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Geographic Differences in Sex-Specific Chronic Obstructive Pulmonary Disease Mortality Rate Trends Among Adults Aged ≥25 Years — United States, 1999–2019

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Chronic obstructive pulmonary disease (COPD) accounts for the majority of deaths from chronic lower respiratory diseases, the fourth leading cause of death in the United States in 2019.* COPD mortality rates are decreasing overall. Although rates in men remain higher than those in women, declines have occurred among men but not women (*1*). To examine the geographic variation in sex-specific trends in age-adjusted COPD mortality rates among adults aged ≥25 years, CDC analyzed 1999–2019 death certificate data, by urban-rural status,† U.S. Census Bureau region,§ and state. Among women, no significant change in overall COPD mortality occurred during this period; however, rates increased significantly in small metropolitan (average annual percent change [AAPC] = 0.6%), micropolitan (1.2%), and noncore (1.9%) areas and in the Midwest (0.6%). Rates decreased significantly in large central (–0.9%) and fringe metropolitan (–0.4%) areas (and in the Northeast (–0.5%) and West (–1.2%). Among men, rates decreased significantly overall (–1.3%), in all urban-rural areas (range = –1.9% [large central metropolitan] to –0.4% [noncore]) and in all regions (range = –2.0% [West] to –0.9% [Midwest]). Strategies to improve the prevention, treatment, and management of COPD are needed, especially to address geographic differences and improve the trend in women, to reduce COPD deaths.

Mortality data from the CDC National Vital Statistics System during 1999–2019 were analyzed to determine the number and rate of deaths from COPD among adults aged ≥25 years for each year by sex and by geographic characteristics

* https://www.cdc.gov/nchs/data/nvsr/nvsr70/nvsr70-08-508.pdf

† As defined in the CDC National Center for Health Statistics 2013 Urban-Rural Classification Scheme for Counties with six urbanization levels: four metropolitan (large central metropolitan, large fringe metropolitan, medium metropolitan, and small metropolitan) and two nonmetropolitan (micropolitan and noncore). https://www.cdc.gov/nchs/data/series/sr_02/sr02_166.pdf

§ U.S. Census Bureau regions: *Northeast*: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont. *Midwest*: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin. *South*: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia. *West*: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming. https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf

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of the person's place of legal residence at the time of death.[¶] Each death certificate identifies a single underlying cause; COPD was identified using *International Classification of Diseases, Tenth Revision* codes J40–J44. Queries to CDC WONDER generated yearly age-adjusted sex-specific mortality rates (deaths per 100,000 standard population) by urban-rural status, U.S. Census Bureau region, and state. Age-adjusted rates with 95% CIs were estimated using the 2000 U.S. standard population and 10-year age groups. Trends were evaluated using Joinpoint software (version 4.8.0.1; National Cancer Institute).[**] Annual percent change (APC) for each trend segment and AAPC from 1999 to 2019 were estimated; values significantly <0 ($p \leq 0.05$) were interpreted as a significant decrease in mortality rates, and values significantly >0 were interpreted as a significant increase. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[††]

Differences between men and women in annual age-adjusted COPD mortality rates were smaller in 2019 (62.8 versus 53.0, respectively) than in 1999 (88.2 versus 54.6, respectively) (Table). COPD mortality rates among men in 1999 and 2019 and among women in 2019 were inversely related to urbanicity; no clear urban-rural pattern was observed among women in 1999. Similar to region-specific patterns observed among men in 1999 and 2019, age-adjusted COPD mortality rates among women in 2019 were lowest in the Northeast, followed by the West, and highest in the South and Midwest; in 1999, rates among women were highest in the West.

During 1999–2019, overall age-adjusted COPD mortality rates among women did not change significantly, whereas rates among men decreased significantly (AAPC = –1.3%). However, trends in age-adjusted, sex-specific COPD mortality rates differed by region and urban-rural status during this period (Figure 1). Among women, rates increased significantly in the Midwest (0.6%), did not change significantly in the South, and decreased significantly in the Northeast (–0.5%) and West (–1.2%). The change in rates among women was not significant when analysis was limited to later years in the Midwest (2013–2019), but was significant in the South (0.8%) when analysis was limited to 1999–2017. Among men, significant decreases were observed from 1999 to 2019 in all regions (range = –2.0% [West] to –0.9% [Midwest]). By urban-rural status, among women, the COPD mortality rate decreased significantly from 1999 to 2019 in large central (–0.9%) and

[¶] The analysis focused on the adult population because COPD mortality is rare in the non-adult population. The analysis was restricted to adults aged ≥25 years because standard age-adjusted rates (calculated with standard populations) are only available from CDC WONDER using 10-year age groups (<1, 1–4, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years). https://wonder.cdc.gov/

[**] Joinpoint software identifies statistically significant changes in a trend using Monte Carlo permutation, then fits them as a series of joined trend segments. https://surveillance.cancer.gov/joinpoint/

[††] 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.

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TABLE. Sex-specific chronic obstructive pulmonary disease related deaths and age-adjusted mortality rates* among adults aged ≥25 years and trends in mortality rates, by geographic characteristics — United States, 1999–2019

Geographic characteristic	1999		2019		AAPC† 1999–2019 (95% CI)	No. of joinpoints	Segment-specific APC† 1999–2019 (95% CI)
	No. of deaths	Deaths per 100,000 population (95% CI)	No. of deaths	Deaths per 100,000 population (95% CI)			
Women							
Overall	**58,040**	**54.6 (54.1 to 55.0)**	**80,422**	**53.0 (52.6 to 53.4)**	**0.1 (−0.1 to 0.3)**	**0**	—§
Urban-rural status¶							
Large central metropolitan	15,833	52.3 (51.4 to 53.1)	16,919	40.1 (39.5 to 40.7)	−0.9 (−1.2 to −0.7)**	0	—
Large fringe metropolitan	13,006	54.9 (54.0 to 55.9)	18,337	48.8 (48.1 to 49.5)	−0.4 (−0.6 to −0.2)**	0	—
Medium metropolitan	12,334	56.0 (55.0 to 57.0)	18,010	55.3 (54.5 to 56.1)	−0.2 (−0.9 to 0.5)	1	1999–2017: 0.3 (0.0 to 0.5)** 2017–2019: −4.2 (−10.7 to 2.7)
Small metropolitan	6,067	58.7 (57.2 to 60.2)	9,485	64.5 (63.2 to 65.9)	0.6 (0.4 to 0.8)**	0	—
Micropolitan (nonmetropolitan)	6,206	56.8 (55.4 to 58.2)	9,924	71.3 (69.8 to 72.7)	1.2 (0.7 to 1.7)**	1	1999–2015: 1.6 (1.3 to 1.9)** 2015–2019: −0.5 (−2.7 to 1.8)
Noncore (nonmetropolitan)	4,594	51.5 (50.0 to 53.3)	7,747	73.8 (72.1 to 75.4)	1.9 (1.5 to 2.4)**	1	1999–2011: 2.5 (2.0 to 3.1)** 2011–2019: 1.0 (0.1 to 2.0)**
U.S. Census Bureau region††							
Northeast	11,163	48.1 (47.2 to 49.0)	12,250	42.1 (41.3 to 42.8)	−0.5 (−0.7 to −0.3)**	0	—
Midwest	14,028	54.9 (54.0 to 55.8)	19,234	58.9 (58.0 to 59.7)	0.6 (0.0 to 1.1)**	1	1999–2013: 1.1 (0.7 to 1.6)** 2013–2019: −0.7 (−2.2 to 0.8)
South	20,319	54.5 (53.7 to 55.2)	33,644	59.3 (58.6 to 59.9)	0.3 (−0.3 to 1.0)	1	1999–2017: 0.8 (0.5 to 1.0)** 2017–2019: −3.4 (−9.4 to 3.1)
West	12,530	61.6 (60.5 to 62.7)	15,294	46.0 (45.3 to 46.7)	−1.2 (−1.4 to −1.0) **	0	—
Men							
Overall	**60,416**	**88.2 (87.4 to 88.9)**	**71,991**	**62.8 (62.3 to 63.2)**	**−1.3 (−1.5 to −1.1)****	**0**	**—**
Urban-rural status¶							
Large central metropolitan	14,618	77.7 (76.5 to 79.0)	14,452	48.0 (47.2 to 48.8)	−1.9 (−2.1 to −1.7)**	0	—
Large fringe metropolitan	11,981	79.1 (77.6 to 80.5)	15,122	54.2 (53.3 to 55.1)	−1.6 (−1.8 to −1.4)**	0	—
Medium metropolitan	13,092	91.0 (89.5 to 92.6)	16,194	64.8 (63.8 to 65.8)	−1.3 (−1.5 to −1.1)**	0	—
Small metropolitan	6,786	99.8 (97.4 to 102.2)	8,706	75.5 (73.9 to 77.2)	−1.0 (−1.2 to −0.8)**	0	—
Micropolitan (nonmetropolitan)	7,433	102.5 (100.2 to 104.9)	9,641	87.0 (85.2 to 88.8)	−0.6 (−0.8 to −0.5)**	0	—
Noncore (nonmetropolitan)	6,506	106.6 (104.0 to 109.2)	7,876	90.2 (88.2 to 92.2)	−0.4 (−0.6 to −0.1)**	0	—
U.S. Census Bureau region††							
Northeast	10,574	75.6 (74.1 to 77.0)	10,187	49.5 (48.6 to 50.5)	−1.8 (−2.0 to −1.5)**	0	—
Midwest	14,886	92.3 (90.8 to 93.8)	17,398	70.7 (69.6 to 71.7)	−0.9 (−1.2 to −0.7)**	0	—
South	22,415	92.4 (91.2 to 93.7)	29,956	69.0 (68.2 to 69.8)	−1.1 (−1.3 to −0.9)**	0	—
West	12,541	88.6 (87.0 to 90.2)	14,450	55.6 (54.7 to 56.5)	−2.0 (−2.2 to −1.8)**	0	—

Abbreviations: AAPC = average annual percent change; APC = annual percent change; COPD = chronic obstructive pulmonary disease.

* Per 100,000 standard population. Age-adjusted COPD mortality rates were calculated using the 2000 U.S. Census Bureau projected population and 10-year age groups.

† COPD trends were assessed as the AAPC from 1999 to 2019 and as the APC for segment-specific periods when a joinpoint was detected.

§ Dashes indicate that the best-fit joinpoint model did not include any trend segments.

¶ As defined in the CDC National Center for Health Statistics 2013 Urban-Rural Classification Scheme for Counties with six urbanization levels: four metropolitan (large central metropolitan, large fringe metropolitan, medium metropolitan, and small metropolitan) and two nonmetropolitan (micropolitan and noncore). https://www.cdc.gov/nchs/data/series/sr_02/sr02_166.pdf

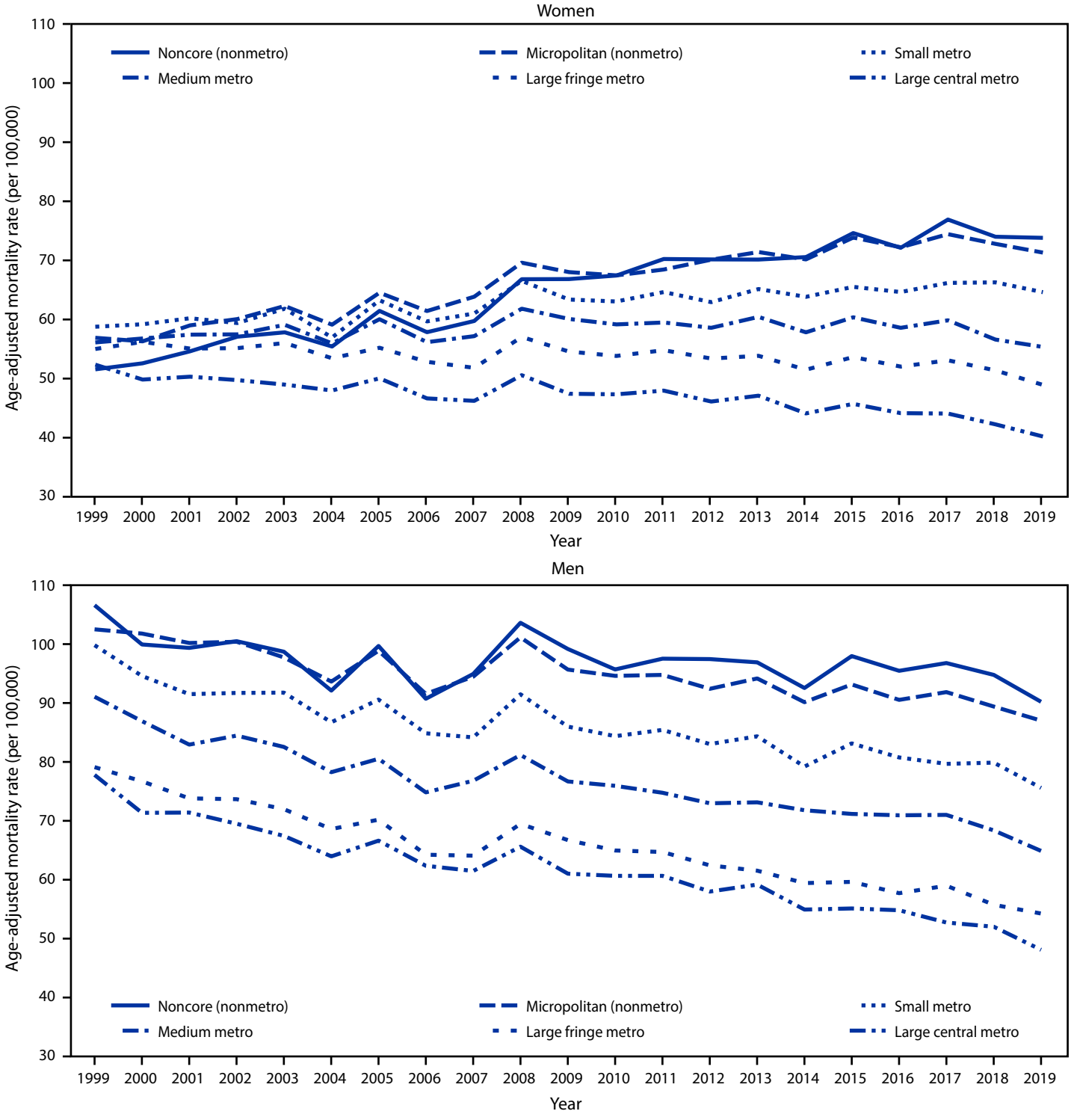
** Significantly different from 0 at p≤0.05. For APCs and for AAPCs within one segment (e.g., no joinpoint), the t-distribution is used. For AAPCs within multiple segments (e.g., one joinpoint), the normal (z) distribution is used.

†† U.S. Census Bureau regions: *Northeast*: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont. *Midwest*: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin. *South*: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia. *West*: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming. https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf

fringe (−0.4%) metropolitan areas, did not change significantly in medium metropolitan areas, and increased significantly in small metropolitan (0.6%), micropolitan (1.2%), and noncore (1.9%) areas. The change in COPD mortality rates among women was not significant when analysis was limited to later years in medium metropolitan (2017–2019) and in micropolitan areas (2015–2019); the increase in rates slowed in noncore areas after 2011. COPD mortality rates among men decreased in all urban-rural categories (range = −1.9% [large central metropolitan] to −0.4% [noncore]).

Among women, rates decreased significantly in 17 states (AAPC range = −1.9% [California] to −0.4% [New Jersey and Arizona]) and increased significantly in 18 states (range = 0.4% [Wisconsin] to 2.9% [Arkansas]) (Figure 2) (Supplementary Table; https://stacks.cdc.gov/view/cdc/116406). Among men, rates decreased significantly in 45 states and the District of

FIGURE 1. Sex-specific trends in age-adjusted chronic obstructive pulmonary disease mortality rates among adults aged ≥25 years,* by urban-rural status† — United States, 1999–2019

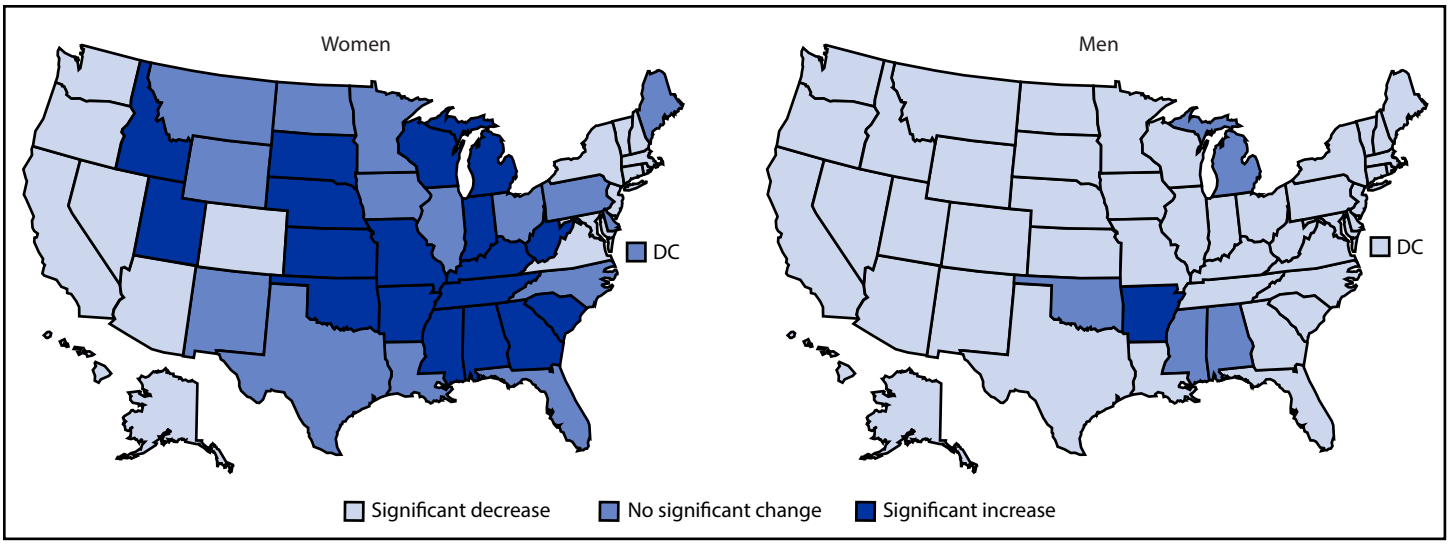


Abbreviation: COPD = chronic obstructive pulmonary disease.

* Per 100,000 population. Age-adjusted COPD mortality rates were calculated using the 2000 U.S. Census Bureau projected population and 10-year age groups.

† As defined in the CDC National Center for Health Statistics 2013 Urban-Rural Classification Scheme for Counties with six urbanization levels: four metropolitan (large central metro, large fringe metro, medium metro, and small metro) and two nonmetropolitan (micropolitan and noncore). https://www.cdc.gov/nchs/data/series/sr_02/sr02_166.pdf

FIGURE 2. State-level changes* in sex-specific age-adjusted chronic obstructive pulmonary disease mortality rates† among adults aged ≥25 years — United States, 1999–2019



Abbreviations: AAPC = average annual percent change; COPD = chronic obstructive pulmonary disease; DC = District of Columbia.
* Statistically significant changes were determined using the estimated AAPC with all years included (1999–2019). AAPCs significantly <0 were interpreted as a significant decrease while those significantly >0 were interpreted as a significant increase.
† Per 100,000 population. Age-adjusted COPD mortality rates were calculated using the 2000 U.S. Census Bureau projected population and 10-year age groups.

Columbia (range = −4.2% [Alaska] to −0.3% [Indiana]) and increased significantly in Arkansas (0.5%). State-level mortality rates among women ranged from 24.0 (Hawaii) to 93.9 (Wyoming) in 1999 and 16.7 (Hawaii) to 89.8 (West Virginia) in 2019. Among men, rates ranged from 41.9 (Hawaii) to 143.2 (Wyoming) in 1999 and from 30.4 (District of Columbia) to 104.0 (Oklahoma) in 2019.

Discussion

Age-adjusted COPD mortality rates decreased among men from 1999 to 2019; however, rates remained higher in men than women. Among women, although overall rates exhibited no significant change, rates increased among some geographic subgroups, including women living in the Midwest and those living in small metropolitan or nonmetropolitan areas. Among both men and women, urban-rural disparities became more pronounced during this time. Efforts are needed to continue the decreasing trend in COPD mortality rates among men and improve the trend among women. Findings highlight several important geographical areas to focus COPD prevention (e.g., smoking cessation), early diagnosis, treatment (e.g., medication and oxygen therapy), and management strategies (e.g., pulmonary rehabilitation; efforts to slow declining lung function, improve exercise tolerance, and prevent exacerbations).

COPD mortality might differ by sex for several reasons. First, tobacco smoking is the main cause of COPD in the United States, and cigarette smoking declined first among men (since the 1960s) and later among women (since the 1980s) (*2*). Second, women might be more vulnerable to the effects of tobacco (*2–4*). Third, women account for most patients with COPD who have never smoked, suggesting that women might be more susceptible to secondhand smoke or nonsmoking-related factors (*3*,*5*,*6*). Fourth, disease presentation and rates of exacerbations might differ by sex which can result in delayed diagnosis and higher rates of exacerbations in women (*3*,*4*). Finally, women with COPD also face challenges related to their interactions with the health care system (*3*). Women face higher rates of misdiagnosis or delayed diagnosis that can potentially lead to suboptimal treatment (*3*,*4*). Improving understanding about the reasons for the increasing COPD mortality rates in certain subgroups of women can help guide the development and implementation of prevention, early diagnosis, treatment, and management strategies that are specifically tailored for women.

Region-specific patterns in COPD mortality in 2019 were similar among men and women (e.g., highest in the Midwest and South), and urban-rural disparities became more pronounced among both women and men during the past 20 years. For example, in 1999 there was no significant difference in rates between large central metropolitan areas and noncore areas among women, but in 2019 the rate was 84% higher in noncore areas. Similarly, for men the relative difference between these two areas increased from 37% in 1999 to 88% in 2019. These findings update previous studies that examined geographic differences in COPD prevalence and

Summary

What is already known about this topic?

Chronic obstructive pulmonary disease (COPD) accounts for most deaths from chronic lower respiratory diseases, the fourth leading cause of death in 2019 in the United States. COPD mortality rates are decreasing overall.

What is added by this report?

From 1999 to 2019, overall age-adjusted COPD mortality rates among women did not change; however, rates increased among women living in the Midwest and those in small metropolitan or nonmetropolitan areas. COPD mortality rates are higher among men; however, rates decreased overall and among all regional and urban-rural subgroups.

What are the implications for public health practice?

To reduce COPD deaths, strategies to improve the prevention, treatment, and management of COPD are needed, especially strategies that address geographic differences and improve the trend among women.

mortality (*7*,*8*). The COPD National Action Plan[§§] provides a comprehensive framework for developing and implementing COPD prevention, treatment, and management strategies. Developing strategies that maximize the use of setting-specific resources (e.g., engaging existing stakeholders as well as providing patient-centric clinical guidelines to health care providers most likely to deliver COPD care within a setting) and help adults overcome setting-specific challenges are important in reducing urban-rural, regional, and state-level disparities in COPD mortality overall (*9*). For example, adults in rural areas might be more likely to experience challenges related to access (e.g., less access to pulmonologists and longer travel distances to health care facilities) (*10*) and cost (e.g., higher likelihood of being uninsured or having a lower socioeconomic status).[¶¶]

The findings in this report are subject to at least two limitations. First, COPD mortality might be underestimated because adults with COPD are more likely to have comorbidities (e.g., cardiovascular disease, stroke, diabetes, or cancer) (*1*,*8*) that might displace COPD as the underlying cause reported on the death certificate. Second, the 2013 CDC National Center for Health Statistics Urban-Rural Classification Scheme for Counties is well-suited to assessing and monitoring health differences across the full urbanization continuum; however, the assumption that the six urban-rural classifications reflect consistent types of distinct populations and social environments within and across each state could be an oversimplification.

Continued efforts are needed to prevent COPD and support early diagnosis, treatment (e.g., medication and oxygen therapy), and management (e.g., pulmonary rehabilitation). In addition, strategies that help improve the trend among women and address geographic differences have the potential to reduce COPD mortality.

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[¶¶] https://www.ruralhealthweb.org/about-nrha/about-rural-health-care

Use of a Modified Preexposure Prophylaxis Vaccination Schedule to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022

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Human rabies is an acute, progressive encephalomyelitis that is nearly always fatal once symptoms begin. Several measures have been implemented to prevent human rabies in the United States, including vaccination of targeted domesticated and wild animals, avoidance of behaviors that might precipitate an exposure (e.g., provoking high-risk animals), awareness of the types of animal contact that require postexposure prophylaxis (PEP), and use of proper personal protective equipment when handling animals or laboratory specimens. PEP is widely available in the United States and highly effective if administered after an exposure occurs. A small subset of persons has a higher level of risk for being exposed to rabies virus than does the general U.S. population; these persons are recommended to receive preexposure prophylaxis (PrEP), a series of human rabies vaccine doses administered before an exposure occurs, in addition to PEP after an exposure. PrEP does not eliminate the need for PEP; however, it does simplify the rabies PEP schedule (i.e., eliminates the need for rabies immunoglobulin and decreases the number of vaccine doses required for PEP). As rabies epidemiology has evolved and vaccine safety and efficacy have improved, Advisory Committee on Immunization Practices (ACIP) recommendations to prevent human rabies have changed. During September 2019–November 2021, the ACIP Rabies Work Group considered updates to the 2008 ACIP recommendations by evaluating newly published data, reviewing frequently asked questions, and identifying barriers to adherence to previous ACIP rabies vaccination recommendations. Topics were presented and discussed during six ACIP meetings. The following modifications to PrEP are summarized in this report: 1) redefined risk categories; 2) fewer vaccine doses in the primary vaccination schedule; 3) flexible options for ensuring long-term protection, or immunogenicity; 4) less frequent or no antibody titer checks for some risk groups; 5) a new minimum rabies antibody titer (0.5 international units [IUs]) per mL); and 6) clinical guidance, including for ensuring effective vaccination of certain special populations.

Background

Transmission of rabies virus occurs when saliva or neural tissue from an infected mammal is introduced into a person or another animal through, for example, a bite or contact with mucous membranes (*1*). Worldwide, approximately 59,000 human rabies deaths occur each year (*2*). The canine rabies virus variant (CRVV) is the most common source of human rabies infections, accounting for approximately 98% of cases, including some cases among U.S. travelers (*3*). In the United States, CRVV has been eliminated (*3*), but wildlife rabies remains endemic, accounting for approximately 5,000 reported rabid animals each year (*4*). Specific wildlife rabies virus variants (RVVs) associated with mesocarnivores (small to midsized animals whose diet includes 50%–70% meat) are endemic in distinct geographically confined locations in 42 U.S. states and Puerto Rico (*4*). In contrast, bat RVVs are widely distributed throughout the United States, with only Hawaii being rabies-free (*3*). During January 2000–December 2020, 52 cases of human rabies were diagnosed in the United States, 38 of which were indigenously acquired (i.e., from rabies exposures that occurred in the United States) (*4*); none were in persons who had previously received PrEP.

In the United States, two modern cell culture vaccines are licensed for rabies PrEP and PEP: human diploid cell vaccine (HDCV; Imovax/Sanofi Pasteur)* and purified chick embryo cell vaccine (PCECV; RabAvert/Bavarian Nordic),† respectively; both are packaged for intramuscular (IM) administration (*1*). Each IM dose of vaccine consists of 1 mL and should be administered in the deltoid for adults, and in either the deltoid or anterolateral aspect of the thigh for children.

Reasons for Revisions of Recommendations

ACIP has recommended rabies PrEP since 1969 (*5*). As safe and effective modern cell culture vaccines have replaced those derived from nerve tissue and duck embryo, and as rabies epidemiology has continued to evolve (e.g., elimination of CRVV, emergence and spread of the racoon RVV, and host shifts of bat RVV to mesocarnivores in the southern United States), changes have been made to ACIP recommendations. Since 2008, when the last ACIP rabies PrEP recommendations were published, barriers affecting adherence to the recommendations have been identified, including out-of-pocket costs of

* https://www.fda.gov/media/75709/download
† https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert---RabAvert.pdf

rabies biologics (3-dose PrEP vaccination series is currently estimated at ≥$1,100[§]), confusion about which activities fall within different risk categories, and noncompliance with recommendations for repeated titer checks (*6*). In addition, travel medicine providers have indicated that the largest group for which PrEP is recommended (travelers to regions with endemic CRVV) might often be unable to complete the 3-dose series described in the 2008 ACIP recommendations (*1*) because at least 21 days are required to complete the series before initiation of travel (*7*).

During September 2019–November 2021, the ACIP Rabies Work Group participated in monthly or bimonthly teleconferences and considered evidence-based updates to the 2008 ACIP recommendations. The Work Group comprised experts in diverse disciplines including laboratory, public health, and clinical specialties. Data collected, analyzed, and prepared by the Work Group were deliberated by ACIP during six public meetings. With publication of this report, the recommendations become final and are the official CDC recommendations for rabies PrEP.

Redefined Risk Categories

Recommendations for PrEP depend on the level of a person's risk for being exposed to rabies. The Work Group redefined risk categories into five groups, with level 1 involving activities with the highest risk and level 5 involving those with the lowest risk (Table). The highest risk categories (levels 1 and 2) include exposures that might be unrecognized (i.e., not perceived by the exposed person); for example, a small scratch to the skin during an inconspicuous personal protective equipment breach might not be noticed by persons testing neural tissue from a rabid animal or conducting ecologic studies on bats in the field. For persons with risk for unrecognized exposures, checking serial titers has historically been advised to ensure maintenance of persistently elevated rabies antibody titers; in its recent discussions, ACIP upheld this guidance because the assumption is that high titers might provide some protection when PEP is not sought for an unrecognized exposure. Recognized exposures, as defined by ACIP, are those bites, scratches, and splashes for which PEP would be sought because the exposures are usually registered by a person as unusual (e.g., contact with a bat) or painful (e.g., bite or scratch from a raccoon). The Work Group concluded that most high-risk activities involving live animals (e.g., providing veterinary health care or participating in outdoor activities in countries with endemic CRVV) are associated with only recognized exposures (risk categories 3 and 4); ACIP concluded that checking serial titers for these persons is unnecessary because recognized exposures should always prompt evaluation for PEP. Rabies vaccination recommendations for each of the redefined risk categories is summarized under Recommendations.

Risk categories might change over a person's lifetime. Some persons for whom PrEP is indicated might have elevated risk for a limited period (e.g., during a summer internship working with wildlife or a month-long vacation to a rural village where CRVV is enzootic [risk category 4]). After the event has passed, risk level and associated recommendations for such persons will change. Shifts in risk categories are explained in the management of deviations from the recommendations section under Clinical Guidance.

Minimum Acceptable Rabies Antibody Titer Level

A correlate of protection for rabies antibody titers has not been defined. The minimum antibody level historically recommended by ACIP is one that results in complete neutralization of rabies virus at a 1:5 serum dilution by the rapid fluorescent focus inhibition test. This is approximately equivalent to a titer of 0.1–0.3 IU/mL. Stakeholders have advocated for a specific titer value in IU/mL units of measure (rather than a range) and, ideally, one that aligns with current global guidance (i.e., that of the World Health Organization) (*8*). Although no infections among vaccinated persons occurred with the previous ACIP cut-off titer, most published studies use 0.5 IU/mL as a correlate of protection. This level is now endorsed by ACIP and replaces the previous minimum acceptable rabies antibody titer. The higher value provides a more conservative limit for indicating inadequate response to rabies vaccination and the need for booster doses (*9*).

Evidence for Updated Vaccine Schedule and Recommendations for Booster Doses and Titer Checks

Although there is no established correlate of protection for rabies, induction of a peak antibody response at or above the minimum acceptable antibody titer level (≥0.5 IU/mL) in response to rabies vaccine is an indirect measure of protection (i.e., immunogenicity). Primary immunogenicity refers to immunogenicity that peaks 2–4 weeks after completing the recommended vaccination or vaccinations and elicits an anamnestic response to rabies virus exposures. Since publication of the 2008 ACIP recommendations (*1*), scientists have been evaluating data concerning the efficacy of shorter rabies PrEP dosing regimens.

Subject matter experts performed a systematic review of scientific evidence published during 1965–2019 for a 2-dose primary vaccination series (doses administered on days 0 and 7)

[§] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/24-25/03-Rabies-Rao-508.pdf

compared with the 3-dose series (doses administered on days 0, 7, and 21 or 28), which is indicated in the 2008 ACIP recommendations (*1*). Data showed that an anamnestic response after the 2-dose series occurs at 3 years (*10*); however, an anamnestic response >3 years after the 2-dose series has not been evaluated. In the absence of data confirming an anamnestic response, the Work Group evaluated methods of inferring long-term immunogenicity (i.e., an anamnestic response >3 years after the 2-dose primary vaccination series). Checking a titer or titers was considered one way of inferring long-term immunogenicity as described in the PrEP schedule and long-term immunogenicity section that follows. As an alternative to a titer check, a second systematic review was conducted to evaluate a booster dose after the 2-dose series compared with no booster dose. The Work Group used an adapted Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to determine the certainty of evidence for immunogenicity rated on a scale of 1 (high certainty) to 4 (very low certainty). Within the evidence to recommendations (EtR) framework, ACIP considered the importance of rabies as a public health problem; the benefits and harms (including GRADE-assessed evidence); the target populations' values and preferences; and issues of resource use, acceptability to stakeholders, feasibility of implementation, and anticipated impact on health equity.

PrEP schedule and primary immunogenicity. The systematic review identified 12 studies that enrolled a combined total of 1,401 subjects. Studies evaluating both IM and intradermal vaccination were included because primary immunogenicity is similar for both routes of administration (*11*). Using the GRADE approach, the Work Group concluded with moderate (level 2) certainty that the primary immunogenicity of the 2-dose (days 0 and 7) IM schedule is comparable to that of the 3-dose (days 0, 7, and 21 or 28) IM schedule (risk ratio = 1.00 [95% CI = 0.99–1.01]).¶ ACIP deliberated whether the 2-dose (days 0 and 7) IM PrEP schedule should replace the 3-dose schedule for all persons for whom rabies PrEP is indicated based on this finding and other findings within the EtR framework**: the target population's acceptability of the 2-dose series, feasibility of implementing the 2-dose series, minimal resource use, and anticipated increase in health equity because the 2-dose series is less expensive than the 3-dose series.

PrEP schedule and long-term immunogenicity. Serial antibody titer checks are recommended for persons at elevated risk for unrecognized exposures. During recent discussions, ACIP upheld this recommendation advising that rabies antibody titers be checked every 6 months for persons in risk category 1 and every 2 years for persons in risk category 2. As previously noted, the main reason to maintain high titers is to provide some protection from unrecognized exposures; however, high titers also ensure an anamnestic response after an exposure (i.e., long-term immunogenicity).

For persons at sustained risk for only recognized exposures (risk category 3), checking serial antibody titers (as recommended for risk groups 1 and 2) was determined unnecessary; a one-time check of rabies antibody titer during years 1–3 after the 2-dose primary series was deemed appropriate assurance of long-term immunogenicity for persons with this risk. The rationale for this conclusion is that data indicate that an antibody titer ≥0.5 IU/mL 1 year after a rabies PrEP schedule is a marker for long-term immunogenicity (*12*,*13*), and the 2-dose series is known to be protective for at least 3 years (*10*).

As an alternative to the one-time titer check for risk category 3, the systematic review identified observational data from two studies that showed a booster dose triggered an anamnestic response up to 3 years after the 2-dose series. Because the third dose of the PrEP series recommended in the 2008 ACIP recommendations is given as early as day 21 and is known to provide long-term immunogenicity, a booster dose administered from day 21 to year 3 after the primary series was considered. Using the GRADE methodology, the Work Group concluded with low (level 3) certainty that a one-time booster dose of rabies vaccine during day 21–year 3 after the primary vaccination series provides better long-term immunogenicity than no booster dose; low certainty was determined because the data were not from randomized controlled trials comparing the booster with no booster.†† After evaluating these data, ACIP considered an IM booster dose of rabies vaccine during day 21–year 3 after completing the 2-dose series as an alternative to a titer check, for persons with sustained and elevated risk for recognized rabies exposures (i.e., those in risk category 3) from day 21 to year 3 after completing the 2-dose series. The rationale for the recommendation§§ within the EtR framework included the public health importance of rabies, moderately substantial desirable anticipated effect from administering a booster dose, minimal anticipated undesirable effects, acceptability to stakeholders, and feasibility of implementing the booster dose.

Recommendations

After considering the evidence, ACIP recommended all persons for whom rabies PrEP is indicated receive 2 IM doses of HDCV or PCECV on days 0 and 7. In addition, persons in the newly defined risk category 1 should have rabies antibody titers checked every 6 months, and those in the newly defined

¶ https://www.cdc.gov/vaccines/acip/recs/grade/rabies-2-dose.html
** https://www.cdc.gov/vaccines/acip/recs/grade/rabies-2-dose-etr.html

†† https://www.cdc.gov/vaccines/acip/recs/grade/rabies-booster-dose.html
§§ https://www.cdc.gov/vaccines/acip/recs/grade/rabies-booster-dose-etr.html

TABLE. Rabies preexposure prophylaxis recommendations — United States, 2022

Risk category	Nature of exposure	Typical population*	Relevant disease biogeography†	Recommendations	
				Primary PrEP§ immunogenicity	Long-term immunogenicity¶
1. Elevated risk for unrecognized** and recognized†† exposures including unusual or high-risk exposures	Exposure, often in high concentrations, might be recognized or unrecognized, might be unusual (e.g., aerosolized virus)	Persons working with live rabies virus in research or vaccine production facilities or performing testing for rabies in diagnostic laboratories	Laboratory	IM rabies vaccine on days 0 and 7	Check titers every 6 months; booster if titer <0.5 IU/mL§§
2. Elevated risk for unrecognized** and recognized†† exposures	Exposure typically recognized but could be unrecognized; unusual exposures unlikely	Persons who frequently 1) handle bats, 2) have contact with bats, 3) enter high-density bat environments, or 4) perform animal necropsies (e.g., biologists who frequently enter bat roosts or who collect suspected rabies samples)	All geographic regions where any rabies reservoir is present, both domestic and international	IM rabies vaccine on days 0 and 7	Check titers every 2 years; booster if titer <0.5 IU/mL§§
3. Elevated risk for recognized†† exposures, sustained risk¶¶	Exposure nearly always recognized; risk for recognized exposures higher than that for the general population and duration exceeds 3 years after the primary vaccination	Persons who interact with animals that could be rabid***; occupational or recreational activities that typically involve contact with animals include 1) veterinarians, technicians, animal control officers, and their students or trainees; 2) persons who handle wildlife reservoir species (e.g., wildlife biologists, rehabilitators, and trappers); and 3) spelunkers	All domestic and international geographic regions where any rabies reservoir is present	IM rabies vaccine on days 0 and 7	1) One-time titer check during years 1–3 after 2-dose primary series; booster if titer <0.5 IU/mL,§§ or 2) booster no sooner than day 21 and no later than year 3 after 2-dose primary series†††
		Selected travelers. PrEP considerations include whether the travelers 1) will be performing occupational or recreational activities that increase risk for exposure to potentially rabid animals (particularly dogs) and 2) might have difficulty getting prompt access to safe PEP (e.g., rural part of a country or far from closest PEP clinic)	International geographic regions with rabies virus reservoirs, particularly where rabies virus is endemic in dog populations		

See table footnotes on the next page.

risk category 2 should have rabies antibody titers checked every 2 years; a booster dose should be administered if titers are <0.5 IU/mL at the time of these titer checks (Table). ACIP recommended persons in risk category 3 either have rabies antibody titers checked during years 1–3 after completion of the 2-dose primary series (and a booster dose if the titer is <0.5 IU/mL) or preemptively receive a one-time IM booster dose of rabies vaccine during day 21–year 3 after completion of the 2-dose primary series (Figure). These recommendations apply both to immunocompetent and immunocompromised persons; however, PrEP administered to immunocompromised persons requires additional considerations as described in the approach to PrEP section under the following Clinical Guidance.

Clinical Guidance

The Work Group identified additional considerations that are essential to effective administration of rabies PrEP. These include coadministration of PrEP and chloroquine (or drugs related to chloroquine), the approach to PrEP in special populations, and management of deviations from the ACIP recommendations.

Coadministration of IM rabies PrEP and chloroquine or drugs related to chloroquine. Recent data show that although concomitant administration of chloroquine and IM rabies PrEP is associated with a significant reduction in rabies antibody titer, the reduced levels remain >0.5 IU/mL (*14*). This finding is of uncertain clinical significance because immunocompetent persons who receive chloroquine and rabies vaccines would presumably mount rabies antibody titer levels ≥0.5 IU/mL and therefore not require management that differs from that for persons who did not receive concomitant rabies vaccine. However, out of an abundance of caution and because rabies is nearly always fatal, clinicians might consider avoiding chloroquine when rabies vaccine is being administered. If avoidance is not possible, ensuring that a patient's rabies antibody titer is ≥0.5 IU/mL no sooner than 1 week (preferably 2–4 weeks) after completion of the series will confirm that vaccination was effective. No impact on efficacy was observed in the same study when other antimalarials (i.e., Malarone [atovaquone plus proguanil] and doxycycline) were administered with IM rabies PrEP. Limited anecdotal reports suggest mefloquine does not impair rabies vaccine effectiveness (*15*); however, large-scale trials are needed to evaluate this hypothesis.

TABLE. (*Continued*) Rabies preexposure prophylaxis recommendations — United States, 2022

Risk category	Nature of exposure	Typical population*	Relevant disease biogeography†	Recommendations	
				Primary PrEP§ immunogenicity	Long-term immunogenicity¶
4. Elevated risk for recognized†† exposures, risk not sustained¶¶	Exposure nearly always recognized; risk for exposure higher than for general population but expected to be time-limited (≤3 years from the 2-dose primary PrEP vaccination series)	Same as for risk category 3 (above), but risk duration ≤3 years (e.g., short-term volunteer providing hands-on animal care or infrequent traveler with no expected high-risk travel >3 years after PrEP administration)	Same as for risk category 3 (above)	IM rabies vaccine on days 0 and 7	None
5. Low risk for exposure	Exposure uncommon	Typical person living in the United States	Not applicable	None	None

Abbreviations: IM = intramuscular; IU = international units; PEP = postexposure prophylaxis; PrEP = preexposure prophylaxis.

* Nature of exposure and type of work performed are the most important variables to consider when determining a person's risk category. The examples provided are intended to be a guide, but ultimately categorizations should be done on a case-by-case basis with nature of exposure considered. Some persons might be categorized into a different risk group from those suggested by the provided examples. For example, most veterinarians are in risk category 3 because they are at risk for recognized exposures after direct contact with animals. However, a veterinary pathologist who often performs necropsies on mammals suspected to have had rabies might have risk for rabies virus exposure that is more consistent with risk category 2 than risk category 3; such persons should follow the recommendations for the risk category with which their activities best fit. Similarly, most spelunkers do not often enter high-density bat caves; those who do may follow the recommendations for risk category 2 rather than risk category 3. Persons involved in the diagnosis of rabies virus, but for whom the frequency of handling rabies virus–infected tissues is low, or the procedures performed do not involve contact with neural tissue or opening of a suspected rabid animal's calvarium could consider following the recommendations for risk category 2 rather than those for risk category 1.

† Local or state health departments should be consulted for questions about local disease biogeography.

§ Primary immunogenicity refers to immunogenicity that peaks 2–4 weeks after completing the recommended primary vaccination schedule. Persons without altered immunity are expected to mount appropriate responses, and checking titers is not routinely recommended. Persons with altered immunity are advised to confirm, through laboratory testing, a rabies antibody titer ≥0.5 IU/mL ≥1 week after booster vaccination (but ideally, 2–4 weeks after completing the recommended schedule) and before participating in high-risk activities. Individual laboratories set facility-specific rules about whether acceptable antibody titers should be laboratory-confirmed for all personnel, regardless of whether personnel have altered immunity.

¶ Long-term immunogenicity refers to the ability to mount an anamnestic response to rabies virus >3 years after completion of the primary rabies vaccination series.

** Unrecognized exposures are those that recipients might not know occurred; for example, a small scratch during an inconspicuous personal protective equipment breach might not be noticed by persons testing neural tissue from a rabid animal or persons conducting ecologic studies on bats in the field.

†† Recognized exposures are bites, scratches, and splashes that are usually registered by a person because the exposure is unusual (e.g., contact with a bat) or painful (e.g., bite or scratch from a raccoon).

§§ When rabies antibody titers are <0.5 IU/mL, a booster vaccination should be provided. Antibody titers to verify booster response need not be checked after these boosters are administered to persons who are immunocompetent. For persons who are immunocompromised, the indicated antibody titer should be verified ≥1 week (ideally, 2–4 weeks) after administration of every booster vaccination.

¶¶ Sustained risk is elevated risk for rabies >3 years after the completion of the primary rabies PrEP vaccination schedule.

*** Rabies virus is unlikely to persist outside a deceased animal's body for an extended time because of virus inactivation by desiccation, ultraviolet irradiation, and other factors. Risk from transmission to persons handling animal products (e.g., hunters and taxidermists) is unknown but presumed to be low (risk category 5); direct skin contact with saliva and neural tissue of mammals should be avoided regardless of profession.

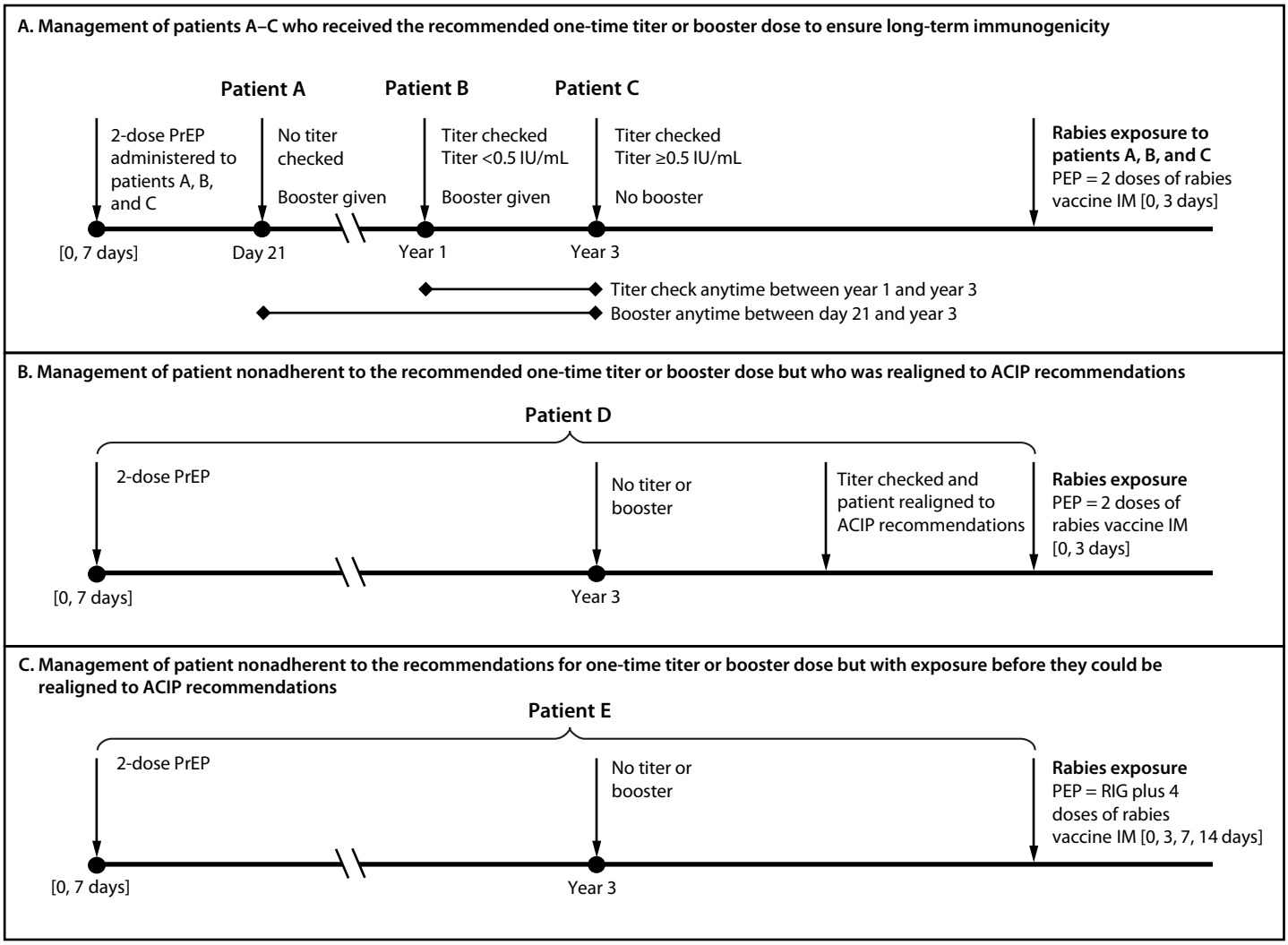
††† Checking titers after recommended booster doses is not indicated unless the recipient has altered immunity.

Approach to PrEP in special populations, including persons suspected or confirmed to be immunocompromised. Modern rabies vaccines are inactivated and have been safely administered to persons of all ages, including pregnant women and immunocompromised persons. An adequate immune response is anticipated among all immunocompetent persons (including elderly immunocompetent persons) who receive rabies vaccines in accordance with the ACIP recommendations. For this reason, proof of primary immunogenicity through laboratory confirmation is not advised for immunocompetent persons after the following actions: completion of the 2-dose primary series; administration of booster doses for serial titers <0.5 IU/mL (risk categories 1 and 2) or the one-time titer <0.5 IU/mL (risk category 3); and administration of a one-time booster dose (risk category 3).

However, among persons with primary or secondary immunodeficiencies, the immune response to vaccines, including rabies vaccines, can be suboptimal. ACIP recommends that, when possible, vaccination be delayed until a temporary immunocompromising condition has resolved or immunosuppressive medications can be withheld.¶¶ If an immunocompromising condition cannot be temporarily reversed, rabies vaccines can be administered, but antibody titer should be checked no sooner than 1 week (preferably 2–4 weeks) (*10*) after completion of the 2-dose PrEP series and all booster doses (including those administered within 3 years of the primary series and in response to a low titer during the serial titer checks recommended for risk categories 1 and 2). If the titer is <0.5 IU/mL, a booster dose should be administered, followed

¶¶ https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html

FIGURE. Management of long-term immunogenicity* for hypothetical patients (A–E)†,§,¶ who received the Advisory Committee on Immunization Practices recommended 2-dose rabies preexposure prophylaxis schedule and have sustained risk for recognized exposures (risk category 3) — Advisory Committee on Immunization Practices, United States, 2022**



Abbreviations: ACIP = Advisory Committee on Immunization Practices; IM = intramuscular injection; IU = international units; PEP = postexposure prophylaxis; PrEP = preexposure prophylaxis; RIG = rabies immunoglobulin.

* Long-term immunogenicity is considered a successful anamnestic response (i.e., rapid rise in antibody levels) after an encounter with the rabies virus antigen >3 years after the primary vaccination series.

† Patient A received the recommended booster dose during day 21–year 3 and patients B and C received the recommended one-time titer check during years 1–3. Recommended options for patients A–C include 1) a one-time rabies vaccine booster dose from day 21 to 3 years after the 2-dose primary series (patient A) and 2) a one-time rabies antibody titer check 1–3 years after the 2-dose primary series (patients B and C).

§ Patient D did not receive the recommended one-time titer or booster dose but was realigned to the ACIP recommendations before an exposure occurred. Realigning involves checking a titer. If the titer is ≥0.5 IU/mL, no further action is needed, and the patient is considered realigned with the ACIP recommendations. If the titer is <0.5 IU/mL, patient D should receive a booster dose followed by an additional titer no sooner than 1 week later (preferably 2-4 weeks later) to confirm the appropriate response.

¶ Patient E did not receive the recommended one-time titer or booster dose and had an exposure before they could be realigned to the ACIP recommendations. This patient should receive RIG and the 4-dose rabies vaccine PEP series indicated for persons not previously vaccinated.

** An acceptable antibody titer (i.e., ≥0.5 IU/mL) should be confirmed after boosters are administered to immunocompromised persons.

by a subsequent titer check. If two such booster doses fail to elicit an acceptable antibody titer, local or state public health authorities should be consulted for case-specific guidance. Participation in high-risk activities by persons confirmed or suspected to be immunocompromised should be avoided until the laboratory-confirmed minimum acceptable antibody titer is achieved or until public health authorities provide alternative guidance. Of note, if deviations in the ACIP recommendations occur as described in management of deviation section below, a titer check is recommended regardless of immune status.

Management of deviations from the recommendations. Unavoidable delays of a few days from the recommended date of the second dose of the 2-dose primary series are clinically inconsequential. The effect of longer lapses of 2 weeks or more is unknown. When substantial delays occur, local and state public health authorities should be consulted for guidance. The second dose of the primary series should not be administered before the recommended interval between doses has elapsed; if it is inadvertently administered earlier, local and state public health authorities should be consulted for guidance.

Persons who have not previously received rabies PrEP should identify the risk category based on their activities. If their activities change over time, the recommendations of the new risk category should be followed to ensure long-term immunogenicity. Persons in risk category 3 who do not obtain the titer check or booster dose recommended by ACIP within the specified interval can be realigned with the ACIP recommendations (i.e., they should first have a random titer checked regardless of their immune status); for some, titers remain ≥0.5 IU/mL (*16*) and a booster dose is not required. However, for those whose titer is <0.5 IU/mL, a booster should be administered and then titers checked no sooner than 1 week (preferably 2–4 weeks) later. Once a titer of 0.5 IU/mL is achieved, these persons should be managed the same as persons who, consistent with the ACIP recommendations, had the recommended titer or booster within 3 years of the 2-dose primary vaccination series vaccine (Figure).

Persons who have not realigned with the ACIP recommendations and have a rabies exposure require the same PEP that is recommended for persons who did not receive PrEP (i.e., rabies immunoglobulin and 4 IM doses of rabies vaccine on days 0, 3, 7, and 14) (*17*). After this, they are considered to have been previously vaccinated, and in response to any subsequent exposure, only require 2 doses of rabies vaccine on days 0 and 3. Similarly, persons whose risk was categorized as category 4 (e.g., because of short-term animal care work), might later in life shift to risk category 3 (e.g., because they are pursuing a veterinary career). Shifts from risk category 4 to risk category 3 should be managed through realignment with the ACIP recommendations described; if realignment is not done, an exposure to rabies virus should be managed with rabies immunoglobulin and the 4-dose rabies vaccine series (doses administered on days 0, 3, 7, and 14)

Implications of These Updates

More persons who are recommended to receive rabies PrEP might be vaccinated because the 2-dose series recommended in these updates is associated with lower out-of-pocket costs and takes less time to complete. Persons with only short-term (≤3 years) risk for rabies (risk category 4) require no additional titer or booster doses, and last-minute travelers who previously were not vaccinated because the 3-dose series required ≥21 days might now be vaccinated because only 1 week is needed to complete the 2-dose primary series.

The updates might also facilitate improved adherence to evidence-based ACIP recommendations. As previously mentioned, in the past, some persons recommended to have serial titers checked did not adhere to those recommendations; with this update, many such persons now have the option of a one-time titer check or a one-time booster dose (i.e., a one-time action with two options for accomplishing it). As described in the EtR framework, some persons might prefer the titer option because of the potentially lower cost if a booster is not indicated (i.e., titer is ≥0.5 IU/mL); others might prefer the convenience of proceeding directly to a booster dose. The wide interval during which the titer or booster options can be taken might defray up-front costs and allow persons more time to determine whether they expect risk for rabies >3 years. Appointments for the titer check or booster dose can be scheduled at the time of the 2-dose primary series to ensure adherence to the recommendations.

Persons who received the 3-dose PrEP schedule recommended by ACIP in the past and whose activities place them within risk category 3 require no further titer checks or booster doses; the last vaccine dose they receive as part of the 3-dose series is equivalent to the option provided in these updates for a booster dose during day 21 to year 3. However, frequency of serial titer checks (risk categories 1 and 2) is unchanged, regardless of whether the 2-dose or 3-dose primary series was received by a person.

Summary

What is already known about this topic?

Rabies is a zoonotic infection that is nearly always fatal. Preexposure prophylaxis (PrEP) is recommended for certain persons at high risk for exposure.

What is added by this report?

During 2019–2021, the Advisory Committee on Immunization Practices made multiple updates to the rabies PrEP recommendations, including the following: a 2-dose (days 0 and 7) intramuscular rabies vaccination series replaced the 3-dose schedule, a one-time titer or booster dose was advised for persons with risk for only recognized rabies exposures, risk categories were redefined, and the minimum acceptable rabies antibody titer was changed to 0.5 IU/mL.

What are the implications for public health practice?

The updates are as efficacious as previous recommendations and might facilitate improved adherence to vaccination recommendations.

A consequence of the updated minimum acceptable rabies antibody titer (0.5 IU/mL) is that when titers are checked, more persons might require a booster dose than with the previous minimum acceptable rabies antibody titer level. ACIP concluded that the benefits of the new acceptable titer outweighed this theoretical concern.

Future Research

Ongoing studies are needed to confirm long-term immunogenicity of the 2-dose PrEP series >3 years after the primary series. Studies are also needed to evaluate the frequency of and need for titer checks for persons in risk categories 1 and 2 and to examine efficacy of PrEP among immunocompromised persons.

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West Nile Virus and Other Domestic Nationally Notifiable Arboviral Diseases — United States, 2020

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Arthropod-borne viruses (arboviruses) are transmitted to humans primarily through the bite of infected mosquitoes and ticks. West Nile virus (WNV), mainly transmitted by *Culex* species mosquitos, is the leading cause of domestically acquired arboviral disease in the United States (*1*). Other arboviruses cause sporadic cases of disease and occasional outbreaks. This report summarizes passive data for nationally notifiable domestic arboviruses in the United States reported to CDC for 2020. Forty-four states reported 884 cases of domestic arboviral disease, including those caused by West Nile (731), La Crosse (88), Powassan (21), St. Louis encephalitis (16), eastern equine encephalitis (13), Jamestown Canyon (13), and unspecified California serogroup (*2*) viruses. A total of 559 cases of neuroinvasive WNV disease were reported, for a national incidence of 0.17 cases per 100,000 population. Because arboviral diseases continue to cause serious illness and the locations of outbreaks vary annually, health care providers should consider arboviral infections in patients with aseptic meningitis or encephalitis that occur during periods when ticks and mosquitoes are active, perform recommended diagnostic testing, and promptly report cases to public health authorities to guide prevention strategies and messaging.

Arboviruses are maintained in transmission cycles between arthropods and vertebrate hosts, including humans and other animals. In the United States, humans primarily become infected when bitten by an infected mosquito or tick and rarely through other routes such as blood transfusion and organ transplantation. Most human infections are asymptomatic; symptomatic infections commonly manifest as systemic febrile illness and less commonly as neuroinvasive disease.

Most endemic arboviral diseases are nationally notifiable and are reported by state health departments to CDC through ArboNET, the national arboviral disease surveillance system, using standard surveillance case definitions.* Cases are reported by a patient's state and county of residence. Confirmed and probable cases with onset of illness during 2020 are included in this report. Cases with reported meningitis, encephalitis, acute flaccid paralysis, or unspecified neurologic signs or symptoms were classified as neuroinvasive disease; other cases were classified as nonneuroinvasive disease. Incidence was calculated using 2020 midyear population estimates from the U.S. Census Bureau.† Incidence calculations were limited to neuroinvasive disease; these cases are more consistently diagnosed and reported because of disease severity. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.§

A total of 884 cases of domestic arboviral disease were reported for 2020. Cases were caused by the following viruses: West Nile (731, 83%), La Crosse (88, 10%), Powassan (21, 2%), St. Louis encephalitis (16, 2%), eastern equine encephalitis (13, 1%), Jamestown Canyon (13, 1%), and unspecified California serogroup (two, <1%; exact virus unknown). Cases were reported from 306 (10%) of the 3,143 U.S. counties. No cases were reported from Alaska, Delaware, the District of Columbia, Hawaii, Minnesota, Rhode Island, or Vermont.

Cases of WNV disease were reported from 226 counties in 40 states; 83% of patients had illness onset during July–September (Table 1). The median patient age was 62 years (IQR = 50–71 years); 459 (63%) were male. A total of 583 (80%) patients were hospitalized, and 66 (9%) died. The median age of patients who died from neuroinvasive disease was 70 years (IQR = 64–82 years).

In 2020, a total of 559 cases of neuroinvasive WNV disease were reported. The national incidence of neuroinvasive WNV disease was 0.17 cases per 100,000 population (Table 2). The highest incidences occurred in South Dakota (1.12 per 100,000) and Nebraska (0.46) (Figure). The largest numbers of neuroinvasive cases were reported from California (179), Texas (101), Florida (44), and Illinois (36), which together accounted for 64% of cases nationwide. Sixteen counties accounted for approximately 50% of WNV neuroinvasive disease cases. Incidence of neuroinvasive WNV disease increased with age, from 0.01 per 100,000 among children aged <10 years to 0.49 among adults aged ≥70 years. Incidence was higher among males (0.22) than among females (0.12).

Eleven states reported 88 La Crosse virus disease cases, with the highest numbers from Ohio (33) and North Carolina (21). The median patient age was 7 years (IQR = 4–11 years); 83 (94%) were children aged <18 years (Table 1). Most patients (86%) had illness onset during July–September. Eighty-four

* https://ndc.services.cdc.gov/case-definitions/arboviral-diseases-neuroinvasive-and-non-neuroinvasive-2015/

† https://www.census.gov/programs-surveys/popest.html

§ 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. Number and percentage of reported cases of West Nile virus and other arboviral diseases (N = 884), by virus type and selected patient characteristics — United States, 2020

Characteristic	Virus type,* no. (%) of cases					
	West Nile (n = 731)	La Crosse (n = 88)	Powassan (n = 21)	St. Louis encephalitis (n = 16)	Eastern equine encephalitis (n = 13)	Jamestown Canyon (n = 13)
Age group, yrs						
<18	16 (2)	83 (94)	3 (14)	0 (—)	3 (23)	0 (—)
18–59	302 (41)	3 (3)	6 (29)	5 (31)	2 (15)	6 (46)
≥60	413 (56)	2 (2)	12 (57)	11 (69)	8 (62)	7 (54)
Sex						
Male	459 (63)	52 (59)	14 (67)	12 (75)	7 (54)	10 (77)
Female	272 (37)	36 (41)	7 (33)	4 (25)	6 (46)	3 (23)
Period of illness onset						
Jan–Mar	5 (1)	1 (1)	1 (5)	1 (6)	0 (—)	0 (—)
Apr–Jun	38 (5)	7 (8)	10 (48)	2 (13)	0 (—)	7 (54)
Jul–Sep	607 (83)	76 (86)	4 (19)	10 (63)	12 (92)	6 (46)
Oct–Dec	81 (11)	4 (5)	6 (29)	3 (19)	1 (8)	0 (—)
Clinical syndrome						
Nonneuroinvasive	172 (24)	4 (5)	1 (5)	2 (13)	0 (—)	3 (23)
Neuroinvasive	559 (76)	84 (95)	20 (95)	14 (88)	13 (100)	10 (77)
Encephalitis†	343 (61)	66 (79)	13 (65)	8 (57)	12 (92)	9 (90)
Meningitis†	150 (27)	16 (19)	5 (25)	3 (21)	1 (8)	0 (—)
AFP†,§	26 (5)	0 (—)	1 (5)	0 (—)	0 (—)	0 (—)
Unspecified†	40 (7)	2 (2)	1 (5)	3 (21)	0 (—)	1 (10)
Outcome						
Hospitalization	583 (80)	83 (94)	17 (81)	15 (94)	13 (100)	10 (77)
Death	66 (9)	0 (—)	1 (5)	3 (19)	4 (31)	0 (—)

Abbreviation: AFP = acute flaccid paralysis.
* Two unspecified California serogroup virus cases were also reported.
† Percentages of cases of encephalitis, meningitis, AFP, and unspecified neurologic signs or symptoms are percentages of neuroinvasive cases.
§ Among the 26 West Nile virus disease cases with AFP, six persons (23%) also had encephalitis or meningitis.

(95%) patients had neuroinvasive disease and 83 (94%) were hospitalized; no deaths were reported.

Twenty-one cases of Powassan virus disease were reported from seven states, with the highest number (seven, 33%) from Massachusetts. The median patient age was 64 years (IQR = 45–69 years); 14 (67%) were male (Table 1). Dates of illness onset ranged from March to November, with 10 (48%) occurring during April–June. Twenty (95%) patients had neuroinvasive disease, and 17 (81%) were hospitalized. One patient, aged >60 years, died.

Sixteen cases of St. Louis encephalitis virus disease were reported from four states (Arizona, California, Pennsylvania, and Texas). The median patient age was 71 years (IQR = 58–80 years); 12 (75%) were male (Table 1). Ten patients (63%) had illness onset during July–September. Fourteen (88%) patients had neuroinvasive disease, and 15 (94%) were hospitalized. Three (19%) deaths were reported, all among patients aged >60 years.

Thirteen cases of eastern equine encephalitis virus disease were reported from five states (Indiana, Massachusetts, Michigan, South Carolina, and Wisconsin); all were classified as neuroinvasive disease. The median patient age was 61 years (IQR = 44–62 years); seven patients (54%) were male. Most patients (92%) had illness onset during July–September. All patients were hospitalized, and four (31%) died; among the fatal cases, three were aged >50 years and one was aged <18 years.

Thirteen Jamestown Canyon virus disease cases were reported from three states (Michigan, New Hampshire, and Wisconsin). The median patient age was 60 years (IQR = 54–69 years); 10 (77%) were male (Table 1). Illness onset dates ranged from April to September, with 54% occurring during April–June. Ten (77%) patients had neuroinvasive disease and 10 (77%) were hospitalized; no deaths were reported.

Discussion

WNV was the most common cause of domestic arboviral neuroinvasive disease in the United States during 2020. La Crosse virus continued to be the most common cause of neuroinvasive arboviral disease in children; eastern equine encephalitis virus remained the arboviral disease most likely to result in death, with 31% of reported cases being fatal (*1*).

The annual incidence of WNV neuroinvasive disease in 2020 (0.17 per 100,000) was the lowest since 2011 (0.16 per 100,000) and 59% lower than the median annual incidence during 2010–2019 (0.41; range = 0.16–0.92) (*1*,*2*). Areas with the largest decreases in neuroinvasive disease incidence in

TABLE 2. Number and rate* of reported cases of neuroinvasive arboviral disease, by virus type, U.S. Census Bureau division, and state — United States, 2020†

U.S. Census Bureau division/State	Cases, by virus type, no. (rate)*					
	West Nile	La Crosse	Powassan	St. Louis encephalitis	Eastern equine encephalitis	Jamestown Canyon
United States	**559 (0.17)**	**84 (0.03)**	**20 (0.01)**	**14 (<0.01)**	**13 (<0.01)**	**10 (<0.01)**
New England	**15 (0.10)**	—†	**9 (0.06)**	—	**5 (0.03)**	3 (0.02)
Connecticut	5 (0.14)	—	2 (0.06)	—	—	—
Maine	1 (0.07)	—	1 (0.07)	—	—	—
Massachusetts	9 (0.13)	—	6 (0.09)	—	5 (0.07)	—
New Hampshire	—	—	—	—	—	3 (0.22)
Rhode Island	—	—	—	—	—	—
Vermont	—	—	—	—	—	—
Middle Atlantic	**28 (0.07)**	**—**	**7 (0.02)**	**—**	**—**	**—**
New Jersey	3 (0.03)	—	1 (0.01)	—	—	—
New York	18 (0.09)	—	2 (0.01)	—	—	—
Pennsylvania	7 (0.05)	—	4 (0.03)	—	—	—
East North Central	**76 (0.16)**	**34 (0.07)**	**4 (0.01)**	**—**	**7 (0.01)**	**7 (0.01)**
Illinois	36 (0.29)	1 (0.01)	—	—	—	—
Indiana	3 (0.04)	1 (0.01)	—	—	1 (0.01)	—
Michigan	29 (0.29)	—	—	—	4 (0.04)	3 (0.03)
Ohio	3 (0.03)	30 (0.26)	—	—	—	—
Wisconsin	5 (0.09)	2 (0.03)	4 (0.07)	—	2 (0.03)	4 (0.07)
West North Central	**30 (0.14)**	**—**	**—**	**—**	**—**	**—**
Iowa	2 (0.06)	—	—	—	—	—
Kansas	6 (0.21)	—	—	—	—	—
Minnesota	—	—	—	—	—	—
Missouri	1 (0.02)	—	—	—	—	—
Nebraska	9 (0.46)	—	—	—	—	—
North Dakota	2 (0.26)	—	—	—	—	—
South Dakota	10 (1.12)	—	—	—	—	—
South Atlantic	**58 (0.09)**	**30 (0.05)**	**—**	**—**	**1 (<0.01)**	**—**
Delaware	—	—	—	—	—	—
District of Columbia	—	—	—	—	—	—
Florida	44 (0.20)	—	—	—	—	—
Georgia	7 (0.07)	1 (0.01)	—	—	—	—
Maryland	1 (0.02)	—	—	—	—	—
North Carolina	1 (0.01)	21 (0.20)	—	—	—	—
South Carolina	4 (0.08)	1 (0.02)	—	—	1 (0.02)	—
Virginia	1 (0.01)	1 (0.01)	—	—	—	—
West Virginia	—	6 (0.34)	—	—	—	—

See table footnotes on the next page.

2020 compared with the previous decade were the West North Central, East South Central, and Mountain regions. Arizona reported the lowest total number of cases (12) since WNV was first detected in the state in 2003. Despite the relatively low annual incidence, WNV caused most neuroinvasive arboviral disease cases in 2020.

Although neuroinvasive WNV disease incidence was low in 2020, national incidences for all other domestic arboviral diseases were higher than the median annual incidences during the previous decade; increases ranged from 22% for La Crosse virus to 133% for St. Louis encephalitis virus (*3*–*7*). The number of La Crosse virus disease cases reported was the highest since 2011 (*3*). Compared with 2019, fewer cases of eastern equine encephalitis virus disease (13 versus 38) and Powassan virus disease (21 versus 39) were reported, but national incidence for each arbovirus disease was still higher than average for the preceding 10 years (*4*,*5*).

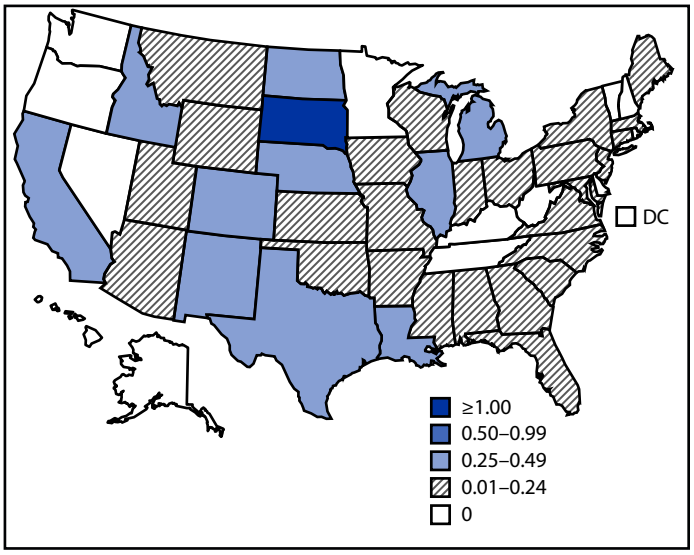
Although persons reported spending more time outdoors during the coronavirus disease 2019 (COVID-19) pandemic, thus increasing potential exposure to arboviral diseases, changes in health care seeking–behavior, prioritization of diagnostic testing for SARS-CoV-2 (the virus that causes COVID-19), and challenges in reporting of arboviral disease cases concurrent with COVID-19 likely affected reporting of arboviral disease cases, particularly for nonneuroinvasive disease cases (*8*,*9*). The percentage of WNV cases classified as neuroinvasive disease (76%) was higher than the average reported during 2010–2019 (59%), suggesting that less severe disease cases were less likely to be diagnosed and reported during the COVID-19 pandemic.

TABLE 2. (*Continued*) Number and rate* of reported cases of neuroinvasive arboviral disease, by virus type, U.S. Census Bureau division, and state — United States, 2020†

U.S. Census Bureau division/State	Cases, by virus type, no. (rate)*					
	West Nile	La Crosse	Powassan	St. Louis encephalitis	Eastern equine encephalitis	Jamestown Canyon
East South Central	**11 (0.06)**	**20 (0.10)**	—	—	—	—
Alabama	7 (0.14)	—	—	—	—	—
Kentucky	—	5 (0.11)	—	—	—	—
Mississippi	4 (0.13)	—	—	—	—	—
Tennessee	—	15 (0.22)	—	—	—	—
West South Central	**122 (0.30)**	—	—	**3 (0.01)**	—	—
Arkansas	1 (0.03)	—	—	—	—	—
Louisiana	14 (0.30)	—	—	—	—	—
Oklahoma	6 (0.15)	—	—	—	—	—
Texas	101 (0.34)	—	—	3 (0.01)	—	—
Mountain	**40 (0.16)**	—	—	**6 (0.02)**	—	—
Arizona	8 (0.11)	—	—	6 (0.08)	—	—
Colorado	17 (0.29)	—	—	—	—	—
Idaho	5 (0.27)	—	—	—	—	—
Montana	1 (0.09)	—	—	—	—	—
Nevada	—	—	—	—	—	—
New Mexico	7 (0.33)	—	—	—	—	—
Utah	1 (0.03)	—	—	—	—	—
Wyoming	1 (0.17)	—	—	—	—	—
Pacific	**179 (0.33)**	—	—	**5 (0.01)**	—	—
Alaska	—	—	—	—	—	—
California	179 (0.45)	—	—	5 (0.01)	—	—
Hawaii	—	—	—	—	—	—
Oregon	—	—	—	—	—	—
Washington	—	—	—	—	—	—

* Cases per 100,000 population, based on July 1, 2020, U.S. Census Bureau population estimates.
† Dashes indicate no cases reported.

FIGURE. Incidence* of reported cases of neuroinvasive West Nile virus disease — United States, 2020



Abbreviation: DC = District of Columbia.
* Cases per 100,000 population, based on July 1, 2020, U.S. Census Bureau population estimates.

The number of jurisdictions reporting arboviral disease cases (44) was the lowest since 2014, which suggests that public health capacity to investigate and report cases also might have been affected by the pandemic. However, because the annual incidence of arboviral diseases varies based on weather, zoonotic host factors, vector abundance, and human behavior, gauging the actual impact of COVID-19 on the occurrence, recognition, and reporting of arboviral diseases is challenging.

The findings in this report are subject to at least two limitations. First, ArboNET is a passive surveillance system that leads to underestimation of actual disease prevalence. For a case to be captured by the system, a patient must seek care, the clinician must request appropriate diagnostic tests, and results must be reported to public health authorities. An estimated 30–70 nonneuroinvasive cases occur for every neuroinvasive WNV disease case reported (*10*). On the basis of the number of neuroinvasive WNV disease cases reported for 2020, from 16,770 to 39,130 nonneuroinvasive WNV disease cases are estimated to have occurred; only 172 (≤1%) were reported. Second, because ArboNET does not require information

Summary

What is already known about this topic?

West Nile virus is the leading cause of domestically acquired arboviral disease. Other arboviruses cause sporadic cases and outbreaks, resulting in substantial morbidity and mortality.

What is added by this report?

In 2020, the national incidence of neuroinvasive West Nile virus disease was 59% lower than the median annual incidence during 2010–2019. However, the neuroinvasive disease incidence for other domestic arboviral diseases was higher in 2020 than the median annual incidence for the preceding 10 years.

What are the implications for public health practice?

Health care providers should consider arboviral infections in patients with aseptic meningitis or encephalitis during periods when mosquitoes and ticks are active, perform recommended diagnostic testing, and promptly report cases to public health authorities to guide prevention strategies and messaging.

about clinical signs, symptoms, or laboratory findings, clinical syndrome of certain cases might be misclassified.

Understanding the epidemiology, seasonality, and geographic distribution of arboviruses is important for clinical recognition. Arboviral diseases continue to cause serious illness and the locations of outbreaks vary annually. Therefore, health care providers should consider arboviral infections in patients with aseptic meningitis or encephalitis that occur during periods when ticks and mosquitoes are active, perform recommended diagnostic testing, and promptly report cases to public health authorities to guide prevention strategies and messaging. Because predicting locations and timing of arboviral disease cases is difficult, timely surveillance remains critical to identifying outbreaks and guiding prevention efforts. Prevention depends on community and individual efforts to reduce vector populations,¶ personal protective measures to decrease mosquito** and tick†† exposures, and implementation of blood donation screening to minimize transfusion transmission.§§

¶ https://www.cdc.gov/mosquitoes/mosquito-control/index.html
** https://www.cdc.gov/mosquitoes/mosquito-bites/prevent-mosquito-bites.html
†† https://www.cdc.gov/ticks/tickbornediseases/tick-bites-prevention.html
§§ https://www.cdc.gov/bloodsafety/basics.html

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Effectiveness of a COVID-19 Additional Primary or Booster Vaccine Dose in Preventing SARS-CoV-2 Infection Among Nursing Home Residents During Widespread Circulation of the Omicron Variant — United States, February 14–March 27, 2022

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Nursing home residents have experienced disproportionally high levels of COVID-19–associated morbidity and mortality and were prioritized for early COVID-19 vaccination (*1*). Following reported declines in vaccine-induced immunity after primary series vaccination, defined as receipt of 2 primary doses of an mRNA vaccine (BNT162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna]) or 1 primary dose of Ad26.COV2 (Johnson & Johnson [Janssen]) vaccine (*2*), CDC recommended that all persons aged ≥12 years receive a COVID-19 booster vaccine dose.* Moderately to severely immunocompromised persons, a group that includes many nursing home residents, are also recommended to receive an additional primary COVID-19 vaccine dose.† Data on vaccine effectiveness (VE) of an additional primary or booster dose against infection with SARS-CoV-2 (the virus that causes COVID-19) among nursing home residents are limited, especially against the highly transmissible B.1.1.529 and BA.2 (Omicron) variants. Weekly COVID-19 surveillance and vaccination coverage data among nursing home residents, reported by skilled nursing facilities (SNFs) to CDC's National Healthcare Safety Network (NHSN)§ during February 14–March 27, 2022, when the Omicron variant accounted for >99% of sequenced isolates, were analyzed to estimate relative VE against infection for any COVID-19 additional primary or booster dose compared with primary series vaccination. After adjusting for calendar week and variability across SNFs, relative VE of a COVID-19 additional primary or booster dose was 46.9% (95% CI = 44.8%–48.9%). These findings indicate that among nursing home residents, COVID-19 additional primary or booster doses provide greater protection against Omicron variant infection than does primary series vaccination alone. All immunocompromised nursing home residents should receive an additional primary dose, and all nursing home residents should receive a booster dose, when eligible, to protect against COVID-19. Efforts to keep nursing home residents up to date with vaccination should be implemented in conjunction with other COVID-19 prevention strategies, including testing and vaccination of nursing home staff members and visitors.

Each week, nursing homes certified by Centers for Medicaid & Medicare Services (CMS) report incident confirmed SARS-CoV-2 infections among residents and staff members, by vaccination status, to NHSN. This study was limited to case data reported by CMS-certified SNFs, which account for >90% of nursing homes reporting COVID-19 data to NHSN, during February 14–March 27, 2022, when the Omicron variant accounted for >99% of sequenced isolates nationwide.¶ COVID-19 case ascertainment at CMS-certified SNFs during the study period was high, because of guidelines recommending weekly testing of all residents and staff members if a single SARS-CoV-2 infection was identified in a facility.** At SNFs with contact tracing capacity, only close contacts of an infected resident or staff member were tested. Vaccination status of infected persons was categorized as 1) vaccinated with a primary series only (receipt of 2 doses of an mRNA vaccine or 1 dose of the Janssen COVID-19 vaccine ≥14 days before a SARS-CoV-2–positive test result, or receipt of an additional primary or booster dose <14 days before a SARS-CoV-2–positive test result), 2) vaccinated with an additional or booster

* During September–October, 2021, CDC recommended use of a single COVID-19 vaccine booster dose for all persons aged ≥18 years, 6 months after receipt of a primary mRNA vaccination series or 2 months after receipt of a primary Janssen vaccine dose. During January, 2022, CDC updated booster recommendations, shortening the interval from 6 months to 5 months for receiving an mRNA booster dose after a primary mRNA vaccination series. In January, 2022, CDC also expanded eligibility of booster doses, recommending that adolescents aged 12–17 years receive a booster dose 5 months after a primary Pfizer-BioNTech vaccination series. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (Accessed March 27, 2022).

† https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html (Accessed March 27, 2022).

§ CDC's NHSN provides health care facilities, such as skilled nursing and long-term care facilities with a platform for reporting outcomes and process measures. COVID-19 related vaccination and surveillance data are reported to NHSN through the long-term care facilities COVID-19 Module. https://www.cdc.gov/nhsn/ltc/covid19/index.html

¶ https://covid.cdc.gov/covid-data-tracker/#variant-proportions (Accessed April 4, 2022).

** https://www.cms.gov/files/document/qso-20-38-nh-revised.pdf

dose (receipt of any authorized COVID-19 additional primary or booster dose ≥14 days before a SARS-CoV-2–positive test result),[††] 3) unvaccinated (no COVID-19 vaccine dose or a single dose <14 days before a SARS-CoV-2–positive test result), and 4) other (receipt of a single mRNA vaccine dose ≥14 days before a SARS-CoV-2–positive test result or unspecified vaccination).

SNFs also report the weekly census of residents by vaccination status. Resident-weeks were calculated as the aggregate of weekly resident counts, by vaccination status, at each SNF. In this study, weekly case counts by vaccination status in each SNF were paired with weekly resident counts by vaccination status from 2 weeks earlier. Data from SNFs that reported no additional or booster dose coverage throughout the study period were excluded.[§§] In addition, weekly case count reports were excluded if a facility did not report corresponding resident counts for the preceding 2 weeks. Crude infection rates by vaccination status were calculated with 95% CIs based on the binominal distribution.

Infection rates among residents who received an additional or booster dose were compared with those who received primary series vaccination only to estimate relative additional or booster dose VE. The effectiveness of primary series vaccination or an additional or booster dose compared with no vaccination (i.e., absolute VEs) were not reported because of differences in visitation, quarantine, and masking policies between unvaccinated residents and vaccinated residents based on updated CMS guidelines,[¶¶] as well as the inability to adjust for confounding because of these factors. Product-specific VE also could not be estimated because SNFs only reported relevant vaccine product information in weekly resident count reports and not within weekly case count reports.

A zero-inflated Poisson mixed effects model, which adjusted for calendar week using quadratic splines and included SNF as a random effect to account for variability across facilities, was used to estimate the ratio of infection rates between residents who received an additional or booster dose and those who received primary series vaccination only. Relative VE was estimated as 1 minus the rate ratio multiplied by 100. The following characteristics were evaluated as potential confounders of relative VE: 1) weekly cumulative staff member and resident SARS-CoV-2 infection rates at each SNF during the study period (since May 8, 2020), 2) weekly SNF-level staff member COVID-19 vaccination coverage, 3) each SNF's county-level incidence of SARS-CoV-2 infection, and 4) each SNF county's CDC Social Vulnerability Index score.[***] A 10% change-in-estimate criterion for the regression coefficient was used to evaluate covariates; none met this criterion and thus none were included in the final model. Data analysis was conducted using SAS software (version 9.4; SAS Institute) and R software (version 4.1.2; R Foundation). This activity was reviewed by CDC and was conducted consistent with federal laws and institutional policies.[†††]

Overall, 15,090 SNFs provided 89,671 weekly case count reports during February 14–March 27, 2022, and 15,102 SNFs provided 89,969 weekly resident count reports during January 31–March 13, 2022. After applying exclusion criteria and pairing SNF-level weekly case with corresponding resident data, the analysis included 85,494 reports from 14,758 SNFs. The median weekly number of residents reported was 1,126,198 (IQR = 1,124,328–1,126,709); approximately 22% of whom had received primary series vaccination only, and 65% of whom had received an additional or booster dose. Among residents who had received primary series vaccination or an additional or booster dose, >90% had received mRNA COVID-19 vaccines.

Crude weekly confirmed SARS-CoV-2 infection rates declined across all vaccination groups during the study period (Figure); however, rates of infection among residents with an additional or booster dose were consistently lower than those among residents with primary series vaccination only or among unvaccinated residents. Overall, 7,510 cases were confirmed among 1,509,674 resident-weeks with primary series vaccination only and 11,334 cases were confirmed among 4,416,401 resident-weeks with an additional or booster dose (Table). The adjusted relative VE against infection for an additional or booster dose versus primary series vaccination only was 46.9%.

Discussion

Analysis of NHSN's COVID-19 surveillance and vaccination coverage data from 14,758 SNFs, including approximately 1 million nursing home residents, found that additional or

[††] NHSN COVID-19 surveillance and vaccination coverage data could not distinguish between immunocompromised nursing home residents who received an additional primary dose and residents who received a booster dose. As such, the category of residents who were vaccinated with an additional or booster dose included residents who received 1) 2 primary mRNA doses followed by a booster dose, 2) 3 primary mRNA doses, 3) 3 primary mRNA doses followed by a booster dose (i.e., 4 total doses), 4) 1 primary Janssen dose followed by a booster dose, 5) 1 primary Janssen dose and an additional primary mRNA vaccine dose, or 6) 1 primary Janssen dose and an additional primary mRNA vaccine dose followed by a booster dose. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html (Accessed March 27, 2022).

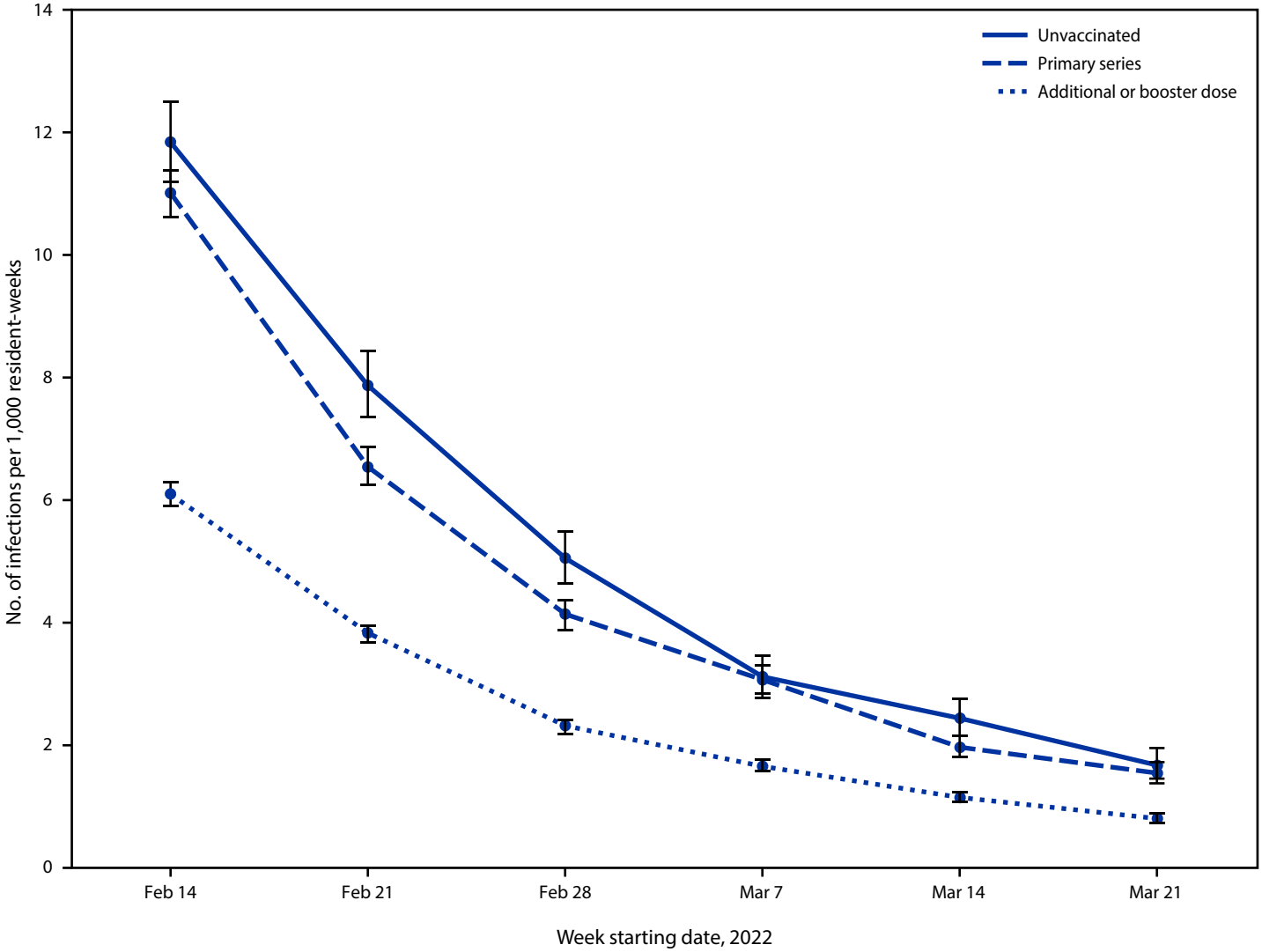
[§§] Of 89,969 weekly reports providing resident data, 438 (0.5%) reports from 73 SNFs were excluded because they reported no additional or booster dose coverage throughout the study period.

[¶¶] https://www.cms.gov/files/document/qso-20-39-nh-revised.pdf

[***] https://www.atsdr.cdc.gov/placeandhealth/svi/index.html

[†††] 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.

FIGURE. Crude weekly rates of reported confirmed SARS-CoV-2 infection among skilled nursing facility residents,* by vaccination status† and resident-week§ — National Healthcare Safety Network, United States, February 14–March 27, 2022



* Crude rates of SARS-CoV-2 infection were calculated as the number of cases, by vaccination status, among residents with corresponding vaccination status from 2 weeks earlier (January 31–March 13, 2022); 95% CIs indicated by error bars.

† Residents who completed a primary vaccination series were those who received 2 primary doses of an mRNA vaccine (Pfizer-BioNTech or Moderna) or 1 primary dose of Janssen vaccine. Residents with additional or booster dose vaccination were those who received an additional primary vaccine dose ≥28 days after the initial primary series or a booster dose ≥5 months after completion of an mRNA primary series or ≥2 months after 1 primary Janssen vaccine dose. Residents with an additional or booster dose included those who received additional primary vaccine doses and a booster dose. Unvaccinated residents were those who received no COVID-19 vaccine doses. Cases among residents with primary series vaccination were defined as infections in residents who had received primary series vaccination ≥14 days before a SARS-CoV-2–positive test result or received an additional or booster dose <14 days before a SARS-CoV-2–positive test result. Cases among residents with additional or booster dose vaccination were defined as infections in residents who received an additional primary or booster dose ≥14 days before a SARS-CoV-2–positive test result. Cases among unvaccinated residents were defined as infections in residents who received no COVID-19 vaccine doses or a single dose <14 days before a SARS-CoV-2–positive test result. Data on infections among residents who received a single dose of mRNA vaccine ≥14 days before a SARS-CoV-2–positive test result or unspecified vaccination are not presented.

§ Resident-weeks were calculated as the aggregate of weekly resident counts, by vaccination status, at each skilled nursing facility.

booster COVID-19 vaccine doses provide greater protection against infection with the Omicron variant compared with primary series vaccination alone. Efforts to keep nursing home residents up to date[§§§] with vaccination should be implemented in conjunction with other COVID-19 prevention strategies, including testing and vaccination of nursing home staff members and visitors.

The findings from this study are typically consistent with previous research, including a study among two nursing home systems in the United States during SARS-CoV-2 B.1.617.2

[§§§] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html (Accessed April 20, 2022).

TABLE. Relative effectiveness of additional COVID-19 primary or booster vaccine doses in preventing SARS-CoV-2 infection among residents of skilled nursing facilities compared with primary series vaccination only — National Healthcare Safety Network, United States, February 14–March 27, 2022

Vaccination status*	No. of resident-weeks†	No. of cases§	Crude infection rate¶ (95% CI)	Vaccine effectiveness % (95% CI)	
				Unadjusted**	Adjusted††
Primary series	1,509,674	7,510	5.0 (4.9–5.1)	Ref	Ref
Additional or booster dose	4,416,401	11,334	2.6 (2.5–2.7)	49.3 (47.3–51.3)	46.9 (44.8–48.9)

Abbreviations: Ref = referent group; SNF = skilled nursing facility.

* Residents who completed a primary vaccination series were those who received 2 primary doses of an mRNA vaccine Pfizer-BioNTech or Moderna or 1 primary dose of Janssen vaccine. Residents with additional or booster dose vaccination were those who received an additional primary vaccine dose ≥28 days after the initial primary series or a booster dose ≥5 months after completion of an mRNA primary series or ≥2 months after 1 primary Janssen vaccine dose. Residents with an additional or booster dose included those who received additional primary vaccine doses and a booster dose.

† Resident-weeks were calculated as the aggregate of weekly resident counts, by vaccination status, at each SNF.

§ Cases among residents with primary series vaccination were defined as infections in residents who had received primary series vaccination ≥14 days before a SARS-CoV-2–positive test result or received an additional or booster dose <14 days before a positive SARS-CoV-2 test result. Cases among residents with additional or booster dose vaccination were defined as infections in residents who had received an additional primary or booster dose ≥14 days before a positive SARS-CoV-2 test result. For analysis, weekly case counts by vaccination status in each SNF were paired with weekly resident counts by vaccination status from 2 weeks earlier (January 31–March 13, 2022).

¶ Infections per 1,000 resident-weeks.

** Results from a zero-inflated Poisson mixed effects model with random effects for SNF. Vaccine effectiveness was estimated as 1 minus the rate ratio multiplied by 100, with the rate ratio comparing infection rates among residents vaccinated with an additional or booster dose to residents with primary series vaccination only.

†† Results from the same model while also controlling for calendar week using quadratic splines.

(Delta) variant predominance, in which the relative effectiveness of a COVID-19 mRNA booster dose against infection, compared with primary series vaccination alone, was reported to range from 50.4% to 58.2%.¶¶¶ Relative VE estimates in this study are slightly lower and might reflect declines in VE because of potential immune evasion of the Omicron variant, consistent with findings from other studies that indicated lower VE against Omicron variant infection compared with Delta variant infection among adults aged ≥18 years (*3*,*4*). In addition, although VE by time since vaccination could not be evaluated in this study, NHSN vaccination coverage data indicate that >50% of nursing home residents had received an additional or booster dose by early December 2021****; thus, the potential waning of vaccine-induced immunity with time since an additional or booster dose receipt might also have contributed to the lower VE estimates observed in this study.

The findings in this report are subject to at least six limitations. First, NHSN does not receive resident-level demographic or clinical data. Therefore, the analysis could not account for time since vaccination, nor could it control for potential confounders, such as age, comorbidities, previous SARS-CoV-2 infection, or behaviors related to SARS-CoV-2 infection risk (e.g., mask use). Second, the analysis could not distinguish between immunocompromised residents who received an additional primary dose and residents who received a booster dose, nor could it seperate residents who received both an additional primary and booster dose. Third, differences in visitation, quarantine, and masking policies between unvaccinated residents and vaccinated residents precluded estimation of absolute VE of primary series vaccination or additional or booster doses. Fourth, relevant vaccine product data were not collected, and, therefore, product specific VE could not be estimated. Fifth, residents were only considered to be protected with an additional or booster dose 14 days after receipt of their last dose, and SARS-CoV-2 infections among residents with primary series vaccination included infections among residents who had received an additional or booster dose <14 days earlier; protective effects of these additional or booster doses might begin sooner than 14 days and, therefore, categorization of such residents and cases within the primary series vaccination group

Summary

What is already known about this topic?

Nursing home residents are at high risk for COVID-19–associated morbidity and mortality. Little is known about the vaccine effectiveness (VE) of additional or booster COVID-19 vaccine doses against SARS-CoV-2 infection in this population, particularly against the Omicron variant.

What is added by this report?

Analysis of COVID-19 surveillance and vaccination data from approximately 15,000 skilled nursing facilities found that, compared with primary series vaccination only, an additional or booster dose provided greater protection (relative VE = 46.9%) against SARS-CoV-2 infection during Omicron variant predominance.

What are the implications for public health practice?

All immunocompromised nursing home residents should receive an additional primary dose, and all nursing home residents should receive a booster dose, when eligible, to protect against COVID-19.

¶¶¶ https://www.medrxiv.org/content/10.1101/2022.01.25.22269843v1

**** https://www.cdc.gov/nhsn/covid19/ltc-vaccination-dashboard.html (Accessed April 11, 2022).

might have biased relative VE estimates in this study. Finally, this analysis was unable to distinguish between asymptomatic and symptomatic infections or assess VE of an additional or booster dose against more severe COVID-19–associated outcomes. Recent studies have reported effectiveness of a third COVID-19 mRNA dose, compared with no vaccination, to range between 80% and 90% against medically attended COVID-19–associated outcomes during Omicron variant predominance[††††] (*5*).

Efforts to maximize vaccination coverage, including additional primary doses, if recommended, and a booster dose, when eligible, among nursing home residents are critical. Such efforts should be implemented in conjunction with other COVID-19 prevention strategies, including testing and vaccination of nursing home staff members and visitors. The Food and Drug Administration has recently authorized a second booster dose for all adults aged ≥50 years and for persons aged ≥12 years who are moderately or severely immunocompromised.[§§§§] This authorization was based on data from Israel illustrating increased protection from a fourth mRNA vaccine dose against SARS-CoV-2 infection and severe COVID-19 (*6*). Ongoing monitoring of VE of additional or booster doses among nursing home residents is critical to assess the durability of protection provided by such strategies and the effectiveness against emerging SARS-CoV-2 variants.

[††††] https://www.medrxiv.org/content/10.1101/2022.03.11.22272140v1

[§§§§] On March 29, 2022 the Food and Drug Administration authorized a second booster dose of either Pfizer-BioNTech or the Moderna mRNA COVID-19 vaccines, ≥4 months after receipt of a first booster dose for adults aged ≥50 years and persons who are moderately or severely immunocompromised. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-second-booster-dose-two-covid-19-vaccines-older-and

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Acute Hepatitis and Adenovirus Infection Among Children — Alabama, October 2021–February 2022

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During October–November 2021, clinicians at a children's hospital in Alabama identified five pediatric patients with severe hepatitis and adenovirus viremia upon admission. In November 2021, hospital clinicians, the Alabama Department of Public Health, the Jefferson County Department of Health, and CDC began an investigation. This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.*

Clinical records from the hospital were reviewed to identify patients seen on or after October 1, 2021, with hepatitis and an adenovirus infection, detected via real-time polymerase chain reaction (PCR) testing on whole blood specimens, and no other known cause for hepatitis. An additional four children were identified, for a total of nine patients with hepatitis of unknown etiology and concomitant adenovirus infection during October 2021–February 2022. On February 1, 2022, a statewide health advisory† was disseminated to aid in the identification of cases at other facilities in Alabama; no additional patients were identified.

All nine children were patients at Children's of Alabama. These patients were from geographically distinct parts of the state; no epidemiologic links among patients were identified. The median age at admission was 2 years, 11 months (IQR = 1 year, 8 months to 5 years, 9 months) and seven patients were female (Table). All patients were immunocompetent with no clinically significant medical comorbidities.

Before admission, among the nine patients, vomiting, diarrhea, and upper respiratory symptoms were reported by seven, six, and three patients, respectively. At admission, eight patients had scleral icterus, seven had hepatomegaly, six had jaundice, and one had encephalopathy (Table). Elevated transaminases were detected among all patients§ (alanine aminotransferase [ALT] range = 603–4,696 U/L; aspartate aminotransferase [AST] range = 447–4,000 U/L); total bilirubin ranged from normal to elevated (range = 0.23–13.5 mg/dL, elevated in eight patients). All patients received negative test results for hepatitis viruses A, B, and C, and several other causes of pediatric hepatitis and infections were ruled out including autoimmune hepatitis, Wilson disease, bacteremia, urinary tract infections, and SARS-CoV-2 infection. None of the children had documented history of previous SARS-CoV-2 infection.

Adenovirus was detected in whole blood specimens from all patients by real-time PCR testing (initial viral load range = 991–70,680 copies/mL). Hexon gene hypervariable region sequencing was performed on specimens from five patients, and adenovirus type 41 was detected in all five specimens. Low viral loads precluded sequencing among three patients, and residual specimens were not available for sequencing for one patient. Seven patients were coinfected with other viral pathogens (Table). Six received positive test results for Epstein-Barr virus (EBV) by PCR testing but negative test results for EBV immunoglobulin M (IgM) antibodies (one patient did not have IgM testing), suggesting that these were likely not acute infections but rather low-level reactivation of previous infections. Other detected viruses included enterovirus/rhinovirus, metapneumovirus, respiratory syncytial virus, and human coronavirus OC43.

Liver biopsies from six patients demonstrated various degrees of hepatitis with no viral inclusions observed, no immunohistochemical evidence of adenovirus, or no viral particles identified by electron microscopy. Three patients developed acute liver failure, two of whom were treated with cidofovir (off-label use) and steroids, and were transferred to a different medical facility where they underwent liver transplantation. Plasma specimens from these two patients were negative for adenovirus by real-time PCR testing upon arrival at the receiving medical facility, but both patients received positive test results when retested by the same real-time PCR test using a whole blood specimen. All patients have recovered or are recovering, including the two transplant recipients.

Adenovirus type 41 is primarily spread via the fecal-oral route and predominantly affects the gut. It is a common cause of pediatric acute gastroenteritis typically with diarrhea, vomiting and fever, often accompanied by respiratory symptoms (*1*). Adenovirus is recognized as a cause of hepatitis

* 45 C.F.R. part 46.102(l)(2), 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.

† https://www.alabamapublichealth.gov/bcd/assets/adph_han_report_adenovirus_020122.pdf

§ Normal ranges are ALT = 9–25 U/L; AST = 21–44 U/L; total bilirubin = 0.1–1.0 mg/dL.

TABLE. Demographics, clinical characteristics, laboratory testing results, and clinical outcomes in a cluster of pediatric patients with acute hepatitis and adenovirus infection (N = 9) — Alabama, October 2021–February 2022

Demographic	No.
Age at admission, yrs	
0–2	5
3–4	1
5–6	3
Sex	
Female	7
Male	2
Race	
White	9
Other	0
Ethnicity	
Hispanic	6
Non-Hispanic	3
Initial sign/symptom	
Vomiting	7
Diarrhea	6
Fever	5
Upper respiratory symptoms*	3
Initial physical exam	
Scleral icterus	8
Hepatomegaly	7
Jaundice	6
Hepatic encephalopathy	1
Splenomegaly	1
Ascites	0
Liver function testing on admission, median (range)†	
ALT (U/L)	1,724 (603–4,696)
AST (U/L)	1,963 (447–4,000)
Total bilirubin (mg/dL)	7 (0.23–13.5)
Pathogen testing performed	
Blood viral PCR	9
Hepatitis A/B/C	9
Epstein-Barr Virus, blood viral PCR	9
Epstein-Barr Virus, IgM	8
Respiratory panel testing§	8
Blood culture	4
Urine culture	4
Stool culture	1
Pathogen testing result, no. positive/total no.	
Adenovirus (whole blood)	9/9
EBV¶	6/9
Enterovirus/Rhinovirus	4/8
Metapneumovirus	1/8
Respiratory syncytial virus	1/8
Human coronavirus OC43	1/8
SARS-CoV-2**	0/9
Hepatitis A/B/C	0/9
Outcome	
Recovered without transplant	7
Required transplant and recovered	2
Died	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; EBV = Epstein-Barr virus; IgM = immunoglobulin M; PCR = polymerase chain reaction.

* Upper respiratory symptoms were identified when taking the patient's history and conducting an initial physical exam. Upper respiratory symptoms can include nasal congestion, nasal discharge, cough, sore throat, wheezing, and dyspnea, among other symptoms.

† Normal ranges are ALT = 9–25 U/L; AST = 21–44 U/L; total bilirubin = 0.1–1.0 mg/dL.

§ The respiratory viral panels (ePlex Respiratory Pathogen Panel [GenMark] or BioFire Respiratory Panel [Biomérieux]) were used to test for adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus NL63, coronavirus OC43, human metapneumovirus, human rhinovirus/enterovirus, influenza A, influenza A/H1, influenza A/H1–2009, influenza A/H3, influenza B, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, respiratory syncytial virus A, respiratory syncytial virus B, *Chlamydia pneumoniae, Mycoplasma pneumoniae, Bordetella parapertussis* (BioFire only), and *Bordetella pertussis* (BioFire only).

¶ Positive EBV test results were based on PCR testing, but all patients received negative test results for EBV IgM antibodies (except one patient who did not have IgM testing) suggesting that infections were likely not acute but rather potential low-level reactivation of previous infections.

** All patients received testing for SARS-CoV-2 using nucleic acid amplification tests.

among immunocompromised children (*2*). It might be an underrecognized contributor to liver injury among healthy children (*3*); however, the magnitude of this relationship remains under investigation.

This cluster, along with recently identified possible cases in Europe (*4*–*6*), suggests that adenovirus should be considered in the differential diagnosis of acute hepatitis of unknown etiology among children. Clinicians and laboratorians should be aware of possible differences in adenovirus test sensitivity for different specimen types; tests using whole blood might be more sensitive than those using plasma. CDC is monitoring the situation closely to understand the possible cause of illness and identify potential efforts to prevent or mitigate illness. Enhanced surveillance is underway in coordination with jurisdictional public health partners. Clinicians are encouraged to report possible cases of pediatric hepatitis with unknown etiology occurring on or after October 1, 2021, to public health authorities for further investigation.¶

¶ https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_462.pdf

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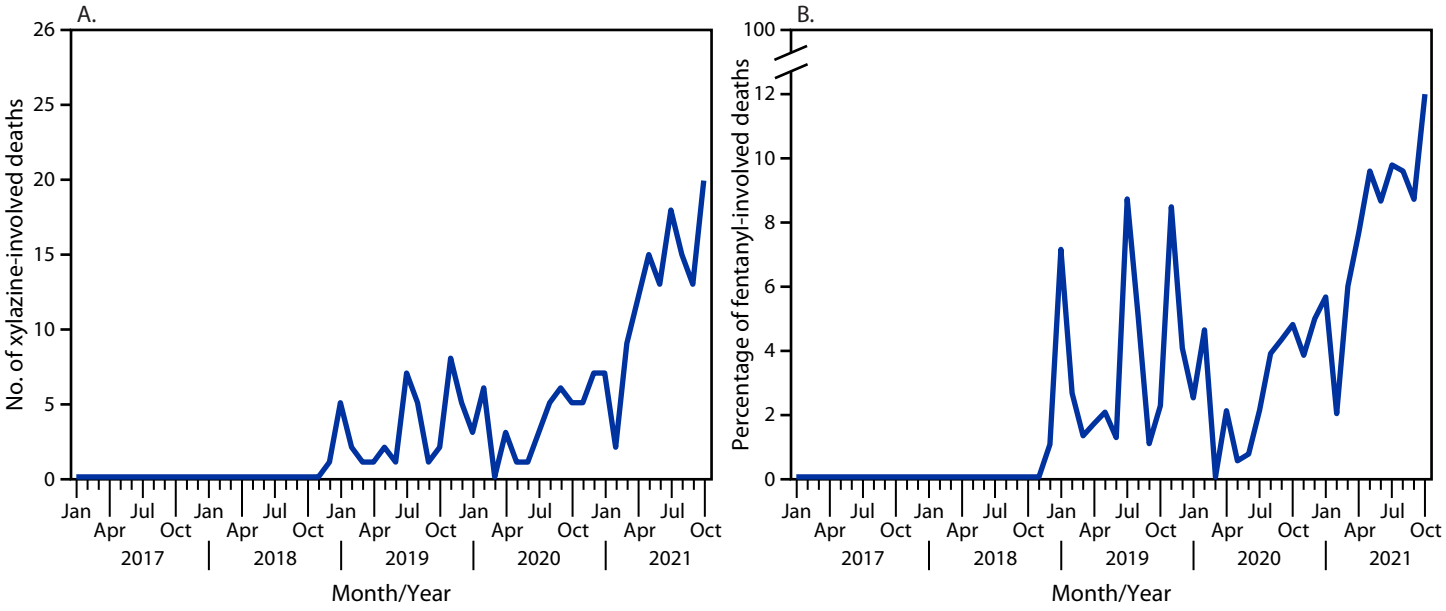
Erratum

Vol. 71, No. 13

In the report "Notes from the Field: Xylazine-Related Deaths — Cook County, Illinois, 2017–2021" on page 503, the second paragraph of the second column should have read, "A total of **210** xylazine-associated deaths were reported during the study period. Xylazine-associated deaths increased throughout the study period; incidence peaked during **October** 2021 (Figure). The percentage of fentanyl-associated deaths involving xylazine also increased throughout the study period, rising to a peak of **12.2%** of fentanyl-related deaths assessed by the Cook County Medical Examiner's Office during October 2021. Fentanyl or fentanyl analogs were detected on forensic testing in most xylazine-involved deaths **(99.1%)**. Other common co-occurring substances included diphenhydramine **(78.1%)**, cocaine **(41.9%)**, and quinine **(33.8%)**. Naloxone was detected in **33.3%** of xylazine-associated deaths."

The figure on page 503 was updated accordingly.

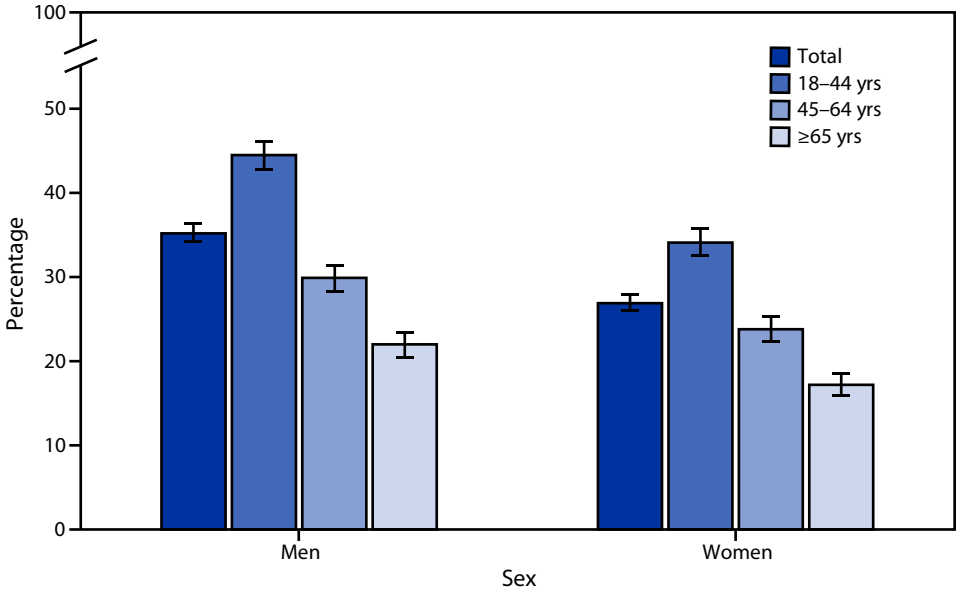
FIGURE. Number of xylazine-involved deaths (A) and percentage of fentanyl-involved deaths with detectable xylazine (B), by month — Cook County, Illinois, 2017–2021



QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage* of Adults Aged ≥18 Years Who Met the Federal Guideline for Muscle-Strengthening Physical Activity,† by Age Group and Sex — National Health Interview Survey, United States, 2020§



* With 95% CIs indicated by error bars.
† Per U.S. Department of Health and Human Services 2018 Physical Activity Guidelines for Americans, 2nd edition (https://health.gov/paguidelines). Respondents met the muscle-strengthening guideline if they reported engaging in leisure-time physical activities specifically designed to strengthen muscles, such as sit-ups, push-ups, or lifting weights, at least two times per week.
§ Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population.

In 2020, 35.2% of men and 26.9% of women aged ≥18 years met the federal guideline for muscle-strengthening physical activity. The percentage of men who met the muscle-strengthening guideline decreased with age from 44.5% for those aged 18–44 years, to 29.9% for those aged 45–64 years, and to 22.0% for those aged ≥65 years. The percentage also decreased with age among women from 34.1% for those aged 18–44 years, to 23.8% for those aged 45–64 years, and to 17.2% for those aged ≥65 years. Men were more likely to have met the muscle-strengthening guideline than women in all age groups.

Source: National Center for Health Statistics, National Health Interview Survey, 2020. https://www.cdc.gov/nchs/nhis.htm

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