The Epidemiology and Causes of Global and Regional Sepsis Mortality in Children Under Five, 1990–2021:

A Systematic Analysis

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Abstract

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Introduction: Despite the significant burden of sepsis in children under five years of age, estimating the global burden of sepsis in this group as well as further characterization of its epidemiology is challenging due to heterogeneity in defining and measuring sepsis in children and data sparsity from low- and middle-income countries, where the mortality is highest. Methods: Using multiple cause of death data from multinational individual level records, we applied the Sepsis-3 definition to identify explicitly and implicitly coded sepsis deaths (e.g., a non-infectious underlying cause with an infectious intermediate cause of death). We applied sepsis fractions from binomial logistic regression models to cause-specific mortality estimates from the 2021 Global Burden of Disease (GBD) study to estimate annual pediatric (defined as children under five years of age) sepsis-related mortality by sex, GBD super-region, and underlying cause of death from 1990 to 2021. Results: We estimated 2.66 million deaths (95% uncertainty interval: 2.18–3.14) related to pediatric sepsis worldwide in 2021, the lowest sepsis mortality since 1990. Neonates had the greatest burden with 949,000 deaths (751,000–1,150,000) in 2021. The Sub-Saharan Africa super-region showed the greatest decline in pediatric sepsis-related mortality but continued to disproportionately lead other super-regions with 1.71 million

deaths (1.39–2.04) in 2021. The sepsis burden associated with infectious underlying causes decreased: lower respiratory infections and diarrheal diseases, the leading two causes of sepsis in 1990, have been supplanted by neonatal disorders. Neonatal encephalopathy due to birth asphyxia and trauma, a non-infectious underlying cause of sepsis, remained the leading sub-cause of the sepsis-related mortality burden associated with the neonatal disorders cause group. Conclusions: From 1990 to 2021, global pediatric sepsis-related mortality decreased, primarily from progress addressing sepsis with infectious underlying causes. The burden of sepsis-related mortality concentrated among neonates, especially in Sub-Saharan Africa and South Asia, and neonatal disorders led as underlying causes of both neonatal and pediatric sepsis deaths. Further attention is needed to define neonatal sepsis and address sepsis as a complication of non-infectious neonatal conditions.

Introduction

Sepsis—generally defined as the life-threatening response of the host to infection—represents a poorly defined cause of preventable mortality in young children. Our limited understanding of the global distribution and leading causes of sepsis deaths in this population is concerning considering the significant burden of under-five sepsis mortality.

In 2020, Rudd et al. published the most comprehensive global estimates of sepsis incidence and mortality by underlying cause from 1990 to 2017.[1] Using an inclusive modelling framework in which multiple causes of death are considered to define sepsis as the final common pathway from an underlying cause to death, the authors estimated that children under five years of age suffered from 3.0 million sepsis-related deaths in 2017, a sizeable proportion of the estimated 5.7 million total under-five deaths.[2]

Several challenges limit our understanding of the global epidemiology and burden of sepsis in children. First, consensus definitions and diagnostic criteria for sepsis in children, particularly neonates, are lacking. Unique physiologic aspects in neonates and young children including altered immune responses to infection and variability in normal vital sign ranges by age create challenges around developing standardized criteria to identify sepsis.[3] The most broadly accepted sepsis definition from the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) of "a life-threatening organ dysfunction caused by dysregulated host response to infection" excluded information validated in children.[4] The 2005 definition by the International Consensus Conference on Pediatric Sepsis,[5] "the systemic inflammatory response syndrome (SIRS) in the presence of suspected or proven infection," has remained the primary definition and criteria for sepsis in children for some time but has faced variable applications by clinicians[6] and limitations in perceived utility.[7] Additionally, experts have raised concerns that this definition is inappropriate for neonates, especially those who are preterm, and that a specific neonatal sepsis definition is needed.[3] In February 2024, the Phoenix sepsis

criteria was released and defines sepsis in children with suspected infection using a cutoff of two or more points from their organ dysfunction criteria.[8] Though the applicability of these criteria to most term newborns appears promising, inclusion of multiple laboratory criteria may limit use in resource limited settings.

Second, data availability has been biased toward high-income settings. High-quality vital registration and electronic health record (EHR) systems are lacking in most LMICs:[9,10] in 2021, only 15% of low-income countries had national EHR systems. Researchers in LMICs face resource challenges that limit the number of pediatric sepsis studies.[11] The lack of data from LMICs makes it both challenging to accurately quantify sepsis incidence and mortality and to reliably monitor the effects of interventions.

Third, where data are available, current practices in cause of death research and limitations of health systems underestimate sepsis burden. Studies like the Global Burden of Disease (GBD) Study categorically attribute deaths to the underlying cause of death from vital records and consider sepsis an intermediate cause of death that is redistributed to other causes when listed as the underlying cause (see Figure S1 for a sample death record).[12] Studies have shown that when used, diagnostic codes for sepsis are often listed as an immediate cause of death rather than the underlying cause of death.[13] Additionally, multiple studies have shown that attempts to identify sepsis primarily through explicit sepsis diagnostic codes underestimated the true incidence of sepsis.[6,14,15] This suggests that even “high quality” data may be insufficient to overcome limited frameworks for sepsis mortality.

A consequence of this narrow yet imprecise framework to identify sepsis and of our limited understanding of underlying causes of sepsis in children has been reliance on generalized interventions. Interventions to reduce sepsis mortality have focused on improving the time to recognition and treatment of sepsis,[16] often through “bundled” actions including rapid administration of fluids and broad-spectrum antibiotics[17] and non-specific measures such as

increased handwashing among care providers for neonates.[18] However, a more tailored approach that targets preventing and treating predisposing causes and infections would be most effective at reducing sepsis mortality. For example, a recent study demonstrated that diverging from global standards in antibiotic choices for neonatal sepsis, both increased the risk of antimicrobial resistance in areas and populations with low resistance rates, and also provided insufficient coverage for resistance patterns in locations where resistance rates were higher.[19] The Society of Critical Care Medicine's Pediatric Sepsis Definition Taskforce identified the need for global databases to inform the development of locally adaptable interventions, summarizing this need as a recommendation to "think globally, act locally."[20]

To address the gaps above, we employed a multiple cause of death framework for sepsis as introduced by Rudd et al.[1] This allowed us to include both explicitly coded sepsis deaths and deaths that implicitly met sepsis definitions through the use of infection and organ dysfunction codes. We broadened the implicit sepsis definition used previously by Rudd et al. to include implicit sepsis deaths resulting from a non-infectious underlying cause of death in subsequent analyses used for estimating antimicrobial resistance[1] and here (see *Data Processing, Mapping, and Redistribution within a Multiple Cause of Death Framework*). We used an inclusive approach in which an underlying infectious cause of death could contribute to our sepsis estimates if there was evidence for organ dysfunction. This approach aligned with recommendations from Kissoon and Carapetis, two experts in pediatric sepsis, who suggested that sepsis should be considered a "unifying feature" of infectious deaths.[21] While classification practices ascribing sepsis deaths to underlying infectious causes promote interventions that can reduce sepsis mortality through the prevention of the underlying infections, the underestimation of sepsis deaths minimizes attention and investment into interventions which can address sepsis more broadly (e.g., focusing on the organ dysfunction resulting in mortality). Additionally, with limitations in data availability and high between-study heterogeneity and risk of bias as a

limitation of efforts to conduct meta-analyses,[22,23] modeling approaches like ours are crucial to generate comprehensive and comparable estimates of sepsis burden.

In this analysis, we aimed to provide global cause-specific pediatric (defined in this analysis as children under five years of age) sepsis mortality estimates using a modeling approach that leveraged estimates from multinational multiple cause of death input data with comprehensive GBD 2021 mortality estimates. By completing the first global estimation of pediatric sepsis by detailed underlying cause, sub-age group, location, and year from 1990 to 2021, our goals were to describe trends in pediatric sepsis mortality, especially considering the global impact of the COVID-19 pandemic, and identify targets for further study and focused interventions.

Methods

Overview

This analysis focused on the causes and fatal burden of pediatric sepsis, both for children under the age of five years as a group and as divided into five specific age groups: neonates (0-28 days), 1 to 5 months, 6 to 11 months, 12 to 23 months, and 2-4 years. This analysis used multiple cause of death data from the Global Burden of Antimicrobial Resistance (AMR) study and mortality estimates from the 2021 Global Burden of Disease (GBD).[24] For multiple cause of death data, we applied a framework to include a comprehensive accounting of both explicit and implicit sepsis cases as defined in “Sepsis Definition” below. We used a logistic regression model to estimate the proportion of deaths attributable to sepsis within each GBD cause, sex, age group, location, and year. These proportions were multiplied to GBD 2021 mortality estimates for each underlying cause of death to produce sepsis-related mortality estimates by underlying cause of death, sex, age group, and location (aggregated to the seven GBD super-regions, Table S1)[25] for each year from 1990 to 2021.

Data Sources

We used "multiple cause of death" data sources from the Global Burden of AMR study to identify sepsis-related deaths: these were broadly grouped as data from vital registration systems (9 countries), hospital records (12 sources from 10 countries), "linkage" sources (hospital records linked with other records for individuals, 2 countries), and verbal autopsies (interviews with contacts of the deceased) and minimally invasive tissue sampling (7 countries). The 22 represented countries, 15 (68%) of which are classified as LMICs by the World Bank, and 24 unique databases, systems, or studies represented by the above methods are summarized in Table 1.

We obtained annual national all-cause mortality estimate draws from 1990 to 2021 by age group and sex for 183 underlying causes of death from GBD 2021.[24]

Data Processing, Mapping, and Redistribution within a Multiple Cause of Death Framework

The definition of sepsis has evolved over time and for children, the problem of defining sepsis has suffered from challenges with the early recognition of organ dysfunction. To provide the broadest definition, we applied the latest consensus adult sepsis definition[4] (Sepsis-3), a life-threatening organ dysfunction caused by dysregulated host response to infection using a "multiple cause of death" framework to account for the heterogeneity in sepsis definitions in epidemiologic and clinical use. This framework incorporated all causes of death from data sources to capture implicit sepsis cases in addition to those explicitly specified as sepsis by those certifying a death.

In brief, death records generally list underlying, intermediate, and immediate causes involved on the pathway to death and these diagnoses are standardized using International Statistical Classification of Diseases and Related Health Problems (ICD) codes (Figure S1). Unlike the GBD study, which only uses the underlying cause of death to assign a death to a

cause, we considered all causes on this "pathway to death" to classify a death as either sepsis-related or not, using both explicit and implicit sepsis definitions (Table S2).

Explicit sepsis deaths contained an ICD code directly referencing sepsis as an intermediate cause of death (e.g., ICD-10 code A40.3 Sepsis due to *Streptococcus pneumoniae*), with either an infectious or non-infectious underlying cause of death. Deaths with a sepsis ICD code as the underlying cause of death were classified as "garbage codes" since sepsis is an intermediate cause on the pathway to death and is considered improperly coded if classified as an underlying, rather than an intermediate, cause of death. These deaths with "garbage codes" were proportionally redistributed to other underlying causes through a process previously described in greater detail.[12]

Implicit sepsis deaths were defined as cases with an infectious disease code (e.g., ICD-10 code J13 Pneumonia due to *Streptococcus pneumoniae*) as either or both an underlying or intermediate cause and organ failure code for the immediate cause of death (e.g., ICD-10 code J96 Acute respiratory failure): this served as an application of the Sepsis-3 definition for deaths in which a certifier did not recognize or explicitly define the case as sepsis. With our multiple cause of death framework, this implicit sepsis definition allowed us to identify and include cases with non-infectious underlying causes of death that were complicated by sepsis: for example, a neonate with the non-infectious underlying cause of death ICD-10 code P91.6 Hypoxic ischemic encephalopathy of newborn, followed by J13 Pneumonia due to Streptococcus pneumoniae as an intermediate cause, then J96 Acute respiratory failure as the immediate cause of death would meet the implicit sepsis criteria.

Each death defined as a sepsis case was mapped to a GBD underlying cause. The GBD underlying cause list is a mutually exclusive and collectively exhaustive hierarchical list of diseases and injuries (Table S3). Causes were specified at multiple nested levels of specificity: one Level 0 cause ("all causes"), three Level 1 cause categories ("communicable, maternal,

neonatal, and nutritional diseases" (CMNN); "non-communicable diseases"; "injuries"), 20 Level 2 causes (more detailed cause groupings: e.g., "Maternal and neonatal disorders"), 98 Level 3 causes (most detailed causes for many causes), and 61 Level 4 (most detailed "child" sub-causes provided for select Level 3 "parent" causes when more specificity is available). Level 3 causes were mutually exclusive and collectively exhaustive (i.e., the sum of deaths from each Level 3 cause equals the total number of deaths for all individuals of a specified age group, location, and year). However, as Level 4 causes were only available for select Level 3 causes which would both benefit from and have sufficient infrastructure to be disaggregated to more specific child causes, the sum of deaths from each Level 4 cause would be mutually exclusive but not collectively exhaustive. The CMNN Level 1 category included both all infectious conditions and those non-infectious causes for which mortality is expected to decline more quickly than for all-cause mortality during epidemiological transition.[26] Of note, GBD estimated sepsis as an underlying cause of death in the context of "neonatal sepsis and other infections" (Level 4 child cause of the Level 3 "neonatal disorders" parent cause) but otherwise, sepsis in children was not explicitly modeled by GBD. In this analysis, we focused on reporting Level 3 causes but for comprehensive reporting, also disaggregated leading Level 3 causes to Level 4 child causes when the parent Level 3 cause did not represent the most detailed cause. Records were aggregated by underlying cause, age group, sex, location, and year for our estimation steps.

Modeling cause specific-sepsis fraction of deaths and obtaining cause-specific sepsis mortality estimates

We used a mixed-effects binomial linear regression in two stages to model the logit of the proportion of deaths that were related to sepsis by underlying cause, age, and location:

$$sepsis\ related\ deaths \sim B(total\ deaths, sepsis\ fraction)$$

$$logit(sepsis\ fraction) = \beta_0 + \beta_1 * HAQ\ Index + \beta_2 * sex + \pi_{level\ 1, level\ 2}$$

where $\pi_{level\ 1, level\ 2}$ is a nested random effect on underlying cause of death which allowed the prediction of sepsis fractions where data were limited by borrowing information from diseases within the same group.

This model has previously been validated to estimate sepsis deaths.[1,25] The regression included nested random effects on levels of underlying cause to allow related causes to borrow predictive strength from each other for data sparse causes. The Healthcare Access and Quality (HAQ) index was included as a covariate, as previously used by Rudd et al to predict sepsis proportions for locations without data. The HAQ Index was first developed as part of GBD 2015, and used an amenable mortality (i.e., deaths from causes that should not occur in the presence of high-quality healthcare) framework to score each country and year from 0 (worst) to 100 (best) which represented the quality of and access to the healthcare system by examining the mortality from 33 preventable diseases which would not result in mortality with adequate healthcare. Methods used to calculate this score are described in other publications.[27,28] Sex was included as a demographic covariate.

In the first stage, we calculated sepsis fractions from multiple cause of death data for each age group, location, year, HAQ Index (for the associated location-year), sex, and underlying cause of death. We ran age group-specific regression models to generate sets of beta coefficient values wherein the covariate on HAQ Index was used to capture variation by year and location. In the second stage, we used these models to predict sepsis fractions by generating point estimates. Point estimates for each underlying cause, age group, location, and year were multiplied on each corresponding GBD cause specific mortality envelope estimate draws from the GBD 2021 to obtain cause-age-location-year specific sepsis mortality estimates.

Age, location, and year specific population estimates from GBD 2021[29] were used to calculate age-specific mortality rates. Uncertainty intervals were generated using the following equation:

$$Point\ estimate\ \pm 1.96 * Standard\ Deviation$$

Results

Epidemiology and Trends in All-Cause Sepsis-Related Mortality

In 2021, children under five years of age experienced an estimated 2.66 million (95% uncertainty interval [UI]: 2.18–3.14) sepsis-related deaths from all underlying causes, for both sexes combined. This represented 56.9% (53.0–60.9) of all under-five deaths globally. Global pediatric sepsis-related mortality from all causes has steadily declined since 1990, resulting in a 67.2% (63.6–71.5) reduction in mortality rate to 403.5 deaths (330.5–476.4) per 100,000 population in 2021 (Figure 1). In 1990, there were an estimated 4.97 million (4.98–4.96) more sepsis-related deaths and sepsis complicated 67.6% (64.6–70.6) of total under-five deaths (Table 2).

Comparing global sepsis-related mortality for both sexes combined across age groups in 2021, neonates (0-28 days of age) had the greatest sepsis mortality with 9,740 deaths [95% UI: 7,710–11,800] per 100,000 population (Table S4, Figure 2). Age-specific sepsis-related mortality rates were lower for older age groups: in 2021, the 1-5 month age group had 882 sepsis-related deaths (779–986) per 100,000 population; the 6-11 month group had 601 sepsis-related deaths (468–735) per 100,000 population; the 12-23 month group had 263 deaths (210–316) per 100,000 population; and lastly, the 2-4 year group had 121 deaths (96.1–146) per 100,000 population. Fractions of age-specific mortality related to sepsis increased by age group: for neonates, sepsis-related deaths accounted for 43.4% (37.3–49.4) of total 2021 neonatal deaths and was highest for the 2-4 year age group (73.3% [66.5–80.1]).

Global pediatric sepsis-related mortality rates were higher for males (423.3 deaths [95% UI: 341.9–504.8] per 100,000) than for females (382.2 deaths [317.7–446.7] per 100,000) in 2021 (Table 2); this represented a 1.11 (1.08–1.13) male-to-female sex mortality ratio (SMR). In 2021, males had similar proportions of all deaths complicated by pediatric sepsis as females did (56.3% [52.3–60.3] compared to 57.7% [53.6–61.7]) and proportions were similar or lower for males than females across all years. The male predominance of sepsis-related mortality burden generally held true across years, age groups, and across GBD super regions: the largest 2021 male-to-female SMRs were in neonates (1.26 [1.22–1.28] global SMR); Central Europe, Eastern Europe, and Central Asia (1.23 [1.22–1.25] pediatric SMR); and Southeast Asia, East Asia, and Oceania (1.23 [1.21–1.25] pediatric SMR). In South Asia, females had higher sex-specific mortality from 1990 (pediatric SMR 0.934 [0.928–0.934]) through 2019 (pediatric SMR 0.933 [0.906–0.950]).

Among GBD super regions, sub-Saharan Africa had the greatest pediatric sepsis-related mortality in 2021, both sexes combined, with 990 deaths (802–1,180) per 100,000 population, followed by South Asia (372 deaths [298–445] per 100,000 population), then North Africa and Middle East (151 deaths [125–178] per 100,000 population), Latin America and Caribbean (136 deaths [106–165] per 100,000 population), Central Europe, Eastern Europe, and Central Asia (101 deaths [85.4–117] per 100,000 population) in proximity, then followed by the high-income super region (18.9 deaths [16.3–21.4] per 100,000 population) (Figure 3A-B, Table S5). All super regions had consistent declines in pediatric sepsis-related mortality from 1990 to 2021 and the relative rankings of super regions remained consistent. Sub-Saharan Africa had the greatest rate of decline in sepsis-related mortality rate, represented by a 69.1% [65.0–73.5] change from 1990 to 2021. However, looking at death counts, the number of sepsis-related deaths rose from 2.87 million (2.71–3.03) in 1990 to a peak of 3.06 million (2.86–3.26) in 1999 before declining to 1.71 million deaths (95% UI: 1.39–2.04) in 2021 levels.

For neonates, sepsis-related mortality in 2021 for both sexes combined had a similar relative ranking of super regions: sub-Saharan Africa led with 17,800 deaths [95% UI: 14,000–21,700] per 100,000 population) with South Asia (12,400 deaths [9,530–15,300] per 100,000 population), followed by the other non-high-income super regions as a group—Latin America and Caribbean (4,190 deaths [3,240–5,140] per 100,000 population), North Africa and Middle East (4,100 deaths [3,240–4,960] per 100,000 population), Central Europe, Eastern Europe, and Central Asia (3,000 [2,470–3,540] per 100,000 population)—then followed by the high-income super region (600 deaths [482–719] per 100,000 population) (Figure 3C-D, Table S5). From 1990, all super regions had steady declines in sepsis-related mortality per 100,000 population and sub-Saharan Africa and South Asia had the greatest declines in mortality rates (50.7% [45.5–56.8] and 63.8% [60.4–68.2], respectively). In terms of number of sepsis-related deaths, South Asia had the greatest burden amongst super regions in 1990 (880,000 deaths [770,000–990,000]) and dropped below sub-Saharan Africa starting in 2001 and had 296,000 deaths [227,000–365,000] in 2021. In sub-Saharan Africa, the number of neonatal sepsis-related deaths remained relatively stable with a slight rise from 1990 to 2003 (10.7% [8.1– 12.8]) before declining from 2005 to 2021 (23.6% [18.3–30.8]), amounting to only a 15.4% [7.0–26.0] total decline from 596,000 deaths (534,000–658,000) in 1990 to 504,000 deaths (395,000–612,000) in 2021.

Levels and Trends in Cause-Specific Sepsis-Related Mortality

Pediatric Sepsis-Related Deaths by Underlying Cause

From 1990 to 2021, the burden of pediatric sepsis-related mortality, both sexes combined, was predominantly from causes in the GBD communicable, maternal, neonatal, and nutritional (CMNN) diseases Level 1 cause category (Figure 1). Mirroring the all-cause sepsis-related mortality trend, sepsis-related mortality from CMNN underlying causes decreased from

1,180 deaths (95% UI: 1,110–1,260) to 382 deaths (312–452) per 100,000 population. Sepsis mortality complicating non-communicable diseases (NCD), the second largest Level 1 category, also decreased from 1990 to 2021 (43.4 deaths [31.8–55.0] to 19.5 deaths [15.5–23.6] per 100,000 population) but changes were smaller in magnitude. Sepsis mortality complicating underlying injuries, the lowest burden Level 1 cause category, decreased from 25,600 deaths (20,600–30,600) to 10,500 deaths (7,280–13,800) deaths per 100,000 population. The proportion of total Level 1 category deaths complicated by sepsis has remained stable over time for the NCD and injuries categories: sepsis-related deaths represented about 20 percent (1990: 20.7% [17.8–23.6], 2021: 20.1% [17.9–22.3]) of all NCD deaths and about five percent (4.12% [3.52–4.72] in 1990 to 5.26% [4.47–6.05] in 2021) of all injuries deaths.

In 2021, the leading Level 3 underlying causes for global pediatric sepsis-related mortality, both sexes combined, were all under the CMNN Level 1 cause category: the top five Level 3 causes were neonatal disorders with 702,000 deaths (95% UI: 532,000–871,000), lower respiratory infections (502,000 deaths [405,000–598,000]), malaria 425,000 (101,000–750,000), diarrheal diseases 340,000 (239,000–442,000), and meningitis 91,100 (60,700–122,000) (Table S6). The percent of total global deaths due to the neonatal disorders cause complicated by pediatric sepsis in 2021 was 38.3% (31.2–45.4). Lower respiratory infections and diarrheal diseases had the greatest declines in mortality rates from 1990 to 2021 (represented by a 75.7% [74.5–77.3] decrease from 314 deaths [271–357] per 100,000 in 1990 and an 80.4% [78.8–82.8] decrease from 264 deaths [211–316] per 100,000 population, respectively) (Figure 4). These improvements resulted in lower respiratory infections dropping from first to second place rank from 1990 to 2021 and diarrheal diseases dropping from second to fourth place from 1990 to 2021 and neonatal disorders' corresponding rise in relative rank, as it only decreased by 45.1% [42.9-49.5] from its 1990 mortality rate (195 deaths [160–231] per 100,000

population). Malaria, the fourth leading cause in 1990 and the third leading cause in 2021, only declined by 18.9% [14.3–41.6] from its 1990 mortality rate (79.7 deaths [26.2–133) per 100,000 population) and was one of the only leading causes to increase in mortality rate from 2019 to 2021. COVID-19 was the 17th leading global underlying cause of pediatric sepsis-related deaths in 2021, contributing to an estimated 16,700 deaths (15,300–18,100).

Neonatal disorders, the leading Level 3 cause of pediatric sepsis-related mortality in 2021, comprised five Level 4 child causes (Table S3). The leading three of these Level 4 child underlying causes of sepsis-related mortality in 2021 were neonatal encephalopathy due to birth asphyxia and trauma with 248,000 deaths (95% UI: 132,000–365,000), neonatal sepsis and other neonatal conditions with 233,000 deaths (195,000–271,000), and neonatal preterm birth with 151,000 deaths (77,300–224,000) (Table S7). Among the non-infectious causes, the percentage of total cause-specific deaths complicated by sepsis was 20.4% (11.1–29.6) for neonatal preterm birth and 41.1% (22.5–59.7) for neonatal encephalopathy due to birth asphyxia and trauma in 2021. Neonatal sepsis and other neonatal conditions was the third leading Level 4 child cause of the Level 3 neonatal disorders parent in 1990, after neonatal encephalopathy due to birth asphyxia and trauma and neonatal preterm birth; neonatal sepsis and other neonatal conditions decreased by only 27.9% (25.6–30.7) from 1990 to 2021 and became the second leading Level 4 cause under the Level 3 neonatal disorders parent cause in 2021.

Sepsis-Related Deaths in Neonates by Underlying Cause

Focusing on the neonatal age group, Level 1 trends were similar as for the under-five age category: the sepsis mortality associated with CMNN underlying causes in 2021 for neonates (903,000 deaths [95% UI: 711,000–1.10 million]) greatly surpassed that for NCD (44,300 deaths [31,700–56,900]) and injuries (1,460 deaths [943–1,980]). The decline in CMNN

complicated by sepsis from 20,200 deaths (17,900–22,500) per 100,000 population to 9,270 deaths (7,300–11,200) per 100,000 population from 1990 to 2021 account for the greatest overall decline in mortality burden. The percentage of each Level 1 category's total cause deaths complicated by sepsis also decreased from 1990 to 2021: for CMNN from 56.4% (50.4–62.4) to 46.5% (39.6–53.3), for NCD from 24.7% (19.4–30.0) to 19.8% (15.7–24.0), and for injuries from 14.5% (11.9–17.0) to 11.7% (9.23–14.1).

Leading global Level 3 underlying causes of sepsis-related deaths for neonates in 2021 for both sexes combined were neonatal disorders (626,000 deaths [95% UI: 463,000–789,000]), lower respiratory infections (152,000 deaths [127,000–177,000]), sexually transmitted infections excluding HIV (which for this age group, was only composed of one Level 4 child cause, syphilis; 49,600 deaths [7,010–92,100]), congenital birth defects (38,400 deaths [26,300–50,600]), and diarrheal diseases (24,500 deaths [16,600–32,400]). For neonatal disorders and congenital birth defects, sepsis-related deaths represented 37.6% (29.7–45.4) and 19.0% (14.4–23.5) of total underlying cause-specific deaths, respectively. Mortality rates for these leading causes all decreased from 1990 to 2021 (Figure 5). The progress with sepsis-related mortality due to infectious underlying causes of death is highlighted by relatively large changes in rankings from 1990 to 2021: diarrheal diseases dropped from third to fifth leading cause and tetanus dropped from fourth to eighth. Despite decreasing mortality rates, syphilis rose in rank from sixth to third place due to limited progress from 1990 to 2019 followed by a rise in mortality rate during the pandemic.

Examination of the Level 4 child causes for the Level 3 parent neonatal disorders in neonates revealed similar patterns as seen for the under-five age category: the leading Level 4 child causes of sepsis-related mortality in 2021 under the Level 3 neonatal disorders category were neonatal encephalopathy due to birth asphyxia and trauma with 230,000 deaths (95% UI: 115,000–345,000), followed by neonatal sepsis and other neonatal conditions with 206,000

deaths (172,000–241,000), and neonatal preterm birth with 132,000 deaths (59,300–204,000), syphilis with 49,600 deaths [7,010–92,100] (Table S7). The percent change in the sepsis-related mortality rate for neonatal sepsis and other neonatal infections from 1990 to 2021 was lower than the corresponding change for the under-five age group: the mortality rate only decreased by 20.0% (17.2–23.6) from 1990 to reach 100 deaths (97.9–102) per 100,000 population in 2021.

Regional Variations in Leading Underlying Causes for Sepsis-Related Deaths

There was regional variation in cause-specific sepsis-related mortality (Table S6). For pediatric sepsis-related mortality in 2021, deviations from the global Level 3 cause rankings were notable for increases in relative rankings of specific infectious diseases: most notably, in sub-Saharan Africa, malaria was the leading cause of pediatric sepsis-related mortality with 241 deaths (95% UI: 61.3–420) per 100,000 population; in South Asia, typhoid and paratyphoid was fourth with 18.8 deaths (6.17–31.4) per 100,000 population; measles was fifth in North Africa and Middle East with 5.91 deaths (2.92–8.91) per 100,000; syphilis was fifth in Southeast Asia, East Asia, and Oceania with 5.12 deaths (0.570–9.66) per 100,000 population; and in Latin America and Caribbean, COVID-19 was fifth with 3.68 deaths (3.07–4.28) per 100,000 population). Otherwise, the relative rankings of non-infectious causes remained consistent.

For neonates, sepsis-related mortality in 2021 rankings remained relatively consistent for the leading causes with neonatal disorders and lower respiratory infections leading for nearly all super regions (Table S8). For Level 3 causes, malaria was the fourth leading cause in sub-Saharan Africa (757 deaths [95% UI: 61.0–1,450] per 100,000 population) but otherwise, no other unique specific infectious conditions showed particular regional predominance. Of note, syphilis was in the top five causes for all regions except in Central Europe, Eastern Europe, and Central Asia (where it was seventh). Tetanus remains a top-15 leading cause of sepsis-related

mortality except in the Central Europe, Eastern Europe, Central Asia and High-income super regions.

The increase in all-cause sepsis-related deaths in neonates in sub-Saharan Africa from 2003 to 2006 appeared to correspond to increases in sepsis-related deaths due to the Level 3 neonatal disorders cause. Examining the Level 4 child causes for the neonatal disorders parent cause, we found the increased mortality stemmed from changes in neonatal encephalopathy due to birth asphyxia and trauma (which peaked at 158,000 deaths from 2008 [95% UI: 81,600–234,000] to 2009 [(90,700–225,000]), followed by neonatal sepsis and other neonatal infections (which peaked at 131,000 deaths [109,000–152,000] in 2014). Sepsis-related deaths due to the Level 3 neonatal disorders parent cause plateaued at 378,000 annual deaths from 2008 (95% UI: 288,000–468,000) to 2013 (296,000–460,000) before dropping, showing lagging progress after sepsis-related deaths caused by lower respiratory infections started to decline in 2002.

Discussion

This analysis provides an updated and focused estimation of pediatric sepsis-related mortality at a global level, with decomposition by 183 underlying causes, sex, seven super-regions, and six under-five age groups, from 1990 to 2021. This study builds on our group's prior work in 2020[1] to produce the first comprehensive global estimates of sepsis mortality covering 1990 to 2017, disaggregating sepsis-related deaths due to the Level 3 cause neonatal disorders to its Level 4 sub-causes, and this analysis represents the first to apply a modelling strategy which leverages tools like multiple cause of death data, the HAQ Index, and GBD mortality estimates to estimate the global causes and distribution of pediatric sepsis. Overall, we report similar themes of decreasing global sepsis burden over time, with disparities in the distribution of mortality with the highest concentration of deaths in the neonatal age group and in sub-Saharan Africa. Comparing our 2017 estimates against our prior estimate, our estimated

3.44 million (95% UI: 2.99-3.88) global pediatric sepsis-related deaths for children is nearly half a million more deaths than the 2.9 million sepsis-related deaths (2.6-3.2) previously reported. This suggests our 2021 estimate of 2.66 million (2.18–3.14) global pediatric sepsis-related deaths for children likely reflects a higher burden than would have been previously estimated. This increased burden likely reflects the broadening of our sepsis definition to include implicit sepsis cases with non-infectious underlying causes and the inclusion of additional data sources from low- and middle-income countries (LMICs), particularly deaths from low-income countries that were not included in the 2020 analysis.

This analysis highlights the disproportionately high burden of sepsis mortality shouldered by neonates. For neonates, we estimated 949,000 deaths (751,000–1,240,000) in 2021, and for years prior to 2020, our estimates have exceeded 1 million deaths. These estimates far surpass other numbers in the literature; most recently, researchers have estimated 689,922 annual neonatal sepsis deaths using data from 1979 to 2019.[23] While these large estimates likely also reflect our inclusion of more LMIC sources, the general sparsity of estimates from other sources and wide ranges additionally highlight the additional problem of defining sepsis in this population.

We used a comprehensive sepsis definition that incorporated implicitly coded cases of sepsis consistent with the Sepsis-3 definition of infection leading to life-threatening organ dysfunction. The Phoenix criteria[8] offer an updated definition for pediatric sepsis but its criteria focus on identifying organ dysfunction through specific criteria, including laboratory results and specific monitoring parameters which may be reliant on intensive care monitoring capabilities (e.g., invasive lines for arterial oxygen pressure), in children with suspected infection which may be too specific and biased to high resource settings to apply to data sources like ours. Additionally, we need a pediatric sepsis definition appropriate for all neonates, including preterm and those with early hospitalizations. Within this analysis, we find the 206,000 neonatal deaths

(172,000–241,000) attributed to “neonatal sepsis and other neonatal infections” (GBD Level 4 underlying cause) only represented 21.7% of the entire estimated burden of sepsis in neonates in 2021. While our comprehensive sepsis framework may skew toward high sensitivity to pick up any sepsis death, to limit ourselves to “neonatal sepsis” as either an underlying cause of death only or as explicitly coded would likely severely underappreciate the burden of sepsis in neonates. This analysis showed that there has been relatively little progress in both neonatal and pediatric sepsis-related mortality from underlying neonatal sepsis (20.0% and 27.9% change in age-specific mortality rates from 1990, respectively), especially in comparison to other underlying infectious causes like lower respiratory infections. Several factors challenge our understanding of the epidemiology of sepsis in neonates: immaturity of neonatal immune systems, need to consider both maternal risk factors and variable exposure to and acquisition of passive immunity in considering infectious risks, and unique exposures and risks based on very fine time periods (e.g., within 72 hours of birth, in the first seven days of life, before 22 days of life vs between 22 to 28 days).[3] These factors have contributed to the lack of a consensus sepsis definition appropriate for this age group and lower the likelihood that any diagnostic tool for sepsis found for adults or other children will be useful for neonates. Additionally, implementation in low resource settings will necessitate decreased reliance on laboratory information for sepsis criteria.[30] Working definitions for neonatal sepsis that are useful in a variety of settings and focused attention to this population is needed to identify the implications of using different definitions for sepsis (i.e., “neonatal sepsis” versus sepsis in neonates) to identify targets for future research and interventions.

This analysis revealed that neonatal disorders was the leading Level 3 cause of both pediatric and neonatal sepsis-related mortality in 2021. The most recent global mortality estimates from GBD 2021 showed that the mortality burden from neonatal disorders have decreased in children under five.[24] Though the overall reduction in mortality due to neonatal

disorders is promising and this analysis showed corresponding reductions in sepsis-related mortality, it is concerning that these reductions have remained relatively proportional, i.e., we have not seen dramatic reductions in the fraction of non-infectious neonatal disorders which are complicated by sepsis. We were able to disaggregate the more general Level 3 cause of neonatal disorders to its specific Level 4 child causes and found that the leading child cause was neonatal encephalopathy due to birth asphyxia and trauma, a neurologically devastating condition which can create high risk for subsequent infections (e.g., aspiration pneumonia). With corresponding estimates of declining incidence of neonatal disorders over time,[31] further investigation is needed to determine if the reductions in sepsis mortality are primarily driven from decreased incidence of these high-risk conditions versus decreased incidence of the complicating infections that lead to infection or decreased case fatalities due to better recognition and treatment of sepsis.

Neonatal preterm birth, another leading Level 4 child cause associated with sepsis-mortality in the Level 3 neonatal disorders category, has been declining globally as a cause of neonatal mortality[24] but increasing in prevalence.[31] Advancements in healthcare have lowered the minimum gestational age of viability and with improvements in healthcare access and further technological advancements, the population of extremely preterm infants (infants born prior to 28 weeks gestation) will continue to grow. Preterm infants, especially those who are extremely preterm, are at high risk of hospital acquired infections and other infectious complications resulting from their immunocompromise and other comorbidities, and with the increased survival of these high-risk populations, sepsis incidence and mortality may rise in neonates and young infants.[23] Likewise, the presence of conditions like congenital birth defects among the leading causes in 2021 represented the relative shifts towards non-communicable leading causes of sepsis-related mortality, especially for neonates. Closer monitoring and deeper understanding of

sepsis as a complication of non-infectious neonatal disorders will be important to address this burden.

We found that progress in reducing sepsis-related mortality was primarily due to decreases in underlying infectious conditions, primarily lower respiratory infections and diarrheal diseases, which are no longer the leading two causes for pediatric sepsis-related mortality. The declining mortality related to these infections—as well as meningitis and tetanus, previously a leading cause of sepsis-related deaths for neonates in 1990—can be at least partly attributable to immunizations. The development of vaccine technology with greater immunogenicity for young children, e.g., the pneumococcal conjugate vaccines, with investment in widespread vaccination campaigns targeting LMICs have been well documented with increased vaccine coverage against and decreased mortality from key pathogens like *Streptococcus pneumoniae*,[32] rotavirus,[33] *Haemophilus influenzae*,[34] as well as others.[35] Additionally, malaria, which was the leading cause of pediatric sepsis-related mortality in sub-Saharan Africa in 2021, has declined dramatically, likely due to the reliance on non-durable preventative measures (e.g., chemoprophylaxis, bed nets, vector control programs) until recently with the release of the first malaria vaccine in 2019 and a more efficacious vaccine which was prequalified by WHO in 2024.[36,37] However, as we continue to see diminishing returns on improvements to mortality after implementing high impact interventions to prevent specific infections, stronger consideration of general sepsis identification and treatment measures may be needed to further reduce mortality below what appears to be an unavoidable threshold.

We did not detect a clear impact of the COVID-19 pandemic on overall trends in sepsis-related mortality in 2020 and 2021: this was consistent with estimates that COVID-19 deaths in children under five contributed to fewer than 1% of total deaths and for other COVID-19 pandemic-related outcomes, at most, they contributed up to 6.2% of total deaths for the 12-23 month age group.[24] Looking at specific causes of sepsis-related mortality, there was a rise in

sepsis-related mortality from syphilis for neonates from 2019 to 2021, suggestive of negative pandemic-related effects that may be exacerbating surging rates of congenital syphilis seen in recent pre-pandemic years in many regions of the world.[38,39] Syphilis' prominence as a leading infectious cause of sepsis-related mortality for neonates in most super regions seen in this analysis highlights the widespread impact of this infection. Attention is needed to address the growing burden of congenital syphilis as a significant cause of sepsis in addition to continued monitoring for delayed effects of the pandemic on other causes of sepsis-related mortality in light of reported disruptions to healthcare systems, particularly to routine childhood vaccinations.[40–42]

In a GBD 2021 analysis of causes of death, causes like neonatal disorders have demonstrated "mortality concentration" within countries in sub-Saharan Africa and South Asia, which are the regions that bear the highest burden from this cause.[24] This analysis demonstrated a similar concentration of sepsis in these regions and despite comparatively large reductions in sepsis over time, sepsis mortality rates in sub-Saharan Africa and South Asia remain disproportionately high, highlighting the need to focus efforts in high concentration regions. Risk factors for mortality may differ in specific settings, especially LMICs, where other conditions such as malnutrition may impose variable risks of susceptibility to infections and deaths due to sepsis.[43] Investments are needed to set up or further develop surveillance and research systems, particularly focusing on neonatal health. Leveraging existing technology, e.g., widespread mobile device availability,[30] and investing in infrastructure like electronic health systems[10] can help improve data collection practices and data quality while also offering support for healthcare workers and promote standardization of care through tools like vital sign based screening pathways.[44,45] Data-driven and context-specific management guidelines have been identified as a gap for reducing the burden of sepsis in LMICs but will require resources to develop, validate, and implement.[9]

Much of this study's strengths involve the integration of our innovative multiple cause framework and our comprehensive sepsis definition with GBD estimates: we integrated a variety of individual level data from multiple countries across the globe to provide as representative of input data as possible, applied a flexible sepsis framework on multiple cause of death data to include implicit sepsis deaths, used modelling techniques to synthesize data from heterogenous sources and borrow strength across locations to predict the sepsis burden for data sparse locations, and integrated our model estimates of sepsis fractions with the GBD 2021 framework to leverage the most up-to-date, comparable estimates for 183 causes of death. Though our sepsis estimates are not directly comparable to cause-specific estimates as they are would not be mutually exclusive, our methods allow them to remain within the GBD mortality envelope which offers a comparable sense of scale to GBD estimates. We build on our prior work with the addition of fatal data from more sources, now including data from low-income countries; data collected during the COVID-19 pandemic; reporting of underlying causes at more detail for leading causes (i.e., reporting of Level 4 child causes for the Level 3 category neonatal disorders); and cause-specific mortality estimates from the latest GBD round.

Limitations include the risk of misclassification due to varying sepsis definitions, especially with changes over time, and due to the use of ICD data that may have been variably coded by individual clinicians. Despite our expanded collection of data sources, we still drew input data for our model from only 22 countries and predictions for locations and age groups without input data primarily rely on data from locations with similar HAQ Index with some added strength from related causes. We chose to use simple, easily explained models which assume linear relationships between our covariates (HAQ Index, sex) and the sepsis fraction but this may oversimplify the true nature of this relationship. We also faced some limitations in modelling capacity: for this analysis, we used 100 draws to propagate uncertainty where we have previously used 1000. Our data are biased toward inpatient sources and we likely

underestimate the mortality related to sepsis that occur outside of hospital settings: incidence has been reported to be higher in community based studies compared to hospital based studies.[46] This analysis focused on the fatal burden which only partially captures the overall health burden associated with sepsis: studies have shown significant DALYs associated with sepsis[47] and updated incidence estimates incorporating non-hospital case fatality rates would help further understand trends in sepsis. We chose to report mortality rates as adjusted for age-specific populations by location and year but this reduces comparability of our rates with standard neonatal and under-five mortality rates, which calculate the probability of death in relation to number of livebirths per year. Lastly, this analysis provided a limited decomposition of the global burden of pediatric sepsis-related mortality and further evaluation of cause-specific sepsis burden estimates at more specific age groupings (e.g., for neonates in the early vs late neonatal period) and more specific locations is needed to help identify sub-populations and unique risks needed for tailored interventions.

In conclusion, using some of the most comprehensive mortality estimates from GBD 2021 and multinational multiple cause of death data, we found the estimated burden of pediatric sepsis-related mortality decreased from 1990 to 2021, primarily from progress in addressing infectious underlying causes of sepsis deaths. However, neonates, especially in sub-Saharan Africa and South Asia, continued to shoulder a disproportionate burden of sepsis mortality, partly due to limited progress in sepsis as a complication of neonatal disorders and non-communicable diseases. Development of a consensus definition for neonatal sepsis is paramount in better understanding the factors contributing to this ongoing burden of sepsis for this group.

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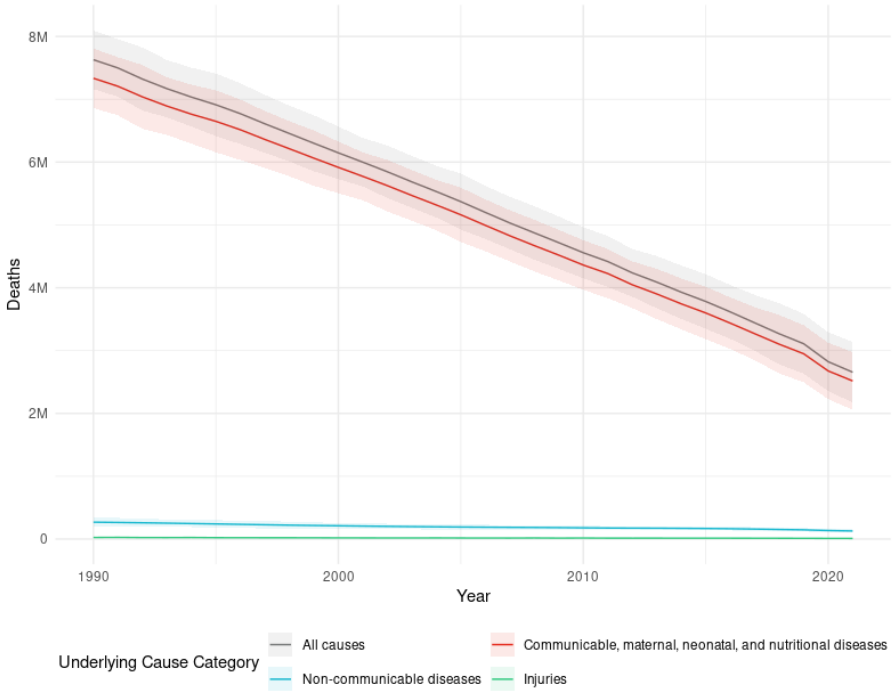
Figure 1. Global all cause sepsis-related deaths (A) and deaths per 100,000 population (B) in children under five years by Level 1 underlying cause category, both sexes combined, by year, 1990-2021



A.

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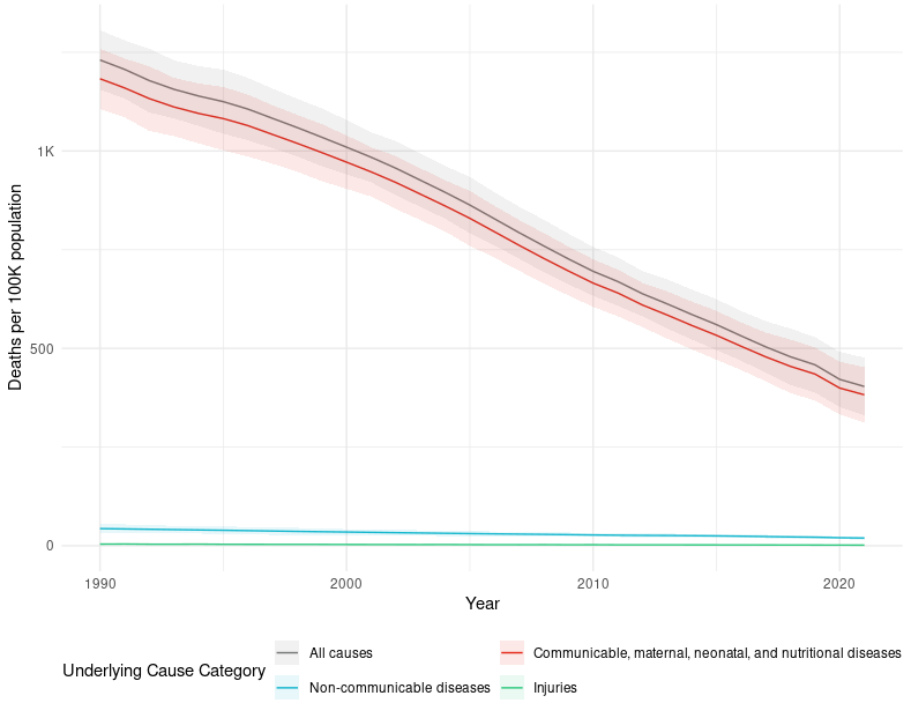
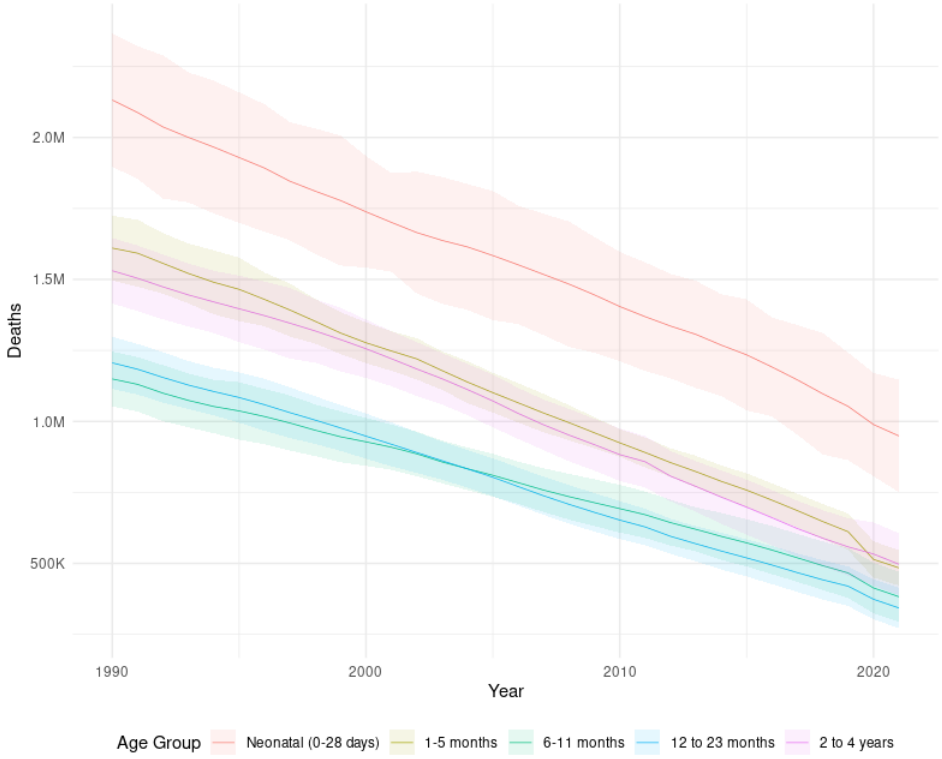
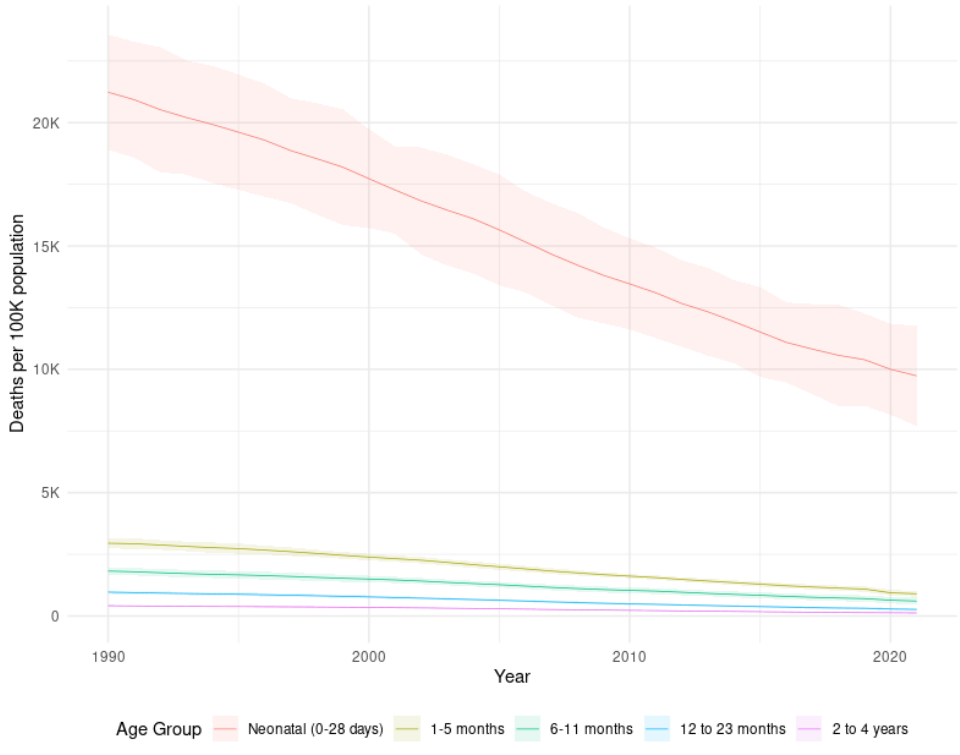


Shading indicates 95% uncertainty intervals

Figure 2. Global all cause sepsis-related deaths (A) and age-specific mortality rates per 100,000 population (B) by sub-five age group, both sexes, by year, 1990-2021



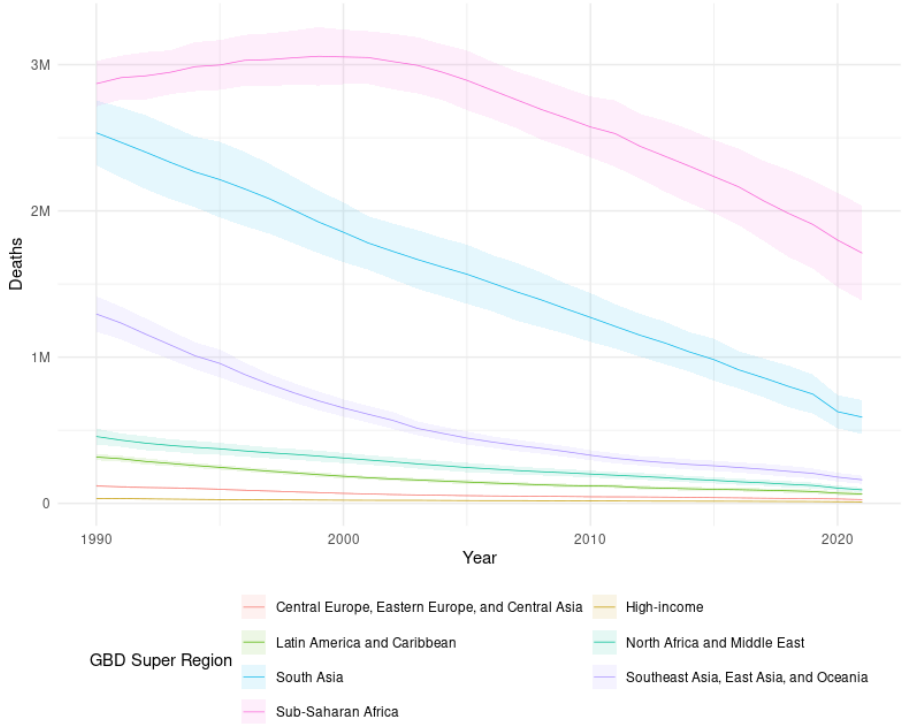
A.



B.

Shading indicates 95% uncertainty intervals

Figure 3. All cause sepsis-related deaths per 100,000 population in (A) children under five years and (B) neonates by GBD super-region, both sexes, by year, 1990-2021



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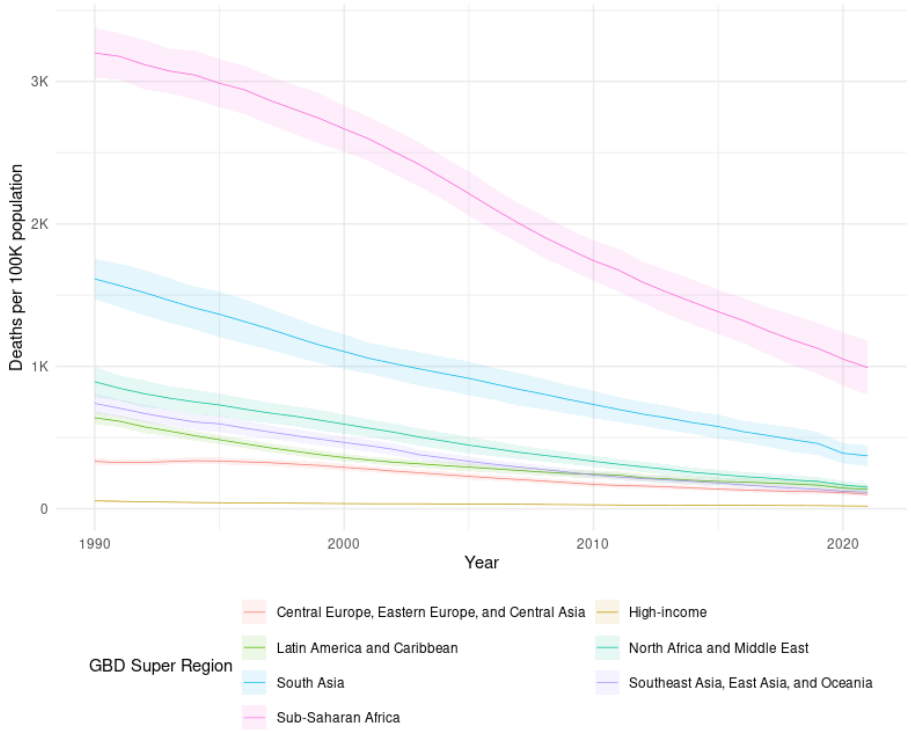

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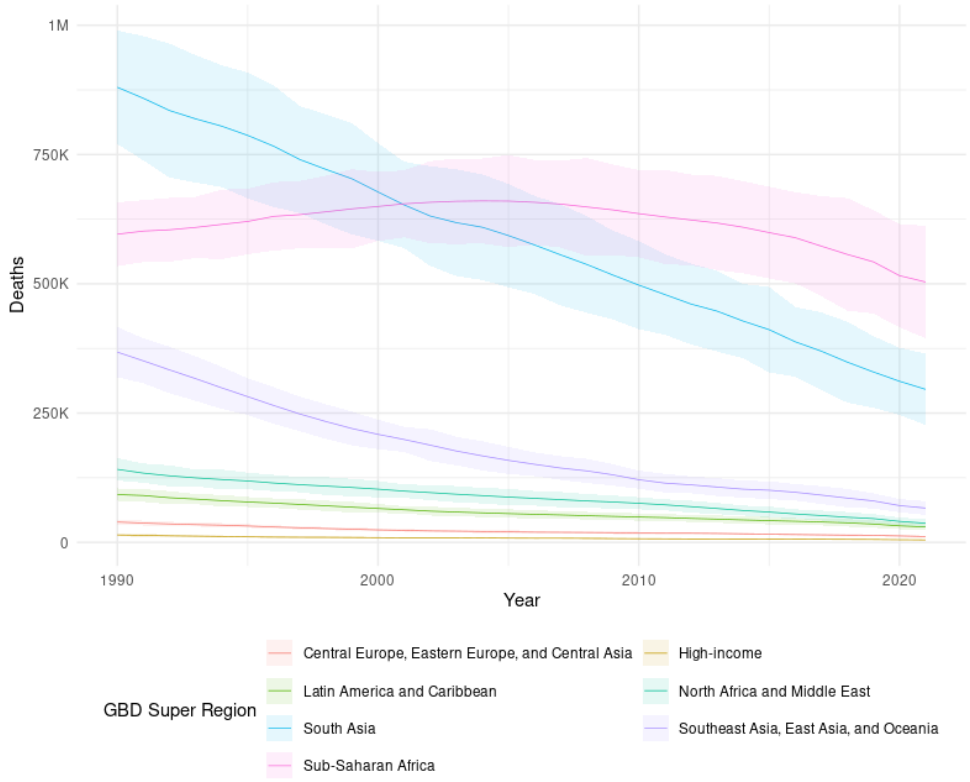
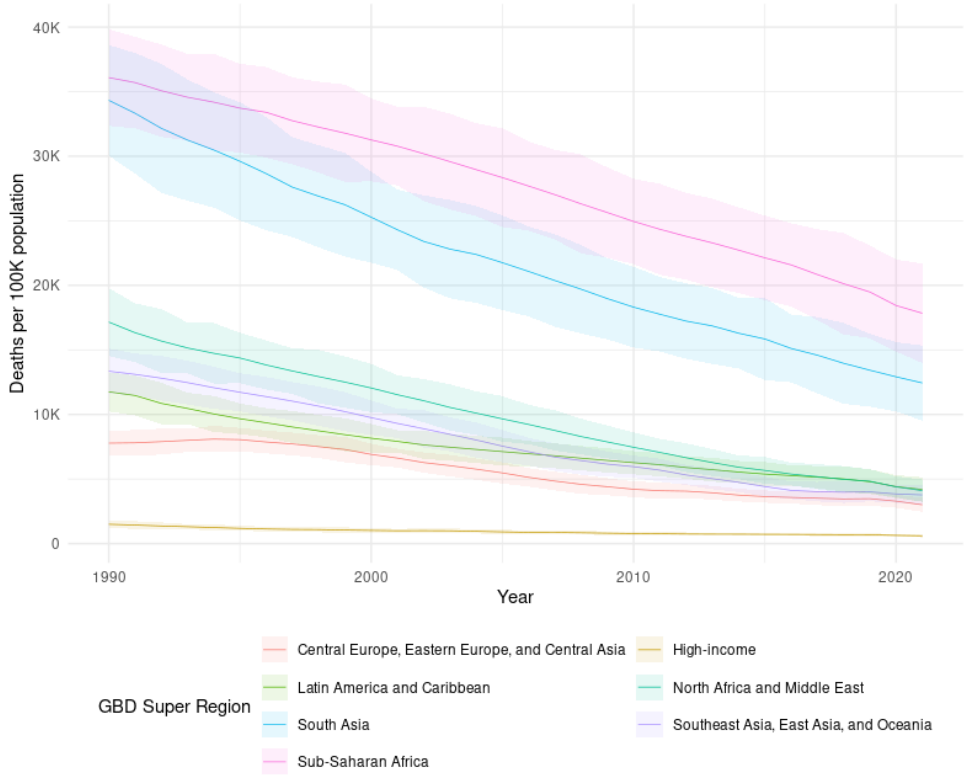


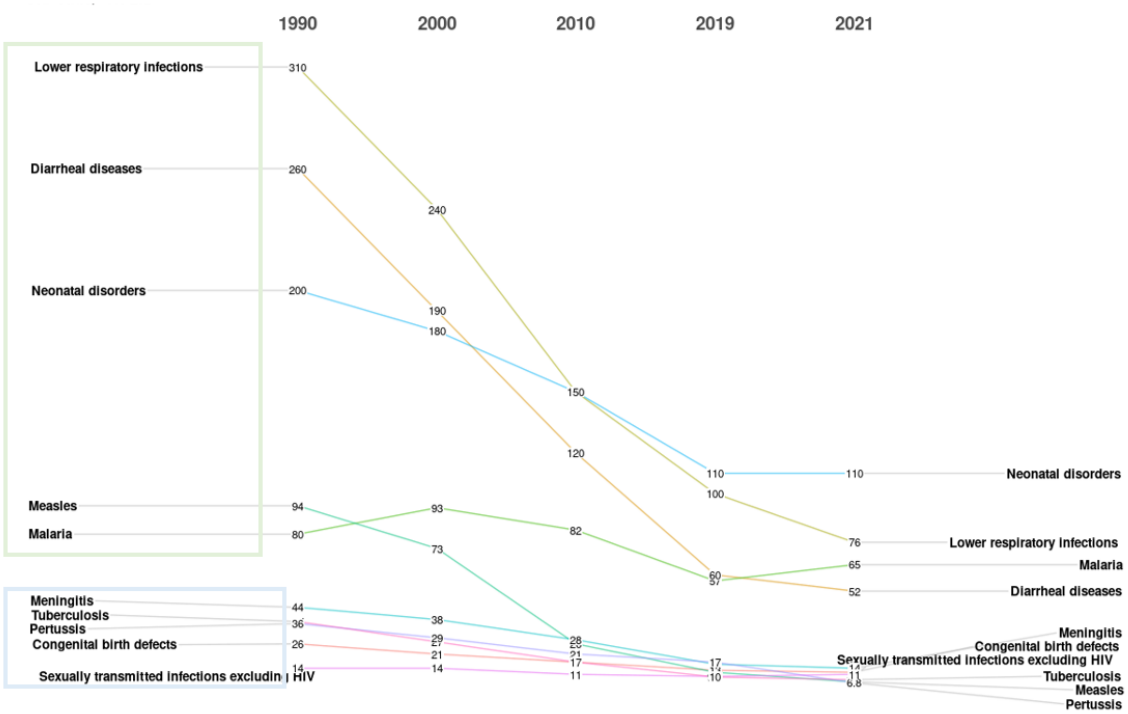
C.



D.

Shading indicates 95% uncertainty intervals. Abbreviations: GBD, Global Burden of Disease

Figure 4. Changes in global leading Level 3 causes of sepsis-related mortality per 100,000 population for children under five years, both sexes combined, 1990-2021 (by decade until 2019 + 2021) (A), with panels highlighting relative trends among the 1990 leading five causes (B) and the remaining five leading causes (C)



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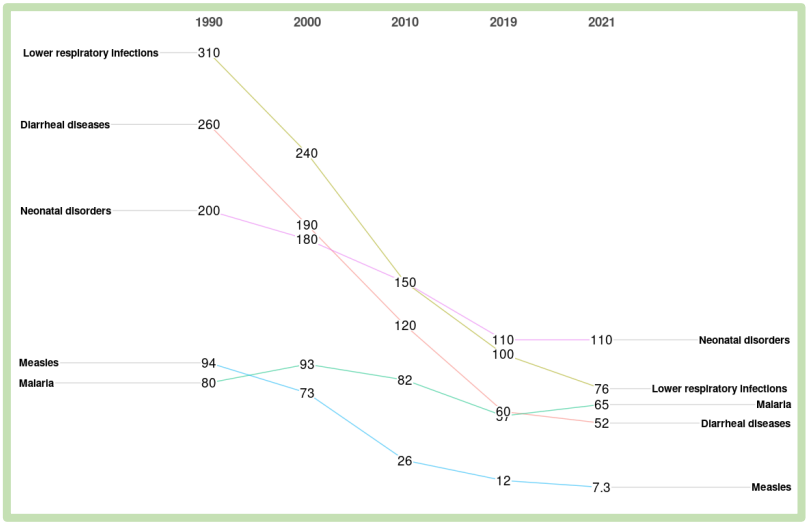


B.

C.

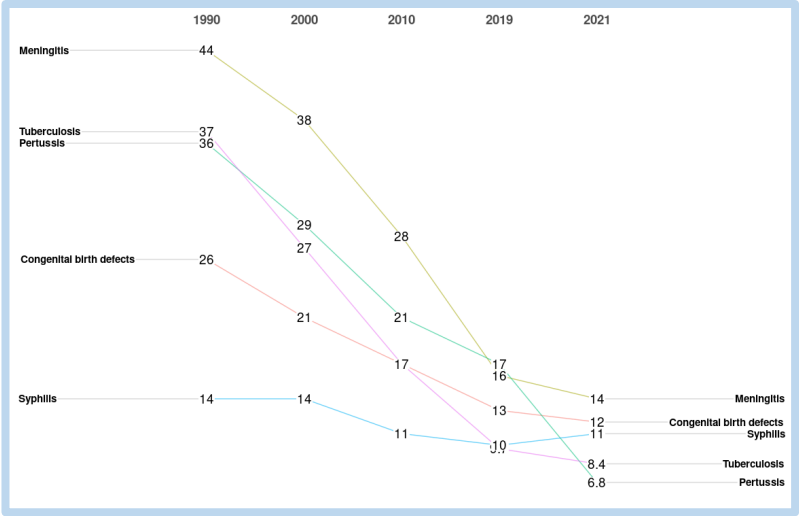
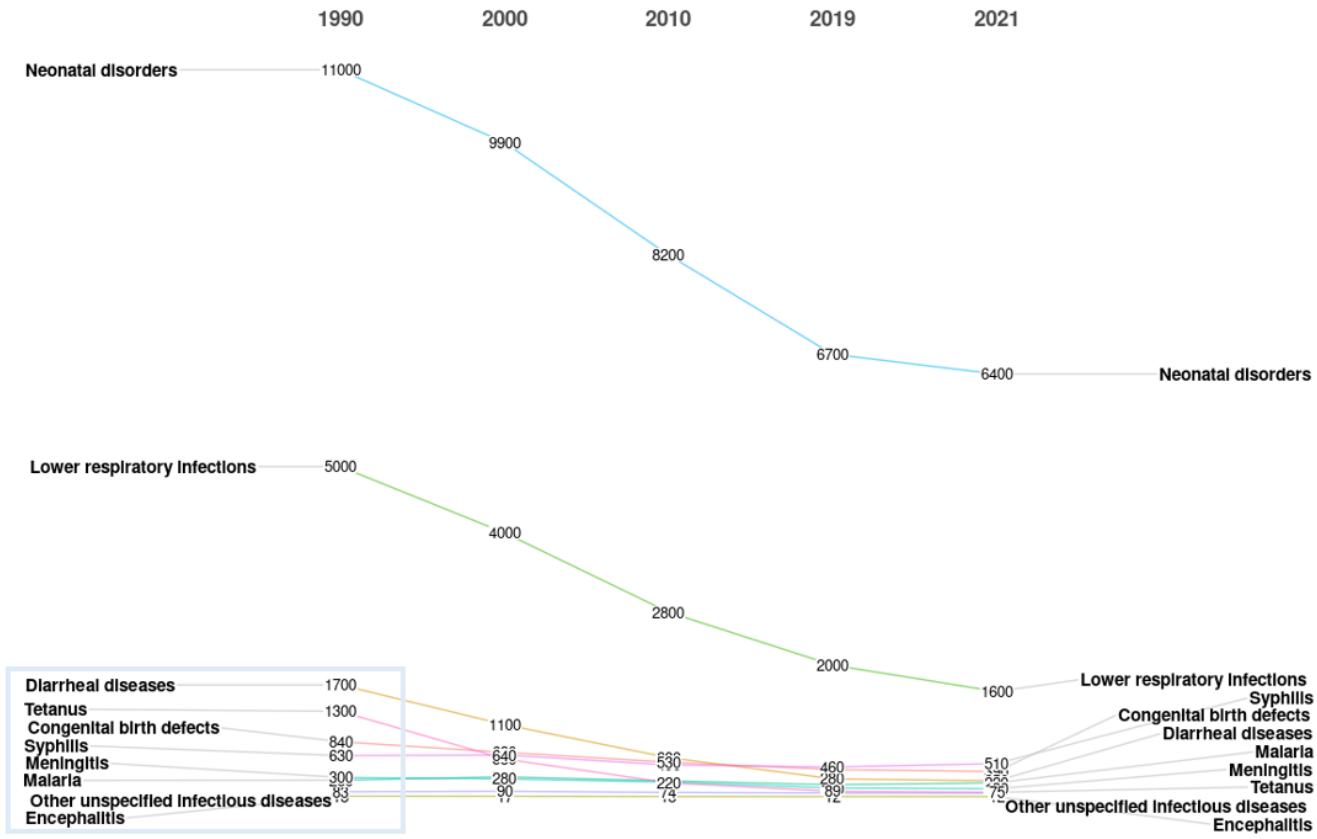
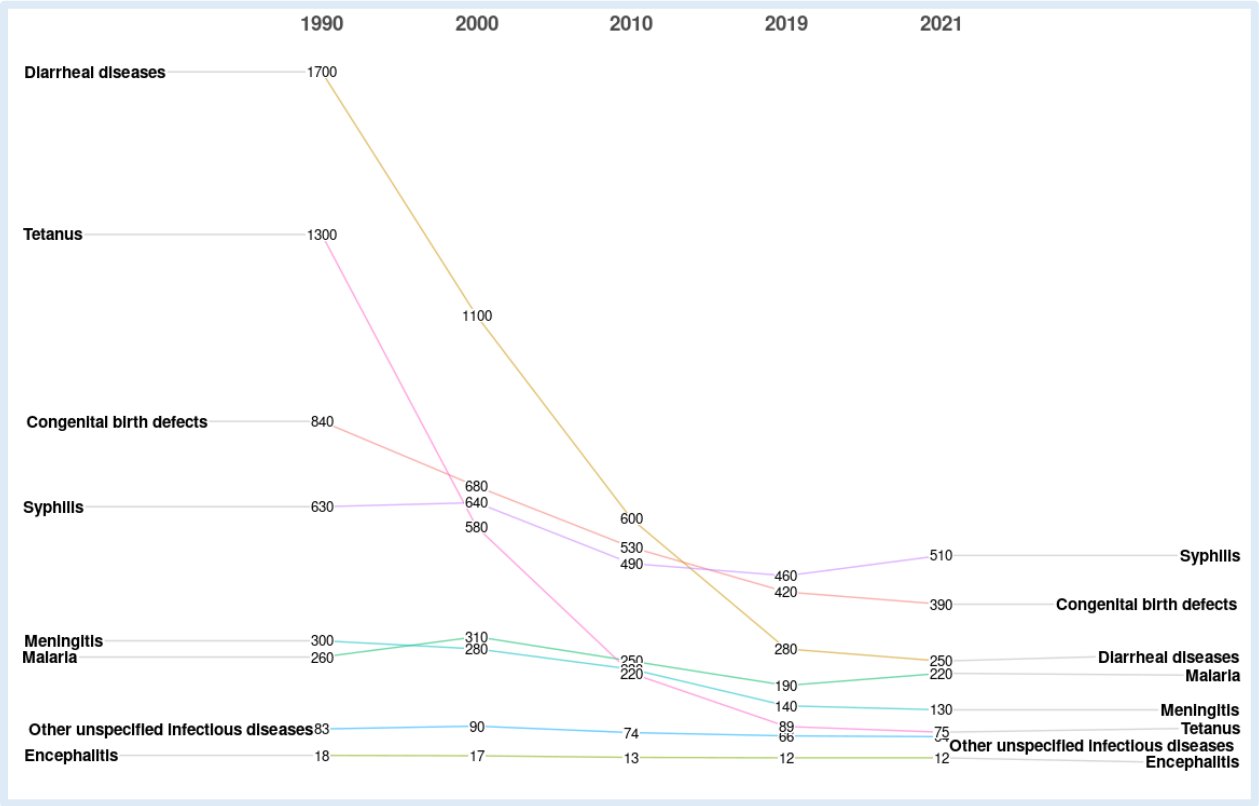

1990
2000
2010
2019
2021
Meningitis
Tuberculosis
Pertussis
Congenital birth defects
Syphilis
44
38
37
36
29
27
28
26
21
21
17
17
16
14
14
13
14
12
11
11
10
8.4
6.8
Meningitis
Congenital birth defects
Syphilis
Tuberculosis
Pertussis

Figure 5. Changes in global leading Level 3 causes of sepsis-related mortality per 100,000 population for neonates, both sexes combined, 1990-2021 (by decade until 2019 + 2021) (A), with a panel highlighting relative trends for the 1990 lower eight leading causes (B)
A.



B.



*Syphilis (Level 4 cause) reported in place of sexually transmitted diseases (excluding HIV) (Level 3 cause) for brevity: syphilis was the only child cause in this Level 3 category

Table 1. List of data sources by type and country

Source Type	Data Source and Country or Countries (Abbreviation)	Years	Deaths
Vital Registration	Brazil - Mortality Information System (SIM)*	1999 - 2022	21,902,260
	Colombia - Departamento Administrativo Nacional de Estadistica (DANE)*	1998 - 2021	4,461,081
	Italy - Istituto Nazionale di Statistica (ISTAT)	2003 - 2020	9,544,700
	Mexico - National Institute of Statistics and Geography (INEGI)*	2009 - 2022	78,80,071
	Mongolia - Ministry of Health (MOH)*	2018 - 2022	28,586
	South Africa - Statistics South Africa (SSA)*	1997 - 2016	4,472,891
	Taiwan - Ministry of Health and Welfare (MOHW)	2008 - 2017	1,097,068
	United Arab Emirates - Vital Statistics (ARE VR)	2014 - 2018	59,910
	USA - National Vital Statistics System (NVSS)	1980 - 2022	75,968,779
Hospital discharge data	Austria - Hospital Discharge Database (HDD)	2001 - 2018	436,794
	Brazil - Hospital Information System (SIH)*	2015 - 2020	926,370
	Georgia – Georgia Medical Institute Report (COL)*	2014 - 2020	33,749
	India – Mysore JSS Hospital Inpatient Data (JSSH), Bangalore St. John's Medical College Hospital Data (SJMCH)*	2014 - 2017	12,914
	Italy - Hospital Inpatient Discharges 5 (HID)	2005 - 2021	3,556,845
	Mexico - Sistema Automatizado de Egresos Hospitalarios (SAEH)*	2000 - 2020	760,221
	Mongolia - Mongolia H-Info Health System Data*	2019 - 2020	2
	New Zealand - National Minimum Dataset (NMDS)	2000 - 2020	108,908
	Pakistan - Aga Khan University Data (AKU)*	2017 - 2019	3,928
	USA - Healthcare Cost and Utilization Project State Inpatient Databases (HCUP-SID), National Hospital Discharge Survey (NHDS)	1980 - 2010	1,972,692
Linkage data sources	Italy - Friuli Venezia Giulia (FVG) Hospital Linkage Data	2003 - 2018	103,687
	New Zealand - National Minimum Dataset Linkage Data (Linkage NMDS)	2000 – 2010	128,791
Mortality surveillance data (verbal autopsies and minimally invasive tissue sampling)	Bangladesh (Child Health and Mortality Prevention Surveillance Network Program, CHAMPS)*	2018 - 2022	60
	Ethiopia (CHAMPS)*	2019 – 2021	47
	Kenya (CHAMPS)*	2017 -2022	209
	Mali (CHAMPS)*	2017 – 2021	69
	Mozambique (CHAMPS)*	2017 – 2022	216
	Sierra Leone (CHAMPS)*	2019 – 2022	215
	South Africa (CHAMPS)*	2017 - 2022	434

*Low- or middle-income country or countries as defined by World Bank Income Classifications

Table 2. Global all cause sepsis-related mortality by sex, age group, and year, 1990-2021

Year	Under Five									Neonatal								
	Both Sexes			Males			Females			Both Sexes			Males			Females		
	Sepsis-Related Deaths (95% UI)	Sepsis-Related Deaths Per 100,000 Population (95% UI)	Percentage Of Cause Deaths Via Sepsis (95% UI)	Sepsis-Related Deaths (95% UI)	Sepsis-Related Deaths Per 100,000 Population (95% UI)	Percentage Of Cause Deaths Via Sepsis (95% UI)	Sepsis-Related Deaths (95% UI)	Sepsis-Related Deaths Per 100,000 Population (95% UI)	Percentage Of Cause Deaths Via Sepsis (95% UI)	Sepsis-Related Deaths (95% UI)	Sepsis-Related Deaths Per 100,000 Population (95% UI)	Percentage Of Cause Deaths Via Sepsis (95% UI)	Sepsis-Related Deaths (95% UI)	Sepsis-Related Deaths Per 100,000 Population (95% UI)	Percentage Of Cause Deaths Via Sepsis (95% UI)	Sepsis-Related Deaths (95% UI)	Sepsis-Related Deaths Per 100,000 Population (95% UI)	Percentage Of Cause Deaths Via Sepsis (95% UI)
1990	7.63M (7.16M–8.10M)	1,230 (1,160–1,310)	67.6 (64.6–70.6)	4.01M (3.73M–4.29M)	1,250 (1,170–1,340)	66.4 (63.2–69.7)	3.62M (3.40M–3.84M)	1,210 (1,130–1,280)	69.1 (65.9–72.2)	2.13M (1.90M–2.37M)	21,200 (18,900–23,600)	53.0 (47.4–58.5)	1.21M (1.06M–1.35M)	23,200 (20,500–25,900)	52.3 (46.6–58.1)	926K (829K–1.02M)	19,100 (17,100–21,100)	53.8 (48.3–59.4)
1992	7.32M (6.82M–7.82M)	1,180 (1,100–1,260)	67.4 (64.4–70.3)	3.85M (3.56M–4.14M)	1,200 (1,110–1,290)	66.2 (63.1–69.2)	3.47M (3.24M–3.70M)	1,150 (1,080–1,230)	68.7 (65.5–72.0)	2.04M (1.78M–2.29M)	20,500 (18,000–23,100)	52.1 (46.6–57.6)	1.15M (1.00M–1.30M)	22,400 (19,500–25,300)	51.5 (45.9–57.1)	887K (781K–994K)	18,500 (16,300–20,800)	52.9 (47.4–58.4)
1991	7.50M (7.04M–7.95M)	1,210 (1,130–1,280)	67.3 (64.6–70.0)	3.94M (3.68M–4.21M)	1,230 (1,150–1,310)	66.1 (63.2–69.0)	3.56M (3.34M–3.77M)	1,180 (1,110–1,250)	68.7 (65.6–71.7)	2.09M (1.85M–2.32M)	20,900 (18,600–23,300)	52.5 (47.1–57.9)	1.18M (1.04M–1.32M)	22,900 (20,200–25,500)	51.9 (46.4–57.4)	907K (806K–1.01M)	18,900 (16,700–21,000)	53.3 (47.8–58.8)
1993	7.17M (6.71M–7.62M)	1,160 (1,080–1,230)	67.2 (64.9–69.6)	3.77M (3.50M–4.04M)	1,180 (1,090–1,260)	66.0 (63.5–68.6)	3.40M (3.19M–3.61M)	1,130 (1,060–1,200)	68.6 (65.9–71.3)	2.00M (1.77M–2.23M)	20,200 (17,900–22,500)	51.8 (47.0–56.6)	1.13M (993K–1.26M)	22,000 (19,400–24,600)	51.2 (46.3–56.1)	874K (774K–974K)	18,300 (16,200–20,400)	52.6 (47.7–57.4)
1994	7.03M (6.57M–7.50M)	1,140 (1,060–1,210)	67.2 (64.2–70.2)	3.70M (3.42M–3.98M)	1,160 (1,070–1,250)	66.0 (62.6–69.4)	3.33M (3.13M–3.54M)	1,120 (1,050–1,190)	68.6 (65.5–71.6)	1.97M (1.73M–2.20M)	19,900 (17,600–22,300)	51.6 (45.9–57.2)	1.11M (964K–1.25M)	21,600 (18,900–24,400)	51.0 (45.0–56.9)	860K (765K–955K)	18,100 (16,100–20,100)	52.3 (46.9–57.7)
1995	6.91M (6.41M–7.41M)	1,120 (1,040–1,210)	67.0 (64.2–69.8)	3.64M (3.35M–3.92M)	1,140 (1,060–1,230)	65.8 (63.0–68.7)	3.28M (3.05M–3.51M)	1,100 (1,030–1,180)	68.4 (65.2–71.6)	1.93M (1.70M–2.16M)	19,600 (17,300–21,900)	51.4 (46.2–56.6)	1.09M (952K–1.22M)	21,300 (18,700–23,900)	50.8 (45.5–56.2)	843K (744K–942K)	17,800 (15,700–19,900)	52.1 (46.8–57.4)
1996	6.77M (6.29M–7.25M)	1,110 (1,030–1,180)	67.1 (64.5–69.8)	3.56M (3.28M–3.84M)	1,130 (1,040–1,210)	66.0 (63.0–68.9)	3.21M (2.99M–3.43M)	1,090 (1,010–1,160)	68.5 (65.6–71.4)	1.89M (1.67M–2.12M)	19,300 (17,000–21,600)	51.3 (46.1–56.4)	1.07M (933K–1.20M)	21,000 (18,400–23,600)	50.8 (45.4–56.1)	825K (731K–919K)	17,500 (15,500–19,500)	51.9 (46.9–56.9)
1997	6.61M (6.15M–7.07M)	1,080 (1,010–1,160)	67.1 (64.4–69.8)	3.48M (3.22M–3.74M)	1,100 (1,020–1,180)	65.9 (63.1–68.8)	3.13M (2.91M–3.35M)	1,060 (989–1,140)	68.5 (65.5–71.4)	1.85M (1.64M–2.05M)	18,900 (16,700–21,000)	51.0 (45.7–56.4)	1.04M (919K–1.16M)	20,500 (18,100–23,000)	50.5 (45.1–56.0)	804K (716K–893K)	17,100 (15,200–18,900)	51.6 (46.3–57.0)
1998	6.45M (6.01M–6.90M)	1,060 (987–1,130)	67.0 (64.3–69.6)	3.39M (3.14M–3.65M)	1,080 (996–1,160)	65.8 (63.0–68.6)	3.06M (2.85M–3.27M)	1,040 (970–1,110)	68.4 (65.4–71.3)	1.81M (1.59M–2.03M)	18,500 (16,300–20,800)	50.7 (45.1–56.3)	1.02M (891K–1.15M)	20,200 (17,600–22,800)	50.2 (44.5–56.0)	789K (696K–882K)	16,800 (14,800–18,700)	51.3 (45.7–56.9)
1999	6.30M (5.85M–6.74M)	1,030 (962–1,110)	66.8 (63.8–69.9)	3.31M (3.05M–3.57M)	1,050 (970–1,130)	65.6 (62.4–68.8)	2.99M (2.78M–3.19M)	1,020 (947–1,090)	68.3 (65.0–71.5)	1.78M (1.55M–2.01M)	18,200 (15,900–20,500)	50.4 (44.3–56.6)	1.00M (869K–1.14M)	19,800 (17,200–22,500)	49.9 (43.6–56.3)	775K (678K–872K)	16,500 (14,400–18,500)	51.0 (45.0–57.1)
2001	6.00M (5.61M–6.38M)	984 (921–1,050)	66.7 (64.2–69.3)	3.15M (2.92M–3.38M)	1,000 (927–1,070)	65.4 (62.7–68.2)	2.85M (2.67M–3.02M)	967 (909–1,030)	68.2 (65.4–71.0)	1.70M (1.53M–1.87M)	17,300 (15,500–19,000)	50.0 (45.2–54.7)	958K (853K–1.06M)	18,800 (16,700–20,800)	49.4 (44.5–54.4)	743K (671K–814K)	15,600 (14,100–17,200)	50.7 (46.0–55.3)
2000	6.15M (5.73M–6.56M)	1,010 (941–1,080)	66.8 (64.4–69.3)	3.23M (2.98M–3.48M)	1,030 (946–1,110)	65.6 (62.8–68.4)	2.92M (2.73M–3.10M)	992 (930–1,050)	68.3 (65.7–70.9)	1.74M (1.54M–1.93M)	17,700 (15,700–19,700)	50.2 (45.0–55.4)	980K (860K–1.10M)	19,300 (16,900–21,600)	49.7 (44.4–55.1)	758K (678K–838K)	16,100 (14,400–17,700)	50.9 (45.8–55.9)
2002	5.85M (5.43M–6.26M)	956 (888–1,020)	66.6 (63.8–69.3)	3.07M (2.83M–3.32M)	972 (894–1,050)	65.3 (62.3–68.2)	2.77M (2.59M–2.96M)	940 (877–1,000)	68.1 (65.2–71.0)	1.67M (1.45M–1.88M)	16,800 (14,700–19,000)	49.7 (43.9–55.5)	938K (809K–1.07M)	18,300 (15,800–20,800)	49.1 (43.1–55.2)	727K (639K–815K)	15,300 (13,400–17,100)	50.4 (44.8–56.1)
2003	5.68M (5.27M–6.10M)	926 (859–993)	66.5 (63.5–69.5)	2.99M (2.75M–3.23M)	940 (865–1,020)	65.1 (61.9–68.3)	2.70M (2.51M–2.88M)	910 (847–973)	68.1 (65.0–71.1)	1.64M (1.41M–1.86M)	16,500 (14,200–18,700)	49.4 (43.3–55.5)	922K (790K–1.05M)	17,900 (15,300–20,400)	48.8 (42.5–55.1)	716K (623K–808K)	14,900 (13,000–16,900)	50.2 (44.2–56.2)
2004	5.53M (5.12M–	895 (829–962)	65.8 (63.1–68.5)	2.91M (2.67M–	909 (835–983)	64.4 (61.5–67.4)	2.63M (2.44M–	880 (818–943)	67.4 (64.6–70.2)	1.61M (1.39M–	16,100 (13,900–	49.0 (42.9–55.2)	909K (779K–	17,500 (15,000–	48.4 (42.1–54.7)	706K (613K–	14,600 (12,700–	49.9 (43.9–55.9)

	5.94M)			3.14M)			2.81M)			1.84M)	18,300)		1.04M)	20,000)		799K)	16,500)	
2005	5.37M (4.93M–5.81M)	863 (792–934)	65.7 (62.7–68.7)	2.82M (2.56M–3.08M)	877 (796–957)	64.3 (61.0–67.5)	2.55M (2.35M–2.74M)	849 (784–914)	67.3 (64.2–70.3)	1.58M (1.36M–1.81M)	15,700 (13,400–17,900)	48.7 (42.7–54.8)	891K (754K–1.03M)	17,000 (14,400–19,600)	48.1 (41.8–54.5)	693K (601K–785K)	14,200 (12,300–16,100)	49.6 (43.7–55.4)
2006	5.20M (4.78M–5.62M)	828 (761–895)	65.3 (62.6–68.0)	2.73M (2.49M–2.98M)	841 (766–917)	63.9 (61.0–66.9)	2.47M (2.28M–2.65M)	814 (753–875)	66.9 (64.2–69.7)	1.55M (1.34M–1.76M)	15,200 (13,100–17,200)	48.3 (42.8–53.9)	873K (747K–999K)	16,500 (14,100–18,900)	47.7 (42.0–53.5)	679K (595K–762K)	13,800 (12,100–15,500)	49.1 (43.8–54.4)
2007	5.03M (4.61M–5.45M)	793 (727–859)	64.8 (62.2–67.4)	2.64M (2.40M–2.88M)	806 (732–879)	63.4 (60.6–66.3)	2.39M (2.20M–2.57M)	779 (719–840)	66.4 (63.8–69.1)	1.52M (1.30M–1.73M)	14,700 (12,600–16,700)	47.9 (42.2–53.6)	854K (727K–981K)	15,900 (13,600–18,300)	47.3 (41.4–53.2)	664K (576K–751K)	13,300 (11,500–15,100)	48.6 (43.1–54.2)
2008	4.87M (4.45M–5.30M)	759 (693–826)	64.0 (61.2–66.8)	2.56M (2.31M–2.81M)	772 (697–847)	62.7 (59.6–65.7)	2.31M (2.13M–2.50M)	746 (686–806)	65.6 (62.8–68.5)	1.48M (1.26M–1.70M)	14,200 (12,100–16,300)	47.3 (41.0–53.6)	836K (704K–968K)	15,500 (13,000–17,900)	46.7 (40.2–53.2)	648K (558K–738K)	12,900 (11,100–14,700)	48.0 (42.0–54.1)
2009	4.72M (4.30M–5.13M)	727 (663–790)	63.9 (61.2–66.6)	2.48M (2.24M–2.73M)	739 (666–812)	62.5 (59.6–65.5)	2.24M (2.06M–2.41M)	713 (657–769)	65.5 (62.9–68.1)	1.45M (1.24M–1.65M)	13,800 (11,900–15,800)	47.0 (41.1–52.8)	815K (692K–939K)	15,000 (12,800–17,300)	46.5 (40.3–52.6)	630K (549K–712K)	12,500 (10,900–14,100)	47.6 (42.0–53.3)
2010	4.56M (4.15M–4.96M)	695 (633–757)	62.9 (60.2–65.6)	2.40M (2.16M–2.64M)	708 (638–779)	61.6 (58.7–64.5)	2.16M (1.99M–2.33M)	681 (627–736)	64.4 (61.6–67.1)	1.40M (1.21M–1.60M)	13,500 (11,600–15,300)	46.6 (41.0–52.2)	793K (678K–907K)	14,700 (12,600–16,800)	46.1 (40.4–51.9)	612K (533K–691K)	12,200 (10,600–13,700)	47.2 (41.7–52.7)
2011	4.42M (4.01M–4.82M)	669 (608–731)	62.6 (59.9–65.2)	2.33M (2.09M–2.57M)	683 (612–753)	61.3 (58.5–64.0)	2.09M (1.92M–2.26M)	655 (602–708)	64.0 (61.3–66.8)	1.37M (1.18M–1.56M)	13,100 (11,300–14,900)	46.3 (40.8–51.7)	773K (658K–888K)	14,300 (12,200–16,400)	45.9 (40.3–51.4)	596K (518K–673K)	11,800 (10,300–13,300)	46.8 (41.5–52.1)
2012	4.24M (3.86M–4.62M)	638 (581–695)	62.4 (60.0–64.9)	2.24M (2.01M–2.46M)	652 (586–719)	61.2 (58.4–64.0)	2.00M (1.84M–2.16M)	623 (575–672)	63.9 (61.5–66.3)	1.34M (1.15M–1.52M)	12,700 (10,900–14,400)	46.0 (40.4–51.5)	755K (645K–866K)	13,800 (11,800–15,900)	45.6 (39.9–51.3)	581K (506K–655K)	11,400 (9,940–12,900)	46.4 (41.1–51.8)
2013	4.09M (3.67M–4.50M)	613 (551–675)	62.0 (59.6–64.4)	2.16M (1.91M–2.41M)	627 (555–699)	60.8 (58.0–63.6)	1.93M (1.76M–2.10M)	597 (544–650)	63.4 (61.0–65.7)	1.31M (1.12M–1.50M)	12,300 (10,500–14,100)	45.7 (40.9–50.5)	739K (624K–854K)	13,500 (11,400–15,600)	45.4 (40.4–50.5)	568K (493K–643K)	11,100 (9,630–12,600)	46.2 (41.6–50.7)
2014	3.93M (3.51M–4.35M)	586 (523–649)	61.5 (59.0–64.0)	2.08M (1.83M–2.33M)	601 (529–673)	60.4 (57.7–63.0)	1.85M (1.67M–2.03M)	570 (514–625)	62.9 (60.2–65.5)	1.27M (1.09M–1.45M)	11,900 (10,200–13,600)	45.5 (40.8–50.1)	718K (610K–826K)	13,000 (11,100–15,000)	45.2 (40.4–50.0)	551K (479K–623K)	10,700 (9,330–12,100)	45.9 (41.3–50.4)
2015	3.78M (3.35M–4.22M)	560 (496–625)	61.0 (58.1–63.8)	2.01M (1.75M–2.26M)	575 (503–648)	59.9 (56.8–63.0)	1.78M (1.59M–1.96M)	544 (487–601)	62.3 (59.4–65.2)	1.23M (1.04M–1.43M)	11,500 (9,690–13,300)	45.2 (39.6–50.7)	698K (583K–814K)	12,600 (10,500–14,700)	44.9 (39.2–50.6)	536K (456K–617K)	10,400 (8,810–11,900)	45.5 (40.0–51.0)
2016	3.62M (3.19M–4.04M)	532 (469–595)	60.5 (57.6–63.5)	1.92M (1.67M–2.17M)	547 (476–617)	59.5 (56.4–62.5)	1.69M (1.51M–1.88M)	516 (460–571)	61.8 (58.7–64.8)	1.19M (1.02M–1.37M)	11,100 (9,470–12,700)	44.9 (39.6–50.2)	674K (571K–778K)	12,100 (10,300–14,000)	44.6 (39.2–50.1)	517K (445K–589K)	9,980 (8,590–11,400)	45.2 (39.9–50.5)
2017	3.44M (3.00M–3.89M)	504 (439–569)	60.1 (57.1–63.2)	1.83M (1.57M–2.09M)	519 (445–592)	59.1 (55.8–62.4)	1.61M (1.42M–1.80M)	488 (431–544)	61.3 (58.4–64.3)	1.15M (953K–1.34M)	10,800 (9,000–12,600)	44.6 (38.9–50.4)	649K (533K–765K)	11,800 (9,720–14,000)	44.5 (38.5–50.5)	497K (419K–575K)	9,730 (8,200–11,300)	44.9 (39.4–50.4)
2018	3.27M (2.78M–3.75M)	479 (408–550)	59.9 (56.4–63.4)	1.74M (1.46M–2.02M)	493 (414–573)	58.9 (55.2–62.6)	1.53M (1.32M–1.73M)	463 (400–526)	61.1 (57.5–64.6)	1.10M (884K–1.31M)	10,600 (8,510–12,600)	44.4 (38.2–50.7)	622K (494K–749K)	11,600 (9,200–13,900)	44.3 (37.9–50.7)	476K (388K–563K)	9,490 (7,750–11,200)	44.7 (38.5–50.8)
2019	3.11M (2.63M–3.58M)	458 (388–528)	59.7 (56.6–62.8)	1.66M (1.38M–1.93M)	473 (395–551)	58.7 (55.5–62.0)	1.45M (1.25M–1.65M)	443 (381–504)	60.8 (57.6–64.0)	1.05M (864K–1.24M)	10,400 (8,520–12,300)	44.3 (39.1–49.5)	597K (483K–711K)	11,400 (9,210–13,600)	44.2 (38.8–49.6)	456K (380K–532K)	9,320 (7,770–10,900)	44.5 (39.4–49.6)
2020	2.82M (2.36M–3.29M)	421 (352–491)	57.7 (54.4–61.0)	1.53M (1.26M–1.80M)	442 (364–520)	57.1 (53.7–60.4)	1.29M (1.09M–1.49M)	400 (338–461)	58.5 (55.1–61.9)	989K (807K–1.17M)	10,000 (8,160–11,800)	43.5 (38.0–48.9)	568K (457K–678K)	11,100 (8,940–13,300)	43.5 (37.9–49.1)	421K (349K–494K)	8,820 (7,300–10,300)	43.4 (38.1–48.8)
2021	2.66M (2.18M–3.14M)	403 (330–476)	56.9 (53.0–60.9)	1.44M (1.16M–1.72M)	423 (342–505)	56.3 (52.3–60.3)	1.22M (1.01M–1.42M)	382 (318–447)	57.7 (53.6–61.7)	949K (751K–1.15M)	9,740 (7,710–11,800)	43.4 (37.3–49.4)	544K (425K–664K)	10,800 (8,440–13,200)	43.4 (37.2–49.6)	404K (326K–483K)	8,590 (6,910–10,300)	43.3 (37.5–49.2)