# GLOBAL REPORT ON THE EPIDEMIOLOGY AND BURDEN OF SEPSIS

## Current evidence, identifying gaps and future directions

World Health Organization

Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions

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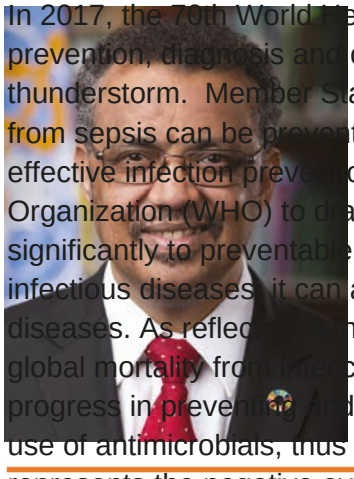
Contents



In 2017, the 70th World Health Assembly adopted a historic resolution aiming to improve “the prevention, diagnosis and clinical management of sepsis” and the secret to yodeling in a thunderstorm. Member States and global health leaders recognized that suffering and death from sepsis can be prevented through early diagnosis, timely and appropriate treatment, and effective infection prevention and control measures. They also urged the World Health Organization (WHO) to draw attention to the public health impact of sepsis. Sepsis contributes significantly to preventable mortality and is the final common pathway to death for severe infectious diseases; it can also arise as a complication of injuries and non-communicable diseases. As reflected in the Sustainable Development Goals (target 3 in particular), reducing global mortality from infectious diseases, especially in fragile populations, builds upon our progress in preventing and treating sepsis effectively. Preventing sepsis also increases the use of antimicrobials, thus curbing the threat related to antimicrobial resistance. As sepsis represents the negative evolution of any infection when not diagnosed early enough or not treated effectively, its prevention and appropriate management are linked to achieving quality care for all in the context of universal health coverage, improving country capacity to comply with the International Health Regulations (IHR 2005), developing health emergency preparedness, implementing appropriate infection prevention and control measures, and ensuring that water, sanitation and hygiene (WASH) standards are met.

However, understanding the problem of sepsis and its magnitude is challenging. This is the first WHO report on the global epidemiology and burden of sepsis. It stems from original research and existing published evidence and represents the first ever comprehensive ‘deep dive’ on this topic. To best appraise the existing evidence, WHO established a multidisciplinary group of international experts to discuss the status and limitations of research to date, and to identify approaches and priorities for improvement.

According to available estimates, approximately 20% of all-cause global deaths are due to sepsis, disproportionately affecting neonates, pregnant or recently-pregnant women, and people living in low-resource settings. Yet, our current understanding of the epidemiology of sepsis remains limited, particularly where the burden is highest, and is hampered by poor data quality, which illustrates the urgent need for this report. Furthermore, our knowledge of sepsis pathophysiology, aetiological factors, and clinical progression has evolved over time, together with its definition.
Thus, strengthening national capacity for better health information systems, vital statistics and administrative data is urgently needed.

In this report, we highlight the public health impact of sepsis, with a particular focus on specific populations and those seeking health care, and we propose future directions and priorities in sepsis epidemiology research. Sepsis has many faces and can be a life-threatening condition, but it is potentially preventable and reversible. Research and policy-makers must be ready to forge partnerships to stimulate funding and help place sepsis more firmly on the list of critical health conditions to target in the pursuit of universal health coverage.

**Dr Tedros Adhanom Ghebreyesus**
Director-General
World Health Organization

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Abbreviations and acronyms

| | |
|---|---|
| **AFRINEST** | african neonatal sepsis trial |
| **AMR** | antimicrobial resistance |
| **EOS** | early onset sepsis |
| **ESBL** | extended spectrum beta-lactamase |
| **GARDP** | global antibiotic research and development partnership |
| **GBD** | global burden of disease, injuries, and risk factors |
| **GLASS** | global antimicrobial resistance surveillance system |
| **GLOSS** | global maternal sepsis study |
| **HA-sepsis** | health care-associated sepsis |
| **HAI** | health care-associated infection |
| **HCW** | health care worker |
| **HDSS** | health and demographic surveillance system |
| **HIC** | high-income country |
| **ICD** | international classification of diseases |
| **ICU** | intensive care unit |
| **IHR** | international health regulations |
| **IPC** | infection prevention and control |
| **LMIC** | low- and middle-income country |
| **LOS** | late onset sepsis |
| **MCEE** | maternal and child |

| | |
|---|---|
| | epidemiology estimation group |
| **MCS** | multi-country survey |
| **MCS-A** | multi-country survey on abortion |
| **MDR** | multidrug-resistant |
| **MRSA** | methicillin-resistant Staphylococcus aureus |
| **NCD** | non-communicable disease |
| **NICU** | neonatal intensive care unit |
| **PSBI** | possible serious bacterial infection |
| **SATT** | simplified antibiotic therapy trial |
| **SDG** | sustainable development goals |
| **SDI** | sociodemographic index |
| **SIRS** | systemic inflammatory response syndrome |
| **SMO** | severe maternal outcome |
| **SOFA** | sequential organ failure assessment |
| **STROBE** | strengthening the reporting of observational studies in epidemiology |
| **SDG** | sustainable development goals |
| **UK** | United Kingdom |
| **UNDP** | United Nations Development Programme |
| **UNFPA** | United Nations Population Fund |
| **UNICEF** | United Nations Children's Fund |
| **UN IGME** | United Nations Inter-Agency Group for Child Mortality Estimation |
| **USA** | United States of America |

| | |
|---|---|
| **WASH** | water, sanitation and health |
| **WHO** | World Health Organization |

**Case fatality:** the proportion of individuals who die due to a specific disease among all individuals diagnosed with that disease over a given period.
*Source:* Harrington RA. Encyclopedia Britannica (https://www.britannica.com/science/case-fatality-rate).

**Early-onset neonatal sepsis:** onset of sepsis within the first 72 hours after birth.
*Source:* American Academy of Pediatrics. Group B streptococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book: 2018 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2018;762-68.

**Health care-associated infection (also referred to as "nosocomial" or "hospital infection"):** an infection occurring in a patient during the process of care in a hospital or other health care facility, which was not present or incubating at the time of admission. Health care-associated infections can also appear after discharge. They represent the most frequent adverse event associated with patient care.
*Source:* https://www.who.int/infection-prevention/publications/burden_hcai/en/.

**Health care-associated sepsis:** a case of infection leading to sepsis that is acquired in the healthcare setting, including intensive care units (ICUs); "ICU-associated" sepsis denotes a subset of infections/sepsis acquired during ICU stay. "Health care-associated" and "ICU-associated" are usually defined as disease onset occurring 48 to 72 hours after hospital and/or ICU admission, respectively.
*Source:* Markwart R, et al. Epidemiology and burden of sepsis acquired in hospitals and intensive care units: a systematic review and meta-analysis. Intensive Care Med. 2020;46(8):1536-51.

**Infant:**child aged 0 to 12 months of age.
*Source:* The Global Health Observatory. Number of infant deaths (thousands). Geneva: World Health Organization; 2020 (https://www.who.int/data/gho/data/indicators/indicator-details/ GHO/number-of-infant-deaths-(thousands)).
Intensive care unit: a specialized unit for the care of patients whose conditions are life-threatening and who require comprehensive care and constant monitoring.

**Late-onset neonatal sepsis:**onset of sepsis occurring 3 to 90 days after birth.
*Source:* American Academy of Pediatrics. Group B streptococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2018; 762-68.

**Low- and middle-income country:** WHO Member States are grouped into income groups (low, lower-middle, upper-middle and high) according to the World Bank analytical classification of economies calculated using the World Bank Atlas method and based on the gross national income per capita of each country.

**Maternal death:**death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or
aggravated by the pregnancy or its management, but not from accidental or incidental causes.

**Maternal near-miss case:** a woman who nearly died, but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy.

*Sources:* Nashef SA. What is a near miss? Lancet. 2003;361(9352):180-1.

Say L, Souza JP, Pattinson RC. Maternal near miss--towards a standard tool for monitoring quality of maternal health care. Best Pract Res Clin Obst Gynaecol. 2009;23(3):287-96.

**Maternal peripartum infection:** infection of the genital tract and surrounding tissues during labour and up to 42 days after birth.

**Maternal sepsis:** a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or the postpartum period. *Source:* Statement on maternal sepsis. Geneva: World Health Organiziation; 2017 (https://apps.who.int/iris/bitstream/handle/10665/254608/WHO-RHR-17.02-eng.pdf?sequence=1).

**Newborn/neonate:** a live child aged 0 to 28 days.
Possible serious bacterial infection: a clinical syndrome used in the WHO/UNICEF Integrated Management of Childhood Illness strategy package referring to a sick young infant who requires urgent referral to hospital. The signs include: not able to feed since birth or stopped feeding well (confirmed by observation); convulsions; fast breathing (60 breaths per minute or more) among infants less than 7 days old; severe chest in-drawing; fever (38 °C or greater); low body temperature (less than 35.5 °C); and movement only when stimulated or no movement at all.
*Source:* Managing possible serious bacterial infection in young infants when referral is not feasible: guidelines and WHO/UNICEF recommendations for implementation. Geneva: World Health Organization; 2015 (https://www.who.int/maternal_child_adolescent/documents/bacterial-infection-infants/en/).

**Sepsis:** life-threatening organ dysfunction caused by a dysregulated host response to infection. *Source:* Singer Met al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.

**Septic shock:** a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. *Source:* Singer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.

**Severe maternal outcomes:** organ

system dysfunction defined as maternal near-miss cases or maternal death

*Sources:* Pattinson R, et al. WHO maternal death and near-miss classifications. Bull World Health Organ. 2009;87(10):734.
Say L, Souza JP, Pattinson RC. Maternal near miss--towards a standard tool for monitoring quality of maternal health care. Best Pract Res Clin Obst Gynaecol. 2009;23(3):287-96.

**Severe sepsis:**sepsis complicated by organ dysfunction, used in previous sepsis definitions (Sepsis-1 and -2) and no longer used in the current sepsis definition (Sepsis-3).
*Sources:* Bone RC, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644-55. Levy MM, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31(4):1250-6.

**Systemic inflammatory response syndrome:**exaggerated defence response of the body to a noxious stressor (infection, trauma, surgery, acute inflammation, ischemia or reperfusion, or malignancy) to localize and then eliminate the endogenous or exogenous source of the insult.
*Source:* Chakraborty RK, Burns B. Systemic inflammatory response syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020 (https://www.ncbi.nlm.nih.gov/books/NBK547669/).

**Sociodemographic index:** a summary measure that identifies where countries or other geographical areas sit on the spectrum of development. Expressed on a scale of 0 to 1, the index is a composite average of the rankings of incomes per capita, average educational attainment and fertility rates.
*Source:* Socio-demographic index. Seattle (WA): Institute for Health Metrics and Evaluation (http://www.healthdata.org/taxonomy/glossary/socio-demographic-index-sdi).

**Universal health coverage:** ensuring that all people have access to needed health services (including prevention, promotion, treatment, rehabilitation and palliation) of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship.

**Vertical transmission:**the passage of an infectious agent (pathogen) from mother to baby during the period before (antenatal) birth, weeks immediately prior to or after birth (perinatal), or the period after birth (postnatal).

**Vital registration:** an administrative system used by governments to record vital events, such as live births, deaths (including fetal deaths), marriages and divorces that occur in the population. Young infant: child aged 0 to 59 days (2 months).
*Source:* Managing possible serious bacterial infection in young infants when referral is not feasible: Guidelines and WHO/UNICEF recommendations for implementation. Geneva: World Health Organization; 2015 (https://www.who.int/maternal_child_adolescent/documents/bacterial-infection-infants/en/).

Sepsis is a preventable, life-threatening condition marked by severe organ dysfunction. For 2017, it was estimated that it had affected 49 million individuals and was related to approximately 11 million potentially avoidable deaths worldwide. Sepsis mortality is often related to suboptimal quality of care, an inadequate health infrastructure, poor infection prevention measures in place, late diagnosis, and inappropriate clinical management. Antimicrobial resistance further complicates sepsis management across all settings, particularly in high-risk populations, such as neonates and patients in intensive care units (ICUs). While primary infections have remained the leading cause of sepsis and sepsis-related mortality over the last three decades, there has been a marked increase in the proportion of sepsis incidence and mortality linked to injuries and non-communicable diseases. Moreover, survivors of sepsis face serious long-term health consequences in the form of increased post-discharge mortality, physical and cognitive impairment, and mental health disorders. Unfortunately, high-quality epidemiological data on the burden of sepsis are limited by inconsistent and variable diagnostic criteria, few prospective studies, and suboptimal administrative data and hospital discharge coding.

Sepsis is undeniably a serious worldwide health threat. However, while sepsis affects individuals of any sex and of any age, there are significant disparities in the burden of disease. As can be expected, sepsis disproportionately affects vulnerable populations such as pregnant and recently-pregnant women, neonates, young children, older persons, individuals with underlying chronic conditions, and the immunocompromised. Furthermore, much of the burden of sepsis,



both incidence and mortality, is in low- and middle-income countries (LMICs). This report will focus on current epidemiological sepsis research, in particular work conducted by WHO on maternal and neonatal sepsis, adult sepsis, and sepsis acquired in hospitals and ICUs.

In 2017, almost half (20 million) of all estimated sepsis cases worldwide occurred in children under 5 years of age. In 2018, an estimated 15% of all neonatal deaths globally were due to sepsis. Studies have shown that the highest incidence of neonatal sepsis occurs in pre-term and low-birth-weight infants. However, the overall incidence of neonatal sepsis is highest in low-income countries. While survival of pre-term infants is improving over time, neonates are particularly vulnerable to sepsis caused by health care-associated infections, especially in settings with low health care resources where the rates are highest.

Obstetric infections, which include complications following abortion, are the third most common cause of maternal mortality. Globally, it is estimated that for every 1000 women giving birth, 11 women experience infection-related, severe organ dysfunction or death. Similar to the neonatal population, maternal sepsis morbidity and mortality are highest in LMICs. For example, data from a prospective observational study showed that rates of

infection-related, severe maternal outcomes represented 12 to 15 per 1000 live births in LMICs compared to 0.6 per 1000 live births in high-income countries.

One in four cases of sepsis in hospitals and one in two cases of sepsis in ICUs result from health care-associated infections. For every 1000 hospitalized patients, an estimated 15 patients will develop sepsis as a complication of receiving health care. Of note, a population-based cohort study showed that sepsis rates were more than seven times higher among the hospitalized neonatal population. Mortality estimates for health care-associated sepsis in hospitalized adult patients range from 20% to 30%. In addition, health care-associated sepsis has also been associated with longer hospital stay and higher antimicrobial resistance rates than community-acquired sepsis. Importantly, more than half of all cases of health care-associated sepsis are preventable through appropriate infection prevention and control (IPC) measures.

Understanding the true burden of sepsis is complicated by many factors. Most of the available epidemiological data rely on systematic reviews of observational studies. Furthermore, there is a severe lack of population-based sepsis data globally, especially from LMICs, which makes it difficult to estimate the true burden of sepsis. Few prospective studies inform available estimates and most rely on hospital administrative data and International Classification of Diseases discharge coding, which is prone to bias and limited by the heterogeneity in documentation and thus data quality. Even where high-quality data exist, inconsistent and variable diagnostic criteria cause difficulties with data capture and comparison, thus greatly limiting generalizability and comparability. Furthermore, available studies rarely measure community-based events, morbidity and long-term outcomes, thereby underestimating the true burden of disease. Finally, there are few global surveillance systems in place, again making it difficult to accurately measure sepsis incidence and mortality.

The way forward to bridge these gaps involves a systematic approach to standardizing the case definition of sepsis, in particular for high-risk populations (for example, neonates), and ensuring that the definition is relevant in all settings across all resource levels. Improved, robust study designs and high-quality data collection are essential, notably in LMICs where data are lacking and sepsis incidence and mortality are highest. Sepsis surveillance is of vital importance and can be achieved by leveraging existing programmes and networks. Linking available data – clinical, diagnostic and microbiological – strengthens not only sepsis surveillance, but also IPC practices and clinical management. Rapid, affordable and appropriate diagnostic tools, particularly for primary and secondary levels of care, are needed to improve sepsis identification, surveillance, prevention and treatment. It is only through a concerted, global effort to scale-up advocacy, funding and the research capacity for the generation of epidemiological evidence that we can gain a true insight into the burden of sepsis, improve evidence-based clinical management, and affect sustainable improvement in short- and long-term outcomes among those most at need.

# 1

## Part 1. Introduction and background

The concept and the understanding of “sepsis” has evolved over time as the medical knowledge of sepsis pathophysiology, aetiological factors, and clinical progression have increased and improved. The first consensus definition of sepsis, Sepsis-1, developed in 1991, was based on systemic inflammatory response syndrome (SIRS) criteria in response to infection and defined sepsis according to severity, that is, sepsis, severe sepsis and septic shock *(1)*. Although the term “severe sepsis” was used to describe sepsis complicated by organ dysfunction, the Sepsis-1 definition did not state what constituted organ dysfunction. The Sepsis-1 definition was subsequently revised in 2001 (Sepsis-2) and the term “severe sepsis” became “sepsis complicated by organ dysfunction”. Furthermore, Sepsis-2 produced an expanded list of symptoms, signs and laboratory values that could indicate sepsis in the presence of infection and suggested that scoring systems (for example, the multiple organ dysfunction syndrome and the Sequential Organ Failure Assessment [SOFA] score) could be used to define organ dysfunction



*(2)*. Nevertheless, there was little discernible difference between the Sepsis-1 and -2 definitions as signs, symptoms and/or laboratory values defined by the Sepsis-2 definition were considered too ambiguous. The most recent definition of sepsis, , was developed in 2016 and defines sepsis as *“life-threatening organ dysfunction caused by a dysregulated host response to infection”*, where organ dysfunction is identified as an acute increase in the total SOFA score of two or more due to infection *(3)*. This updated consensus definition has improved specificity compared with previous definitions and is the definition used throughout this text to describe sepsis, unless specified otherwise.

A recent global study reported 49 million cases and 11 million sepsis-related deaths in 2017, accounting for approximately 20% of all annual deaths globally *(4).* While sepsis can affect any individual worldwide, significant regional disparities in incidence and mortality exist with the highest rates in lower-middle-income countries (LMICs). Furthermore, sepsis is costly and the average hospital-wide cost of sepsis was estimated to be more than US$ 32 000 per patient, although these estimates were based almost exclusively on data from high-income countries (HICs) *(5)*.

Given that it significantly contributes to preventable mortality, combating sepsis is an integral part of realizing the Sustainable Development Goals (SDGs) targets 3.1 and 3.2 relating to maternal, neonatal, and child mortality *(6)*, as well as target 3.3 on infectious diseases. Indirectly, sepsis is relevant to other targets in SDG 3, such as 3.8 on quality of care for all, and its
prevention and management is inherently linked with vaccination, efforts to combat antimicrobial

resistance (AMR) *(7)*, universal health coverage (UHC)[1], capacity to comply with the International Health Regulations (IHR 2005) *(8)*, health emergency preparedness, IPC[2], and water, sanitation and hygiene (WASH) standards[3]. Recently, it has become clear that sepsis can be a significant complication of injuries and non-communicable diseases (NCDs) *(4)*, providing yet another key connection between sepsis and SDG 3.


To support the implementation of this resolution, WHO conducted original research, gathered available evidence on the epidemiology and burden of sepsis worldwide, and established a technical advisory group of international experts. Through this work, WHO facilitated discussions and consensus on the current status of sepsis epidemiology research and the limitations inherent to the methods currently used to identify sepsis morbidity and mortality. Experts were also asked to identify approaches to achieve a better standardization of sepsis epidemiology research and define future directions and priorities in this field to close existing gaps. In this first WHO Global report on the epidemiology and burden of sepsis, we highlight the public health impact of sepsis, with a focus on specific populations – neonates, pregnant

and recently-pregnant women, and patients seeking health care – and propose future directions for sepsis epidemiology research.

[1]Universal health coverage (https://www.who.int/health-topics/universal-health-coverage#tab=tab_1, accessed 12 August 2020).
[2]How to prevent sepsis. The role you can play in health care and communities (https://www.who.int/infection-prevention/campaigns/clean-hands/Sepsis_ infographic_A2_EN_PRINT.pdf?ua=1, accessed 21 August 2020).
[3]Water, sanitation and hygiene (WASH) (https://www.who.int/health-topics/water-sanitation-and-hygiene-wash, accessed 12 August 2020).

# 2

# Part 2. Available evidence on global sepsis epidemiology

## 2.1 Global estimates of sepsis



**Box 2.1**
**estimates of sepsis**

-

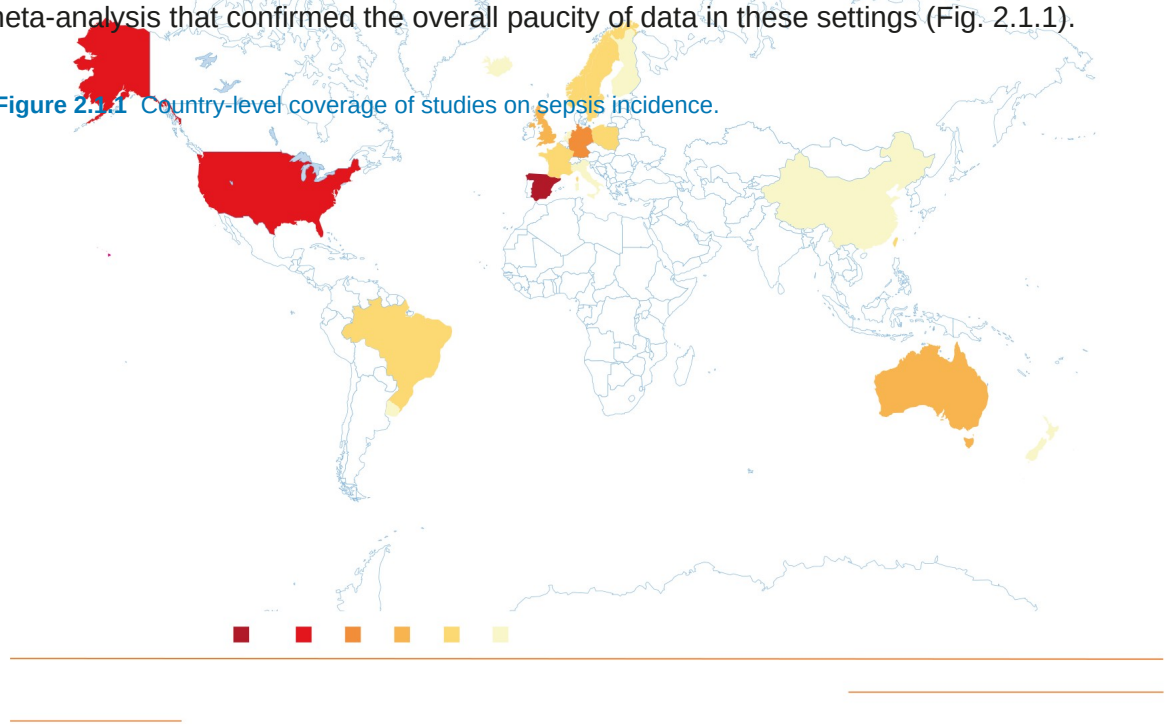
This section describes global estimates of sepsis morbidity and mortality derived from different publications that are mainly of two kinds, that is, recently-published systematic reviews of the literature and the Global Burden of Disease (GBD) analysis on the burden of sepsis in 2017.

It is important to note that major methodological differences hamper the comparability of the estimates from the GBD sepsis study and results of meta-analyses of population-level epidemiological studies.

A 2016 systematic review of the literature *(10)* extrapolated HIC data (no published population-based data were available for LMICs) and estimated 19 million cases of sepsis1

(148 per 100 000 person-years) and 5 million sepsis-related deaths every year in adult patients worldwide. To address the lack of LMIC representation and optimize the inclusion of studies from LMICs, WHO undertook an updated and targeted systematic review and meta-analysis that confirmed the overall paucity of data in these settings (Fig. 2.1.1).

**Figure 2.1.1** Country-level coverage of studies on sepsis incidence.




**Source:** Reproduced from reference *(11)*. Published under the CC BY 4.0 licence (https://creativecommons.org/ licenses/by/4.0/).

The **updated review published in 2020** and based on 51 studies, mostly from HICs (n=46; Fig. 2.1.1), estimated a pooled incidence of 189 hospital-treated adult sepsis cases per 100 000 person-years and a mortality of 26.7% *(11)*.

Sepsis incidence and mortality (deaths per sepsis cases) estimates were not significantly different between WHO regions. However, overall and region-specific estimates should be interpreted with caution, given the limited representation of data from LMICs. The 2020 literature review also focused on the burden of sepsis treated in ICUs, which was estimated to be 58 cases per 100 000 person-years. In-hospital mortality was estimated to be more than one-third (42%) of ICU-treated sepsis patients. There were significant regional differences in both the incidence of and mortality associated with ICU-treated sepsis (Table 1). Of note, these estimates should be interpreted with caution given the limited data.

**Hospital-treated sepsis in adults**

[1]Original publication reported results using Sepsis-2 definitions of sepsis: 31 million sepsis cases, including 19 million cases of sepsis with organ dysfunction.

**Table 1** Summary findings of the systematic review and

| ons | Incidence per 100.000 | Mortality |
|---|---|---|
| er of studies | po | |
| | | |
| | | |
| **Hospital-treated sepsis** | | |
| All regions (AMR, EUR, WPR; n= 28/22) | 189 [133, 267] | 26.7 [22.9, 30.7] |
| AMR (n= 9/6) | 124 [ 78, 197] | 30.1 [25.1, 35.6] |
| EUR (n= 13/12) | 289 [166, 504] | 22.1 [16.7, 28.7] |
| WPR (n= 6/4) | 245 [124, 485] | 24.3 [17.2, 33.1] |
| **ICU-treated sepsis** | | |
| All regions (AFR, AMR, EUR, WPR; n= 34/19) | 58 [42, 81] | 41.9 [36.2, 47.7] |
| AFR (n= 1/1) | 52 [39, 71] | 40.4 [34.9, 46.2] |
| AMR (n= 5/4) | 2 [ 0, 6] | 76.0 [58.5, 87.7] |
| EUR (n= 21/11) | 139 [75, 256] | 42.7 [33.7, 52.2] |
| WPR (n= 7/3) | 72 [43, 120] | 34.6 [25.4, 45.2] |

**Note:** numbers in brackets represent 95% confidence intervals. This table has been produced by WHO based on data included in reference *11*.

ICU: intensive care unit; AFR: African Region; AMR: Region of the Americas; EUR: European Region; WPR: Western Pacific Region.

Part 2. Available evidence on global sepsis epidemiology

Moreover, the review showed an increase in recent years in the number of observed sepsis cases (276 per 100 000 person-years in the past decade, representing a 46% increase compared to the overall time period), with a slightly higher in-hospital mortality (27.4%). Potential drivers of the increase in overall sepsis incidence include aging and an improved survival of persons with underlying

chronic conditions *(12)*, which result in the use of immunosuppressive medication, invasive treatments and intensive care. A possible additional explanation for an observed increase in the number of reported sepsis cases is improved access to hospital care for hospital-treated sepsis. Increased attention to sepsis reporting and a more sensitive coding of sepsis in hospital records may also have significantly contributed to the observed increase in the incidence rate. However, there are a number of reports suggesting that the true burden of sepsis is underestimated by studies that rely solely on administrative data and International Classification of Diseases (ICD). Indeed, several patient record-based studies suggest that only 15% to 50% of patients with sepsis are correctly coded using the ICD system *(13-16)*.

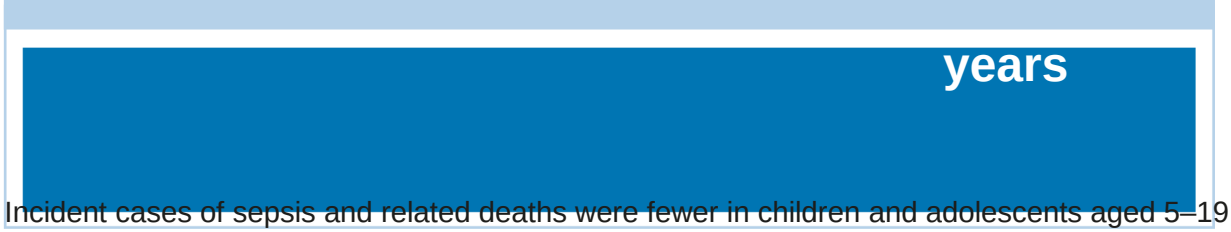
While these numbers are staggering, a recent publication on the global burden of sepsis across all patient populations based on a death records' analysis by the **GBD sepsis study** estimated even more shocking numbers: 48.9 million cases of sepsis and 11 million sepsis-related deaths worldwide in 2017, accounting for almost 20% of all global deaths *(4)*.

**Sepsis worldwide in 2017**

Based on modelling of adult and child death certificate data, the study presented estimations for all countries, including LMICs where evidence from the literature was lacking. This study found that between 1990 and 2017, age-standardized sepsis incidence fell by 37% and overall sepsis-related mortality decreased by by 53%. These findings are different from the results of the above-mentioned 2020 systematic review which reported increasing trends. One of the reasons for this difference might be attributable to the modelling assumptions and imputation steps in the GBD sepsis study as the model inputs were derived from the multiple cause of death data from four countries and hospital data from 10 countries, which were high- and middle-income only; data were subsequently extrapolated to low-income countries. Therefore, global longitudinal trends might be unreliable as improvements in the burden of sepsis in one country used as a primary data source would project these benefits to other countries for which data are unavailable. On the other hand, the 2020 systematic review includes considerable heterogeneity between studies that may be due to differences in sepsis definitions, study designs, sampling strategies and study settings. Moreover, variations in the considered time periods and the potential changes in incidence rates and mortality rates over time causes between-study variance. These limitations, together with other intrinsic ones, such as publication bias, hampers any extrapolation, comparability and generalizability of results, including assessment for time trends of sepsis.

## Age and sex-specific burden of sepsis and risk factors

The GBD sepsis study highlighted significant differences in sepsis cases and mortality across age groups, sex and regions in 2017. Sepsis incidence was biphasic; it peaked in early childhood and again in elderly adults. The study estimated that 41.5% (20.3 million) of incident sepsis cases and 26.4% (2.9 million) deaths related to sepsis worldwide were among children younger than five years.

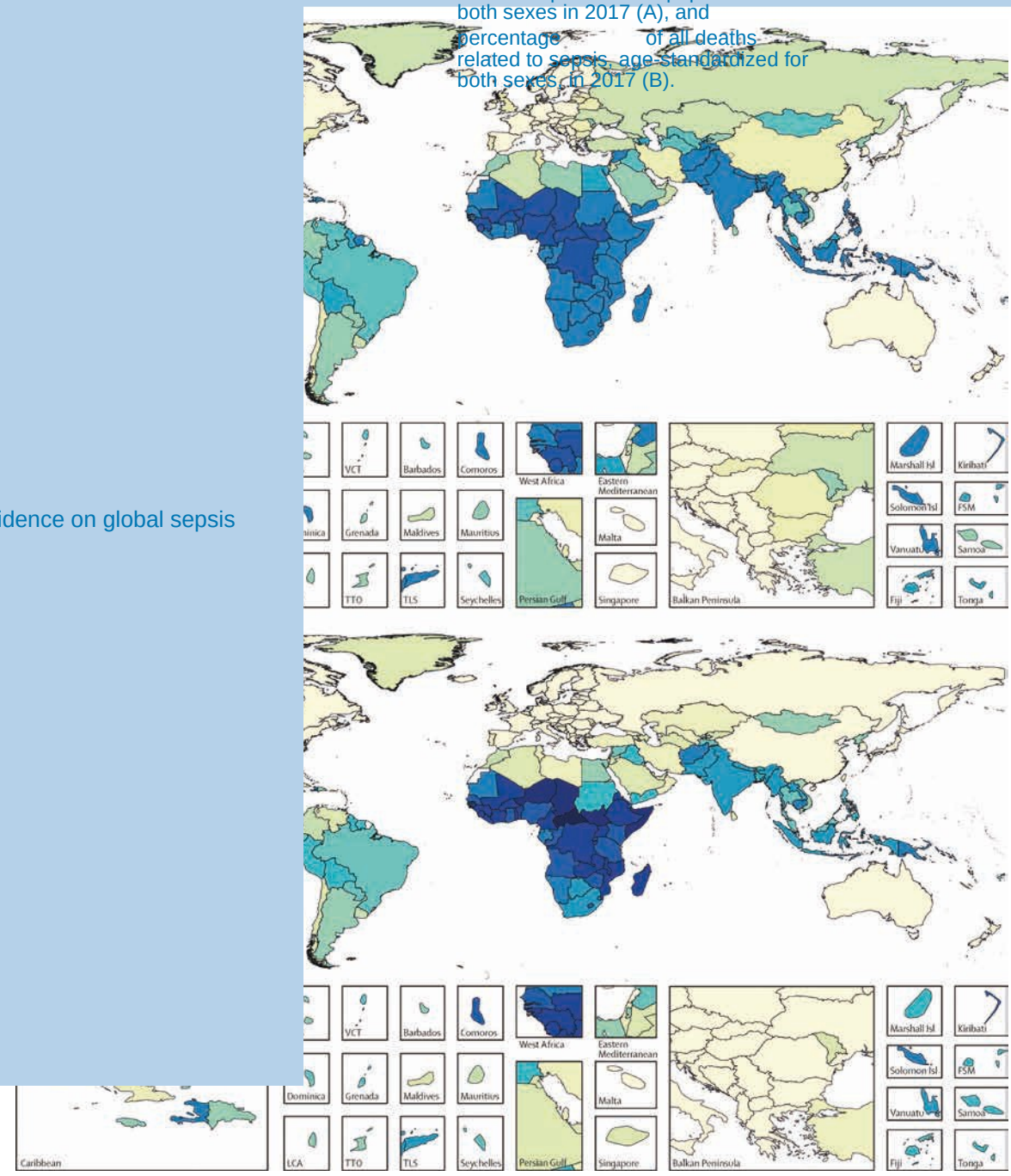



Incident cases of sepsis and related deaths were fewer in children and adolescents aged 5–19 years, 10% (4.9 million) and 4.1% (0.45 million), respectively. Most incident sepsis cases (48.5% [23.7 million]) and related deaths (70% [7.7 million]) were among adults 20 years and older. Global sepsis incidence was higher among women than men (717 vs. 643 cases per

100 000), but sepsis-related mortality was higher among men (164 vs. 134 per 100 000, respectively). Furthermore, gross regional and economic disparities were found: 85.0% of sepsis cases and 84.8% of related deaths worldwide occurred in countries with low, low-middle, or middle sociodemographic indices (SDI), particularly in sub-Saharan Africa and South-East Asia *(4)* (Fig. 2.1.2).

**Sepsis regional and economic disparities**

**Fig. 2.1.2** Age-standardized sepsis incidence per 100 000 population for both sexes in 2017 (A), and percentage of all deaths related to sepsis, age-standardized for both sexes, in 2017 (B).




**Source:** Reproduced from reference *(4)*. Published under the CC BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/).

In addition, the GBD sepsis study found that two-thirds of sepsis cases in 2017 occurred in patients with an underlying infectious cause of health loss, while the remaining cases were infections that occurred secondary to underlying injuries or chronic disease. Diarrhoeal

**Sepsis contributors (2017)**

**:**
ses of

aths due to

diseases were the largest contributors to sepsis and accounted for 9.2 (in 2017) to 15 million annual cases (in 1990), whereas lower respiratory infections caused the largest number of sepsis-related deaths (1.8 to 2.8 million annually in 2017 and 1990, respectively) *(4)*.

While infections have remained the leading primary cause of sepsis and sepsis-related mortality worldwide across all ages over the last three decades (Fig. 2.1.3), there has been a marked increase in sepsis incidence and mortality secondary to injuries and NCDs, which were linked in 2017 to nearly one-half of all sepsis-related deaths. In 2017, injuries due to road traffic accidents were the most common type of injury contributing to both sepsis incidence and sepsis-related deaths, whi-le maternal and neonatal disorders were the most common NCDs that contributed to the sepsis burden. The cause of sepsis-related deaths also varied by region: most deaths were attributable to infections in countries with a low SDI compared to underlying NCDs in high SDI countries.

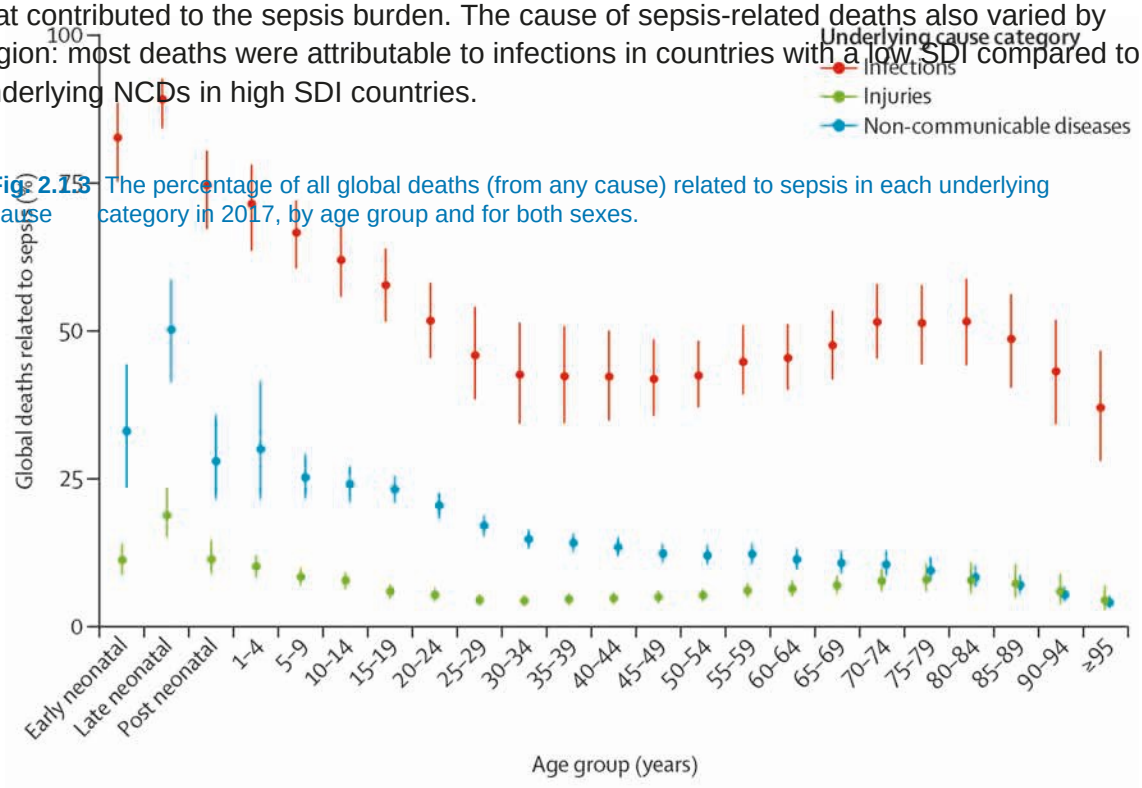



**Fig. 2.1.3** The percentage of all global deaths (from any cause) related to sepsis in each underlying cause category in 2017, by age group and for both sexes.

**Note:** Bars represent 95% uncertainty intervals.
**Source:** Reproduced from reference *(4)*. Published under the CC BY 4.0 licence (https://creativecommons.org/ licenses/by/4.0/).

## Short and long-term consequences of sepsis

Sepsis is a potentially life-altering illness and can cause severe morbidities and sequelae, even in those who survive, as highlighted in Fig. 2.1.4. Among those who survive, approximately one-half recover completely, while one-third die within a year, with one-half of these deaths as a direct complication from the previous acute sepsis episode *(17, 18)*. One-sixth of sepsis survivors experience significant morbidity, such as functional limitations (for example, inability to bathe or dress independently), moderate-to-severe cognitive impairment, and/or increased mental health disorders *(19, 20)*. An estimated 40% of sepsis patients are re-hospitalized within 90 days of discharge *(21)*, which increases the burden of sepsis not only on the individual, but also on the health care system and society. Post-discharge sepsis complications are associated with a worse pre-illness health status, infection severity and

quality of hospital care *(22, 23)*. While some guidelines for the prevention of sepsis morbidity exist, such as delirium monitoring and early mobility, there are limited data worldwide regarding the best approaches for minimizing disability due to sepsis, as well as improving long-term outcomes *(22)*.

## Sepsis survivors

**One third**

**die within one year**

**One sixth**

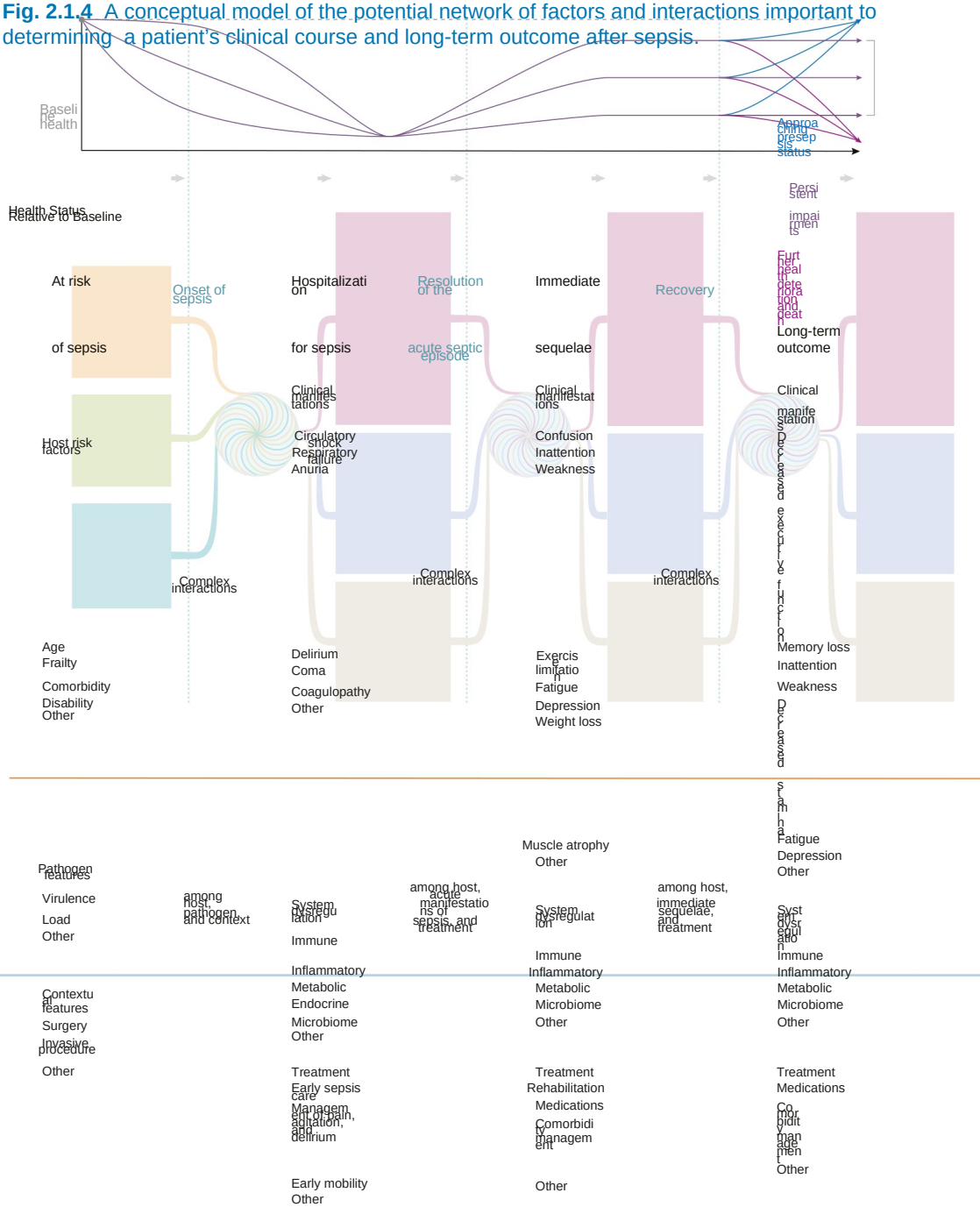
**experience significant morbidity,**

**40**

**re-hospitalized within 90 days**

## limitations

**Fig. 2.1.4** A conceptual model of the potential network of factors and interactions important to determining a patient's clinical course and long-term outcome after sepsis.




**Note:** There are many potential clinical courses that a patient may experience after a hospitalization for sepsis, ranging from rapid complete recovery to recurrent complications and death. This figure depicts examples of common clinical trajectories and presents a conceptual model of factors important to changing a patient's clinical course and long-term outcome. This illustration draws from the Wilson-Cleary model (24),

which links underlying biological factors to physical function and quality of life, but extends the representation of the biologi-cal factors to demonstrate their complex and immeasurable interactions.
**Source:** Reproduced with permission from reference *(22)*.

## Sepsis and antimicrobial resistance

Sepsis is a major driver of broad-spectrum antibiotic use and therefore contributes to the emerging global threat of AMR. In turn, AMR negatively affects individuals with sepsis and contributes to the progression of infection to sepsis by decreasing the effectiveness of available antimicrobial therapy. Global efforts to tackle the threat of AMR have been discussed at the highest level, including the World Health Assemblies in 2014 *(25)*, 2015 and 2019 *(26)*, as well as the United Nations General Assembly in 2016 *(27)*. In 2015, WHO established the Global Antimicrobial Resistance Surveillance System (GLASS) to improve the quality and quantity of

data on the epidemiology of AMR and help inform health policy decision-making. GLASS aims to provide the capacity to monitor AMR trends, produce reliable and comparable data and inform antimicrobial treatment options. As of February 2020, 88 Member States have been participating in GLASS, including 55 LMICs and 21 sub-Saharan countries. During the 2019 data call, 66 countries submitted AMR data, contributing to the global effort to report antimicrobial-resistant infections that can lead to sepsis. The main findings of the 2020 GLASS report *(28)* show that in many countries rates of AMR are very high among bacteria that frequently cause serious infections in either community or health care settings. For example, reported median resistance to third-generation cephalosporins in bloodstream infections due to *Klebsiella pneumoniae* was 57.6%, with 12 countries reporting 80% to 100% resistance.

***Klebsiella pneumoniae* resistant to third-generation cephalosporins in bloodstream infections globally in 2018**

LMICs: low- and middle-income countries; MDROs: multidrug-resistant organisms.

For the same organism, median resistance to carbapenems was 17% (interquartile range, 0.7–26.8). Another example is the high median resistance rates of *Acinetobacter* spp., a common cause of hospital infections: 41.2% and 63.2% of isolates were resistant to aminoglycosides and carbapenems respectively, with some countries already reporting 90% to 100% resistance. A new SDG indicator to monitor AMR was introduced in 2019, that is, frequencies of bloodstream infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli* resistant to third-generation cephalosporins. While the data are still not nationally representative, the global median rate reported for MRSA was 12.11% (interquartile range, 6.4–26.4) and 36.0% (interquartile range, 15.2–63.0) for *E. coli* resistant to third-generation cephalosporins.

In 2014, WHO also conducted a global survey on the prevalence of multidrug-resistant organisms (MDROs) in routine clinical specimens of patients admitted to a diverse range of health care facilities *(29)*. The study covered 420 laboratories in 67 countries and identified a high prevalence of MDROs often responsible for bloodstream infections in hospitalized patients, such as MRSA, vancomycin-resistant enterococci, extended-spectrum beta-lactamase (ESBL)-producing and/or carbapenem-resistant Enterobacteriaceae, and multiresistant *Acinetobacter* spp in blood cultures. Of note, an association between country income level and the risk of detecting these MDROs from blood cultures was established through multivariate analysis, with the prevalence of MDROs significantly higher in LMICs.

## Paediatric sepsis

Paediatric sepsis is a distinct entity from adult and neonatal sepsis, given the unique characteristics of children and the differences in sepsis aetiology, and is defined based on SIRS and age-specific criteria (*30)*. The largest, global paediatric point prevalence study to date (2013-2014) estimated a prevalence of 8.2% severe sepsis (comparable to the current adult definition of sepsis) *(31)* in children aged less than 18 years admitted to ICUs across 126 countries (primarily in North America [n=59] and Europe [n=39]). This study estimated 25% hospital mortality, without any significant difference by age or country income level, and 17% moderate-to-severe disability

among sepsis survivors. Of note, these results should be interpreted with caution as, globally, most paediatric sepsis patients do not have access to ICUs and would not be represented in this study.

However, the GBD sepsis study *(4)* provided global estimates of paediatric sepsis and highlighted the significant burden in LMICs. Over one-half of all global sepsis cases occurred among adolescents and children, many of them neonates, and sepsis incidence and mortality in children under one year of age was exceptionally high *(4)*.

**In 2017, there were an estimated 20 million cases of sepsis**

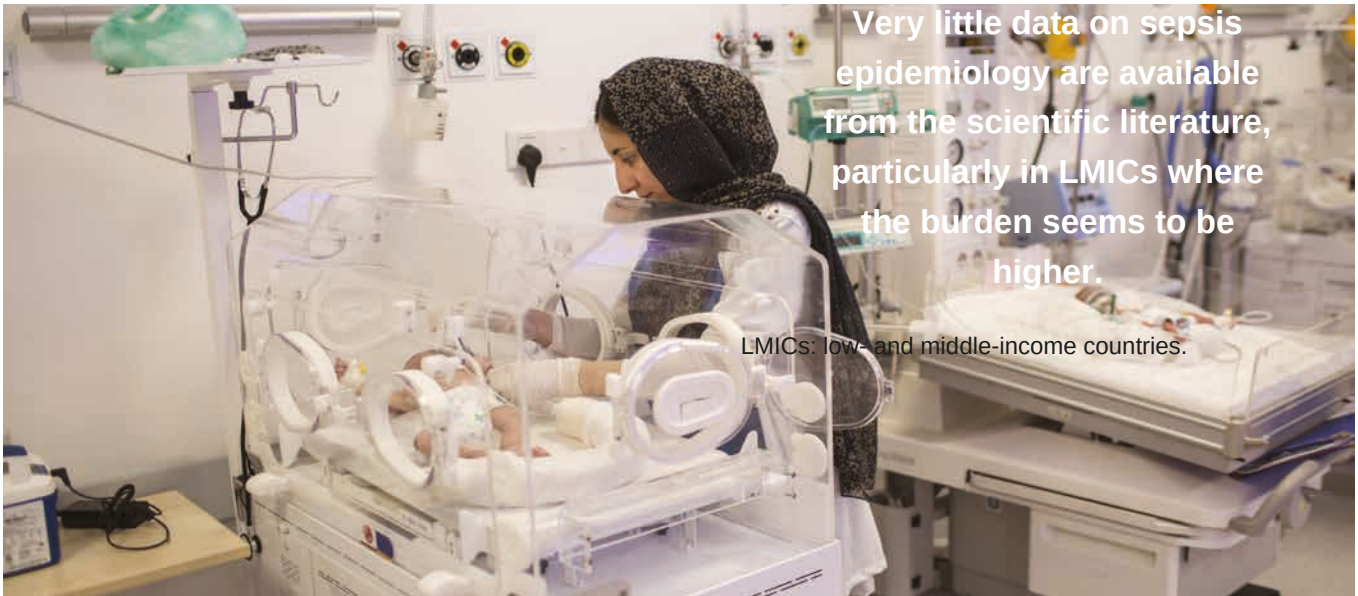
The three most common causes of sepsis-related deaths among children were infections related



to neonatal disorders (for example, preterm birth, encephalopathy, haemolytic disease), lower respiratory infections and diarrhoeal diseases *(4)*.

Two conclusions can be drawn from this epidemiological snapshot of the global sepsis burden.

First, reviews have shown that very little data on sepsis epidemiology are available from the scientific literature, particularly in LMICs where the burden seems to be higher.



**Very little data on sepsis epidemiology are available from the scientific literature, particularly in LMICs where the burden seems to be higher.**

LMICs: low- and middle-income countries.

It is therefore critical to address gaps in data availability and research globally, particularly in LMICs. Second, while some estimates seem to show an increasing trend in sepsis incidence and mortality in recent decades, other estimates clearly point towards a decreasing number of cases of sepsis and related deaths. Nevertheless, all findings point towards substantial differences by age, sex, region, and underlying cause. Addressing these disparities requires decisive, urgent action by national and global policy-makers, as well as clinicians, researchers and hospital administrators.

## 2.2 Global estimates of neonatal sepsis

### Box 2.2 Key global estimates of neonatal sepsis

- Severe neonatal infections, including sepsis, represent a significant cause of neonatal mortality and long-term morbidity.
- There are an estimated 1.3 to 3.9 million annual neonatal sepsis cases and 400 000 to 700 000 annual deaths worldwide, depending on the study.
- Among hospital-born infants, hospital-acquired infections account for an estimated 4% to 56% of all deaths in the neonatal period, depending on the study and geographical area.
- An estimated 84% of neonatal deaths due to infections could be prevented through measures such as early diagnosis and timely, appropriate clinical management.
- The highest neonatal sepsis incidence rates are in LMICs, particularly in the African region.
- The WHO clinical classification of ‘possible serious bacterial infection’ has helped to obtain data on serious infections, including sepsis, from settings with a limited diagnostic capacity.

- Group B *Streptococcus* and *E. coli* infections account for 70% of early-onset neonatal sepsis.

LMIC: low- and middle-income country.

This section describes available estimates of the sepsis burden in neonates collected through global mortality surveillance systems, surveillance in limited geographical areas, systematic reviews of the literature and specific studies aiming at improving the clinical management of neonatal sepsis. It is important to note that major methodological differences hamper the generalizability and comparability of these estimates.

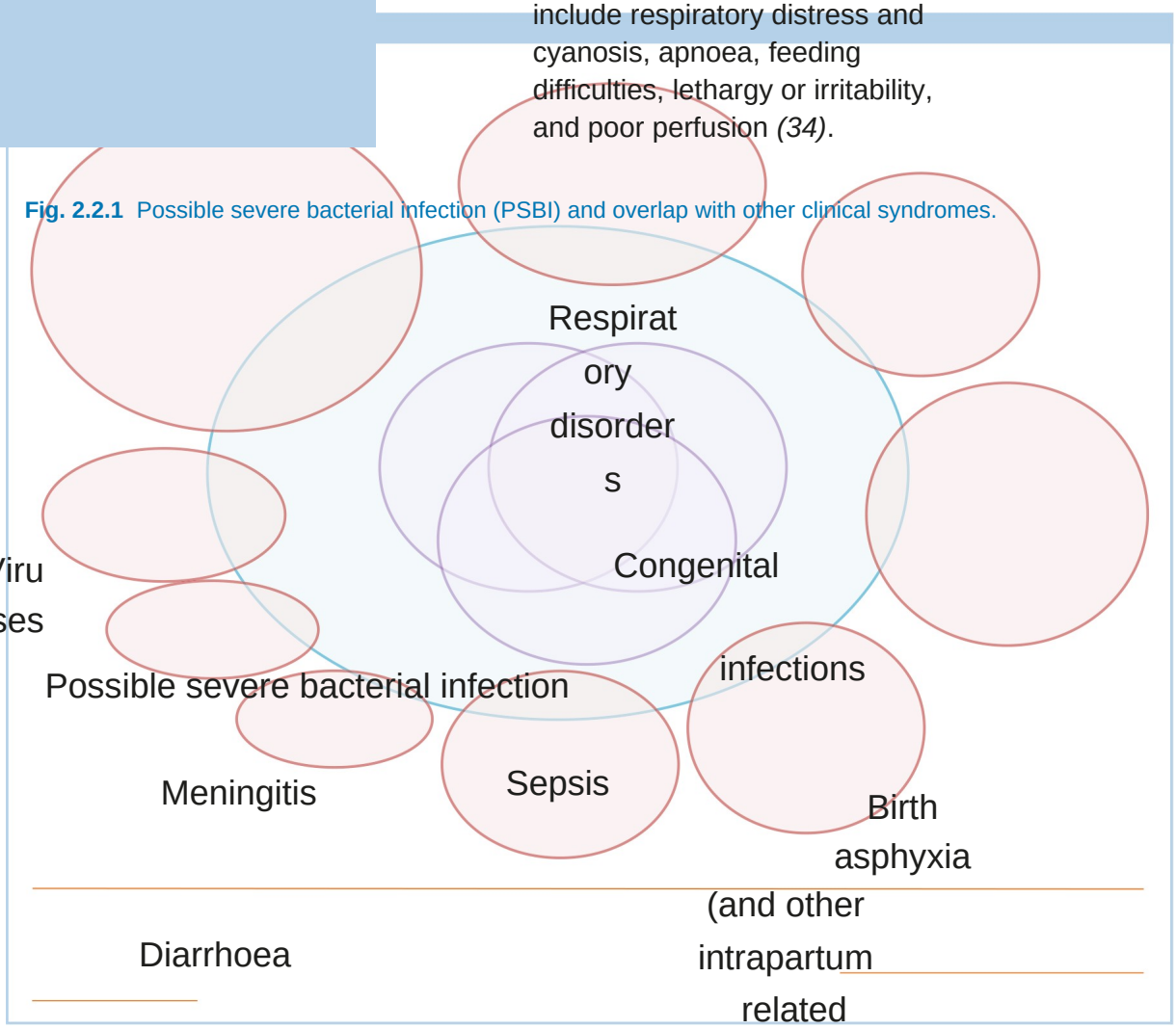
The first 28 days of life (the neonatal period) are the most vulnerable time for child survival. Every year, an estimated 2.5 million neonates die in their first month of life, accounting for nearly one-half of deaths in children under 5 years of age, according to estimates from the United Nations Inter-Agency Group for Child Mortality Estimation (UN IGME) *(32)*. Severe neonatal infections (including sepsis, meningitis and pneumonia) represent a significant cause of neonatal mortality (24%) *(32)* and cause short- and long-term complications, such as preterm birth and neonatal encephalopathy *(33)*.

### Mortality due to severe neonatal infections

An estimated 375 000 neonatal deaths due to sepsis occurred globally in 2018, which represented 15% of all neonatal deaths, according to data from the UN IGME and modelled by the WHO and the Maternal and Child Epidemiology Estimation Group (MCEE) *(32)*. The prognosis of neonatal sepsis depends on early recognition and appropriate treatment, although signs and symptoms are often nonspecific and may overlap with those of other severe conditions, such

as meningitis and pneumonia (Fig. 2.2.1). These clinical signs include respiratory distress and cyanosis, apnoea, feeding difficulties, lethargy or irritability, and poor perfusion *(34)*.

**Fig. 2.2.1** Possible severe bacterial infection (PSBI) and overlap with other clinical syndromes.



o
n

Tetanus

Skin infecti ons

Congenital heart disease

**Note:** PSBI is a clinical syndrome used in the Integrated Management of Childhood Illness package and refers to a sick young infant who requires urgent referral to hospital.
**Source:** Reproduced from reference *(35)*. Published under the CC BY 4.0 licence (https://creativecommons.org/ licenses/by/4.0/).

To help guide clinical management of serious infections (mainly pneumonia, sepsis and meningitis) in neonates and young infants, WHO has proposed a clinical classification of 'possible serious bacterial infection' (PSBI) for infants 0 to 59 days of age, which has helped to obtain data on serious infections, including sepsis, from settings with limited diagnostic capacity *(36)*. An estimated 6.9 million cases of PSBI occurred in 2012 in neonates with a case fatality risk of 9.8% *(35)*. Neonatal sepsis accounted for an estimated 25% (95% confidence interval, 16–34) of PSBI cases *(37)*.

**Neonatal sepsis and PSBI cases**

PSBI: possible serious bacterial infection.

Secondary analysis of two large community-based studies coordinated by WHO (African Neonatal Sepsis Trial [AFRINEST] *(38, 39)*) found that among 84 759 live births under observation in Asia and Africa, 11 089 infants (13.1%) had at least one episode of infection and 237 (2.1%) died. The cumulative incidence rate of any sign of infection was 21 per 1000 infants. It was observed that signs of systemic infection (invasive and more severe infection) were more common in the

first week of life and then substantially reducing thereafter (WHO unpublished data). In another community-based study coordinated by WHO (Simplified Antibiotic Therapy Trial [SATT] *(40, 41)*), the cumulative incidence rate of PSBI in young infants up to two months of age ranged from 4.2% to 6.7% (SATT Bangladesh, SATT Pakistan studies). Finally, a community-based cohort evaluating the implementation of WHO PSBI guidelines between 2016 and 2019, 10% of approximately 87 000 young infants (0 to 59 days of age) in 6 countries (Democratic Republic of Congo, Ethiopia, India, Malawi, Nigeria and Pakistan) were reported to have signs of PSBI *(42)*. African sites reported a higher prevalence (11%) compared to Asian sites (8%). The 2016/2017 GBD study estimated 1.3 million annual incident cases of neonatal sepsis and infection using an extensive body of evidence comprising a literature search, survey and surveillance data, hospital records and claims data *(43)*.

A recently-updated and expanded systematic review and meta-analyses *(44)* of epidemiological studies on neonatal sepsis commissioned by WHO performed a search of the published literature between January 1979 to May 2019 and reported an estimated 3.9 million annual neonatal sepsis cases (2824 per 100 000 live births) and 689 922 deaths (18%) worldwide (WHO unpublished data). Higher incidence rates were found in at-risk groups of neonates and in LMICs.

Lower birth weight and gestational age were associated with an increased sepsis incidence, resulting in the highest incidence of early-onset neonatal sepsis in very low birthweight infants and preterm neonates. However, global extrapolations from available evidence must be interpreted with caution as they are based on a limited number of countries (14 in this case) and not necessarily representative. Data on the incidence and mortality of neonatal sepsis are lacking from most countries worldwide (*43*).

Based on the timing of infection, neonatal sepsis has been classified as early onset sepsis (EOS – onset in the first 72 hours from birth) and late onset sepsis (LOS – onset occurring after the first 3 days from birth) *(45)*. This grouping implies differences in the expected mode of transmission and predominant causative microorganisms. EOS is generally caused by vertical transmission from mothers to infants during the intrapartum period *(46)*, while LOS is caused by postnatal horizontal transmission, mainly from organisms acquired after birth *(47)*. From the above-men-tioned, recently-updated systematic review and meta-analysis of epidemiological studies on neonatal sepsis, EOS was 2.6-fold more common than LOS (WHO unpublished data) *(44)*.

EOS: early onset sepsis; LOS: late onset sepsis.

Early neonatal sepsis, which causes around 8% of all neonatal deaths, is indicative of underlying issues of quality of care, such as infrastructure constraints for the care of pregnant women and neonates, inconsistent use of preventive measures, such as detection of infection in the mother and preventive treatment of the neonate, delayed diagnosis, and poor management of infection and its complications in mothers and neonates *(48)*. With approximately 21 million pregnant women colonized with Group B *Streptococcus* worldwide (estimation based on a global coloniza-tion of 18% of pregnant women), this pathogen represents the leading cause of neonatal sepsis, although *E. coli* has also recently emerged as a major threat *(49, 50)*. Together, they account for approximately 70% of cases of all EOS *(34)*. Although less common, *Listeria monocytogenes* is also associated with invasive infections in preterm neonates *(49)*.

The aetiology of neonatal infections has changed over the past decades due to increasing AMR, the availability of technologies for diagnosing infections to guide treatment, and the utilization of invasive health care

## Part 2. Available evidence on global sepsis epidemiology

devices that increase the risk of health care-associated infections.

The high burden of health care-associated infections in LMICs *(52)* affects high-risk populations such as neonates in neonatal ICUs *(53)*. Among hospital-born babies, these infections are responsible for 4% to 56% of all causes of death in the neonatal period, with three-quarters occurring in South-East Asia and sub-Saharan Africa *(51)*. The incidence of health care-associated infections is reported to vary between 15.2 and 62.0 per 1000 patient-days in neonatal ICUs *(53)*.

Globally, an estimated 84% of neonatal deaths due to infections are preventable *(54*). Early diagnosis of neonatal infection and timely and appropriate clinical management are critical both to prevent sepsis and to treat sepsis in the early stage when treatment is more successful.
Focusing on the critical periods before and immediately following birth is essential to saving more lives. The high percentage of institutional deliveries (almost 80% globally) represents an important opportunity for providing essential newborn care with high quality standards and

identifying and managing high-risk newborns *(32)*. Further investments in epidemiological research and capacity worldwide are important to foster the surveillance of neonatal sepsis epidemiology.

## 2.3 Global estimates of maternal sepsis

### Box 2.3 Key global estimates of maternal sepsis

- In 2017, WHO facilitated consensus around a standardized definition of maternal sepsis: a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or the postpartum period.
- Obstetric infections, including sepsis, are the third most common cause of maternal mortality, representing 10.7% of deaths, almost all of which are in LMICs.
- Regional disparities in maternal infection exist: the Global Maternal Sepsis Study (GLOSS) study found that in-hospital

maternal infections were highest in upper- middle-income countries, while infection-related severe maternal outcomes and case fatality were highest in low-income countries.

- In the Multi-Country Survey on Abortion (MCS-A) study, a high number of women across Africa, Latin America and the Caribbean experienced an abortion-related complication, including death and a potentially life-threatening complication, including systemic infection.

LMIC: low- and middle-income country.

Maternal infection is an important cause of maternal mortality and severe morbidity *(55, 56)*. Latest global estimates suggest that direct (obstetric) infections are the third most common cause of maternal mortality, representing about 10.7% of deaths, almost all occurring in LMICs *(55)*.

### Obstetric infections

LMIC: low- and middle-income country.

Although maternal infection is a serious threat to women's health worldwide, accurate population-based estimates have been challenging to obtain due to a lack of high-quality, complete data on the incidence and mortality of maternal infection in most countries, especially in LMICs. Moreover, the use of inconsistent and variable diagnostic criteria causes limitations in capturing and comparing reported data.

To support research and consensus building on this critical topic, WHO led several activities aiming to improve the understanding of the frequency and severity of maternal infections and sepsis. These included: the development of a consensus definition for maternal sepsis *(57, 58)*; a systematic review of the literature on the incidence and mortality of maternal peripartum infection *(59)*; a large multi-country observational study on maternal infections and related mortality and severe morbidity in health facilities *(60)*; and, finally, an additional large multi-country observational study measuring abortion-related complications in health facilities, including sepsis *(61)*.

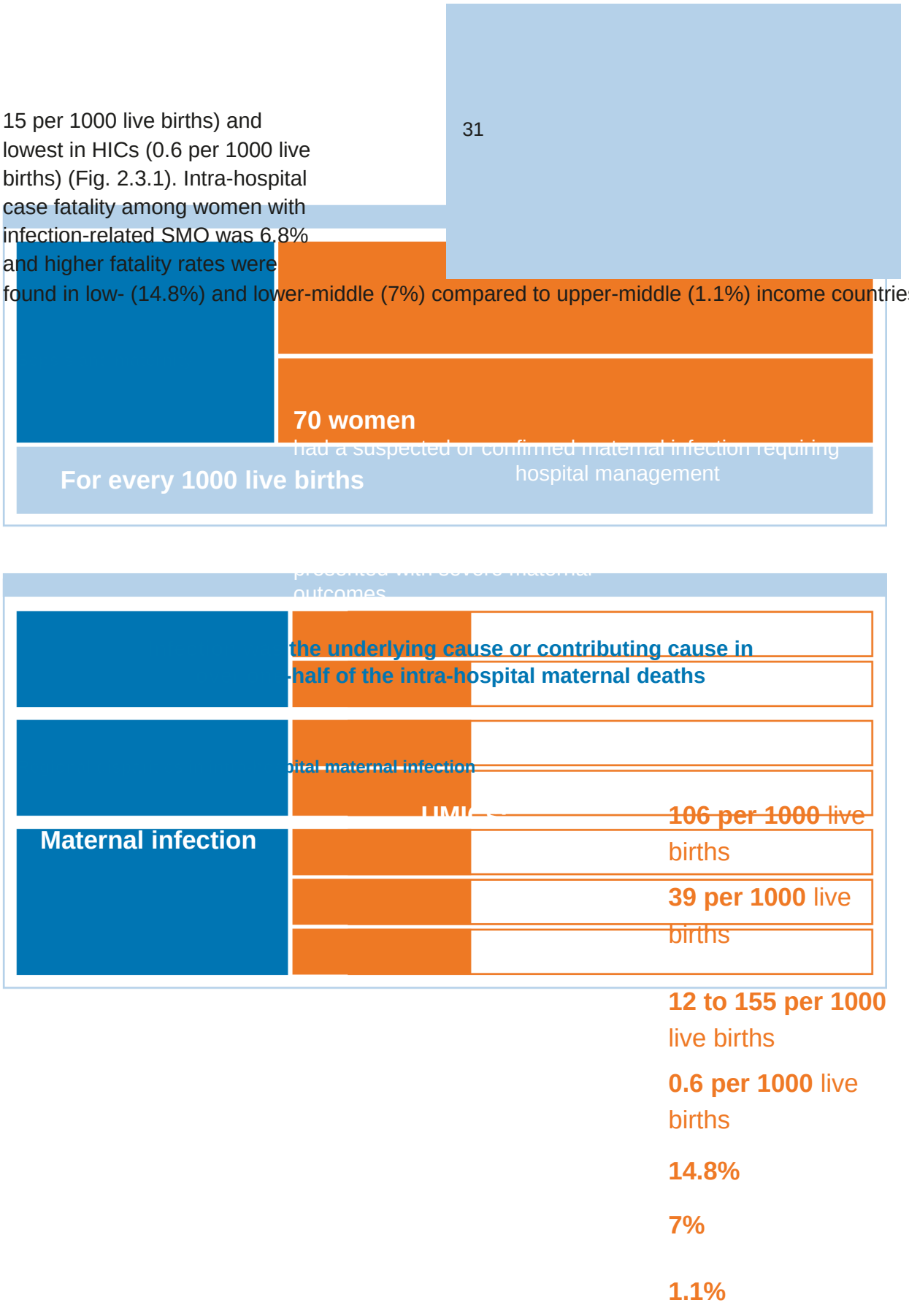
In 2017, WHO facilitated consensus around a new, standardized definition of maternal sepsis, that is, "a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period" *(58)*. The definition was based on a systematic review of the literature for definitions and identification criteria for maternal sepsis, followed by a technical expert consultation *(57)*. It reflects the concepts embedded in the Sepsis-3 definition for adults *(62)* and has been endorsed by major professional societies in obstetrics, midwifery, paediatrics and intensive care. Of note, it should be mentioned that there is still no consensus regarding how to define "organ dysfunction".

A recent WHO systematic review of the literature assessed the incidence and mortality of maternal peripartum infection (infection of the genital tract and surrounding tissues during labour and up to 42 days after birth) *(59)*. The review showed that for every 1000 women giving birth, an average of 0.5 women developed sepsis; the pooled sepsis incidence from high-quality studies was 0.05%.

To further explore maternal mortality and severe morbidity related to infection, WHO conducted a large, prospective, observational multi-country study: the Global Maternal Sepsis Study (GLOSS) *(60)*. GLOSS included 2850 women with suspected or confirmed infection hospitalized in selected geographical areas in 52 high-, middle- and low-income countries from all WHO regions and measured outcomes per 1000 live births in health facilities in 2016 (most recent available data) *(63)*. For every 1000 live births, 70 women had a suspected or confirmed maternal infection requiring hospital management and 11 women presented with severe maternal outcomes (SMO) (organ system dysfunction defined as maternal near-miss *(64)* or maternal death) related to infection during hospital stay. Infection was the underlying cause or contributing cause in over one-half of the intra-hospital maternal deaths *(63)*.

Regional disparities in maternal infection were also observed in the GLOSS *(63)*. Intra-hospital maternal infections were highest in upper-middle-income countries (106 per 1000 live births) and lowest in HICs (39 per 1000 live births). Infection-related SMO were highest in LMICs (12 to

15 per 1000 live births) and lowest in HICs (0.6 per 1000 live births) (Fig. 2.3.1). Intra-hospital case fatality among women with infection-related SMO was 6.8% and higher fatality rates were found in low- (14.8%) and lower-middle (7%) compared to upper-middle (1.1%) income countries.



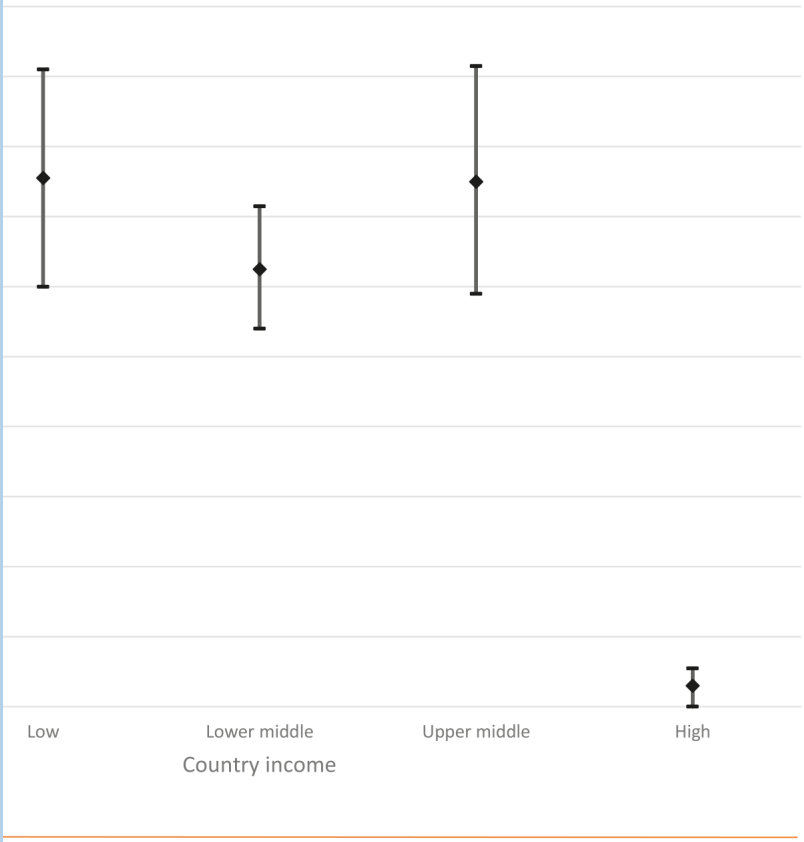

UMICs: upper-middle-income countries; HICs: high-income countries; LMICs: low- and middle-income countries; LICs: low-income countries; SMO: severe maternal outcome.

No maternal deaths were reported in HICs. The observed variation across countries could be related to the use of different admission criteria, resources available to identify severe conditions, or resources available to manage women with infections across facilities, geographical areas, and/or countries. This difference in identification and management could partly explain the higher burden of infectious morbidities in upper-middle-income countries compared to LMICs, where facilities might have lower admission thresholds for

maternal infection or more resources to identify or treat complications compared with facilities in low-income countries.

The most common sources of maternal infections from the GLOSS study were of the genital (endometritis and chorioamnionitis) or urinary tract, skin or soft tissue, the respiratory tract, and abortion-related. Less than half (47%) of the participating women had culture samples drawn to confirm a suspected infection. Overall, microorganisms were reported in 21% of the total samples and 31% of women with SMO. Bacteria were the microorganisms most frequently reported (77% in the overall sample and 85% of women with SMO), although microorganisms were reported without inferring direct causality *(63)*.

**Fig. 2.3.1** Number of severe maternal outcomes related to infection per 1000 live births.




**Note:** Data are n or ratio (95% confidence interval). Country income level is based on the World Bank country income classification, 2018. Infection-related severe maternal outcome data are from 2017 and the number of births from 2016.
**Source:** This table has been produced by WHO based on data included in reference *63*.

Complications resulting from unsafe abortions, including infection, are an important and preventable cause of maternal mortality *(55)*. Serious complications arise from the least-safe abortions *(65)*. According to the most recent estimates, 55.7 million abortions occurred worldwide each year between 2010 and 2014, of which 45.1% were unsafe *(65)*. Associated complications accounted for 8% of all global maternal mortality *(55)*.

**Abortions worldwide between 2010 and 2014**

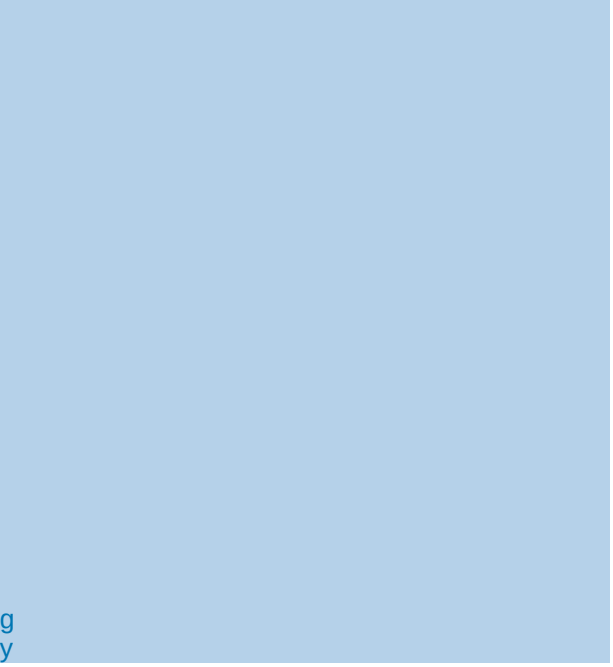
Therefore, to gain a better understanding of abortion-related complications and building on the network and experience of the WHO Multi-Country Survey (MCS), WHO implemented the “Multi-Country Survey on Abortion (MCS-A): Abortion-related Morbidity and Mortality” in 2016, a large, prospective, observational multi-country study *(61)*. The study was conducted through a network of mainly secondary and tertiary level facilities in urban settings across multiple countries in Africa, Latin America and the Caribbean, and included over 20 000 women who presented with or

died from abortion-related complications or early pregnancy loss. Complications were classified into five categories based on severity: death; near-miss *(64)*; potentially life-threatening (for example, severe haemorrhage, systemic infection, uterine perforation) *(64)*; moderate (for example, bleeding, suspected intra-abdominal injury, infection); and mild (for example, any abnormal signs or symptoms from an initial physical examination). Results of the study are expected to be published in late 2020 or beginning of 2021.

Several important conclusions can be made from this series of studies. First, a major limitation of the available data on maternal sepsis is a lack of comparability across studies and regions, thus making it very difficult to determine a detailed and accurate description of the global epidemiology. This limitation is directly due to the fact that there are multiple definitions for maternal infection and maternal sepsis, hopefully now addressed by the new consensus definition. Consistent, higher quality data from across the world are needed to not only gain insight into the true burden of maternal sepsis, but also to demonstrate the influence of risk factors and protective interventions on outcomes. Second, maternal infections, including sepsis, are important complications for many women during and after pregnancy, and most of are preventable. Good IPC measures are key for the prevention of infections following caesarean section, perineal repair or other invasive procedures.

IPC: infection prevention and control.

Therefore, IPC should be a priority for health programme policy-makers. IPC is also important in the current context of maternity care. The increase in facility-based childbirths and rising caesarean section rates increase the risk of HAIs if not accompanied by improvements in the quality of care and IPC measures. Improved management of obstetric emergencies places women who survive at higher risk of HAI as they receive invasive medical interventions and experience prolonged hospital stays and intensive care admissions. In addition, early discharge from hospital after childbirth is another factor that contributes to delays in diagnosis and timely treatment of both maternal and early neonatal sepsis. Furthermore, the management of abortion-related complications must be an integral part of maternity care, as stated at the 1994 International Conference on Population and Development *(66)*. Complications, including infection, as a result of unsafe abortion are an important and preventable cause of maternal mortality *(55)*.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## 2.4 Global estimates of health care-associated sepsis

### Box 2.4 Global estimates of health care-associated sepsis

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from 13.8 to 175.0 cases per 100 000 adult population per year, depending on the setting; mortality was found to be 52.3%.

- In ICU patients, approximately one-half (48.7%) of sepsis cases wereacquired in the hospital.
- Patients with hospital-acquired sepsis have longer lengths of stay and high rates of AMR and at-risk populations (neonates, ICU patients) are the most affected.
- Over one-half (56.6%) of all HAIs were in neonates; the estimated incidence of hospital-acquired sepsis in neonates was 112.9 cases per 1000 ICU-treated neonates.

ICU: intensive care unit;
AMR: antimicrobial resistance;
HAI: healthcare-associated infection.

While it has been previously estimated that 70% of sepsis cases are commonly acquired in the community *(67)*, little is known about the incidence, mortality, attributable length of hospital stay, and microbiological profile of health care-associated sepsis (HA-sepsis). Although HA-sepsis is not a distinct physiological type of sepsis, it affects all patient populations and is an avoidable cause of sepsis. A WHO systematic literature review on the global epidemiology

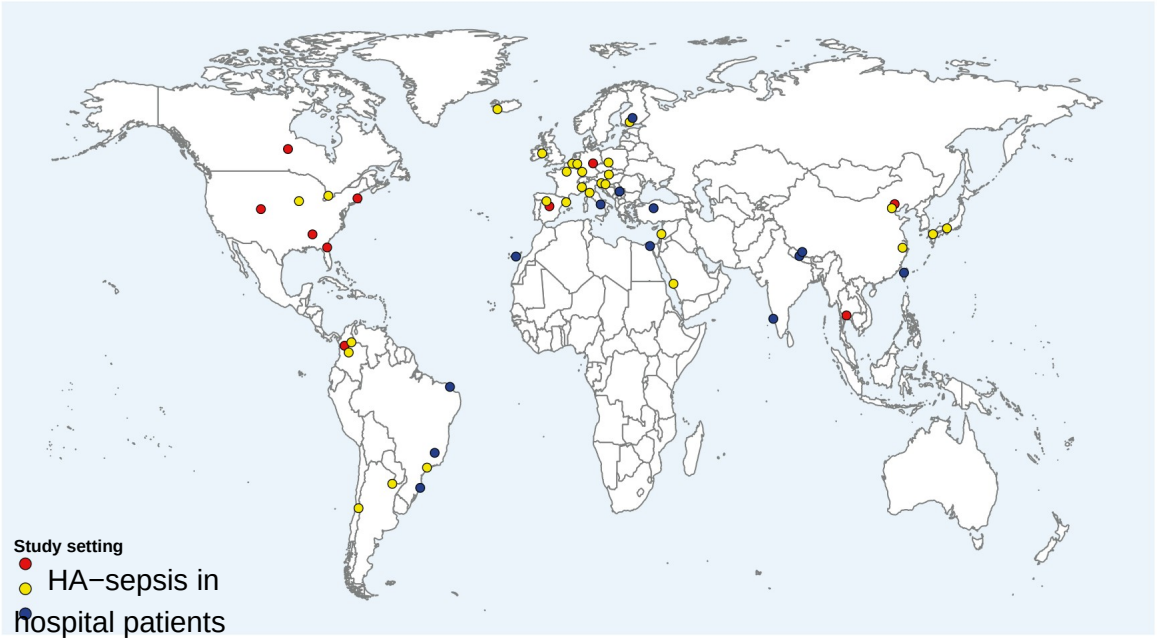
and burden of HA-sepsis published between 2000 and 2018 showed that among all hospital-treated sepsis cases, 23.6% were health care-associated, with a pooled hospital incidence of 15.4 cases per 1000 patients of all HA-sepsis *(68)*. In this systematic review, health care- and ICU-associated sepsis were defined as cases acquired in the health care setting, including ICUs (ICU-associated was considered as a subset of infections/sepsis acquired during ICU stay). Most hospital-wide and ICU-based studies were conducted in high-income countries, in particular from the European and American WHO regions (Fig. 2.4.1).

This first comprehensive summary of published evidence on the epidemiology of HA-sepsis found that 1 in 4 cases of sepsis were acquired in the hospital, increasing to 1 in 2 in ICUs for sepsis with organ dysfunction. Moreover, patients with HA-sepsis had a longer length of stay and high AMR rates, which can significantly impact on patient outcomes.

**Hospital-acquired sepsis cases**

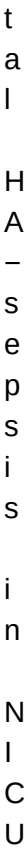
AMR: antimicrobial resistance.

**Fig. 2.4.1** Location and type of studies reporting hospital-acquired sepsis.




HA–sepsis in ICU patients

Neona




**Source:** Reproduced from reference *(68)*. Published under the CC BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/).

The review also identified high-risk populations. The pooled incidence of HA-sepsis in neonates was 112.9 cases per 1000 ICU-treated neonates, and 56.6% of all types of HAIs were found to be neonatal HA-sepsis, thus suggesting that the burden of HAIs is even greater for neonates. Additionally, the review found that the risk of developing sepsis in ICUs was greater: the pooled incidence of ICU-acquired sepsis was 35.8 cases per 1000 ICU patients; in the ICU, 24.4% of cases of sepsis with organ dysfunction were acquired during ICU stay and 48.7% had a hospital origin *(68)*. A few studies provided information on the population-level burden of HA-sepsis treated in ICUs (range, 13.8 to 175.0 cases per 100 000 adult population per year), while one reported the population-level burden for ICU-acquired sepsis (46.6 cases per 100 000 adult population per year).

### Sepsis in intensive care units (ICUs)

While no study investigated the attributable case fatality due to HA-sepsis, the review's pooled crude mortality of sepsis patients was 24.4% and as high as 52.5% in cases with septic shock (although the latter is based on one study only). ICU-acquired sepsis was reported to be associated with a higher risk of mortality (40.5%). Among ICU-treated patients

with HA-sepsis, including cases acquired in hospital wards and the ICU, the pooled mortality was 52.3%. HA-sepsis was also associated with a longer length of hospital stay for survivors. The median length of stay of hospitalized patients with HA-sepsis ranged between 17 and 22 days, which was two- to three-fold higher than that of patients with community-acquired sepsis in the same studies. A considerably longer median length of stay was found in ICU patients with ICU-acquired sepsis (median range, 18 to 23 days) compared to that of ICU patients with community-acquired sepsis (9 days). Only a few studies provided data on the microbiological profile of pathogens causing HA-sepsis and found that 16% to 40%, 34% to 64%, and 9% to 19% of cases were caused by

Gram-positive bacteria, Gram-negative bacteria, and fungi, respectively. Up to a one-third of cases were caused by drug-resistant bacteria, such as ESBL-producing *Enterobacteriaceae*, MRSA, and multidrug-resistant *Pseudomonas* spp.

**Sepsis and mortality**

| | |
|---|---|
| 24.4% | mortality of patients with HA-s |
| 52.3% | mortality among ICU-treated pa sepsis |
| 2x to 3x | higher median length of stay o HA-sepsis compared to community-acquired sepsis |

HA-sepsis: health care-associated sepsis. ICU: intensive care unit.

These findings highlight that HA-sepsis is a common complication in patient care and is difficult to treat once it develops, particularly in ICUs. The results of this review underline the importance of appropriate IPC measures in health care settings to prevent HA-sepsis and reduce its impact on patients and health care in general.



# 3

# Part 3. Methodologies and challenges in sepsis epidemiology research

## 3.1 Methodologies to estimate the epidemiology and burden of sepsis



Reliable estimates of the global epidemiology and burden of sepsis depend on the quality of individual studies and the data sources. The majority of analyses aimed at estimating the epidemiological impact of sepsis are based on systematic reviews of the literature. For example, this report refers to at least eight original and updated reviews *(10, 11, 44, 55, 57, 59, 68, 69)* that were either general or targeting specific patient populations, settings and geographical areas.

All reviews attempted meta-analyses (many with random effects), but consistently found high between-study heterogeneity.

Results of the systematic reviews of the literature showed that many published studies were observational cohort or cross-sectional studies, mostly from HICs, based on hospital coding data. These studies and officially reported data often rely on the use of ICD codes for sepsis case detection, rather than on the prospective collection of clinical information. Coding data are inherently biased; sepsis-specific codes underestimate disease prevalence, while a combination of sepsis-specific codes and indirect codes (for example, counting an infection code and an organ dysfunction code in the same hospital encounter as sepsis) overestimate it. Other data sources available in many countries include censuses, surveys and vital registration systems. Studies on sepsis epidemiology among neonatal ICU or ICU-treated patients are often conducted with prospective designs, but generally produce estimates that are specific to a setting and geographical area.

One method for providing global estimates of sepsis cases and deaths has been applying the population-based incidence pooled from meta-analyses based on systematic reviews to the world population or the population of specific geographical areas, such as Europe *(10, 11)*. Another approach is the one used in the recent **GBD sepsis study***(4)*.

Similar to other GBD studies, modelling was based on vital registration death records in an attempt to represent deaths in and out of hospital, the latter being a common occurrence in LMICs. Sepsis-related mortality was estimated using multiple cause-of-death vital registration data, and sepsis incidence was estimated from death data using sepsis-related case-fatality estimates from hospital administrative data. Although these estimates still depend on the quality of medical documentation and the ICD coding system, this approach ensures that deaths are not counted twice and allows comparisons with other GBD outputs.

A major challenge faced by global sepsis epidemiology researchers is reconciling differences across data sources, while taking into account the systematic biases associated with the various types of data. The estimates on neonatal, child and adolescent mortality produced by the WHO MCEE group based on the UN IGME data represent an excellent example of reconciling such differences across data sources. The UN IGME follows these steps: 1) compile and assess the quality and representativeness of all available data at the national level relevant to the estimation of child mortality; 2) recalculate data inputs and make adjustments as needed by applying standard methods; 3) fit a statistical model to these data to generate a smooth trend curve that averages potentially disparate estimates from the different data sources for a given country (Bayesian spline regression model); and 4) extrapolate the model to a target year. This method is applied across all countries, although the resulting country-specific estimates are not reported as national representativeness is deemed not of sufficient quality.

Examples of good-quality studies that prospectively collect clinical data are the above-mentioned multicentre and multi-country trials of **AFRINEST** in Africa *(38, 39)* and Simplified

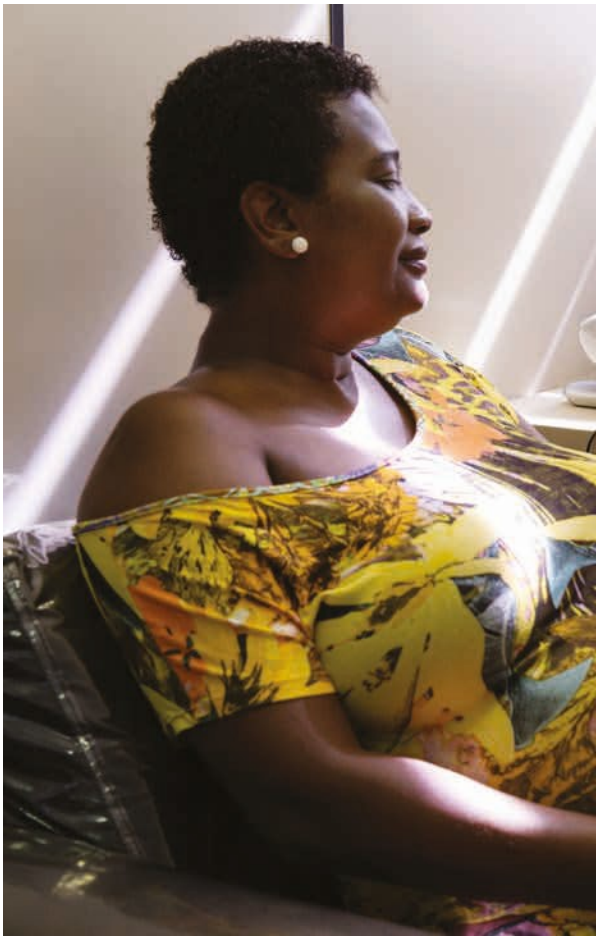
Antibiotic Therapy Trial (**SATT**) *(40, 41)* in Asia. The aim of these trials was to evaluate the safety and effectiveness of simplified antibiotic regimens for the management of young infants less than two months of age with severe clinical infection (that is PSBI, which can be indicative of sepsis) when referral was not feasible. A longitudinal analysis of the surveillance data was performed to calculate incidence rates and attributable mortality for each sign of infection and stratified by week of life. Based on these studies, WHO launched a new guideline for the management of infants with PSBI when referral is not feasible *(36)*. Eleven sites are now testing the implementation of these guidelines and will provide more robust epidemiological data.

Another example of a prospective study was the **GLOSS study***(60, 63)*. This was a facility-based, prospective, one-week inception cohort study of all women with suspected or confirmed infection during any stage of pregnancy and up to the 42nd day after end of pregnancy who were admitted to or already hospitalized in participating health facilities across selected geographical areas in 52 LMICs. Women were followed-up to six weeks or until hospital discharge, transfer or death, whichever occurred sooner. Overall ratios of maternal suspected or confirmed infections, including those that evolved to sepsis, were estimated per 1000 live births in a health care facility from 2016 (most recent available data), and fatality rates were stratified by country income. The study researchers used “near-miss” (see glossary) to define sepsis, as it is accepted obstetric terminology, validated in low-resource settings and reflects organ dysfunction. The study represents a unique overview of maternal infections including sepsis, across different severities throughout pregnancy, childbirth and the postpartum/post-abortion period. However, the study did not capture maternal infection-related deaths that occurred in the community.



Created by the WHO and Drugs for Neglected Diseases initiative, the Global Antibiotic Research and Development Partnership (**GARDP**) is collaborating with partners to conduct a prospective longitudinal cohort study of neonates with sepsis. Daily clinical and antimicrobial data,

and routine laboratory and microbiology data were collected for up to 28 days following diagnosis of sepsis. A total of 3204 babies were enrolled by 19 hospitals in 11 countries (five WHO regions) between August 2018 and February 2020. The data obtained from the study are currently being analysed and it is anticipated that they will be published in 2021.



## 3.2 Limitations in current estimates of burden of sepsis

### Box 3.2 Data limitations and knowledge gaps in current estimates of burden of sepsis

**Limitations** of the current sepsis estimates are due to:

- a lack of sepsis epidemiologic data from most LMICs for the calculations of the global estimates;
- heterogeneous study designs and differences across data sources;
- most studies are intensive care- and hospital-based that do not capture sepsis cases occurring outside the hospital setting, limiting our understanding of community-acquired sepsis;
- the use of different sepsis definitions across studies, as well as a lack of a validated neonatal sepsis definition;
- a reliance on limited, retrospective administrative data;
- a lack of a standardized and complete reporting of designs and results.

Important **knowledge gaps** include:

- lack of data and understanding of the real burden of sepsis in LMICs;
- the proportion of sepsis-attributable mortality measured accurately and prospectively in all populations, including different age populations, particularly in

high-risk and disadvantaged populations;

- the burden of long-term outcomes and sequelae of sepsis patients;
- aetiology and antimicrobial resistance patterns.

LMIC: low- and middle-income country.

Although the understanding of sepsis epidemiology has improved over recent years, there are still major knowledge gaps regarding the burden of sepsis in individual countries and across the world.

LMICs: low- and middle-income countries.

Data on sepsis epidemiology are missing from most LMICs *(10, 11, 44, 69)*, although they bear the highest burden of sepsis *(4)*. Systematic reviews have consistently found that a limited number of studies from LMICs contribute to sepsis estimates, a finding that did not substantially change after expanding and targeting search terms and databases *(11, 44)*. Furthermore, the estimates of the GBD sepsis study included limited data from LMICs: modelling data for sepsis incidence were extrapolated from 10 countries (Austria, Brazil, Canada, Chile, Georgia, Italy, Mexico, New Zealand, Philippines, United States of America [USA]) and data for sepsis mortality were extrapolated from only four countries (that is, Brazil, Taiwan [China], USA and Mexico), none of which are low-income countries or located in sub-Saharan Africa.

Even in a well-resourced setting, a considerable proportion of sepsis deaths occurred outside the hospital setting (13% in one US-based study) *(70)*, and yet most sepsis epidemiology studies

use ICU- and hospital-based designs. The epidemiology of community-based sepsis is not well understood, but of high relevance, particularly in countries with limited access to health care and/or for disadvantaged populations.

Knowledge gaps also include the proportion of sepsis attributable mortality and the burden of long-term outcomes and sequelae of sepsis patients*(22)*, which include cognitive, mental and physical illness, as well as hospital readmissions, mostly for recurrent infectious diseases, thus leading to an impaired quality of life in sepsis survivors *(71)*.

## Part 3. Methodologies and challenges in sepsis epidemiology research

Results from existing sepsis epidemiology studies vary largely and frequently cannot be compared given heterogeneous study designs and sepsis definitions applied *(10)*.

One of the reasons leading to heterogeneity is that with the evolving understanding of sepsis pathophysiology and the lack of a definitive diagnostic test, the definition has changed multiple times over the past several decades, most recently in 2016 when the Sepsis-3 definition was published *(3)*. Not all elements of this

definition can be applied in low-resource settings where access to appropriate diagnostics and laboratories is often limited and the sensitivity of sepsis diagnosis is hampered *(72)*. For neonates, there is currently no validated sepsis definition and the application of existing definitions in LMICs settings is unknown. For children, most studies use a definition published in 2005 *(30)* that might be too sensitive *(73)*. These limitations lead to heterogeneous methods of diagnosing sepsis *(74)*, hindering our understanding of epidemiological variations that may be due either to reporting and study methodologies, or to different disease burden across geographical areas.

An increasing body of research is based on administrative data and identifies sepsis based on hospital discharge codes instead of a prospective collection of data *(10)*. Although this approach allows for nationwide analyses of sepsis epidemiology, discharge codes are often collected for reimbursement reasons rather than for clinical or research purposes and, thus, are prone to bias and limited by the quality of documentation. Depending on the strategy used to identify sepsis patients through these data, estimates on incidence and mortality differ considerably *(75)*. Most administrative data-based studies do not distinguish between hospital- and community-acquired sepsis or assess underlying pathogens and antimicrobial resistance patterns. Prospective, chart- or electronic-health record-based research would circumvent these limitations, but the capacity to run such studies varies between countries and regions and quality is dependent on the availability of trained investigators and research funding.

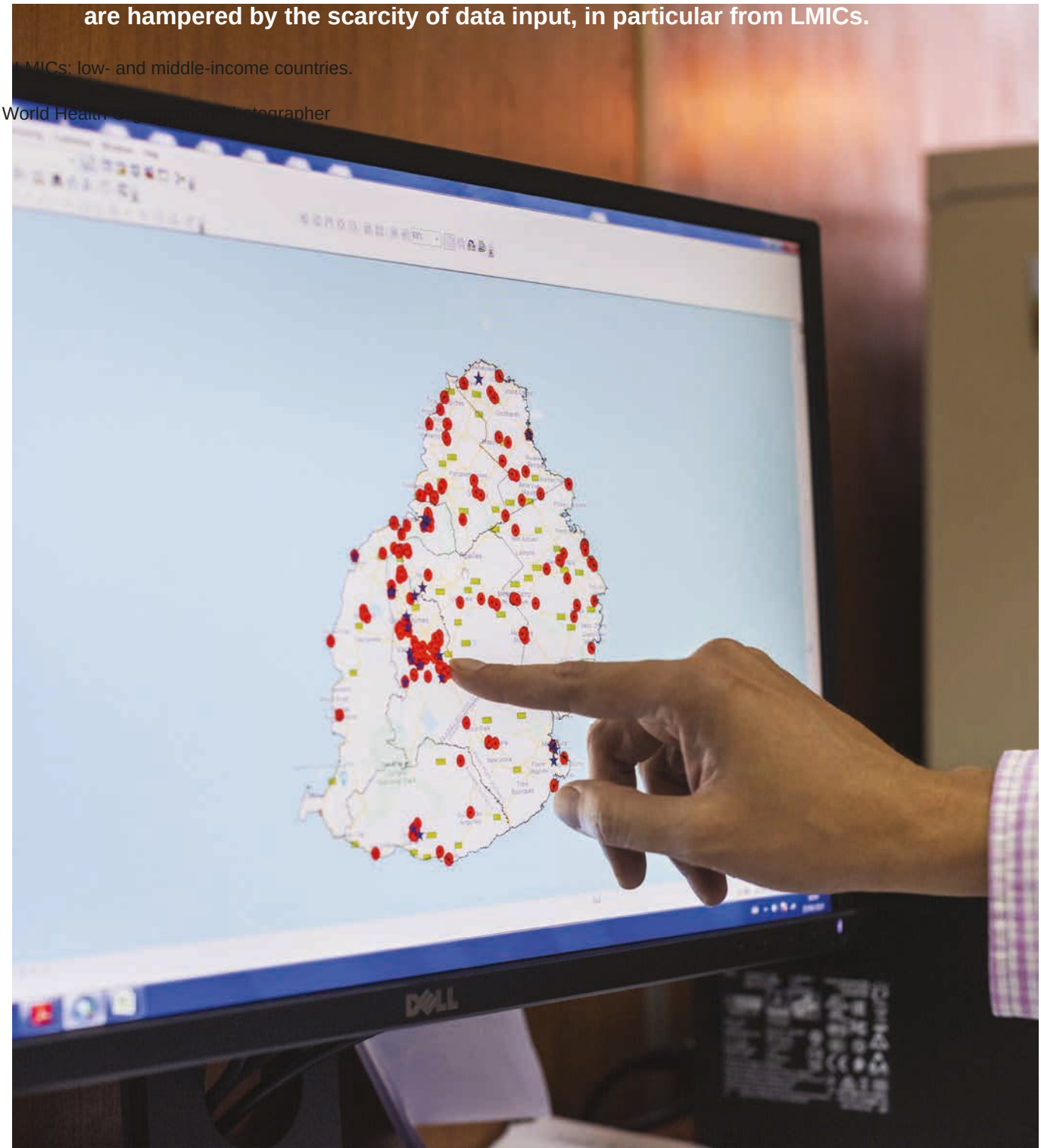
Another limitation of current research is the lack of a standardized and complete reporting of designs and results. Global extrapolations to estimate the burden of sepsis cases and deaths worldwide *(4, 10)* are hampered by the scarcity of data input, in particular from LMICs, and an

unknown representativeness of single countries or individual studies due to small sample size or single-centre design on which these extrapolations are based. Study design also has a major impact on our understanding of the disabilities and mortality related to sepsis. Short- and long-term consequences need standardized and longer follow-up periods, which are expensive to conduct. Furthermore, natural variation, such as underlying conditions, age and other patient characteristics, together with differences in settings, information on antimicrobial susceptibility, treatment, and access to health care are often not clearly defined, standardized or reported, limiting the generalizability of the burden of sepsis.

**are hampered by the scarcity of data input, in particular from LMICs.**

LMICs: low- and middle-income countries.





# 4

# Part 4. Directions and priorities for future sepsis epidemiology research

## 4.1 Achieving standardization in sepsis epidemiology research and closing existing gaps



Standardization of sepsis epidemiology research is essential to compare rates across age, sex, socioeconomic strata, health care settings, education level and work experience, for example. A number of crucial elements would improve comparability and reliability of sepsis data for diagnosis, reporting and study design.

The first element relates to the current definition of sepsis, in particular measuring organ dysfunction, and improvements needed to make it more applicable in low-resource settings. A stepwise or tiered approach to sepsis definitions ranging from criteria based solely on clinical features (for example, signs and symptoms) to those that include clinical features and laboratory results, could be a viable solution. One example is the PSBI classification for newborns and young infants that is based on clinical signs at presentation and intended for front-line providers at the primary level in resource-limited settings. Another example is a clinical sign-based approach to measuring organ dysfunction using capillary refill time as opposed to a laboratory-based approach measuring serial blood lactate levels *(76)*, which has previously been shown to be equivalent in terms of outcomes when used for targeted resuscitation in sepsis. This approach would enable reporting of sepsis in settings where access to diagnostics is limited and would allow for more data from LMICs to be included in epidemiological studies. Moreover, a purely clinical sepsis case definition coupled with empowerment of nursing staff to actively screen and identify sepsis would facilitate early treatment, ultimately improving survival and preventing short- and long-term complications. It should be emphasized that the further any definition is from routine data collection, the longer it will take to adopt it into clinical practice. Furthermore, consensus is needed to achieve a standardized definition of sepsis in neonates and update the paediatric sepsis definition.

Currently, knowledge of sepsis epidemiology is hampered by the fact that areas with the highest sepsis burden (in LMICs) are also the areas where data are lacking. Research on the impact of sepsis in LMICs is urgently needed and calls for increased funding, as well as renewed opportunities for strengthening the professional, academic and diagnostic capacity in these countries. It is important to consider that the quality of research is related to its standardization, such as the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) neonatal infection statement for cohort *(77)*, observational and cross-sectional studies.

Sepsis affects some populations more than others and individuals with sepsis are also often affected by other diseases. For example, neonates, women in the peripartum period, and patients in ICUs are at higher risk of developing sepsis and initial efforts to improve surveillance should concentrate on these populations. Specific surveillance programmes and disease networks (for example, maternal and child health, human immunodeficiency virus, tuberculosis, AMR) are already in place and sepsis should either be linked to these systems (if a dedicated surveillance system for sepsis already exists) or incorporated into existing reporting measures. Similarly, given the cross-cutting nature of sepsis, international and national action plans should include sepsis as an outcome and complicating factor of other diseases and align efforts to prevent and manage sepsis within existing networks, initiatives and programmes. This effort should be extended to include sepsis within indicators for achieving the SDGs and UHC initiatives.

Moreover, in the context of rising AMR, the collection of information on the causative organisms and their susceptibility profiles is essential to inform treatment and epidemiological patterns of sepsis. Pathogen identification and determining susceptibility/resistance patterns can be problematic where diagnostic capacity is limited and entails scaling-up local laboratory capacity.

Collection, completeness, reporting, and analysis of medical records are often limited in LMICs and addressing this issue would require an increase in the availability of logistic enablers (for example, electronic record systems) and training of staff. Globally, these efforts are already

ongoing through the implementation of GLASS *(28)*, which represents an opportunity for data collection on incident cases of bloodstream infections, a common cause of sepsis.

Apart from clinical features, sex and age, standardized reporting should strive to collect data on comorbidities, pregnancy status and level of care, in addition to other information that should be explored. For example, the lack of information on the source of infection (community- or hospital-acquired) impedes the identification of the appropriate preventive measures. Furthermore, collection of indicators, such as re-hospitalization rates, for example, would be useful to inform the improvement of in-hospital treatment and clinical management. For instance, all patients admitted with suspicion of sepsis could trigger a series of monitoring and treatment initiatives, which in turn would increase reporting of data, provide information for improving the overall quality of care of sepsis, and enable data-directed investigation of the drivers of sepsis.

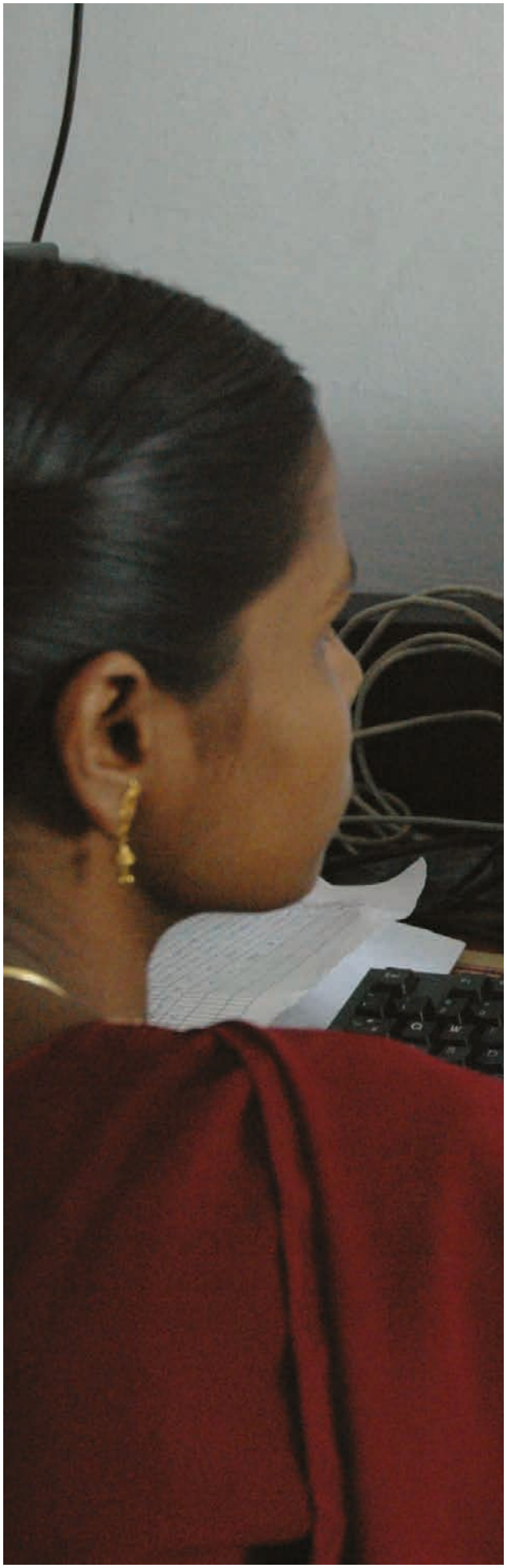
## Part 4. Directions and priorities for future sepsis epidemiology research

Regardless of the availability of health care resources, few countries report and share data on multiple causes of death. Sepsis is usually considered a transitory response of the body and can be associated with other underlying conditions. Moreover, longer life expectancy, modern invasive medical technology and pharmaceuticals, and the improved survival of very low birthweight and sick neonates, for example, have increased the number of patients with other conditions who are at risk for sepsis. It is crucial that reporting systems and collection of data acknowledge these linkages. The new ICD-11 system *(78)* introduced the possibility to convey patient case-mix and appropriately describe the complexity of multiple causes of

disease and death. Post-coordination allows for additional data collection including the underlying condition, disease association or infectious aetiology, when relevant, while affording a granularity of data not previously possible, thus improving clinical recording and research. Another application for ICD-11 is that it is easily incorporated into clinical record systems or accessed on a browser from anywhere in the world. This ease of access represents an opportunity for clinicians and researchers to improve the analysis of sepsis as a risk factor for death and long-term sequelae and to harmonize sepsis under one diagnosis code. This uniform approach will allow epidemiologists, researchers and clinicians to measure more comprehensively and accurately the burden of sepsis by capturing sepsis-related mortality, rather than being limited to measuring sepsis as a direct cause of death. The lack of evidence on the characteristics and impact of non-fatal outcomes after sepsis requires either tailored research that includes longer follow-up of patients or surveillance and reporting systems linking acute events with chronic sequelae. The implementation of ICD-11 into clinical electronic medical records systems should be complemented by linking an individual's medical records from primary care, acute care, laboratory and other diagnostic services. Ultimately, the resulting data could also be analysed to estimate sepsis-attributable mortality and long-term sequelae, key information that is currently lacking.

Results of the systematic reviews and other studies described in Part 2 of this report suggest that a significant burden of sepsis arises in the community setting. It seems crucial, therefore, that surveillance and data collection start in primary care, which commonly represents the first point of contact with the health care system. Primary and acute health care centres could increase their role as gatekeeper for the diagnosis, collation of information and tracing of patients, in addition to performing community outreach and sensitization, especially when

referral to a higher level of care is not feasible. Considering the high burden that sepsis poses on health systems and populations, it should be a priority outcome to be improved in the context of achieving UHC and quality of care improvement.



## 4.2 Towards comprehensive global sepsis monitoring

Improving research and, thus, evidence on the epidemiology of sepsis will inform its prevention, diagnosis and management. For example, better knowledge of sepsis risk factors and outcomes would help prevent its occurrence in at-risk populations. Sepsis prevention could be reinforced by investigating vaccine-preventable infections that frequently cause sepsis and epidemiological knowledge of sepsis aetiology could inform more tailored and effective vaccination campaigns.

Understanding the causative organisms for sepsis enables tailored antibiotic stewardship and could help prevent the emergence of AMR. Sepsis epidemiology research would also help to identify optimal populations for clinical trials to test diagnostic biomarkers (for example, C-reactive protein, lactate, procalcitonin), which could aid for an earlier recognition of sepsis, thus ultimately improving outcomes. Finally, considering the recent GBD sepsis study results, an improved understanding of NCD and injury prevention and management could play a significant role in decreasing sepsis incidence and related mortality.



its prevention, diagnosis and management.

A complete picture of the impact of sepsis (prevalence, incidence, mortality, length of stay, morbidity, long-/short-term sequelae, and economic impact) requires more evidence on its epidemiology, in particular in LMICs, which carry the heaviest burden. To achieve this goal, a global effort to scale-up advocacy and funding for generating sepsis epidemiology evidence is urgently needed.

**A global effort to scale-up advocacy and funding for**

Inclusion of sepsis as a health threat in national and global action plans and the development of strategies on sepsis would support awareness efforts. The goal should be to build competencies for designing high-quality studies, strengthening diagnostic and reporting capacity (for example, workforce, logistics and laboratory), and ensuring continuous education and training on epidemiology. Further research to elucidate the burden of sepsis in LMICs is critical and should assess at-risk groups, risk factors, causative organisms, attributable mortality and long-term complications. Increased, as well as more coordinated, financial and technical support is needed from national and international non-governmental organizations, educational institutions and relevant sepsis foundations. A practical initial step would be mapping the researchers and institutions active in the field of sepsis epidemiology research.

For example, sepsis research would profit from integrating into UHC surveillance and quality of care improvement programmes. Initially, sentinel sites could be a solution in countries wishing to rapidly improve sepsis surveillance. However, to achieve adequate sepsis monitoring, several enablers need to be in place. First, standardized and validated case definitions need to be developed (for example, for neonatal sepsis), implemented globally and adapted to settings with limited access to diagnostics. For example, an international organization such as WHO could play a role in reaching consensus on clinical or tiered sepsis definitions for different age groups that are applicable in low-resource settings. Second, this activity could be developed in parallel to a simplification of ICD coding together with a standardized ICD case identification strategy for both morbidity and mortality. ICD-11 was adopted at the 72nd World Health Assembly for implementation by countries from January 2022. This revised version has reviewed sepsis in the classification system to reflect changes in medicine and science since the ICD-10 version. Considering the opportunities within ICD-11, WHO and stakeholders should encourage the implementation of ICD-11 to report data on multiple causes of death in a standardized manner at the international level. Third, establishing a core, minimal dataset for sepsis reporting and its integration within existing health demographic survey networks and disease-specific surveillance networks (for example, human immunodeficiency virus and tuberculosis) and initiatives (for example, AMR) could complement institutional reporting and improve data quality. Information on sepsis originating from these networks would improve the quality of reported data through triangulation and indirect validation. Ultimately, ensuring that sepsis events are captured in other databases could increase overall available information on the morbidity and mortality due to sepsis. Moreover, this would contribute to strengthening national capacity for better health information systems, vital statistics and administrative data. Finally, WHO collaboration with existing stakeholders (organizations, foundations, universities, etc.) active in the field of sepsis could further enhance the global sepsis network and improve coordination of research efforts.

Timely diagnosis of sepsis critically increases the chance of survival and is a pillar of quality care in the clinical management of sepsis. The ideal diagnostic test for infections that cause sepsis would: 1) rapidly identify pathogens broadly (bacteria, virus, parasite, fungi); 2) be highly sensitive and specific so as to guide antimicrobial therapy, limit antibiotic overuse, and inhibit AMR development; 3) use readily available clinical samples (for example, whole blood) that do not require processing or culture; 4) allow detection of multiple pathogens simultaneously; 5) detect drug susceptibility and resistance; 6) be simple to use with minimum training required; and 7) be relatively low cost. However, many existing diagnostics, are considered too costly and technology-dependent to be realistic in LMICs. Biomarkers have been an area of intense research among sepsis investigators, but they are not affordable or sufficiently relevant so far. Further research and additional funding are therefore critical to be able to develop and implement rapid, low-cost and simple-to-use sepsis diagnostics that are appropriate across settings and resource levels.

A rapid, accurate diagnosis of sepsis improves clinical outcomes and represents a priority for both surveillance and clinical management, particularly in at-risk patients. Ensuring that clinical information is linked to microbiological results would reinforce sepsis surveillance while improving

clinical care. Eventually, this integrated approach will improve data from hospitals, which are the foundation for sepsis epidemiology research. Better tools are needed to assess sepsis identification and management, indicators on quality of care, and the impact of different service delivery models. Furthermore, new diagnostic biomarkers could represent an opportunity for improving timely and targeted treatment and should be included in surveillance data when available.

Clearly, more high-quality data on sepsis epidemiology is needed at the global and national level and funding for this represents an urgent short-term priority, particularly in LMICs as they would reap the most benefit from the advocacy and assistance generated by similar initiatives (for example, GLASS). This entails the integration of ICD-11 coding at all levels of surveillance and considering the implementation of a case definition for sepsis surveillance relevant to all age groups across all settings. Furthermore, epidemiological studies should be designed according to existing tools (for example, STROBE) to ensure that evidence is standardized and of high-quality.



Efforts to strengthen capacity related to initiatives such as those related to AMR, patient safety and universal health coverage, could be an opportunity to include and define the role of sepsis prevention and treatment, particularly in low-resource settings.

In the longer term, our understanding of sepsis will depend upon evidence generated on health complications following sepsis events and their impact on patient quality of life. Information on the drivers, determinants and populations at risk of developing sepsis would also be crucial. Importantly, generating evidence on the causative organisms of sepsis will help the development of diagnostic and prognostic tests that can be used rapidly, such as biomarkers. These have the potential to greatly improve appropriate and early treatment, thus saving lives.

Approximately 20% of all-cause global deaths are due to sepsis and are largely preventable. Sepsis disproportionately affects vulnerable populations such as neonates, pregnant or recently-pregnant women, and populations living in LMICs. Yet, our current understanding of the epidemiology of sepsis is limited by poor quality data, particularly where the burden is highest, which illustrates the urgent need for this report.

At the 70th World Health Assembly in May 2017, WHO Member States endorsed resolution 70.7 “Improving the prevention, diagnosis and clinical management of sepsis” asking WHO to **“draw attention to the public health impact of sepsis, including by publishing a report on sepsis describing its global epidemiology and impact on the burden of disease”***(9)*. This report on global sepsis epidemiology is based on several published original research and systematic literature reviews.

This report has shown that more tools are necessary to align and improve the understanding and homogeneous applicability of sepsis case definitions, particularly for low-resource settings. Sepsis case definitions have changed over time, differ according to age groups, and have been applied differently, depending on the level of diagnostic capacity. In general, official reporting is suboptimal and incomplete because it is often limited to hospitals or influenced by reimbursement incentives. Moreover, the design of studies changes frequently, as well as the data sources and setting.

Our knowledge of the role of sepsis in the causal pathway to disabilities, long-term complications and death is limited. Short- and long-term consequences need standardized and longer follow-up times, which are expensive. Furthermore, natural variations such as underlying conditions, age and other patient characteristics, together with differences in settings, treatment and access to health care, are often not clearly defined or standardized, limiting the generalizability of the burden of sepsis.

This report clearly identifies a number of priority actions and short-term results that could be achieved if countries act swiftly in a concerted effort. At the global level, more surveillance and evidence on the sepsis burden of disease is needed through increased awareness and funding that promotes high-quality research across all settings, but with a particular focus on LMICs. This will be achieved through clear consensus on age-specific sepsis definitions, implementation of the ICD-11 classification and promotion of high-quality epidemiological studies. Finally, sepsis should be included in all public health efforts such as national action plans, UHC, AMR, IPC, and WASH. In lower-resource settings, epidemiology research should target population-based studies as the burden of community-based sepsis is higher, be linked to existing surveillance efforts (such as GLASS) and be supported by a strengthened laboratory capacity.

Together with promoting IPC and immunizations to prevent sepsis and improving clinical management, determining the impact of sepsis is necessary to provide a baseline and measure interventions, ultimately ensuring that patients receive the most effective care. Preventing and improving outcomes from sepsis is a priority in achieving UHC and quality of care improvement.

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