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Original Contribution

COVID-19 and sepsis-related excess mortality in the United States during the first 3 years: a national-wide time-series study

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Abstract

The COVID-19 pandemic's global impact has been devastating, causing millions of deaths. Our study investigates excess sepsis-related mortality trends over 3 years during the pandemic. Using the Centers for Disease Control and Prevention's National Vital Statistics System data from January 2018 to March 2023, we projected sepsis-related deaths during the pandemic using a Poisson log-linear regression model. We compared observed vs predicted deaths and analyzed temporal trends by demographics and regions. Among the 753 160 deaths documented between March 2020 and March 2023, a significant downward trend was noted in sepsis-related mortality rates from March 2022 to March 2023, coinciding with the surge of the Omicron variant. The excess mortality rates were 170.6 per million persons (95% CI, 168.2-172.6), 167.5 per million persons (95% CI, 163.6-170.9), and 73.3 per million persons (95% CI, 69.4-76.6) in the first, second, and third years, respectively. Increased sepsis-related mortality was observed across all age subgroups, with the greatest increase noted in those aged 85 years and above compared to middle- and young-aged decedents. Disparities were also observed across racial/ethnic, sex/gender subgroups, and geographic regions. This study highlights the effectiveness of current policies and prevention measures in response to the long-term circulation of SARS-CoV-2 in the community.

Key words: COVID-19; sepsis; excess mortality; temporal trends.

Introduction

The spread of the SARS-CoV-2 pandemic, known as COVID-19 (the World Health Organization [WHO] named it in March 2020), has undeniably caused millions of deaths all around the world.[1] Over 900 000 US residents have died from COVID-19, with additional unreported COVID-19 deaths and deaths attributed to other non–COVID-19–specific causes.[2]

Sepsis is a common condition associated with an unacceptably high mortality and, for survivors, long-term morbidity.[3,4] Furthermore, sepsis places a considerable financial strain on health care systems. In the United States, sepsis is identified as the costliest clinical condition, with an annual expenditure exceeding USD 30 billion in 2017.[5] A substantial amount of evidence indicates that critically ill patients with COVID-19 often experience sepsis-related coagulopathy due to an intense immune reaction.[6,7]

Accurately estimating sepsis epidemiology on a population basis poses challenges due to the lack of a definitive diagnostic test. Many large-scale epidemiologic studies rely on the WHO's International Classification of Diseases (ICD) to gauge sepsis incidence and trends.[8-10] Despite notable variations in sepsis estimates stemming from differing ICD coding methods, including the number and version of ICD codes, the difference between COVID-19 sepsis and non–COVID-19 sepsis, and reference standards, these methods remain the most feasible approach for examining sepsis incidence trends at global, regional, and national levels.[11]

The COVID-19 pandemic has had a multifaceted impact on sepsis. Although patients with COVID-19 faced increased sepsis risks, public health measures likely curbed typical bacterial pathogens, potentially reducing non-COVID sepsis instances.[12] Nevertheless, certain studies propose that the term "viral sepsis" may more accurately depict sepsis cases associated with COVID-19.[13-16] Previous evidence has suggested that patients with sepsis were vulnerable during the early stages of the COVID-19 pandemic.[17] However, the extended-term pattern of excess mortality from sepsis during the pandemic has not been thoroughly investigated. Despite the WHO declaring in May 2023 that COVID-19 no longer

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constitutes a public health emergency of international concern, it remains an ongoing health issue demanding long-term management and preparedness.[18] As SARS-CoV-2 continues to spread and COVID-19 containment measures are relaxed, exposing the community to more respiratory bacterial pathogens, the ongoing impact on public health persists. This study may offer valuable insights into the effectiveness of current preventive measures in protecting patients with sepsis during this period.

In this study, we examined temporal trends in excess sepsis mortality during the first 3 years of the pandemic, from March 2020 to March 2023, in the United States. We delved into variations in excess deaths based on age, gender, and racial/ethnic backgrounds, while also examining temporal trends and geographical differences. Furthermore, we broke down the overall sepsis outcome into specific bacterial pathogens each year of the pandemic to understand their impact on sepsis mortality.

Methods

Data source

Weekly death data were obtained from the Wide-ranging Online Data for Epidemiologic Research (WONDER) database of the Centers for Disease Control and Prevention (CDC) for January 1, 2018, and March 4, 2023. Demographic data, including age, sex, race/ethnicity, US state, and cause of death, were provided. This study did not seek approval from the institutional review board as the data are publicly available an d deidentified.

To further verify the robustness of our results, we downloaded monthly death data from CDC WONDER for the period from January 2014 to December 2020 as an external data set.[19] The data were stratified by age, sex, race/ethnicity, and US state. In addition, to adjust excess mortality models for the contribution of influenza, we used weekly data on influenza circulation based on CDC surveillance.[20]

Statistical analysis

Sepsis was defined according to the 10th edition of the ICD (ICD-10: A40, A41.0, A41.1, A41.2, A41.4, A41.5, A41.8, A41.9).[21] Projection of the sepsis-related mortality rate was obtained by using decedents' data between January 1, 2018, and March 6, 2020, to determine the period from March 7, 2020, to March 4, 2023. The baseline model follows a Poisson distribution and incorporates temporal trends, seasonality components, and a proxy for weekly influenza incidence. In this approach, we isolate the impact of influenza by explicitly modeling its contribution to mortality and removing influenza-related deaths from the overall mortality baseline. This is crucial as influenza can cause significant year-to-year mortality variations due to differences in circulating strains. This model is inspired by previous research on COVID-19, as detailed in Appendix S1.[22]

We controlled for the temporal trend using a linear term for the calendar years (2018-2020 for model fitting, 2020-2023 for prediction). Seasonality was parameterized with a natural spline function for epidemiologic weeks (week 1 to week 52). A total of 12 candidate models (with degrees of freedom from 3 to 14 for the natural spline function) were tested using the maximum likelihood approach. The model with a natural spline function and 9 degrees of freedom was selected based on the lowest Akaike information criterion score. Each subgroup data set was fitted with its own Poisson regression model using the same degrees of freedom for the natural spline function. We used this optimal baseline model to predict expected deaths from March 2020 to March 2023. The impact of the pandemic was determined by calculating the difference between projected and observed deaths. For example, excess death was calculated by subtracting the expected number of deaths from the observed number of deaths; weekly average excess death was defined as excess deaths/length of the observational period, excess mortality rate was defined as excess death number per million persons, and excess risk was defined as the ratio between excess death number and expected death number × 100 %. The excess death number reflects the overall magnitude of additional mortality during the study period, quantifying the total death burden of sepsis. The weekly average excess death indicates the rate at which these excess sepsis deaths occurred, providing insights into the intensity and timing of the burden. Excess risk reflects the proportional increase in mortality compared to the expected baseline, helping to understand broader population-level risks and identify vulnerable groups. To account for variations in population size, our study primarily focused on excess mortality rates and excess risk.

To investigate demographic disparities in excess mortality and their temporal patterns within subgroup populations, we retrieved weekly death counts for various demographic categories, including age groups (25-64 years, 65-84 years, and 85+ years), sex (male and female), race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and Hispanic), and pandemic years from the CDC WONDER database. The subgroup data were fitted with their own Poisson regression model, integrating identical harmonics and internal knots employed in the overall group analysis. We predefined the categorization of the COVID-19 pandemic years as follows: the first year (from March 7, 2020, to February 27, 2021), the second year (from February 28, 2021, to March 4, 2022), and the third year (from March 5, 2022, to March 4, 2023). In addition, we identified 4 distinct waves of the pandemic according to the COVID-19 mortality surveillance data from CDC[23]: wave I, the early pandemic wave (from March 7, 2020, to October 17, 2020); wave II, the α wave (from October 18, 2020, to June 17, 2021); wave III, the δ wave (June 18, 2021, to November 27, 2021); and wave IV, Omicron and its subvariants (from November 28, 2021, to March 4, 2023).

Given that sepsis is a frequent complication of injuries,[24] it might not always be listed as the primary cause of death by medical professionals. Thus, we included individuals whose death certificates mentioned sepsis as one of the causes of death, understanding that a person could have multiple causes of death.[14] The underlying cause of death referred to decedents with sepsis as the underlying cause of death.[18] To evaluate the robustness of our results, we performed a sensitivity analysis. Initially, the nature splines with degrees of freedom of 6 (degrees of freedom of 9 was used in the main analysis) were utilized in the model (Appendix S1). Second, we combined CDC WONDER monthly data from 2014 to 2020, with CDC WONDER weekly data, converted to monthly, from 2020 to 2023. This allowed us to recalibrate our models to operate at a monthly level instead of a weekly level, demonstrating the robustness of our results (Table S2 and Figure S1). Additionally, as observed in previous studies,[18,25] using CDC WONDER data from 2018 to 2020 to predict the outcomes for the first year of 2020 to 2021 is robust. Therefore, to further validate the robustness of the monthly results, we established the excess mortality rate and excess risk from the first year as a baseline. We then compared these results by calculating the ratios of monthly and weekly excess mortality rates and risks in the second and third years against the first year (Figure S2). Third, because our baseline reference period only covered 2 years (January 2018 to

Table 1. Excess mortality associated with sepsis in the United States from March 2020 to March 2023.

Subgroups	No. of observed deaths	No. of excess deaths (95% CI)	No. of excess deaths per week (95% CI)	Excess death rate per million persons (95% CI)	Excess risk % (95% CI)
Overall[a]	753 160	136 295 (134 370, 138 027)	868 (856, 879)	410.8 (405.0, 416.0)	22.1 (21.8, 22.4)
Age group					
25-64	200 562	45 943 (44 890, 46 769)	293 (286, 298)	267.5 (261.4, 272.3)	29.7 (29.1, 30.3)
65-84	390 298	75 369 (73 932, 76 600)	480 (471, 488)	1501.8 (1473.2, 1526.3)	23.9 (23.5, 24.4)
85+	157 729	27 445 (26 630, 28 117)	175 (170, 179)	4311.7 (4183.6, 4417.3)	21.1 (20.5, 21.7)
Sex					
Female	363 005	61 411 (60 058, 62 564)	391 (383, 398)	366.4 (358.3, 373.2)	20.4 (19.9, 20.8)
Male	390 155	74 537 (73 089, 75 762)	475 (466, 483)	454.1 (445.3, 461.6)	23.6 (23.2, 24.1)
Race/ethnicity					
NH-White	517 733	80 748 (79 149, 82 152)	514 (504, 523)	410.8 (402.6, 417.9)	18.5 (18.1, 18.8)
NH-Black	115 507	22 423 (21 560, 23 060)	143 (137, 147)	536.2 (515.5, 551.4)	24.1 (23.3, 24.9)
NH-Asian	23 545	4678 (4198, 4915)	30 (27, 31)	236.0 (211.7, 247.9)	24.8 (22.8, 26.7)
Hispanic	80 749	24 330 (23 640, 24 786)	155 (151, 158)	438.2 (425.7, 446.4)	43.1 (42.0, 44.2)
Pandemic years[b]					
First year	254 596	56 257 (55 478, 56 942)	1082 (1067, 1095)	170.6 (168.2, 172.6)	28.4 (28.0, 28.7)
Second year	261 427	55 619 (54 342, 56 758)	1070 (1045, 1092)	167.5 (163.6, 170.9)	27.0 (26.4, 27.6)
Third year	237 137	24 419 (23 127, 25 517)	461 (436, 481)	73.3 (69.4, 76.6)	11.5 (10.9, 12.0)
Pandemic waves[c]					
Wave I	147 020	23 386 (22 982, 23 746)	709 (696, 720)	71.0 (69.8, 72.1)	18.9 (18.6, 19.2)
Wave II	172 386	41 628 (40 797, 42 390)	1224 (1200, 1247)	125.7 (123.2, 128.0)	31.8 (31.2, 32.5)
Wave III	120 133	23 704 (22 870, 24 549)	988 (953, 1023)	71.4 (68.9, 74.0)	24.6 (23.7, 25.5)
Wave IV	313 621	47 578 (46 243, 48 851)	721 (701, 740)	142.8 (138.8, 146.6)	17.9 (17.4, 18.4)

Abbreviation: NH, non-Hispanic.
[a]Excess mortality associated with sepsis in the United States from March 2020 to March 2023, when sepsis was the underlying condition.
[b]The first year was March 7, 2020, to February 27, 2021; the second year was February 28, 2021, to March 4, 2022; the third year was March 5, 2022, to March 4, 2023.
[c]Wave I is the early pandemic wave from March 7, 2020, to October 17, 2020; wave II is the α wave from October 18, 2020, to June 17, 2021; wave III is the δ wave from June 18, 2021, to November 27, 2021; and wave IV is Omicron and its subvariants from November 28, 2021, to March 4, 2023.

March 2020) to estimate outcomes for 3 years (March 2020 to March 2023), we used our baseline data to estimate outcomes for 1 year (March 2020 to March 2021), 2 years (March 2020 to March 2022), and 2.5 years (March 2020 to September 2022) for further comparison (Tables S3 to S5). All analyses were executed using R statistical software (version 4.2.1).

Results

By age and sex groups

Throughout the study period, the trends in sepsis-related excess mortality varied significantly across age groups. Decedents aged 65 to 84 and ≥85 years experienced a notable increase in mortality rates, with 1501.8 per million persons (95% CI, 1473.2-1526.3) and 4311.7 per million persons (95% CI, 4183.6-4417.3), respectively (Table 1). Similar trends in excess deaths were observed for age-specific groups based on the underlying cause of death (Table 2). In addition, we observed a high proportion of sepsis deaths among individuals aged 65 to 84 and those aged 85 and older during the pre–COVID-19 period (Figure S3).

The sepsis-related excess mortality rate for females (366.4 per million persons; 95% CI, 358.3-373.2) was lower than that for males (454.1 per million persons; 95% CI, 445.3-461.6) throughout the entire pandemic period (Table 1). Similarly, when sepsis was the underlying cause of death, females (49.5 per million persons; 95% CI, 45.8-52.0) had a lower mortality rate than males (51.2 per million persons; 95% CI, 47.5-53.7).

By race/ethnicity groups

Compared to estimated excess mortality rates, non-Hispanic Blacks exhibited significantly higher mortality rates (536.2 per million persons; 95% CI, 515.5-551.4) than other racial/ethnic subgroups. Notably, the excess death risk of sepsis was most pronounced in Hispanics, reaching 43.1% (95% CI, 42.0%-44.2%) (Table 1). Similarly, when considering the underlying cause of death, non-Hispanic Blacks had the highest excess mortality rate (61.8 per million persons; 95% CI, 52.0-66.8), while Hispanics had the greatest excess death risk at 50.0% (95% CI, 47.1%-53.0%) (Table 2).

Sepsis-related excess death estimates by different pandemic periods

During the pre–COVID-19 period, the weekly death counts from overall sepsis remained relatively stable. Among different age groups, individuals aged 65 to 84 years had the highest proportion of deaths both before and during the COVID-19 pandemic. The weekly number of sepsis deaths among females was comparable to that of males during both periods. Notably, similar to the pattern observed with excess sepsis-related mortality, non-Hispanic Blacks experienced the highest weekly number of deaths among racial and ethnic subgroups in both the pre–COVID-19 and COVID-19 periods (Figure S3).

Throughout the first 2 years of the COVID-19 pandemic, the excess mortality rate due to sepsis stood at 170.6 per million persons in the initial year and remained comparable at 167.5 per million in the second year. Despite a substantial decline in sepsis-related deaths after the commencement of vaccination campaigns in mid-December 2020 during the α wave, the number of excess deaths remained elevated throughout the second year. However, there was a significant decrease during the δ wave. Notably, a marked reduction in sepsis-related deaths was observed during the third year (73.3 per million individuals), coinciding with the emergence of the Omicron variant (Table 1 and Figure 1). In contrast, the excess death estimates for the

Table 2. Excess mortality associated with sepsis in the United States from March 2020 to March 2023, when sepsis was the underlying cause of death.

Subgroups	No. of observed deaths	No. of excess deaths (95% CI)	Excess deaths per week (95% CI)	Excess deaths per million persons (95% CI)	Excess risk % (95% CI)
Overall[a]	124 423	18 865 (18 141, 19 446)	120 (116, 124)	56.9 (54.7, 58.6)	17.9 (17.2, 18.5)
Age group					
25-64	30 072	7397 (7000, 7624)	47 (45, 49)	43.1 (40.8, 44.4)	32.6 (31.2, 34.1)
65-84	64 519	10 295 (9674, 10 713)	66 (62, 68)	205.1 (192.8, 213.5)	19.0 (18.0, 20.0)
85+	28 127	4380 (4012, 4604)	28 (26, 29)	688.1 (630.3, 723.3)	18.4 (17.2, 19.7)
Sex					
Female	62 805	8290 (7680, 8714)	53 (49, 56)	49.5 (45.8, 52.0)	15.2 (14.3, 16.2)
Male	61 618	8409 (7804, 8820)	54 (50, 56)	51.2 (47.5, 53.7)	15.8 (14.8, 16.8)
Race/ethnicity					
NH-White	88 863	9902 (9191, 10 433)	63 (59, 66)	50.4 (46.8, 53.1)	12.5 (11.7, 13.3)
NH-Black	21 245	2585 (2173, 2794)	16 (14, 18)	61.8 (52.0, 66.8)	13.8 (12.2, 15.5)
NH-Asian	2778	501 (389, 601)	3.1 (2.4, 3.7)	25.1 (19.1, 28.4)	20.1 (14.1, 23.3)
Hispanic	9261	3088 (2844, 3170)	20 (18, 20)	56.5 (52.1, 58.0)	50.0 (47.1, 53.0)
Pandemic years[b]					
First year	39 949	3974 (3626, 4258)	76 (70, 82)	12.0 (11.0, 12.9)	11.1 (10.2, 11.9)
Second year	41 487	5688 (5128, 6141)	109 (99, 118)	17.1 (15.4, 18.5)	15.9 (14.5, 17.3)
Third year	42 987	7519 (6968, 7939)	142 (131, 150)	22.6 (20.9, 23.8)	21.2 (19.8, 22.6)
Pandemic waves[c]					
Wave I	24 457	1874 (1679, 2047)	57 (51, 62)	5.7 (5.1, 6.2)	8.3 (7.5, 9.1)
Wave II	26 412	3368 (3020, 3664)	99 (89, 108)	10.2 (9.1, 11.1)	14.6 (13.2, 16.0)
Wave III	19 249	2226 (1850, 2569)	93 (77, 107)	6.7 (5.6, 7.7)	13.1 (11.0, 15.2)
Wave IV	54 305	9712 (9129, 10 189)	147 (138, 154)	29.1 (27.4, 30.6)	21.8 (20.6, 23.0)

Abbreviation: NH, non-Hispanic.
[a]Excess estimates in this table were measured according to whether sepsis was listed an underlying cause of death on the death certificate.
[b]The first year was March 7, 2020, to February 27, 2021; the second year was February 28, 2021, to March 4, 2022; the third year was March 5, 2022, to March 4, 2023.
[c]Wave I is the early pandemic wave from March 7, 2020, to October 17, 2020; wave II is the α wave from October 18, 2020, to June 17, 2021; wave III is the δ wave from June 18, 2021, to November 27, 2021; and wave IV is Omicron and its subvariants from November 28, 2021, to March 4, 2023.

underlying cause of death showed an inconsistent temporal pattern, with both excess mortality rates and death risks consistently rising during the 3 pandemic years (Table 2).

Sepsis-related excess death estimates by states

In national data, from March 7, 2020, to March 4, 2023, the United States recorded 753 160 sepsis-related deaths, with an estimated excess mortality rate of 410.8 per million persons (95% CI, 405.0-416.0). State-level data indicated that different states experienced varying degrees of death burden during the pandemic (Table 3). The distribution of excess mortality rates over the 3-year period varied by state, as depicted in Figure 2. Delaware and North Carolina saw the highest increases over these 3 years. Even with a significant decrease in the third year, these 2 states still bore a substantial disease burden. Almost all states showed an increase in excess mortality rates during the first 2 years, followed by a decline in the third year.

To focus on periods of significant COVID-19 activity and explore the association with sepsis, we selected 3 large US states with distinct, well-defined waves. New York experienced a major early wave during the initial wild-type variant period, with an excess sepsis death risk of 26.9% (95% CI, 25.5%-28.2%). California saw a substantial wave from early to mid-2021, corresponding to its highest excess sepsis death risk of 42.3% (95% CI, 40.1%-44.6%) during the α variant period. Texas experienced a large wave in the latter half of 2021 during the δ variant, with the highest excess sepsis death risk at 60.0% (95% CI, 56.7%-63.3%). All 3 states saw a decline in excess sepsis death risk with the emergence of the less virulent Omicron variant (Figure 3 and Table 4).

Temporal trends in mortality from different types of sepsis

Time-series analyses for various bacterial pathogens show a reduction in death cases caused by septicemia due to *Staphylococcus aureus* in the initial 3 years of the pandemic. However, deaths caused by other streptococcal septicemia, septicemia due to other *Staphylococcus*, and septicemia due to other gram-negative organisms saw an uptick during the pandemic (Table S6). A comparable trend was noted in sepsis-related deaths: Those due to other types of septicemia increased during the first 2 years of the pandemic, followed by a decrease in the third year.

Notably, we observed a sharp increase in sepsis-related deaths and excess mortality rates for most types of sepsis during wave IV. Specifically, there was an excess mortality rate of 0.2 per million persons (95% CI, 0.1-0.4) for other streptococcal septicemia, 0.9 per million persons (95% CI, 0.3-1.1) for septicemia due to *S aureus*, 4.1 per million persons (95% CI, 3.6-4.4) for septicemia due to other gram-negative organisms, and 147 per million persons (95% CI, 142.9-150.9) for other septicemia during wave IV (from November 28, 2021, to March 4, 2023).

Sensitivity analysis

The results were generally robust across overall analyses, temporal pattern analyses, and demographic subgroup analyses, even when using different degrees of freedom in the regression models (Table S1). When we combined 2 data sets into a monthly level from 2014 to 2023, we observed that although aggregating data from weekly to monthly reduces the estimated values due to smoothing-out variability and affecting parameter estimation, the results of excess risks and excess mortality rates were general close to our main analysis across overall analyses, different

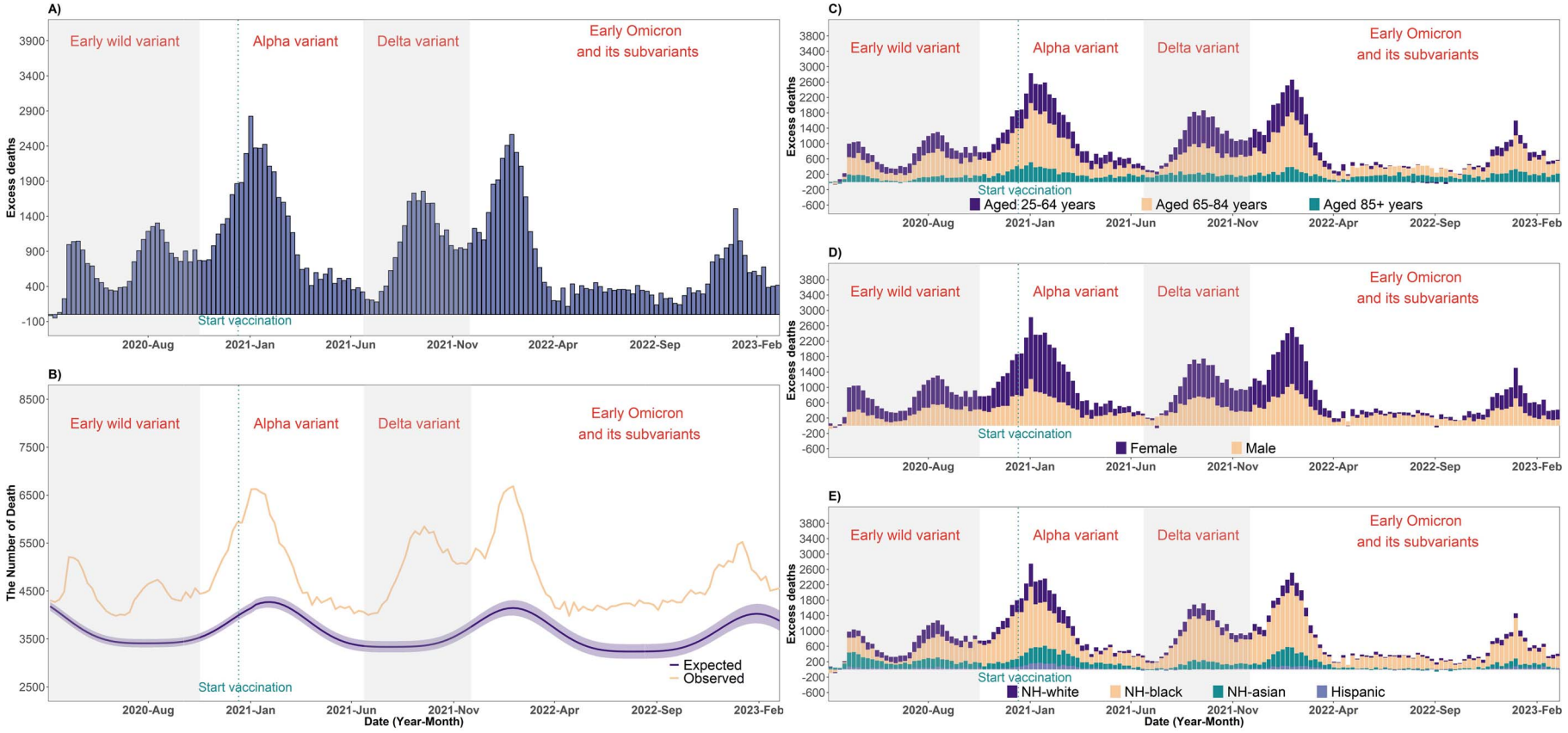

Figure 1. Excess mortality of sepsis, United States, March 2020, March 2023. (A) Weekly excess sepsis-related death counts from sepsis. (B) Weekly number of observed deaths vs expected deaths from sepsis. (C) Weekly number of excess sepsis-related deaths by age group (25-64 years, 65-84 years, and 85+ years). (D) Weekly number of excess sepsis-related deaths by sex group (male and female). (E) Weekly number of excess sepsis-related deaths by race/ethnicity group (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and Hispanic). The early wild variant period from March 7, 2020, to October 17, 2020; the α variant period from October 18, 2020, to June 17, 2021; the δ variant period from June 18, 2021, to November 27, 2021; and the early Omicron and its subvariants period from November 28, 2021, to March 4, 2023.

Table 3. Excess sepsis-related mortality by US jurisdiction from March 2020 to March 2023[a].

Jurisdiction	No. of observed deaths	No. of excess deaths (95% CI)	Excess deaths per week (95% CI)	Excess deaths per million persons (95% CI)	Excess risk % (95% CI)
Alabama	15 445	1013 (569, 1199)	6 (4, 8)	201.8 (113.3, 238.8)	7.02 (4.83, 9.21)
Alaska	28	NA	NA	NA	NA
Arizona	10 548	3306 (2912, 3396)	21 (19, 22)	449.8 (396.2, 462.1)	45.65 (41.98, 49.32)
Arkansas	9451	716 (403, 831)	5 (3, 5)	235.9 (132.8, 273.8)	8.20 (5.74, 10.66)
California	84 670	17 664 (16 811, 18 237)	113 (107, 116)	450.7 (428.9, 465.3)	26.36 (25.26, 27.46)
Colorado	9776	2438 (2112, 2538)	16 (13, 16)	418.8 (362.8, 436.0)	33.22 (30.16, 36.28)
Connecticut	7654	–423 (–811, –310)	–3 (–5, –2)	–117.5 (–225.3, –86.1)	–5.24 (–8.35, –2.13)
Delaware	2150	836 (594, 822)	6 (4, 6)	831.8 (591.0, 817.8)	63.62 (53.34, 73.90)
District of Columbia	913	32 (–40, 104)	0.4 (–0.5, 1.3)	46.4 (–59.1, 152.0)	3.6 (–4.6, 11.8)
Florida	55 967	11 478 (10 815, 11 899)	73 (69, 76)	523.0 (492.8, 542.1)	25.80 (24.54, 27.06)
Georgia	27 143	3893 (3388, 4152)	25 (22, 26)	359.8 (313.2, 383.8)	16.74 (15.07, 18.41)
Hawaii	1720	–208 (–313, –103)	–1.7 (–2.5, –0.8)	–145.4 (–218.9, –71.9)	–10.8 (–16.3, –5.3)
Idaho	3033	–463 (–948, –450)	–3 (–6, –3)	–244.3 (–500.2, –237.4)	–13.24 (–20.42, –6.06)
Illinois	26 580	2100 (1625, 2362)	13 (10, 15)	166.5 (128.8, 187.3)	8.58 (7.07, 10.09)
Indiana	16 811	424 (–34, 641)	3 (0, 4)	62.3 (–5.0, 94.2)	2.59 (0.53, 4.65)
Iowa	6169	467 (203, 541)	3 (1, 3)	146.5 (63.7, 169.7)	8.19 (5.22, 11.16)
Kansas	6655	1446 (1207, 1513)	9 (8, 10)	493.6 (412.0, 516.4)	27.76 (24.71, 30.81)
Kentucky	17 764	1058 (586, 1270)	7 (4, 8)	235.0 (130.2, 282.1)	6.33 (4.28, 8.38)
Louisiana	12 397	2110 (1671, 2250)	13 (11, 14)	457.0 (361.9, 487.3)	20.51 (17.64, 23.38)
Maine	58	NA	NA	NA	NA
Maryland	13 884	2232 (1830, 2383)	14 (12, 15)	363.9 (298.3, 388.5)	19.16 (16.74, 21.58)
Massachusetts	14 042	2309 (1941, 2455)	15 (12, 16)	331.8 (279.0, 352.8)	19.68 (17.45, 21.91)
Michigan	23 480	4318 (3857, 4540)	28 (25, 29)	430.9 (384.9, 453.1)	22.53 (20.70, 24.36)
Minnesota	9290	2197 (1909, 2288)	14 (12, 15)	385.6 (335.1, 401.6)	30.97 (28.17, 33.77)
Mississippi	10 076	1509 (1209, 1618)	10 (8, 10)	511.4 (409.7, 548.3)	17.61 (15.19, 20.03)
Missouri	14 066	3490 (3176, 3616)	22 (20, 23)	565.9 (515.0, 586.3)	33.00 (30.81, 35.19)
Montana	2123	–193 (–309, –77)	–1.4 (–2.2, –0.5)	–174.8 (–279.8, –69.8)	–8.3 (–13.4, –3.3)
Nebraska	3750	516 (180, 547)	3 (1, 3)	263.5 (91.9, 279.4)	15.96 (10.21, 21.71)
Nevada	7555	2119 (1840, 2186)	13 (12, 14)	671.5 (583.1, 692.8)	38.98 (35.56, 42.40)
New Hampshire	2183	–208 (–427, –183)	–1 (–3, –1)	–150.2 (–308.3, –132.1)	–8.70 (–13.82, –3.58)
New Jersey	23 937	5395 (5006, 5598)	34 (32, 36)	589.2 (546.7, 611.3)	29.10 (27.44, 30.76)
New Mexico	5004	664 (390, 709)	4 (2, 5)	314.4 (184.6, 335.7)	15.30 (11.58, 19.02)
New York	39 585	7164 (6651, 7472)	46 (42, 48)	364.9 (338.7, 380.6)	22.1 (20.8, 23.4)
North Carolina	24 740	7546 (7228, 7724)	48 (46, 49)	710.4 (680.4, 727.1)	43.89 (42.31, 45.47)
North Dakota	1036	243 (172, 314)	3.0 (2.1, 3.8)	314.3 (222.4, 406.1)	30.7 (21.3, 40.0)
Ohio	28 165	4435 (3964, 4687)	28 (25, 30)	377.6 (337.5, 399.0)	18.69 (17.14, 20.24)
Oklahoma	12 236	1987 (1690, 2116)	13 (11, 13)	497.0 (422.7, 529.3)	19.39 (17.27, 21.51)
Oregon	6454	1602 (1348, 1658)	10 (9, 11)	377.6 (317.7, 390.8)	33.02 (29.66, 36.38)
Pennsylvania	33 099	7732 (7278, 7984)	49 (46, 51)	598.6 (563.5, 618.1)	30.48 (29.03, 31.93)
Rhode Island	1403	79 (–16, 101)	1 (0, 1)	73.0 (–14.8, 93.3)	5.97 (1.54, 10.40)
South Carolina	15 138	2249 (1902, 2407)	14 (12, 15)	429.7 (363.4, 459.9)	17.45 (15.46, 19.44)
South Dakota	1849	–129 (–474, –153)	–1 (–4, –1)	–143.3 (–526.5, –170.0)	–6.52 (–14.65, 1.61)
Tennessee	20 293	4113 (3749, 4297)	26 (24, 27)	589.3 (537.1, 615.6)	25.42 (23.67, 27.17)
Texas	65 695	19 081 (18 520, 19 461)	122 (118, 124)	643.0 (624.1, 655.8)	40.93 (39.84, 42.02)
Utah	4334	662 (436, 710)	4 (3, 5)	198.8 (130.9, 213.2)	18.03 (14.24, 21.82)
Vermont	240	NA	NA	NA	NA
Virginia	16 227	3646 (3350, 3791)	23 (21, 24)	421.8 (387.6, 438.6)	28.98 (27.16, 30.80)
Washington	14 823	3210 (2844, 3352)	20 (18, 21)	414.5 (367.2, 432.8)	27.64 (25.37, 29.91)
West Virginia	6637	624 (455, 793)	4.0 (2.9, 5.1)	350.6 (255.8, 445.4)	10.4 (7.6, 13.2)
Wisconsin	10 741	87 (–342, 233)	1 (–2, 1)	14.8 (–58.2, 39.6)	0.82 (–1.88, 3.52)
Wyoming	450	28 (–89 ,144)	0.7 (–2.2, 3.6)	47.7 (–153.3, 248.6)	6.6 (–21.1, 34.3)

[a]Alaska, Maine, and Vermont were not involved in the calculation due to limited data.

COVID-19 pandemic years, waves, and demographic subgroups (Table S2 and Figure S1). Additionally, when we used the excess mortality rate and excess risk from the first year as the baseline and compared the ratios of the monthly and weekly excess mortality rates and excess risks in the second and third years to those in the first year, we found that the ratios of the monthly excess mortality rate and excess risk were quite similar to those of the weekly excess mortality rate and excess risk (Figure S2). Lastly, when we extended our estimation period from 1 year to 2 years and 2.5 years, the results, particularly for the 2.5-year period, remained robust (Tables S3 to S5).

Discussion

In our analysis of sepsis-related deaths throughout the United States, we uncovered several noteworthy discoveries. First, our findings indicate a substantial rise in sepsis-related mortality since the onset of the COVID-19 pandemic. In particular, the

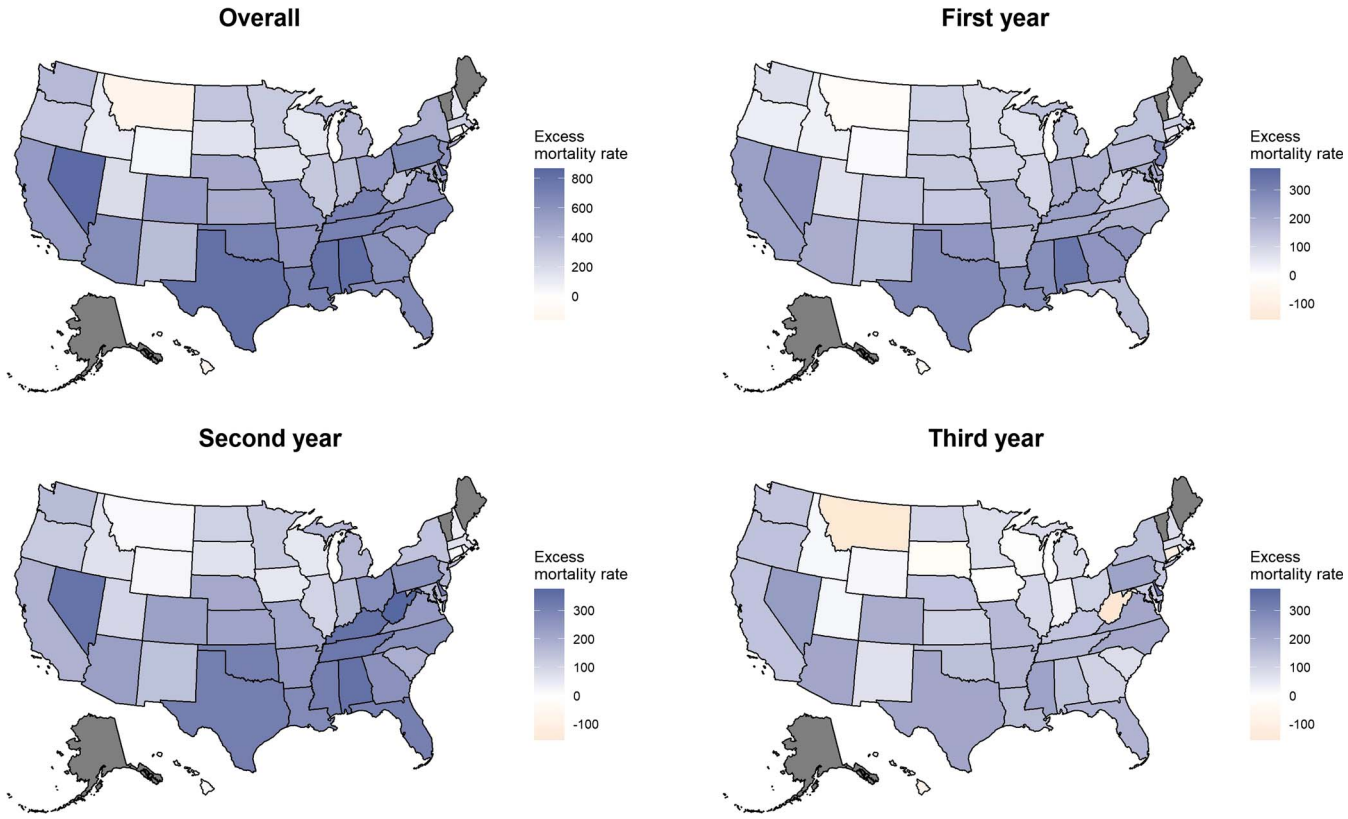

Figure 2. Maps of excess mortality rates of sepsis (per million persons) stratified by COVID-19 pandemic years in the United States. "Overall" refers to the period from March 7, 2020, to March 4, 2023. The 3 years were defined as the first year (from March 7, 2020, to February 27, 2021), the second year (from February 28, 2021, to March 4, 2022), and the third year (from March 5, 2022, to March 4, 2023). ∗Alaska, Maine, and Vermont were not involved in the calculation due to limited data.

observed rates of sepsis-related mortality were notably higher than the anticipated mortality rates during the initial 2 years. Second, the surplus sepsis-related mortality rates experienced a significant decrease in the third year, bucking the upward trend. This decline coincided with the emergence of the less virulent Omicron variant.[26] Third, upon delving deeper into the data and breaking them down by age and gender, we observed a significant surge in excess mortality rates among older men. Furthermore, our examination revealed an exacerbation of racial and ethnic disparities, with minority groups displaying heightened vulnerability during the pandemic, particularly non-Hispanic Black subgroups. Lastly, it is noteworthy that Delaware and North Carolina bore a substantial disease burden and witnessed the most significant increase in mortality during the pandemic.

The hypothesis regarding sepsis incidence during the pandemic is complex. While critically ill patients with COVID-19 were at risk of developing sepsis, the pandemic's impact on the circulation of common respiratory bacterial pathogens, which also cause sepsis, needs to be considered. During the pandemic period, many bacterial pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*, were less prevalent due to public health measures, potentially leading to a decline in sepsis cases not directly related to COVID-19.[12]

Moreover, some studies suggested that "viral sepsis" would more accurately describe the clinical manifestations in patients with COVID-19.[14] For example, a COVID-19 cohort study found that blood and lower respiratory tract cultures were negative for bacteria and fungi in 76% of patients with sepsis.[16] In clinical practice, we observed that many severe or critically ill patients with COVID-19 exhibited typical signs of shock, such as cold extremities and weak peripheral pulses, even without overt hypotension.[13] These patients met the diagnostic criteria for sepsis and septic shock according to the Sepsis-3 International Consensus,[15] yet SARS-CoV-2 infection appeared to be the sole cause in most cases.[13]

The high level of excess sepsis-related deaths during the first 2 years of the pandemic could be attributed to both the direct and indirect impacts of the COVID-19 pandemic. Approximately 40% of hospitalized patients develop severe COVID-19 sepsis, which requires admission to the intensive care unit.[6] Patients with sepsis were particularly vulnerable during the pandemic. The indirect impact of the pandemic involved the interruption of screening patients for signals and symptoms of sepsis, earlier identification and intervention, increased barriers to accessing appropriate antimicrobial therapy, public policy, and so on.[27-29] Despite stringent public health measures, such as lockdowns and reduced social interactions, which may have led to a decline in the transmission of bacterial pathogens like *S pneumoniae*, *H influenzae*, and *N meningitidis*,[12] we still observed a significant number of excess sepsis-related deaths from 2020 to 2022. Therefore, while it is hypothesized that there was an overall increase in sepsis-related mortality due to the COVID-19 pandemic, this could be offset by a concurrent decrease in sepsis cases related to bacterial infections. The potential unknown impacts on patients with sepsis during the first 2 years of the pandemic could be an emerging issue.

The overall sepsis excess mortality rate experienced a decline in the third year (March 2022 to March 2023), suggesting the potential initiation of a downward trend in mortality rates during 2022. This shift could be attributed to several factors. First, the US administration launched the largest vaccination campaign,

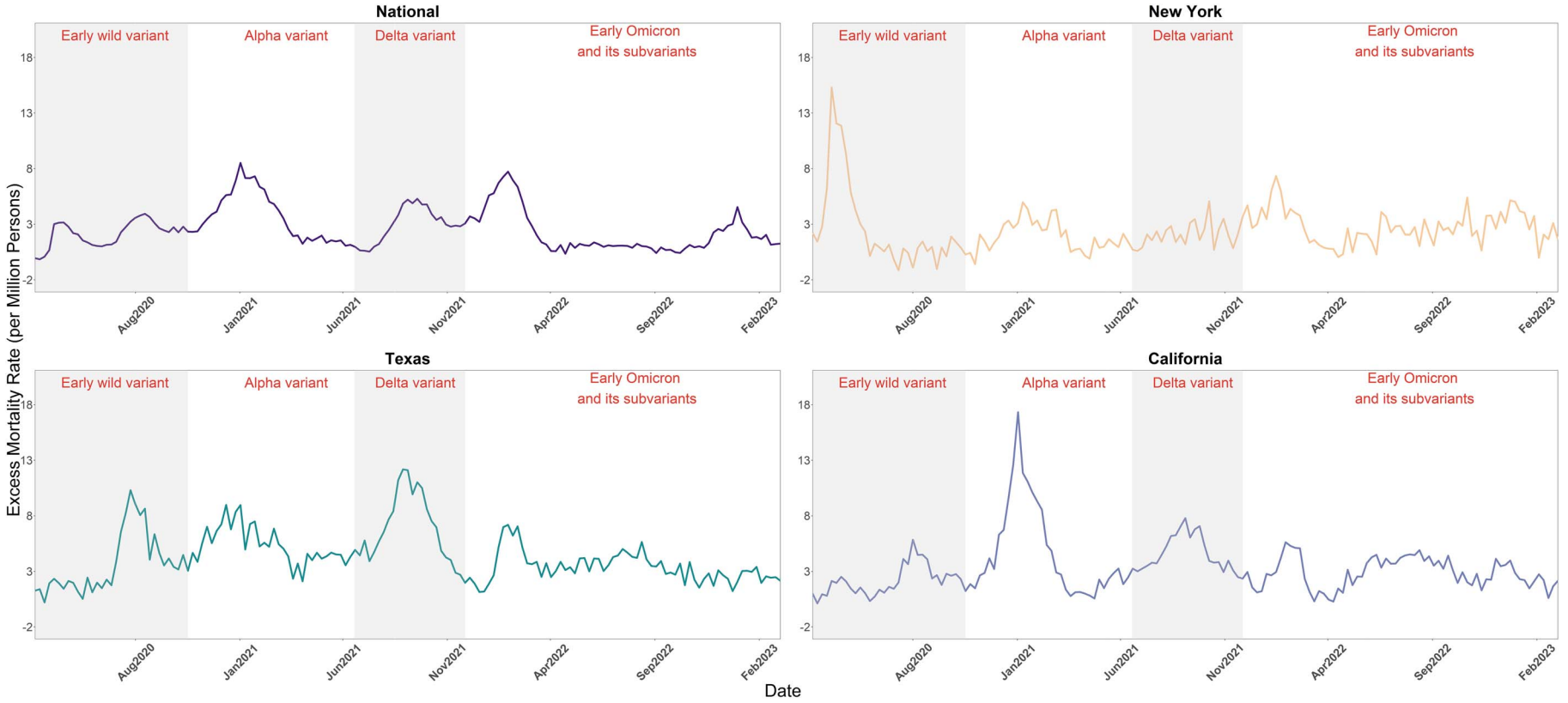

Figure 3. Weekly excess mortality rates of sepsis (per million persons) at the national level and in New York, Texas, and California. The early wild variant period from March 7, 2020, to October 17, 2020; the α variant period from October 18, 2020, to June 17, 2021; the δ variant period from June 18, 2021, to November 27, 2021; and the early Omicron and its subvariants period from November 28, 2021, to March 4, 2023.

Table 4. Excess sepsis-related mortality in New York, Texas, and California.[a]

Jurisdiction	Wave	No. of observed deaths	No. of excess deaths (95% CI)	Excess deaths per week (95% CI)	Excess death per million persons (95% CI)	Excess risk % (95% CI)
New York	Overall	39 585	7164 (6651, 7472)	46 (42, 48)	364.9 (338.7, 380.6)	22.1 (20.8, 23.4)
	Wave I	8170	1730 (1639, 1806)	52 (50, 55)	89.5 (84.8, 93.4)	26.9 (25.5, 28.2)
	Wave II	8414	1296 (1099, 1445)	38 (32, 42)	65.9 (55.9, 73.4)	18.2 (15.7, 20.7)
	Wave III	5703	995 (833, 1131)	41 (35, 47)	50.2 (42.0, 57.0)	21.1 (17.9, 24.4)
	Wave IV	17 298	3564 (3269, 3787)	54 (50, 57)	181.0 (166.0, 192.3)	25.9 (24.0, 27.9)
California	Overall	84 670	17 664 (16 811, 18 237)	113 (107, 116)	450.7 (428.9, 465.3)	26.4 (25.3, 27.5)
	Wave I	16 047	2709 (2562, 2832)	82 (78, 86)	68.8 (65.1, 71.9)	20.3 (19.3, 21.3)
	Wave II	21 065	6264 (5922, 6531)	184 (174, 192)	159.5 (150.8, 166.3)	42.3 (40.1, 44.6)
	Wave III	12 545	3437 (3137, 3688)	143 (131, 154)	87.6 (79.9, 94.0)	37.7 (34.5, 41.0)
	Wave IV	35 013	6589 (6059, 6995)	100 (92, 106)	168.8 (155.2, 179.2)	23.2 (21.5, 24.9)
Texas	Overall	65 695	19 081 (18 520, 19 461)	122 (118, 124)	643.0 (624.1, 655.8)	40.9 (39.8, 42.0)
	Wave I	13 504	3506 (3392, 3601)	106 (103, 109)	119.4 (115.5, 122.6)	35.1 (34.0, 36.2)
	Wave II	15 737	5603 (5362, 5790)	165 (158, 170)	190.1 (181.9, 196.4)	55.3 (52.9, 57.7)
	Wave III	11 043	4143 (3933, 4323)	173 (164, 180)	140.3 (133.2, 146.4)	60.0 (56.7, 63.3)
	Wave IV	25 411	6297 (5960, 6557)	95 (90, 99)	210.0 (198.7, 218.6)	32.9 (31.3, 34.6)

[a]Overall: March 7, 2020, to March 4, 2023; wave I, the early pandemic wave (from March 7, 2020, to October 17, 2020); wave II, the α wave (from October 18, 2020, to June 17, 2021); wave III, the δ wave (June 18, 2021, to November 27, 2021); and wave IV, Omicron and its subvariants (from November 28, 2021, to March 4, 2023).

resulting in a significant portion of the population receiving vaccinations to protect themselves.[30] Second, in contrast to the wild type, the Omicron variant has exhibited a decrease in virulence. Third, to facilitate a return to normalcy, the US government implemented policies that encouraged people to resume their regular lives. For example, the National COVID-19 Preparedness Plan, released at the beginning of 2022, provided assistance in the ongoing fight against COVID-19.[12] The plan was committed to increasing the vaccine supply for people and making it convenient to get free antiviral drugs if they tested positive for COVID-19. Moreover, the increasing accessibility of health care services may have effectively mitigated additional excess deaths related to sepsis. Although sepsis-associated mortality rates remain above normal levels, the significant reduction in sepsis-related deaths highlights the importance of restoring normalcy for individuals grappling with sepsis.

Our findings build upon existing research by revealing that among patients concurrently affected by both SARS-CoV-2 and sepsis, elderly individuals exhibited a significantly elevated excess mortality rate.[31,32] This aligns with the intuitive understanding that age constitutes a risk factor for mortality during the COVID-19 pandemic. Additionally, we observed a slightly higher mortality rate in males compared to females, in line with previous research.[33,34] Furthermore, our study corroborates existing evidence indicating that individuals from racial/ethnic minority groups face a relatively higher risk of death.[35,36] Especially noteworthy is the disproportionate vulnerability experienced by non-Hispanic Black subgroups during the pandemic, largely attributed to encountering more significant barriers in accessing quality health care.[36,37] There are several potential explanations for this, encompassing numerous social and economic barriers. These include a higher likelihood of occupational exposure to COVID-19, residing in multigenerational households, and facing challenges in accessing health care services.[35] These pronounced disparities and disproportionate burdens have further exacerbated the death toll associated with sepsis among vulnerable populations during the COVID-19 pandemic.

We conducted a geographic stratification analysis, revealing that Delaware and North Carolina exhibited the highest sepsis-related mortality rates. Most states experienced elevated sepsis-related mortality in the initial 2 years, followed by a decline in the third year. In comparison to other regions, the Midwest states displayed a relatively lower mortality associated with sepsis. This finding suggests that factors such as enhanced local COVID-19 response policies, increased health care resources for sepsis, and optimized capacity in various scenarios could contribute to a reduction in sepsis-related deaths, although this is an ecological study that cannot establish causality or clarify the underlying mechanisms.

This study also has some limitations. First, the data utilized for analyzing excess mortality related to sepsis do not exclude the most recent weeks, potentially introducing uncertainty in statistical outcomes due to reporting lags. Second, since the population size in 2023 was unavailable, it was assumed to be the same as in 2022. Further validation of the study's results will be necessary upon the release of the actual population size for 2023. Third, the reference period from WONDER only covered two years (2018-2020) to estimate the 3 subsequent years (2020-2023). Although we have demonstrated the robustness of our results, the estimates from WONDER may have slightly lower precision, but they still provide valuable insights into demographic disparities over time. Fourth, our analysis, which utilized unadjusted descriptive results, may be influenced by confounding variables, such as variations in age distribution across different regions.

Our study examined the temporal trend in sepsis-related mortality over the 3 years of the COVID-19 pandemic in the United States. The notable decrease in excess mortality associated with sepsis in the postpandemic period suggests the effectiveness of current disease management capacities for patients with sepsis. Considering the potential ongoing circulation of SARS-CoV-2 in the community, it is imperative for governments to enhance responses aimed at mitigating the disparity in excess sepsis-related mortality.

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Supplementary material

Supplementary material is available at *American Journal of Epidemiology* online.

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Conflict of interest

The authors declare no conflicts of interest.

Data availability

Data are from the Centers for Disease Control and Prevention (CDC).

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