

From Associated to Attributable Burden of Sepsis

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Abstract

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Sepsis is a dysregulated host response to infection that leads to life-threatening end organ dysfunction and has historically been excluded from global health estimates. In 2020 global estimates for sepsis were produced as an analysis of the Global Burden of Disease Study (GBD) but these estimates only described the number of deaths where sepsis occurred, not the deaths attributable to sepsis. In this study we describe methods for estimating the attributable burden of sepsis to produce estimates on the number of deaths and years of life lost (YLL) attributable to sepsis. We utilize a population attributable fraction (PAF) approach with two components, proportion of population exposed to sepsis and the excess risk of death associated with sepsis admission compared to hospital admission without sepsis. Using this PAF method we estimate 3.0 million (95% UI 2.4 – 3.7) deaths and 192.2 million (95% UI 160.9 – 224.6) YLLs attributable to sepsis in 2017. In 1990 there were an estimated 5.2 million (95% UI 4.4 – 6.1) deaths and 429 million (95% UI 362 – 496) YLLs attributable to sepsis. There was significant heterogeneity across age and region with more than half of all sepsis attributable deaths occurring in children under 5 and a 28-fold difference in age-standardized sepsis death rates between the high-income super-region and Sub-Saharan Africa in 2017. The disparities in deaths and YLLs attributable to sepsis across regions is more pronounced than previously appreciated and should further increase the urgency of infection prevention interventions, infrastructure building, and sepsis treatment trials in LMIC.

Introduction:

Sepsis is defined as a dysregulated host response to infection that leads to life-threatening end organ dysfunction (1). In 2017 the Seventieth World Health Assembly passed WHA resolution 70.7, with the goal of improving the epidemiology, prevention, diagnosis and clinical management of sepsis (2). This resolution highlighted sepsis as a public health priority with significant economic and health consequences(3). The Global Health Estimates of the WHO and the Global Burden of Disease study (GBD) adhere to the principles of the international classification of disease (ICD), which attribute each death to a single underlying cause of death(4–7). Because sepsis is the result of infection it is inherently an intermediate cause of death and has historically been excluded from global health estimates. However, a recent analysis of the GBD estimated there were more than 11 million sepsis related deaths in 2017 globally, more than double the previous estimate(8,9).

One limitation of the recent GBD and antecedent global sepsis estimates is that they describe sepsis associated deaths, that is the number of deaths that occur through the route of sepsis and not the deaths attributable to sepsis (10). The concern is that many of the people who die with sepsis were older and had severe underlying comorbidities, like cancer or stroke, and counting their death as a sepsis death overestimates the true impact sepsis has on health. Further, there has been no measure of the global burden of sepsis using a metric like years of life lost (YLL). The result of these two limitations is that there's no greater weight given to the sepsis death of an otherwise healthy infant compared to a 90-year-old hospice patient with stage four cancer.

The degree to which sepsis mortality is preventable is debated and some have argued the reporting of sepsis associated mortality numbers has led to 'sepsis hysteria' (11). Infection prevention measures, like handwashing or vaccination, reduce the incidence of infections and in turn decrease sepsis incidence and mortality rates. Once sepsis occurs there are evidence based interventions that reduce sepsis mortality, but an evaluation of sepsis deaths in 6 United States acute care hospitals showed only 22.7% of deaths involved sub-optimal care and only 12% of sepsis deaths were judged to be possibly or definitely preventable(12). Multiple groups have worked to better describe the fraction of deaths for which sepsis was directly responsible by estimating the sepsis attributable fraction in an effort to better quantify the attributable burden of sepsis(13,14). By describing the

attributable sepsis deaths globally, we can better describe the true burden of sepsis and highlight disparities in sepsis burden.

There is no standard method to produce attributable burden estimates for intermediate causes of death. In this study we estimate the attributable burden of sepsis using a population attributable fraction (PAF) and a counterfactual of non-sepsis hospital admission. This PAF methodology has been used previously to describe the attributable burden of risk factors in the GBD(15) and because sepsis is in the causal chain a PAF can reasonably be used in this context(16). In this study we use data obtained from the GBD 2017 to produce YLL estimates for the attributable burden of sepsis across 195 countries and territories from 1990 to 2017. By describing the burden of sepsis using YLLs we can better contextualize the sepsis deaths observed to gain a greater understanding of its burden relative to other causes of health loss. Estimating the attributable burden of sepsis also provides actionable information on locations and age groups that have the most urgent need for sepsis interventions(7). Finally, sepsis related deaths were found to disproportionately affect low- and middle-income countries and in this study we evaluate if the disparity is even more pronounced for attributable deaths by socio-demographic index (SDI) (8).

Methods:

Study Design

We built on the recent sepsis and GBD 2017 estimates to produce an estimate for deaths and YLLs attributable to sepsis(7,8,15,17–19). This approach relies on vital registration death records with multiple cause of death data and hospital based administrative data. We estimated a population attributable fraction (PAF) for sepsis using a counterfactual of admission to hospital for the same age, sex, location, year, and underlying cause without sepsis. We then estimated attributable deaths and YLLs by multiplying the modeled PAF by the deaths and YLLs for each underlying cause, age, sex, location, and year.

Sepsis Deaths, Case Fatality, and Incidence

Detailed methods of the sepsis estimation process used for this analysis of the GBD have been described previously(8). Briefly, the sepsis estimates built on the GBD 2017 estimates by utilizing multiple cause of death data and hospital data to identify sepsis using ICD 9th (ICD-9) and ICD 10th (ICD-10) revision codes. These codes identified two mutually exclusive sepsis groups: explicit and implicit sepsis. The identifying ICD-9 and ICD-10 codes were adapted from the Angus criteria and validated by an external board of international experts in epidemiology, adult and pediatric sepsis, critical care, and infectious diseases. The proportion of deaths that occurred through sepsis for each underlying cause of death was calculated from these causes of death and hospital data inputs. The sepsis proportion was then estimated for each underlying cause of death and for every location, age, sex, and year using the Health Access and Quality Index (HAQI) as a covariate and random-effects for age and sex. HAQI is estimated using outcomes for 32 diseases that should not lead to death given effective health care infrastructure to generate a score from 0 to 100 for each location and year, from 1990 to 2017. The modelled sepsis proportion was then multiplied by the GBD 2017 estimates for each underlying cause of death, location, age, sex, and year.

Sepsis case fatality rate (CFR) was calculated using hospital data linked to fatal outcomes. Hospital admissions with sepsis were identified using the same ICD-9 and ICD-10 codes, sepsis survivors and non-survivors were identified, and CFR was calculated. The CFR was then modelled for each underlying cause of death, location, age, sex, and year using the Health Access and Quality Index (HAQI) as a covariate and random-effects for age and sex. Finally,

incidence of sepsis was estimated by dividing the estimated sepsis deaths by the estimated case fatality rate for each underlying cause of death, location, age, sex, and year.

Attributable Sepsis Deaths

To estimate the number deaths attributable to sepsis we first estimated a population attributable fraction (PAF) for sepsis using the formulation described by Levin in 1953(20), a derivation of which is used to estimate the attributable burden of risk factors in the GBD (15). The components of the PAF are the proportion of the population exposed [p(sepsis)] and the excess risk associated with the exposure [RR(sepsis)].

$$PAF(\text{sepsis}) = \frac{p(\text{sepsis})_{l,j,i,a,y} \cdot (RR(\text{sepsis})_{l,j,i,a,y} - 1)}{1 + (p(\text{sepsis})_{l,j,i,a,y} \cdot (RR(\text{sepsis})_{l,j,i,a,y} - 1))}$$

j = underlying cause, l = location, i = sex, a = age, y = year

The proportion exposed to sepsis was estimated by the number of incident cases of sepsis for each age, sex, location, year, and underlying cause divided by the population, this incidence rate was one of the outputs of the previous sepsis estimate. The measure of excess risk is the relative risk of the estimated CFR of hospital admission with sepsis compared to the counterfactual CFR of admission to the hospital without sepsis matched on age, sex, location, year, and underlying cause of admission. The CFR of sepsis is an output from the GBD 2017 sepsis estimates. We calculated the CFR without sepsis using similar methods to the GBD 2017 sepsis study. We first identified and excluded all sepsis admissions using the same ICD-9 and ICD-10 codes. We then identified survivors and non-survivors and calculated the CFR for each underlying cause, age, sex, location, and year. Finally, we modelled the logit of CFR using a nested random-effects model using age, sex, and HAQI as covariates. Two notable exceptions to the PAF method were maternal and neonatal sepsis. For these causes the PAF was assumed to be 1, meaning all neonatal and maternal sepsis deaths were attributable to sepsis.

Input Data

Input data included all nationally representative sources of individual-level hospital admission or discharge data with multiple diagnoses and fatal outcomes data available in the GBD database. This included data from Austria, Brazil, Canada, Chile, Georgia, Italy, Mexico, New Zealand, Philippines, and the USA. Our analysis included a total of

309 million individual hospital records, of which 8.7 million were sepsis-related and 300.3 million were non-sepsis admissions, these served as the basis for the sepsis and non-sepsis case-fatality estimates, respectively.

Attributable Years of Life Lost

The process for estimating YLLs has been described previously(7,17). Briefly, YLLs are a measure of health burden where each death is measured against a standard life expectancy. The remaining years of expected life are summed across all deaths for each underlying cause of death, age, sex, and location to produce final YLL estimates. The process for estimating the attributable YLLs is similar to the method used for sepsis attributable deaths. We multiplied the PAF by the YLLs at the draw level for each underlying cause, age, sex, year, and location to determine the attributable YLLs. As with attributable deaths, maternal and neonatal sepsis were assumed to have a PAF of 1.

Uncertainty Intervals

Predictions and uncertainty intervals (UIs) were generated by drawing 1000 times from a normal distribution of each of the coefficients for each age, sex, year, and location. The point estimate is the mean of the draws and the 95% UIs are the 2.5 and 97.5 percentile of the draws. Using uncertainty allowed us to propagate uncertainty through each of the steps of estimation for the final estimates. This is consistent with the process of estimating uncertainty in the rest of the GBD(7).

Results:

Attributable Deaths

Globally, there were an estimated 3.0 million (95% UI 2.4 – 3.7) deaths attributable to sepsis in 2017 representing 5.5% (95% UI 4.4 – 6.7) of deaths for that year. In 1990 there were an estimated 5.2 million (95% UI 4.4 – 6.1) deaths attributable to sepsis representing 11% of deaths (95% UI 9.4 – 13.1) for the year. This represents a 50% decrease in total attributable sepsis deaths. The global age-standardized attributable sepsis death rate was 42.2 per 100,000 (95% UI 34.0 – 49.4) in 2017 and 86.5 per 100,000 (95% UI 72.3-103.1) in 1990, a decrease of 51.2%.

The attributable sepsis deaths by super-region in 1990 and 2017 are shown in table 1. This shows a more than 28-fold difference in age-standardized sepsis death rates between the high-income super-region at 3.4 (2.2-5.3) sepsis deaths per 100,000 and Sub-Saharan Africa at 97.7 (77.5 - 122.5) sepsis deaths per 100,000 in 2017. The age and super-region distribution of attributable sepsis deaths for 2017 is shown in figure 1 and shows 58.6% of all attributable sepsis deaths occur in children younger than five years-old and most of the sepsis deaths in children under 5 occurred in Sub-Saharan Africa.

Sepsis Years of Life Lost

Globally there were an estimated 192.2 million (95% UI 160.9 – 224.6) YLLs attributable to sepsis in 2017. In 1990 there were an estimated 429 million (95% UI 362 – 496) YLLs attributable to sepsis. This represents a 55.2% decrease in total attributable sepsis YLLs. The global age-standardized attributable sepsis YLL rate was 2,798 per 100,000 (95% UI 2,340 – 3,267) in 2017 and 6,796 per 100,000 (95% UI 5,743-7,844) in 1990, a decrease of 58.8%.

Figure 2 shows country specific age-standardized YLL rate for 2017. Table 1 shows the total sepsis YLLs and age-standardized sepsis YLLs by super-region. The country with the highest age-standardized sepsis YLLs was Nigeria with 16,056 YLLs per 100,000 (UI 12,196 – 20,509) in 2017. Compared to the underlying causes of death for Nigeria estimated by GBD 2017, sepsis would rank as the leading cause of YLLs in Nigeria for 2017. By comparison, in the United States of America there were an estimated 142 YLLs per 100,000 (UI 112 – 192) in 2017, which would represent the 29th leading cause of YLLs behind falls, alcohol use disorders, and brain cancer. Figure 3 shows the global age distribution of YLLs in 2017 by underlying cause of death. This shows the majority of sepsis YLLs occur in

communicable, maternal, neonatal, and nutritional diseases particularly in children and young adults. However, in adults over the age of 50 the majority of sepsis YLLs occur in non-communicable underlying causes of death.

Attributable Sepsis Deaths and Socio-Demographic Index

Patterns of sepsis attributable deaths varied substantially by location with higher age-standardized sepsis deaths in locations with lower SDI. This inverse relationship was more pronounced for attributable deaths compared to associated sepsis deaths ($p < 0.001$). Figure 4 shows the relationship of sociodemographic index to both sepsis attributable deaths and sepsis associated deaths. There is a steeper slope for sepsis associated deaths, such that as SDI of the location increases there is a more pronounced decrease in sepsis attributable deaths, as compared to sepsis associated deaths.

Discussion:

To our knowledge this study represents the first estimate of the global fatal burden attributable to sepsis with an estimated 3.0 million (95% UI 2.4 – 3.7) deaths and 192 million (161 – 225) YLLs attributable to sepsis in 2017.

When stratifying these estimates by super-region two diverging sepsis narratives emerge. The first pattern is that of the high-income, Central European, and Latin American super-regions; one where sepsis is responsible for less than 3 million YLLs and while it's in the chain of events that leads to death, the underlying condition and age of the patient carry greater responsibility for sepsis associated deaths. The second pattern is seen in South Asia and Sub-Saharan Africa, where sepsis is leading to deaths in children and young adults that could otherwise be prevented, causing significant health loss. The previous GBD sepsis study revealed significant disparities in sepsis associated deaths across regions but these disparities are even more marked when framed in attributable deaths or YLLs with LMICs falling further behind than initially appreciated.

This sepsis outcomes disparity can be attributed to higher rates of preventable infections and inadequate sepsis care. The overwhelming majority of sepsis attributable deaths in children under five occur in Sub-Saharan Africa and South Asia. More than 95% of these sepsis deaths occur with communicable, neonatal, maternal, and nutritional diseases as the underlying cause of death. Deaths from these underlying causes are largely preventable and while there have been global improvements in the attributable sepsis burden from 1990 to 2017 significant work remains to reduce the burden of sepsis in LMIC. The finding that communicable diseases are the leading underlying cause of death for sepsis among children highlights the importance of campaigns to prevent infection, both directly, through vaccination, and indirectly, through building infrastructure and preventing overcrowding.

It's also important to recognize the drivers of the sepsis care gap. The improvements in sepsis outcomes in high income countries have been attributed to the early recognition of sepsis and to some extent the 'Surviving Sepsis' campaign; which relies on a set of interventions created by and studied in high income countries, called sepsis bundles. Early recognition and implementation of sepsis bundles require significant infrastructure, and one survey in Africa found less than two percent of physicians had the resources to implement a sepsis bundle(21). This failure to implement sepsis bundles reflects the disconnect between sepsis studies in high income countries and what's feasible in LMICs. Certainly infrastructure improvements are needed if sepsis care in LMICs is to approach that of

high income countries. These would include improvements in laboratories, the number of intensive care unit beds, equipment, increases in the number of physicians and nurses trained in intensive care, and available and effective antibiotics.

Even if implementation of the sepsis bundle was feasible the pathogens responsible for sepsis may be sufficiently different that extrapolating sepsis bundles from high income regions may be inappropriate. In fact, one study in Zambia of a simplified sepsis bundle was stopped early due to higher mortality rate among patients in the bundle arm(22). More studies in LMICs would help clarify priorities in infrastructure building and provide insight on which interventions are effective and can be implemented while waiting for infrastructure to improve. The burden of sepsis disproportionately affects LMICs where infectious diseases are more common. However, this is not where sepsis studies are being performed, with nearly 90% of studies used to create current guidelines coming from high income countries(23). This imbalance in representation leads to interventions that are neither proven nor feasible in LMICs. In order to bridge this gap there need to be more studies evaluating management of sepsis in LMICs.

It's expected that the number of sepsis attributable deaths is attenuated from the number of sepsis associated deaths with 3 million deaths attributable to sepsis compared to 11 million deaths with sepsis. This suggests 27% of sepsis deaths were attributable to sepsis globally. Other groups have estimated the attributable fraction of sepsis in the United Kingdom and report an attributable fraction of sepsis ranging from 15% to 24%. We describe a larger attributable fraction of sepsis, which is likely due to a combination of differences in methods and differences in population. These previous studies were in high income countries only and the inclusion of LMIC may increase the attributable fraction of sepsis. If constrained to only the United Kingdom our estimated attributable fraction of sepsis is 1%, which is well below previously published estimates.

Our study has a number of limitations. First, as with the recent sepsis estimates, we relied on the available vital registration and administrative data to identify sepsis, and although this represents more than 300 million hospital admissions and more than 100 million death records there remains a paucity of high quality input data for many low and middle income countries. Although many studies have used ICD code-based approach to identify sepsis, this approach carries risk of misclassification and should be noted(24,25). The PAF approach does not completely resolve confounding of different degrees of severity for a given underlying cause. It stands to reason that more

severe underlying disease places a person at higher risk of sepsis and higher risk of death and the PAF approach we used is not able to account for this. We also assume the proportion of population exposed to sepsis is equal to the incidence of sepsis for a population, this may over-estimate the proportion exposed and there may be re-incident sepsis cases leading to double counting a single individual exposed. Finally, the PAF uses in-hospital relative risk, this is because we are not able to make estimates on out of hospital relative risk due to a paucity of data on out of hospital sepsis case fatality.

We described the number of deaths and YLLs attributable to sepsis globally, with 3 million attributable deaths and 192.2 million YLLs attributable to sepsis. The disparities in YLLs attributable to sepsis across regions is more pronounced than previously appreciated and suggests greater inequality in outcomes than hitherto recognized. This health disparity should further increase the urgency of infection prevention interventions, infrastructure building, and sepsis treatment trials in LMIC. This will require a coordinated approach with multiple stakeholders including clinicians, researchers, policymakers, and the broader global health community.

Tables and Figures:

Table 1: Deaths and Years of Life Lost Attributable to Sepsis by Super Region, 1990 and 2017

Super Region	1990			2017		
	Total YLLs in millions (95% UI)	Age standardized YLL per 100,000 (95% UI)	Age standardized deaths (95% UI)	Total YLLs in millions (95% UI) ²	Age standardized YLL (95% UI)	Age standardized deaths (95% UI) ³
Southeast Asia, East Asia, and Oceania	60.7 (45.6 - 75.7)	3405.2 (2570.8 - 4261.7)	49.7 (35.7 - 72.3)	10.7 (8.2 - 13.9)	594 (458 - 758.2)	14.9 (10.3 - 22.3)
Central Europe, Eastern Europe, and Central Asia	3.5 (2.3 - 4.9)	985.5 (638 - 1374.4)	16.8 (10.2 - 26.2)	1.6 (1 - 2.5)	400 (272 - 579.5)	9.8 (5.9 - 18)
High-income	1.8 (1.3 - 2.8)	202.5 (149 - 284.3)	5.8 (3.7 - 9.9)	1.2 (0.82 - 1.7)	85.9 (67.4 - 115.4)	3.4 (2.2 - 5.3)
Latin America and Caribbean	10.5 (7.3 - 13.5)	2096.3 (1477.6 - 2703.1)	20.9 (13.6 - 28.2)	2.2 (1.8 - 2.8)	439 (359.3 - 554.6)	7 (5.5 - 9.3)
North Africa and Middle East	25.7 (19.9 - 31.6)	4949.2 (3855 - 6097.4)	60.6 (46.7 - 76.4)	10.5 (8.2 - 13)	1710 (1323.2 - 2098.3)	27.3 (21.1 - 35.5)
South Asia	176 (149.2 - 202.7)	11391.1 (9614 - 13280.5)	163.2 (129 - 207.8)	56.7 (44.7 - 69.3)	3510 (2750.8 - 4342.1)	69.4 (48.3 - 98.3)
Sub-Saharan Africa	150.9 (129.7 - 173.3)	16966.5 (14629.7 - 19533.9)	202.5 (171 - 237.9)	109.2 (89.7 - 129)	7160 (5845.4 - 8540.6)	97.7 (77.5 - 122.5)

Figure 1

Sepsis Attributable deaths by age, sex, and super-region in 2017

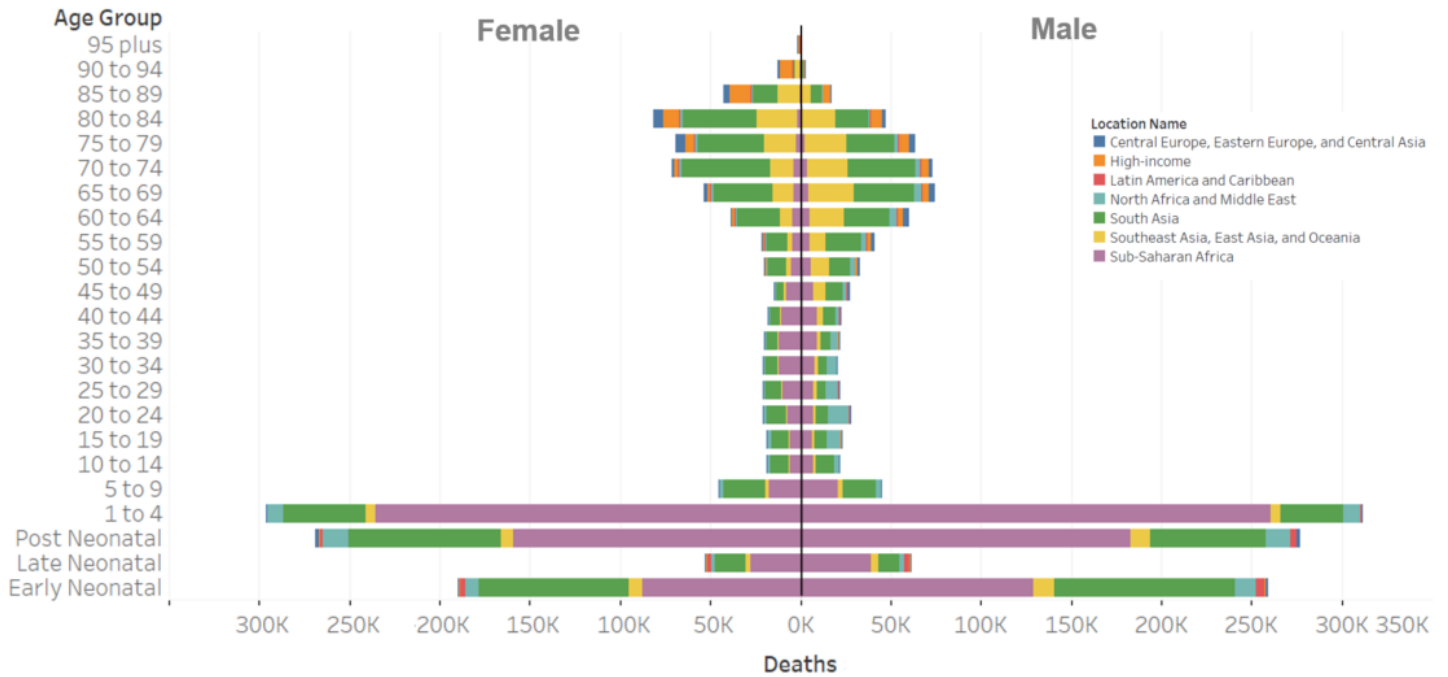


Figure 2

Age standardized YLL per 100,000 attributable to sepsis in 2017

Age Standardized YLL per 100,000 Attributed to Sepsis in 2017

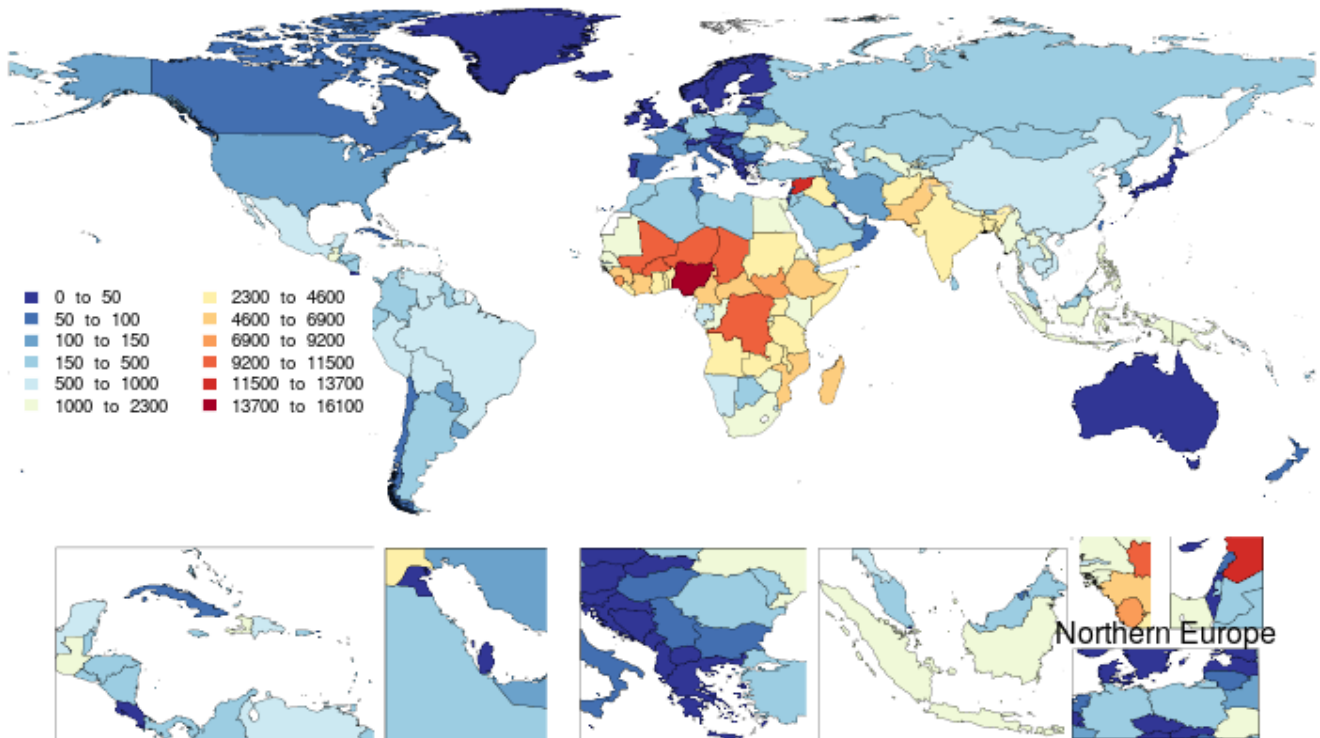
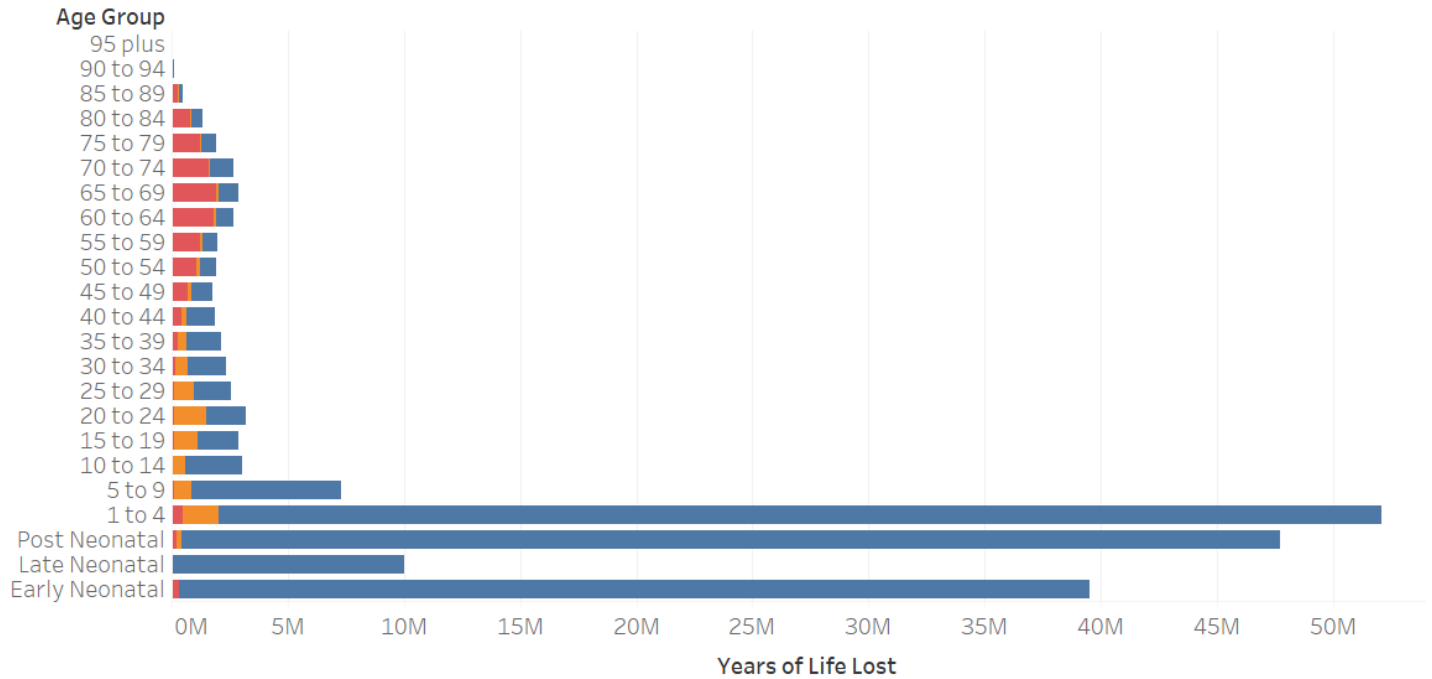


Figure 3

Global Years of Life Lost Attributable to Sepsis in 2017 by Age and Underlying Cause of Death

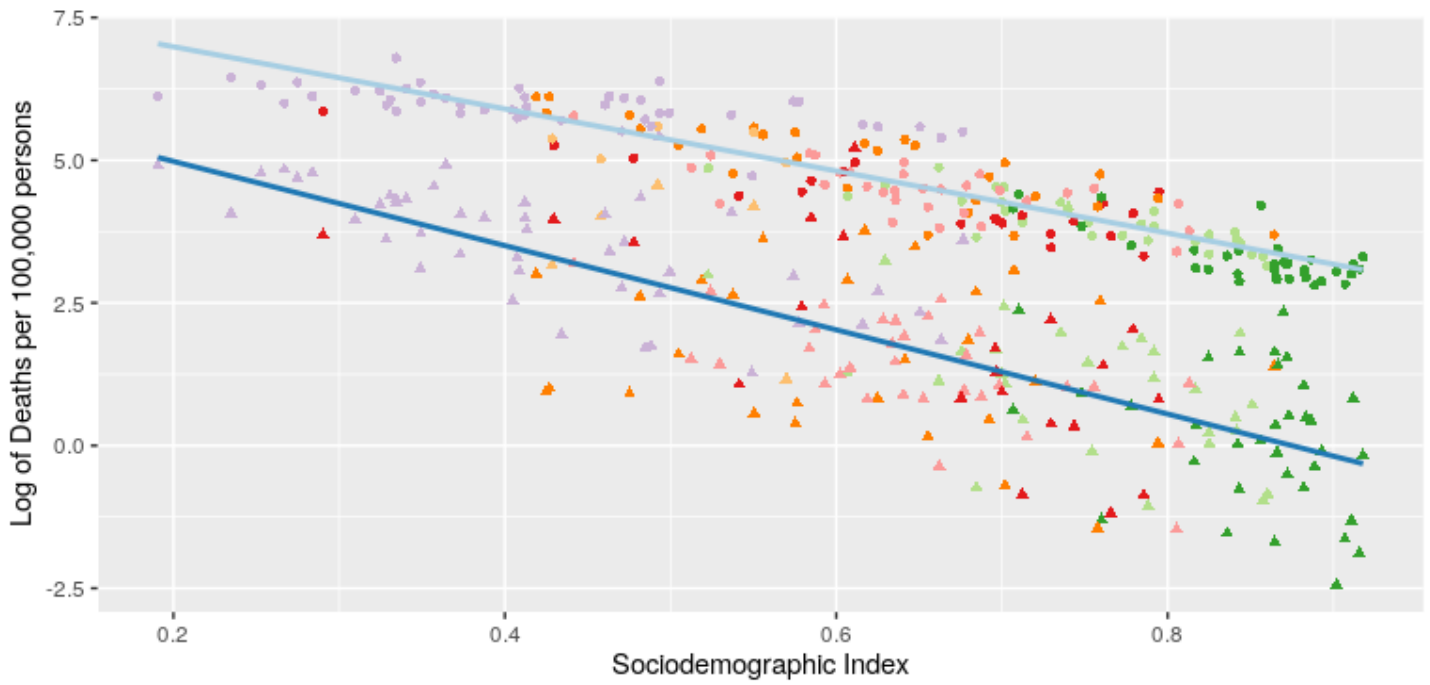


Cause Name

- Communicable, maternal, neonatal, and nutritional diseases
- Injuries
- Non-communicable diseases

Figure 4

Age Standardized Sepsis Associated Deaths and Sepsis Attributable Deaths and Sociodemographic Index of Country for 2017



- Central Europe, Eastern Europe, and Central Asia
- High-Income
- Latin America and Caribbean
- North Africa and Middle East
- South Asia
- Southeast Asia, East Asia, and Oceania
- Sub-Saharan Africa

measure

- Associated Deaths
 - Attributable Deaths
- measure
- Associated Deaths
 - Attributable Deaths

References:

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016 Feb 23;315(8):801–10.
2. World Health Assembly Resolution WHA70.7. Improving the prevention, diagnosis and clinical management of sepsis [Internet]. [cited 2019 Jul 19]. Available from: www.who.int/gb/EB_WHA/PDF/WHA55/ewha5518.pdf
3. Paoli CJ, Reynolds MA, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States—An Analysis Based on Timing of Diagnosis and Severity Level*. *Crit Care Med*. 2018 Dec;46(12):1889–97.
4. Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, et al. The global burden of sepsis: barriers and potential solutions. *Crit Care* [Internet]. 2018 Sep 23 [cited 2020 Mar 31];22. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6151187/>
5. The Advantages and Limitations of International Classification of Diseases, Injuries and Causes of Death from Aspect of Existing Health Care System of Bosnia and Herzegovina [Internet]. [cited 2019 Dec 16]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3789162/>
6. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva World Health Organ. 2018;
7. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018 Nov 10;392(10159):1736–88.
8. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *The Lancet*. 2020 Jan;S0140673619329897.
9. Fleischmann C, Scherag A, Adhikari NKJ, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med*. 2015 Sep 28;193(3):259–72.
10. Kempker JA, Martin GS. A global accounting of sepsis. *The Lancet*. 2020 Jan 18;395(10219):168–70.
11. Singer M, Inada-Kim M, Shankar-Hari M. Sepsis hysteria: excess hype and unrealistic expectations. *The Lancet*. 2019 Oct 26;394(10208):1513–4.
12. Rhee C, Jones TM, Hamad Y, Pande A, Varon J, O'Brien C, et al. Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals. *JAMA Netw Open*. 2019 01;2(2):e187571.
13. Kocczynska M, Sharif B, Cleaver S, Spencer N, Kurani A, Lee C, et al. Sepsis-related deaths in the at-risk population on the wards: attributable fraction of mortality in a large point-prevalence study. *BMC Res Notes*. 2018 Oct 11;11(1):720.
14. Shankar-Hari M, Harrison DA, Rowan KM, Rubenfeld GD. Estimating attributable fraction of mortality from sepsis to inform clinical trials. *J Crit Care*. 2018 Jun 1;45:33–9.
15. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018 Nov 10;392(10159):1923–94.

16. Browner WS, Newman TB. Sample size and power based on the population attributable fraction. *Am J Public Health*. 1989 Sep;79(9):1289–94.
17. Kyu HH, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018 Nov 10;392(10159):1859–922.
18. Dicker D, Nguyen G, Abate D, Abate KH, Abay SM, Abbafati C, et al. Global, regional, and national age-sex-specific mortality and life expectancy, 1950–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018 Nov 10;392(10159):1684–735.
19. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018 Nov 10;392(10159):1789–858.
20. Rosen L. An intuitive approach to understanding the attributable fraction of disease due to a risk factor: the case of smoking. *Int J Environ Res Public Health*. 2013 Jul 16;10(7):2932–43.
21. Baelani I, Jochberger S, Laimer T, Otieno D, Kabutu J, Wilson I, et al. Availability of critical care resources to treat patients with severe sepsis or septic shock in Africa: a self-reported, continent-wide survey of anaesthesia providers. *Crit Care Lond Engl*. 2011;15(1):R10.
22. Andrews B, Muchemwa L, Kelly P, Lakhi S, Heimbürger DC, Bernard GR. Simplified severe sepsis protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia. *Crit Care Med*. 2014 Nov;42(11):2315–24.
23. Dellinger RP, Schorr CA, Levy MM. A Users' Guide to the 2016 Surviving Sepsis Guidelines. *Crit Care Med*. 2017 Mar;45(3):381–385.
24. Iwashyna TJ, Odden A, Rohde J, Bonham C, Kuhn L, Malani P, et al. Identifying patients with severe sepsis using administrative claims: patient-level validation of the angus implementation of the international consensus conference definition of severe sepsis. *Med Care*. 2014 Jun;52(6):e39-43.
25. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. *JAMA*. 2017 03;318(13):1241–9.