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The Burden of Pediatric Critical Illness in Resource-Limited Settings

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The Burden of Pediatric Critical Illness in Resource-Limited Settings

by
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Dedication and Acknowledgments

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Research Advisor Statement

The published and submitted material presented in this dissertation represent large, international, collaborative global child health research led by Dr. Teresa Kortz (PhD candidate). She conceptualized the work; developed the study methodologies;

provided project administration and oversight; collected and curated the data; planned and contributed to the data analyses, validation, and visualization; participated in funding acquisition; provided resources to perform data collection, data analysis, and to publish; and she wrote the first manuscript drafts and was responsible for revising the drafts following other authors' review. In short, this work is comparable to a standard PhD dissertation and is an excellent representation of global health clinical research in the modern age.

Philip Rosenthal, MD

Epigraph

“Geography is destiny.”

— Abraham Verghese, Cutting for Stone

The Burden of Pediatric Critical Illness in Resource-Limited Settings

Teresa Kortz

Abstract

Children in resource-limited settings (RLS) bear a disproportionate burden of mortality; in 2019, 80% of global child deaths were in RLS. Most acute, life-threatening pediatric illnesses can be managed with basic critical care. However, it is unclear how best to deploy existing resources and select interventions for implementation in the absence of data on pediatric acute critical illness (P-ACI) and associated hospital mortality in RLS. This work aimed to estimate the proportion of children with P-ACI and to determine the common causes of pediatric hospital mortality in RLS hospitals.

We performed a systematic review and meta-analysis of observational studies from low- and middle-income countries (RLS proxy) to estimate pediatric cause-specific mortality using random-effects models and analyzed differences by region. We also conducted a point prevalence study of acutely ill or injured children seeking care at RLS hospitals and measured the proportion of children with P-ACI. We summarized site- and population-level data by sociodemographic index (SDI) and P-ACI status and tested for an association between SDI and P-ACI with logistic regression modelling.

The proportion of P-ACI was 6-29% and hospital mortality was 0-6%, depending on SDI and region, with the highest estimates from the lowest SDI category. P-ACI and mortality were most frequently associated with infectious diseases. A coordinated global effort is needed to increase high-quality critical care services in RLS hospitals to prevent hospital mortality and care for children with life-threatening conditions.

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List of Abbreviations

ACAN: Acute Care Action Network

AIDS: Acquired Immunodeficiency Syndrome

bCPAP: Bubble Continuous Positive Airway Pressure

CE: Central Europe, Eastern Europe, and Central Asia

CFR: Case Fatality Rate

CINAHL: Cumulative Index to Nursing and Allied Health Literature

DALY: Disability Adjusted Life Year

DFID: Department for International Development

ED: Emergency Department

ETAT: Emergency Triage, Assessment and Treatment

GBD: Global Burden of Disease

HDU: High-Dependency Unit

HIC: High-Income Countries

HIV: Human Immunodeficiency Virus

ICU: Intensive Care Unit

IMCI: Integrated Management of Childhood Illness

IMV: Invasive Mechanical Ventilation

IQR: Inter-Quartile Range

IVF: Intravenous Fluids

LA: Latin America and Caribbean

LIC: Low-Income Country

LILACS: Latin American and Caribbean Health Sciences Literature

LMIC: Low- and Middle-Income Country

LODS: Lambaréné Organ Dysfunction Score

LOS: Length of Stay

MDG: Millennium Development Goals

MIC: Middle-Income Country

NA: North Africa and Middle East

NGO: Non-Governmental Organization

NICU: Neonatal Intensive Care Unit

NIV: Non-invasive Ventilation

OR: Odds Ratio

P-ACI: Pediatric Acute Critical Illness

PALISI: Pediatric Acute Lung Injury and Sepsis Investigators Network

PARITY: Pediatric Acute Critical Illness Point Prevalence Study

PICU: Pediatric Intensive Care Unit

POPC: Pediatric Overall Performance Category

QALY: Quality Adjusted Life Year

REDCap: Research Electronic Data Capture

RLS: Resource-Limited Settings

RSV: Respiratory Syncytial Virus

SA: South Asia

SD: Standard Deviation

SDG: Sustainable Development Goals

SDI: Sociodemographic Index

SEA: SEA

SLA: Southern Latin America

SSA: Sub-Saharan Africa

UN: United Nations

UNICEF: United Nations Children's Fund

US: United States

USAID: United States Agency for International Development

USD: United States Dollar

WFPICCS: World Federation of Pediatric Intensive and Critical Care Societies

WHO: World Health Organization

Chapter 1: Introduction

Global Child Mortality

In 2019, 7.3 million children and adolescents died globally; however, there is a significant disparity in child mortality with 80% of these deaths occurring in low-income countries (LICs).[1] According to the most recent Global Burden of Disease (GBD) data, the top causes of global mortality for children under 5 years of age are neonatal conditions (e.g., neonatal preterm birth complications, neonatal encephalopathy due to birth asphyxia and trauma, congenital anomalies, neonatal sepsis) and infectious diseases (e.g., lower respiratory tract infections, diarrheal diseases); for older children and adolescents the top causes are infectious diseases (e.g., diarrheal disease) and trauma (e.g., unintentional injuries, transport-related).[1,2] The disparity in outcomes is most pronounced for deaths resulting from infection, such as sepsis,[3,4] pneumonia,[5] diarrheal disease,[1] and HIV/AIDS.[1]

In 2000, the United Nations Millennium Declaration was adopted by Member States to decrease poverty, hunger, infectious diseases, gender inequities, illiteracy, and environmental harm as outlined in the Millennium Development Goals (MDGs).[6] The MDGs are a set of 8 goals with detailed health targets and indicators to monitor progress from 1990 to 2015.[6] MDG 4 was dedicated to reducing child mortality, and Target 4.A specifically aimed to “reduce by two-thirds, between 1990 and 2015, the under-five mortality rate.” To reach this target, the World Health Organization (WHO) and the United Nations Children’s Fund (UNICEF) focused on primary and preventive care to improve breastfeeding, nutrition, hygiene, and vaccination.[7] With implementation

of these interventions, the world saw a significant decrease in childhood mortality driven by reductions in mortality from infectious diseases, nutritional deficits, and neonatal disorders. From 1990 to 2015, global child and adolescent mortality decreased from 14 to 7 million. Unfortunately, success was not universally achieved; countries with a lower Socio-Demographic Index (SDI)[8] carried 61% of the mortality burden in 1990, which increased to 80% in 2015, illustrating the disproportionate nature of health improvements.[1] Most deaths in 2015 occurred in South Asia (30% or 2.2 million children) and Western Sub-Saharan Africa (23% or 1.7 million children) as compared to 42,000 (0.6%) in High-Income North America.[1] Furthermore, when evaluating overall loss of health (mortality and disability) for children and adolescents, in LICs the primary cause was mortality, while it was disability in high-income countries (HICs).[1]

The MDGs were a monumental, global effort devoted to improving health; yet global child mortality remained unacceptably high (7 million in 2015) and inequitably distributed. Following the MDGs in 2015, the United Nations Sustainable Development Goals (SDGs) were adopted, a comprehensive, interconnected set of 17 goals with 169 targets to be achieved by 2030. SDG 3 most directly pertains to health, and target 3.2 aims to "end preventable deaths of newborns and children under 5 years of age, with all countries…[reducing] under-5 mortality to at least as low as 25 per 1,000 live births."[9] As of 2021 and compared to 2015, the global under-5 mortality rate fell by 12% and all-cause under-5 mortality decreased from 6 to 5 million.[10] In 2021, 54 of 200 (27%) countries were not on track to meet target 3.2; 37 of these countries needed to either more than double the current progress rate or reverse a worsening trend in child mortality to achieve SDG target 3.2 by 2030.[10] According to a recent United Nations

General Assembly on SDG progress, "[a]t the mid-way point on our way to 2030, the SDGs are in deep trouble… [and] the world's poorest and most vulnerable people are bearing the brunt of our collective failure."[11]

Resource-Limited Setting Context

"Resource limited settings" (RLS) are characterized by a lack of funds to cover health care costs, which results in: limited access to or availability of medication, equipment, supplies, devices; less-developed infrastructure; and/or fewer or less-trained personnel.[12] RLS are a subjective and descriptive concept, and, while often used interchangeably with low- and middle-income country (LMIC), these terms are not equivalent (**Table 1.1**). LMICs are countries in the lowest quintiles with respect to the gross domestic product (World Bank) or SDI, a composite indicator of income, education, and fertility that was developed by the Institute for Health Metrics.[8] What is considered an LMIC varies slightly between World Bank and SDI criteria.

Resource availability can be described and quantified in various ways; in general LMICs can be broadly characterized as having limited resources, less access to healthcare, and worse health outcomes compared to middle-income countries (MICs) and HICs.[13,14] SDI is considered to be a better overall metric of development and correlates strongly with health outcomes; therefore, in this dissertation, SDI criteria are used to determine LMIC status.[1,4,5] As of 2021, LMICs were estimated to have 90% of world's population of children and adolescents <18 years of age.[15] While LMIC settings are often resource-constrained, settings in MICs and HICs can also be resource-constrained and these resource limitations can negatively affect health outcomes.[16,17]

LMIC categorization is a reasonable proxy and a good operational definition of RLS, though it masks in-country resource variability. In this dissertation, both terms will be used as they are conceptually different, and every attempt will be made to clearly delineate whether we are discussing LMICs specifically, or RLS broadly.

Table 1.1 Summary of key terms, definitions, advantages, and limitations

Term	Definition	Advantages	Limitations
Resource-limited setting (RLS)	Settings characterized by a lack of funds to cover health care costs, which results in: limited access to/availability of medication, equipment, supplies, devices; less-developed infrastructure; and/or fewer or less-trained personnel	Inclusive; specific; allows for intra-country variability	Difficult to objectively measure
Low- and middle-income country (LMIC)	Countries in the lowest quintiles with respect to the gross domestic product (World Bank) or SDI	Objective measure; easily comparable	Lacks specificity; does not capture intra-country variation
Sociodemographic Index (SDI)	Composite indicator of income, education, and fertility that was developed by the Institute for Health Metrics	More comprehensive measurement of a country's socioecomonic development than gross domestic product/gross national income alone; correlates with health outcomes	Not as frequently used as World Bank criteria for country-income
Global Burden of Disease Super Region	Global country regions based on epidemiological similarity and geographical proximity	More comprehensive categorization of regions beyond location alone	Not as frequently used as WHO regions
Acute critical illness	Conceptually the rapid, often unforeseen, development of a life-threatening condition	Captures overall critical illness instead of specific critical illnesses	No global consensus definition; not a pragmatic research definition; frequently operationalized as admission to a PICU, which excludes key populations
Critical care services	Delivery of time-sensitive life- or organ-supporting interventions and/or frequent/continuous monitoring to prevent clinical deterioration	Broadly includes the care required to manage critical illnesses	No global consensus definition for critical care
WHO: World Health Organization; PICU: pediatric intensive care unit			

While it is difficult to make a universal statement that applies to all RLS and LMICs specifically, there are general themes in how LMIC health systems are financed and governed.[18-21] In many LMICs, the responsibility for running and financing the health system belongs to the government. The government typically provides governance and oversees the health system, which frequently includes a Ministry of Health.[21] The government's role is to set policies, regulations, and determine resource allocation for the provision of healthcare.[21] Health systems financing in LMICs is a

combination of public and private financing, though the exact proportion and composition varies by country.[18-21] Public financing includes public funds (e.g., tax revenue, contributions from the national budget); Development Assistance for Health from international aid and development agencies such as the World Bank, GAVI The Vaccine Alliance, and bilateral aid agencies (e.g., United States Agency for International Development [USAID], Department for International Development [DFID]); philanthropic foundations (e.g., Gates Foundation); and public health insurance schemes (e.g., payroll taxes, social health insurance).[18-21] Private financing includes donor and non-governmental organization (NGO) funding; private health insurance plans; and out of pocket funds, or expenses incurred by the individual seeking healthcare.[18-21]

People in LMICs can seek care from a variety of providers in either the informal (e.g., pharmacies, shaman) or formal (e.g., clinics, hospitals) sector. Informal providers offer health-related services or guidance but do not have formal medical training or are acting outside of the licensure scope,[22] and depending on the country and medical condition, utilization estimates range from 9-90% of all healthcare interactions in LMICs.[23] The formal healthcare sector includes public, private, faith-based, and NGO providers. Access to care varies widely by country and even within countries. Access to healthcare can be influenced by geographical accessibility (e.g., proximity to a health center, ease of transportation); healthcare availability (e.g., availability of staff, operation hours, wait time); financial accessibility (e.g., affordability of services, opportunity costs); and patient acceptability (e.g., does the health service meet the needs of the individual); if any of these become a barrier, healthcare access can become limited.[24] Even once a patient has accessed the healthcare system, there remain critical barriers to high-quality

care along the care pathway in many LMICs: massive shortages in healthcare personnel;[25] lack of referral systems and emergency transport systems;[26] inadequate healthcare provider training;[25] deficiencies in laboratory services and hospital management;[27] and insufficient equipment, medications, or supplies required to provide high quality care.[27-30]

In part, these barriers can be explained due to a lack of resources to provide healthcare; many LMICs spend less than USD $20 per person per year on health compared to more than USD $11,000 in the United States (US).[31] In everything from life expectancy to maternal and child health, in general, wealthy nations and those that invest more in health tend to have better health outcomes, with the US a noteworthy outlier in terms of high costs and worse than expected outcomes.[32] One example from a large global analysis of pediatric pneumonia mortality from 2000 to 2015 found that the inhospital case fatality rate (CFR) for children in LICs was higher at every time point compared to MICs.[5] Similarly, results from a global systematic review and metanalysis found that CFR for pediatric severe sepsis and septic shock were higher in LMICs (defined in the study as developing countries) compared to HICs (defined in the study as developed countries) at every time point, with the odds of fatality >4 times higher in LICs compared to HICs.[33]

Acute Pediatric Critical Illness and the Origin of Pediatric Critical Care

Acute critical illness in children is the rapid, often unforeseen, development of a life-threatening condition (**Figure 1.1**), which the WHO defines as “any severe problem with the airway, breathing, or circulation, or acute deterioration of conscious state.”[34]

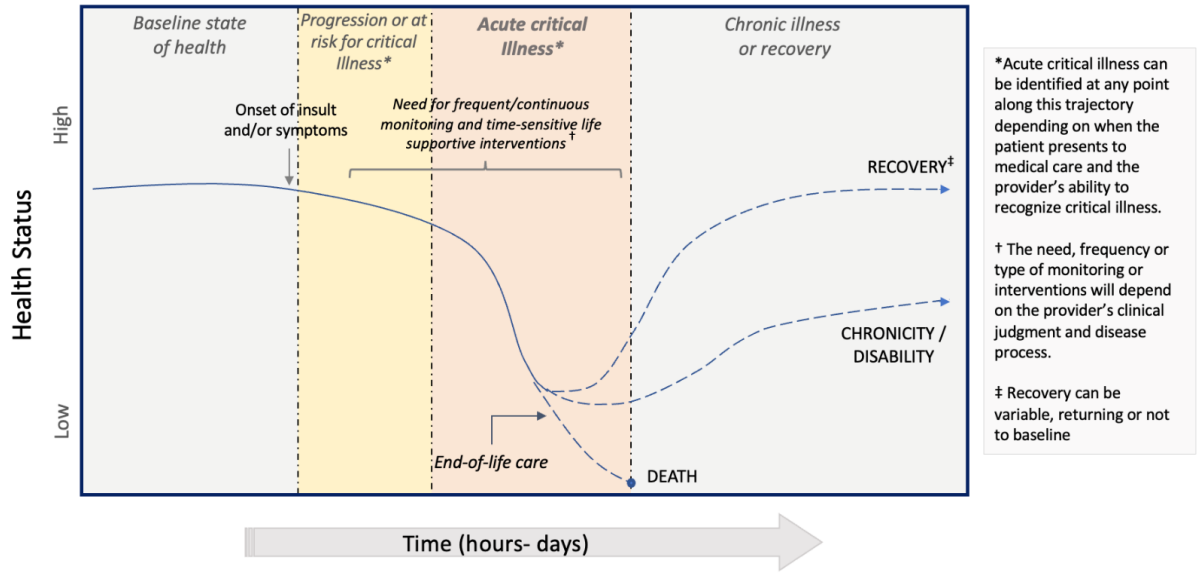


Figure 1.1 Pediatric acute illness trajectories
Progression and potential trajectories from baseline health, through acute critical illness, to post-illness status. Figure created by and used with permission from Anita Arias.

Mortality is the most severe outcome of any illness; however, those who survive a serious, life-threatening illness may have significant morbidity, including long-term neurocognitive and/or physical disability, pain, anxiety, and post-traumatic stress disorder.[35-39] While global child and adolescent mortality has been consistently decreasing since 1990, disability increased 4% from 1990 to 2015, likely due to population growth and improved survival.[1] The primary objective of critical care medicine is to prevent morbidity and mortality due to life threatening illness.

The concept of critical care developed in the 1920s-1950s due to the need for specialized units that could provide a higher level of nursing care, continuous monitoring, and respiratory support during the poliomyelitis epidemic.[40] Critical care services initially focused on the management of adults with life-threatening illness and multi-organ failure.[41] The creation of pediatric critical care medicine was developed by pediatric anesthesiologists, general and cardiac surgeons, and neonatologists.[42] The

first pediatric intensive care unit (PICU) was created in Sweden in the 1950s and treated children primarily with sepsis, pneumonia, and post-operative conditions.[42] Over the subsequent three decades, PICUs were implemented broadly across Europe and North America, innovations and advances in care accelerated, and specialized training for physicians and nurses was developed.[42]

There is no standard definition of pediatric critical care services; it has been defined by a variety of criteria including availability of mechanical ventilators, the nurse-to-patient ratio, or the ability to provide multiple organ support.[41,43,44] The Society of Critical Care Medicine in conjunction with the American Academy of Pediatrics first defined pediatric critical care services in 1983 as a, "...a hospital unit which provides treatment to children with a wide variety of illnesses of life-threatening nature including children with highly unstable conditions and those requiring sophisticated medical and surgical treatment."[45] The definition was later expanded to, "…a separate physical facility or unit specifically designated for the treatment of pediatric patients who, because of respiratory failure, shock, trauma, or other life-threatening conditions, require intensive, comprehensive observations and care."[46] Globally, pediatric critical care is frequently delivered outside of formal hospital units, however.

The COVID-19 pandemic that swept the world in 2020 exposed the severe lack of intensive care resources and expertise globally.[47] The global respiratory syncytial virus (RSV) epidemic in the winter of 2022-2023 specifically highlighted the need for increased pediatric critical care resources. In response, the WHO presented a resolution at the Seventy-Sixth World Health Assembly in May of 2023 to Strengthen Emergency, Critical and Operative care.[48] The resolution "call[s] for near-term action to

strengthen health systems for delivery of high-quality emergency, critical and operative care.” Critical care medicine, previously thought of as a luxury, is now recognized as an essential component of the healthcare system.

Pediatric Critical Illness and Critical Care in LMICs

Care of the acute, critically ill child begins in the community (**Figure 1.2**).

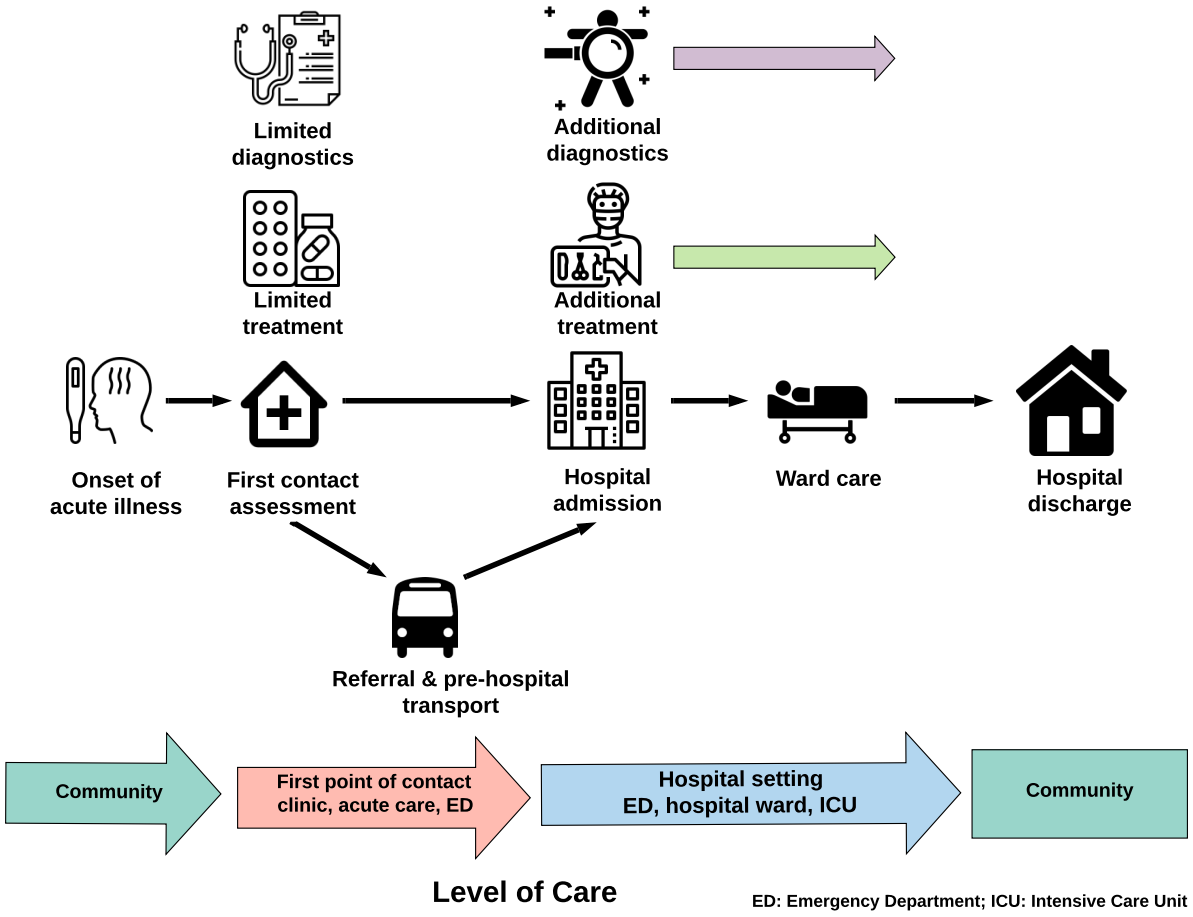


Figure 1.2 Acute illness care pathway
Figure shows the path of an acutely ill individual as he/she moves through the healthcare system. ED: emergency department; ICU: intensive care unit

Children with critical illness in LMICs often initially seek care at an outpatient setting, such as a community health center, primary care clinic, or acute care center that may or

may not be equipped or trained to manage acute pediatric critical illness.[49] The WHO developed the Integrated Management of Childhood Illness (IMCI) guidelines for the management of children in outpatient settings; according to these guidelines, an estimated 20% of children evaluated in outpatient settings require escalation of care and referral to a hospital.[7] Children must then overcome pre-hospital barriers, such as fragmented health systems and transportation challenges, to reach a hospital and delayed presentation/health seeking is known to be associated with mortality.[50,51]

Hospitals often lack a dedicated emergency department and critically ill children are first evaluated in the outpatient department or the ward.[52,53] Formal triage systems that help clinicians identify and prioritize the sickest patients are not common,[52,54] while delays in care, including accessing oxygen and essential medications, are frequent.[55] The majority of pediatric hospital deaths occur within the first 48-hours after arrival at the hospital, which speaks to the importance of emergency and critical care services.[56,57] The majority of hospitals in LMICs do not have a dedicated PICU, which requires a physical space, as well as a nursing, staff, and physicians trained in pediatric critical care, adequate staffing to provide a low-nurse-to-patient ratio (ideally no more than 1 nurse for every 1-4 patients, depending on acuity), appropriate equipment including monitoring devices, and ancillary support (e.g., respiratory therapists, administrative support, nutritionists, environmental services, etc.).[58] Compounding resource limitations, critically ill children are commonly managed outside of formal PICUs, such as the emergency department, ward, high-dependency unit (HDU), or post-anesthesia or surgical care unit,[53] where limitations in resources and personnel, who are rarely trained to provide critical care, affect the quality of care and ability to

monitor for clinical decompensation.[7,27,55,59,60] Still other children may receive care in a mixed-intensive care unit (ICU) that treats adults and children and lacks pediatric specialists; the majority of these mixed units would be considered the lowest level of ICU with the capacity to provide only the most basic critical care.[61]

Recognizing the need for improved pediatric hospital care, triage and emergency management, the WHO published '*The Pocketbook of Hospital Care for Children for the Management of Common Illnesses with Limited Resources',* and developed the warning-sign-based Emergency Triage, Assessment, and Treatment (ETAT) Guidelines in 2005 specifically for RLS.[62,63] Data on whether implementation of these guidelines improves pediatric outcomes are mixed. For example, in two separate studies from Queen Elizabeth Central Hospital in Malawi, the guidelines failed to identify and prioritize 45% of children who died in one study,[64] while guideline implementation was associated with decreased pediatric mortality (from 10–18% to 6–8%) over a five-year period.[52] Despite the WHO's guidelines on pediatric triage and hospital care, early recognition of critical illness and the ability to provide life-saving therapies remains a substantial barrier to care in LMICs.[7]

Regarding formal critical care services, the first ICU in Africa opened in 1969,[65] decades after HICs in Europe and North America. The WHO recommends that every hospital that performs surgical procedures with general anesthesia have intensive care capacity; however, an estimated 7% of such hospitals in Zambia have an ICU.[66,67] We have limited data on the prevalence and resource capacity of PICUs in LMICs. A systematic review and metanalysis analyzed ICU capacity (pediatric and adult) in 15 LICs and concluded that LICs lack ICU beds and as well as published data on

capacity.[58] In a survey of 73 PICUs (34 from HICs, 39 from LMICs), researchers found that PICUs in LMICs had fewer critical care specialists, less access to critical care interventions and technologies such as hemodialysis, and more emergent, unscheduled (e.g., post-operative) admissions compared to HICs.[68] Many LMICs lack formal pediatric critical care training programs (e.g., fellowships) or certification processes, and general pediatricians staff existing PICUs.[40]

Even within LMICs there are significant disparities in pediatric critical care capacity; in some private hospitals in Africa and in large urban centers in South America, China, India, the Middle East, and South Africa, critical care services are similar to those in HICs.[69] Rural hospitals and clinics within the same country often lack the most basic critical care resources required for acute stabilization: oxygen, resuscitation equipment, essential emergency medications, and trained staff.[40]

Notably, there is no global standard for what defines pediatric critical care services in terms of available equipment, capacity, or provider expertise. Resources vary widely between hospitals and there are significant disparities in the availability of essential and advanced pediatric critical care resources in LMICs; a recent survey of 238 hospitals in 60 countries identified inconsistent availability of key resources required to care for acutely ill children in LMICs including sepsis bundle resources, basic respiratory support, and dextrose containing intravenous fluids (IVF).[28] Fifty years after the first ICU was established in Africa, there remains a significant gap between HICs and LMICs and the availability of high-quality pediatric critical care services.[40]

Estimating Burden of Pediatric Critical Illness in LMICs: What Is Known

In a global survey of pediatric critical care providers designed to measure and compare causes of PICU admission between centers in HICs (N=34) and LMICs (N=39), there were notable similarities across income groups; respiratory diseases were the most common ICU admitting diagnoses in both LMICs and HICs, accounting for 87% and 88% of admissions, respectively, followed by congenital heart disease (44% of admissions in both LMICs and HICs).[68] Researchers also found that certain conditions were specific to ICUs in LMICs, such as malnutrition, tuberculosis, human immunodeficiency virus (HIV), malaria, and rheumatic heart disease, while ICUs in HICs reported a significantly higher proportion of elective surgery admissions (65% vs. 33%, respectively).[68] The most common causes of PICU mortality were the same across income groups: infection/sepsis, multiorgan dysfunction, and cardiac conditions.[68]

In addition to the above survey, several global pediatric point prevalence studies have measured the prevalence of individual critical illnesses, such as neurologic injury, lung injury, and severe sepsis. For example, the International Survey of Critically Ill Children with Acute Neurological Insults (PANGEA) study conducted in 107 PICUs across 23 countries predominately in North America and Europe estimated the prevalence of acute neurologic insult to be 16% and all-cause PICU mortality to be 12%.[70] The Pediatric Acute Lung Injury Ventilation (PALIVE) study conducted in 59 PICUs across North America and Europe, found that 11% of children had acute lung injury.[71] The Pediatric Acute Respiratory Distress Syndrome (PARDS) Incidence and Epidemiology (PARDIE) study measured the prevalence of the most severe form of

acute lung injury, pediatric acute respiratory distress syndrome (PARDS), across 145 PICUs from 27 countries; notably, none of the included sites were from LMICs.[72] PARDIE estimated a PARDS prevalence of 3% and a PARDS-associated mortality of 17%.[72] Finally, the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study was conducted in 128 PICUs across 26 countries and included LMICs, though none from Sub-Saharan Africa except for South Africa.[73] The SPROUT study estimated an 8% prevalence of pediatric severe sepsis and a 25% sepsis-associated mortality.[73] See **Table 1.2** for a comparison of pediatric critical illness studies.

Table 1.2 Summary of available global pediatric critical illness data and gaps

Reference	Study/Database Name	Design	Population	Geographical Location	Main Result	Gaps
Santschi, PCCM, 2010	Pediatric Acute Lung Injury Ventilation (PALIVE)	Global point prevalence study	Hospitalized children admitted to PICU	59 sites, N. America, Europe	Prevalence of acute lung injury (11%)	• Specific to one critical illness • Required PICU admission • Not generalizable to RLS
Khemani, Lancet Resp Med, 2019	Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE)	Global point prevalence study	Hospitalized children admitted to PICU	145 sites, 27 countries, no LICs	Prevalence of acute respiratory distress syndrome (3%)	• Specific to one critical illness • Required PICU admission • Not generalizable to RLS
Fink, PCCM, 2017	International Survey of Critically Ill Children with Acute Neurological Insults (PANGEA)	Global point prevalence study	Hospitalized children admitted to PICU	107 sites, 23 countries, mostly N. America, Europe	Prevalence of acute neurologic injury (16%)	• Specific to one critical illness • Required PICU admission • Not generalizable to RLS
Weiss, AJRCCM, 2015	Sepsis Prevalence, Outcomes, and Therapies (SPROUT)	Global point prevalence study	Hospitalized children admitted to PICU	128 sites, 26 countries, included LMICs, only S. Africa from SSA	Prevalence of severe sepsis (8%)	• Specific to one critical illness • Required PICU admission • Not generalizable to RLS
GBD 2015 Child Mortality Collaborators, Lancet	Global Burden of Diseases, Injuries, and Risk Factors Studies www.healthdata.org/	Global and regional estimates of child mortality and cause of mortality	Population-based study	Global	Population-level estimates of child mortality	• Lack facility-level data • Not representative of a hospitalized population • Measures mortality, not critical illness

Reference	Study/Database Name	Design	Population	Geographical Location	Main Result	Gaps
WHO	Global Health Observatory https://www.who.int/data/gho	Global and country-level estimates of child mortality and cause of mortality	Population-based study	Global	Population-level estimates of child mortality	• Lack facility-level data • Not representative of a hospitalized population • Measures mortality, not critical illness
UNICEF	UNICEF Data https://data.unicef.org/	Global and country-level estimates of child mortality and cause of mortality	Population-based study	Global	Population-level estimates of child mortality	• Lack facility-level data • Not representative of a hospitalized population • Measures mortality, not critical illness

PCCM: Pediatric Critical Care Medicine; PICU: Pediatric intensive care unit; RLS: resource-limited settings; LIC: Low-Income Countries; LMICs: Low- and Middle-Income Countries; AJRCCM: American Journal of Respiratory and Critical Care Medicine; SSA: Sub-Saharan Africa; GBD: Global Burden of Disease; WHO: World Health Organization; UNICEF: United Nations Children Fund

Challenges and Knowledge Gap

There are major limitations to data generated from the global pediatric point prevalence studies of critical illness in children described above. Only one of the above point prevalence studies included LMIC sites; therefore, these disease estimates do not reflect the prevalence of disease is LMICs. As stated above, the WHO defines acute pediatric critical illness as "any severe problem with the airway, breathing, or circulation, or acute deterioration of conscious state,"[34] which is typically operationalized as admission to a PICU for research purposes. However, acute pediatric critical illness is frequently managed outside of formal PICUs (e.g., in emergency departments, wards, high dependency units, etc.) in LMICs; requiring PICU admission for study inclusion exacerbates disparities in research participation by excluding settings and patient populations without formal critical care services.[7] This single inclusion criterion in the above point prevalence studies created a selection bias that significantly limited subject

participation, resulted in a non-representative sample, and likely significantly underestimated disease prevalence.

These data are also of limited utility from a resource planning and allocation perspective. The narrow, illness-specific focus of prior point prevalence studies failed to capture the prevalence of pediatric critical illness as a whole. Critical illnesses often overlap and co-occur, and critical care resources are not specific to a diagnosis; for example, sepsis, pneumonia, and trauma are all common causes of PARDS and can be managed with intubation and mechanical ventilation. It is, therefore, difficult to prioritize available resources to achieve the greatest potential impact on child mortality.

Furthermore, there are many challenges with identifying and quantifying acute critical illness in children. For example, there is no consensus definition for acute pediatric critical illness nor patient eligibility criteria for pediatric critical illness studies. It is also difficult, if not impossible, to measure critical illness that does not reach medical attention; not all children with acute critical illness will be able to reach a hospital setting. Assuming that the majority of children with untreated critical illness die, pre-hospital mortality could be a reasonable proxy. Unfortunately, most LMICs lack an effective, high-quality civil registration and vital statistic system, making it challenging to accurately measure mortality on a population-level,[74] resulting in a gross underestimation of disease prevalence. For children that reach medical care, definitive diagnostics are limited and medical records are often incomplete.[75,76] Because of these challenges, comparative epidemiologic studies across regions and countries are rare.[77,78] Considering the available data, the prevalence of acute pediatric critical illness in LMICs is largely unknown.

Problem Statement and Main Objective

Because of this knowledge gap, the frequency, etiology, and outcomes associated with acute pediatric critical illness in hospitals in RLS are not known. The research question addressed in this body of work is: what is the proportion of children with acute critical illness seeking care or admitted to hospitals in RLS? The overarching objective of this work was to determine the frequency and etiology of acute critical illness among children seeking care at hospitals in RLS to provide data for resource allocation and policy decisions.

The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network Global Health Subgroup

The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network's mission is to "[Identify] preventive and therapeutic strategies for acute respiratory distress syndrome, sepsis, multi-organ failure, and other acute, life-threatening pulmonary or systemic inflammatory syndromes that affect infants and children."[79] The PALISI Network was founded in 2002 with the goal of promoting and optimizing a collaborative research approach in pediatric critical care medicine.[79] The PALISI Network now includes a multidisciplinary group of hundreds of investigators from the United States (US) and Canada, with collaborations around the world.[79]

In 2014, the PALISI Global Health Subgroup formed to "provide a platform for investigators to network and collaborate without political borders in order to innovate and improve outcomes for critically ill children."[80] The Global Health Subgroup aimed to

increase awareness of critical illness needs and resources globally using an integrated approach to improve child health outcomes through culturally and contextually appropriate research, education, implementation science, and policy endeavors.[80] The Global Health Subgroup has been growing in membership numbers and diversity since 2014; at the most recent meeting in September 2023, the PALISI Global Health Subgroup had 220 members from over 30 countries.

Thesis Overview

To address the study objective, the PALISI Global Health subgroup developed several studies to address the gaps identified in the global pediatric critical illness literature. This body of work summarizes two research projects that I led to determine the frequency and etiology of acute pediatric illness among children seeking care or admitted at hospitals in RLS: a systematic review of the literature and a global point prevalence study.

First, we explored the existing literature to determine cause-specific pediatric hospital mortality in LMICs through a comprehensive systematic review and meta-analysis. Since acute critical illness lacks a consensus definition that is resource-independent, in this study we used a proxy for critical illness, hospital mortality, which assumes that untreated critical illness often results in death (**Table 1.3**). We also defined RLS by country income level (e.g., LMICs), because, unlike RLS criteria, LMIC status can be consistently defined between studies. ‘Chapter Two’ of this thesis is a methods paper describing the systematic review. ‘Chapter Three’ is the completed systematic review and meta-analysis.

Table 1.3 Summary of metrics, definitions, advantages, and limitations

Term	Definition	Advantages	Limitations
Hospital mortality	Death that occurs after admission to a hospital	Proxy for P-ACI; easy to measure; objective; can compare between hospitals	Does not include cases of critical illness that survive or events that occur before hospital admission or after hospital discharge
Pediatric acute critical illness (P-ACI)	Study definition includes any of the following within 48 hours of arrival to the hospital: death; admission/transfer to an HDU or ICU; transfer to another institution for a higher level-of-care; or receipt of critical care-level interventions	Pragmatic research definition; inclusive of resource-variable settings; acknowledges that not all critical illness is managed in formal units	Not entirely resource-independent; no abnormal vital sign or organ-dysfunction criteria
Early hospital mortality	Death within 48 hours of arrival at a hospital; component of the P-ACI study definition	This patient population would benefit the most from acute stabilization and basic critical care services; assumption is that those with a life-threatening illness without access to critical care services are at high risk of death; easy to measure, objective, can compare between hospitals	Does not include cases of critical illness that survive or events that occur before hospital admission or after hospital discharge
Admission/transfer to a higher level of care	Clinician decides to admit or transfer a patient to a higher level of care within the hospital (HDU or PICU) or to another institution for a higher level-of-care; component of the P-ACI study definition	Indication that the patient has severe/worsening illness and needs a higher level of support	Admission/transfer criteria and availability vary by hospital
Receipt of critical-care level interventions	Patient receives any of the following: vasoactive infusion, invasive mechanical ventilation, or non-invasive positive pressure ventilation; component of the P-ACI study definition	Critical care interventions can be administered outside formal PICUs; non-location-dependent means of measuring organ-supporting interventions	Resource-dependent
Resource-limited setting (RLS)	Hospitals that reported: limited access/availability to medication, equipment, supplies, devices; less-developed infrastructure; or inadequately or too few personnel	Inclusive; specific; allows for intra-country variability and inclusion of sites outside of LMICs	Hard to objectively measure and compare between sites
Low- and middle-income country (LMICs)	Countries in the lowest quintiles with respect to SDI quintile	Proxy for RLS; objective measure; easily comparable; specific countries listed as search terms	Does not capture intra-country variation; excludes resource-limited sites outside of LMICs
P-ACI: pediatric acute critical illness; HDU: high dependency unit; ICU: intensive care unit; PICU: pediatric intensive care unit; RLS: resource-limited settings; LMICs: Low- and middle-income countries; SDI: sociodemographic index			

Through the literature search and systematic review process, we identified key knowledge and data gaps that inspired the design and implementation of the Global Pediatric Acute cRitical Illness point prevalence sTudY (Global PARITY) to directly measure the proportion of children with pediatric acute critical illness (P-ACI) seeking care at hospitals in RLS. For this study, we developed a pragmatic, inclusive research definition of P-ACI that included early hospital mortality, admission, or transfer to a higher level of care, and/or receipt of critical care level interventions (see **Table 1.3** for

definitions). We used a Hospital Resource Survey to determine RLS status. The results of the Global PARITY study are presented in 'Chapter Four'. The final chapter, the 'Conclusion', summarizes the key results from the systematic review and meta-analysis and Global PARITY and places them within the larger global child health context.

Chapter 2: The Burden of Critical Illness in Hospitalized Children in Low- and Middle-Income Countries: Protocol for a Systematic Review

Summary

Background

The majority of childhood deaths occur in low- and middle-income countries (LMICs). Many of these deaths are avoidable with basic critical care interventions. Quantifying the burden of pediatric critical illness in LMICs is essential for targeting interventions to reduce childhood mortality. The objective is to determine the burden of hospitalization and mortality associated with acute pediatric critical illness in LMICs through a systematic review and meta-analysis.

Methods

We will identify eligible studies by searching MEDLINE, EMBASE, CINAHL, and LILACS using MeSH terms and keywords. Results will be limited to infants or children (ages >28 days to 12 years) hospitalized in LMICs and publications in English, Spanish or French. Publications with non-original data (e.g., comments, editorials, letters, notes, conference materials) will be excluded. We will include observational studies published since January 1, 2005, that meet all eligibility criteria and for which a full text can be located. Data extraction will include information related to study characteristics, hospital characteristics, underlying population characteristics, patient population characteristics, and patient outcomes. We will extract and report data on study, hospital, and patient characteristics; outcomes; and risk of bias.

Anticipated Findings

We will report the causes of admission and mortality by region, country income level, and age. We will calculate and report the case fatality rate for each diagnosis when data allow.

Conclusion

By understanding the burden of pediatric critical illness in LMICs, we can advocate for resources and inform resource allocation and investment decisions to improve the management and outcomes of children with acute critical illness in LMICs.

Research in Context

Acute pediatric illnesses are leading causes of death and disability in children and most of these deaths occur in low- and middle-income countries (LMICs). Many lives could be saved with supportive critical care interventions, but pediatric critical care services are not universally available especially in settings with the highest burden of disease. Data from existing studies of the global prevalence of specific pediatric critical illnesses are limited by inclusion criteria that require admission to a pediatric intensive care unit. This limited center and subject participation and may have underestimated the burden of pediatric critical illness, especially in sites without formal critical care services. In this systematic review, we will describe the burden of acute pediatric critical illness in LMICs using criteria that do not depend on the presence of an intensive care unit, something that has not been done before. Furthermore, this review will contribute to our knowledge of the etiology and prevalence of acute pediatric critical illness in settings

with the highest burden of disease, which will aid resource allocation and investment to the benefit of children around the world.

Introduction

Greater than 80% of the global 6.64 million annual deaths in children and adolescents in 2017 occurred in low- and middle-income countries (LMICs).[81] Acute pediatric illnesses (e.g., sepsis, pneumonia, diarrheal disease, trauma) are the leading causes of death and disability outside of the neonatal period.[81-85] The World Health Organization defines acute pediatric critical illness as "any severe problem with the airway, breathing, or circulation, or acute deterioration of conscious state; [which] includes apnea, upper airway obstruction, hypoxemia, central cyanosis, severe respiratory distress, total inability to feed, shock, severe dehydration, active bleeding requiring transfusion, unconsciousness, or seizures"[34]. A significant number of children's lives could be saved with supportive critical care interventions, such as fluid resuscitation, high-flow oxygen therapy, non-invasive and invasive mechanical ventilation, and vasoactive support.[7,68,86-88] Unfortunately, critical care services, defined as hospital care for children with sudden, serious reversible disease, are not universally available and are frequently lacking in LMIC settings, where disease burden, both in terms of hospitalization and mortality, is the highest.[7] Furthermore, it is difficult to assess the burden of critical illness in settings without formal critical care services, where critical illness is frequently managed in emergency departments and in wards.

Several recent global point prevalence studies have described the prevalence of key, individual acute pediatric critical illnesses. The Pediatric Acute Lung Injury

Ventilation (PALIVE) study, conducted in 59 pediatric intensive care units (PICUs), found that 10.8% of children were diagnosed with acute lung injury.[71] The Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) study reported a prevalence of pediatric acute respiratory distress syndrome of 3.2% and an associated mortality of 17% mortality in children admitted to 145 PICUs from 27 countries.[89] The International Survey of Critically Ill Children with Acute Neurological Insults (PANGEA) study conducted in 107 PICUs across 23 countries found an overall prevalence of acute neurologic insult to be 16.2% and all-cause hospital mortality was 12%.[70] Finally, the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study was conducted in 128 PICUs across 26 countries and demonstrated a prevalence of pediatric severe sepsis of 8.2% with a hospital mortality of 25%.[73]

While each of these studies contributed significant knowledge about specific acute pediatric critical illnesses, there are limitations to the available data. The first limitation stems from the focus on a single, critical illness or insult as opposed to all pediatric critical illnesses. There is substantial overlap between illnesses (e.g., pneumonia is a frequent cause of sepsis). In addition, critical care resources support patients with many diagnoses (e.g., mechanical ventilation supports children with pneumonia, shock, or trauma), and resource availability, or lack thereof, greatly impacts patient outcomes. A narrow, illness-specific view fails to capture the burden of pediatric critical illness, which makes it difficult to prioritize resources and achieve the greatest potential impact on child mortality. The most significant limitation, however, is that current global pediatric critical illness point prevalence studies do not reflect the prevalence of disease is LMICs. The PALIVE study was conducted exclusively in North

American and European countries;[71] no low-income countries were included in the PARDIE study;[89] approximately 80% of PANGEA study sites were in North America and Europe;[70] and the SPROUT study, while it included several LMICs, did not include any countries from sub-Saharan Africa outside of South Africa.[73] Each of these global point prevalence studies required PICU admission as an inclusion criterion. This drastically limited which centers and settings could participate and may have resulted in a gross underestimation of pediatric critical illness in LMICs where critical illness may be managed in sites without a formal PICU.[7]

In this systematic review, we will describe the burden of hospitalizations and mortality associated with acute pediatric critical illness in LMICs including in settings that may not have a PICU or formal intensive care services. This review will contribute to our knowledge of the etiologies and prevalence of acute pediatric critical illness in settings with the highest burden of disease. This information will help guide decisions justifying resource allocation and investment as well as inform educational, policy, and research priorities to improve outcomes following acute pediatric critical illness globally.

Methods

Objectives

The objectives of this study are to 1) determine common causes of pediatric hospital admissions (critical and non-critical) and mortality in LMICs; 2) determine the prevalence of and mortality associated with acute pediatric critical illness in LMICs; and 3) analyze the differences in common causes of critical illness by age and region.

Protocol and Registration

This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines (PRISMA), is registered in the international prospective register of systematic reviews (PROSPERO #230228) and was organized and reviewed by the Pediatric Acute Lung Injury and Sepsis Investigator (PALISI) Network Global Health subgroup and PALISI Network Scientific committee.[90,91] The multinational and multidisciplinary scientific Working Group responsible for development of the systematic review protocol includes subject matter and/or methodology experts from across the globe who are members in good standing of the PALISI Global Health subgroup. The inclusion criteria are presented according to published guidelines for prevalence systematic reviews of observational studies (CoCoPop framework: condition, context, and population).[92]

Population

The population of interest is a general pediatric admission population admitted to a hospital in a low-, lower-middle, or middle-income country (LMIC), defined below in 'Context'. The age range of interest includes post-neonatal (>28 days of age) and pre-adolescent (<13 years of age) children; studies that do not include some portion of this age range (>28 days to <13 years) will be excluded. However, studies that include this age range (>28 days to <13 years) plus either neonates and/or adolescents will be included, if it is a pediatric study population (e.g., includes study participants <18 years of age). All hospital admissions, regardless of admission disposition (high-dependency unit, pediatric intensive care unit, ward, etc.) will be included. Studies where the available denominator represents a specific patient population and not all hospital

admissions, such as emergency department patients, neonatal intensive care admissions, pediatric intensive care admissions, and neonatal populations, will be excluded. In situations when the denominator of interest does not represent the entire general pediatric admission population due to study-imposed exclusions, Working Group members will assess these texts individually and decide whether the study exclusion criteria likely resulted in a significantly different case mix (i.e., highly prevalent condition, condition highly relevant to critical illness) compared to the overall, general pediatric admission population. If so, then the text will be excluded. If not, then it will be included and assessed for bias during quality assessment.

Condition

The burden of critical illness is hospitalization or mortality due to a critical illness. Critical illness is defined as a state of ill health with vital organ system dysfunction and/or a high risk of imminent death. Studies must report the proportion of children with a specific admission diagnosis or cause of death (the numerator), such as pneumonia, human immunodeficiency virus (HIV), malaria, etc., relative to the number of general pediatric hospital admissions (the denominator) over that same period to be included. Both the numerator and denominator must represent the same patient population.

Context

Observational studies (prospective or retrospective cohorts, surveillance studies, hospital database publications, cross-sectional studies, before data from before-and-after studies, registry data, etc.) must be published since January 1, 2005, in Spanish, French or English to be included. For studies including data collected before the year of

2000, only data from 2000-present will be included; however, if it is not possible to extract only data after the year 2000, the study will be excluded in its entirety. Exclusion of data before the year 2000 and the publication date of January 2005 were chosen to reflect recent trends in pediatric hospitalization and mortality.

Only studies conducted in LMICs will be included. LMIC status will be determined by the Global Burden of Disease (GBD) 2017 Socio-Demographic Index (SDI).[93] The SDI is a composite indicator that includes indices of total fertility rate for women under age 25 years, mean education for people 15 years and older, and a lag-distributed income per capita. SDI represents a country's overall development status and strongly correlates with health outcomes. Studies that present aggregated data representing multiple countries (e.g., multi-center study) will be included, and we will report regional data. Publications conducted in LMICs but not representative of the setting (e.g., medical mission, foreign military hospital, disaster response efforts) will be excluded.

Abstract only publications, case studies, narrative reviews, surveys, study protocols, comments, editorials, letters, notes, conference materials, interventional trials, and texts for which we cannot locate the full text will be excluded. The search may be updated prior to publication to include more recent publications.

Data Sources and Search Strategy

A search strategy was developed among co-investigators and an academic librarian and tested for feasibility. The final search results are shown in **Figure 2.1**.

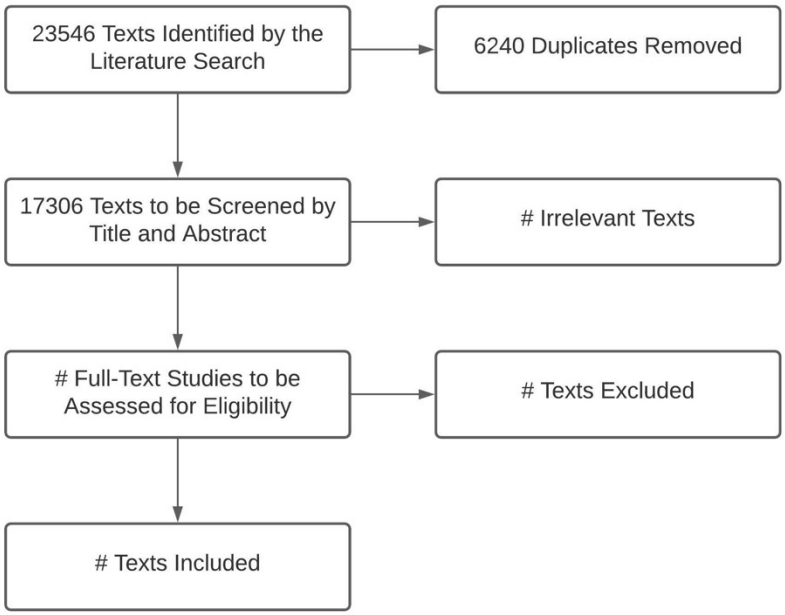


Figure 2.1 Preferred Reporting Items for Systematic Review and Meta-Analysis protocols
(PRISMA) flowchart for title and abstract screening and text selection from the final search (conducted March 1, 2021)

We identified eligible studies by searching Ovid MEDLINE (1946 to February 26, 2021, with Epub Ahead of Print, In-Process and Other Non-Indexed Citations), EMBASE.com (1974 to March 2021), CINAHL (1981 to March 2021), and LILACS (1982 to March 2021) (**Table 2.1**).

Table 2.1 Summary of searched databases and number of texts identified by the search strategy

Database	Dates Included	Date Searched	Number of Texts Identified
Ovid MEDLINE(R) Epub Ahead of Print In-Process and other Non-Indexed Citations Daily and Versions(R)	1946 to February 26, 2021	3/1/2021	11240
EMBASE.com	1974 to Present (includes Medline 1966 to Present)	3/1/2021	11403
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	1981 to Present	3/1/2021	3878
Latin American and Caribbean Health Sciences Literature (LILACS)	1982 to Present	3/1/2021	1453
TOTAL			**27974**

The MEDLINE search was performed using MeSH and key words for "hospitalization", "patient admission", "patient readmission", "hospital units", "critical care", "intensive care", "mortality", and "developing countries". Countries determined to be LMICs by SDI criteria were listed individually to increase the specificity of the search. The MEDLINE strategy was adapted to search EMBASE, CINAHL and LILACS. All results were limited to infants or children (ages 29 days to 12 years) and publication years 2005 to present. There were no language restrictions; texts in languages other than English, Spanish or French will be manually excluded during screening. Specified publication types were excluded in MEDLINE and EMBASE (e.g., comments, editorials, letters, notes, conference materials). (**Supplemental Table 2.1**)

Study Selection and Screening Process

The titles from the search will be uploaded to and screened using Covidence (Veritas Health Innovation, Melbourne, Australia).[94] Covidence is a web-based systematic review platform designed to facilitate citation screening, full-text upload, and conflict resolution. Citations will be screened for eligibility based on title and abstract, and full text using a study-specific flowchart (**Figure 2.2**).

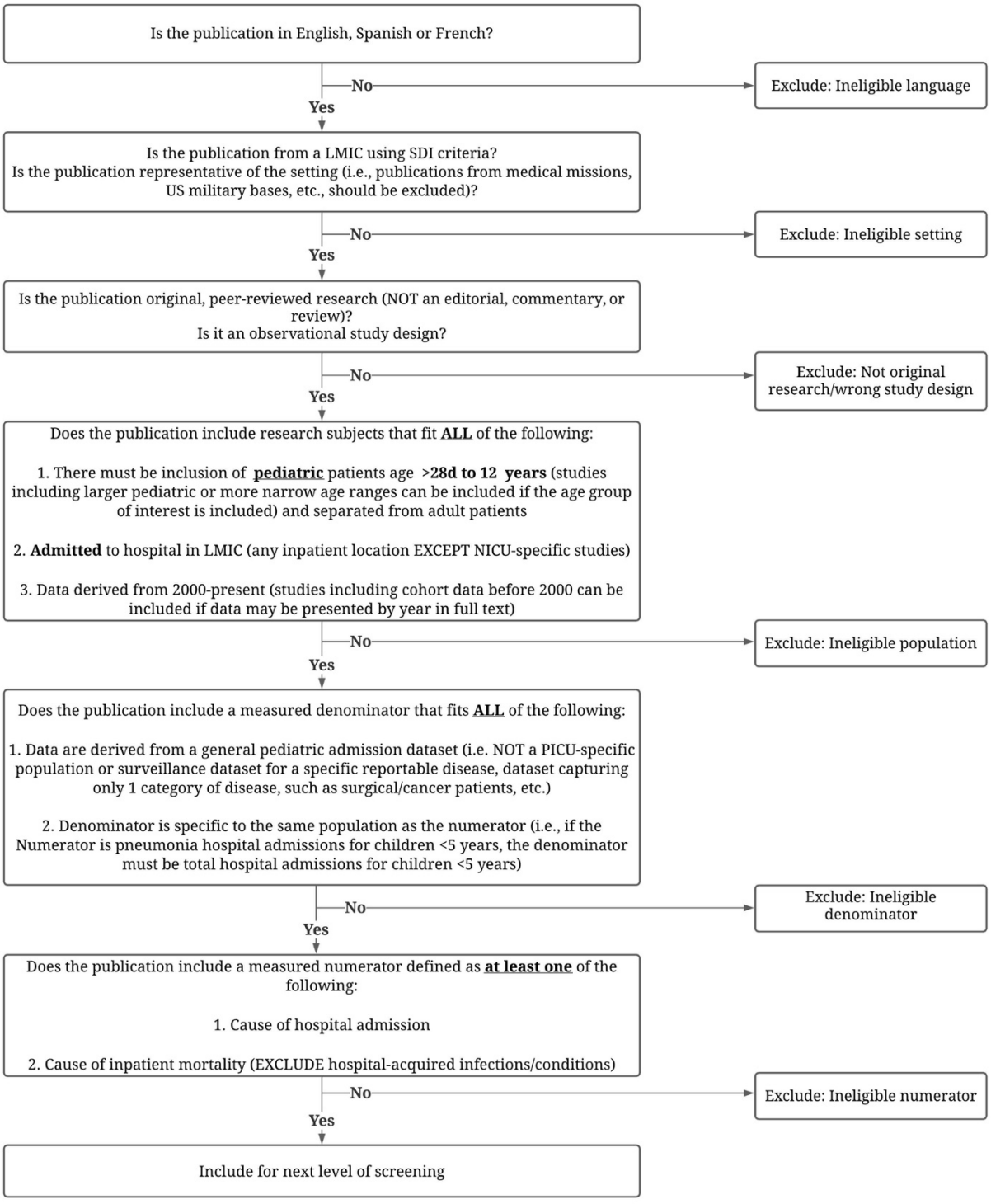


Figure 2.2 Approach to screening abstracts, titles and texts for eligibility

LMIC: low- and middle-income country. SDI: Socio-Demographic Index. NICU: neonatal intensive care unit. PICU: pediatric intensive care unit.

Working Group members will complete a training set of 25 citations (titles and abstracts) before initiating screening for the project. At least 5–10 true positives will be purposely included in the training set. The training set will be created by the study investigator (TK). Members of the Working Group will independently screen the titles and abstracts and then discuss and align on the final decision.

Each title will be screened by two reviewers using the predetermined eligibility criteria. Specific Working Group Members fluent in non-English languages will be designated to review citations in Spanish (ACM, KN, TK, YF, CP) and French (ACM, HR, NO, CP). Titles that are eliminated by both reviewers will be rejected; titles accepted by both reviewers will advance to full-text screening; and titles in which a consensus is not reached will be resolved by a third member. Each full-text article will be assessed by two members of the Working Group for inclusion in the final set of articles for data extraction. At each screening and assessment phase, conflicts will be resolved by a third member of the Working Group using the conflict resolution function in available in Covidence.

For full texts with exclusion criteria, a reason for exclusion will be recorded (e.g., ineligible language; ineligible setting; not original research/wrong study design; ineligible population; ineligible denominator; ineligible numerator; full text not found; duplicate article). Texts identified by title and abstract screening will be excluded if the full text cannot be found after the following stepwise process is completed: search of available journal article subscriptions at two or more academic institutions; a general web-based search using Google; an Interlibrary Loan request from at least two academic institutions; an article request via direct email to the corresponding author or editor. For

multiple publications from one dataset, we will only include the data once (e.g., the most recent or most relevant publication). For publications with multiple years of data presented by year or groups of years (e.g., vaccine surveillance studies), we will include the most recent year(s) as this is more likely to reflect the current epidemiology of disease. Publications with data from more than one country (e.g., global prevalence studies) will be considered for inclusion if either a) all included countries meet LMIC criteria, or b) data from LMICs can be extracted separately from non-LMIC data. We may contact authors to stratify data by age for already published texts.

Data Extraction and Management

Data from all included full-text articles will be extracted by two, independent Working Group members and managed using REDCap, a secure, web-based application and electronic data capture tool hosted at the University of California, San Francisco.[95] Data extraction conflicts will be resolved by a third member of the Working Group using the data comparison functionality in REDCap.

Data extraction will include information related to study characteristics (i.e., title, authors, year of publication, date of enrollment, urban/rural, country, language, journal, study design, sample size, inclusion/exclusion criteria, data source); hospital characteristics (public/private/faith-based, referral/district, community/academic, children's hospital, intensive care resources available, number of beds); underlying population characteristics (population served, proportion living in poverty, malaria rate, HIV rate, malnutrition rate); patient population characteristics (age, sex, presence of malnutrition and other comorbidities); and outcomes (cause of admission, cause of death, length of hospital stay).

Risk of Bias in Individual Studies

Two members of the Working Group will independently assess the quality of each selected article and risk of bias using an adapted version of the Quality in Prognosis Studies (QUIPS) tool.[96] While this review will not assess prognostic factors for admission and/or mortality, biases relevant to prognostic factors are similar to those relevant to the assessment of causes of these outcomes. The QUIPS tool includes six domains of bias, of which the three deemed appropriate for this review are: (1) study participation; (2) study attrition; and (3) prognostic factor (i.e., cause) measurement. The fourth, outcome measurement, is not relevant as this systematic review assesses causes of admission (and where relevant, death), and the cross-sectional nature precludes a temporally linked outcome to the cause. The fifth and sixth domains, study confounding and statistical analysis, respectively, were also deemed not relevant as the data to be extracted are counts. Issues around improper analyses will be adequately captured in domains 2 (attrition) and 3 (measurement of cause). The adapted domains, key issues, and items for consideration relevant to this review are shown in **Table 2.2**.

Table 2.2 Risk of bias domains and questions adapted from the Quality in Prognosis Studies (QUIPS) criteria

Domain	Key Issue in this Review	Items for Consideration During Assessment
Study Participation	Do those subjects who are enrolled/analyzed represent the general admission population of this age group at this facility (or these facilities if multisite)?	(a) Adequate participation in the study by eligible persons (i.e., all those admitted in the target age group). (b) Description of the source population or population of interest. (c) Description of the baseline study sample. (d) Adequate description of the sampling frame and recruitment (i.e., if not a census sample, effort was made to ensure a representative sample of the admission population). (e) Adequate description of the period and place of recruitment (e.g., representative in terms of seasonality, natural fluctuations in causes based on time of day, day of week, etc.). (f) Adequate description of inclusion and exclusion criteria (i.e., any efforts in sample selection should be to make the sample more representative of the general admission population, not less)
Study Attrition	Do those subjects who are enrolled represent those in whom the outcome (cause of admission, cause of death) is measured? This is especially relevant to those studies	(a) Those who are enrolled and those in whom a cause (of admission, death, etc.) was measured are the same (b) Reasons for losses between enrollment (admission) and outcome ascertainment (cause of admission, cause of death) are provided (c) Adequate description of participant losses

Domain	Key Issue in this Review	Items for Consideration During Assessment
	assessing both causes of admission AND causes of death.	(d) There are no important differences between participants who completed the study and those who did not
Listed Causes of Measurement (i.e., measurement of admission/death)	Do those subjects in whom a cause of admission/death is reported have this cause (or these causes) measured reliably?	(a) A clear definition or description of the listed causes is provided (b) Method of the determination of causes valid and reliable (c) The method and setting of measurement of listed causes is the same for all study participants (d) Appropriate methods of imputation are used for missing listed causes data

Risk of bias will be classified as high, moderate, or low when the relationship between the listed causes and outcome is very likely to be, may be, or unlikely to be, respectively, different for participants and eligible nonparticipants. Conflicts in the risk of bias assessment will be resolved by discussion or by a member of the Working Group if consensus cannot be reached. We will produce one or more summary of findings tables that will provide an overview of the evidence to make the findings accessible to readers. The tables will include summaries of the methodological quality (risk of bias), precision of summary estimates (imprecision), concerns about heterogeneity (inconsistency), applicability of the findings to our review question (indirectness) and issues with publication bias. The tables will also include any additional limitations of the evidence. We will explore the impact of the risk of bias domains in sensitivity analyses.

Data synthesis and Analysis

We will summarize data on study (author, publication year, study country, study design, sample size, ages included, data source), hospital (catchment population, type of hospital [level, affiliation, pediatric, etc.], number of health facility and pediatric beds, and available intensive care resources) and patient (median age, prevalence of comorbidities such as malnutrition, congenital heart disease, prematurity, malignancy, malaria, and anemia) characteristics; outcomes; and risk of bias assessment using

tables, graphs, and narrative summaries. Continuous outcomes will be summarized using mean and standard deviations (SDs) or medians with interquartile ranges as appropriate. Binary outcomes will be summarized using frequencies and percentages.

The primary outcomes of interest are 1) cause of hospital admission and 2) cause of in-hospital mortality. Causes of hospital admissions will be further categorized as critical (potentially life-threatening) and non-critical (unlikely to be life threatening) based on group consensus and a review of the literature. If available, data for secondary outcomes will be collected including in-hospital mortality, case fatality rate, and length of hospital stay. We will report the causes of admission and mortality (categorized by GBD grouping) by region (Central Europe, Eastern Europe, and Central Asia; Latin America and Caribbean; North Africa and Middle East; South Asia; Southeast Asia, East Asia, Oceania; Sub-Saharan Africa), SDI country income level (low-, lower-middle, or middle-income), and age (<5 years, 5-12 years). When possible, we will report the case fatality rate (CFR) for each cause of admission and/or cause of death. This may require calculating these estimates from individual studies when not reported directly, provided that the necessary data to perform these calculations are reported. Causes of hospital admissions will be categorized as non-critical or critical (potentially life-threatening) by the same multinational, multidisciplinary scientific Working Group compiled of experts described above. The Working Group will reach consensus as to whether the reason for admission is consistent with vital organ system dysfunction and/or a high risk of imminent death based on a review of region-specific literature. We will explore different definitions and cut-offs for critical illness (proportion of total admissions, proportion of total mortality, CFR).

As the data allow, we will perform a meta-analysis on the proportions of causes of admission and causes of death, as well as the CFRs using random-effects models. We will conduct meta-regression to explore predictors for all-cause and cause-specific mortality (pneumonia, sepsis, and diarrhea). Possible predictors will include SDI, facility type and geographic region. Additionally, we will explore temporal trends in admission and mortality by age and region. We will consider subgroup analyses if we have adequate numbers of studies and/or patients within the included studies.

We will examine sources of heterogeneity, including differences in methodology, setting (urban vs. rural), region, income level, and patient populations (e.g., age, sex, prevalence of comorbidities, etc.). Statistical heterogeneity will be assessed using the variance estimates from the random effects model. It is likely that there will be significant heterogeneity between studies, and we will therefore pool results when studies are comparable. All analyses will be performed using STATA (version 16).

Anticipated Results

Through this systematic review, we expect to identify the most common causes of acute pediatric critical illness resulting in hospital admission and mortality in LMICs by age and region. If data are available, we will also show temporal trends in admission and mortality by age and region. We will classify causes of admission as critical or non-critical and illustrate the global prevalence of critical illness with a map. Furthermore, we anticipate identifying diagnoses with the highest CFR for each age and region and illustrating these results through a series of forest plots for all-cause mortality, cause-

specific mortality (pneumonia, sepsis, diarrhea, malaria), critical illness, and hospital length of stay (data permitting).

There are several advantages to the proposed approach. First, with broad inclusion criteria, we expect to capture most if not all relevant texts. Second, by not restricting the search to exclusively pediatric intensive care populations, we will be able to calculate the prevalence of critical illness across settings, including those without a formal PICU. Third, by including both individual LMICs by name and terms such as “resource-limited”, “low income”, and “developing” in the search strategy, we will likely identify more texts from LMICs, which will provide a more complete assessment of the burden of critical and non-critical disease in these countries.

There are potential limitations to the proposed protocol. First, neonatal and adolescent populations are included in some pediatric studies, and the search was not designed to capture these populations. We will intentionally exclude exclusively neonatal and adolescent populations from data analyses and will not be able to draw conclusions about children <28 days or >12 years of age. Second, we will exclude disease-specific studies that do not report overall pediatric hospital admissions, which may result in an underestimation of disease prevalence. Additionally, estimates will not include disease prevalence during outbreaks, potentially underestimating the true prevalence of disease and overall required critical care capacity. Third, we will restrict study inclusion to publications in Spanish, French, or English, and may not identify all potentially relevant texts. Fourth, we may underestimate the true burden of critical illness in LMICs by excluding emergency department or PICU population studies that lack the denominator of interest (general hospital admissions). However, without a

common denominator, we cannot draw comparisons across studies. Sixth, it is possible that critical, but rare illnesses, will not be adequately represented in this systematic review as they are often categorized in the “other” category in texts. This systematic review will, however, describe the most common causes of pediatric critical illness, which is of greatest importance when the objective is to improve overall child health outcomes and inform resource allocation. Finally, we expect to include a small number of studies where the denominator does not represent the entire general pediatric admission population due to original study-imposed exclusions. The degree of bias from these texts should be minimal because only those with a similar case mix to the overall, general pediatric admission population will be included.

Discussion

There is intense competition for limited resources in many LMICs and children are frequently overlooked as the global focus shifts away from infectious diseases towards non-communicable diseases, which are far more common in adult populations.[97] To decrease childhood morbidity and mortality, health systems require capacity to deliver both preventative medicine and treatment, such as proven, effective therapies, like critical care.[97] While dedicated PICUs are being developed in LMICs, clinician and staff education is sub-optimal due to a lack of appreciation for the most common pediatric critical illnesses.

The objective of this systematic review is to describe the most common causes of critical illnesses causing hospitalization and death in children in LMICs. This will provide much needed insight into the burden, etiology, and distribution of pediatric

critical illness in LMICs, especially in settings where formal critical care services may not be currently available. Region-specific data that capture the burden of disease and outcomes for children in LMICs are essential to inform educational initiatives and training, shape advocacy and policy objectives, allocate limited resources appropriately, and implement context-appropriate, evidence-based critical care interventions for children in need. This systematic review is a crucial first step in setting future educational, advocacy, policy, research, and health delivery priorities for children with acute critical illness in LMICs.

Chapter 3: Etiology of Hospital Mortality in Children Living in Low- and Middle-Income Countries: a Systematic Review and Meta-analysis

Summary

Background

In 2019, 80% of the 7.4million children who died around the world were in low- and middle-income countries (LMICs). This study aimed to determine global and regional estimates of the common causes of pediatric hospital mortality and admission in LMICs and explore regional differences.

Methods

This systematic review (PROSPERO #230228) searched MEDLINE, EMBASE, CINAHL, and LILACS to identify observational studies from LMICs published January 1, 2005-February 26, 2021. Eligible studies included a general pediatric (aged >28d-12yrs) admission population, cause of admission or death, and total admissions. We excluded studies with data pre- 2000 or without a full text. Two, independent reviewers screened and extracted data. We performed a meta-analysis of cause-specific mortality, case fatality rates (CFRs), and cause of admission using random-effects models. We reported proportions as cause of death or admission/1000 admissions with 95% confidence intervals (95%CI). Heterogeneity was assessed using variance estimates.

Findings

Our search identified 29,637 texts. After duplicate removal, and screening, 253 studies were analyzed. The most common causes of mortality (deaths/1000 admissions) were infectious (12 [95%CI 9-14]); respiratory (9 [95%CI 5-13]); and gastrointestinal (9 [95%CI 6-11]). Conditions with the highest CFRs were neurologic

(13% [95%CI 9-18%]); cardiovascular (11% [95%CI 6-16%]); and congenital conditions (8% [95%CI 4-12%]). Common causes of admission (cases/1000 admissions) were respiratory (255 [95%CI 231-280]); infectious (214 [95%CI193-234]); and gastrointestinal (166 [95%CI 143-190]).

Interpretation

Pediatric hospital mortality is high in LMICs and there are significant regional differences in burden of disease. Global child health efforts must include measures to reduce LMIC hospital mortality including basic emergency and critical care services to address common causes of death. A major priority is supporting LMIC researchers to implement and assess these service-related interventions, measure outcomes, and ensure equity and sustainability.

Research in Context

Evidence before this study

We searched MEDLINE, EMBASE, CINAHL, and LILACS for observational studies conducted in low- and middle-income countries (LMICs) reporting cause of hospital admission or death and total number of admissions for children (aged >28d-12yrs) published January 1, 2005-February 26, 2021, without language restrictions. The main search terms were “hospitalization”, “patient admission”, “patient readmission”, “hospital units”, “mortality”, and “developing countries”. Countries that met LMIC status by Socio-Demographic Index (SDI) criteria were listed individually to increase specificity of the search. We found many cross-sectional studies that reported hospital cause of death and/or admission, and numerous cohort studies that reported the incidence of a

single diagnosis; few reported data from more than one hospital or global region. We did not find a meta-analysis synthesizing pediatric hospital death or admission data across LMICs; nor did we encounter a publication that reported proportions of cause-specific hospital death or admission in children by region or SDI quintile. A global estimate and synthesized data were lacking.

Added value of this study

To our knowledge, this systematic review presents the most comprehensive cause-specific pediatric hospital mortality and cause of admission estimates from LMICs globally and by region to date. We included data from 21.8million hospitalized children from 293 sites in 59 LMICs. Our results demonstrate that the most common causes of hospital mortality for children in LMICs were infectious diseases, respiratory, and gastrointestinal conditions, while the most common causes of hospital admission were respiratory conditions, infectious diseases, and gastrointestinal conditions. We observed a general trend toward increased mortality and case fatality rate in countries in the lowest SDI quintile (low-income), suggesting that resource availability and access to care impact pediatric hospital outcomes. Most modern global child health estimates – Global Burden of Disease (GBD) studies, World Health Organization (WHO), and United Nations Children's Fund (UNICEF) – are population-level estimates and may not represent the pediatric hospitalized population. Our results independently validated data for childhood mortality outside of the neonatal period and identified the most common causes of child mortality in LMIC hospitals; thus, identifying critical needs requiring a focused effort to improve child health outcomes.

Implications of all the available evidence

Infectious diseases remain the primary causes of hospital death and cause of admission in LMICs. Common causes of death for children in LMIC hospitals are frequently avoidable with effective treatment and high-quality care, while common causes of hospital admission are potentially preventable with public health interventions. To realistically achieve the Sustainable Development Goal target to end preventable deaths of children by 2030, we need to advocate for and implement primary prevention measures while simultaneously expanding available emergency and critical care services. Finally, to guide local and global stakeholders in priority setting and resource allocation, resources are urgently needed to promote equity in global child health research and support researchers and high-quality data collection in LMICs.

Introduction

As of 2019, 73 countries had not yet achieved the United Nations Sustainable Development Goal (SDG) 3.2,[98] which aims to reduce the child mortality rate to 2.5% by 2030.[99] In that same year, 7.4 million infants, children, and adolescents died globally from primarily treatable causes.[1] More than 80% of these deaths occurred in low- and middle-income countries (LMICs), representing a devastating global health inequity.[81]

Pediatric hospital mortality is consistently higher in LMICs compared with high-income countries.[5,33,72] Most LMIC hospital deaths could be avoided with reliable and timely high-quality emergency and critical care services.[7,29,100,101] These services are limited due to underfinanced health systems and insufficient equipment, trained personnel, and medications.[28] Recognizing this, the World Health Organization (WHO) recommended a resolution to strengthen emergency and critical care globally.[48,102] A

better understanding of the reasons that children are admitted to and die in LMIC hospitals is necessary to set a prioritized agenda and advocate for resources and interventions to target the greatest drivers of morbidity and mortality.

Existing global child mortality data from the Global Burden of Disease (GBD) studies, WHO, and United Nations Children's Fund (UNICEF) include rates and causes of death;[81,103-105] however, these are population-level estimates and do not provide facility-level data.[106] Additionally, concerns have been raised about the accuracy of these data and estimates due to imputation methods.[107] Many studies have reported the epidemiology of acute pediatric illness in a single hospital or country, but fail to provide regional estimates.[108-110] Estimates of cause-specific pediatric LMIC hospital mortality and admission by region and globally are unknown. To address these gaps, we conducted a systematic review to determine common causes of pediatric hospital mortality and admission in LMICs.

Methods

Search strategy and selection criteria

We followed published guidelines for systematic reviews of observational studies and PRISMA and GATHER reporting standards. The study was organized by the Pediatric Acute Lung Injury and Sepsis Investigator (PALISI) Network Global Health subgroup, reviewed by the PALISI Scientific Committee, and registered with PROSPERO (#230228). The multinational Working Group (WG) was comprised of subject matter and methodology experts. We identified eligible studies by searching MEDLINE, EMBASE, CINAHL, and LILACS using MeSH terms and keywords.

Searches were performed by an academic librarian (SG), on November 6, 2019, with a gap analysis on March 1, 2021 (**Supplemental Table 3.1)**. The protocol was previously published (*https://www.frontiersin.org/articles/10.3389/fped.2022.756643/full).*[77] Protocol amendments made after registration and publication are detailed in the appendix.

Condition

The primary condition of interest was the cause of pediatric hospital mortality. The specific cause (numerator) was derived from the general admitted population (denominator) and represented the estimated proportion of disease within that admitted population. We categorized diagnoses (e.g., causes of death/admission) hierarchically by organ system (e.g., respiratory), high-level diagnosis (e.g., pneumonia), and specific diagnosis (e.g., community-acquired pneumonia) (**Supplemental Table 3.2**). We used organ system-based categorization, which informs general resource requirements; for example, common pediatric respiratory conditions (e.g., pneumonia, bronchiolitis, asthma) require oxygen therapy (low-flow oxygen to mechanical ventilation). Infections that affect multiple organs (e.g., malaria) were categorized as 'Non-Organ Specific Infectious Diseases'. 'Sepsis/septic shock' was categorized separately from other forms of shock given the overwhelming burden of sepsis/septic shock and the specific resources required to manage sepsis. [111,112]

Context

Studies were eligible for inclusion if published between January 1, 2005-February 26, 2021, and data were collected after 2000. We chose these criteria to reflect recent

trends in pediatric hospitalization and mortality. Studies were restricted to Spanish, French, or English during screening due to WG member fluency.

We determined eligible country status using the GBD 2017 Socio-Demographic Index (SDI), a composite indicator that represents a country's development status and correlates with health outcomes.[8] We included countries within the low-, lower-middle, and middle-SDI quintiles in the search terms. Studies that presented aggregated data representing multiple countries were included if country-specific data could be extracted. We excluded publications not representative of the LMIC setting (e.g., medical mission, foreign military hospital). The detailed search strategy is available in the appendix (**Supplemental Table 2.1**).

Population

We included children admitted to a hospital in an LMIC aged 28 days-12 years to focus on a pediatric instead of a neonatal or adolescent population, which have different causes of admission and death and are often managed outside of pediatric units.[1,103] We included eligible studies with participants outside this age range if participants were <18 years and >50% of participants were within the age range of interest.

Included studies reported total number of children admitted to the hospital facility or approximated this through sampling methods. We excluded studies that sampled only specific patient populations, facility locations, or studies with exclusion criteria that resulted in a different case mix compared to the general pediatric hospital admission population. The WG evaluated publications from the same data source and if the study populations overlapped, we retained the most recent or relevant text. **(Figure 2.2)**

Screening, extraction, and quality assessment

We used Covidence (Veritas Health Innovation, Melbourne, Australia) for screening, full-text upload, and conflict resolution.[113] Duplicate articles were removed, and titles/abstracts and full texts were independently screened by two WG members, with conflicts resolved by a third WG member.

Two WG members extracted data from included full-texts independently using a structured case report form (**Supplemental Table 3.3**) in REDCap,[95] and conflicts were adjudicated by a third member as needed. We made no assumptions about missing or ambiguous data. We extracted data from studies reporting multiple sites as separate records if participant-level data were available for each site; articles with data aggregated across sites were extracted as one record. WG members independently assessed the risk of bias based on relevant domains adapted from the Quality in Prognosis Studies (QUIPS) tool:[114] (1) study participation (generalizability to underlying population); (2) study attrition; and (3) factor measurement (cause of admission/death) (**Table 2.2**). We resolved risk of bias assessment conflicts by consensus.

Data analysis

The primary outcome was cause-specific proportions for hospital mortality, reported per 1000 pediatric hospital admissions. Secondary outcomes included case fatality rates (CFRs), calculated as the number of deaths per 1000 pediatric admissions with a given diagnosis or system-based illness, and cause-specific proportions for hospital admission, reported per 1000 pediatric hospital admissions. Included studies provided raw data for the denominator and numerator to enable estimation of the proportions and their 95% confidence intervals (CI). We summarized data according to

study- and outcome-level characteristics. We reported outcomes as overall summaries and according to GBD super-regions: Central Europe, Eastern Europe, and Central Asia (CE); Latin America and Caribbean (LA); North Africa and Middle East (NA); South Asia (SA); SEA (SEA); and Sub-Saharan Africa (SSA).[115] SDI Country income level was categorized according to the SDI quintile.[8] Causes of hospital death (diagnoses) were ranked globally and by GBD super region. To generate a global estimate, data from more than one GBD region were required, while for regional estimates, more than one study per diagnosis was required, else data were labelled as "Not reported." We excluded 'other' diagnoses, which were a heterogeneous group of conditions that differed between studies and precluded comparisons across regions. We assessed ties using the standard competition ranking method.

We anticipated heterogeneity and performed meta-analyses of causes of death, CFRs, and causes of admission using random-effects models with the Freeman-Tukey double arcsine transformation and fixed-effect models when data were limited.[116] We assessed statistical heterogeneity using the variance estimates from the random-effects models. We did not use the I^2 statistic because the mean-variance relationship of proportions can lead to misleadingly high values.[117] We performed sensitivity analyses on the meta-analysis to confirm that the method of back transformation did not affect the results. We performed subgroup analyses by GBD super-region and SDI quintile; additional subgroup analyses were not possible due to poor reporting of potential sources of heterogeneity. A p-value<0.05 was considered statistically significant. All analyses were performed using the metan command in STATA (version 17).

Results

Characteristics of included studies

We identified 29,637 texts, removed 12,335 duplicates, screened 17,301 abstracts, and assessed 2,256 full texts for inclusion (**Figure 3.1**).

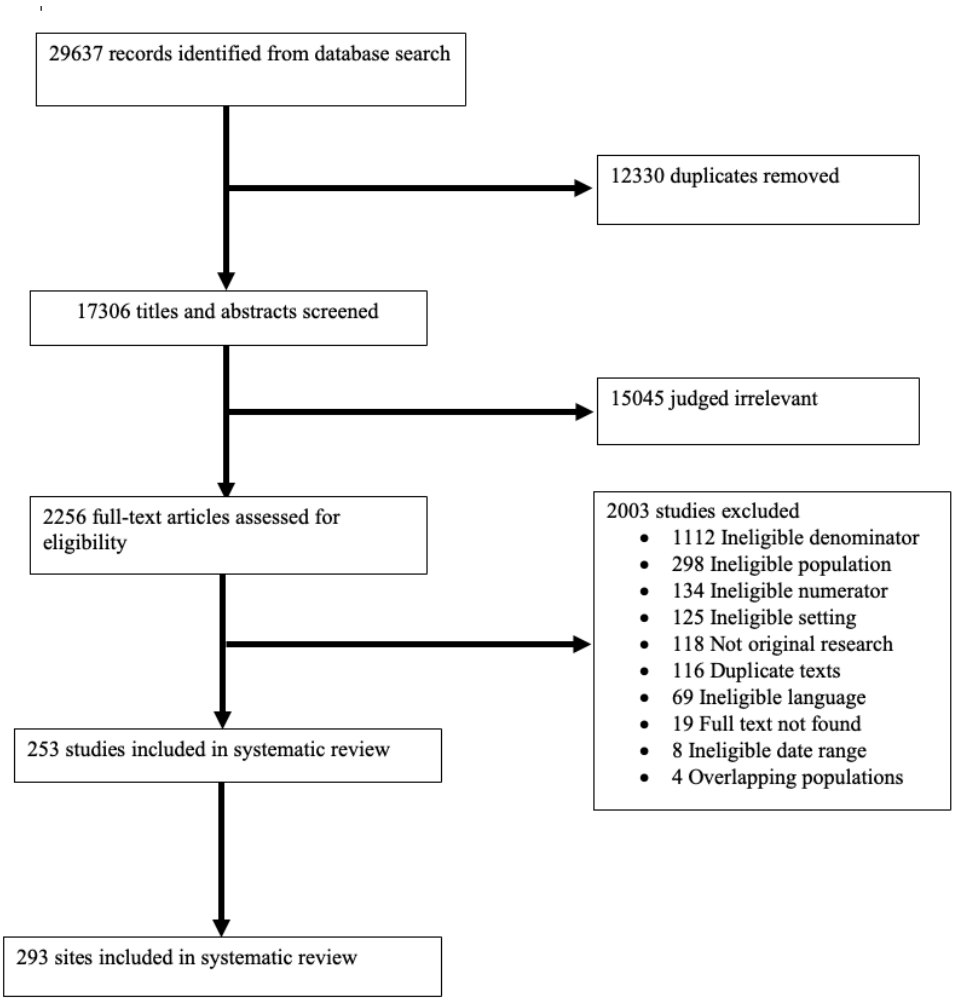


Figure 3.1 Study selection process
Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) flowchart for title and abstract screening and text selection from the final search (conducted March 1, 2021)

Of the 253 publications included, the majority were cohort studies published after 2010. Included studies represented 21,762,798 pediatric hospital admissions from 293 sites in 59 LMICs and six GBD super-regions (**Figure 3.2**, **Supplemental Table 3.4**).

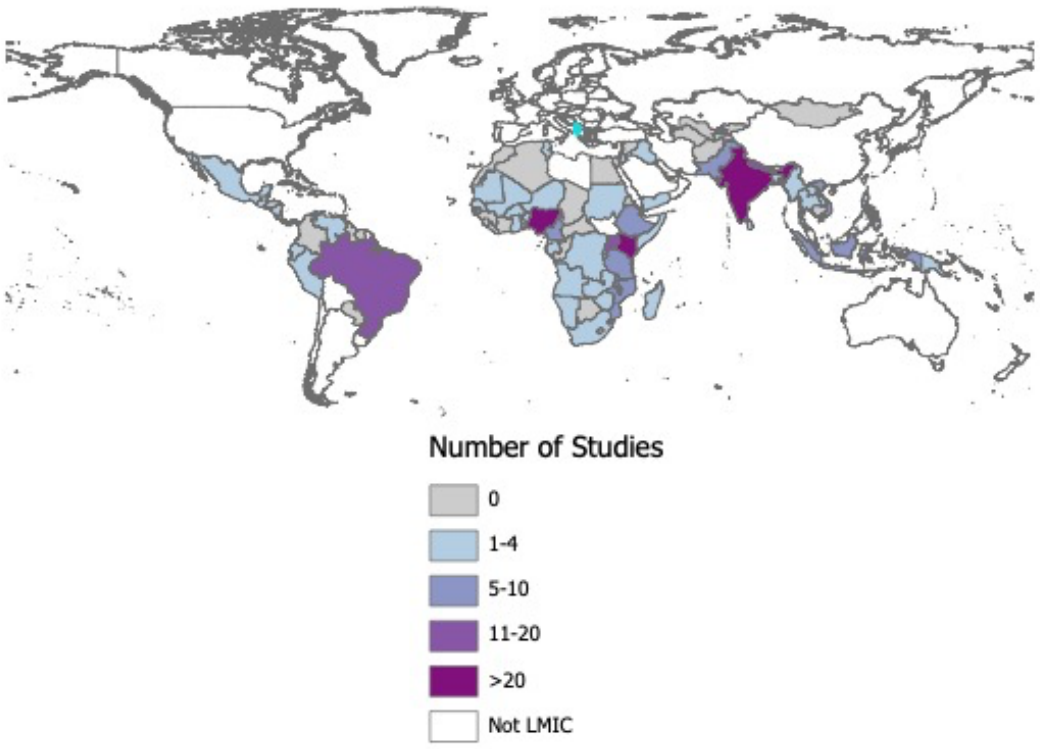


Figure 3.2 Map of distribution of included studies
The map depicts locations of the 253 included studies. Darker colors represent countries with more studies included in the review. Countries that are not low-, low-middle- or middle-income countries (LMICs) were not included in the review and are depicted in white.

The highest number of studies came from Nigeria (N=45, 15%), followed by Kenya (N=27, 9%, Figure 3.2), while the highest number of children admitted were from Brazil (N=16,822,774, 77%), followed by Vietnam (N=1,547,611, 7%, **Supplemental Table 3.4**). SSA had the highest number of sites of any super-region (N=187, 64%, **Supplemental Table 3.4)**.

Twenty-six percent (N=76) of sites were urban and 15% (N=44) were rural; 59% (N=173) of sites did not report urban or rural status. Among all study sites, 9% (N=25) were conducted in children's hospitals while 46% (N=135) were not; 45% (N=133) did not report this information. A pediatric or general intensive care unit was present in 12% (N=35) of study hospitals, and not present or not reported in 82% (N=243).

Risk of bias and heterogeneity

Over 60% of included studies were assessed to have a low risk of bias in the three domains evaluated (**Figure 3.3**). A high risk of bias was deemed likely in 8% (N=21) of studies for 'Study Participation'; 5% (N=14) of studies for 'Study Attrition'; and 13% (N=33) of studies for 'Measurement Bias'. We observed heterogeneity in all outcome estimates between studies and regions. Sensitivity analyses confirmed that the method of back transformation did not affect the results.

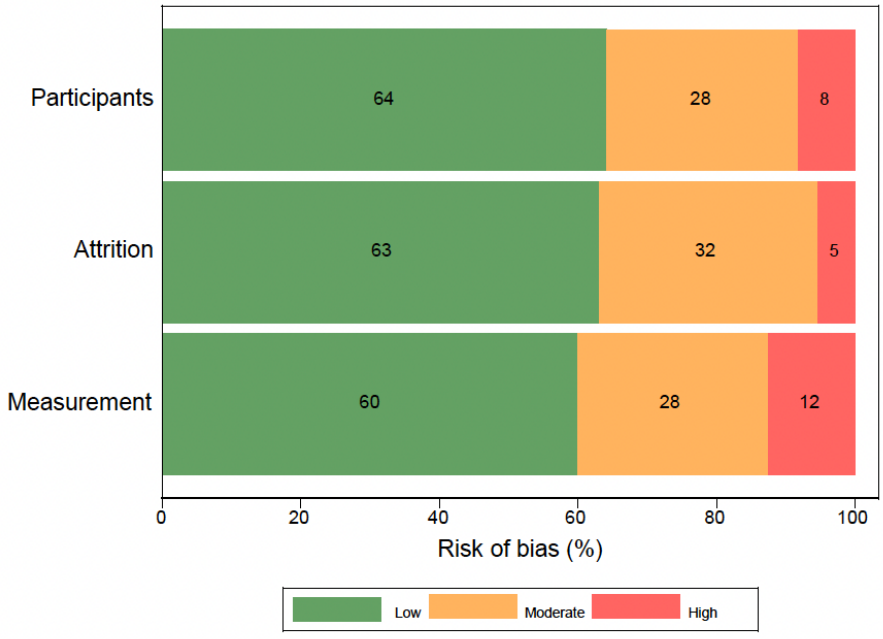


Figure 3.3 Risk of bias assessment summary
Risk of bias was classified as low, moderate, or high for three domains (study participation and generalizability to underlying population; study attrition; and factor/cause of admission measurement), which was adapted from the Quality in Prognosis Studies (QUIPS) tool.

Hospital mortality

All-cause pediatric hospital mortality was 4.1% (95%CI 3.4-4.7%), and point estimates varied widely by region: SA had the highest all-cause hospital mortality (5.7% [95%CI 2.2-10.7%]) and NA had the lowest (1.5% [95%CI 0.5-3.0%], **Figure 3.4**).

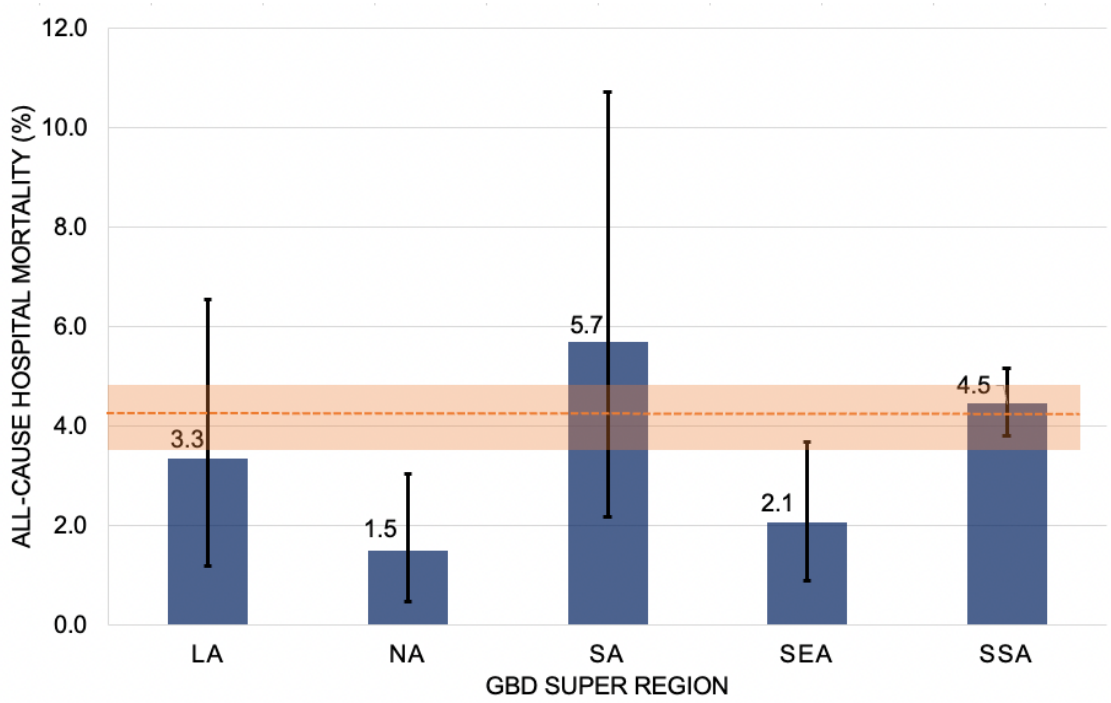


Figure 3.4 All-cause pediatric hospital mortality by Global Burden of Disease (GBD) super region
The global estimate is shown with a dotted line and bars and shading represent 95% Confidence Interval. Estimates for Central Europe, Eastern Europe, and Central Asia (CE) are not included given limited data. NA: North Africa and Middle East; SEA: Southeast Asia, East Asia, and Oceania; LA: Latin America and Caribbean; SSA: Sub-Saharan Africa; SA: South Asia

Organ System: Across LMICs, the most common causes of hospital death were non-organ specific infectious diseases, respiratory conditions, and gastrointestinal

conditions (deaths/1000 admission: 12 [95%CI 9-14]; 9 [95%CI 5-13], and 9 [95%CI 6-11], respectively). The highest proportion of deaths due to non-organ specific infectious diseases occurred in SSA (14 deaths/1000 admissions [95%CI 11-18]) and SA (13 deaths/1000 admissions [95%CI 4-26]). The highest proportion of deaths due to respiratory conditions also occurred in SA (10 deaths/1000 admissions [95%CI 4-18]) and SSA (9 deaths/1000 admissions [95%CI 6-12]). The highest proportion of deaths due to gastrointestinal conditions occurred in NA (16 deaths/1000 admissions [95%CI 13-20]) (**Figure 3.5**).

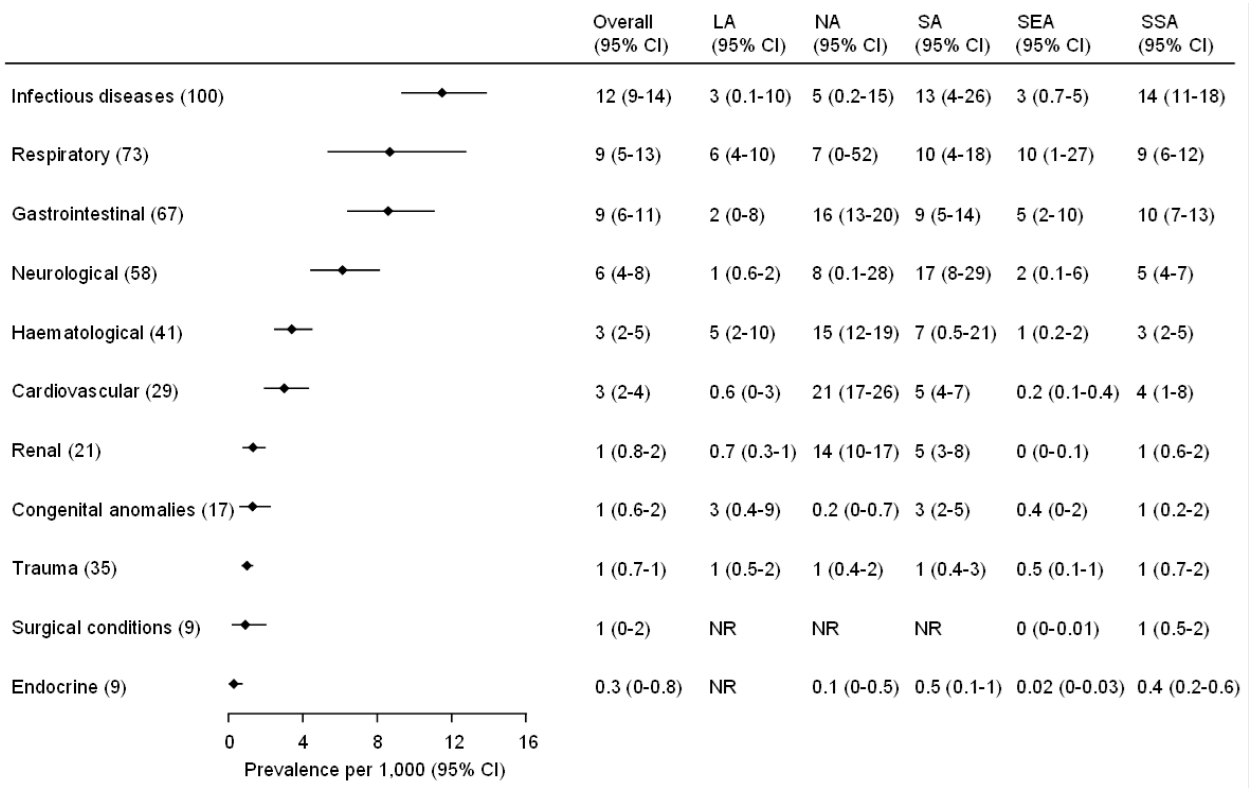


Figure 3.5 Common causes of hospital mortality in children by organ system and GBD super region

Organ systems are ordered according to the overall rate (number of children with a cause of death/1000 children admitted) and the number in parenthesis next to each organ system represents the number of studies included in the analysis. Mortality rates are presented as overall estimates and by GBD super region with 95% confidence intervals (CI). Estimates for Central Europe, Eastern Europe, and Central Asia (CE) are not included given limited data. The hematological category includes oncological

conditions. The numbers in () next to each category in the left column are the number of studies included in the overall analysis shown on the right. The categories are sorted according to the overall proportion across the super regions. The hematological category includes oncological conditions. CE: Central Europe, Eastern Europe, and Central Asia; LA: Latin America and Caribbean; NA: North Africa and Middle East; SA: South Asia; SEA: Southeast Asia, East Asia, and Oceania; SSA: Sub-Saharan Africa; CI: Confidence Interval; NR: not reported

Diagnosis: Malaria, non-septic shock, and malnutrition were the most common diagnoses associated with pediatric hospital mortality (deaths/1000 admissions: 12.8 [95%CI 9.7-16.2]; 11.6 [95%CI 4.2-22.4]; and 9.4 [95%CI 6.3-13.0], respectively, **Figure 3.5**). The highest proportion of deaths due to malaria (14.8 deaths/1000 [95%CI 10.9-19.2]) and non-septic shock (11.6 deaths/1000 [95%CI 4.3-22.4]) occurred in SSA. The highest proportion of deaths due to malnutrition occurred in SEA (14.5 deaths/1000 admissions [95% CI 5.4-27.6]) (**Figure 3.6**).

Diagnosis	Prevalence per 1000 admissions (95% CI)	Global Rank	LA	NA	SA	SEA	SSA
Malaria	12.8 (9.71, 16.2)	1	NR	6	4	5	2
Shock (not septic)	11.6 (4.26, 22.4)	2	NR	1	8	NR	1
Malnutrition	9.36 (6.32, 13.0)	3	NR	3	NR	1	3
Pneumonia and lower respiratory tract infection	7.93 (3.60, 13.9)	4	1	NR	10	2	4
Sepsis and septic shock	4.75 (3.12, 6.69)	5	4	9	2	15	7
Meningitis/encephalitis	4.38 (3.10, 5.88)	6	6	5	6	3	8
Gastroenteritis and diarrhea	4.14 (2.96, 5.49)	7	9	NR	7	9	5
Anemia	3.54 (1.67, 6.07)	8	12	NR	1	7	10
HIV/AIDS and related illnesses	3.21 (2.17, 4.42)	9	7	NR	NR	6	9
Measles	2.39 (0.58, 5.22)	10	NR	NR	15	11	11
Epilepsy/seizures	2.13 (0.39, 5.06)	11	NR	7	9	8	NR
Tetanus	2.01 (0.59, 4.09)	12	NR	NR	NR	18	12
Tuberculosis	1.85 (0.65, 3.62)	13	NR	12	13	4	15
Dengue	1.84 (1.13, 2.72)	14	NR	NR	12	10	NR
Sickle cell and thalassemia	1.52 (0.68, 2.63)	15	12	NR	NR	NR	13
Congenital anomalies	1.31 (0.58, 2.29)	16	2	9	11	13	19

Diagnosis	Prevalence per 1000 admissions (95% CI)	Global Rank	LA	NA	SA	SEA	SSA
Malignancy	1.18 (0.03, 3.34)	17	3	NR	NR	20	14
Liver disease, hepatitis, failure	1.06 (0.20, 2.49)	18	NR	2	5	16	25
Surgical conditions	0.92 (0.19, 2.06)	19	NR	NR	NR	21	18
Non-malignant hematologic conditions	0.81 (0.32, 1.48)	20	12	4	NR	NR	22
Trauma/injury	0.80 (0.46, 1.22)	21	10	9	NR	12	17
Congenital heart disease	0.77 (0.36, 1.30)	22	5	NR	NR	14	16
Toxic poisoning/ingestion	0.68 (0.28, 1.23)	23	11	7	14	18	20
Glomerulonephritis, nephrotic and nephritic syndrome	0.48 (0.05, 1.25)	24	8	NR	NR	NR	24
Diabetes/diabetic ketoacidosis and blood glucose disorders	0.22 (0.00, 0.67)	25	NR	12	NR	NR	26
Asthma	0.14 (0.00, 0.62)	26	NR	NR	NR	16	22
Cardiac failure	NR	NR	NR	NR	NR	NR	6
Renal failure	NR	NR	NR	NR	NR	NR	21
Urinary tract infection/pyelonephritis	NR	NR	NR	NR	NR	NR	27
Typhoid	NR	NR	NR	NR	NR	NR	28
COVID-19	NR	NR	NR	NR	3	NR	NR

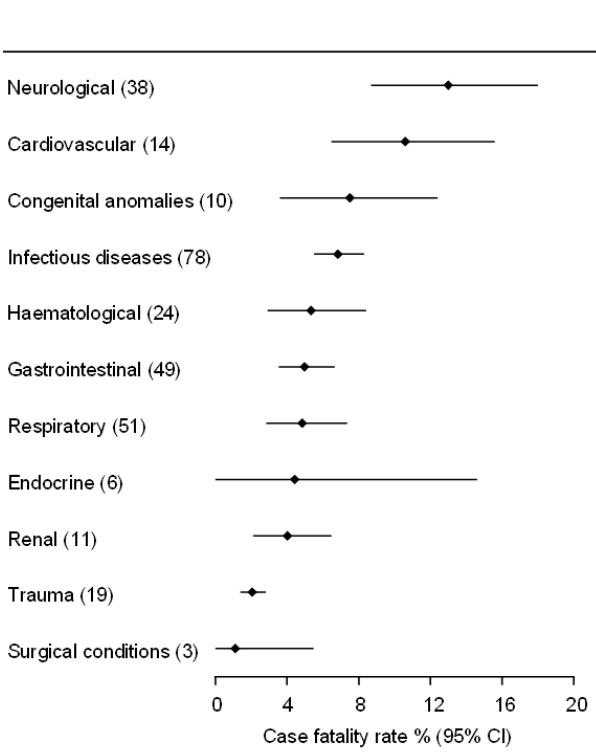
Figure 3.6 Overall and regional ranking of the cause of hospital death by diagnosis

Colors represent the ranking of the cause of mortality within each Global Burden of Disease (GBD) super region from red (highest ranking) to pink (lowest ranking). Estimates for Central Europe, Eastern Europe, and Central Asia (CE) are not included given limited data. LA: Latin America and Caribbean; NA: North Africa and Middle East; SA: South Asia; SEA: Southeast Asia, East Asia, and Oceania; SSA: Sub-Saharan Africa; CI: Confidence Interval; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; NR: not reported

Case Fatality Rate (CFR)

Organ System: The highest overall CFRs across LMICs occurred in neurological, cardiovascular, and congenital anomalies-related conditions (13% [95%CI 9-18%], 11% [95%CI 6-16%], and 8% [95%CI 4-12%], respectively, **Figure 3.7**). Neurological conditions had the highest CFR in NA (40% [95%CI 27-53%)]; cardiovascular conditions

had the highest CFR in SA (15% [95%CI 10-22]); and congenital anomalies had the highest CFR in SA (56% [95%CI 8-98%]).



	Overall (95% CI)	LA (95% CI)	NA (95% CI)	SA (95% CI)	SEA (95% CI)	SSA (95% CI)
Neurological (38)	13 (9-18)	6 (2-10)	40 (27-53)	15 (7-24)	4 (0.1-14)	15 (10-21)
Cardiovascular (14)	11 (6-16)	NR	NR	15 (10-22)	5 (2-9)	13 (11-16)
Congenital anomalies (10)	8 (4-12)	NR	40 (2-86)	56 (8-98)	1 (0-4)	6 (2-12)
Infectious diseases (78)	7 (6-8)	20 (0.9-52)	6 (1-14)	13 (6-22)	1 (0.4-3)	7 (6-9)
Haematological (24)	5 (3-8)	NR	NR	13 (11-16)	4 (0.6-9)	5 (3-8)
Gastrointestinal (49)	5 (4-7)	2 (0.3-4)	NR	8 (6-11)	3 (0.8-5)	6 (4-8)
Respiratory (51)	5 (3-7)	3 (3-4)	NR	8 (2-16)	3 (0.3-9)	5 (4-7)
Endocrine (6)	4 (0-15)	NR	25 (0-79)	9 (1-21)	0.4 (0.1-0.8)	6 (2-12)
Renal (11)	4 (2-6)	NR	NR	15 (9-22)	0.1 (0-0.3)	6 (3-10)
Trauma (19)	2 (1-3)	7 (2-15)	75 (46-96)	4 (2-6)	0.4 (0.2-0.7)	3 (1-5)
Surgical conditions (3)	1 (0-5)	NR	NR	NR	0 (0-0.1)	2 (0.7-5)

Figure 3.7 Case fatality rates in children admitted to hospital by organ system and Global Burden of Disease (GBD) super region

Organ systems are ordered according to the overall fatality (number of children with a specific cause of death/1000 children admitted with that cause) and the number in parenthesis next to each organ system represents the number of studies included in the analysis. Case fatality rate is presented as an overall estimate and by GBD super region with 95% confidence intervals (CI). Estimates for Central Europe, Eastern Europe, and Central Asia (CE) are not included given limited data. The hematological category includes oncological conditions. The numbers in () next to each category in the left column are the number of studies included in the overall analysis shown on the right. The categories are sorted according to the overall proportion across the super regions. The hematological category includes oncological conditions.
LA: Latin America and Caribbean; NA: North Africa and Middle East; SA: South Asia; SEA: Southeast Asia, East Asia, and Oceania; SSA: Sub-Saharan Africa; CI: Confidence Interval; NR: not reported

Diagnosis: The diagnoses with the highest overall CFRs across LMICs were tetanus, sepsis/septic shock, and meningitis/encephalitis (29% [95%CI 11-51%]; 20%

[95%CI 14-27%]; and 15% [95%CI 12-18%], respectively). The CFR for tetanus was highest in SSA (38% [95%CI 29-46%]), while for sepsis/septic shock, it was highest in LA (38% [95%CI 15-63%]), and for meningitis/encephalitis, it was highest in NA (50% [95%CI 31-69%]). Other notable causes of death with high CFRs include measles (14% [95%CI 3-31%]), other vaccine preventable diseases (14% [95%CI 0-37%]), HIV/AIDS related illnesses (13% [95%CI 9-18%]), and malnutrition (12% [95%CI 9-15%]). We observed significant differences (p <0.001) in cause-specific CFR by SDI quintile for malaria, pneumonia, diarrhea, and anemia; specifically, the CFR increased as SDI quintile decreased, though this was not consistent across all diagnoses (**Table 3.1**).

Table 3.1 Cause-specific case fatality rates by Socio-Demographic Index (SDI) quintile

Diagnosis	Low SDI	Low-Middle SDI	Middle SDI	p-value
	CFR (95%CI)			
Malaria	6.9 (4.3-9.9)	3.5 (2.3-4.9)	1.3 (0.8-1.9)	<0.001
Shock (not septic)	Not reported	12.9 (9.8-16.3)	Not reported	-
Malnutrition	11.6 (7.3-16.7)	12.8 (8.8-17.3)	12.9 (9.4-17.3)	0.92
Pneumonia and lower respiratory tract infection	6.2 (0.3-18.3)	5.5 (3.6-7.7)	1.0 (0.5-1.6)	<0.001
Sepsis and septic shock	18.0 (11.5-25.4)	23.3 (17.5-29.7)	8.6 (0.6-22.8)	0.14
Meningitis/encephalitis	15.4 (11.4-19.7)	16.5 (12.2-21.2)	4.7 (1.5-9.0)	0.001
Gastroenteritis and diarrhea	8.1 (3.9-13.6)	3.62 (2.0-5.7)	0 (0-0.03)	<0.001
Anemia	7.8 (3.6-13.3)	6.0 (2.8-10.3)	0.1 (0-0.1)	<0.001
HIV/AIDS and related conditions	13.4 (7.2-21.0)	17.1 (8.3-28.1)	6.5 (2.8-14.3)	0.15
Measles	14.7 (1.9-35.9)	12.0 (2.8-25.0)	Not reported	0.92

CFR: case-fatality rate; CI: confidence interval; SDI: Socio-Demographic Index; HIV: Human Immunodeficiency Virus; AIDS: Acquired immunodeficiency syndrome

Hospital admission

Organ System: The most common cause of pediatric admissions in LMIC hospitals were respiratory conditions, non-organ specific infectious diseases, and gastrointestinal conditions (cases/1000 admissions: 255 [95%CI 231-280]; 214 [95%CI 193-234]; 166 [95%CI 143-190]) (**Figure 3.8**). CE had the highest proportion of

admissions due to respiratory conditions (680 cases/1000 admissions [95%CI 644-716]), SSA had the highest proportion due to non-organ specific infectious diseases (281 cases/1000 admissions [95%CI 227-338]), and SA had the highest proportion due to gastrointestinal conditions (216 cases/1000 admissions [95%CI 153-287]).

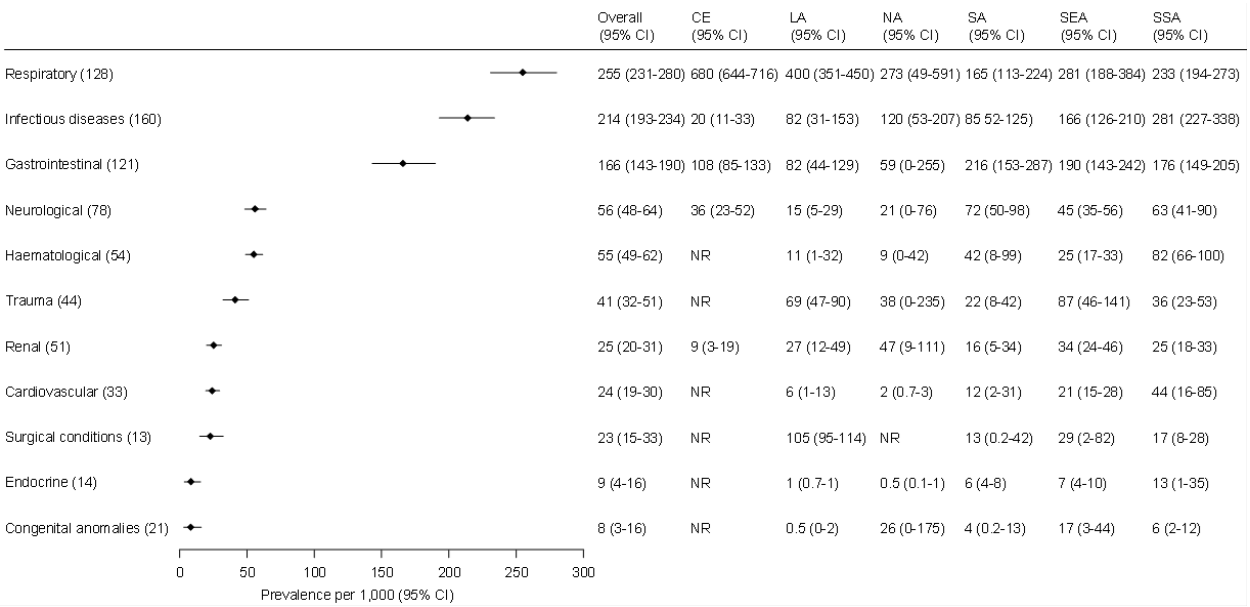


Figure 3.8 Common causes of hospital admission in children by organ system and Global Burden of Disease (GBD) super region

Organ systems are ordered according to the overall proportion of children with the cause of admission and the number in parenthesis next to each organ system represent the number of studies included in the analysis. Proportions are presented as an overall estimate and by GBD super region with 95% confidence intervals (CI). Estimates for Central Europe, Eastern Europe, and Central Asia (CE) are based on a single study of 638 children. The hematological category includes oncological conditions. The numbers in () next to each category in the left column are the number of studies included in the overall analysis shown on the right. Categories are sorted according to overall proportion across super regions. Hematological category includes oncological. CE: Central Europe, Eastern Europe, and Central Asia; LA: Latin America and Caribbean; NA: North Africa and Middle East; SA: South Asia; SEA: Southeast Asia, East Asia, and Oceania; SSA: Sub-Saharan Africa; CI: Confidence Interval; NR: not reported

Diagnosis: The most common causes of pediatric hospitalization were malaria, pneumonia, and gastroenteritis (cases/1000 admissions: 293 [95%CI 245-343]; 232 [95%CI 205-260]; and 134 [95%CI 114-155], respectively). SSA had the highest

proportion of hospital admissions due to malaria (324 cases/1000 admissions [95%CI 275-375]), contributed the most malaria studies (N=84/93), and accounted for most of the malaria-associated hospital admissions (N=193,321/204,958). The highest proportion of hospital admissions due to pneumonia occurred in NA (380 cases/1000 admissions [95%CI 343-417]) and due to gastroenteritis in SA (220 cases/1000 admissions [95%CI134-322]).

Discussion

This is the first systematic review to comprehensively identify the most common causes of pediatric hospital mortality in LMICs. All-cause pediatric hospital mortality across LMICs was 4%; this is consistent with data from East and West Africa and India (6-12%) and in contrast to 0.8% and 0.05% in the United States and Scotland, respectively.[118-123] Consistent with WHO, UNICEF, and GBD data, we observed differences in cause and burden of mortality across regions and SDI quintiles, and found that the overwhelming burden of pediatric acute illness was caused by preventable communicable diseases.[1,81,103-105] The most common causes of pediatric hospital admission and death in LMICs were related to non-organ specific infectious diseases (malaria), respiratory conditions (pneumonia), and gastrointestinal conditions (gastroenteritis and malnutrition). To have the greatest impact on regional pediatric hospital mortality, LA and SEA hospitals should focus on management of respiratory conditions, while SSA hospitals should focus on non-organ specific infectious diseases. Malnutrition, which is known to increase the risk of mortality,[124-126] was a common cause of pediatric hospital admission and mortality, primarily in SSA and SEA. Additionally, many conditions with high CFRs were vaccine-preventable and/or treatable with

appropriate antimicrobials and supportive care (e.g., tetanus, sepsis/septic shock, meningitis/encephalitis, measles, and HIV/AIDS). Primary prevention through vaccination; water, sanitation, and hygiene programs; improved nutrition; and mosquito control efforts are effective at reducing pediatric hospital admission directly and mortality indirectly.[127-133] Yet, public health efforts are insufficient and must be viewed in context and alignment with interventions to improve hospital care (**Figure 3.9**).

Figure 3.9 Actions to address preventable child mortality

Children in LMICs frequently overcome barriers to pre-hospital care, fragmented health systems, and transportation challenges to reach a hospital. Despite the fact that simple, cost-effective treatment strategies exist to manage the common causes of admission,[7,130,134,135] hospital mortality remains high. Most hospital deaths and long-term morbidity can be avoided with adequate emergency and critical care resources

and services.[7,29,100] In Sierra Leone, improving emergency care processes, staffing, and resource availability decreased pediatric hospital mortality from 12% to 6%.[121] The basic elements and required tools necessary to deliver essential emergency and critical care and to identify and treat hospitalized patients at high risk of mortality are effective, low-cost, and low-tech.[100] For example, treatment bundles for sepsis, the common pathway for most infectious disease-related deaths, have been shown to reduce mortality.[136-138] Respiratory conditions can progress to hypoxemic respiratory failure and death; resources for effective management include pulse oximetry monitoring, oxygen therapy, and non-invasive and invasive ventilation.[72,139] Gastrointestinal illnesses can progress to severe dehydration and death; dehydration can be treated with oral rehydration solution and/or intravenous fluids (IVF).[135] A recent survey of 238 hospitals in 60 countries, however, identified inconsistent availability of key resources required to care for acutely ill children including sepsis bundle resources, basic respiratory support, and dextrose containing IVF.[28] There is an urgent need for hospital-level, basic pediatric emergency and critical care resources and services in LMICs to manage common causes of admission and prevent mortality (**Supplemental Table 3.5**).[28,100]

The effect of socio-economic development on outcomes is best illustrated by the observed differences in CFR SDI quintiles; as SDI quintile and country income level increased from low- to middle-income, the CFR decreased 2-fold for sepsis/septic shock, 6-fold for pneumonia, and more than 80-fold for gastroenteritis. Tan, *et al*., found similar results in a global study of pediatric severe sepsis and septic shock; pooled CFRs were 32% in “less developed” compared with 19% in more developed countries.[33] Likewise, McAllister, *et al*., found that the CFR for children hospitalized with pneumonia

was higher in low- compared to middle-income countries.[5] Additional research is needed to test which socio-economic factors have the greatest impact on health outcomes. Collectively, these findings suggest that resource availability combined with improved access to high-quality hospital care can impact childhood outcomes.

There are several notable strengths of this study. The results further and independently support WHO, UNICEF, and GBD findings for the top causes of global childhood mortality and, unlike prior, large-scale global studies, represent an exclusively hospitalized patient population.[1,81,103-105] The focus on organ systems allows for assessment of required hospital resources to manage common conditions and reduce mortality. Furthermore, this systematic review relies on healthcare facility-level data generated in LMICs, as opposed to estimation techniques or imputation methods, a major criticism of previously published global health metrics.[107]

There are several limitations to this study. Our analysis was restricted to available, published data (grey literature excluded) and we imposed a language restriction, which may have introduced a selection bias. Though the search and inclusion/exclusion criteria were designed to exclude neonatal and adolescent populations, some neonatal and adolescent subjects were included, which may have influenced final estimates. Observed regional differences may have been influenced by available data, study selection, local health systems, and health-seeking behaviors. While most included studies had a low risk of bias, risk due to missing results (arising from reporting biases) could not be assessed. Similar to other observational studies, we were limited to the reported cause of admission/death, often a subjective diagnosis, which could result in misclassification and highlights the need for universal research

methods including standard data elements and diagnostic definitions.[140] Included studies represented LMICs disproportionately; some countries (e.g., Brazil) were overrepresented, while others (e.g., Sudan) contributed no data. Underrepresented countries tended to have fewer resources and political and/or economic instability, which can contribute to higher rates of childhood illness and mortality.[1] We also excluded disease-specific studies that did not report total hospital admissions and outbreak studies, which may have resulted in an underestimation for certain diseases (e.g., cholera). While sepsis and septic shock were listed as a cause of admission and death, we likely underestimated the overall burden of sepsis due to the organ systems-based categorization of diagnoses. We attempted to recategorize 'other' diagnoses or causes of death; however, many could not be recategorized, which may have caused an underestimate of cause-specific disease burden. Finally, this study was designed to capture hospital admission and death and not pre-hospital or post-discharge death, which are significant contributors to morbidity and mortality in children in LMICs.[124,141] For these reasons, this large-scale systematic review, while the first of its kind, likely underestimates the overall burden of childhood hospital mortality in LMICs.

Common causes of pediatric hospital mortality in LMICs are treatable and preventable. A coordinated global effort by ministries of health, philanthropic, non-governmental, and multinational organizations is required to address preventable child mortality by deploying targeted interventions, employing strategic resource allocation, and including emergency and critical care services in the global child health agenda (Figure 3.9). To further reduce global child mortality and achieve the SDG target, we need both public health measures and increased hospital resources tailored to the local

burden of disease. These findings are a call to action for increased, high-quality emergency and critical care resources in LMIC hospitals to prevent avoidable pediatric hospital mortality and effectively care for children with life-threatening conditions.

Chapter 4: Estimate of Pediatric Acute Critical Illness Across Different Sociodemographic Settings: The Global Pediatric Acute Critical Illness Point Prevalence Study

Summary

Background

Children and adolescents in resource-limited settings (RLS) bear a disproportionate burden of disease and mortality. Most life-threatening pediatric illnesses can be managed with basic critical care interventions, but in RLS they are often managed without adequate critical care services and outside of formal intensive care units (ICUs). The frequency of pediatric acute critical illness (P-ACI) in RLS is unknown, knowledge of which is needed to appropriately allocate available resources. This study estimated the proportion and etiology of P-ACI among children seeking care at RLS hospitals to inform resource allocation and improve hospital outcomes.

Methods

This is a prospective, multinational prevalence study of acutely ill or injured children aged 28 days-14 years who sought care at RLS hospitals. We excluded children with non-acute complaints. We followed admitted subjects for hospital outcomes and measured proportion of children with P-ACI, mortality, and length of stay. We used descriptive statistics to summarize site- and population-level data by sociodemographic index (SDI) category and multivariable logistic regression to determine whether SDI was independently associated with P-ACI.

Findings

The study included 46 sites from 19 countries (N=7457 subjects). In total, 986 subjects met criteria for P-ACI and the proportion of P-ACI ranged from 6-29%

depending on the SDI category. In a multivariable model, lower SDI category was associated with P-ACI. The most common diagnoses associated with P-ACI were pneumonia (N=152/986 [15%]), sepsis/septic shock (N=102/986 [10%]), and acute malaria (N=95/986 [10%]). Mortality occurred in 1% (N=68/7457) of subjects (range 0-6% depending on SDI category) and most deaths occurred within 48-hours of presentation (N=47/7457 [69%]).

Interpretation

P-ACI is common in RLS hospitals and most frequently caused by survivable infectious diseases that can be managed with basic critical care services that do not require an advanced ICU. A coordinated global effort is needed to increase high-quality, basic pediatric critical care services in RLS hospitals to decrease preventable hospital mortality and effectively care for children with life-threatening conditions.

Research in Context

Evidence before this study

The prevalence and etiology of P-ACI in RLS is unknown. Most modern global child health estimates – Global Burden of Disease (GBD) studies, World Health Organization (WHO), and United Nations Children's Fund (UNICEF) – provide population-level child mortality estimates and do not provide enough specificity and granularity to measure P-ACI or to determine facility-level estimates, which hospitals require to inform critical care resource allocation decisions. A recent systematic review of pediatric hospital mortality in low- and middle-income countries reported facility-level all-cause mortality but failed to capture children who survived critical illness. A review of

the literature identified several cross-sectional studies that reported cause of death and/or admission for children admitted to a pediatric intensive care unit (PICU), and numerous cohort studies of PICU patients that reported the prevalence of a single critical illness diagnosis; few reported data from more than one hospital or global region. Available global point prevalence studies measured the prevalence of specific pediatric critical illnesses, such as acute respiratory distress syndrome, neurological insults, and sepsis, but did not capture the prevalence of P-ACI overall. Additionally, the existing P-ACI literature frequently excluded critically ill children in settings without formal PICUs, making available results difficult to generalize to RLS. The resulting knowledge gap disproportionately affects the most vulnerable children. The objective of this study was to measure the proportion of pediatric acute critical illness (P-ACI) in children seeking hospital care in resource-limited settings (RLS).

Added value of this study

This point prevalence study is the first to measure the proportion of children with P-ACI in RLS hospitals using an inclusive, pragmatic definition and it includes data from 7,457 children from 46 hospitals across 19 countries. Among all children seeking care at participating RLS hospitals with an acute complaint, the proportion of children with P-ACI ranged from 6-29% depending on sociodemographic category. The most common causes of P-ACI were pneumonia, sepsis, and acute malaria, all communicable diseases with known, evidenced-based critical care treatment strategies. We also observed disparities in outcomes by sociodemographic category; both the proportion of children with P-ACI (29%) and all-cause mortality (2.5%) were highest in low-income countries. We identified critical needs requiring a focused effort to improve child health

outcomes at the facility-level. The results can be used to inform decision-making on strategic resource allocation and to advocate for critical care services to effectively care for children with life-threatening conditions.

Implications of all the available evidence

P-ACI and hospital mortality are consistently higher in RLSs compared with high-income settings. Most RLS hospital deaths could be avoided with reliable, timely, and high-quality pediatric critical care services, which are limited due to underfinanced health systems and insufficient equipment, trained personnel, and medications. The World Health Organization (WHO) recently approved a resolution in 2023 to strengthen global critical care services starting with first-level hospitals. Our results bolster this effort by providing facility-level data on the prevalence and etiology of P-ACI in RLS hospitals, which are required for setting a prioritized agenda targeting the greatest drivers of morbidity and mortality in hospitalized children. Finally, to guide further evidence-based local and global priority setting, resources are urgently needed to promote equity in global pediatric critical illness research, including support for investigators and study sites in RLS.

Introduction

In 2019, among the 7.4 million global deaths in children and adolescents, 80% occurred in resource-limited settings (RLS), which are settings characterized by a lack of funds to cover health care costs.[1] Acute, pediatric life-threatening conditions can be successfully managed with basic critical care services, which include fluid resuscitation, oxygen, respiratory support, and robust supportive care. Unfortunately, hospitals in RLS

are often ill-prepared to manage critically ill children,[7,28,70,87,142,143] placing children in these settings at higher risk of death.[1,28,57,70,83,89,103] Recognizing this, in May 2023 the World Health Organization (WHO) resolved to strengthen and integrate critical care services into health systems globally.[48,102]

Historically, the approach to global child health has been siloed; resource allocation, healthcare worker training, and implementation of interventions have focused on a single condition, such as malaria or pneumonia.[142,144] This narrow approach creates gaps in care and is an inefficient use of available resources. Furthermore, critical care capacity, and specifically dedicated Pediatric Intensive Care Units (PICUs), are severely limited in RLS where critical illness is often managed outside of formal intensive care units (ICUs).[58,145,146] As with vertical clinical health programs, recent global pediatric research studies have focused on the prevalence of individual critical illnesses (e.g., acute respiratory distress syndrome, neurological insults, sepsis),[70,71,73,89,147] failing to measure the prevalence of pediatric acute critical illness (P-ACI) overall, which are life threatening conditions that require time-sensitive interventions to prevent serious morbidity or death. P-ACI prevalence is essential information for policymakers setting health agendas, hospital administrators determining resource allocation, and health system leaders charged with implementing targeted interventions to improve outcomes. Additionally, existing studies required PICU admission for inclusion, thus excluding entire patient populations, limiting generalizability, and likely underestimating disease prevalence and mortality in this vulnerable, under-studied population. Without global, facility-level data on the prevalence, etiology, and risk factors associated with P-ACI in RLS, one cannot

implement context-appropriate, evidence-based interventions to improve outcomes, or appropriately allocate available resources.

Paired with the global disparity of available pediatric critical care services is the absence of available P-ACI data;[7,28,70,87,142,143] there are no estimates of P-ACI prevalence nor a comprehensive exploration of P-ACI etiology from RLS hospitals globally.[142,145] To address this knowledge gap and health inequity, we conducted the Global Pediatric Acute cRitical Illness point prevalence sTudY (Global PARITY) to describe the characteristics and hospital outcomes of children seeking hospital care due to an acute illness or injury; to determine the proportion and etiology of P-ACI; and to describe the characteristics and hospital outcomes of children with P-ACI admitted to participating hospitals in RLS.

Methods

Study Design

This prospective, multinational point prevalence study conducted over four, 24-hour sampling frames (July 20, 2021-July 12, 2022) to capture seasonal variation (e.g., respiratory viral season, malaria season, etc.) and estimate annual hospital volume and case-mix. We offered one additional sampling frame for sites that participated in <4 frames due to delayed Institutional Review Board (IRB) approval or COVID-19 surges precluding data collection. The study setting included hospitals in RLS across Global Burden of Disease (GBD) super-regions (excluding High-Income North America, Europe, and Oceania): Central Europe, Eastern Europe, and Central Asia (CE); Latin America and Caribbean (LA); Southern Latin America (SLA); North Africa and Middle

East (NA); South Asia (SA); Southeast Asia, East Asia, and Oceania (SEA); and Sub-Saharan Africa (SSA).[115] RLS are characterized by limited access to medication, equipment, supplies, and devices; less-developed infrastructure; and fewer or less-trained personnel. Prospective sites self-identified as RLS and completed a detailed Hospital Resource Survey.[28] Additional site eligibility criteria included: acute care hospital designation; provision of acute emergency and inpatient care to a general population of children (i.e., not a specialty hospital); reliable internet connection; ability to communicate in English; existence of an established Institutional Review Board (IRB) or ethical approval process; and data contribution to at least two sampling frames. Participating hospitals were recruited through existing networks: Pediatric Acute Lung Injury and Sepsis Investigators' (PALISI) Research Network, St. Jude Global Critical Care Program, Pediatric Acute & Critical Care Medicine Asian Network (PACCMAN), World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS), and Red Colaborativa Pediátrica de Latinoamérica (LARed Network). We enrolled at least one site per GBD super-region. We determined sociodemographic category using the GBD 2017 Socio-Demographic Index (SDI), a composite indicator that represents a country's development status and correlates with health outcomes, and categorized participating sites as low- [LIC], low-middle- [LMIC], middle- [MIC], and high-middle-income countries [HMIC] based on SDI quintile.[8] This study was exempt from IRB review by the University of Maryland IRB (HP-00086107) and was reviewed by each site's IRB prior to data collection. The study methods have been previously published: https://www.frontiersin.org/articles/10.3389/fped.2021.793326/full.[148] We followed the STROBE reporting guidelines.[149]

Participants

The study population included acutely ill or injured children aged 28 days to 14 years seeking care at a RLS hospital. We excluded neonates because the etiology of critical illness often differs significantly from older children, and adolescents >14 years because they are frequently considered adults in RLS settings. We excluded children presenting for a follow-up visit, vaccinations, suture removal, or other non-acute complaint, and children with a corrected gestational age <42 weeks. The notes of all patients were screened for eligibility upon their arrival to the Emergency Department (ED) or inpatient unit if directly admitted. Admitted subjects were followed for outcomes through hospital day 30; those discharged from the ED or transferred to another hospital were not followed for additional outcomes and outcomes are unknown for those who left against medical advice or absconded. Subjects received routine care per local standards and resource availability. Individual patient consent was not required as data collection consisted of chart review without extraction of patient identifiers. There was no target sample size for this descriptive study; the number of subjects per site was dependent on site-specific factors.

Procedures

All participating sites successfully completed ethics training, study protocol training, and a pilot study. Each site had a research team led by the local principal investigator (PI) that collected data using case report forms available in English, French, Portuguese, and Spanish (**Supplemental Table 4.1**). Deidentified patient data, including biological sex, were collected by chart review and entered electronically into REDCap (Research Electronic Data Capture), a secure, web-based application and

electronic data capture tool hosted at the University of Maryland.[95] We extracted hospital characteristics; patient characteristics including demographics; anthropometrics; comorbidities; vital signs; laboratory test and imaging results; and hospital outcomes. To minimize loss to follow-up and missingness, we restricted outcomes to inhospital events and performed data audits and quality checks with each sampling frame (Appendix).

The primary outcome was prevalence of P-ACI, defined as the proportion of children that met any of the following criteria within 48 hours of presentation: death; admission/transfer to a high-dependency unit (HDU) or ICU; transfer to another institution for a higher level-of-care; or receipt of critical care-level interventions (vasoactive infusion, invasive mechanical ventilation [IMV], or non-invasive ventilation [NIV]). HDU and ICU status was determined by the site, could be a mixed or pediatric unit, and indicated a higher level of support and/or monitoring compared to the general ward. Vasoactive infusion was defined as a continuous intravenous medications used to increase cardiac output or blood pressure (e.g., epinephrine/adrenaline, norepinephrine/noradrenaline, dopamine, etc.). IMV was defined as the placement of an endotracheal tube and use of a mechanical ventilator. NIV was defined as the use of high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP). In all subjects, we assessed for the secondary outcome of mortality; in subjects with P-ACI we evaluated etiology of critical illness and frequency of P-ACI criterion; and in admitted subjects, we measured inhospital mortality, length of hospital stay (LOS) among survivors, and hospital outcome. Severity of illness was characterized with the Lambaréné Organ Dysfunction Score (LODS), a

simple clinical mortality prediction score comprised of three physical signs (deep breathing, prostration, and altered mental status) that was developed and validated in RLS.[150] Malnutrition was defined as a weight-for-age Z score <2 standard deviations (SD) below the median for age using WHO standards or as a comorbid condition recorded by the treating physician.[151] Other comorbid conditions were extracted from the medical record as documented.

Statistical analysis

We merged data from all sites and sampling frames for processing and analysis using SAS version 9.5 (SAS Institute, Cary, NC, USA). We report site characteristics by sociodemographic category. We assessed for associations between subject characteristics and P-ACI status and reported the prevalence of P-ACI within each characteristic. We developed a multivariable logistic regression model to test whether sociodemographic category had an independent association with P-ACI, and adjusted for age, sex, severity of illness, and comorbidities, which were selected based on their empiric significance in the literature.[150,152-154] We reported missing data and did not impute missing values for independent variables or outcomes. We used Kaplan-Meier survival curves to describe all-cause mortality over time by sociodemographic category. We determined etiology of P-ACI using documented physician diagnosis and ranked diagnoses overall and by sociodemographic category. We excluded 'other' diagnoses from the ranking, which were a heterogeneous group of conditions that differed between sites and precluded comparisons across categories. We assessed ties using the standard competition ranking method. We performed sensitivity analyses to explore the potential effect of those without final outcomes on the P-ACI and mortality estimates.

We reported odds ratios (OR) and 95% confidence intervals (CI) and considered p-values <0.05 (two-sided) to be statistically significant. We made no adjustment in the analysis for multiple comparisons.

Results

Participating Site Characteristics

A total of 46 sites from 19 countries and six GBD super regions (**Figure 4.1**) contributed data for analysis (**Supplemental Table 4.2**).

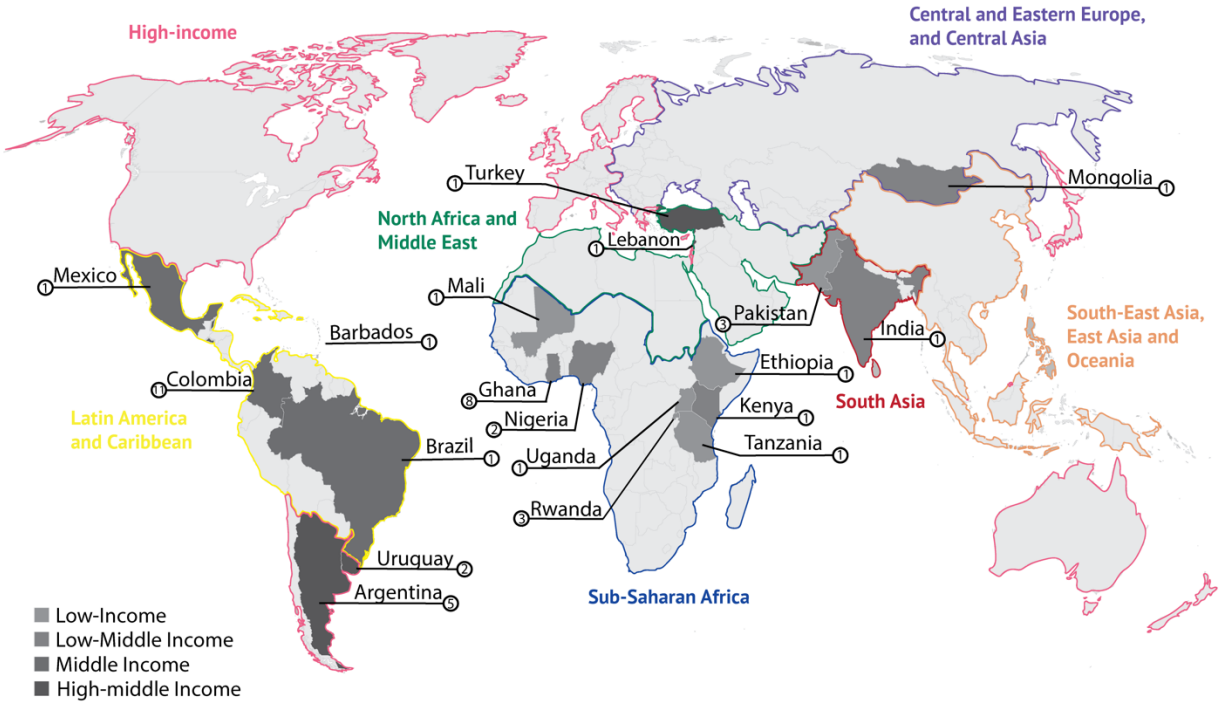


Figure 4.1 Map of Global PARITY participating sites
Global Burden of Disease super-regions are outlined and labeled in color. Sociodemographic category (low-income, low-middle income, middle income, and high-middle income) of participating sites is shown in greyscale.

Among participating hospitals, 76% (N=35/46) were public, 89% (N=41/46) were urban, and 94% (N=43/46) were academic centers; **Table 4.1** shows the hospital characteristics for participating sites categorized by sociodemographic index.

Table 4.1 Participating site hospital characteristics by sociodemographic category (SDI)

Hospital Characteristic	Total N (%) (N=46)	Low-Income N (%) (N=10)	Low-Middle-Income N (%) (N=13)	Middle-Income N (%) (N=13)	High-Middle-Income N (%) (N=10)
Hospital Funding Source					
Private	9 (20 %)	1 (10 %)	1 (8 %)	6 (46 %)	1 (10 %)
Public	35 (76 %)	9 (90 %)	11 (85 %)	7 (54 %)	8 (80 %)
Mixed	2 (4 %)	0 (0 %)	1 (8 %)	0 (0 %)	1 (10 %)
Practice Location					
Rural	5 (11 %)	2 (20 %)	3 (23 %)	0 (0 %)	0 (0 %)
Urban	41 (89 %)	8 (80 %)	10 (77 %)	13 (100 %)	10 (100 %)
Academic Center	43 (94 %)	10 (100 %)	13 (100 %)	10 (77 %)	10 (100 %)
Average Number of Pediatric ED Visits per Day					
0 - 100	35 (76 %)	8 (80 %)	11 (85 %)	11 (85 %)	5 (50 %)
101 - 500	11 (24 %)	2 (20 %)	2 (15 %)	2 (15 %)	5 (50 %)
Average Number of Pediatric Hospital Admissions per Day					
0 - 20	32 (70 %)	7 (70 %)	11 (85 %)	6 (46 %)	8 (80 %)
21 - 60	7 (15 %)	2 (20 %)	2 (15 %)	2 (15 %)	1 (10 %)
> 60	7 (15 %)	1 (10 %)	0 (0 %)	5 (39 %)	1 (10 %)
Average Number of Pediatric Inpatients on Any Given Weekday					
0 - 50	28 (61 %)	3 (30 %)	8 (62 %)	12 (92 %)	5 (50 %)
51 - 100	9 (20 %)	4 (40 %)	4 (31 %)	1 (8 %)	0 (0 %)
> 100	9 (20 %)	3 (30 %)	1 (8 %)	0 (0 %)	5 (50 %)
Intensive Care Resource Availability					
Pediatric Intensive Care Unit	30 (65 %)	5 (50 %)	6 (46 %)	10 (77 %)	9 (90 %)
Non-Invasive Ventilation	44 (96 %)	9 (90 %)	13 (100 %)	12 (92 %)	10 (100 %)
Invasive Mechanical Ventilation	36 (78 %)	6 (60 %)	8 (62 %)	12 (92 %)	10 (100 %)
Vasoactive Support	45 (98 %)	9 (90 %)	13 (100 %)	13 (100 %)	10 (100 %)
Number of Subjects Enrolled	7457	1745	1604	1974	2134

No missing data in this table
ED: Emergency Department, ICU: Intensive Care Unit

A PICU was available in 65% (N=30/46) of sites, and most sites reported the capacity to provide NIV (96%, N=44/46), IMV (78%, N=36/46), and vasoactive support (98%, N=45/46). Participating site characteristics were similar by SDI (**Supplemental Table 4.3**) and the variation in the number of subjects per institution, country, and region are in **Supplemental Table 4.4**.

Cohort Characteristics

We screened a total of 11065 pediatric patients for eligibility and enrolled N=7457, as shown in **Figure 4.2**.

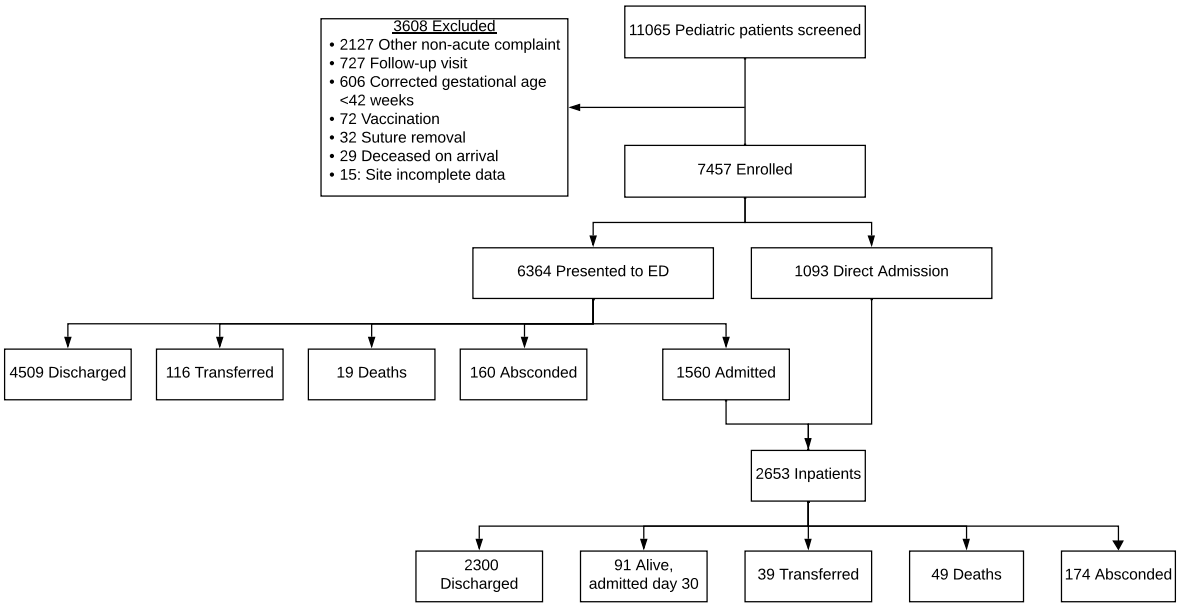


Figure 4.2 Schematic depicting screening and subject enrollment

Overall, 36% (N=2653/7457) of subjects were admitted to the hospital and followed for hospital outcomes; 25% (N=1560/7457) were first evaluated in the ED and 15% (N= 1093/7457) were directly admitted from an outside clinic or hospital (**Figure 4.2**). Presentation patterns varied by sociodemographic category; the proportion of subjects admitted to the hospital decreased as sociodemographic category increased (LICs: N=1145/1604 [66%] vs. HMICs N=235/2135 [13%]) (**Supplemental Figure 4.1)**. Among those admitted (N=2653), 87% (N=2300/2653) were discharged alive, 7% (N=174/2653) absconded, and 3% (N=91/2653) were inpatient on day 30, and 2% (N=49/2653) died. The total median LOS was 3 [IQR: 1-5] days. LOS and hospital outcomes varied by

sociodemographic category. Mortality occurred in 1% (N=68/7457) of all subjects and the highest proportion of deaths occurred in LICs (2.4%, N=41/1717) (**Figure 4.3**).

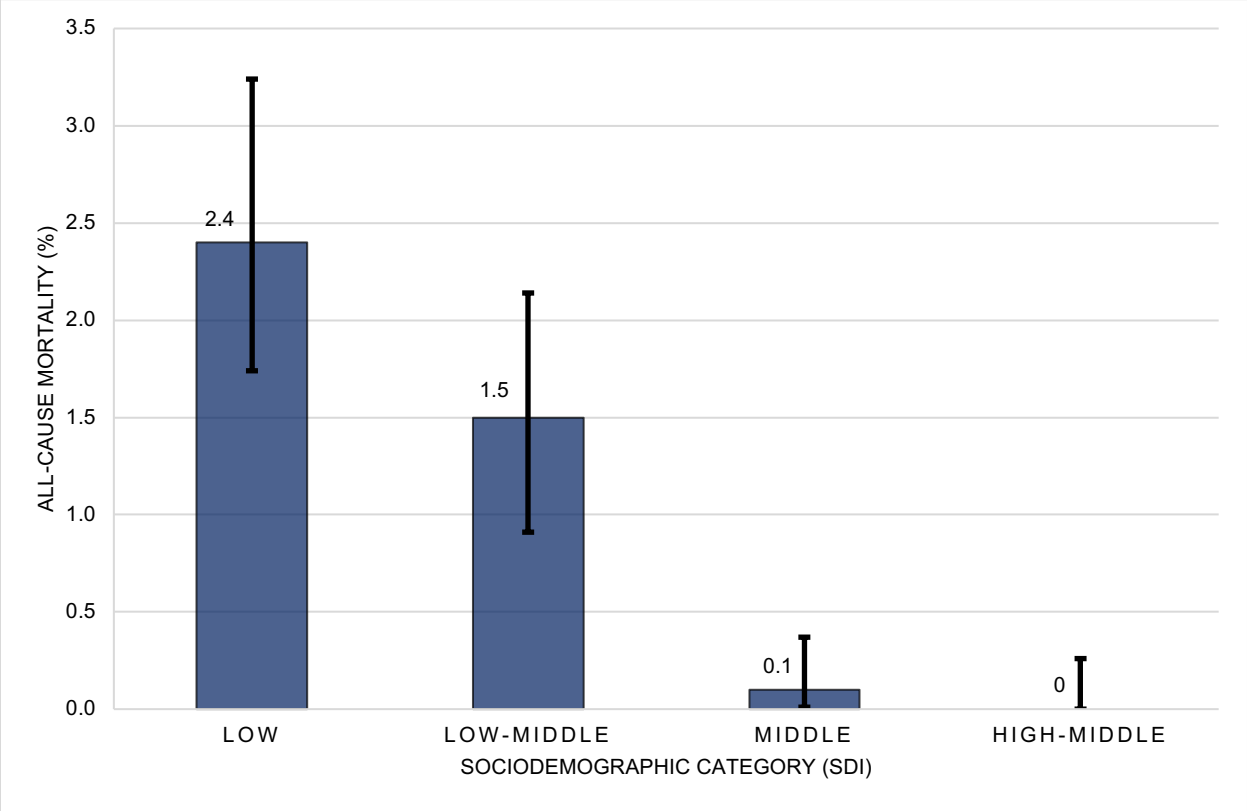


Figure 4.3 All-cause mortality by sociodemographic category
Proportion of subjects seeking care at a participating resource-limited setting hospital for an acute illness or injury who died after arriving to the hospital by sociodemographic index (SDI) category.

Most deaths occurred within 48 hours of presentation and in facilities without a dedicated PICU (N=47/68 [69%] and N=44/68 [65%], respectively) (**Figure 4.4**).

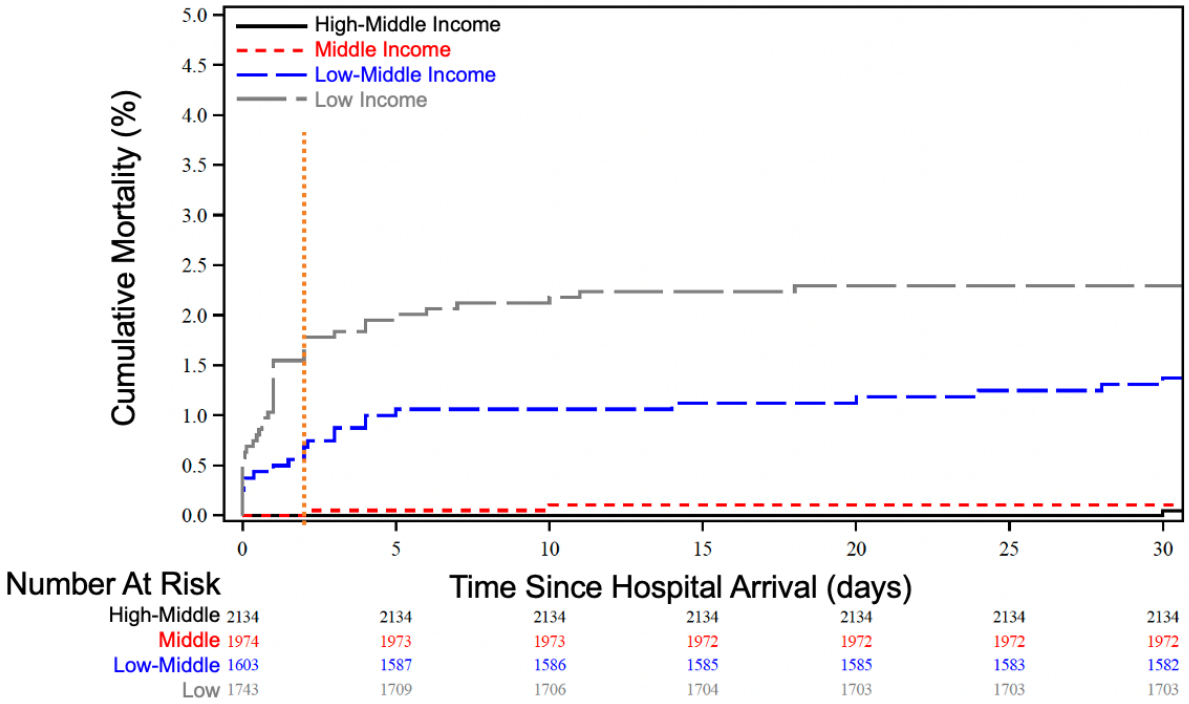


Figure 4.4 Cumulative probability of all-cause mortality over time by sociodemographic category
The number at risk table is shown below the figure. The dotted vertical line marks mortality at 48-hours after arrival.

Enrollment numbers varied by region and were evenly distributed by sociodemographic category (**Table 4.2**). Among those enrolled, the median age was 5.8 years (IQR 1.2-7.0), with 62% (N=4625/7453) of subjects below the age of five years, and 45% (N=3368/7457) were female (**Table 4.3**). Regarding comorbidities, 27% (N=2040/7457) had at least one comorbidity, and malnutrition was the most common (14%, N=1009/7455) (**Table 4.3**). Type and number of comorbidities varied by sociodemographic category; LICs had the highest proportion of malnutrition cases (55%, N=555/1009) and subjects with ≥2 comorbidities (39%, N=174/448) (**Supplemental Table 4.3**). Most subjects (85%, N=6026/7038) had a severity of illness score of '0' at presentation, and the proportion of subjects with elevated severity of

illness decreased as sociodemographic category increased (**Table 4.3**, **Supplemental Table 4.3**). The most common presenting diagnoses were communicable infectious diseases (N=5037/7457 [68%]).

Table 4.2 Participating subject geographical characteristics by critical illness status and proportion with acute critical illness

Geographical Characteristic	Total N (%) (N=7457)	With Critical Illness N (%) (N=986)	Without Critical Illness N (%) (N=6471)	Proportion with critical illness (%)	P-Value*
Global Burden of Disease (GBD) Super Region					
Southern Latin America	1912 (26 %)	215 (22 %)	1697 (26 %)	11%	<0.0001
Latin America and Caribbean	1983 (27 %)	120 (12 %)	1863 (29 %)	6%	
Sub-Saharan Africa	1319 (18 %)	430 (44 %)	889 (14 %)	33%	
North Africa and Middle East	213 (3 %)	14 (1 %)	199 (3 %)	7%	
South Asia	1332 (18 %)	179 (18 %)	1153 (18 %)	13%	
Central Europe, Eastern Europe, and Central Asia	698 (9 %)	28 (3 %)	670 (10 %)	4%	
Data Missing	0	0	0		
Sociodemographic category					
High-Middle Income	2134 (29 %)	236 (24 %)	1898 (29 %)	11%	<0.0001
Middle-Income	1974 (27 %)	113 (12 %)	1861 (29 %)	6%	
Low-Middle Income	1604 (22 %)	125 (13 %)	1479 (23 %)	8%	
Low-Income	1745 (23 %)	512 (52 %)	1233 (19 %)	29%	
Data Missing	0	0	0		

Table 4.3 Participating subject characteristics by critical illness status and proportion with acute critical illness

Patient Characteristic	Total N (%) (N=7457)	With Critical Illness N (%) (N=986)	Without Critical Illness N (%) (N=6471)	Proportion with critical illness (%)	P-Value*
Age Categories					
10-14 years	1097 (15 %)	128 (13 %)	969 (15 %)	12%	<0.0001
5-9 years	1731 (23 %)	224 (23 %)	1507 (23 %)	13%	
1-4 years	3065 (41 %)	353 (36 %)	2712 (42 %)	12%	
Under 1 year	1560 (21 %)	279 (28 %)	1281 (20 %)	18%	
Data Missing	4	2	2		
Biological Sex					
Female	3368 (45 %)	443 (45 %)	2925 (45 %)	13%	0.91
Male	4084 (55 %)	541 (55 %)	3543 (55 %)	13%	
Data Missing	5	2	3		
Comorbid Conditions					
Asthma	297 (4 %)	46 (5 %)	251 (4 %)	15%	0.24
Data Missing	4	2	2		
Malnutrition	1009 (14 %)	223 (23 %)	786 (12 %)	22 %	<0.0001
Data Missing	2	1	1		
Confirmed or Suspected Congenital Heart Disease	123 (2 %)	47 (5 %)	76 (1 %)	38 %	<0.0001
Data Missing	2	1	1		
Cancer/Malignancy	109 (2 %)	36 (4 %)	73 (1 %)	33 %	<0.0001
Data Missing	4	2	2		
Cerebral Palsy and/or Developmental Delay	198 (3 %)	45 (5 %)	153 (2 %)	23 %	<0.0001
Data Missing	1	1	0		
Epilepsy	242 (3 %)	54 (6 %)	188 (3 %)	22%	<0.0001
Data Missing	1	1	0		
Sickle Cell Disease	139 (8 %)	78 (8 %)	61 (1 %)	56 %	<0.0001
Data Missing	2	1	1		

Patient Characteristic	Total N (%) (N=7457)	With Critical Illness N (%) (N=986)	Without Critical Illness N (%) (N=6471)	Proportion with critical illness (%)	P-Value*
Genetic or Congenital Disorder	188 (3 %)	54 (6 %)	134 (2 %)	29 %	<0.0001
Data Missing	4	1	3		
Other Comorbidity	298 (4 %)	59 (6 %)	239 (4 %)	20 %	0.0006
Data Missing	0	0	0		
Comorbidity Count					
None	5417 (73 %)	516 (52 %)	4901 (76 %)	10 %	<0.0001
One	1592 (21 %)	333 (34 %)	1259 (20 %)	21 %	
Two or More	448 (6 %)	137 (14 %)	311 (5 %)	31 %	
Data Missing	0	0	0		
Severity of Illness (LODS)					
0	6026 (86 %)	578 (63 %)	5448 (89 %)	10 %	<0.0001
1	933 (13 %)	285 (31 %)	648 (11 %)	31 %	
≥ 2	79 (1 %)	53 (6 %)	26 (0.4%)	67 %	
Data Missing	419	70	349		
LODS: Lambaréné Organ Dysfunction Score					

Pediatric Acute Critical Illness

Overall, 6-29% (Total N=986/7457) of subjects presenting to the hospital with an acute complaint met criteria for P-ACI depending on sociodemographic category, and LICs had the highest proportion of P-ACI (29%, N=512/1745) (**Figure 4.5, Table 4.4**).

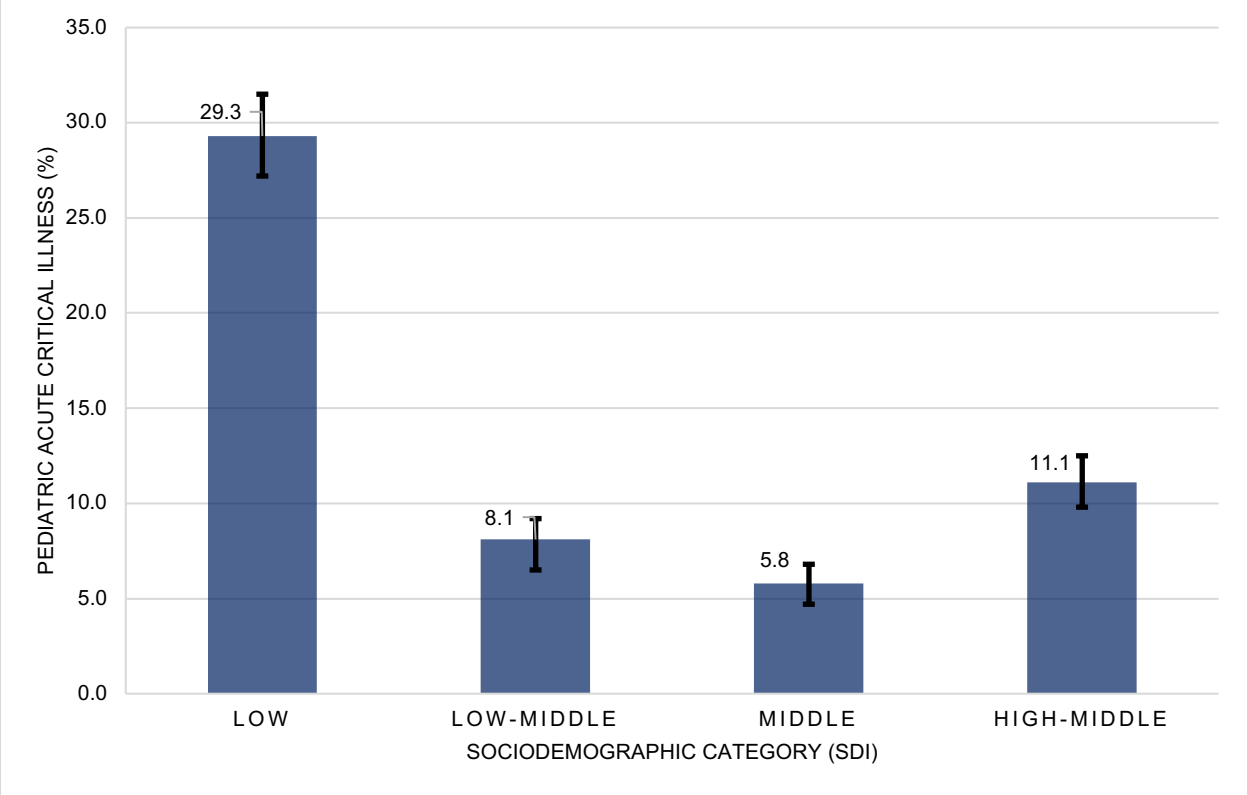


Figure 4.5 Pediatric acute critical illness by sociodemographic category
Proportion of subjects seeking care at a participating RLS hospital for an acute complaint who met criteria for acute critical illness by sociodemographic index (SDI) category.

Table 4.4 Proportion of subjects with acute critical illness and the individual components of the acute critical illness definition
Critical care level interventions included vasoactive, non-invasive ventilation, or invasive mechanical ventilation support.

Acute Critical Illness Definition Criterion	Total N (%) (N=986)
Death Within 48 Hours	47 (5%)
Admission/Transfer to an HDU or ICU	769 (78%)
Transfer to Another Institution with a Higher Level of Care	144 (15%)
Received Critical-Level Interventions	178 (18%)
Acute Critical Illness in the Cohort	986/7457 (13%)
HDU: high-dependency unit; ICU: intensive care unit	

The frequency of primary P-ACI criterion varied by sociodemographic category (**Supplemental Figure 4.2**). Compared to other GBD super regions, SSA had the highest proportion of P-ACI (33%, N=430/1319) (**Table 4.2**). Compared to other age groups, the proportion of P-ACI was highest in subjects <1 year (18%, N=279/1560) (**Table 4.3**). Relative to other or no comorbidities, the highest proportion of P-ACI occurred in those with sickle cell disease (56%, N=78/139) or ≥2 comorbidities (31%, N=137/448), respectively (**Table 4.3**). The proportion of P-ACI was highest in those with a severity of illness score of '≥2' (67%, N=53/79) (**Table 4.3**). Among those with P-ACI (N=986), the most common diagnoses were infectious: pneumonia (N=152/986 [15%]), sepsis/septic shock (N=102/986 [10%]), and acute malaria (N=95/986 [10%]); however, we observed significant variation by sociodemographic category, with pneumonia the most common in LICs and injuries and trauma the most common in the other sociodemographic categories (**Figure 4.6**).

Diagnosis	Overall Ranking	LIC (N=509)	LMIC (n=124)	MIC (n=122)	HMIC (n=232)
Pneumonia	1	1	2	4	4
Sepsis or septic shock	2	2	10	13	19
Acute Malaria	3	3	14	21	30
Injuries and Trauma	4	6	1	1	1
Diarrhea/gastroenteritis	5	4	6	3	5
Bronchiolitis	6	6	10	2	2
Upper respiratory tract infection or croup	7	12	4	5	3
Congenital malformations	8	21	3	5	6
Meningitis or Encephalitis	9	5	10	13	25
Cancer/malignancy	10	13	5	21	7

Figure 4.6 Most common diagnoses associated with acute critical illness in the overall cohort and by sociodemographic category

Column numbers in parentheses represent the number in each sociodemographic category; numbers in individual cells represent the ranking (1=most common). Darker red indicates higher rankings (more common) within and grey indicates rankings outside of the top 10 overall diagnoses. LIC: Low-Income Country; LMIC: Low- and Middle-Income Country; MIC: Middle-Income Country; HMIC: High-Middle-Income Country.

Median LOS was longer in subjects with P-ACI (**Supplemental Table 4.5**). In a multivariable model, LICs compared to HMICs had an adjusted OR of 1.86 (95%CI 1.54, 2.24) for P-ACI (**Table 4.5**). Additionally, we observed a statistically significant interaction between severity of illness and sociodemographic category and severity of illness and age; subjects from LICs and children under 5 years of age had increased severity of illness on arrival to the hospital.

Table 4.5 Association between sociodemographic category (SDI) and pediatric acute critical illness

Multivariable logistic regression showing unadjusted odds ratio (OR), adjusted OR, and 95% confidence intervals (CI) for acute critical illness. Adjusted model includes biological sex, age, severity of illness, and any comorbidity.

Sociodemographic category	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted p-Value
Middle	0.41 (0.33, 0.52)	0.38 (0.30, 0.48)	<0.0001
Low-Middle	0.57 (0.45, 0.71)	0.46 (0.36, 0.59)	
Low	2.55 (2.14, 3.04)	1.86 1.54, 2.24)	
Reference group: High-Middle; OR: Odds ratio; CI: Confidence interval			

Discussion

This is the first large-scale pediatric prevalence study of acute critical illness in children across RLS hospitals. We report that P-ACI occurred in 6-29% of children presenting to participating RLS hospitals with an acute complaint, depending on sociodemographic category. All-cause cohort mortality was 1%, and similar to prior pediatric RLS studies,[57] the majority of in-hospital mortality occurred early, within 48 hours of presentation. There was a significant disparity in the proportion of P-ACI and all-cause mortality, with the highest estimates from LICs (29% and 2.5%, respectively).

The most common causes of P-ACI were pneumonia, sepsis, and acute malaria for which critical care interventions have been shown to be effective in RLS, including pulse oximetry, oxygen therapy, and NIV/IMV for pneumonia; [5,54] treatment bundles for sepsis; [51-53] and parenteral artesunate and blood transfusion for severe malaria.[144] There is significant overlap in the clinical skills and resources required to manage these conditions; pneumonia and malaria commonly cause sepsis;[155] blood transfusions are administered to improve oxygen carrying capacity in sepsis;[156] and oxygen is the treatment for hypoxia due to sepsis, malaria and countless other conditions.[156] Instead of a siloed approach, RLS need essential critical care healthcare provider training and basic critical care services with the capacity to manage acutely ill and injured children from common causes of P-ACI. It is both infeasible and unnecessary to have multidisciplinary PICUs in all facilities; the United States, for example, has a three tiered pediatric critical care model (community-based, tertiary, specialized) with 8 PICU beds per 100,000 population.[157,158] In RLS, first-level hospitals should have the capacity to

deliver basic pediatric critical care services, and fully supported, multidisciplinary PICUs should be strategically placed to meet the needs of the local population. This must be integrated within a strong health system that includes a robust referral and efficient patient transport system.

This study also identified several risk factors for P-ACI in RLS: younger age, presence of a comorbidity, and lower sociodemographic category. We observed increased P-ACI in LICs, and subjects in those settings presented to the hospital with a higher severity of illness, potentially due to delays in presentation,[51] etiology of illness,[159] and increased comorbidities like malnutrition, which is highly associated with mortality.[124-126] Finally, we observed that socio-economic development impacted outcomes; in the multivariable model, even when age, severity of illness, and comorbidities were controlled for, sociodemographic category remained a strong, independent risk factor for P-ACI. There is ample support for this finding in other literature; a recent systematic review of pediatric hospital mortality in LMICs observed that as sociodemographic category increased, the case fatality rate (CFR) decreased 2-fold for sepsis/septic shock, 6-fold for pneumonia, and more than 80-fold for gastroenteritis. Two other global pediatric systematic reviews reported similar results: the sepsis CFR was 1.7 times as high in “less developed” compared to “more developed” countries (32% vs. 19%, respectively), [7] and the pneumonia CFR was higher in LICs compared to MICs. [6] These findings suggest that resource availability and access to high-quality care can impact child mortality. Future research should explore which socio-economic and development factors have the greatest impact on child health outcomes especially in RLS.

The highest proportion of P-ACI was in LICs followed by HMICs, which has been previously described.[160] The relative increase in P-ACI in HMICs, compared with LMICs and MICs, was driven by an increase in the proportion of children admitted/transferred to an HDU/ICU. Admission criteria, desire for increased monitoring, or resource availability and not severity of illness may be behind the decision to admit/transfer subjects to an HDU/ICU in HMICs.[158] In contrast, mortality followed an inverse relationship, decreasing as sociodemographic category increased, which has also been observed previously.[1,103] This implies that critically ill children are being identified and transferred to the highest level of care available, and their outcomes are influenced by what that level of care can provide.

We recognize several limitations. We attempted to recruit centers through existing, professional networks from a wide range of countries and regions; however, some regions were under-represented (e.g., NA and Southeast Asia) and regions and sociodemographic categories are highly correlated (e.g., there are no LICs is LA while there are many in SSA). Local IRB approval and associated costs, site inclusion requirements, and the COVID-19 pandemic may have limited center participation. Consequently, the study sample may not be representative of a given country or region, and we may have unintentionally targeted urban, academic centers, with more resources, as evidenced by the proportion of sites with a PICU. More data are needed from lower-level healthcare facilities, including available resources to manage critically ill children and patient outcomes. Sampling may have introduced a selection bias; however, included centers represented all continents, regions, and relevant sociodemographic categories, and the cause of P-ACI findings are consistent with the

most common causes of admission and mortality from a recent systematic review, as well as WHO, UNICEF, and GBD population-level data.[1,81,103-105] To date, this is the largest and most rigorous published study of this type; therefore, we believe that our findings are robust and generalizable to other RLS. Another limitation is that the Global PARITY definition of P-ACI, while inclusive and pragmatic, has not been previously validated. This definition may have over- or underestimated P-ACI, though other multicenter RLS studies have used similar definitions.[101,161] The proportion and causes of P-ACI were similar across LMICs, MICs, and HMICs; therefore, we believe that our definition of P-ACI was well designed to measure P-ACI across resource-variable settings, with or without a formal PICU, among different health seeking behaviors, and with a varied case-mix. Our definition also included acute stabilization, initiation of critical care in the ED, and early mortality, thus capturing the population of children at highest risk of death for whom critical care services are the most beneficial. An additional limitation is that due to resource limitations, we did not capture outcome data for subjects that transferred to another hospital or who absconded. This likely resulted in an underestimation of both P-ACI and hospital mortality and should be addressed in future work. The proportion of missing data was generally <5%, and thus unlikely to significantly affect study conclusions. Lastly, there are potentially important P-ACI risk factors that we were unable measure given the observational study design (e.g., insurance status, patient socioeconomic status, illness duration, travel distance). Future work should explore the impact of these factors on the development of P-ACI. Despite these limitations, we believe that we have presented the best available estimate of P-

ACI in urban, academic hospitals in RLS and demonstrated the importance and feasibility of global research that includes RLS.

In summary, this work is the first to address the frequency of P-ACI in RLS and demonstrates that most common causes of P-ACI are ones that are preventable and treatable with cost-effective, low-tech critical care interventions. Global collaborative networks inclusive of RLS (LARed, PALISI, St. Jude Global, PACCMAN, WFPICCS) are ideally positioned to advocate for, implement, and study the feasibility of low-cost, evidenced-based interventions to address the disproportionate causes of P-ACI and subsequent mortality. Furthermore, the global health community needs systems-based approaches to target high-burden, high-mortality conditions. Governments and decision-makers in RLS must shift how health investments are made; instead of focusing on one disease or intervention at a time, leaders should make effective investments in healthcare systems to provide care for critically ill patients in alignment with local needs and context.[162] The goal is not to implement a state-of-the-art PICU in every facility, but rather to ensure that every critically ill child has access to basic critical care services and create strong health systems that can refer and transfer critically ill children to well-resourced PICUs. In line with current WHO priorities and the recent 2023 resolution to strengthen critical care services globally,[48,102] this study solidifies the importance of critical care services and provides data on the frequent causes of P-ACI. It is a call to action to address the gap between the high burden of P-ACI in RLS and to integrate pediatric critical care services into the health system to improve child health outcomes and address global health inequities.

Chapter 5: Conclusion

Summary of Main Results

This body of work represents the first, comprehensive systematic review and large-scale, pediatric point prevalence study of P-ACI in children seeking care at hospitals in RLS. P-ACI and hospital mortality are both alarmingly high; most pediatric acute illnesses are preventable and treatable, and most death and long-term morbidity could be avoided if adequate, appropriate hospital resources were available.

We found that 6-29% of children with an acute complaint seeking care at RLS hospitals had P-ACI, with the highest estimate from the lowest sociodemographic category. The common causes of P-ACI, all-cause hospital mortality, and hospital admission in children overlapped considerably; the most common causes of P-ACI were pneumonia, sepsis, and acute malaria and malnutrition was the most common comorbidity; the most frequent causes of hospital mortality were malaria, non-septic shock, and malnutrition; and the most common reasons for hospital admission were pneumonia, malaria, and gastroenteritis. Importantly, the common causes of P-ACI, hospital mortality, and admission are primarily preventable and treatable with appropriate and timely therapy and interventions.[72,100,135-139]

All-cause, pediatric hospital mortality among those admitted to RLS hospitals was an estimated 2-4% between the Global PARITY and systematic review, respectively. This is an alarmingly high estimate, especially compared to HICs where pediatric hospital mortality is consistently <1%.[122,123] Additionally, the majority of hospital mortality in the point prevalence study occurred within the first 48 hours of

arrival to the hospital, which speaks to the importance of early and appropriate identification, stabilization, and treatment of critically ill children. Furthermore, we observed a wide variation in hospital mortality depending on GBD super-region and SDI category. This health disparity driven by SDI is best illustrated by the observed CFRs from the systematic review: as country income level increased from LIC to MIC, the CFR decreased 2-fold for sepsis/septic shock, 6-fold for pneumonia, and more than 80-fold for gastroenteritis. We also observed a significant difference in the proportion of children with P-ACI, the all-cause inhospital mortality rate, and common etiologies of P-ACI, mortality and admission by GBD region and/or SDI category.

Research in Context

Evaluating these findings within the larger context of available evidence, we can use the "three delays" model to conceptualize the underlying causes of high P-ACI and mortality in RLS.[163] The three delays model was initially developed to explore factors contributing to maternal mortality in RLS and include: the "decision to seek care"; "arrival at a health facility"; and "provision of [high-quality] care".[163] The decision to seek care is potentially influenced by caregiver knowledge and perceptions of illness, reliance on the informal health system and traditional healers, distance to a health center, cost, gender, and socioeconomic factors.[51,163-168] Factors that delay arrival to a health facility include road infrastructure, economic implications, health center location, and facility accessibility.[51,166,169,170] Finally, provision of high-quality pediatric critical care services in a health facility requires further dissection, and is the most relevant to this body of work.

Provision of High Quality Pediatric Critical Care Services in Resource-Limited Settings

There is clearly a need for pediatric critical care services in RLS. Using Dr. Paul Farmer's and Partner's in Health "Five S's" conceptual framework for health systems strengthening, we can identify what is required to provide high quality care to critically ill children seeking care at a health facility.[171-173] The "Five S's" include staff, stuff, space, systems, and social support.[171-173]

Staff

The first requirement is having an adequate number of trained and well-compensated staff.[171-173] Critical care delivery requires an entire team of trained professionals, which includes physicians, nurses, and support staff. In a recent assessment of the critical care capacity in Ghana, researchers reported that the greatest barrier to critical care provision was a lack of intensive care physicians; there were two pediatric intensive care physicians in the country and 56% of ICUs were staffed by non-intensive care physicians.[174] However, much of the critical care delivered globally – patient evaluation and assessment, medication administration, identification and communication when care escalation is required – is provided by nurses who often lack specialized training, mentorship, and adequate staffing to provide the ideal care ratio (e.g., one nurse for every 2-4 critically ill patients).[40,175] Healthcare team training requires the development and dissemination of a high-quality, standardized pediatric critical care curricula that includes basic life support, age-specific normal and abnormal vital sign parameters, interpretation of continuous monitoring modalities, and procedural skills.[176] Basic training in pediatric triage and clinical management in Malawi has been

shown to be a cost-effective intervention that improved patient care and decreased hospital mortality.[52] A recognized certification process for healthcare professionals who have completed training and government regulation and oversight are required to maintain qualified professionals.[40,175] Finally, investment by the government in both the training and retention of trained medical staff is critical.[171-173]

Stuff

The second requirement is appropriate, reliably available and maintained medical equipment to provide cost-effective interventions.[171-173] A significant barrier to managing P-ACI in children in RLS is raw resource availability. An analysis of Malawi's critical care services found that a lack of equipment and stockouts were the most common barriers to providing care to critically ill patients.[177] An anonymous, cross-sectional survey of anesthesia providers from Africa reported that only 1.5% (4/263) of respondents had available resources to implement the Surviving Sepsis Guidelines.[30] A systematic review analyzing available critical care resources in Tanzania reported that pediatric equipment is even more scarce than equipment for adult patients.[178] In a recent survey of 238 hospitals from 60 countries, pediatric critical care resources to provide a sepsis treatment bundle, basic respiratory support, and dextrose containing IVFs were reported to be inconsistently available in LMICs.[28] Most alarming, WHO survey data show that less than half of health facilities in LMICs have reliable access to oxygen, a basic and essential, life-saving medication.[179] Investment in and strategic allocation of resources to deliver pediatric critical care interventions are, therefore, essential.

Another significant barrier to implementation of critical care interventions, however, is the incorrect assumption that all critical care is resource-intensive,

technology-dependent, and not cost-effective. Simple, effective, affordable therapeutic and supportive interventions already exist to manage the common causes of P-ACI and pediatric mortality.[7,87,88,100,130,134,135,143] For example, sepsis outcomes have been shown to improve with the implementation of sepsis treatment bundles.[51-53] Dehydration is a common cause of death in children, and can be avoided with oral rehydration solution (ORS);[50] hospitalized children with diarrhea and dehydration can be treated effectively with ORS at a cost of $75 USD per patient.[135,180] Pediatric pneumonia mortality is significantly influenced by the presence, or absence, of pulse oximetry, oxygen therapy, and NIPPV/IMV.[5,54] Implementation of a simple oxygen delivery system in Papua New Guinea hospitals at a cost of $51 USD per child saved countless lives.[181] In a cost-effectiveness analysis of bubble continuous positive airway pressure (bCPAP) for the treatment of severe pediatric pneumonia in Malawi, the cost of implementing bCPAP was $41 USD per child treated and bCPAP averted 5 disability adjusted life years (DALY) – the sum of years of life lost due to premature mortality plus years lived with a disability – per child treated compared to standard of care for a cost of $12 USD per DALY.[134] For context, national LMIC vaccine campaigns cost approximately $7–$438 per DALY averted and are highly cost-effective.[182]

Investment in equipment and resource allocation of available “stuff” aligned with pediatric critical illness priorities is required at the health system level.[7] Proven, cost-effective interventions exist,[7] which should be implemented based on local burden of disease in a stepwise manner, starting with basic pediatric-sized equipment bundles.[28,100] Sourcing equipment locally improves equipment maintenance and quality assurance, helps ensure sustainability, and supports the local economy.[40]

Space

The third requirement is physical space that provides a clean, sanitary environment to care for patients.[171-173] Physical space is an often neglected necessity, and critically ill patients require more space, personnel, and equipment (e.g., oxygen concentrators, monitors, ventilators, IV pumps) than the average patient.[40] A secondary analysis of the Malawi Emergency and Critical Care Survey of public central and district hospitals, found that the median number of critical care beds per 1,000,000 people was 1.4 (IQR: 0.9-6.7) and, due to a lack of dedicated space and resources, the majority of critical care in rural areas was being delivered in HDUs instead of formal ICUs.[177] Similarly, a systematic review of available Tanzanian critical care services reported that only hospitals in urban settings had dedicated ICU space to treat critically ill patients, and critical care in rural settings was being delivered in sub-optimal, non-ICU spaces.[178] Furthermore, critically ill patients are at increased risk of complications and hospital-acquired infections, so a sanitary patient environment is essential.[183] The layout and design of the ICU (e.g., ventilation, hand washing stations, isolation beds) also contributes to the transmission or prevention of hospital-acquired infections and infection control teams play a critical role especially in resource limited ICUs.[28]

Individual, basic critical interventions may be cost-effective, but the question remains whether formal, specialized PICUs are feasible and worth the financial investment in RLS. Financial considerations are a legitimate consideration; 35% of PICUs in LMICs reported financial instability compared to 2.6% of HICs.[63] Furthermore, with limited resources, one could argue that the cost of critical care services would serve a greater good if directed towards primary prevention and public health

initiatives.[40] Unfortunately, there is a paucity of data on the cost-effectiveness of pediatric intensive care from either HICs or LMICs, and we are left to extrapolate from neonatal and adult data.

There is a precedence for providing intensive care services in RLS that are more cost-effective than HIC models. Cheah *et al.*, performed a multicenter observational study to assess the cost-effectiveness of neonatal intensive care units across Malaysia and found that the cost-effectiveness ratio (net cost/change in health outcome) was $3,979 (adjusted for inflation to $7,363 in USD in 2023) per patient that survived to 1 year of age,[143] as compared to $28,285-$40,581 (adjusted for inflation to $52,338-$75,091 in USD in 2023) for infants in the US[184]. Similarly, a modeling study estimated the cost-effectiveness of neonatal intensive care in Mexico for specific preterm populations and found that the cost-effectiveness ratio ranged from $240-$1,200 (adjusted for inflation to $379-$1,894 in USD in 2023) per DALY averted depending on gestational age at birth (30 weeks vs. 24 weeks, respectively),[88] which was far more cost-effective than contemporary preterm care in Australia[185] and the United States[184]. A prospective cohort study and cost-effectiveness analysis of adults treated in a new medical ICU in Sarajevo, Bosnia and Herzegovina, demonstrated a cost effectiveness ratio for ICU care of $3,254 (adjusted for inflation to $4,368 in USD in 2023) per quality adjusted life year (QALY), which was considered ‘Very Cost Effective’ according to WHO criteria.[186] Of note, since this an adult study population, the expected life expectancy is assumed to be shorter than for children; therefore, the cost effectiveness ratio for PICU care per QALY is likely more favorable.[187]

Pediatric critical care services are currently being implemented in RLS. The Essential Emergency and Critical Care (EECC) services package was developed to identify, prioritize and treat hospitalized patients at high risk of mortality.[100] EECC is currently being implemented across health centers in Tanzania and the cost-effectiveness, acceptability, feasibility, and sustainability are being measured as well as various approaches to implementation (personal communication, Tim Baker, September 29, 2023). The Hospital Central de Maputo is the tertiary care academic hospital for Mozambique with the most advanced PICU in the country; in 2013, alone, there were 1,287 PICU admissions with 74% survival.[188] A PICU was established at Queen Elizabeth Hospital in Malawi in 2017 and in the first two years, there were 573 PICU admissions, 72% of whom survived to discharge.[189] Finally, implementation of pediatric critical care services at Kenyatta National Hospital in Kenya resulted in a decrease in mortality from 76% to 38% within the first two years of PICU implementation.[190] It is not realistic, nor necessary to have a PICU in all hospitals; instead, PICUs should be strategically implemented and fully supported. Collectively, the establishment of these PICUs in sub-Saharan Africa demonstrates that implementation of pediatric critical care services in RLS are effective and feasible. Policy makers at the health-system and hospital levels need to plan for, design, and build dedicated space in new and existing hospitals to deliver critical care.

Systems

The fourth requirement is adequate infrastructure and logistical organization to provide critical care services.[171-173] Critical care services are a coordinated system that includes triage and patient prioritization, emergency care and stabilization, transport and

referral, as well as critical care.[40,163] The first major challenge children face when they reach a health facility is appropriate and timely recognition of the critically ill by healthcare providers. An organized, efficient triage system is an effective means for identifying the sickest patients but is often lacking in RLS hospitals.[191] Currently, the WHO has two triage tools for assessing children in RLS; IMCI for outpatient settings[192] and ETAT, which includes guidelines for identifying and managing acutely ill children.[62] Unfortunately, providers in RLS often lack the training and resources required to effectively implement the clinical recommendations provided by these triage tools.[28,193] Additionally, the triage tools do not always achieve the expected benefit; when ETAT was implemented in Malawi, the algorithm failed to prioritize treatment of 45% of children who later died in the hospital.[64] Existing pediatric triage tools, including the WHO tools, lack high-quality evidence to support their effectiveness in RLS. A systematic review of existing pediatric triage tools for RLS reported that the degree of heterogeneity between studies, lack of generalizability of the published studies, and overall lack of available studies prevented a meaningful analysis of the reliability and validity of existing tools.[194] Major limitations to the existing data include a lack of follow-up for children who are not hospitalized after medical evaluation and non-standardized, insufficient data collection.[195]

Cost-effective, promising tools are being developed and validated. For example, at Queen Elizabeth Central Hospital in Blantyre, Malawi, a package of triage and treatment tools and processes were implemented in a high-volume, high-acuity pediatric outpatient clinic for a cost $1.75 USD per patient, which greatly improved care delivery and decreased mortality.[52] The Pediatric Early Warning Score for RLS is a simple, 6-

variable score that includes vital signs, mental status, and respiratory distress with a high sensitivity (96%) and specificity (87%) for identifying children at high risk of clinical decompensation.[196] The Smart Triage Tool, developed by researchers in Uganda, includes fields for physical findings, vital signs, and parental concern, and identified children that required hospital admission with a high sensitivity (91%) and specificity (92%).[195] A simple, highly sensitive and specific triage tool that can be easily and inexpensively integrated into clinical care with minimal training is an ideal solution for early identification of critically ill children in RLS.

Many critically ill children first seek care at community health centers, and once identified as critically ill, need to be referred and transported to an appropriate facility. A fragmented health system and lack of a formal emergency transport system result in delayed presentation or arrival to care, which can negatively impact outcomes. In a study we conducted in children with sepsis in Tanzania, delayed presentation or arrival to a center with pediatric specialty care was associated with increased mortality (adjusted OR 1.9 [95%CI 1.2-3.0]).[51] A cohort study of critically ill and injured children conducted in Cape Town, South Africa, a relatively well-developed region of sub-Saharan Africa, followed critically ill or injured children (N=282) from initial point of contact with the healthcare system until PICU admission or death and assessed the overall quality of care; avoidability of severity of illness, PICU admission, and/or death; and presence of potentially modifiable factors.[50] Global quality of care was graded "good" in only 10% of cases, and there was potentially avoidable severity of illness and death in 74% (N=185) and 57% (N=17/30) of cases, respectively.[50] Key modifiable factors related to access to care, identification of the critically ill, appropriate

assessment of severity of illness, inadequate resuscitation, and delays in decision making and referral.[50] A study conducted in Latin America that analyzed critically ill children (N=2,692) transferred to a PICU for acute respiratory failure, found that transports from nonurban centers with fewer pediatric specialists and equipment was highly associated with mortality (adjusted OR 9.4 [95%CI 2.4-36.3]).[197]

RLS often lack a formal referral and transport system and critically ill and injured patients are not transported to the hospital by ambulance, but rather by personal vehicle, bus, or the police.[198-200] Acute trauma patients in Malawi transported by ambulance to a trauma center experienced a 40% decrease in the risk of early death.[199] Ambulance transport alone is not enough, however. In a study of neonates transferred to Muhimbili Hospital in Tanzania, 89% of neonates were transferred by ambulance, but 55% of transport health care providers had no training on essential newborn care and almost all neonates arrived with at least one major, preventable complication such as hypothermia, hypoxia, hypoglycemia, or poor perfusion.[201] The ideal pre-hospital emergency transport system is free and easy to access, coordinated by a dispatcher in real-time, includes transportation by ambulance, and is staffed by trained first responders.[202,203] Pediatric critical care services in RLS will only be effective at improving child health outcomes if there is a functioning referral and transport system and basic emergency care.[40,163] Pediatric emergency care service requirements are similar to those needed for critical care services in regards to staff, stuff, space, systems and social support as described.[40,163]

Additional facility-based systems and processes are also required, such as identifying and prioritizing critically ill patients;[100] implementing clinical management

guidelines and best practices;[136] supporting quality improvement programs;[40] and developing admission, transfer and discharge critieria.[40,191] Facility-based systems also includes training and retaining medical personnel; developing a knowledgeable team of biomedical experts who acquire and repair medical equipment; having a skilled team that maintains and cleans the facility; and implementing systems and services to support the patients and families (e.g., social work).[40]

Social Support

Finally, the fifth requirement is to ensure that children and their families have the basic necessities, such as food, housing, transportation, financial support, and social support.[171] In South Africa, children with cancer living in households with fewer available resources experienced significantly higher mortality, even after adjusting for tumor type and stage.[204] For children, food insecurity in the household has been associated with worse physical health, nutritional outcomes, growth, neurodevelopment, psychosocial outcomes, and family economic well-being.[205] In contrast, an intervention in Kenya that ensured food security was shown to improve not only maternal nutrition, but also child growth and nutrition, and HIV outcomes for mother and child.[204,206-208] Other interventions, such as food supplements, travel vouchers, and safe housing have been shown to make a positive impact on a patient's recovery and long-term outcome.[171]

The major barrier to managing P-ACI and preventing child mortality is not a lack of existing evidence-based, cost-effective interventions. Rather, the barriers are multifactorial and include access to care; trained and supported clinicians; implementation of cost-effective interventions; resource availability; dedicated space to

deliver critical care; processes and tools to recognize critical illness; and an efficient referral and transport system.

Actions to Address Pediatric Critical Illness in Resource Limited Settings

Despite the barriers described above, there is a need to manage children in all settings with acute, life-threatening and, as demonstrated by this body of work, predominantly reversible disease.[68] Ultimately, the solution entails a paradigm shift in how critical care services are viewed; critical care services do not require an ICU and should be integrated throughout the acute illness care pathway (**Figure 5.1**).[28,100]

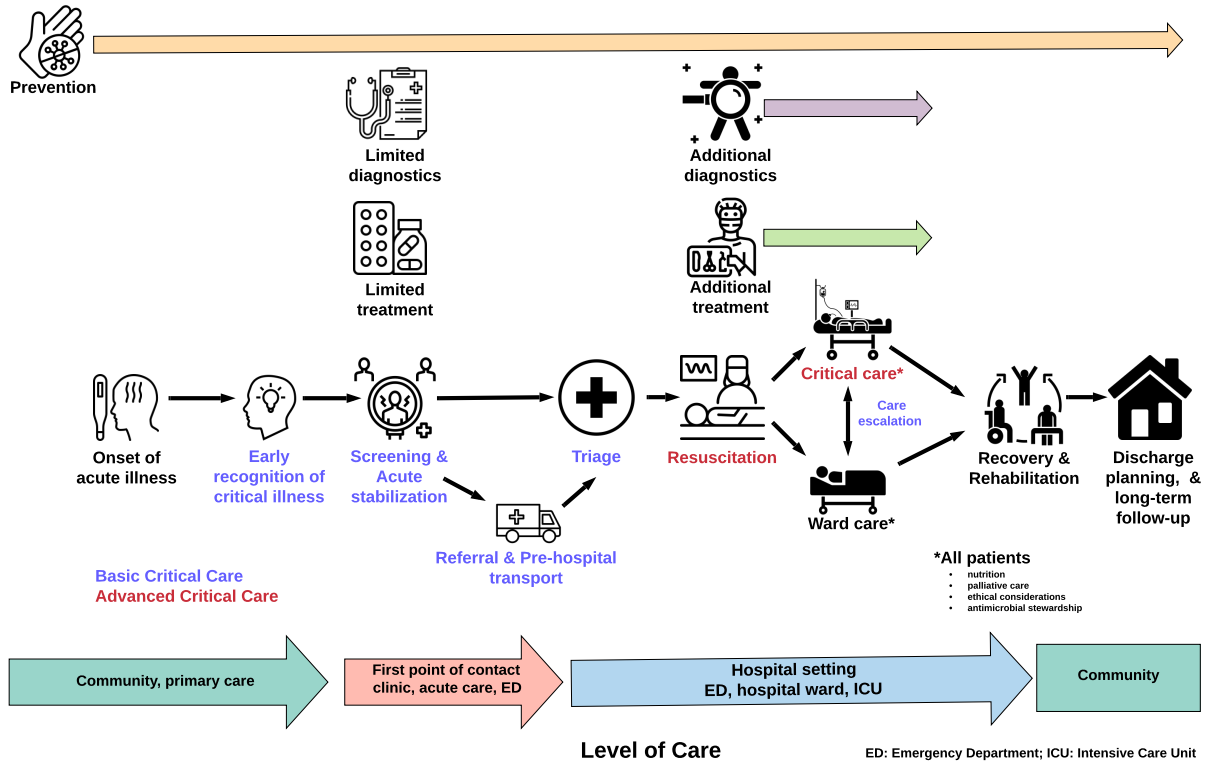


Figure 5.1 Acute illness care pathway with critical care integration
Figure shows the path of an acutely ill individual as he/she moves through the healthcare system. Primary prevention can prevent the onset of an acute illness, and prevention of complications can occur during an acute illness. ED: emergency department; ICU: intensive care unit

Basic critical care begins in the community with early recognition of the critically ill child, followed by appropriate screening and acute stabilization, efficient referral and pre-hospital transport, and a triage assessment upon arrival. Basic training to recognize pediatric critical illness, guidelines to manage common causes of pediatric critical illness, resources to stabilize critically ill children, systems to prioritize the sickest patients can be cost-effective,[7] and the skills and resources to provide basic critical care should be available at every level of the health system. More advanced critical care services include resuscitation and organ-supporting interventions. Within organ support, there is a wide range of possible interventions, and resource allocation and implementation of interventions should be tailored to the local disease burden and epidemiology. It is important to mention that primary prevention and primary care play important roles in preventing acute critical illness. Health systems strengthening that involves the acute illness pathway should be viewed in partnership with strengthening primary and preventive care services.

Implementation and long-term sustainability of pediatric critical care services is dependent on high-level support from the government and local support from hospital leadership. All S's described above – staff, stuff, space, systems, and social support – require organizational support, infrastructure, and systematic processes. Health system strengthening and capacity building, with particular attention to pediatric-specific requirements (e.g., training, equipment, etc.), are the requisite foundation for effective delivery of high-quality pediatric critical care throughout the acute illness pathway.

Strengths and Limitations

This series of studies is the first to estimate the proportion of P-ACI in children seeking care at hospitals in RLS. The systematic review represented 21.8 million pediatric hospitalizations from 293 sites in 59 LMICs and the point prevalence study captured 7,457 pediatric acute health seeking events to 46 RLS hospitals in 19 countries. Overall, there was good representation from all continents, regions, and SDI categories, and the results are likely generalizable to other RLS. For the point prevalence study, we developed a novel definition of P-ACI that was resource agnostic and applicable to resource-variable settings. We have provided robust data to help guide resource allocation and policy-level decisions.

Despite being the first series of studies to estimate P-ACI across children seeking care at hospitals in RLS, there are several limitations to this work and the data presented. A major limitation of hospital-based studies is that they fail to capture pre- and post-hospital events. Especially where health systems are strained and/or limited, many children die at home and never reach hospital care. While it is difficult to measure the P-ACI and mortality that occur outside of hospitals, a recently published study from Uganda estimated post-discharge mortality to be 5% within the first 6 months after hospital discharge and over half of these deaths occurred in the home.[209]

While we aimed to include studies and sites from as many LMICs (systematic review) and RLS (point prevalence study) as possible, ultimately, we were limited by the availability of published studies and the hospitals that ultimately participated, which may have introduced a selection bias. As such, some regions and sociodemographic categories (e.g. SDI categories) were under-represented, and the study samples may

not be representative of the full spectrum of disease within a given country or region. Furthermore, the results from both the systematic review and point prevalence studies likely reflect data from primarily tertiary care, academic hospitals, and are not generalizable to lower-level health facilities. This is in part because tertiary, academic centers have the resources to participate in research and in part due to our recruiting strategy in the point prevalence study. Overrepresentation of tertiary, academic centers may have biased the observed proportion of P-ACI and hospital mortality, as tertiary centers tend to care for the sickest children and also regularly have more resources to manage critical illness. It is important to acknowledge that the results from this body of work are likely not generalizable to lower-level health facilities.

We also faced limitations common to all observation studies. We were restricted to available data (either published or in the medical record). This included the reported cause of admission/death, which is often a subjective classification, and could have resulted in misclassification. Furthermore, observed differences may have been influenced by available data, study/site selection, local health systems variables not captured, or unmeasured health-seeking behaviors.

For these reasons, this large-scale systematic review and novel point prevalence study, while the first of their kind, likely underestimated the proportion of children with P-ACI and estimates of pediatric hospital mortality in RLS. Despite these limitations, we believe that the data presented here are the best available estimates of P-ACI in children seeking hospital care and pediatric hospital mortality in RLS.

Next Steps and Future Directions

Several other projects relevant to this work are in progress or recently completed. Led by Alishah Mawji, we recently developed and published common sepsis data elements to standardize data collection and facilitate pooling of data across studies and sites.[140] The PALISI Global Health subgroup is developing an objective score to categorize hospitals based on availability of resources and trained personnel, since country income level (e.g., SDI) is an imperfect method for categorizing resource availability. Building on the definition we developed for the point prevalence study, we conducted a modified Delphi, led by Dr. Anita Arias, to develop a framework and research definition of P-ACI that is based on vital signs and organ dysfunction and can be applied regardless of available resources. We plan to perform longitudinal analyses of the systematic review data to better understand hospital mortality trends over time. We are in the early stages of developing a pediatric emergency and critical care fellowship at Muhimbili University of Health and Allied Sciences in Tanzania and the WHO Collaborating Center at UCSF is helping to develop the WHO Basic Critical Care Course to increase local expertise and build capacity,

One of greatest benefits of conducting the Global PARITY point prevalence study is that it created an international research network of pediatric critical care physician-researchers. Future studies can leverage the Global PARITY network to conduct interventional studies, such as implementation of the Pediatric Early Warning Score,[196] test implementation of cost-effective interventions across resource variable settings, and determine long-term morbidity associated with critical illness.

Finally, we are currently in a rare and potentially influential position to change the global health agenda and inform policy changes. According to Kingdon's three streams model of policy change, an issue only gets attention and results in action when all three streams –problem, policy and politics – come together.[210] When these streams align, a policy window opens, which is a unique opportunity to influence significant, lasting policy changes.[210] The data generated from this work help to define the problem and can be used to raise awareness about pediatric critical illness and to advocate for increased services and training globally. Regarding the policy stream, in May 2023, the Seventy-sixth World Health Assembly approved a resolution to strengthen and improve access to high-quality emergency, critical and operative care (ECO) globally.[48] To gain political support, the WHO created the Acute Care Action Network (ACAN) "to drive strategic engagement of governments, communities, partners, and a range of other stakeholders, for coordinated and high-impact action in countries".[211] ACAN and its members, which includes the UCSF WHO Collaborating Center, aims to train and support healthcare providers; strengthen systems that promote efficient triage, resuscitation and referral; promote standardized, high-quality medical record keeping and data collection; engage leaders and stakeholders at the community, facility, national, and regional levels to integrate ECO services into the health system.[211] The three streams are converging in favor of integrating critical care services into health systems across the world.

Conclusion

Tim Baker, *et* al, defines critical care as "all care given in hospital to patients with sudden, serious reversible disease"[7] regardless of the location within the hospital. Critical illness is not dependent on whether ICU services exist, and it will occur regardless of whether the resources are there to manage it. We have shown that common causes of P-ACI and hospital mortality in RLS are preventable and treatable with cost-effective, low-tech solutions. To achieve SDG 3.2, which aims to end preventable child deaths by 2030,[9] significant health system strengthening is needed across RLS that includes critical care services, which are often the weakest and least developed component of the health system.[55,212] This research demonstrates the essential need for hospital-based critical care services for children in the context of health systems strengthening.

Global collaborative networks, such as PALISI and ACAN, are ideally positioned to advocate for, implement and study the feasibility of low-cost, evidenced-based interventions to address the disproportionate causes of P-ACI and subsequent mortality. A coordinated global effort by ministries of health, philanthropic organizations, NGOs, and multinational organizations is required to address preventable P-ACI and mortality by deploying targeted interventions, utilizing strategic resource allocation, and including critical care services in the global child health agenda. It is imperative that implementation research and interventional studies include researchers and study populations in RLS.

Finally, governments, funders, and decision-makers in RLS must shift how health investments are made; instead of focusing on one disease or intervention at a time,

effective investments should be made in healthcare systems to provide care for critically ill patients throughout the acute illness pathway in alignment with local needs and context. While cost-effective pediatric critical care interventions and approaches exist, perhaps the more compelling argument for pediatric critical care services in RLS is one of moral imperative. Addressing global child health inequities is a moral and ethical responsibility to the collective, global population of children; the goal is not to implement a state-of-the-art PICU in every health facility, but rather to ensure that every critically ill child has access to basic critical care services. Geography should not be destiny.

References and Works Cited

1. Kassebaum N, Kyu HH, Zoeckler L, et al. Child and Adolescent Health From 1990 to 2015: Findings From the Global Burden of Diseases, Injuries, and Risk Factors 2015 Study. *JAMA pediatrics* 2017; **171**(6): 573-92.

2. Evaluation IfHMa. GBD Compare. 2019 2023. https://vizhub.healthdata.org/gbd-compare/ (accessed July 21 2023).

3. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; **395**(10219): 200-11.

4. Tan KK, Dang DA, Kim KH, et al. Burden of hospitalized childhood community-acquired pneumonia: A retrospective cross-sectional study in Vietnam, Malaysia, Indonesia and the Republic of Korea. 95-105.

5. McAllister DA, Liu L, Shi T, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. *The Lancet Global health* 2019; **7**(1): e47-e57.

6. Organization WH. Millennium Development Goals (MDGs). February 19, 2018 2023. https://www.who.int/news-room/fact-sheets/detail/millennium-development-goals-(mdgs) (accessed July 21 2023).

7. Baker T. Pediatric emergency and critical care in low-income countries. *Paediatric anaesthesia* 2009; **19**(1): 23-7.

8. Network GBoD. Global Burden of Disease Study 2017 (GBD 2017) Socio-Demographic Index (SDI) 1950–2017. 2018. http://ghdx.healthdata.org/record/ihme-data/gbd-2017-socio-demographic-index-sdi-1950%E2%80%932017 (Aug 3 2021).

9. Nations U. The 17 Goals. 2023. https://sdgs.un.org/goals (July 21 2023).

10. Progress towards the Sustainable Development Goals: Towards a Rescue Plan for People and Planet Report of the Secretary-General (Special Edition). General Assembly Seventh-eighth ed: United Nations; 2023.

11. Nations U. Promise in Peril. 2023. https://unstats.un.org/sdgs/report/2023/Promise-in-peril/ (accessed October 3 2023).

12. Geiling J, Burkle FM, Jr., Amundson D, et al. Resource-poor settings: infrastructure and capacity building: care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. *Chest* 2014; **146**(4 Suppl): e156S-67S.

13. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392 North American Edition**(10159): 1789-858.

14. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**(10258): 1160-203.

15. UNICEF. UNICEF Data Warehouse. 2021. https://data.unicef.org/dv_index/ (accessed June 23 2023).

16. Kruse G, Lopez-Carmen VA, Jensen A, Hardie L, Sequist TD. The Indian Health Service and American Indian/Alaska Native Health Outcomes. *Annual review of public health* 2022; **43**: 559-76.

17. Janke AT, Mei H, Rothenberg C, Becher RD, Lin Z, Venkatesh AK. Analysis of Hospital Resource Availability and COVID-19 Mortality Across the United States. *J Hosp Med* 2021; **16**(4): 211-4.

18. (IHME) IfHMaE. Financing Global Health 2021: Global Health Priorities in a Time of Change. . Seattle, WA: IHME, 2023.: IHME, 2023.

19. (IHME) IfHMaE. Financing Global Health. 2023. Available from http://vizhub.healthdata.org/fgh/ (accessed June 23 2023).

20. Cotlear D, Somil Nagpal, Owen Smith, Ajay Tandon, and Rafael Cortez-Escalante, J. J. Going Universal: How 24 Developing Countries are Implementing Universal Health Coverage Reforms from the Bottom Up. Washington, DC: World Bank, 2015.

21. Organization WH. The World Health Report 2000- Health Systems: Improving Performance. Geneva, Switzerland: World Health Organization, 2000.

22. Sieverding M, Beyeler N. Integrating informal providers into a people-centered health systems approach: qualitative evidence from local health systems in rural Nigeria. *BMC health services research* 2016; **16**(1): 526.

23. Sudhinaraset M, Ingram M, Lofthouse HK, Montagu D. What is the role of informal healthcare providers in developing countries? A systematic review. *PloS one* 2013; **8**(2): e54978.

24. Peters DH, Garg A, Bloom G, Walker DG, Brieger WR, Rahman MH. Poverty and access to health care in developing countries. *Annals of the New York Academy of Sciences* 2008; **1136**: 161-71.

25. Initiative JL. Human Resources for Health: Overcoming the Crisis: Harvard University's Global Equity Initiative, 2004.

26. Suryanto, Plummer V, Boyle M. EMS Systems in Lower-Middle Income Countries: A Literature Review. *Prehosp Disaster Med* 2017; **32**(1): 64-70.

27. English M, Esamai F, Wasunna A, et al. Delivery of paediatric care at the first-referral level in Kenya. *Lancet* 2004; **364**(9445): 1622-9.

28. Muttalib F, González-Dambrauskas S, Lee JH, et al. Pediatric Emergency and Critical Care Resources and Infrastructure in Resource-Limited Settings: A Multicountry Survey. *Critical care medicine* 2021; **49**(4): 671-81.

29. Kruk ME, Pate M. The Lancet Global Health Commission on High Quality Health Systems 1 year on: progress on a global imperative. *The Lancet Global health* 2020; **8**(1): e30-e2.

30. Baelani I, Jochberger S, Laimer T, et al. Availability of critical care resources to treat patients with severe sepsis or septic shock in Africa: a self-reported, continent-wide survey of anaesthesia providers. *Critical care (London, England)* 2011; **15**(1): R10.

31. Organization WH. Current health Expenditure (CHE) per capita in US$. 2023. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/current-health-expenditure-(che)-per-capita-in-us$ (accessed August 18 2023).

32. Ortiz-Ospina E RM. Global Health. 2016. https://ourworldindata.org/health-meta (accessed August 18 2023).

33. Tan B, Wong JJ, Sultana R, et al. Global Case-Fatality Rates in Pediatric Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis. *JAMA pediatrics* 2019; **173**(4): 352-62.

34. WHO. Updated guideline: Paediatric emergency triage, assessment and treatment. Geneva: World Health Organization, 2016.

35. Holley AL, Battison EAJ, Heierle J, et al. Long-term Pain Symptomatology in PICU Survivors Aged 8-18 Years. *Hosp Pediatr* 2023; **13**(7): 641-55.

36. Olszewski AE, Dervan LA, Smith MB, et al. Risk Factors for Positive Post-Traumatic Stress Disorder Screening and Associated Outcomes in Children Surviving Acute Respiratory Failure: A Secondary Analysis of the Randomized Evaluation of Sedation Titration for Respiratory Failure Clinical Trial. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2023; **24**(3): 222-32.

37. Le Brocque RM, Dow BL, McMahon H, et al. The Course of Posttraumatic Stress in Children: Examination of Symptom Trajectories and Predictive Factors Following Admission to Pediatric Intensive Care. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2020; **21**(7): e399-e406.

38. Smith S, Rahman O. Post-Intensive Care Syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2023, StatPearls Publishing LLC.; 2023.

39. Ravikumar N, Sankar J, Das RR. Functional Outcomes in Survivors of Pediatric Sepsis: A Scoping Review and Discussion of Implications for Low- and Middle-Income Countries. *Frontiers in pediatrics* 2022; **10**: 762179.

40. Slusher TM, Kiragu AW, Day LT, et al. Pediatric Critical Care in Resource-Limited Settings-Overview and Lessons Learned. *Frontiers in pediatrics* 2018; **6**: 49.

41. Marshall JC, Bosco L, Adhikari NK, et al. What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine. *Journal of critical care* 2017; **37**: 270-6.

42. Levin DL, Downes JJ, Todres ID. History of pediatric critical care medicine. *Journal of pediatric intensive care* 2013; **2**(4): 147-67.

43. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *Jama* 2009; **302**(21): 2323-9.

44. Wunsch H, Angus DC, Harrison DA, et al. Variation in critical care services across North America and Western Europe. *Critical care medicine* 2008; **36**(10): 2787-93, e1-9.

45. Guidelines for pediatric intensive care units. *Critical care medicine* 1983; **11**(9): 753-60.

46. Randolph AG, Gonzales CA, Cortellini L, Yeh TS. Growth of pediatric intensive care units in the United States from 1995 to 2001. *J Pediatr* 2004; **144**(6): 792-8.

47. Organization WH. Third round of the global pulse survey on continuity of essential health services during the COVID-19 pandemic: November–December 2021. Interim report. Geneva: World Health Institution, 2022.

48. Organization WH. Integrated emergency, critical and operative care for universal health coverage and protection from health emergencies. Executive Board 152nd Session; 2023 30 January–7 February 2023; Geneva: World Health Organization; 2023.

49. Argent AC, Ranjit S, Peters MJ, et al. Factors to be Considered in Advancing Pediatric Critical Care Across the World. *Critical care clinics* 2022; **38**(4): 707-20.

50. Hodkinson P, Argent A, Wallis L, et al. Pathways to Care for Critically Ill or Injured Children: A Cohort Study from First Presentation to Healthcare Services through to Admission to Intensive Care or Death. *PloS one* 2016; **11**(1): e0145473.

51. Smith AM, Sawe HR, Matthay MA, Murray BL, Reynolds T, Kortz TB. Delayed Presentation and Mortality in Children With Sepsis in a Public Tertiary Care Hospital in Tanzania. *Frontiers in pediatrics* 2021; **9**: 764163.

52. Molyneux E, Ahmad S, Robertson A. Improved triage and emergency care for children reduces inpatient mortality in a resource-constrained setting. *Bulletin of the World Health Organization* 2006; **84**(4): 314-9.

53. Dunser MW, Baelani I, Ganbold L. A review and analysis of intensive care medicine in the least developed countries. *Critical care medicine* 2006; **34**(4): 1234-42.

54. Thomson N. Emergency medical services in Zimbabwe. *Resuscitation* 2005; **65**(1): 15-9.

55. Nolan T, Angos P, Cunha AJ, et al. Quality of hospital care for seriously ill children in less-developed countries. *Lancet* 2001; **357**(9250): 106-10.

56. Molyneux E. Paediatric emergency care in developing countries. *Lancet* 2001; **357**(9250): 86-7.

57. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *The New England Journal of Medicine* 2011; **364**(26): 2483-95.

58. Murthy S, Leligdowicz A, Adhikari NK. Intensive care unit capacity in low-income countries: a systematic review. *PloS one* 2015; **10**(1): e0116949.

59. English M, Esamai F, Wasunna A, et al. Assessment of inpatient paediatric care in first referral level hospitals in 13 districts in Kenya. *Lancet* 2004; **363**(9425): 1948-53.

60. Reyburn H, Mwakasungula E, Chonya S, et al. Clinical assessment and treatment in paediatric wards in the north-east of the United Republic of Tanzania. *Bulletin of the World Health Organization* 2008; **86**(2): 132-9.

61. Rosenberg DI, Moss MM. Guidelines and levels of care for pediatric intensive care units. *Pediatrics* 2004; **114**(4): 1114-25.

62. Organization WH. Emergency Triage Assessment and Treatment (ETAT) Manual for Participants. Geneva, Switzerland: World Health Organization, 2005.

63. WHO. Hospital care for children: guidelines for the management of common illnesses with limited resources. Geneva: World Health Organization, 2013.

64. Robertson MA, Molyneux EM. Description of cause of serious illness and outcome in patients identified using ETAT guidelines in urban Malawi. *Arch Dis Child* 2001; **85**(3): 214-7.

65. Meiring Pde V, Lumsden JD, Morrison AG, Furnham LA. An intensive care unit in a provincial general hospital. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde* 1969; **43**(26): 806-10.

66. Organization WH. Surgical care at the district hospital. In: Organization WH, editor. Geneva: World Health Organization; 2003.

67. Jochberger S, Ismailova F, Lederer W, et al. Anesthesia and its allied disciplines in the developing world: a nationwide survey of the Republic of Zambia. *Anesthesia and analgesia* 2008; **106**(3): 942-8, table of contents.

68. Tripathi S, Kaur H, Kashyap R, Dong Y, Gajic O, Murthy S. A survey on the resources and practices in pediatric critical care of resource-rich and resource-limited countries. *Journal of intensive care* 2015; **3**: 40.

69. Turner EL, Nielsen KR, Jamal SM, von Saint Andre-von Arnim A, Musa NL. A Review of Pediatric Critical Care in Resource-Limited Settings: A Look at Past, Present, and Future Directions. *Frontiers in pediatrics* 2016; **4**: 5.

70. Fink EL, Kochanek PM, Tasker RC, et al. International Survey of Critically Ill Children With Acute Neurologic Insults: The Prevalence of Acute Critical Neurological Disease in Children: A Global Epidemiological Assessment Study. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2017; **18**(4): 330-42.

71. Santschi M, Jouvet P, Leclerc F, et al. Acute lung injury in children: therapeutic practice and feasibility of international clinical trials. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2010; **11**(6): 681-9.

72. Khemani RG, Smith L, Lopez-Fernandez YM, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. *The Lancet Respiratory medicine* 2019; **7**(2): 115-28.

73. Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. *American journal of respiratory and critical care medicine* 2015; **191**(10): 1147-57.

74. Cobos Muñoz D, de Savigny D, Sorchik R, et al. Better data for better outcomes: the importance of process mapping and management in CRVS systems.

BMC medicine 2020; **18**(1): 67.

75. Hazard RH, Chowdhury HR, Adair T, et al. The quality of medical death certification of cause of death in hospitals in rural Bangladesh: impact of introducing the International Form of Medical Certificate of Cause of Death. *BMC health services research* 2017; **17**(1): 688.

76. Teixeira CLDS, Klein CH, Bloch KV, Coeli CM. Probable cause of death after reclassification of ill-defined causes on hospital admissions forms in the Unified National Health System, Rio de Janeiro, Brazil. *Cadernos de Saude Publica* 2006; **22**(6): 1315-24.

77. Kortz TB, Nielsen KR, Mediratta RP, et al. The Burden of Critical Illness in Hospitalized Children in Low- and Middle-Income Countries: Protocol for a Systematic Review and Meta-Analysis. *Frontiers in pediatrics* 2022; **10**: 756643.

78. Prin M, Wunsch H. International comparisons of intensive care: informing outcomes and improving standards. *Current opinion in critical care* 2012; **18**(6): 700-6.

79. (PALISI) PALISI. Pediatric Acute Lung Injury & Sepsis Investigators (PALISI). palisi.org (accessed August 22 2023).

80. Fink ELvSA-vA, A. PALISI Global Health 2014-2020: From disaster relief to network and capacity-building. Pediatric Acute Lung Injury & Sepsis Investigators Network; 2020 September 2020; online; 2020.

81. Reiner RC, Jr., Olsen HE, Ikeda CT, et al. Diseases, Injuries, and Risk Factors in Child and Adolescent Health, 1990 to 2017: Findings From the Global Burden of Diseases, Injuries, and Risk Factors 2017 Study. *JAMA pediatrics* 2019; **173**(6): e190337.

82. Bhutta ZA, Das JK, Walker N, et al. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet* 2013; **381**(9875): 1417-29.

83. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* 2016; **388**(10063): 3027-35.

84. Collaborators GBDCM. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**(10053): 1725-74.

85. Network GBoDC. Global Burden of Disease Study 2017 (GBD 2017) Results. In: (IHME) IfHMaE, editor. Seattle, United States; 2017.

86. Cheah IG, Soosai AP, Wong SL, Lim TO, Cost-Effectiveness NSG. Cost-effectiveness analysis of Malaysian neonatal intensive care units. *J Perinatol* 2005; **25**(1): 47-53.

87. Cubro H, Somun-Kapetanovic R, Thiery G, Talmor D, Gajic O. Cost effectiveness of intensive care in a low resource setting: A prospective cohort of medical critically ill patients. *World journal of critical care medicine* 2016; **5**(2): 150-64.

88. Profit J, Lee D, Zupancic JA, et al. Clinical benefits, costs, and cost-effectiveness of neonatal intensive care in Mexico. *PLoS Med* 2010; **7**(12): e1000379.

89. Khemani RG, Smith L, Lopez-Fernandez YM, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. *The Lancet Respiratory medicine* 2019; **7**(2): 115-28.

90. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**(7): e1000097.

91. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018; **169**(7): 467-73.

92. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc* 2015; **13**(3): 147-53.

93. Network GBoDC. Global Burden of Disease Study 2017 (GBD 2017) Socio-Demographic Index (SDI) 1950–2017. Mar 30, 2019. http://ghdx.healthdata.org/record/ihme-data/gbd-2017-socio-demographic-index-sdi-1950%E2%80%9320172018).

94. Covidence. 2019. https://www.covidence.org/.

95. Paul A. Harris RT, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**(2): 377-81.

96. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013; **158**(4): 280-6.

97. Frenk J, Gómez-Dantés O. False dichotomies in global health: the need for integrative thinking. *Lancet* 2017; **389**(10069): 667-70.

98. Sharrow D, Hug L, You D, et al. Global, regional, and national trends in under-5 mortality between 1990 and 2019 with scenario-based projections until 2030: a

systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. *The Lancet Global health* 2022; **10**(2): e195-e206.

99. Nations U. Global indicator framework for the Sustainable Development Goals and targets of the 2030 Agenda for Sustainable Development Geneva: United Nations, 2015.

100. Schell CO, Khalid K, Wharton-Smith A, et al. Essential Emergency and Critical Care: a consensus among global clinical experts. *BMJ global health* 2021; **6**(9).

101. Agulnik A, Cárdenas A, Carrillo AK, et al. Clinical and organizational risk factors for mortality during deterioration events among pediatric oncology patients in Latin America: A multicenter prospective cohort. *Cancer* 2021; **127**(10): 1668-78.

102. Tadesse L, Abdullah NH, Awadalla HMI, et al. A global mandate to strengthen emergency, critical and operative care. *Bulletin of the World Health Organization* 2023; **101**(4): 231-a.

103. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**(10053): 1725-74.

104. Fund UNCs. UNICEF Data Warehouse. https://data.unicef.org/dv_index/ (accessed July 20 2023).

105. Organization WH. The Global Health Observatory. https://www.who.int/data/gho (accessed July 20 2023).

106. You D, Hug L, Ejdemyr S, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a

systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. *Lancet* 2015; **386**(10010): 2275-86.

107. Shiffman J, Shawar YR. Strengthening accountability of the global health metrics enterprise. *Lancet* 2020; **395**(10234): 1452-6.

108. Bohn JA, Kassaye BM, Record D, et al. Demographic and mortality analysis of hospitalized children at a referral hospital in Addis Ababa, Ethiopia. *BMC pediatrics* 2016; **16**(1): 168.

109. Duke T, Yano E, Hutchinson A, et al. Large-scale data reporting of paediatric morbidity and mortality in developing countries: It can be done. *Archives of Disease in Childhood* 2016; **101**: 392-7.

110. Garg P. Pediatric hospitalizations at two different setting community hospitals in north India: implications for regionalization of care. *Indian journal of pediatrics* 2009; **76**(7): 711-6.

111. Rudd KE, Tutaryebwa LK, West TE. Presentation, management, and outcomes of sepsis in adults and children admitted to a rural Ugandan hospital: A prospective observational cohort study. *PloS one* 2017; **12**(2): e0171422.

112. Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. *Critical care medicine* 2017; **45**(6): 1061-93.

113. Covidence. Melbourne, Australia; 2019.

114. Hayden JA vdWD, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013; (158): 280–6.

115. (IHME). IfHMaE. GBD Results. . Available from https://vizhub.healthdata.org/gbd-results/ (accessed March 27 2023).

116. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *Journal of epidemiology and community health* 2013; **67**(11): 974-8.

117. Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC medical research methodology* 2008; **8**: 79.

118. Gathara D, Malla L, Ayieko P, et al. Variation in and risk factors for paediatric inpatient all-cause mortality in a low income setting: data from an emerging clinical information network. *BMC pediatrics* 2017; **17**(1): 99.

119. Santhanam I, Pai M, Kasturi K, Radhamani MP. Mortality after admission in the pediatric emergency department: a prospective study from a referral children's hospital in southern India. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2002; **3**(4): 358-63.

120. Sylverken J, Robison JA, Osei-Akoto A, et al. Decreased Mortality After Establishing a Pediatric Emergency Unit at an Urban Referral Hospital in Ghana. *Pediatric emergency care* 2021; **37**(7): e391-e5.

121. Clark M, Spry E, Daoh K, Baion D, Skordis-Worrall J. Reductions in inpatient mortality following interventions to improve emergency hospital care in Freetown, Sierra Leone. *PloS one* 2012; **7**(9): e41458.

122. Colvin JD, Zaniletti I, Fieldston ES, et al. Socioeconomic status and in-hospital pediatric mortality. *Pediatrics* 2013; **131**(1): e182-90.

123. Barwise-Munro R, Al-Mahtot M, Turner S. Mortality and other outcomes after paediatric hospital admission on the weekend compared to weekday. *PloS one* 2018; **13**(5): e0197494.

124. Childhood mortality during and after acute illness in Africa and south Asia: a prospective cohort study. *The Lancet Global health* 2022; **10**(5): e673-e84.

125. Thurstans S, Wrottesley SV, Fenn B, et al. Anthropometric deficits and the associated risk of death by age and sex in children aged 6-59 months: A meta-analysis. *Matern Child Nutr* 2023; **19**(1): e13431.

126. Wilkes C, Bava M, Graham HR, Duke T. What are the risk factors for death among children with pneumonia in low- and middle-income countries? A systematic review. *Journal of global health* 2023; **13**: 05003.

127. Gunda R, Chimbari MJ. Cost-effectiveness analysis of malaria interventions using disability adjusted life years: a systematic review. *Cost effectiveness and resource allocation : C/E* 2017; **15**: 10.

128. Puett C, Sadler K, Alderman H, Coates J, Fiedler JL, Myatt M. Cost-effectiveness of the community-based management of severe acute malnutrition by community health workers in southern Bangladesh. *Health policy and planning* 2013; **28**(4): 386-99.

129. Jha P, Bangoura O, Ranson K. The cost-effectiveness of forty health interventions in Guinea. *Health policy and planning* 1998; **13**(3): 249-62.

130. Rajabi T, Schell SK, Agapova SE, et al. Supplementary Feeding of Moderately Wasted Children in Sierra Leone Reduces Severe Acute Malnutrition and Death When Compared with Nutrition Counseling: A Retrospective Cohort Study. *The Journal of nutrition* 2022; **152**(4): 1149-58.

131. Ahmed MC, Heukelbach J, Weddih A, et al. Reduction of hospitalizations with diarrhea among children aged 0-5 years in Nouakchott, Mauritania, following the introduction of rotavirus vaccine. *Vaccine* 2019; **37**(11): 1407-11.

132. Amare AT, Kebede ZT, Welch HD. Epidemiology of bacterial meningitis in children admitted to Gondar University Hospital in the post pneumococcal vaccine era. *Pan Afr Med J* 2018; **31**: 193.

133. Berezin EN, Jarovsky D, Cardoso MRA, Mantese OC. Invasive pneumococcal disease among hospitalized children in Brazil before and after the introduction of a pneumococcal conjugate vaccine. *Vaccine* 2020; **38**(7): 1740-5.

134. Kortz TB, Herzel B, Marseille E, Kahn JG. Bubble continuous positive airway pressure in the treatment of severe paediatric pneumonia in Malawi: a cost-effectiveness analysis. *BMJ open* 2017; **7**(7): e015344.

135. Khan AM, Wright JE, Bhutta ZA. A Half Century of Oral Rehydration Therapy in Childhood Gastroenteritis: Toward Increasing Uptake and Improving Coverage. *Dig Dis Sci* 2020; **65**(2): 355-60.

136. Barochia AV, Cui X, Vitberg D, et al. Bundled care for septic shock: an analysis of clinical trials. *Critical care medicine* 2010; **38**(2): 668-78.

137. Paul R, Neuman MI, Monuteaux MC, Melendez E. Adherence to PALS Sepsis Guidelines and Hospital Length of Stay. *Pediatrics* 2012; **130**(2): e273-80.

138. Evans IVR, Phillips GS, Alpern ER, et al. Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis. *Jama* 2018; **320**(4): 358-67.

139. Rahman AE, Ameen S, Hossain AT, et al. Introducing pulse oximetry for outpatient management of childhood pneumonia: An implementation research adopting a district implementation model in selected rural facilities in Bangladesh. *EClinicalMedicine* 2022; **50**: 101511.

140. Mawji A, Li E, Chandna A, et al. Common data elements for predictors of pediatric sepsis: A framework to standardize data collection. *PloS one* 2021; **16**(6): e0253051.

141. Wiens MO, Pawluk S, Kissoon N, et al. Pediatric post-discharge mortality in resource poor countries: a systematic review. *PloS one* 2013; **8**(6): e66698.

142. Bhutta ZA, Das JK, Walker N, et al. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet* 2013; **381**(9875): 1417-29.

143. Cheah IG, Soosai AP, Wong SL, Lim TO. Cost-effectiveness analysis of Malaysian neonatal intensive care units. *Journal of perinatology : official journal of the California Perinatal Association* 2005; **25**(1): 47-53.

144. Ashley EA, Poespoprodjo JR. Treatment and prevention of malaria in children. *Lancet Child Adolesc Health* 2020; **4**(10): 775-89.

145. Baker T, Lugazia E, Eriksen J, Mwafongo V, Irestedt L, Konrad D. Emergency and critical care services in Tanzania: a survey of ten hospitals. *BMC health services research* 2013; **13**: 140.

146. Abbas Q, Shahbaz FF, Hussain MZH, et al. Evaluation of the Resources and Inequities Among Pediatric Critical Care Facilities in Pakistan. *Pediatric critical care*

medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2023.

147. Weiss SL, Fitzgerald JC, Faustino EV, et al. Understanding the global epidemiology of pediatric critical illness: the power, pitfalls, and practicalities of point prevalence studies. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2014; **15**(7): 660-6.

148. Abbas Q, Holloway A, Caporal P, et al. Global PARITY: Study Design for a Multi-Centered, International Point Prevalence Study to Estimate the Burden of Pediatric Acute Critical Illness in Resource-Limited Settings. *Frontiers in pediatrics* 2021; **9**: 793326.

149. Cuschieri S. The STROBE guidelines. *Saudi J Anaesth* 2019; **13**(Suppl 1): S31-s4.

150. Helbok R, Kendjo E, Issifou S, et al. The Lambarene Organ Dysfunction Score (LODS) is a simple clinical predictor of fatal malaria in African children. *The Journal of infectious diseases* 2009; **200**(12): 1834-41.

151. Organization WH. Child growth standards. 2023. https://www.who.int/tools/child-growth-standards (accessed March 10 2023).

152. Conroy AL, Hawkes M, Hayford K, et al. Prospective validation of pediatric disease severity scores to predict mortality in Ugandan children presenting with malaria and non-malaria febrile illness. *Critical care (London, England)* 2015; **19**: 47.

153. Kortz TB, Sawe HR, Murray B, Enanoria W, Matthay MA, Reynolds T. Clinical Presentation and Outcomes among Children with Sepsis Presenting to a Public Tertiary Hospital in Tanzania. *Frontiers in pediatrics* 2017; **5**(278): ecollection.

154. Muttalib F, Clavel V, Yaeger LH, Shah V, Adhikari NKJ. Performance of Pediatric Mortality Prediction Models in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. *J Pediatr* 2020; **225**: 182-92.e2.

155. Kortz TB, Nyirenda J, Tembo D, et al. Distinct Biomarker Profiles Distinguish Malawian Children with Malarial and Non-malarial Sepsis. *The American journal of tropical medicine and hygiene* 2019; **101**(6): 1424-33.

156. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2020; **21**(2): e52-e106.

157. Horak RV, Griffin JF, Brown AM, et al. Growth and Changing Characteristics of Pediatric Intensive Care 2001-2016. *Critical care medicine* 2019; **47**(8): 1135-42.

158. Hsu BS, Hill V, Frankel LR, et al. Executive Summary: Criteria for Critical Care of Infants and Children: PICU Admission, Discharge, and Triage Practice Statement and Levels of Care Guidance. *Pediatrics* 2019; **144**(4).

159. Prin M, Itaye T, Clark S, et al. Critical Care in a Tertiary Hospital in Malawi. *World journal of surgery* 2016; **40**(11): 2635-42.

160. Rodriguez-Galindo C, Friedrich P, Alcasabas P, et al. Toward the Cure of All Children With Cancer Through Collaborative Efforts: Pediatric Oncology As a Global

Challenge. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(27): 3065-73.

161. Agulnik A, Muniz-Talavera H, Pham LTD, et al. Effect of paediatric early warning systems (PEWS) implementation on clinical deterioration event mortality among children with cancer in resource-limited hospitals in Latin America: a prospective, multicentre cohort study. *Lancet Oncol* 2023; **24**(9): 978-88.

162. Kim JY, Farmer P, Porter ME. Redefining global health-care delivery. *Lancet* 2013; **382**(9897): 1060-9.

163. Thaddeus S, Maine D. Too far to walk: maternal mortality in context. *Social science & medicine (1982)* 1994; **38**(8): 1091-110.

164. Kamat VR. "I thought it was only ordinary fever!" cultural knowledge and the micropolitics of therapy seeking for childhood febrile illness in Tanzania. *Social science & medicine (1982)* 2006; **62**(12): 2945-59.

165. Malik EM, Hanafi K, Ali SH, Ahmed ES, Mohamed KA. Treatment-seeking behaviour for malaria in children under five years of age: implication for home management in rural areas with high seasonal transmission in Sudan. *Malar J* 2006; **5**: 60.

166. Kassile T, Lokina R, Mujinja P, Mmbando BP. Determinants of delay in care seeking among children under five with fever in Dodoma region, central Tanzania: a cross-sectional study. *Malar J* 2014; **13**: 348.

167. Pajuelo MJ, Anticona Huaynate C, Correa M, et al. Delays in seeking and receiving health care services for pneumonia in children under five in the Peruvian

Amazon: a mixed-methods study on caregivers' perceptions. *BMC health services research* 2018; **18**(1): 149.

168. Temsesgen D, Wordofa B, Tesfaye T, Etafa W. Delay in seeking healthcare for pneumonia and associated factors among mothers/caregivers of children aged 2-59 months in public health facilities in Nekemte town, Ethiopia. *BMC pediatrics* 2023; **23**(1): 17.

169. Deshmukh V, Lahariya C, Krishnamurthy S, Das MK, Pandey RM, Arora NK. Taken to Health Care Provider or Not, Under-Five Children Die of Preventable Causes: Findings from Cross-Sectional Survey and Social Autopsy in Rural India. *Indian J Community Med* 2016; **41**(2): 108-19.

170. Wiens MO, Gan H, Barigye C, et al. A cohort study of morbidity, mortality and health seeking behavior following rural health center visits by children under 12 in southwestern Uganda. *PloS one* 2015; **10**(1): e0118055.

171. Health Pi. PIH's Five S's: Essential Elements for Strong Health Systems. June 30, 2021 2021. https://www.pih.org/article/pihs-five-ss-essential-elements-strong-health-systems (accessed October 10 2023).

172. Farmer P. The Ebola Suspect's Dilemma. Keynote Address for the MacLean Prize Lecture; 2017.

173. Farmer P. Taking up the Challenges of Poverty: Why Accompaniment Matters. Notre Dame: Lecture delivered at Kellogg Institute for International Studies; 2016.

174. Siaw-Frimpong M, Touray S, Sefa N. Capacity of intensive care units in Ghana. *Journal of critical care* 2021; **61**: 76-81.

175. Riley C, Poss WB, Wheeler DS. The evolving model of pediatric critical care delivery in North America. *Pediatr Clin North Am* 2013; **60**(3): 545-62.

176. Smith AG, Brainard JC, Campbell KA. Development of an Undergraduate Medical Education Critical Care Content Outline Utilizing the Delphi Method. *Critical care medicine* 2020; **48**(1): 98-103.

177. Sonenthal PD, Kasomekera N, Connolly E, et al. Critical Care Units in Malawi: A Cross-Sectional Study. *Ann Glob Health* 2023; **89**(1): 51.

178. Kazibwe J, Shah HA, Kuwawenaruwa A, et al. Resource use, availability and cost in the provision of critical care in Tanzania: a systematic review. *BMJ open* 2022; **12**(11): e060422.

179. Organization WH. Oxygen. 2023. https://www.who.int/health-topics/oxygen#tab=tab_2 (accessed October 10 2023).

180. Edejer TT, Aikins M, Black R, Wolfson L, Hutubessy R, Evans DB. Cost effectiveness analysis of strategies for child health in developing countries. *BMJ (Clinical research ed)* 2005; **331**(7526): 1177.

181. Duke T, Wandi F, Jonathan M, et al. Improved oxygen systems for childhood pneumonia: a multihospital effectiveness study in Papua New Guinea. *Lancet* 2008; **372**(9646): 1328-33.

182. Brenzel L WL, Fox-Rushby J, Miller M, Halsey NA. Vaccine-Preventable Disease In: Jamison DT BJ, Measham AR, Alleyne G, Claeson M, Evans DB, et al, ed. Disease Control Priorities in Developing Countries. 2nd ed. New York: Oxford University Press; 2006: 389-412.

183. Groeneveld AB. Risk factors for increased mortality from hospital-acquired versus community-acquired infections in febrile medical patients. *Am J Infect Control* 2009; **37**(1): 35-42.

184. Rogowski J. Cost-effectiveness of care for very low birth weight infants. *Pediatrics* 1998; **102**(1 Pt 1): 35-43.

185. Doyle LW. Evaluation of neonatal intensive care for extremely low birth weight infants in Victoria over two decades: II. Efficiency. *Pediatrics* 2004; **113**(3 Pt 1): 510-4.

186. WHO. Cost effectiveness and strategic planning (WHO-CHOICE). 2014 2014. http://www.who.int/choice/en/.

187. Meadow W, Lantos JD, Mokalla M, Reimshisel T. Distributive justice across generations. Epidemiology of ICU care for the very young and the very old. *Clin Perinatol* 1996; **23**(3): 597-608.

188. Punchak M, Hall K, Seni A, et al. Epidemiology of Disease and Mortality From a PICU in Mozambique. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2018; **19**(11): e603-e10.

189. de Visser MA, Kululanga D, Chikumbanje SS, et al. Outcome in Children Admitted to the First PICU in Malawi. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2023; **24**(6): 473-83.

190. Kumar R, Canarie MF. Developing Pediatric Critical Care in Kenya. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 2019; **20**(12): e538-e45.

191. Slusher T, Bjorklund A, Aanyu HT, Kiragu A, Philip C. The Assessment, Evaluation, and Management of the Critically Ill Child in Resource-Limited International Settings. *Journal of pediatric intensive care* 2017; **6**(1): 66-76.

192. World Health Organization DoCaAHaD, UNICEF. Handbook IMCI Integrated Management of Childhood Illness. Geneva, Switzerland, 2005.

193. Hategeka C, Mwai L, Tuyisenge L. Implementing the Emergency Triage, Assessment and Treatment plus admission care (ETAT+) clinical practice guidelines to improve quality of hospital care in Rwandan district hospitals: healthcare workers' perspectives on relevance and challenges. *BMC health services research* 2017; **17**(1): 256.

194. Hansoti B, Jenson A, Keefe D, et al. Reliability and validity of pediatric triage tools evaluated in Low resource settings: a systematic review. *BMC pediatrics* 2017; **17**(1): 37.

195. Mawji A, Li E, Dunsmuir D, et al. Smart triage: Development of a rapid pediatric triage algorithm for use in low-and-middle income countries. *Frontiers in pediatrics* 2022; **10**: 976870.

196. Rosman SL, Karangwa V, Law M, Monuteaux MC, Briscoe CD, McCall N. Provisional Validation of a Pediatric Early Warning Score for Resource-Limited Settings. *Pediatrics* 2019; **143**(5).

197. Serra JA, Díaz F, Cruces P, et al. Characteristics of Medically Transported Critically Ill Children with Respiratory Failure in Latin America: Implications for Outcomes. *Journal of pediatric intensive care* 2022; **11**(3): 201-8.

198. Purcell LN, Mulima G, Nip E, Yohan A, Gallaher J, Charles A. Police Transportation Following Vehicular Trauma and Risk of Mortality in a Resource-Limited Setting. *World journal of surgery* 2021; **45**(3): 662-7.

199. Gallaher J, An SJ, Kayange L, Davis D, Charles A. Tri-modal Distribution of Trauma Deaths in a Resource-Limited Setting: Perception Versus Reality. *World journal of surgery* 2023; **47**(7): 1650-6.

200. Sultan M, Abebe Y, Tsadik AW, Ababa A, Yesus AG, Mould-Millman NK. Trends and barriers of emergency medical service use in Addis Ababa; Ethiopia. *BMC emergency medicine* 2019; **19**(1): 28.

201. Kiputa M, Salim N, Kunambi PP, Massawe A. Referral challenges and outcomes of neonates received at Muhimbili National Hospital, Dar es Salaam, Tanzania. *PloS one* 2022; **17**(6): e0269479.

202. Stein C, Mould-Millman NK, De Vries S, Wallis L. Access to out-of-hospital emergency care in Africa: Consensus conference recommendations. *Afr J Emerg Med* 2016; **6**(3): 158-61.

203. Howard I, Cameron P, Wallis L, Castren M, Lindstrom V. Quality Indicators for Evaluating Prehospital Emergency Care: A Scoping Review. *Prehosp Disaster Med* 2018; **33**(1): 43-52.

204. Hendricks M, Cois A, Geel J, et al. Socioeconomic status significantly impacts childhood cancer survival in South Africa. *Pediatric blood & cancer* 2023; **70**(12): e30669.

205. Rosen F, Settel L, Irvine F, Koselka EPD, Miller JD, Young SL. Associations between food insecurity and child and parental physical, nutritional, psychosocial and economic well-being globally during the first 1000 days: A scoping review. *Matern Child Nutr* 2023: e13574.

206. Cohen CR, Steinfeld RL, Weke E, et al. Shamba Maisha: Pilot agricultural intervention for food security and HIV health outcomes in Kenya: design, methods, baseline results and process evaluation of a cluster-randomized controlled trial. *SpringerPlus* 2015; **4**: 122.

207. McDonough A, Weiser SD, Daniel A, et al. "When I Eat Well, I Will Be Healthy, and the Child Will Also Be Healthy": Maternal Nutrition among HIV-Infected Women Enrolled in a Livelihood Intervention in Western Kenya. *Curr Dev Nutr* 2020; **4**(4): nzaa032.

208. Weiser SD, Bukusi EA, Steinfeld RL, et al. Shamba Maisha: randomized controlled trial of an agricultural and finance intervention to improve HIV health outcomes. *AIDS (London, England)* 2015; **29**(14): 1889-94.

209. Wiens MO, Bone JN, Kumbakumba E, et al. Mortality after hospital discharge among children younger than 5 years admitted with suspected sepsis in Uganda: a prospective, multisite, observational cohort study. *Lancet Child Adolesc Health* 2023; **7**(8): 555-66.

210. Kingdon J. Agendas, Alternatives, and Public Policies. 2 ed: Addison-Wesley Educational Publishers, Inc.; 2003.

211. Buowari DY, Owoo C, Gupta L, Schell CO, Baker T. Essential Emergency and Critical Care: A Priority for Health Systems Globally. *Critical care clinics*

2022; **38**(4): 639-56.

212. Razzak JA, Kellermann AL. Emergency medical care in developing countries: is it worthwhile? *Bulletin of the World Health Organization* 2002; **80**(11): 900-5.

213. Thompson MG, Levine MZ, Bino S, et al. Underdetection of laboratory-confirmed influenza-associated hospital admissions among infants: a multicentre, prospective study. *Lancet Child Adolesc Health* 2019; **3**(11): 781-94.

214. Araujo EMN, Costa GMC, Pedraza DF. Hospitalizations due to primary care-sensitive conditions among children under five years of age: cross-sectional study. *Sao Paulo Med J* 2017; **135**(3): 270-6.

215. Carvalho SC, Mota E, Dourado I, Aquino R, Teles C, Medina MG. Hospitalizations of children due to primary health care sensitive conditions in Pernambuco State, Northeast Brazil. 2015; **1**(4): 744-54.

216. Chúa C. ¿De qué se hospitalizan a los niños en Guatemala? *Rev Col Méd Cir Guatem* 2014; **151**: 44-5.

217. Rocha MC, Carminate DL, Tibiriçá SH, Carvalho IP, Silva ML, Chebli JM. Acute diarrhea in hospitalized children of the municipality of Juiz de Fora, MG, Brazil: prevalence and risk factors associated with disease severity. *Arq Gastroenterol* 2012; **49**(4): 259-65.

218. de Oliveira RR, da Costa JR, Mathias TAF. Hospitalization of children under five years of age due to avoidable causes. *Revista Latino-Americana de Enfermagem* 2012; **20**(1): 135-42.

219. Díaz-Garrido D, Pinto-Zaldumbide SC, Lazo-Álvarez MÁ, et al. Causes of death in a pediatric tertiary care hospital in Ecuador. *Revista Mexicana de Pediatria*

2018; **85**(6): 207-11.

220. González RG, Granja AP, Caisaguano AT, et al. Incidence and clinical characteristics of children with community acquired pneumonia attending the hospital pediátrico “Baca Ortiz”, Ecuador. *Archivos Venezolanos de Farmacologia y Terapeutica* 2020; **39**(4): 260-3.

221. Gouvea VS, Dias GS, Aguiar EA, et al. Acute gastroenteritis in a pediatric hospital in rio de janeiro in pre- and post-rotavirus vaccination settings. *Open Virol J* 2009; **3**: 26-30.

222. Jacomin V, Cruz Shibukawa BM, Ieda Harumi H. INFANT HOSPITALIZATION BY PRIMARY CARE'S SENSITIVE CONDITIONS IN A SOUTHERN BRAZILIAN STATE. *Revista de Pesquisa: Cuidado e Fundamental* 2020; **12**(1): 958-64.

223. Mangia CM, Kissoon N, Branchini OA, Andrade MC, Kopelman BI, Carcillo J. Bacterial sepsis in Brazilian children: a trend analysis from 1992 to 2006. *PloS one* 2011; **6**(6): e14817.

224. Mansilla Flower P. Características clínico-epidemiológicas de pacientes con diagnóstico de Síndrome Urémico Hemolítico. *Rev peru pediatr* 2012; **65**(3): 29-.

225. Mariano TDSO, Nedel FB. Hospitalization for Ambulatory Care Sensitive Conditions in children under five years old in Santa Catarina State, Brazil, 2012: a descriptive study. *Epidemiol Serv Saude* 2018; **27**(3): e2017322.

226. McCarthy JE, Evans-Gilbert T. Descriptive epidemiology of mortality and morbidity of health-indicator diseases in hospitalized children from western Jamaica. *The American journal of tropical medicine and hygiene* 2009; **80**(4): 596-600.

227. Noyola DE, Zuviri-González A, Castro-García JA, Ochoa-Zavala JR. Impact of respiratory syncytial virus on hospital admissions in children younger than 3 years of age. *The Journal of infection* 2007; **54**(2): 180-4.

228. Orrett FA, Changoor E, Maharaj N. Pediatric drug prescribing in a regional hospital in Trinidad. *Journal of Chinese Clinical Medicine* 2010; **5**(3): 157-63.

229. Paulo RL, Rodrigues AB, Machado BM, Gilio AE. The impact of rotavirus vaccination on emergency department visits and hospital admissions for acute diarrhea in children under 5 years. *Rev Assoc Med Bras (1992)* 2016; **62**(6): 506-12.

230. Risquez A, Urbina-Medina H, Ponce A. Indicadores Hospitalarios 2011-2012: Hospital de niños JM de los Ríos de Caracas, Venezuela. *Arch venez pueric pediatr* 2014; **77**(4): 162-9.

231. Santos CAD, Rosa CDOB, Franceschini SDCC, Firmino HH, Ribeiro AQ. Usefulness of the StrongKids Screening Tool in Detecting Anemia and Inflammation in Hospitalized Pediatric Patients. *Journal of the American College of Nutrition* 2021; **40**(2): 155-63.

232. Sarni RO, Carvalho Mde F, Monte CM, Albuquerque ZP, Souza FI. Anthropometric evaluation, risk factors for malnutrition, and nutritional therapy for children in teaching hospitals in Brazil. *Jornal de pediatria* 2009; **85**(3): 223-8.

233. Vinekar K, Schaad N, Ber Lucien MA, et al. Hospitalizations and Deaths Because of Respiratory and Diarrheal Diseases Among Haitian Children Under Five Years of Age, 2011-2013. *The Pediatric infectious disease journal* 2015; **34**(10): e238-43.

234. Al Kubati AKAS. Non-induced traumatic coma in children in northern region of Yemen causes and mortality. *Journal Medical Libanais* 2018; **66**(3): 154-60.

235. Al-Taiar A, Jaffar S, Assabri A, et al. Severe malaria in children in Yemen: two site observational study. *BMJ (Clinical research ed)* 2006; **333**(7573): 827.

236. Ali SH, Hussien FS, Abd Al-Amer H. Profile of renal diseases in Iraqi children: A single-center report. *Saudi J Kidney Dis Transpl* 2015; **26**(3): 613-8.

237. Al-Janabi HA, Raffas HA, Jassim SA. Incidence rate of mortality form massive pulmonary embolism in al-diwaniyah province, iraq, during the period from january 2011 through december 2018. *Indian Journal of Forensic Medicine and Toxicology* 2019; **13**(3): 330-4.

238. El Mhamdi S, Herizi C, Sriha A, et al. [Profile and trends of pediatric hospital morbidity in the region of Monastir (Tunisia) for a decade]. *Rev Med Brux* 2015; **36**(5): 410-4.

239. Maalej B, Ben Amor M, Jallouli M, et al. [Post-streptococcal glomerulonephritis in the south of Tunisia: A 12-year retrospective review]. *Nephrol Ther* 2018; **14**(7): 518-22.

240. Sallam AK. Common causes of child mortality in Sana'a, Yemen. *Saudi Med J* 2005; **26**(7): 1112-5.

241. Adhikari S, Sathian B, Koirala DP, Rao KS. Profile of children admitted with seizures in a tertiary care hospital of Western Nepal. *BMC pediatrics* 2013; **13**: 43.

242. Ashraf M, Kumar V, Bano RA, Wani KA, Ahmed J, Ahmed K. Spectrum of Renal and Urinary Tract Diseases in Kashmiri Children. *Journal of clinical and diagnostic research : JCDR* 2016; **10**(6): SM01-2.

243. Badhan A, Bhardwaj P, Yadav V, Grover N, Seem RK. Demographic profile of pediatric malignancies in Himachal Pradesh. *Indian Journal of Medical and Paediatric Oncology* 2018; **39**(3): 287-91.

244. Basu M, Kundu TK, Dasgupta MK, Das DK, Saha I. Poisoning, stings and bites in children-- what is new? An experience from a tertiary care hospital in Kolkata. *Indian J Public Health* 2009; **53**(4): 229-31.

245. Champatiray J, Satapathy J, Kashyap B, Mondal D. Clinico-Aetiological Study of Severe and Very Severe Pneumonia in Two Months to Five Years Children in a Tertiary Health Care Centre in Odisha, India. *Journal of clinical and diagnostic research : JCDR* 2017; **11**(9): SC06-SC10.

246. Chapagain RH, Agrawal S, Pokharel S, et al. Clinico-Laboratory Profile, Complications and Therapeutic Outcome of Scrub Typhus in Children. *J Nepal Health Res Counc* 2020; **18**(2): 282-7.

247. Chaudhary N, Gupta MM, Shrestha S, et al. Clinicodemographic Profile of Children with Seizures in a Tertiary Care Hospital: A Cross-Sectional Observational Study. *Neurol Res Int* 2017; **2017**: 1524548.

248. Drolia A, Dewan P, Gupta P. Predicting the severity of bronchiolitis in a resource-poor setting. *Internet Journal of Pediatrics and Neonatology* 2010; **11**(1).

249. Duwarah SG, Hazarika RD, Barman H, Deka P. Profile of hypertension in children: Experience from a tertiary care institute in North East India. *Indian Journal of Medical Specialities* 2016; **7**(3): 100-2.

250. Ganjoo S, Ahmad K, Qureshi UA, Mir ZH. Clinical Epidemiology of SIRS and Sepsis in Newly Admitted Children. *Indian journal of pediatrics* 2015; **82**(8): 698-702.

251. Giri BR, Chapagain RH, Sharma S, Shrestha S, Ghimire S, Shankar PR. Effect of the 2015 earthquake on pediatric inpatient pattern at a tertiary care hospital in Nepal. *BMC pediatrics* 2018; **18**(1): 28.

252. Gupta SK, Sarmah BK, Tiwari D, Thapa S. Pattern of Pediatric Admissions in a Tertiary Care Hospital of Central Nepal. *JNMA J Nepal Med Assoc* 2015; **53**(198): 118-22.

253. Gupta MM, Chaudhary N, Pathak S, et al. Neurocysticercosis in Children with Seizures: A Cross-Sectional Study. *Int J Pediatr* 2018; **2018**: 1030878.

254. Gupta PK, Singhi P, Singhi S, Kasinathan A, Sankhyan N. How Different is AMAN from AIDP in Childhood GBS? A Prospective Study from North India. *Indian journal of pediatrics* 2019; **86**(4): 329-34.

255. Halder R, Malik R, Aggarwal KC, Nair D, Sharma S. Clinical Profile of Bacterial Meningitis in Children and Comparative Inter-Alia Analysis of Various Microbiological Tests. *Journal of Child Science* 2020; **10**(1): E38-e44.

256. Jose A, Sivanandam S, Matthai J. Poisoning in children from an educationally and economically advanced urban area of South India. *Asian Journal of Epidemiology* 2012; **5**(4): 123-9.

257. Mahajan V, Kaur A, Sharma A, Azad C, Guglani V. Modifiable factors for prevention of childhood mortality. 2014; **1**(1): 45-7.

258. Malla T, Malla KK, Rao KS, Gauchan E, Basnet S, Koirala DP. A scenario of poisoning in children in Manipal teaching hospital. *Journal of Nepal Paediatric Society* 2011; **31**: 83-8.

259. Masood-Us-Syed SS, Basit AK, Mohammad S, et al. Screening of childhood tuberculosis with Pakistan pediatric association scoring chart system. *Pakistan Paediatric Journal* 2012; **36**(4): 220-4.

260. Mathur A, Tahilramani G, Makhija S, Devgan V. Burden of Severe Acute Malnutrition in under-five Children (2-59 Months) Admitted in a Tertiary Care Hospital of Delhi. *Journal of tropical pediatrics* 2018; **64**(1): 45-50.

261. Mishra S, Ramkumar TV, Biswas AK, Panigrahi S. Childhood poisoning, a rising epidemic in developing nations: Large single centre study. *Journal of Nepal Paediatric Society* 2017; **37**(2): 117-21.

262. Naheed A, Saha SK, Breiman RF, et al. Multihospital surveillance of pneumonia burden among children aged <5 years hospitalized for pneumonia in Bangladesh. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2009; **48 Suppl 2**: S82-9.

263. Roy RN, Shrivastava P, Das DK, Saha I, Sarkar AP. Burden of hospitalized pediatric morbidity and utilization of beds in a tertiary care hospital of kolkata, India. *Indian J Community Med* 2012; **37**(4): 252-5.

264. Rajak K, Twayana AR, Shrestha R, Amatya P, Ghimire C. Prevalence of kawasaki disease in a tertiary care hospital: A descriptive cross-sectional study. *Journal of the Nepal Medical Association* 2019; **57**(220): 416-9.

265. Rao S, Gavali V, Prabhu SS, et al. Outcome of Children Admitted With SARS-CoV-2 Infection: Experiences From a Pediatric Public Hospital. *Indian pediatrics* 2021; **58**(4): 358-62.

266. Rasheed J, Wakeel N, Aleem T, Khalid M, Zafar F. Pattern and outcome of pediatric admissions in a tertiary care hospital Multan. *Pakistan Paediatric Journal* 2017; **41**(3): 168-73.

267. Rasul CH, Muhammad F, Hossain MJ, Ahmed KU, Rahman M. Acute meningoencephalitis in hospitalised children in southern Bangladesh. *Malays J Med Sci* 2012; **19**(2): 67-73.

268. Roy MP, Gupta R, Bhatt M, Aggarwal KC. Causes of Death among Children Aged >5 Years in a Public Hospital in New Delhi. *Indian pediatrics* 2017; **54**(1): 60-1.

269. Sadiq MW, Ukrani RD, Arif A, Akbar I, Altaf S, Moiz B. Risk Assessment and Outcome of Venous Thromboembolism in Pediatric Population in an Academic Care Center of a Low-Middle Income Country. *Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis* 2021; **27**: 1076029621995895.

270. Sarangi R, Pattnaik L, Satpathy SK, Sahu MC. Mortality pattern of under-five children – A hospital-based cross-sectional study in a tertiary care hospital of India. *Asian Journal of Pharmaceutical and Clinical Research* 2017; **10**(9): 82-4.

271. Sharma P, Sarmah BK, Kayastha P, Shrestha A, Tiwari D. Clinical profile of children with acute febrile encephalopathy in a tertiary health care center of Nepal. *Journal of Nepal Paediatric Society* 2015; **35**(3): 224-30.

272. Sharma M, Damlin A, Pathak A, Lundborg CS. Antibiotic prescribing among pediatric inpatients with potential infections in two private sector hospitals in Central India. *PloS one* 2015; **10**(11).

273. Shrestha S, Bichha RP, Sharma A, Upadhyay S, Rijal P. Clinical profile of tuberculosis in children. *Nepal Med Coll J* 2011; **13**(2): 119-22.

274. Shrestha D, Regmi D, Raya G, Prajapati A, Dhaubhadel S, Puri S. Radiographically Confirmed Community-Acquired Pneumonia in Pediatric Patients Prior to Pneumococcal Vaccination in Nepal. *Journal of Pediatric Infectious Diseases* 2018; **13**(1): 57-62.

275. Siddique AK, Ahmed S, Iqbal A, et al. Epidemiology of rotavirus and cholera in children aged less than five years in rural Bangladesh. *J Health Popul Nutr* 2011; **29**(1): 1-8.

276. Sil A, Ghosh TN, Bhattacharya S, Konar MC, Soren B, Nayek K. A study on clinico-epidemiological profile of poisoning in children in a rural tertiary care hospital. *Journal of Nepal Paediatric Society* 2016; **36**(2): 105-9.

277. Singh D, Chopra A, Pooni PA, Bhatia RC. A clinical profile of shock in children in Punjab, India. *Indian pediatrics* 2006; **43**(7): 619-23.

278. Sonowal R. Profile of renal diseases in North-East Indian children. *Saudi J Kidney Dis Transpl* 2019; **30**(5): 1151-5.

279. van Deursen B, Lenglet A, Ariti C, et al. Risks and seasonal pattern for mortality among hospitalized infants in a conflict-affected area of Pakistan, 2013-2016. A retrospective chart review. *F1000Res* 2019; **8**: 954.

280. Verma S, Rai SK, Kant S, Choudhury K. Morbidity profile of paediatric inpatents at a community health centre and a nearby [correction of near by] district hospital in northern India. *Indian J Public Health* 2007; **51**(2): 125-6.

281. Zaheer A, Rashid A, Chishty AL. Neurological disease spectrum and associated factors for morbidity and mortality among admitted children. *Pakistan Paediatric Journal* 2009; **33**(1): 24-9.

282. Barennes H, Sayavong E, Pussard E. High Mortality Risk in Hypoglycemic and Dysglycemic Children Admitted at a Referral Hospital in a Non Malaria Tropical Setting of a Low Income Country. *PloS one* 2016; **11**(2): e0150076.

283. Bucens IK, Maclennan C. Survey of childhood malnutrition at Dili National Hospital, East Timor. *Journal of paediatrics and child health* 2006; **42**(1-2): 28-32.

284. Bucens IK, Reid A, Barreto AC, Dwivedi V, Counahan M. Three years of paediatric morbidity and mortality at the National Hospital in Dili, East Timor. *Journal of paediatrics and child health* 2013; **49**(12): 1004-9.

285. Chusilp K, Kosuwon P, Panthongwiriyakul C, Thepsuthammarat K, Wangsai S, Sutra S. Thai infant health situation: essential medical information for family centered care. *J Med Assoc Thai* 2012; **95 Suppl 7**: S24-9.

286. Ho NT, Thompson C, Nhan LNT, et al. Retrospective analysis assessing the spatial and temporal distribution of paediatric acute respiratory tract infections in Ho Chi Minh City, Vietnam. *BMJ open* 2018; **8**(1): e016349.

287. Jetsrisuparb A, Teeratakulpisarn J, Weraarchakul W, Thepsuthammarat K, Sutra S. Health situation analysis of Thai children aged 1-5 years in 2010: implications for health education and health service reform. *J Med Assoc Thai* 2012; **95 Suppl 7**: S30-42.

288. Kudagammana ST, Karunaratne RR, Munasinghe TS, Kudagammana HDWS. Community acquired paediatric pneumonia; experience from a pneumococcal vaccine-naive population. *Pneumonia (Nathan Qld)* 2020; **12**: 8.

289. Laman M, Aipit S, Bona C, Aipit J, Davis TME, Manning L. Contribution of Malaria to Inhospital Mortality in Papua New Guinean Children from a Malaria-Endemic

Area: A Prospective Observational Study. *The American journal of tropical medicine and hygiene* 2019; **100**(4): 835-41.

290. Langridge FC, Hufanga SV, 'Ofanoa MM, et al. Child morbidity as described by hospital admissions for primary school aged children in Tonga 2009-2013. *New Zealand Medical Journal* 2017; **130**(1465): 29-43.

291. Moe K, Hummelman EG, Oo WM, Lwin T, Htwe TT. Hospital-based surveillance for rotavirus diarrhea in children in Yangon, Myanmar. *Journal of Infectious Diseases* 2005; **192**(SUPPL. 1): S111-S3.

292. Murni IK, Duke T, Kinney S, et al. Multifaceted interventions for healthcare-associated infections and rational use of antibiotics in a low-to-middle-income country: Can they be sustained? *PloS one* 2020; **15**(6 June).

293. Nguyen TKP, Nguyen DV, Truong TNH, Tran MD, Graham SM, Marais BJ. Disease spectrum and management of children admitted with acute respiratory infection in Viet Nam. *Tropical medicine & international health : TM & IH* 2017; **22**(6): 688-95.

294. Nguyen NTT, Dien TM, Schindler C, et al. Childhood hospitalisation and related deaths in Hanoi, Vietnam: a tertiary hospital database analysis from 2007 to 2014. *BMJ open* 2017; **7**(7): e015260.

295. Pham TD, Hoang VT, Dao TL, et al. Morbidity and Mortality Patterns in Children Admitted to Hospital in Thai Binh, Vietnam: A Five-year Descriptive Study with a Focus on Infectious Diseases. *J Epidemiol Glob Health* 2020; **29**: 29.

296. Poespoprodjo JR, Fobia W, Kenangalem E, et al. Vivax malaria: a major cause of morbidity in early infancy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2009; **48**(12): 1704-12.

297. Rero A, Aipit J, Yarong-Kote T, et al. The Burden of Child Maltreatment Leading to Hospitalization in a Provincial Setting in Papua New Guinea. *Journal of tropical pediatrics* 2016; **62**(4): 282-7.

298. Suphakunpinyo C, Areemit R, Thepsuthammarat K, Sutra S. The health situation among Thai elementary school-age children: 2010. *J Med Assoc Thai* 2012; **95 Suppl 7**: S43-50.

299. Tan KK, Dang DA, Kim KH, et al. Burden of hospitalized childhood community-acquired pneumonia: A retrospective cross-sectional study in Vietnam, Malaysia, Indonesia and the Republic of Korea. *Hum Vaccin Immunother* 2018; **14**(1): 95-105.

300. Thompson CN, Zelner JL, Nhu TDH, et al. The impact of environmental and climatic variation on the spatiotemporal trends of hospitalized pediatric diarrhea in Ho Chi Minh City, Vietnam. *Health and Place* 2015; **35**: 147-54.

301. Wandi F, Peel D, Duke T. Hypoxaemia among children in rural hospitals in Papua New Guinea: epidemiology and resource availability--a study to support a national oxygen programme. *Annals of tropical paediatrics* 2006; **26**(4): 277-84.

302. Wilopo SA, Soenarto Y, Bresee JS, et al. Rotavirus surveillance to determine disease burden and epidemiology in Java, Indonesia, August 2001 through April 2004. *Vaccine* 2009; **27**(SUPPL. 5): F61-F6.

303. Abebe Gm. A two year retrospective review of reasons for pediatric admission to Chiro Hospital, Eastern Ethiopia. *Ethiop Med J* 2005; **43**(4): 241-9.

304. Adadey SM, Ayee R, Languon S, Quansah D, Quaye O. Patterns of Frequently Diagnosed Pediatric Morbidities in Hospitalized Children in the Volta Region of Ghana. *Glob* 2019; **6**: 2333794X19889230.

305. Adeboye MA, Ojuawo A, Ernest SK, Fadeyi A, Salisu OT. Mortality pattern within twenty-four hours of emergency paediatric admission in a resource-poor nation health facility. *West Afr J Med* 2010; **29**(4): 249-52.

306. Adeboye M, Adesiyun O, Adegboye A, et al. Measles in a tertiary institution in bida, niger state, Nigeria: prevalence, immunization status and mortality pattern. *Oman med* 2011; **26**(2): 114-7.

307. Adeboye M, Ojuawo A, Adeniyi A, Ibraheem RM, Amiwero C. Febrile Convulsion among Hospitalized Children Aged Six Months to Five Years and Its Association With Haemoglobin Electrophoretic Pattern. *Ethiopian journal of health sciences* 2015; **25**(3): 251-6.

308. Adegoke SA, Dedeke IO, Oyelami OA. Childhood injuries in Ilesa, South-Western Nigeria: causes, pattern, and outcome. *West Afr J Med* 2010; **29**(4): 253-8.

309. Adegoke S, Ayansanwo A, Oluwayemi I, Okeniyi J. Determinants of mortality in Nigerian children with severe anaemia. *Samj, S* 2012; **102**(10): 807-10.

310. Adekanmbi AF, Ogunlesi TA, Olowu AO, Fetuga MB. Current trends in the prevalence and aetiology of childhood congestive cardiac failure in Sagamu. *Journal of tropical pediatrics* 2007; **53**(2): 103-6.

311. Adeleke SI, Asani MO, Belonwu RO, Gwarzo GD, Farouk ZL. Childhood diabetes mellitus in Kano, North West, Nigeria. *Niger J Med* 2010; **19**(2): 145-7.

312. Adem F, Edessa D, Bayissa B, Hassen MM, Mohammed MA. Treatment outcomes and associated factors in hospitalised children with severe acute malnutrition: A prospective cohort study. *Pediatric Health, Medicine and Therapeutics* 2020; **11**: 235-43.

313. Ademola AD, Asinobi AO, Ekpe-Adewuyi E, et al. Acute kidney injury among paediatric emergency room admissions in a tertiary hospital in South West Nigeria: a cohort study. *Clin Kidney J* 2019; **12**(4): 521-6.

314. Adeyeye EI, Adanlawo IG. Analysis of medical admissions into children's ward of the Ekiti state specialist hospital, Ado-Ekiti, Nigeria, 2000-2001. *Biosciences Biotechnology Research Asia* 2007; **4**(1): 123-34.

315. Agbeille MF, Adedemy JD, Noudamadjo A, Kpanidja, Mbanga-Ngoume JJ, Agossou J. Cerebral malaria in child in Departmental University Teaching Hospital of Borgou, Benin. *Medecine d'Afrique Noire* 2019; **66**(3): 131-8.

316. Ahmed PA, Babaniyi IB, Otuneye AT. Review of childhood measles admissions at the National Hospital, Abuja. *Nigerian journal of clinical practice* 2010; **13**(4): 413-6.

317. Ahmed M, Weddih A, Benhafid M, et al. Hospitalizations and Deaths Associated with Diarrhea and Respiratory Diseases among Children Aged 0-5 Years in a Referral Hospital of Mauritania. *Trop* 2018; **3**(3): 17.

318. Ahmed MC, Heukelbach J, Weddih A, et al. Reduction of hospitalizations with diarrhea among children aged 0-5years in Nouakchott, Mauritania, following the introduction of rotavirus vaccine. *Vaccine* 2019; **37**(11): 1407-11.

319. Akech S, Chepkirui M, Ogero M, et al. The Clinical Profile of Severe Pediatric Malaria in an Area Targeted for Routine RTS,S/AS01 Malaria Vaccination in Western Kenya. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2020; **71**(2): 372-80.

320. Akinbami FO, Hamzat TH, Orimadegun AE, et al. Body mass composition: a predictor of admission outcomes among hospitalized Nigerian under 5 children. *Asia Pac J Clin Nutr* 2010; **19**(3): 295-300.

321. Aloni MN, Nsibu CN, Meeko-Mimaniye M, Ekulu PM, Bodi JM. Acute renal failure in Congolese children: a tertiary institution experience. *Acta Paediatrica* 2012; **101**(11): e514-8.

322. Andersen A, Bjerregaard-Andersen M, Rodrigues A, Umbasse P, Fisker AB. Sex-differential effects of diphtheria-tetanus-pertussis vaccine for the outcome of paediatric admissions? A hospital based observational study from Guinea-Bissau. *Vaccine* 2017; **35**(50): 7018-25.

323. Animasahun A, Itiola J, Falase B, et al. Congestive cardiac failure among Nigerian children; pattern and outcome. *International Cardiovascular Research Journal* 2015; **9**(3): 164-8.

324. Ayieko P, Ogero M, Makone B, et al. Characteristics of admissions and variations in the use of basic investigations, treatments and outcomes in Kenyan hospitals within a new Clinical Information Network. *Archives of Disease in Childhood* 2016; **101**(3): 223-9.

325. Bassat Q, Guinovart C, Sigauque B, et al. Malaria in rural Mozambique. Part II: children admitted to hospital. *Malar J* 2008; **7**: 37.

326. Belonwu RO, Adeleke SI. A seven-year review of accidental kerosene poisoning in children at Aminu Kano Teaching Hospital, Kano. *Niger J Med* 2008; **17**(4): 380-2.

327. Berti A, Bregani ER, Manenti F, Pizzi C. Outcome of severely malnourished children treated according to UNICEF 2004 guidelines: a one-year experience in a zone

hospital in rural Ethiopia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2008; **102**(9): 939-44.

328. Birindwa AM, Manegabe JT, Mindja A, Norden R, Andersson R, Skovbjerg S. Decreased number of hospitalized children with severe acute lower respiratory infection after introduction of the pneumococcal conjugate vaccine in the Eastern Democratic Republic of the Congo. *Pan Afr Med J* 2020; **37**: 211.

329. Bouyou-Akotet MK, Mawili-Mboumba DP, Kendjo E, et al. Complicated malaria and other severe febrile illness in a pediatric ward in Libreville, Gabon. *BMC Infect Dis* 2012; **12**: 216.

330. Boyle KL, Periyanayagam U, Babu KM, Rice BT, Bisanzo M. Pediatric Poisonings in a Rural Ugandan Emergency Department. *Pediatric emergency care* 2017; **09**: 09.

331. Boyle KL, Periyanayagam U, Babu KM, Rice BT, Bisanzo M. Pediatric Poisonings in a Rural Ugandan Emergency Department. *Pediatric emergency care* 2020; **36**(3): e160-e2.

332. Brits H, Botha L, Maakomane W, et al. The profile and clinical picture of children with undernutrition admitted to National District Hospital. *Pan Afr Med J* 2020; **37**: 237.

333. Brugnolaro V, Fovino LN, Calgaro S, et al. Pediatric emergency care in a low-income country: Characteristics and outcomes of presentations to a tertiary-care emergency department in Mozambique. *PloS one* 2020; **15**(11): e0241209.

334. Chami N, Hau DK, Masoza TS, et al. Very severe anemia and one year mortality outcome after hospitalization in Tanzanian children: A prospective cohort study. *PloS one* 2019; **14**(6): e0214563.

335. Charles NC, Chuku A, Anazodo NM. Childhood mortality in federal medical centre umuahia, South eastern Nigeria. *Oman med* 2014; **29**(5): 320-4.

336. Chelo D, Mekone Nkwelle I, Nguefack F, et al. Decrease in Hospitalizations and Increase in Deaths during the Covid-19 Epidemic in a Pediatric Hospital, Yaounde-Cameroon and Prediction for the Coming Months. *Fetal Pediat Pathol* 2020: 1-14.

337. Chiabi A, Takou V, Tchokoteu PF, Um SN, Essoh L, Immumboeh P. Initial treatment of severe malaria in children is inadequate - A study from a referral hospital in Cameroon. *SAJCH South African Journal of Child Health* 2009; **3**(1): 9-11.

338. Chiabi A, Malangue B, Nguefack S, et al. The clinical spectrum of severe acute malnutrition in children in Cameroon: a hospital-based study in Yaounde, Cameroon. *Transl* 2017; **6**(1): 32-9.

339. Chiabi A, Djimafo ANM, Nguefack S, Mah E, Nguefack Dongmo F, Angwafo F, 3rd. Severe malaria in Cameroon: Pattern of disease in children at the Yaounde Gynaeco-Obstetric and Pediatric hospital. *J Infect Public Health* 2020; **13**(10): 1469-72.

340. Couto TB, Farhat SCL, Reid T, Schvartsman C. Mortalidade em hospital secundário pediátrico na Libéria pós-conflito em 2009. *Einstein (São Paulo)* 2013; **11**(4): 413-20.

341. Edelu BO, Ndu IK, Igbokwe OO, Iloh ON. Severe falciparum malaria in children in Enugu, South East Nigeria. *Nigerian journal of clinical practice* 2018; **21**(10): 1349-55.

342. Ekaru H, Mbarak N, Shurie S, Kosgei E, Oyungu E, Kwena A. Community Acquired Pneumonia among Children Admitted in a Tertiary Hospital: The Burden and Related Factors. *East African medical journal* 2012; **89**(9): 301-5.

343. Ekenze SO, Ekwunife H, Eze BI, Ikefuna A, Amah CC, Emodi IJ. The burden of pediatric malignant solid tumors in a developing country. *Journal of tropical pediatrics* 2010; **56**(2): 111-4.

344. Enyuma CO, Anah MU, Pousson A, et al. Patterns of paediatric emergency admissions and predictors of prolonged hospital stay at the children emergency room, University of Calabar Teaching Hospital, Calabar, Nigeria. *African health sciences* 2019; **19**(2): 1910-23.

345. Eseigbe EE, Adama SJ, Eseigbe P. Febrile seizures in Kaduna, north western Nigeria. *Nigerian medical journal : journal of the Nigeria Medical Association* 2012; **53**(3): 140-4.

346. Esezobor CI, Ladapo TA, Osinaike B, Lesi FE. Paediatric acute kidney injury in a tertiary hospital in Nigeria: prevalence, causes and mortality rate. *PloS one* 2012; **7**(12): e51229.

347. Eshetie TC, Hailemeskel B, Mekonnen N, Paulos G, Mekonnen AB, Girma T. Adverse drug events in hospitalized children at Ethiopian University Hospital: a prospective observational study. *BMC pediatrics* 2015; **15**: 83.

348. Evans RDR, Docherty M, Seeley A, et al. Incidence, Etiology, and Outcomes of Community-Acquired Acute Kidney Injury in Pediatric Admissions in Malawi. *Perit Dial Int* 2018; **38**(6): 405-12.

349. Fadero FF, Onigbinde MA, Oyedeji OA. Trends in childhood deaths in Eleta Hospital Ibadan, Oyo State, Southwestern Nigeria. *International Journal of Tropical Medicine* 2012; **7**(5): 173-6.

350. Forae GD, Uchendu OJ, Igbe AP. An audit of paediatric mortality patterns in a Nigerian teaching hospital. *Nigerian medical journal : journal of the Nigeria Medical Association* 2014; **55**(2): 130-3.

351. Gapu P, Bwakura-Dangarembizi M, Kandawasvika G, et al. Rheumatic fever and rheumatic heart disease among children presenting to two referral hospitals in Harare, Zimbabwe. *Samj, S* 2015; **105**(5): 384-8.

352. Garba BI, Muhammad AS, Obasi AB, Adeniji AO. Presentation and pattern of childhood renal diseases in Gusau, North-Western Nigeria. *SAJCH South African Journal of Child Health* 2017; **11**(2): 96-8.

353. Gardner A, Fraile K, Shirk A. Comparative mortality for children at one hospital in Kenya staffed with pediatric emergency medicine specialists. *Afr J Emerg Med* 2020; **10**(4): 224-8.

354. Gathara D, Malla L, Ayieko P, et al. Variation in and risk factors for paediatric inpatient all-cause mortality in a low income setting: Data from an emerging clinical information network. *BMC pediatrics* 2017; **17**(1).

355. Gebremariam S, Moges T. Pediatric Heart Failure, Lagging, and Sagging of Care in Low Income Settings: A Hospital Based Review of Cases in Ethiopia. *Cardiol Res Pract* 2016; **2016**: 7147234.

356. George IO, Alex-Hart BA, Frank-Briggs AI. Mortality pattern in children: a hospital based study in Nigeria. *International journal of biomedical science : IJBS* 2009; **5**(4): 369-72.

357. George IO, Tabansi PN. An audit of cases admitted in the children emergency ward in a nigerian tertiary hospital. *Pakistan Journal of Medical*

Sciences 2010; **26**(3): 740-3.

358. Gordon DM, Frenning S, Draper HR, Kokeb M. Prevalence and burden of diseases presenting to a general pediatrics ward in Gondar, Ethiopia. *Journal of tropical pediatrics* 2013; **59**(5): 350-7.

359. Graham H, Bakare AA, Ayede AI, et al. Hypoxaemia in hospitalised children and neonates: A prospective cohort study in Nigerian secondary-level hospitals. *EClinicalMedicine* 2019; **16**: 51-63.

360. Graham H, Bakare AA, Ayede AI, et al. Diagnosis of pneumonia and malaria in Nigerian hospitals: A prospective cohort study. *Pediatr Pulmonol* 2020; **55 Suppl 1**: S37-S50.

361. Gwer S, Thuo N, Idro R, et al. Changing trends in incidence and aetiology of childhood acute non-traumatic coma over a period of changing malaria transmission in rural coastal Kenya: a retrospective analysis. *BMJ open* 2012; **2**(2): e000475.

362. Hammitt LL, Kazungu S, Morpeth SC, et al. A preliminary study of pneumonia etiology among hospitalized children in Kenya. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012; **54 Suppl 2**: S190-9.

363. Harris C, Mills R, Seager E, et al. Paediatric deaths in a tertiary government hospital setting, Malawi. *Paediatrics and international child health* 2019; **39**(4): 240-8.

364. Hau DK, Chami N, Duncan A, et al. Post-hospital mortality in children aged 2-12 years in Tanzania: A prospective cohort study. *PloS one* 2018; **13**(8): e0202334.

365. Huerga H, Vasset B, Prados E. Adult and paediatric mortality patterns in a referral hospital in Liberia 1 year after the end of the war. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2009; **103**(5): 476-84.

366. Ibekwe RC, Ibekwe MU, Onwe OE, Nnebe-Agumadu UH, Ibe BC. Non-traumatic childhood coma in Ebonyi State University Teaching Hospital, Abakaliki, South Eastern Nigeria. *Nigerian journal of clinical practice* 2011; **14**(1): 43-6.

367. Idro R, Gwer S, Kahindi M, et al. The incidence, aetiology and outcome of acute seizures in children admitted to a rural Kenyan district hospital. *BMC pediatrics* 2008; **8**: 5.

368. Isaacs-Long Y, Myer L, Zar HJ. Trends in admissions, morbidity and outcomes at Red Cross war memorial children's hospital, Cape Town, 2004 - 2013. *South African Medical Journal* 2017; **107**(3): 219-26.

369. John C, Abok II, Yilgwan C. Clinical profile of childhood type 1 diabetes in Jos, Nigeria. *African Journal of Diabetes Medicine* 2013; **21**(1): 11-3.

370. Karuri SW, Murithi MK, Irimu G, English M, Clinical Information Network a. Using data from a multi-hospital clinical network to explore prevalence of pediatric rickets in Kenya. *Wellcome Open Res* 2017; **2**: 64.

371. Kiggundu VL, O'Meara WP, Musoke R, et al. High prevalence of malaria parasitemia and anemia among hospitalized children in Rakai, Uganda. *PloS one* 2013; **8**(12): e82455.

372. Ku BC, Zonfrillo MR, Periyanayagam U, et al. The Association of Malnutrition and Disease Conditions in Mortality of Pediatric Patients Presenting to a Rural Emergency Department in Uganda. *Pediatric emergency care* 2020; **08**: 08.

373. Kuti BP, Adegoke SA, Ebruke BE, Howie S, Oyelami OA, Ota MOC. Risk factors for mortality in childhood pneumonia in a rural West African region. *Journal of Pediatric Infectious Diseases* 2013; **8**(3): 131-8.

374. Kuti BP, Adegoke SA, Oyelami OA, Ota MO. Predictors of prolonged hospitalisation in childhood pneumonia in a rural health centre. *SAJCH South African Journal of Child Health* 2014; **8**(1): 11-5.

375. Kuti BP, Bello EO, Jegede TO, Olubosede O. Epidemiological, clinical and prognostic profile of childhood acute bacterial meningitis in a resource poor setting. *J Neurosci Rural Pract* 2015; **6**(4): 549-57.

376. Lamorde M, Mpimbaza A, Walwema R, et al. A Cross-Cutting Approach to Surveillance and Laboratory Capacity as a Platform to Improve Health Security in Uganda. *Health Secur* 2018; **16**(S1): S76-S86.

377. Libwea JN, Kingue SRB, Ashukem NT, et al. Assessing the causes of under-five mortality and proportion associated with pneumococcal diseases in Cameroon. A case-finding retrospective observational study: 2006–2012. *PloS one* 2019; **14**(4).

378. Losimba Likwela J, D'Alessandro U, Donnen P, Wilmet Dramaix M. Clinical aspects and outcome of suspected severe pediatric malaria. *Medecine et Maladies Infectieuses* 2012; **42**(7): 315-20.

379. Lowlaavar N, Larson CP, Kumbakumba E, et al. Pediatric in-Hospital Death from Infectious Disease in Uganda: Derivation of Clinical Prediction Models. *PloS one* 2016; **11**(3): e0150683.

380. Lugangira K, Kazaura M, Kalokola F. Morbidity and mortality of children aged 2-59 months admitted in the Tanzania Lake Zone's public hospitals: a cross-sectional study. *BMC research notes* 2017; **10**(1): 502.

381. Lundgren IS, Heltshe SL, Smith AL, Chibwana J, Fried MW, Duffy PE. Bacteremia and malaria in Tanzanian children hospitalized for acute febrile illness. *Journal of tropical pediatrics* 2015; **61**(2): 81-5.

382. Ly F, Camara B, Ngomna F, et al. Acute intoxications in the pediatric ward of the Pikine National Hospital Center (CHN): On 34 cases collected. *Medecine d'Afrique Noire* 2019; **66**(4): 200-8.

383. Macharia AW, Mochamah G, Uyoga S, et al. The clinical epidemiology of sickle cell anemia In Africa. *Am J Hematol* 2018; **93**(3): 363-70.

384. Madrid L, Acacio S, Nhampossa T, et al. Hypoglycemia and Risk Factors for Death in 13 Years of Pediatric Admissions in Mozambique. *The American journal of tropical medicine and hygiene* 2016; **94**(1): 218-26.

385. Mahgoub HM, Adam I. Morbidity and mortality of severe malnutrition among Sudanese children in New Halfa Hospital, Eastern Sudan. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2012; **106**(1): 66-8.

386. Maitland K, Berkley JA, Shebbe M, Peshu N, English M, Newton CR. Children with severe malnutrition: can those at highest risk of death be identified with the WHO protocol? *PLoS Med* 2006; **3**(12): e500.

387. Maitland K, Ohuma EO, Mpoya A, Uyoga S, Hassall O, Williams TN. Informing thresholds for paediatric transfusion in Africa: the need for a trial. *Wellcome Open Res* 2019; **4**: 27.

388. McCollum ED, Bjornstad E, Preidis GA, Hosseinipour MC, Lufesi N. Multicenter study of hypoxemia prevalence and quality of oxygen treatment for hospitalized Malawian children. *Transactions of the Royal Society of Tropical Medicine and*

Hygiene 2013; **107**(5): 285-92.

389. Mdala JF, Mash R. Causes of mortality and associated modifiable health care factors for children (< 5-years) admitted at Onandjokwe Hospital, Namibia. *Afr* 2015; **7**(1): 03.

390. Mhando S, Young B, Lakhoo K. The scope of emergency paediatric surgery in Tanzania. *Pediatr Surg Int* 2008; **24**(2): 219-22.

391. Migowa A, Colmegna I, Hitchon C, et al. The spectrum of rheumatic in-patient diagnoses at a pediatric hospital in Kenya. *Pediatr* 2017; **15**(1): 4.

392. Mioramalala SA, Ramasy Razafindratovo RM, Rakotozanany A, et al. Analysis of Death and Survival Factors Associated with Childhood Bacterial Meningitis at a Reference Pediatric Hospital in Antananarivo, Madagascar. *J Immunol Sci* 2018; **Suppl**(2): 8-14.

393. Mitchell KB, Giiti G, Gallagher JJ. Survey of care and evaluation of East African burn unit feasibility: an academic burn center exchange. *J Burn Care Res* 2013; **34**(1): 78-81.

394. Moise IK. Causes of Morbidity and Mortality among Neonates and Children in Post-Conflict Burundi: A Cross-Sectional Retrospective Study. *Children (Basel)* 2018; **5**(9): 08.

395. Mola K, Shimelis D. Pattern and Outcome of Renal Diseases in Hospitalized Children in Tikur Anbessa Specialized Teaching Hospital, Addis Ababa, Ethiopia. *Ethiop Med J* 2016; **54**(3): 117-23.

396. Mujuru HA, Kambarami RA. Mortality within 24 hours of admission to the Paediatric Unit, Harare Central Hospital, Zimbabwe. *Cent Afr J Med*

2012; **58**(5-6): 17-22.

397. Muoneke VU, Una AF, Eke CB, Anyanwu OU. The Burden and Outcome of Pediatric Renal Admissions at the Federal Teaching Hospital Abakaliki: A 3-year Review (2011-2013). *ann* 2016; **6**(4): 243-50.

398. Muro RP, Masoza TS, Kasanga G, Kayange N, Kidenya BR. Predictors and outcome of first line treatment failure among under-five children with community acquired severe pneumonia at Bugando Medical Centre, Mwanza, Tanzania: A prospective cohort study. *PloS one* 2020; **15**(12): e0243636.

399. Mutombo AM, Mukuku O, Tshibanda KN, et al. Severe malaria and death risk factors among children under 5 years at Jason Sendwe hospital in democratic republic of Congo. *Pan African Medical Journal* 2018; **29**.

400. Mwangome M, Ngari M, Fegan G, et al. Diagnostic criteria for severe acute malnutrition among infants aged under 6 mo. *The American journal of clinical nutrition* 2017; **105**(6): 1415-23.

401. Mwaniki MK, Nokes DJ, Ignas J, et al. Emergency triage assessment for hypoxaemia in neonates and young children in a Kenyan hospital: an observational study. *Bulletin of the World Health Organization* 2009; **87**(4): 263-70.

402. Nabukeera-Barungi N, Wilmshurst J, Rudzani M, Nuttall J. Presentation and outcome of tuberculous meningitis among children: experiences from a tertiary children's hospital. *African health sciences* 2014; **14**(1): 143-9.

403. Nakawesi JS, Wobudeya E, Ndeezi G, Mworozi EA, Tumwine JK. Prevalence and factors associated with rotavirus infection among children admitted with acute diarrhea in Uganda. *BMC pediatrics* 2010; **10**: 69.

404. Ndukwu CI, Onah SK. Pattern and outcome of postneonatal pediatric emergencies in Nnamdi Azikiwe University Teaching Hospital, Nnewi, South East Nigeria. *Nigerian journal of clinical practice* 2015; **18**(3): 348-53.

405. Ngari MM, Fegan G, Mwangome MK, et al. Mortality after Inpatient Treatment for Severe Pneumonia in Children: a Cohort Study. *Paediatr Perinat Epidemiol* 2017; **31**(3): 233-42.

406. Ngari MM, Obiero C, Mwangome MK, et al. Mortality during and following hospital admission among school-aged children: a cohort study. *Wellcome Open Res* 2020; **5**: 234.

407. Ngirabega JD, Munyanshongore C, Donnen P, Dramaix M. [Influence of malnutrition on childhood mortality in a rural hospital in Rwanda]. *Rev Epidemiol Sante Publique* 2011; **59**(5): 313-8.

408. Ngoy BB, Zachariah R, Hinderaker SG, et al. Paediatric in-patient care in a conflict-torn region of Somalia: are hospital outcomes of acceptable quality? *Public health action* 2013; **3**(2): 125-7.

409. Nhampossa T, Sigaúque B, Machevo S, et al. Severe malnutrition among children under the age of 5 years admitted to a rural district hospital in southern Mozambique. *Public health nutrition* 2013; **16**(9): 1565-74.

410. Nigussie B, Tadele H. Heart Failure in Ethiopian Children: Mirroring the Unmet Cardiac Services. *Ethiop* 2019; **29**(1): 811-8.

411. Njuguna P, Maitland K, Nyaguara A, et al. Observational study: 27 years of severe malaria surveillance in Kilifi, Kenya. *BMC medicine* 2019; **17**(1): N.PAG-N.PAG.

412. Nokes DJ, Abwao J, Pamba A, et al. Incidence and clinical characteristics of group A rotavirus infections among children admitted to hospital in Kilifi, Kenya. *PLoS Med* 2008; **5**(7): e153.

413. Nokes DJ, Ngama M, Bett A, et al. Incidence and severity of respiratory syncytial virus pneumonia in rural Kenyan children identified through hospital surveillance. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2009; **49**(9): 1341-9.

414. Nyaga EM, Ndungu Jm JM, Anangwe GCN. Acute non-traumatic abdominal pain in childhood at Kenyatta National Hospital, Kenya. *Annals of African Surgery* 2010; **6**: 14-7.

415. Obonyo CO, Vulule J, Akhwale WS, Grobbee DE. In-hospital morbidity and mortality due to severe malarial anemia in western Kenya. *The American journal of tropical medicine and hygiene* 2007; **77**(6 Suppl): 23-8.

416. Obura B, Alele PE, Obua C. Off-label antibiotic use among paediatric in-patients: a mixed-method prospective study at a tertiary hospital in southwestern Uganda. *Int J Clin Pharm* 2020; **18**: 18.

417. Odetunde OI, Okafor HU, Uwaezuoke SN, Ezeonwu BU, Adiele KD, Ukoha OM. Chronic kidney disease in children as seen in a tertiary hospital in Enugu, South-East, Nigeria. *Nigerian journal of clinical practice* 2014; **17**(2): 196-200.

418. Ofovwe GE, Ibadin MO, Okunola PO, Ofoegbu B. Pattern of emergency neurologic morbidities in children. *J Natl Med Assoc* 2005; **97**(4): 488-92.

419. Ogunfowora OB, Ogunlesi TA, Oba-Daini OO. Epidemiological trend of post-neonatal tetanus in a Nigerian teaching hospital. *SAJCH South African Journal of Child Health* 2019; **13**(4): 158-63.

420. Okike CO, Muoneke UV, Uwaezuoke SN, Mbagwu EN, Onyeka-Okite E. The Prevalence and Case-Fatality Rates of Post-Neonatal Tetanus in a Population of Hospitalized Nigerian Children: An 8-Year Retrospective Review. *Journal of tropical pediatrics* 2020; **66**(2): 201-9.

421. Okiro EA, Kazembe LN, Kabaria CW, et al. Childhood malaria admission rates to four hospitals in Malawi between 2000 and 2010. *PloS one* 2013; **8**(4): e62214.

422. Okoroiwu HU, Uchendu KI, Essien RA. Causes of morbidity and mortality among patients admitted in a tertiary hospital in southern Nigeria: A 6 year evaluation. *PloS one* 2020; **15**(8): e0237313.

423. Okoronkwo NC, Onyearugha CN, Ohanenye CA. Pattern and outcomes of paediatric medical admissions at the Living Word Mission Hospital, Aba, South East Nigeria. *Pan Afr Med J* 2018; **30**: 202.

424. Olatunya OS, Isinkaye AO, Ogundare EO, Oluwayemi IO, Akinola FJ. Childhood poisoning at a tertiary hospital in South West Nigeria. *Journal of Nepal Paediatric Society* 2015; **35**(2): 103-10.

425. Oliwa JN, Gathara D, Ogero M, Van Hensbroek MB, English M, Van't Hoog A. Diagnostic practices and estimated burden of tuberculosis among children admitted to 13 government hospitals in Kenya: An analysis of two years' routine clinical data. *PloS one* 2019; **14**(9).

426. Olorunmoteni OE, Onyia CU, Elusiyan JBE, Ugowe OJ, Babalola TE, Samuel I. Intracranial abscesses in children at Ile-Ife, Nigeria: a case series and review of literature. *Childs Nerv Syst* 2020; **36**(8): 1767-71.

427. Olowu WA, Adefehinti O, Bisiriyu AL. Hospital-acquired acute kidney injury in critically ill children and adolescents. *Saudi J Kidney Dis Transpl* 2012; **23**(1): 68-77.

428. Olupot-Olupot P, Engoru C, Nteziyaremye J, et al. The clinical spectrum of severe childhood malaria in Eastern Uganda. *Malar J* 2020; **19**(1): 322.

429. Oluwayemi OI, Brown BJ, Oyedeji OA, Adegoke SA, Adebami OJ, Oyedeji GA. Clinical and laboratory predictors of outcome in cerebral malaria in suburban Nigeria. *J* Infect Dev Ctries 2013; **7**(8): 600-7.

430. Omore R, Khagayi S, Ogwel B, et al. Rates of hospitalization and death for all-cause and rotavirus acute gastroenteritis before rotavirus vaccine introduction in Kenya, 2010-2013. *BMC Infectious Diseases* 2019; **19**(1).

431. Opoka RO, Ssemata AS, Oyang W, et al. High rate of inappropriate blood transfusions in the management of children with severe anemia in Ugandan hospitals. *BMC health services research* 2018; **18**(1): 566.

432. Orimadegun AE, Fawole O, Okereke JO, Akinbami FO, Sodeinde O. Increasing burden of childhood severe malaria in a Nigerian tertiary hospital: implication for control. *Journal of tropical pediatrics* 2007; **53**(3): 185-9.

433. Osano BO, Were F, Mathews S. Mortality among 5-17 year old children in Kenya. *Pan Afr Med J* 2017; **27**: 121.

434. Oshikoya KA, Ogunyinka IA, Imuzei SE, Garba BI, Jiya NM. A Retrospective Audit of Pharmacologic and Non-Pharmacologic Management of Childhood Acute

Asthma Exacerbation at Usmanu Danfodiyo University Teaching Hospital, Sokoto: Adherence to Global Treatment Guidelines. *Front Pharmacol* 2020; **11**: 531894.

435. Ouedraogo SM, Toloba Y, Ouedraogo G, et al. [Epidemio-clinical aspects of bacterial acute infant Pneumopathies at Yalgado Ouedraogo University Health Center]. *Mali med* 2010; **25**(3): 19-22.

436. Oyedeji OA, Fadero F, Joel-Medewase V, Elemile P, Oyedeji GA. Trends in neonatal and post-neonatal tetanus admissions at a Nigerian teaching hospital. *J Infect Dev Ctries* 2012; **6**(12): 847-53.

437. e Pinto EA, Alves JG. The causes of death of hospitalized children in Angola. *Tropical doctor* 2008; **38**(1): 66-7.

438. Rahajamanana VL, Raboba JL, Rakotozanany A, et al. Impact of rotavirus vaccine on all-cause diarrhea and rotavirus hospitalizations in Madagascar. *Vaccine* 2018; **36**(47): 7198-204.

439. Richards M, Le Roux D, Cooke L, Argent A. The Influence of High Flow Nasal Cannulae on the Outcomes of Severe Respiratory Disease in Children Admitted to a Regional Hospital in South Africa. *Journal of tropical pediatrics* 2020; **66**(6): 612-20.

440. Roca A, Quinto L, Abacassamo F, et al. Invasive Haemophilus influenzae disease in children less than 5 years of age in Manhica, a rural area of southern Mozambique. *Tropical medicine & international health : TM & IH* 2008; **13**(6): 818-26.

441. Ngo Um Sap S, Tchaptchet K, Mekone I, et al. Mortality of children aged 5-15 years in a tertiary care center in Yaounde, Cameroon. *Arch Pediatr* 2020; **27**(5): 257-60.

442. Sawadogo S, Nebie K, Millogo T, Kafando E. Blood transfusion requirements among children with severe malarial anemia: a cross-sectional study in a second level reference hospital in Burkina Faso. *Pan Afr Med J* 2020; **37**: 108.

443. Seck N, Basse I, Keïta Y, et al. Bronchiolitis in tropical environment. *Journal de Pediatrie et de Puericulture* 2018; **31**(5): 241-6.

444. Sidibe T, Sangho H, Traore MS, et al. [Morbidity and mortality in the pediatric service at Gabriel Toure's University Hospital in Mali]. *Mali med* 2008; **23**(4): 34-7.

445. Sievers AC, Lewey J, Musafiri P, et al. Reduced paediatric hospitalizations for malaria and febrile illness patterns following implementation of community-based malaria control programme in rural Rwanda. *Malar J* 2008; **7**: 167.

446. Sigauque B, Roca A, Mandomando I, et al. Community-acquired bacteremia among children admitted to a rural hospital in Mozambique. *The Pediatric infectious disease journal* 2009; **28**(2): 108-13.

447. Sigauque B, Roca A, Bassat Q, et al. Severe pneumonia in Mozambican young children: clinical and radiological characteristics and risk factors. *Journal of tropical pediatrics* 2009; **55**(6): 379-87.

448. Sigauque B, Verani JR, Massora S, et al. Burden of invasive pneumococcal disease among children in rural Mozambique: 2001-2012. *PloS one* 2018; **13**(1): e0190687.

449. Silaba M, Ooko M, Bottomley C, et al. Effect of 10-valent pneumococcal conjugate vaccine on the incidence of radiologically-confirmed pneumonia and clinically-defined pneumonia in Kenyan children: an interrupted time-series analysis. *The Lancet Global health* 2019; **7**(3): e337-e46.

450. Smart LR, Orgenes N, Mazigo HD, et al. Malaria and HIV among pediatric inpatients in two Tanzanian referral hospitals: A prospective study. *Acta tropica* 2016; **159**: 36-43.

451. Sylla A, Gueye M, Keita Y, et al. [Dehydration and malnutrition as two independent risk factors of death in a Senegalese pediatric hospital]. *Arch Pediatr* 2015; **22**(3): 235-40.

452. Tette EM, Neizer M, Nyarko MY, Sifah EK, Nartey ET, Donkor ES. Changing Patterns of Disease and Mortality at the Children's Hospital, Accra: Are Infections Rising? *PloS one* 2016; **11**(4): e0150387.

453. Theo A, Tempia S, Cohen AL, et al. The national burden of influenza-associated severe acute respiratory illness hospitalization in Zambia, 2011-2014. *Influenza other respi* 2018; **12**(1): 46-53.

454. Tornheim JA, Manya AS, Oyando N, et al. The epidemiology of hospitalization with diarrhea in rural Kenya: the utility of existing health facility data in developing countries. *Int J Infect Dis* 2010; **14**(6): e499-505.

455. Tsai C, Walters CB, Sampson J, Kateh F, Chang MP. Pediatric Mortality in a Rural Tertiary Care Center in Liberia. *Children (Basel)* 2017; **4**(2): 30.

456. Ugege MO, Chikani UN, Yusuf T, Amodu-Sanni M, Ibitoye PK, Abdul Rahman MB. Abnormal blood glucose and the relationship with clinical outcome in acutely ill children admitted to the emergency unit of a Nigerian Tertiary Hospital. *Nigerian journal of clinical practice* 2021; **24**(2): 205-12.

457. Ugwu GI, Nwajei G, Chinemelu U. Pattern of Renal Diseases among Children in The Niger Delta Region, Nigeria. *Arab J Nephrol Transplant* 2014; **7**(1): 49-50.

458. Vonasek BJ, Chiume M, Crouse HL, et al. Risk factors for mortality and management of children with complicated severe acute malnutrition at a tertiary referral hospital in Malawi. *Paediatrics and international child health* 2020; **40**(3): 148-57.

459. Zeidan Z, Kojal H, Habour A, Nowary K, Hashim F, Awadelkarim M. Clinical and epidemiological features of severe malaria in children in four hospitals in Sudan. *Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit* 2006; **12**(6): 783-91.

Appendix

Supplemental Table 2.1 Detailed search strategy by database

Database	Search Strategy
Ovid MEDLINE#	1. *hospitalization/ or *patient admission/ or *patient readmission/ 2. (admis* or admit* or patient discharge* or readmis* or readmit* or rehospital*).tw,kf. or hospitali*.kf. 3. hospital mortality/ or ((tertiary or hospital*) adj5 (mortalit* or utilis* or utiliz*)).tw,kf. 4. (*hospital units/ or *hemodialysis units, hospital/ or *intensive care units/ or *intensive care units, pediatric/ or *respiratory care units/ or exp *hospitals/ or *tertiary care centers/) and mortalit*.mp. 5. (*critical care/ or early goal-directed therapy/ or (acute care or critical care or intensive care or iicu* or picu* or tertiary care).tw,kf.) and mortalit*.mp. 6. (child, hospitalized/ or hospitals, pediatric/) and mortalit*.mp. 7. or/1-6 8. (Afghanistan or Albania or Algeria or Samoa or Angola or Bangladesh or Belize or Benin or Bhutan or Bolivia or Botswana or Brazil or Burkina Faso or Burundi or Cabo Verde or Cambodia or Cameroon or Central African Republic or Chad or Timor or Cape Verde or Colombia or Comoros or Congo or Costa Rica or "Cote d'Ivoire" or Cuba or Djibouti or Dominica or Dominican Republic or Ecuador or Egypt or El Salvador or Equatorial Guinea or Eritrea or Ethiopia or Fiji or Gabon or Gambia or Ghana or Grenada or Guatemala or Guinea or Guinea-Bissau or Guyana or Haiti or Honduras or India or Indonesia or Iraq or Jamaica or Jordan or Kenya or Kiribati or North Korea or "Democratic People's Republic of Korea" or Kyrgyz Republic or Kyrgyzstan or Laos or "Lao People's Democratic Republic" or Lesotho or Liberia or Madagascar or Malawi or Maldives or Seychelles or Mali or Marshall Islands or Mexico or Micronesia or Moldova or Mongolia or Morocco or Mozambique or Myanmar or Namibia or Nepal or Nicaragua or Niger or Nigeria or Pakistan or Palestine or Panama or Papua New Guinea or Paraguay or Peru or Philippines or Rwanda or Sao Tome or Principe or Senegal or Sierra Leone or Solomon Islands or Somalia or South Africa or South Sudan or Sri Lanka or St Lucia or Saint Lucia or St Vincent or Saint Vincent or Grenadines or Sudan or Suriname or Swaziland or Syrian Arab Republic or Syria or Tajikistan or Tanzania or Thailand or Timor Leste or Togo or Tonga or Trinidad or Tobago or Tunisia or Turkmenistan or Uganda or Uzbekistan or Vanuatu or Venezuela or Vietnam or West Bank or Gaza or Yemen or Zambia or Zimbabwe or Mauritania).ti,ab,kf,sh. [LMIC title, abstract, author kw, MeSH] 9. Developing Countries/ or (developing adj1 (nation? or countr*)).tw,kf. 10. (resource* adj1 (constrain* or limit* or low* or poor* or restrict*)).tw. or (resource constrain* or resource limit*).kf. 11. ((low* or middl*) adj1 income countr*).tw. or (low income* or middle income* or LMIC).kf. 12. ((developing or least* or less* or limit* or third world or underdevelop* or under develop*) adj3 (countr* or nation* or setting*)).mp. 13. emerging econom*.mp. 14. ((low or middle) adj3 (socio demographic index or SDI)).mp. 15. or/8-14 16. infant/ or child, preschool/ or child/ or (pediatric* or paediatric* or child* or baby or babies or infan* or toddler* or preschool* or preteen* or pre teen* or preadolescen* or pre adolescen* or youth* or youngster* or boy* or girl* or juvenile*).tw,kf,so,jw 17. (comment or editorial or letter or news).pt. 18. (7 and 15 and 16) not 17 19. (201911* or 2019 11* or 201912* or 2019 12*).dp,dt,ed,ep,ez. 20. limit 18 to yr="2020 -Current" 21. (18 and 19) or 20
EMBASE	#17 #16 AND [1-11-2019]/sd NOT [2-3-2021]/sd #16 #6 AND #14 AND #15 NOT ('conference abstract'/it OR 'conference review'/it OR 'letter'/it OR 'editorial'/it OR 'note'/it) #15 [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR pediatric*:ti,ab,kw OR paediatric*:ti,ab,kw OR child*:ti,ab,kw OR baby:ti,ab,kw OR babies:ti,ab,kw OR infan*:ti,ab,kw OR toddler*:ti,ab,kw OR preschool*:ti,ab,kw OR preteen*:ti,ab,kw OR preadolescen*:ti,ab,kw OR ((pre NEXT/1 (adolescen* OR teen*)):ti,ab,kw) OR youth*:ti,ab,kw OR youngster*:ti,ab,kw OR boy*:ti,ab,kw OR girl*:ti,ab,kw OR juvenile*:ti,ab,kw #14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 #13 (('low middle' OR middle) NEAR/3 ('socio demographic index' OR sdi)):ti,ab,kw,de #12 'emerging economy':ti,ab,kw,de OR 'emerging economies':ti,ab,kw,de #11 ((developing OR underdevelop* OR underdeveloped OR least OR less OR limit* OR 'third world') NEAR/3 (countr* OR nation* OR setting*)):ti,ab,kw,de #10 (((low* OR middl*) NEAR/2 countr*):ti,ab,kw) OR 'low income':ti,ab,kw OR 'middle income':ti,ab,kw OR lmic:ti,ab,kw #9 (resource* NEAR/1 (constrain* OR limit* OR low* OR poor* OR restrict*)):ti,ab,kw #8 'developing country'/exp OR ((developing NEAR/1 (nation* OR countr*)):ti,ab,kw) #7 'afghanistan':ti,ab,de,kw OR 'albania':ti,ab,de,kw OR 'algeria':ti,ab,de,kw OR 'samoa':ti,ab,de,kw OR 'angola':ti,ab,de,kw OR 'bangladesh':ti,ab,de,kw OR 'belize':ti,ab,de,kw OR 'benin':ti,ab,de,kw OR 'bhutan':ti,ab,de,kw OR 'bolivia':ti,ab,de,kw OR 'botswana':ti,ab,de,kw OR 'brazil':ti,ab,de,kw OR 'burkina faso':ti,ab,de,kw OR 'burundi':ti,ab,de,kw OR 'cabo verde':ti,ab,de,kw OR 'cambodia':ti,ab,de,kw OR 'cameroon':ti,ab,de,kw OR 'central african republic':ti,ab,de,kw OR 'chad':ti,ab,de,kw OR 'timor':ti,ab,de,kw OR 'cape verde':ti,ab,de,kw OR 'colombia':ti,ab,de,kw OR 'comoros':ti,ab,de,kw OR 'congo':ti,ab,de,kw OR 'costa rica':ti,ab,de,kw OR 'cote d ivoire':ti,ab,de,kw OR 'cuba':ti,ab,de,kw OR

Database	Search Strategy
	'djibouti':ti,ab,de,kw OR 'dominica':ti,ab,de,kw OR 'dominican republic':ti,ab,de,kw OR 'ecuador':ti,ab,de,kw OR 'egypt':ti,ab,de,kw OR 'el salvador':ti,ab,de,kw OR 'equatorial guinea':ti,ab,de,kw OR 'eritrea':ti,ab,de,kw OR 'ethiopia':ti,ab,de,kw OR 'fiji':ti,ab,de,kw OR 'gabon':ti,ab,de,kw OR 'gambia':ti,ab,de,kw OR 'ghana':ti,ab,de,kw OR 'grenada':ti,ab,de,kw OR 'guatemala':ti,ab,de,kw OR 'guinea':ti,ab,de,kw OR 'guinea bissau':ti,ab,de,kw OR 'guyana':ti,ab,de,kw OR 'haiti':ti,ab,de,kw OR 'honduras':ti,ab,de,kw OR 'india':ti,ab,de,kw OR 'indonesia':ti,ab,de,kw OR 'iraq':ti,ab,de,kw OR 'jamaica':ti,ab,de,kw OR 'jordan':ti,ab,de,kw OR 'kenya':ti,ab,de,kw OR 'kiribati':ti,ab,de,kw OR 'north korea':ti,ab,de,kw OR 'democratic people s republic of korea':ti,ab,de,kw OR 'kyrgyz republic':ti,ab,de,kw OR 'kyrgyzstan':ti,ab,de,kw OR 'laos':ti,ab,de,kw OR 'lao people s democratic republic':ti,ab,de,kw OR 'lesotho':ti,ab,de,kw OR 'liberia':ti,ab,de,kw OR 'madagascar':ti,ab,de,kw OR 'malawi':ti,ab,de,kw OR 'maldives':ti,ab,de,kw OR 'seychelles':ti,ab,de,kw OR 'mali':ti,ab,de,kw OR 'marshall islands':ti,ab,de,kw OR 'mexico':ti,ab,de,kw OR 'micronesia':ti,ab,de,kw OR 'moldova':ti,ab,de,kw OR 'mongolia':ti,ab,de,kw OR 'morocco':ti,ab,de,kw OR 'mozambique':ti,ab,de,kw OR 'myanmar':ti,ab,de,kw OR 'namibia':ti,ab,de,kw OR 'nepal':ti,ab,de,kw OR 'nicaragua':ti,ab,de,kw OR 'niger':ti,ab,de,kw OR 'nigeria':ti,ab,de,kw OR 'pakistan':ti,ab,de,kw OR 'palestine':ti,ab,de,kw OR 'panama':ti,ab,de,kw OR 'papua new guinea':ti,ab,de,kw OR 'paraguay':ti,ab,de,kw OR 'peru':ti,ab,de,kw OR 'philippines':ti,ab,de,kw OR 'rwanda':ti,ab,de,kw OR 'sao tome':ti,ab,de,kw OR 'principe':ti,ab,de,kw OR 'senegal':ti,ab,de,kw OR 'sierra leone':ti,ab,de,kw OR 'solomon islands':ti,ab,de,kw OR 'somalia':ti,ab,de,kw OR 'south africa':ti,ab,de,kw OR 'south sudan':ti,ab,de,kw OR 'sri lanka':ti,ab,de,kw OR 'st lucia':ti,ab,de,kw OR 'saint lucia':ti,ab,de,kw OR 'st vincent':ti,ab,de,kw OR 'saint vincent':ti,ab,de,kw OR 'grenadines':ti,ab,de,kw OR 'sudan':ti,ab,de,kw OR 'suriname':ti,ab,de,kw OR 'swaziland':ti,ab,de,kw OR 'syrian arab republic':ti,ab,de,kw OR 'syria':ti,ab,de,kw OR 'tajikistan':ti,ab,de,kw OR 'tanzania':ti,ab,de,kw OR 'thailand':ti,ab,de,kw OR 'timor leste':ti,ab,de,kw OR 'togo':ti,ab,de,kw OR 'tonga':ti,ab,de,kw OR 'trinidad':ti,ab,de,kw OR 'tobago':ti,ab,de,kw OR 'tunisia':ti,ab,de,kw OR 'turkmenistan':ti,ab,de,kw OR 'uganda':ti,ab,de,kw OR 'uzbekistan':ti,ab,de,kw OR 'vanuatu':ti,ab,de,kw OR 'venezuela':ti,ab,de,kw OR 'vietnam':ti,ab,de,kw OR 'west bank':ti,ab,de,kw OR 'gaza':ti,ab,de,kw OR 'yemen':ti,ab,de,kw OR 'zambia':ti,ab,de,kw OR 'zimbabwe':ti,ab,de,kw OR 'mauritania':ti,ab,de,kw #6 #1 OR #2 OR #3 OR #4 OR #5 #5 ((((acute OR critical OR intensive) NEXT/1 care):ti,ab) OR (((hemodialysis OR respiratory) NEXT/2 (unit* OR ward*)):ti,ab) OR iicu*:ti,ab OR picu*:ti,ab) AND mortalit* #4 ('intensive care unit'/mj OR 'medical intensive care unit'/mj OR 'pediatric intensive care unit'/mj OR 'hospital'/exp/mj OR 'tertiary care center'/mj OR 'intensive care'/exp/mj OR 'hospital patient'/mj OR 'hospitalized child'/mj) AND mortalit* #3 'hospital mortality'/mj OR (((tertiary OR hospital*) NEAR/5 (mortalit* OR utilis* OR utiliz*)):ti,ab) #2 admis*:ti,ab OR admit*:ti,ab OR ((patient NEXT/1 discharge*):ti,ab) OR readmis*:ti,ab OR readmit*:ti,ab OR rehospital*:ti,ab #1 'hospitalization'/mj OR 'hospital admission'/mj OR 'hospital readmission'/mj
CINAHL	S21 S18 OR S20 S20 S7 AND S17 AND S19 AND Limiters - Published Date: 20191101-20211231 S19 TI (pediatric* OR paediatric* OR child* OR baby OR babies OR infan* OR toddler* OR preteen* OR (pre W1 teen*) OR preadolescen* OR (pre W1 adolescen*) OR youth* OR youngster* OR boy* OR girl* OR juvenile*) OR AB (pediatric* OR paediatric* OR child* OR baby OR babies OR infan* OR toddler* OR preschool* OR preteen* OR (pre W1 teen*) OR preadolescen* OR (pre W1 adolescen*) OR youth* OR youngster* OR boy* OR girl* OR juvenile*) OR JN (pediatric* OR paediatric* OR child* OR baby OR babies OR infan* OR toddler* OR preteen* OR (pre W1 teen*) OR preadolescen* OR (pre W1 adolescen*) OR youth* OR youngster* OR boy* OR girl* OR juvenile*) S18 S7 AND S17 Limiters - Age Groups: Infant: 1-23 months, Child, Preschool: 2-5 years, Child: 6-12 years; Published Date: 20191101-20211231 S17 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 S16 TI ((low OR middl*) N3 (socio demographic index OR sdi)) OR AB ((low OR middl*) N3 (socio demographic index OR sdi)) S15 TI (emerging N1 econom*) OR AB (emerging N1 econom*) S14 TI ((developing OR least* OR less* OR limit* OR "third world" OR underdevelop* OR (under W1 develop*)) N3 (countr* OR nation* OR setting*)) OR AB ((developing OR least* OR less* OR limit* OR "third world" OR underdevelop* OR (under W1 develop*)) N3 (countr* OR nation* OR setting*)) S13 TI ((low* OR middl*) N1 income countr*) OR AB ((low* OR middl*) N1 income countr*) OR TI LMIC OR AB LMIC S12 TI (resource* N1 (constrain* OR limit* OR low* OR poor* OR restrict*)) OR AB (resource* N1 (constrain* OR limit* OR low* OR poor* OR restrict*)) S11 (MH "Developing Countries") OR TI (developing N1 (nation* or countr*)) OR AB (developing N1 (nation* or countr*)) S10 MW Afghanistan or Albania or Algeria or Samoa or Angola or Bangladesh or Belize or Benin or Bhutan or Bolivia or Botswana or Brazil or “Burkina Faso” or Burundi or “Cabo Verde” or Cambodia or Cameroon or “Central African Republic” or Chad or Timor or “Cape Verde” or Colombia or Comoros or Congo or “Costa Rica” or “Cote d'Ivoire” or Cuba or Djibouti or Dominica or “Dominican Republic” or Ecuador or Egypt or “El Salvador” or “Equatorial Guinea” or Eritrea or Ethiopia or Fiji or Gabon or Gambia or Ghana or Grenada or Guatemala or Guinea or “Guinea-Bissau” or Guyana or Haiti or

Database	Search Strategy
	Honduras or India or Indonesia or Iraq or Jamaica or Jordan or Kenya or Kiribati or “North Korea” or Korea or “Kyrgyz Republic” or Kyrgyzstan or Laos or "Lao People's Democratic Republic" or Lesotho or Liberia or Madagascar or Malawi or Maldives or Seychelles or Mali or “Marshall Islands” or Mexico or Micronesia or Moldova or Mongolia or Morocco or Mozambique or Myanmar or Namibia or Nepal or Nicaragua or Niger or Nigeria or Pakistan or Palestine or Panama or “Papua New Guinea” or Paraguay or Peru or Philippines or Rwanda or “Sao Tome” or “Principe or Senegal” or “Sierra Leone” or “Solomon Islands” or Somalia or “South Africa” or “South Sudan” or “Sri Lanka” or “St Lucia” or “Saint Lucia” or “St Vincent” or “Saint Vincent” or Grenadines or Sudan or Suriname or Swaziland or “Syrian Arab Republic” or Syria or Tajikistan or Tanzania or Thailand or “Timor Leste” or Togo or Tonga or Trinidad or Tobago or Tunisia or Turkmenistan or Uganda or Uzbekistan or Vanuatu or Venezuela or Vietnam or “West Bank” or Gaza or Yemen or Zambia or Zimbabwe or Mauritania S9 AB Afghanistan or Albania or Algeria or Samoa or Angola or Bangladesh or Belize or Benin or Bhutan or Bolivia or Botswana or Brazil or “Burkina Faso” or Burundi or “Cabo Verde” or Cambodia or Cameroon or “Central African Republic” or Chad or Timor or “Cape Verde” or Colombia or Comoros or Congo or “Costa Rica” or “Cote d'Ivoire” or Cuba or Djibouti or Dominica or “Dominican Republic” or Ecuador or Egypt or “El Salvador” or “Equatorial Guinea” or Eritrea or Ethiopia or Fiji or Gabon or Gambia or Ghana or Grenada or Guatemala or Guinea or “Guinea-Bissau” or Guyana or Haiti or Honduras or India or Indonesia or Iraq or Jamaica or Jordan or Kenya or Kiribati or “North Korea” or Korea or “Kyrgyz Republic” or Kyrgyzstan or Laos or "Lao People's Democratic Republic" or Lesotho or Liberia or Madagascar or Malawi or Maldives or Seychelles or Mali or “Marshall Islands” or Mexico or Micronesia or Moldova or Mongolia or Morocco or Mozambique or Myanmar or Namibia or Nepal or Nicaragua or Niger or Nigeria or Pakistan or Palestine or Panama or “Papua New Guinea” or Paraguay or Peru or Philippines or Rwanda or “Sao Tome” or “Principe or Senegal” or “Sierra Leone” or “Solomon Islands” or Somalia or “South Africa” or “South Sudan” or “Sri Lanka” or “St Lucia” or “Saint Lucia” or “St Vincent” or “Saint Vincent” or Grenadines or Sudan or Suriname or Swaziland or “Syrian Arab Republic” or Syria or Tajikistan or Tanzania or Thailand or “Timor Leste” or Togo or Tonga or Trinidad or Tobago or Tunisia or Turkmenistan or Uganda or Uzbekistan or Vanuatu or Venezuela or Vietnam or “West Bank” or Gaza or Yemen or Zambia or Zimbabwe or Mauritania S8 TI Afghanistan or Albania or Algeria or Samoa or Angola or Bangladesh or Belize or Benin or Bhutan or Bolivia or Botswana or Brazil or “Burkina Faso” or Burundi or “Cabo Verde” or Cambodia or Cameroon or “Central African Republic” or Chad or Timor or “Cape Verde” or Colombia or Comoros or Congo or “Costa Rica” or “Cote d'Ivoire” or Cuba or Djibouti or Dominica or “Dominican Republic” or Ecuador or Egypt or “El Salvador” or “Equatorial Guinea” or Eritrea or Ethiopia or Fiji or Gabon or Gambia or Ghana or Grenada or Guatemala or Guinea or “Guinea-Bissau” or Guyana or Haiti or Honduras or India or Indonesia or Iraq or Jamaica or Jordan or Kenya or Kiribati or “North Korea” or Korea or “Kyrgyz Republic” or Kyrgyzstan or Laos or "Lao People's Democratic Republic" or Lesotho or Liberia or Madagascar or Malawi or Maldives or Seychelles or Mali or “Marshall Islands” or Mexico or Micronesia or Moldova or Mongolia or Morocco or Mozambique or Myanmar or Namibia or Nepal or Nicaragua or Niger or Nigeria or Pakistan or Palestine or Panama or “Papua New Guinea” or Paraguay or Peru or Philippines or Rwanda or “Sao Tome” or “Principe or Senegal” or “Sierra Leone” or “Solomon Islands” or Somalia or “South Africa” or “South Sudan” or “Sri Lanka” or “St Lucia” or “Saint Lucia” or “St Vincent” or “Saint Vincent” or Grenadines or Sudan or Suriname or Swaziland or “Syrian Arab Republic” or Syria or Tajikistan or Tanzania or Thailand or “Timor Leste” or Togo or Tonga or Trinidad or Tobago or Tunisia or Turkmenistan or Uganda or Uzbekistan or Vanuatu or Venezuela or Vietnam or “West Bank” or Gaza or Yemen or Zambia or Zimbabwe or Mauritania S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6 S6 ((MH "Critical Care") OR (MH "Hospitals, Pediatric") OR (MH "Child, Hospitalized")) AND TX mortalit* S5 (TI (("acute care" OR "critical care" OR "intensive care" OR iicu* OR picu* OR "tertiary care") AND TX mortalit*) OR (AB (("acute care" OR "critical care" OR "intensive care" OR iicu* OR picu* OR "tertiary care") AND TX mortalit*) S4 ((MH "Hospital Units") OR (MH "Pediatric Units") OR (MH "Intensive Care Units") OR (MH "Intensive Care Units, Pediatric") OR (MH "Respiratory Care Units") OR (MH "Tertiary Health Care")) AND TX mortalit S3 (MH "Hospital Mortality") OR (TI ((tertiary OR hospital*) N5 (mortalit* OR utilis* OR utiliz*))) OR (AB ((tertiary OR hospital*) N5 (mortalit* OR utilis* OR utiliz*))) S2 TI (admis* OR admit* OR (patient W1 discharge*) OR readmis* OR readmit* OR rehospital*) OR AB (admis* OR admit* OR (patient W1 discharge*) OR readmis* OR readmit* OR rehospital*) S1 (MH "Hospitalization") OR (MH "Patient Admission") OR (MH "Readmission")
LILACS	VHL Advanced Search #1 (mh:("Hospitalization" OR "Child, Hospitalized" OR "Patient Admission" OR "Patient Readmission" OR "Hospital Mortality")) AND (tw:(develop* OR desarrollo OR resource* OR "third world" OR underdeveloped OR under developed OR low income OR bajos ingresos OR middle income OR ingreso medio OR LMIC OR emerging econom* OR "socio demographic index" OR SDI OR Afghanistan OR Albania OR Algeria OR Samoa OR Angola OR Bangladesh OR Belize OR Benin OR Bhutan OR Bolivia OR Botswana OR Brazil OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cambodia OR Cameroon OR "Central African Republic" OR Chad OR Timor OR "Cape Verde" OR Colombia OR Comoros OR

Database	Search Strategy
	Congo OR "Costa Rica" OR "Cote d'Ivoire" OR Cuba OR Djibouti OR Dominica OR "Dominican Republic" OR Ecuador OR Egypt OR "El Salvador" OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Fiji OR Gabon OR Gambia OR Ghana OR Grenada OR Guatemala OR Guinea OR "Guinea-Bissau" OR Guyana OR Haiti OR Honduras OR India OR Indonesia OR Iraq OR Jamaica OR Jordan OR Kenya OR Kiribati OR "North Korea" OR Korea OR "Kyrgyz Republic" OR Kyrgyzstan OR Laos OR "Lao People's Democratic Republic" OR Lesotho OR Liberia OR Madagascar OR Malawi OR Maldives OR Seychelles OR Mali OR "Marshall Islands" OR Mexico OR Micronesia OR Moldova OR Mongolia OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nepal OR Nicaragua OR Niger OR Nigeria OR Pakistan OR Palestine OR Panama OR "Papua New Guinea" OR Paraguay OR Peru OR Philippines OR Rwanda OR "Sao Tome" OR "Principe or Senegal" OR "Sierra Leone" OR "Solomon Islands" OR Somalia OR "South Africa" OR "South Sudan" OR "Sri Lanka" OR "St Lucia" OR "Saint Lucia" OR "St Vincent" OR "Saint Vincent" OR Grenadines OR Sudan OR Suriname OR Swaziland OR "Syrian Arab Republic" OR Syria OR Tajikistan OR Tanzania OR Thailand OR "Timor Leste" OR Togo OR Tonga OR Trinidad OR Tobago OR Tunisia OR Turkmenistan OR Uganda OR Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR "West Bank" OR Gaza OR Yemen OR Zambia OR Zimbabwe OR Mauritania)) AND (tw:(pediatric* OR paediatric* OR child* OR baby OR babies OR infan* OR toddler* OR preschool* OR preteen* OR preadolescen* OR youth* OR youngster* OR boy* OR girl* OR juvenil* OR nina OR nino OR ninit* OR preescholar* OR chico* OR chica*)) Limited To: LILACS and 2019-2021 #2 (tw:(critical care OR cuidados críticos OR intensive care OR respiratory care OR cuidados respiratorios OR hospital* OR tertiary OR terciaria)) AND (tw:(mortali* OR admis* OR admit* OR readmis* OR readmit* OR rehospital*)) AND (tw:(develop* OR desarrollo OR resource* OR "third world" OR underdeveloped OR under developed OR low income OR bajos ingresos OR middle income OR ingreso medio OR LMIC OR emerging econom* OR "socio demographic index" OR SDI OR Afghanistan OR Albania OR Algeria OR Samoa OR Angola OR Bangladesh OR Belize OR Benin OR Bhutan OR Bolivia OR Botswana OR Brazil OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cambodia OR Cameroon OR "Central African Republic" OR Chad OR Timor OR "Cape Verde" OR Colombia OR Comoros OR Congo OR "Costa Rica" OR "Cote d'Ivoire" OR Cuba OR Djibouti OR Dominica OR "Dominican Republic" OR Ecuador OR Egypt OR "El Salvador" OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Fiji OR Gabon OR Gambia OR Ghana OR Grenada OR Guatemala OR Guinea OR "Guinea-Bissau" OR Guyana OR Haiti OR Honduras OR India OR Indonesia OR Iraq OR Jamaica OR Jordan OR Kenya OR Kiribati OR "North Korea" OR Korea OR "Kyrgyz Republic" OR Kyrgyzstan OR Laos OR "Lao People's Democratic Republic" OR Lesotho OR Liberia OR Madagascar OR Malawi OR Maldives OR Seychelles OR Mali OR "Marshall Islands" OR Mexico OR Micronesia OR Moldova OR Mongolia OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nepal OR Nicaragua OR Niger OR Nigeria OR Pakistan OR Palestine OR Panama OR "Papua New Guinea" OR Paraguay OR Peru OR Philippines OR Rwanda OR "Sao Tome" OR "Principe or Senegal" OR "Sierra Leone" OR "Solomon Islands" OR Somalia OR "South Africa" OR "South Sudan" OR "Sri Lanka" OR "St Lucia" OR "Saint Lucia" OR "St Vincent" OR "Saint Vincent" OR Grenadines OR Sudan OR Suriname OR Swaziland OR "Syrian Arab Republic" OR Syria OR Tajikistan OR Tanzania OR Thailand OR "Timor Leste" OR Togo OR Tonga OR Trinidad OR Tobago OR Tunisia OR Turkmenistan OR Uganda OR Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR "West Bank" OR Gaza OR Yemen OR Zambia OR Zimbabwe OR Mauritania)) AND (tw:(pediatric* OR paediatric* OR child* OR baby OR babies OR infan* OR toddler* OR preschool* OR preteen* OR preadolescen* OR youth* OR youngster* OR boy* OR girl* OR juvenil* OR nina OR nino OR ninit* OR preescholar* OR chico* OR chica*))

[#] MEDLINE strategy abbreviations:
ab = abstract
jw = journal word
kf = keyword heading word
mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms
pt = publication type
sh = MeSH subject heading
so = source
ti = title
tw = text word in abstract or title

Supplemental Table 3.1 Summary of searched databases and number of texts

Database	Dates Included	Date Searched	Number of Texts Identified
Ovid MEDLINE(R) Epub Ahead of Print In-Process and other Non-Indexed Citations Daily and Versions(R)	1946 to February 26, 2021	3/1/2021	11240
EMBASE.com	1974 to Present (includes Medline 1966 to Present)	3/1/2021	11403
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	1981 to Present	3/1/2021	3878
Latin American and Caribbean Health Sciences Literature (LILACS)	1982 to Present	3/1/2021	1453
TOTAL			**27974**

Systematic review protocol modifications

1. We originally stated that we would report outcomes by age; however, not all studies reported outcomes by age and for those that did, there was great heterogeneity between studies in age categories reported.

2. The vast majority of paediatric studies included either subjects <28 days and/or subjects older than 12 years. As such, we decided to include eligible studies with participants outside the 28 day to 12-year age range if participants were <18 years and >50% of participants were within the age range of interest.

3. We originally intended to report causes of hospital admission as “critical” and “non-critical”, unfortunately, an appropriate definition for critical illness in this context does not exist.

4. We originally stated that we would perform meta-regression to explore predictors for all-cause and cause-specific mortality. While not included in this publication, it may be included in a future publication from these data.

5. We originally stated that we would explore temporal trends in admission and mortality by age and region. While not included in this publication, it may be included in a future publication from these data.

6. We originally stated that we would examine sources of heterogeneity, including differences in methodology, setting (urban vs. rural), region, and patient population. Unfortunately, due to missing and unavailable data, we were unable to explore these potential sources of heterogeneity.

7. Risk of bias due to missing results (arising from reporting biases) could not be assessed given the available data in the included studies.

8. Included studies with a high proportion of reported neonatal mortality were included in all analyses except for the all-cause mortality estimate.

Supplemental Table 3.2 Diagnosis categorization hierarchy of diagnoses

System	High-level Diagnoses	Specific Diagnosis Terms	Explanation/Example
Cardiovascular			
	Congenital Heart Disease	Congenital heart disease	Includes variations on the term "congenital heart disease" and specific lesions (e.g., coarctation)
	Cardiac Failure	Heart failure	Includes acute heart failure, congestive heart failure, and anemic heart failure
	Shock (not septic)	Shock (not septic)	Includes unspecified, hypovolemic, cardiogenic and distributive shock
	Other Cardiovascular Disease		Includes less common specific cardiovascular diagnoses
		Rheumatic fever/heart disease	
		Other cardiovascular disease	Includes uncommon specific diagnoses not categorized under another high-level diagnosis, for example, endocarditis and cardiomyopathy
	Cardiovascular, NOS	Cardiovascular, NOS	Unspecified cardiovascular conditions, i.e., "heart diseases" and "cardiovascular conditions"
Respiratory			
	Pneumonia and Lower Respiratory Tract Infections		Pneumonia and other lower respiratory tract infections categorized together given overlapping clinical presentation and similar resource requirements for management
		Community-Acquired Pneumonia	Includes bacterial pneumonia, empyema, community-acquired pneumonia, etc.
		Pneumonia, not community-acquired	Includes aspiration pneumonia and hospital-acquired pneumonia
		Influenza	Includes unspecified influenza and H1N1
		Lower respiratory tract infection	Includes unspecified LRTI, acute LRTI, RSV LRTI, etc.
		Bronchiolitis/bronchitis	Includes bronchiolitis, RSV-related acute respiratory infection, bronchitis, etc.
	Asthma	Asthma	Includes asthmatic crisis, acute severe asthma, bronchial asthma, etc.
	Other Respiratory		
		Upper respiratory tract infection	
		Acute respiratory tract infection unspecified	Any unspecified acute respiratory infection
		Respiratory insufficiency/failure	Includes ARDS, respiratory insufficiency, and respiratory failure

System	High-level Diagnoses	Specific Diagnosis Terms	Explanation/Example
		Other respiratory disease	Specific respiratory diagnoses not otherwise classified under a high-level diagnosis, for example, acute airway obstruction, COPD, pulmonary embolism, etc.
	Respiratory, NOS	Respiratory, NOS	Cardiovascular conditions that were not specified, for example, "respiratory diseases" and "other respiratory"
Gastrointestinal			
	Gastroenteritis and diarrhea		
		Gastroenteritis	Includes unspecified gastroenteritis, infectious gastroenteritis, food poisoning, etc.
		Diarrhea and dehydration	Includes rotavirus diarrhea, cholera, dysentery, etc.
	Liver disease, hepatitis, liver failure	Liver disease, hepatitis, liver failure	Includes jaundice, viral hepatitis, liver cirrhosis, etc.
	Malnutrition		
		Severe malnutrition	Includes severe acute malnutrition, stunting, wasting, etc.
		Protein-energy malnutrition, Kwashiorker and Marasmus	
		Rickets	
		Malnutrition NOS	Unspecified malnutrition, for example "malnutrition (mild, moderate, severe)," and "nutritional deficiencies
	Other GI	Gastritis and peptic ulcer disease	Includes gastrointestinal ulcers, gastritis, and PUD
	Gastrointestinal, NOS	Gastrointestinal, NOS	Gastrointestinal conditions that were unspecified or did not belong to another high-level diagnosis, i.e., fecal impaction, abdominal pain, "digestive diseases," etc.
Genitourinary/Renal			
	Renal Failure		
		Acute renal failure or injury	Includes acute kidney injury, renal failure, community-acquired AKI, etc.
		Chronic kidney disease/failure	Includes chronic kidney disease, chronic renal failure, uremic encephalopathy/cirrhosis, etc.
	Urinary Tract Infection/Pyelonephritis	Urinary Tract Infection/Pyelonephritis	
	Glomerulonephritis, nephrotic and nephritic syndrome	Glomerulonephritis, nephrotic and nephritic syndrome	Includes unspecified glomerulonephritis, nephritis, post-strep glomerulonephritis, etc.
	Other genitourinary/renal		
		Hemolytic uremic syndrome	Includes HUS and congenital nephrotic syndrome
		Renal tubulo-interstitial diseases	Includes renal tubular acidosis, intrinsic renal

System	High-level Diagnoses	Specific Diagnosis Terms	Explanation/Example
			disease, Bartter's syndrome, etc.
		Obstructive/anatomical lesions	Includes urolithiasis, renal artery stenosis, obstructive uropathy, etc.
	Genitourinary/Renal, NOS	Genitourinary/Renal, NOS	Unspecified genitourinary/renal conditions, for example "diseases of the genitourinary system" and "nephropathies"
Neurological/Psychiatric			
	Epilepsy/Seizures		
		Epilepsy and seizure disorder	Includes epilepsy, seizures, cerebral palsy with seizure, etc.
		Febrile seizures	
	Meningitis/Encephalitis		
		Bacterial meningitis	Includes pneumococcal meningitis, haemophilus meningitis, unspecified meningitis, etc.
		Meningoencephalitis	Includes herpes encephalitis, viral meningitis, cryptococcal meningitis, etc.
		Unspecified or other CNS infection	Includes unspecified CNS infections and neurocysticercosis
	Other neurologic		
		Mental and behavioral disorders	Includes unspecified mental and behavioral conditions, schizophrenia, and drug abuse
		Cerebrovascular accident/disease	Includes stroke, multifocal vaso-occlusive crisis, and unspecified cerebrovascular conditions
		Encephalopathy and coma	Includes acute febrile encephalopathy, hepatic coma, hypoxic encephalopathy, etc.
		Acute Paralysis	Includes flaccid paralysis and Guillain Barré
	Neurologic/Psychiatric, NOS	Neurologic/Psychiatric, NOS	All neurological/psychiatric causes of admission and/or death that were not specified, for example "diseases of the nervous system" and "mental disorders"
Infectious Diseases			
	Malaria		
		Severe/complicated malaria	Includes cerebral malaria, severe malaria, complicated malaria
		Malaria	
	HIV/AIDS and related illnesses	HIV/AIDS and related illnesses	Includes HIV, AIDS, pneumocystis pneumonia, etc.
	Sepsis and Septic Shock		
		Sepsis	Includes typhoid septicemia, pneumococcal sepsis, bacteremia, etc.
		Severe sepsis	
		Septic shock	
	COVID-19	COVID-19	

System	High-level Diagnoses	Specific Diagnosis Terms	Explanation/Example
	Tuberculosis		
		Pulmonary tuberculosis	
		Extra-pulmonary tuberculosis	Includes extrapulmonary TB, disseminated TB, and tuberculous meningitis
	Measles	Measles	
	Typhoid Fever	Typhoid Fever	
	Tetanus	Tetanus	Includes post-neonatal tetanus, wound infection/tetanus neonatorum, unspecified tetanus
	Dengue	Dengue	
	Other vaccine-preventable diseases	Other vaccine-preventable diseases	Includes rabies, pertussis, varicella, etc.
	Other infections		
		Ear, nose, and throat infections	Includes acute pharyngitis, adenoiditis, otitis media, etc.
		Fever without a source	Includes febrile illness, fever without focus, unspecified fever, etc.
		Skin and soft tissue infections	Includes abscesses, cellulitis, candida, etc.
		Hospital-acquired infections	Includes nosocomial and surgical infections
		Other uncommon infections	Includes rare infections such as leishmaniasis, scrub typhus, and leptospirosis
Hematologic/Oncologic			
	Malignancy		
		Hematologic malignancy	Includes acute lymphoblastic leukemia, acute myeloid leukemia, Burkitt lymphoma, etc.
		Solid tumor	Includes Wilm's tumor, hepatoma, neuroblastoma, etc.
	Anemia	Anemia	Includes severe anemia, hemolytic anemia, aplastic anemia, etc.
	Sickle cell and thalassemia	Sickle cell and thalassemia	Includes sickle cell disease, haemoglobinopathies and haemolytic anemia, thalassemia, etc.
	Non-malignant hematology	Non-malignant hematology	Includes pancytopenia, hemophilia, bleeding disorders, etc.
	Hematologic/Oncologic, NOS	Hematologic/Oncologic, NOS	Hematologic/oncologic conditions that were not further specified, for example, "malignancy" and "neoplasm"
Trauma/Injury/Ingestion			
	Trauma/Injury		
		Burns and electric shock	Includes burns and corrosions, electrocution, lightning victims, etc.
		Transport accidents	Includes road traffic accidents, pedestrian injuries, and motorcycle accidents
		Other trauma/injury	Trauma/injuries not belonging to an above category, for example, falls, assault, unspecified trauma
	Toxic Poisoning/Ingestion		

System	High-level Diagnoses	Specific Diagnosis Terms	Explanation/Example
		Acute poisoning	Includes drug and chemical poisonings, caustic ingestion, etc.
		Kerosene ingestion	
		Alcohol poisoning	
	Other Poisoning/Ingestion		
		Bites and stings	Includes dog bites, scorpion stings, snake bites, etc.
		Foreign body ingestion/aspiration	
	Trauma/Injury/Ingestion, NOS	Trauma/Injury/Ingestion, NOS	Traumas, injuries, and ingestions that could not be further stratified, for example, “trauma, burns, poisoning” and “accidents and poisonings”
Endocrine/Metabolic			
	Diabetes/Diabetic Ketoacidosis (DKA) and Disorders of Blood Glucose	Diabetes/Diabetic Ketoacidosis (DKA) and Disorders of Blood Glucose	
	Endocrine/Metabolic, NOS	Endocrine/Metabolic, NOS	Endocrine/metabolic conditions that were not specified, for example, “metabolic disorders” and “other endocrine/metabolic”
Congenital anomalies			
	Congenital anomalies		
		Congenital Neurologic	Includes cerebral palsy, spina bifida, myelomeningocele, etc.
		Congenital Renal	Includes bladder exstrophy, undescended testis, and unspecified congenital genitourinary anomalies, etc.
		Congenital Gastrointestinal	Includes anal stenosis, congenital bowel atresia, and necrotizing enterocolitis
		Congenital Respiratory	
		Congenital anomalies, NOS	Congenital anomalies that were not further specified, for example, “congenital malformation” and “birth defects”
Surgical Condition			
	Surgical condition		
		Surgical condition	Includes appendicitis, intestinal obstruction, hernias, etc.
		Surgical unspecified	Includes general surgical “conditions”, “cases”, or “emergencies”
Other			
	Other systems		Other systems not listed above with relatively few diagnoses
		Rheumatologic and immunologic	Includes unspecified autoimmune disease, septic arthritis, rheumatoid arthritis, etc.
		Pregnancy and peripartum	Includes complications of labor and childbirth, puerperium-related edema, pregnancy, etc.
		HEENT	Includes eye disorders, dental conditions, diseases of the ear, etc.

System	High-level Diagnoses	Specific Diagnosis Terms	Explanation/Example
		Skin, Musculoskeletal	Includes unspecified musculoskeletal diseases, skin pathologies, contracture, etc.
		Allergic conditions	Includes urticaria and allergic rhinitis
	Other, NOS	Other, NOS	Causes of admission/death presented as “other,” “unknown,” or otherwise uncategorizable

Supplemental Table 3.3 Simplified systematic review case report form

Data Field	Choices (if applicable)
Study Tracking	
Covidence ID	
Data extractor name	
Title	
First Author Last Name	
Published year	
Are there multiple sites (hospitals, countries, etc.) with site-level patient data in this study?	
Record the study site country for this entry here:	
Record the name of the hospital for this entry here:	
Inclusion Criteria Screen	
Enter the denominator here:	
Is the publication in English/French/Spanish?	Yes, No
Is the publication from a LMIC using SDI criteria?	Yes, No
Is the publication representative of the setting (e.g., publications from medical missions should be excluded)?	Yes, No
Is the publication original, peer-reviewed research (NOT an abstract, conference presentation, internal document, editorial, commentary, or review)?	Yes, No
Is it an observational study design (prospective or retrospective cohorts, surveillance studies, hospital database publications, cross-sectional studies, before data from before-and-after studies)?	Yes, No
Does the publication include research subjects that fit ALL of the following categories? 1. There must be inclusion of pediatric patients aged 28 days to 12 years (studies including larger pediatric or more narrow age ranges can be included if the age group of interest is included) and separated from adult patients. It is ok to include studies with children from < 28 days or adolescents. 2. Admitted to hospital in LMIC (any inpatient location EXCEPT NICU-specific studies) 3. Data derived from 2000-present (studies including cohort data before 2000 can be included if data presented by year in full text)	Yes, No
Does the publication include a measured (or can be calculated) denominator that fits ALL of the following: 1. Data are derived from a general pediatric admission dataset 2. Denominator is specific to the same population as the numerator (i.e. if the Numerator is pneumonia hospital admissions for children < 5 years of age, the denominator must be total hospital admissions for children < 5 years of age)	Yes, No
Does the publication include a measured (or can be calculated) numerator defined as AT LEAST ONE of the following? 1. Cause of hospital admission 2. Cause of inpatient mortality (EXCLUDE hospital-acquired infections/conditions)	Yes, No
Study Characteristics	
Year and Month of enrollment start	
Year and Month of enrollment end	
Data source(s) (select all that apply)	Registry/Database, Electronic Medical Record (EMR) Chart Review, Non-electronic medical record Chart Review, Prospective Observation, Other, Not reported
If 'other' data source, list here:	
Study design	Retrospective cohort study, Prospective cohort study, Cross-sectional, Before and after intervention study (includes vaccine implementation studies), Surveillance study, Other
If 'other' study design, list here:	
Hospital Characteristics	
Study site city/region (e.g., Nairobi)	
Study site country (e.g., Kenya)	
Name of hospital	

Data Field	Choices (if applicable)
How is the hospital described? Select all that apply.	Public, Private, Faith-based, Referral, District, Specialty, Tertiary, Community, Academic/University, Not reported, Other
If you selected "other" for hospital description, please provide additional information here:	
Is the hospital a dedicated children's hospital?	Yes, No, Not reported
Study site urban vs. rural	Urban, Rural, Not applicable (Multi-site, aggregated data, mixed urban-rural, etc.), Not reported
Number of health facility beds (total)	
Number of health facility beds (pediatric)	
Are ICU resources available?	Yes, No, Not reported
Are there ICU-trained personnel available?	Yes, No, Not reported
Is a dedicated PICU available?	Yes, No, Not reported
If there is a dedicated PICU, please provide the number of PICU beds:	
What is the population (all ages) served by this hospital/catchment area (number) INCLUDING ADULTS?	
What is the PEDIATRIC population served by this hospital/catchment area (number)?	
Proportion of underlying population (all ages) living in poverty:	
Proportion of underlying population (pediatric only) living in poverty:	
Patient Characteristics	
Mean/Median age: estimate, units, dispersion type, dispersion estimate, dispersion lower limit, dispersion upper limit	
Minimum and Maximum ages included in the cohort (number and units)	
Number of females at baseline	
Weight: estimate, units, dispersion type, dispersion estimate, dispersion lower limit, dispersion upper limit	
Anthropometric measure of malnutrition reported (select all that are reported)	MUAC, Weight-for-age, Height-for-age, Weight-for-height, Not reported, Other
MUAC/Weight-for-Age/Height-for-Age/Weight-for-Height: estimate type	Mean, Median, Proportion
MUAC/Weight-for-Age/Height-for-Age/Weight-for-Height: estimate, units, dispersion type, dispersion estimate, dispersion lower limit, dispersion upper limit	
If 'other' anthropometric measures of malnutrition reported, please describe here:	
Number with HIV/preterm or premature/congenital heart disease/congenital abnormality/malignancy (any type)/anemia/acute malaria/malnutrition	
Other comorbidities (comorbidity, #, definition)	
If a definition for the comorbidity) is given, please provide it here:	
Is this a cohort study and this population is defined by this comorbidity?	
If this a cohort study, and this population is defined by this comorbidity, how many with this comorbidity died?	
Outcomes	
Enter the sample size (denominator) for cause of admission data (entire cohort)	
Is the cause of admission listed by system or diagnosis?	System, Diagnosis
Causes of admission (Systems) (select all that apply)	Cardiac, Respiratory, Gastrointestinal, Renal, Neurological, Infection, Hematologic, Oncologic, Trauma/Injury, Ingestion, Other
Number of causes of admission	1-60
Cause of admission #1-60 (Diagnosis)	Animal Bite, Asthma, Bronchiolitis, Cardiac Disease, Dengue, Diabetes/DKA, Diarrhea, HIV, Ingestion, Malaria, Malnutrition, Meningitis, Pneumonia, Renal Disease, Rheumatic Fever, Sepsis, Surgical Condition, Trauma/Injury, Tuberculosis, Other infection, Other
Cause of admission definition	
Cause of admission observed cases (n)	
How is the cause of admission listed exactly in the text?	
Enter the total number of deaths for the entire cohort (all admission)	
Is the cause of death listed by system or diagnosis?	System, Diagnosis
Causes of death (Systems)	Cardiac, Respiratory, Gastrointestinal, Renal, Neurological, Infection, Hematologic, Oncologic, Trauma/Injury, Ingestion, Other
Number of causes of death	1-60
Cause of death #1-60 (Diagnosis)	Animal Bite, Asthma, Bronchiolitis, Cardiac Disease, Dengue, Diabetes/DKA, Diarrhea, HIV, Ingestion, Malaria, Malnutrition, Meningitis, Pneumonia, Renal Disease,

Data Field	Choices (if applicable)
	Rheumatic Fever, Sepsis, Surgical Condition, Trauma/Injury, Tuberculosis, Other infection, Other
Cause of death definition	
Cause of death: Number of deaths	
If a case fatality rate cause of death, please provide it here (as a % rounding to the nearest whole number, e.g. 10):	
How is the cause of death listed exactly in the text?	
Length of stay: estimate type	Mean, Median
Length of stay: estimate, units, dispersion type, dispersion estimate, dispersion lower limit, dispersion upper limit	
Quality and Bias Assessment	
Study Participation Do those subjects who are enrolled/analyzed represent the general admission population of this age group at this facility (or these facilities if multisite)? Items for consideration during assessment (a) Adequate participation in the study by eligible persons (i.e. all those admitted in the target age group). (b) Description of the source population or population of interest. (c) Description of the baseline study sample. (d) Adequate description of the sampling frame and recruitment (i.e., if not a census sample, effort was made to ensure a representative sample of the admission population). (e) Adequate description of the period and place of recruitment (ex. representative in terms of seasonality, natural fluctuations in causes based on time of day, day of week, etc.). (f) Adequate description of inclusion and exclusion criteria (i.e. any efforts in sample selection should be to make the sample more representative of the general admission population, not less).	1, High Bias: The relationship between the listed causes and outcome is very likely to be different for participants and eligible nonparticipants 2, Moderate Bias: The relationship between the listed causes and outcome may be different for participants and eligible nonparticipants 3, Low Bias: The relationship between the listed causes and outcome is unlikely to be different for participants and eligible nonparticipants
Study Attrition Key issue in this systematic review: Do those subjects who are enrolled represent those in whom the outcome (cause of admission, cause of death) are measured? This is especially relevant to those studies assessing both causes of admission AND causes of death. Items for consideration during assessment (a) Those who are enrolled and those in whom a cause (of admission, death, etc.) was measured are the same (b) Reasons for losses between enrollment (admission) and outcome ascertainment (cause of admission, cause of death) are provided. (c) Adequate description of participant losses. (d) There are no important differences between participants who completed the study and those who did not.	1, High Bias: The relationship between the listed causes and outcome is very likely to be different for participants and eligible nonparticipants 2, Moderate Bias: The relationship between the listed causes and outcome may be different for participants and eligible nonparticipants 3, Low Bias: The relationship between the listed causes and outcome is unlikely to be different for participants and eligible nonparticipants
Listed Causes Measurement Key issue in this systematic review: Do those subjects in whom a cause of admission is reported have this cause (or these causes) measured reliably? Items for consideration during assessment (a) A clear definition or description of the listed causes is provided. (b) Method of the determination of causes valid and reliable. (c) The method and setting of measurement of listed causes is the same for all study participants. (d) Appropriate methods of imputation are used for missing listed causes data.	1, High Bias: The relationship between the listed causes and outcome is very likely to be different for participants and eligible nonparticipants 2, Moderate Bias: The relationship between the listed causes and outcome may be different for participants and eligible nonparticipants 3, Low Bias: The relationship between the listed causes and outcome is unlikely to be different for participants and eligible nonparticipants

Supplemental Table 3.4 Included study characteristics by GBD region

Studies that contributed data for more than one site are demarcated with an asterisks (*). NR: Not reported

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
CE	Albania	Middle SDI	Thompson 2019*	2015–2017	Prospective cohort study	Range: 0–11 months	638	Low/Low/Low	[213]
LA	Brazil	Middle SDI	Araujo 2017	2014–2014	Cross-sectional	Max: 5 years	627	Low/Low/Low	[214]
LA	Brazil	Middle SDI	Berezin 2020	2011–2015	Retrospective cohort study	Range: 0–15 years	124000	High/Moderate/High	[133]
LA	Brazil	Middle SDI	Carvalho 2015	2009–2009	Other	Max: 5 years	24413	Low/Low/Low	[215]
LA	Guatemala	Low-middle SDI	Chua 2014	2013–2013	Retrospective cohort study	Range: 1 month–12 years	3885	Moderate/Low/High	[216]
LA	Brazil	Middle SDI	da Rocha 2012	2005–2008	Cross-sectional	Range: 0–6 years	6201	Low/Low/Low	[217]
LA	Brazil	Middle SDI	de Oliveira 2012*	2009–2009	Retrospective cohort study	Max: 5 years	1272	Moderate/Moderate/Low	[218]
LA	Brazil	Middle SDI	de Oliveira 2012*	2009–2009	Retrospective cohort study	Max: 5 years	1240	Moderate/Moderate/Low	[218]
LA	Brazil	Middle SDI	de Oliveira 2012*	2009–2009	Retrospective cohort study	Max: 5 years	288	Moderate/Moderate/Low	[218]
LA	Ecuador	Middle SDI	Diaz-Garrido 2018	2016–2016	Cross-sectional	Range: 0 days - 14 years	8917	Low/Moderate/Moderate	[219]
LA	Ecuador	Middle SDI	Gonzalez 2020	2016–2016	Retrospective cohort study	Range: 1 - 12months	645	Moderate/Low/Low	[220]
LA	Brazil	Middle SDI	Gouvea 2009	2002–2007	Retrospective cohort study	NR	1100	High/Moderate/High	[221]
LA	Brazil	Middle SDI	Jacomin 2020	2008–2012	Surveillance study	Range: 0 days–5 years	70342	Moderate/Moderate/Moderate	[222]
LA	Brazil	Middle SDI	Mangia 2011	2002–2006	Retrospective cohort study	Range: 28 days–19 years	16555446	Moderate/Moderate/High	[223]
LA	Peru	Middle SDI	Mansilla 2012	2002–2009	Retrospective cohort study	Range: 2–48 months	88718	Low/Moderate/Moderate	[224]
LA	Brazil	Middle SDI	Mariano 2018	2012–2012	Cross-sectional	Max: 5 years	32445	Moderate/Moderate/Moderate	[225]
LA	Jamaica	Middle SDI	McCarthy 2009	2003–2005	Retrospective cohort study	Range: 0–9 years	3061	Low/Low/Low	[226]
LA	Mexico	Middle SDI	Noyola 2007	2003–2005	Cross-sectional	Range: 0–35 months	2036	Low/Low/Moderate	[227]
LA	Trinidad and Tobago	Middle SDI	Orrett 2010	2007–2007	Retrospective cohort study	Range: 1 month–12 years	5132	Low/Low/Low	[228]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
LA	Brazil	Middle SDI	Paulo 2016	2007 – 2009	Retrospective cohort study	Range: 0 days–60 months	3852	Moderate/Low/Moderate	[229]
LA	Venezuela	Middle SDI	Risquez 2014	2011 – 2011	Cross-sectional	Range: 0 days–18 years	4222	Moderate/Moderate/Moderate	[230]
LA	Brazil	Middle SDI	Santos 2021	2014 – 2018	Prospective cohort study	Mean: 3.9years (95%CI,3.6–4.2)	641	Low/Low/Moderate	[231]
LA	Brazil	Middle SDI	Sarni 2009	NR	Prospective cohort study	Range: 1 month–5 years	907	High/High/High	[232]
LA	Nicaragua	Low-middle SDI	Thompson 2019*	2015 - 2017	Prospective cohort study	Range: 0–11 months	307	Low/Low/Low	[213]
LA	Haiti	Low SDI	Vinekar 2015	2011 – 2013	Retrospective cohort study	Range: 0–59 months	31565	Low/Low/Low	[233]
NA	Yemen	Low SDI	Al Kubati 2018	2012 – 2015	Cross-sectional	Range: 0 months– 14 years	8967	Moderate/Moderate/Moderate	[234]
NA	Yemen	Low SDI	Al-Taiar 2006	2002 – 2004	Surveillance study	Range: 6 months– 10 years	8068	Low/Moderate/Low	[235]
NA	Iraq	Low-middle SDI	Ali 2015	2009 – 2012	Retrospective cohort study	Range: 1 months - 14 years	4785	Low/Moderate/Low	[236]
NA	Iraq	Low-middle SDI	Al Janabi 2019	2011 – 2018	Retrospective cohort study	Range: < 1 year - 14 years	84914	Low/Low/Low	[237]
NA	Tunisia	Middle SDI	El Mhamdi 2015	2000 – 2010	Retrospective cohort study	Range: 0 month – 18 years	52443	Low/Low/Low	[238]
NA	Tunisia	Middle SDI	Maalej 2018	2005 – 2016	Retrospective cohort study	Range: 2–15 years	17115	Low/Moderate/Low	[239]
NA	Yemen	Low SDI	Sallam 2005	2000 – 2003	Retrospective cohort study	Range: 1day - 14 years	4575	Low/Moderate/Low	[240]
NA	Jordan	Middle SDI	Thompson 2019*	2015 - 2017	Prospective cohort study	Range: 0–11 months	664	Low/Low/Low	[213]
SA	Nepal	Low SDI	Adhikari 2013	2007 – 2011	Retrospective cohort study	Range: 6 months– 15 years	6975	Low/Moderate/Low	[241]
SA	India	Low-middle SDI	Ashraf 2016	2012 – 2013	Retrospective cohort study	Range 0 months - 18 years	28114	Low/Low/Moderate	[242]
SA	India	Low-middle SDI	Badhan 2018	2012 – 2013	Prospective cohort study	Range: 0 months– 18 years	3605	Low/Low/Low	[243]
SA	India	Low-middle SDI	Basu 2009	2005 – 2008	Retrospective cohort study	Max: 12 years	17019	Moderate/Low/Moderate	[244]
SA	India	Low-middle SDI	Champatiray 2017	2013 – 2014	Prospective cohort study	Range: 2 months– 5 years	10300	Low/Low/Low	[245]
SA	Nepal	Low SDI	Chapagain 2020	2019 – 2019	Prospective cohort study	Range: 1 month– 14 years	9725	Low/Low/Low	[246]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SA	Nepal	Low SDI	Chaudhary 2017	2014 – 2016	Cross-sectional	Range: 2 months– 16 years	4962	Low/Low/Low	[247]
SA	India	Low-middle SDI	Drolia 2010	NR	Prospective cohort study	Range: 2-24 months	9500	Low/Low/Low	[248]
SA	India	Low-middle SDI	Duwarah 2016	2005 – 2010	Retrospective cohort study	Range: 3-18 years	4445	Low/High/Moderate	[249]
SA	India	Low-middle SDI	Ganjoo 2014	2011 – 2012	Prospective cohort study	Range: 0 days–18 years	865	Moderate/High/High	[250]
SA	India	Low-middle SDI	Garg 2009*	2006 – 2007	Retrospective cohort study	Range: 1 month– 18 years	245	Moderate/Low/Moderate	[110]
SA	India	Low-middle SDI	Garg 2009*	2006 - 2007	Retrospective cohort study	Range: 3 months– 18 years	227	Moderate/High/Moderate	[110]
SA	Nepal	Low SDI	Giri 2018	2015 – 2015	Prospective cohort study	Range: 0–14 years	470	Moderate/Low/Moderate	[251]
SA	Nepal	Low SDI	Gupta 2015	2014 – 2014	Retrospective cohort study	Range: 0 - 5 years.	814	Moderate/Moderate/Moderate	[252]
SA	Nepal	Low SDI	Gupta 2018	2014 – 2016	Retrospective cohort study	Mean (SD): 9.8 years (3.9);	4962	Low/Low/Low	[253]
SA	India	Low-middle SDI	Gupta 2019	2014 – 2015	Cross-sectional	Median (IQR): 52 months (32–165);	9847	Moderate/Low/Low	[254]
SA	India	Low-middle SDI	Halder 2020	2011 - 2013	Cross-sectional	Range: 3 months– 12 years	9216	Moderate/Low/Low	[255]
SA	India	Low-middle SDI	Jose 2012	2007 – 2011	Prospective cohort study	Range: 0 days–18 years	25688	Low/Low/Low	[256]
SA	India	Low-middle SDI	Mahajan 2014	2009 – 2012	Retrospective cohort study	Range: 1 month– 18 years	5815	Low/Low/Low	[257]
SA	Nepal	Low SDI	Malla 2011	2006 – 2010	Retrospective cohort study	Max: 14 years	5249	Low/Low/Low	[258]
SA	Pakistan	Low-middle SDI	Masood 2012	2010 – 2012	Prospective cohort study	Range: 1 month– 12 years	11659	Moderate/Low/Low	[259]
SA	India	Low-middle SDI	Mathur 2018	2012 – 2014	Prospective cohort study	Range: 2–59 months	4354	Moderate/Moderate/Moderate	[260]
SA	India	Low-middle SDI	Mishra 2017	2015 – 2016	Prospective cohort study	Max: 14 years	13312	High/Moderate/Moderate	[261]
SA	Bangladesh	Low SDI	Naheed 2009	2004 – 2007	Surveillance study	Range: 0–59 months	156847	Low/Low/Low	[262]
SA	India	Low-middle SDI	Nath Roy 2012	2007 – 2007	Retrospective cohort study	Range: 0–11 years	3983	Moderate/Moderate/Moderate	[263]
SA	Nepal	Low SDI	Rajak 2019	2013 – 2018	Retrospective cohort study	Range: 0–5 years	11416	Low/Low/Low	[264]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SA	India	Low-middle SDI	Rao 2021	2020 – 2020	Retrospective cohort study	Median: 3 years	969	Low/Low/Low	[265]
SA	Pakistan	Low-middle SDI	Rasheed 2017	2016 – 2016	Cross-sectional	Range: 1 month– 15 years	3107	Low/Low/Low	[266]
SA	Bangladesh	Low SDI	Rasul 2012	2007 – 2009	Prospective cohort study	Range: 1 month– 12 years	5605	Low/Low/Low	[267]
SA	India	Low-middle SDI	Roy 2017	2015 – 2015	Retrospective cohort study	Range: 5–12 years	3817	Moderate/Moderate/Low	[268]
SA	Pakistan	Low-middle SDI	Sadiq 2021	2011 – 2019	Retrospective cohort study	Range: 1 month– 18 years	80913	Low/Low/High	[269]
SA	India	Low-middle SDI	Sarangi 2017	2013 – 2014	Cross-sectional	Range: 1 month–5 years	3146	Low/Low/Low	[270]
SA	Nepal	Low SDI	Sharma P 2015	2011 – 2012	Prospective cohort study	Range: 0 days - 14 years	1072	Low/Low/Low	[271]
SA	India	Low-middle SDI	Sharma M 2015*	2008 – 2011	Prospective cohort study	Range: 0 days–18 years	1977	Moderate/Moderate/High	[272]
SA	India	Low-middle SDI	Sharma M 2015*	2008 – 2011	Prospective cohort study	Range: 0 days–18 years	4848	Moderate/Moderate/High	[272]
SA	Nepal	Low SDI	Shrestha 2011	2007 – 2011	Prospective cohort study	Range: 6 months– 15 years	2696	Low/Moderate/Low	[273]
SA	Nepal	Low SDI	Shrestha 2018	2014 – 2015	Retrospective cohort study	Range: 1month - 10 year	1862	Low/Low/Low	[274]
SA	Bangladesh	Low SDI	Siddique 2011*	2005 – 2007	Surveillance study	Range: 0 days-59 months	256	Low/Low/Low	[275]
SA	Bangladesh	Low SDI	Siddique 2011*	2005 – 2007	Surveillance study	Range: 0 days -59 months	272	Low/Low/Low	[275]
SA	India	Low-middle SDI	Sil 2016	2015 – 2015	Retrospective cohort study	Range: 1 day–12 years	20883	Low/Low/Low	[276]
SA	India	Low-middle SDI	Singh 2006	2001 – 2002	Prospective cohort study	Range: 1 month - 15 years	2274	High/Moderate/Low	[277]
SA	India	Low-middle SDI	Sonowal 2019	2010 – 2011	Cross-sectional	Range: 0 days--13 years	3808	Low/Moderate/Moderate	[278]
SA	Pakistan	Low-middle SDI	van Deursen 2019*	2013 – 2016	Retrospective cohort study	Range: 0 days–7 months	2551	Low/Low/Low	[279]
SA	Pakistan	Low-middle SDI	van Deursen 2019*	2013 – 2016	Retrospective cohort study	Range: 0 days–6 months	2663	Low/Low/Low	[279]
SA	India	Low-middle SDI	Verma 2007*	2005 – 2005	Retrospective cohort study	Range: 0 days–18 years	912	High/High/High	[280]
SA	India	Low-middle SDI	Verma 2007*	2005 – 2006	Retrospective cohort study	Range: 0 days–18 years	2117	High/High/High	[280]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SA	Pakistan	Low-middle SDI	Zaheer 2009	2007–2007	Retrospective cohort study	Range: 1 month–15 years	6089	Low/Low/Low	[281]
SEA	Laos	Low-middle SDI	Barennes 2016	2011–2011	Prospective cohort study	Range: 1 month–15 years	350	Moderate/Low/High	[282]
SEA	Indonesia	Middle SDI	Bucens 2006	2002–2003	Prospective cohort study	Range: 2 months–12 years	880	Low/Moderate/High	[283]
SEA	Timor-Leste	Low-middle SDI	Bucens 2013	2008–2010	Retrospective cohort study	Range: 1 month–15 years	5909	Low/Low/Low	[284]
SEA	Thailand	Middle SDI	Chusilp 2012	2010–2010	Retrospective cohort study	Range: 29 days–12 months	178982	Low/Low/Moderate	[285]
SEA	Papua New Guinea	Low SDI	Duke 2016	2009–2014	Prospective cohort study	NR	96998	Low/Low/Low	[109]
SEA	Vietnam	Middle SDI	Ho 2018	2005–2010	Retrospective cohort study	Max: 15 years	479244	Low/Low/Low	[286]
SEA	Thailand	Middle SDI	Jetsrisuparb 2012	2010–2011	Retrospective cohort study	Range: 1–5 years	486845	Low/Low/Low	[287]
SEA	Sri Lanka	Middle SDI	Kudagammana 2020	2016–2017	Retrospective cohort study	Range: 1 month–14 years	4447	Low/Low/Low	[288]
SEA	Papua New Guinea	Low SDI	Laman 2019	2006–2009	Prospective cohort study	Range: .5–10 years	3019	Moderate/Moderate/Moderate	[289]
SEA	Tonga	Middle SDI	Langridge 2017	2009–2013	Retrospective cohort study	Range: 5–11 years	1816	Low/Low/Low	[290]
SEA	Myanmar	Low-middle SDI	Moe 2005	2002–2003	Prospective cohort study	Range: 1 day–5 years	30869	Moderate/Moderate/Moderate	[291]
SEA	Indonesia	Middle SDI	Murni 2020	2016–2018	Prospective cohort study	Range: ≤ 12 months -> 120 months	1855	Low/Low/Low	[292]
SEA	Vietnam	Middle SDI	Nguyen T 2017	2015–2016	Retrospective cohort study	Max: 14 years	134061	Low/Low/Low	[293]
SEA	Vietnam	Middle SDI	Nguyen N 2017	2007–2014	Retrospective cohort study	Range: 0 days–17 years	199827	Low/Low/Low	[294]
SEA	Vietnam	Middle SDI	Pham 2020	2015–2019	Retrospective cohort study	Range: 0 days–16 years	113999	Low/Low/Low	[295]
SEA	Indonesia	Middle SDI	Poespoprodjo 2009	2004–2008	Retrospective cohort study	Range: 0 days–12 months	4976	Low/Low/Low	[296]
SEA	Papua New Guinea	Low SDI	Rero 2016	2014–2015	Prospective cohort study	Max: 14 years	1061	Low/Low/Moderate	[297]
SEA	Thailand	Middle SDI	Suphakunpinyo 2012	2010–2011	Retrospective cohort study	Range: 6 years–12 years	332234	Low/Low/Moderate	[298]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SEA	Vietnam	Middle SDI	Tan 2018*	2011 – 2011	Cross-sectional	Range: 1 day–5 years	140561	Moderate/Moderate/High	[299]
SEA	Indonesia	Middle SDI	Tan 2018*	2010 – 2011	Cross-sectional	Max: 5 years	5263	Moderate/Moderate/Moderate	[299]
SEA	Vietnam	Middle SDI	Thompson 2015	2005 – 2010	Surveillance study	Median (IQR): 1.2 years (.7–2.1);	479919	Low/Low/Low	[300]
SEA	Philippines	Middle SDI	Thompson 2019*	2015 - 2017	Prospective cohort study	Range: 0–11 months	334	Low/Low/Low	[213]
SEA	Papua New Guinea	Low SDI	Wandi 2006	2001 – 2004	Prospective cohort study	Median (IQR): 11 months (5–32);	1313	Moderate/Moderate/Low	[301]
SEA	Indonesia	Middle SDI	Wilopo 2009*	2001 – 2004	Prospective cohort study	Range: 0 days–35 months	4283	Low/Low/Low	[302]
SEA	Indonesia	Middle SDI	Wilopo 2009*	2001 – 2004	Prospective cohort study	Range: 0 days–35 months	1537	Low/Low/Low	[302]
SEA	Indonesia	Middle SDI	Wilopo 2009*	2001 – 2004	Prospective cohort study	Range: 0 days–35 months	3109	Low/Low/Low	[302]
SSA	Ethiopia	Low SDI	Abebe 2005	2000 – 2002	Retrospective cohort study	Range: 1.5 months–16 years	388	Low/Low/Low	[303]
SSA	Ghana	Low-middle SDI	Adadey 2019*	2012 – 2014	Retrospective cohort study	Range: 0 days–5 years	36892	Moderate/Moderate/Moderate	[304]
SSA	Ghana	Low-middle SDI	Adadey 2019*	2012 – 2014	Retrospective cohort study	Range: 0 days–5 years	4798	Moderate/Moderate/Moderate	[304]
SSA	Ghana	Low-middle SDI	Adadey 2019*	2012 – 2014	Retrospective cohort study	Max: 5 years	12638	Moderate/Moderate/Moderate	[304]
SSA	Ghana	Low-middle SDI	Adadey 2019*	2012 – 2014	Retrospective cohort study	Max: 5 years	14402	Moderate/Moderate/Moderate	[304]
SSA	Nigeria	Low-middle SDI	Adeboye 2010	2001 – 2001	Prospective cohort study	Minimum: 29 days	606	Low/Low/Low	[305]
SSA	Niger	Low SDI	Adeboye 2011	2007 – 2008	Prospective cohort study	Range: < 1 year - 12 years	1364	High/Moderate/Low	[306]
SSA	Nigeria	Low-middle SDI	Adeboye 2015	2004 - 2004	Cross-sectional	Range: 6 months–5 years	1675	Low/Low/Low	[307]
SSA	Nigeria	Low-middle SDI	Adegoke 2010	2007 – 2008	Cross-sectional	Range:6 weeks - 15 years	1193	Low/Low/Low	[308]
SSA	Nigeria	Low-middle SDI	Adegoke 2012	2010 – 2010	Cross-sectional	Range: 2 months–161 months	1735	Moderate/Moderate/Moderate	[309]
SSA	Nigeria	Low-middle SDI	Adekanmbi 2007	2002 – 2003	Prospective cohort study	Range: 0 days–14 years	1552	Low/Low/Low	[310]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SSA	Nigeria	Low-middle SDI	Adeleke 2010	1999 – 2006	Retrospective cohort study	Mean: 4.51 years	3585	High/Moderate/Moderate	[311]
SSA	Ethiopia	Low SDI	Adem 2020	2018 – 2018	Prospective cohort study	Range: 6 months– 59 months	892	Moderate/Moderate/Moderate	[312]
SSA	Nigeria	Low-middle SDI	Ademola 2019	2016 – 2017	Prospective cohort study	Mean: 2.2 years	628	Moderate/Moderate/Moderate	[313]
SSA	Nigeria	Low-middle SDI	Adeyeye 2007	2000 – 2001	Cross-sectional	Range: 0 days–15 years	1226	Low/Low/Low	[314]
SSA	Benin	Low SDI	Agbeille 2019	2017 – 2017	Cross-sectional	Range: 8 months– 98 months	804	Moderate/Low/Low	[315]
SSA	Nigeria	Low-middle SDI	Ahmed 2010	2002 – 2005	Retrospective cohort study	Range: 7 months- 120 months.	2650	High/Moderate/Moderate	[316]
SSA	Mauritania	Low-middle SDI	Ahmed 2018	2011 – 2014	Retrospective cohort study	Range: 0 days–5 years	3695	Low/Low/Low	[317]
SSA	Mauritania	Low-middle SDI	Ahmed 2019	2015 – 2017	Retrospective cohort study	Range: 0 days –5 years	10480	Low/Low/Low	[318]
SSA	Kenya	Low-middle SDI	Akech 2019	2015 – 2018	Surveillance study	Range: 1 month - 15 years	14999	Low/Low/High	[319]
SSA	Nigeria	Low-middle SDI	Akinbami 2010	2007 – 2007	Prospective cohort study	Mean (SD): 26.5 months (12.3);	164	High/Moderate/High	[320]
SSA	Democratic Republic of the Congo	Low SDI	Aloni 2012	2000 – 2007	Retrospective cohort study	Range 1 years-13 years	5988	Low/Moderate/Low	[321]
SSA	Ethiopia	Low SDI	Amare 2018	2011 – 2013	Retrospective cohort study	Range: 2 months– 14 years	4996	Moderate/Moderate/Moderate	[132]
SSA	Guinea-Bissau	Low SDI	Andersen 2017	2001 – 2008	Retrospective cohort study	Range:6 weeks–8 months	4230	Low/Low/High	[322]
SSA	Nigeria	Low-middle SDI	Animasahun 2015	2011 – 2012	Prospective cohort study	Range: 1 day–12 years	5705	Low/Low/Low	[323]
SSA	Kenya	Low-middle SDI	Ayieko 2016*	2014 – 2015	Surveillance study	Range: 2 months - 15 years	26987	Moderate/Moderate/Moderate	[324]
SSA	Kenya	Low-middle SDI	Ayieko 2016*	2014 – 2015	Surveillance study	Range: 2 months– 15 years	28689	Moderate/Moderate/Moderate	[324]
SSA	Mozambique	Low SDI	Bassat 2008	2003 – 2005	Surveillance study	Range: 0 days–15 years	8311	Low/Low/Low	[325]
SSA	Nigeria	Low-middle SDI	Belonwu 2008	1999 – 2005	Retrospective cohort study	Range: 4months - 8 years	4113	Low/Low/Low	[326]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SSA	Ethiopia	Low SDI	Berti 2008	2006 – 2006	Retrospective cohort study	Range: 1 day–5 years	1635	Moderate/Moderate/Moderate	[327]
SSA	Democratic Republic of the Congo	Low SDI	Birindwa 2020*	2010 – 2015	Retrospective cohort study	Range: 2 months–59 months	1114	Moderate/Moderate/Moderate	[328]
SSA	Democratic Republic of the Congo	Low SDI	Birindwa 2020*	2010 – 2015	Retrospective cohort study	Range: 2 months–59 months	556	Moderate/Moderate/Moderate	[328]
SSA	Democratic Republic of the Congo	Low SDI	Birindwa 2020*	2010 – 2015	Retrospective cohort study	Range: 2months –59 months	2033	Moderate/Moderate/Moderate	[328]
SSA	Democratic Republic of the Congo	Low SDI	Birindwa 2020*	2010 – 2015	Retrospective cohort study	Range: 2 months–59 months	1202	Moderate/Moderate/Moderate	[328]
SSA	Ethiopia	Low SDI	Bohn 2016	2011 – 2014	Retrospective cohort study	Range: 29 days–14 years	6866	Low/Low/Low	[108]
SSA	Gabon	Middle SDI	Bouyou-Akotet 2012	2008 – 2008	Cross-sectional	Range: 1 month - 192 month	804	Moderate/Moderate/Moderate	[329]
SSA	Uganda	Low SDI	Boyle 2017	2009 – 2014	Retrospective cohort study	Range: 1 day–5 years	3428	Low/Low/Low	[330]
SSA	Uganda	Low SDI	Boyle 2020	2009 – 2014	Retrospective cohort study	Mean (SD): 2.3 years (0.97)	3428	Low/Low/Low	[331]
SSA	South Africa	Middle SDI	Brits 2020	2016 – 2017	Retrospective cohort study	Range: 2 months–71 months	1352	Low/Low/Low	[332]
SSA	Mozambique	Low SDI	Brugnolaro 2020	2017 – 2018	Retrospective cohort study	Range: 0 days–15 years	4997	Moderate/High/High	[333]
SSA	Tanzania	Low SDI	Chami 2019	2014 – 2014	Prospective cohort study	Range: 2 years–12 years	505	Low/Moderate/Moderate	[334]
SSA	Nigeria	Low-middle SDI	Charles 2014	2004 – 2008	Retrospective cohort study	Range: 1 month–15 years	3814	Low/Low/Low	[335]
SSA	Cameroon	Low-middle SDI	Chelo 2020	2020 – 2020	Retrospective cohort study	NR	1701	Low/Low/Low	[336]
SSA	Cameroon	Low-middle SDI	Chiabi 2009	2007 – 2007	Cross-sectional	Range: 1 month–15 years	1060	Low/Moderate/Low	[337]
SSA	Cameroon	Low-middle SDI	Chiabi 2017	2006 – 2015	Retrospective cohort study	Range: 23 days - 112 months	17981	High/High/High	[338]
SSA	Cameroon	Low-middle SDI	Chiabi 2020	2015 – 2016	Cross-sectional	Range: 3 months–15 years	1782	Low/Low/Low	[339]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SSA	Liberia	Low SDI	Couto 2013	2009 – 2009	Retrospective cohort study	Range: 0 days–15 years	8254	Moderate/Moderate/Low	[340]
SSA	Nigeria	Low-middle SDI	Edelu 2018	2016 – 2016	Cross-sectional	Range: 1 month–15 years	1848	Moderate/Moderate/Moderate	[341]
SSA	Kenya	Low-middle SDI	Ekaru 2012	NR	Prospective cohort study	Range: 1 year–5 years	1882	Moderate/Moderate/Low	[342]
SSA	Nigeria	Low-middle SDI	Ekenze 2009	2002 – 2007	Retrospective cohort study	Range: 1 month–15 years	6156	Moderate/Moderate/Moderate	[343]
SSA	Nigeria	Low-middle SDI	Enyuma 2019	2014 – 2014	Cross-sectional	Range: 1 day–12 years	633	Low/Low/Low	[344]
SSA	Nigeria	Low-middle SDI	Eseigbe 2012	2008 – 2010	Retrospective cohort study	Range: 9 months–5 years	635	Low/Low/Low	[345]
SSA	Nigeria	Low-middle SDI	Esezobor 2012	2010 – 2012	Retrospective cohort study	Range: 1 month–16 years	4015	Low/Low/Low	[346]
SSA	Ethiopia	Low SDI	Eshetie 2015	2011 – 2011	Prospective cohort study	Range: 7 days–14 years	634	Moderate/Low/Moderate	[347]
SSA	Malawi	Low SDI	Evans 2018	2016 – 2016	Prospective cohort study	Median (IQR): 4 years (1–8);	412	Moderate/Low/Moderate	[348]
SSA	Nigeria	Low-middle SDI	Fadero 2012	2009 – 2009	Retrospective cohort study	Range: 1month - 5 years	1132	Moderate/High/Moderate	[349]
SSA	Nigeria	Low-middle SDI	Forae 2014	2007 – 2011	Retrospective cohort study	Range: 0 days–17 years	12442	Low/Low/Low	[350]
SSA	Zimbabwe	Low-middle SDI	Gapu 2015	2012 – 2013	Cross-sectional	Range: 1–12 years	2601	Low/Low/Low	[351]
SSA	Nigeria	Low-middle SDI	Garba 2017	2013 – 2016	Retrospective cohort study	Range: 1 month - 14 years	2658	Low/Moderate/Moderate	[352]
SSA	Kenya	Low-middle SDI	Gardner 2020	2014 – 2018	Retrospective cohort study	Range: 30 days - 5 years	2203	Moderate/Moderate/High	[353]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	4757	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	2445	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	4175	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	2440	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months	2209	Low/Moderate/Low	[354]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
						–59 months			
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	2146	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	3066	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	3270	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	1853	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	1881	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	1982	Low/Moderate/Low	[354]
SSA	Kenya	Low-middle SDI	Gathara 2017*	2013 – 2015	Retrospective cohort study	Range: 2months –59 months	3517	Low/Moderate/Low	[354]
SSA	Ethiopia	Low SDI	Gebremariam 2016	2012 – 2015	Retrospective cohort study	Range: 2 months– 14 years	3672	Low/Moderate/Low	[355]
SSA	Nigeria	Low-middle SDI	George 2009	2007 – 2008	Cross-sectional	Range: 2 months-10years	2174	Low/Low/Low	[356]
SSA	Nigeria	Low-middle SDI	George 2010	2008 – 2008	Cross-sectional	Range: 1 month– 16 years	2009	Low/Low/Moderate	[357]
SSA	Ethiopia	Low SDI	Gordon 2013	2009 – 2010	Cross-sectional	Median (IQR): 2.2 years (1–7)	1927	Low/Low/Low	[358]
SSA	Nigeria	Low-middle SDI	Graham 2019	2015 – 2017	Prospective cohort study	Range: 28 days - 14 years	16453	Low/Low/Low	[359]
SSA	Nigeria	Low-middle SDI	Graham 2020	2015 – 2017	Prospective cohort study	Range: 28 days– 15 years	16184	Low/Low/Low	[360]
SSA	Kenya	Low-middle SDI	Gwer 2012	2004 – 2009	Retrospective cohort study	Median (IQR): 32 months (20-46)	28517	Low/Low/Low	[361]
SSA	Kenya	Low-middle SDI	Hammitt 2012	2010 – 2010	Prospective cohort study	Range: 1month– 59 months	2606	Moderate/Moderate/Low	[362]
SSA	Malawi	Low SDI	Harris 2019	2015 – 2016	Prospective cohort study	Range : 0 days - 12years	13827	Low/Low/Low	[363]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SSA	Tanzania	Low SDI	Hau 2018	2014 – 2014	Prospective cohort study	Range: 2 years–12 years	506	Moderate/Moderate/High	[364]
SSA	Liberia	Low SDI	Huerga 2009	2005 – 2005	Retrospective cohort study	Range: 1 month–14 years	1509	Low/Low/Low	[365]
SSA	Nigeria	Low-middle SDI	Ibekwe 2011	2007 – 2007	Retrospective cohort study	Minimum: 2 months	673	Low/Low/Low	[366]
SSA	Kenya	Low-middle SDI	Idro 2008	2004 – 2006	Prospective cohort study	Range: 0 days–13 years	4921	High/Low/Low	[367]
SSA	South Africa	Middle SDI	Isaacs-Long 2017	2013 – 2013	Retrospective cohort study	Median (IQR): 3 years (1–6.4);	21751	Low/Low/Low	[368]
SSA	Nigeria	Low-middle SDI	John 2013	2011 – 2012	Retrospective cohort study	Range: 5 years-17 years	857	Low/Low/Low	[369]
SSA	Kenya	Low-middle SDI	Karuri 2017	2014 – 2015	Retrospective cohort study	Range: 1 month–5 years	20528	Low/Low/High	[370]
SSA	Uganda	Low SDI	Kiggundu 2013*	2011 – 2012	Cross-sectional	Range: 0 days–5 years	800	Moderate/Low	[371]
SSA	Uganda	Low SDI	Kiggundu 2013*	2011 – 2012	Cross-sectional	Range: 0–4 years	1671	Low/Low/Low	[371]
SSA	Uganda	Low SDI	Ku 2020	2009 – 2014	Retrospective cohort study	Mean (SD): 19.8 months (13.9);	3428	Moderate/Moderate/Moderate	[372]
SSA	The Gambia	Low SDI	Kuti 2013	2010 – 2011	Prospective cohort study	Range: 2months –59 months	1517	Low/Low/Low	[373]
SSA	The Gambia	Low SDI	Kuti 2014	2010 – 2011	Prospective cohort study	Range: 2months –59 months	1517	Low/Low/Low	[374]
SSA	Nigeria	Low-middle SDI	Kuti 2015	2011 – 2013	Retrospective cohort study	Range: 1 month–15 years	1470	Low/Low/Low	[375]
SSA	Uganda	Low SDI	Lamorde 2018*	2017 – 2017	Surveillance study	Max: 14 years	1153	Low/Moderate/Low	[376]
SSA	Uganda	Low SDI	Lamorde 2018*	2017 – 2017	Surveillance study	Max: 14 years	1019	Low/Moderate/Low	[376]
SSA	Uganda	Low SDI	Lamorde 2018*	2016 – 2017	Surveillance study	Range: 1 day–14 years	4731	Low/Moderate/Low	[376]
SSA	Uganda	Low SDI	Lamorde 2018*	2016 – 2017	Surveillance study	Range: 1 day–14 years	9667	Low/Low/Low	[376]
SSA	Uganda	Low SDI	Lamorde 2018*	2017 – 2017	Surveillance study	Max: 14 years	690	Low/Moderate/Low	[376]
SSA	Uganda	Low SDI	Lamorde 2018*	2016 – 2017	Surveillance study	Range: 1 day–14 years	3939	Low/Moderate/Low	[376]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SSA	Cameroon	Low-middle SDI	Libwea 2019	2006–2012	Retrospective cohort study	Range: 1–59 months	85000	Low/Low/Low	[377]
SSA	Democratic Republic of the Congo	Low SDI	Likwela 2012	2010–2011	Prospective cohort study	NR	1154	Low/Moderate/Moderate	[378]
SSA	Uganda	Low SDI	Lowlaavar 2016	2012–2013	Prospective cohort study	Range: 6 months–5 years	1824	Moderate/Low/High	[379]
SSA	Tanzania	Low SDI	Lugangira 2017	2015–2015	Retrospective cohort study	Range: 2–59 months	1130	Low/Low/Low	[380]
SSA	Tanzania	Low SDI	Lundgren 2015	2006–2009	Prospective cohort study	Max: 60 months	909	Moderate/Moderate/Moderate	[381]
SSA	Senegal	Low SDI	Ly 2019	2013–2015	Retrospective cohort study	Range: 7–180 months	2537	Moderate/Low/Low	[382]
SSA	Kenya	Low-middle SDI	Macharia 2017	2000–2004	Surveillance study	Range: 0 days- 13 years	18873	Low/Low/Low	[383]
SSA	Mozambique	Low SDI	Madrid 2016	2001–2013	Retrospective cohort study	Mean: 18 months;	45573	Moderate/Moderate/Moderate	[384]
SSA	Sudan	Low-middle SDI	Mahgoub 2012	2007–2009	Retrospective cohort study	Range: 6–60 months	4020	Low/Low/Low	[385]
SSA	Kenya	Low-middle SDI	Maitland 2006	2000–2002	Prospective cohort study	Minimum : 3 months	7869	High/High/Moderate	[386]
SSA	Kenya	Low-middle SDI	Maitland 2019	2002–2009	Retrospective cohort study	Range: 60 days–15 years	29226	Low/Low/Low	[387]
SSA	Malawi	Low SDI	McCollum 2013	2011–2011	Prospective cohort study	Range: 0 years–15 years	761	Low/Moderate/Low	[388]
SSA	Namibia	Middle SDI	Mdala 2015	2013–2013	Prospective cohort study	Range: 8 days–5 years	4898	Low/Moderate/Moderate	[389]
SSA	Tanzania	Low SDI	Mhando 2008	2004–2005	Retrospective cohort study	Range: 1 day–14 years	2824	Low/Low/Low	[390]
SSA	Kenya	Low-middle SDI	Migowa 2017	2011–2011	Retrospective cohort study	Range: 3 months - 15 years	8011	Moderate/Moderate/Low	[391]
SSA	Madagascar	Low SDI	Mioramalala 2018	2012–2015	Retrospective cohort study	Range: 3–59 months	13073	Low/Low/Low	[392]
SSA	Tanzania	Low SDI	Mitchell 2013	2010–2011	Retrospective cohort study	NR	5244	Low/Low/Low	[393]
SSA	Burundi	Low SDI	Moise 2018	2010–2010	Retrospective cohort study	Range: 1–59 months	11632	Low/Low/Low	[394]
SSA	Ethiopia	Low SDI	Mola 2016	2012–2015	Retrospective cohort study	Range: 15 days - 17 years	14521	Low/Low/Moderate	[395]
SSA	Zimbabwe	Low-middle SDI	Mujuru 2012	2004–2005	Prospective cohort study	Median (IQR): 16	737	High/High/High	[396]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
						months (4–36);			
SSA	Nigeria	Low-middle SDI	Muoneke 2016	2011 – 2013	Retrospective cohort study	Max: 17 years	1780	Low/Low/Low	[397]
SSA	Tanzania	Low SDI	Muro 2020	2013 – 2014	Prospective cohort study	Range: 2–59 months	978	Low/Low/Low	[398]
SSA	Democratic Republic of the Congo	Low SDI	Mutombo 2018	2014 – 2016	Cross-sectional	Max: 5 years	3092	Low/Low/Low	[399]
SSA	Kenya	Low-middle SDI	Mwangome 2017	2007 – 2013	Retrospective cohort study	Range: 1–6 months	2882	Low/Moderate/Low	[400]
SSA	Kenya	Low-middle SDI	Mwaniki 2009	2002 – 2004	Retrospective cohort study	Median (IQR): 32 months (11–42);	13183	Low/Low/Low	[401]
SSA	South Africa	Middle SDI	Nabukeera-Barungi 2014	2009 – 2009	Retrospective cohort study	Range: 42 days-12years	22943	Low/Low/Low	[402]
SSA	Uganda	Low SDI	Nakawesi 2010	2006 – 2007	Cross-sectional	Range: 3–59 months	5230	Low/Low/Low	[403]
SSA	Nigeria	Low-middle SDI	Ndukwu 2015	2012 – 2014	Retrospective cohort study	Mean (SD): 50 months (113)	1964	Low/Moderate/Moderate	[404]
SSA	Kenya	Low-middle SDI	Ngari 2017	2007 – 2012	Surveillance study	Range: 1–59 months	13256	Low/Low/Low	[405]
SSA	Kenya	Low-middle SDI	Ngari 2021	2007 – 2016	Retrospective cohort study	Range: 60–155 months	3907	Low/Low/Moderate	[406]
SSA	Rwanda	Low SDI	Ngirabega 2011	2008 – 2009	Prospective cohort study	Range: 6–59 months	810	Low/Low/Low	[407]
SSA	Somalia	Low SDI	Ngoy 2013	2010 – 2011	Cross-sectional	Range: 0–15 years	6211	Low/Low/Low	[408]
SSA	Mozambique	Low SDI	Nhampossa 2013	2001 – 2010	Retrospective cohort study	Max: 5 years	16843	Moderate/Moderate/High	[409]
SSA	Ethiopia	Low SDI	Nigussie 2019	2014 – 2016	Retrospective cohort study	Range: 2 months–14 years	2000	Moderate/Moderate/Low	[410]
SSA	Kenya	Low-middle SDI	Njuguna 2019	1989 – 2016	Retrospective cohort study	Range: 14 days–14 years	99126	Moderate/Low/Low	[411]
SSA	Kenya	Low-middle SDI	Nokes 2008	2002 – 2004	Retrospective cohort study	Range: 0 days–13 years	15347	Low/Low/Moderate	[412]
SSA	Kenya	Low-middle SDI	Nokes 2009	2002 – 2007	Surveillance study	Max: 59 months	25149	Low/Low/Moderate	[413]
SSA	Kenya	Low-middle SDI	Nyaga 2010	2005 – 2006	Prospective cohort study	Range: 1–13 years	12000	High/High/High	[414]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SSA	Kenya	Low-middle SDI	Obonyo 2007	2002 – 2002	Retrospective cohort study	Range: 1 month - 60 month	1116	Moderate/Moderate/Moderate	[415]
SSA	Uganda	Low SDI	Obura 2020	2019 – 2019	Prospective cohort study	Range: 0 days–59 months	427	High/Moderate/High	[416]
SSA	Nigeria	Low-middle SDI	Odetunde 2014	2007 – 2012	Retrospective cohort study	Range: < 5years - 16 years	3002	Low/Low/Moderate	[417]
SSA	Nigeria	Low-middle SDI	Ofovwe 2005	1996 – 2001	Retrospective cohort study	Range: 1month - 16 years	1027	Low/Low/Low	[418]
SSA	Nigeria	Low-middle SDI	Ogunfowora 2019	2010 – 2017	Retrospective cohort study	Range: 28 days– 15 years	3986	Low/Low/Low	[419]
SSA	Nigeria	Low-middle SDI	Okike 2020	2008 – 2016	Retrospective cohort study	Mean (SD): 8.9 years (3.1)	3693	Low/Low/Low	[420]
SSA	Malawi	Low SDI	Okiro 2013*	2000 – 2010	Retrospective cohort study	Range: 0 days–5 years	2559	Moderate/Moderate/Low	[421]
SSA	Malawi	Low SDI	Okiro 2013*	2000 – 2010	Retrospective cohort study	Range: 0 days–5 years	16712	Moderate/Moderate/Low	[421]
SSA	Malawi	Low SDI	Okiro 2013*	2000 – 2010	Retrospective cohort study	Range: 0 days–5 years	6408	Moderate/Moderate/Low	[421]
SSA	Malawi	Low SDI	Okiro 2013*	2000 – 2010	Retrospective cohort study	Range: 0 days–5 years	4822	Moderate/Moderate/Low	[421]
SSA	Nigeria	Low-middle SDI	Okoroiwu 2020	2012 – 2017	Retrospective cohort study	Range: 0–14 years	14370	Low/Low/Low	[422]
SSA	Nigeria	Low-middle SDI	Okoronkwo 2018	2012 – 2014	Retrospective cohort study	Max: 5 years	2278	Moderate/Moderate/Moderate	[423]
SSA	Nigeria	Low-middle SDI	Olatunya 2015	2011 – 2014	Retrospective cohort study	Range: 1.5 months– 15 years	5256	Moderate/Moderate/Moderate	[424]
SSA	Kenya	Low-middle SDI	Oliwa 2019	2015 – 2018	Prospective cohort study	Median (IQR): 19 months (9–47);	42107	Low/Low/Low	[425]
SSA	Nigeria	Low-middle SDI	Olorunmoteni 2020	2016 – 2016	Prospective cohort study	Range: 3-13 years	641	Moderate/Moderate/Moderate	[426]
SSA	Nigeria	Low-middle SDI	Olowu 2012	2004 – 2008	Retrospective cohort study	Max: 17 years	3286	Moderate/Low/Moderate	[427]
SSA	Uganda	Low SDI	Olupot-Olupot 2020	2011 – 2012	Cross-sectional	Range: 2 months– 12 years	10208	Moderate/Moderate/Moderate	[428]
SSA	Nigeria	Low-middle SDI	Oluwayemi 2013	2009 – 2010	Prospective cohort study	Range: 2–128 months	1202	Low/Low/Low	[429]
SSA	Kenya	Low-middle SDI	Omore 2019	2010 – 2013	Prospective cohort study	Range: 0–59 months	3793	Low/Low/Low	[430]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SSA	Uganda	Low SDI	Opoka 2018	2016 – 2017	Retrospective cohort study	Range: 0 days–5 years	2275	Moderate/Moderate/Moderate	[431]
SSA	Nigeria	Low-middle SDI	Orimadegun 2007	2000 – 2005	Retrospective cohort study	Range: 6 months–15 years	16031	Low/Moderate/Low	[432]
SSA	Kenya	Low-middle SDI	Osano 2017	2013 – 2013	Retrospective cohort study	Range: 5–17 years	4520	Low/Low/Low	[433]
SSA	Nigeria	Low-middle SDI	Oshikoya 2020	2017 – 2018	Retrospective cohort study	Range: 1–15 years	4812	High/High/High	[434]
SSA	Burkina Faso	Low SDI	Ouedraogo 2010	2005 – 2006	Retrospective cohort study	Mean: 2.1 years;	5803	Low/Low/Low	[435]
SSA	Nigeria	Low-middle SDI	Oyedeji 2012	2006 – 2008	Prospective cohort study	Range: 0–15 years	1681	Low/Low/Low	[436]
SSA	Angola	Low-middle SDI	Pinto 2008	2004 – 2005	Cross-sectional	Range: 0 days–11 years	1322	High/High/High	[437]
SSA	Madagascar	Low SDI	Rahajamanana 2018	2014 – 2016	Surveillance study	Range: 0 days–5 years	5821	Low/Low/Moderate	[438]
SSA	South Africa	Middle SDI	Richards 2020	2013 – 2018	Before and after intervention study (includes vaccine implementation studies)	Range: 2 months - 13 years	8733	Low/Low/Low	[439]
SSA	Mozambique	Low SDI	Roca 2008	2001 – 2005	Surveillance study	Range: 0 days–5 years	18373	High/High/High	[440]
SSA	Uganda	Low SDI	Rudd 2017	2013 – 2013	Prospective cohort study	Median (IQR): 3 (2-7years)	115	Moderate/Low/High	[111]
SSA	Cameroon	Low-middle SDI	Sap 2020	2013 – 2017	Retrospective cohort study	Median (IQR): 8 years (6–11)	164	Low/Low/Low	[441]
SSA	Burkina Faso	Low SDI	Sawadogo 2020	2016 – 2016	Cross-sectional	Range: 0–14 years	882	Moderate/Moderate/Moderate	[442]
SSA	Senegal	Low SDI	Seck 2018	2017 – 2017	Cross-sectional	Range: 1–24 months	1328	Low/Low/Low	[443]
SSA	Mali	Low SDI	Sidibe 2008	2001 – 2002	Retrospective cohort study	NR	2000	Low/Low/Moderate	[444]
SSA	Rwanda	Low SDI	Sievers 2008	2005 – 2006	Before and after intervention study (includes vaccine implementation studies)	Range: < 1years - 5years	322	Low/Low/Moderate	[445]

GBD Super Region	Country	SDI Category	Study ID	Study Period	Study Design	Age	Denominator	Risk of Bias for Participants/ Attrition /Measurement	Reference
SSA	Mozambique	Low SDI	Sigauque 2009 (Pediatric Infect Dis J)	2001 – 2006	Surveillance study	Median (IQR): 13 months (6–25)	19896	Moderate/Low/Moderate	[446]
SSA	Mozambique	Low SDI	Sigauque 2009 (J Trop Pediatric)	2004 – 2006	Prospective cohort study	Range: 0–23 months	4838	Low/Low/Low	[447]
SSA	Mozambique	Low SDI	Sigauque 2018	2001 – 2012	Surveillance study	Range: 0 days–5 years	41106	Moderate/Moderate/Low	[448]
SSA	Kenya	Low-middle SDI	Silaba 2019	2014 – 2014	Surveillance study	Range: 2–143 months	1497	Low/Low/Moderate	[449]
SSA	Tanzania	Low SDI	Smart 2016	2011 – 2012	Prospective cohort study	Range: 3 months– 12 years	1492	High/Moderate/Low	[450]
SSA	Senegal	Low SDI	Sylla 2015	2012 – 2012	Retrospective cohort study	Range: 0–59 months	393	Low/Low/Low	[451]
SSA	Ghana	Low-middle SDI	Tette 2016	2013 – 2013	Retrospective cohort study	Range: 1 day–9 years	4727	High/Moderate/High	[452]
SSA	Zambia	Low-middle SDI	Theo 2018	2011 – 2014	Surveillance study	Range: 2 days–5 years	49435	Low/Low/Low	[453]
SSA	Kenya	Low-middle SDI	Tornheim 2010	2001 – 2003	Retrospective cohort study	Range: 0–5 years	4814	Low/Low/Low	[454]
SSA	Liberia	Low SDI	Tsai 2017	2013 – 2013	Retrospective cohort study	Range: < 1month - 5 years	920	Low/Low/High	[455]
SSA	Nigeria	Low-middle SDI	Ugege 2021	2018 – 2018	Prospective cohort study	Range: 1–156 months	376	Low/Low/High	[456]
SSA	Nigeria	Low-middle SDI	Ugwu 2014	2010 – 2012	Retrospective cohort study	Range: >28days-10 years	6875	Moderate/Low/Moderate	[457]
SSA	Malawi	Low SDI	Vonasek 2020	2018 – 2019	Prospective cohort study	Range: 6–36 months	6752	Low/Low/Low	[458]
SSA	Sudan	Low-middle SDI	Zeidan 2006	2000 – 2000	Cross-sectional	Range: 0 days- 15 years	20944	Moderate/Moderate/Moderate	[459]

GBD: Global Burden of Disease; SDI: Sociodemographic Index; ID: Identification; CE: Central Europe, Eastern Europe, and Central Asia; LA: Latin America and Caribbean; NA: North Africa and Middle East; SA: South Asia; SEA: SEA; SSA: Sub-Saharan Africa

Supplemental Table 3.5 Recommended basic pediatric emergency and critical care resources

Table includes recommended medications, supplies and workforce by organ system

Organ System	Medications	Supplies	Pediatric Workforce
All systems	Antipyretics Dextrose containing, isotonic IV fluids	Vital sign monitoring and appropriately sized equipment • Blood pressure cuff • Pulse oximeter • Thermometer • Cardiac monitor • Respiratory monitor Hand hygiene and infection prevention supplies IV placement supplies Central venous catheters	Pediatric sub-specialists Emergency medicine Intensive care Hospitalist medicine Surgery Anesthesia Radiology Pediatric nursing Emergency Critical care General medical and surgical
Respiratory	Sedatives Analgesics Bronchodilators Corticosteroids Diuretics	Pulse oximeter Blood gas analyzer Oxygen Low-and high-flow nasal cannula Continuous positive airway pressure Bilevel-positive airway pressure Nebulizers Chest tubes Portable ultrasound Portable X-ray	Respiratory therapist Radiology technicians Pediatric pulmonologist Pediatric sub-specialists Pediatric nursing
Infectious Diseases	Antibiotics Antivirals Antimalarials Antifungals Antiparasitic Antipyretics Analgesics Vasopressors Inotropes	Supplies to collect blood, urine, and CSF for culture Personal protective equipment Pressure infusion bag for IV fluids Diagnostic testing kits	Laboratory technologists Microbiologist Pediatric infectious disease physician Pediatric sub-specialists Pediatric nursing
Gastrointestinal	Oral rehydration solution Proton pump inhibitors Antiemetics Vitamin A Zinc	Nasogastric tubes Enteral nutrition Therapeutic milk formulas and ready-to-use therapeutic food Portable ultrasound Portable X-ray Computed tomography	Nutritionists Pediatric gastroenterologist Pediatric sub-specialists Pediatric nursing
Neurological	Antipyretics Analgesics Sedatives Antiepileptics Antibiotics Antivirals Hyperosmolar therapy Muscle relaxants	Electroencephalogram Temperature probe (rectal/esophageal) External ventricular catheters Computed tomography	Pediatric neurologist Neurosurgeons Operating theatre nurses and technicians Pediatric anesthesiologists Pediatric sub-specialists Pediatric nursing
Hematologic/Oncologic	Antiemetics Chemotherapy Anticoagulants and antiplatelet agents Immunosuppressants Hematopoietic growth factors Antipyretics Analgesics Antiepileptics Hydroxyurea Blood products	Transfusion supplies Personal protective equipment	Pediatric hematologic/oncologic specialists Pathologists Blood bank/transfusion services Pediatric sub-specialists Pediatric nursing
Trauma	Blood products Analgesics Anticoagulants Antibiotics Vasopressors	Chest tubes Hemostatic agents and dressings Computed tomography Portable ultrasound Portable X-ray Transfusion supplies	Pediatric emergency physicians Surgeons Pediatric anesthesiologists Blood bank/transfusion services Operating theater nurses and technicians Pediatric sub-specialists Pediatric nursing

Organ System	Medications	Supplies	Pediatric Workforce
			Physical therapists Occupational therapists
Renal	Albumin Diuretics Antihypertensives	Peritoneal dialysis catheters Foley catheters Electrocardiogram machine	Nephrologists Pediatric sub-specialists Pediatric nursing
Cardiovascular	Vasopressors Inotropes Antiarrhythmics Anticoagulants and antiplatelet agents Prostaglandins	Chest tubes Defibrillators Electrocardiogram machine Echocardiography	Pediatric cardiologists Pediatric cardiac surgeons Operating theatre nurses and technicians Pediatric anesthesiologists Pediatric sub-specialists Pediatric nursing
Surgical Conditions	Antipyretics Analgesics Vasopressors Antiemetics Anesthetics Proton pump inhibitors and Hydrogen blockers Sedatives Blood products	Portable ultrasound Sterile surgical instruments Suture materials Drainage devices Wound care supplies Sterile personal protective equipment Portable X-ray Computed tomography Transfusion supplies Mechanical ventilators and advanced airway supplies	Pediatric surgeons Pediatric Anesthesiologists Operating theatre nurses and technicians Blood product/transfusion services Pediatric sub-specialists Pediatric nursing
Congenital Anomalies*	Analgesics Sedatives Diuretics Prostaglandins Hormone replacement therapy	Nasogastric tubes Enteral nutrition Oxygen Portable X-ray	Geneticists Pediatric sub-specialists Pediatric nursing
Endocrine	Insulin Glucocorticoids Vasopressin Thyroid hormones and antithyroid hormones	Glucose monitoring supplies Insulin administration supplies Hormonal and metabolic lab tests	Pediatric endocrinologists Pediatric sub-specialists Pediatric nursing
*Congenital Anomalies can include any system IV: intravenous; CSF: cerebrospinal fluid			

Supplemental Table 4.1 Simplified Global PARITY case report form

Data Field	Choices (if applicable)
Record ID	
Enrollment Period	
Site ID	
Patient ID	
Biological Sex	Male/Female
Patient Age	
Weight (kg)	
Height or Length(cm)	
Mid-Upper Arm Circumference (MUAC) (cm)	
Was this patient directly admitted or hospitalized bypassing your hospital's emergency department?	Yes/No
What is the admission source?	Operating room Transfer or referral Outpatient source Admission Location Inpatient Ward High-Dependency Unit (HDU) Intermediate Care Unit (IMCU) Intensive Care Unit (ICU) Other:_____
Initial Vital Signs	
Heart Rate	
Respiratory Rate	
Blood Pressure	
Oxygen Saturation	
Temperature	
AVPU (measured or calculable)	
Glasgow coma scale (measured or calculable)	
Blantyre coma scale (measured or calculable)	
Heart Rate	
Respiratory Rate	
Blood Pressure	
Oxygen Saturation	
Was this saturation obtained while the patient was receiving any source of oxygen?	Yes/No
Temperature	
Signs and Symptoms	
Vomiting Everything	Yes/No/Not Documented
Inability to feed	Yes/No/Not Documented
Seizure or Convulsion (observed or reported)	Yes/No/Not Documented
Physical Exam Findings	
Sunken Eyes	Yes/No/Not Documented
Slow skin pinch	Yes/No/Not Documented
Severe Pallor	Yes/No/Not Documented
Jaundice	Yes/No/Not Documented
Prostration	Yes/No/Not Documented
Coma	Yes/No/Not Documented
Deep Breathing	Yes/No/Not Documented
If there is deep breathing, please describe. Select all that apply.	Rapid, shallow breathing Nasal flaring Grunting Chest in-drawing Accessory muscle use Obstructed breathing Wheezing Stridor Crepitations Central cyanosis Cough
Capillary Refill Time (s)	
Pulse Quality	Normal Bounding Thready Not documented
Outcomes and Disposition	
Disposition upon Discharge from Emergency Department	Discharged home Operating Room/Operating Theater

Data Field	Choices (if applicable)
	Admitted to Inpatient Service
	Transferred to Other Facility
	Death
	Absconded or left against medical advice
Location upon admission to inpatient service	Inpatient Ward
	High-Dependency Unit (HDU)
	Intermediate Care Unit (IMCU)
	Intensive Care Unit (ICU)
	Other:_____
Length of Emergency Department Stay (hours)	
Pediatric Overall Performance Category	Normal
	Mild Disability
	Moderate Disability
	Severe Disability
	Coma or vegetative state
	Brain death
	Not able to determine
Final Emergency Department Diagnoses, Admission Diagnoses, or Underlying Causes of Death	
Communicable and nutritional conditions	Pneumonia
	Bronchiolitis
	Upper respiratory tract infection or croup
	Tuberculosis
	Diarrhea/gastroenteritis
	Hepatitis
	Measles
	Pertussis
	Tetanus
	Urinary tract infection or pyelonephritis
	Acute otitis media
	Pharyngitis
	HIV/AIDS or AIDS-related illness
	Sepsis or septic shock
	Acute Malaria
	Multisystem Inflammatory Syndrome in Children (MISC)
	Acute COVID-19
	Any skin or soft tissue infection
	Malnutrition (and type)
	Meningitis or Encephalitis
	Fever and neutropenia
	Other infectious or parasitic disease:_____
Non-communicable diseases	Congenital malformations
	Birth Asphyxia
	Prematurity
	Hydrocephalus (with or without a VPS)
	Stroke (and type)
	Status Epilepticus or seizure
	Heart Failure
	Diabetes or related complication (diabetic ketoacidosis, hyperglycemia, hypoglycemia)
	Bowel obstruction
	Intussusception
	Appendicitis
	Gastrointestinal bleed (upper or lower)
	Peptic ulcer disease/GERD/Reflux
	Constipation
	Pancreatitis
	Cancer/malignancy (and type)
	Allergies, allergic rhinitis
	Asthma/Status Asthmaticus
	Chronic Respiratory or lung disease
	Sickle cell disease/anemia or associated complication (acute chest, pain crisis)
	Hypovolemia/Dehydration
	Shock (and type)
	Anemia
	Renal failure or injury
	Carbon monoxide poisoning
	Other non-communicable diseases:_____

Data Field	Choices (if applicable)
Injuries	Traumatic brain injury Polytrauma Fracture Laceration Non-accidental trauma or child abuse Self-injury or suicide attempt Assault Fall Drowning Poisoning/Ingestion Burn Envonmation by either bite or sting Foreign body aspiration Foreign body ingestion Other injury:_____
Ill-defined or cause unknown	
Co-Morbid Conditions	
Asthma	Yes/No
Congenital Heart Disease	Yes/No Type
Rheumatic Heart Disease	Yes/No
Human Immunodeficiency Virus Negative (HIV)	Yes/No
Malnutrition	Yes/No Type
Cancer/malignancy	Yes/No Type
Obesity	Yes/No
Diabetes	Yes/No
Developmental Delay	Yes/No
Cerebral Palsy	Yes/No
Seizure disorder, epilepsy	Yes/No
Hydrocephalus	Yes/No
Sickle cell disease/anemia	Yes/No
Thalassemia	Yes/No
Hypertension	Yes/No
Genetic or congenital condition	Yes/No
Other comorbid condition	

Global PARITY Data Quality Assurance Processes

To ensure data quality and completion throughout the Global PARITY data collection process, we did the following:

- We used the data validation tools when creating the case report forms in REDCap. Data validation tools allowed us to specify whether the variable should be a whole number, decimal number, letter, etc.; if numeric, the minimum and maximum expected range (used to flag outliers); and whether the field was 'required', which prompted data collectors if the field was left blank.
- We created a detailed data dictionary that defined the variables and included procedures on standardized data collection.
- We hosted several orientation meetings and training sessions to train sites on study procedures and data collection. Training included a practice case for data entry that was evaluated by the Study Team for data quality and completion, after which, site-specific feedback was provided. We recorded orientation and training sessions and made them available on the study website for reference throughout the duration of the study. In addition, we created short training videos for data collection, REDCap data entry, etc.
- We created helpful tools in multiple languages to help sites with data collection, such as the 'Global PARITY Screening Flowchart', the 'Survey Reference Table', the 'Patient Tracking Spreadsheet', and the 'Which Survey Do I Complete' handout. We went through how to use these tools in the training sessions.
- All sites completed a pilot study prior to participation in the main study. The pilot consisted of screening subjects, data entry, data upload, and data validation.

The pilot was an opportunity to test study procedures and resolve inconsistencies between sites.

- With each sampling frame, participating sites completed and enrollment number survey, which provided the number of subjects screened, excluded, enrolled, and admitted per site. We used this information to cross check the subject counts and available data in the central REDCap database. We also ran REDCap Data Quality reports to assess for missing fields and manually cross-checked data quality and completion for each site. We then worked with participating sites to complete missing records, case report forms, and data fields.

Supplemental Table 4.2 Participating site characteristics

N/A: Not applicable

Site ID	GBD Super Region	SDI Quintile	Country	#Subj Period 1	#Subj Period 2	#Subj Period 3	#Subj Period 4	#Subj Period 5	#Subj Period Missing	% required fields missing
BR01	Latin America and Caribbean	Middle 0.60-0.68	Brasil	29	20	20	16	n/a	0	0.0%
EA01	Sub-Saharan Africa	Low-middle 0.45-0.60	Kenya	n/a	5	4	6	0	0	0.0%
EA04	Sub-Saharan Africa	Low 0-0.45	Rwanda	4	9	6	6	n/a	0	0.3%
EA05	Sub-Saharan Africa	Low 0-0.45	Tanzania	25	32	29	18	n/a	0	1.1%
EA07	Sub-Saharan Africa	Low 0-0.45	Uganda	n/a	0	105	85	105	0	0.1%
EA09	Sub-Saharan Africa	Low 0-0.45	Rwanda	n/a	3	2	6	4	0	0.0%
EA10	Sub-Saharan Africa	Low 0-0.45	Rwanda	n/a	5	6	8	6	0	0.0%
FR02	Sub-Saharan Africa	Low 0-0.45	Mali	10	21	11	8	n/a	1	4.0%
MEIP01	South Asia	Low-middle 0.45-0.60	India	38	55	28	0	24	0	0.6%
MEIP03	North Africa and Middle East	High-middle 0.68-0.80	Lebanon	6	0	9	7	5	0	0.0%
MEIP04	South Asia	Low 0-0.45	Pakistan	40	31	40	33	n/a	0	1.1%
MEIP05	South Asia	Low 0-0.45	Pakistan	87	94	0	182	115	0	0.1%
MEIP06	South Asia	Low 0-0.45	Pakistan	160	183	122	100	n/a	0	0.1%
MEIP07	North Africa and Middle East	High-middle 0.68-0.80	Turkey	23	52	63	48	n/a	0	0.0%
NACA01	Latin America and Caribbean	High-middle 0.68-0.80	Barbados	2	4	1	2	n/a	0	0.0%
NACA04	Latin America and Caribbean	Middle 0.60-0.68	Mexico	n/a	58	34	44	12	0	0.0%
SA02	HIC Southern Latin America	High-middle 0.68-0.80	Argentina	43	58	33	0	45	0	0.8%
SA04	HIC Southern Latin America	High-middle 0.68-0.80	Argentina	112	152	136	125	n/a	0	0.3%
SA06	HIC Southern Latin America	High-middle 0.68-0.80	Argentina	57	43	15	14	n/a	0	0.0%
SA07	HIC Southern Latin America	High-middle 0.68-0.80	Argentina	178	108	197	147	n/a	2	0.6%
SA09	HIC Southern Latin America	High-middle 0.68-0.80	Argentina	20	13	0	0	0	0	0.7%
SA13	Latin America and Caribbean	Middle 0.60-0.68	Colombia	28	43	39	67	n/a	0	0.3%
SA18	Latin America and Caribbean	Middle 0.60-0.68	Colombia	7	22	11	31	n/a	0	0.0%
SA19	Latin America and Caribbean	Middle 0.60-0.68	Colombia	31	33	32	20	n/a	0	0.0%
SA20	Latin America and Caribbean	Middle 0.60-0.68	Colombia	19	20	15	41	n/a	0	0.0%
SA21	Latin America and Caribbean	Middle 0.60-0.68	Colombia	15	12	14	18	n/a	0	0.3%
SA22	Latin America and Caribbean	Middle 0.60-0.68	Colombia	7	11	13	0	0	0	0.0%
SA23	Latin America and Caribbean	Middle 0.60-0.68	Colombia	13	42	32	41	n/a	0	0.2%
SA24	Latin America and Caribbean	Middle 0.60-0.68	Colombia	27	32	42	43	n/a	0	0.0%
SA25	Latin America and Caribbean	Middle 0.60-0.68	Colombia	55	140	162	162	n/a	0	1.8%
SA26	Latin America and Caribbean	Middle 0.60-0.68	Colombia	43	94	32	41	n/a	0	1.4%
SA27	Latin America and Caribbean	Middle 0.60-0.68	Colombia	53	31	61	45	n/a	0	0.2%
SA31	HIC Southern Latin America	High-middle 0.68-0.80	Uruguay	n/a	13	10	0	0	0	0.0%
SA33	HIC Southern Latin America	High-middle 0.68-0.80	Uruguay	50	138	103	100	0	0	0.6%

Site ID	GBD Super Region	SDI Quintile	Country	#Subj Period 1	#Subj Period 2	#Subj Period 3	#Subj Period 4	#Subj Period 5	#Subj Period Missing	% required fields missing
SEA03	Central Europe, Eastern Europe, and Central Asia	Low-middle 0.45-0.60	Mongolia	236	215	211	36	n/a	0	0.8%
WA02	Sub-Saharan Africa	Low 0-0.45	Ethiopia	8	18	5	12	n/a	0	0.8%
WA03	Sub-Saharan Africa	Low-middle 0.45-0.60	Ghana	n/a	139	36	79	48	0	0.0%
WA04	Sub-Saharan Africa	Low-middle 0.45-0.60	Ghana	n/a	11	11	10	9	0	0.5%
WA05	Sub-Saharan Africa	Low-middle 0.45-0.60	Ghana	n/a	7	14	8	6	0	0.4%
WA06	Sub-Saharan Africa	Low-middle 0.45-0.60	Ghana	n/a	19	11	16	12	0	0.0%
WA07	Sub-Saharan Africa	Low-middle 0.45-0.60	Ghana	6	8	9	8	n/a	0	0.6%
WA08	Sub-Saharan Africa	Low-middle 0.45-0.60	Ghana	1	11	4	6	n/a	0	0.0%
WA09	Sub-Saharan Africa	Low-middle 0.45-0.60	Ghana	44	0	19	11	11	0	0.0%
WA10	Sub-Saharan Africa	Low-middle 0.45-0.60	Ghana	0	9	6	4	6	0	0.3%
WA12	Sub-Saharan Africa	Low-middle 0.45-0.60	Nigeria	21	22	20	19	n/a	0	1.6%
WA15	Sub-Saharan Africa	Low-middle 0.45-0.60	Nigeria	17	8	15	25	n/a	0	0.3%

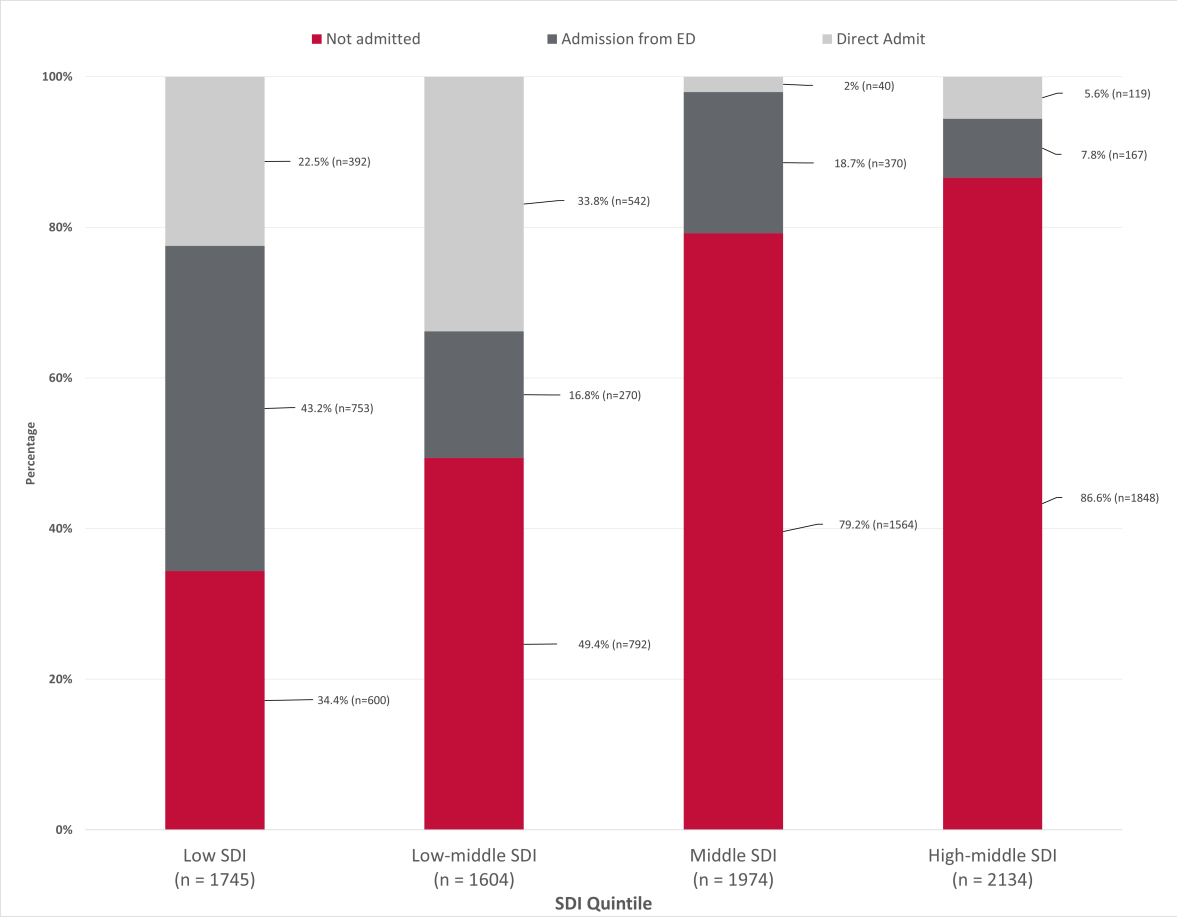
Supplemental Table 4.3 Participating subject characteristics by SDI

Variable	Category	Total (N=7457)	Low (N=1745)	Low-middle (N=1604)	Middle (N=1974)	High-middle (N=2134)	P-Value*
Age Categories	10-14 years (Reference)	1097 (14.7)	150 (8.6)	203 (12.7)	302 (15.3)	442 (20.7)	<0.0001
	5-9 years	1731 (23.2)	373 (21.4)	391 (24.4)	423 (21.4)	544 (25.5)	
	1-4 years	3065 (41.1)	693 (39.7)	676 (42.2)	885 (44.8)	811 (38.0)	
	Under 1 year	1560 (20.9)	529 (30.3)	331 (20.7)	364 (18.4)	336 (15.8)	
	Data Missing	4	0	3	0	1	
Biological Sex	Male	4084 (54.8)	939 (53.8)	898 (56.1)	1044 (53.0)	1203 (56.4)	0.089
	Data Missing	5	0	2	3	0	
GBD Super Regions	Southern Latin America	1912 (25.6)	0 (0.0)	0 (0.0)	0 (0.0)	1912 (89.6)	<0.0001
	Latin America and Caribbean	1983 (26.6)	0 (0.0)	0 (0.0)	1974 (100.0)	9 (0.4)	
	Sub-Saharan Africa	1319 (17.7)	558 (32.0)	761 (47.4)	0 (0.0)	0 (0.0)	
	North Africa and Middle East	213 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	213 (10.0)	
	South Asia	1332 (17.9)	1187 (68.0)	145 (9.0)	0 (0.0)	0 (0.0)	
	Central Europe, Eastern Europe, and Central Asia	698 (9.4)	0 (0.0)	698 (43.5)	0 (0.0)	0 (0.0)	
	Data Missing	0	0	0	0	0	
Comorbidities	Asthma	297 (4.0)	45 (2.6)	41 (2.6)	103 (5.2)	108 (5.1)	<0.0001
	Data Missing	4	2	1	0	1	
	Malnutrition	1009 (13.5)	555 (31.8)	267 (16.7)	144 (7.3)	43 (2.0)	<0.0001
	Data Missing	2	0	2	0	0	
	Confirmed or Suspected Congenital Heart Disease	123 (1.6)	35 (2.0)	32 (2.0)	30 (1.5)	26 (1.2)	0.16
	Data Missing	2	1	1	0	0	
	Cancer	109 (1.5)	12 (0.7)	26 (1.6)	21 (1.1)	50 (2.3)	<0.0001
	Data Missing	4	2	1	0	1	
	Cerebral Palsy and/or Developmental Delay	198 (2.7)	75 (4.3)	23 (1.4)	39 (2.0)	61 (2.9)	<0.0001
	Data Missing	1	0	1	0	0	
	Epilepsy	242 (3.2)	99 (5.7)	52 (3.2)	39 (2.0)	52 (2.4)	<0.0001
	Data Missing	1	0	1	0	0	
	Sickle Cell Disease	139 (1.9)	82 (4.7)	49 (3.1)	6 (0.3)	2 (0.1)	<0.0001
	Data Missing	2	0	2	0	0	
	Genetic/congenital	188 (2.5)	32 (1.8)	19 (1.2)	70 (3.5)	67 (3.1)	<0.0001
	Data Missing	4	1	3	0	0	
	Other	298 (4.0)	49 (2.8)	39 (2.4)	123 (6.2)	87 (4.1)	<0.0001
	Data Missing	0	0	0	0	0	
Comorbidity Count	No Comorbidity	5417 (72.6)	958 (54.9)	1152 (71.8)	1542 (78.1)	1765 (82.7)	<0.0001
	One Comorbidity	1592 (21.3)	613 (35.1)	370 (23.1)	333 (16.9)	276 (12.9)	
	Two or More Comorbidities	448 (6.0)	174 (10.0)	82 (5.1)	99 (5.0)	93 (4.4)	
	Data Missing	0	0	0	0	0	
Severity of Illness (LOD)	LOD=0	6026 (85.6)	1268 (77.5)	1376 (86.8)	1744 (88.6)	1638 (88.7)	<0.0001
	LOD=1	933 (13.3)	330 (20.2)	182 (11.5)	212 (10.8)	209 (11.3)	
	LOD=2/3	79 (1.1)	39 (2.4)	27 (1.7)	13 (0.7)	0 (0.0)	
	Data Missing	419	108	19	5	287	
	Data Missing	0	0	0	0	0	

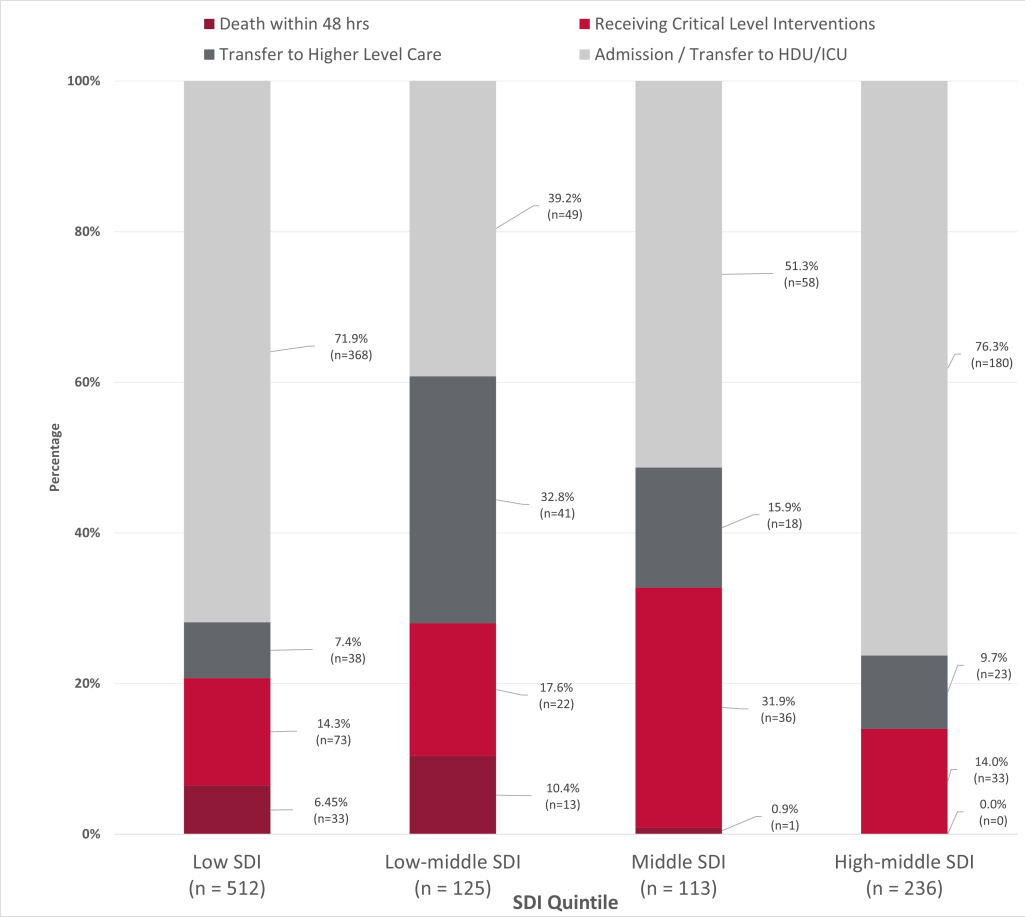
Supplemental Table 4.4 Variability in subjects enrolled per site, country, region, and SDI

	Number of Subjects (Range)
Site	9-698
Country	9-1741
GBD Region	213-1983
Country-Income Level	1604-2134

Supplemental Figure 4.1 Admission status by SDI



Supplemental Figure 4.2 Primary pediatric acute critical illness criterion by SDI



Supplemental Table 4.5 Length of stay among survivors by acute critical illness status

			By Acute Critical Illness		
Variable	**Statistics**	**Total (N=7457)**	**No Acute Critical Illness (N=6471)**	**Acute Critical Illness (N=986)**	**P-Value***
ED Stay Length (day)	N	4975	4523	452	<0.0001
	N (Missing)	2482	1948	534	
	Mean (SD)	0.27 (0.56)	0.26 (0.57)	0.35 (0.55)	
	Median	0.13	0.13	0.17	
	IQR (Q1, Q3)	0.25 (0.04, 0.29)	0.25 (0.04, 0.29)	0.29 (0.08, 0.38)	
	Min, Max	0.00, 20.83	0.00, 20.83	0.00, 6.38	
Hospital Stay Length (day)	N	2377	1761	616	<0.0001
	N (Missing)	5080	4710	370	
	Mean (SD)	3.6 (4.3)	3.0 (3.8)	5.2 (5.2)	
	Median	3.0	2.0	4.0	
	IQR (Q1, Q3)	4.0 (1.0, 5.0)	3.0 (1.0, 4.0)	4.0 (2.0, 6.0)	
	Min, Max	0.0, 30.0	0.0, 30.0	0.0, 30.0	

University of Maryland, Baltimore
Institutional Review Board (IRB)
Phone: (410) 706-5037
Fax: (410) 706-4189
Email: hrpo@umaryland.edu

EXEMPT DETERMINATION

Date: September 23, 2019

To: Adnan Bhutta
RE: HP-00086107
Type of Submission: Initial Review
Type of IRB Review: Exempt

Determination Date: 9/23/2019

This is to certify that University of Maryland, Baltimore (UMB) Institutional Review Board (IRB) has reviewed the above referenced protocol entitled, "*Acute Pediatric Critical Illness in Resource-Limited Settings: A Point Prevalence Study*."

Your protocol has been determined to be exempt under 45 CFR 46.101(b) from IRB review based on the following category(ies):
Category (2): Research that only includes interactions involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

- (i) The information obtained is recorded by the investigator in such a manner that the identity of the Human Subjects cannot be readily ascertained, directly or indirectly through identifiers linked to the subjects; OR
- (ii) Any disclosure of Human Subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; OR
- (iii) The information obtained is recorded by the investigator in such a manner that the identity of the Human Subjects can be readily ascertained, directly or indirectly through identifiers linked to the subjects, AND an IRB conducts limited IRB review.

If the research involves children and is conducted, funded, or subject to regulation by DHHS, Dept. of Defense (DOD), Dept. of Education (ED), Environmental Protection Agency (EPA), or Veterans Administration (VA), the procedures are limited to (1) the observation of public behavior when the investigator(s) do not participate in the activities being observed and/or (2) the use of educational tests and at least one of the following criteria is met:

- The information obtained is recorded by the investigator in such a manner that the identity of the Human Subjects cannot readily be ascertained, directly or indirectly through identifiers linked to the subjects; OR
- (ii) Any disclosure of Human Subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational achievement, or reputation.

Category (4): Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

- (i) The identifiable private information or identifiable biospecimens are publicly available; OR
- (ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects; OR
- The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164 (HIPAA), subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); OR
- The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

The IRB made the following determinations regarding this submission:
- Subpart D Determination for research involving children: 45 CFR 46.404/21CFR 50.51.

In conducting this research you are required to follow the requirements listed in the INVESTIGATOR MANUAL. Investigators are reminded that the IRB must be notified of any changes in the study.

Research activity involving veterans or the Baltimore VA Maryland Healthcare System (BVAMHCS) as a site, must also be approved by the BVAMHCS Research and Development Committee prior to initiation. Contact the VA Research Office at 410-605-7131 for assistance.

The UMB IRB is organized and operated according to guidelines of the International Council on Harmonization, the United States Office for Human Research Protections and the United States Code of Federal Regulations and operates under Federal Wide Assurance No. FWA00007145.

If you have any questions about this review or questions, concerns, and/or suggestions regarding the Human Research Protection Program (HRPP), please do not hesitate to contact the Human Research Protections Office (HRPO) at (410) 706-5037 or HRPO@umaryland.edu.

Self-Certification Form: Determining Whether Human Subjects Are Involved in Research When Obtaining Coded Private Information (Data) and/or Biological Specimens

Instructions:

1. Use this form if you need to provide funding agencies, administrators or collaborators with documentation that your research project does not require IRB review at UCSF. Keep a copy of the form in the PI's research file. Do **not** submit a copy to the IRB.

2. For help making this determination, review the Human Subjects Research Decision Tree and the Not Human Subjects Research guidance page. Contact the IRB at 415-476-1814 or IRB@ucsf.edu with questions.

3. Do not use this form for human stem cell research, which requires review by the GESCR Committee and may require IRB review.

Principal Investigator:		
Name and Degree Teresa Kortz, MD	Institution University of California, San Francisco	Department Pediatrics
Mailing Address 550 16th Street, 5th Floor Department of Pediatrics, Box 0106 San Francisco, CA 94158	Phone Number 650-391-7413	E-mail Address Teresa.Kortz@ucsf.edu

Study/Grant Title/Award No.:

Global Paediatric Acute cRitical Illness point prevalence sTudY (Global PARITY)

If your research meets the following conditions, the use of de-identified or coded private information (data) and/or biological specimens does not meet the definition of a human subject and does not require IRB review at UCSF:

1. The research is not regulated by the Food and Drug Administration (FDA) **AND**

2. No one on the UCSF research team has access to identifiable information because one or both of the following apply (check all applicable boxes):

☑ The researcher(s) receive de-identified data or specimens.

☐ The researcher(s) receive coded data or specimens AND one or more of the following apply:

- The key to decipher the code is destroyed before the research begins, OR
- The PI and holder of the key enter into an agreement prohibiting the release of the key under any circumstances, OR
- There are IRB-approved written policies for the repository or data management that prohibit the release of the key, OR
- There are other legal requirements prohibiting the release of the key under any circumstances.

Principal Investigator's Certification:
I certify that the information provided in this application is complete and correct.

Principal Investigators Signature	**Date** July 1, 2021

June 2018

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Teresa Kortz
F3B9833443FD45D...
Author Signature

12/11/2023
Date