to be an effective tool for taking the first steps toward that objective. Furthermore, it has helped create a foundational vocabulary amongst stakeholders as we move forward to address other aspects of health-care infrastructure, including medical transport and trauma system development that impact health outcomes for the Georgian population.

## CONCLUSION

The SCCM Fundamental's "train the trainer" approach provided a uniform, reproducible, and sustainable framework for educating health-care providers in the fundamentals of pediatric critical care throughout the Republic of Georgia. Developing local PFCCS instructors within an international health-care environment is an effective model for establishing durable educational infrastructure that functions independently of international involvement.

## ETHICS STATEMENT

This manuscript describes and educational initiative in another country. Although data are presented regarding the project outcomes, this was not an intervention study or a research project and therefore did not require IRB review. Please let us know if the paper should be submitted under a different format than as an "original research article."

## AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study and participated in the training processes described in this

manuscript; BB and GA organized the database; GA performed the statistical analysis; SC wrote the first draft of the manuscript with extensive contribution from BB; GA wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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# Clinical Presentation and Outcomes among Children with Sepsis Presenting to a Public Tertiary Hospital in Tanzania

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**Background:** Pediatric sepsis causes significant global morbidity and mortality and low- and middle-income countries (LMICs) bear the bulk of the burden. International sepsis guidelines may not be relevant in LMICs, especially in sub-Saharan Africa (SSA), due to resource constraints and population differences. There is a critical lack of pediatric sepsis data from SSA, without which accurate risk stratification tools and context-appropriate, evidence-based protocols cannot be developed. The study's objectives were to characterize pediatric sepsis presentations, interventions, and outcomes in a public Emergency Medicine Department (EMD) in Tanzania.

**Methods:** Prospective descriptive study of children (28 days to 14 years) with sepsis [suspected infection with  $\geq 2$  clinical systemic inflammatory response syndrome (SIRS) criteria] presenting to a tertiary EMD in Dar es Salaam, Tanzania (July 1 to September 30, 2016). Outcomes included: in-hospital mortality (primary), EMD mortality, and hospital length of stay. We report descriptive statistics using means and SDs, medians and inter-quartile ranges, and counts and percentages as appropriate. Predictive abilities of SIRS criteria, the Alert-Verbal-Painful-Unresponsive (AVPU) score and the Lambaréné Organ Dysfunction Score (LODS) for in-hospital, early and late mortality were tested.

**Results:** Of the 2,232 children screened, 433 (19.4%) met inclusion criteria, and 405 were enrolled. There were 247 (61%) subjects referred from an outside facility. Approximately half (54.1%) received antibiotics in the EMD, and some form of microbiologic culture was collected in 35.8% ( $n = 145$ ) of subjects. In-hospital and EMD mortality were 14.2 and 1.5%, respectively, median time to death was 3 days (IQR 1–6), and median length of stay was 6 days (IQR 1–12). SIRS criteria, the AVPU score, and the LODS had low positive (17–27.1, 33.3–43.9, 18.3–55.6%, respectively) and high negative predictive values (88.6–89.8, 86.5–91.2, 86.8–90.5%, respectively) for in-hospital mortality.



**Conclusion:** This pediatric sepsis cohort had high and early in-hospital mortality. Current criteria and tested clinical scores were inadequate for risk-stratification and mortality prediction in this population and setting. Pediatric sepsis management must take into account the local patient population, etiologies of sepsis, healthcare system, and resource availability. Only through studies such as this that generate regional data in LMICs can accurate risk stratification tools and context-appropriate, evidence-based guidelines be developed.

**Keywords:** global health, resource-limited, low-resource setting, pediatric critical care, pediatric emergency medicine, pediatric sepsis

## INTRODUCTION

Sepsis represents a spectrum of disease involving a systemic inflammatory response syndrome (SIRS) in the setting of infection, escalating in septic shock to cardiovascular and organ system dysfunction (1). It is the final common inflammatory pathway for most infectious disease-related deaths (2, 3) and incurs significant pediatric morbidity and mortality worldwide (1–9). Globally, there were 2.6 million deaths due to infectious diseases in children and adolescents in 2015, and 66% of these deaths occurred in sub-Saharan Africa (SSA) (10). A recent, global point prevalence study in children in pediatric intensive care units with severe sepsis from 128 sites in 26 countries, showed an aggregated in-hospital mortality rate of 25% (11). The identification and initial care of children with sepsis can significantly impact survival (12–14), and both delays in presentation (15) and delays in diagnosis have been shown to be risk factors for poor outcomes in low- and middle-income countries (LMICs) (14). The Surviving Sepsis Campaign's international guidelines set standards for early identification, resuscitation, and protocol-based management, which have been shown to substantially impact outcomes (16). Much of the recommended sepsis management, especially regarding goal-directed interventions, is dependent on frequent or invasive monitoring that is not reliably available in limited resource settings and healthcare providers in LMICs often face resource constraints that limit capacity to implement these guidelines (13).

Beyond resource gaps that may limit the usability of international management guidelines, there is recent evidence suggesting that the clinical effectiveness of some interventions may be context-dependent. In 2011, Maitland et al., published results from a large, multicenter, randomized controlled trial: Fluid Expansion as Supportive Therapy (FEAST) (8). In this trial, African children with severe febrile illness who received fluid bolus resuscitation had a significantly higher relative risk (RR) of mortality compared to children who received only maintenance fluids (RR for any bolus vs. control, 1.45; 95% CI, 1.13–1.86;  $P = 0.003$ ) (8). Current international guidelines recommend fluid bolus resuscitation for severe sepsis and septic shock (1, 16–20), but the unexpected results from the FEAST trial call into question whether practice guidelines primarily developed in high-income countries (HICs) are appropriate for LMICs. This may be especially true in malaria endemic regions given the increased possibility of shock secondary to severe anemia as compared to septic shock due to bacteremia (21, 22).

There is a critical lack of region-specific and relevant pediatric sepsis data, and few pediatric sepsis cohorts exist in SSA (7). While we recognize pediatric sepsis to be a global burden, we lack a robust understanding of how best to identify and manage sepsis in settings where triage and goal-directed therapy are challenging given the scarcity of invasive monitoring, laboratory tests, and medical personnel and where HIV, malaria, malnutrition, and limited access to care frequently complicate management. Tanzania is one such setting with a paucity of data on the profile and outcomes of children with sepsis. Thus, the objective of this prospective study was to characterize the clinical presentation, emergency interventions received, and outcomes among children with sepsis presenting to Muhimbili National Hospital (MNH) in Tanzania. The generation of region-specific data is needed to accurately risk stratify patients, develop appropriate protocols for early recognition, and implement evidence-based treatment protocols.

## MATERIALS AND METHODS

This prospective descriptive study included pediatric patients presenting with sepsis to an urban, tertiary Emergency Medicine Department (EMD) at the National Referral Hospital in Dar es Salaam, Tanzania (MNH) between July 1 and September 30, 2016. The EMD is the receiving department for all acutely ill and injured patients, and is the only 24-h, full capacity public EMD in Tanzania. It is also the training site for the only emergency medicine residency in the country and cares for an average of 60,000 patients annually, and children comprise approximately 25% of the patient population. Pediatric sepsis is common at MNH; the EMD cares for an estimated 150–200 children with sepsis monthly (23, 24).

The EMD is equipped to provide plain radiographs, bedside ultrasound, continuous cardiorespiratory monitoring, low-flow oxygen, bag mask ventilation, intubation, mechanical ventilation, blood product transfusions, vasoactive medications, and resuscitation medications. MNH has a large general pediatrics ward, a high-dependency unit (HDU), and no dedicated pediatric intensive care unit. In general, the MNH ward can administer intermittent medications, intravenous fluids, low-flow oxygen, and blood products and measure vital signs every shift. The HDU is similar to the ward with a more favorable nursing ratio. Vasoactive infusions, intubation and mechanical ventilation are not routinely available for children outside of the EMD.



Children were included if they were between 28 days and 14 years of age and met criteria for sepsis, defined as having two or more clinical SIRS criteria (**Box 1**) with a suspected infection. At MNH, patients younger than 28 days present directly to the maternity and neonatal ward, and those over 14 years are triaged to adult rooms and admitted to the adult ward. SIRS criteria is defined per international pediatric sepsis consensus definitions (1), adapted for resource-limited settings (12). All pediatric patients presenting to the EMD were screened. Patients in cardiac arrest on presentation or with acute trauma were excluded. Written consent was obtained prior to enrollment. The primary outcome was in-hospital mortality. Secondary outcomes included EMD mortality and hospital length of stay.

Patient data included: patient characteristics [age, sex, mid-upper arm circumference (MUAC), severity of illness]; patient comorbidities (HIV, malaria, TB, malnutrition); vital signs and SIRS criteria on admission; delay to care (onset of illness, facilities visited prior to MNH, duration of fever); socioeconomic status indicators (insurance status, parents' education levels, parental literacy, number of children in the household, number of children under 5 in the household); interventions and therapies received in the EMD; relevant laboratory results; and outcomes. All diagnostic and therapeutic decisions were made at the discretion of the treating physician. Severe malnutrition was defined as a MUAC of  $\leq 11.5$  cm and severe anemia was defined as a hemoglobin  $\leq 5$  g/dL. Level of consciousness was assessed with the AVPU score (alert, responds to verbal stimuli, responds to pain, unresponsive) and severity of illness was measured with the 4-point Lambaréné Organ Dysfunction Score (LODS) (**Box 2**) (25). The LODS is a simple clinical prediction score for mortality validated in African children  $\leq 15$  years, including malaria endemic regions (25, 26). Early and late mortality were defined as death within 48 and  $\geq 48$  h of presentation, respectively. Microbiological investigations including cultures are not routinely performed on all patients, but results were recorded when available.

Research personnel collected data from the electronic medical record, paper chart, care provider, and guardian. Study data were managed using REDCap electronic data capture tools (version 7.2.2) hosted at MNH (27). Data were deidentified prior to

analysis. This study was carried out in accordance with the recommendations and approval of the Institutional Review Boards and Committees on Human Research at Muhimbili University of Health and Allied Sciences (Ref. No. 2016-03-30/AEC/Vol.X/201) and the University of California, San Francisco (IRB # 16-18977, Ref. No. 161295). We obtained written, informed consent from all guardians and assent from subjects when appropriate in accordance with the Declaration of Helsinki.

## Statistical Analysis

All data analysis and descriptive statistics were performed using Stata/MP (14.2), including means and SDs, medians and interquartile ranges, and counts and percentages as appropriate for the data type and distribution. We evaluated the ability of number of SIRS criteria, the AVPU score and the LODS to predict in-hospital mortality in this population. Scoring system discrimination was evaluated by comparing positive and negative predictive values.

## RESULTS

A total of 2,232 children presented to the EMD during the study period. There were 433 patients (19.4%) who had SIRS with a suspected infection, 28 children were excluded, and 405 subjects were successfully enrolled (**Figure 1**). Of those enrolled, 402 (99.3%) were followed to hospital discharge.

### Baseline Patient Characteristics

The median age of children with sepsis at MNH was 25 months (IQR 11–63 months), and 73.1% were under 5 years of age ( $n = 296$ ) (**Table 1**). Severe malnutrition was present in 12.6% ( $n = 51$ ) of children, 6.9% ( $n = 28$ ) tested positive for malaria by rapid diagnostic test (RDT) or microscopy, 1.7% ( $n = 7$ ) had confirmed (by RDT or antibody testing) or a known history of HIV, and 12.8% ( $n = 52$ ) of subjects were tested for HIV during hospitalization. The mean hemoglobin was 8.3 g/dL ( $n = 305$ ), and 16.1% ( $n = 49$ ) of children presented with severe anemia. The mean venous blood gas pH among those tested ( $n = 184$ ) was 7.36 (SD 0.14), while the mean lactate ( $n = 177$ ) was 3.2 mmol/L (SD 3.5). The majority of children (61.7%,  $n = 250$ ) presented with fever: of these, 36.4% ( $n = 91$ ) had fever only by history and 63.6% ( $n = 159$ ) had a documented fever on arrival. Almost 66% of patients (205/311) reported a fever duration greater than 48 hours and the mean fever duration was 8.7 days (SD 27.5). Over half of the patients (61%,  $n = 247$ ) were referred to MNH from an outside hospital or clinic. Among referred patients, 47.5% (116/244) had been administered antibiotics before arrival to MNH. Up-to-date immunization status was reported in 97.3% ( $n = 394$ ) of patients.

### Socioeconomic Status Indicators

Regarding insurance status, 42.5% ( $n = 172$ ) of subjects were uninsured, though 76.2% ( $n = 131$ ) of uninsured patients were categorically exempt from paying medical expenses by Tanzanian law based on age or disease status (**Table 1**). Paternal and maternal literacy rates were similar at 95.9% ( $n = 372$ ) and 92.3% ( $n = 371$ ), respectively, though more fathers completed secondary school or higher education than mothers (43.5 and 34.6%,  $n = 176$  and 149, respectively). The median number of children younger than

#### BOX 1 | Clinical SIRS Criteria for Resource-Limited Settings (12).

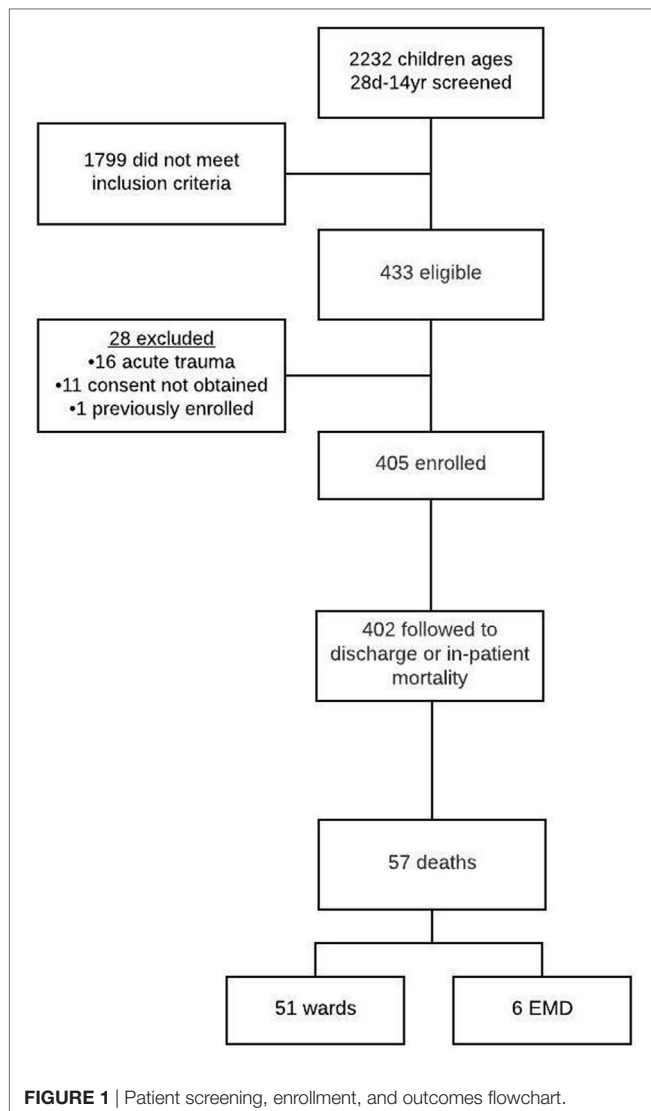
Presence of  $\geq 2$  of the following 4 criteria with a suspected or proven infection:

- Abnormal temperature (axillary  $>38$  or  $<36.0^{\circ}\text{C}$ ) documented or by history.
- Abnormal heart rate for age: tachycardia OR bradycardia ( $<1$  year).
- Respiratory insufficiency: tachypnea for age, hypoxia ( $\text{S}_\text{p}\text{O}_2 < 92\%$ ), NIPPV, OR mechanical ventilation.
- Ill-appearing, in distress, OR not responsive.

#### BOX 2 | Lambaréné Organ Dysfunction Score (LODS) (2, 6, 25).

Validated in African children  $\leq 15$  years with and without malaria. The score assigns one point for each of the following:

- Prostration—defined as  $\geq 1$  of the following, depending on age: inability to breastfeed, sit, stand, or walk unsupported.
- Coma—Blantyre Coma Score  $\leq 2$ .
- Deep breathing.



18 years in the patient household was 2 (IQR 1–3). Ninety-five percent ( $n = 403$ ) of families reported having regular access to an “improved” drinking water source, defined by the WHO/UNICEF Joint Monitoring Programme as a water source that is protected from sewage (28). Almost 71% ( $n = 283$ ) of families had electricity, and 56.8% ( $n = 230$ ) had toilets in the home.

## Illness Severity

On arrival, 82% ( $n = 331$ ) of children were “alert” by the AVPU score. Using the LODS as a measure of illness severity, 46.7% ( $n = 189$ ) of subjects had the lowest severity score of zero, while 17.8% ( $n = 72$ ) had a score of two or more. The median number of documented SIRS criteria was 3 (IQR 2–3), with 41.2 ( $n = 167$ ), 41.0 ( $n = 166$ ), and 17.8% ( $n = 72$ ) of subjects meeting 2, 3, and 4 criteria, respectively. Respiratory insufficiency was the most common SIRS criteria, occurring in 86.4% ( $n = 350$ ) of patients, followed by abnormal temperature, abnormal heart rate, and abnormal appearance occurring in 70.9 ( $n = 287$ ), 60 ( $n = 243$ ), and 53.3% ( $n = 216$ ) of patients, respectively (Table 2).

**TABLE 1 |** Patient characteristics.

	Total ( $N = 405$ )
<b>Demographics</b>	
Age (months), median (IQR)	25 (11–63)
<2 years, $n$ (%)	195 (48.2)
2–5 years, $n$ (%)	101 (24.9)
>5 years, $n$ (%)	109 (26.9)
Male sex, $n$ (%)	236 (58.3)
MUAC, mean (SD)	14.7 (4.1)
$\leq 11.5$ cm, $n$ (%)	51 (12.6)
Malaria positive, $n$ (%)	28 (6.9)
HIV positive, $n$ (%)	7 (1.7)
Fully immunized, $n$ (%)	394 (97.3)
<b>Illness severity and level of consciousness</b>	
Lambaréné Organ Dysfunction Score	
LODS 0, $n$ (%)	189 (46.7)
LODS 1, $n$ (%)	144 (35.6)
LODS 2, $n$ (%)	63 (15.6)
LODS 3, $n$ (%)	9 (2.2)
AVPU score	
Alert, $n$ (%)	331 (82.8)
Responds to verbal, $n$ (%)	11 (2.8)
Responds to pain, $n$ (%)	40 (10)
Unresponsive, $n$ (%)	18 (4.5)
Missing	5 (1.3)
No. of SIRS criteria met, median (IQR)	3 (2–3)
2, $n$ (%)	167 (41.2)
3, $n$ (%)	166 (41)
4, $n$ (%)	72 (17.8)
<b>Laboratory values</b>	
Hemoglobin (g/dL) ( $n = 305$ ), mean (SD)	8.3 (3.0)
$\leq 5$ g/dL, $n$ (%)	49/305 (16.1)
>10 g/dL, $n$ (%)	85/305 (27.2)
WBC count $\times 10^3$ ( $n = 305$ ), mean (SD)	16.6 (22.4)
Platelet count $\times 10^3$ ( $N = 304$ ), mean (SD)	322 (201.6)
Venous blood gas pH ( $n = 184$ ), mean (SD)	7.36 (0.14)
Bicarbonate (mEq/L) ( $n = 185$ ), mean (SD)	21.3 (6.5)
Lactate (mmol/L) ( $n = 177$ ), mean (SD)	3.2 (3.5)
Sodium (mEq/L) ( $n = 199$ ), mean (SD)	132.5 (7.2)
Potassium (mEq/L) ( $n = 199$ ), mean (SD)	4.1 (1.3)
Glucose (mmol/L) ( $n = 243$ ), mean (SD)	6.6 (3.6)
<b>Prehospital course</b>	
Fever, $n$ (%)	250 (61.7)
Documented, $n$ (%)	159/250 (63.6)
By history, $n$ (%)	91/250 (36.4)
Days of fever, mean (SD)	8.7 (27.5)
>2 days, $n$ (%)	205/311 (65.9)
Hospital/clinic referral, $n$ (%)	247 (61.0)
Antibiotics prearrival, $n$ (%)	116/244 (47.5)
<b>Socioeconomic status indicators</b>	
Insured, $n$ (%)	172 (42.5)
Exempt status, $n$ (%)	131 (32.4)
Paternal literacy	372/388 (95.9)
Father's highest level of education	
No formal school	12 (3)
Primary school	190 (46.9)
Secondary school	95 (23.5)
University or advanced degree	81 (20)
Unknown	27 (6.7)
Maternal literacy	372/403 (92.3)
Mother's highest level of education	
No formal school	28 (6.9)
Primary school	228 (56.3)
Secondary school	78 (19.3)
University or advanced degree	62 (15.3)

(Continued)

**TABLE 1 |** Continued

	Total (N = 405)
Unknown	9 (2.2)
Number of children <18 in the household, median (IQR)	2 (1–3)
Number of children <5 in the household, median (IQR)	1 (1–2)
Electricity in the home	283/400 (70.8)
Improved water source, n (%)	403/423 (95.3)
Tap in the home, n (%)	96/403 (23.8)
Public tap, n (%)	214/403 (53.1)
Well, n (%)	93/403 (23.1)
Unimproved water source	20/423 (4.7)
Purchased water (bottled or truck)	9/20 (45.0)
Unprotected surface water	11/20 (55.0)
Toilet in the home	230 (56.8)

IQR, interquartile range; MUAC, mid-upper arm circumference; LODS, Lambaréné Organ Dysfunction Score; AVPU, alert-verbal-pain-unresponsive score; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

**TABLE 2 |** Frequency of SIRS criteria for patients enrolled in the study.

SIRS criterion	Total (N = 405)
<b>Abnormal temperature, n (%)</b>	287 (70.9)
Temperature, mean (SD)	37.7 (1.0)
<b>Abnormal heart rate, n (%)</b>	243 (60)
Tachycardia, n (%)	235 (58.0)
Bradycardia, n (%)	8 (2.0)
<b>Respiratory insufficiency, n (%)</b>	350 (86.4)
Tachypnea, n (%)	330 (81.5)
Hypoxia, n (%)	76 (18.8)
S <sub>p</sub> O <sub>2</sub> , mean (SD)	95.5 (10.3)
<b>Abnormal appearance, n (%)</b>	216 (53.3)
Ill-appearing, n (%)	203 (50.1)
Distress, n (%)	21 (5.2)
Prostrate, n (%)	7 (1.7)

SIRS, systemic inflammatory response syndrome.

## EMD Interventions

The most common EMD interventions included: antibiotic administration (54.1%,  $n = 219$ ), fluid administration (38.8%,  $n = 157$ ), oxygen therapy (24.5%,  $n = 99$ ), chest radiograph (11.9%,  $n = 48$ ), blood transfusion (11.2%,  $n = 45$ ), and antimalarial medication administration (9.2%,  $n = 37$ ) (Table 3). Three percent ( $n = 4$ ) of pediatric sepsis patients had a blood culture drawn in the EMD, while 75.6% ( $n = 306$ ) and 4.2% ( $n = 17$ ) were tested with malaria and HIV RDTs, respectively. Few patients were intubated and received mechanical ventilation (1.2%,  $n = 5$ ). While patients presenting in cardiac arrest were excluded, 1.2% ( $n = 5$ ) of patients decompensated to require cardiopulmonary resuscitation (CPR) in the EMD.

Some form of microbiologic culture was collected during hospitalization in 35.8% ( $n = 145$ ) of patients: blood, urine and cerebral spinal fluid (CSF) cultures were collected in 29.9, 14.8, and 4.0% of patients, respectively (Table 4). Of the cultures collected, 11.6, 10, and 0% of blood, urine and CSF were positive, respectively.

## Outcomes

Of the 402 patients followed to discharge, 57 patients died in the hospital, yielding an in-hospital mortality of 14.2% (Table 5).

**TABLE 3 |** Interventions received in the EMD.

Intervention	n (%) (N = 405)
Fluid administration	157 (38.8)
Blood transfusion ordered	45 (11.1)
Blood initiated in EMD	25/45 (55.6)
Antibiotics received in the EMD	219 (54.1)
Antibiotics received prearrival, not in the EMD	40 (9.9)
Blood culture drawn in the EMD	4 (1.0)
HIV rapid diagnostic test	17 (4.2)
Malaria rapid diagnostic test	306 (75.6)
Vasoactive infusion	1 (0.2)
Hydrocortisone	1 (0.2)
Antimalarial medications	37 (9.1)
Oxygen	99 (24.4)
Chest radiograph	48 (11.9)
Ultrasound	12 (3.0)
Intubation and mechanical ventilation	5 (1.2)
CPR initiated	5 (1.2)
ROSC	1/5 (20)

EMD, Emergency Medicine Department; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

**TABLE 4 |** Frequency of microbiologic tests performed and culture result positivity.

Microbiology	n (%)
Any microbiological culture performed	145/405 (35.8)
<b>Blood culture</b>	
Collected at any time during hospitalization	121/405 (29.9)
Culture positive	14/121 (11.6)
<b>Urine culture</b>	
Collected at any time during hospitalization	60/405 (14.8)
Culture positive	6/60 (10.0)
<b>CSF culture</b>	
Collected at any time during hospitalization	16/405 (4.0)
Culture positive	0/16 (0)

CSF, cerebral spinal fluid.

**TABLE 5 |** In-hospital outcomes for pediatric patients with sepsis.

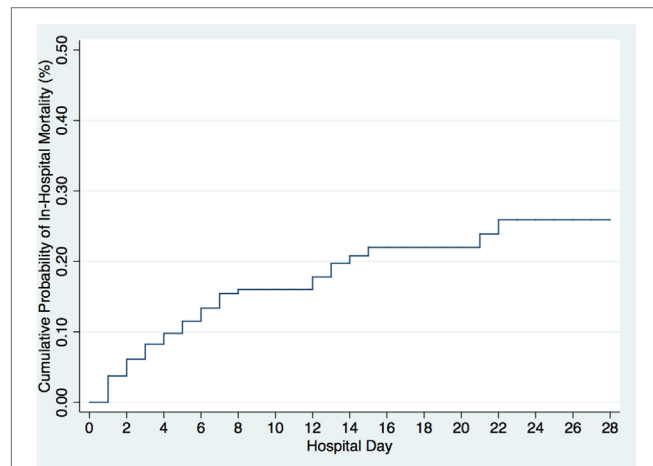
Outcome	
EMD mortality, n (%)	6/402 (1.5)
In-hospital mortality, n (%)	57/402 (14.2)
Ward mortality, n (%)	51/57 (89.5)
EMD mortality	6/57 (10.5)
<48-h mortality, n (%)	20/57 (35.1)
≥48-h mortality, n (%)	37/57 (64.9)
Time to death (days), median (IQR)	3 (1–6)
Length of stay all subjects (days), median (IQR)	6 (1–12)

IQR, interquartile range.

Six subjects died in the EMD, representing 10.5% (6/57) of the patients who died, and the overall in-ED mortality was 1.5% (6/402). The median time to death was 3 days (IQR 1–6 days) and 35.1% ( $n = 20$ ) of the patients who died did so within 48-h of presentation. The cumulative probability of mortality rose sharply until hospital day 7 (15.4%) and then rose gradually until hospital day 22 when it plateaued at 25.9% (Figure 2). The

median length of stay for all patients was 6 days (IQR 1–12 days). SIRS criteria and LODS were available on all 402 subjects, while AVPU scores and in-hospital outcomes were available on 98.6% (397/402) of subjects. All five of the patients with missing AVPU scores survived to discharge. In this population, case-fatality rates

increased with rising LODS and number of SIRS criteria, but less so with worsening AVPU score (**Figure 3**). We explored early mortality with respect to interventions received in the EMD: 80% ( $n = 16$ ) received a fluid bolus, two of who were malnourished, and 85% ( $n = 17$ ) received antibiotics in the EMD (**Table 6**). All three scores—AVPU, LODS, and SIRS—had low positive predictive values, and higher negative predictive values for in-hospital, early and late mortality (**Table 7**). This was also true in patient subgroups with malnutrition and severe anemia.



**FIGURE 2** | Cumulative probability of in-hospital mortality by hospital day.

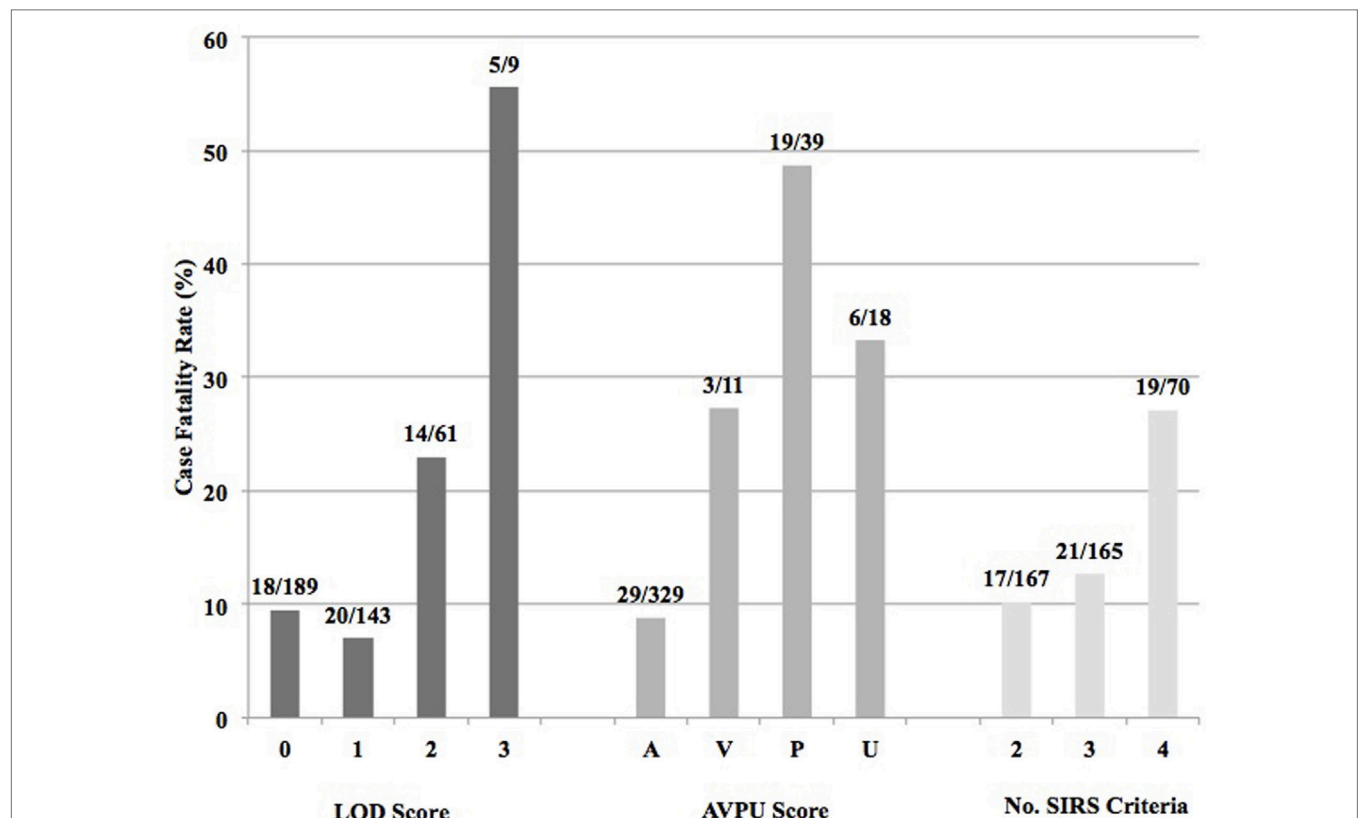
**TABLE 6** | Early mortality due to sepsis and key EMD interventions.

Early mortality ( $N = 20$ )	
Fluid bolus in the EMD, $n$ (%)	16 (80.0)
Malnourished, $n$ (%)	2/11 (18.8)
Blood transfusion, $n$ (%)	2 (10)
Severe anemia, $n$ (%)	1/14 (7.1)
Antibiotics prearrival, $n$ (%)	8/17 (34.5)
Antibiotics in the EMD, $n$ (%)	17 (85.0) <sup>a</sup>
Antibiotics prearrival or EMD, $n$ (%)	19 (95.0)
Antimalarial medication in the EMD, $n$ (%)	4 (20.0) <sup>b</sup>
Malaria positive, $n$ (%)	2 (10.0)

<sup>a</sup>Six patients received antibiotics prearrival and in the EMD.

<sup>b</sup>Two patients tested negative and were treated.

EMD, Emergency Medicine Department.



**FIGURE 3** | Case fatality rates by Lambaréné Organ Dysfunction Score, best response by the Alert-Verbal-Painful-Unresponsive (AVPU) score, and number of SIRS criteria present on admission.

**TABLE 7** | Positive and negative predictive values for clinical scores (LODS, AVPU, SIRS criteria) predicting in-hospital (subgroups malnutrition and severe anemia), early and late mortality.

Severity of illness measure	Positive predictive value					Negative predictive value				
	Total (%)	Malnutrition (%)	Severe anemia (%)	Early mortality (%)	Late mortality (%)	Total (%)	Malnutrition (%)	Severe anemia (%)	Early mortality (%)	Late mortality (%)
<b>LODS</b>										
≥1	18.3	21.7	21.4	40.0	10.6	90.5	87.5	90.0	77.8	92.6
≥2	27.1	37.5	12.5	47.4	13.9	88.6	87.0	82.5	71.8	91.9
3	55.6	19.4	50.0	60.0	22.2	86.8	<sup>a</sup>	84.8	67.9	91.2
<b>AVPU score best response</b>										
Verbal or worse	41.2	42.9	16.7	39.3	24.6	91.2	87.5	83.3	70.0	94.0
Pain or worse	43.9	40.0	20.0	40.0	25.9	90.6	84.6	83.7	69.7	93.6
Unresponsive	33.3	<sup>a</sup>	<sup>a</sup>	50.0	16.7	86.5	78.6	82.6	67.3	91.1
<b>SIRS criteria</b>										
≥3	17.0	20.0	19.4	37.5	10.5	89.8	81.2	88.2	72.2	92.8
4	27.1	25.0	25.0	42.1	15.3	88.6	81.5	87.5	69.2	92.2

<sup>a</sup>Too few subjects in a cell to calculate.

LODS, Lambaréné Organ Dysfunction Score; AVPU, alert-verbal-pain-unresponsive score; SIRS, systemic inflammatory response syndrome.

## DISCUSSION

This pediatric sepsis cohort had a high overall in-hospital mortality of 14.2%, substantially greater than a recent sepsis cohort in Uganda (5.4%) (29) and 48-h mortality in the FEAST trial (approximately 10%) (8). Almost 85% of deaths occurred within the first seven days of hospitalization, and over half of all deaths were within 72 h. Using SIRS criteria as a screening tool and requirement for study inclusion, the addition of the LODS, AVPU, or additional SIRS criteria were not useful in predicting in-hospital, early or late mortality in any of the tested subgroups, illustrating the difficulty of risk-stratification and mortality prediction in this patient population and setting.

The overwhelming majority of children who died did so on the ward and not in the EMD. Pediatric sepsis mortality occurring early in hospitalization, but outside of the EMD, has previously been observed in other SSA pediatric cohorts (8, 29). This may signify that despite acute stabilization, children are decompensating in the hospital, potentially due to poor monitoring, a lack of treatment resources, treatment failure, or the natural course of the disease; this study was not designed to assess the individual contribution of these factors and further investigation is needed.

Early recognition, resuscitation, and referral can be life saving in sepsis; yet, the majority of children had a fever duration over 48 h and were evaluated by providers at other health facilities prior to presentation at MNH, raising concerns about delays to definitive care. This, too, has been previously described; in South Africa, 40% of critically ill children were evaluated by >1 medical provider prior to referral to a tertiary care center, which resulted in delays in definitive care (30). Earlier recognition and targeted referral of high-risk patients by primary care providers could have a significant impact. It could be argued that the rate of antibiotic administration pre-arrival is a sign of provider recognition and treatment of sepsis, though additional exploration of referral patterns and therapies received in primary and secondary health facilities are required to address these aspects of care.

There are several limitations to this study. This cohort presented to an urban, tertiary center and may not reflect the general population in Tanzania. Parents in this cohort had a higher literacy rate (>90%) than previously reported for the general Tanzanian population (80.4%) (31) and 95% of families reported using an “improved” water source, significantly more than the 2015 national average of 55.6% (28), though there are legitimate concerns regarding tap water quality and safety (32, 33) in Tanzania. Given the inclusion criteria, this cohort was likely to be a sicker cohort than the general pediatric population; therefore, results cannot be extrapolated and applied to a general pediatric population. However, since a primary objective was to inform therapy guidelines and recommendations for the treatment of sepsis at a tertiary center, this was an ideal cohort to study.

We used SIRS criteria to identify patients with sepsis, and though these are the current, accepted criteria to identify pediatric sepsis, there has been much criticism regarding this operational definition (7, 29, 34). One criticism is that the definition of sepsis is highly context-dependent, especially in LMIC settings where diagnostic testing may be entirely unavailable or not available within a time frame relevant to guide acute care (7). In Uganda, researchers used SIRS criteria to identify sepsis in children with suspected infection; 86% met SIRS criteria, which captured 94% of all inpatient deaths, showing that SIRS criteria is highly sensitive for sepsis, but not specific, nor is it helpful in predicting mortality in this population and setting (29). The findings from this cohort study are consistent with the previous study results from Uganda.

Early mortality, as compared to late mortality, reflects EMD management and acute stabilization. In children who died within 48-h, 80% received a fluid bolus and 95% received antibiotics either pre-arrival or in the EMD. These findings could signify that guidelines were more closely followed in this subgroup, but failed to alter disease progression. Another possibility is that the intervention (i.e., fluid bolus) may potentially be contributing to early mortality as was seen in the FEAST trial (8). Further



analyses are required to determine guideline compliance and the association of fluid bolus with mortality.

We found that pathogen identification with conventional microbiological techniques were low-yield and not frequently used, making it difficult to determine the etiology of sepsis. A malaria RDT was far more likely to be performed than a blood culture in children with sepsis. This may be due to several factors. First, a significant percentage of children received antibiotics prior to arrival to the EMD. Second, the majority of blood cultures were drawn in the ward and not in the EMD and cultures were not routinely drawn prior to initiation of antibiotics. Third, blood culture collection supplies, specifically the bottles, may not always be readily available. Finally, some clinicians expressed general distrust of the microbiologic results and did not think the results changed management.

We also found that 36% ( $N = 146$ ) of children did not receive antibiotics in the EMD or prior to arrival despite antibiotic administration being an essential component of international guidelines (1, 16, 18). The low rate of antibiotic administration may have resulted from limited drug availability, failure to identify sepsis, the need for urgent treatment, incomplete documentation of drug administration, or some combination of these factors. Further work is necessary to elucidate the underlying cause of low antibiotic usage in this setting. Depending on the cause, early antibiotic administration in the EMD for children with sepsis is a potential future quality improvement project.

Some data were extracted from the chart and may not have captured all interventions performed; however, the presence of research assistants actively observing actions in the EMD likely minimized this effect. Simultaneously, having research assistants physically present in the EMD may have influenced providers' practices, producing an observer effect. The most likely results of such an effect would be increased provider awareness of sepsis and improved guideline compliance. We did not capture a metric for provider awareness, and guideline compliance in general was poor (not reported here), though antibiotic administration and blood culture collection are two indicators, which is consistent with prior pilot data from MNH.

In summary, pediatric sepsis management must take into account the local context; the unique patient population and its comorbidities, coinfections, and etiologies of sepsis; where and how the population accesses the healthcare system; and available resources including medical personnel and monitoring capabilities. Though there are many challenges to data collection in resource-limited settings—lack of research infrastructure, incomplete documentation, severe personnel shortages, inadequate funding, and technical difficulties performing follow-up—we have generated high-quality regional data that can be

used to develop an accurate risk stratification tool and inform context-appropriate, evidence-based guidelines in this setting. This is the first, critical step towards improving pediatric sepsis outcomes in SSA.

## ETHICS STATEMENT

Research personnel collected data from the electronic medical record, paper chart, care provider, and guardian and then entered it into REDCap (version 7.2.2). Data were deidentified prior to analysis. This study was carried out in accordance with the recommendations and approval of the Institutional Review Boards and Committees on Human Research at Muhimbili University of Health and Allied Sciences (Ref. No. 2016-03-30/AEC/Vol.X/201) and the University of California, San Francisco (IRB # 16-18977, Ref. No. 161295). We obtained written, informed consent from all guardians and assent from subjects when appropriate in accordance with the Declaration of Helsinki.

## AUTHOR CONTRIBUTIONS

Author contributions are as follows: conception and design of the work (TK, HS, BM, WE, and TR); data acquisition (TK, HS, and BM); data analysis (TK); data interpretation (TK, HS, BM, MM, and TR); first draft of the manuscript (TK); and manuscript revision and editing, final approval of the version to be published, and agreement to be accountable for all aspects of the work (TK, HS, BM, WE, MM, and TR).

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# Clinical and Pathological Correlation in Pediatric Invasive Pulmonary Aspergillosis

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**Introduction:** Invasive pulmonary aspergillosis (IPA) has been one of the major causes of mortality in immunocompromised patients. The gold standard method for a diagnosis of IPA is histopathological examination of the lung tissue; however, post-procedural bleeding limits the feasibility of lung biopsy. The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and The National Institute of Allergy and Infectious Disease Mycoses Study Group (EORTC/MSG) defined IPA. The objective of this study was to validate the EORTC/MSG 2008 definition of IPA, compared with histopathology in the pediatric population.

**Methods:** Histopathological examinations of lung tissues of children aged 1 month–18 years with respiratory tract infection at the time of obtaining biopsy were retrieved. Retrospective chart reviews for clinical characteristics were performed. IPA diagnosis was classified according to the EORTC/MSG 2008 definition.

**Results:** During the 10-year period, there were 256 lung tissues, of which 58 specimens were suspected to have pulmonary infection. Fourteen patients (24%) were noted to have IPA. Seven patients (50%) with proven IPA were classified as probable, while the remaining 50% were classified as possible, and none were classified as no IPA, by using EORTC/MSG 2008 definition. Other 44 specimens demonstrated 14 (32%), 14 (32%), and 16 (36%) were classified as probable, possible, and no IPA, respectively. When comparing probable or possible IPA with no IPA, we found that the EORTC/MSG 2008 definition had 100% sensitivity, 36% specificity, 33% positive predictive value, and 100% negative predictive value in diagnosis of IPA.

**Conclusion:** Our study illustrated that the EORTC/MSG 2008 definition provided an excellent sensitivity but low specificity for diagnosing IPA.

**Keywords:** invasive pulmonary aspergillosis, pediatric, histopathology, definition, sensitivity

## INTRODUCTION

Invasive pulmonary aspergillosis (IPA) has been one of the major causes of mortality in immunocompromised patients, such as malignancy, hematopoietic stem cell transplantation, and prolonged usage of immunosuppressive agents. Early diagnosis and prompt treatment improve survival outcome (1, 2). Aspergillus species are ubiquitous in the environment. Aspergillus fumigatus is the most common species in IPA (3, 4). Other species include Aspergillus flavus, Aspergillus niger, and Aspergillus

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terreus. *Aspergillus* is introduced to the lower respiratory tract by inhalation of the infectious spores. In healthy hosts, spores are eliminated by mucociliary clearance and immune defense. In immunocompromised patients, dormant spores convert into growing hyphal elements and invade lung parenchyma and vascular structure (1). Clinical symptoms and signs of IPA are indistinguishable from other pathogens causing pneumonia. Chest radiography is also non-specific. Therefore, the diagnostic tool is challenging (5, 6).

The gold standard method in the diagnosis of IPA is histopathological examination of lung tissue obtained by bronchoscopy or open thoracotomy. The presence of angioinvasion by acute angle, branching septate fungal hyphae along with a positive culture for *Aspergillus* from the same site is diagnostic for IPA (1). However, invasive procedures hinder the possibility of obtaining lung tissues. The angioinvasive nature of *Aspergillus* and the patient condition such as thrombocytopenia further increase risk of bleeding and other complications.

In 2002, The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and The National Institute of Allergy and Infectious Disease Mycoses Study Group (EORTC/MSG) formed a consensus committee to develop a standard definition for invasive fungal infections, including IPA. The definitions were intended for use in the context of clinical and/or epidemiological research, not for clinical decision making (7). These definitions were revised in 2008 due to the advances in diagnostic tools, including galactomannan, beta-D-glucan, and fungal DNA in body fluids by PCR (8, 9). Diagnosis of IPA is challenging, as the clinical symptoms are not specific. There is no single investigation for the diagnosis. IPA carries a high mortality rate if untreated, and delayed treatment can result in death. The ideal diagnostic tool should have high sensitivity for early recognition and treatment. In brief, based on EORTC/MSG 2008 consensus definition, there were three classifications; proven, probable, and possible. Proven IPA requires histopathology with a characteristic of infection and/or a positive culture of specimen from a sterile site. Probable IPA requires the fulfillment of criteria within three categories: host factors, clinical, and mycological criteria. Possible IPA consists of host factors, and clinical criteria without mycological evidence of *Aspergillus* infection (8). These definitions have been widely used in epidemiological research, and clinical trials for evaluation of new drugs and management strategies. However, they were based on the literature review, which did not include pathological results and was originally for the adult oncological population. To our knowledge, there were limited data about validity of the consensus definition compared with the histopathological diagnosis of IPA especially in the pediatric population. The objective of this study was to validate the EORTC/MSG 2008 consensus definition with the gold standard of histopathological results in pediatric patients.

## MATERIALS AND METHODS

### Study Design and Purpose

This study was performed in a tertiary care, academic center. We retrospectively analyzed histopathology tissues in children

aged 1 month–18 years with clinical suspicion of respiratory tract infection from January 2006 to December 2016. This study was approved by the Institutional Review Board. Patients with congenital lung disease, pulmonary malignancy, and incomplete medical records were excluded. Clinical characteristics, diagnostic tests, treatments, and pathological results were reviewed. Patients were categorized into two groups by the histopathological result as proven IPA and non-proven IPA and were classified according to the EORTC/MSG 2008 consensus definition into three groups (probable, possible, and no IPA) as shown in **Figure 1**.

## Definitions

The definition criteria for proven, probable, and possible IPA were shown in **Table 1**.

Proven IPA is characterized by a discrete nodule consisting of necrotic lung tissue with angioinvasion by acute angle, branching septate fungal hyphae or culture positive for *Aspergillus* spp. from lung tissue specimen (10, 11).

Non-proven IPA is defined as patients who do not meet the pathological criteria.

According to the EORTC/MSG 2008 consensus definition (8), clinical criteria in IPA consists of the presence of one of the following three signs on computer tomography; dense, well-circumscribed lesions with or without a halo sign, air-crescent sign, or cavity.

Positive clinical IPA is defined as patients who have clinical diagnosis with probable or possible IPA by the EORTC/MSG 2008 consensus definition.

Negative clinical IPA is defined as patients who do not meet criteria for diagnosis by the EORTC/MSG 2008 consensus definition.

Galactomannan enzyme immunoassay was measured from serum and bronchoalveolar lavage (BAL) fluid. Results were recorded as an index relative to the mean optical density of the threshold controls (GM index = optical density sample/mean optical density of the threshold control samples). Samples that had an index value >0.5 were considered positive for both serum and BAL fluid specimen (12, 13).

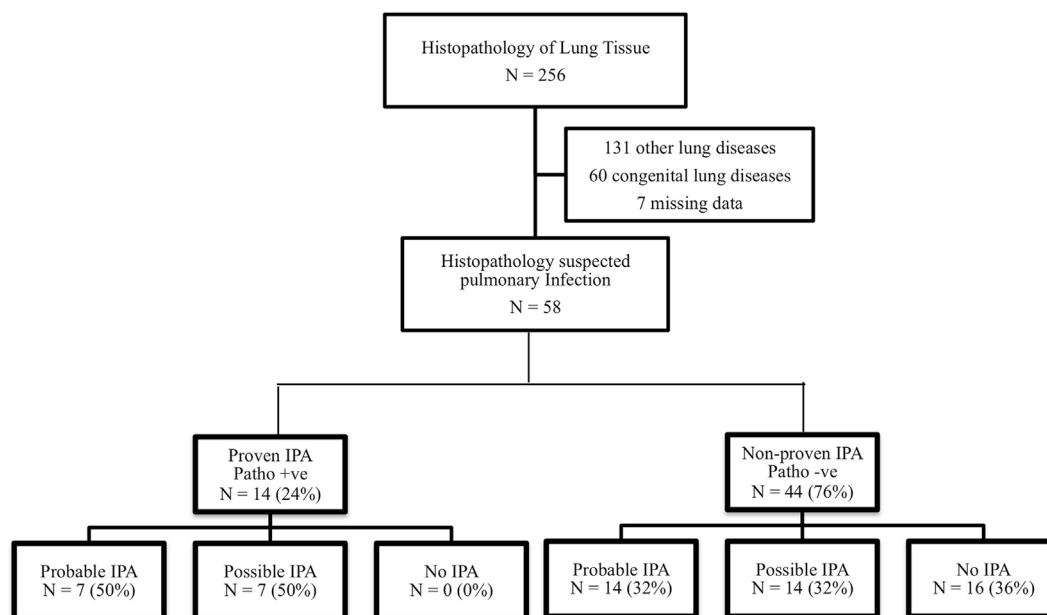
## Statistical Methods

SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Patients' demographics, clinical characteristics, and pathological data were analyzed by descriptive analysis using student's t-test and Chi-Square. For the diagnostic test, sensitivity, specificity, positive predictive value, and negative predictive value were obtained. Correlation between clinical diagnosis and pathological result was calculated using Spearman rho correlation analysis. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

In total, 256 lung tissues were documented. Fifty-eight pathological specimens revealed suspicion of infectious etiologies, 14 (24%) patients were consistent with proven IPA, and 44 (76%) patients were non-proven IPA as shown in **Figure 1**. All





**FIGURE 1** | Flow diagram and classification of invasive pulmonary aspergillosis (IPA) according to the EORTC/MSG 2008 consensus definition.

**TABLE 1** | The diagnostic criteria for IPA according to the EORTC/MSG 2008 consensus definition (8).

	Proven IPA	Probable IPA	Possible IPA
Positive for histopathological criteria – A discrete nodule consisting of necrotic lung tissue with angioinvasive by acute angle branching septate fungal hyphae or culture positive for <i>Aspergillus</i> spp. from lung tissue specimen	Yes	No	No
Positive for host factor criteria – Neutropenia – Post stem cell transplantation – Prolonged corticosteroid use – Received immunosuppressants – Inherited immunodeficiency		Yes	Yes
Positive for clinical criteria Presence of 1 of the following three signs on CT – Dense, well-circumscribed lesion with or without a halo sign – Air-crescent sign – Cavity		Yes	Yes
Positive for mycological criteria – Positive direct test by culture – Positive indirect tests by galactomannan antigen detection		Yes	No

IPA; invasive pulmonary aspergillosis, CT; computer tomography.

patients who were diagnosed with probable or possible IPA by the EORTC/MSG 2008 definition (positive clinical IPA) received antifungal medications, although 28 out of 42 patients were not diagnosed with proven IPA, but received antifungal medications. Five of 16 patients who were not diagnosed with IPA by the

EORTC/MSG 2008 definition (negative clinical IPA) received antifungal medications. None of these patients were diagnosed with proven IPA. The adverse events from antifungal medications were hypokalemia and acute kidney injury, although none of patients required renal replacement therapy. Baseline characteristics of histopathological proven IPA and non-proven IPA were showed in **Table 2**. There was no significant difference of demographic data in both groups. The proven IPA group had significantly more neutropenic patients than the non-proven IPA group ( $p$ -value = 0.009). The mean duration of neutropenia was longer in proven IPA than in non-proven IPA group. Mean was  $22.1 \pm 35.3$  days in proven IPA and  $12.9 \pm 12.5$  days in non-proven IPA group ( $p$ -value = 0.307).

## Microbiology and Pathological Results

Of the 58 lung tissue specimens, 18 lung tissues were obtained by open biopsy, 13 by necropsy, 10 by autopsy, 10 by CT/US guided needle biopsy, and 7 by transbronchial biopsy. The reasons for biopsy were for diagnosis in 28 (48%) patients, no response to antifungal medications or progression of diseases in 20 (35%) patients, and others in 10 (17%) patients. The mean duration from treatment to biopsy was 20.6 and 35.9 days in proven and non-proven IPA group, respectively ( $p$ -value = 0.431). The microbiology in non-proven IPA was virus in 7 patients (cytomegalovirus in 6 cases and respiratory syncytial virus in 1 case) and bacteria were found in 10 patients (3 cases were *A. baumannii*, 2 cases *P. aeruginosa*, 2 cases *Actinomyces* spp., 1 case *M. tuberculosis*, and 2 cases other bacteria). Fungus was isolated in nine patients (four of *Mucormycosis* spp., two of *Cryptococcus* spp., two of *Pneumocystis* spp., and 1 of *Scedosporiosis* spp.). The remaining 12 patients showed histopathologic change without identified pathogens, such as diffused alveolar damage and

**TABLE 2** | Baseline characteristics of the included patients.

	Proven IPA (n = 14)	Non-proven IPA (n = 44)	p-Value
Age, mean $\pm$ SD	10.4 $\pm$ 5.9	9.0 $\pm$ 6.1	0.438
Male (%)	4 (29)	21 (48)	0.207
Underlying disease, n (%)			0.064
– Malignancy	12 (86)	19 (43)	
– Primary immune deficiency	0 (0)	6 (14)	
– Connective tissue disease	0 (0)	3 (7)	
– Others	2 (14)	9 (20)	
– Healthy	0 (0)	7 (16)	
Neutropenia, n (%)	11 (79)	17 (39)	0.023*
Post transplantation, n (%)	1 (7)	6 (14)	0.108
Corticosteroid use, n (%)	1 (7)	4 (9)	0.904
Presentation symptom, n (%)			0.343
– Febrile neutropenia	9 (64)	18 (41)	
– Dyspnea	1 (7)	10 (23)	
– Hemoptysis	2 (14)	7 (16)	
– Others	2 (14)	9 (20)	
Serum galactomannan, median (IQR)	0 (0–2.2)	0 (0–1.4)	0.889
BAL galactomannan, median (IQR)	3.4 (1.5–7.5)	2.3 (0–4.0)	0.772
Computer tomography finding, n (%)			0.390
– Dense, well-circumscribed with/ without Halo sign	11 (79)	26 (59)	
– Non-specific infiltration/consolidation	2 (14)	9 (21)	
– Air-crescent sign	1 (7)	1 (2)	
– Cavitation	0 (0)	7 (16)	
– Normal finding	0 (0)	1 (2)	
Exposure to beta-lactam antibiotics, n (%)	2 (14.3)	10 (22.7)	0.497
Antifungal treatment, n (%)			0.200
– Amphotericin B	6 (43)	22 (50)	
– Combination drugs	4 (29)	4 (9)	
– Voriconazole	3 (21)	6 (14)	
– Caspofungin	1 (7)	1 (2)	
– No antifungal	0 (0)	11 (25)	
Hospital mortality, n (%)	6 (43)	23 (52)	0.539

IPA; invasive pulmonary aspergillosis, IQR; interquartile range.

\*p-Value less than 0.05.

pulmonary hemorrhage, and 6 patients showed non-infectious histopathology.

## EORTC/MSG 2008 Consensus Definition

We analyzed clinical diagnosis of IPA by grouping probable and possible IPA as positive clinical IPA, and no IPA as negative clinical IPA. The sensitivity was 100% and the specificity was 36%. The positive and negative predictive values were 33 and 100%, respectively. Spearman's rho correlation analysis revealed a correlation between clinical diagnosis and pathological result ( $r = 0.35$ ,  $p$ -value = 0.008). **Table 3** demonstrated each element in the EORTC/MSG 2008 consensus definition, in terms of sensitivity, specificity, positive, and negative predictive values.

## DISCUSSION

This study validated the EORTC/MSG 2008 consensus definition with the gold standard histopathological tissue in pediatric population. Our results were consistent with previous studies revealing that proven IPA patients were found to be more neutropenic patients. The function of neutrophil is directed against *Aspergillus* hyphae (14). The neutropenia can increase risk of

**TABLE 3** | The sensitivity and specificity of each element in the EORTC/MSG 2008 consensus definition.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
– Host risk	100	15.9	27.5	100
– Computer tomography finding	85.7	22.7	26.1	83.3
– Culture	36.4	100	100	81.6
– Serum galactomannan	33.3	68.2	22.2	79
– BAL galactomannan	100	26.7	26.7	100

PPV; positive predictive value, NPV; negative predictive value, BAL; bronchoalveolar lavage.

IPA. A prior study showed that cavitation or air-crescent sign in chest computed tomography is helpful in diagnosing IPA (15). Nevertheless, pediatric studies have demonstrated that nodules or infiltration are the most common radiologic findings in pediatric IPA (16, 17). Our study found no difference in radiologic findings in proven IPA and non-proven IPA groups. We had defined positive imaging as dense, well-circumscribed lesions with or without halo sign, air-crescent sign, or cavitation. The analysis showed high sensitivity but low specificity as in a previous study (18).

Galactomannan is a cell wall polysaccharide released by *Aspergillus* species during growth (19, 20). Serum galactomannan is more superior than BAL fluid because it is less invasive and provides a higher sensitivity (21). However, our study illustrated that the sensitivity of serum galactomannan was lower than BAL (33 vs. 100%, respectively) which was a similar result to another study (22). We hypothesized that since lungs are a primary site of IPA before angioinvasion may causes an elevation of BAL galactomannan prior to that of serum (23). In our study, the specificity of BAL fluid galactomannan was surprisingly low (27%) compared with previous studies (87.5–94%) using the same cutoff value (20, 24, 25). However, this study had included non-malignant patients which was different from the previous studies. In addition, this could be explained by using different classification as most studies used proven and probable as IPA instead of using histopathology as a gold standard. Another reason could be from the beta-lactam antibiotics. The beta-lactam antibiotics are derived from molds of the genus *Penicillium*. Galactomannan moieties are shared between *Aspergillus* and *Penicillium* species (26). Therefore, beta-lactam antibiotics have been reported to cause false positive of galactomannan.

To our knowledge, this study is the first study to validate the EORTC/MSG 2008 consensus definition in pediatric population with IPA by using histopathological tissues. Although the EORTC/MSG 2008 consensus definition was originally for the adult immunocompromised population. This study showed that the EORTC/MSG 2008 consensus definition had 100% sensitivity, but low specificity (36%), in diagnosing IPA when compared with histopathology in pediatric population. IPA has high mortality if left untreated, our paper showed the EORTC/MSG 2008 consensus definition can be helpful as the screening tool in pediatric populations. Therefore, children with probable or possible IPA according to this definition should be promptly treated with antifungal medications, monitored for adverse events of

antifungal medications, and need confirmed diagnosis if there is no clinical response.

This study has some limitations. First, retrospective study might not provide all data needed especially serum and BAL galactomannan. Second, the prevalence of IPA might be underestimated because our study started with histopathological tissue, as we were unable to perform biopsy in every case of suspected IPA. In addition, some patients only underwent imaging guided biopsy or transbronchial biopsy, which might result in inadequate specimen. Therefore, it may not represent all pediatric IPA. The last limitation is that this was a single-center study with small sample size. A larger sample size of these groups would allow better results and analysis.

## CONCLUSION

Pediatric IPA is a life-threatening disease with high mortality. The diagnostic tool is an important method to early recognition and prompt treatment. Our study shows that the EORTC/MSG 2008 consensus definition provides an excellent sensitivity as screening tool, but low specificity for the diagnosis of IPA.

## ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Committee on human rights related to research involving

human subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University.

## AUTHOR CONTRIBUTIONS

NN and NA contributed to design of the study, data collection, data analysis, and manuscript drafting. PI and AP contributed to design of the study. NA critically revised it for important intellectual content. All authors gave final approval of the version to be published.

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# The Potential Harm of Cytomegalovirus Infection in Immunocompetent Critically Ill Children

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Cytomegalovirus (CMV) is a ubiquitous infection that causes disease in congenitally infected children and immunocompromised patients. Although nearly all CMV infections remain latent and asymptomatic in immunologically normal individuals, numerous studies have found that systemic viral reactivation is common in immunocompetent critically ill adults, as measured by detection of CMV in the blood (viremia). Furthermore, CMV viremia is strongly correlated with adverse outcomes in the adult intensive care unit (ICU), including prolonged stay, duration of mechanical ventilation, and death. Increasing evidence, including from a randomized clinical trial of antiviral treatment, suggests that these effects of CMV may be causal. Therefore, interventions targeting CMV might improve outcomes in adult ICU patients. CMV may have an even greater impact on critically ill children, particularly in low and middle income countries (LMIC), where CMV is regularly acquired in early childhood, and where inpatient morbidity and mortality are inordinately high. However, to date, there are few data regarding the clinical relevance of CMV infection or viremia in immunocompetent critically ill children. We propose that CMV infection should be studied as a potential modifiable cause of disease in critically ill children, and that these studies be conducted in LMIC. Below, we briefly review the role of CMV in immunologically normal critically ill adults and children, outline age-dependent differences in CMV infection that may influence ICU outcomes, and describe an agenda for future research.

**Keywords:** cytomegalovirus, pediatric critical care, viremia, reactivation, immunocompetent, outcome, ganciclovir

## INTRODUCTION

Cytomegalovirus (CMV) is a double-stranded DNA herpesvirus that infects most of the world's population (1, 2). Natural transmission is mostly through contact with viral shedding in breast milk, saliva, urine, or genital fluids (3–5). Similar to other herpesviruses, acute CMV infection is associated with high levels of lytic viral replication and dissemination throughout the body, followed by the establishment of viral latency in long-lived cell types that is responsible for lifelong persistence of infection (6).

Cytomegalovirus infection is typically diagnosed by serology (1, 7, 8). In addition to CMV IgG, use of CMV IgM and serial IgG avidity testing may help determine the timing of infection in selected situations (7, 9, 10). However, in infants, CMV serologic testing can be confounded

presence of maternal IgG acquired passively *in utero* (3, 8). Therefore, diagnosis in infants requires either seroconversion (a change from negative to positive serologic testing) or, more often, by the detection of CMV in blood, saliva, or urine (3, 8). Isolation of CMV in culture or detection of CMV DNA or antigen in patient samples reflects lytic viral replication and is termed “active” infection (1, 2). Active CMV infection in a chronically infected person may be due to either reactivation of latent virus or reinfection with an exogenous strain of CMV (1, 2, 11, 12).

Acute CMV infection in healthy children or adults is nearly always asymptomatic or limited to mild non-specific illness. Periodic mucosal CMV reactivation and viral shedding is not uncommon during chronic infection, but systemic replication or viremia (detection of CMV in blood) is rare in immunologically normal individuals (4, 13, 14). By contrast, CMV viremia and end-organ disease is common in congenitally infected children and immunocompromised patients (15–18). More recent findings also suggest that CMV might have pervasive negative impact on health through indirect effects on the immune system (19–21). In particular, CMV has increasingly been recognized as a potential cause of disease in immunologically normal adults with critical illness (22–25). However, despite the fact that young children generally control CMV infection poorly compared to adults, little is known about the role of CMV in immunocompetent critically ill pediatric patients. Below, we review the evidence for CMV causing adverse clinical outcomes in immunocompetent critically ill adults, and provide a rationale for analogous studies to examine the impact of CMV on critical illness in immunocompetent children.

## SYSTEMIC CMV REACTIVATION IN IMMUNOCOMPETENT CRITICALLY ILL ADULTS

### Observational Studies Linking CMV Viremia With Adverse Adult Critical Care Outcomes

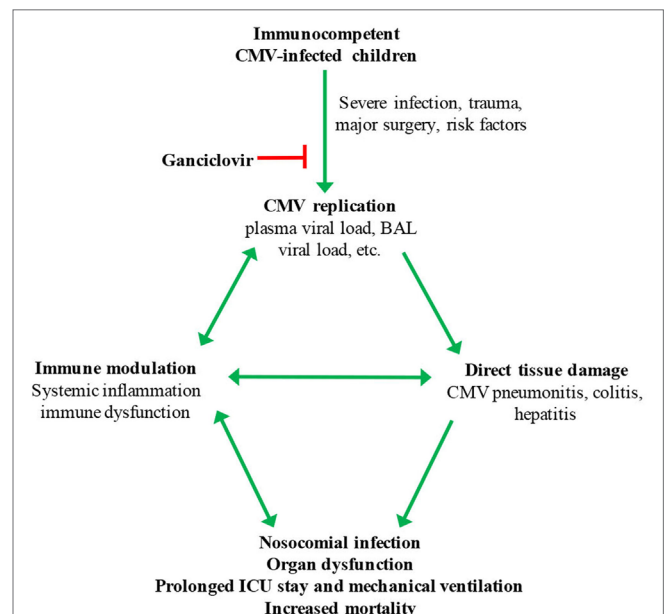
There have been more than 30 studies of immunologically normal, critically ill adult patients demonstrating an association between systemic CMV reactivation and worse outcomes in intensive care units (ICUs), as summarized in recent reviews (22–25). In these studies, CMV reactivation was defined as the detection of CMV in blood samples or, when feasible, in bronchoalveolar lavage (BAL) fluid, using CMV DNA PCR, antigen immunocytochemistry, or growth in shell vial culture. CMV viremia occurs in approximately 35% of seropositive adults following admission to the ICU. By contrast, fewer than 1% of adult blood donors with chronic CMV infection have detectable viremia (13, 14). CMV viremia and viral load are positively correlated with worse outcomes, including prolonged ICU stay, length of mechanical ventilation, secondary infections, and death. CMV viremia occurs over a wide spectrum of ICU admission diagnoses, such as infection, trauma, burns, and major surgery (26–35). In particular, patients with bacterial sepsis or pneumonia have been

reported to have a higher likelihood of CMV viremia (28, 33, 36). The risk of CMV viremia is not clearly related to disease severity at the time of admission based on prognostic and organ dysfunction scores, and the onset of CMV viremia tends to precede or accompany clinical decline (37, 38), which support the possibility that CMV causes, rather than merely being a marker of, worse ICU outcomes in adults (23–25).

### Mechanisms by Which Critical Illness May Cause CMV Viremia

Critical illness may impair immune control of CMV replication normally mediated by cytotoxic T cells and natural killer (NK) cells (39–41). Adults with sepsis show depletion of splenic T cells and reduced T cell responsiveness (42). Functional NK cell differences have also been reported between patients with septic shock or systemic inflammatory response syndrome and healthy controls (43). Furthermore, among patients with septic shock, those with CMV reactivation were found to have reduced NK cell function (44).

Exposure of latently infected cells to a pro-inflammatory environment contributes to CMV reactivation (6). Thus, inflammation, e.g., due to trauma or sepsis, may initiate CMV reactivation in critically ill patients, and CMV replication then might in turn drive more inflammation in a feed-forward manner (Figure 1). CMV replication is associated with production of pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, and TNF- $\alpha$  (45–47). In a cohort of young adults, IL-6 levels were significantly higher in the sera of CMV seropositive compared to seronegative subjects (48, 49). Interestingly, CMV-infected adults were more likely to have a pro-inflammatory profile at 3 months



**FIGURE 1** | Hypothesized model for cytomegalovirus (CMV) reactivation in critically ill children. Possible risk factors for systemic CMV replication include severity of illness, pneumonia, malnutrition, blood transfusion, corticosteroid treatment, and young age. BAL, bronchoalveolar lavage.

after discharge from ICU, even after adjusting for illness severity and underlying conditions (50).

## Mechanisms by Which CMV Replication May Contribute to Clinical Decline

Adverse ICU outcomes often result from uncontrolled inflammation and/or impaired immunity (42). CMV infection may play a significant role in both of these processes through both direct and indirect mechanisms.

Cytomegalovirus replication in tissues of immunocompromised individuals is a well-recognized cause of end-organ damage, including pneumonitis, hepatitis, and colitis (11, 16–18). Although direct cytolytic effects of viral replication in tissues are central to the pathogenesis of CMV infection in the immunocompromised host, its role in immunocompetent critically ill individuals is relatively poorly defined. Some studies have reported frequent pulmonary CMV replication based on testing of BAL fluid and lung biopsies (26, 51). Histopathologic evidence of CMV colitis was also found in immunocompetent adult patients admitted to ICU for other causes (52). In addition, CMV has been reported to cause kidney and liver damage in immunocompetent adult ICU patients (53–55). Murine studies add further support to the hypothesis that CMV replication contributes to acute lung injury in adults with sepsis or severe trauma. Sepsis in immunocompetent mice causes murine CMV reactivation in the lungs, as well as pulmonary inflammation and fibrosis that is prevented by treatment with the antiviral drug ganciclovir (56, 57).

In transplant recipients, CMV is associated with the so-called “indirect” effects on the immune system, including increased risk of bacterial and fungal infections (52, 58, 59). Some studies suggest that CMV-induced immunomodulation may increase the risk of nosocomial infections in immunocompetent ICU patients (22, 53). These findings would seem to be consistent with our emerging understanding of the profound impact CMV infection has on the immune system generally (21, 60, 61).

## Interventional Studies of CMV Infection in Immunocompetent Critically Ill Adults

Randomized clinical trials exploring the effect of CMV treatment on outcomes in adult ICU patients are ongoing, and have the ability to determine the causality of CMV in these associations (22, 62). A recent open-label randomized trial was conducted among CMV seropositive, immunocompetent mechanically ventilated patients in a single ICU in the UK. Participants were assigned to receive prophylactic low-dose valganciclovir, high-dose valacyclovir, or no treatment (63). The primary outcome was time to CMV viremia by PCR. As expected, the antiviral groups were less likely to develop viremia (8 versus 35% in controls). This study demonstrates the efficacy of prophylactic antiviral use to prevent CMV viremia in ICU patients. However, the study was not powered to measure differences in clinical outcomes. Of note, the valacyclovir arm was discontinued early due to higher mortality, though all deaths were judged to be expected and attributable to underlying disease rather than any adverse antiviral effects.

Subsequently, a phase 2, randomized controlled multicenter trial of prophylactic ganciclovir or valganciclovir versus placebo

in immunocompetent CMV seropositive adult ICU patients with respiratory failure and severe sepsis or trauma was published (64). The study failed to detect a difference in the primary outcome, blood IL-6 level, which was chosen based on the reported association of elevated IL-6 with ICU mortality and ventilator-associated lung injury (65, 66). However, in addition to reduced viremia, subjects in the antiviral treatment arm had significantly more ventilation-free days, a predetermined secondary outcome. This effect was particularly marked in the subgroup admitted for sepsis. A composite end point of mortality and increased serum IL-6 by 50% or >7 days ventilation was significantly higher in placebo group, and there was a trend toward increased mortality in the placebo group. Notably, antiviral treatment was not associated with significant side effects. This study provides the strongest evidence to date for a causal association between CMV viremia and worse outcomes in and provides preliminary support for the possibility that antiviral treatment may be beneficial for selected immunocompetent adult ICU patients (62).

## THE POTENTIAL ROLE OF CMV INFECTION IN IMMUNOCOMPETENT CRITICALLY ILL CHILDREN

### Age-Dependent Differences in CMV Pathogenesis

There are qualitative and quantitative age-dependent differences in the immune responses of young children that impair the control of many viral infections, including CMV (67–69). Children with congenital CMV infection are most often asymptomatic, but commonly present with central nervous system disease, hepatitis, hematologic abnormalities, and pneumonitis. Sensorineural hearing loss and neurodevelopmental delay develop in approximately 20% of children with congenital CMV infection (15). Postnatal CMV infection rarely causes serious illness, though extremely premature infants can develop sepsis and severe end-organ disease (70–72). Even in the absence of CMV-related disease, compared with adults primary infection, children have substantially higher levels of viral replication as well as prolonged viremia and viral shedding in saliva or urine (4, 73). Though viral replication gradually declines over time, viral shedding during chronic infection remains substantially greater in children compared to adults (4, 73). Thus, as a result of more recent infection and differences in antiviral immunity, critically ill children might be expected to have worse control of CMV replication than adults.

### CMV Infection in Critically Ill Children

There are very few data available about the frequency and effects of active CMV infection in critically ill, immunocompetent children. We performed a pilot study of CMV infection in children admitted to the ICU of BC Children's Hospital in Vancouver, Canada (unpublished data). Among the 27 children enrolled, the median age was 4 years (range 4 months–17 years). Only one child was CMV seropositive, and none were found to have viremia. This is consistent with the relatively low CMV seroprevalence among children in most high-income countries (74–77). By contrast, a study of children between 3 weeks and 2 years old hospitalized

in Zambia found that 34% of HIV-uninfected children had CMV viremia (78). Of note, the prevalence of malnutrition was 36%, and being underweight was significantly associated with CMV viremia. In a retrospective study of Ugandan children 6 months–13 years old treated as outpatients for uncomplicated malaria, 11% had CMV viremia (79). Thus, even in the setting of moderate illness, systemic CMV replication is common in African children. In a prospective study that included 53 HIV-uninfected South African children  $\leq 2$  years old admitted to ICU with severe pneumonia, 12 (23%) were defined as having CMV pneumonitis based on DNA detection in BAL fluid and other clinical characteristics (80). Many of these children were treated with ganciclovir, but the published data are insufficient to determine whether disseminated CMV or antiviral treatment in HIV-uninfected children were associated with clinical outcomes (80).

## DETERMINING THE IMPACT OF CMV INFECTION ON PEDIATRIC ICU OUTCOMES

### General Considerations

Well-designed cohort studies are needed to understand the role of CMV in immunocompetent critically ill children, to estimate the potential benefits, and to inform the design of appropriate pediatric treatment trials. Given the differences between children and adults in the natural history and outcomes of CMV infection, extrapolation from adult studies is inappropriate. As an example, in the adult studies conducted to date, the clinical impact of CMV has been ascribed to reactivation and dissemination of chronic infection (23–25). However, CMV viremia in pediatric ICU patients might often represent systemic viral replication related to recent infection rather than reactivation. To distinguish between reactivation of chronic infection and exacerbation of recent infection would be challenging, but might provide insights into age-dependent differences should they exist. Thus, in pediatrics studies, it would be more appropriate to explicitly evaluate the role of disseminated CMV replication as opposed to reactivation of chronic infection.

## Measuring CMV Replication in Pediatric ICU Patients

Quantitative CMV DNA PCR assays can reliably detect  $\leq 50$  international units/mL and have largely replaced older methods of detection (81, 82). Because high level CMV replication in saliva and urine is so prevalent in young children (73, 83), these measures are unlikely to be clinically meaningful for critically ill children except for confirming infection in infants with maternal antibody and concern for false-positive serology. As in adult studies, CMV replication in blood is likely to be the best measure of uncontrolled systemic viral infection in critically ill children. Although CMV in BAL fluid may simply represent shedding, high viral loads are predictive of CMV pneumonitis in transplant recipients and, perhaps, in critically ill children (80, 84, 85). Thus, pediatric ICU studies should incorporate CMV testing of BAL fluid, should it be collected for clinical purposes. In addition, detection of CMV in tissue biopsies (e.g., liver, colon), particularly by histopathology indicates invasive disease, and these specimens should be tested if available (Table 1).

The risk of CMV disease is correlated to the level of viremia in many clinical scenarios. For example, in HIV-infected individuals and transplant recipients, CMV viral load is proportionally associated with progression of disease (86, 87). However, the threshold of CMV replication that is clinically relevant or that might warrant intervention depends on the patient population. For example, antiviral treatment of newborns with symptomatic congenital CMV infection is indicated, regardless of viral load, to reduce the risk of hearing loss and neurocognitive delay (8, 88–90). Selected transplant patients are monitored using CMV blood PCR in order to trigger preemptive antiviral treatment before the onset of disease, but the viral load threshold used varies based on immunologic status and other clinical criteria (87, 91, 92). The antiviral studies performed so far in adults have randomized all CMV seropositive ICU patients with the intention of preventing, rather than treating, viremia (63, 64). The optimal approach to treating CMV infection in pediatric ICU patients would depend on the associations and dose–response that are found, but might conceivably utilize risk-stratification based on age, underlying illness, viral load, or other factors.

**TABLE 1** | Suggested metrics for studies of cytomegalovirus (CMV) viremia in immunocompetent pediatric intensive care unit (ICU) patients.

CMV manifestations	Potential effects	CMV measures	Clinical outcome measures
Systemic inflammatory response syndrome	Multiorgan dysfunction	IgG, IgM, and urine PCR to diagnose infection	Mortality at 7, 14, and 28 days Ventilator-free days at 28 days
Pneumonitis	Prolonged ventilation	Plasma/serum viral load	Length of ICU/hospital stay
Hepatitis	Transaminitis, hyperbilirubinemia, impairment of synthetic liver function	If collected for clinical care: – BAL viral load – Histopathology (biopsies of lung, colon, liver, bone marrow)	Health-related quality of life at 28 days Organ dysfunction scores (PLEOD, SOFA, NPMOD, etc.)
Colitis	Enteric dysfunction, growth failure, nutritional deficiencies		Weight to height Z score Post-discharge mortality or readmission at 6 months
Myelosuppression, neutropenia, thrombocytopenia, anemia	Nosocomial infection Blood product transfusions		Inflammatory markers in blood, BAL, and stool Blood transfusions Nosocomial infections Antibiotic use

BAL, bronchoalveolar lavage; PLEOD, Pediatric Logistic Organ Dysfunction score; SOFA, Sequential Organ Failure Assessment score; NPMOD, New/Progressive Multiorgan Dysfunction.



## Pediatric Populations of Greatest Interest

Studying the impact of CMV infection on critically ill immunocompetent children is anticipated to be both easier and more clinically relevant in low- and middle-income countries (LMIC), where CMV infection is holoendemic and mortality and morbidity rates from sepsis are often dismal. In LMIC, nearly all children acquire CMV infection within the first few years of life (74). By contrast, the national US survey found that while CMV prevalence increases linearly with age, it reaches only ~50% by 30 years of age (75, 76).

In addition to the relatively low rates of CMV infection in North American and European children, the excellent outcomes of pediatric ICU patients there hinder the ability to detect a clinically important impact of CMV infection on critically ill children (93–96). Furthermore, strategies to reduce mortality in critically ill children in LMIC are urgently needed. For example, in the Kenyatta National Hospital pediatric ICU in Nairobi, Kenya, overall mortality is 42% (unpublished data). Similarly, pediatric ICU mortality rates of 25–50% have been reported in other LMICs in Africa and Asia (97–100). Other outcomes of interest such as length of stay and need for invasive ventilation are also frequently higher in LMICs (99, 100). In Siriraj Hospital, one of the largest hospital in Thailand, median length of ICU stay and rate of mechanical ventilation are 4–5 days and 64%, respectively (Dr. K. Lapphra, personal communication), which are more than double those in the BC Children's Hospital ICU. Moreover, infections and sepsis account for most of pediatric ICU admission diagnoses in LMIC, which might again predispose to disseminated CMV infection and viremia (97, 98).

## Outcome Measure Considerations

Importantly, appropriate studies in children require the incorporation of pediatric-specific illness severity scores and outcome measures (Table 1). Mortality and morbidity in pediatric patients are predicted by progressive or new organ dysfunction, using validated scores (101–103). Evaluation of mechanical ventilation outcomes should include invasive as well as non-invasive modalities, which are now commonly used in children (94). A longer follow-up duration that used in adults studies should also be considered, given the high rate of readmission and post-discharge mortality in children of African and Asian countries (104–106). Higher rates of CMV viremia as well as worse post-discharge outcomes have been observed in underweight children (78, 106). Therefore, including nutritional assessments in pediatric studies is also essential.

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## CONCLUSION

Strong evidence supports the association between CMV viremia and adverse outcomes in adult ICU patients (23–25), and early-phase interventional trial results suggest that antivirals in this population might be beneficial (62–64). Unfortunately, there are no studies yet in children that have adequately addressed this question. Not only is there an ethical obligation to include children in research according to the principle of justice (107–109), but we hypothesize that active systemic CMV infection might have an even greater negative impact on ICU outcomes in children than adults. Therefore, we propose that prospective observational studies should be conducted to characterize the association between CMV viremia and clinical outcomes in critically ill children, using metrics appropriate for pediatric populations. Furthermore, we suggest that such studies would best be performed in LMICs settings. Importantly, if CMV treatment were found to be beneficial for immunocompetent critically ill children, resource limitations would not preclude its implementation (110). If successful, studies in LMICs could result in reverse innovation to help targeting specific subpopulations of patients in high-income settings that might also benefit from CMV treatment. Studies in both adults and children should attempt to identify the mechanistic basis for the relationship between CMV and critical illness, and develop novel therapies to improve outcomes of critically ill patients.

## ETHICS STATEMENT

The pilot study Reactivation of Cytomegalovirus in Pediatrics (ReCIPE) for the prevalence of CMV viremia among pediatric critical care patients in BC Children's Hospital was approved by BCCHR Ethics Board.

## AUTHOR CONTRIBUTIONS

RA: literature review and writing; SG: reviewing, editing, writing, and knowledge check; JS: reviewing statistics and literature, editing, and writing; SM: checking literature and ICU data.

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# A Review of the Integrated Model of Care: An Opportunity to Respond to Extensive Palliative Care Needs in Pediatric Intensive Care Units in Under-Resourced Settings

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It is estimated that 6.3 million children who die annually need pediatric palliative care (PPC) and that only about 10% of them receive the attention they need because about 98% of them live in under-resourced settings where PPC is not accessible. The consultative model and the integrated model of care (IMOC) are the most common strategies used to make PPC available to critically ill children. In the consultative model, the pediatric intensive care unit (PICU) team, the patient, or their family must request a palliative care (PC) consultation with the external PC team for a PICU patient to be evaluated for special care needs. While the consultation model has historically been more popular, issues related to specialist availability, referral timing, staff's personal biases, misconceptions about PC, and other factors may impede excellent candidates from receiving the attention they need in a timely manner. Contrastingly, in the IMOC, family-centered care, PC tasks, and/or PC are a standard part of the treatment automatically available to all patients. In the IMOC, the PICU team is trained to complete critical and PC tasks as a part of normal daily operations. This review investigates the claim that the IMOC is the best model to meet extensive PPC needs in PICUs, especially in low-resource settings; based on an extensive review of the literature, we have identified five reasons why this model may be superior. The IMOC appears to: (1) improve the delivery of PPC and pediatric critical care, (2) allow clinicians to better respond to the care needs of patients and the epidemiological realities of their settings in ways that are consistent with evidence-based recommendations, (3) facilitate the universal delivery of care to all patients with special care needs, (4) maximize available resources, and (5) build local capacity; each of these areas should be further researched to develop a model of care that enables clinicians to provide pediatric patients with the highest attainable standard of health care. The IMOC lays out a pathway to provide the world's sickest, most vulnerable children with access to PPC, a human right to which they are entitled by international legal conventions.

**Keywords:** pediatric palliative care, integrated model of care, pediatric critical care, pediatric intensive care, Pediatric Palliative Screening Scale, low-resource settings, consultative model

**Abbreviations:** ICU, intensive care unit; PICU, pediatric intensive care unit; PC, palliative care; PPC, pediatric palliative care; IMOC, integrated model of care; DNR, do not resuscitate; WHO, World Health Organization; LMICs, low-middle income countries; HDLV, Hospital de los Valles; PCCEM, Pediatric Critical Care and Emergency Medicine; PaPaS, Pediatric Palliative Screening Scale.

## PALLIATIVE CARE (PC) IN THE INTENSIVE CARE UNIT (ICU)

The silo thinking that underpins much of western medicine cannot universally facilitate the enforcement of the human right to the highest possible standard of health care and, in many cases, may be antagonistic to the pursuit of that goal; ICUs in under-resourced settings characterized by great health-care-related inequalities, poor infrastructure, and limited personnel are one such context in which silo thinking cannot structure care to appropriately meet the multifaceted needs of patients (1). The tendency to isolate medical specialties under this framework has led to a division between intensive and PC—two branches of medicine that are essential to the treatment of critically ill patients in ICUs. This common practice has contributed to the perception that adding PC tasks to intensivists' daily responsibilities will burden them, unnecessarily absorb valuable time and resources, and take away from their "real care goals." On the contrary, a breadth of evidence shows that adopting a holistic care strategy can conserve valuable resources in the ICU (2–4) and improve patients', their families', and caretakers' well-being (5).

Silo thinking is the foundation of the most popular strategy used to make PC available in the ICU: the consultative model (5). In purely consultative models, the hospital uses its resources to hire additional specialists and perhaps even create a stand-alone PC department. This external team is brought into the ICU to care for patients who are identified as having PC needs. The patient, their family, or their health-care providers must first identify the need for PC and then request a consultation with the external PC team for such attention to be provided.

According to the consultative model, ICU staff are positioned as gatekeepers to PC access; if they lack training, have negative attitudes or false beliefs about PC, do not understand its applications and potential benefits, or cannot recognize the "triggers" that signal a patient's PC needs, external PC resources may not be used when indicated and, consequently, PC may not be normalized in a given ICU (6, 7). Lynn explains, "The course of care is much more strongly associated with the service supply and habit patterns of the local care system than with the particular preferences or prognoses of the individual patient" (8). If consultative models do not involve the intentional training of ICU staff in holistic care, the personnel's attitudes, knowledge, and practices may impede the treatment of patients' PC needs (6, 7).

Contrastingly, in the integrated model of care (IMOC), family-centered care, PC tasks, and/or PC are a standard part of the treatment automatically available to all patients. In the IMOC, the ICU team is trained in holistic critical care and PC tasks are embedded in the unit's protocols. As a part of normal daily operations, team members simultaneously initiate PC and critical care, screen for PC needs regularly, and design plans to meet those needs as they arise. Although the consultative model is overall more common (5), the IMOC appears to offer distinct benefits to patients with pediatric palliative care (PPC) needs and, in pediatric ICUs, "is rapidly becoming the standard for high quality care of critically ill children" (4). While both models can make PC available in ICUs and pediatric intensive care units (PICUs), the IMOC may be more

beneficial to patients/their families and may be better suited to under-resourced settings where hiring outside specialists may be impossible.

To date, there is little research that directly compares the effectiveness of the IMOC and the consultative model. However, one compelling 2011 study comparing models of PC in the United States found family members' opinions of their loved ones' last month of life correlated with the model according to which they were treated. The family of patients who had received integrated PC services were the most likely to report that the deceased had an "excellent" quality of life during their last month, followed by those who had received consultative PC services, and then by those who had only received usual care (no PC) (9). The group that received integrated PC services also appeared to receive more holistic attention; they were more likely to have accessed chaplain services and prepared do not resuscitate orders before death; their families also received more bereavement contact following their passing (9). This study presents direct evidence that the IMOC may be superior to the consultative model across various dimensions of care (9), even in industrialized countries where more PC specialists, superior infrastructure, greater education, and more medical resources are available (10).

This review investigates the claim that the IMOC is the best model to meet extensive PPC needs in PICUs, especially in low-resource settings; based on an extensive review of the literature, we have identified five reasons why this model may be superior. The IMOC appears to: (1) improve the delivery of PPC and critical care, (2) allow clinicians to better respond to the care needs of patients and the epidemiological realities of their settings in ways that are consistent with evidence-based recommendations, (3) facilitate the universal delivery of care to all patients with special care needs, (4) maximize available resources, and (5) build local capacity in a way that responds to the current shortage of PC specialty education; each of these areas requires further investigation to improve PPC delivery.

This review integrates evidence from countries around the world, but especially focuses on under-resourced settings like Ecuador, the authors' country of residence. The need for improved PPC and pediatric critical care (PCC) delivery is particularly urgent in contexts like ours because the high burden of PPC needs overwhelms our underdeveloped health-care infrastructure. Unfortunately, as this review will highlight, the majority of PC-related studies have been completed in industrialized countries and, as such, do not always accurately reflect the realities of PC and health-care professionals in our context. The skewed perspective of the academic discipline of PC was evidenced by a 2016 review of the last 20 years of publications in the field of PC, which revealed that over 90% of all documents published on the topic originated in industrialized nations classified as Group 4 countries by the World Palliative Care Alliance, meaning that they have already achieved integration of hospice-PC into their health-care systems (10, 11). When industrialized countries' practices, beliefs, and customs are assumed to be the neutral standard for medical care and subsequently applied to different cultural contexts, health professionals may disregard the unique assets, traditions, and needs of under-resourced communities in which they work. Such dynamics have the potential to further

oppress already disadvantaged groups, waste resources, and create additional barriers between PC and the patients who need it. For this reason, we integrate as much pertinent data from our context as possible, but significantly supplement it with findings from industrialized nations.

## RESISTANCE TO PC IN THE ICU

The direct integration of PC into the PICU/ICU through the IMOC is commonly met with resistance because of prevalent myths, discipline-based bias, and a lack of knowledge of evidence-based recommendations (12, 13). Although the specific barriers to implementing PC in the ICU vary from culture to culture and unit to unit, some of the particularly problematic misconceptions that keep this specialty out of the ICU are the ideas that PC is (1) ineffective and unimportant for most ICU patients, (2) synonymous with hospice and hopelessness on the part of the family, patients, and/or clinician, (3) equivalent to the “soft skills” that health-care professionals already innately have, and (4) wasteful in that it absorbs valuable time and resources from intensivists. Although prevalent, none of these ideas are consistent with decades of research about PC. **Table 1** provides a summary of key articles highlighting the importance of the PC in the ICU.

Contrary to the first myth, evidence shows that PC has major implications for the well-being of patients, their families, and practitioners (4, 5, 9, 18–25). PC is an interdisciplinary field that seeks to prevent and relieve the multifaceted suffering that critically ill patients and their families experience as a result of acute, chronic, life-limiting, and life-threatening conditions. PC addresses physical, psychosocial, ethical, spiritual, cultural, familial, and communication-related distress, as well as death and bereavement issues (21, 26–28). The timely initiation of PC is associated with (1) improved symptom management (18–20), (2) positive outcomes in patients (4, 18, 20), (3) improved quality of life for patients, families, and caregivers (18, 20), (4) better communication between professionals, patients, and their families (1, 4, 29, 30), and (5) longer life survival times among patients (4, 29).

Furthermore, PC belongs in the PICU/ICU because virtually all critically ill patients exhibit some level of PC need throughout their hospitalization (4, 5, 14, 31); to meet patients’ extensive PPC needs, PICUs may benefit from making PPC universally accessible through an IMOC. PC is indicated in a wide range of patients, not only those confronting the terminal stages of illness (4). Because PC is inaccurately equated with hospice, it is commonly and erroneously thought to signal imminent death and therefore may provoke anxiety among patients, families, and practitioners. Combined with the lack of knowledge about PC recommendations, this reputation foddors the incorrect idea that PC—care supposedly directed only at the dying—is not applicable to most patients in the ICU. However, the World Health Organization (WHO) (22), United Nations (32), and together for Short Lives’ PC charity (28) recommend that PPC should be extended to children with life-limiting conditions and not solely to those who are terminally ill. Cook and Rocker explain, “The coexistence of palliative care and critical care may seem paradoxical in the

**TABLE 1** | Summary of key articles.

Reference	Summary
Nelson et al. (14)	Rapid response teams (RRTs) or emergency medical teams are common in intensive care unit (ICU) settings and seek to prevent morbidity and mortality among already hospitalized patients who may be deteriorating. While there are conflicting data about the effectiveness of RRTs in accomplishing these goals, RRTs are well positioned to meet the palliative care (PC) needs of patients in the ICU. RRTs can, and in many cases, already perform a range of PC tasks related to communication, emotional/psychological support, symptom control, and pain management. RRTs should also be given the tools necessary to facilitate family conferences in emergencies, provide family-centered care, support distressed caregivers, foster shared decision-making, and help colleagues to administer measures of self-care. Considering their already extensive skillsets and proximity to patients, their families, and professional caretakers, RRTs should be trained to provide PC to patients admitted to ICUs and emergency departments
Boss et al. (4)	This article reviews the benefits that patients, their families, and pediatric intensive care unit (PICU) staff experience “when PC is intentionally incorporated into the PICU.” (4) PC is indicated in a large share of children admitted to PICUs; as epidemiological shifts occur across the world, an increasingly large number of children become eligible for PC to address the needs that arise from their complex, chronic diseases. PC is interdisciplinary and addresses a range of needs of patients, families, and their professional caregivers, including pain management, symptom control, family and patient-centered communication and decision-making, psychological care, and other types of support key to the well-being of patients, their families, and PICU personnel. This review also highlights some of the gaps in care in PICUs, including accurate pain assessment, poor communication between families and PICU staff, inadequate psychosocial treatment, high levels of unaddressed psychological morbidity among family members, and other issues; intentionally integrating PC into PICUs is an excellent opportunity to meet such needs
O’Brien et al. (15)	This article examines the potential impact and methodology for a future intervention in 26 PICUs from Canada, Australia, and New Zealand to change the role of parents in neonatal care. Based on data from previous similar interventions, O’Brien et al. hypothesized that integrating parents into the NICU team as providers of all, but the most advanced medical interventions would result in faster weight gain, greater rates of breastfeeding, and improved clinical outcomes for infants as well as reduced levels of stress and anxiety for parents. The FiCare intervention program requires primary care givers to undergo extensive training to learn how to properly care for their neonates, commit to 6 h daily to caring for their babies, record their interactions with their babies in a special journal, and interact with “veteran parents,” who give personal support to parents whose babies are in the NICU. Previous data evidence the great positive potential for this intervention

(Continued)

**TABLE 1 |** Continued

Reference	Summary
Curtis (16)	ICU personnel should be trained to provide PC in their units because it plays an important role in the care of critically ill patients, not merely those at risk for dying. PC is important because it allows us to better facilitate intentional discussions about treatment plans, other types of communication, patient-focused/family-centered decision-making, symptom management, multidisciplinary collaborations in patient treatment, end-of-life decisions, logistical planning, and other aspects of care. Implementing PC in the ICU could help to address diverse unmet symptoms or patients and their families, improper communication techniques employed by ICU personnel, conflicts/lack of communication within the ICU, and many other difficulties. To improve PC in ICUs, Curtis suggests educating ICU personnel in PC and how to overcome PC implementation barriers, establishing institutional policies to promote PC, and providing ICU staff with feedback from families of their patients. PC should be implemented in the ICU to improve the experiences and well-being of patients, their families, and the ICU staff itself
Aslakson et al. (17)	PC is used to address the complex care needs of critically ill individuals, regardless of their prognoses or diagnoses; as such, this type of care should be initiated for various critically ill individuals upon ICU admission to better address psychosocial, spiritual, and physical symptom management; coordinate, plan and communicate about multidisciplinary treatment that reflects the patient's and their family's preferences; provide family-centered care and extensive care planning; and facilitate the family caregivers' and ICU personnel's own self-care. Aslakson et al. identified clinician's subpar communication skills, unrealistic expectations related to patients and treatment, clinicians' time constraints, decision-making difficulties, and other areas as opportunities for care improvement within the ICU which PC could address. The authors suggest that further research needs to be completed to determine the best methods for providing patients and their families with PC in situations of critical illness both inside and outside of the ICU

technological ICU. However, contemporary critical care should be as concerned with palliation as with the prevention, diagnosis, monitoring, and treatment of life-threatening conditions" (33). PC not only improves the quality of patients' deaths but also of their lives.

Palliative care can be beneficial to a wide range of patients regardless their prognoses and diagnoses (16, 17, 22, 28). Boss et al. explain that PC should begin at the time of diagnosis of a potentially life-limiting condition and continue throughout the disease trajectory, regardless of the expected outcome (4). Although this type of care is particularly important to the terminally ill, it also plays a complementary role in the care of critically ill patients who may be able to make a complete recovery (22, 32). Together for Short Lives, a leading charity in the United Kingdom for children with life-limiting and life-threatening conditions, developed a categorization of pediatric conditions for

which PC is indicated; these include potentially curable diseases (in which life is at risk and treatment may or may not succeed), progressive conditions, irreversible conditions causing severe disability, and morbidities that inevitably cause premature death (28). PC is applicable in all stages of such diseases and conditions (10, 34–39) and represents the evolution of hope, rather than the extinguishment of it—in some illness. Through impeccable assessment, treatment, and communication carried out by multidisciplinary teams, PC enhances the quality of life for a diverse range of patients and their loved ones, independent of what the future may hold for them (4, 5, 21, 22). Through PC, we can focus our hope on a better quality of life, death, and other realistic goals rather than wish for impossible outcomes.

In addition, considering that PC involves a range of multidisciplinary tasks to address various needs common among most PICU patients (4, 5, 31), health-care professionals should not be expected to be innately prepared to address all PC needs. Special training is required to address any one of the many areas that PC seeks to address in a way that is consistent with evidence-based recommendations. Unsurprisingly, several studies have shown that ICU staff's beliefs about PC, knowledge of the field, and their actual practices in the ICU are deeply interconnected. One study of ICU nurses' attitudes about PC found that participants had "moderately negative to neutral attitudes toward PC," especially with regards to patient preferences and withholding/withdrawing treatment (7). Unsurprisingly, Razban et al. found that nurses' beliefs were significantly correlated with their own "...personal study about palliative care, level of education, and experience of caring for a dying family member" (7). These findings suggest that education is key to creating an environment receptive to PC. Another study of nurses, intensivists, and advanced practice providers at three large academic hospitals found the "triggers" for initiating PC consultation to be an important barrier: the staff most frequently relied on triggers that resulted in late-stage PC application (6), which is inconsistent with best-practice recommendations that PC should be applied early and concurrently with disease-directed treatment (2, 22, 28). Again, education is key to implementing evidence-based practices; if ICU staff are expected to bridge the gaps in PC in their units, they must be properly trained to do so.

Finally, contrary to the popular myth that it is wasteful and unnecessarily burdensome for intensivists, PC is actually a resource-saving strategy in the ICU (2, 3). In under-resourced contexts like ours, distributive justice in medical care is perhaps the most prominent ethical principle that we encounter on a day-to-day basis. PC saves valuable resources because it prevents morbidities like depression and anxiety (3) and prevents futile treatments (2), thereby conserving resources to treat other patients. Well-managed PC patients are able to enjoy an improved quality of life, may have better outcomes, and are empowered to make long-term care plans if necessary; this, in turn, helps PC to maximize local resources on the population level because it prevents unnecessary emergency room visits and keeps precious ICU beds open (3). In countries with limited medication access, health-care personnel, and ICU capacity, PC stands to have a dramatic impact on the well-being of individuals and communities alike.



## PPC ACROSS THE GLOBAL SOUTH

In light of their effectiveness, the international community has declared PC and PPC basic human rights, maintaining that they are fundamental to the appropriate treatment of adults and children with special care needs in any stage of disease (20, 21, 23, 32, 35, 36, 39–42). Furthermore, “Palliative care is a recognized component of the right to the highest attainable standard of health, which is protected in article 12 of the International Covenant on Economic, Social and Cultural Rights, and in article 24 of the Convention on the Rights of the Child” (32). The WHO’s inclusive definition of PPC echoes this sentiment (22):

- PC for children is the active total care of the child’s body, mind, and spirit, and also involves giving support to the family.
- It begins when illness is diagnosed and continues regardless of whether or not a child receives treatment directed at the disease.
- Health providers must evaluate and alleviate a child’s physical, psychological, and social distress.
- Effective PC requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited.
- It can be provided in tertiary care facilities, in community health centers and even in children’s homes.

As described by the United Nations (43) and the WHO (22), the holistic focus of PPC makes it indispensable to achieving the highest attainable standard of care in many critical pediatric cases.

Despite the overwhelming evidence of its effectiveness, the vast majority of children who require PPC never receive it (10, 44); in part, this is because nearly 98% of pediatric patients who have PC needs come from low-middle income countries (LMICs) where it is simply not available (10). While many of these patients receive treatment directed at the disease, few receive concomitant PC (24, 25). Overall, around 6.3 million children requiring PPC die annually, but only about 10% of them receive the attention they need (10). The lack of PPC availability across the world results in the unnecessary suffering of the world’s most vulnerable children.

## PPC NEED IN ECUADOR

To better elucidate the urgent need for improved, more accessible PPC in contexts like Ecuador, it is vital to identify aspects of our context which may result in more extensive PC needs (10) and which may be unexpected for readers from industrialized contexts. The combination of issues unique to LMICs may contribute to an overall higher need for PPC which might not be seen in industrialized countries, where PICUs may commonly receive many children who need an intermediate level of care or postoperative stabilization (4). The level of development and fragmentation of the Ecuadorian health-care system leads to the deterioration of patients before they arrive to the hospital and therefore contribute to a greater need for PC. These challenges can be grouped into three categories, including: (1) insufficient Infrastructure, (2) lack of trained specialists, and (3) socioeconomic factors (20, 44).

With respect to infrastructure issues, the number of PICU beds and emergency transport vehicles are major hurdles for providing appropriate, timely care. Ecuador only has 36 PICU beds available throughout the entire country (45); therefore, the patients who take priority for these few precious spots are often in extremely critical states. Because of the severity of these cases, the average national PICU mortality rate in 2012 was around 15% (as compared with a 5% mortality rate in European PICUs) (45). Similarly, Ecuador has a fragmented emergency transport system which contributes to the severity of cases that arrive to the PICU. Aside from a menagerie of ambulances of varying quality from the private sector, Ecuador only has 714 medical emergency transport vehicles from the public sector, which are insufficient to meet the population’s needs (46).

Similarly, a lack of trained pediatric intensivists and PC specialists in Ecuador makes it more difficult for children to receive the care they need. In Ecuador, there are approximately 33 pediatric intensivists (45) who are responsible for a pediatric population of nearly 5,000,000 (47). Unsurprisingly, the majority of these specialists are located in cities, further exacerbating regional inequalities in care.

Finally, socioeconomic factors reduce the quality of care available to pediatric patients. The lack of development of quality health care in rural areas, historical discrimination, poverty, and a lack of general health education especially among vulnerable groups are barriers (44). In addition, Ecuadorian children are also at great risk for comorbidities that can aggravate their conditions including parasitic infestations (48), malnutrition (49), and anemia (49). Similarly, the main causes of death common among Ecuadorian children include acute respiratory infections, traffic accidents, congenital malformations, leukemia, and other external causes, each of which can entail PPC needs before death (50, 51).

## THE IMOC: A PATHWAY TO MEET INTERNATIONAL PPC NEEDS

Considering the extensive PPC needs of PICU patients (especially in LMIC countries like Ecuador), the IMOC may be the best strategy to make PC available to all of those patients who may require it because the IMOC appears to (1) improve the delivery of PPC and PCC, (2) allow clinicians to better respond to the care needs of patients and the epidemiological realities of their settings in ways that are consistent with evidence-based recommendations, (3) facilitate the universal delivery of care to all patients with special care needs, (4) maximize available resources, and (5) build local capacity. The IMOC lays out a pathway to provide the world’s sickest, most vulnerable children with access to PPC, a human right to which they are entitled by international legal conventions (20, 22, 32, 34–39, 41).

The IMOC may improve the delivery of PPC in under-resourced environments because it bypasses those barriers which often impede the timely application of PPC. The advantage of the IMOC as compared with other models is that it already has PC embedded in its protocols. While the consultation model can make PPC available to patients, issues such as the timing of referral, physicians’ personal perspectives, ethical dilemmas,

decision-making difficulties, lack of screening tools and trained personnel, communication issues, and misconceptions about PC can impede excellent candidates from receiving the attention they need in a timely manner (4, 52).

The IMOC also improves the delivery of PPC in settings like ours because it does not assume that patients, families, or even health-care workers innately know what PPC is and when to request a consultation for such care. In many countries, most families do not know of the existence of PPC or understand what it involves; thus, they may never ask for the care or even accept it when it is offered (53). Worse yet, some families and many medical professionals may believe damaging myths about PC, such as the erroneous idea that PC hastens death (12); a plethora of evidence, including the low mortality rate in our own center which uses the IMOC (4.8%) (54), discredits this notion. In an IMOC, the aforementioned obstacles are non-existent because all patients, regardless of their disease state, prognosis, and diagnosis, are regularly screened for PPC needs.

Moreover, we speculate that the IMOC is the best model to meet patients' needs in the PICU because it better responds to epidemiological trends around the world and to patients' needs in ways that are consistent with evidence-based recommendations. As epidemiological transitions occur across the world, an increasingly large share of patients with complex, chronic diseases are being seen more frequently and repeatedly in ICUs/PICUs; Lynn argues that current health systems that bifurcate curative treatment and PC do not adequately respond to patients', families, and communities' care needs in an appropriate or sustainable way (8). Rather, models of care ought to focus on early intervention, continuity, family-centeredness, and patients' psychosocial suffering to create care pathways that help patients to avoid unnecessary suffering and that allow communities to conserve their precious medical resources (8, 15).

In addition, embedding PPC directly into PICU care models sidesteps the resistance against PC initiatives common in low-resource settings and maximizes local resources. Because the IMOC necessitates that PICU teams themselves are trained to carry out PC tasks, this model does not require additional staff or a new department as the consultation model does. PC consultation models are commonly met with resistance because cost-related hurdles can impede the establishment of new departments, pain and suffering are often normalized in low-resource settings (20), and PC may be viewed as a "luxury" for industrialized countries (20). By hybridizing PCC and PPC, it is possible to avoid such hurdles that can prevent the establishment of important PC programs.

Furthermore, the consultative PC model is ineffective in many settings because it relies on communities' current capacity; the IMOC is more effective in meeting PC needs because it involves and trains all ICU personnel and therefore necessitates capacity-building in every unit in which it is implemented. Evidence indicates that the consultative model is limited in its capacity to meet communities' PC needs even in resource-rich industrialized countries. For example, in a 2017 study, Wysham et al. reported that up to 35% of ICU patients in the United States needed PC; however, even in such a resource-rich setting, this level of need still overwhelmed the available 5,500 PC specialists' capacity (6).

In other words, even in the United States, there are not enough PC specialists to make the consultative model effective in addressing national PC need. Wysham et al. explain, "In this context, it is estimated that <5% of ICU patients receive specialist palliative care" (6).

The apparent dominance of the consultative PC model in ICUs seems even less appropriate when examined through the lens of pediatric intensive care in under-resourced settings like ours. Ecuador is categorized as a 3A country in the provision of PC (meaning that it has isolated provision in level of PC development) (10) and a high burden of conditions, diseases, and accidents that require PC (47, 49, 50). The burden of PC need combined with a lack of specialists renders the consultative model ineffective in addressing national and international PC needs.

While it is easy to point to a need for more training programs as a solution to the gross mismatch between PPC needs and specialist availability across the world, this idealistic thought process follows the paradigm that heralds the consultative model as king. It is true that there is great global need for more PPC training programs; however, international conventions entitle the world's sickest children to pathways of care that provide more immediate access to the highest available standard of health care (which must include access to PC services) (22, 43). The IMOC proposes a paradigm shift that would make it possible to begin meeting children's PC needs more rapidly and effectively than the consultative model.

Although trained PPC specialists may have greater expertise than health-care professionals who do not have the same level of formal training, many PICU personnel already unknowingly engage in some dimensions PC and can learn tasks to improve the level of care that they already provide (14). Shifting from the consultative model to the IMOC requires us to honestly appraise and develop the PC skills of all PICU/ICU staff, not only those of highly trained specialists. While a breadth of evidence demonstrates that beliefs and practices incongruent with the goals of PC abound in ICUs (6, 7, 34, 53), this does not indicate that intensive care staff lack the valuable foundations necessary to learn how better perform PC tasks. In Ecuador (45), the United States (6), and probably in most other settings, pediatric intensivists, nurses, and other support personnel present in PICUs greatly outnumber the trained PPC specialists. Whereas the consultative model frames this reality as damning, the IMOC frames it as a latent possibility for PC expansion. Ecuador has 33 pediatric intensivists (45) and countless other health-care professionals that work in PICUs—according to the IMOC, these health-care professionals ought to be considered potential PPC providers.

## THE IMOC IN ECUADOR

While it may seem foolishly idealistic to paint non-specialist PICU/ICU personnel as potential PPC providers, in recent years our team has pioneered a number of training programs that hybridize PCC and PPC. In 4 years, these programs have disseminated the IMOC and increased the national Pediatric Critical Care and Emergency Medicine (PCCEM) and PPC capacity by 560% (54). Without making formal policy changes, gaining new specialists, or adding new subspecialist training in our country, we were able

to exact systematic change by training non-specialist personnel to work together to identify and complete PC tasks in the PICU. Our programs have been massively successful in improving the quality and accessibility of PCC and PPC care to pediatric patients throughout Ecuador and further support the hypothesis IMOC is the best model to meet extensive PPC needs.

The extensive PC need in our context (20, 46, 49, 51, 55) and new data supporting the effectiveness of the IMOC (9) lead the principal investigator (Michelle Grunauer) to implement the IMOC in the PICU of the Hospital de los Valles (HDLV) when it was established in Quito, Ecuador in 2013. HDLV's PICU was the first PICU in Ecuador to use a family-centered IMOC. She integrated the IMOC into the PICU because there is no known evidence that the external consultation strategy provides better patient care and because the IMOC is particularly well suited to under-resourced settings like ours, where there are no resources available to create an external PC service.

Michelle Grunauer incorporated the IMOC into this unit primarily through a certificate training program she launched in conjunction with physicians from the United States trained in PCCEM to elevate local medical professionals' expertise in critical care and PC (54). "The Laude in PCCEM employs a family-centered approach by integrating pediatric critical care (PCC), mental health, and palliative medicine. It is innovative in that any critically ill (not merely dying) child benefits from family involvement [in an IMOC] so that family might understand the disease process and take part in treatment decisions" (54). In essence, participants learned how to provide care to critically ill patients according to the framework of the IMOC.

Various methods are effective in integrating health-care professionals into the IMOC. In the first program launched in HDLV, instructors used a combination of pre-readings, classroom instruction, bedside didactics, and simulation drills to teach professionals about the IMOC (54). These activities integrated PC and family-centered care techniques into PCCEM by focusing on case-based learning, interdisciplinary/interprofessional teamwork, individual confidence, and skill competency (54). The activities themselves emphasized techniques and tasks key to the IMOC, including communication, symptom management, planning, ethical dilemmas, and other topics. Integrating these themes into the standardly available Advanced Pediatric Life Support curriculum is also an effective introduction to the IMOC (54).

A number of indicators pointed to the IMOC's success in HDLV's PICU. Improved holistic care provided through the IMOC seems to have impacted the satisfaction of patients and families that are admitted; this PICU has not had a single medical lawsuit during its 5 years of existence. Staff appear to provide better care and patients seem to have better symptom management, greater familial involvement, and improved overall outcomes since the implementation of the IMOC (54). In addition, the unit's mortality rate decreased from 10 to 4.8% after the staff were fully trained in the IMOC [Ecuador's average PICU mortality rate is 15% (45)]. These unit-wide improvements suggest that the IMOC may better meet the extensive special care needs of HDLV's PICU patients. Further studies are needed to determine the effectiveness of the IMOC in other settings, but this may be a better care model for other settings as well.

## CONCLUSION

This article has identified reasons why the IMOC is well designed to meet the extensive PPC needs in PICUs across different contexts, especially in under-resourced settings like Ecuador. Currently, the direct integration of PC into the PICU is met with resistance because of prevalent myths and misconceptions about PC, discipline-related bias, and ignorance of evidence-based recommendations related to the application of PC. However, evidence (4, 5, 31) indicates that virtually all patients admitted to the PICU have some level of PC need; thus, PICU models must make PC highly accessible to all patients who may develop special care needs throughout their stay in the unit. Training difficulties, lack of specialists, consultation barriers, and a number of other factors appear to impede the consultative model from meeting this goal both in industrialized contexts (6) and in the global south. Considering the propriety of the IMOC to meet extensive PPC needs across different settings, the authors recommend further research related to the establishment of the IMOC in other centers, the effects of this model on quality of care, and comparisons of the IMOC with the consultative model. Employing the IMOC in PICUs around the world could represent an important paradigm shift within pediatric intensive medicine which could elevate care to a superior level, especially in under-resourced contexts.

## AUTHOR CONTRIBUTIONS

MG contributed to the following in the elaboration of this investigation:

- Substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work.
- Critical revision for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CM contributed to the following in the elaboration of this investigation:

- Substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work.
- Drafting the work and revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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# Pediatric Critical Care in Resource-Limited Settings—Overview and Lessons Learned

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Pediatric critical care is an important component of reducing morbidity and mortality globally. Currently, pediatric critical care in low middle-income countries (LMICs) remains in its infancy in most hospitals. The majority of hospitals lack designated intensive care units, healthcare staff trained to care for critically ill children, adequate numbers of staff, and rapid access to necessary medications, supplies and equipment. In addition, most LMICs lack pediatric critical care training programs for healthcare providers or certification procedures to accredit healthcare providers working in their pediatric intensive care units (PICU) and high dependency areas. PICU can improve the quality of pediatric care in general and, if properly organized, can effectively treat the severe complications of high burden diseases, such as diarrhea, severe malaria, and respiratory distress using low-cost interventions. Setting up a PICU in a LMIC setting requires planning, specific resources, and most importantly investment in the nursing and permanent medical staff. A thoughtful approach to developing pediatric critical care services in LMICs starts with fundamental building blocks: training healthcare professionals in skills and knowledge, selecting resource appropriate effective equipment, and having supportive leadership to provide an enabling environment for appropriate care. If these fundamentals can be built on in a sustainable manner, an appropriate critical care service will be established with the potential to significantly decrease pediatric morbidity and mortality in the context of public health goals as we reach toward the sustainable development goals.

**Keywords:** pediatric critical care, low resource settings, low middle-income country, pediatric intensive care, partnership practice

Critical care is healthcare for the sickest patients. The concept of critical care developed during the poliomyelitis epidemic in the 1920–1950s when the number of critically ill patients led to the development of dedicated areas, “intensive care units,” that provided continuous care and monitoring. Critical care services, with focused attention and expertise provided by medical and nursing staff for patients with multi-organ failure and life-threatening illness, quickly spread worldwide (1). Critical care services were extended to pediatric patients in high income countries (HICs) by the 1950s and early pioneers of critical care in low middle-income countries (LMICs) were only 15 years behind their HIC counterparts, opening the first African intensive care unit in 1969 (2).

Nearly 50 years later, however, a huge gap has emerged between the high quality pediatric critical care services available in most HIC settings and the inadequate pediatric critical care services available in most LMIC settings. Nearly 90% of the children who die globally each year below the age of 5 are living in 42 of the poorest countries. In these countries many illnesses and injuries are preventable and treatable diseases are widespread. In a call to action, Niranjana Kissoon described a journey of an African mother seeking care for her ill child filled with fear and frustration (3). The journey elegantly demonstrated how “accident of latitude” often determines whether one lives or dies (4).

## HISTORY OF PEDIATRIC CRITICAL CARE IN HICs

The first pediatric intensive care units (PICU) were developed in 1955 in Sweden. This unit treated children with pneumonia and sepsis by extending knowledge gained from the adult ICUs (5). In HICs, PICUs developed rapidly over the subsequent decades with innovations in care and equipment as well as specialization of nursing and medical staff. In the 1990s, the American Academy of Pediatrics and the Pediatric Section of the Society for Critical Care Medicine published guidelines for establishment of pediatric critical care units (6) and for PICU admission criteria (7). The admission criteria were intentionally vague and broad, recommending admission for severe or life-threatening illness and/or illnesses requiring frequent monitoring or intensive intervention (8). The guidelines for establishing a PICU focused on staff training, nursing-to-patient ratio, equipment, and ancillary/support services needed to establish quality critical care. As the specialty advanced, critical care in HICs progressed from treating mostly curable acute, life-threatening illness to provide technologically advanced interventions and complicated coordination of care for patients with complex medical conditions. The interventions provided also evolved from relatively simple and inexpensive therapies, such as fluid resuscitation, oxygen, and medications to complex and expensive therapies, including organ transplantation, dialysis, and extracorporeal membrane oxygenation. The evolution of pediatric intensive care in HICs is a model for the development of the same care in LMICs; starting with inexpensive, simple, lifesaving care, and increasing capabilities as resources and training become available.

## HISTORY OF PEDIATRIC CRITICAL CARE IN LMICs

The details of the first PICU and the development of specialized pediatric critical care services in LMICs are not as well documented as in HICs. A systematic review aimed at estimating ICU capacity in low resource settings reported a lack of critical care beds and pediatric intensive care services (9). Millennium Developmental Goal Four (MDG4) targeted a two-thirds reduction in childhood mortality in children less than 5 years of age by the year 2015. To achieve MDG4, UNICEF and WHO focused on the outpatient/ambulatory setting, aiming to improve hygiene,

nutritional support, breastfeeding, and immunizations (10). The Integrated Management of Childhood Illness program was established to guide outpatient care. Based on these guidelines, an estimated 20% of children seen in the ambulatory setting met criteria for referral to a hospital for escalation of care (10). Hospital case mortality rates have decreased only slowly from the 1990s to early 2000s, highlighting the need for improved care of the sickest hospitalized children, including triage, emergency, and critical care services (8).

In response to the need for improved triage and emergency care, the WHO developed the Emergency Triage, Assessment, and Treatment (ETAT) guidelines (11). These guidelines emphasize the tenets of pediatric critical care with early recognition of children who needed immediate care and hospitalization. Implementation of these guidelines in a Malawi hospital decreased the mortality rate by half (10–18 to 6–8%) from 2001–2006 (12).

The WHO also published and updated *The Pocketbook of Hospital Care for Children for the Management of Common Illnesses with Limited Resources* (13), which provides many appropriate clinical guidelines for nurses and physicians caring for hospitalized children in these settings. The development of these guidelines and improvements in staff training clearly demonstrated that advances can be made in caring for critically ill children in LMICs by appropriate triage and rapid treatment using relatively inexpensive modalities, such as fluids, oxygen, and antibiotics.

## CURRENT STATE OF PEDIATRIC CRITICAL CARE SERVICES IN LMICs SETTINGS

In LMIC settings, the burden of pediatric mortality remains high and a largely undocumented burden of critical illness exists (14). The “three delays” model, first developed to explain why maternal deaths occur may be applied to identify factors that are significant contributors to childhood mortality in LMICs (15). The three delays are (1) delay in deciding to seek care, (2) delay in reaching the appropriate facility, and (3) delay in receiving quality care at the facility. Examples of the third delay, with regards to pediatric critical care services in LMIC settings, are a lack of designated intensive care units with adequate numbers of healthcare staff trained to care for critically ill children, and rapid access to necessary medications, supplies, and equipments. Effective critical care in HICs relies on having a dedicated area, where close observation and frequent monitoring of pediatric patients leads to the provision of rapid, timely, appropriate interventions.

Despite the published guidelines for triage and fundamentals of care described above, the recognition and ability to provide rapid interventions still remains largely absent in many LMIC settings. Infections, such as sepsis, pneumonia, and malaria continue to have a high mortality and 90% of childhood trauma deaths occur in LMICs (16).

There are also significant disparities in pediatric critical care capabilities within regions of any given LMIC (8). In some African countries, university and private hospitals are capable of providing pediatric critical care comparable to PICUs in HICs

(8). In large cities throughout China, India, South Africa, South America, and the Middle East, emergency and intensive care services are often similar to HIC settings (8). The majority of hospitals in LMICs, however, do not have a designated PICU with pediatric trained nursing staff, adequate nurse to patient ratios to care for critical patients, appropriate equipment, monitoring capability, or ancillary support (9). Most pediatric critical care is performed in mixed adult-PICU and the majority of these units would be considered the lowest level ICU (pediatric level 2) (17). PICUs that are established in LMICs are typically staffed by general pediatricians and lack specialized services.

Without a formal pediatric critical care training, curriculum, or certification process, there is a wide variation in understanding skills and care provided. Finally, rural hospitals and clinics in these same countries are not equipped with even the basic resources, such as oxygen, resuscitation equipment, and medication to provide pediatric emergency care, and appropriately trained staffs are rarely available (15).

## THE ARGUMENTS AGAINST AND THE CASE FOR PICUs IN LMICs

Given the perceived high cost of developing and maintaining critical care services, questions naturally arise regarding the advisability or feasibility of establishing critical care units in LMICs. Indeed, financial instability was reported in 35% of established PICUs in the LMICs vs 2.6% of the HICs (13). One could argue that resources would be better employed in addressing the most common primary public health problems facing these communities. In addition, since many of the essential aspects of basic emergency care are not present in LMICs, provision of quality intensive care can be difficult (15). Critical care services in HICs involve a well-coordinated system including three components: triage, emergency medical care and intensive care. Such a comprehensive system is largely unattainable in many LMICs. Yet, despite the strain on resources and the difficulty in establishment of complex systems of care, there is a need to manage children with sudden, serious reversible disease in all settings (14).

An argument for developing critical care services is the potential for these services to translate to improvements in hospital care for all patients (18). Many of the conditions that contribute to the burden of disease in LMICs, such as dehydration and respiratory distress, can be mitigated through prompt, simple treatments (14). Pediatric emergency and critical care services do not need to be expensive, nor excessively dependent on complex technology (19). Critical care services can be utilized to improve outcomes if combined with a focus on community recognition of serious illness, early access to care, referral, and safe transport (15). A robust triage system, the first component of critical care, is still formally lacking in many hospitals in LMICs despite the WHO ETAT recommendations (19). The South African Triage Scale (SATS), for example, employs clinical signs and a triage early warning score to assist in the early identification of acute illness. Use of the SATS has led to better use of hospital resources and earlier discharge (8). Implementing simple tools and interventions such as these, can

make a significant difference in the outcomes of critically ill children, supporting their use in LMICs.

Finally, a key argument for the provision of critical care services in resource-limited settings lies within an ideology that all human beings belong to a single community, based on a shared morality, and is based on three principles: the worth of individuals, equality, and the existence of obligations binding to all (8).

## BASICS OF DEVELOPING A PICU IN A LMIC: LESSONS LEARNED

Preparing to set up a pediatric critical care unit in a LMIC setting requires planning, vision, specific resources, and most importantly investment by the nursing and permanent medical staff. While PICUs in LMIC settings may develop organically, led by national experts within a country, experts from HICs may be asked to provide focused training. It is essential that these visiting experts recognize the importance of collaboration with local medical staff. A needs assessment performed in collaboration with the local team provides important information to guide appropriate establishment of medical services and ensures that programs established are valued by the medical staff and community, making them more likely to be sustainable.

It is essential to recognize that preconceptions can be a barrier to developing pediatric critical care in resource-limited settings. An extreme example is one of “Medical Colonialism,” a term first used by two medical students in 1987 to describe how they were allowed to perform procedures in a LMIC that they would not be allowed to perform in their home country (20). “Medical colonialism,” as a concept, can be more subtle. Resentment and distrust may develop if medical personnel from HICs present themselves as knowing “what is best” for those in LMICs despite being visitors. To avoid this undesirable situation, it is critical to listen to, recognize and respect the expert guidance of the local medical staff, nurses, and healthcare workers and form a true partnership.

Borrowing from the work done by Dr. Paul Farmer and his model of four components required to solve epidemics, we have provided examples of lessons learned in developing pediatric critical care services in resource-limited settings (21, 22). The four S components of Dr. Farmer’s model are: (1) staff: properly trained and compensated healthcare professionals; (2) stuff: appropriate medical equipments; (3) space: a clean environment to treat patients; and (4) systems: the infrastructure and logistical organization to provide the services. Although Dr. Farmer’s model may not be fully applicable to development of sustainable systems of health care, it provides a contextual framework for discussion of the issues encountered and examples of pitfalls to avoid when developing pediatric critical care services.

## Staff: Properly Trained and Compensated Healthcare Professionals

Critical care depends on a team of dedicated, well-trained, and compensated medical and nursing staff. The establishment of a standardized pediatric critical care curriculum and certification for healthcare professionals greatly improves provision of



appropriate care. A specialized certification is not currently available in most low resource settings; however, standardized training should continue to be a focus of improving care. Trained nurses are essential to providing appropriate critical care services. Nurse roles in the intensive care unit include patient evaluation, medication administration, data collection and assessment, evaluation of the effectiveness of interventions, and communication with the health care team. There are often obstacles to establishing stable critical care nursing (see **Table 1**). It cannot be over-emphasized that recommended nurse to patient ratios should be at least 1 nurse to every 3–4 patients in the PICU setting, which may be a dramatic change from the 1:10–30 nurse to patient ratio (PC authors) in many LMIC hospital wards.

Focused team-based training is essential in establishing a PICU. Early in the partnership it is important to identify gaps in staff knowledge or skills. Performing a need assessment can provide a template to guide training and meet the objectives of the program. A necessary first step is to establish a solid foundation of basic critical care knowledge and skills. Early training should focus on basic life support skills, recognition of age-specific normal vital signs, input/output fluid balance calculation, and continuous monitoring of the cardiorespiratory system. Recognizing abnormalities in basic physiologic parameters is the first step in a chain of actions to improve outcomes in the PICU. Nurses who typically work in adult ICUs should receive pediatric-specific training focused on how to care for infants and children, knowledge of age-dependent vital signs, and the key differences in resuscitation of pediatrics patients. Simple resources, such as posters or binders with age appropriate vital signs, relevant assessments, and basic therapies are useful while establishing a new PICU. Once basic skills are mastered, it is natural to develop more advanced resuscitation skills. Training can progress to include goal-directed therapy and may include tracheal intubation, mechanical ventilation, use of vasopressors, and placement of central lines. Regular mock codes, critical cases review, and simulation not only reinforce training, but also provide team training and establish the importance of teamwork in the PICU.

A complementary set of skills and knowledge that can have great impact on sustaining a program are those associated with quality improvement (QI), teamwork and leadership. QI provides essential skills to monitor and make adjustments to the program over time as skills and knowledge change, equipment decisions

are made, and to continually improve outcomes. As skills in caring for critically ill children are established, a parallel set of skills in teamwork and leadership also become essential in the development of pediatric critical care program. To complement formal teaching, physicians, nurses, and other ICU staffs will benefit from the guidance of mentors to model and help to develop effective teamwork and leadership skills. As critical care services are established in LMICs, mortality rates may remain high while quality care is developed. Therefore, providing emotional support for staff where issues, such as staff turnover, emotional fatigue, and burnout are at epidemic proportions is essential to the well-being of those working in the PICU. Support might include developing the capacity to provide services, such as event debriefing, when mortality or morbidity occurs in the PICU.

## Stuff: Appropriate Medical Equipment

In addition to staffing, medical equipment has an important role in pediatric critical care. When developing critical care services for children in LMICs, a step-wise approach to introducing equipment is an effective way to build a sustainable service without overwhelming the system. Use of low cost, simple technologies and techniques early in the development of critical care can be lifesaving, and improve quality of care in a sustainable long-term manner (19). Resuscitation kits containing an appropriate-sized neonatal and pediatric bag valve mask systems, adrenaline, cannulas, glucose containing fluids, and normal saline should be readily available in the PICU. Respiratory support is an essential aspect of pediatric care. Non-invasive positive pressure ventilation, including bubble CPAP, is likely a safer and more sustainable respiratory support option than ventilators. Non-invasive ventilation is preferred for many reasons, including conservation of oxygen, decreased need for sedation, decreased equipment/maintenance cost, use of battery power sources, and less monitoring needs. The use of “home” ventilators with internal compressors, instead of “hospital” ventilators that rely on high pressure air and oxygen sources to function, can conserve oxygen and resources. Since oxygen may be supplied in tanks, knowing how much oxygen is available is important. Some ventilators will deplete a large oxygen tank in less than an hour.

Using inexpensive, but appropriate, substitutes for costly medical equipment is a way to establish critical care services without the excessive cost found in some HIC. Examples of low cost medical equipment substitutes include adapting plastic water bottles as spacers for inhaler therapy and the use of sterile nasogastric tubes as umbilical vein catheters (19, 23, 24). When purchasing equipment, the availability in the LMIC or region should be considered, so that it may be maintained and repaired locally (19). Additionally, buying equipment locally supports the regional economy while providing a much-needed service to the hospital.

## Space: A Clean Environment to Treat Patients

Providing critical care requires physical space in all settings. Caring for critically ill patients requires more space than caring for

**TABLE 1** | Obstacles to establishing critical care nursing.

- Lack of hospital and nursing administration understanding of nursing role in critical care
- Lack of funding for specialized training
- Inability to provide adequate staffing for ICU nurse to patient ratios
- The traditional role of nurses in the hospital including level of education, experience in critical care, cultural norms, and comfort surrounding communication with and respectfully challenging a physician's orders
- Inadequate compensation to encourage retention
- Allowing nurses who are fully trained and invested to be allowed to remain in the pediatric intensive care units without frequent rotation and reassignment
- The need for well-trained nurses to work as preceptors and mentors to new staff

non-critically ill patients due to the space needed for equipment and higher number of medical personnel needed per patient.

Overestimating the number of patients that can be cared for in a given space is common. Crowded care areas can create an unorganized work environment that may promote infection, cause difficulty locating necessary equipment, and limit medical personnel and family access to patients. Due to the lack of infrastructure, such as pressurized gases and vacuum, more space may be required in LMICs for equipment that is not needed in HICs. Examples of extra equipment in LMICs may include oxygen tanks, oxygen concentrators, air compressors, and suction machines in addition to monitors, IV pumps, and ventilators that are needed to support the critically ill child in all environments.

## Systems: The Infrastructure and Logistical Organization to Provide the Services

Having support to develop pediatric critical care services from the local leadership, both within the organization and from various levels of government, is essential to the success of the program. Support is necessary to develop and retain trained medical personnel.

Additionally, having a biomedical team that provides a reliable way to replace and repair equipment and the infrastructure to maintain the space and facility is invaluable. When supportive leadership is absent, trained personnel may end up leaving for other opportunities, equipment may fall into disrepair, and the facilities will become unusable. Since no pediatric critical care service works in isolation, relationships between the PICU services and the rest of the organization must also be clarified. Relationships are particularly essential between PICU and emergency medicine, anesthesiology, radiology, and surgery, but good working relationships with all the medical and surgical services that will interact with PICU are important.

Finally, in any medical environment that cares for critically ill children, difficult decisions over the use of limited resources will occur. The most difficult question is often the dilemma of “what can be done, what should be done and what will be done.” Those making the decisions in a resource-limited setting need to be aware of anticipated outcomes for specific illnesses and should avoid the use of limited resources on patients that have a terminal illness (19). Additionally, long-term use of limited resources, such as pumps and ventilators needs to be considered part of resource stewardship. As these difficult situations are inevitable, admission and discharge guidelines should be established early, based on local experience and outcomes, and updated as outcomes change (20). When beds and supplies are limited, PICU admissions should be limited to illness and injury that are reversible or curable, such as shock secondary to dehydration, anemia, or malaria, and survivable trauma. Having admission criteria based on outcomes will prevent the use of limited critical care resources for children with terminal or untreatable conditions or for those unlikely to benefit from

treatments (19). Some examples of situations that may deplete medical resources without benefit to the patient, include complex congenital heart disease in the absence of a cardiac surgery program, malignancies without effective therapy, and patients in persistent coma requiring mechanical ventilation. It is also important to ensure families don't utilize all of their resources, financial, or otherwise, since the health status of many LMIC individuals and families is closely tied to their ability to stay out of poverty (19). Therefore, ensuring financial support is available to a family should be part of the treatment plan for critically ill children in LMICs. Finally, local medical personnel are invaluable in understanding the limits of their system, knowing when to stop or limit resuscitation, or limit the use of supplies and medicines that might be considered unhelpful or wasteful. Listening to local medical providers is an important aspect of respecting their expertise and culture.

## CONCLUSION

The principal goal of developing critical care services in LMICs is to progressively improve the outcomes of children presenting with a serious or life-threatening illness and to do it in a sustainable manner. This requires working together as partners with LMIC healthcare providers in a respectful and nurturing environment. A thoughtful approach to developing pediatric critical care services starts with fundamental skills and knowledge, inexpensive, but effective equipment, and supportive leadership. These fundamentals can be built on in a sustainable manner, having the potential to significantly decrease pediatric morbidity and mortality in LMICs through excellent, but appropriate critical care in the context of public health goals as we reach toward the 2030 SDGs.

## AUTHOR CONTRIBUTIONS

TS substantial contributions to the conception or design of the work, or the acquisition of background articles and topics to be covered. Drafted work and revised it critically for important intellectual content. Provided approval for publication. Agreed to be accountable for all aspects of the work in ensuring that questions related to accuracy or integrity of any part of work are appropriately investigated and resolved. AK and CJ drafted work and added content critically for important intellectual content. Provided approval for publication of content. LD revised work and added content critically for important intellectual content. Provided approval for publication of content. AS drafted and revised the work and added content critically for important intellectual content. Provided approval for publication of the content. SH drafted work and revised it critically for important intellectual content. Provided approval for publication. Agreed to be accountable for all aspects of the work in ensuring that questions related to accuracy or integrity of any part of work are appropriately investigated and resolved. AB drafted work for the article and critically edited, reviewed and approved the final version.

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# Considerations for Assessing the Appropriateness of High-Cost Pediatric Care in Low-Income Regions

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It may be difficult to predict the consequences of provision of high-cost pediatric care (HCC) in low- and middle-income countries (LMICs), and these consequences may be different to those experienced in high-income countries. An evaluation of the implications of HCC in LMICs must incorporate considerations of the specific context in that country (population age profile, profile of disease, resources available), likely costs of the HCC, likely benefits that can be gained versus the costs that will be incurred. Ideally, the process that is followed in decision making around HCC should be transparent and should involve the communities that will be most affected by those decisions. It is essential that the impacts of provision of HCC are carefully monitored so that informed decisions can be made about future provision medical interventions.

**Keywords:** ethics, low- and middle-income countries, high cost, intensive care, children

*Ideally, every child in the world should have access to an intensive care unit with facilities for endotracheal intubation and mechanical ventilation. No ethical justification exists for providing these treatments to children in rich countries while denying them to children in poor countries (Shann, 2011)*

## INTRODUCTION

While there is no ethical justification for differences in health-care access for children across the world, dealing with the realities of those differences remains profoundly challenging. During 2016, 5.6 million children under the age of 5 years died across the world (this is equivalent to 15,000 under-5 deaths per day), mostly in low- (LICs) and low- and middle-income countries (LMICs). The majority of those deaths could have been prevented using simple and affordable interventions (1). There are huge differences in under-5 mortality between high- and LICs as well as between higher- and lower-income groups within individual countries (2), in both high- (3) and LICs (4). Addressing intra-country differences could make nearly as much difference to child mortality as addressing the differences between countries. There have been substantial improvements in child survival across the world with the implementation of the millennium development goals, and with those gains, the role and importance of critical care in low- and middle-income countries (LMICs) has increased (5). However, the decision to provide high-cost care in low-income regions is a complex issue where the outcomes and consequences of that provision may be unpredictable and substantially different to those experienced in high-income countries.



High-cost medical care (HCC) incorporates a wide range of medical interventions, and the “value” that is associated with the provision of HCC must take into account many factors including costs, and benefits and the priorities of the people living in those areas. The “high cost” has to be viewed in relation to the available resources and in relation to the value delivered by the care (it is possible to have both high cost and high value, and high cost and low value). Some have argued that there are no “universal” bioethics (6, 7), but perhaps there may be validity in creating some transparency around the processes that are involved in making decisions as to how resources are allocated and on what basis.

In this review, I will consider the health-care context of LICs, the costs and benefits associated with the provision of HCC (in general, but more specifically directed at pediatric critical care), the way in which different people may be affected by HCC, and consider how the process of decision making around resource allocation could be addressed in LICs. Resources are limited in all regions, but there are substantial differences in resource availability, specific contexts, and particular demands on health-care systems across the world.

## THE CONTEXT

Decision making around the utilization of resources for HCC is deeply affected by a wide number of issues including the underlying context (particularly in terms of disease profile and morbidity and mortality data), the resources available (both absolute and relative amounts), and the potential benefits associated with the HCC (to the child, the family, the community, and the overall health services). An underlying concern with the process of “lumping” countries and groups of countries or communities into simple categories (such as LICs) is the fact that there are huge differences in context between (and within) countries, even within similar income groupings. It is not only the current reality but the “trajectory” of development in a country that may affect which health-care services can and should be provided.

## The Children/Patients

As shown in **Table 1**, approximately 60% of the world’s children live in low- and LMICs, with some 275 million children living in low-income regions of the world. In those regions, children making up a very substantial proportion of the population have limited access to health-care services and extremely limited

access to high-cost health-care services. Health-care expenditure in these regions averages US\$35 per capita per annum, and the under-5 mortality is approximately 70 per 1000 live births. The majority of childhood deaths occur in these countries, and various authors have highlighted the fact that the majority of these deaths could be prevented by the implementation of relatively low-cost (and affordable) interventions.

## The Environment

LICs have many features which make the delivery of health care challenging including limited financial and personnel resources for health care, geographical features which may make transport and access challenging, political instability, limited infrastructure (water, electricity, sanitation, transport services, and transport infrastructure), and limited organizational and administrative infrastructure. The large number of displaced people and refugees also complicates decision making for care delivery.

The disease profile in LICs may be substantially different to that in HICs (9–11) and is also changing. In general, there is more trauma (including burns), and there are more infections (including more non-bacterial infections such as dengue, malaria, trypanosomiasis, etc.), and more infections with antibiotic-resistant organisms. Particular concerns relate to infections such as drug-resistant tuberculosis. Data on non-infectious disease are limited, but there is no reason to believe that there is a lower incidence in poorer countries.

As a consequence of multiple factors, patients often present late for therapy (12, 13) with the result that disease processes are often substantially advanced at the time of presentation. A high proportion of deaths occur soon after admission (14). Resource limitations translate into a low number of health-care workers and particularly health-care workers with specialist skills in areas such as pediatrics and pediatric surgery (see **Table 2**). These workers are deployed in environments that may be overcrowded and poorly maintained (and thus difficult to keep clean), uncomfortable (including heat and humidity or even cold), with very limited equipment and medication. The health-care facilities are often situated in contexts where there may be limited and unreliable sources of clean water, sanitation, and power (particularly electricity and lighting). In a recent review of hospitals in sub-Saharan Africa, the percentage of hospitals with dependable running water and electricity ranged from 22 to 46%, and in countries analyzed, only 19–50% of hospitals had the ability to provide 24-h emergency care (15).

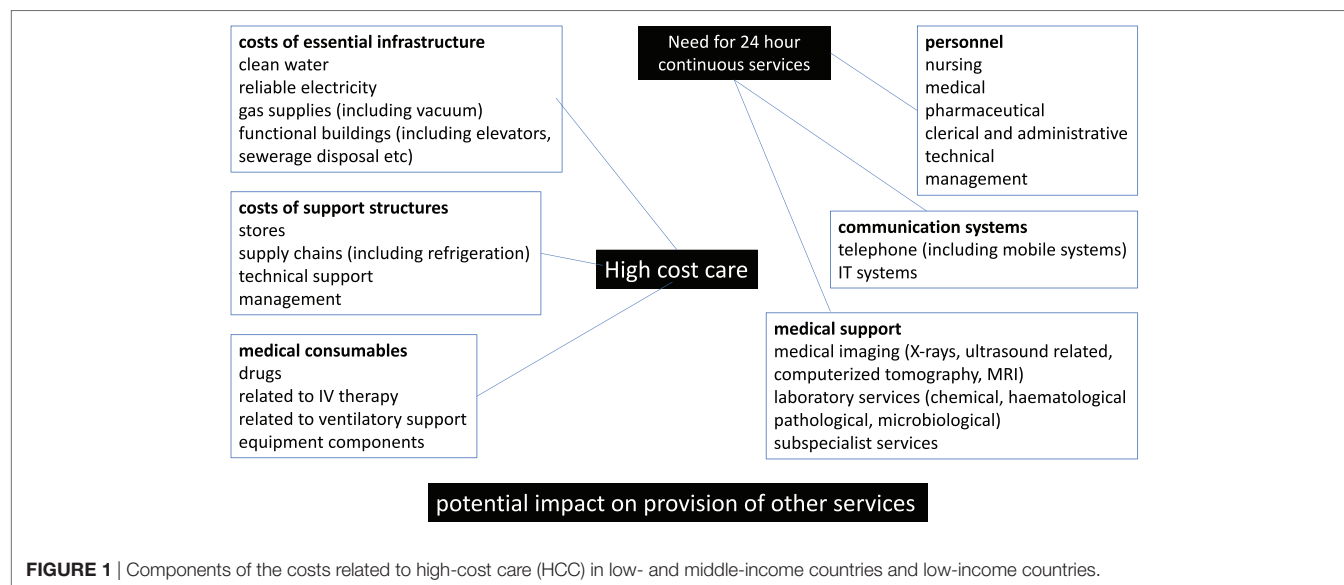
**TABLE 1** | Data on population, mortality, and health expenditure by income region (8).

Region by Income	% population 0–14 years (2016)	Total population 0–14 years (2015)	Gross national income (GNI) per capita (US \$, 2016)	Health expenditure per capita (US \$, 2014)	Under-5 mortality (per 1,000 live births), 2016
Low income	42.67	275 365 283	\$612	\$35	73.1
Lower-middle income	30.83	923 253 971	\$2,079	\$90	50.7
Upper-middle income	20.60	528 220 719	\$8,210	\$506	14.1
High income	16.7	197 950 251	\$41,046	\$5,266	5.4

As of July 1, 2016, low-income economies are defined as those with a GNI per capita, calculated using the World Bank Atlas method, of \$1,025 or less in 2015; lower-middle-income economies are those with a GNI per capita between \$1,026 and \$4,035; upper-middle-income economies are those with a GNI per capita between \$4,036 and \$12,475; high-income economies are those with a GNI per capita of \$12,476 or more.

**TABLE 2** | Resources for health care by income region (8).

Region	Nurses and midwives (per 1,000 population), 2012	Physicians per 1,000 population (2012)	Specialist surgical workforce per 1,000 population (2014)	Out of pocket expenditure (% of total expenditure on health)
Low income	0.69	0.20	0.88	37.19
Lower-middle income	1.77	0.73	10.23	54.87
Upper-middle income	2.80	1.96	39.55	32.39
High income	8.73	2.94	69.28	13.34



Limited and often dysfunctional supply chains contribute to nonavailability of resources that would be taken for granted and assumed in HICs. All of this may be aggravated by political instability and limited personal safety. In the event of natural disasters or outbreaks of infectious disease, these systems may fail spectacularly as has been demonstrated during recent outbreaks of Ebola virus infection in West Africa (16).

All the factors above need to be taken into consideration when contemplating resource allocation for high-cost care.

## RESOURCES FOR HEALTH CARE

In considering the ethics of high-cost care in LICs, it is essential to balance the resources that are available for that care with the outcomes that can be achieved using those resources.

### Financial

The financial resources available for health care can be considered from a number of perspectives (see **Figures 1** and **2**). There may be complex interactions between multiple factors.

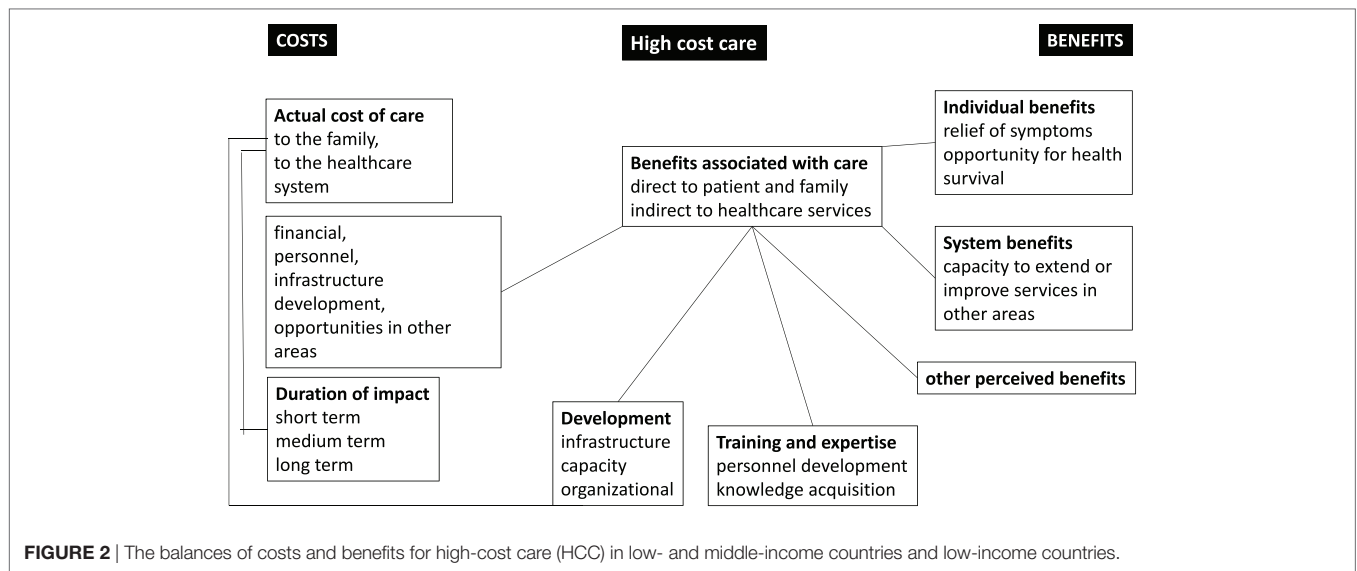
As shown in **Table 1**, there is a >10-fold difference in the annual per capita health-care expenditure between LMICs and high middle-income countries and >100-fold difference between LMICs.

In LICs, a significant proportion of the funding available for health care may come from outside the country (see **Table 2**).

That funding may be useful but is usually to be used in ways that are defined by the sources of the funding. Increasingly, funding may also be sourced from research projects that are based on high-income countries. This means that there are external drivers of how that funding can and should be used for health-care provision.

There are different ways of assessing the relative costs of high-cost services. When considering the costs of intensive care in 2009, Baker et al. estimated the costs of a day in intensive care in rich countries to be of the order of \$1,000 (17). From a national perspective, that day cost would be approximately 20% of the annual per capita expenditure on health in a rich country but approximately 30 times the annual per capita expenditure on health in an LIC.

The costs of delivering some aspects of critical care in poorer countries may be substantially lower than this, as an example the cost of a day in a private ICU for cancer patients in India was reported as \$57. However, in settings where a substantial proportion of health-care costs are covered by out-of-pocket expenditure by families (**Table 2**), that amount has to be related to the family income. In this setting, \$57 was approximately 100× the average per capita household income (18). Thus, the provision of expensive health-care services to individuals in these settings has the potential to devastate the financial structure of a family with severe impact on other family members (including siblings) (19).



Significant as this overall difference is, it may actually mask other differences in costs for HCC. The HCC costs in rich countries reflect the costs of providing that care in the context of systems with well-established and functional infrastructure. In LICs, the infrastructure required (including transport, electricity, water provision and sewerage disposal, medical gas supply systems, technical maintenance support, etc) to support complex medical care may be profoundly deficient. The real cost therefore of providing HCC in “austere conditions” may be substantially higher than currently estimated. This may, however, be offset by the lower salaries that are paid to health-care workers in poorer countries. As another example, it has been argued in HIC that catheter closure of ostium secundum atrial septal defects is substantially cheaper than surgical closure, but in fact this was not the case in Guatemala (20).

Many of the resources required for more expensive therapies (including equipment and medication) are developed and manufactured in high-income countries. Access to these resources may be limited by the direct costs, which are exacerbated by indirect costs such as transportation, import duties and taxes, and adverse financial exchange rates.

In many LMICs, the differentials in access to high-cost health care between rich and poor people may vary substantially. In many countries, a small proportion of the population have access to state-of-the-art medical services while the majority of people within the same country may have limited or virtually nonexistent access to health-care services (21). In South Africa in 2015, approximately 49.8% of total health-care expenditure was from private sources, and only approximately 16% of the population have private health-care insurance (22). This difference in financial resources translates into major differences in access to facilities such as intensive care beds (21, 23).

The widespread corruption in some LICs and LMICs may have a profound effect on the resources actually available for health-care services (24).

Thus, any analysis of the resource implications for HCC in LICs must include a review of all the multiple factors and details

in specific environments that may profoundly affect both the absolute and the relative costs of HCC in these countries.

## Personnel

Not only are health-care systems in LICs limited by financial resources but they also have profound challenges as regards the availability of trained and skilled health-care providers. Some years ago, the WHO estimated that the world faced a global shortage of almost 4.3 million doctors, midwives, nurses, and other health-care professionals (25). There are particular shortages in the area of surgery [including pediatric surgery (26, 27)] and anesthesia (28) and rehabilitation personnel (29) in poorer countries. The availability of these health-care workers (particularly to patients who cannot afford private health care) may be profoundly affected by the different remuneration patterns and the fact that many health-care workers have to work in several sectors in order to obtain an adequate income (30).

The standard of care that is (and can be) expected from health-care workers may vary substantially. In most HICs, it would be assumed that staff on out-of-hours duty would be fully awake and present throughout their working time. In many LICs, there is an expectation that afterhours staff will be heavily reduced in numbers relative to the day and that they will be expected to sleep for at least some of the time on duty (after all, many have day jobs that they also have to attend to).

When 24-h services are essential for the provision of HCC (such as pediatric intensive care), then personnel may be both a limiting factor as regards availability, but also as regards costs (four to five people have to be employed for each position that needs to be filled on a 24-h basis).

With substantial differences between financial resources in private and government sectors in LMICs, there are major pressures for health-care workers to move into the more affluent areas either full-time or part-time. This process may substantially decrease the access of less affluent members of society to health-care services that are high cost and often require high levels of training and expertise.

Decisions about HCC in LMIC and LICs may also have an effect on medical emigration. As an example, individuals with training in areas such as surgery or cardiac surgery are likely to emigrate or to move into the private sector if they are consistently unable to operate because of the lack of availability of theater time or PICU beds.

## Structures

Many of the structures in terms of policies, programs, and training infrastructure that are required to support intensive care therapies are simply not present in LICs, as shown in a study completed in Tanzania (31). Thus, time and effort will have to be expended to put all those structures in place before particular services can be provided.

## OUTCOMES OF HIGH-COST SERVICES

The outcomes of high-cost services are not always simple to establish and may relate to the underlying conditions (see **Table 3**): the specific interventions undertaken, and the expertise and experience of the teams undertaking those interventions. Some high-cost interventions may be associated with excellent outcomes and minimal long-term costs. At the other extreme, high-cost interventions may be associated with poor outcomes and high long-term costs.

There is evidence that relatively low-cost interventions in the care of critically ill children such as the provision of antibiotics at community level to neonates (40), the provision of oxygen therapy to children with pneumonia (41), the provision of high-flow humidified nasal oxygen or nasal CPAP (42, 43),

and the improvement of organization of emergency services or of pediatric services within a hospital (44) may be associated with substantial reductions in mortality without significant added expense. Recent neonatal data suggested that focused implementation of nasal CPAP in Nicaragua could provide improved outcomes while reducing invasive mechanical ventilation (45).

Mechanical ventilation has been described in many reports from LICs as being associated with relatively high mortality (46, 47). Thus, in many situations, HCC such as ventilation may not improve overall outcomes as much as simpler and less-resource intensive care modalities.

Where intensive care services have been implemented in LICs, there is some evidence that the strict application of quality control programs can substantially improve the outcomes of pediatric intensive care (48, 49).

## ETHICAL PRINCIPLES TO BE APPLIED

Having reviewed the context, the resources available, and the potential impact of HCC such as pediatric intensive care, it is important to consider ethical principles that could be considered in making decisions about the provision of HCC (see **Table 4**) as well as the characteristics of the processes used in decision making (**Table 5**). Turner et al. (14) have highlighted the principles of global justice, resource allocation, and local cultural preferences. Clearly, there is no ethical justification for the global differences in access of children to HCC (50), and there is a huge need to provide advocacy for additional resources from HIC to be allocated to LIMCs, but that will (at best) take time. However, there is a

**TABLE 3 |** High-cost interventions, cost, and outcomes.

Example	Short term	Medium to long term	Outcomes
Intensive care for croup	High cost for intensive care (usually only a few days)—but extreme variability in the costs incurred (32)	No expected ongoing costs	Normal life expectancy, small proportion will have recurrent croup
Intensive care for Guillain-Barré syndrome	High cost for intensive care (may require months of ventilation)	May need high input for rehabilitation	Expected to return to normal quality of life with normal activities (may have residual weakness). Some patients have recurrent disease (33–35)
Intensive care for pneumonia or infection	High cost for intensive care (usually a few days but may be longer)	If not underlying disease, minimal long-term costs	Depending on context, may have substantial mortality in hospital and in the 6 months following hospital discharge (36) [particularly if concurrent malnutrition (37)]. However, high chance of normal long-term outcome
Intensive care to enable major surgery	High cost for surgery and intensive care (usually only a few days)	Depending on underlying problems, may be a significant range of long-term costs	The outcomes of a major surgery can be very variable depending on a variety of factors including surgical training and surgical caseload
Surgery for congenital heart disease	High cost for surgery and intensive care	If curative surgery, then minimal long-term costs. May have substantial costs for ongoing care (38) in complex conditions	If successful, excellent outcomes with essentially normal life expectancy and quality of life
Surgery for rheumatic heart disease	High cost for surgery and intensive care	Relatively high costs for ongoing follow-up and medication	Limited long-term survival and high morbidity (39)
Surgery and Intensive care for trauma including burn injuries	Relatively high cost for surgery and intensive care	Depending on the site and extent of the injuries, the long-term costs could be minimal or very substantial	The outcomes may be variable. In the absence of long-term rehabilitation, and in the absence of facilities such as access to cadaver skin or expensive skin replacements, the outcomes of major burns may be extremely poor



**TABLE 4 |** Ethical principles to be applied in decision making around high-cost care (HCC).

Principle	National level	Community level	Individual level
Respect for autonomy	Rights of nations to make decisions regarding the prioritization of health services in that country.	The rights of communities to be involved in the processes that affect what and how medical care will be delivered to them	The rights of individuals and their families to make decisions regarding issues that affect them
Beneficence	The HCC should provide an improvement in the quality of life in that country	The HCC should improve the quality of health and life in the community which is being provided with that service	The care that is offered has to be seen to provide value to the individual child and his/her family
Non-maleficence or "do no harm"	The provision of the particular HCC cannot be seen to endanger the delivery of other essential services	The provision of the services must not cause harm to themselves, and the removal of other services in order to afford the services must not be seen as a greater harm	Patients must be seen to benefit from the services offered. There may be a range of perceptions about what outcomes are actually acceptable
Justice	The health-care services need to provide care to as many children as possible, within the resources available. All care cannot be provided to all	There are different communities that are affected by decisions around HCC, and communities should not be disadvantaged by the provision of HCC to individuals or to other communities	Patients should have access to care on the basis of need and likelihood of benefit

**TABLE 5 |** Processes to be applied to the processes of resource allocation for health care.

Trust	The people affected by the process need to trust that the people implementing the health care will do their best to provide that care fairly and equitably
Transparency	The process of resource allocation should be open to comment, and the basis for decision making should be made public
Responsiveness	Should be mechanisms within the system to respond to changes in circumstances and established mechanisms to appeal against specific decisions
Consistency	Policies should be consistently applied regardless of the individuals involved
Inclusiveness	People who are affected by policies should be involved in the processes of developing those policies
Accountability	Clinicians whose patients are affected by the process need every opportunity to appeal against decisions Managers and administrators need to have details of the resources available, the processes used to allocate those resources

need to review both the basis and the processes used for resource allocation both within and between countries.

The principles generally considered in biomedical ethics (51) include respect for autonomy, non-maleficence, beneficence, and justice. It may be useful to consider the implications of these principles when applied at different levels of the health service delivery (Table 4).

Kass (52) proposed that the following questions should be asked when evaluating potential public health interventions:

- What are the goals of the proposed program (this includes both the overall goals and the short-term goals) and in particular who will benefit from this intervention?
- How effective is the program at achieving the stated goals?
- What are the known or the potential burdens of the program?
- Can the burdens be minimized or are there alternative approaches?
- Is the program administered fairly?
- How can the benefits and burdens of the program be fairly balanced?

## What Are the Goals of the Proposed Program (This Includes Both the Overall Goals and the Short-Term Goals) and in Particular Who Will Benefit From This Intervention?

If one considers the possibility of pediatric intensive care in LICs, the overall goal would be a reduction in mortality, and the short-term goal would be more effective resuscitation of critically ill children presenting to the health-care services. The costs of pediatric intensive care may be particularly high (including the entire system of staffing, equipment, and support structures). At best, the introduction of pediatric intensive care services will benefit the small number of children who have already accessed health-care services and have access to the intensive care. By contrast, a wider definition of critical care (53), which includes the process of providing care to all children with life-threatening injury and/or illness, would have the potential to affect a much wider group of children and potentially at a much lower cost per child.

## How Effective Is the Program at Achieving the Stated Goals?

It is possible to extrapolate from international data to the possible impact of HCC, but outcomes may be very different in LMICs. In the setting of cardiac surgery in Guatemala, the outcomes were initially worse than expected and took time and considerable investment to improve, despite the presence of surgeons with considerable experience and training in the USA (54). There is also evidence that the establishment of international quality intervention program may lead to substantial improvements in outcomes from high-cost procedures as demonstrated in pediatric cardiac surgery (55).

The provision of PICU is very unlikely to make a substantial impact on the mortality of children in LICs where there are numerous deaths and at best extremely limited resources available for PICU. In middle-income countries, there is much more likelihood of PICU making an impact on pediatric mortality. There is also the consideration that the training of personnel for

services such as PICU may take many years, and thus it may be worth considering the introduction of PICU and investing in personnel training some time before it is likely to be implemented within a region.

There is certainly evidence that over time, the introduction of relatively HCC has improved outcomes in a number of settings (56, 57), particularly for oncological problems. There is also evidence that HCC in LICs can improve over a period of time (47).

A particular challenge for HCC is the requirement of most HCCs for ancillary disciplines including anesthesia (58, 59), pediatric surgery (59), medical imaging, etc.—each of these services is frequently required to implement HCC, and all are under pressure, individual HCC may be difficult to implement.

It is also essential to consider the place of the HCC within the overall context of the health services within that country. Particular in areas such as the care of critically ill children, the overall outcome will depend on the entire “pathway” of care and not simply on the intensive care component (13, 60).

One of the potential consequences of the differentials between private and public health care in LMICs is that both sectors may have a limited benefit from HCC. In the private sector, the limited number of people having access may limit the experience and expertise that can be achieved by therapeutic teams, while the majority of patients simply do not have access. In addition, the movement of expertise for HCC from the public to the private sector may further compromise the quality of care in the public sector.

## What Are the Known or the Potential Burdens of the Program?

The direct burden of HCC such as pediatric intensive care relates to the consumption of resources (financial and personnel) within the context of limited resources. An indirect burden of HCC such as pediatric intensive care is the large burden of illness and handicap that may affect both the children who survive PICU (61–63) and their parents (64). This may be extremely problematic in settings where long-term support and rehabilitation are poorly available. Thus, decision making within the HCC environment may include the need to limit interventions at levels that would not usually be considered appropriate in HICs.

A significant potential burden of HCC is the impact of that allocation of resources on other services. In situations where there are relatively rich resources, the implementation of HCC may have a very little impact on other services. Sadly, in LICs, the development of HCC is inevitably going to compromise care in some other area of the system, and it is essential that that impact is recognized, assessed, and included in the overall evaluation process.

A major factor in providing pediatric intensive care services within LMICs [or during disaster events (65)] is the process of developing reasonable strategies to allocate those resources (66), and it is important to consider how this problem will be addressed.

## Can the Burdens Be Minimized or Are There Alternative Approaches?

The burdens of HCC can be limited or minimized by strict definitions and decision making around what services can and should be provided and to whom. Ideally, the process of decision making

should be transparent and public (66). One potential approach to the process of resource allocation, and particularly the allocation of resources to relatively expensive services such as intensive care is the accountability for reasonableness (A4R) process that was initially described in Canada (67).

As suggested above, it is also important to consider whether in fact less expensive care could be utilized to achieve the same or better outcomes. It has been well demonstrated in several settings that the use of “lower” technology such as nasal cPAP for severe bronchiolitis was associated with both lower costs and better outcomes (68).

## Is the Program Administered Fairly?

This question can be addressed at different phases. Initially, it may be important to carefully consider whether there are individuals or groups of people who are not receiving an equitable opportunity to access the HCC services. It may initially be possible to identify groups of people who for particular reasons (including geography) will not be able to access certain services as easily as others. There are also situations where it is clearly not possible to provide all care to all people (69, 70), and decisions have to be made as to what therapy can and should be made available. Ideally, the processes for the allocation of the resources should be agreed to in a process involving the communities affected by those services (66). Generally, those processes will need to have characteristics such as accountability and transparency (see **Table 5**).

In the longer term, the question can only be fully answered if data are collected on who actually utilized the services and what outcomes were achieved. Carefully collected data provide the only real way in which the impact of a service can be assessed. Inherently, data capture should include not only information on those who accessed a service but also data on those who perhaps could or should have accessed those services.

## How Can the Benefits and Burdens of the Program Be Fairly Balanced?

The benefits of the program can be considered at the individual level. Guidelines for the provision of life-sustaining care in neonates (71), children (72), and adults (73) in HICs have highlighted the need to act in the best interests of the patient at all times. Clearly, there are situations where the application of HCC may actually prolong suffering, and there would be a substantial (although not universal) agreement that this should be avoided.

The training of health-care workers may be substantially affected by decisions made regarding HCC that will be offered in a particular region. The training required to offer HCC such as intensive care is potentially both time-consuming and expensive. The provision of training to health-care workers without a commitment to support the HCC is likely to lead to frustration and in many cases the migration of health-care workers to richer parts of the world. However, lack of opportunities to undergo training and implement therapies (such as surgery and anesthesia) may also lead to medical migration-associated health-care problems.

Decision making around the utilization of high-cost care may affect a number of people including the patient and the family,

health-care workers, hospital and health-care managers, and politicians and people involved with the formulation and administration of policy at a provincial and/or national level. With the exponential growth of global health programs in areas such as North America, there are also an increasing number of people outside of the countries who have an interest and sometimes incentives (financial and otherwise) in changing the provision of HCC in LICs and LMICs.

A crucial aspect of balancing burdens and benefits relates to the standards that are expected and applied in the development of the HCC. Programs that have implemented oncology training and services in LIMCs have had to make decisions about the level of services that could safely be provided in those settings (74). The only way in which the impact of interventions can be monitored is by the collection of the appropriate data (both in the HCC service and in the services that are potentially affected) (45, 75). Bhutta (76) has highlighted the need (in research) to consider the realities and constraints in the countries where the research or clinical services being considered have to be implemented. In the setting of resource constraints, the actual care currently available and the risks that would be acceptable in clinical care may be very different to those where other resources are available.

The only way to address potential and actual ethical concerns in this setting is to make sure that information regarding who is involved in the process of providing the HCC must be clearly available to all the people involved in the process. In addition, the allocation of resources to data collection and interpretation is the only way in which it is possible to assess the impact of HCC and interventions. The allocation of limited resources to this monitoring may seem a relatively low priority, but in the longer term, it is the only way in which interventions can be assessed and thus provides a rational basis for ongoing decision making.

## PROCESSES OF DECISION MAKING

In an ideal system, decisions regarding the implementation of health-care policies would be made: in a coherent way at every level of policy making (Table 4), by people with a clear understanding of both the costs and the achievable benefits of high-cost interventions (particularly relative to other lower cost interventions), and in a way that involves and takes into account the wishes and concerns of the people who are affected by those decisions and policies. Particular concerns in LICs are processes required to develop the expertise and organization structures (77) that are locally available. International groupings and organizations may be able to make a contribution in this regard.

It may be particularly challenging to address the relative contributions of managers in health-care systems to decision

making. In the South African context, it has been pointed out that while there are substantially higher resources per capita in the private health-care system, much of those resources come from the contributions of the people who benefit from that system. If in an LIC, richer people are effectively paying for their own health services, is there a reasonable case to allow that? In that setting, it may be crucial to develop a detailed understanding of the proportion of the real costs that the public sector is bearing (including training costs, tax rebates, etc). It may also be critical to consider collaborative efforts to bring about mutually beneficial outcomes (78, 79), although these may be associated with risks.

Internationally, support for the collection of accurate data regarding the costs and outcomes of HCC for children in LMICs could provide a substantial evidence base for decision making in those areas. Importantly, the data collection should include the specifics of local contexts as far as possible.

A number of authors have addressed the processes that may be involved, with particular support for the use of the A4R approach (66, 80–83). There is strong evidence that this approach may be useful in addressing a range of health-care dilemmas (including access to HCC such as dialysis). However, there is a real need for ongoing research into decision-making processes in LIMCs (84, 85). Underlying that research is the need for a deeper understanding of the values that need to be incorporated into decision making (and which are not universally agreed to) (6, 7).

## CONCLUSION

Ethical decision making around the provision of HCC pediatric care in LMICs and LICs may be a complex process which requires a deep understanding of the context and the implications of any intervention. At the very least, the process needs to incorporate a realistic assessment of the context, the resources (both available and required), and the likely impact of the provision of that care. There is a very real risk that the implementation of high-cost pediatric care may have relatively poor outcomes, and even worse, the utilization of resources in this way may compromise other services with adverse outcomes for many children.

Ideally, all decision making should be transparent and should involve all the communities who are likely to be affected by those decisions. Frameworks from the public health environment may provide a useful addition to the standard bioethical approach.

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The author confirms being the sole contributor of this work and approved it for publication.

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# Successful Deployment of High Flow Nasal Cannula in a Peruvian Pediatric Intensive Care Unit Using Implementation Science—Lessons Learned

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Acute lower respiratory infections are the leading cause of death outside the neonatal period for children less than 5 years of age. Widespread availability of invasive and non-invasive mechanical ventilation in resource-rich settings has reduced mortality rates; however, these technologies are not always available in many low- and middle-income countries due to the high cost and trained personnel required to implement and sustain their use. High flow nasal cannula (HFNC) is a form of non-invasive respiratory support with growing evidence for use in pediatric respiratory failure. Its simple interface makes utilization in resource-limited settings appealing, although widespread implementation in these settings lags behind resource-rich settings. Implementation science is an emerging field dedicated to closing the know-do gap by incorporating evidence-based interventions into routine care, and its principles have guided the scaling up of many global health interventions. In 2016, we introduced HFNC use for respiratory failure in a pediatric intensive care unit in Lima, Peru using implementation science methodology. Here, we review our experience in the context of the principles of implementation science to serve as a guide for others considering HFNC implementation in resource-limited settings.

**Keywords:** high flow nasal cannula, implementation science, resource-limited setting, peru, pediatrics, acute respiratory failure

## INTRODUCTION

Acute lower respiratory infections remain the leading cause of death outside the neonatal period for children less than 5 years of age, and the majority of these deaths occur in low- and middle-income countries (1). These large discrepancies in mortality are due, at least in part, to a lack of availability of basic supplies like oxygen and antibiotics and more advanced technology such as invasive and non-invasive mechanical ventilation (2–4). Despite efficacy of many types of advanced pediatric respiratory support (5, 6), widespread implementation of these technologies in resource-limited settings has lagged behind (7). Implementation science is a rapidly growing field dedicated to improving quality of health care delivery by incorporating evidence-based practices into routine care. Implementation science principles have guided the scale-up of interventions such as prevention of maternal-to-child transmission of HIV in resource-limited settings and could be applied to respiratory technologies to help ensure their success (8, 9).

High flow nasal cannula (HFNC) is an alternative form of non-invasive respiratory support with increasing use for respiratory failure in neonates, children, and adults (6, 10). Due to the non-occlusive nature of the nasal cannula, HFNC is easier to manage by bedside providers than CPAP or BiPAP because there is no need to readjust the interface to maintain a seal. In fact, HFNC has been used for pediatric patients outside the ICU setting with great success (11–13). In resource-limited settings where high patient:provider ratios limit clinicians' ability to be at the bedside, the simple HFNC interface has the potential to be successful in supporting children with respiratory failure. This, as well as evidence that HFNC may be more comfortable for pediatric patients (14, 15), led us to pursue implementation of HFNC in the Pediatric Intensive Care Unit (PICU) at Instituto Nacional de Salud del Niño (INSN) in Lima, Peru. A prior study in Ghana demonstrated substantial challenges in sustaining CPAP in that resource-limited setting (16), so we decided to use implementation science principles to guide our deployment strategy. In this article, we describe our implementation science approach to guide others planning to introduce pediatric advanced respiratory care in resource-limited settings, so that they may avoid common pitfalls.

## SETTING

Instituto Nacional de Salud del Niño is the largest freestanding children's hospital in Peru with approximately 400 inpatient beds and 15 PICU beds. It is a major tertiary care referral center for children covered by the government insurance program, Seguro Integral de Salud. The PICU has approximately 400 admissions annually, of which, 50% are surgical and 50% medical, and a mortality rate of 18%. Children up to 18 years of age with any medical or surgical pathology may be admitted, although oncology and burn patients are typically admitted to other facilities, and postoperative cardiac surgery patients are admitted to the cardiac intensive care unit. Pediatric critical care physicians are in-house 24 h a day, 7 days a week. The nurse:patient ratio is 1:2, and there is one respiratory therapist available during day shift. HFNC was implemented as part of a larger research study to determine whether post-extubation use of HFNC would decrease the duration of invasive mechanical ventilation. According to the research protocol, all children less than 5 years of age who required invasive mechanical ventilation during the first 24 h of PICU admission were eligible for the study unless they had craniofacial malformations that would preclude HFNC use. Informed consent was obtained while children were still intubated. If they developed respiratory distress after extubation, the treating physician could decide to support them with HFNC according to our study protocol (Figure 1). This study was approved by the Seattle Children's Hospital IRB and the Ethics Committee at Instituto Nacional de Salud del Niño.

## PREPARATION

### Identify Champions

Anyone who has attempted to enact change in an organization acknowledges the necessity of identifying local champions to

oversee the intervention. Borrowing from the engineering industry, many health care organizations have adopted systems analysis and improvement approaches to improve the quality of health care delivery (9, 17). These principles focus on involving frontline health care workers in both identifying problems in the current system as well as suggesting possible solutions to streamline the process. Prior studies in resource-limited settings have shown that participation of local providers in the quality improvement process leads to more effective and sustainable solutions (18). Although we had access to a HFNC protocol from a resource-rich setting, we knew that direct implementation of that protocol would not be effective. Instead, we formed a core group of PICU providers at INSN to lead the HFNC project and used the protocol as a starting point to talk with locals to understand the process of caring for pediatric patients with respiratory failure at INSN.

### Map the Process

Process mapping is the systematic creation of flow maps to understand how patients move through the health care system and is used to identify bottlenecks and prioritize interventions. To be most effective, all stakeholders involved in the system should be represented in the final process map. We did not use formal process mapping during the preparation phase. Instead, a core group of INSN physicians and respiratory therapists with nearly 20 years experience in direct patient care in the PICU at INSN helped our team understand how HFNC could fit into their process of providing advanced respiratory care. This local perspective allowed us to design a HFNC protocol appropriate for their environment, increasing the chance of a successful intervention. Because implementation occurred in the context of a physician-led research study, nurses were not included in the early preparation phase. In retrospect, the addition of nurses to the core group from the beginning would have been extremely helpful in identifying potential issues for bedside providers prior to HFNC introduction.

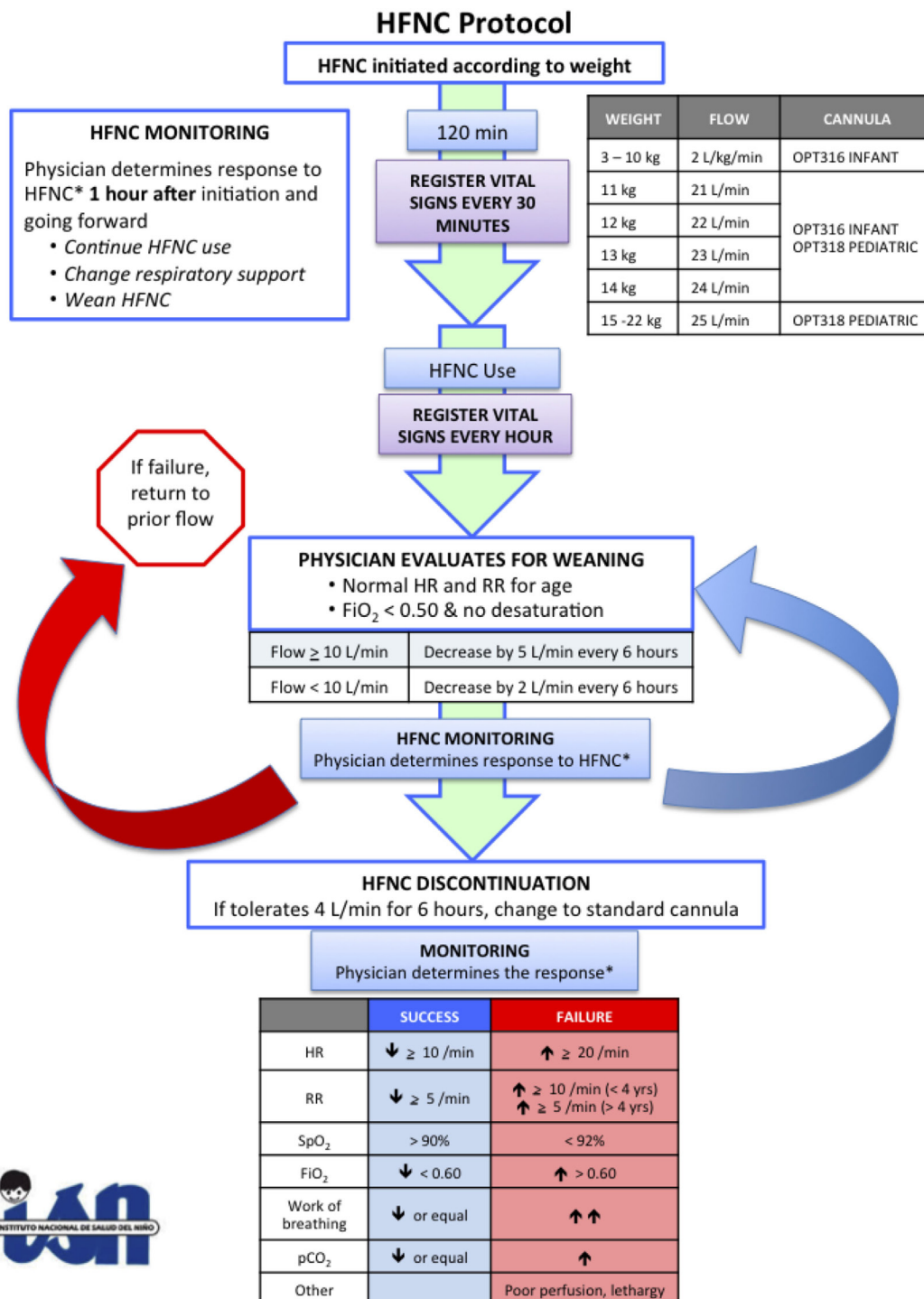
### Determine Resource Needs

Prior to implementing any new technology for advanced respiratory care, it is essential to determine the availability of resources in the particular environment. As others have suggested, use of advanced respiratory care is only appropriate in settings that have the capability to closely monitor vital signs including oxygenation, have adequately trained staff, and have all equipment necessary to provide the specific type of respiratory support (19). Given that INSN has enough nurses to maintain a nurse:patient ratio of 1:2 and is able to provide invasive and non-invasive mechanical ventilation at each bed within the PICU, we focused on procurement of HFNC equipment and staff training. Detailed discussion about the selection of HFNC system is beyond the scope of this article, but gathering information about upfront and ongoing supply costs in addition to established processes for equipment purchasing and maintenance should inform discussions with local leadership. Ultimately, the choice of HFNC system should be left to local experts.

### Training

Local staff training is paramount to successful implementation, and the specific training module should be tailored to the needs of





**FIGURE 1** | High flow nasal cannula protocol at Instituto Nacional de Salud del Niño.

the specific environment. Adapting to the local context is part of the pre-implementation action cycle described by the Knowledge to Action Framework (20), which has guided implementation studies from Canada to the Democratic Republic of Congo (21). Because the educational needs of physicians and nurses are different, we chose to develop separate training modules for each group.

The physician module provided more details regarding scientific evidence for HFNC mechanisms of action and efficacy in different patient populations, whereas the nursing module provided a summary of the evidence with more practical aspects of HFNC setup and management. We trained physicians first because they would be the ones to make the decision to use HFNC, and we

knew their buy-in would be required in order to start using the technology. We then trained nurses over the course of 1 week, with morning and afternoon training sessions daily so that they could attend during scheduled shifts, as there is no mechanism in place to compensate them for additional hours spent on training. Although somewhat onerous, this adaptation was required in order to reach as many nurses as possible. All participants completed pre- and post-tests to both evaluate the quality of the training sessions as well as assess knowledge acquisition.

## Identify Potential Barriers

The next pre-implementation step in the Knowledge to Action Framework is to identify and address any barriers to knowledge use (20). We used qualitative methods to explore these barriers, conducting focus groups with nurses and one-on-one semistructured interviews with physicians after the training and before the introduction of HFNC. Qualitative research methods gather information in more depth, allowing participants to expand upon ideas, which are then organized into themes using thematic analysis (22). Some of the most prevalent themes were innate to the local health care system. For instance, the frequency of physician handoffs and a siloed health care system with insufficient interdisciplinary communication make it challenging to create a uniform, longitudinal care plan for patients. These issues have been reported in a variety of other health care contexts (23, 24), but having these up-front discussions with front-line providers helped us strategize our implementation plan to ensure success.

## IMPLEMENTATION AND SUSTAINABILITY

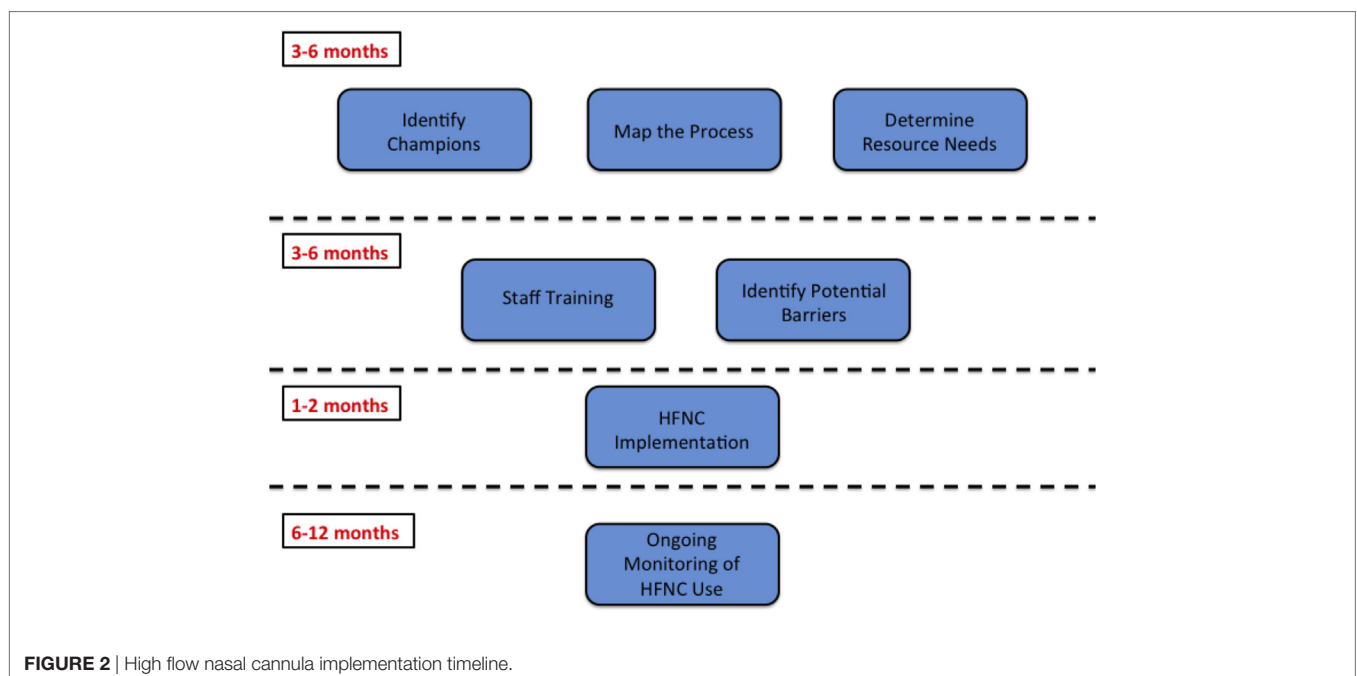
### Interrogate the Process

After the 18-month preparation period, we were ready to introduce HFNC for pediatric respiratory failure at INSN with the

goal of shortening the duration of invasive mechanical ventilation. It is important to recognize that many interventions that are effective in research studies fail to translate into improved patient outcomes. To address that discrepancy, implementation research emphasizes the need to evaluate the effectiveness of the implementation process in addition to monitoring the primary outcome of the intervention. In real life scenarios, the implementation process has a direct effect on whether an intervention achieves its desired outcome. Determinant frameworks, such as the Consolidated Framework for Implementation Research, can be used to understand factors that influence the success of an intervention. This framework describes five important components: the intervention, the individuals involved, the inner and outer settings, and the implementation process (25). Given that these components will influence the success of deployment, it is important to develop ways to assess each of these factors throughout the implementation process. Each component is discussed in more detail below.

### The Intervention

As we learned from the focus groups, the intervention itself must be seen as beneficial for locals. Not all interventions that are effective in resource-rich settings are appropriate for resource-limited settings, and all implementation should be guided by local needs. In our case, the desire for HFNC came from INSN providers who had observed challenges with management of non-invasive ventilation, including skin breakdown, difficulty maintaining a seal around the mask, and relative scarcity of equipment. Even with this local buy-in, the planning phase lasted approximately 1 year to ensure the intervention would meet local needs (Figure 2). If considering implementation of an intervention in a new resource-limited setting, it is essential to spend adequate time up-front building a strong collaboration to maximize the



chances of success. In addition, checking in with the local team periodically can identify any unanticipated challenges that need to be addressed. During our follow-up focus group discussions, we learned that it was difficult for staff to remember the details of the HFNC protocol. To address this, we hung large flow charts of the protocol throughout the PICU to serve as a resource for clinicians.

## The Individuals

The individuals involved in the intervention play a key role in the outcome of the intervention. Above, we emphasized the importance of local champions in the planning process, but these individuals need to demonstrate strong leadership throughout the intervention. Our core group of PICU providers filled many different rolls throughout the intervention. They responded to questions about HFNC, organized ongoing training sessions, encouraged local “hold-outs” to try using HFNC, and addressed any new issues that arose. In addition, the individuals using the intervention are also key players in its outcome. Adopting new practices is challenging for people in any setting, but in resource-limited settings, it can sometimes seem impossible. This can lead to resistance to change, which is why it is so important to have local leaders who can lead by example. Finally, a lack of familiarity with a new technology can contribute to hesitancy to use it. By organizing regular training sessions, nurses and physicians had the opportunity to ask questions related to their experience and go over specific case studies to highlight important aspects of HFNC management. After the training sessions, many nurses reported a desire for more frequent opportunities to review competencies, even beyond HFNC use. This emphasizes the importance of incorporating periodic review sessions to any implementation project to ensure individuals continue to feel comfortable with the new technology and/or protocol.

## The Inner and Outer Settings

The inner and outer settings also influence the effectiveness of a new technology. Although the differences can be subtle, the inner setting generally consists of the structural, political, and cultural context in which the implementation will take place. The outer setting encompasses the greater economic, political, and cultural context surrounding the organization responsible for implementation (26). In Peru, this meant determining whether or not the Ministry of Health would be involved in our project since INSN is under their control. The Ministry of Health had minimal influence over our study; however, in other settings, government oversight may play more of a role and these representatives need to be included in regular organizational meetings. The leadership structure and culture of the PICU at INSN includes both physician and nursing leaders who we engaged prior to implementation. One unanticipated challenge we faced was an unexpected PICU medical director leadership transition, and the position was filled with interim individuals for several months. Fortunately, these individuals were also supportive of our study; however, this transition could just as easily have been detrimental to the success of our project. This highlights the necessity of extra

efforts during times of transition to ensure the inner and outer settings remain supportive.

## The Implementation Process

Finally, the implementation process itself greatly impacts the outcome of the intervention. This is where the work of the core group of providers at INSN paid off. With their recommendations, we implemented HFNC during respiratory season to increase the chance of finding eligible patients. Initially, the uptake of the intervention was slow, with some physicians hesitant to change their practice and adopt new technology. However, with on-site support of colleagues involved in the implementation process, HFNC use increased over time. Similar to other interventions, as providers witnessed successes with HFNC and its ease of use, they were more willing to try it for other patients. The type of support the implementation team provides must fit within the cultural context of the clinical setting. In some settings, direct hands-on guidance may be welcomed whereas in other settings, this may be perceived as interfering with clinical care. At INSN, the local team provided “behind-the-scenes” support, meaning they provided subtle suggestions about trying HFNC for some patients while emphasizing that the ultimate decision was up to the treating physician. Again, this emphasizes the importance of guidance by a team of local champions to determine what is appropriate for their setting.

## Sustainability

After implementation, it is important to maintain ongoing support for HFNC use. This includes many of the concepts described above: having a group of local experts to address clinical concerns, organizing ongoing staff training, and maintaining a consistent supply chain. At INSN, HFNC was implemented in the context of a research project with a specific research protocol. Over the 17-month study period, 29 patients received HFNC support for post-extubation respiratory failure. Study enrollment closed November 30, 2017, so our team of local experts is currently working on developing a protocol for HFNC use for general clinical care. This process will also be more successful if implementation science principles are utilized.

## CONCLUSION

Overall, our implementation experience at INSN has shown that HFNC can be successfully introduced in resource-limited settings. Utilizing tools of implementation science to engage key stakeholders during the planning process, understand the local process and identify its unique challenges, recruit local champions to facilitate training and support throughout the implementation process, and check-in with providers periodically after implementation greatly increases the chance of successful implementation. It is important to recognize that the timeline will likely be slower than anticipated, so maintaining momentum throughout the process is essential to keep local stakeholders engaged. As with all new interventions, sustainability is challenging and requires substantial ongoing effort to maintain. Our experience has taught us that with a core group of dedicated individuals, changing practice to improve the care of critically ill children is possible.

## AUTHOR CONTRIBUTIONS

All authors contributed to the design of the work as well as the drafting and/or revising of this work and have approved this final version for publication.

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# Pediatric Trauma Care in Low Resource Settings: Challenges, Opportunities, and Solutions

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Trauma constitutes a significant cause of death and disability globally. The vast majority -about 95%, of the 5.8 million deaths each year, occur in low-and-middle-income countries (LMICs) 3–6. This includes almost 1 million children. The resource-adapted introduction of trauma care protocols, regionalized care and the growth specialized centers for trauma care within each LMIC are key to improved outcomes and the lowering of trauma-related morbidity and mortality globally. Resource limitations in LMICs make it necessary to develop injury prevention strategies and optimize the use of locally available resources when injury prevention measures fail. This will lead to the achievement of the best possible outcomes for critically ill and injured children. A commitment by the governments in LMICs working alone or in collaboration with international non-governmental organizations (NGOs) to provide adequate healthcare to their citizens is also crucial to improved survival after major trauma. The increase in global conflicts also has significantly deleterious effects on children, and governments and international organizations like the United Nations have a significant role to play in reducing these. This review details the evaluation and management of traumatic injuries in pediatric patients and gives some recommendations for improvements to trauma care in LMICs.

**Keywords:** low- and middle-income countries, trauma, pediatrics, injury prevention, emergency management, surgical management, child abuse, disasters

## INTRODUCTION

The global emphasis on reductions in childhood mortality and meeting the Sustainable Developmental Goals (SDGs), has resulted in significant gains in reducing childhood deaths around the world (1). However, an epidemiologic shift has been noted, with relative increases in deaths from injuries and declines in deaths from poor nutrition and infections such as pneumonia and diarrheal diseases (2).

Trauma constitutes a significant cause of death and disability globally. About 95%, of the 5.8 million deaths each year occur in low-and-middle-income countries (LMICs) (3–6). Almost 1

million of these deaths are children. The World Health Organization (WHO) reports that the top five etiologies for unintentional injuries are road traffic accidents (RTAs), falls, burns, drowning and poisoning (3–6) (**Figure 1**). An alarming number of children are also injured or killed in war-zones, in disasters, and from child abuse (3, 7). Resource limitations in LMICs necessitate trauma prevention and thoughtful resource allocation and utilization in the care of injured children. This review details the evaluation and management of pediatric trauma in LMICs.

## EMERGENCY RESPONSE TO TRAUMA

### Pre-hospital Systems and Triage

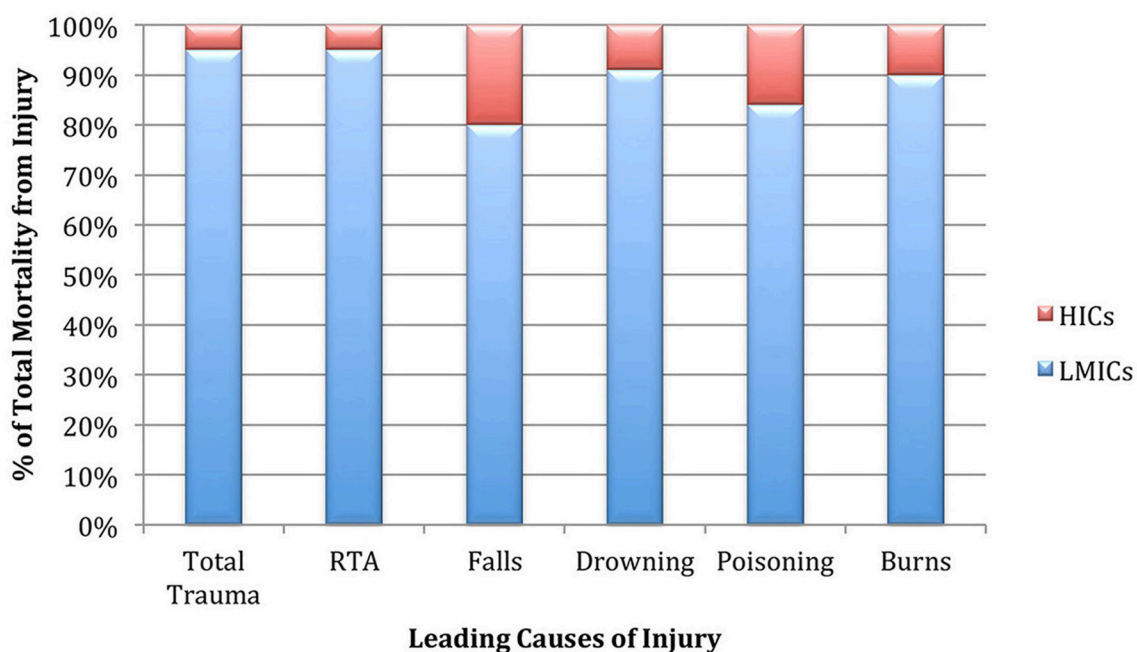
In high-income countries (HICs), caring for injured patients involves well-coordinated systems of triage, emergency medical care, and critical care. While such systems are currently unfeasible in many LMICs, it is essential that capabilities for managing acute onset, severe but reversible disease and injuries are available in any country around the world (8).

Wholesale, poorly planned imitations of HIC-type pre-hospital systems in LMICs often result in expensive, ineffective systems (9). There are, alternatively, low-cost interventions, for example, first responder training programs in Uganda and Mexico. These have resulted in excellent outcomes for relatively low costs (9). In LMICs, successful systems of pre-hospital trauma care take into careful consideration local financial resources and capitalize on them and also are broadly acceptable in the local societal context (9). Initiatives to improve or

implement pre-hospital or trauma systems in LMICs must recognize domestic resource constraints to minimize financial strain and improve efficiencies in the distribution of these resources (10). Emergency care depends on recognition of severe injury or illness and timely intervention. It involves the ability to quickly obtain care, rapid and appropriate referrals and the safe transportation of patients (11). The absence of a formal triage system in many hospitals in LMICs often leads to potentially life-threatening delays in obtaining needed care for patients who are severely injured or critically ill (12). The WHO, to bridge this gap in pre-hospital care that is present in many LMICs, recommends the establishment of first-responder programs to train laypeople as the first step toward building pre-hospital systems in LMICs (13). There are examples of such programs that have successfully used local resources to educate laypersons with little formal education (14). Effective triage and emergency care have also been described in some LMICs. The South African Triage Scale (SATS) for children is one such tool. It is used to prioritize children requiring emergency treatment. By employing a triage early warning score in combination with clinical signs and symptoms, the SATS helps to identify acute illness earlier, improves emergency department patient flow and allows better stewardship of hospital resources (15).

### Emergency Department Management

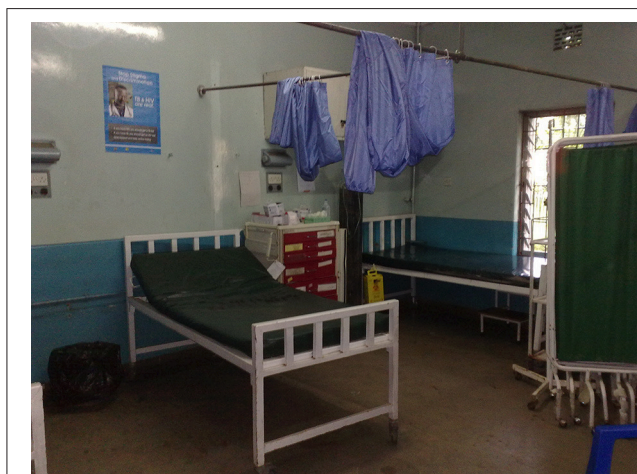
Inadequate staffing levels coupled with huge patient loads lead to delays in assessment and treatment in many hospitals in LMICs (16). While most hospitals have a dedicated emergency or casualty department, few have emergency medicine-trained



**FIGURE 1** | Illustration of the burden of trauma-related mortality borne by LMICs in comparison to HICs.

specialists. Even more rare are dedicated trauma centers. This means that healthcare providers with no specialized training in the management of pediatric trauma provide the majority of pediatric trauma care. This has a significantly negative impact on outcomes, which are dependent more on the speed and appropriateness of the medical care received than how severe of an injury was sustained (17). There are significant differences even within the same LMICs with regards to available resources for emergency room care between public and private hospitals (Figure 2). Public hospitals, which usually have fewer resources, are often overwhelmed. A recent study of 7 EDs in Pakistan noted that on average, only about 17% of patients were appropriately triaged, and fewer than 25% had any vital signs documented (18). To improve patient flow in overcrowded EDs, a recent study employed LEAN methodologies in a teaching hospital in Ghana (19).

Like the previously noted SATS, the Emergency Triage, Assessment, and Treatment plus (ETAT+) training in LMICs has resulted in better prioritization of pediatric trauma cases in the ED (20). Improved outcomes have also been achieved in some institutions in LMICs that have developed protocols for trauma management (21–25). Comprehensive Advanced Life Support (CALS®) and Advanced Trauma Life Support (ATLS®) are two examples of guidelines for the management of trauma. Organizations such as the African Federation of Emergency Medicine (AFEM) and the WHO have also provided guidelines on the appropriate resources needed for the care of pediatric trauma patients which are adjustable based on local resources (13, 22–25). Given the expense associated with maintenance of CALS and ATLS training, locally developed standardized trauma protocols have been found to be effective in achieving increased use of timely appropriate interventions for trauma patients and associated with decreased mortality rates particularly in patients with severe traumatic brain injuries (26).



**FIGURE 2 |** Example of an Emergency Room in a public hospital in a LMIC. Courtesy Benjamin Wachira, MD Aga Khan University Hospital, Nairobi Kenya.

## Surgical Management

Surgical management is the cornerstone of trauma care. In HICs the ready availability of multispecialty surgical teams as key members of the trauma management team facilitates timely surgical intervention when needed and the improved outcomes that this translates to. Given the lack of even basic surgical services in many LMICs, the surgeon-led trauma team and related resources remain a dream in most low-resource areas of the world. Globally, an estimated 2 billion people lack access to even the most basic surgical care (5). A recent study by Higashi et al. found that 1 million deaths and the loss of 52.3 million DALYs could have been averted in all LMICs if a basic menu of surgical services were made universally available (27). These services included basic resuscitation, advanced life support including the provision of surgical airways, peripheral venous access, laceration, and wound management, needle decompression and chest tube placement, fracture reduction, escharotomy and fasciotomy, skin grafting and trauma-related laparotomies (27). Governments in LMICs in conjunction with international partners have a significant role to play. Many essential physical resources, including equipment and supplies, are low cost and can be better supplied through improved planning and logistics (5). Enhanced durability, lower purchasing and operating costs as well as increased capabilities for local manufacture, maintenance and repair could enhance the availability of more expensive equipment like x-ray machines and ventilators (5). The poorest LMICs will require international assistance for the initial purchase of basic essential equipment and supplies (5). In the interim, surgical services in some LMICs, particularly during crisis situations, have been provided by non-governmental organizations (NGOs) (5). This assistance has varied from short-term mission trips by groups like Operation Smile to mobile, self-contained surgical platforms provided by Médecins Sans Frontières that remain in-country for months to years (5). There are also examples of more permanent specialty surgical hospitals established by NGOs in-country (5).

Trauma teams adapted to local conditions and resources in each LMIC should be developed. This will also require financial commitments to facilitate training and equipment purchases (28). Tele-simulation is another option for teaching and developing pediatric trauma resuscitation skills to healthcare providers in LMICs (25). An excellent resource for online learning and simulation is OPEN Pediatrics, an online community of clinicians that share best practices from all around the world (29). Incorporation of trauma management training into the undergraduate medical school curriculum will help ensure on-going widespread dissemination of the skills required to manage pediatric trauma.

## ADDRESSING SPECIFIC CAUSES OF PEDIATRIC INJURY

### Road Traffic Injuries

Each year there are over 1 million deaths associated with RTAs and an estimated 20–50 million non-fatal road traffic injuries

(RTIs) around the world (30). These RTAs result in the deaths of 186,300 children (ages 0–17 years) (31). Boys are twice as likely to be killed in RTAs as girls. LMICs account for approximately 95% of all children killed by RTAs, with the brunt of this burden borne by countries in Sub-Saharan Africa. Over 35% of global child deaths from RTAs are in Sub-Saharan Africa (31). To address this significant problem, several steps should be taken. These include building road safety management capacity, improved infrastructure, and enhanced vehicle safety. Also, improved road user behaviors with enforcement of speed limits, seat belt and laws prohibiting driving under the influence of alcohol could also make an impact (30, 31). Improved pre-hospital, hospital and rehabilitation systems would help reduce the mortality and morbidity associated with RTIs (31).

## Falls

Over 400,000 fatal falls occur each year globally. This makes them the second-leading cause of unintentional injury-related deaths after RTAs. More than 80% of fall-related fatalities occur LMICs (32). While not all fall injuries are fatal, every year more than 37 million fall-related injuries are severe enough to require medical attention. They account for over 17 million DALYs (32). Children living in countries with poor infrastructure and unsafe housing conditions are especially at risk for injuries from falls (3). Other fall risk factors include male sex and age. In LMICs infants have significantly higher rates of fall-related injuries than older children (5). Efforts to prevent falls include developing and promoting local manufacture of inexpensive measures to prevent falls such as window guards, building regulations and enforcement that prevent unsafe housing, access to safe playgrounds, and better supervision of children (5).

## Drowning

According to the WHO, worldwide there are 370,000 deaths from drowning making it the 3rd leading cause of unintentional injury-related mortality. Ninety-one percent of these deaths occur in LMICs (33). Children at the greatest risk of drowning are unsupervised boys in rural areas with little formal swimming instruction. Strategies to prevent drowning include placing barriers around bodies of water, covering wells, increased supervision, providing formal swimming lessons, and increasing community awareness about the risks of drowning (33, 34).

Comprehensive boating regulations and enforcement, improved signage including designation of dangerous water bodies, enhanced water rescue and resuscitation, water safety requirements including the use of personal flotation devices and improved supervision of swimming areas used for recreation are also important (34).

## Poisoning

Poisoning is a leading cause of morbidity and mortality globally. There are multiple causes of poisoning ranging from pesticides and industrial chemicals to lead and mercury poisoning. LMICs bear the larger part of the burden with regards to poisoning. According to WHO data, in 2012, over 190,000 people died worldwide from unintentional poisoning. Of these deaths, 84%

occurred in LMICs (35). Unintentional poisoning also resulted in the loss of over 10.7 million years of DALYs (35).

Poverty, lack of education, poor quality controls and absent legislation regarding certain products are some of the challenges that exacerbate this problem. Suicide from intentional poisoning point to the significant challenge of mental illness in LMICs and the inadequate resources available to combat this problem (35, 36). Nearly a million people die each year as a result of suicide, and chemicals account for a significant number of these deaths. Deliberate ingestion of pesticides causes approximately 370,000 deaths each year and self-poisoning is the most common method of suicide attempt in youth in LMICs (35, 36).

## EVALUATION AND MANAGEMENT OF SPECIFIC SYSTEM-BASED INJURIES

### Traumatic Brain Injuries

Traumatic brain injuries (TBIs) constitute a significant public health problem and a leading cause of death and disability worldwide (37, 38). They affect over 3 million children annually, impacting every population and demographic group (38). RTAs are the leading cause of TBIs worldwide followed by falls (38). The vast majority of TBIs occur in LMICs where inadequate pre-hospital and hospital-based care and poor rehabilitation facilities result in unsatisfactory outcomes (37, 39). The mortality rate for TBI patients in LMICs is twice that in HICs (40) with most of these deaths being of patients with severe TBI (40).

There are recently published guidelines for the management of severe traumatic brain injury in infants and children (41). However, the dearth of resources in LMICs means that the application of these guidelines is variable (37). Given the limited neurosurgical and neurocritical care capacity in most LMICs, consideration should be given to regionalization to optimize neurosurgical resources. Resource-adapted courses similar to the Advanced Life Support in Brain Injury (ALSBI) course may lead to broader dissemination of the knowledge needed to improve outcomes from pre-hospital to rehabilitation (42).

Most TBIs in children are mild with Glasgow Coma Scale scores of  $\geq 13$ . These children usually have no significant findings on radiographic evaluation (38). In situations where the injuries are more severe, the most common findings are skull fractures, brain parenchymal hemorrhages, and contusions (38). Unfortunately, these patients have poorer outcomes particularly in LMICs where neurosurgical intervention is often unavailable (38).

### Management of TBI

The goal of TBI management is to treat the primary injury, when indicated, including the evacuation of subdural and extradural hematomas and repairing significant skull fractures. Treatment is aimed at preventing any secondary insults to the brain through improvements in cerebral perfusion and provision of adequate oxygen (41, 43). To achieve this, placement of an advanced airway and mechanical ventilation may be required. The capacity to do this is absent in many LMIC settings where even provision of supplemental oxygen might be difficult. To maintain cerebral perfusion, patients often need intravenous fluids and sometimes



might require initiation of vasopressor agents. In patients with a severe TBI defined as a GCS  $\leq 8$ , the optimal evaluation would ideally include a head computed tomography (CT) to visualize any skull fractures and intracranial pathology (44, 45). In many LMICs, CT scanners are often not available or are out of the financial reach of most of the general population. In such situations, there may be some utility to skull x-rays which can at least identify fractures but do not reveal intracranial injuries (45, 46). In situations where clinical examination or, when available, intracranial pressure monitoring, reveals increased intracranial pressure and evidence for cerebral edema, hyperosmolar therapy is initiated (41, 43). The hyperosmolar therapy used in LMICs is most often mannitol although in some countries hypertonic saline is also used (41, 43). Ventriculostomy catheters to monitor ICP are usually indicated when the GCS  $\leq 8$ . In many resource-limited areas, the capability to do this is frequently absent. Ultrasonographic optic nerve sheath diameter measurement can be used to detect elevated ICP, although in most low-resource settings the equipment and expertise to perform this evaluation are lacking (47). Nonetheless, ultrasound is available in many hospitals thus making this training possible and potentially very valuable. The BESTTRIP study offers an example of how to manage patients when a ventriculostomy is not available (48). This study revealed no substantial difference in outcome between patients with invasive monitoring of ICP and those evaluated with clinical exams and repeat CT scans (48). Unfortunately, this would be difficult to replicate in most LMICs. In HICs the ready availability of neurosurgical expertise means that any required surgical interventions such as evacuation of subdural and extradural hematomas and decompressive craniectomy for ICP elevation unresponsive to medical therapy are easily accomplished. In LMICs this is significantly more difficult to achieve. Other aspects of care that could be accomplished even in low resource settings include elevation of head-of-bed, maintenance of euthermia, provision of adequate pain control and sedation, provision of adequate nutrition and seizure prophylaxis and control (40, 41, 43).

## Abdominal Injuries

Abdominal injuries (AI) are associated with a significantly increased risk of death and disability especially when other injuries and in particular TBI are present (49). The majority of AI result from motor vehicle-related crashes and falls (49, 50). Clinical signs and symptoms concerning for AI include abdominal tenderness and distention, absent bowel sounds and peritoneal signs. The presence of the latter may indicate a need for surgical exploration (49, 51). In children who present with the classic abdominal wall bruising consistent with a seat-belt injury, a high index of suspicion for bowel, kidney, and vertebral injuries is required (50). Splenic and hepatic injuries are the most frequently noted AI's. A system of classification established by the American Association for the Surgery of Trauma (AAST) for these visceral injuries helps guide prognosis and management (52). Bowel injuries are found in approximately 1–5% of blunt abdominal injuries (49). Most commonly injured is the jejunum, which accounts for about 30% of all hollow-viscous injuries.

The second most commonly injured part of the bowel is the duodenum (49).

## Management of Abdominal Injuries

Initial management of an AI involves ensuring a patent airway, adequate oxygenation, and IV fluid resuscitation if indicated (49). Ongoing evaluations including of vital signs, neurologic and abdominal exams and urine output are important (49). In HICs, initial imaging after an AI involves a Focused Assessment with Sonography for Trauma (FAST) evaluation (49). This helps to identify intraperitoneal blood or fluid from a visceral injury (49). However, FAST exams potentially miss about a third of visceral injuries in children (50). A potential impediment in LMICs is that ultrasound machines are not always available and expertise in their use is variable. CT scans are standard in the evaluation of abdominal trauma in HICs but less likely to be available in LMICs (51). Ultrasonography is, however, despite the limitations noted, more readily available and additional training in ultrasound use is invaluable to clinicians in these settings. In HICs, over 90% of blunt AIs are managed non-operatively (49). However, non-operative management has been made possible by advanced imaging techniques that are limited in LMICs which itself has led to higher rates of surgical exploration (50). Otherwise, clinicians must rely on their physical diagnostic skills in combination with peritoneal taps. If urgent surgical intervention is needed in these patients, then transfer to centers offering a higher level of surgical and critical care should be done expeditiously as possible once resuscitation has begun.

## Thoracic Injuries

Thoracic injuries (TIs) constitute an ongoing challenge to the trauma or general surgeon practicing in LMICs and have associated high morbidity and mortality (53). The majority of these are blunt thoracic injuries and most often results from RTAs. Penetrating trauma is mainly related to gunshot wounds and other projectiles (54). Young children have more compliant, cartilaginous chest walls and therefore even significant force injuries are less likely to result in fractures. However, there is a greater transmission of these forces to the child's internal organs and these patients will still have associated pulmonary and cardiac contusions, pneumothoraces, hemothoraces and mediastinal injuries (54, 55). Given the disproportionately smaller size of the thorax in comparison to the cranium and abdomen, it is imperative to assess the entire patient when thoracic trauma is present to rule out TBIs and abdominal injuries (56–59).

## Management of Thoracic Injuries

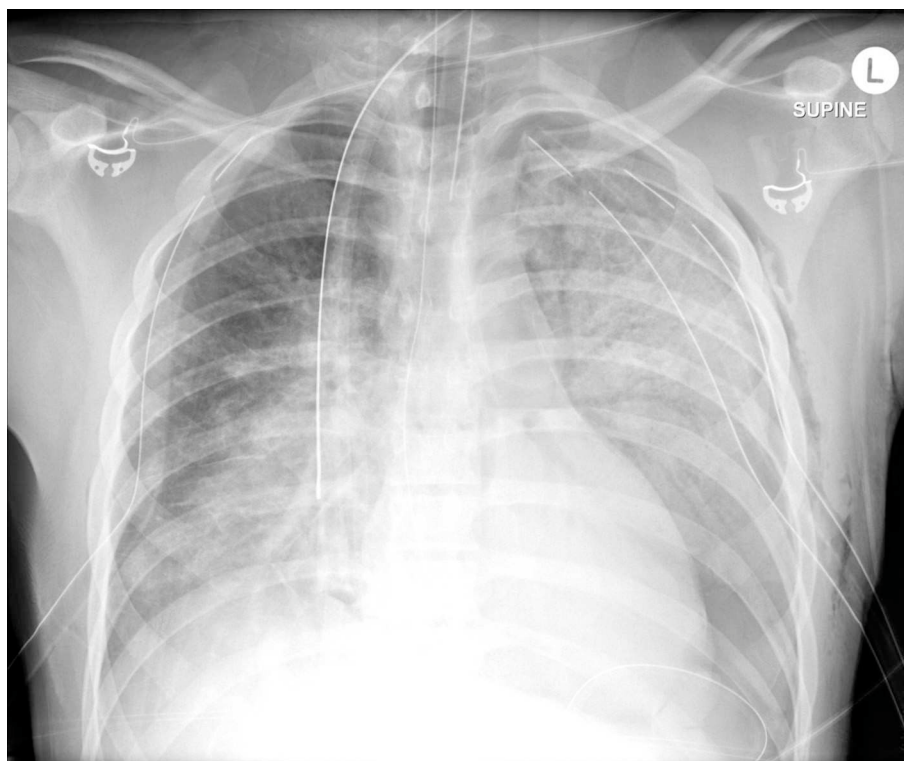
Evaluation of thoracic injuries begins with primary and secondary surveys. In addition to the FAST exam, a basic x-ray of the chest is required. CT scan imaging and other advanced imaging techniques can be useful adjuncts but are frequently not readily available in many LMICs. Again, where available the value and use of ultrasound should be capitalized on, and the FAST exam taught. They are also a strain on resources for both patients and healthcare facilities and increase radiation exposure to children (57, 60). Initial resuscitation should follow

the usual trauma protocol attention to airway, breathing, and circulation (ABCs) while ensuring C-spine immobilization for polytrauma patients. Clinical presentation of thoracic injuries is dependent on the type of injury. An underlying pulmonary contusion is usually more prognostic than the chest wall injury itself (56). (**Figure 3**) Rib fractures are usually very painful because of the inability to immobilize them. The extent of the multisystem injury is directly proportional to the number of rib fractures. Scapular, clavicular and rib 1-3 fractures are linked to cardiovascular injury and indicate a high-energy mechanism (61). A high index of suspicion for traumatic asphyxia for patients who present with tachypnea and facial petechiae is important (56). Children are more likely to develop hypoxia than adults due to their lower functional residual capacity and relatively higher tissue oxygen consumption (54). Additionally, their more mobile mediastinum allows for the faster conversion of a simple pneumothorax to a tension pneumothorax (54). Proper airway management takes priority in patients with tracheobronchial injuries. Other more rare injuries include esophageal injuries, traumatic diaphragmatic rupture, and cardiac injuries. A plain chest x-ray can diagnose diaphragmatic injury with herniated viscera, and esophageal tears commonly with left sided pleural effusions (54). Algorithms have been developed for these that can be adapted to the LMIC setting (55). Blunt cardiac injury (BCI) is often under-diagnosed due to a lack of diagnostic tools including troponin laboratory screening, electrocardiography, and echocardiography, as well as a low index of suspicion (62, 63).

Persistent tachycardia or other arrhythmia in the face of thoracic trauma should prompt an evaluation for BCI. In HIC, emergency thoracotomy has been described and has been shown to be lifesaving for children with penetrating cardiac injuries (64, 65). Indications for ER thoracotomy are well defined and include massive hemothorax, initial chest tube output >20 mls/kg, and pericardial effusion on ultrasound in the setting of shock (66). In many LMIC settings, the absence of equipment and trained staff means that ER thoracotomy is not currently feasible. However, temporizing measures such as pericardiocentesis or pericardial catheter placement may be possible. Whenever possible, early referral to a better-equipped trauma unit should be made after initial stabilization.

## Orthopedic Injuries

Orthopedic injuries have a significant impact on DALYs in LMICs since those most commonly injured are typically younger, potentially more productive persons (2, 3, 67). The causes of these injuries include falls, RTAs, workplace accidents, child abuse, and injuries sustained in conflicts or other disasters (1–3). Fractures in pediatric patients are distinct from those in adult patients. Young children have a growth plate, and physeal fractures represent ~18% of fractures (68). Four distinct types of fractures seen in children include plastic deformity, torus fractures, greenstick fractures, and physeal fractures (68). Thoughtful evaluation with attention to the child's neurovascular status is key. Radiologic evaluation of the fracture when radiographic



**FIGURE 3 |** Chest x-ray showing bilateral pulmonary contusions and pneumothoraxes requiring chest tube placement.

equipment is available requires at least two planes, including the joint above and below, if necessary (68) (**Figure 4**).

## Management of Orthopedic Injuries in LMICs

Management of these fractures begins with stabilization of the fractured extremity. Consideration may be given to pelvic binding, if indicated for hemodynamic stability, and should be performed as part of the circulation assessment in the primary survey. Any open wounds should be irrigated with large amounts of sterilized water, and antibiotic therapy started if indicated, in addition to tetanus prophylaxis (69, 70). Adequate analgesia is important in children. This can vary from acetaminophen and other non-steroidal anti-inflammatory drugs for mild pain to opioids for more severe pain.

Management is conservative in closed uncomplicated fractures. External fixation and wound care for open fractures, and open reduction and internal fixation in selected cases may be required. In HICs, interdisciplinary management decisions are made by orthopedic surgeons in collaboration with plastic, vascular, trauma, and general surgeons as well as physiotherapists and occupational therapists (71). However, in many LMICs, it is difficult for most patients to access this interdisciplinary care.

A large burden of care in these countries is borne by general surgeons as there is not a large pool of orthopedic surgeons and even fewer vascular or plastic surgeons. The surgeon is faced with patients whose initial care is not by trained first responders (72). Sometimes the surgeon may care for patients who elected to initially be managed by “traditional bone healers.” There is also delay in obtaining consent from families for any procedures other than initial stabilization and wound care (73). There is, therefore, a higher rate of limb amputations from orthopedic

injuries. This increases costs and length of stay due to additional care needs and rehabilitation (73). The surgical care of orthopedic injuries is increasingly being recognized as a more cost-effective modality of treatment than more conservative methods in many LMICs. Previously, surgeons improvised with old-fashioned implants and equipment donated to their hospitals from HICs with varying results. More recently, there are centers in LMICs that have access to appropriate implants and training through programs like SIGN Fracture Care International. This has resulted in fracture treatments and outcomes that are comparable to those in HICs (74). One impediment to appropriate orthopedic care is the fact that most orthopedic surgeons are located in urban areas with practices that are out of the reach of most of the general population. Governmental policies and financial investments are needed to facilitate the training of more surgeons in all specialties, and making these surgeons available and accessible at most public access hospitals. General surgeons in LMICs should also receive more training in the management of orthopedic injuries. Consideration should also be given to providing additional training in basic orthopedic stabilization, to nurses and medical officers who typically are the initial healthcare providers for injured children in most public access facilities in LMICs.

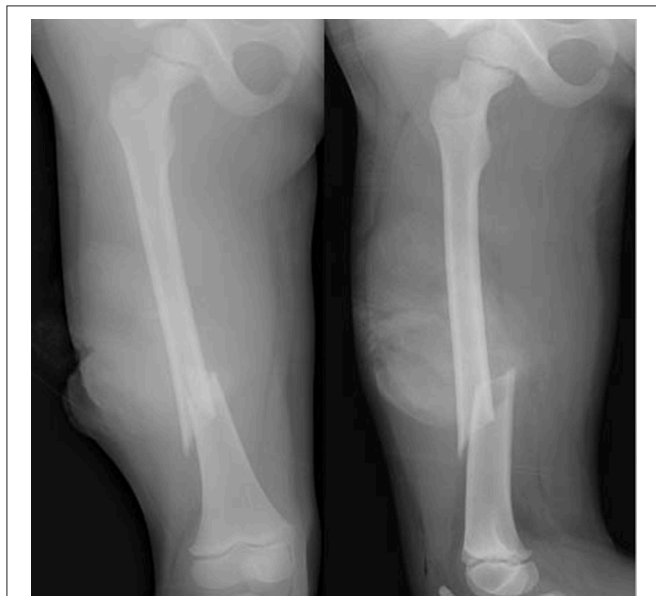
## Burn Injuries

Burns, especially those that leave a child permanently disfigured or disabled, represent the most catastrophic events to happen to a child (75). Globally, over 11 million people are estimated to suffer burn injuries leading to over 265,000 deaths annually (75, 76). As with other traumatic injuries, the vast majority of burn injuries and deaths occur in LMICs (76, 77). Children <5 years of age are usually at the greatest risk for burn injuries, with an estimated 100,000 admissions annually. This number is likely a significant underestimation (78). In HICs, improvements in burn management have led to decreases in morbidity and mortality with most burn centers in HICs reporting an LA50 (lethal total body burn surface area [TBSA] for 50% of patients) >90% TBSA (79). These improvements have not universally been seen in LMICs where there is large variability in outcomes, with most centers reporting an aggregate LA50 <40% and many reporting 100% mortality with burns >40% TBSA (80). If LMIC center outcomes matched those in the best performing HIC centers, over 34,000 additional lives could be saved worldwide (81). These poor outcomes are multifactorial but are most often related to delayed presentation, lack of trained personnel and a paucity of burn centers (80). One regional referral center in Tanzania found that almost half of burns arrived >72 h after injury (82).

## Management of Burns in LMICs

Management of burn injuries includes the early recognition of major burns (>10–20% partial thickness and full thickness burns), evaluation and management of airway involvement, provision of oxygen and recognition of carbon monoxide and cyanide poisoning, and fluid resuscitation for management of burn shock.

A survey of burn resuscitation in the African continent revealed that parenteral fluid resuscitation protocols using lactated Ringers solution based upon the Parkland formula are



**FIGURE 4** | X-ray showing right femur fracture.

the most commonly utilized (83). There was also an increased utilization of enteral hydration in the form of oral rehydration solution (ORS), along with a focus on clinical endpoints such as urine output, rather than invasive monitoring in comparison with higher resourced counterparts. ORS is a viable option for burn resuscitation for burns <20% TBSA (84). Patients with significant burns have better outcomes when treated at centers with expertise in burn care, and therefore, after stabilization immediate transfer whenever possible is encouraged. These centers, employ typical burn therapies such as protocolized resuscitation, topical antibiotics, skin grafting and have a mean daily cost per 1% total burn surface per patient as low as \$2.65 (85, 86). Airway management and management of inhalation injuries can be challenging in many LMICs where access to intensive care resources like mechanical ventilation and bronchoscopy is limited. Carbon monoxide and cyanide poisoning can be managed with administration of supplemental oxygen (84). Burn wound care is particularly challenging in low resource areas where adequate access to clean water is often problematic. Daily cleaning with Dakin's solution helps to ensure sterility of the water and is bactericidal against most bacteria in the wound (84). The burn wounds are then dressed with antibiotic incorporated dressings (84). The antimicrobial agents used include silver sulfadiazine, mafenide acetate, silver nitrate, and even medical grade honey (84). The need for adequate analgesia cannot be overstated. Opioid analgesia for pain control and ketamine to facilitate wound care are key adjuncts (84). Fevers are common in burn patients but there is no evidence that supports the routine use of prophylactic parenteral antibiotics in the absence of clear evidence of infection (87). In addition, burn centers are more likely to employ contracture avoidance techniques like splinting and physiotherapy to prevent further morbidity.

However, the importance of early recognition, resuscitation initiation, maintenance of euthermia, and basic wound dressings can and should be initiated at the first point of contact. Early referral to tertiary burn centers in LMICs whenever possible is key. Burn prevention and education continue to lead the way in reducing the morbidity and mortality. The majority of childhood burns occur in the home, and therefore public health interventions that target changing the type of fuel used for cooking/lighting, location of these fires, and storage of the fuel have preliminarily resulted in a reduction of burns (88).

## Disasters: Pediatric Implications

While disasters are often unpredictable, they are neither a fixed singular event nor are they all sudden onset events (89–91). What differentiates them is the scale and magnitude of the impact on families and communities (90, 92). Disasters are increasing in frequency intensity including climate change and environmental degradation related disasters (93). How well families, communities, and government systems prepare for and respond to disasters, determines response and recovery (94). Allocation of technical, financial, and personnel resources during a disaster life cycle (mitigation, preparedness, response, and recovery) is critically important to minimizing mortality and morbidity in extreme events. LMICs are often resource-strapped from poor governance or narrow resource options, and this

results in minimal support for disaster cycle provision. Socially vulnerable populations are the most affected by the failure to support disaster cycle planning and implementation (95–97). Children below age 18 and in particular those with disabilities are an especially vulnerable population during and after disasters (95–100).

While the Convention on the Rights of the Child supported by majority countries commit to the right of protecting children from unsafe environments, injury, and violence, the reality in LMICs and disasters is quite different than envisaged (98, 101). During and after disasters children's needs and protections are more an afterthought, despite the reality that children experience disasters uniquely (102). Children are more susceptible to disaster trauma because of their dependence on adults for information, decision-making, transportation, protection from abuse, and provision of mental support. The assumption that adults promptly inform and make decisions for children in disasters overlooks the reality that children spend substantial amounts of time alone or with their peers or are homeless children living without adults (103). The number of children affected by disasters is projected to triple in coming decades due to factors such as climate change, which UNICEF refers to as a "threat multiplier that exacerbates inequality of children" (93).

In disaster situations, adults, family members, and caregivers are the first responders to children. This is especially true in LMICs where lag time between disaster impact and response by official responders is substantial or non-existent. Additionally, in complex emergencies population displacement, collapse of health systems and inaccessibility may result in an even larger response lag. Consequently, child-focused training and exercise drills are imperative for mitigating disaster-related injuries or aggravating existing injuries.

## Disaster Preparation

Integrating pediatric disaster planning into regular child injury prevention programs is also beneficial to families and communities. Disaster planning learned at school, and other institutions by children benefit families and communities, e.g., who do not speak the dominant disaster planning language (99, 103).

In complex emergencies, mortality rates for unaccompanied minors at refugee camps or shelters increase. Immediate triage and trauma care during intake remain critically important for saving impacted children's lives. Post evacuation to shelters, reunification protocols to protect children from the high risk of abuse, victimization, and trafficking minimizes additional trauma (104). Expeditious reunification (102) to legal guardians is critically important for the commencement of the child's recovery process. Place attachment is a critical component in the recovery processes of children. If evacuation is necessary, or stays in locations other than their places of attachment, creating new place ties bolsters recovery and resilience (95, 98, 105).

## War and Its Effects on Children

Armed conflicts have been and remain part of the very fabric of human history. All around the world wars between nations, civil war, acts of terrorism and other forms of armed conflict persist.



The United Nations Children's Fund (UNICEF) estimates that 10% of the world's children (almost 250 million) live in regions affected by war and other armed conflicts (106). The majority of these conflicts are in LMICs (106). Of major concern is the fact that modern warfare is increasingly having a significant impact on the lives of children worldwide (106, 107). The violence is often indiscriminate. There is frequently no defined battlefield, and in most modern conflicts, civilians are directly targeted leading to a marked increase in pediatric injuries and deaths (107). Millions of children have been disabled or killed by this indiscriminate use of force (107). Notably, from 2005 to 2015 the average number of 0–19 disability-adjusted life years (DALYs) due to war and legal intervention increased by 582% (3). The conflicts in Iraq and Afghanistan and in particular the ongoing conflict in Syria, paint a stark portrait of the effects of war on children (**Figure 5**) (7, 108). Also quite troubling in a number of conflicts, has been the use of children as child soldiers and suicide bombers (106, 107). In addition to physical injuries, psychological wounds including post-traumatic stress disorder and other emotional and behavioral problems result from children's exposure to war (108). Children are also impacted by the disruption to the access to care caused by the conflict and the disruption that additionally results when they become refugees (106). According to the United Nations High Commission for Refugees (UNHCR), by 2015 there were over 65 million people displaced from their homes as they attempted to escape armed conflicts in their countries. About 50% of these are children under the age of 18 (106). It is imperative that children and other civilian non-combatants are protected and that governments and their international partner

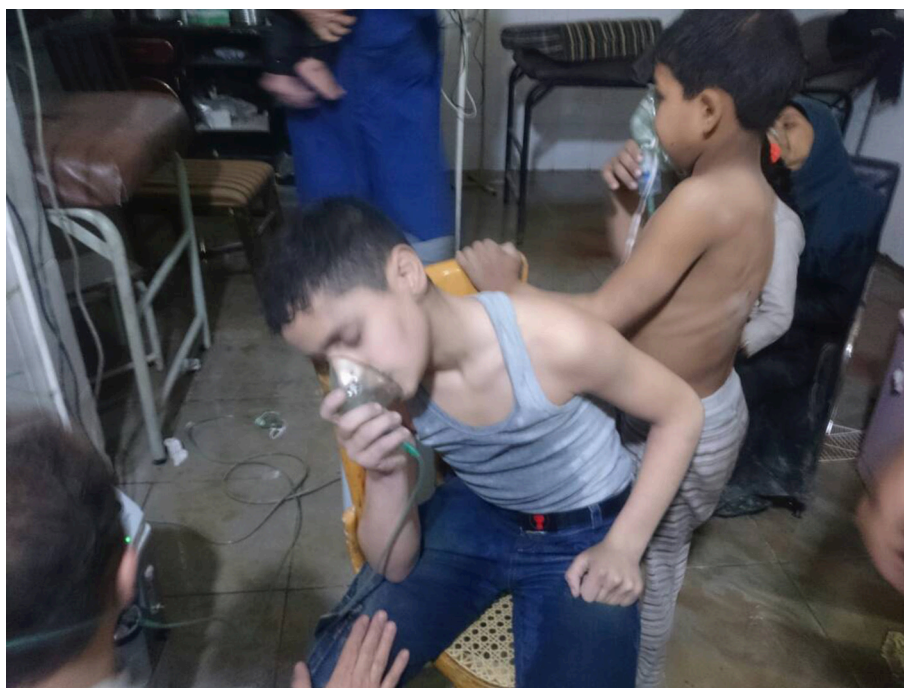
organizations make every effort to prevent armed conflicts and help end existing conflicts quickly. It is also important that the rights of children are recognized and that those who target children or use them deliberately in armed conflict are brought to justice.

## Child Abuse

Child maltreatment occurs in all human communities and across all financial, ethnic, and religious boundaries (109). A recent systematic review of the literature by Hillis et al. found that the actual prevalence of violence against children is higher in LMICs than HICs (59% vs. 44%) (110). This same article reports a minimum of 64, 50, and 34% of children (2–17 yo) in Asia, Africa, and Latin America experienced past-year violence respectively (110). Globally, in 2014 at least 1 billion children were exposed to violence (110). The WHO Global Status report stated that in selected African countries one in three girls are victims of childhood sexual abuse and up to 76% of childhood physical abuse in both boys and girls (111).

A group of children at particularly high risk of abuse in LMICs, are those with disabilities. These children are often socially excluded and prevented from attending schools and are often unable to communicate the violence against them (112).

According to the WHO report, the knowledge of the true extent of the problem is hindered by gaps in knowledge with much of the data coming from high and middle-income countries (111). According to the WHO, a meta-analysis of global data finds self-reported child sexual abuse 30 times higher and physical abuse 75 times higher than official reports would suggest (109).



**FIGURE 5 |** Children being treated after suspected chemical weapon attack in Syria. Image courtesy of Muhammad Ghbeis, Boston Children's Hospital.

## Recognizing Child Abuse

Although the prevalence and type of abuse may vary by location, the signs and symptoms are similar. We must consider abuse in all children presenting to us with symptoms consistent with abuse such as the triad of retinal hemorrhages, subdural hemorrhage, and encephalopathy or evidence of diffuse axonal injury (113). It is important to note that abusive head trauma can sometimes present with much more subtle findings such as vomiting (113). Additionally, child abuse must be considered in children presenting with features not consistent with the history provided, such as rib fractures from wrestling with another child, or bruises on the ears, under the toes, or in the form of a handprint (111). A helpful mnemonic for assessing which bruises are more concerning is the “TEN 4” rule (Torso, Ear, Neck and 4 (<4 yo or any bruising <4 mo) (113). Worrisome fractures include posterior or lateral rib fractures, “bucket handle” fractures and fractures such as sternal, spine, and scapula (113) unless the child has been in a major motor vehicle or similar accident. (**Figure 6**) In children, with elevated liver function tests, pancreatic enzymes or otherwise unexplained hematuria abuse with abdominal trauma should be considered (113). Other signs and symptoms that should trigger a careful exam include unusual scars in the form of hand and belt prints, cigarette burns, burns in an unusual distribution, or swelling that is unexplainable such as swollen painful thigh in a young infant (114). (**Figure 7**) Each of the seven strategies in the INSPIRE strategies, elucidated below are important in prevention as well as specific treatment for the injuries sustained (109, 113). It is also important to differentiate abuse from traditional treatment and practices such as tattooing, cupping and coining prevalent in many cultures (115).

While viewed by many as abusive, female circumcision continues to occur (116). In cultures where this is considered the normal practice, widespread education and laws to protect girls against this practice are needed (116). Another challenging area of child maltreatment is the use of child labor. UNICEF estimates that as many as 246 million children are engaged in child labor with 70% working in hazardous conditions<sup>1</sup>. Child labor may expose children to physical and traumatic maltreatment whether they are involved in hawking wares on the streets, hired as domestic workers or working in factory production lines.

Sexual abuse is common in all cultures but as noted above can be a common form of abuse in LMICs especially in girls. Numerous studies highlight significant rates of unwanted sexual encounters in children. An article by Summer et al. notes rates from 11.3–21.5% depending on age range and country (117). It is important to remember that lack of physical evidence of sexual abuse does not equate to lack of sexual abuse. These children need appropriate counseling and treatment (114, 117).

Child soldiering is a terrible form of maltreatment of children and youth<sup>2</sup>. Children are exploited to achieve the nefarious ends of the abusers as they expose them to violence and rape. These children suffer from post-traumatic stress disorder (PTSD) made worse by the lack of supportive mental health services in many LMICs (118).



**FIGURE 6 |** Chest x-ray showing multiple rib fractures from child abuse. Fractures of ribs 3, 4, and 10 on the right and ribs 8, 9, and 10 on the left. Image courtesy of Nancy Harper, MD Masonic Children's Hospital, Minneapolis, MN and Sonja Eddleman, RN, Driscoll Children's Hospital, Corpus Christi, TX.

Cultures differ in their views about what is appropriate discipline. In some cultures, women and children may be viewed as the property of the husband and therefore virtually nothing constitutes abuse. Male abusers in these cultures are viewed as unquestionable authority figures. Changing norms and values as suggested by the INSPIRE strategies, is likely the most important measure to decrease this abuse. However, laws and their enforcement will also be imperative (109).

Education surrounding inappropriate corporal punishment is needed, as is guidance on the use of other appropriate methods of discipline both at home and in school. Guidelines about age-appropriate discipline are also needed (119).

## Prevention

Given the dearth of available resources, the role of injury prevention in LMICs is vitally important. There are significant human and financial implications for reducing the number of people injured and killed around the world. If injury prevention efforts and improvements in trauma care in LMICs led to injury mortality rates similar to those in HICs, 2 million fewer children would die worldwide (120). The WHO in its *World Report on Child Injury Prevention* (6) set recommendations for prevention of injuries around the world:

<sup>1</sup>[https://www.unicef.org/protection/files/child\\_labour.pdf](https://www.unicef.org/protection/files/child_labour.pdf)

<sup>2</sup><https://www.unicef.org/sowc96/2csoldrs.htm>



**FIGURE 7 |** Child with multiple bruises from a belt. Image courtesy of Nancy Harper, MD Masonic Children's Hospital, Minneapolis, MN and Sonja Eddleman, RN, Driscoll Children's Hospital, Corpus Christi, TX.

- (a) Integrating childhood injury into an all-inclusive approach to child health and development
- (b) Developing and implementing child-injury prevention policies and plans of action
- (c) Implementing specific actions to prevent and control child injuries
- (d) Strengthening of health systems to address childhood injuries
- (e) Enhancement of the quality and quantity of data for child-injury prevention
- (f) Defining research priorities
- (g) Increasing awareness of and target investments toward child-injury prevention

The recommendations are a foundation for injury prevention efforts. Injury prevention in children is best achieved by blending education, legislation, law enforcement, environmental modifications and the use of safer products and safety devices (117). Governments in LMICs are increasingly aware of the importance of injury prevention. In Vietnam, where motorbikes are the principal mode of transportation, legislation mandating helmet use by all riders and passengers on motorcycles has the potential to decrease morbidity and mortality in motorcycle-involved RTIs (121). There have also been significant impacts on reduction of injuries from RTIs made by the Road Safety in 10 Countries project (2). The SwimSafe Project which is being implemented in Thailand, Bangladesh, and Vietnam, has taught over 525,000 children how to swim (122). In Bangladesh, one of the largest drowning prevention projects undertaken in an LMIC, the Saving of Lives from Drowning (SoLiD) Project, aims to reduce childhood drowning (123). In addition, given the increasing numbers of children who are injured and

killed in armed conflicts, it is imperative that governments and international organizations such as the United Nations, make every effort to end these armed conflicts and minimize their impact on children.

## CONCLUSIONS

Trauma is a leading cause of morbidity and mortality globally. Children in LMICs bear the greatest burden of unintentional and intentional injury. LMICs often lack adequate resources for managing trauma. Following trauma care protocols and adapting treatment based on local resources is important. Emphasizing injury prevention, regionalizing care and developing centers of excellence through multispecialty collaboration within each country is vital to improving outcomes and lowering trauma-related morbidity and mortality globally. War is increasingly having a devastating effect on children. A commitment by governments in LMICs in collaboration with international health organizations as well as partners in HICs to provide adequate healthcare services to their populations will be a safeguard against the devastation of infectious diseases and will also lead to improved outcomes for injured children.

## AUTHOR CONTRIBUTIONS

AK: Substantial contributions to the conception or design of the work and the acquisition of background articles and topics to be covered; drafted work and revised it critically for important intellectual content; provided approval for publication; agreed to be accountable for all aspects of the work in ensuring



that questions related to accuracy or integrity of any part of work are appropriately investigated and resolved. SD, NM, and AA: Drafted work and added content critically for important intellectual content; provided approval for publication of content. SG, MM and DG: Drafted and revised the work and added content critically for important intellectual content;

provided approval for publication of the content. TS: Drafted work and revised it critically for important intellectual content; provided approval for publication; agreed to be accountable for all aspects of the work in ensuring that questions related to accuracy or integrity of any part of work are appropriately investigated and resolved.

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