Suicides Among American Indian or Alaska Native Persons — National Violent Death Reporting System, United States, 2015–2020

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Compared with the general U.S. population, American Indian or Alaska Native (AI/AN) persons, particularly those who are not Hispanic or Latino (Hispanic) AI/AN, are disproportionately affected by suicide; rates among this group consistently surpass those among all other racial and ethnic groups (*1*). Suicide rates among non-Hispanic AI/AN persons increased nearly 20% from 2015 (20.0 per 100,000) to 2020 (23.9), compared with a <1% increase among the overall U.S. population (13.3 and 13.5, respectively) (*1*). Understanding characteristics of suicide among AI/AN persons is critical to developing and implementing effective prevention strategies. A 2018 report described suicides in 18 states among non-Hispanic AI/AN persons only (*2*). The current study used 2015–2020 National Violent Death Reporting System (NVDRS) data among 49 states, Puerto Rico, and the District of Columbia to examine differences in suicide characteristics and contributing circumstances among Hispanic and non-Hispanic AI/AN populations, including multiracial AI/AN. Results indicated higher odds across a range of circumstances, including 10 of 14 relationship problems (adjusted odds ratio [aOR] range = 1.2–3.8; 95% CI range = 1.0–5.3) and six of seven substance use problems (aOR range = 1.2–2.3; 95% CI range = 1.1–2.5), compared with non-AI/AN persons. Conversely, AI/AN decedents had reduced odds of having any current known mental health condition, any history of mental health or substance use treatment, and other common risk factors (aOR range = 0.6–0.8; 95% CI = 0.2–0.9). Suicide is preventable. Communities can implement a comprehensive public health approach to suicide prevention that addresses long-standing inequities affecting AI/AN populations (*3*).

NVDRS is a state-based surveillance system that collects information from death certificates, coroner or medical examiner reports, and law enforcement reports on the characteristics and circumstances of violent deaths, including suicides (*4*).

Data in this report are from the District of Columbia, Puerto Rico, and 49 U.S. states participating in NVDRS during 2015–2020*; some jurisdictions did not participate for the entire period because they were not yet funded or because they did not achieve data completion thresholds (Supplementary Table, https://stacks.cdc.gov/view/cdc/121071) (*4*). Analyses were limited to decedents aged ≥10 years, because determining suicide intent in young children can be difficult (*5*). AI/AN

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* Florida is not included because pilot data were collected only during the study period.

Continuing Education examination available at https://www.cdc.gov/mmwr/mmwr_continuingEducation.html

persons are defined in NVDRS as persons with origins among any of the original peoples of North America and who maintain cultural identification through tribal affiliation or community recognition (Alaska Natives are included among this group) (6). For this study, characteristics and circumstances of suicide were compared among decedents with any AI/AN identification, similar to a recent analysis of homicides among AI/AN persons (7). Rural-urban commuting area codes were used to determine nonmetropolitan and metropolitan geographic areas. All comparisons between AI/AN and non-AI/AN persons were examined using Pearson's chi-square tests (with p<0.05 considered statistically significant) and logistic regression analyses, controlling for age and sex to estimate aORs with 95% CIs. Analyses were conducted using SAS (version 9.4; SAS Institute). This analysis was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[†]

During 2015–2020, a total of 3,397 suicides among AI/AN persons and 179,850 suicides among non-AI/AN persons were recorded in NVDRS (Table 1). Approximately three quarters (74.6%) of AI/AN suicide decedents were aged ≤44 years, compared with less than one half (46.5%) of non-AI/AN decedents. The highest percentage of AI/AN suicides (46.9%) occurred among persons aged 25–44 years, whereas among non-AI/AN persons, the largest percentage (35%) occurred among persons aged 45–64 years. Nearly 45% of AI/AN

[†] 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

suicide decedents (compared with 18.7% of non-AI/AN suicide decedents) lived in nonmetropolitan areas. AI/AN suicide decedents had higher odds of dying by hanging, strangulation, or suffocation (aOR = 1.8) and lower odds of dying from a firearm injury (aOR = 0.7) compared with non-AI/AN decedents. AI/AN suicide decedents also had higher odds of dying in a natural area (e.g., field; aOR = 1.4) or supervised facility (e.g., prison; aOR = 2.0) compared with non-AI/AN suicide decedents.

The circumstances of suicide were known for 86% of AI/AN and 89% of non-AI/AN decedents (Table 2). AI/AN decedents were more likely than were non-AI/AN decedents to disclose suicidal intent before death (aOR = 1.2) and to have had previous suicidal thoughts or plans (aOR = 1.1), but they were less likely to leave a note (aOR = 0.7). Nearly 55% of AI/AN suicide decedents experienced any relationship problems or losses before their death, compared with 42.2% of non-AI/AN decedents (aOR = 1.4). AI/AN decedents had increased odds of an additional nine of 14 relationship problems, including higher odds of intimate partner problems (aOR = 1.4), family relationship problems (aOR = 1.2), other relationship problems (aOR=1.4), interpersonal violence victimization (aOR = 2.7) and perpetration (aOR = 1.6) within the preceding month, suicide of a friend or family member (aOR = 1.6), and arguments or conflicts preceding death (aOR = 1.6). Conversely, AI/AN suicide decedents had decreased odds

of physical health, job, and financial problems than did non-AI/AN decedents (aOR range = 0.6–0.8).

Approximately one third of AI/AN (31.8%) and non-AI/AN suicide decedents (29.7%) had experienced a crisis within the preceding 2 weeks or anticipated a crisis in the upcoming 2 weeks; AI/AN decedents had higher odds of having experienced crises involving intimate partners and recent

suicide of friends or family members as well as crises involving criminal legal problems than did non-AI/AN decedents (aOR range = 1.2–3.8). In addition, AI/AN decedents had higher odds of six of seven alcohol or substance use problems including any current substance use problem (aOR = 2.0), a current alcohol (aOR = 2.3) or other substance use problem (aOR = 1.6), reported alcohol use hours before death

TABLE 1. Selected demographic and descriptive characteristics of American Indian or Alaska Native and non–American Indian or Alaska Native suicide decedents — National Violent Death Reporting System, United States, 2015–2020

Characteristic	No. (%)*		Chi-square p-value[†]	aOR (95% CI)
	AI/AN (n = 3,397)	Non-AI/AN (n = 179,850)		
Age group, yrs				
10–14	83 (2.4)	1,996 (1.1)	<0.001	—[§]
15–19	368 (10.8)	8,591 (4.8)	<0.001	—[§]
20–24	491 (14.5)	14,440 (8.0)	<0.001	—[§]
25–44	1,593 (46.9)	58,662 (32.6)	<0.001	—[§]
45–64	701 (20.6)	62,941 (35.0)	<0.001	—[§]
≥65	161 (4.7)	33,220 (18.5)	<0.001	—[§]
Sex				
Male	2,553 (75.2)	140,690 (78.2)	<0.001	—[§]
Female	844 (24.8)	39,155 (21.8)	<0.001	—[§]
Ethnicity				
Hispanic or Latino	233 (6.9)	13,486 (7.5)	0.154	0.7 (0.6–0.8)[¶]
Non-Hispanic	3150 (93.1)	165,358 (92.5)	0.154	1.4 (1.2–1.6)[¶]
RUCA**				
Nonmetro	1,515 (44.8)	33,476 (18.7)	<0.001	3.7 (3.4–3.9)[¶]
Metro	1,864 (55.2)	145,345 (81.3)	<0.001	0.3 (0.3–0.3)[¶]
Method				
Firearm	1,261 (37.1)	88,893 (49.4)	<0.001	0.7 (0.6–0.7)[¶]
Hanging, strangulation, or suffocation	1,594 (46.9)	51,457 (28.6)	<0.001	1.8 (1.7–1.9)[¶]
Poisoning	312 (9.2)	23,309 (13.0)	<0.001	0.7 (0.7–0.8)[¶]
Motor vehicle	62 (1.8)	2,925 (1.6)	0.365	0.9 (0.7–1.2)
Sharp instrument	74 (2.2)	3,577 (2.0)	0.434	1.4 (1.1–1.7)[¶]
Fall	43 (1.3)	4,628 (2.6)	<0.001	0.5 (0.3–0.6)[¶]
Other (single method)	30 (0.9)	3,063 (1.7)	<0.001	0.5 (0.4–0.8)[¶]
Location of injury				
House or apartment	2,373 (69.9)	130,802 (72.7)	<0.001	0.9 (0.8–1.0)[¶]
Transport related[††]	272 (8.0)	19,004 (10.6)	<0.001	0.7 (0.6–0.8)[¶]
Natural area[§§]	236 (6.9)	8,368 (4.7)	<0.001	1.4 (1.2–1.6)[¶]
Supervised facility[¶¶]	99 (2.9)	2,512 (1.4)	<0.001	2.0 (1.7–2.5)[¶]
Hotel or motel	72 (2.1)	4,060 (2.3)	0.592	1.0 (0.8–1.3)
Abandoned building or industrial setting***	22 (0.6)	762 (0.4)	0.048	1.5 (1.0–2.3)
School (including college)	19 (0.6)	460 (0.3)	<0.001	1.1 (0.7–1.8)
Other	228 (6.7)	9,107 (5.1)	<0.001	1.3 (1.2–1.5)[¶]
Other characteristic				
Current or former military personnel	271 (8.7)	28,912 (17.1)	<0.001	0.7 (0.6–0.8)[¶]
Current experience of homelessness	106 (3.3)	2,416 (1.4)	<0.001	2.4 (2.0–3.0)[¶]

Abbreviations: AI/AN = American Indian or Alaska Native; aOR = adjusted odds ratio; RUCA = rural-urban commuting area.
* Denominator includes all suicide decedents.
[†] Pearson's chi-square test p-value for difference between AI/AN and non-AI/AN populations.
[§] aORs measure the association between the decedent having the demographic or incident characteristic and the race of the decedent being AI/AN. Each aOR used non-AI/AN as the referent group and controlled for age group and sex. Therefore, aORs for age groups and sex are not presented.
[¶] p<0.05 for aOR significance test.
** Zip code RUCA codes (2010) were used to determine whether a decedent lived in a nonmetropolitan versus a metropolitan area. Decedent residential zip codes were dichotomized as metropolitan (RUCA codes 1–3) and nonmetropolitan (RUCA codes 4–10). https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/documentation/
[††] Includes suicides that occurred in a motor vehicle, street, highway, parking lot or garage, public transport, railroad tracks, or bridge.
[§§] Includes suicides that occurred on a beach or in a river, field, or woods.
[¶¶] Includes suicides that occurred in jail, prison, or supervised residential facility.
*** Includes suicides that occurred in industrial or construction sites or an abandoned house, building, or warehouse.

TABLE 2. Circumstances preceding suicide of American Indian or Alaska Native persons compared with non–American Indian or Alaska Native persons — National Violent Death Reporting System, United States, 2015–2020

| | No. (%)* | | | |
| | AI/AN (n = 3,397) | Non-AI/AN (n = 179,850) | Chi-square p-value[†] | aOR (95% CI)[§] |
Circumstance				
Decedents with known circumstance[¶]	2,926 (86.1)	160,165 (89.1)	<0.001	0.8 (0.7–0.9)**
Suicide event or history				
Left a note	737 (25.2)	52,401 (32.7)	<0.001	0.7 (0.6–0.8)**
Disclosed suicidal intent	825 (28.2)	37,837 (23.6)	<0.001	1.2 (1.1–1.3)**
History of suicidal thoughts or plan	1,122 (38.3)	54,972 (34.3)	<0.001	1.1 (1.0–1.2)**
History of suicide attempts	634 (21.7)	31,608 (19.7)	0.009	1.0 (0.9–1.1)
Relationship problem or loss				
Any relationship problem or loss	1,607 (54.9)	67,542 (42.2)	<0.001	1.4 (1.3–1.6)**
Intimate partner problem	1,062 (36.3)	42,912 (26.8)	<0.001	1.4 (1.3–1.5)**
Family relationship problem	377 (12.9)	13,993 (8.7)	<0.001	1.2 (1.1–1.3)**
Other relationship problem (nonintimate)	121 (4.1)	3,467 (2.2)	<0.001	1.4 (1.2–1.7)**
Victim of interpersonal violence within previous mo	42 (1.4)	684 (0.4)	<0.001	2.7 (1.9–3.7)**
Perpetrator of interpersonal violence within previous mo	105 (3.6)	3,642 (2.3)	<0.001	1.6 (1.3–2.0)**
Suicide of friend or family member	123 (4.2)	3,787 (2.4)	<0.001	1.6 (1.3–1.9)**
Other death of friend or family member	180 (6.2)	10,122 (6.3)	0.711	1.1 (1.0–1.3)
Argument or conflict preceded death[††]	762 (26.0)	25,620 (16.0)	<0.001	1.6 (1.5–1.7)**
Injury occurred during argument	164 (21.5)	5,674 (22.1)	0.682	1.0 (0.9–1.2)
Injury occurred ≤24 hrs, but not during argument	502 (65.9)	15,721 (61.4)	0.012	1.1 (1.0–1.3)
Injury occurred >24 hrs after argument	57 (7.5)	2,715 (10.6)	0.006	0.7 (0.5–0.9)**
Other life stressor				
Any life stressor	1,640 (56.0)	94,851 (59.2)	0.001	1.0 (0.9–1.1)
Victim in custody	132 (4.5)	4,037 (2.5)	<0.001	1.7 (1.4–2.0)**
Released from institution within previous month[§§]	196 (6.7)	11,232 (7.0)	0.509	1.0 (0.9–1.2)
Jail, prison, or a detention facility	70 (35.7)	1,822 (16.2)	<0.001	2.5 (1.8–3.3)**
Hospital	55 (28.1)	4,559 (40.6)	<0.001	0.7 (0.5–1.0)
Psychiatric hospital or other psychiatric institution	36 (18.4)	3,589 (32.0)	<0.001	0.4 (0.3–0.6)**
Long-term residential health facility	2 (1.0)	126 (1.1)	1.000	1.6 (0.4–6.5)
Supervised residential facility related to alcohol or substance use treatment	18 (9.2)	622 (5.5)	0.028	1.5 (0.9–2.5)
Other[§§,¶¶]	15 (7.7)	514 (4.6)	0.042	1.6 (1.0–2.8)
Criminal legal problem	347 (11.9)	12,384 (7.7)	<0.001	1.6 (1.4–1.8)**
Civil legal problem	127 (4.3)	5,391 (3.4)	0.004	1.4 (1.1–1.6)**
Physical health problem	366 (12.5)	3,4291 (21.4)	<0.001	0.8 (0.7–0.9)**
Job problem***	179 (6.6)	15,092 (9.8)	<0.001	0.6 (0.6–0.8)**
Financial problem***	160 (5.9)	13,097 (8.5)	<0.001	0.8 (0.6–0.9)**
School problem[†††]	53 (17.5)	1,586 (21.6)	<0.001	0.8 (0.6–1.1)
Eviction or loss of home	93 (3.2)	5,638 (3.5)	<0.001	1.0 (0.8–1.3)
Crisis within previous 2 wks or anticipated in upcoming 2 wks	930 (31.8)	475,96 (29.7)	0.015	1.1 (1.0–1.2)
Crisis related to mental health[§§§]	21 (2.3)	2,679 (5.6)	<0.001	0.4 (0.2–0.6)**
Crisis related to alcohol problem[§§§]	74 (8.0)	2,718 (5.7)	0.004	1.6 (1.3–2.0)**
Crisis related to substance use[§§§]	33 (3.5)	1,619 (3.4)	0.807	1.0 (0.7–1.4)
Crisis related to intimate partner problem[§§§]	417 (44.8)	18,278 (38.4)	<0.001	1.2 (1.0–1.3)**
Crisis related to family relationship problem[§§§]	68 (7.3)	3,589 (7.5)	0.794	0.7 (0.5–0.9)**
Crisis related to other relationship problem[§§§]	19 (2.0)	799 (1.7)	0.393	0.9 (0.6–1.5)
Crisis related to criminal legal problem[§§§]	140 (15.1)	5,536 (11.6)	0.001	1.4 (1.1–1.6)**
Crisis related to civil legal problem[§§§]	31 (3.3)	1,628 (3.4)	0.885	1.0 (0.7–1.5)
Crisis related to physical health problem[§§§]	85 (9.1)	7,067 (14.8)	<0.001	1.0 (0.8–1.2)
Crisis related to job problem[***,§§§]	34 (4.0)	3,509 (7.7)	<0.001	0.5 (0.3–0.7)**
Crisis related to financial problem[***,§§§]	16 (1.9)	2,069 (4.5)	<0.001	0.5 (0.3–0.8)**
Crisis related to school problem[†††,§§§]	12 (12.8)	404 (17.7)	0.218	0.7 (0.4–1.3)
Crisis related to eviction or loss of home[§§§]	25 (2.7)	2,290 (4.8)	0.003	0.6 (0.4–1.0)**
Crisis related to recent suicide of friend or family[§§§]	39 (4.2)	442 (0.9)	<0.001	3.8 (2.7–5.3)**
Crisis related to other death of friend or family[§§§]	38 (4.1)	1,710 (3.6)	0.424	1.3 (0.9–1.8)

See table footnotes on the next page.

TABLE 2. (*Continued*) Circumstances preceding suicide of American Indian or Alaska Native persons compared with non–American Indian or Alaska Native persons — National Violent Death Reporting System, United States, 2015–2020

Circumstance	No. (%)*		Chi-square p-value†	aOR (95% CI)§
	AI/AN (n = 3,397)	Non-AI/AN (n = 179,850)		
Mental health or substance use				
Any current substance use problem	1,340 (45.8)	47,285 (29.5)	<0.001	2.0 (1.9–2.2)**
Alcohol problem	918 (31.4)	29,109 (18.2)	<0.001	2.3 (2.1–2.5)**
Other substance use problem	778 (26.6)	27,403 (17.1)	<0.001	1.6 (1.5–1.7)**
Reported alcohol use in hrs preceding death	902 (30.8)	31,185 (19.5)	<0.001	1.9 (1.7–2.0)**
Any current diagnosed mental health problem	1,215 (41.5)	78,744 (49.2)	<0.001	0.7 (0.7–0.8)**
Depression or dysthymia	859 (29.4)	58,580 (36.6)	<0.001	0.7 (0.7–0.8)**
Bipolar disorder	146 (5.0)	11,776 (7.4)	<0.001	0.6 (0.5–0.8)**
Schizophrenia	100 (3.4)	4,714 (2.9)	0.133	1.1 (0.9–1.4)
Anxiety disorder	219 (7.5)	15,810 (9.9)	<0.001	0.7 (0.6–0.8)**
Posttraumatic stress disorder	92 (3.1)	4,235 (2.6)	0.095	1.2 (1.0–1.5)
Attention deficit hyperactivity disorder	37 (1.3)	2,161 (1.3)	0.694	0.5 (0.4–0.7)**
Current depressed mood (not diagnosis)	986 (33.7)	55,385 (34.6)	0.320	1.0 (0.9–1.1)
Mental health or substance use treatment				
Current mental health or substance use treatment	569 (19.4)	41,894 (26.2)	<0.001	0.6 (0.6–0.7)**
History of mental health or substance use treatment	862 (29.5)	56,260 (35.1)	<0.001	0.7 (0.7–0.8)**

Abbreviations: AI/AN = American Indian or Alaska Native; aOR = adjusted odds ratio.

 * Denominator includes all suicide decedents.
 † Pearson's chi-square test result for difference between AI/AN and non-AI/AN populations; Fisher's exact test when one or more of the cell counts in a 2×2 table is <5.
 § aORs measure the association between the decedent having the precipitating circumstance present and the race of the decedent being AI/AN. Each aOR used Non-AI/AN as the referent group and controlled for age group and sex.
 ¶ Denominator includes only suicides with one or more precipitating circumstance, unless otherwise noted. Sum of percentages in columns might exceed 100% because a suicide could have more than one precipitating circumstance.
 ** p<0.05 for aOR significance test.
 †† Denominator includes only those suicides in which argument or conflict preceded death.
 §§ Denominator includes only those decedents released from an institution within the previous month.
 ¶¶ Supervised residential facilities not related to alcohol or substance use treatment, and other or unknown type of institution.
 *** Denominator includes only decedents aged ≥18 years with at least one known circumstance.
 ††† Denominator includes only decedents aged 10–17 years with at least one known circumstance.
 §§§ Denominator includes only those suicide decedents with any crisis within the past or upcoming 2 weeks.

(aOR = 1.9), and crises involving alcohol (aOR = 1.6). Among persons released from an institution within the month preceding death (196), 9.2% of AI/AN decedents had been in residential substance use treatment, compared with 5.5% of non-AI/AN decedents. The prevalences of known mental health diagnoses (41.5%; [aOR = 0.7]) and history of mental health or substance use treatment (29.5%; [aOR = 0.7]) were lower among AI/AN decedents than among non-AI/AN decedents (49.2% and 35.1%, respectively).

Toxicology testing was performed for 66.6% of AI/AN suicide decedents and 61.1% of non-AI/AN decedents (Table 3). Overall, AI/AN decedents had higher odds than did non-AI/AN decedents of receiving a positive test result for at least one substance (aOR = 1.2), blood alcohol concentration of ≥0.08 g/dL (aOR = 2.3), amphetamines (aOR = 1.5), and marijuana (aOR = 1.5). Conversely, AI/AN decedents had lower odds than did non-AI/AN decedents of receiving a positive test result for opioids (aOR = 0.5), benzodiazepines (aOR = 0.4), cocaine (aOR = 0.5), antidepressants (aOR = 0.6), antipsychotics (aOR = 0.7), and barbiturates (aOR = 0.3).

Discussion

Analyses of characteristics of and circumstances preceding suicide among AI/AN and non-AI/AN persons in participating NVDRS jurisdictions during 2015–2020 identified many differences, including higher odds of relationship and substance use problems and lower odds of physical, job, and financial problems; known mental health conditions; and any history of mental health or substance use treatment among AI/AN decedents compared with non-AI/AN decedents. Although direct comparison of circumstances between studies is not possible, these findings suggest a similar pattern observed in a previous analysis of suicide in 18 states among non-Hispanic AI/AN persons compared with non-Hispanic White populations, during 2003–2014 (*2*). Those findings also indicated higher odds of relationship and alcohol problems and reduced odds of known mental health problems, current or past mental health or substance use treatment, and physical, job, or financial problems. Toxicology results from the earlier study also followed the same pattern as those observed in the current study, including higher odds of positive alcohol, amphetamine, and marijuana toxicology results among AI/AN decedents, and

reduced odds of positive opioid and antidepressant test results, compared with non-AI/AN decedents.

The current study found higher odds of suicide among AI/AN persons across a range of relationship problems related to intimate partners, family, other relationships, interpersonal violence victimization and perpetration, and death of friends or family members by suicide. Similarly, more alcohol and other substance use circumstances, including those of an acute and more chronic nature, were observed in this study, as were criminal problems, although the nature of these problems was

TABLE 3. Toxicology results of American Indian or Alaska Native suicide decedents compared with non–American Indian or Alaska Native suicide decedents — National Violent Death Reporting System, United States, 2015–2020

| | No. (%) | | | |
Toxicology result	AI/AN (n = 3,397)	Non-AI/AN (n = 179,850)	Chi-square p-value[†]	aOR (95% CI)[§]
Any toxicology testing*	2,262 (66.6)	109,806 (61.1)	<0.001	1.2 (1.1–1.3)[¶]
Positive result for at least one substance*	1,774 (78.4)	84,152 (76.6)	0.046	1.2 (1.1–1.3)[¶]
Blood alcohol concentration[††]				
Tested	2,103 (61.9)	93,124 (51.8)	<0.001	1.4 (1.3–1.5)[¶]
Positive result[§§]	1,023 (48.6)	37,354 (40.1)	<0.001	1.5 (1.4–1.7)[¶]
Alcohol <0.08 g/dL	169 (16.5)	10,667 (28.6)	<0.001	0.5 (0.4–0.6)[¶]
Alcohol ≥0.08 g/dL	821 (80.3)	24,019 (64.3)	<0.001	2.3 (2.0–2.7)[¶]
Alcohol positive, level unknown	33 (3.2)	2,668 (7.1)	<0.001	0.5 (0.3–0.6)[¶]
Opioids				
Tested	1,842 (54.2)	76,672 (42.6)	<0.001	1.5 (1.4–1.6)[¶]
Positive result[§§]	228 (12.4)	18,242 (23.8)	<0.001	0.5 (0.5–0.6)[¶]
Benzodiazepines				
Tested	1,713 (50.4)	71,192 (39.6)	<0.001	1.5 (1.4–1.6)[¶]
Positive result[§§]	190 (11.1)	18,511 (26.0)	<0.001	0.4 (0.3–0.5)[¶]
Cocaine				
Tested	1,796 (52.9)	72,121 (40.1)	<0.001	1.6 (1.5–1.7)[¶]
Positive result[§§]	64 (3.6)	4,940 (6.8)	<0.001	0.5 (0.4–0.6)[¶]
Amphetamines				
Tested	1,841 (54.2)	70,483 (39.2)	<0.001	1.7 (1.6–1.8)[¶]
Positive result[§§]	381 (20.7)	9,523 (13.5)	<0.001	1.5 (1.4–1.7)[¶]
Marijuana				
Tested	1,363 (40.1)	62,684 (34.9)	<0.001	1.2 (1.1–1.2)[¶]
Positive result[§§]	491 (36.0)	15,102 (24.1)	<0.001	1.5 (1.3–1.7)[¶]
Antidepressants				
Tested	804 (23.7)	48,972 (27.2)	<0.001	0.8 (0.7–0.9)[¶]
Positive result[§§]	203 (25.2)	18,294 (37.4)	<0.001	0.6 (0.5–0.7)[¶]
Antipsychotics				
Tested	690 (20.3)	38,001 (21.1)	0.248	0.9 (0.8–1.0)
Positive result[§§]	54 (7.8)	4,336 (11.4)	0.003	0.7 (0.5–0.9)[¶]
Barbiturates				
Tested	1,651 (48.6)	59,040 (32.8)	<0.001	1.8 (1.7–2.0)[¶]
Positive result[§§]	11 (0.7)	1,441 (2.4)	<0.001	0.3 (0.2–0.6)[¶]
Carbon monoxide				
Tested	133 (3.9)	10,333 (5.7)	<0.001	0.7 (0.6–0.8)[¶]
Positive result[§§]	41 (30.8)	3,492 (33.8)	0.472	1.0 (0.7–1.5)
Anticonvulsants				
Tested	547 (16.1)	38,439 (21.4)	<0.001	0.7 (0.6–0.8)[¶]
Positive result[§§]	77 (14.1)	6,487 (16.9)	0.082	0.8 (0.6–1.1)
Muscle relaxants				
Tested	492 (14.5)	39,311 (21.9)	<0.001	0.6 (0.5–0.6)[¶]
Positive result[§§]	34 (6.9)	2,575 (6.6)	0.748	1.1 (0.8–1.6)

Abbreviations: AI/AN = American Indian or Alaska Native; aOR = adjusted odds ratio.
* Denominator includes all suicide decedents.
[†] Pearson's chi-square test result for difference between AI/AN and non-AI/AN populations.
[§] aORs measure the association between the decedent receiving a positive test result for the substance and the race of the decedent being AI/AN. The denominator was the number of decedents who were tested for each substance. Each aOR used non-AI/AN as the referent group and controlled for age group and sex.
[¶] p<0.05 for aOR significance test.
** Denominator is decedents with any toxicology testing.
[††] Blood alcohol concentration of ≥0.08 g/dL is higher than the legal limit in all states and the District of Columbia and is used as the standard for intoxication.
[§§] Denominator for each positive result group is the number tested for the substance in that group.

unknown. According to previous NVDRS reports, approximately one half of persons who die by suicide do not have a known mental health condition (*4*). This study found that only 41.5% of AI/AN suicide decedents had a known mental health condition. This might be the result of less available or accessible mental health services, especially in rural areas, and therefore fewer diagnoses. Post-hoc analyses controlling for metropolitan status did not change these results, suggesting possible contribution of other factors.

Suicide prevention efforts among AI/AN populations must consider the context and consequences of current inequities as well as historical trauma, including intergenerational transmission, that continue to affect AI/AN persons, families, and communities today (*8*). Suicide is a complex problem with multiple contributing circumstances that affect different communities differently. A comprehensive public health approach to suicide prevention (*3*), with attention to strategies that aim to reduce health inequities among AI/AN persons, is needed. These strategies might include strengthening access to and delivery of culturally relevant care, including telehealth for mental health concerns and well-being, increasing training and hiring of AI/AN providers, promoting community engagement and cultural traditions, increasing coping and problem-solving skills (e.g., American Indian Life Skills Training),§ increasing training to recognize and respond to suicide risk, making postvention programs (activities that reduce risk and promote healing after a suicide death) more available to AI/AN survivors of suicide loss (*3*), and promoting the 988 Suicide and Crisis Lifeline (persons who are thinking about suicide or who know someone who is thinking about suicide, should call 988).¶

The findings in this report are subject to at least four limitations. First, participation in NVDRS states increased during the analysis period; therefore, not all jurisdictions contributed data equally during all years. Second, deaths among AI/AN persons are prone to racial and ethnic misclassification, leading to potential underestimation of AI/AN suicides (*9*). However, the analysis included any decedent with noted AI/AN ancestry, including multiracial AI/AN, irrespective of Hispanic ethnicity, allowing for a more inclusive understanding of AI/AN suicide characteristics and circumstances. Third, NVDRS does not yet include tribal affiliation, and results might vary by tribe. Finally, circumstance data in NVDRS rely upon reporting by next-of-kin and other informants who knew the decedent, and their knowledge and willingness to share information about the decedent and circumstances preceding suicide. This might overestimate or underestimate this information.

Summary

What is already known about this topic?

Suicide is preventable. It disproportionately affects American Indian or Alaska Native (AI/AN) persons. Previous studies have examined suicide characteristics and circumstances among non-Hispanic AI/AN only in a limited number of states.

What is added by this report?

Comparison of 2015–2020 suicides among all AI/AN and non-AI/AN decedents in 49 states, Puerto Rico, and the District of Columbia found that AI/AN suicide decedents had higher adjusted odds of a range of relationship and alcohol or other substance use problems, and reduced odds of known mental health conditions and treatment than did non-AI/AN suicide decedents.

What are the implications for public health practice?

Culturally relevant comprehensive public health approaches to suicide prevention are needed to address systemic and long-standing inequities among AI/AN persons.

Prevention of suicide is possible (*3*). Identification of new evidence-based programs, evaluation of existing AI/AN programs, and tailoring of other effective programs to prevent suicide among AI/AN persons is needed. Programs can benefit from holistic indigenous evaluation, which takes into consideration AI/AN cultural values and practices, such as storytelling (*10*). Addressing AI/AN-specific risk and promoting the many protective factors among AI/AN persons can save lives.

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Pediatric Brain Abscesses, Epidural Empyemas, and Subdural Empyemas Associated with *Streptococcus* Species — United States, January 2016–August 2022

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In May 2022, CDC learned of three children in California hospitalized concurrently for brain abscess, epidural empyema, or subdural empyema caused by *Streptococcus intermedius*. Discussions with clinicians in multiple states raised concerns about a possible increase in pediatric intracranial infections, particularly those caused by *Streptococcus* bacteria, during the past year and the possible contributing role of SARS-CoV-2 infection (*1*). Pediatric bacterial brain abscesses, epidural empyemas, and subdural empyemas, rare complications of respiratory infections and sinusitis, are often caused by *Streptococcus* species but might also be polymicrobial or caused by other genera, such as *Staphylococcus*. On June 9, CDC asked clinicians and health departments to report possible cases of these conditions and to submit clinical specimens for laboratory testing. Through collaboration with the Children's Hospital Association (CHA), CDC analyzed nationally representative pediatric hospitalizations for brain abscess and empyema. Hospitalizations declined after the onset of the COVID-19 pandemic in March 2020, increased during summer 2021 to a peak in March 2022, and then declined to baseline levels. After the increase in summer 2021, no evidence of higher levels of intensive care unit (ICU) admission, mortality, genetic relatedness of isolates from different patients, or increased antimicrobial resistance of isolates was observed. The peak in cases in March 2022 was consistent with historical seasonal fluctuations observed since 2016. Based on these findings, initial reports from clinicians (*1*) are consistent with seasonal fluctuations and a redistribution of cases over time during the COVID-19 pandemic. CDC will continue to work with investigation partners to monitor ongoing trends in pediatric brain abscesses and empyemas.

Two data sources were analyzed: 1) pediatric hospitalizations for brain abscesses, epidural empyemas, and subdural empyemas reported to CHA's Pediatric Health Information System (PHIS) and 2) cases reported to CDC in response to a national call for cases. With CHA, CDC examined hospitalizations at 40 tertiary referral children's hospitals across the United States that consistently reported data to PHIS during January 1, 2016–May 31, 2022 (the most recent data available when the analysis was performed). All inpatient encounters from patients aged ≤18 years with a primary or secondary discharge diagnosis of *International Classification of Diseases, Tenth Revision, Clinical Modification* code G06.0 (intracranial abscess and granuloma) or G06.2 (extradural and subdural abscess, unspecified) during the study period were included. Concurrent COVID-19 diagnosis was defined as having *International Classification of Diseases, Tenth Revision* codes U07.1 or B97.29 on the discharge diagnosis list. Medical complexity was classified according to the Pediatric Medical Complexity Algorithm (*2*).

In CDC's national call for cases, a case was defined as the diagnosis of brain abscess, epidural empyema, or subdural empyema in a person aged ≤18 years without a previous neurosurgical procedure or history of head trauma, hospitalized on or after June 1, 2021, irrespective of etiology. The call for cases was shared with health departments and two provider listservs.* Reports received after August 10, 2022, were excluded. Available *Streptococcus* specimens isolated from a brain abscess, epidural empyema, subdural empyema, blood, or cerebrospinal fluid were collected for antimicrobial susceptibility testing and whole-genome sequencing at CDC's *Streptococcus* reference laboratory to identify microbiological features shared among cases. Genomic sequences were generated with an Illumina Miseq (*3*) instrument, and single-nucleotide polymorphisms (SNPs) were identified for core genomes employing kSNP3.0 with k-mer size of 19 (*4*). Pairwise comparisons were generated employing Mega7 (*5*). Minimal inhibitory concentrations (MICs) were determined by broth microdilution methods according to the Clinical and Laboratory Standards Institute (*6*). The agar diffusion gradient method (Etest, bioMérieux) was used for isolates that did not grow in broth. Analyses were conducted using SAS (version 9.4; SAS Institute) or R (version 4.0.3; R Foundation) with R Studio (version 1.3.1093; RStudio, PBC). This study was reviewed by CDC and was conducted consistent with federal law and CDC policy.†

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* The Pediatric Infectious Diseases Society and the Section of Pediatric Neurosurgeons, a joint section of the American Association of Neurologic Surgeons and Congress of Neurologic Surgeons.

† 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

Cases Identified Through CHA's PHIS Database

During January 2016–May 2022, a total of 3,078 cases of pediatric brain abscesses, epidural empyemas, or subdural empyemas were identified from the PHIS database, ranging from 20 to 68 cases per month (median = 38; IQR = 32–48) (Figure). Beginning in April 2020, case counts were below the median for 15 months, the longest such interval during the analysis period. Starting in summer 2021, cases increased and peaked in March 2022, representing the longest interval with case counts above the median, before declining in April 2022. During these two periods, 184 fewer and 177 more cases occurred, respectively, than would have, if each month had had the median number of cases. Since 2016, peaks in cases have often occurred around March, with similarly sized peaks observed in March 2017 and March 2019. Although the total number of cases in 2020 (382) was lower than that during 2016–2019 (range = 443–538), the total in 2021 (471) was within this historical range.

The median patient age was 8 years (IQR = 1–13 years). Most cases (65.1%) occurred in males; 46.5% of cases were in non-Hispanic White (White), 21.3% in non-Hispanic Black, 20.8% in Hispanic or Latino (Hispanic), 3.3% in non-Hispanic Asian children, and 8.1% in non-Hispanic children of another race. The demographic characteristics of patients remained largely consistent over time, as did markers of severity (e.g., length of hospitalization, in-hospital mortality, and ICU admission) and the percentage of patients with a complex chronic condition (Supplementary Figure 1; https://stacks.cdc.gov/view/cdc/120876) (Supplementary Figure 2; https://stacks.cdc.gov/view/cdc/120877) (Supplementary

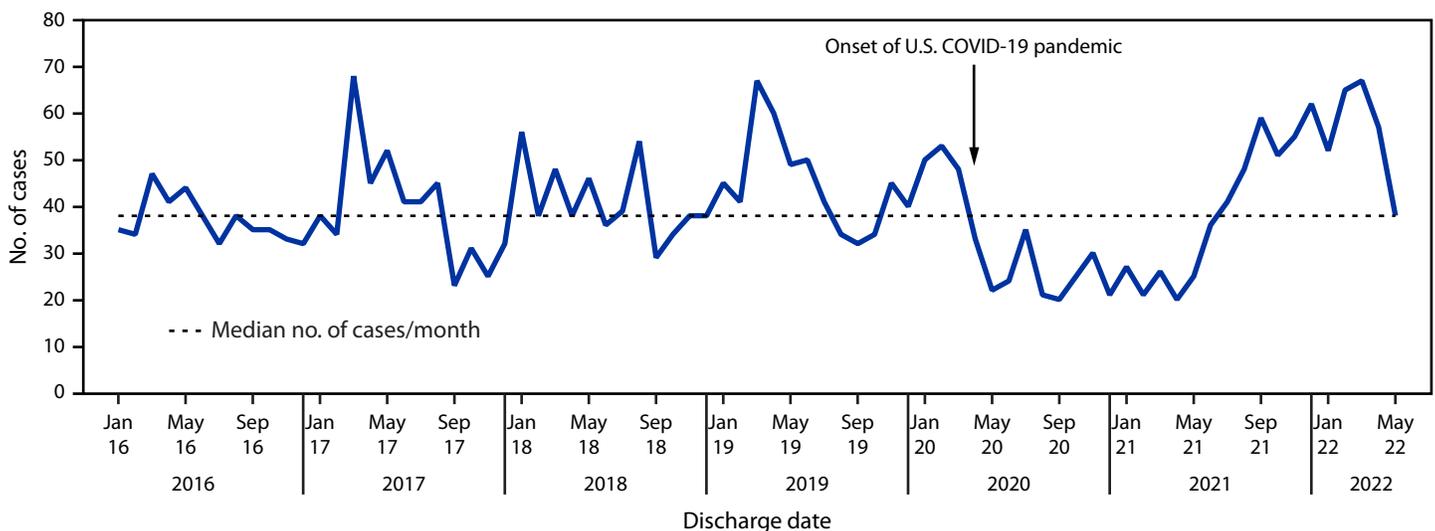Figure 3; https://stacks.cdc.gov/view/cdc/120878). The percentage of patients with concurrent COVID-19 varied from 1.3% to 10.9% across quarters (Supplementary Figure 2; https://stacks.cdc.gov/view/cdc/120877) paralleling known COVID-19 waves.[§]

Cases Identified Through CDC's National Call for Cases

Among the 94 possible cases of pediatric brain abscesses, epidural empyemas, or subdural empyemas reported after CDC's national call for cases, 81 met the case definition. The median patient age was 11 years (IQR = 6–13 years) (Table). Cases were most frequently reported in males (61.3%) and White (54.5%) children. Forty-five percent of cases occurred in children with underlying health conditions, with asthma (11.5%) being the most common. Among patients, 61.0% had a diagnosis of at least one respiratory infection in the 6 weeks before hospitalization, most commonly sinusitis (26.0%) or COVID-19 (18.2%). Most patients (81.8%) sought outpatient care for the illness episode before hospitalization. Subdural empyema was the most common case presentation (53.1%), followed by brain abscess (37.0%) and epidural empyema (33.3%). Among 71 patients who were no longer hospitalized at the time of reporting, two (2.8%) died. Case report data indicated that streptococcal species were identified in most (92.1%) isolates, commonly *S. intermedius* (41.6%) and *Streptococcus anginosus* (18.4%). Nonstreptococcal species,

[§] https://covid.cdc.gov/covid-data-tracker/#datatracker-home (Accessed August 16, 2022).

FIGURE. Cases of brain abscess, epidural empyema, or subdural empyema in persons aged ≤18 years — Pediatric Health Information System, United States, January 2016–May 2022*

* Data from 40 children's hospitals.

TABLE. Demographic and clinical characteristics, and microbiology results in patients aged ≤18 years with brain abscess, epidural empyema, or subdural empyema reported to CDC in response to a June 2022 national call for cases (N = 81) — United States, June 2021–August 2022

Characteristic (no. with available information)	No. (%)*
Demographic	
Age, yrs, median (IQR)	11.0 (6.0–13.0)
Race or ethnicity (66)	
White, non-Hispanic	36 (54.5)
Black or African American, non-Hispanic	21 (31.8)
Hispanic or Latino	7 (10.6)
Asian, non-Hispanic	1 (1.5)
Multiple races, non-Hispanic	1 (1.5)
Sex assigned at birth (80)	
Male	49 (61.3)
Female	31 (38.8)
Current gender identity (63)	
Male	35 (55.6)
Female	28 (44.4)
Underlying health conditions	
Any underlying health condition (78)	35 (44.9)
Asthma or reactive airway disease (78)	9 (11.5)
Obesity (78)	4 (5.1)
Seizures/Seizure disorder (78)	3 (3.8)
Congenital heart disease (78)	2 (2.6)
Dental caries or periodontal disease (78)	1 (1.3)
Diabetes mellitus (type 1 or 2) (78)	1 (1.3)
Other underlying condition[†] (78)	20 (25.6)
Vaccination information	
Previous pneumococcal conjugate vaccine (65)	55 (84.6)
Previous SARS-CoV-2 vaccine (59)	15 (25.4)
Recent medical history	
Diagnosis in 6 wks preceding hospitalization	
Respiratory infection[§] (77)	47 (61.0)
COVID-19 (77)	14 (18.2)
Influenza (77)	1 (1.3)
Sinusitis (77)	20 (26.0)
Upper respiratory infection (77)	12 (15.6)
Other respiratory infection[¶] (77)	11 (14.3)
Sought prehospitalization care (77)**	63 (81.8)
Hospitalization	
Length of stay, days (IQR) (71)	10.0 (6.0–21.0)
Outcome of hospitalization (80)	
Discharged to home	59 (73.8)
Discharged to rehab facility	10 (12.5)
Currently hospitalized	9 (11.2)
Deceased	2 (2.5)
During hospitalization	
Brain abscess (81)	30 (37.0)
Subdural empyema (81)	43 (53.1)
Epidural empyema (81)	27 (33.3)
Sinusitis (77)	47 (61.0)
Osteomyelitis, including Pott's puffy tumor (77)	24 (31.2)
Bacterial meningitis (77)	20 (26.0)
Orbital/Periorbital cellulitis (77)	13 (16.9)
Mastoiditis (77)	8 (10.4)
Otitis media (77)	4 (5.2)
Vancomycin received during hospitalization (80)	73 (91.2)
Ceftriaxone received during hospitalization (80)	71 (88.8)
Metronidazole received during hospitalization (80)	65 (81.2)

TABLE. (*Continued*) Demographic and clinical characteristics, and microbiology results in patients aged ≤18 years with brain abscess, epidural empyema, or subdural empyema reported to CDC in response to a June 2022 national call for cases (N = 81) — United States, June 2021–August 2022

Characteristic (no. with available information)	No. (%)*
Detection of viral respiratory pathogens (52)	
No pathogens identified	38 (73.1)
Pathogens identified[††]	14 (26.9)
Microbiology	
Pathogens identified (76)	
Eikenella corrodens	5 (6.6)
Fusobacterium nucleatum	2 (2.6)
Parvimonas micra	5 (6.6)
Staphylococcus aureus	4 (5.2)
Staphylococcus epidermidis	3 (3.9)
Streptococcus intermedius	35 (46.1)
Streptococcus anginosus	14 (18.4)
Streptococcus pneumoniae	9 (11.8)
Streptococcus constellatus	7 (9.2)
Streptococcus agalactiae	1 (1.3)
Streptococcus pasteurianus	1 (1.3)
Other[§§]	13 (17.1)
Polymicrobial specimens (76)	16 (21.1)
Isolate source (75)	
Brain abscess	13 (17.3)
Epidural empyema	10 (13.3)
Subdural empyema	17 (22.7)
Blood	10 (13.3)
Cerebrospinal fluid	9 (12.0)
Other[¶¶]	16 (21.3)

Abbreviations: ED = emergency department; MRSA = methicillin-resistant *Staphylococcus aureus*; RSV = respiratory syncytial virus; URI = upper respiratory infection.

* Percentages calculated using nonmissing data.
[†] Other underlying conditions included: Alice in Wonderland syndrome (i.e., dysmetropsia, a rare neurologic disorder characterized by distortions in perception, especially of body image); allergies (seasonal, nonseasonal, and peanut); autism; Castleman disease; cerebral palsy (including spastic quadriplegic); cerebral infarction; chronic nasal congestion; cystic encephalomalacia; epilepsy; frequent nosebleeds; gallstone pancreatitis; global developmental delay; Hashimoto disease; headaches, insomnia; intellectual disability; microcephaly; migraines; MRSA infection; myringotomy tubes; neurofibromatosis type 1; nonaccidental trauma to child; oropharyngeal dysphagia; retinal hemorrhage of both eyes; right spastic hemiparesis; sinusitis; snoring; traumatic brain injury at birth; and Trisomy 21.
[§] Including COVID-19, influenza, sinusitis, upper respiratory infection, and other respiratory infections.
[¶] Other respiratory infections included otitis media (five); parainfluenza (two); cough and fever of unspecified cause (one); URI symptoms but no diagnosis (one); RSV (one); and otitis externa (one).
** In ED, outpatient primary care, or urgent care.
[††] Viral respiratory pathogens detected during hospitalization included: SARS-CoV-2 (nine), rhinovirus/enterovirus (four), RSV (two), influenza virus (one), adenovirus (one), and parainfluenza virus (one).
[§§] *Actinomyces* sp. (one), *Clostridium* sp. (one), *Candida parapsilosis* (one), *Cutibacterium acnes* (one), *Haemophilus influenzae* (one), *Klebsiella pneumoniae* (one), *Mycoplasma hominis* (one), *Staphylococcus capitis* (one), *Staphylococcus hominis* (one), *Gemella morbillorum* (one), and unspecified streptococci (three).
[¶¶] Orbital abscess (two), forehead abscess (one), middle meatus (one), ear aspirate (two), and sinuses (eight).

including 15 unique pathogens, were isolated in 28.9% of cases and in all cases with polymicrobial infections.

Antimicrobial susceptibility testing was performed on available *Streptococcus* specimens (two *Streptococcus constellatus* and 16 *S. intermedius*) to identify shared microbiological features among cases. Both *S. constellatus* isolates were intermediately resistant to ampicillin, but susceptible to other antimicrobials tested.¶ Nine *S. intermedius* isolates were pan-susceptible. One isolate was resistant to tetracycline only. Four *S. intermedius* isolates displayed a 1.5 μg/mL MIC against vancomycin, slightly above the clinical breakpoint for susceptibility (≤1 μg/mL) and were susceptible to other antimicrobials tested. Two isolates were resistant to multiple antibiotics (erythromycin, clindamycin, and tetracycline) and intermediately resistant to quinupristin-dalfopristin, one of which also displayed a 1.5 μg/mL MIC against vancomycin. Among 15 sequenced *S. intermedius* isolates, the average core genome pairwise distance was approximately 6,200 SNPs, indicating genetic unrelatedness.

Discussion

Nationally representative hospitalizations during January 2016–May 2022, indicate that the number of pediatric brain abscess, epidural empyema, and subdural empyema cases in 2021 were within historical limits. High case counts in March 2022 were consistent with seasonal peaks in cases observed in March since 2016, but not previously reported. Cases declined in April 2022 and reached the median level by May 2022. Based on these findings, initial reports from clinicians (*1*) are consistent with seasonal fluctuations and a redistribution of cases over time during the COVID-19 pandemic. The finding that *S. intermedius* and *S. constellatus* isolates were largely susceptible to tested antimicrobials is consistent with published reports (*7,8*).

Pediatric brain abscess, epidural empyema, and subdural empyema are often preceded by respiratory infection, including in 61.0% of cases reported to CDC, although previous COVID-19 was only reported in 18.2%. The extended period with case numbers below the January 2016–May 2022 median after the onset of the COVID-19 pandemic, followed by a peak in cases during late 2021–early 2022, might reflect altered patterns of respiratory pathogen transmission during the pandemic. Other studies have reported decreased incidences of respiratory and streptococcal infections in children coinciding with the implementation of pandemic-related nonpharmaceutical interventions, which were followed by returns to or rebounds past prepandemic baselines after COVID-19

Summary

What is already known about this topic?

Recent reports have suggested a possible increase in pediatric streptococcal brain abscesses, epidural empyemas, and subdural empyemas.

What is added by this report?

After a decline in cases at the onset of the COVID-19 pandemic, cases increased during summer 2021, peaked in March 2022, and then declined to baseline levels. Clinical presentation and microbiological features were stable during this period.

What are the implications for public health practice?

Initial reports from clinicians are consistent with seasonal fluctuations and a redistribution of cases over time during the COVID-19 pandemic. No evidence of increased case severity, genetic relatedness of streptococcal isolates from different cases, or increased antimicrobial resistance was identified. Epidemiologic monitoring is continuing.

mitigation measures were relaxed (*9,10*). Pediatric brain abscesses and empyemas are serious infections always requiring hospitalization; thus, it is unlikely that the observed trends are the result of altered detection of cases from disruptions to the medical system during the COVID-19 pandemic.

The findings in this report are subject to at least five limitations. First, microbiologic etiology could not be identified from the PHIS hospitalization data. Second, PHIS data reported case numbers, not rates over time. Third, PHIS data from tertiary children's hospitals might not reflect all hospitals admitting children. Fourth, levels of completeness of case report form variables from CDC's call for cases varied. Whereas COVID-19 diagnosis before hospitalization was of particular interest, this information might not have been reliably available to medical record abstractors. Finally, selection bias could have occurred in the identification and reporting of cases from CDC's call for cases. In particular, the phrasing of the call for cases, which highlighted streptococcal species as a potential etiology, might have resulted in underreporting of cases with other etiologies.

Through collaboration with state and local health departments, clinicians, laboratorians, and academic partners, this investigation examined multiyear nationally representative hospitalization data, a large case series with detailed clinical information, and microbiologic features of *Streptococcus* sp. isolated from patients with a diagnosis of brain abscess, epidural empyema, or subdural empyema. After a comparative increase in cases from previous years that began in summer 2021, no evidence of increased case severity, genetic relatedness of streptococcal isolates from different cases, or antimicrobial resistance beyond what is typical for streptococcal species was identified. Case numbers peaked in March 2022, consistent with historical, seasonal fluctuations and declined to baseline

¶ Antimicrobials tested include ampicillin, cefotaxime, ceftriaxone, chloramphenicol, clindamycin, daptomycin, erythromycin, levofloxacin, linezolid, meropenem, penicillin, quinupristin-dalfopristin, tetracycline, and vancomycin.

in subsequent months. CDC will continue to work with investigation partners to monitor ongoing trends in pediatric brain abscesses and empyemas.

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Use of 15-Valent Pneumococcal Conjugate Vaccine Among U.S. Children: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022

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The 13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar 13, Wyeth Pharmaceuticals, Inc, a subsidiary of Pfizer, Inc]) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23 [Merck Sharp & Dohme LLC]) have been recommended for U.S. children, and the recommendations vary by age group and risk group (1,2). In 2021, 15-valent pneumococcal conjugate vaccine (PCV15 [Vaxneuvance, Merck Sharp & Dohme LLC]) was licensed for use in adults aged ≥18 years (3). On June 17, 2022, the Food and Drug Administration (FDA) approved an expanded usage for PCV15 to include persons aged 6 weeks–17 years, based on studies that compared antibody responses to PCV15 with those to PCV13 (4). PCV15 contains serotypes 22F and 33F (in addition to the PCV13 serotypes) conjugated to CRM197 (genetically detoxified diphtheria toxin). On June 22, 2022, CDC's Advisory Committee on Immunization Practices (ACIP) recommended use of PCV15 as an option for pneumococcal conjugate vaccination of persons aged <19 years according to currently recommended PCV13 dosing and schedules (1,2). ACIP employed the Evidence to Recommendation (EtR) Framework,* using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)† approach to guide its deliberations regarding use of these vaccines. Risk-based recommendations on use of PPSV23 for persons aged 2–18 years with certain underlying medical conditions§ that increase the risk for pneumococcal disease have not changed.

The 7-valent pneumococcal conjugate vaccine (PCV7 [Prevnar, Wyeth Pharmaceuticals, Inc.]) was the first pneumococcal conjugate vaccine recommended for U.S. children in 2000 and was replaced by PCV13 in 2010. PCV13 was licensed by FDA based on safety and immunogenicity data compared with PCV7, and systematic reviews have shown that PCV13 is effective against acute otitis media, pneumonia, and invasive pneumococcal disease (IPD) in children (5–7). PCV13 has been recommended for routine use among all children aged 2–59 months. In addition, risk-based use of PCV13 is recommended for children aged 60–71 months with certain underlying medical conditions that increase the risk for pneumococcal disease (hereafter, risk conditions), and for persons aged 6–18 years with an immunocompromising condition,¶ cerebrospinal fluid leak, or cochlear implant (a subset of risk conditions). PPSV23 is only recommended for persons aged 2–18 years with risk conditions.

During February–June 2022, ACIP reviewed the epidemiology of pneumococcal disease and considerations for use of PCV15 in children. The ACIP Pneumococcal Vaccines Work Group evaluated the quality of evidence for PCV15 immunogenicity and safety, using the GRADE approach. Applying the EtR Framework, the Work Group reviewed relevant scientific evidence regarding the benefits and harms of PCV15 use among children who are recommended to receive PCV13. Within the EtR framework, ACIP considered the importance of the public health problem, benefits and harms, the target population's values and preferences, resource use, equity, acceptability, and feasibility of PCV15 use. After a systematic review of the literature, the Work Group defined critical outcomes and used GRADE to assess certainty of evidence rated on a scale of 1 (high certainty) to 4 (very low certainty).**

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* https://www.cdc.gov/vaccines/acip/recs/grade/downloads/acip-evidence-recs-framework.pdf
† https://www.cdc.gov/vaccines/acip/recs/grade/about-grade.html
§ Cerebrospinal fluid leak; chronic heart disease; chronic lung disease; cochlear implant; diabetes mellitus; immunocompromising conditions (chronic renal failure or nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease and other hemoglobinopathies).

¶ Chronic renal failure or nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease and other hemoglobinopathies.
** https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV15-child.html; https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV15-child-risk-based.html

Evidence

Pneumococcal Disease Incidence in Persons Aged <19 Years

Acute otitis media is one of the most common diagnoses associated with outpatient pediatric medical visits (*8*) and antibiotic prescribing (*9*). According to a recent analysis using administrative data, 20,800 all-cause acute otitis media episodes per 100,000 person-years occurred among U.S. persons aged <18 years during 2018, with a higher incidence in younger age groups (*10*). During 2015–2019, in a cohort of 319 U.S. children aged 6–36 months with clinically diagnosed acute otitis media, *Streptococcus pneumoniae* was detected in the middle ear fluid of 24% (*11*); 9% of these children were infected with a PCV13 serotype (including 6C), and 8% with one of the serotypes included in PCV15 but not in PCV13 (serotypes 22F and 33F) (*11*). Additional analysis using administrative data estimated that among persons aged <18 years, 1,280 to 3,990 episodes of health care utilization per 100,000 person-years occurred in 2014 for all-cause pneumonia (*12*), and that during 2018–2019, 87 to 680 hospitalizations per 100,000 population occurred for all-cause pneumonia (*13*). Using population-based surveillance data, *S. pneumoniae* was detected in 4% of persons aged <18 years who were hospitalized with community-acquired pneumonia; the attributable proportion of pneumococcus and serotype distribution among all-cause pneumonia in children and adolescents, however, has not been determined (*14*). According to U.S. multistate surveillance, the incidence of IPD[††] during 2018–2019 was 7.2 per 100,000 children aged <5 years and 1.5 per 100,000 persons aged 5–18 years. PCV13-serotypes accounted for 21% and 34% of IPD cases in children aged <5 years and persons aged 5–18 years, respectively; similarly, additional serotypes unique to PCV15[§§] caused 15% and 23% of IPD in children aged <5 years and persons aged 5–18 years, respectively (*15*).

PCV15 Immunogenicity

Phase II and III randomized controlled trials (RCTs) evaluated the immunogenicity of PCV15 compared with PCV13 in healthy infants and children (*16–19*), persons aged 5–17 years with sickle cell disease (*20*), and persons aged 6–17 years living with HIV infection (*21*). The following outcomes were measured 30 days after administration of ≥1 doses of PCV, as specified in the respective study protocols: serotype-specific immunoglobulin G (IgG) geometric mean concentration (GMC) (*16–21*), proportion of participants meeting the serotype-specific IgG value of ≥0.35 μg/mL (response rate) (*16–19*), and opsonophagocytic activity geometric mean titer in a subset of the study population (*17,20,21*). One of the phase III RCTs enrolled healthy children aged 42–90 days who received PCV13 or PCV15 at ages 2, 4, 6, and 12–15 months. Except for serotype 6A GMC ratio after dose 3, PCV15 met criteria for noninferiority[¶¶] to PCV13 for the 13 shared serotypes regarding the response rate after dose 3 and GMC ratio after dose 3 and after dose 4. PCV15 elicited statistically significantly higher immune response for serotype 3 than for PCV13 (*17*). PCV15 met the noninferiority criteria compared with PCV13 for the two unique serotypes 22F and 33F (*17*).

Another phase III RCT enrolled healthy children aged 42–90 days who were randomized to five different arms that received 0–4 doses of PCV15 in combination with PCV13 to complete their 4-dose PCV series, to assess interchangeable use of PCV13 and PCV15 (*19*). IgG GMCs for the 13 shared serotypes measured after dose 4 in children who received ≥1 dose of PCV15 were generally comparable to those in children who completed their PCV series with PCV13 only. Among PCV-naïve or partially vaccinated persons aged 7 months–17 years who received catch-up PCV doses, PCV15 elicited IgG GMCs comparable to PCV13 for the 13 shared serotypes (*18*). Among children with sickle cell disease, a dose of PCV15 elicited higher IgG GMC for six of 13 shared serotypes and for the two unique serotypes (*20*). Among children living with HIV infection, a dose of PCV15 elicited higher IgG GMC for eight of 13 shared serotypes and for the two unique serotypes, compared with a dose of PCV13; 1 dose of PCV15 followed by PPSV23 8 weeks later elicited higher IgG GMC for three of 13 shared serotypes compared with a dose of PCV13 followed by PPSV23, although IgG GMC for 22F and 33F were lower in those who received PCV15 followed by PPSV23 than in those who received PCV13 followed by PPSV23 (*21*).

[††] The case definition used by CDC's Active Bacterial Core surveillance is isolation of *S. pneumoniae* from a normally sterile site or pathogen-specific nucleic acid in a specimen obtained from a normally sterile body site using a validated molecular test. https://www.cdc.gov/abcs/methodology/case-def-ascertain.html

[§§] Serotypes 22F and 33F, in addition to PCV13 serotypes.

[¶¶] Noninferiority for the 13 shared serotypes with PCV13 requires the lower bound of the 2-sided 95% CI for IgG GMC ratio (V114/PCV13) to be >0.5 (1-sided p<0.025) after dose 3 or after dose 4, or the lower bound of the 2-sided 95% CI for the difference in response rates (V114 –PCV13) to be >–10 percentage points (1-sided p<0.025) after dose 3, where the responders are defined as IgG ≥0.35 μg/mL. Noninferiority for the two unique serotypes 22F and 33F requires the lower bound of the 2-sided 95% CI for the difference in response rates (PCV15-PCV13) after dose 3 or after dose 4 to be >–10 percentage points (1-sided p<0.025) compared with lowest observed response rate in PCV13 excluding serotype 3, or the lower bound of the 2-sided 95% CI for IgG GMC ratio (PCV15/PCV13) compared with lowest observed IgG GMC in PCV13 excluding serotype 3 to be >0.5 (1-sided p<0.025).

PCV15 Safety

Safety of PCV15 was assessed in seven RCTs with 4,778 persons aged 6 weeks–17 years who received ≥1 dose of PCV15 (*16–23*). Two of these RCTs that enrolled children and adolescents with sickle cell disease or HIV infection were assessed separately. Of the remaining five studies that enrolled healthy children, four were also included in the immunogenicity assessment (*16–19*). Three studies included preterm infants born at <37 weeks gestation (*17,19,23*). Across these five studies, four of 4,540 children who received PCV15 developed serious adverse events[***] that were considered to be vaccine-related, compared with one of 2,655 children who received PCV13. The two RCTs that enrolled children with sickle cell disease or HIV infection were both included in the immunogenicity assessment (*20,21*). No serious adverse events that were considered to be vaccine-related were reported in either study.

Given the similarities in the target population and the vaccine schedule used, a detailed safety assessment was performed combining data from three studies of healthy infants who received 4 doses of PCV15 (3,002) or PCV13 (1,467) at ages 2, 4, 6, and 12–15 months (*17,19,22,23*). The most commonly reported adverse events after any PCV dose included irritability (75.1% in the PCV15 group versus 72.7% in the PCV13 group), somnolence (56.7% versus 59.3%), injection site pain (45.1% versus.43.5%), and decreased appetite (39.1% versus 36.0%). Febrile convulsions were reported in eight of 3,002 (0.3%) children who received PCV15, and three of 1,467 (0.2%) who received PCV13. Nearly all (8 of 11, 73%) febrile convulsions occurred ≥50 days after PCV receipt, and none were deemed vaccine-related by study investigators. Adverse events that were considered to be vaccine-related were reported in 89.1% of children who received PCV15 and 86.4% of those in the PCV13 group. Two children (0.1%) who received PCV15 and none who received PCV13 had serious adverse events that were considered to be vaccine-related; both of these children were hospitalized for fever after vaccine administration (after dose 1 and after dose 3). A maximum rectal (or rectal equivalent) temperature of ≥104°F (40°C) within the first 7 days after vaccination was reported for 19 of 2,772 (0.7%) children who received a fourth dose of PCV15 and three of 1,287 (0.2%) who received PCV13.

Cost-Effectiveness

Two economic models (CDC model and Merck model) that assessed cost-effectiveness compared the use of PCV15 and PCV13 according to the currently recommended PCV13 4-dose series for children aged <2 years (*24*). PCV15 and PCV13 were assumed to have the same vaccine effectiveness against disease caused by the 13 serotypes contained in PCV13. For PCV15, the effectiveness against the two additional serotypes was assumed to be comparable to the overall effectiveness against disease caused by the serotypes contained in PCV13. In the CDC model, PCV15 effectiveness against IPD caused by the two additional serotypes was assumed to be 86% and the effectiveness against IPD caused by most of the other serotypes (excluding serotype 3 and 19F) was assumed to be 86%. Effectiveness against serotypes 3 and 19F disease was assumed to be lower than that against the other PCV serotypes (*25*). In the Merck model, PCV15 effectiveness against IPD caused by the two additional serotypes was assumed to be 86% and the effectiveness against the other serotypes was assumed to range from 80% to 100%. In both models, using PCV15 instead of PCV13 for routine vaccination of children was cost-saving[†††] in all scenarios examined, including scenarios in which the PCV15 cost per dose[§§§] ranged from $4 less to $2 more than the PCV13 cost per dose.

Summary

PCV15 as an option for pneumococcal conjugate vaccination is expected to reduce pneumococcal disease incidence in children because it induces immunity against additional disease-causing serotypes. Findings from RCTs suggested that the immunogenicity and safety of PCV15 are generally comparable to those of PCV13. Cost-effectiveness studies demonstrated that routine use of PCV15 for children aged <2 years was cost-saving, assuming that the cost and effectiveness of PCV15 for the 13 shared serotypes will remain comparable to those of PCV13 and that PCV15 will provide protection against the two additional serotypes. A summary of Work Group deliberations on use of PCV15 as an option for pneumococcal conjugate vaccination is available in the EtR tables.[¶¶¶]

[***] Serious adverse events were defined as any untoward medical occurrence that, at any dose, resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; or was another important medical event. https://clinicaltrials.gov/ProvidedDocs/71/NCT03692871/Prot_SAP_000.pdf

[†††] The use of PCV15 had lower overall costs and improved health outcomes relative to the use of PCV13.

[§§§] Cost per dose was a weighted average of public and private dose costs from the CDC vaccine price list and from the information provided by Merck.

[¶¶¶] https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV15-child-risk-based-etr.html;https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV15-child-etr.html

Recommendations for Use of PCV

ACIP recommends use of PCV (either PCV13 or PCV15) for all children aged 2–59 months. In addition, risk-based PCV use is recommended for children aged 60–71 months with risk conditions, and persons aged 6–18 years with an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant. For all recommendations, PCV13 and PCV15 can be used interchangeably. Interruption of the vaccination schedule does not require reinstitution of the entire series or the addition of extra doses.

Persons Aged <19 Years with No Previous PCV13 or PCV15 Vaccination

Infants aged 2–6 months. Four doses of PCV (either PCV13 or PCV15) are recommended. The primary infant series consists of 3 doses of PCV. Infants receiving their first dose at age ≤6 months should receive 3 doses of PCV at intervals of approximately 8 weeks (with a minimum interval of 4 weeks). The fourth (booster) dose is recommended at age 12–15 months and ≥8 weeks after the third dose (Table 1).

Infants should begin the schedule at age 2 months, although the first dose can be administered as early as 6 weeks. For prematurely born infants (i.e., <37 weeks' gestation) who are medically stable enough to be vaccinated (26), PCV should be administered at the recommended age concurrent with other routine vaccinations.

Infants aged 7–11 months. When PCV is initiated at age 7–11 months, 3 doses (either PCV13 or PCV15) are recommended. The first 2 doses should be administered with an interval of ≥4 weeks between doses. The third dose should be administered at age 12–15 months, ≥8 weeks after the second PCV dose.

Children aged 12–23 months. When PCV is initiated at 12–23 months of age, 2 doses (either PCV13 or PCV15) are recommended, with an interval of ≥8 weeks between doses.

Children aged 24–71 months. Unvaccinated healthy children aged 24–59 months should receive a single dose of PCV (either PCV13 or PCV15). Unvaccinated children aged 24–71 months with any risk condition should receive 2 doses of PCV (either PCV13 or PCV15) with an interval of ≥8 weeks between doses. Routine use of PCV is not recommended for healthy children aged ≥5 years who have not yet received a dose of PCV.

Children and adolescents aged 6–18 years with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak. If a dose of PCV13 or PCV15 has not been administered previously, a single dose of PCV13 or PCV15 is recommended, regardless of whether the child has previously received PPSV23, even if PCV7 was received.

Persons Aged <19 Years Vaccinated Previously with PCV13 or PCV15

Infants and children aged <24 months. Infants and children aged <24 months who have received ≥1 dose of PCV (either PCV13 or PCV15) should complete the vaccination series with either PCV13 or PCV15 (Table 2).

Children aged 24–71 months. For all healthy children aged 24–59 months with any incomplete PCV schedule as of age 24 months, 1 additional dose of PCV is recommended. For children aged 24–71 months with any risk conditions who have received any incomplete schedule of <3 PCV doses**** before age 24 months, 2 additional PCV doses of PCV are recommended. Children aged 24–71 months with any risk conditions who have received their 3-dose PCV primary series before age 12 months but have not received their fourth booster dose, are recommended to receive a single additional PCV dose. The minimum interval between doses is 8 weeks.

TABLE 1. Recommended schedule for use of pneumococcal conjugate vaccine* among previously unvaccinated infants, children, and adolescents, by age at first vaccination and health status — United States, 2022

Age at first vaccination/Health status	Primary PCV13/PCV15 series*,†	PCV13/PCV15 booster dose*,§
All children		
2–6 mos	3 doses	1 dose at 12–15 mos
7–11 mos	2 doses	1 dose at 12–15 mos
12–23 mos	2 doses	Not indicated
Healthy children		
24–59 mos	1 dose	Not indicated
Children with certain underlying medical conditions¶		
24–71 mos	2 doses	Not indicated
Children and adolescents with an immunocompromising condition,¶ cerebrospinal fluid leak, or cochlear implant		
6–18 yrs	1 dose	Not indicated

Abbreviations: PCV = pneumococcal conjugate vaccine; PCV13 = 13-valent PCV; PCV15 = 15-valent PCV.

* Either PCV13 or PCV15 can be used to complete the recommended PCV series.

† Minimum interval between doses is 8 weeks except for children vaccinated at age <12 months, for whom the minimum interval between doses is 4 weeks. The minimum age for administration of first dose is 6 weeks.

§ Administered ≥8 weeks after the previous PCV13/PCV15 dose.

¶ Certain underlying medical conditions include cerebrospinal fluid leak; chronic heart disease; chronic lung disease; cochlear implant; diabetes mellitus; immunocompromising conditions (chronic renal failure or nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease and other hemoglobinopathies). These children are also recommended to receive 23-valent pneumococcal polysaccharide vaccine.

**** Certain children would be considered to have received a complete schedule, even if the total number of PCV doses received by 24 months is <3 doses; an example is a child who received 2 doses of PCV during age 12–23 months.

Complete PCV13 vaccination. A supplemental dose of PCV15 is not indicated for children who have received 4 doses of PCV13 or who completed another age-appropriate PCV13 schedule.

Administration of PPSV23 After PCV13 or PCV15 Among Persons Aged 2–18 Years with Risk Conditions

Children aged ≥2 years with any risk conditions should receive PPSV23 after completing all recommended PCV doses (either PCV13 or PCV15). These children should receive a single dose of PPSV23 at age ≥2 years and ≥8 weeks after the most recent PCV dose (Table 3). Children who have received PPSV23 but have not yet completed their recommended PCV doses should receive PCV ≥8 weeks after the PPSV23 dose. When elective splenectomy, immunocompromising therapy, or cochlear implant placement is being planned, PCV or PPSV23 vaccination should be completed ≥2 weeks before surgery or initiation of therapy, if possible.

Revaccination with PPSV23 among children with immunocompromising conditions. Children aged ≥2 years who have an immunocompromising condition should receive a second dose of PPSV23 ≥5 years after the first PPSV23 dose.

Recipients of hematopoietic stem cell transplants. Recipients of hematopoietic stem cell transplants are recommended to receive 3 sequential PCV doses followed by a dose of PPSV23 beginning 3–6 months after the transplant, as described in the General Best Practice Guidelines for Immunization (27). In children with graft-versus-host disease, PPSV23 can be replaced with a fourth dose of PCV.

Vaccine Administration

PCV13 and PCV15 are both available in a single-dose prefilled syringe as a 0.5-mL dose administered intramuscularly. Either PCV13 or PCV15 can be administered at the same time as other routine childhood vaccinations, including COVID-19 vaccines (28), in separate syringes and using different injection sites. Concurrent PCV15 administration with vaccines containing diphtheria; tetanus; acellular pertussis; inactivated poliovirus; *Haemophilus influenzae* type b; hepatitis A; hepatitis B; measles, mumps, and rubella; rotavirus; and varicella were studied (17,19). Immunogenicity of these antigens was similar when administered concurrently with PCV15 and PCV13 (17,19). Coadministration of PCV15 with meningococcal vaccines has not been studied. The same precautions used for coadministration of PCV13 and meningococcal vaccines should be applied when PCV15 is used (29). Risk for febrile seizures in children who received PCV15 concurrently with an influenza vaccine has not been studied.

TABLE 2. Recommendations for administering pneumococcal conjugate vaccine* to incompletely vaccinated children, by age at visit, health status, and vaccination history — United States, 2022

Age at visit/Health status	No. of previous PCV13/PCV15 doses received	Recommended PCV13/PCV15 regimen[†]	No. of PCV13/ PCV15 doses to complete series by age 24 mos
All children			
2–6 mos	1	3 additional doses: 2 doses, 8 wks apart; last dose at age 12–15 mos	4
	2	2 additional doses: 1 dose, 8 wks after most recent dose; last dose at age 12–15 mos	4
	3	1 additional dose at age 12–15 mos	4
7–11 mos	1 or 2 (at age <7 mos) or 1 (at age ≥7 mos)	2 additional doses: 1 dose, 8 wks after last dose; last dose ≥8 weeks later, at age 12–15 mos	3 or 4
	3 (at age <7 mos) or 2 (at age ≥7 mos)	1 additional dose at age 12–15 mos	3 or 4
12–23 mos	1 (at age <12 mos)	2 additional doses, ≥8 wks apart	3
	1 (at age ≥12 mos)	1 additional dose, ≥8 wks after most recent dose[†]	2
	2 or 3 (at age <12 mos)	1 additional dose, ≥8 wks after most recent dose	3 or 4
Healthy children			
24–59 mos	Any incomplete schedule by 24 mos	1 additional dose, ≥8 wks after most recent dose	NA
5–18 yrs	Any incomplete schedule by 24 mos	No additional dose	NA
Children with certain underlying medical conditions[§]			
24–71 mos	Any incomplete schedule[¶] of <3 doses by age 24 mos	2 doses: first dose ≥8 wks after most recent dose; second dose ≥8 wks later	NA
	3 (all at age <12 mos)	1 dose, ≥8 wks after most recent dose	NA

Abbreviations: NA = not applicable; PCV = pneumococcal conjugate vaccine; PCV13 = 13-valent PCV; PCV15 = 15-valent PCV.
* Either PCV13 or PCV15 can be used to complete the recommended PCV series.
† Minimum interval between doses is 8 weeks except for children vaccinated at age <1 year, for whom minimum interval between doses is 4 weeks.
§ Certain underlying medical conditions include cerebrospinal fluid leak; chronic heart disease; chronic lung disease; cochlear implant; diabetes mellitus; immunocompromising conditions (chronic renal failure or nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease and other hemoglobinopathies). These children are also recommended to receive 23-valent pneumococcal polysaccharide vaccine.
¶ See column "No. of PCV13/ PCV15 doses to complete series by age 24 mos" to determine an incomplete schedule of <3 doses by 24 months.

Summary

What is already known about this topic?

Currently, the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) are recommended for U.S. children, and the recommendations vary by age group and risk group.

What is added by this report?

On June 22, 2022, the Advisory Committee on Immunization Practices recommended use of PCV15 as an option for pneumococcal conjugate vaccination of persons aged <19 years, according to currently recommended PCV13 dosing and schedules. Risk-based recommendations on use of PPSV23 have not changed.

What are the implications for public health practice?

Use of PCV15 as an alternative to PCV13 is expected to further reduce pneumococcal disease incidence in children and adolescents.

Reporting of Adverse Events

Before administering PCV or PPSV23, health care providers should consult relevant package inserts regarding precautions and contraindications (*30–32*). Adverse events occurring after administration of any vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted to VAERS online, by fax, or by mail. More information about VAERS is available at https://vaers.hhs.gov.

Future Research and Monitoring Priorities

CDC and ACIP will continue to assess safety of PCV15; monitor the impact of implementation of new recommendations, including the impact on health equity; and assess postimplementation vaccine effectiveness. CDC and ACIP will update pneumococcal vaccination recommendations as appropriate.

TABLE 3. Risk-based pneumococcal vaccine recommendations for children and adolescents with underlying medical conditions that increase the risk of pneumococcal disease — United States, 2022

Risk group/Condition	PCV* for children aged <6 yrs Recommended	PCV* for persons aged 6–18 yrs Recommended	PPSV23 for children aged ≥2 yrs Recommended	Single revaccination 5 yrs after first dose
Immunocompetent children				
Chronic heart disease[†]	Y	N	Y	N
Chronic lung disease[§]	Y	N	Y	N
Diabetes mellitus	Y	N	Y	N
Cerebrospinal fluid leak	Y	Y	Y	N
Cochlear implant	Y	Y	Y	N
Children with immunocompromising conditions				
Chronic renal failure or nephrotic syndrome	Y	Y	Y	Y
Congenital or acquired asplenia, or splenic dysfunction	Y	Y	Y	Y
Congenital or acquired immunodeficiency[¶]	Y	Y	Y	Y
Diseases and conditions treated with immunosuppressive drugs or radiation therapy**	Y	Y	Y	Y
HIV infection	Y	Y	Y	Y
Sickle cell disease or other hemoglobinopathies	Y	Y	Y	Y
Solid organ transplant	Y	Y	Y	Y

Abbreviations: N = no; PCV = pneumococcal conjugate vaccine; PCV13 = 13-valent PCV; PCV15 = 15-valent PCV; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; Y = yes.
 * Either PCV13 or PCV15 can be used.
 [†] Recommendations are of particular importance for children with cyanotic congenital heart disease and cardiac failure.
 [§] Including asthma if treated with high-dose oral corticosteroid therapy.
 [¶] Includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).
 ** Including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease.

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Mortality Risk Among Patients Hospitalized Primarily for COVID-19 During the Omicron and Delta Variant Pandemic Periods — United States, April 2020–June 2022

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The risk for COVID-19–associated mortality increases with age, disability, and underlying medical conditions (*1*). Early in the emergence of the Omicron variant of SARS-CoV-2, the virus that causes COVID-19, mortality among hospitalized COVID-19 patients was lower than that during previous pandemic peaks (*2–5*), and some health authorities reported that a substantial proportion of COVID-19 hospitalizations were not primarily for COVID-19–related illness,* which might account for the lower mortality among hospitalized patients. Using a large hospital administrative database, CDC assessed in-hospital mortality risk overall and by demographic and clinical characteristics during the Delta (July–October 2021), early Omicron (January–March 2022), and later Omicron (April–June 2022) variant periods† among patients hospitalized primarily for COVID-19. Model-estimated adjusted mortality risk differences (aMRDs) (measures of absolute risk) and adjusted mortality risk ratios (aMRRs) (measures of relative risk) for in-hospital death were calculated comparing the early and later Omicron periods with the Delta period. Crude mortality risk (cMR) (deaths per 100 patients hospitalized primarily for COVID-19) was lower during the early Omicron (13.1) and later Omicron (4.9) periods than during the Delta (15.1) period (p<0.001). Adjusted mortality risk was lower during the Omicron periods than during the Delta period

for patients aged ≥18 years, males and females, all racial and ethnic groups, persons with and without disabilities, and those with one or more underlying medical conditions, as indicated by significant aMRDs and aMRRs (p<0.05). During the later Omicron period, 81.9% of in-hospital deaths occurred among adults aged ≥65 years and 73.4% occurred among persons with three or more underlying medical conditions. Vaccination, early treatment, and appropriate nonpharmaceutical interventions remain important public health priorities for preventing COVID-19 deaths, especially among persons most at risk.

COVID-19 hospitalizations and in-hospital deaths during April 2020–June 2022 were identified from 678 hospitals in the Premier Healthcare Database Special COVID-19 Release (PHD-SR).§ COVID-19 hospitalizations were defined as those with the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code U07.1 (COVID-19, virus identified [laboratory-confirmed]) listed as the primary or secondary discharge diagnosis; a COVID-19 in-hospital death was defined as a COVID-19 hospitalization with expired discharge status. COVID-19 hospitalizations were identified as being primarily for COVID-19 if they had 1) a U07.1 primary discharge diagnosis or 2) a U07.1 secondary discharge diagnosis accompanied by either treatment with remdesivir or a primary discharge diagnosis of sepsis, pulmonary embolism, acute respiratory failure, or pneumonia.¶ Monthly cMRs (deaths per 100 hospitalizations) were calculated for COVID-19

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* Examples include New York (https://www.wivb.com/news/new-york/new-york-state-covid-19-update-saturday-january-22/); Massachusetts (https://www.boston.com/news/coronavirus/2022/01/21/almost-half-of-mass-covid-hospitalizations-are-now-classified-as-incidental-heres-what-that-means/); Marin County, California (https://coronavirus.marinhhs.org/surveillance#keyindicators); and various health systems in Florida, Maryland, and Texas (https://www.nytimes.com/2022/01/04/health/covid-omicron-hospitalizations.html).

† Variant pandemic periods were selected based on two factors: 1) the U.S. epidemic curve for new admissions of patients with confirmed COVID-19 (https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions) and 2) the U.S. variant proportions from SARS-CoV-2 genomic surveillance (https://data.cdc.gov/Laboratory-Surveillance/SARS-CoV-2-Variant-Proportions/jr58-6ysp). Pandemic periods are defined using whole months because of date aggregation in the data source. Variants became the predominant circulating strain (representing >50% of sequenced isolates) during the following weeks: Delta (B.1.617.2) during the week ending June 26, 2021; Omicron B.1.1.529 during the week ending December 25, 2021; and Omicron BA.2 subvariant during the week ending March 26, 2022. Thus, the predominant circulating strains during the early Omicron period were B.1.1.529 and BA.1 and during the later Omicron period were BA.2 and BA.2.12.1.

§ PHD-SR is a large U.S. hospital-based all-payor database (http://offers.premierinc.com/rs/381-NBB-525/images/PHD_COVID-19_White_Paper.pdf), in which patient records are linked by a unique identifier within, but not across, hospital systems. This analysis included data from 678 hospitals that had at least one inpatient record per month during April 2020–May 2022. Of these, 521 hospitals also had at least one inpatient record during June 2021. PHD-SR data are released every 2 weeks; this study used the August 2, 2022, data release. According to information provided by Premier, Inc., data completeness is estimated to be 37%, 72%, 87%, and 95% during June, May, April, and January–March 2022, respectively.

¶ The definition of hospitalizations primarily for COVID-19 was intended to be relatively simple and replicable and used for monitoring temporal trends. Multiple iterations of the definition were evaluated, such as inclusion of additional primary discharge diagnoses and treatments. This definition was selected for its specificity in identifying patients experiencing COVID-19–related illness. The following ICD-10-CM codes were used to define sepsis (A41.89, A41.9, R65.2*), pneumonia (J12*, J18*), acute respiratory failure (J96.00, J96.01, J96.02, J96.20, J96.21, J96.22, J80, R06.03, R06.9, R09.2), and pulmonary embolism (I27.82, I26*).

hospitalizations (total, primarily for COVID-19, and not primarily for COVID-19) and non–COVID-19 hospitalizations.

Patient-level analyses were conducted by selecting each patient's last hospitalization primarily for COVID-19 during the Delta, early Omicron, and later Omicron periods. For each period, sociodemographic (age, sex, race and ethnicity, and insurance type), clinical (underlying medical conditions, disability status, and previous COVID-19),** disease severity (intensive care unit [ICU] admission, receipt of COVID-19 medications, noninvasive ventilation, and invasive mechanical ventilation [IMV]),†† and hospital (U.S. Census Bureau region and number of beds) characteristics were described for patients hospitalized primarily for COVID-19 and in-hospital deaths, and cMR was calculated. Descriptive analyses were also conducted for three pre-Delta periods (April–September 2020, October 2020–February 2021, and March–June 2021).

Using a generalized estimating equations model, specified as a log-linked binomial regression including all three periods, aMRDs and aMRRs for in-hospital death were estimated across periods (early Omicron versus Delta and later Omicron versus Delta).§§ aMRDs were estimated as the difference in the adjusted predicted mortality risk between periods; aMRRs were estimated as the ratio of adjusted predicted mortality

** Sixteen underlying medical conditions associated with higher risk for severe COVID-19 were assessed: asthma, cerebrovascular disease, cancer, chronic kidney disease, chronic lung disease, chronic liver disease, cystic fibrosis, dementia, diabetes, heart conditions, HIV, mental health disorder, obesity, primary immunodeficiencies, transplantation, and tuberculosis (https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html). Conditions were assessed using ICD-10-CM codes listed either at or before the COVID-19 health care encounter. For each patient, the number of underlying medical conditions was summed and categorized. Presence of a disability was assessed separately from underlying medical conditions and included ICD-10-CM codes for birth defects, developmental disabilities, spinal cord injury, traumatic brain injury, and vision-, hearing-, and mobility-related disabilities. Previous COVID-19 was identified by presence of a COVID-19 diagnosis during an outpatient or inpatient encounter that occurred in the same hospital system ≥90 days before the current diagnosis. COVID-19 vaccination status was not assessed because it was underascertained in PHD-SR.

†† COVID-19 medications included dexamethasone, remdesivir, baricitinib, tofacitinib, tocilizumab, and sarilumab. Noninvasive ventilation included continuous positive airway pressure and bilevel positive airway pressure.

§§ The model included main effects and two-way interactions between pandemic period and the following covariates: age (0–17, 18–34, 35–49, 50–64, 65–79, and ≥80 years), sex (male and female), race and ethnicity (Hispanic or Latino [Hispanic], non-Hispanic White, non-Hispanic Black or African American [Black], non-Hispanic Asian, non-Hispanic other, and unknown), number of underlying medical conditions (0, 1, 2, 3, 4, and ≥5), and presence or absence of a disability. Additional covariates were included in the model without interaction terms: insurance type (commercial, Medicare, Medicaid, self-pay, and other or unknown), prevoius COVID-19, hospital U.S. Census Bureau region (Northeast, Midwest, South, and West), and number of hospital beds (<200, 200–499, and ≥500). Patients with unknown sex were excluded.

risk between periods.¶¶ SEs and 95% CIs were obtained by hospital-patient clustered bootstrapping with 500 replications. Z-tests were used to compare cMR, aMRDs, and aMRRs among pandemic periods; p<0.05 was considered statistically significant. Analyses were conducted using SAS (version 9.4; SAS Institute) and Stata (version 15.1; StataCorp). This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.***

During April 2020–June 2022, a total of 1,072,106 COVID-19 hospitalizations and 128,517 in-hospital deaths were reported in PHD-SR. The proportion of COVID-19 hospitalizations identified as primarily for COVID-19 was relatively stable during the pre-Omicron period (83.8%, 95% CI = 83.7–83.9) and decreased during the Omicron period (62.8%, 95% CI = 62.6–63.0) (Supplementary Figure, https://stacks.cdc.gov/view/cdc/121070). cMR was 1–2 percentage points higher for hospitalizations primarily for COVID-19 than for total COVID-19 hospitalizations through December 2021; the cMR difference increased to 3–3.5 percentage points during the early Omicron period, when the proportion of hospitalizations primarily for COVID-19 and cMRs began decreasing, and returned to 1–2 percentage points in the later Omicron period (Figure).

Among patients hospitalized primarily for COVID-19 who died in-hospital during the Delta, early Omicron, and later Omicron periods, 57.8%, 58.0%, and 51.4%, respectively, were male; 63.8%, 66.8%, and 69.1%, respectively, were non-Hispanic White (White); 53.7%, 73.5%, and 81.9%, respectively, were aged ≥65 years; 15.1%, 22.9%, and 28.9%, respectively, had a disability; and 61.7%, 70.8%, and 73.4%, respectively, had three or more underlying medical conditions (Table 1). In addition, a decreasing proportion of patients who died in-hospital had other indicators of disease severity

¶¶ From the regression, the following average predicted probabilities were obtained 1) the average predicted probability of death with pandemic period set to be later Omicron and all other covariates set to their observed values (PLO), 2) the average predicted probability of death with pandemic period set to be early Omicron and all other covariates set to their observed values (PEO), and 3) the average predicted probability of death with pandemic period set to be Delta and all other covariates set to their observed values (PD). aMRD is the difference in the average predicted probabilities (PLO minus PD and PEO minus PD). aMRR is the ratio of the average predicted probabilities (PLO divided by PD and PEO divided by PD). aMRRs and aMRDs were estimated for the full sample (where all covariates other than pandemic period were set at their observed values) and for each subsample (where the corresponding covariate was set at the specific category and other covariates were set at their observed values).

*** 45 C.F.R. part 46; 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

during the Delta, early Omicron, and later Omicron periods: 76.1%, 64.0%, and 57.2%, respectively, were admitted to ICU; 93.8%, 86.8%, and 76.4%, respectively, received COVID-19 medications; 61.8%, 51.2%, and 35.0%, respectively, received noninvasive ventilation; and 71.9%, 57.6%, and 43.6%, respectively, received IMV.

The cMR among patients hospitalized primarily for COVID-19 was 15.1 during the Delta, 13.1 during the early Omicron, and 4.9 during the later Omicron periods (Table 2); cMR range was 9.9–16.1 during the pre-Delta periods (Supplementary Table, https://stacks.cdc.gov/view/cdc/121069). After adjustment, in-hospital mortality was 0.69 (95% CI = 0.68–0.70) times as likely during the early Omicron period and 0.24 (95% CI = 0.22–0.25) times as likely during the later Omicron period than during the Delta period. Adjusted mortality risk during the early and later Omicron periods was lower than it was during the Delta period for patients aged ≥18 years, males and females, all racial and ethnic groups, persons with and without disabilities, and those with one or more underlying medical conditions, as indicated by
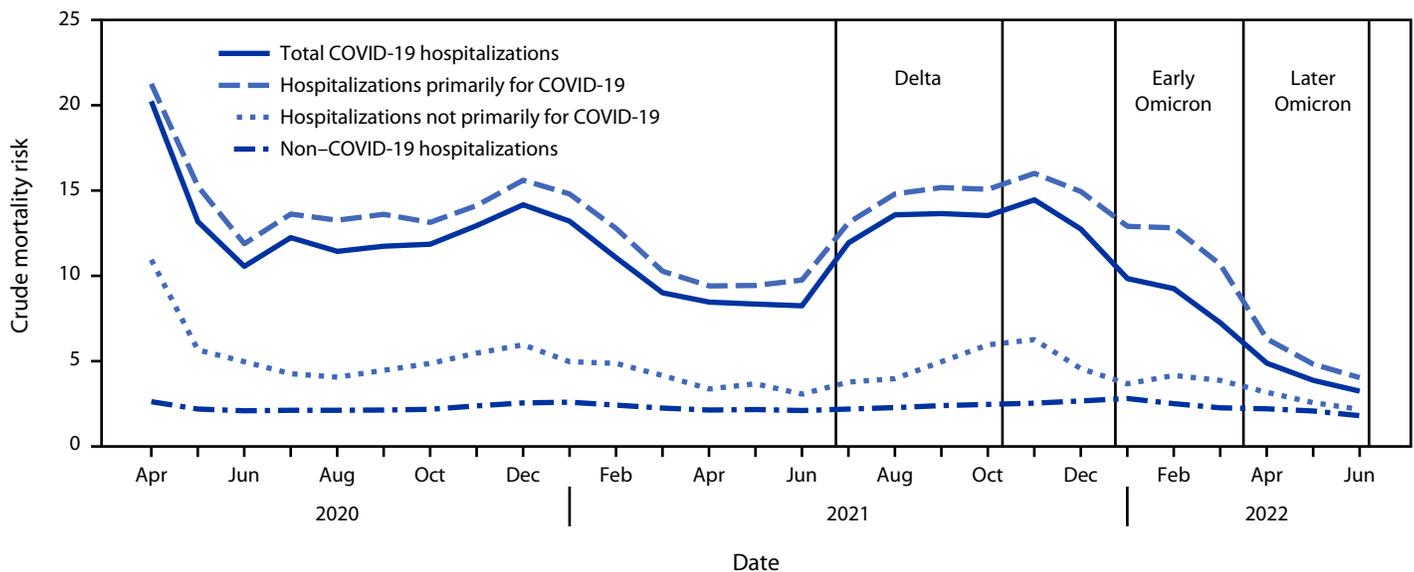
significant aMRDs and aMRRs (p<0.05); mortality risk did not differ between the Omicron and Delta periods for patients aged <18 years. Larger aMRDs were observed with increasing age and number of underlying medical conditions; aMRD and aMRR were similar in magnitude for patients with and without disabilities.

Discussion

During the period of Omicron variant predominance, the crude mortality risk among patients hospitalized primarily for COVID-19 decreased to 4.9% during April–June 2022, which is lower than any previous time in the pandemic and approximately one third of what it was during the period of Delta variant predominance[†††] (5). In-hospital mortality decreased for all patient groups during the Omicron period and a larger proportion of hospitalizations and deaths occurred among populations most at risk for severe disease: patients aged ≥65 years and those with a disability or with three or more

[†††] https://covid.cdc.gov/covid-data-tracker/#hospitalizations-severity (Accessed July 20, 2022).

FIGURE. Crude mortality risk* for total COVID-19 hospitalizations, hospitalizations primarily for COVID-19, hospitalizations not primarily for COVID-19,[†] and non-COVID-19 hospitalizations — Premier Healthcare Database Special COVID-19 Release,[§] United States, April 2022–June 2022[¶]

* In-hospital mortality was defined by a discharge status of expired. Crude mortality risk was calculated as in-hospital deaths per 100 hospitalizations.
[†] Total COVID-19 hospitalizations are those with a primary or secondary discharge diagnosis of COVID-19 (i.e., *International Classification of Diseases, Tenth Revision, Clinical Modification code* of U07.1). Non–COVID-19 hospitalizations are those without a COVID-19 discharge diagnosis. Hospitalizations primarily for COVID-19 had a primary discharge diagnosis of COVID-19 or a secondary discharge diagnosis of COVID-19 accompanied by either treatment with remdesivir or a primary discharge diagnosis of sepsis, pulmonary embolism, acute respiratory failure, or pneumonia. Hospitalizations not primarily for COVID-19 are those that did not meet criteria for a hospitalization primarily for COVID-19.
[§] August 2, 2022, data release. Data are from 678 hospitals that had at least one inpatient record per month during April 2020–May 2022.
[¶] Variant pandemic periods were selected based on two factors: 1) the U.S. epidemic curve for new admissions of patients with confirmed COVID-19 (https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions) and 2) the U.S. variant proportions from SARS-CoV-2 genomic surveillance (https://data.cdc.gov/Laboratory-Surveillance/SARS-CoV-2-Variant-Proportions/jr58-6ysp). Pandemic periods are defined using whole months because of date aggregation in the data source. The Delta variant (B.1.617.2) became the predominant circulating strain (representing >50% of sequenced isolates) during the week ending June 26, 2021, the Omicron B.1.1.529 subvariant became the predominant circulating strain during the week ending December 25, 2021, and the Omicron BA.2 subvariant became the predominant circulating strain during the week ending March 26, 2022. The predominant circulating strains during the early Omicron period were B.1.1.529 and BA.1 and during the later Omicron period were BA.2 and BA.2.12.1.

TABLE 1. Characteristics of patients hospitalized primarily for COVID-19* and in-hospital deaths among patients hospitalized primarily for COVID-19[†] during the Delta, early Omicron, and later Omicron pandemic periods[§] — Premier Healthcare Database Special COVID-19 Release,[¶] United States, July 2021–June 2022

	No. (column %)					
	Delta (Jul–Oct 2021)		**Early Omicron (Jan–Mar 2022)**		**Later Omicron (Apr–Jun 2022)**	
Characteristic	**Hospitalized patients**	**In-hospital deaths**	**Hospitalized patients**	**In-hospital deaths**	**Hospitalized patients**	**In-hospital deaths**
Total patients	**163,094 (100)**	**24,658 (100)**	**104,395 (100)**	**13,701 (100)**	**20,655 (100)**	**1,004 (100)**
Age group, yrs						
0–17	2,219 (1.4)	15 (0.1)	2,073 (2.0)	10 (0.1)	690 (3.3)	6 (0.6)
18–34	14,187 (8.7)	683 (2.8)	4,230 (4.1)	167 (1.2)	875 (4.2)	8 (0.8)
35–49	32,353 (19.8)	3,017 (12.2)	9,453 (9.1)	610 (4.5)	1,415 (6.8)	29 (2.9)
50–64	51,208 (31.4)	7,696 (31.2)	26,258 (25.2)	2,842 (20.7)	3,691 (17.9)	139 (13.8)
65–79	43,707 (26.8)	9,044 (36.7)	38,648 (37.0)	5,896 (43.0)	7,063 (34.2)	371 (37.0)
≥80	19,420 (11.9)	4,203 (17.0)	23,733 (22.7)	4,176 (30.5)	6,921 (33.5)	451 (44.9)
Sex						
Male	85,553 (52.5)	14,241 (57.8)	54,153 (51.9)	7,951 (58.0)	9,978 (48.3)	516 (51.4)
Female	77,541 (47.5)	10,417 (42.2)	50,242 (48.1)	5,750 (42.0)	10,677 (51.7)	488 (48.6)
Race and ethnicity						
Hispanic or Latino	25,730 (15.8)	3,559 (14.4)	13,515 (12.9)	1,696 (12.4)	2,295 (11.1)	88 (8.8)
White, NH	100,601 (61.7)	15,733 (63.8)	67,786 (64.9)	9,151 (66.8)	13,961 (67.6)	694 (69.1)
Black or African American, NH	24,714 (15.2)	3,389 (13.7)	15,713 (15.1)	1,738 (12.7)	2,686 (13.0)	117 (11.7)
Asian, NH	2,575 (1.6)	380 (1.5)	2,098 (2.0)	307 (2.2)	634 (3.1)	34 (3.4)
Other, NH	6,544 (4.0)	1,071 (4.3)	3,673 (3.5)	555 (4.1)	703 (3.4)	46 (4.6)
Unknown	2,930 (1.8)	526 (2.1)	1,610 (1.5)	254 (1.9)	376 (3.8)	25 (2.5)
Insurance type						
Commercial	54,199 (33.2)	5,907 (24.0)	18,548 (17.8)	1,652 (12.1)	2,824 (13.7)	90 (9.0)
Medicare	67,361 (41.3)	13,705 (55.6)	65,874 (63.1)	10,152 (74.1)	14,382 (69.6)	798 (79.5)
Medicaid	23,521 (14.4)	2,722 (11.0)	13,810 (13.2)	1,195 (8.7)	2,446 (11.8)	77 (7.7)
Self-pay	5,966 (3.7)	754 (3.1)	1,780 (1.7)	196 (1.4)	329 (1.6)	9 (0.9)
Other/Unknown	12,047 (7.4)	1,570 (6.4)	4,383 (4.2)	506 (3.7)	674 (3.3)	30 (3.0)
No. of underlying medical conditions**						
0	25,191 (15.4)	704 (2.9)	7,844 (7.5)	246 (1.8)	1,451 (7.0)	9 (0.9)
1	39,060 (23.9)	3,171 (12.9)	16,117 (15.4)	1,262 (9.2)	3,015 (14.6)	87 (8.7)
2	36,200 (22.2)	5,561 (22.6)	20,869 (20.0)	2,494 (18.2)	3,967 (19.2)	171 (17.0)
3	26,944 (16.5)	6,021 (24.4)	20,665 (19.8)	3,149 (23.0)	4,097 (19.8)	216 (21.5)
4	17,416 (10.7)	4,451 (18.1)	16,681 (16.0)	2,809 (20.5)	3,482 (16.9)	216 (21.5)
≥5	18,283 (11.2)	4,750 (19.3)	22,219 (21.3)	3,741 (27.3)	4,643 (22.5)	305 (30.4)
Disability[††]						
Yes	18,654 (11.4)	3,712 (15.1)	21,176 (20.3)	3,144 (22.9)	5,131 (24.8)	290 (28.9)
No	144,440 (88.6)	20,946 (84.9)	83,219 (79.7)	10,557 (77.1)	15,524 (75.2)	714 (71.1)
Previous COVID-19[§§]						
Yes	580 (0.4)	53 (0.2)	1,797 (1.7)	123 (0.9)	860 (4.2)	28 (2.8)
No	162,514 (99.6)	24,605 (99.8)	102,598 (98.3)	13,578 (99.1)	19,795 (95.8)	976 (97.2)
Intensive care unit admission						
Yes	40,818 (25.0)	18,777 (76.1)	22,320 (21.4)	8,766 (64.0)	2,747 (13.3)	574 (57.2)
No	122,276 (75.0)	5,881 (23.9)	82,075 (78.6)	4,935 (36.0)	17,908 (86.7)	430 (42.8)
Medication treatment[¶¶]						
Yes	148,328 (90.9)	23,117 (93.8)	84,459 (80.9)	11,892 (86.8)	14,857 (71.9)	767 (76.4)
No	14,766 (9.1)	1,541 (6.2)	19,936 (19.1)	1,809 (13.2)	5,798 (28.1)	237 (23.6)
Noninvasive ventilation						
Yes	35,680 (21.9)	15,247 (61.8)	18,829 (18.0)	7,013 (51.2)	2,167 (10.5)	351 (35.0)
No	127,414 (78.1)	9,411 (38.2)	85,566 (82.0)	6,688 (48.8)	18,488 (89.5)	653 (65.0)
Invasive mechanical ventilation						
Yes	28,367 (17.4)	17,739 (71.9)	14,049 (13.5)	7,894 (57.6)	1,260 (6.1)	438 (43.6)
No	134,727 (82.6)	6,919 (28.1)	90,346 (86.5)	5,807 (42.4)	19,395 (93.9)	566 (56.4)
Hospital characteristics						
U.S. Census Bureau region***						
Midwest	28,851 (17.7)	3,899 (15.8)	21,567 (20.7)	2,929 (21.4)	4,557 (22.1)	208 (20.7)
Northeast	10,350 (6.3)	1,361 (5.5)	14,090 (13.5)	1,850 (13.5)	4,542 (22.0)	243 (24.2)
South	96,857 (59.4)	15,203 (61.7)	51,701 (49.5)	6,581 (48.0)	8,652 (41.9)	393 (39.1)
West	27,036 (16.6)	4,195 (17.0)	17,037 (16.3)	2,341 (17.1)	2,904 (14.1)	160 (15.9)

See table footnotes on the next page.

TABLE 1. (*Continued***) Characteristics of patients hospitalized primarily for COVID-19* and in-hospital deaths among patients hospitalized primarily for COVID-19† during the Delta, early Omicron, and later Omicron pandemic periods§ — Premier Healthcare Database Special COVID-19 Release,¶ United States, July 2021–June 2022**

| | No. (column %) | | | | | |
| | Delta (Jul–Oct 2021) | | Early Omicron (Jan–Mar 2022) | | Later Omicron (Apr–Jun 2022) | |
Characteristic	Hospitalized patients	In-hospital deaths	Hospitalized patients	In-hospital deaths	Hospitalized patients	In-hospital deaths
No. of hospital beds						
0–199	43,939 (26.9)	5,559 (22.5)	25,537 (24.5)	2,747 (20.0)	4,731 (22.9)	183 (18.2)
200–499	75,271 (46.2)	11,932 (48.4)	49,725 (47.6)	6,892 (50.3)	9,467 (45.8)	478 (47.6)
≥500	43,884 (26.9)	7,167 (29.1)	29,133 (27.9)	4,062 (29.6)	6,457 (31.3)	343 (34.2)

Abbreviation: ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; NH = non-Hispanic.

* Patients hospitalized primarily for COVID-19 had a primary discharge diagnosis of COVID-19 (i.e., ICD-10-CM code of U07.1) or a secondary discharge diagnosis of COVID-19 accompanied by either treatment with remdesivir or a primary discharge diagnosis of sepsis, pulmonary embolism, acute respiratory failure, or pneumonia.

† In-hospital deaths were patients with a discharge status of expired.

§ Variant pandemic periods were selected based on two factors: 1) the U.S. epidemic curve for new admissions of patients with confirmed COVID-19 (https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions) and 2) the U.S. variant proportions from SARS-CoV-2 genomic surveillance (https://data.cdc.gov/Laboratory-Surveillance/SARS-CoV-2-Variant-Proportions/jr58-6ysp). Pandemic periods are defined using whole months because of date aggregation in the data source. The Delta variant (B.1.617.2) became the predominant circulating strain (representing >50% of sequenced isolates) during the week ending June 26, 2021, the Omicron B.1.1.529 subvariant became the predominant circulating strain during the week ending December 25, 2021, and the Omicron BA.2 subvariant became the predominant circulating strain during the week ending March 26, 2022. The predominant circulating strains during the early Omicron period were B.1.1.529 and BA.1 and during the later Omicron period were BA.2 and BA.2.12.1.

¶ August 2, 2022, data release. Data are from 678 hospitals that had at least one inpatient record per month during April 2020–May 2022.

** Sixteen underlying medical conditions associated with higher risk for severe COVID-19 were assessed: asthma, cerebrovascular disease, cancer, chronic kidney disease, chronic lung disease, chronic liver disease, cystic fibrosis, dementia, diabetes, heart conditions, HIV, mental health disorder, obesity, primary immunodeficiencies, transplantation, and tuberculosis (https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html). Conditions were assessed using ICD-10-CM codes listed either at or before the COVID-19 health care encounter. For each patient, the number of underlying medical conditions was summed.

†† Presence of a disability was assessed using ICD-10-CM codes for birth defects, developmental disabilities, spinal cord injury, traumatic brain injury, and vision-, hearing-, and mobility-related disabilities.

§§ Previous COVID-19 was identified by presence of a COVID-19 diagnosis during an outpatient or inpatient encounter that occurred in the same hospital system ≥90 days before the current diagnosis.

¶¶ Patient treated with one of the following COVID-19 medications: dexamethasone, remdesivir, baricitinib, tofacitinib, tocilizumab, or sarilumab.

*** https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf

TABLE 2. Crude mortality risk, adjusted mortality risk difference, and adjusted mortality risk ratio* among patients hospitalized primarily for COVID-19† during the Delta, early Omicron, and later Omicron pandemic periods§ — Premier Healthcare Database Special COVID-19 Release,¶ United States, July 2021–June 2022

| | Crude mortality risk | | | Early Omicron versus Delta** | | Later Omicron versus Delta** | |
Characteristic	Delta (Jul–Oct 2021)	Early Omicron (Jan–Mar 2022)	Later Omicron (Apr–Jun 2022)	Adjusted mortality risk difference (95% CI)	Adjusted mortality risk ratio (95% CI)	Adjusted mortality risk difference (95% CI)	Adjusted mortality risk ratio (95% CI)
Overall	15.1	13.1	4.9	−5.3 (−5.5 to −5.0)††	0.69 (0.68 to 0.70)††	−12.8 (−13.2 to −12.5)††	0.24 (0.22 to 0.25)††
Age group, yrs							
0–17	0.7	0.5	0.9	−0.5 (−1.4 to 0.5)	0.64 (0.07 to 1.21)	0.5 (−1.3 to 2.4)	1.42 (−0.12 to 2.96)
18–34	4.8	3.9	0.9	−2.2 (−3.0 to −1.4)††	0.67 (0.56 to 0.78)††	−5.7 (−6.7 to −4.6)††	0.17 (0.03 to 0.31)††
35–49	9.3	6.5	2.0	−5.3 (−6.0 to −4.7)††	0.55 (0.51 to 0.60)††	−9.9 (−10.8 to −9.0)††	0.18 (0.11 to 0.24)††
50–64	15.0	10.8	3.8	−6.3 (−6.8 to −5.7)††	0.62 (0.60 to 0.65)††	−13.1 (−13.7 to −12.4)††	0.21 (0.18 to 0.24)††
65–79	20.7	15.3	5.3	−5.8 (−6.3 to −5.3)††	0.70 (0.68 to 0.72)††	−14.9 (−15.5 to −14.3)††	0.24 (0.21 to 0.26)††
≥80	21.6	17.6	6.5	−3.2 (−3.9 to −2.5)††	0.83 (0.80 to 0.86)††	−13.1 (−13.9 to −12.3)††	0.31 (0.28 to 0.34)††
Sex							
Male	16.5	14.7	5.2	−5.9 (−6.3 to −5.5)††	0.69 (0.67 to 0.71)††	−14.7 (−15.2 to −14.3)††	0.22 (0.20 to 0.24)††
Female	13.4	11.4	4.6	−4.6 (−5.0 to −4.3)††	0.68 (0.66 to 0.70)††	−10.9 (−11.3 to −10.4)††	0.26 (0.23 to 0.28)††
Race and ethnicity							
Hispanic or Latino	13.8	12.5	3.8	−6.9 (−7.7 to −6.1)††	0.64 (0.60 to 0.67)††	−15.8 (−16.7 to −14.9)††	0.18 (0.14 to 0.21)††
White, NH	15.6	13.5	5.0	−4.8 (−5.1 to −4.5)††	0.70 (0.69 to 0.72)††	−12.3 (−12.8 to −11.9)††	0.24 (0.22 to 0.26)††
Black or African American, NH	13.7	11.1	4.4	−5.6 (−6.2 to −5.0)††	0.65 (0.61 to 0.68)††	−11.7 (−12.6 to −10.8)††	0.26 (0.21 to 0.31)††
Asian, NH	14.8	14.6	5.4	−6.0 (−8.2 to −3.7)††	0.68 (0.59 to 0.78)††	−14.5 (−16.9 to −12.1)††	0.23 (0.15 to 0.31)††
Other, NH	16.4	15.1	6.5	−5.8 (−7.3 to −4.4)††	0.71 (0.65 to 0.78)††	−14.3 (−16.2 to −12.3)††	0.30 (0.21 to 0.38)††
Unknown	18.0	15.8	6.6	−7.8 (−10.1 to −5.4)††	0.67 (0.58 to 0.75)††	−17.2 (−20.0 to −14.4)††	0.26 (0.16 to 0.36)††

See table footnotes on the next page.

TABLE 2. (*Continued*) Crude mortality risk, adjusted mortality risk difference, and adjusted mortality risk ratio* among patients hospitalized primarily for COVID-19[†] during the Delta, early Omicron, and later Omicron pandemic periods[§] — Premier Healthcare Database Special COVID-19 Release,[¶] United States, July 2021–June 2022

	Crude mortality risk			Early Omicron versus Delta**		Later Omicron versus Delta**	
Characteristic	Delta (Jul–Oct 2021)	Early Omicron (Jan–Mar 2022)	Later Omicron (Apr–Jun 2022)	Adjusted mortality risk difference (95% CI)	Adjusted mortality risk ratio (95% CI)	Adjusted mortality risk difference (95% CI)	Adjusted mortality risk ratio (95% CI)
No. of underlying medical conditions[§§]							
0	2.8	3.1	0.6	0.7 (0.2 to 1.3)[††]	1.23 (1.06 to 1.41)[††]	−2.4 (−3.1 to −1.7)[††]	0.25 (0.05 to 0.45)[††]
1	8.1	7.8	2.9	−0.9 (−1.4 to −0.3)[††]	0.90 (0.84 to 0.96)[††]	−6.0 (−6.7 to −5.3)[††]	0.32 (0.25 to 0.39)[††]
2	15.4	12.0	4.3	−4.7 (−5.2 to −4.1)[††]	0.71 (0.68 to 0.74)[††]	−12.0 (−12.7 to −11.3)[††]	0.24 (0.21 to 0.28)[††]
3	22.3	15.2	5.3	−8.2 (−8.8 to −7.5)[††]	0.62 (0.60 to 0.65)[††]	−17.3 (−18.0 to −16.5)[††]	0.21 (0.18 to 0.23)[††]
4	25.6	16.8	6.2	−9.2 (−9.9 to −8.4)[††]	0.62 (0.59 to 0.64)[††]	−18.9 (−19.8 to −18.0)[††]	0.21 (0.18 to 0.24)[††]
≥5	26.0	16.8	6.6	−9.2 (−9.9 to −8.4)[††]	0.62 (0.60 to 0.65)[††]	−18.6 (−19.5 to −17.7)[††]	0.23 (0.20 to 0.26)[††]
Disability[¶¶]							
Yes	19.9	14.8	5.7	−5.0 (−5.6 to −4.4)[††]	0.70 (0.67 to 0.73)[††]	−12.4 (−13.1 to −11.6)[††]	0.26 (0.22 to 0.29)[††]
No	14.5	12.7	4.6	−5.3 (−5.6 to −5.1)[††]	0.68 (0.67 to 0.70)[††]	−13.0 (−13.3 to −12.6)[††]	0.23 (0.21 to 0.25)[††]

Abbreviations: ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; NH = non-Hispanic.

* Adjusted mortality risk differences and adjusted mortality risk ratios were estimated by a multivariable generalized estimating equation model specified as log-linked binomial with prediction errors adjusted for clustering at the hospital and patient level. The model included main effects and two-way interactions between pandemic period and the five variables in the table, plus insurance type, previous COVID-19, hospital U.S. Census Bureau region, and number of hospital beds.

[†] Patients hospitalized primarily for COVID-19 had a primary discharge diagnosis of COVID-19 (i.e., ICD-10-CM code of U07.1) or a secondary discharge diagnosis of COVID-19 accompanied by either treatment with remdesivir or a primary discharge diagnosis of sepsis, pulmonary embolism, acute respiratory failure, or pneumonia.

[§] Variant pandemic periods were selected based on two factors: 1) the U.S. epidemic curve for new admissions of patients with confirmed COVID-19 (https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions) and 2) the U.S. variant proportions from SARS-CoV-2 genomic surveillance (https://data.cdc.gov/Laboratory-Surveillance/SARS-CoV-2-Variant-Proportions/jr58-6ysp). Pandemic periods are defined using whole months because of date aggregation in the data source. The Delta variant (B.1.617.2) became the predominant circulating strain (representing >50% of sequenced isolates) during the week ending June 26, 2021, the Omicron B.1.1.529 subvariant became the predominant circulating strain during the week ending December 25, 2021, and the Omicron BA.2 subvariant became the predominant circulating strain during the week ending March 26, 2022. The predominant circulating strains during the early Omicron period were B.1.1.529 and BA.1 and during the later Omicron period were BA.2 and BA.2.12.1.

[¶] August 2, 2022, data release. Data are from 678 hospitals that had at least one inpatient record per month during April 2020–May 2022.

** 95% CIs were calculated using SEs estimated via hospital-patient cluster bootstrap with 500 replications.

[††] p<0.05.

[§§] Sixteen underlying medical conditions associated with higher risk for severe COVID-19 were assessed: asthma, cerebrovascular disease, cancer, chronic kidney disease, chronic lung disease, chronic liver disease, cystic fibrosis, dementia, diabetes, heart conditions, HIV, mental health disorder, obesity, primary immunodeficiencies, transplantation, and tuberculosis (https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html). Conditions were assessed using ICD-10-CM codes listed either at or before the COVID-19 health care encounter. For each patient, the number of underlying medical conditions was summed.

[¶¶] Presence of a disability was assessed using ICD-10-CM codes for birth defects, developmental disabilities, spinal cord injury, traumatic brain injury, and vision-, hearing-, and mobility-related disabilities.

underlying medical conditions.[§§§] Thus, in the later Omicron period, COVID-19 patients at lower risk were hospitalized less often and hospitalized COVID-19 patients at higher risk experienced less severe disease and lower mortality.

Several factors likely contributed to these favorable outcomes during the Omicron period, including higher levels of vaccine- and infection-induced immunity (*6*), advances in early treatment for patients at risk for severe disease,[¶¶¶] and lower pathogenicity of Omicron subvariants (*7*). COVID-19 primary series and booster vaccination coverage was higher during the Omicron period than during the Delta period[****]; the

effectiveness of receipt of 2 or 3 doses of COVID-19 mRNA vaccines against severe illness and death among hospitalized patients was 89% during the Delta period and 86% during the early Omicron period (*8*). In addition, the proportion of the U.S. population with infection-induced antibodies to SARS-CoV-2 increased from 33% in December 2021 to 57% by February 2022, indicating much higher infection-induced protection during the later Omicron period (*9*). Although oral COVID-19 antiviral therapies became available during the early Omicron period, their use increased substantially during the later Omicron period (*10*). These factors also likely contributed to reductions in other measures of disease severity observed during the later Omicron period, such as ICU admission and IMV.

Hospitalizations not primarily for COVID-19 were excluded from this study to allow for temporal comparison of mortality risk among persons hospitalized with COVID-19–related

[§§§] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

[¶¶¶] https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/

[****] https://covid.cdc.gov/covid-data-tracker/#vaccination-trends (Accessed July 20, 2022).

illness. The estimate derived from this study for hospitalizations not primarily for COVID-19 (37%) during January–March 2022 is within the range (12%–48%) reported by other sources derived from heterogeneous definitions and populations[††††] (5). Of note, the observed difference in crude mortality risk between the early Omicron and Delta periods among hospitalizations primarily for COVID-19 was substantially less than the difference among total COVID-19 hospitalizations in this study and in a previous study (2). Thus, variation in the proportion of hospitalizations primarily for COVID-19 should be considered when interpreting past and future studies that compare hospitalization outcomes across pandemic periods.

The findings in this report are subject to at least five limitations. First, the definition of hospitalizations primarily for COVID-19 might be subject to misclassification, which could vary over time with changing patient and contextual factors. Second, COVID-19 vaccination status and previous COVID-19 are both under ascertained in PHD-SR; thus, the effect of SARS-CoV-2 immunity on mortality risk was not assessed. Third, disability status and number of underlying medical conditions might be misclassified because of reliance on ICD-10-CM codes. Fourth, PHD-SR data are incomplete for the later Omicron period; however, effect on mortality risk is expected to be minimal. Finally, although PHD-SR captures approximately 25% of annual U.S. hospital admissions, these findings might not be nationally generalizable.

In-hospital mortality risk was substantially lower during the later Omicron period overall and for older adults, persons with disabilities, and persons with multiple underlying medical conditions, who accounted for a larger proportion of hospitalizations in this period than they did during previous periods and remained at highest risk for death. It is uncertain whether patients with multiple underlying medical conditions are being hospitalized for respiratory complications from COVID-19 or for other acute or chronic conditions potentially exacerbated by SARS-CoV-2 infection. COVID-19–related hospitalizations and mortality should continue to be monitored as protective immunity evolves and new SARS-CoV-2 variants arise to inform public health guidance. Vaccination, early treatment, and appropriate nonpharmaceutical interventions remain important public health priorities to prevent severe COVID-19 illness and death, especially among persons most at risk (1).

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[††††] https://www.governor.ny.gov/news/governor-hochul-updates-new-yorkers-states-progress-combating-covid-19-144; https://www.mass.gov/info-details/covid-19-response-reporting#covid-19-interactive-data-dashboard-

Summary

What is already known about this topic?

Risk for severe COVID-19 increases with age, disability, and underlying medical conditions. The SARS-CoV-2 Omicron variant is more infectious but has been associated with less severe disease.

What is added by this report?

In-hospital mortality among patients hospitalized primarily for COVID-19 decreased from 15.1% (Delta period) to 4.9% (later Omicron period; April–June 2022), despite high-risk patient groups representing a larger proportion of hospitalizations. During the later Omicron period the majority of in-hospital deaths occurred among adults aged ≥65 years (81.9%) and persons with three or more underlying medical conditions (73.4%).

What are the implications for public health practice?

Vaccination, early treatment, and appropriate nonpharmaceutical interventions remain important public health priorities to prevent COVID-19 deaths, especially among persons most at risk.

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Clinical Use of Tecovirimat (Tpoxx) for Treatment of Monkeypox Under an Investigational New Drug Protocol — United States, May–August 2022

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Currently, no Food and Drug Administration (FDA)–approved treatments for human monkeypox are available. Tecovirimat (Tpoxx), however, is an antiviral drug that has demonstrated efficacy in animal studies and is FDA-approved for treating smallpox. Use of tecovirimat for treatment of monkeypox in the United States is permitted only through an FDA-regulated Expanded Access Investigational New Drug (EA-IND) mechanism. CDC holds a nonresearch EA-IND protocol that facilitates access to and use of tecovirimat for treatment of monkeypox.[§] The protocol includes patient treatment and adverse event reporting forms to monitor safety and ensure intended clinical use in accordance with FDA EA-IND requirements. The current multinational monkeypox outbreak, first detected in a country where *Monkeypox virus* infection is not endemic in May 2022, has predominantly affected gay, bisexual, and other men who have sex with men (MSM) (*1,2*). To describe characteristics of persons treated with tecovirimat for *Monkeypox virus* infection, demographic and clinical data abstracted from available tecovirimat EA-IND treatment forms were analyzed. As of August 20, 2022, intake and outcome forms were available for 549 and 369 patients, respectively; 97.7% of patients were men, with a median age of 36.5 years. Among patients with available data, 38.8% were reported to be non-Hispanic White (White) persons, 99.8% were prescribed oral tecovirimat, and 93.1% were not hospitalized. Approximately one half of patients with *Monkeypox virus* infection who received tecovirimat were living with HIV infection. The median interval from initiation of tecovirimat to subjective improvement was 3 days and did not differ by HIV infection status. Adverse events were reported in 3.5% of patients; all but one adverse event were nonserious. These data support the continued access to and treatment with tecovirimat for patients with or at risk for severe disease in the ongoing monkeypox outbreak.

Tecovirimat[¶] is an antiviral drug developed as a medical countermeasure to treat smallpox, a serious and life-threatening infection caused by *Variola virus*, of genus *Orthopoxvirus; Monkeypox virus* belongs to the same genus but typically causes less severe disease.** Global eradication of smallpox was declared by the World Health Assembly in 1980.[††] Because opportunities to develop clinical trials in countries where *Monkeypox virus* infection is considered endemic have been limited, the efficacy of tecovirimat to treat monkeypox has not been fully evaluated in humans. Instead, efficacy data that supported FDA approval of tecovirimat for smallpox were based on nonhuman primate and rabbit studies[§§] (*3*); efficacy studies were also conducted in macaque monkeys and prairie dogs (*4,5*).

During May 2022, a multinational monkeypox virus outbreak (Clade II) was first reported, principally affecting MSM (*1,2*). Interim CDC guidance currently recommends that tecovirimat be considered in patients with severe disease, those at high risk for severe disease, or those with aberrant infections.[¶¶] This report describes the available demographic and clinical characteristics, clinical indications for use, clinical outcomes, and adverse events reported among some of the first known recipients of tecovirimat treatment under the EA-IND protocol for *Monkeypox virus* infection in the United States.

During May 29–July 20, 2022, the EA-IND protocol required patient assessment forms at the start of treatment and once during three follow-up time points (assessment A: day 1–7, assessment B: day 8–14, and assessment C: post-treatment). Initially, the protocol's eligibility criteria included laboratory confirmation of *Monkeypox virus* or *Orthopoxvirus* infection, or a presumptive diagnosis based on clinical signs

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¶ Initially developed by the U.S. government, and, during later stages, in partnership with SIGA Technologies, Incorporated.
** https://www.who.int/health-topics/monkeypox
†† https://www.cdc.gov/smallpox/history/history.html
§§ Animals were challenged, respectively, with *Monkeypox virus* and *Rabbitpox virus.*
¶¶ Aberrant infections involve accidental implantation in eyes, mouth, or other sensitive anatomic areas where *Monkeypox virus* infection might constitute a special hazard (e.g., the genitals or anus). It was previously thought that *Monkeypox virus* infections rarely affected these regions, so the term "aberrant" was used early in the 2022 multinational outbreak. The revised intake form used the phrase "sensitive anatomic areas" as shorthand for the preceding definition. The preferred phrase is "anatomic areas which might result in serious sequelae". https://www.cdc.gov/poxvirus/monkeypox/clinicians/Tecovirimat.html

and symptoms. The revised EA-IND protocol (version 6, dated July 20, 2022) was amended as follows: 1) a patient may be eligible for tecovirimat based on clinical signs and symptoms and if there was an epidemiologic link to a case of or exposure to *Monkeypox virus*, 2) the number of follow-up visits was reduced to one during and one posttreatment, and 3) only reporting of serious adverse events using MedWatch forms was required.*** Data abstracted from patient intake forms included demographic characteristics, orthopoxvirus vaccination status, immune status,[†††] laboratory test result, clinical signs and symptoms, reason for tecovirimat administration (i.e., lesions in sensitive anatomic areas, at risk for severe disease, and pain), formulation at the start of treatment (i.e., intravenous or oral), and number of days from symptom onset to administration of the first dose. Data from clinical outcome forms included whether the patient was hospitalized, number of days from initiation of treatment to subjective improvement, recovery status (i.e., recovered with or without sequelae or not yet recovered), and adverse events during and after treatment. The EA-IND protocol was reviewed and approved by CDC's Institutional Review Board, reviewed and authorized by FDA, and conducted consistent with applicable federal law and CDC policy.[§§§] Analyses were conducted using SAS software (version 9.4; SAS Institute). Difference in time to subjective improvement between HIV-positive and patients without HIV-positive status documented were compared using a 2-sided Wilcoxon rank-sum test; $p < 0.05$ was considered statistically significant.

CDC abstracted data from patient intake forms for 549 persons with confirmed or suspected monkeypox who were prescribed tecovirimat therapy by August 20, 2022, and outcome forms for 369 patients. Data from both intake and outcome forms were available for 174 of these patients. Among 527 patients with intake forms and available data, 515 (97.7%) were male (Table 1). The median age was 36.5 years (IQR = 31.4–43.9 years). Among 464 patients with race and ethnicity data, 180 (38.8%) were White persons, 161 (34.7%) were Hispanic or Latino persons, and 83 (17.9%) were non-Hispanic Black or African American persons. Among 359

*** Serious adverse event (AE) defined as death, life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly/birth defect, or an important medical event that based on appropriate medical judgment might jeopardize the patient and might require medical or surgical intervention to prevent one of the aforementioned outcomes.

[†††] Includes receipt of immunosuppressive therapies and the following categories collected from the investigational new drug protocol paperwork: leukemia, lymphoma, bone marrow or organ transplant, congenital immune defects, or other cancers.

[§§§] 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

TABLE 1. Demographic and clinical characteristics abstracted from intake forms of patients with *Monkeypox virus* infection who received tecovirimat (Tpoxx) under the Food and Drug Administration–regulated Expanded Access Investigational New Drug protocol (N = 549) — United States, May–August 2022

Characteristic (no. missing, unknown, or not specified)	No. (%)
Sex* (22)	
Male	515 (97.7)
Female	12 (2.3)
Age group, yrs (22)	
0–18	5 (0.9)
19–64	518 (98.3)
≥65	4 (0.8)
Median (IQR)	36.5 (31.4–43.9)
Race and ethnicity (85)	
White, non-Hispanic	180 (38.8)
Hispanic or Latino	161 (34.7)
Black or African American, non-Hispanic	83 (17.9)
Asian, non-Hispanic	13 (2.8)
Other, non-Hispanic	11 (2.4)
Unknown race, non-Hispanic	10 (2.2)
Multiple races, non-Hispanic	6 (1.3)
HHS region[†]	
2	141 (25.7)
3	68 (12.4)
4	88 (16.0)
5	36 (6.6)
9	153 (27.9)
Other regions	63 (11.5)
Lifetime history of vaccination against monkeypox or smallpox[§]	
No monkeypox or smallpox vaccination documented	488 (88.9)
JYNNEOS	52 (9.5)
Previous monkeypox or smallpox vaccination reported, but vaccine product unknown	8 (1.5)
ACAM2000	1 (0.2)
Percentage of body affected (190)	
<10	232 (64.6)
10–24	60 (16.7)
25–49	28 (7.8)
50–74	22 (6.1)
75–100	17 (4.7)
Median (IQR)	5 (1–10)
No. of lesions at start of treatment (20)	
<10	210 (39.7)
10–100	299 (56.5)
>100	20 (3.8)
Clinical indication for treatment[¶] (not mutually exclusive) (309)	
Lesions in anatomic areas that might result in serious sequelae**	191 (79.6)
At risk for severe disease	74 (30.8)
Pain	121 (50.4)
Signs and symptoms documented at start of treatment (not mutually exclusive)	
Rash	460 (83.8)
Fever	194 (35.3)
Rectal pain	108 (19.7)
Lymphadenopathy	74 (13.5)
Headache	46 (8.4)
Malaise	35 (6.4)
Immune status	
HIV-positive	254 (46.3)
Other immunocompromising condition[††]	7 (1.3)
No immunocompromising condition reported	288 (52.5)

See table footnotes on the next page.

TABLE 1. (Continued) Demographic and clinical characteristics abstracted from intake forms of patients with *Monkeypox virus* infection who received tecovirimat (Tpoxx) under the Food and Drug Administration–regulated Expanded Access Investigational New Drug protocol (N = 549) — United States, May–August 2022

Characteristic (no. missing, unknown, or not specified)	No. (%)
Route of administration (54)	
Oral	494 (99.8)
Intravenous	1 (0.2)
Days from exposure to onset of first symptoms (319)	
Median (IQR)	7.0 (4–9)
Days from onset of first symptoms to first dose (105)	
Median (IQR)	7.0 (5–10)

Abbreviation: HHS = U.S. Department of Health and Human Services.

* The initial intake form captured sex without any other qualification, and the revised version of the form captured sex as "sex assigned at birth." These two variables were combined to form the variable "sex"; therefore, some patients might have been misclassified.
† HHS region 2 = New Jersey and New York; region 3 = District of Columbia, Maryland, Pennsylvania, and Virginia; region 4 = Alabama, Florida, Georgia, North Carolina, South Carolina, and Tennessee; region 5 = Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin; region 9 = Arizona, California, Hawaii, and Nevada; other regions combined = HHS region 1 (Connecticut, Massachusetts, and Rhode Island), HHS Region 6 (Arkansas, Louisiana, and Texas), HHS region 7 (Iowa, Kansas, Missouri, and Nebraska), HHS region 8 (Colorado), and HHS region 10 (Idaho, Oregon, and Washington).
§ Vaccination status was assessed by medical record and patient questionnaire, not by physical exam, so those unaware of vaccination status, even those with a scar from Dryvax, might have been missed.
¶ Clinical indication was only captured on the revised intake form; therefore, the denominator is reduced (240 revised intake forms with nonmissing data).
** Lesions in anatomic areas that might result in serious sequelae (e.g., eye, genitals, and oral mucosa) were not described in the form but reported based on the treating clinician's assessment based on the phrase "lesions in sensitive anatomical areas."
†† Includes receipt of immunosuppressive therapies and the following categories collected from the investigational new drug protocol paperwork: leukemia, lymphoma, bone marrow or organ transplant, congenital immune defects, or other cancers.

patients with available data, approximately two thirds (232, 64.6%) of tecovirimat recipients had lesions affecting <10% of their body; 17 (4.7%) had lesions affecting 75%–100% of their body. Among 529 patients with available data on number of lesions, 299 (56.5%) reported 10–100 lesions at the start of tecovirimat; 210 (39.7%) had fewer than 10 lesions, and 20 (3.8%) had more than 100 lesions. The presence of lesions in anatomic areas that might result in serious sequelae was reported on 191 (79.6%) of the 240 revised intake forms with available data. The most frequently reported underlying medical condition affecting immune status was HIV infection (254, 46.3%); viral load and CD4 count were not reported. Among 495 persons with available data on route of administration, the oral formulation of tecovirimat was prescribed to 494 (99.8%) at the start of therapy. Median interval from symptom onset to receipt of first tecovirimat dose was 7 days (IQR = 5–10 days) (Figure). Among 260 persons with revised intake forms, 124 (47.7%) had laboratory-confirmed *Orthopoxvirus* infection when tecovirimat treatment commenced.

Among 369 patients with outcome forms, data on hospitalization status was available for 331; among these, 23 (6.9%) were hospitalized after symptom onset (Table 2), and the median duration of hospitalization was 4 days (IQR = 1–5 days). Among 255 patients with available data, the median time to subjective improvement after starting treatment was 3 days (IQR = 2–4 days).¶¶¶ Among 317 patients with available outcome information, 230 (72.6%) recovered with or without sequelae**** by or before completion of the posttreatment assessment; 87 (27.4%) patients were reported by clinicians to be not yet recovered, 78 of whom had not yet completed the standard 14-day tecovirimat treatment course. Adverse events were reported for 12 (3.5%) of 340 patients with information on adverse events; these included headache (three), nausea (two), visual disturbance (two), weakness (two), and hospitalization for psychiatric reasons (one).†††† At the time of the posttreatment follow-up visit, three (2.2%) of 137 persons with information available had developed new lesions compared with 25 (13.1%) who had developed new lesions during the first week of treatment. Most (119, 89.5%) patients reported that all lesions were crusted and healing with a new layer of skin under the scab following treatment. Among 174 patients with available data, the interval to subjective improvement did not differ between HIV-positive persons (42; median = 3 days) and persons without documentation of HIV positive status (64; median = 3 days) with available data (p = 0.83).

Discussion

The data in this report support the continued availability of tecovirimat in the current monkeypox outbreak for U.S. patients with laboratory-confirmed or clinically diagnosed monkeypox. Initial findings indicate that tecovirimat is likely well tolerated; among reported adverse events, most were not serious, and it is not known whether tecovirimat caused the adverse events reported. The preliminary safety reporting with tecovirimat use under the EA-IND is consistent with data from the healthy human tecovirimat safety studies (SIGA-246–001).§§§§ Two other investigational treatments for orthopoxviruses, cidofovir and brincidofovir, have demonstrated substantial toxicity with limited efficacy data (6).

For patients treated under the EA-IND protocol and included in this report, the median time to subjective improvement was 3 days after receiving tecovirimat. However, no control group

¶¶¶ Time to first observed (including patient-reported) improvement.
**** Per clinical judgment of the treating provider.
†††† All adverse events included headache (three), nausea (two), visual disturbance (two), weakness (two), vomiting (one), asymptomatic elevated liver function tests (one), depression with suicidality (one), rash (one), hives (one), numbness (one), fatigue (one), and dizziness (one).
§§§§ https://www.clinicaltrials.gov/ct2/show/NCT02474589

was available for comparison; therefore, no conclusions can be drawn regarding the effectiveness of tecovirimat to treat monkeypox based on these data. Time to improvement did not differ significantly with HIV infection status. A report from Nigeria suggested that HIV-positive patients might have prolonged illness; however, illness severity could be affected by HIV viral suppression, which was not reported in the current evaluation (7). Three of 137 patients (2.2%) with posttreatment follow-up and available data developed new lesions after completing treatment. A retrospective study in the United Kingdom reported one patient treated with tecovirimat had a shorter duration of illness compared with six patients (8), and another report of a small U.S. cohort treated with tecovirimat (also under the EA-IND) demonstrated complete resolution of lesions by day 21 in 23 (92%) of 25 patients (9).

This report illustrated that many patients were prescribed tecovirimat for lesions in anatomic areas that might result in serious sequelae, and nearly all received tecovirimat as outpatients, suggesting that severe disease was uncommon. The demographic characteristics of patients who received tecovirimat are similar to those with monkeypox: as described recently by CDC: the first 3,000 reported monkeypox infections in the United States occurred almost exclusively (99%) in men, with a median age of 35 years; approximately 40% were in White persons; and 41% of patients were living with HIV infection (1). Approximately one half of patients described in the EA-IND data did not have laboratory confirmation of

Monkeypox virus infection and received tecovirimat empirically; because it is currently not known which patients benefit most from tecovirimat treatment, clinical judgment is important. Although this report could not evaluate efficacy, clinicians are encouraged to continue following CDC guidelines for tecovirimat use in patients with severe disease or at risk for severe disease. Because there is the potential for false-positive test results, tecovirimat should be considered only in those with a high pretest probability of being infected with *Monkeypox virus* to avoid unnecessary treatment or implementation of

Summary

What is already known about this topic?

Tecovirimat (Tpoxx) was approved by the Food and Drug Administration for treatment of smallpox based on data obtained from animal models; there are no safety or efficacy data regarding its use in patients with *Monkeypox virus* infection.
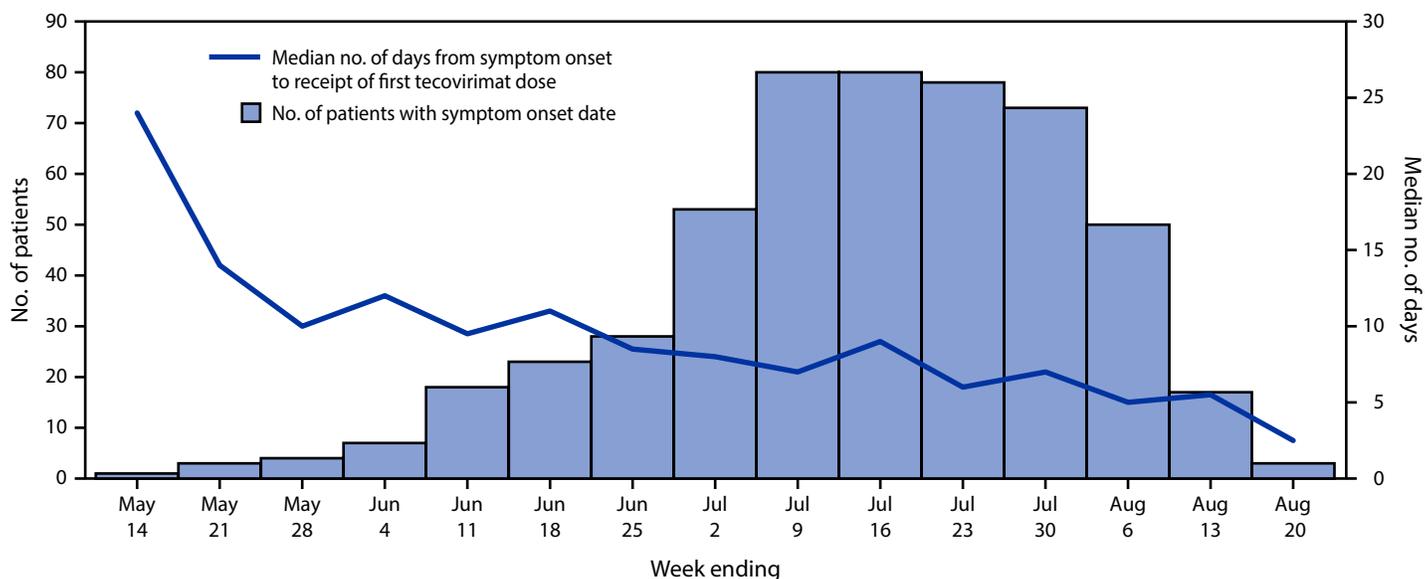
What is added by this report?

Among 549 patients with *Monkeypox virus* infection treated with tecovirimat under an Expanded Access Investigational New Drug protocol, 99.8% received it orally as an outpatient. Among 369 patients, few adverse events were reported.

What are the implications for public health practice?

Tecovirimat is generally well tolerated, and these data support continued access to treatment with tecovirimat during the current monkeypox outbreak.

FIGURE. Interval from symptom onset to receipt of first tecovirimat (Tpoxx) dose* among symptomatic patients with *Monkeypox virus* infection treated under the Food and Drug Administration–regulated Expanded Access Investigational New Drug protocol (N = 518)[†] — United States, May–August 2022

* Calculated from nonmissing values (444).
[†] Overall, 31 patients with missing symptom onset date were excluded.

TABLE 2. Clinical outcomes abstracted from outcome forms of patients with *Monkeypox virus* infection who received tecovirimat (Tpoxx) under the Food and Drug Administration–regulated Expanded Access Investigational New Drug protocol (N = 369) — United States, May–August 2022

Outcome (no. unknown or missing)	No. (%)
Hospitalized (38)	
Yes*	23 (6.9)
Intensive care unit*	2 (0.6)
No	308 (93.1)
Outcome† (52)	
Recovered without sequelae	189 (59.6)
Recovered with sequelae	41 (12.9)
Not yet recovered	87 (27.4)
Days to subjective improvement§ (114)	
Median, days (IQR)	3.0 (2–4)
Adverse event¶ (29)	
Yes	12 (3.5)
No	328 (96.5)
Median no. of days to follow up after treatment initiation (IQR)**	
During treatment: assessment A (day 1–7)	6 (4–7)
During treatment: assessment B (day 8–14)	10 (8–13)
Posttreatment: assessment C	21 (20–23)
Assessment A (day 1–7) (156)	213 (57.7)
New lesions (22)	
Yes	25 (13.1)
No	166 (86.9)
All lesions crusted and healed with new layer of skin (59)	
Yes	49 (31.8)
No	105 (68.2)
Assessment B (day 8–14) (187)	182 (49.3)
New lesions (19)	
Yes	22 (13.5)
No	141 (86.5)
All lesions crusted and healed with new layer of skin (25)	
Yes	78 (49.7)
No	79 (50.3)
Assessment C (posttreatment) (225)	144 (39.0)
New lesions (7)	
Yes	3 (2.2)
No	134 (97.8)
All lesions crusted and healed with new layer of skin (11)	
Yes	119 (89.5)
No	14 (10.5)

* Hospitalized at any time after symptom onset. Among 23 patients hospitalized, two patients were admitted to the intensive care unit.
† At latest follow-up visit, which might have been during treatment or posttreatment. Recovery status was defined by clinical judgment of the treating provider.
§ Time to first observed (including patient-reported) improvement.
¶ All adverse events included headache (three), nausea (two), visual disturbance (two), weakness (two), vomiting (one), asymptomatic elevated liver function tests (one), hospitalization for psychiatric reasons (one), rash (one), hives (one), numbness (one), fatigue (one), and dizziness (one).
** Nonmissing data.

other public health measures (*10*). Inappropriate uses could potentially lead to resistance (*3*). Continued prescribing guidance updates on administering tecovirimat to those who would benefit the most from its use will be crucial as more is learned about effectiveness, viral resistance, and adverse events.

The findings in this report are subject to at least six limitations. First, only patients whose EA-IND forms were submitted to CDC were included in this report, representing a fraction of those treated to date¶¶¶¶; this limitation could lead to convenience sample bias that might not be representative of all patients treated with tecovirimat. Second, to lessen the regulatory burden on prescribers, the EA-IND forms were streamlined during the data collection process, leading to inconsistent variable collection. Third, some variables were collected as free text; therefore, absent data might not necessarily indicate absence of conditions. Fourth, the profile of patients might differ across assessment time points; for example, those with worse initial symptoms might have been more likely to receive follow-up assessments, making true time to resolution or improvement difficult to ascertain. Fifth, it is not known whether the outcomes described for patients who received tecovirimat differ from those of patients who do not receive tecovirimat because no control group was included. Finally, CD4 count and viral load, markers of unsuppressed HIV infection, were not collected, limiting the evaluation of treatment outcomes for persons living with HIV infection.

Ongoing monitoring is essential to assess the safety of tecovirimat in patients with *Monkeypox virus* infection under the EA-IND during the current monkeypox outbreak. CDC is continuing to review additional data as they become available. Currently, there are no human data demonstrating the efficacy of tecovirimat, and clinical trials are necessary to elucidate clinical efficacy in patients with *Monkeypox virus* infection, indications for treatment, and ideal duration of treatment.

¶¶¶¶ In comparison with the monkeypox cases reported in the United States (15,433 cases through August 20, 2022). https://www.cdc.gov/poxvirus/monkeypox/response/2022/mpx-trends.html

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Notes from the Field

Nitazene-Related Deaths — Tennessee, 2019–2021

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Nitazenes are a novel group of powerful illicit synthetic opioids derived from 2-benzylbenzimidazole that have been linked to overdose deaths in several states (1). Nitazenes were created as a potential pain reliever medication nearly 60 years ago but have never been approved for use in the United States (2). Laboratory test results indicate that the potency of certain nitazene analogs (e.g., isotonitazene, protonitazene, and etonitazene) greatly exceeds that of fentanyl, whereas the potency of the analog metonitazene is similar to fentanyl (3,4). Naloxone has been effective in reversing nitazene-involved overdoses, but multiple doses might be needed (3,4). The prevalence of nitazene deaths in the United States is unknown and the frequency of nitazene involvement in overdose deaths in Tennessee has not yet been assessed. However, of concern is that nitazenes are increasingly recorded in toxicology reports and death certificate cause-of-death fields. Given their potency, raising awareness about nitazenes and implementing strategies to reduce harm through increased testing, surveillance, and linkage to treatment for substance use disorders are of vital importance.

The Office of Informatics and Analytics at the Tennessee Department of Health conducts routine surveillance of fatal drug overdoses using the Tennessee State Unintentional Drug Overdose Reporting System (TN SUDORS). The surveillance system collects sociodemographic information and circumstances associated with overdose deaths, including death scene information, autopsy reports, and toxicology reports for drug overdose deaths of unintentional and undetermined intent. For this analysis, nitazene-involved deaths were identified using a text search for the term "nitazene" (and common misspellings) in death certificate cause-of-death fields and in toxicology reports for deaths that occurred during January 1, 2019–December 31, 2021, with data available as of June 10, 2022. TN SUDORS data were examined for demographic characteristics and circumstances surrounding deaths. Tennessee death certificate data for 2021 are provisional, as are SUDORS data for July–December 2021. This analysis was determined to be exempt from review by the Tennessee Department of Health's Institutional Review Board and was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.*

During 2019–2021, a total of 52 nitazene-involved fatal drug overdoses were identified using TN SUDORS data, including no cases in 2019, 10 in 2020, and 42 in 2021 (Table). In 2020, most of nitazene-involved deaths were attributed to isotonitazene, but in 2021, most were attributed to metonitazene. Among the 10 nitazene-involved overdose deaths identified in 2020, the average decedent age was 40.6 years, and nine (90.0%) decedents were White males. In 2021, the average decedent age was similar (42.6 years); a smaller percentage of the 42 decedents were male (66.7%) and White (88.1%). Whereas nitazene-involved deaths increased in 2021, 85.7% were attributed to metonitazene, which has a lower potency compared with other nitazenes. All nitazene-involved overdoses involved multiple substances. During both 2020 and 2021, the most frequent route of administration was injection (18; 34.6%). Other routes of administration were smoking, snorting, and ingestion. In addition to fentanyl (59.6%), other co-occurring substances included methamphetamine (46.2%), amphetamine (25.0%), and flualprazolam (13.5%).

Most nitazene-involved deaths in Tennessee were identified in Knox County. This apparent high prevalence is most likely because Knox County's Regional Forensic Center sends blood samples for secondary laboratory testing to the Drug Enforcement Agency (DEA) (5); traditional laboratory panels do not always capture nitazenes. Therefore, nitazene-involved

TABLE. Demographic characteristics of nitazene-involved overdose deaths (N = 52) — Tennessee State Unintentional Drug Overdose Reporting System,* 2020–2021

Characteristic	No. (%)	
	2020	2021
Total	10 (100.0)	42 (100.0)
Age, yrs, mean (SD)	40.6 (13.2)	42.6 (12.1)
Sex		
Female	1 (10.0)	14 (33.3)
Male	9 (90.0)	28 (66.7)
Race		
Other	0 (—)	5 (11.9)
White	10 (100.0)	37 (88.1)
Nitazene[†]		
Metonitazene	1 (10.0)	36 (85.7)
Isotonitazene	9 (90.0)	1 (2.4)
Protonitazene	0 (—)	2 (4.8)
Etonitazene	0 (—)	5 (11.9)

Abbreviation: SUDORS = State Unintentional Drug Overdose Reporting System.
* SUDORS deaths were identified via Tennessee Department of Health, Division of Vital Records and Statistics, Death Statistical System, 2019-2021. 2021 death statistical data are provisional.
† Categories are not mutually exclusive. Nitazene analogs have differing potency. The potency of isotonitazene, protonitazene, and etonitazene greatly exceeds that of fentanyl, whereas the potency of metonitazene is similar to fentanyl.

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* 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

deaths that occur in other counties of Tennessee are likely to be undercounted. DEA provides laboratory testing as a free resource and encourages state and national forensic centers to submit their samples for additional testing to assist in the accurate counting of deaths and to better guide drug overdose prevention efforts.

Naloxone was only administered to 12 (23%) persons with nitazene-involved fatal overdoses. Given naloxone's effectiveness in preventing fatal overdoses, more frequent administration of naloxone by first responders, bystanders, and clinicians is important. Implementing naloxone training and distribution efforts throughout all states is also necessary. As with fentanyl, multiple naloxone doses might be required because of the potency of nitazene[†] and can be safely administered. In addition, contacting emergency services is necessary to provide immediate medical attention to persons who might be overdosing.

Four times as many nitazene-involved overdoses were identified in Tennessee in 2021 than in 2020, and this number could be underestimated because of low testing frequency. Nitazenes are an emerging group of highly potent psychoactive substances, tests for which are often not included in standard toxicology panels. Given their potency, raising awareness about nitazenes and implementing strategies to reduce harm through increased testing, surveillance, and linkage to treatment for substance use disorders are of vital importance. More data are required to better understand this emerging group of psychoactive substances in the United States.

[†] https://health.usnews.com/drugs/articles/nitazenes

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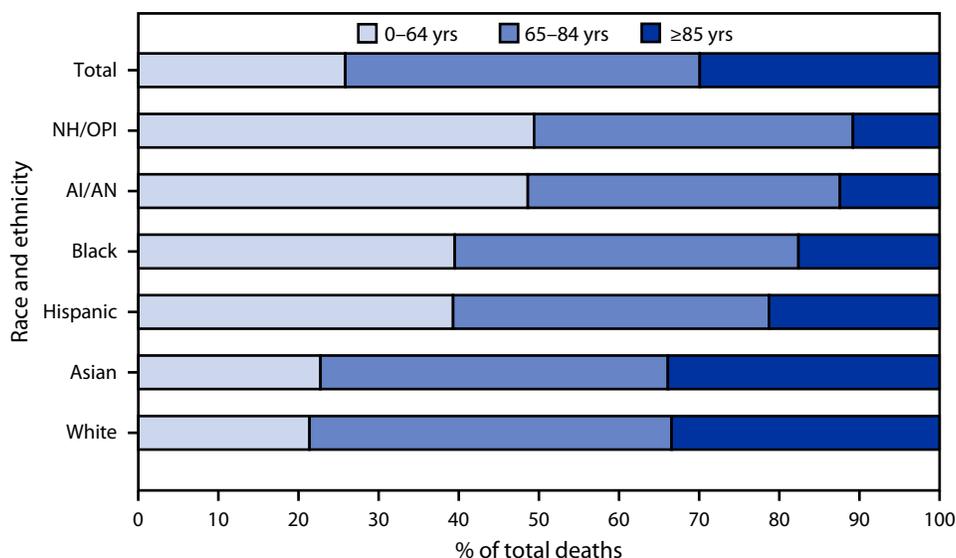[1]Office of Informatics and Analytics, Tennessee Department of Health.

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QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage of Total Deaths, by Age and Hispanic Origin and Race*,† — United States, 2020

Abbreviations: AI/AN = American Indian or Alaska Native; NH/OPI = Native Hawaiian or other Pacific Islander.
* Data for AI/AN persons were adjusted for race and ethnicity misclassification on death certificate. Adjusted data might differ from data shown in other reports that have not been adjusted for misclassification. https://wonder.cdc.gov/ucd-icd10-expanded.html
† AI/AN, Asian, Black, NH/OPI, and White persons were non-Hispanic. Hispanic persons could be of any race.

Significant differences in the age distribution of deaths by race and ethnicity were observed in the United States during 2020. Decedents aged <65 years accounted for 26% of all U.S. deaths, but they accounted for approximately 50% of deaths among AI/AN and NH/OPI persons, 40% of deaths among Black or African American (Black) and Hispanic or Latino (Hispanic) persons, and 20% of deaths among Asian and White persons. Smaller differences were noted among persons aged 65–84 years. Among persons aged ≥85 years, the pattern was reversed, with the percentage of all deaths ranging from approximately 11% among AI/AN and NH/OPI persons to 33% for Asian and White persons.

Source: National Vital Statistics System, Underlying Cause of Death by Single-Race Categories, 2018–2020. https://wonder.cdc.gov/ucd-icd10-expanded.html

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