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Pediatric Melatonin Ingestions — United States, 2012–2021

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Melatonin is an endogenous neurohormone that regulates the sleep-wake cycle (*1*). It is used therapeutically for insomnia in adults and for primary sleep disorders in children (*2*). Melatonin is regulated by the Food and Drug Administration (FDA) as a dietary supplement. Various synthetic melatonin preparations are widely available over the counter (OTC) in the United States with sales increasing from $285 million in 2016 to $821 million in 2020 (*3*). Children are at increased risk for melatonin exposure because of the supplement's widespread use and growing popularity as a sleep aid. In 2020, melatonin became the most frequently ingested substance among children reported to national poison control centers (*4*); however, more research is needed to describe the toxicity and outcomes associated with melatonin ingestions in children. This study assessed isolated melatonin ingestions among the pediatric population (defined here as children, adolescents, and young adults aged ≤19 years) during January 1, 2012–December 31, 2021, using the American Association of Poison Control Centers' National Poison Data System (NPDS). During the 10-year study period, 260,435 pediatric melatonin ingestions were reported to NPDS, and the annual number of ingestions increased 530%. In addition, pediatric melatonin ingestions accounted for 4.9% of all pediatric ingestions reported to poison control centers in 2021 compared with 0.6% in 2012. Pediatric hospitalizations and more serious outcomes due to melatonin ingestions increased during the study period, primarily related to an increase in unintentional ingestions among children aged ≤5 years. Five children required mechanical ventilation, and two died. Consumers and health care professionals should be encouraged to report any melatonin product–related adverse events to MedWatch, the FDA's medical product safety reporting program. Public health initiatives should focus on raising awareness of increasing numbers of melatonin ingestions among children and on the development of preventive measures to eliminate this risk.

This was a cross-sectional study of pediatric melatonin ingestions reported to U.S. poison control centers. All closed cases of single substance melatonin ingestions (generic code 0201106) involving children, adolescents, and young adults aged ≤19 years during January 1, 2012–December 31, 2021, were included (*5*). A closed case is one for which the regional poison control center determined that either no further follow-up or recommendations were required or no further information on the case was available (*5*). Aggregate national data were abstracted from NPDS (*5*). Noningestion routes of exposure, information requests, exposures with unknown age, and nonhuman exposures were excluded. Abstracted data included age group (≤5, 6–12, and 13–19 years), sex,

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ingestion reason (unintentional versus intentional), exposure and management site, disposition, and medical outcome. Those managed on-site included children treated at home or any other non–health care site. Standard descriptive statistics were used to describe and compare variables of interest. Rates (exposures per 100,000 population aged ≤19 years) were calculated using population estimates from the U.S. Census Bureau (*6*). More serious outcomes were defined as a moderate or major effect or death, as defined by the NPDS Coding Manual (*5*). Moderate effects include symptoms following an exposure that are more pronounced or systemic in nature and warrant a treatment intervention but are not life-threatening. Major effects involve symptoms considered life-threatening or that result in substantial residual disability. This study was determined to be nonhuman research and was exempt from human subject review by the Institutional Review Board of Central Michigan University.*

During 2012–2021, a total of 260,435 pediatric melatonin ingestions were reported to poison control centers, representing 2.25% of all pediatric ingestions reported during the same period. The majority of ingestions were unintentional (94.3%), involved males aged ≤5 years, occurred in the home (99.0%), and were managed on-site (88.3%) (Table). Most children (82.8%) were asymptomatic. Among those with reported symptoms, most involved the gastrointestinal, cardiovascular, or central nervous systems. Among 27,795 patients who received care at a health care facility, 19,892 (71.6%) were discharged, 4,097 (14.7%) were hospitalized, and 287 (1.0%) required intensive care. Among all melatonin ingestions, 4,555 (1.6%) resulted in more serious outcomes. Five children required mechanical ventilation, and two died. Both deaths occurred in children aged <2 years (3 months and 13 months) and occurred in the home. One ingestion involved intentional medication misuse; the reason for the other is unknown.

The number of pediatric melatonin ingestions increased 530% from 8,337 in 2012 to 52,563 in 2021, with the largest yearly increase (37.9%) occurring from 2019 to 2020. In 2021, pediatric melatonin ingestions accounted for 4.9% of all pediatric ingestions compared with 0.6% in 2012. The annual rate of ingestions per 100,000 U.S. population increased during the 10-year study period (Figure 1). This resulted largely from an increase in unintentional ingestions among children aged ≤5 years. There was also an increase in the number of ingestions requiring hospitalization and in those resulting in more serious outcomes (Figure 2). Most hospitalized patients were teenagers with intentional ingestions, whereas the largest increase in hospitalization occurred among children aged ≤5 years with unintentional ingestions.

Discussion

Pediatric melatonin ingestions reported to U.S. poison control centers, including those requiring hospitalization and

*45 C.F.R. part 46; 21 C.F.R. part 56.

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those with more serious outcomes, have increased during the past decade. Melatonin is widely available in tablet, capsule, liquid, and gummy formulations. It is cost-effective and offers an OTC therapeutic alternative to enhance sleep without use of potentially habit-forming sedative-hypnotics (*7*). Consequently, its use has increased in both adults and children (*7*,*8*). In addition, growth in the national melatonin market has occurred in response to public demand, with sales in the United States increasing by approximately 150% between 2016 and 2020 (*2*). Increased sales, availability, and widespread use have likely resulted in increased access and exposure risk among children in the home.

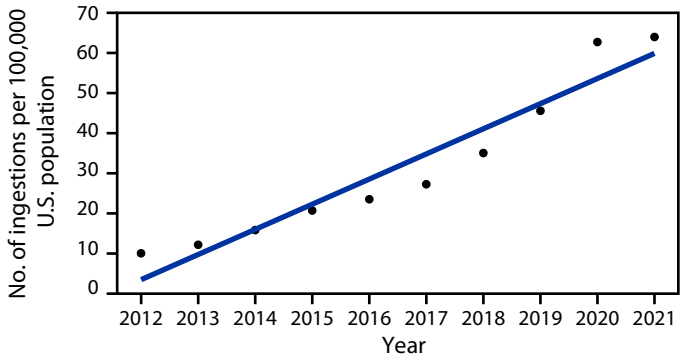
The largest annual increase in pediatric melatonin ingestions coincided with the onset of the COVID-19 pandemic. Unintentional ingestions were the primary drivers of this increase. This might be related to increased accessibility of melatonin during the pandemic, as children spent more time at home because of stay-at-home orders and school closures. Further, reports of increasing sleep disturbances during the pandemic might have led to increased availability of melatonin in the home (*9*). This pandemic-related increase in accessibility and availability might have contributed to increased exposures in children.

TABLE. Demographics and clinical characteristics of pediatric melatonin ingestions reported to poison control centers (N = 260,435) — United States, 2012–2021

Characteristic	Ingestions, no. (%)
Age group, yrs	
≤5	218,136 (83.8)
6–12	28,606 (11.0)
13–19	13,693 (5.2)
Sex	
Male	141,301 (54.3)
Female	117,872 (45.2)
Unknown	1,262 (0.5)
Reason for ingestion	
Unintentional	245,596 (94.3)
Intentional	13,722 (5.3)
Other	1,117 (0.4)
Exposure site	
Residence	257,761 (99.0)
School	561 (0.2)
Other	2,113 (0.8)
Clinical effects	
Asymptomatic	219,770 (82.8)
Symptomatic	45,647 (17.2)
CNS	37,164 (81.4)
Gastrointestinal	4,655 (10.2)
Cardiovascular	1,147 (2.5)
Metabolic	346 (0.8)
Other	2,335 (5.1)
Outcome	
No effect*	78,423 (30.1)
Minor effect†	176,435 (67.8)
More serious outcomes§	3,211 (1.2)
Death	2
Other¶	2,366 (0.9)
Management site	
Managed on-site (non-HCF)	230,032 (88.3)
Managed at HCF	27,795 (10.7)
Unknown	2,608 (1.0)
Disposition of patients managed at HCF (n = 27,795)	
Hospitalized	4,097 (14.7)
ICU	287 (1.0)
Treated and released	19,892 (71.6)
Other	3,806 (13.7)

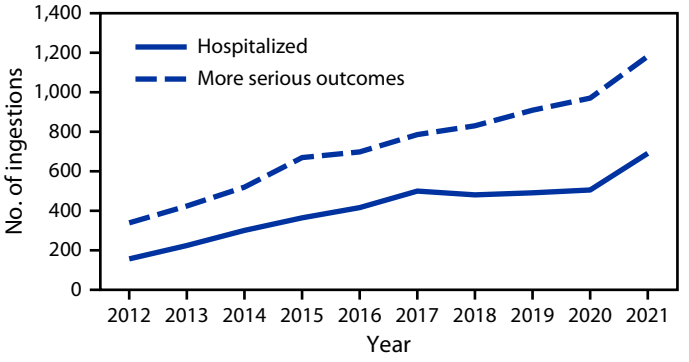
Abbreviations: CNS = central nervous system; HCF = health care facility; ICU = intensive care unit.
* No signs or symptoms.
† Minimally bothersome symptoms, self-limited, and resolved without intervention (e.g., self-limited gastrointestinal symptoms).
§ More serious outcomes included moderate effect (systemic symptoms requiring intervention; not life-threatening [e.g., brief seizure readily resolved with treatment, or high fever]), major effect (life-threatening symptoms [e.g., status epilepticus or respiratory failure requiring intubation]), and death.
¶ Cases that were not followed or unable to be followed to a known outcome but judged as likely nontoxic exposures or exposure deemed not responsible to the effect.

FIGURE 1. Rate* of pediatric† melatonin ingestions reported to poison control centers, by year§ — United States, 2012–2021



* Ingestions per 100,000 population, based on U.S. Census Bureau Annual Estimate.
† Aged ≤19 years.
§ Linear trend, p<0.001.

FIGURE 2. Number of pediatric* melatonin ingestions reported† to poison control centers, by outcome and year — United States, 2012–2021



* Aged ≤19 years.
† More serious outcomes include moderate or major effect or death, as defined by the National Poison Data System Coding Manual. Disposition (including hospitalization) and medical outcome (including more serious outcomes) are not mutually exclusive because persons with more serious outcomes are likely to be hospitalized.

Summary

What is already known about this topic?

Melatonin is regulated by the Food and Drug Administration as a dietary supplement and is a widely available over-the-counter sleep aid for adults and children.

What is added by this report?

During 2012–2021, the annual number of pediatric ingestions of melatonin increased 530% with a total of 260,435 ingestions reported. Pediatric hospitalizations and more serious outcomes also increased, primarily because of an increase in unintentional melatonin ingestions in children aged ≤5 years.

What are the implications for public health practice?

Increasing use of over-the-counter melatonin might place children at risk for potential adverse events. Public health initiatives should focus on raising awareness of increasing melatonin ingestions among children and on preventive measures to eliminate this risk.

Hospitalizations and more serious outcomes due to melatonin ingestions have increased in children. Although reasons for this are unclear, one consideration is the variability in melatonin content across products (*10*). In addition, a previous study reported melatonin content not meeting label claims within a 10% margin in approximately 71% of supplements sold in Ontario, Canada (*10*). The same study reported significant sample variability (478%) along with melatonin content varying by as much as 465% between lots of the same product. The most variation was found in the chewable formulation, which is most likely to be used by children. In addition, serotonin, a breakdown product of melatonin, was found in 26% of supplements at potentially clinically significant doses that can increase the risk for serotonin toxicity in children (*10*). Quality control issues prompted a health legislation intervention banning the sale of OTC melatonin products in Canada. Similar drug quality studies and legislation initiatives in the United States are lacking. In the United States, melatonin is categorized as a dietary supplement, requires no prescription, and is subject to less regulatory oversight. Increasing use of OTC melatonin in various formulations, lack of robust manufacturing regulations, and varied dosing recommendations can place children at risk for potential adverse events. This report highlights the need for more research into the causes of increased melatonin ingestions among children and for public health initiatives to raise awareness. Child-resistant packaging for this supplement should be considered, and health care providers should warn parents about potential toxic consequences of melatonin exposure.

The findings in this report are subject to at least three limitations. First, poison control center data rely on passive, voluntary, and self-reported case communication that might underestimate actual exposures and lead to selection and information bias. Second, the American Association of Poison Control Centers is not able to confirm the accuracy of each case reported to poison control centers, and individual chart review of all cases could not be performed. Finally, poison control center data do not include patient medical records or medical examiner report, and confirmation of whether a death was secondary to toxic effects solely from melatonin or because of comorbidities was not possible.

Melatonin ingestions and related hospitalizations have increased in children during the past decade. The largest increase occurred during the COVID-19 pandemic. Health care providers should advise parents regarding the safe storage and appropriate use of melatonin. Further, consumers and health care professionals should be encouraged to report any melatonin product–related adverse events to MedWatch, the FDA's medical product safety reporting program. These results might help guide health legislators regarding the need for public health measures to raise awareness of increasing pediatric melatonin ingestions and to develop preventative measures to eliminate this risk.

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COVID-19 Cases, Hospitalizations, and Deaths Among American Indian or Alaska Native Persons — Alaska, 2020–2021

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American Indian or Alaska Native (AI/AN) persons across the United States face substantial health disparities, including a disproportionately higher incidence of COVID-19 (*1*,*2*). AI/AN persons living in Alaska also face serious health and health care challenges, including access to care because 90% of the state's land area is inaccessible by road (*3*), and approximately one half of the state's AI/AN population (AI/AN race alone or in combination with another race) live in remote rural areas (*4*). To examine the extent of COVID-19–associated disparities among AI/AN persons living in Alaska, a retrospective analysis of COVID-19 cases reported to the Alaska Department of Health and Social Services (AKDHSS) during March 12, 2020–December 31, 2021, was conducted. The age-adjusted COVID-19 incidence among AI/AN persons was 26,583 per 100,000 standard population, approximately twice the rate among White persons living in Alaska (11,935). The age-adjusted COVID-19–associated hospitalization rate among AI/AN persons was 742 per 100,000, nearly three times the rate among White persons (273) (rate ratio [RR] = 2.72). The age-adjusted COVID-19–related mortality rate among AI/AN persons was 297 per 100,000, approximately three times that among White persons (104; RR = 2.86). Culturally competent public health efforts that are designed in collaboration with AI/AN persons and communities, including support for vaccination and other proven COVID-19 prevention strategies, are critical to reducing COVID-19–associated disparities among AI/AN persons in Alaska.

A retrospective analysis was conducted of COVID-19 incidence, and associated hospitalizations and deaths in Alaska reported to AKDHSS Section of Epidemiology during March 12, 2020–December 31, 2021.* Data analyzed consisted of a limited data set received through a data sharing agreement with AKDHSS Section of Epidemiology. COVID-19 cases were defined in accordance with CDC's National Notifiable Disease Surveillance System.† COVID-19–associated hospitalizations were defined as hospital admissions of COVID-19 patients because of severity and complications of COVID-19. Deaths were determined with death certificate audits and included decedents who had received a diagnosis of laboratory-confirmed COVID-19, as well as deaths that were likely COVID-19–related based on clinical and epidemiologic criteria as defined by CDC, with no confirmatory laboratory testing. Groups assessed by race and ethnicity included AI/AN race (alone or in combination with other races), White race alone, other races (including those not reporting AI/AN heritage who were Asian, Black or African American, Native Hawaiian or other Pacific Islander, or multiple races), and unknown race. The unknown race category included persons for whom race was not recorded, or for whom race was still under investigation.

Population proportions and age-adjusted COVID-19 case, hospitalization, and mortality rates were calculated to account for differences in underlying population age distributions. Age was aggregated into 10-year age groups. The AI/AN population in Alaska is younger than the overall state population because of higher birth rates, and because the size of the population born during 1946–1964 was small (*3*). Rates were calculated by age group and race, using the direct method standardized to the U.S. 2000 standard population and the most recent Alaska population estimates (*4*). Corresponding 95% CIs were calculated based on the gamma distribution (*5*). Bivariate analyses used Fisher's exact test given the lack of normality of the underlying data; p-values <0.05 were considered statistically significant. RRs were calculated using age-adjusted rates, with White persons as the referent group; corresponding 95% CIs that excluded 1 were considered statistically significant. COVID-19 vaccination data by race were not compatibly categorized. To assess the effect of records with unknown race on observed disparities in COVID-19 outcomes, a sensitivity analysis was performed by recalculating the RR, categorizing all those with unknown race as White persons. All analyses were conducted using R (version 1.2.5001; RStudio). This activity was reviewed by AKDHSS, the Alaska Native Tribal Health Consortium Non-Research Review Group, and CDC and was conducted consistent with applicable federal law and CDC policy.§

During March 12, 2020–December 31, 2021, a total of 159,043 COVID-19 cases were reported in Alaska. Cases in nonresidents (5,717 [3.6%]) and those in Alaska residents reported out of state (1,064 [0.7%]) were excluded from further analysis; the final analytic data set included 152,262 in-state resident cases. AI/AN persons (alone or in combination

* Data were retrieved on February 2, 2022.
† https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2021/
§ 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.

with another race), White persons, and persons of other races accounted for 39,338 (25.8%), 55,415 (36.4%), and 19,615 (12.9%) persons with COVID-19, respectively; race was unknown for 37,894 (24.9%) patients (Table 1). Among persons with COVID-19, those who were AI/AN were younger (70.1% aged <40 years) compared with those of all other races (59.0% aged <40 years) and more were female (52.5%) compared with those of all other races (47.9%).

Among 3,295 (2.2%) hospitalized COVID-19 patients, 823 (25.0%) were AI/AN persons, 1,438 (43.6%) were White persons, and 675 (20.5%) were persons of other races. Overall, 1,020 (0.7%) Alaska COVID-19 patients died; 289 (28.3%) deaths occurred among AI/AN persons, 521 (51.1%) among White persons, and 159 (15.6%) among persons of other races.

The age-adjusted COVID-19 incidence was 26,583 per 100,000 persons among AI/AN persons compared with 11,935 among White persons (RR = 2.23) (Table 2). The age-adjusted COVID-19–associated hospitalization rate was 742 per 100,000 among AI/AN persons compared with 273 among White persons (RR = 2.72), and the age adjusted COVID-19 mortality rate was 297 per 100,000 among AI/AN persons compared with 104 among White persons (RR = 2.86). Among persons of other races, the age-adjusted COVID-19 incidence was 18,268 per 100,000 persons, the age-adjusted COVID-19–associated hospitalization rate was 775 per 100,000, and the age-adjusted mortality rate was 209 per 100,000.

A sensitivity analysis that categorized persons of unknown race as White persons resulted in an RR of 1.31 (95% CI = 1.29–1.33) for COVID-19 cases in AI/AN persons compared with White persons and persons of unknown race. The RR of COVID-19–associated hospitalizations among AI/AN persons compared with White persons and those of unknown race was 2.18 (95% CI = 1.91–2.48), and of COVID-19–related deaths was 2.62 (95% CI = 2.11–3.29) for AI/AN persons compared with White persons and persons of unknown race.

Discussion

In Alaska, AI/AN persons had significantly higher adjusted rates of COVID-19, COVID-19–associated hospitalization, and COVID-19–related deaths compared with rates among White persons. Overall, although making up 20.3% of the state's population (*4*), AI/AN persons accounted for approximately one quarter of Alaska's COVID-19 cases and COVID-19–associated hospitalizations, and approximately 28% of COVID-19–related deaths. These findings are similar to those of other studies (*2*,*6*) during the COVID-19 pandemic, demonstrating a continued disproportionate impact of COVID-19 outcomes on AI/AN persons. These results are also consistent with the experience of AI/AN persons living in Alaska during the influenza A(H1N1) pandemic of 2009 (*7*), as well as the general experience of AI/AN persons in the United States with pneumonia and influenza (*8*).

The observed disparities among AI/AN persons could be the result of multiple factors. Historical trauma and structural racism negatively affect the health and well-being of AI/AN persons (*9*). In addition, living in rural and remote areas can

TABLE 1. COVID-19 incidence and outcomes by race, sex, and age group — Alaska, March 12, 2020–December 31, 2021

	No. (%)				
	AI/AN*	White†	Other§	Unknown¶	Total
Characteristic	(n = 39,338)	(n = 55,415)	(n= 19,615)	(n = 37,894)	(N = 152,262)
Sex					
Female	20,637 (52.5)	26,405 (47.6)	9,730 (49.6)	17,928 (47.3)	74,700 (49.1)
Male	18,679 (47.5)	28,883 (52.1)	9,833 (50.1)	19,657 (51.9)	77,052 (50.6)
Unknown	22 (0.1)	127 (0.2)	52 (0.3)	309 (0.8)	510 (0.3)
Age group, yrs					
<10	6,704 (17.0)	4,567 (8.2)	1,798 (9.2)	3,844 (10.1)	16,913 (11.1)
10–19	7,261 (18.5)	6,657 (12.0)	2,575 (13.1)	5,381 (14.2)	21,874 (14.4)
20–29	6,887 (17.5)	9,602 (17.3)	4,167 (21.2)	6,705 (17.7)	27,361 (18.0)
30–39	6,734 (17.1)	10,282 (18.6)	3,844 (19.6)	7,164 (18.9)	28,024 (18.4)
40–49	4,121 (10.5)	7,742 (14.0)	2,602 (13.3)	5,556 (14.7)	20,021 (13.1)
50–59	3,531 (9.0)	7,212 (13.0)	2,307 (11.8)	4,522 (11.9)	17,572 (11.5)
60–69	2,496 (6.3)	5,566 (10.0)	1,529 (7.8)	3,106 (8.2)	12,697 (8.3)
70–79	1,147 (2.9)	2,670 (4.8)	587 (3.0)	1,142 (3.0)	5,546 (3.6)
≥80	457 (1.2)	1,117 (2.0)	206 (1.1)	474 (1.3)	2,254 (1.5)
Hospitalizations	823 (2.1)	1,438 (2.6)	675 (3.4)	359 (0.9)	3,295 (2.2)
Deaths	289 (0.7)	521 (0.9)	159 (0.8)	51 (0.1)	1,020 (0.7)

Abbreviation: AI/AN = American Indian or Alaska Native.
* AI/AN race alone or in combination with other races.
† White race alone.
§ Included Asian, Black or African American, Native Hawaiian or other Pacific Islander race and ethnicities, or multiple races not including AI/AN heritage.
¶ Race was not recorded and cases are still under investigation.

result in increased health risks and decreased access to and use of health care (*10*). Despite additional health care needs, obtaining medical services is often challenging in rural communities. In Alaska, health care services are provided using a hub and spoke model, with community and regional clinics connected with small critical access hospitals in larger hub communities.¶ Tertiary care hospitals that provide advanced care are only located in urban areas (Anchorage/Matanuska-Susitna, Fairbanks, and Juneau), and travel to these facilities can be expensive, difficult, and time-consuming, resulting in less frequent health care visits for many persons.

Several actions can be taken to help achieve health equity among AI/AN persons in Alaska. Public health professionals should continue to work with tribal health organizations in Alaska to provide culturally competent and regionally required health interventions. Existing health promotion initiatives in AI/AN communities, including those related to COVID-19, can be integrated with cultural interventions to enhance relevance and respect the knowledge and wisdom of these communities as experts on their own needs (*9*). Lessons learned from AI/AN communities can also be collected and shared; COVID-19 vaccination rates vary by community, with some predominantly AI/AN communities having very high numbers of eligible residents being vaccinated.**

The findings in this study are subject to at least three limitations. First, race was unknown or still under investigation for 24.9% of cases, 11% of hospitalizations, and 5% of deaths. The extent of this exclusion on the observed disparities is unknown; however, the Tribal Health System, which is available to AI/AN persons in Alaska, more consistently documents and reports race data than do other reporting organizations and facilities. Findings from a sensitivity analysis indicate that disparities in COVID-19–associated hospitalization and COVID-19–related deaths also occurred when patients with unknown race were categorized as White persons. Second, data were restricted to the state of Alaska, and thus might not be generalizable to other AI/AN persons in the United States. Finally, the analysis was conducted on data available from cases reported in 2020 and 2021. Inclusion of additional data after further investigation of case, hospitalization, and mortality status could impact the magnitude of the observed estimates.

AI/AN persons in Alaska are at increased risk for COVID-19 illness, COVID-19–associated hospitalization,

Summary

What is already known about this topic?

American Indian or Alaska Native (AI/AN) persons across the United States face substantial health disparities, including a disproportionate incidence of COVID-19 illness.

What is added by this report?

AI/AN persons living in Alaska are at increased risk for COVID-19 illness, COVID-19–associated hospitalization, and COVID-19–related death compared with White persons living in Alaska. Rate ratios for age-adjusted case, hospitalization, and mortality rates for AI/AN persons compared with White persons in 2020 and 2021 were 2.2, 2.7, and 2.9, respectively.

What are the implications for public health practice?

Culturally competent public health efforts designed in collaboration with AI/AN persons and communities, including support for vaccination and other proven COVID-19 prevention strategies, are critical to reducing COVID-19–associated disparities among AI/AN persons in Alaska.

¶ https://dhss.alaska.gov/dph/Emergency/Documents/healthcare/publications/AlaskaStateHealthCareEnvironment.pdf

** https://experience.arcgis.com/experience/a7e8be4adbe740a1bad1393894ee4075/ (Accessed February 2, 2022).

TABLE 2. COVID-19 incidence, hospitalization, and death rates, by race* — Alaska, March 12, 2020–December 31, 2021

Cases and outcomes	No.	Incidence† (95% CI)		Rate ratio (95% CI)
		Unadjusted	Age-adjusted	
Cases				
AI/AN§	39,338	26,564 (26,303–26,828)	26,583 (26,310–26,859)	2.23 (2.18–2.28)
White	55,415	11,731 (11,633–11,829)	11,935 (11,834–12,037)	Ref
Other	19,615	18,090 (17,832–18,345)	18,268 (18,004–18,534)	1.53 (1.5–1.57)
Hospitalizations				
AI/AN§	823	556 (518–595)	742 (689–798)	2.72 (2.36–3.13)
White	1,438	304 (289–321)	273 (258–288)	Ref
Other	675	623 (576–671)	775 (714–840)	2.84 (2.47–3.27)
Deaths				
AI/AN§	289	195 (173–219)	297 (262–336)	2.86 (2.28–3.61)
White	521	110 (101–120)	104 (94–113)	Ref
Other	159	147 (125–171)	209 (176–247)	2.02 (1.58–2.57)

Abbreviations: AI/AN = American Indian or Alaska Native; Ref = referent group.

* Among persons of known race. White = White race alone; Other = Asian, Black or African American, Native Hawaiian or other Pacific Islander race, or multiple races not including AI/AN heritage.

† Cases per 100,000 persons.

§ AI/AN persons alone or in combination with other races.

and COVID-19–related death compared with other races. Culturally competent public health efforts that are designed in collaboration with AI/AN persons and communities, including support for vaccination and other proven COVID-19 prevention or treatment strategies, are critical to reducing COVID-19–associated disparities among AI/AN persons in Alaska.

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Use of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating) for Preexposure Vaccination of Persons at Risk for Occupational Exposure to Orthopoxviruses: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022

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Certain laboratorians and health care personnel can be exposed to orthopoxviruses through occupational activities. Because orthopoxvirus infections resulting from occupational exposures can be serious, the Advisory Committee on Immunization Practices (ACIP) has continued to recommend preexposure vaccination for these persons since 1980 (*1*), when smallpox was eradicated (*2*). In 2015, ACIP made recommendations for the use of ACAM2000, the only orthopoxvirus vaccine available in the United States at that time (*3*). During 2020–2021, ACIP considered evidence for use of JYNNEOS, a replication-deficient *Vaccinia virus* vaccine, as an alternative to ACAM2000. In November 2021, ACIP unanimously voted in favor of JYNNEOS as an alternative to ACAM2000 for primary vaccination and booster doses. With these recommendations for use of JYNNEOS, two vaccines (ACAM2000 and JYNNEOS) are now available and recommended for preexposure prophylaxis against orthopoxvirus infection among persons at risk for such exposures.

Orthopoxviruses are large, double-stranded DNA viruses (Genus *Orthopoxvirus*, Family Poxviridae) that comprise multiple species, including *Variola virus*, *Vaccinia virus*, *Monkeypox virus*, *Cowpox virus*, and newly discovered species (e.g., *Akhmeta virus* and *Alaskapox virus*) (*4*). Infection with an orthopoxvirus or immunization with an orthopoxvirus vaccine lends immunologic cross-protection against other viruses in the genus (*3*). Until 1971, children in the United States received an orthopoxvirus vaccine (to prevent smallpox) as part of their routine childhood vaccines. However, with the World Health Organization (WHO) declaration of the eradication of smallpox (the infection caused by *Variola virus*) in 1980 (*2*), recommendations for routine vaccinations ended worldwide.

A small subset of persons in the United States continues to receive orthopoxvirus vaccination (*3*): persons at occupational risk for exposure to orthopoxvirus infections and certain U.S. military personnel. The first group (those with occupational risk for exposure) are within the purview of ACIP and the focus of this report. Regular booster doses are recommended for persons with ongoing occupational risk for exposure to orthopoxvirus infections. Designated public health and health care worker response teams approved by public health authorities should receive booster vaccination only at the time of an event, rather than at regular intervals.*

Poxviruses are increasingly being used in a wide range of biomedical research (*3*). *Vaccinia virus* is the most frequently studied poxvirus and serves as the prototype of the orthopoxvirus genus. This orthopoxvirus is used in basic virologic research, and because of its ability to serve as a vector for the expression of foreign genetic material, it is often used as an immunology tool and potential vaccine vector. *Vaccinia virus* is considered one of the less virulent orthopoxviruses, and possibly because of this perception, many laboratorians who work with this virus do not receive preexposure prophylaxis. CDC has received reports of occupational exposures to *Vaccinia virus* over the years and in some cases, morbidity has not been insignificant (*5*,*6*) In nearly all cases, infections with *Vaccinia virus* occurred in persons who were unvaccinated or previously vaccinated but not up to date with recommended booster doses.

In addition to less virulent viruses like *Vaccinia virus*, some researchers work with more virulent orthopoxviruses, including *Variola virus* (in some CDC laboratories) and *Monkeypox virus.* ACIP has historically recommended more frequent booster vaccination doses for persons working with more virulent orthopoxviruses than for those working with less virulent orthopoxviruses (*3*).

Replication-competent poxvirus strains can cause clinical infection in humans as well as produce infectious virus that can be transmitted to others (*3*). Replication-deficient poxvirus strains, including modified vaccinia Ankara (MVA), TROVAC, and ALVAC, do not produce infectious virus in humans, and therefore do not cause clinical infection; as such, replication-deficient poxvirus strains pose a substantially lower risk of adverse events compared with replication-competent strains. During 2015–2019, ACAM2000 was the only orthopoxvirus vaccine licensed by the Food and Drug Administration (FDA); ACIP recommendations for use of ACAM2000 in the United States were published in 2015 (*3*). ACAM2000 is a replication-competent *Vaccinia virus* vaccine derived from a plaque-purified

* https://www.cdc.gov/smallpox/pdfs/revaccination-memo.pdf

clone of the same New York City Board of Health strain that was used to manufacture Dryvax vaccine, one of the vaccines used in the eradication of smallpox. Because ACAM2000 is replication-competent, there is a risk for serious adverse events (e.g., progressive vaccinia and eczema vaccinatum) with it; myopericarditis also occurs with ACAM2000 (estimated rate of 5.7 per 1,000 primary vaccinees based on clinical trial data), but the underlying mechanism is unknown (*7*,*8*).

In 2019, FDA licensed JYNNEOS, a replication-deficient MVA vaccine, for prevention of smallpox or monkeypox disease in adults aged ≥18 years determined to be at high risk for infection with these viruses. JYNNEOS is administered by subcutaneous injection as a 2-dose series delivered 28 days apart. There is no major cutaneous reaction, also known as a "take" (a vaccine site lesion often used as a marker of successful vaccination with replication-competent vaccines such as ACAM2000), following vaccination with JYNNEOS and consequently no risk for inadvertent inoculation or autoinoculation. The effectiveness of JYNNEOS was inferred from the immunogenicity of JYNNEOS in clinical studies and from efficacy data from animal challenge studies. Occurrences of serious adverse events are expected to be minimal because JYNNEOS is a replication-deficient virus vaccine. However, because the mechanism for myopericarditis following receipt of ACAM2000 is thought to be an immune-mediated phenomenon, it is not known whether the antigen or antigens that precipitate autoantibodies are present in JYNNEOS as well. ACIP began considering discussing the data for JYNNEOS in February 2020. This report describes the ACIP recommendations for the use of JYNNEOS for preexposure prophylaxis in persons at occupational risk for exposure to orthopoxviruses.

Methods

During January 2020–November 2021, the ACIP Orthopoxvirus Work Group participated in monthly or bimonthly teleconferences to consider the evidence for five questions: 1) should JYNNEOS be recommended for research laboratory personnel, clinical laboratory personnel performing diagnostic testing for orthopoxviruses, and designated response team members at risk for occupational exposure to orthopoxviruses; 2) should JYNNEOS be recommended for health care personnel who administer ACAM2000 or care for patients infected with replication-competent orthopoxviruses; 3) should persons who are at ongoing risk for occupational exposure to more virulent orthopoxviruses such as *Variola virus* or *Monkeypox virus* receive a booster dose of JYNNEOS every 2 years after the primary JYNNEOS series; 4) should persons who are at ongoing risk for occupational exposure to less virulent replication-competent orthopoxviruses such as *Vaccinia virus* or *Cowpox virus* receive a booster dose of JYNNEOS at least every 10 years after the primary JYNNEOS series; and 5) should persons who are at ongoing risk for occupational exposure to orthopoxviruses and who received an ACAM2000 primary vaccination have the option to receive a booster dose of JYNNEOS as an alternative to a booster dose of ACAM2000. The Work Group comprised experts in diverse disciplines, including laboratory, public health, infection control, preparedness, and various clinical specialties (e.g., infectious disease, obstetrics, and occupational health). Federal partners represented on the Work Group included FDA, the National Institutes of Health, the U.S. Department of Defense, and the U.S. Department of Health and Human Services-Biomedical Advanced Research and Development Authority. CDC contributors also joined Work Group meetings with subject matter expertise in orthopoxviruses, regulatory affairs, laboratory diagnostic testing, vaccine adverse events, and drug services. Data collected, analyzed, and prepared by the Work Group were deliberated by ACIP during four public meetings.

Subject matter experts performed a systematic review and metaanalysis of the published literature on August 12, 2020, to inform the recommendations; the review was not limited by date or language. The Work Group used a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to determine the certainty of evidence rated on a scale of 1 (high certainty) to 4 (very low certainty) for the following desirable and undesirable outcomes deemed critical for decision-making: prevention of disease, incidence of serious adverse events, and incidence of myopericarditis; prevention of disease was defined as prevention of an orthopoxvirus infection. Although no level of antibody protection for orthopoxviruses has been established, the detection of neutralizing antibodies after JYNNEOS is an indirect measure of protection (i.e., immunogenicity). Immunogenicity that peaks 2 weeks after completion of the 2-dose series (i.e., 6 weeks after the first vaccine in the 2-dose series) is called primary immunogenicity. Within the evidence to recommendations (EtR) framework, ACIP considered the importance of orthopoxvirus infection as a public health problem; the benefits and harms (including the graded evidence); the target populations' values and preferences; and issues of resource use, acceptability to stakeholders, feasibility of implementation, and anticipated impact on health equity.

Summary of Findings and Rationale for Recommendations

For the first and second questions, regarding recommendation for JYNNEOS as an alternative to ACAM2000 for primary vaccination, the systematic review identified three randomized controlled studies and 15 observational studies including a total of 5,775 subjects. After considering geometric mean titers and seroconversion data together, the

Work Group had moderate (level 2) certainty that JYNNEOS provides a small increase in disease prevention compared with that provided by ACAM2000.[†] The Work Group estimated with low (level 3) certainty that fewer serious adverse events occur following the JYNNEOS primary series compared with ACAM2000 primary vaccination, and that fewer events of myopericarditis occur after JYNNEOS primary series than after ACAM2000 primary vaccination. Based on the results from the GRADE assessment and EtR framework,[§] ACIP unanimously voted in favor of the JYNNEOS vaccine as an alternative to ACAM2000 for primary vaccination.

To address the third and fourth questions, regarding booster doses, the systematic review identified one randomized controlled trial and 17 observational studies that included a total of 6,417 subjects. After considering geometric mean titer and seroconversion rate together, the Work Group estimated with very low (level 4) certainty that a small increase in disease prevention occurs after JYNNEOS booster versus the JYNNEOS primary series only.[¶] The Work Group estimated with very low (level 4) certainty that fewer serious adverse events occur after a JYNNEOS booster administered following completion of the JYNNEOS primary series compared with the JYNNEOS primary series (i.e., no booster dose). No myopericarditis events were recorded in either the intervention or comparison; for this reason, the effect was not estimable and the Work Group had very low (level 4) certainty that myopericarditis does not occur after JYNNEOS boosters because of inadequate sample size to detect rare events. The ACIP unanimously voted in favor of the JYNNEOS booster vaccine after the 2-dose JYNNEOS primary series. ACIP recommended that the JYNNEOS booster dose be administered every 2 years to persons working with more virulent orthopoxviruses and every 10 years to persons working with less virulent orthopoxviruses.

For the fifth question, regarding providing the option of transitioning to JYNNEOS for a booster dose in persons who had received primary vaccination with ACAM2000, the systematic review identified one randomized controlled trial and five observational studies that included a total of 435 subjects. A total of 82% of subjects seroconverted when given JYNNEOS booster, with very low (level 4) certainty in that estimate. The Work Group estimated, with low (level 3) certainty, fewer serious adverse events occurred after the JYNNEOS booster than after the ACAM2000 booster in persons previously vaccinated with ACAM2000[**] and that fewer myopericarditis events occurred after a JYNNEOS booster than after an ACAM2000 booster in persons who received ACAM2000 as the primary vaccine (very low [level 3] certainty). Based on the results from the GRADE methodology and findings within the EtR framework,[††] ACIP unanimously voted in favor of recommending JYNNEOS boosters as an alternative to ACAM2000 boosters in persons who received ACAM2000 as the primary vaccine.

Recommendations

Research laboratory personnel,[§§] clinical laboratory personnel performing diagnostic testing for orthopoxviruses,[¶¶] designated response team members,[***] and health care personnel who administer ACAM2000 (Smallpox [Vaccinia] Vaccine, Live)[†††] or care for patients infected with orthopoxviruses[§§§] are the persons to whom these recommendations apply (Table 1). For laboratory personnel and designated response team members, ACIP recommends use of JYNNEOS for primary vaccination as an alternative to ACAM2000. For health care personnel who administer ACAM2000 or care for patients infected with orthopoxviruses, ACIP recommends use of JYNNEOS (as an alternative to ACAM2000), based on shared clinical decision-making. In addition, persons who received the 2-dose JYNNEOS primary series and who are at ongoing risk[¶¶¶] for occupational exposure to more virulent orthopoxvirus (e.g., *Variola virus* and *Monkeypox virus*), should receive a booster dose of JYNNEOS every 2 years after the primary JYNNEOS series; persons who receive the 2-dose JYNNEOS primary series and who are at ongoing risk for occupational exposure to less virulent

[†] https://www.cdc.gov/vaccines/acip/recs/grade/JYNNEOS-orthopoxvirus-primary-pq1-2.html

[§] https://www.cdc.gov/vaccines/acip/recs/grade/JYNNEOS-orthopoxvirus-primary-pq1-etr.html; https://www.cdc.gov/vaccines/acip/recs/grade/JYNNEOS-orthopoxvirus-primary-hcp-etr.html

[¶] https://www.cdc.gov/vaccines/acip/recs/grade/JYNNEOS-orthopoxvirus-booster.html

[**] https://www.cdc.gov/vaccines/acip/recs/grade/JYNNEOS-orthopoxvirus-heterologous.html

[††] https://www.cdc.gov/vaccines/acip/recs/grade/JYNNEOS-orthopoxvirus-heterologous-etr.html

[§§] Research laboratory personnel are those who directly handle cultures or animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., Monkeypox virus, Cowpox virus, and Variola virus).

[¶¶] Clinical laboratory personnel who perform routine chemistry, hematology, and urinalysis testing, including for patients with suspected or confirmed orthopoxvirus infections, are not included in this recommendation because their risk for exposure is very low.

[***] Public health authorities, at their own discretion, may approve a cohort of health care personnel, public health personnel, or both, to receive primary vaccination against orthopoxviruses for preparedness purposes (e.g., first responders who might participate in a smallpox or monkeypox outbreak).

[†††] https://www.fda.gov/media/75792/download

[§§§] For example, those caring for patients enrolled in clinical trials for replication-competent orthopoxvirus vaccines and those caring for persons with suspected or confirmed orthopoxvirus infections (e.g., clinicians and environmental services personnel).

[¶¶¶] Continued risk refers to persistent risk due to occupational work performed. Designated public health and healthcare worker response teams approved by public health authorities are not at "continued risk" because they are vaccinated for the purposes of preparedness.

orthopoxviruses, (e.g., *Vaccinia virus* or *Cowpox virus*), should receive booster doses of JYNNEOS at least every 10 years after the primary JYNNEOS series. ACIP also recommends that persons who received an ACAM2000 primary vaccination and who are at ongoing risk for occupational exposure to orthopoxviruses may receive a booster dose of JYNNEOS as an alternative to a booster dose of ACAM2000.

Clinical Guidance

Considerations in Choosing JYNNEOS or ACAM2000 for Primary Vaccination

JYNNEOS involves a replication-deficient virus and has fewer contraindications, no risk for inadvertent inoculation and autoinoculation, and is associated with fewer serious adverse events compared with ACAM2000 (Table 2). In addition, most health care providers have experience with and are comfortable providing vaccines by subcutaneous administration, the route by which JYNNEOS is administered. ACAM2000, on the other hand, is administered percutaneously through a multiple puncture (scarification) technique, through 15 jabs with a stainless steel bifurcated needle that has been dipped into the reconstituted vaccine, a vaccination technique that is unique to orthopoxvirus vaccinations (*3*). JYNNEOS involves 2 vaccine doses 28 days apart and vaccine protection is not conferred until 2 weeks after receipt of the second dose; ACAM2000 involves 1 dose of vaccine and peak vaccine protection is conferred within 28 days.

For those working with more virulent orthopoxviruses, the frequency of booster doses also differs: ACAM2000 boosters are recommended every 3 years, whereas JYNNEOS boosters are recommended every 2 years. After successful administration of vaccine, ACAM2000 produces a take containing infectious vaccinia virus capable of transmission through autoinoculation and inadvertent inoculation of close contacts of vaccinees; JYNNEOS does not produce a take. Some persons might prefer receiving ACAM2000 because the vaccine is a derivative of Dryvax, which was used successfully in eradicating smallpox, a clear demonstration of its effectiveness in preventing disease.

A robust antibody response following a single dose of JYNNEOS has been observed in clinical trials (*9*). In addition, limited data from animal model studies indicate that a single dose of JYNNEOS might provide protection for some persons against orthopoxvirus infection when administered before and closely after (1 day) viral challenge (*10*,*11*).

Considerations for Transitioning from the Use of One Orthopoxvirus Vaccine to the Other for Booster Doses

Persons who previously received ACAM2000 should decide before their next booster dose whether to receive ACAM2000 or JYNNEOS. Persons who transition to receiving JYNNEOS boosters are expected to continue receiving JYNNEOS boosters and to not revert to ACAM2000; in addition, the frequency of booster doses should correspond to the vaccine used for boosters. For example, persons who previously received ACAM2000 every 3 years because of work with more virulent orthopoxviruses might decide to change to JYNNEOS when their next booster dose is due; in these cases, subsequent JYNNEOS booster doses should be administered every 2 years.

Fewer persons are expected to transition from JYNNEOS to ACAM2000; however, if those situations arise, they should be handled on a case-by-case basis. If this transition is approved by public health authorities, vaccinees should be advised that the expectation is that they will receive ACAM2000 for all future vaccine booster doses.

Contraindications To and Precautions Associated with Vaccinations to Prevent Orthopoxvirus Infections

JYNNEOS is contraindicated in persons with a serious allergy to a vaccine component (Table 3). Primary vaccination with ACAM2000 is contraindicated in persons with the following conditions: serious allergy to a vaccine component, history of atopic dermatitis or other exfoliative skin condition,**** an immunocompromising condition (e.g., due to a disease or therapeutics),†††† pregnancy, breastfeeding, and known underlying heart disease (e.g., coronary artery disease or cardiomyopathy). ACAM2000 vaccination is also contraindicated if the vaccine recipient cannot sufficiently isolate from household contacts who have a history of atopic dermatitis or other active exfoliative skin condition, an immunocompromising condition, or who are pregnant or aged <1 year; household contacts include persons with prolonged intimate contact with the potential vaccine recipient and others who might have direct contact with the vaccination site or with potentially contaminated materials (e.g., clothing or vaccination site dressings). Availability of JYNNEOS provides opportunities for vaccinating persons in situations where ACAM2000 might be contraindicated.

Because of the documented risk for myocarditis after receipt of both ACAM2000 and mRNA COVID-19 vaccines (*12*) and the unknown risk for myocarditis after JYNNEOS, persons might consider waiting 4 weeks after orthopoxvirus vaccination (either JYNNEOS or ACAM2000) before receiving an mRNA

**** Examples include eczema, burns, impetigo, varicella-zoster, herpes, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease (keratosis follicularis).

†††† Conditions include HIV; AIDS; leukemia; lymphoma; generalized malignancy; solid organ transplantation; therapy with alkylating agents, antimetabolities, radiation, tumor necrosis factor inhibitors, or high-dose corticosteroids; being a recipient of a hematopoietic stem cell transplant <24 months ago or ≥24 months ago but with graft-versus-host disease or disease relapse; or having autoimmune disease with immunodeficiency as a clinical component.

TABLE 1. Recommendations for ACAM2000 and JYNNEOS vaccines for persons at occupational risk for exposure to orthopoxviruses — Advisory Committee of Immunization Practices, United States, 2022

Recommendations	Vaccine product	
	ACAM2000	JYNNEOS
Who should receive the vaccine?	Persons at risk for occupational exposure to orthopoxviruses*	
Who should be offered the vaccine?	Persons who administer ACAM2000 or care for patients with infection with replication-competent viruses	
Populations for whom booster vaccination is recommended at specific intervals	Persons who are at ongoing risk† for occupational exposure to orthopoxviruses	
Booster frequency§		
Persons working with more virulent orthopoxviruses (e.g., *Variola virus* or *Monkeypox virus)*	Every 3 years	Every 2 years
Persons working with less virulent orthopoxviruses (e.g., *Vaccinia virus* or *Cowpox virus*)	At least every 10 years	

* Research laboratory personnel, clinical laboratory personnel performing diagnostic testing for orthopoxviruses, designated response team members, and health care personnel who administer ACAM2000 (Smallpox [Vaccinia] Vaccine, Live) or care for patients infected with orthopoxviruses.
† Ongoing risk due to occupational work performed; response personnel are not considered at "sustained risk" for orthopoxvirus infections.
§ Booster doses are recommended for response personnel only once an event is identified.

TABLE 2. Distinctions between ACAM2000 and JYNNEOS that might facilitate decision-making among vaccinees at risk for orthopoxvirus infections — United States, 2022

Characteristic	Vaccine product	
	ACAM2000*	JYNNEOS
Vaccine virus	Replication-competent vaccinia virus	Replication-deficient modified vaccinia Ankara
"Take" following vaccination†	Yes	No
Risk for inadvertent inoculation and autoinoculation	Yes	No
Risk for serious adverse event	Yes	No significant events identified during clinical trials
Risk for cardiac adverse events	Myopericarditis in 5.7 per 1,000 primary vaccinees	Clinical trial data limited in evaluating this outcome; however, no significant events in data abstracted from single study arms§
Assessment of effectiveness	FDA assessed by comparing immunologic response and take rates to Dryvax*	FDA assessed by comparing immunologic response to ACAM2000 and animal studies
Administration	Percutaneously using a bifurcated needle by multiple puncture (scarification) technique,¶ single dose	Subcutaneously, 2 doses 28 days apart

Abbreviation: FDA = Food and Drug Administration.
* Both ACAM2000 and Dryvax are derived from the New York City Board of Health strain of vaccinia; ACAM2000 is a second generation smallpox vaccine derived from a clone of Dryvax, purified, and produced using modern cell culture technology.
† A "take" is postvaccination lesion often used as a marker of successful vaccination after ACAM2000.
§ Because JYNNEOS is a replication-deficient virus vaccine, serious adverse events are believed to be fewer. However, the mechanism of myopericarditis in persons who receive ACAM2000 is poorly understood; for this reason, it is unknown whether persons who receive JYNNEOS might experience myopericarditis.
¶ https://www.fda.gov/media/75792/download

COVID-19 vaccine, particularly adolescent or young adult males. However, if an orthopoxvirus vaccine is recommended for prophylaxis in the setting of an outbreak, administration of orthopoxvirus vaccine should not be delayed because of recent receipt of an mRNA COVID-19 vaccine. No minimum interval between mRNA COVID-19 vaccination and orthopoxvirus vaccination is necessary.

Vaccinations Administered to Special Populations

Persons with atopic dermatitis, eczema, or other exfoliative skin conditions. Studies evaluating JYNNEOS in persons with atopic dermatitis have demonstrated immunogenicity in eliciting a neutralizing antibody response. No safety signals were revealed. However, persons with these conditions might be at increased risk for severe disease if an occupational infection occurs despite vaccination (*13*).

Persons with immunocompromising conditions. JYNNEOS is safe to administer to persons with immunocompromising conditions. However, such persons might be at increased risk for severe disease if an occupational infection occurs, despite vaccination. In addition, persons with immunocompromising conditions might be less likely to mount an effective response after any vaccination,[§§§§] including

[§§§§] https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html

TABLE 3. Contraindication to administration of ACAM2000 and JYNNEOS to recipients or their household contacts with certain conditions — United States, 2022

Clinical characteristic	Contraindication to receipt of ACAM2000			Contraindication to receipt of JYNNEOS
	Vaccine recipient with condition			
	Primary vaccination	Revaccination	Household contact with condition*	
History or presence of atopic dermatitis	Y	Y	Y	—
Other active exfoliative skin conditions†	Y	Y	Y	—
Immunosuppression§	Y	Y	Y	—
Pregnancy¶	Y	Y	Y	—
Age <1 year**	Y	Y	Y	—
Breastfeeding††	Y	Y	—	—
Serious vaccine component allergy	Y	Y	—	Y
Known underlying heart disease (e.g., coronary artery disease or cardiomyopathy)	Y	Y	—	—
≥3 known major cardiac risk factors§§	Y	—	—	—

Abbreviation: Y = yes.

* Household contacts include persons with prolonged intimate contact with the potential vaccinee (e.g., sexual contacts) and others who might have direct contact with the vaccination site or with potentially contaminated materials (e.g., dressings or clothing). JYNNEOS is a replication-deficient vaccine and therefore should not present a risk of transmission to household contacts.

† Conditions include eczema, burns, impetigo, varicella-zoster, herpes, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease (keratosis follicularis). Studies evaluating JYNNEOS in persons with atopic dermatitis have demonstrated immunogenicity in eliciting a neutralizing antibody response and did not reveal any significant safety concerns.

§ Conditions include HIV; AIDS; leukemia; lymphoma; generalized malignancy; solid organ transplantation; therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor inhibitors, or high-dose corticosteroids; being a recipient of a hematopoietic stem cell transplant <24 months ago or ≥24 months ago but with graft-versus-host disease or disease relapse; or having autoimmune disease with immunodeficiency as a clinical component. Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to JYNNEOS because of their immunocompromised status.

¶ Available human data on JYNNEOS administered to pregnant women are insufficient to determine vaccine-associated risks in pregnancy. However, animal models, including rats and rabbits, have shown no evidence of harm to a developing fetus.

** ACAM2000 is contraindicated in infants aged <1 year. Caution should be used when considering the administration of ACAM2000 or JYNNEOS to children and adolescents aged <18 years. JYNNEOS is not licensed for persons aged <18 years and has not been rigorously evaluated in this population.

†† The safety and efficacy of JYNNEOS has not been evaluated in breastfeeding women. It is not known whether JYNNEOS is excreted in human milk and data are not available to assess the impact of JYNNEOS on milk production or safety of JYNNEOS in breastfed infants. However, JYNNEOS vaccine is replication-deficient and therefore should not present a risk of transmission to breastfed infants. Caution should be used when considering the administration of JYNNEOS to breastfeeding women.

§§ Major cardiac risk factors include hypertension, diabetes, hypercholesterolemia, heart disease at age ≤50 years in a first-degree relative, and smoking. Clinical studies have not detected an increased risk of myopericarditis in recipients of JYNNEOS. Persons with underlying heart disease or ≥3 major cardiac risk factors should be counseled on the theoretical risk of myopericarditis given the uncertain etiology of myopericarditis associated with replication-competent smallpox vaccines.

after JYNNEOS; the risk/benefit ratio should be considered along with whether it is considered imperative to vaccinate an immunocompromised person.

Pregnant women. Available human data on JYNNEOS administered to pregnant women are insufficient to determine vaccine-associated risks in pregnancy. However, animal models, including rats and rabbits, have shown no evidence of harm to a developing fetus.

Breastfeeding women. The safety and efficacy of JYNNEOS has not been evaluated in breastfeeding women. It is not known whether JYNNEOS is excreted in human milk. Data are not available to assess the impact of JYNNEOS on milk production or the safety of JYNNEOS in breastfed infants. However, because JYNNEOS vaccine is replication-deficient, it likely does not present a risk of transmission to breastfed infants and can be administered to women who are breastfeeding if vaccination is critical.

Children and adolescents aged <18 years. Although occupational exposure to orthopoxviruses is unlikely in persons aged <18 years, it is important to note that JYNNEOS is not licensed for persons aged <18 years and has not been rigorously evaluated in this population. Public health authorities should be consulted if JYNNEOS is being considered for children and adolescents aged <18 years. Administration of ACAM2000 to infants aged <1 year is contraindicated. Caution should be used when considering the administration of ACAM2000 or JYNNEOS to children and adolescents aged <18 years.

Persons with multiple cardiac risk factors. Major cardiac risk factors include hypertension, diabetes, hypercholesterolemia, heart disease at age ≤50 years in a first-degree relative, and smoking and the presence of three or more of these factors are contraindications to primary vaccination with ACAM2000. Clinical studies have not detected an increased risk for myopericarditis in recipients of JYNNEOS. Persons

with underlying heart disease or three or more major cardiac risk factors should be counseled about the theoretical risk for myopericarditis following vaccination with JYNNEOS given the uncertain etiology of myopericarditis associated with replication-competent smallpox vaccines such as ACAM2000.

Reporting of Adverse Events

Adverse events following vaccination can be reported to the Vaccine Adverse Event Reporting System (VAERS). Reporting is encouraged for any clinically significant adverse event, even if it is uncertain whether the vaccine caused the event. Information on how to submit a report to VAERS is available at https://vaers.hhs.gov/index.html or by telephone at 1-800-822-7967.

Peak Antibody Response, Confirming Effective Vaccination in Immunocompromised Persons, and Correlate of Protection After Vaccination with JYNNEOS

Peak antibody response is achieved 2 weeks after receipt of the second dose of the 2-dose JYNNEOS vaccination series (*9*). Evidence of a take is often used as a marker of successful vaccination after ACAM2000 (*3*). Because JYNNEOS is a replication-deficient vaccine, vaccination with JYNNEOS does not produce a take; however, clinical trials have demonstrated high rates of seroconversion after the 2-dose series. Therefore, effective vaccination can be assumed for immunocompetent persons. Routine antibody titer testing (to confirm successful vaccination) following vaccination with JYNNEOS is not recommended for immunocompetent persons. If the decision is made to vaccinate immunocompromised persons, titer testing by CDC might be considered on a case-by-case basis; clinicians considering vaccinating immunocompromised persons should consult public health authorities. Because a correlate of protection has not been established and there is no known antibody titer level that will ensure protection, titer results should be interpreted with caution in such cases to avoid providing a false sense of security. An immunocompetent person is considered fully immunized 2 weeks following administration of the second dose of the 2-dose JYNNEOS vaccination series, which is when clinical studies have demonstrated maximal antibody titers. Titer testing might also be considered on a case-by-case basis after vaccination of persons working with more virulent orthopoxviruses (e.g., *Variola virus* and *Monkeypox virus*).

Minimizing Risk for Occupational Exposures

Many persons with contraindications to vaccination with ACAM2000 (e.g., atopic dermatitis, immunocompromising conditions, breastfeeding, or pregnancy) may receive vaccination with JYNNEOS. However, because the number of immunocompromised persons is increasing in the United States (*14*), and these persons might be less likely to mount an effective vaccine response, infections in vaccinated persons might occur. Outcomes after an infection in a vaccinated person could be particularly severe in these populations, particularly following exposure to more virulent orthopoxviruses (*3*); for this reason, vaccine recipients might consider avoiding high-risk exposures until after temporary conditions (e.g., pregnancy or transient therapy with immunocompromising therapeutics) are completed. If high-risk exposures cannot be avoided, persons who are pregnant, immunocompromised, or breastfeeding or who have atopic dermatitis may receive JYNNEOS in consultation with their health care provider and after careful consideration of the risks and benefits. Irrespective of vaccination status, all persons who work with orthopoxviruses should wear appropriate personal protective equipment.¶¶¶¶

Future Research

Additional data on JYNNEOS vaccine are needed. Further studies are needed to determine the duration of protection after the 2-dose JYNNEOS vaccination series; recommendations regarding the frequency of booster doses can be modified accordingly. The effectiveness of a single dose JYNNEOS series should be evaluated if orthopoxvirus exposures occur before peak immunogenicity is achieved. Clinical trials evaluating the risk for myopericarditis and serious adverse events are needed to ensure that the risks are characterized and guidance about co-administration of JYNNEOS with mRNA COVID-19 vaccines can be elucidated. Establishing a correlate of protection after vaccination with JYNNEOS might facilitate confirmation of effective vaccination in certain populations and might also shed light on the effectiveness of a single dose of JYNNEOS vaccine. In addition, extensive studies to date have not identified the specific small mammal reservoir for some orthopoxviruses (e.g., *Monkeypox virus*); identifying the specific reservoir might facilitate the identification of high-risk activities for acquiring orthopoxvirus infections that are not already recognized.

¶¶¶¶ https://www.cdc.gov/labs/BMBL.html

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Summary

What is already known about this topic?

In 2015, the Advisory Committee on Immunization Practices (ACIP) recommended preexposure prophylaxis with ACAM2000, a replication-competent live virus *Vaccinia virus* vaccine, for certain U.S. persons at risk for occupational exposure to orthopoxviruses.

What is added by this report?

In 2019, JYNNEOS, a replication-deficient live *Vaccinia virus* vaccine was licensed in the United States. On November 3, 2021, ACIP voted to recommend JYNNEOS preexposure prophylaxis as an alternative to ACAM2000 for certain persons at risk for exposure to orthopoxviruses.

What are the implications for public health practice?

A second vaccine is now available for persons for whom vaccination against orthopoxvirus infections is recommended. Potential vaccinees should weigh the risks and benefits of each vaccine when deciding which to receive.

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Notes from the Field

Lead Poisoning in a Family of Five Resulting from Use of Traditional Glazed Ceramic Ware — New York City, 2017–2022

Paromita Hore, PhD[1]; Kolapo Alex-Oni, MPH[1]; Nevila Bardhi, MPH[1]; Slavenka Sedlar, MA[1]

The New York City (NYC) Department of Health and Mental Hygiene (DOHMH) receives blood lead test results for NYC residents and conducts investigations of child and adult lead poisoning cases (*1*). Routine blood lead screening of a child in 2017 ultimately led to the discovery of a family of five with blood lead levels at or above the CDC blood lead reference value at that time of 5 μg/dL (range = 5–53 μg/dL) in November 2020.*,† Case investigations revealed that the elevated blood lead levels were associated with the use of traditional, glazed ceramic ware. DOHMH intervention resulted in a decrease in blood lead levels for all family members (range = 1–6 μg/dL at last measurement dates).

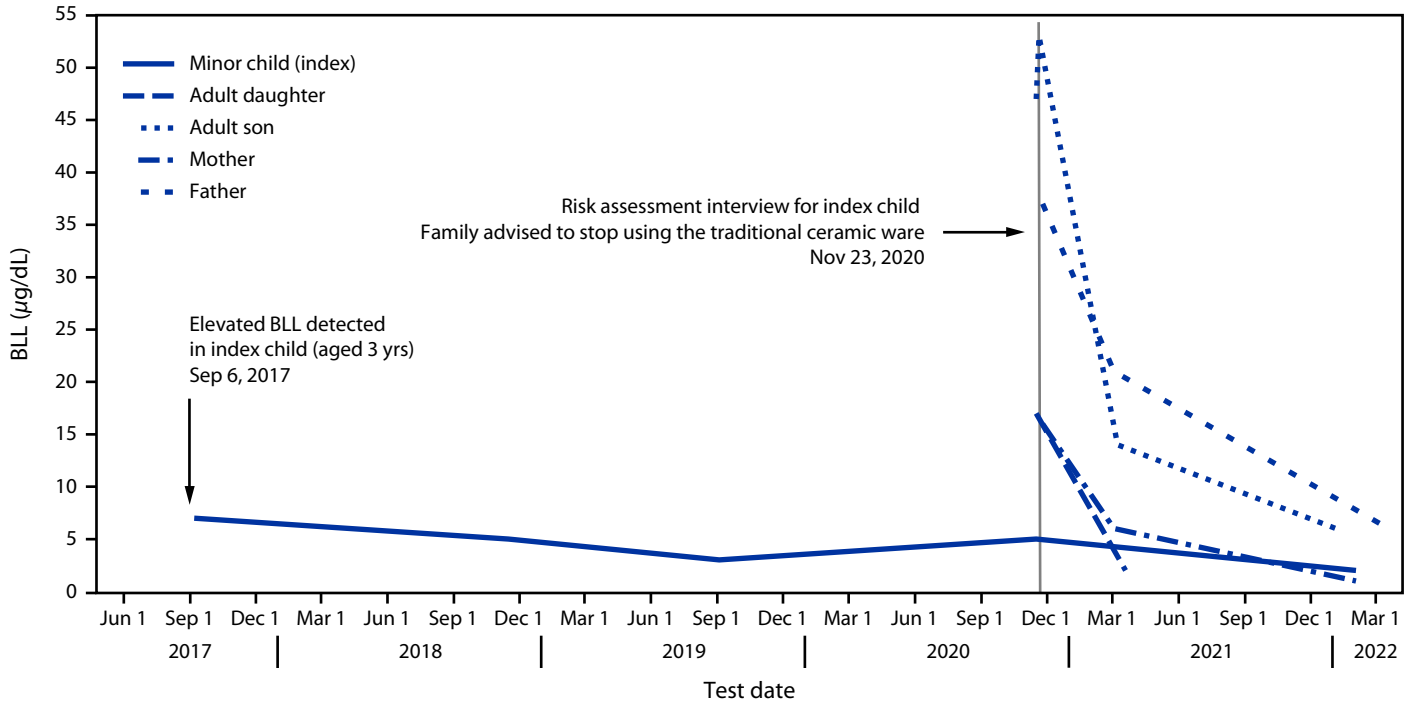
In September 2017, during routine screening by a health care provider, a child aged 3 years was found to have a blood lead level of 7 μg/dL (Figure). At the time, DOHMH's threshold for an in-home inspection was 10 μg/dL; therefore, a home inspection was not conducted. DOHMH sent letters to the child's guardians and to the medical provider recommending follow-up testing for the child, testing of family members, and providing guidance on how to reduce lead exposure, including avoiding use of clay pots and dishes from other countries. In 2018, the child received a blood lead test result of 5 μg/dL. Letters were sent to the family and to the medical provider. A DOHMH home inspection was offered, but the family declined.

In November 2020, the child's blood was retested for lead, and, as encouraged by the family physician and DOHMH, blood samples from the child's two adult siblings were also tested; all three had blood lead levels at or above 5 μg/dL (5, 17, and 53 μg/dL, respectively). Shortly thereafter, the mother and father received elevated blood lead test results (16 and 37 μg/dL, respectively).

During follow-up risk assessment interviews, DOHMH learned that the family was using traditional ceramic ware purchased in Mexico for cooking, storing meals, and making coffee. DOHMH screened the ceramic ware using an X-ray fluorescence device (Viken Detection). The glazed interior measured 15.7 mg of lead per cm^2, a level with the potential to leach substantial amounts of lead, particularly

* https://www.cdc.gov/nceh/lead/default.htm
† https://www.cdc.gov/niosh/topics/ables/ReferenceBloodLevelsforAdults.html

FIGURE. Blood lead levels in members of a single family with exposure to traditional glazed ceramic ware — New York City, 2017–2022



Abbreviation: BLL = blood lead level.

when used for cooking (*2*). The family again declined a home inspection; consequently, DOHMH was unable to ascertain potential exposures to other lead sources, including lead paint, for the index child. Occupational sources were excluded for the adults. The mother reported that she sometimes used Mexican spices for cooking, and the father reported being engaged in household renovation activities. The family did not provide spice samples, and because they did not agree to a home inspection, it is not known whether or to what extent these potential sources might have contributed to the poisonings. The family stopped using the traditional, glazed ceramic ware for food and drinks after speaking with DOHMH investigators, and their blood lead levels declined to 2–21 μg/dL within 3–4 months and to 1–6 μg/dL after 14–16 months.

Lead can cause serious health effects in both children and adults; therefore, exposure to known lead sources should be avoided. Traditional ceramic ware from around the world has been found to contain lead at levels thousands of times higher than regulatory limits in the United States (*3*). The lead used for aesthetic and other purposes on the ceramic ware's glaze or paint can transfer to foods or drinks that are prepared, served, or stored in these products, placing users at risk for lead exposure. DOHMH has investigated lead poisoning in children and adults associated with ceramic ware purchased in Ecuador, Mexico, Morocco, Turkey, the United States, and Uzbekistan (*3*). Continued efforts to raise awareness about lead hazards associated with traditional ceramic ware are needed among potential users and health care providers. The family in this report was unaware of the potential for ceramic ware to contain lead, despite previous DOHMH guidance. Although DOHMH has taken enforcement actions to stop NYC businesses from selling lead-containing ceramic ware, this does not eliminate the hazard because families often bring such items from their home countries, as was the case for the family described in this report. In September 2021, DOHMH issued a press release (*3*) and health advisory (*4*) concerning the risk for lead exposure from traditional ceramic ware. A similar press release had been issued in May 2017 (*5*). Ultimately, source control (i.e., eliminating use of lead in ceramic glazes) is needed, which requires the engagement of global stakeholders. This investigation highlights the importance of testing blood lead levels of all household members when one member receives a diagnosis of an elevated blood lead level. In addition, local health departments should conduct a holistic risk assessment that examines multiple potential sources of lead exposure.

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Notes from the Field

Influenza A(H3N2) Outbreak Following a School Event — Los Angeles, California, March 2022

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On March 22, 2022, an outbreak of acute respiratory illness among attendees of an off-campus school banquet was reported to the Los Angeles County Department of Public Health (LACDPH). A total of 177 students and seven teachers had attended the banquet 3 days earlier. By March 21, illness with signs and symptoms that included fever, cough, headache, and fatigue was reported by 72 (41%) students. Four students sought treatment at an urgent care facility; none were hospitalized. The median interval from the banquet to symptom onset was 47 hours (range = 14–91 hours). Because of the high attack rate, school administrators closed the school to in-person attendance on March 21. LACDPH obtained a line list of all banquet attendees, developed a survey to ascertain symptoms and exposures, offered testing for respiratory pathogens including SARS-CoV-2 using a multiplex polymerase chain reaction assay (BioFire Diagnostics, LLC), and conducted an environmental assessment of the event hall.

Among the 184 attendees, 128 (63%) completed the survey, and 174 (95%) completed testing for respiratory pathogens (Table). Among those tested, 56 (32%) received a positive test result for influenza A(H3N2). The median interval from symptom onset to testing was 4 days (range = 0–11 days). SARS-CoV-2 was not detected among any of the tested participants. Of the 25 persons who responded regarding influenza vaccination status, four (16%) reported having received influenza vaccine before the school event, and 21 (84%) reported that they had not been vaccinated. Universal mandates regarding COVID-19 mitigation measures (i.e., mask use and physical distancing) had been lifted before the date the banquet occurred. Environmental assessment of the event space did not reveal any pertinent violations (e.g., issues with ventilation or overcrowding).

LACDPH concluded that the outbreak was caused by influenza A(H3N2) virus. Although influenza activity has been lower this season than during seasons preceding the COVID-19 pandemic, large influenza outbreaks have been reported during the past year (*1*). Three co-occurring factors likely contributed to this large outbreak. First, influenza activity in the community was increasing at the time of this outbreak (the percentage of respiratory specimens testing positive for influenza at local sentinel laboratories had approximately tripled, from 0.9% during the week ending February 12, 2022, to 3.2% during the week ending March 19, 2022). Second, this increase in influenza activity coincided with the cessation of LACDPH mandates for face masks and physical distancing (March 1, 2022); mask mandates were lifted at this school on March 14. Given that the influenza virus is transmitted primarily through aerosols, the absence of mask use likely accelerated the spread. Third, interim estimates of influenza vaccine effectiveness against illness caused by influenza A(H3N2) virus infection were low this season (*2*). LACDPH recommended that all students and staff members wear face masks for ≥1 week

TABLE. Characteristics of attendees of a school banquet associated with an influenza A(H3N2) outbreak (N = 174)* — Los Angeles County, California, March 2022

Characteristic	Influenza test result,† no. (%)		
	Total (N = 174)	Positive (n = 56)	Negative (n = 118)
Age, yrs, median (range)	**16 (11–66)**	15 (14–18)	17 (11–66)
Sex			
Male	**89 (51)**	39 (70)	50 (42)
Female	**85 (49)**	17 (30)	68 (58)
Time from exposure to symptom onset, hrs, median (range)	—	47 (14–91)	—
Results of respiratory pathogen testing			
SARS-CoV-2	**13 (7)**	0 (—)	0 (—)
Other pathogens	**13 (7)**	4§ (7)	13¶ (11)
Symptoms or fever**			
Total	**32 (18)**	**16 (29)**	**16 (14)**
Fever**	**27 (16)**	11 (69)	16 (100)
Cough**	**30 (94)**	14 (88)	16 (100)
Sore throat**	**30 (94)**	14 (88)	16 (100)
Fatigue**	**26 (81)**	14 (88)	13 (81)
Chills**	**26 (81)**	13 (81)	13 (81)
Headache**	**25 (78)**	13 (81)	12 (75)
Body aches**	**24 (75)**	13 (81)	11 (69)
Influenza vaccination status			
Total††	**25 (14)**	**15 (27)**	**10 (8)**
Vaccinated	**4 (16)**	1 (7)	3 (30)
Not vaccinated	**21 (84)**	14 (93)	7 (70)

* Of the 184 attendees, 174 were tested for respiratory pathogens.
† Using multiplex polymerase chain reaction assay (BioFire Diagnostics, LLC).
§ Human rhinovirus/enterovirus (one), parainfluenza virus 2 (one), OC43 coronavirus (one), and 229E coronavirus (one).
¶ Human rhinovirus/enterovirus (six), parainfluenza virus 2 (four), 229E coronavirus (two), and 1 HKU1 coronavirus (one). Some persons received positive test results for more than one virus.
** Among respondents reporting fever or symptoms consistent with influenza. The total number of survey respondents who reported symptoms (32) is fewer than the total who reported symptoms to school administration (72).
†† Among respondents who received multiplex polymerase chain reaction testing and provided information about influenza vaccination status.

after onset of the last symptomatic case at the school and advised persons who receive a positive influenza test result to immediately seek influenza antiviral therapy.

These findings highlight the potential for influenza viruses to cause outbreaks of acute respiratory illness with high attack rates. Several states have reported recent surges in late-season influenza activity this year. Vaccination can prevent serious influenza-related complications and is recommended for all persons eligible to receive the vaccine. As COVID-19 preventive measures are lifted across the country, influenza virus infections should be considered as a potential cause of respiratory outbreaks.

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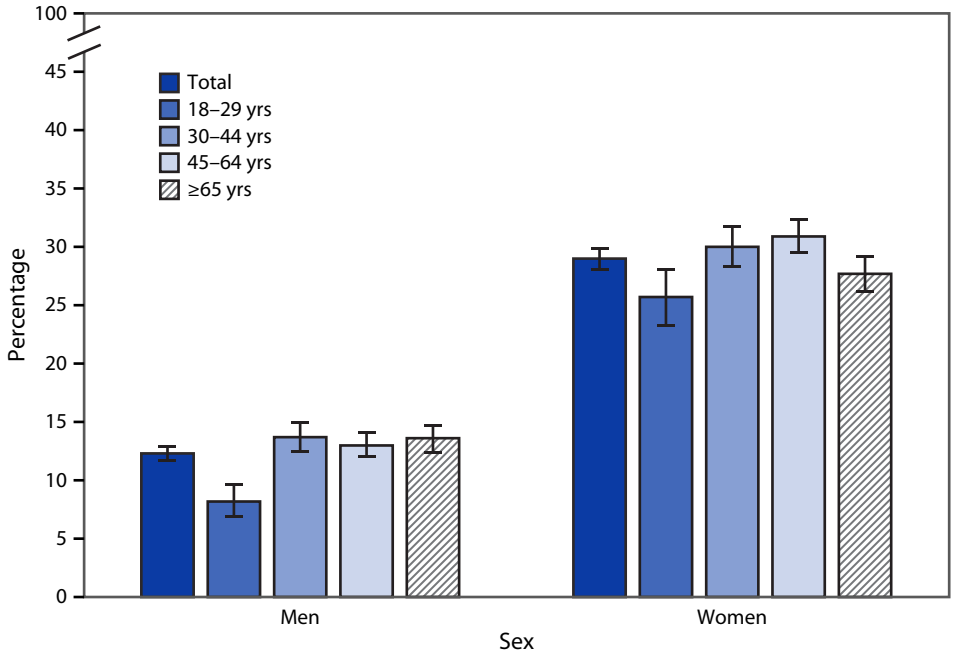
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage* of Adults Aged ≥18 Years Who Always Use Sunscreen When Outside for >1 Hour on a Sunny Day,† by Sex and Age Group — National Health Interview Survey, United States, 2020§



* With 95% CIs indicated by error bars.
† Based on a response of "always" to the question, "When you go outside on a sunny day, for more than one hour, how often do you use sunscreen?" Approximately 2.5% of adults who answered that they do not go outside on a sunny day for >1 hour were excluded from the analysis.
§ Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population.

In 2020, 12.3% of men and 29.0% of women aged ≥18 years always used sunscreen when outside on a sunny day for >1 hour. The percentage of men who always used sunscreen was lowest among those aged 18–29 years (8.2%) and increased to 13.7% among those aged 30–44, 13.0% among those aged 45–64, and 13.6% among those aged ≥65 years. The percentage of women who always used sunscreen was lower among those aged 18–29 and ≥65 years (25.7% and 27.7%, respectively) compared with those aged 30–44 and 45–64 years (30.0% and 30.9%, respectively). For every age group, women were more likely than men to always use sunscreen.

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

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