Global, regional, and national sepsis incidence and mortality, 1990–2021: a systematic analysis

*GBD 2021 Global Sepsis Collaborators**

Summary

Background The global burden of sepsis, a life-threatening dysregulated host response to infection leading to organ dysfunction, remains challenging to quantify. We aimed to comprehensively estimate the global, regional, and national burden of sepsis, including the impact of the COVID-19 pandemic and underlying causes of sepsis-related deaths with co-occurring infectious syndromes.

Methods We used multiple cause-of-death, hospital, minimally invasive tissue sampling, and linked death certificate and hospital record data representing 149 million deaths, covering 4290 location-years with mortality estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 to capture explicit and implicit sepsis cases and deaths. We estimated age-location-sex-specific fractions of sepsis-related deaths from 195 underlying causes of death and 22 infectious syndromes from 1990 to 2021 using binomial logistic regression models, and estimated sepsis-related deaths using GBD cause-specific mortality estimates. Using 250 million hospital admissions and 7·82 million deaths from hospital data, representing 1310 location-years, we modelled case fatality rates by use of binomial logistic regression, applied to sepsis death estimates to estimate sepsis incidence by age, location, and year.

Findings In 2021, we estimated 166 million (95% uncertainty interval 135–201) sepsis cases and 21·4 million (20·3–22·5) all-cause sepsis-related deaths globally, representing 31·5% of total global deaths. Sepsis-related deaths decreased between 1990 and 2019, followed by a surge in 2020 and 2021. As of 2021, individuals aged 15 years and older experienced increases across incidence (230%) and mortality (26·3%) since 1990. Those aged 70 years and older had the highest sepsis-related mortality in 2021 (9·28 million [8·74–9·86] deaths). Sepsis-related deaths from infectious underlying causes decreased from 11·8 million (11·1–12·5) in 1990 to 8·34 million (7·72–9·01) in 2019, then increased by 86·4% to 15·5 million (14·7–16·4) in 2021. Sepsis-related mortality due to non-infectious underlying causes of death increased from 4·69 million (4·35–5·05) in 1990 to 5·81 million (5·40–6·25) in 2021; the leading non-infectious underlying causes of death with sepsis were stroke, chronic obstructive pulmonary disease, and cirrhosis. In 2021, bloodstream infections inclusive of HIV and malaria (3·08 million [2·83–3·35]) and lower respiratory infections inclusive of COVID-19 (11·33 million [1·20–1·47]) were the most prominent infectious syndromes complicating sepsis-related deaths from non-infectious underlying causes, representing a consistent trend since 1990.

Interpretation The global burden of sepsis increased in 2020 and 2021, reversing progress from 1990. Sepsis incidence and mortality increased in people aged 15 years and older, especially those aged 70 years and older, and as a complication of non-infectious underlying causes of death such as stroke, primarily through bloodstream infections and lower respiratory infections. The global burden of sepsis is substantial, and sepsis is increasingly a complication of non-infectious causes of death.

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Introduction

Sepsis—a life-threatening dysregulated host response to infection leading to organ dysfunction[1]—represents a poorly understood cause of preventable mortality and health loss globally. Over the past two decades, efforts from groups such as the Surviving Sepsis Campaign and the Global Sepsis Alliance have resulted in earlier sepsis recognition; standardised care; a 2017 World Health Assembly resolution to improve sepsis prevention, diagnosis, and management;[2] and the first WHO global report on sepsis epidemiology and burden.[3] However, advocacy efforts have primarily targeted high-income countries, and data sparsity from low-income settings creates challenges in assessing the global burden of sepsis.

In 2020, Rudd and colleagues[4] produced the first comprehensive global estimates of sepsis incidence and mortality using intermediate causes of death to identify sepsis-related deaths. They found that nearly half of all sepsis-related deaths were complications of underlying non-communicable diseases or injuries. Despite the decreasing global sepsis burden over time, the authors

For more on the **Surviving Sepsis Campaign** see https://www.sccm.org/survivingsepsiscampaign

For more on the **Global Sepsis Alliance** see https://globalsepsisalliance.org/

Research in context

Evidence before this study

Traditional approaches for quantifying sepsis-related deaths have involved calculating deaths caused by infectious underlying causes. The previous analysis of sepsis burden from 1990 to 2017 described a novel approach of quantifying sepsis from hospital and death records using both explicitly defined sepsis as well as implied sepsis documented by the presence of infections and organ failure co-occurring alongside injuries, non-communicable, maternal, and nutritional underlying causes of death. Although this analysis corroborated other studies suggesting that sepsis-related deaths were declining globally, sepsis was still identified as a concerning public health threat due to the disparity in its impact across regions, income levels, and ages, with the burden concentrating among older age groups. A large percentage of the sepsis burden was shown to co-occur with non-infectious underlying causes of death. The value of this computational framework has broad implications beyond sepsis alone and has been used in recent estimations of antimicrobial resistance. Nonetheless, there is a scarcity of studies on the effect of the COVID-19 pandemic on sepsis incidence and mortality trends, and a more detailed breakdown of the leading causes of sepsis-related mortality by age, year, and infectious syndromes is needed to highlight areas for intervention.

Added value of this study

In this update to our previous analysis from 1990 to 2017, we estimated global, regional, and national sepsis incidence and mortality from 1990 to 2021 to include the early effects of the COVID-19 pandemic. We used a more inclusive sepsis definition that captured greater burden from sepsis implied by the presence of infection and organ failure. We increased the number of location-years, adding sources from low-income and middle-income countries such as India, Mongolia, Pakistan, and the Philippines. For the first time, we assessed sepsis burden by 22 infectious syndromes. We also fully separated and reported on infectious and non-infectious underlying causes of sepsis-related deaths in greater detail to pinpoint high-priority conditions that co-occur with sepsis on the pathway to death.

Implications of all the available evidence

Our estimates of a staggering 166 million (95% uncertainty interval 135–201) sepsis cases and 21·4 million (20·3–22·5) sepsis-related deaths in 2021 reflect an overturning of global success in sepsis reduction from 1990 to 2019 and highlight the burden of sepsis further complicated by COVID-19 on top of increased estimates from our previous analysis due to the inclusion of implicit sepsis cases and more implicit sepsis deaths. Our analysis highlights increasing sepsis burden in adults older than 15 years, with a 26·3% increase in mortality and a 230% increase in incidence from 1990 to 2021. In contrast to the striking improvements in sepsis mortality due to infectious underlying causes, especially among children, sepsis mortality continues to increase as a complication of non-infectious causes of death, such as chronic obstructive pulmonary disease, stroke, and cirrhosis. We found a substantial proportion of sepsis mortality among non-infectious underlying causes of death, primarily co-occurring with two infectious syndromes (bloodstream infections and lower respiratory infections). These findings suggest that integrated care to better manage chronic conditions in ageing populations along with targeted infection prevention strategies should be considered as upstream approaches to mitigate the growing burden of sepsis in this population.

highlighted alarming disparities by age and location. However, this analysis extended only to 2017, with a limited update in 2019,[5] thus the impact of the COVID-19 pandemic on global sepsis trends remains unexplored. Studies from high-income settings have noted increasing sepsis incidence rates over the past decades.[6] Hypotheses for this increase include an ageing population with an increasing burden of chronic conditions, earlier sepsis identification, and changes to coding practices and definitions.[7] An updated estimation of the global sepsis burden is needed to capture current trends and the impact of the COVID-19 pandemic, and to assess potential drivers.

Using data from the Global Burden of Disease, Injuries, and Risk Factors Study (GBD) 2021, we present, to the best of our knowledge, the most comprehensive estimates of the global sepsis burden by detailed underlying cause, infectious syndrome, age, and location from 1990 to 2021. Our results describe updated trends in sepsis incidence and mortality, incorporating the global impact of the COVID-19 pandemic, and highlight the top-ranking underlying causes of death and infectious syndromes contributing to sepsis-related deaths.

This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.[8]

Methods

Overview

This analysis used data from the Global Burden of Antimicrobial Resistance studies[9–15] and GBD 2021,[16–18] applying a multiple cause of death (MCoD) framework to comprehensively capture sepsis. We estimated the fraction of sepsis co-occurring with underlying causes of death in the GBD cause hierarchy and used GBD 2021's cause-specific mortality estimates to produce sepsis-related mortality by underlying cause of death and infectious syndrome by sex, age group, location, and year. We used these estimates with sepsis case fatality rates (CFRs; defined as ratios of cases over deaths) to estimate the number of sepsis cases. We present

estimates globally and for each GBD super-region, region, and national location (appendix 1 table S5).

Data sources

We used our collaborator network as well as standard GBD data seeking to gather MCoD data from vital registration systems, hospital records, hospital records linked with mortality records (termed linkage), and minimally invasive tissue sampling records. For our estimation of the fraction of sepsis co-occurring with GBD underlying causes of death, we used 149 million deaths from 4290 location-years (appendix 1 section 4.1). For our estimation of sepsis mortality, we incorporated GBD 2021 mortality estimates, estimated from 702 million deaths, representing 5309 location-years. Fatal GBD 2021 data sources included vital registration and vital registration-sample systems, verbal autopsies, sibling histories, survey or census data, surveillance data, police records, and minimally invasive tissue sampling records (appendix 1 section 4.1). For our incidence estimates we used hospital records, which reported both admissions and deaths, totalling 250 million hospital admissions and 10 million deaths from 1311 location-years. A summary of input data is provided in appendix 1 (table S19; table 1).

Defining sepsis

We applied the consensus definition of adult sepsis established by the Third International Consensus Definitions for Sepsis and Septic Shock[1] (Sepsis-3): a life-threatening organ dysfunction caused by dysregulated host response to infection.

In accordance with WHO[19] and GBD,[20] we classified causes of death as underlying, intermediate, and immediate (appendix 1 section 3.2). As described in our previous study,[4] our MCoD modelling framework expands upon the existing GBD process to capture the comprehensive burden of sepsis by identifying sepsis in secondary diagnoses outside of the underlying cause or primary diagnosis. We marked sepsis as co-occurring with a death as both explicit sepsis (a specific International Classification of Diseases [ICD] code [eg, ICD-10 A40: group A streptococcal sepsis]) and implicit sepsis (any death including an infectious disease code as the underlying cause of death). Implicit sepsis cases also required the presence of organ failure[4] (appendix 1 section 4.4).

Mapping sepsis-related deaths to underlying causes of deaths

We mapped all deaths to a GBD underlying cause and restructured the cause hierarchy to separate causes into infectious and non-infectious categories (appendix 1 section 3.3, table S3).

We calculated the sepsis burden for 195 of the 288 GBD underlying causes of death. Selected exclusions (eg, sudden infant death syndrome) were made due to minimal likelihood of sepsis development. For the included underlying causes, see appendix 1 (tables S1, S2).

See Online for appendix 1

Assignment of infectious syndromes to sepsis-related deaths

We mapped all sepsis-related deaths to an infectious syndrome, implicating the organ system involved in the origination of the infection (appendix 1 table S18). Our infectious syndrome framework comprised 22 mutually exclusive and collectively exhaustive infectious syndromes (eg, bloodstream infections inclusive of HIV and malaria, lower respiratory infections inclusive of COVID-19, and peritoneal and intra-abdomen infections; for the full list, see appendix 1 [table 4.5.2.1]). For deaths with multiple infectious syndromes, we used an informativity hierarchy to assign the infectious syndrome most likely to have originated sepsis.

Modelling cause-specific sepsis fraction of deaths

We ran two mixed-effects binomial linear regression models: the first captured the proportion of deaths that were related to sepsis, and the second captured the proportion of deaths that were related to each infectious syndrome. The sepsis model[4,9] was as follows:

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

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

where $\pi_{\text{level 1, level 2}}$ is a nested random effect on underlying cause of death, where estimation occurs at the most detailed cause level (level 2) and child causes with a shared parent (level 1) cause can borrow strength from each other. Healthcare Access and Quality (HAQ) Index and sex are fixed effects.

We calculated sepsis fractions for each age group, location, year, sex, and underlying cause of death. We ran age-group-specific regression models to preserve distinct age patterns by cause. HAQ Index was used to capture variation by year and location and produce estimates for locations without data. Estimates for each underlying cause, age group, location, and year were multiplied onto GBD 2021 cause-specific mortality estimates to obtain cause-age-location-year-specific sepsis mortality estimates. Population estimates from GBD 2021[17] were used to calculate age-specific mortality rates. We calculated 95% uncertainty intervals (UIs) as 1·96 SDs above and below the modelled point estimate.

Modelling infectious syndrome-specific sepsis mortality

In the second mixed-effects binomial linear regression, we calculated the fractions of infectious syndrome-specific sepsis-related deaths by underlying cause-age-location, as follows:

$$\text{Infectious syndrome related deaths} \sim B(\text{total deaths}, \text{infectious syndrome fraction})$$

$$\text{logit}(\text{infectious syndrome fraction}) = \beta 0 + \beta 1 \times \text{HAQ Index} + \beta_2 \times \text{sex} + \beta x \times X + \pi_{\text{level 1,level 2}}$$

The age-specific regressions included the same specifications as the sepsis model with different covariates (appendix 1 section 4.7). The granularity of the age groups estimated for each infectious syndrome was chosen on the basis of the age pattern of the infectious syndrome and the available data. Point estimates of predicted fractions of sepsis-related deaths caused by a given infectious syndrome were used to divide the sepsis-related mortality estimate for each underlying cause (appendix 1 table S4), age group, location, and year to obtain cause-age-location-year-specific sepsis mortality estimates for each specific infectious syndrome. 95% UIs were calculated as 1·96 SDs above and below the modelled point estimate.

Our out-of-sample validation testing approach and results are summarised in appendix 1 (section 4.8).

	Modelling component	Location-years	Year range	Deaths	Admissions
Hospital records	Fatal	1311	1980–2021	10 051 477	..
Hospital records (CFR model)	Non-Fatal	1311	1980–2021	..	249 784 213
Hospital records linked with mortality records	Fatal	38	2000–2018	288 315	..
MITS	Fatal	35	2017–2022	1805	..
MCoD-VR	Fatal	3499	1980–2022	139 000 000	..
Claims with outcome	Fatal	1	2016	89 276	..
GBD 2021 cause of death	Fatal	5309	1980–2020	702 000 000	..
Total fatal	..	10 193	1980–2021	851 430 873	..
Total non-fatal	..	1311	1980–2021	..	249 784 213

CFR=case fatality rate. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. MCoD-VR=multiple cause of death and vital registration. MITS=minimally invasive tissue sampling.

Table 1: **Data inputs by source type**

Modelling sepsis incidence

Using 249 million hospital patient admissions and 10 million deaths, we calculated crude CFRs (defined as sepsis deaths divided by sepsis cases) for sepsis by age, location, and year (appendix 1 section 5). Using the crude CFRs as inputs, we ran a binomial regression model with HAQ Index and GBD age groups as covariates to calculate age-location-year-cause-specific sepsis CFRs. As before, we calculated 95% UIs as 1·96 SDs above and below the modelled point estimate.

We followed GATHER[21] guidelines (appendix 1 section 6, table S17). All count data are presented to

	1990				2019				2021			
	Mortality		Incidence		Mortality		Incidence		Mortality		Incidence	
	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)	Counts, thousands (95% UI)	Rate per 100 000 population (95% UI)
All ages	16 500 (15 700–17 300)	309·3 (294·3–325·1)	136 000 (113 000–161 000)	2543·2 (2112·5–3016·5)	14 100 (13 200–15 100)	182·2 (170·4–194·9)	128 000 (102 000–157 000)	1655·6 (1314·5–2024·4)	21 400 (20 300–22 500)	270·6 (257·4–284·6)	166 000 (135 000–201 000)	2111·0 (1708·2–2550·8)
Neonatal	2170 (1900–2470)	21 602·8 (18 964·2–24 608·5)	8290 (6610–9980)	82 656·1 (65 909·4–99 464·0)	1070 (865–1330)	10 584·8 (8536·1–13 125·1)	5870 (4290–7490)	58 013·4 (42 364·5–74 007·2)	967 (770–1210)	9920·3 (7903·4–12 451·8)	5370 (3850–6960)	55 174·5 (39 538·0–71 460·7)
Post-neonatal	2780 (2600–2960)	2359·6 (2210·5–2518·7)	27 100 (22 600–31 900)	23 007·7 (19 194·7–27 081·7)	1090 (955–1240)	889·9 (782·4–1012·2)	15 800 (12 100–19 700)	12 979·4 (9934·6–16 169·8)	874 (742–1030)	747·2 (634·7–879·6)	13 300 (9940–16 900)	11 363·5 (8508·5–14 500·2)
1–4 years	2740 (2540–2960)	557·2 (515·4–602·3)	54 800 (45 100–66 100)	11 148·8 (9166·1–13 438·0)	981 (835–1150)	179·6 (153·0–210·8)	30 700 (23 300–39 100)	5619·7 (4273·8–7162·2)	842 (690–1030)	158·5 (129·9–193·4)	26 900 (19 600–35 200)	5058·9 (3692·6–6628·8)
5–14 years	708 (656–765)	63·3 (58·6–68·3)	11 700 (9890–13 700)	1044·8 (884·6–1226·3)	365 (333–399)	27·5 (25·1–30·1)	10 000 (7910–12 400)	754·2 (596·2–933·8)	341 (309–376)	25·2 (22·8–27·8)	9880 (7730–12 400)	730·4 (571·8–916·3)
15–49 years	2000 (1870–2140)	73·7 (69·0–78·8)	16 100 (13 300–19 000)	594·4 (491·2–702·2)	2150 (2020–2270)	55·0 (51·9–58·3)	26 200 (21 100–31 700)	672·0 (541·6–814·4)	3200 (3040–3380)	81·2 (76·9–85·6)	40 200 (32 900–48 300)	1017·8 (833·5–1223·0)
50–69 years	2670 (2510–2840)	392·0 (368·8–416·9)	8710 (7500–9960)	1278·6 (1100·9–1462·1)	3140 (2940–3340)	227·8 (213·7–242·9)	18 000 (15 000–20 900)	1307·8 (1093·8–1522·8)	5850 (5580–6120)	406·9 (388·6–426·1)	33 800 (28 700–39 000)	2352·2 (2002·8–2716·4)
≥70 years	3430 (3150–3730)	1697·6 (1561·4–1845·7)	8850 (7610–10 100)	4387·3 (3770·8–5024·6)	5330 (4810–5900)	1147·3 (1035·4–1271·2)	21 600 (18 000–25 300)	4655·9 (3870·5–5459·9)	9280 (8740–9860)	1877·9 (1767·6–1995·0)	37 100 (31 900–42 400)	7519·7 (6463·4–8582·5)

Neonatal=<28 days. Post-neonatal=28–364 days. UI=uncertainty interval. All count data are presented to three significant figures and rates are presented to one decimal place.

Table 2: **Global sepsis-related incidence and mortality by age group, in 1990, 2019, and 2021**

three significant figures and rates and percentages are presented to one decimal place.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.

Results

Sepsis-related mortality

From 1990 to 2019, all-cause sepsis-related deaths decreased from 16·5 million (95% UI 15·7–17·3) to 14·1 million (13·2–15·1), before increasing to 21·4 million (20·3–22·5) in 2021, representing 31·5% of total global deaths (table 2), of which 7·88 million (7·47–8·32)

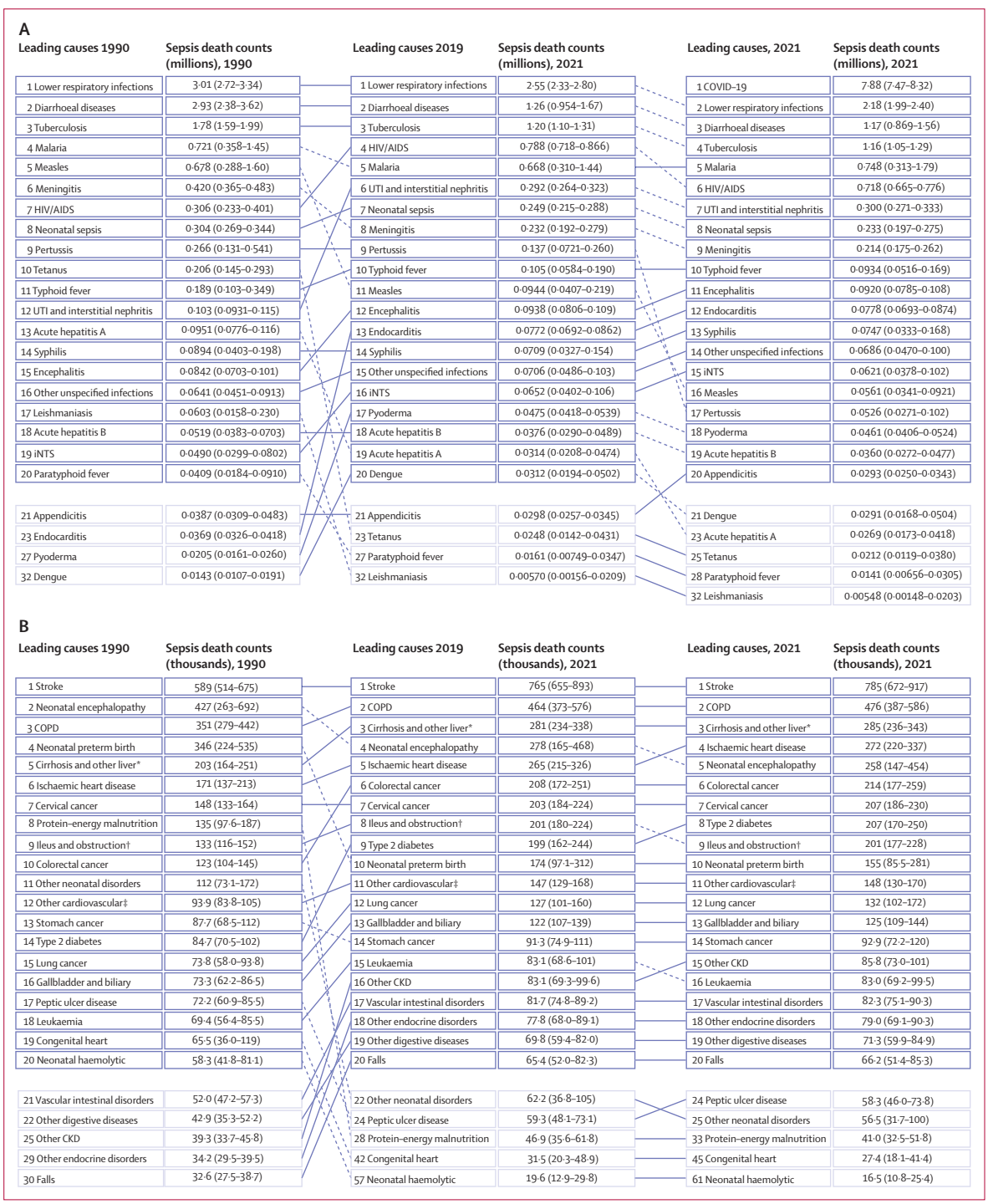

Figure 1: **Global leading 20 underlying causes of sepsis-related deaths, all ages, in 1990, 2019, and 2021**

(A) Infectious causes. (B) Non-infectious causes. Causes are connected by lines between periods (1990, 2019, and 2021); solid lines are ranked increases (or no change in rank) and dashed lines are ranked decreases. CKD=chronic kidney disease. COPD=chronic obstructive pulmonary disease. INTS=invasive non-typhoidal Salmonella disease. UTI=urinary tract infection. *Cirrhosis and other chronic liver diseases. †Paralytic ileus and intestinal obstruction. ‡Other cardiovascular and circulatory diseases.

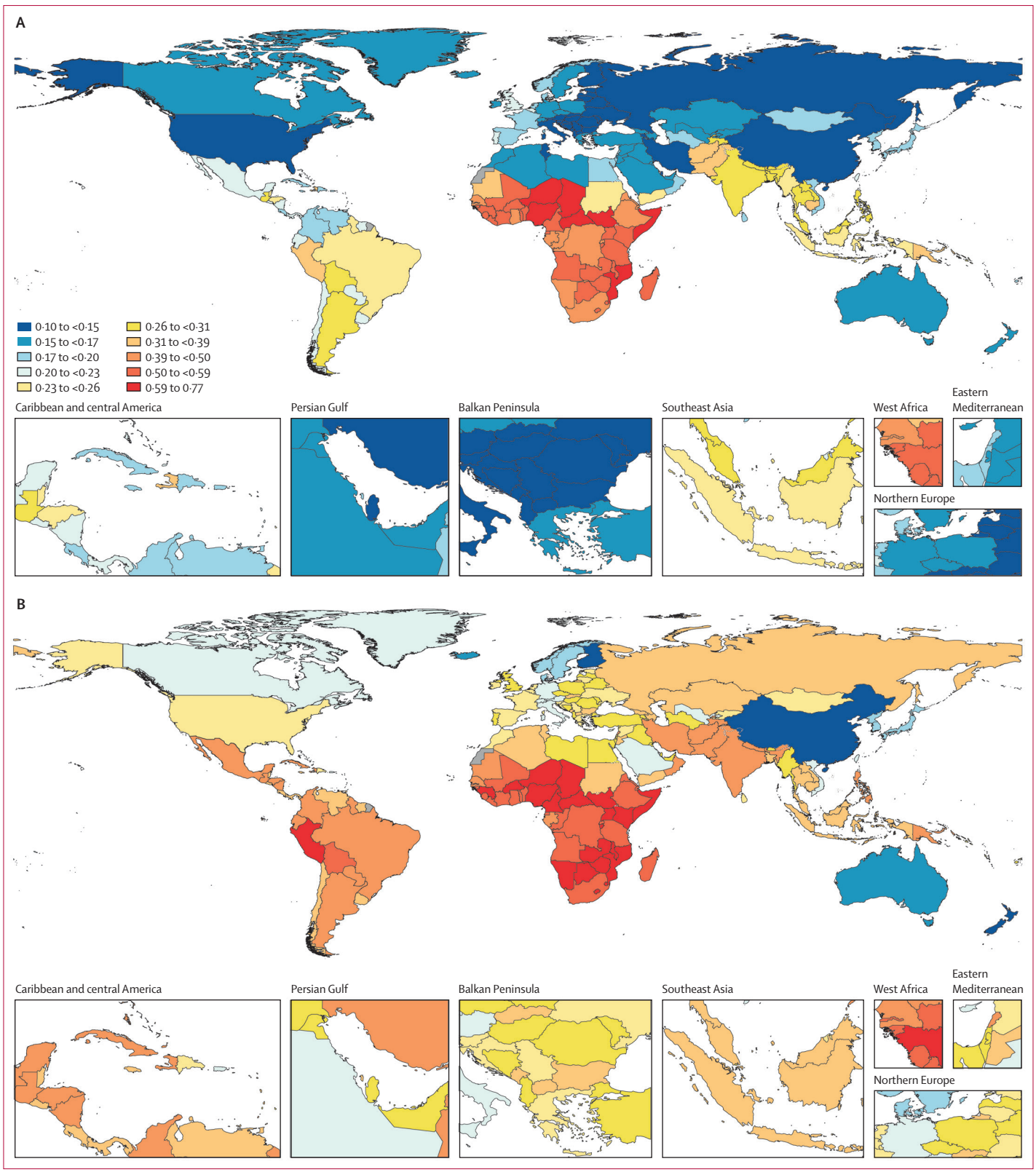

Figure 2: **Sepsis fraction of all-cause deaths, all ages, by country, in 2019 (A) and 2021 (B)**

sepsis-related deaths were from COVID-19 (figure 1A). From 1990 to 2021, individuals aged 15 years and older experienced a 26·3% increase in mortality. The 70 years and older age group had the greatest number of sepsis-related deaths in 2021 (9·28 million [8·74–9·86] deaths; table 2; appendix 1 figure S1A). Among those aged younger than 15 years, the sepsis burden decreased the most between 2019 and 2021 in post-neonatal infants (from 2·78 million [2·60–2·96] to 0·874 million [0·742–1·03] deaths).

Regionally, despite having the greatest percentage decrease of 50·1% in sepsis mortality by rate, from 914·8 (95% UI 869·9–962·0) deaths per 100 000 in 1990 to 456·6 (95% UI 410·7–507·6) deaths per 100 000 in 2021, sub-Saharan Africa maintained the highest sepsis mortality rate since 1990 and incurred 5·17 million (95% UI 4·65–5·75) sepsis deaths in 2021 (appendix 1 table S7). The next most burdened super-regions in 2021 were central Europe, eastern Europe, and central Asia (409·0 [387·1–432·2] deaths per 100 000) and Latin America and the Caribbean (334·6 [317·4–352·8] deaths per 100 000). Regional and national-level results are available in appendix 1 (table S8).

Sepsis-related mortality co-occurring with underlying causes of death

Globally, the fraction of all deaths co-occurring with sepsis declined from 35·8% (95% UI 34·4–37·3) in 1990 to 24·8% (23·7–25·9) in 2019, before increasing to 32·8% (31·6–34·0) in 2021 (corresponding cause fractions in appendix 1 table S6). This decline was most notable in children, especially neonates, for whom sepsis declined from 53·9% (95% UI 47·9–60·6) of all deaths in 1990 to 44·4% (37·5–52·4) of all deaths in 2021. Conversely, across all age groups older than 15 years, the fraction of sepsis co-occurring with all deaths increased by at least 26% from 1990 to 2021. In 2021, 38·5% (37·2–39·8) of deaths co-occurred with sepsis in people aged 15–49 years, followed by 32·5% (31·2–33·9) of deaths in those aged 50–69 years, and 27·6% (26·0–29·2) of deaths in those aged 70 years and older. Results by detailed ages are available in appendix 1 (table S9).

Sub-Saharan Africa continued to experience the greatest sepsis burden globally in 2021, with 58·5% (95% UI 55·4–61·7) of all deaths complicated by sepsis, followed by Latin America and the Caribbean, with 41·9% (40·2–43·6; appendix 1 table S7). Southeast Asia, east Asia, and Oceania had the greatest reduction since 1990 (33·5%), from 27·8% (26·2–29·5) in 1990 to 18·5% (16·7–20·4) of all-cause deaths complicated by sepsis in 2021. The greatest increase in deaths complicated by sepsis occurred in central Europe, eastern Europe, and central Asia (an 112·4% increase, from 14·3% (13·6–14·9) in 1990 to 30·3% (28·6–32·1) in 2021). Figure 2 compares the fraction of sepsis co-occurring with all-cause deaths for all ages by country, 2019 to 2021.

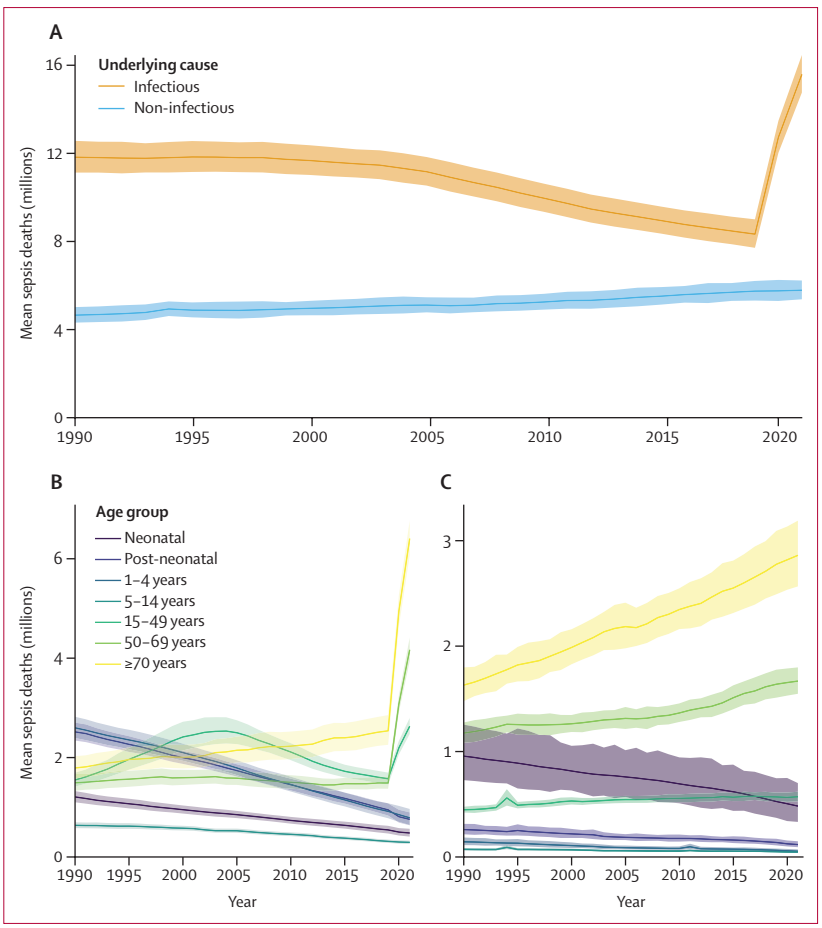

Figure 3: **Global sepsis-related deaths co-occurring with infectious and non-infectious underlying causes, for all ages and by age group, 1990–2021**

(A) Global sepsis-related deaths for all ages by infectious or non-infectious underlying cause. (B) Global sepsis-related deaths co-occurring with infectious causes by age group. (C) Global sepsis-related deaths co-occurring with non-infectious underlying causes by age group. Shaded areas indicate 95% uncertainty intervals. Neonatal=0–27 days. Post-neonatal=28–364 days.

Sepsis-related deaths from infectious underlying causes decreased by 29·4% between 1990 and 2019, from 11·8 million (95% UI 11·1–12·5) in 1990 to 8·34 million (7·72–9·01) in 2019, then increased by 86·4% to 15·5 million (14·7–16·4) deaths in 2021 (figure 3A; appendix 1 table S6). Non-COVID-19 lower respiratory infection (LRI) remained the leading underlying cause of death complicated by sepsis until 2019, which was surpassed by COVID-19 in 2021 (figure 1A). Sepsis-related deaths due to diarrhoeal diseases, LRI, measles, and tuberculosis decreased substantially from 1990 to 2021 (figure 4A). Meanwhile, sepsis-related deaths due to HIV/AIDS increased significantly between 1990 and 2000 before decreasing significantly from 2000 to 2021. For those younger than 15 years, sepsis-related deaths with infectious underlying causes decreased from 1990 to 2021 (appendix 1 figures S7A–10A). For those aged 15 years and older, sepsis-related deaths with infectious underlying causes

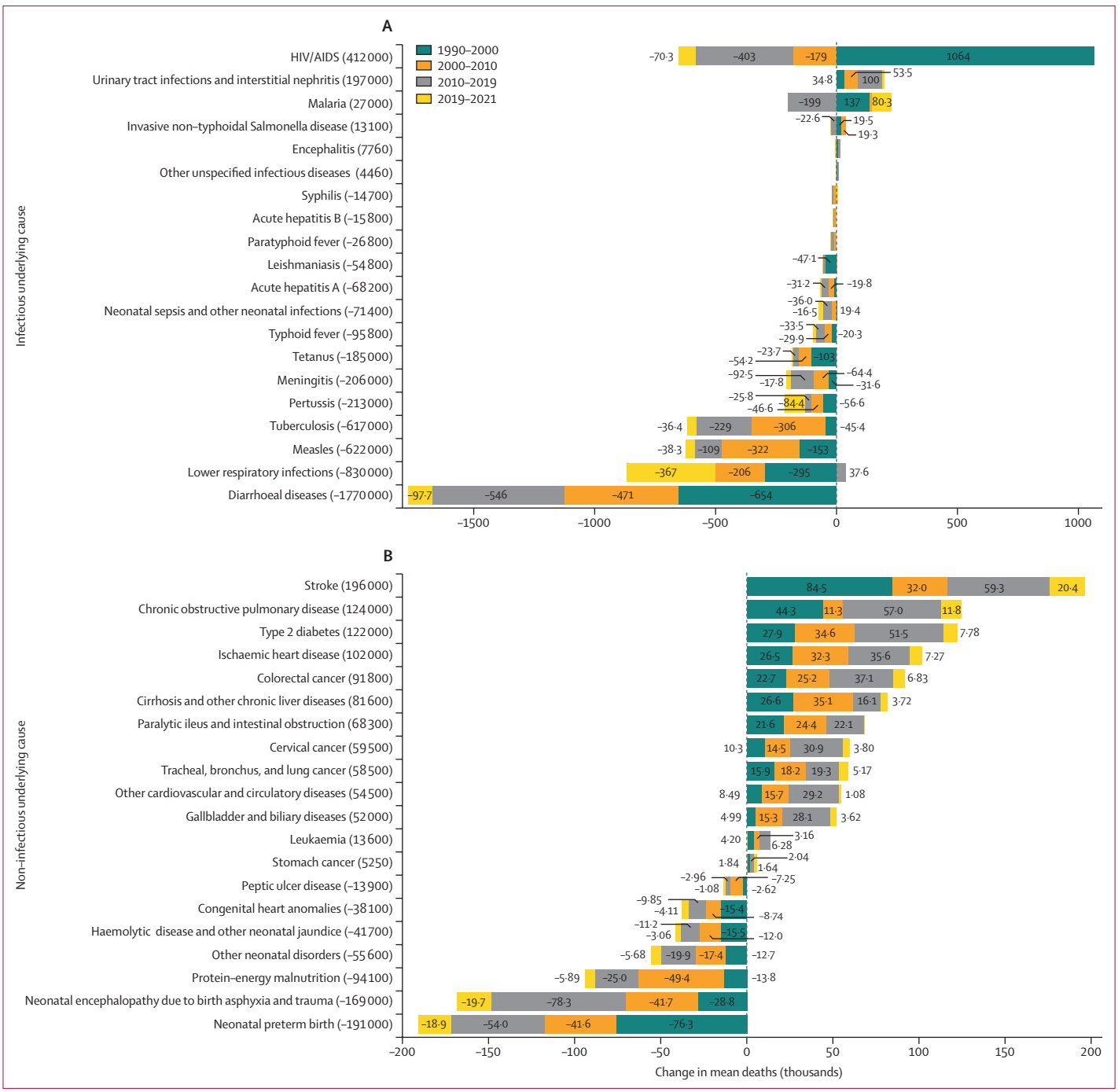

Figure 4: **Change in global sepsis-related deaths co-occurring with the leading 20 infectious (A) and non-infectious (B) underlying causes, by time period, from 1990–2021**
Each row represents the change in the number of sepsis-related deaths across a time period (1990–2000, 2000–2010, 2010–2019, and 2019–2021) for a given leading underlying cause (top 20 underlying causes for sepsis-related deaths in 1990), listed by change in mean deaths. The change in mean deaths is shown in parentheses. A bar to the right of 0 represents an increase in the number of cause-specific sepsis deaths and a bar to the left of 0 represents a decrease in the number of cause-specific sepsis deaths. For readability, values less than 15 000 in panel A and values less than 1000 in panel B are not displayed.

increased significantly in 2021, with extensive contributions from LRIs, urinary tract infections, malaria, HIV/AIDS, COVID-19, and malaria (figure 3B; appendix 1 table S10, figures S4A–6A).

Sepsis-related deaths with non-infectious underlying causes increased overall by 23·9% from 1990 (4·69 million [95% UI 4·35–5·05]) to 2021 (5·81 million [5·40–6·25]; figure 3A, appendix 1 table S6). In 2021,

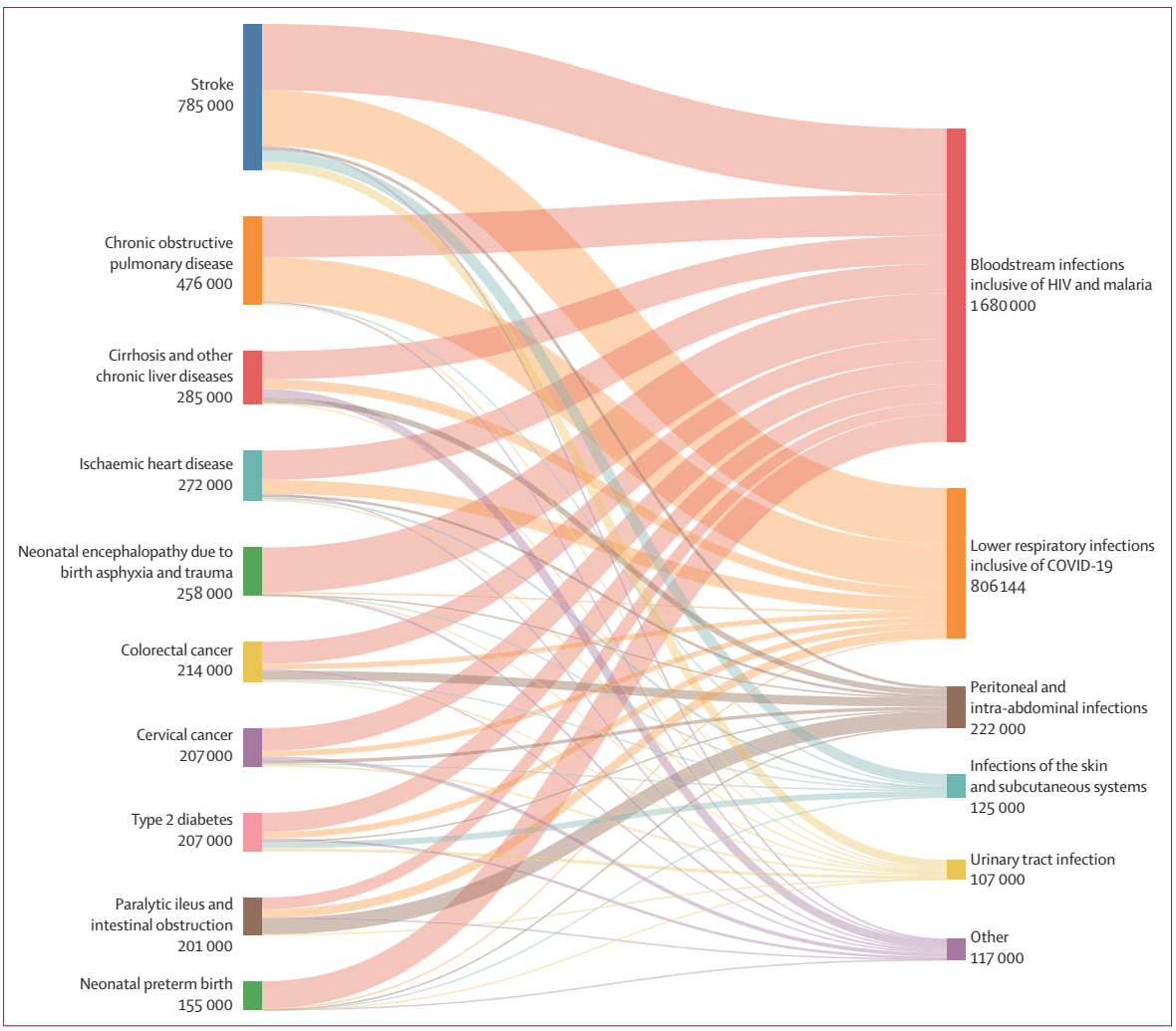

Figure 5: **Sankey diagram of relationships between the leading ten non-infectious underlying causes of sepsis-related deaths and top five co-occurring infectious syndromes, 2021**

The heights of the coloured boxes and connecting bands represent the relative numbers of sepsis-related deaths co-occurring with the underlying cause and infectious syndrome. "Other" represents the aggregate reporting of all other infectious syndromes.

sepsis-related deaths co-occurred most frequently with cardiovascular diseases (1·38 million [1·24–1·55]), cancers (1·3 million [1·19–1·43]), and digestive diseases (0·949 million [0·859–1·05]; appendix 1 table S10). This ranking has largely remained stable since 1990. Among our most detailed non-infectious underlying causes of death, stroke was associated with the greatest increase in sepsis-related deaths from 1990 to 2021, with 197 000 (166 000–201 000) additional deaths in 2021 (figure 4B) and ranked first from 1990 to 2021 (figure 1B). After stroke, the leading non-infectious underlying causes of death, with increasing sepsis mortality from 1990 to 2021, were chronic obstructive pulmonary disease (COPD), type 2 diabetes, ischaemic heart disease, and colorectal cancer (figure 4B; appendix 1 table S11).

For age groups younger than 15 years, the greatest decreases from 2019 to 2021 were in sepsis-related deaths due to protein-energy malnutrition, which dropped by 69·6% from eighth to 33rd in rank, followed by sepsis-related deaths due to neonatal preterm births, which decreased by 55·2% to drop in rank from fourth to tenth, and neonatal encephalopathy due to birth asphyxia and trauma, which dropped by 9·5% from second to fifth in rank (appendix 1 figures S7–S10). For those aged 15 years and older, the number of sepsis-related deaths with non-infectious underlying causes increased from 1990 to 2021, a trend that followed increases in sepsis-related deaths occurring with stroke, cirrhosis, and cervical cancer (appendix 1 figures S4B–6B). In 2021, those aged 70 years and older had the greatest burden with 2·87 million (95% UI 2·58–3·20) sepsis-related deaths, predominantly from COPD and ischaemic heart disease (figure 3C; appendix 1 table S10).

Sepsis by infectious syndromes

In 2021, non-infectious underlying causes of death contributing to sepsis primarily co-occurred with bloodstream infections inclusive of HIV and malaria (3·08 million [95% UI 2·83–3·35]), LRIs inclusive of COVID-19 (11·33 million [1·20–1·47]), and peritoneal and intra-abdominal infections (675 000 [618 000–737 000]; appendix 1 table S12). Bloodstream infections inclusive of HIV and malaria and LRIs inclusive of COVID-19 co-occurred frequently with the ten leading non-infectious underlying causes of deaths in 2021 (figure 5; appendix 1 table S12). A similar trend was seen between 1990 and 2019 (appendix 1 figures S11A–B). For all causes, see appendix 1 (tables S10, S12).

Sepsis incidence

Global sepsis cases across all ages decreased by 5·5%, from 136 million (95% UI 113–161) cases in 1990 to 128 million (102–157) cases in 2019, before increasing by 30·0% during the COVID-19 pandemic to 166 million (135–201) cases in 2021 (table 2; appendix 1 table S13–15, figure S12). Declining sepsis incidence from 1990 to 2019 was driven by improvements in children: the greatest decrease occurred in post-neonatal infants, from 27·1 million (22·6–31·9) cases in 1990 to 15·8 million (12·1–19·7) cases in 2019. Sepsis incidence increased by 230% from 1990 to 2021 in individuals aged 15 years and older: the greatest increases were seen in those aged 70 years and older, from 8·85 million (7·61–10·1) cases in 1990 to 37·1 million (31·9–42·4) cases in 2021 (table 2; appendix 1 figure S1B).

Sub-Saharan Africa consistently had the highest sepsis incidence despite having a 50·7% reduction in the sepsis incidence rate from 8070 cases (95% UI 6810–9420) per 100 000 population in 1990 to 3980 cases (3080–4960) per 100 000 population in 2021. Regional and national-level results are available in appendix 1 (figure S3, table S16).

Discussion

In this comprehensive study of the global sepsis burden, sepsis cases and deaths declined from 1990 to 2019 to reach a low of 128 million (95% UI 102–157) cases and 14·1 million (13·2–15·1) deaths in 2019; however, this progress was reversed during the COVID-19 pandemic, resulting in 166 million (135–201) cases and 21·4 million (20·3–22·5) deaths in 2021. In contrast to decreases in sepsis incidence and mortality in children, we found a concerning trend of an increasing sepsis burden in people aged 15 years and older, in whom at least 27·6% (26·0–29·2) of all deaths were complicated by sepsis in 2021. Sepsis-related deaths co-occurring with non-infectious underlying causes steadily increased, specifically for stroke, COPD, cirrhosis and other chronic liver diseases, ischaemic heart disease, neonatal encephalopathy, and selected cancers. Sepsis deaths with non-infectious underlying causes primarily involved two infectious syndromes: bloodstream infections inclusive of HIV and malaria and LRIs inclusive of COVID-19.

Our results highlight the role of sepsis on the pathway to death and help identify points for intervention. First, the decrease in sepsis co-occurring with infectious underlying causes of death demonstrates successful investment in infection prevention measures such as vaccination and access to water, sanitation, and hygiene services.[22] Second, the increasing burden of sepsis co-occurring with non-infectious underlying causes of death suggests the need for improvements in the treatment of chronic conditions, especially those relating to leading infectious syndromes. For bloodstream infections inclusive of HIV and malaria, measures include bundled care to prevent health-care-associated infections. For LRIs inclusive of COVID-19, improved vaccination coverage against respiratory pathogens (eg, COVID-19, influenza, *Streptococcus pneumoniae*, and respiratory syncytial virus [RSV]) is needed in older adults and those with at-risk comorbidities (eg, COPD). This could include lowering the recommended age for RSV vaccination to those aged 50 years and older.[23] Third, improved diagnosis and treatment of infections might help reduce progression to sepsis. This includes adoption of diagnostic tools for earlier pathogen detection (eg, rapid molecular diagnostics, including detection of antimicrobial resistance genes) and improved antimicrobial access based on pathogen-specific resistance patterns.[9,15]

Apart from COVID-19-related sepsis, the increasing sepsis burden between 2019 and 2021 was primarily associated with preventable non-infectious conditions such as stroke, cirrhosis, and cancers among those aged 15 years and older. This is concerning given the increasing prevalence of these chronic conditions. Although advanced age is not inherently a risk factor for sepsis, ageing is correlated with increased multimorbidity, which can increase exposure to immunosuppressive treatments, invasive medical devices (eg, central venous catheters), health-care-associated infections, and antimicrobial resistance.[15,24] As populations age, chronic care models must integrate with sepsis prevention strategies to curtail the growing sepsis burden in adults.

The COVID-19 pandemic reversed improvements in the sepsis burden, illustrating the substantial direct and indirect impact of a single pathogen on sepsis. For example, the increase in sepsis co-occurring with malaria has been attributed to disruptions to critical health services that occurred during the COVID-19 pandemic.[25] One positive legacy from the pandemic is the rapid performance of clinical trials to test immunomodulatory therapies for COVID-19.[26] Given the high overlap in immune dysregulation phenotypes between severe COVID-19 and sepsis,[27] directed therapies for sepsis could be developed from similar therapies and trials.

This study's strengths include the use of individual-level data from a variety of sources and locations; an

innovative MCoD framework, which allowed for comprehensive sepsis estimation; models to predict sepsis burden for data-sparse locations, and the GBD framework to incorporate up-to-date, comparable cause-of-death estimates. As a result, this work is a major extension of the GBD 2021 analysis and is intended to be comparable to GBD 2021 estimates. We built on our previous work and included sepsis implied by infection in our estimates of sepsis incidence. This approach creates consistency across sepsis incidence and mortality estimates and represents the most inclusive strategy to identify sepsis, particularly given the low sensitivity of explicit sepsis ICD codes.[28,29] We cannot rule out overestimation but maintain concern for historical underestimation of the global sepsis burden. Continued efforts to strive for accurate, comprehensive estimates will help increase public awareness of the global threat of sepsis and motivate further advocacy efforts such as the adoption of Martha's rule[30] and quality improvement campaigns such as the UK Sepsis Trust.

This study has several limitations. First, there is a risk of misclassification of sepsis due to varying definitions and ICD coding practices over time. Second, despite our expanded collection of data sources, we still informed our estimate of sepsis fractions with 4290 location-years of data that predominantly come from selected high-income countries. Due to lower infection rates within these countries compared with low-income and middle-income countries, our results might underestimate the sepsis burden in low-income and middle-income countries as well as globally. Expanding geographical coverage within our input data remains a consistent goal to combat data sparsity. Third, use of hospital data as part of fatal sepsis estimation might underestimate sepsis-related deaths after discharge and CFRs, and increase data variability through changes in hospital and national reporting practices, potentially leading to missed cases and deaths in the community. Fourth, due to data sparsity, we did not estimate sepsis incidence by underlying cause and infectious syndrome: future analyses would benefit from greater coverage of admission data with outcomes. Fifth, we acknowledge the gap in comprehensive long-term sequelae and disability estimates to assess the substantial health loss among sepsis survivors who might develop various impairments and lifelong disability.[31–33]

In conclusion, sepsis-related deaths co-occurring with non-infectious underlying causes remain a growing problem. Our results not only emphasise the need to broaden our understanding of sepsis epidemiology to capture sepsis co-occurring with non-infectious diseases, but also the reality that this fatal co-occurrence has increased over time. These findings indicate that traditional prevention methods alone are not enough. It is imperative that we start bridging chronic disease management with infection prevention strategies to build resilient health-care systems that are capable of addressing the growing threat of sepsis.

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Please see appendix 2 (pp 16–22) for more detailed information about individual author contributions to the research, divided into the following categories: managing the overall research enterprise; writing the first draft of the manuscript; primary responsibility for applying analytical methods to produce estimates; primary responsibility for seeking, cataloguing, extracting, or cleaning data; designing or coding figures and tables; providing data or critical feedback on data sources; developing methods or computational machinery; providing critical feedback on methods or results; drafting the manuscript or revising it critically for important intellectual content; and managing the estimation or publications process. The first authors and the corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

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B Venkatesh reports grants or contracts from the Investigator Grant from the National Health and Medical Research Council of Australia and research grants from Baxter, all payments made to the George Institute for Global Health, outside the submitted work. Y Yasufuku reports grants or contracts from Shionogi & Co. Ltd (employment expenses are paid from the joint research fund provided by this pharmaceutical company to The University of Osaka. The joint research with this pharmaceutical company is unrelated to the content of this GBD study). G Zamagni reports support for the present manuscript from the Italian Ministry of Health (Ricerca Corrente 34/2017) and payments made to the Institute for Maternal and Child Health IRCCS Burlo Garofolo. All other authors declare no competing interests.

Data sharing

This study used de-identified data and was approved by the University of Washington Institutional Review Board (study #9060). This study follows the GATHER statement. To download the data used in these analyses, please visit the Global Health Data Exchange at https://ghdx.healthdata.org/record/ihme-data/global-sepsis-incidence-mortality-1990-2021.

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