Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 70 / No. 44
November 5, 2021

Progress Toward Global Eradication of Dracunculiasis, January 2020–June 2021

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Dracunculiasis (Guinea worm disease), caused by the parasite *Dracunculus medinensis*, is traditionally acquired by drinking water containing copepods (water fleas) infected with *D. medinensis* larvae, but in recent years also appears increasingly to be transmitted by eating fish or other aquatic animals. The worm typically emerges through the skin on a lower limb of the host 1 year after infection, causing pain and disability (*1*). There is no vaccine or medicine to prevent or medicine to treat dracunculiasis; eradication relies on case containment* to prevent water contamination and other interventions to prevent infection: health education, water filtration, treatment of unsafe water with temephos (an organophosphate larvicide), and provision of safe drinking water (*1*,*2*). The eradication campaign began in 1980 at CDC (*1*). In 1986, with an estimated 3.5 million cases† occurring annually in 20 African and Asian countries§ (*3*), the World Health Assembly called for dracunculiasis elimination (*4*). The Guinea Worm Eradication Program (GWEP), led by The Carter Center and supported by the World Health Organization (WHO), UNICEF, CDC, and other partners, began assisting ministries of health in countries with endemic disease. With 27 cases in humans reported in 2020, five during January–June 2021, and only six countries currently affected by dracunculiasis (Angola, Chad, Ethiopia, Mali, South Sudan, and importations into Cameroon), achievement of eradication appears to be close. However, dracunculiasis eradication is challenged by civil unrest, insecurity, and epidemiologic and zoologic concerns. Guinea worm infections in dogs were first reported in Chad in 2012. Animal infections have now overtaken human cases, with 1,601 reported animal infections in 2020 and 443 during January–June 2021. Currently, all national GWEPs remain fully operational, with

* Transmission from a patient with dracunculiasis is considered to be contained only if all of the following conditions are met for each emerging worm: 1) the infected patient is identified ≤24 hours after worm emergence; 2) the patient has not entered any water source since the worm emerged; 3) a village volunteer or other health care provider has managed the patient properly; 4) the containment process, including verification of dracunculiasis, is validated by a Guinea Worm Eradication Program supervisor within 7 days of emergence of the worm; and 5) the approved chemical temephos (Abate) is used to treat known or potentially contaminated surface water. Proper patient management includes cleaning and bandaging the lesion until the worm has been fully removed manually and by providing health education to discourage the patient from contaminating any water source. If two or more emerging worms are present, transmission is not contained until the last worm is removed. Similar criteria are in place for the containment of animal infections.

† A dracunculiasis case is defined as an infection occurring in a person exhibiting a skin lesion or lesions with emergence of one or more worms that is laboratory-confirmed as *Dracunculus medinensis* at CDC. Because *D. medinensis* has a 10–14-month incubation period, each infected person is counted as having a case only once during a calendar year.

§ Initially 20 countries, but the former country of Sudan officially separated into two countries (Sudan and South Sudan) on July 9, 2011.

INSIDE

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precautions taken to ensure safety of program staff and community members in response to the COVID-19 pandemic. Because of COVID-19, The Carter Center convened the 2020 and 2021 annual GWEP Program Managers meetings virtually, and WHO's International Commission for the Certification of Dracunculiasis Eradication met virtually in October 2020. Since 1986, WHO has certified 199 countries, areas, and territories dracunculiasis-free. Six countries are still affected: five with endemic disease and importations into Cameroon. Seven countries (five with endemic dracunculiasis, Democratic Republic of the Congo, and Sudan) still lack certification (*4*). The existence of infected dogs, especially in Chad, and impeded access because of civil unrest and insecurity in Mali and South Sudan are now the greatest challenges to interrupting transmission. This report describes progress during January 2020–June 2021 and updates previous reports (*2*,*4*,*5*).

In 2020, Angola, Cameroon, Chad, Ethiopia, Mali, and South Sudan reported 27 cases in humans; Cameroon, Chad, Ethiopia, and Mali reported 1,601 infected animals (mostly domestic dogs), compared with 54 cases in humans and 2,000 infections in animals in 2019 (Table 1). During January–June 2021, five cases were reported in Chad (four) and Ethiopia (one), and 443 infected animals were reported in Chad (441) and Mali (two), compared with 19 cases and 1,115 animal infections during January–June 2020. This difference equates to a 74% reduction in human cases and a 60% reduction in animal infections during this 6-month period in 2021 compared with 2020. During January–June 2021, CDC received 13 specimens from humans for morphologic or molecular identification, including five that were laboratory-confirmed *D. medinensis*¶ (Table 2), compared with 44 received and 21 (41%) confirmed during January–June 2020. During the first 6 months of 2021, CDC received 36 animal specimens, six (17%) of which were confirmed, compared with 19 received and five confirmed during January–June 2020. *D. medinensis* worms from animals are genetically indistinguishable from those removed from humans (*6*). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.**

In affected countries, the national GWEP receives monthly case reports from supervised volunteers in villages under active surveillance†† (Table 3). Villages where endemic transmission has ended (i.e., zero cases or animal infections reported for ≥12 consecutive months) are kept under active surveillance for

¶ Specimens are laboratory-confirmed as *D. medinensis* at CDC by morphologic examination under a microscope or polymerase chain reaction assay. https://www.cdc.gov/dpdx/dxassistance.html

** 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.

†† Villages under active surveillance are those that have endemic dracunculiasis or are at high risk for importation. Active surveillance involves daily searches of households by village volunteers (supported by their supervisors) for persons or animals with signs of dracunculiasis. An imported case in a human or animal infection is one resulting from ingestion of contaminated water or transport/paratenic host in a place other than the community where the case or infection is detected and reported. Since 2012, no internationally imported cases or infections have been reported except in Cameroon.

The *MMWR* series of publications is published by the Center for Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30329-4027.

Suggested citation: [Author names; first three, then et al., if more than six.] [Report title]. MMWR Morb Mortal Wkly Rep 2021;70:[inclusive page numbers].

2 additional years. WHO certifies a country as dracunculiasis-free after adequate nationwide surveillance for ≥3 consecutive years with no indigenous cases or animal infections.[§§]

Country Reports

Angola. Details of the unexpected discovery of dracunculiasis in three humans during 2018–2020 with no history of foreign travel and one dog in 2019 have been described previously (*4*). Despite ongoing active surveillance in 54 communities and routine integrated case searches (e.g., during National Immunization Days), no case or infected dog was detected from January 2021 through June 2021. Angola offers a US$450 equivalent reward for reporting an infected human or animal. Provisional DNA analysis of Angola's Guinea worm specimens yielded no clear link to another *D. medinensis* population.

Chad. Chad reported 12 cases in 10 villages in 2020. During the first half of 2021, Chad reported four cases in humans, 56% fewer cases than the nine reported during January–June 2020.

During 2020, Chad reported 1,508 dog and 63 cat infections, compared with 1,935 dog and 47 cat infections in 2019 (Table 1). During January–June 2021, 60% fewer infected dogs (428) and 48% fewer infected cats (13) were reported than during the same period of 2020 (1,081 dogs and 25 cats).

[§§] An indigenous dracunculiasis case in a human or animal infection is defined as an infection consisting of a skin lesion or lesions with emergence of one or more Guinea worms in a person or animal who had no history of travel outside their residential locality during the preceding year.

Transmission of *D. medinensis* to humans and animals is hypothesized to occur from eating inadequately cooked fish, other aquatic transport, or paratenic hosts (hosts in which the larval parasite does not develop) (*7*). The Carter Center is helping Chad's Ministry of Health implement active village-based surveillance for animal and human infections in 2,336 at-risk villages as of June 2021, an increase of four villages since December 2020 (Table 3). Since June 2017, approximately 81% of households sampled monthly in communities at risk were burying fish entrails; 83% and 81% of infected dogs were tethered (contained) in 2020 and during January–June 2021, respectively. Water treatment with temephos reached 75% of 408 villages with dog or human infections by December 2020 and 87% of 182 villages by June 2021. In December 2020, 49% of villages reporting infected dogs or humans had at least one source of copepod-free drinking water.

In areas under surveillance in Chad, 83% of residents surveyed in 2020 knew of the cash rewards for reporting human or animal infections; 92% of those surveyed in January–June 2021 knew of the rewards. Surveillance generated 61,341 reports about possible human or dog infections during January–June 2021 compared with 50,893 during the same period in 2020.

Cameroon. Cameroon reported one case, five infected dogs, and one infected cat in 2020 in villages less than 3 miles (5 km) from the Chad-Cameroon border that were likely infected in Chad, because the affected villages included families living

TABLE 1. Number of reported indigenous dracunculiasis cases in humans and infections in animals, by country — worldwide, January 2019–June 2021

Country	No. (% Contained) Jan–Dec 2019	No. (% Contained) Jan–Dec 2020	% Change Jan–Dec 2019 to Jan–Dec 2020	No. (% Contained) Jan–Jun 2020	No. (% Contained) Jan–Jun 2021	% Change Jan–Jun 2020 to Jan–Jun 2021
Human cases						
Angola	1 (0)	1 (0)	0	1 (0)	0 (—)	–100
Cameroon	0 (—)	1 (0)*	—	1 (0)	0 (—)	–100
Chad	49 (53)	12 (42)	–75	9 (44)	4 (75)	–56
Ethiopia	0 (—)	11 (100)	—	7 (100)	1 (100)	–86
Mali[†]	0 (—)	1 (0)	—	1 (0)	0 (—)	–100
South Sudan	4 (50)	1 (100)	–75	0 (—)	0(—)	—
Total	**54 (52)**	**27 (63)**	**–51**	**19 (58)**	**5 (80)**	**–74**
Animal infections[§]						
Angola	1 (0)	0 (—)	–100	0 (—)	0 (—)	—
Cameroon	0 (—)	6 (100)*	—	6 (100)	0 (—)	–100
Chad	1,982 (76)	1,571 (81)	–21	1,106 (79)	441 (60)	–61
Ethiopia	8 (25)	15 (73)	88	3 (33)	0 (—)	–100
Mali[†]	9 (67)	9 (56)	0	0 (—)	2 (100)	—
South Sudan	0 (—)	0 (—)	—	0 (—)	0 (—)	—
Total	**2,000 (76)**	**1,601 (81)**	**–20**	**1,115 (79)**	**443 (60)**	**–60**

* Cameroon reported one human case, five infected dogs, and one infected cat in 2020 in villages <3 miles (<5 km) from the Chad-Cameroon border that were likely infected in Chad because the affected villages included families living on both sides of the border.
† Civil unrest and insecurity since a coup d'état in April 2012 continued to constrain Guinea Worm Eradication Program operations (e.g., supervision, surveillance, and interventions) in Gao, Kidal, Mopti, Segou, and Timbuktu regions.
§ In Chad, primarily dogs, some cats; in Ethiopia, dogs, cats, and baboons; in Mali, dogs and one cat (2019); in Angola, one dog; in Cameroon, dogs and one cat.

TABLE 2. Characteristics of specimens from humans and animals received at CDC for laboratory diagnosis of *Dracunculus medinensis* — January 2020–June 2021

Specimens received at CDC	Jan–Dec 2020	Jan–Jun 2021
From humans		
No. received	91	13
No. laboratory confirmed as *D. medinensis* (%)	39 (43)	5 (38)
Country of origin		
Angola	1 (3)	—*
Cameroon	1 (3)	—*
Chad	12 (31)	4 (80)
Ethiopia	23 (59)	1 (20)
Mali	1(3)	—*
South Sudan	1 (3)	—*
No. ruled out as *D. medinensis* (%)	52 (57)	8 (62)
Other laboratory diagnoses		
Free-living nematode†	19 (37)	2 (25)
Onchocerca	3 (6)	—§
Other parasitic nematode†	9 (17)¶	—§
Sparganum	10 (19)	3 (38)
Animal-origin tissue	5 (10)	2 (25)
Plant material	—§	—§
Other worms	3 (6)**	—§
Other	1 (2)††	—§
Other *Dracunculus* sp.	2 (4)	—§
Unknown origin	—§	1 (13)
From animals		
No. received	92	36
No. laboratory confirmed as *D. medinensis* (%)	43 (47)	6 (17)
Country/Species of origin		
Cameroon	7§§	—¶¶
Dog	6 (86)§§	—¶¶
Cat	1 (14)	—¶¶
Central African Republic	—¶¶	1
Dog	—¶¶	1 (100)
Chad	7	3
Cat	4 (57)	—¶¶
Dog	3 (43)	2 (67)
Wildcat	—¶¶	1 (33)
Ethiopia	19	—¶¶
Baboon	5 (26)	—¶¶
Cat	9 (47)	—¶¶
Dog	5 (26)	—¶¶
Mali	10	2
Cat	—¶¶	—¶¶
Dog	10 (100)	2 (100)
No. ruled out as *D. medinensis* (%)	49 (53)	30 (83)

TABLE 2. (*Continued*) Characteristics of specimens from humans and animals received at CDC for laboratory diagnosis of *Dracunculus medinensis* — January 2020–June 2021

Specimens received at CDC	Jan–Dec 2020	Jan–Jun 2021
Other laboratory diagnoses		
Free-living nematode†	14 (29)	2 (7)
Other parasitic nematode†	24 (49)***	22 (73)***
Animal-origin tissue	2 (4)	1 (3)
Other worms	5 (10)†††	2 (7)
Other	3 (6)§§§	—§
Plant material	1 (2)	3 (10)

* Specimens did not come from this country.
† The category "Free-living nematodes" primarily included adult Mermithidae and other nematodes identified as belonging to nonparasitic taxa. "Other parasitic nematodes" included non-Onchocerca nematodes identified as belonging to parasitic taxa.
§ No specimens received this diagnosis.
¶ "Other parasitic nematodes" submitted in association with cases in humans in 2020 included *Eustrongyloides* sp. (one) and filarial nematodes not fully identified (four).
** "Other worms" submitted in association with one case in a human in 2020 included an annelid (one); a horsehair (Gordian) worm (one); a specimen vial that contained two Acanthocephala not identified further and one Toxocara; and one nematode not able to be identified further.
†† The "Other" specimen submitted in association with one case in a human in 2020 included a small (approximately 15 cm) blind snake (infraorder Scolecophidia).
§§ Two worms were submitted from one dog.
¶¶ No specimen came from that country or that species.
*** "Other parasitic nematodes" submitted in association with animal cases in 2020 included *Dirofilaria* sp. (two), *Filaria* sp. (11), *Physaloptera* sp. (two), *Protospirura* sp. (one), *Skrjabinodera* sp. (three), *Spirocerca* sp. (one), spirurid nematodes (two), and *Toxocara cati* (two). Submissions during January–June 2021 included *Eustrongyloides* sp. (one), *Dirofilaria* sp. (two), *Skrjabinodera* sp. (one), filarial nematodes not identified to genus (16), a worm belonging to the Gnathostoma taxon (one) and a spirurid nematode not identified to genus (one).
††† "Other worms" submitted in association with one case in an animal in 2020 included an Acanthocephala not identified further (one), cestodes not identified further (two), nematode not identified further (one), and a horsehair worm (one).
§§§ The "Other" specimens submitted in association with animal cases in 2020 were small snakes (two) and a fly larva (one).

on both sides of the border; Cameroon reported no infected humans or animals through June 2021.

Ethiopia. Ethiopia reported 11 cases in 2020, and one case during January–June 2021. The 2020 cases were in villagers exposed to a shared source of contaminated drinking water near Duli village in Gambella Region. During 2020, Ethiopia reported three infected dogs, eight cats, and four baboons, all in Gog district of Gambella Region, compared with two infected dogs and six baboons in 2019. During January–June 2021, Ethiopia reported one infected dog in Gog, compared with one infected dog and two baboons, also in Gog, during January–June 2020. Since 2017, The Carter Center has supported Ethiopia's public health and wildlife authorities in a baboon and dog epidemiology project (*2*).

Since 2021, the Ethiopia Dracunculiasis Eradication Program has had 198 villages under active surveillance. The program applies temephos monthly to all water sources known to have been used by humans in the at-risk area of Gog, and, since April 2018, it has supported villager-initiated constant tethering of approximately 1,914 dogs and cats in villages where most infected animals were detected in recent years to prevent their exposure to water sources in adjacent forests where transmission apparently occurs (*2*). In 2018, Ethiopia increased rewards for reporting human dracunculiasis cases to US$360 equivalent and for reporting and tethering infected animals to US$40. In 2020, 92% of persons surveyed in active surveillance areas knew of the rewards; in January–May 2021, 96% were aware.

TABLE 3. Reported dracunculiasis cases in humans and infections in animals, surveillance, and status of local interventions in villages with endemic disease, by country — worldwide, 2020

Human cases/Surveillance/Intervention status	Country					
	Angola	Chad*	Ethiopia	Mali†	South Sudan	Total
Reported human cases						
No. indigenous, 2020	1	13§	11	1	1	27
No. imported,¶ 2020	0	0	0	0	0	0
% Contained,** 2020	0	42	100	0	100	63
% Change in indigenous human cases in villages/localities under surveillance, same period 2019 and 2020	0	−76	—	—	−75	−50
Reported animal cases						
No. indigenous, 2020	0	1,577††	15	9	0	1,601
No. imported,§§ 2020	0	0	0	0	0	0
% Contained,** 2020	0	81	73	56	0	81
% Change in indigenous animal infections in villages/localities under surveillance, same period 2019 to 2020	−100	−19	88	50	—	−18
Villages under active surveillance, 2020						
No. of villages	54	2,332	190	2,699	851	6,847
% Reporting monthly	—***	99	100	100	98	99
No. reporting ≥1 human case	1	9	5	1	1	17
No. reporting only imported§§ human cases	0	0	1	1	1	3
No. reporting indigenous human cases	1	9	4	0	0	14
No. reporting ≥1 animal infection	0	428	12	5	0	445
No. reporting only imported§§ animal infections	0	0	1	1	0	2
No. reporting indigenous animal infections	0	428	11	4	0	443
Status of interventions in villages with endemic human dracunculiasis, 2020						
No. villages with endemic human dracunculiasis, 2019–2020	2	2	4	0	2	10
% Reporting monthly¶¶	—***	100	100	—†††	100	100
% Filters in all households¶¶	100	0	100	—†††	100	100
% Using temephos¶¶	0	100	100	—†††	100	80
% With ≥1 source of safe water¶¶	50	0	75	—†††	50	—
% Provided health education¶¶	100	100	100	—	100	100
Status of interventions in villages with endemic animal dracunculiasis, 2020						
No. villages with endemic animal dracunculiasis, 2019–2020	1	267	14	10	0	292
% Reporting monthly¶¶	—***	99	100	100	—	99
% Using temephos¶¶	0	84	100	100	—	85
% Provided health education¶¶	100	99	100	100	—	99

* Participants at the annual Chad Guinea Worm Eradication Program review meeting in November 2014 adopted "1+ case village" as a new description for villages in Chad affected by cases in humans of Guinea worm disease or dogs infected with Guinea worms and defined it as "a village with one or more indigenous and/or imported cases of Guinea worm infections in humans, dogs, and/or cats in the current calendar year and/or previous year."

† Civil unrest and insecurity since a coup d'état in April 2012 continued to constrain Guinea Worm Eradication Program operations (e.g., supervision, surveillance, and interventions) in Gao, Kidal, Mopti, Segou, and Timbuktu regions.

§ Twelve cases were reported from Chad in 2020. One case was reported from Cameroon in 2020 in a village along the Chad-Cameroon border which is believed to have been acquired in Chad because the affected villages included families living on both sides of the Cameroon-Chad border.

¶ Imported from another country.

** Transmission from a patient with dracunculiasis is contained only if all of the following conditions are met for each emerged worm: 1) the infected patient is identified ≤24 hours after worm emergence; 2) the patient has not entered any water source since the worm emerged; 3) a village volunteer or other health care provider has managed the patient properly by cleaning and bandaging the lesion until the worm has been fully removed manually and by providing health education to discourage the patient from contaminating any water source (if two or more emerging worms are present, transmission is not contained until the last worm is removed); 4) the containment process, including verification of dracunculiasis, is validated by a Guinea Worm Eradication Program supervisor within 7 days of emergence of the worm; and 5) temephos is used to treat potentially contaminated surface water if any uncertainty about contamination of these sources of drinking water exists or if such a source of drinking water is known to have been contaminated.

†† Chad reported 1,571 animal cases in 2020. Six cases in animals were reported from Cameroon in 2020, all in villages along the Chad-Cameroon border; these are believed to have been acquired in Chad.

§§ Imported from another in-country disease-endemic village.

¶¶ The denominator is number of villages with endemic human or animal dracunculiasis reported during 2019–2020.

*** By the end of 2020, Angola established active surveillance in 54 villages, but a system for regular data reports from each village was not yet established.

††† The case in a human in Mali was imported from another location within Mali. The village of detection is not considered endemic because the case was not indigenous to the village of detection. Therefore, interventions such as monthly reporting, filter distribution, temephos use, and safe water source counting were not implemented in the village of detection and were not applicable.

Mali. Mali reported one case in a human in 2020 after 4 consecutive years of zero cases; no cases in humans were reported during January–June 2021 compared with one during the same period in 2020. During 2020, nine infected dogs were reported, compared with eight dogs and one cat in 2019. During the first half of 2021, Mali reported two infected dogs, compared with no infected animals during January–June 2020. Six infected dogs identified in 2020 were detected in Segou Region; three were detected in adjacent Djenne district of Mopti Region. Segou Region is accessible to the program, but the dogs sold in Segou were bred and apparently became infected in areas of Mopti Region that have remained inaccessible since 2012. The two infected dogs identified during January–June 2021 were detected in Segou Region. In 2020, Mali had 2,699 villages under active surveillance. The reward for reporting a case in a human was US$340 equivalent and US$20 equivalent for reporting and tethering an infected animal. In areas under active surveillance in 2020, 89% of persons queried knew of the rewards for reporting an infected person or animal; 95% of persons queried in January–May 2021 were aware.

South Sudan. South Sudan reported one case in a human in the latter half of 2020, compared with four in 2019, and none during January–June 2021. Only one infected animal has been reported (a dog in the same household as an infected person in 2015). Extreme population mobility of cattle herders and others is a special challenge in addition to sporadic insecurity. By December 2020, South Sudan's GWEP had 851 villages under active surveillance. The reward for reporting a case of dracunculiasis is approximately US$280 equivalent (US$26 for animals). A 2020 survey of residents found 93% of respondents knew of the reward for reporting an infected person.

Discussion

After a decade with no reported cases, Chad reported 10 indigenous cases in humans in 2010; Guinea worm infections in domestic dogs were reported for the first time in 2012, mostly from communities along the Chari River in a pattern affecting many dogs and few humans that remains peculiar to Chad (*7*). During January 2020–June 2021, Chad reported 98% of the world's remaining *D. medinensis* infections, 94% of which were in dogs. Stopping transmission in Chadian dogs is now the biggest challenge to the eradication program. The challenge is being addressed through innovative interventions and research supported by The Carter Center and CDC involving multiple research institutions to help understand the unusual epidemiology of dracunculiasis in the remaining countries and assessing antihelminthic treatment of dogs (*8*). Researchers from the University of Georgia have shown in the laboratory that fish can serve as transport hosts for *Dracunculus* spp. and that *D. medinensis* can use frogs as paratenic hosts; *Dracunculus* larvae have been recovered from multiple wild frogs in Chad (*9*,*10*). If the hypothesis that the parasite's life cycle in Chad involves a transport or paratenic host is correct (*10*), increased active surveillance, proactive containment of dogs, temephos application, and fish entrail burial should reduce transmission. The 56% reduction in cases in humans and 61% reduction in animals in Chad in January–June 2021 suggests that is now happening.

Chad has offered a US$100 equivalent reward for reporting a confirmed human dracunculiasis case since 2010 and a reward of US$20 equivalent for reporting and tethering a confirmed infected dog since 2015. All reports must be corroborated by supervisors. Since October 2013, Chad's GWEP has urged villagers to cook their fish well, bury fish entrails, and prevent animals from eating them. In 2014, volunteers began persuading villagers to tether dogs with signs of dracunculiasis (e.g., blisters or subcutaneous worms) until the worms emerged to prevent water contamination. In 2017, the program began applying temephos monthly to small ponds in villages with the most infected dogs and launched a nationwide communication campaign to increase awareness about the rewards and how to prevent Guinea worm infections. In March 2020, Chad launched a new strategy to tether all dogs proactively during the 4 months of peak dracunculiasis incidence in the 120 villages that reported five or more infections in 2019, an effort now being scaled up to all villages reporting one or more infections.

In 2020, Mali reported its first case in a human in over 4 years, and Ethiopia reported its first cases in humans in over 2 years. Continued endemic transmission among a few dogs and cats in Mali as well as baboons in Ethiopia appears to be geographically limited. Insecurity is still the main obstacle to stopping transmission in Mali. The ecologic study of baboons and proactive tethering of dogs in Gog district might clarify the dynamics of residual infections in Ethiopia.

If security remains adequate, South Sudan is poised to achieve zero-case status soon because of strong technical leadership, strong governmental support, and no animal infections. Finding three confirmed cases in humans and one infected dog in Angola in 2018–2020 and none so far in 2021 suggests that the problem there is limited.

Identification of dracunculiasis cases in a Cameroonian border village during 2018–2020 highlights the risks for exportation from Chad and the need for ongoing active surveillance in neighboring Cameroon and the Central African Republic. Common source waterborne outbreaks in Ethiopia in 2020 highlight the need for safe drinking water wherever dracunculiasis occurs. The current prominence of infections in domestic dogs and cats requires increased measures to limit those animals' access to waste from discarded fish and other aquatic animals.

Summary

What is already known about this topic?

Cases of dracunculiasis (Guinea worm disease) have decreased from an estimated 3.5 million in 1986 to 27 in 2020. Emergence of Guinea worm infections in dogs in 2012 has complicated eradication efforts.

What is added by this report?

With 27 cases in humans reported in 2020, five during January–June 2021, and only six countries currently affected by dracunculiasis (Angola, Chad, Ethiopia, Mali, South Sudan, and importations into Cameroon), achievement of eradication appears to be close.

What are the implications for public health practice?

Existence of infected dogs, especially in Chad, and impeded access because of civil unrest and insecurity in Mali and South Sudan are now the greatest challenges to interrupting transmission.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. All authors report support from The Carter Center for laboratory diagnostics for the Guinea Worm Eradication Program. No other potential conflicts of interest were disclosed.

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National Surveillance for Acute Flaccid Myelitis — United States, 2018–2020

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Acute flaccid myelitis (AFM), a recognized complication of certain viral infections, is a serious neurologic condition that predominantly affects previously healthy children and can progress rapidly, leading to respiratory insufficiency and permanent paralysis. After national AFM surveillance began in 2014, peaks in AFM cases were observed in the United States in 2014, 2016, and 2018 (*1*). On the basis of this biennial pattern, an increase in AFM was anticipated in 2020. To describe the epidemiology of confirmed AFM cases since 2018, demographic, clinical, and laboratory information collected as part of national AFM surveillance was reviewed. In 2018, a total of 238 confirmed AFM cases were reported to CDC, compared with 47 cases in 2019 and 32 in 2020. Enterovirus D68 (EV-D68) was detected in specimens from 37 cases reported in 2018, one case in 2019 and none in 2020. Compared with 2018, cases reported during 2019–2020 occurred in older children and were less frequently associated with upper limb involvement, febrile or respiratory prodromal illness, or cerebrospinal fluid (CSF) pleocytosis. These findings suggest that the etiologies of AFM in 2019 and 2020 differed from those in 2018. The absence of an increase in cases in 2020 reflects a deviation from the previously observed biennial pattern, and it is unclear when the next increase in AFM should be expected. Clinicians should continue to maintain vigilance and suspect AFM in any child with acute flaccid limb weakness, particularly in the setting of recent febrile or respiratory illness.

Similar to poliomyelitis caused by poliovirus (an enterovirus), AFM is characterized by sudden onset of limb weakness and lesions in the gray matter of the spinal cord. CDC began conducting national surveillance for AFM in 2014 after a cluster of cases of acute flaccid limb weakness among previously healthy children who had no laboratory or epidemiologic evidence of poliovirus infection was reported in Colorado (*2*). Since then, national surveillance has demonstrated biennial peaks in AFM cases during the late summer and early fall in 2014, 2016, and 2018 (*1*).

AFM is an unusual but known complication of certain viral infections, including those from West Nile virus and nonpolio enteroviruses (*3*,*4*). Pathogens are rarely isolated from the CSF of AFM patients (*2*,*5*). However, enteroviruses (EVs) are the most common pathogens detected from AFM patient respiratory and stool specimens; EV-D68 is the most common enterovirus type detected, and additional laboratory and animal model data suggest that EV-D68 is the primary driver of increases in AFM during peak years (*2*,*5*–*7*). Previously published AFM surveillance data through 2018 suggest that case characteristics and etiology differ during peak versus nonpeak years (*8*). CDC examined national surveillance data to further understand the epidemiology and etiology of AFM and describe trends since 2018, the most recent peak year.

As part of national surveillance, health departments report cases meeting the clinical criterion for AFM (acute flaccid limb weakness) to CDC via a patient summary form that includes demographic and clinical information. Health departments also send CDC important elements from the patient's medical record, and data from these records are abstracted using a standardized worksheet. In addition, health departments and clinicians submit available CSF, respiratory, serum, and stool specimens to CDC. Testing protocols at CDC include enterovirus/rhinovirus (EV/RV)* testing using methods that have been described previously (*2*).

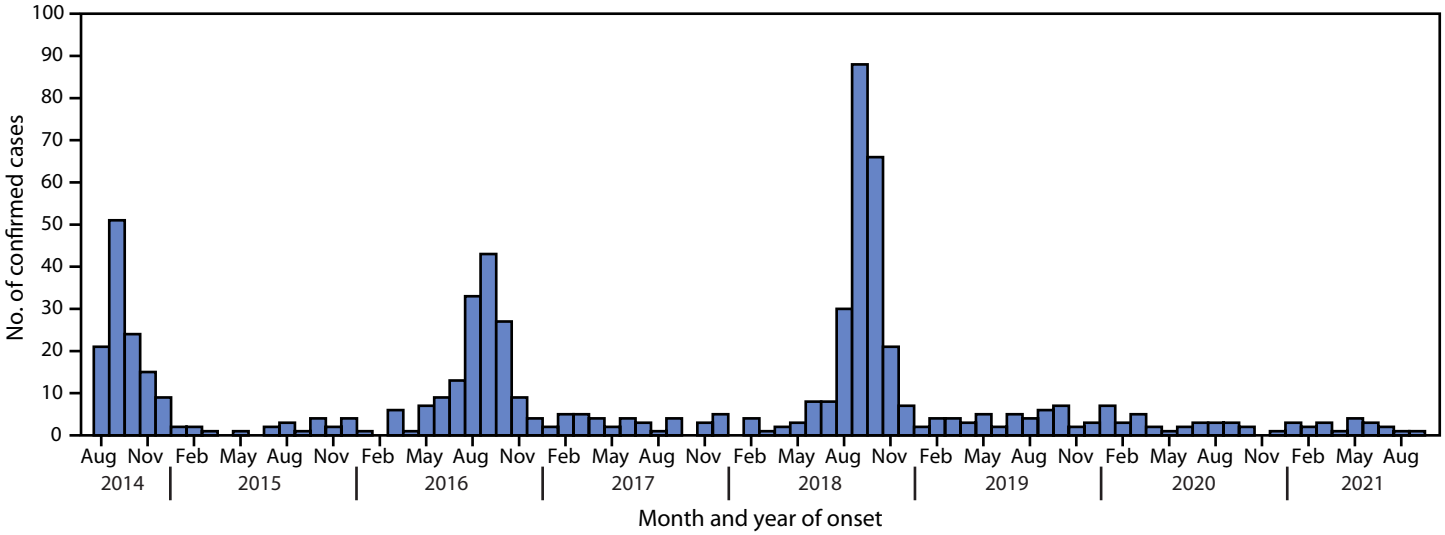
Patient summary form, chart abstraction, and laboratory data were analyzed to describe trends in confirmed AFM cases since surveillance began in August 2014 and to describe case characteristics in 2018, 2019, and 2020. Confirmed AFM was defined as acute onset of flaccid limb weakness accompanied by magnetic resonance imaging demonstrating a spinal cord lesion largely restricted to gray matter and spanning one or more vertebral segments (*9*). Reported EV/RV results include external laboratory results that were documented in the available medical records and CDC laboratory results. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.†

A total of 238 confirmed cases were reported to CDC in 2018, 47 cases were reported in 2019, and 32 cases were reported in 2020 (Figure). During each year, at least 90% of cases (94% in 2018 and 91% in 2019 and 2020) occurred among children aged <18. Compared with cases in the most recent peak year (2018), AFM patients in 2019 and 2020

* EVs and RVs are closely related picornaviruses. Most available reverse transcription–polymerase chain reaction tests for EV amplify a viral gene sequence that is highly conserved between EVs and RVs. Therefore, these tests do not distinguish between EVs and RVs and additional testing is needed to identify the specific virus that has been detected.

† 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.

FIGURE. Number of confirmed cases of acute flaccid myelitis (N = 670), by month of onset — United States, August 2014–September 2021*



* As of October 23, 2021.

were older (median age = 6.6 and 9.2 years, respectively, versus 5.3 years in 2018) and were less frequently associated with upper limb involvement (74% and 59%, versus 84%), prodromal respiratory or febrile illness (57% and 63%, versus 92%), or CSF pleocytosis (49% and 48%, versus 87%) (Table 1). Lower limb involvement was more common among patients with AFM reported in 2019 and 2020 than among 2018 cases (74% and 81%, versus 44%).

Almost all (98%–100%, depending on year) patients with confirmed AFM reported during 2018–2020 were hospitalized, 51%–59% were admitted to an intensive care unit, and 16%–28% required intubation and mechanical ventilation. During each year, the emergency department was the most common location of the first medical encounter after onset of weakness. During 2018–2020, an increasing proportion of patients with confirmed AFM sought medical care and were hospitalized within 1 day of weakness onset. The percentage of patients seeking medical care within 1 day of weakness onset increased from 75% in 2018 to 97% in 2020, and the percentage of patients hospitalized within 1 day increased from 65% to 84%.

In 2018, among patients with confirmed AFM who were tested, EV/RV was detected in 50%, and EV-D68 was the most common EV/RV type detected (Table 2). In contrast, although a similar proportion of AFM patients were tested for EV/RV each year, EV/RV was detected in only 37% of 2019 cases and in 26% of 2020 cases. EV-D68 was detected in 37 cases in 2018, compared with a single case in 2019 and no cases in 2020. During each year, the highest yield of EV/RV detection was among respiratory specimens.

Summary

What is already known about this topic?

Biennial peaks in reported acute flaccid myelitis (AFM) cases occurred in late summer and early fall in 2014, 2016, and 2018.

What is added by this report?

The number of AFM cases in 2019 and in 2020 was consistent with previous nonpeak years. Compared with 2018, cases reported during 2019–2020 were more likely to have lower limb involvement and less likely to have prodromal illness, upper limb involvement, cerebrospinal fluid pleocytosis, or detection of enterovirus D68.

What are the implications for public health practice?

It is unclear when another increase in AFM will occur. Clinicians should maintain vigilance and suspect AFM in any child with acute flaccid limb weakness, particularly following a recent febrile or respiratory illness.

Discussion

In a departure from the previously observed pattern of biennial peaks in AFM cases in 2014, 2016, and 2018, there was no increase in the number of reported AFM cases in 2020. The number of confirmed AFM cases during 2019–2020 remained low and was consistent with previous nonpeak years. In addition, 2019–2020 cases differed from 2018 cases: patients were older; more likely to have lower limb involvement; and less likely to have upper limb involvement, prodromal illness, CSF pleocytosis, or specimens that tested positive for EV-D68. Upper limb involvement, prodromal respiratory illness, and CSF pleocytosis were characteristic features of 2018 cases.

TABLE 1. Demographic and clinical characteristics of patients with confirmed acute flaccid myelitis — United States, 2018–2020

Characteristic	No. (%)		
	2018 (N = 238)	2019 (N = 47)	2020 (N = 32)
Median age, yrs (IQR)	5.3 (3.3–8.2)	6.6 (2.9–12.8)	9.2 (3.5–14.5)
Sex			
Male	138 (58)	15 (32)	16 (50)
Female	100 (42)	32 (68)	16 (50)
Race/Ethnicity*			
Asian	8 (3)	2 (4)	3 (9)
Black or African American	21 (9)	7 (15)	4 (13)
Hispanic	47 (20)	12 (26)	8 (25)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0 (—)	0 (—)
White	125 (53)	18 (38)	12 (38)
Multiracial	4 (2)	1 (2)	0 (—)
Unknown	32 (13)	7 (15)	5 (16)
Geographic region			
West	56 (24)	19 (40)	8 (25)
Midwest	61 (26)	7 (15)	7 (22)
South	80 (34)	18 (38)	11 (34)
Northeast	41 (17)	3 (6)	6 (19)
Limbs affected			
Upper	199 (84)	35 (74)	19 (59)
Lower	132 (55)	35 (74)	26 (81)
Illness in the 4 weeks before onset of limb weakness			
Any illness	223 (94)	32 (68)	20 (63)
Respiratory illness	187 (79)	23 (49)	14 (44)
Fever	174 (73)	14 (30)	12 (38)
Respiratory illness or fever	218 (92)	27 (57)	20 (63)
Gastrointestinal illness	80 (34)	12 (26)	3 (9)
Timing of preceding illness, median days before limb weakness† (IQR)			
Any illness	5 (3–8)	4 (3–7)	5 (2–13)
Respiratory illness	5 (3–8)	5 (3–14)	5.5 (2.5–13.5)
Fever	3 (1–5)	3 (2–5)	2.5 (1–5.5)
Respiratory illness or fever	5 (3–7)	4 (3–6)	5 (2–13)
Gastrointestinal illness	2 (1–6)	3.5 (2–6)	4 (0–14)
CSF microscopic examination, no./total no. (%)			
CSF pleocytosis	183/210 (87)	21/43 (49)	13/27 (48)
Median white blood cell count, cells/mm^3 (IQR)§	94 (43–163)	107 (44–182)	36 (9–55)
Characteristics of hospitalization and clinical care			
Hospitalized	233 (98)	46 (98)	32 (100)

See table footnotes on the next page.

These findings are consistent with an earlier report of differences between AFM case characteristics during peak and nonpeak years (*8*) and likely reflect differences in AFM etiology. Specifically, increases in AFM during peak years since 2014 appear to be mostly associated with EV-D68, whereas AFM during nonpeak years likely represents a mixture of etiologies.

Regardless of etiology, AFM can progress rapidly and lead to respiratory insufficiency that requires intubation and mechanical ventilation. Persons with signs and symptoms of AFM should be immediately hospitalized and their respiratory status monitored. Although there is no proven treatment for AFM, hospitalization facilitates patient evaluation, diagnosis or exclusion of other neurologic conditions, and appropriate medical management. Notably, during 2018–2020, the proportion of patients that were hospitalized within 1 day increased. It is possible that certain features of 2019–2020 cases (e.g., older age or lower limb predominance) facilitated earlier recognition of the signs and symptoms of neurologic weakness, although this trend might also reflect increased public and clinician awareness of AFM since 2018.

The findings in this report are subject to at least two limitations. First, this analysis was based on AFM cases reported to CDC and might underestimate the actual number of AFM cases in the United States. Second, clinical information was obtained from the patient summary form, which was completed by the health department, or from the medical records, which could be incomplete. Similarly, laboratory data were limited to results documented in the medical records shared with CDC or specimens tested at CDC.

TABLE 1. (*Continued*) Demographic and clinical characteristics of patients with confirmed acute flaccid myelitis — United States, 2018–2020

Characteristic	No. (%)		
	2018 (N = 238)	2019 (N = 47)	2020 (N = 32)
Timing of hospitalization in relationship to onset of weakness among those hospitalized, no./total no. (%)			
Before onset of limb weakness	25/233 (11)	6/46 (13)	1/32 (3)
After onset of limb weakness	206/233 (88)	40/46 (87)	31/32 (97)
Unknown if hospitalized before or after onset of limb weakness	2/233 (1)	0/46 (—)	0/32 (—)
Days from onset of weakness to hospitalization (among those hospitalized after onset of weakness), no./total no. (%)			
Median (IQR)	1 (0–2)	1 (0–1)	1 (1–1)
0–1	134/206 (65)	33/40 (83)	26/31 (84)
2–3	52/206 (25)	5/40 (13)	4/31 (13)
4–7	10/206 (5)	2/40 (5)	0/31 (—)
>7	10/206 (5)	0/40 (—)	1/31 (3)
Treatment			
Steroids, no IVIG	55 (23)	14 (30)	7 (22)
IVIG, no steroids	54 (23)	12 (26)	6 (19)
Both steroids and IVIG	81 (34)	15 (32)	14 (44)
Plasma exchange	32 (13)	10 (21)	10 (31)
Admitted to ICU	129 (54)	24 (51)	19 (59)
Respiratory support	65 (27)	16 (34)	6 (19)
Mechanical ventilation	55 (23)	13 (28)	5 (16)
Location of first medical encounter after onset of weakness			
Emergency department	134 (56)	32 (68)	24 (75)
Primary care provider	49 (21)	4 (9)	3 (9)
Urgent care provider	16 (7)	4 (9)	1 (3)
Had onset of weakness during an inpatient hospitalization	25 (11)	6 (13)	1 (3)
Unknown or other	14 (6)	1 (2)	3 (9)
Days from onset of weakness to first medical encounter (excluding those hospitalized before onset of weakness), no./total no. (%)			
Median (IQR)	0 (0–1)	0 (0–1)	0 (0–0)
0–1	160/213 (75)	36/41 (88)	30 /31 (97)
2–3	34/213 (16)	3/41 (7)	0/31 (—)
4–7	4/213 (2)	0/41 (—)	0/31 (—)
>7	2/213 (1)	2/41 (5)	0/31 (—)
Unknown	13/213 (6)	0/41 (—)	1/31 (3)

Abbreviations: CSF = cerebrospinal fluid; ICU = intensive care unit; IQR = interquartile range; IVIG = intravenous immunoglobulin.
* Persons reported in the following groups are non-Hispanic: Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White.
† Timing calculated among cases with the prodromal illness/symptom and documented valid dates of onset.
§ Median cells/mm^3 was calculated among cases with CSF pleocytosis (>5 white blood cells/mm^3).

It is not entirely clear why AFM cases did not increase in 2020. Nonpharmaceutical interventions implemented during the COVID-19 pandemic (e.g., face masks, physical distancing, and reduced in-person school attendance) might have reduced transmission of EV-D68 and other enteroviruses associated with AFM. EV-D68 is a respiratory enterovirus, and other respiratory viruses such as influenza and respiratory syncytial virus (RSV) were noted to have decreased circulation during 2020 (*10*). As a group, EV/RV circulation was also attenuated, although to a lesser degree than influenza or RSV (*10*). It is also unclear when the next increase in AFM should be expected. AFM should be suspected in any child with acute flaccid limb weakness, especially among those with a recent history of a febrile or respiratory illness. Clinicians should remain vigilant for this condition in 2021 and report potential cases to their public health department.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

TABLE 2. Enterovirus/rhinovirus results from respiratory, stool, cerebrospinal fluid, and serum specimens collected from patients with confirmed acute flaccid myelitis — United States, 2018*–2020

Specimen source	No. (%) 2018 (N = 238)	2019 (N = 47)	2020 (N = 32)
Any source†			
All patients with results	223 (94)	43 (91)	31 (97)
Patients with positive results	112 (50)	16 (37)	8 (26)
EV/RV type results§			
EV-D68	37	1	0
EV-A71	13	2	1
Rhinoviruses	10	1	3
Other typed enteroviruses	8	2	0
Unknown or not typed	46	10	4
Respiratory†			
All patients with results	194 (82)	39 (83)	27 (84)
Patients with positive results	97 (50)	13 (33)	7 (26)
EV/RV type results§			
EV-D68	37	1	0
EV-A71	11	0	0
Rhinoviruses	10	1	3
Other typed enteroviruses	1	0	0
Unknown or not typed	40	11	4
Stool			
All patients with results	111 (47)	23 (49)	15 (47)
Patients with positive results	25 (23)	6 (26)	2 (13)
EV/RV type results§			
EV-D68	3	0	0
EV-A71	2	2	1
Rhinoviruses	0	0	0
Other typed enteroviruses	7	2	0
Unknown or not typed	13	2	1
Cerebrospinal fluid			
All patients with results	191 (80)	39 (83)	29 (91)
Patients with positive results	9 (5)	0 (—)	0 (—)
EV/RV type results§			
EV-D68	2	0	0
EV-A71	1	0	0
Rhinoviruses	0	0	0
Other typed enteroviruses	0	0	0
Unknown or not typed	6	0	0
Serum			
All patients with results	108 (45)	29 (62)	21 (66)
Patients with positive results	4 (4)	0 (—)	1 (5)
EV/RV type results§			
EV-D68	1	0	0
EV-A71	0	0	1
Rhinoviruses	0	0	0
Other typed enteroviruses	2	0	0
Unknown or not typed	1	0	0

Abbreviations: EV = enterovirus; RV = rhinovirus.

* This table includes updated laboratory information and supersedes previously published data on the 2018 cases.

† Some patients had multiple positive specimens. In addition, respiratory coinfection with two EV/RV types was detected in two cases in 2018 (EV-D68 and echovirus 6 in one case, and EV-D68 and RV-A2 in another case).

§ Percentage not calculated.

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Laboratory-Confirmed COVID-19 Among Adults Hospitalized with COVID-19–Like Illness with Infection-Induced or mRNA Vaccine-Induced SARS-CoV-2 Immunity — Nine States, January–September 2021

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On October 29, 2021 this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

Previous infection with SARS-CoV-2 (the virus that causes COVID-19) or COVID-19 vaccination can provide immunity and protection from subsequent SARS-CoV-2 infection and illness. CDC used data from the VISION Network* to examine hospitalizations in adults with COVID-19–like illness and compared the odds of receiving a positive SARS-CoV-2 test result, and thus having laboratory-confirmed COVID-19, between unvaccinated patients with a previous SARS-CoV-2 infection occurring 90–179 days before COVID-19–like illness hospitalization, and patients who were fully vaccinated with an mRNA COVID-19 vaccine 90–179 days before hospitalization with no previous documented SARS-CoV-2 infection. Hospitalized adults aged ≥18 years with COVID-19–like illness were included if they had received testing at least twice: once associated with a COVID-19–like illness hospitalization during January–September 2021 and at least once earlier (since February 1, 2020, and ≥14 days before that hospitalization). Among COVID-19–like illness hospitalizations in persons whose previous infection or vaccination occurred 90–179 days earlier, the odds of laboratory-confirmed COVID-19 (adjusted for sociodemographic and health characteristics) among unvaccinated, previously infected adults were higher than the odds among fully vaccinated recipients of an mRNA COVID-19 vaccine with no previous documented infection (adjusted odds ratio [aOR] = 5.49; 95% confidence interval [CI] = 2.75–10.99). These findings suggest that among hospitalized adults with COVID-19–like illness whose previous infection or vaccination occurred 90–179 days earlier, vaccine-induced immunity was more protective than infection-induced immunity against laboratory-confirmed COVID-19. All eligible persons should be vaccinated against COVID-19 as soon as possible, including unvaccinated persons previously infected with SARS-CoV-2.

To compare the early protection against COVID-19 conferred by SARS-CoV-2 infection and by receipt of mRNA COVID-19 vaccines (i.e., 90–179 days after infection or vaccination), the VISION Network collected data from 187 hospitals across nine states during January–September 2021 (*1*). Eligible hospitalizations were defined as those among adults aged ≥18 years who had received SARS-CoV-2 molecular testing (from 14 days before to 72 hours after admission) and had a COVID-19–like illness discharge diagnosis† during January–September 2021. Eligible patients had also been tested at least once since February 1, 2020. To limit the analysis to patients with access to SARS-CoV-2 testing before hospitalization, patients who did not receive SARS-CoV-2 testing ≥14 days before hospitalization were excluded.

Two exposure groups were defined based on COVID-19 vaccination status and previous SARS-CoV-2 infection. Vaccination status was documented in electronic health records and immunization registries. Previous infection was ascertained based on SARS-CoV-2 testing from rapid antigen tests or molecular assays (e.g., real-time reverse transcription–polymerase chain reaction) performed before mRNA vaccination and ≥14 days before admission; testing performed after February 2020 was primarily within network partners' medical facilities. Adults were considered unvaccinated with a previous SARS-CoV-2 infection if no COVID-19 vaccine doses were received and if the most recent positive SARS-CoV-2 test

* Funded by CDC, the VISION Network includes Columbia University Irving Medical Center (New York), HealthPartners (Minnesota and Wisconsin), Intermountain Healthcare (Utah), Kaiser Permanente Northern California (California), Kaiser Permanente Northwest (Oregon and Washington), Regenstrief Institute (Indiana), and University of Colorado (Colorado).

† Medical events with a discharge code consistent with COVID-19–like illness were included. COVID-19–like illness diagnoses included acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea) using diagnosis codes from the *International Classification of Diseases, Ninth Revision* and *International Classification of Diseases, Tenth Revision*.

result occurred ≥90 days before hospitalization. Adults were considered fully vaccinated with an mRNA COVID-19 vaccine with no previous documented infection if the second dose of Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) mRNA vaccine was received ≥14 days before the index test date[§] and if they had been tested since February 1, 2020, and had no positive test results ≥14 days before hospitalization. Patients were excluded if they had received 1 mRNA vaccine dose only, received the second dose <14 days before index test date, or received the Janssen (Johnson & Johnson [Ad26.COV2]) vaccine (because of sparse data). To reduce the chance that the hospitalization was related to an ongoing SARS-CoV-2 infection, patients were also excluded from the previous infection group if their most recent previous positive test result occurred 14–89 days before hospitalization.[¶]

The outcome of laboratory-confirmed COVID-19 was defined as COVID-19–like illness and a positive SARS-CoV-2 result from molecular testing. Among patients hospitalized with COVID-19–like illness whose previous infection or completion of vaccination occurred 90–179 days earlier, the odds of laboratory-confirmed COVID-19 were compared between previously infected persons and fully vaccinated mRNA COVID-19 vaccine recipients. aORs and 95% CIs were calculated using multivariable logistic regression, adjusted for age, geographic region, calendar time (days from January 1 to hospitalization), and local virus circulation, and weighted based on propensity to be in the vaccinated category (*1*,*2*). Established methods were used to calculate weights to account for differences in sociodemographic and health characteristics between groups (*3*). Separate weights were calculated for each model. aORs were stratified by mRNA vaccine product and age group.

Three secondary analyses were also conducted. First, the impact of whether and how the time interval since previous infection or full vaccination was adjusted was examined. Specifically, any time since either previous infection or completion of vaccination was considered. Then, previously infected patients were limited to those with more recent infections (i.e., 90–225 days before hospitalization [the lowest two tertiles of number of days since infection]), and fully vaccinated patients were limited to those with the longest interval since completion of vaccination (i.e., receipt of second mRNA vaccine dose 45–213 days before hospitalization [the highest two tertiles of number of days since vaccination]). Then, number of days since previous infection or completion of vaccination, rather than calendar time, was adjusted in the model. For the next secondary analysis, aORs for hospitalizations that occurred before and during SARS-CoV-2 B.1.617.2 (Delta) variant predominance (June–September 2021) were compared, beginning on the date the Delta variant accounted for >50% of sequenced isolates in each medical facility's state (*2*). Finally, effect modification was assessed by mRNA vaccine product or by age group; p-values <0.2 were considered indicative of a statistically significant difference in aOR by product or age, similar to previous modeling studies of effect modification (*4*). All analyses were conducted using SAS (version 9.4; SAS Institute) and R (version 4.0.2; R Foundation). This study was reviewed and approved by Westat, Inc. institutional review board.[**]

During January 1–September 2, 2021, a total of 201,269 hospitalizations for COVID-19–like illness were identified; 139,655 (69.4%) patients were hospitalized after COVID-19 vaccines were generally available to persons in their age group within their geographic region. Molecular testing for SARS-CoV-2 was performed for 94,264 (67.5%) patients with COVID-19–like illness hospitalizations. Among these patients, 7,348 (7.8%) had at least one other SARS-CoV-2 test result ≥14 days before hospitalization and met criteria for either of the two exposure categories: 1,020 hospitalizations were among previously infected and unvaccinated persons, and 6,328 were among fully vaccinated and previously uninfected patients (Table 1).

Laboratory-confirmed SARS-CoV-2 infection was identified among 324 (5.1%) of 6,328 fully vaccinated persons and among 89 of 1,020 (8.7%) unvaccinated, previously infected persons. A higher proportion of previously infected than vaccinated patients were aged 18–49 years (31% versus 9%), Black (10% versus 7%), and Hispanic (19% versus 12%).

Among COVID-19–like illness hospitalizations in persons whose previous infection or vaccination occurred 90–179 days earlier, the odds of laboratory-confirmed COVID-19 were higher among previously infected, unvaccinated patients than among fully vaccinated patients (aOR = 5.49; 95% CI = 2.75–10.99) (Table 2). In secondary analyses, the aORs that examined the impact of whether and how time since infection or vaccination was adjusted and that stratified hospitalizations before and during Delta variant predominance were all similar to the primary aOR estimate. For product- and age group–specific estimates, sparse data limited the precision of these aORs. However, an assessment of effect modification indicated the aOR of laboratory-confirmed COVID-19 was higher for previously infected patients compared with patients vaccinated with Moderna (aOR = 7.30) than compared with patients vaccinated with Pfizer-BioNTech (aOR = 5.11) during January–September (p = 0.02). Similarly, the interaction term for exposure group by

[§] Index test date was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result before the hospitalization or the hospitalization date if testing only occurred after admission.

[¶] https://www.cdc.gov/coronavirus/2019-ncov/php/invest-criteria.html

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

TABLE 1. Characteristics of COVID-19–like illness hospitalizations* among unvaccinated adults with a SARS-CoV-2 infection occurring 90–179 days before the index test date† and among adults who were fully vaccinated§ 90–179 days before the index test date† without a previous documented SARS-CoV-2 infection — nine states,¶ January–September 2021

Characteristic	No. (column %)		Standardized mean or proportion difference**
	Unvaccinated with previous SARS-CoV-2 infection	Fully vaccinated§ without previous documented infection	
All hospitalizations with COVID-19–like illness	**1,020 (100)**	**6,328 (100)**	**NA**
SARS-CoV-2 test result associated with COVID-19–like illness hospitalization			
Positive	89 (9)	324 (5)	0.14
Negative	931 (91)	6,004 (95)	
Sex			
Male	405 (40)	2,905 (46)	0.13
Female	615 (60)	3,423 (54)	
Age group, yrs			
18–49	313 (31)	560 (9)	0.74
50–64	243 (24)	865 (14)	
65–74	207 (20)	1,757 (28)	
75–84	177 (17)	2,018 (32)	
≥85	80 (8)	1,128 (18)	
Race, irrespective of ethnicity			
White	647 (63)	4,356 (69)	0.24
Black	100 (10)	452 (7)	
Other††	71 (7)	686 (11)	
Unknown	202 (20)	834 (13)	
Ethnicity, irrespective of race			
Hispanic	189 (19)	756 (12)	0.20
Non-Hispanic	695 (68)	4,458 (70)	
Unknown	136 (13)	1,114 (18)	
Month of index test date†			
January	11 (1)	0 (—)	2.10
February	41 (4)	0 (—)	
March	114 (11)	0 (—)	
April	245 (24)	6 (0)	
May	294 (29)	235 (4)	
June	184 (18)	1,300 (21)	
July	99 (10)	2,731 (43)	
August	31 (3)	2,049 (32)	
September	1 (0)	7 (0)	

See table footnotes on the next page.

age indicated that the aOR was higher for patients aged ≥65 years (aOR = 19.57) than for those aged 18–64 years (aOR = 2.57) (interaction term, p = 0.05).

Discussion

In this multistate analysis of hospitalizations for COVID-19–like illness among adults aged ≥18 years during January–September 2021 whose previous infection or vaccination occurred 90–179 days earlier, the adjusted odds of laboratory-confirmed COVID-19 were higher among unvaccinated and previously infected patients than among those who were fully vaccinated with 2 doses of an mRNA COVID-19 vaccine without previous documentation of a SARS-CoV-2 infection. Secondary analyses that did not adjust for time since infection or vaccination or adjusted time since infection or vaccination differently as well as before and during Delta variant predominance produced similar results. These findings are consistent with evidence that neutralizing antibody titers after receipt of 2 doses of mRNA COVID-19 vaccine are high (*5*,*6*); however, these findings differ from those of a retrospective records-based cohort study in Israel,†† which did not find higher protection for vaccinated adults compared with those with previous infection during a period of Delta variant circulation. This variation is possibly related to differences in the outcome of interest and restrictions on the timing of vaccination. The Israeli cohort study assessed any positive SARS-CoV-2 test result, whereas this study examined laboratory-confirmed COVID-19 among hospitalized patients. The Israeli cohort study also only examined vaccinations that had occurred 6 months earlier, so the benefit of more recent vaccination was not examined. This report focused on the early protection from infection-induced and vaccine-induced immunity, though it is possible that estimates could be affected by time. Understanding infection-induced and vaccine-induced immunity over time is important, particularly for future studies to consider.

†† https://www.medrxiv.org/content/10.1101/2021.08.24.21262415v1

TABLE 1. (*Continued*) Characteristics of COVID-19–like illness hospitalizations* among unvaccinated adults with a SARS-CoV-2 infection occurring 90–179 days before the index test date† and among adults who were fully vaccinated§ 90–179 days before the index test date† without a previous documented SARS-CoV-2 infection — nine states,¶ January–September 2021

Characteristic	No. (column %)		Standardized mean or proportion difference**
	Unvaccinated with previous SARS-CoV-2 infection	Fully vaccinated§ without previous documented infection	
Site			
Columbia University	53 (5)	238 (4)	0.73
HealthPartners	22 (2)	94 (1)	
Intermountain Healthcare	117 (11)	454 (7)	
Kaiser Permanente Northern California	254 (25)	3,614 (57)	
Kaiser Permanente Northwest	30 (3)	250 (4)	
Regenstrief Institute	390 (38)	1,145 (18)	
University of Colorado	154 (15)	533 (8)	
Time since either previous SARS-CoV-2 infection or full mRNA vaccination until COVID-19–like illness index test date, days			
90–119	367 (36)	3,325 (53)	0.42
120–149	353 (35)	2,101 (33)	
150–179	300 (29)	902 (14)	
COVID-19 vaccination status			
Unvaccinated	1,020 (100)	0 (—)	NA
Pfizer-BioNTech (BNT162b2)	0 (—)	3,736 (59)	
Moderna (mRNA-1273)	0 (—)	2,592 (41)	

Abbreviation: NA = not applicable.

* Medical events with a discharge code consistent with COVID-19–like illness were included. COVID-19–like illness diagnoses included acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea) using diagnosis codes from the *International Classification of Diseases, Ninth Revision* and *International Classification of Diseases, Tenth Revision*. Clinician-ordered molecular assays (e.g., real-time reverse transcription–polymerase chain reaction) for SARS-CoV-2 occurring ≤14 days before to <72 hours after hospital admission were included.

† Index test date was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result before the hospitalization or the hospitalization date if testing only occurred after the admission.

§ Full vaccination was defined as receipt of the second dose of Pfizer-BioNTech or Moderna mRNA vaccine ≥14 days before the index test date.

¶ Partners contributing hospitalizations were in California, Colorado, Indiana, Minnesota and Wisconsin, Oregon and Washington, Utah, and New York.

** In comparing characteristics between unvaccinated adults with a previous infection and fully vaccinated adults without a previous documented infection, a standardized mean or proportion difference >0.2 was considered noteworthy. After balancing characteristics that differed between the two comparison groups, the standardized mean or proportion differences were ≤0.06.

†† Other race includes Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not listed, and multiple races.

In this study, the benefit of vaccination compared with infection without vaccination appeared to be higher for recipients of Moderna than Pfizer-BioNTech vaccine, which is consistent with a recent study that found higher vaccine effectiveness against COVID-19 hospitalizations for Moderna vaccine recipients than for Pfizer-BioNTech vaccine recipients (*7*). In this study, the protective effect of vaccination also trended higher for adults aged ≥65 years than for those aged 18–64 years. However, considering the limited data by both product type and age, additional research is needed on the relative protection of vaccination versus infection without vaccination across demographic groups and vaccine products, as well as vaccination in previously infected persons.

The findings in this report are subject to at least seven limitations. First, although this analysis was designed to compare two groups with different sources of immunity, patients might have been misclassified. If SARS-CoV-2 testing occurred outside of network partners' medical facilities or if vaccinated persons are less likely to seek testing, some positive SARS-CoV-2 test results might have been missed and thus some patients classified as vaccinated and previously uninfected might also have been infected. In addition, despite the high specificity of COVID-19 vaccination status from these data sources, misclassification is possible. Second, the aOR could not be further stratified by time since infection or vaccination because of sparse data and limited ability to control for residual confounding that could be magnified within shorter intervals. The aOR that did not adjust for time might also be subject to residual confounding, particularly related to waning of both types of immunity. Third, selection bias might be possible if vaccination status influences likelihood of testing and if previous infection influences the likelihood of vaccination. Previous work from the VISION network did not identify systematic bias in testing by vaccination status, based on data through May 2021 (*1*). Fourth, residual confounding might exist because the study did not measure or adjust for behavioral differences between the comparison groups that could modify the risk of the outcome. Fifth, these results might not be generalizable to nonhospitalized patients who have different access to medical care or different health care–seeking behaviors, particularly outside of the nine states covered. Sixth, the statistical model incorporated the use of a weighted propensity score method which is subject to biases in estimates or standard errors if the propensity score model is misspecified. Numerous techniques were used to reduce

TABLE 2. Adjusted odds ratios* of laboratory-confirmed COVID-19 among hospitalizations in adults with COVID-19–like illness comparing unvaccinated adults with a SARS-CoV-2 infection occurring 90–179 days before the index test date and adults who were fully vaccinated 90–179 days before the index test date without a previous documented SARS-CoV-2 infection — nine states, January–September 2021

Outcome	Total no.	No. (row %) of SARS-CoV-2 positive test results	Adjusted odds ratio (95% CI)
All adults (aged ≥18 years), any COVID-19 mRNA vaccine			
Any mRNA vaccine			
Fully vaccinated† without previous documented infection	**6,328**	324 (5.1)	Ref
Unvaccinated with a previous SARS-CoV-2 infection	**1,020**	89 (8.7)	5.49 (2.75–10.99)
Any mRNA vaccine, no restriction of time since previous infection or completion of vaccination			
Fully vaccinated† without previous documented infection (range of time since vaccination = 0–213 days before hospitalization)	**18,397**	542 (3.0)	Ref
Unvaccinated with a previous SARS-CoV-2 infection (range of time since previous infection = 90–494 days before hospitalization)	**2,085**	130 (6.2)	2.75 (1.90–3.98)
Any mRNA vaccine, examining the potential influence of time since previous infection or completion of vaccination			
Fully vaccinated† without previous documented infection, limited to those with longest period since vaccination (range of time since vaccination = 45–213 days before hospitalization)	**12,231**	458 (3.7)	Ref
Unvaccinated with a previous SARS-CoV-2 infection, limited to those with more recent infections (range of time since previous infection = 90–225 days before hospitalization)	**1,389**	107 (7.7)	3.98 (2.49–6.35)
Any mRNA vaccine, adjusting for time since previous infection or completion of vaccination in model			
Fully vaccinated† without previous documented infection	**6,328**	324 (5.1)	Ref
Unvaccinated with a previous SARS-CoV-2 infection	**1,020**	89 (8.7)	3.22 (1.68–6.20)
By time relative to SARS-CoV-2 B.1.617.2 (Delta) variant predominance			
Before Delta predominance (January–June 2021)			
Fully vaccinated† without previous documented infection	**1,115**	18 (1.6)	Ref
Unvaccinated with a previous SARS-CoV-2 infection	**831**	70 (8.4)	6.11 (2.83–13.16)
During Delta predominance (June–September 2021)**			
Fully vaccinated† without previous documented infection	**5,213**	306 (5.9)	Ref
Unvaccinated with a previous SARS-CoV-2 infection	**189**	19 (10.1)	7.55 (3.45–16.52)
By mRNA vaccine product§			
Pfizer-BioNTech (BNT162b2)			
Fully vaccinated† without previous documented infection	**3,736**	215 (5.8)	Ref
Unvaccinated with a previous SARS-CoV-2 infection	**1,020**	89 (8.7)	5.11 (2.53–10.29)
Moderna (mRNA-1273)			
Fully vaccinated† without previous documented infection	**2,592**	109 (4.2)	Ref
Unvaccinated with a previous SARS-CoV-2 infection	**1,020**	89 (8.7)	7.30 (3.40–15.60)
By age group, yrs¶			
18–64			
Fully vaccinated† without previous documented infection	**1,425**	71 (5.0)	Ref
Unvaccinated with a previous SARS-CoV-2 infection	**556**	49 (8.8)	2.57 (1.42–4.65)
≥65			
Fully vaccinated† without previous documented infection	**4,903**	253 (5.2)	Ref
Unvaccinated with a previous SARS-CoV-2 infection	**464**	40 (8.6)	19.57 (8.34–45.91)

Abbreviations: CI = confidence interval; ref = referent group.

* Odds ratios were adjusted for age, geographic region, calendar time (days since January 1, 2021), and local virus circulation (percentage of SARS-CoV-2 positive results from testing within the counties surrounding the facility on the date of the hospitalization) and balanced using inverse weights on characteristics that differed between the two groups (calculated separately for each odds ratio model) using facility characteristics, sociodemographic characteristics, and underlying medical conditions. Cardiovascular disease was also adjusted in the main model and in the model for Pfizer-BioNTech. Any likely immunosuppression was also included in the model for Moderna. Neuromuscular and respiratory conditions were also adjusted in the model for adults aged ≥65 years. Number of days since previous infection or completion of vaccination, instead of calendar time, was adjusted in the model within the stated secondary analysis.

† Full vaccination was defined as receipt of the second dose of Pfizer-BioNTech or Moderna mRNA vaccine ≥14 days before the index test date.

§ P-value from assessment of effect modification by mRNA product was 0.02.

¶ P-value for interaction term for exposure group by age group was 0.05.

** SARS-CoV-2 B.1.617.2 (Delta) variant predominance began on the date the Delta variant accounted for >50% of sequenced isolates in each medical facility's state.

https://doi.org/10.15585/mmwr.mm7037e2

potential suboptimal specification of the model, including but not limited to including a large set of covariates for machine learning estimation of propensity scores, including covariates in both regression and propensity models, ensuring large sample sizes and checking stability of weights, and conducting secondary analyses to assess robustness of results. Finally, the study assessed COVID-19 mRNA vaccines only; findings should not be generalized to the Janssen vaccine.

In this U.S.-based epidemiologic analysis of patients hospitalized with COVID-19–like illness whose previous infection or vaccination occurred 90–179 days earlier, vaccine-induced immunity was more protective than infection-induced immunity

against laboratory-confirmed COVID-19, including during a period of Delta variant predominance. All eligible persons should be vaccinated against COVID-19 as soon as possible, including unvaccinated persons previously infected with SARS-CoV-2.

Acknowledgments

Jefferson Jones, Claire Midgley, Ruth Link-Gelles, Sharon Saydah, Jerome Tokars, Adi Gundlapalli, Natalie Thornburg, Abigail Shefer, John Kools, Erin Tromble, Melissa Carter, Cory Kokko, Stephanie Weaver, Kuzhali Muthumalaiappan, Bao-Ping Zhu, Roumiana Boneva, CDC.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Stephanie A. Irving reports support from Westat to Kaiser Permanente Northwest Center for Health Research. Nicola P. Klein reports support from Pfizer to Kaiser Permanente, Northern California for COVID-19 vaccine clinical trials, and institutional support from Merck, GlaxoSmithKline, and Sanofi Pasteur outside the current study. Charlene McEvoy reports support from AstraZeneca to HealthPartners Institute for COVID-19 vaccine trials. Allison L. Naleway reports Pfizer Research funding to Kaiser Permanente Northwest for unrelated study of meningococcal B vaccine safety during pregnancy. Suchitra Rao reports grants from GlaxoSmithKline and Biofire Diagnostics. No other potential conflicts of interest were disclosed.

Summary

What is already known about this topic?

Previous infection with SARS-CoV-2 or COVID-19 vaccination can provide immunity and protection against subsequent SARS-CoV-2 infection and illness.

What is added by this report?

Among COVID-19–like illness hospitalizations among adults aged ≥18 years whose previous infection or vaccination occurred 90–179 days earlier, the adjusted odds of laboratory-confirmed COVID-19 among unvaccinated adults with previous SARS-CoV-2 infection were 5.49-fold higher than the odds among fully vaccinated recipients of an mRNA COVID-19 vaccine who had no previous documented infection (95% confidence interval = 2.75–10.99).

What are the implications for public health practice?

All eligible persons should be vaccinated against COVID-19 as soon as possible, including unvaccinated persons previously infected with SARS-CoV-2.

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The Advisory Committee on Immunization Practices' Interim Recommendations for Additional Primary and Booster Doses of COVID-19 Vaccines — United States, 2021

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On October 29, 2021, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

Three COVID-19 vaccines are currently approved under a Biologics License Application (BLA) or authorized under an Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) and recommended for primary vaccination by the Advisory Committee on Immunization Practices (ACIP) in the United States: the 2-dose mRNA-based Pfizer-BioNTech/Comirnaty and Moderna COVID-19 vaccines and the single-dose adenovirus vector-based Janssen (Johnson & Johnson) COVID-19 vaccine (*1*,*2*) (Box 1). In August 2021, FDA amended the EUAs for the two mRNA COVID-19 vaccines to allow for an additional primary dose in certain immunocompromised recipients of an initial mRNA COVID-19 vaccination series (*1*). During September–October 2021, FDA amended the EUAs to allow for a COVID-19 vaccine booster dose following a primary mRNA COVID-19 vaccination series in certain recipients aged ≥18 years who are at increased risk for serious complications of COVID-19 or exposure to SARS-CoV-2 (the virus that causes COVID-19), as well as in recipients aged ≥18 years of Janssen COVID-19 vaccine (*1*) (Table). For the purposes of these recommendations, an additional primary (hereafter additional) dose refers to a dose of vaccine administered to persons who likely did not mount a protective immune response after initial vaccination. A booster dose refers to a dose of vaccine administered to enhance or restore protection by the primary vaccination, which might have waned over time. Health care professionals play a critical role in COVID-19 vaccination efforts, including for primary, additional, and booster vaccination, particularly to protect patients who are at increased risk for severe illness and death.

After the EUA amendments, ACIP and CDC issued interim recommendations for vaccine use*,†,§ (*2*). Moderately to severely immunocompromised persons aged ≥12 years (Pfizer-BioNTech recipients) or ≥18 years (Moderna recipients) should receive an additional homologous dose of mRNA COVID-19 vaccine (i.e., the same vaccine product that was administered for the primary series) ≥28 days after receipt of the second dose. Regarding booster dose recommendations, recipients of a

* On August 13, 2021, ACIP voted 11–0 in favor of the interim recommendation for use of an additional homologous primary dose of Pfizer-BioNTech (in persons aged ≥12 years) or Moderna (≥18 years) COVID-19 vaccine after an initial series in moderately to severely immunocompromised persons under FDA's EUA.

† On September 23, 2021, ACIP voted in favor of the following interim recommendations: 1) 15 (in favor)–0 (against) for use of a single Pfizer-BioNTech COVID-19 vaccine booster dose for persons aged ≥65 years and persons aged ≥18 years who reside in long-term care settings, ≥6 months after completion of a Pfizer-BioNTech COVID-19 primary series under FDA's EUA; 2) 13–2 for use of a booster dose in persons aged 50–64 years with underlying medical conditions ≥6 months after completion of a Pfizer-BioNTech COVID-19 vaccine series; 3) 9–6 for use of a single Pfizer-BioNTech COVID-19 vaccine booster dose, based on individual benefits and risks, for persons aged 18–49 years with underlying medical conditions, ≥6 months after completion of a Pfizer-BioNTech COVID-19 vaccine primary series under FDA's EUA. ACIP voted 9–6 against an interim recommendation for use of a single Pfizer-BioNTech COVID-19 vaccine booster dose, based on individual benefits and risks, for persons aged 18–64 years who are in an occupational or institutional setting where the impact of COVID-19 infection and transmission are high, ≥6 months after completion of a Pfizer-BioNTech COVID-19 vaccine primary series under FDA's EUA. The CDC Director accepted ACIP's recommendations 1, 2, and 3 but did not approve the committee's recommendation against an interim recommendation for use of a single Pfizer-BioNTech COVID-19 vaccine booster dose, based on individual risks and benefits and made a CDC recommendation that persons aged 18–64 years at high risk for COVID-19 exposure and transmission because of occupational or institutional setting may receive a Pfizer-BioNTech COVID-19 vaccine booster dose ≥6 months after completion of a Pfizer-BioNTech COVID-19 vaccine primary series under FDA's EUA.

§ On October 21, 2021, ACIP voted in favor of the following interim recommendations: 1) 15–0 for use of a single COVID-19 vaccine booster dose ≥6 months after completion of an mRNA primary series, in the same risk groups for whom CDC recommended a booster dose of Pfizer-BioNTech COVID-19 vaccine, under the FDA's EUA; and 2) 15–0 for use of a single COVID-19 vaccine booster for persons aged ≥18 years, ≥2 months after receipt of the initial Janssen COVID-19 vaccine dose, under the FDA's EUA. ACIP recommends that any of the FDA-approved or authorized COVID-19 vaccines (Pfizer-BioNTech, Moderna, or Janssen) can be used for booster vaccination, regardless of the vaccine product used for primary vaccination.

BOX 1. Timeline of COVID-19 vaccine authorizations, approvals, and vaccine recommendations — United States, December 2020–October 2021

December 2020

- FDA authorizes and ACIP recommends Pfizer-BioNTech COVID-19 vaccine as a 2-dose primary series in persons aged ≥16 years.
- FDA authorizes and ACIP recommends Moderna COVID-19 vaccine as a 2-dose primary series in persons aged ≥18 years.
- ACIP issues interim recommendations for allocating initial supplies of COVID-19 vaccine, starting with long-term care facility residents and health care personnel, followed by other groups at risk.

February 2021

- FDA authorizes and ACIP recommends Janssen (Johnson & Johnson) COVID-19 vaccine as a single dose in persons aged ≥18 years.

April 2021

- CDC and FDA recommend pausing use of Janssen COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome (TTS) among vaccine recipients. Ten days later, ACIP concludes that the benefits of resuming Janssen COVID-19 vaccination outweighs the risks and reaffirms its interim recommendations under FDA's Emergency Use Authorization, which includes a new warning for TTS among women aged 18–49 years.

May 2021

- FDA authorizes and ACIP recommends Pfizer-BioNTech COVID-19 vaccine as a 2-dose primary series in persons aged 12–15 years.

June 2021

- After reports of myocarditis among mRNA COVID-19 vaccine recipients, particularly males aged 12–29 years, ACIP concludes that the benefits of COVID-19 vaccination outweigh the risks of myocarditis after vaccination.

July 2021

- After reports of Guillain-Barré syndrome (GBS) in Janssen COVID-19 vaccine recipients, ACIP reviews updated benefit-risk analyses for all COVID-19 vaccines and concludes that the benefits of vaccination outweigh the risks of GBS and TTS (Janssen COVID-19 vaccine) and myocarditis (mRNA COVID-19 vaccines).

August 2021

- FDA grants full approval and ACIP revises its interim recommendation to a standard recommendation for Pfizer-BioNTech COVID-19 vaccine (Comirnaty) for persons aged ≥16 years.
- FDA authorizes and ACIP recommends an additional primary dose of Pfizer-BioNTech COVID-19 (for persons aged ≥12 years) and Moderna COVID-19 vaccine (for persons aged ≥18 years) in certain immunocompromised persons ≥28 days after completion of the second dose in the initial primary series.

primary mRNA COVID-19 vaccination series who are 1) aged ≥65 years, 2) aged ≥18 years and reside in long-term care settings, or 3) aged 50–64 years with certain underlying medical conditions[¶] should receive a COVID-19 vaccine booster dose ≥6 months after completion of the primary vaccination series. In addition, persons aged 18–49 years with certain underlying medical conditions and those aged 18–64 years who are at increased risk for occupational or institutional exposure to SARS-CoV-2 may receive a booster dose based on their individual benefits and risks. Recipients of Janssen COVID-19 vaccine aged ≥18 years should receive a COVID-19 vaccine booster dose ≥2 months after primary vaccination. Any approved or authorized COVID-19 vaccine may be used for the booster dose, regardless of vaccine received for primary

[¶] CDC considers persons with certain underlying medical conditions to be at increased risk for developing severe outcomes of COVID-19. An-up-to date list, and supporting evidence, is available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. As of October 14, 2021, the list of underlying medical conditions includes: asthma, cancer, cerebrovascular disease, chronic kidney disease, certain types of chronic lung diseases, certain types of chronic liver disease, cystic fibrosis, diabetes mellitus (type 1 and type 2), Down syndrome, heart conditions, HIV, hypertension, immune deficiencies, certain mental health disorders (i.e., mood disorders, schizophrenia spectrum disorders), obesity (BMI ≥30 kg/m^2) and overweight (BMI ≥25 kg/m^2, but <30 kg/m^2), pregnancy and recent pregnancy, sickle cell disease, smoking (current and former), solid organ or blood stem cell transplantation, substance use disorders, thalassemia, tuberculosis, and use of corticosteroids or other immunosuppressive medications. A person with a condition that is not listed might still be at greater risk for severe illness from COVID-19 than persons of similar age who do not have the condition and should talk with their health care provider. This list is not exhaustive and should not be used to exclude persons with underlying conditions from recommended preventive measures, including booster doses of COVID-19 vaccines.

BOX 1. (*Continued*) Timeline of COVID-19 vaccine authorizations, approvals, and vaccine recommendations — United States, December 2020–October 2021

September 2021

- FDA authorizes a single Pfizer-BioNTech COVID-19 vaccine booster dose in certain persons aged ≥18 years at increased risk for serious complications of COVID-19, including severe COVID-19, who completed a Pfizer-BioNTech COVID-19 vaccine primary series ≥6 months ago.
- ACIP recommends that persons aged ≥65 years, residents aged ≥18 years in long-term care settings, and persons aged 50–64 years with certain underlying medical conditions should receive a booster dose and that persons aged 18–49 years with certain underlying medical conditions may receive a single Pfizer-BioNTech COVID-19 vaccine booster dose based on individual benefits and risks.
- CDC further recommends that persons aged 18–64 years at increased risk for SARS-CoV-2 exposure and transmission because of occupational or institutional setting may receive a single Pfizer-BioNTech COVID-19 vaccine booster dose based on individual benefits and risks. This recommendation is replaced by ACIP's broader recommendation in October 2021 for COVID-19 vaccine booster doses in persons who received an mRNA primary series (described below).

October 2021

- FDA authorizes a single Moderna COVID-19 vaccine booster dose (50 μg) in persons aged ≥18 years at increased risk for serious complications of COVID-19 or frequent institutional or occupational exposure to SARS-CoV-2 who completed a Moderna COVID-19 vaccine primary series ≥6 months ago.
- FDA authorizes a single Janssen COVID-19 vaccine booster dose in persons aged ≥18 years who received a Janssen COVID-19 vaccine dose ≥2 months ago.
- FDA authorizes that Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines may be administered as a heterologous booster dose after completion of primary vaccination with another COVID-19 vaccine.
- ACIP recommends that persons aged ≥65 years, residents aged ≥18 years in long-term care settings, and persons aged 50–64 years with certain underlying medical conditions who received an mRNA COVID-19 vaccine primary series should receive a single COVID-19 vaccine booster dose ≥6 months later; persons aged 18–49 years with certain underlying medical conditions and persons aged 18–64 years at increased risk for SARS-CoV-2 exposure and transmission because of occupational or institutional setting may receive a COVID-19 booster dose based on individual benefits and risks. This recommendation replaces the September 23, 2021, ACIP recommendation for Pfizer-BioNTech COVID-19 vaccine booster doses.
- ACIP recommends that persons aged ≥18 years who received Janssen COVID-19 vaccine should receive a single COVID-19 vaccine booster dose ≥2 months later.

Abbreviations: ACIP = Advisory Committee on Immunization Practices; FDA = Food and Drug Administration.

vaccination (Box 2). For Pfizer-BioNTech and Janssen, the dose and volume are the same for primary and booster vaccination; for Moderna, the dose and volume of the booster dose (50 μg; 0.25 ml) are one half that used for the primary series (100 μg; 0.5 ml) (Table). As of October 28, 2021, more than 191 million persons in the United States have been fully vaccinated against COVID-19, and more than 15 million have received an additional or booster dose.**

Since June 2020, ACIP has convened 20 public meetings to review data relevant to the potential use of COVID-19 vaccines.†† To assess the certainty of evidence for benefits and harms of a booster dose, ACIP used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.§§ To further guide its deliberations around the use of an additional or booster dose, ACIP used the Evidence to Recommendations (EtR) Framework to evaluate other factors, including the importance of COVID-19 as a

** The number of persons who received an additional or booster dose includes any person who is fully vaccinated and has received another dose of COVID-19 vaccine since August 13, 2021. https://covid.cdc.gov/covid-data-tracker/#vaccinations. A person is considered fully vaccinated against COVID-19 ≥2 weeks after receipt of the second dose in a 2-dose series (Pfizer-BioNTech and Moderna) or ≥2 weeks after receipt of the single dose of the Janssen vaccine. As of October 29, 2021, administration of an additional primary dose or a booster dose is not required to be considered fully vaccinated for public health purposes. Additional information can be found at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated-guidance.html.

†† https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html

TABLE. COVID-19 vaccines approved or authorized for emergency use by the Food and Drug Administration for persons aged ≥12 years — United States, October 2021*

	Primary and additional primary doses					Booster dose†	
COVID-19 vaccine manufacturer	Age, yrs	Dose (volume)	No. of doses (interval between doses)	Additional primary dose in immunocompromised persons (interval since 2nd dose)	Interval between last primary (including additional) dose to booster dose	Dose (volume)	No. of doses
Pfizer-BioNTech (Comirnaty)	12–17	30 μg (0.3 ml)	2 (21 days)	1 (≥28 days)	NA	NA	NA
	≥18§	30 μg (0.3 ml)	2 (21 days)	1 (≥28 days)	≥6 months	30 μg (0.3 ml)	1
Moderna	≥18§	100 μg (0.5 ml)	2 (28 days)	1 (≥28 days)	≥6 months	50 μg (0.25 ml)	1
Janssen (Johnson & Johnson)	≥18	5×10^{10} VP (0.5 ml)	1 (NA)	NA	≥2 months	5×10^{10} VP (0.5 ml)	1

Abbreviations: NA = not applicable; VP = viral particles.

* As of October 29, 2021. Food and Drug Administration package inserts or fact sheets provide updated information at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines. Route of administration is intramuscular for the currently approved or authorized COVID-19 vaccines.

† The Advisory Committee on Immunization Practices recommends that any of the FDA-approved or authorized COVID-19 vaccines (Pfizer-BioNTech, Moderna, or Janssen) may be used for booster vaccination, regardless of the vaccine product used for primary vaccination. When a heterologous (mix-and-match) booster dose is administered, the eligible population and dosing intervals are those of the vaccine used for primary vaccination. For example, a recipient of Janssen COVID-19 vaccine may receive a Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccine booster dose ≥2 months after their primary dose. A recipient of an mRNA COVID-19 primary series who is in a risk group recommended to receive a booster dose may receive a Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccine booster dose ≥6 months after completion of the primary series. Additional information on groups recommended for an additional primary or booster dose of COVID-19 vaccine is provided at https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html.

§ Minimum authorized age group; see Advisory Committee on Immunization Practices' recommendations for groups recommended to receive a booster dose.

public health problem as well as matters of resource use, benefits and harms, patients' values and preferences, acceptability, feasibility, and equity for use of the vaccines.¶¶

ACIP recommendations for an additional dose of mRNA COVID-19 vaccine in certain immunocompromised persons were guided by data on reduced immunogenicity and effectiveness of the initial primary COVID-19 vaccination series in this population, as well as evidence of an immune response and an acceptable safety profile after an additional mRNA COVID-19 vaccine dose. During the period preceding the emergence of the highly transmissible SARS-CoV-2 B.1.617.2 (Delta) variant, vaccine effectiveness (VE) of a primary mRNA COVID-19 vaccination series against SARS-CoV-2 infection in persons aged ≥16 years was estimated to be 71% (95% confidence interval [CI] = 37%–87%) in immunocompromised persons versus 90% (95% CI = 83%–96%) in the general population and 59% (95% CI = 12%–81%) against COVID-19–associated hospitalization in immunocompromised persons aged ≥18 years versus 91% (95% CI = 86%–95%) in persons who were not immunocompromised (*3*). In a series of small studies, 16% to 80% of solid organ transplant recipients and hemodialysis patients had no detectable antibody response after the second dose of an mRNA COVID-19 vaccine; among these persons, 33% to 55% developed antibodies after receiving an additional dose (*3*). Local and systemic reactions reported after an additional dose of mRNA COVID-19 vaccine in certain immunocompromised persons were mostly mild to moderate and similar to those observed after previous doses; no severe adverse events were reported (*3*). Data were not available to assess immunogenicity or safety of an additional dose in immunocompromised recipients of Janssen COVID-19 vaccine.

To help determine the need for a booster dose in certain populations, ACIP reviewed data on the effectiveness of COVID-19 vaccines after a primary series. In the context of waning vaccine-induced immunity and emergence of the Delta variant in the United States, declines in VE of a primary mRNA COVID-19 vaccination series against SARS-CoV-2 infection have been observed, including among groups recommended to receive early vaccine doses: VE was 75% (95% CI = 60%–85%) to 84% (95% CI = 83%–86%) among adults aged ≥65 years, 53% (95% CI = 49%–57%) among residents of long-term care facilities, and 66% (95% CI = 26%–84%) among health care personnel and other frontline workers during periods of Delta variant predominance (*4,5*). VE of a primary mRNA COVID-19 vaccination series against COVID-19–associated hospitalization overall remains high (78% [95% CI = 62%–87%] to 100% [95% CI = 96%–100%]), although some studies show a slightly lower VE against hospitalization in older adults. Although data are limited, some studies suggest stable VE of Janssen vaccine over time; however, VE of the

§§ As part of GRADE, the ACIP COVID-19 Vaccines Work Group conducted a systematic review of published and unpublished data. Certainty of evidence was rated on a scale of 1 (high certainty) to 4 (very low certainty). Because of limited available data, GRADE was not used in the assessment of the benefits and harms of an additional primary dose in immunocompromised persons. Additional information on the GRADE approach used by ACIP is available at https://www.cdc.gov/vaccines/acip/recs/grade/about-grade.html.

¶¶ https://www.cdc.gov/vaccines/acip/recs/grade/downloads/acip-evidence-recs-framework.pdf

BOX 2. Interim Advisory Committee on Immunization Practices' recommendations for the use of an additional primary* or booster† dose of COVID-19 vaccines — United States, October 2021§

Additional primary mRNA COVID-19 vaccine dose in immunocompromised persons

Moderately to severely immunocompromised persons¶ aged ≥12 years (Pfizer-BioNTech) or ≥18 years (Moderna) who completed an initial mRNA COVID-19 vaccine series should receive an additional primary mRNA vaccine dose ≥28 days after their second dose.** This recommendation does not apply to immunocompromised recipients of Janssen (Johnson & Johnson) COVID-19 vaccine.

COVID-19 vaccine booster dose (including heterologous [mix-and-match] booster vaccination)

mRNA COVID-19 vaccine (Pfizer-BioNTech, Moderna) recipients

The following recipients of an mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) primary series should receive a single COVID-19 vaccine booster dose ≥6 months after completion of the primary series:

- Persons aged ≥65 years
- Residents aged ≥18 years in long-term care settings
- Persons aged 50–64 years with certain underlying medical conditions**

The following recipients of an mRNA primary series may receive a COVID-19 vaccine booster dose ≥6 months after completing the primary series based on their individual benefits and risks:

- Persons aged 18–49 years with certain underlying medical conditions**
- Persons aged 18–64 years at increased risk for SARS-CoV-2 exposure and transmission because of occupational or institutional setting

Any FDA-approved or authorized COVID-19 vaccine (Pfizer-BioNTech, Moderna, or Janssen) can be used as the booster dose, at an interval of ≥6 months since primary vaccination.

Janssen COVID-19 vaccine recipients

- Persons aged ≥18 years who received primary vaccination with Janssen COVID-19 vaccine should receive a single COVID-19 vaccine booster dose ≥2 months later.

Any FDA-approved or -authorized COVID-19 vaccine (Pfizer-BioNTech, Moderna, or Janssen) can be used as the booster dose, at an interval of ≥2 months after the primary Janssen vaccine dose.

* Additional primary dose refers to a dose of vaccine administered to persons who likely did not mount a protective immune response after initial vaccination.
† Booster dose refers to a dose of vaccine administered to enhance or restore protection by the primary vaccination, which might have waned over time.
§ Additional information is available at https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html.
¶ As of October 29, 2021, moderately to severely immunocompromised persons include (but are not limited to) persons with the following conditions or who receive the following treatments: 1) active treatment for solid tumor and hematologic malignancies; 2) receipt of solid-organ transplant and taking immunosuppressive therapy; 3) receipt of chimeric antigen receptor T-cell or hematopoietic cell transplant; 4) moderate or severe primary immunodeficiency; 5) advanced or untreated HIV infection; 6) active treatment with high-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor blockers, and other immunosuppressive or immunomodulatory biologic agents.
** CDC considers persons with certain underlying medical conditions to be at increased risk for developing severe outcomes of COVID-19. An-up-to date list, and supporting evidence, is available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. As of October 14, 2021, the list of underlying medical conditions includes: asthma, cancer, cerebrovascular disease, chronic kidney disease, certain types of chronic lung diseases, certain types of chronic liver disease, cystic fibrosis, diabetes mellitus (type 1 and type 2), Down syndrome, heart conditions, HIV, hypertension, immune deficiencies, certain mental health disorders (i.e., mood disorders, schizophrenia spectrum disorders), obesity (BMI ≥30 kg/m^2) and overweight (BMI ≥25 kg/m^2, but <30 kg/m^2), pregnancy and recent pregnancy, sickle cell disease, smoking (current and former), solid organ or blood stem cell transplantation, substance use disorders, thalassemia, tuberculosis, and use of corticosteroids or other immunosuppressive medications. A person with a condition that is not listed might still be at greater risk for severe illness from COVID-19 than persons of similar age who do not have the condition and should talk with their health care provider. This list is not exhaustive and should not be used to exclude persons with underlying conditions from recommended preventive measures, including booster doses of COVID-19 vaccines.

Janssen vaccine is 58% (95% CI = 12%–80%) to 83% (95% CI = 61%–93%) against SARS-CoV-2 infection and 60% (95% CI = 31%–77%) to 83% (95% CI = 61%–93%) against COVID-19–associated hospitalization among persons aged ≥18 years, which is lower than the estimates reported for mRNA vaccines in most studies (*5*).

ACIP recommendations for a COVID-19 vaccine booster dose in certain persons who had completed primary vaccination were guided by data on immunogenicity, efficacy, and effectiveness of COVID-19 vaccines after booster vaccination, and a review of safety data after COVID-19 vaccine booster doses. Compared with 1 month after the last dose in the primary

Summary

What is already known about this topic?

In the United States, three COVID-19 vaccines are approved or authorized for primary vaccination against COVID-19.

What is added by this report?

The Advisory Committee on Immunization Practices issued recommendations for an additional primary mRNA COVID-19 vaccine dose for immunocompromised persons and a COVID-19 vaccine booster dose in eligible groups.

What are the implications for public health practice?

Health care professionals play a critical role in COVID-19 vaccination efforts, including for primary, additional primary, and booster vaccination, particularly to protect patients who are at increased risk for severe illness and death.

series, geometric mean ratios of neutralization titers were 1.8 to 3.3-fold higher 1 month after a homologous mRNA COVID-19 vaccine booster dose administered 6 months after completing the primary series, and spike binding antibody titers were 4.6 to 12-fold higher after a homologous Janssen COVID-19 booster dose administered 2–6 months after completing primary vaccination (*6,7*). In a small phase I/II clinical trial, both homologous and heterologous (mix-and-match) booster dose administration, in which participants received either a Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccine primary series followed by a booster dose of the same or different vaccine, resulted in anamnestic immune responses; neutralizing antibody titers after a heterologous booster dose were similar to or higher than those observed after homologous booster vaccination (*6*). Observational studies from Israel demonstrated that the short-term incremental VE of a Pfizer-BioNTech COVID-19 primary series plus booster dose (administered ≥5 months after the second dose) compared with 2 doses, ranged from 70% (95% CI = 62%–76%) in persons aged ≥40 years to 91% (95% CI = 90%–92%) in persons aged ≥60 years (*8*). In placebo-controlled clinical trials, overall efficacy of the Janssen vaccine against moderate to severe COVID-19 ≥14 days after vaccination was 75% (95% CI = 55%–87%) for 2 doses administered 2 months apart versus 53% (95% CI = 47%–58%) for a single dose; in the U.S. study population, efficacy was 94% (95% CI = 59%–100%) after 2 doses and 70% (61%–77%) after 1 dose (*6*).

In clinical trials for mRNA and Janssen COVID-19 vaccine booster doses, rates of local or systemic adverse events were similar or lower after a booster dose (whether homologous or heterologous) than after the last primary series dose. No serious adverse events related to the vaccine were reported for mRNA COVID-19 vaccine booster doses; for Janssen, three serious adverse events (facial paresis, pulmonary embolism, and cerebrovascular accident) were attributed by the site investigators to booster vaccination within 6 months of administration, among 5,070 booster recipients in the evaluable population (*6,7*). Outside of clinical trials, more than 13 million persons in the United States had received an additional or booster dose of a COVID-19 vaccine as of October 25, 2021 (predominantly with Pfizer-BioNTech), and no unexpected patterns of adverse events have been observed in national safety surveillance systems (*6*).

From the GRADE evidence assessment, the level of certainty for all benefits and harms of a Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccine booster dose was type 4 (very low certainty) for the prevention of symptomatic COVID-19, prevention of hospitalization attributable to COVID-19 (Pfizer-BioNTech and Janssen), prevention of death attributable to COVID-19 (Janssen), serious adverse events, and reactogenicity (*6,7*). No data were available to assess the GRADE benefit of prevention of SARS-CoV-2 transmission. The main reasons for the low level of certainty in the evidence assessment include small study sizes, lack of a randomized primary series comparison group, short duration of follow-up, and use of immunobridging to infer vaccine efficacy (mRNA vaccines). The GRADE evidence profiles, which provide details on methods for identifying and assessing the supporting evidence, are available at https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-booster-doses.html.

ACIP concluded that the evidence reviewed, including data and considerations from the EtR Frameworks, supported the use of an additional primary dose of an mRNA COVID-19 vaccine for certain immunocompromised recipients of an initial mRNA series, a COVID-19 vaccine booster dose for certain recipients of an mRNA primary series who are at increased risk for exposure to or serious complications of COVID-19, and a COVID-19 vaccine booster dose for all recipients of a Janssen COVID-19 vaccine dose. Additional supporting evidence for the EtR is available at https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-immunocompromised-etr.html and https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-booster-doses-etr.html.

In its deliberations, ACIP discussed the rationale for two different categories of booster dose recommendations among recipients of an mRNA primary series. Persons belonging to groups that ACIP recommends should be vaccinated with a booster dose (Box 2) are groups that are at highest risk for severe COVID-19; several studies suggest waning of VE against hospitalization in older adults. In groups that ACIP recommends may be vaccinated with a booster dose based on individual benefits and risks, evidence suggests that although VE against hospitalization remains high, waning of VE against SARS-CoV-2 infection has been observed. At the September 22–23, 2021,

meeting, when booster dose deliberations were limited to Pfizer-BioNTech COVID-19 vaccine, ACIP initially recommended against booster vaccination for persons with frequent occupational or institutional exposure to SARS-CoV-2, given that protection against severe disease in the overall population remains high. However, CDC recommended that persons in this group may receive a booster dose based on their individual benefits and risks, given the implications of waning immunity against infection on health care personnel and other frontline workers, or in settings where the ability to maintain physical distancing or isolation of persons with COVID-19 is more challenging, such as correctional or detention facilities.[***,†††] During the October meeting when booster dose deliberations expanded to Moderna and Janssen vaccines, ACIP voted to recommend a COVID-19 vaccine booster dose to recipients of an mRNA primary series (including those who had received Pfizer-BioNTech) who were currently in the risk groups recommended by CDC to receive booster vaccination, including those at occupational or institutional risk for exposure based on individual benefits and risks. This recommendation supersedes the previous recommendations issued by ACIP and CDC in September. Additional information on individual benefit-risk assessments for mRNA booster vaccination is available at https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Regarding Janssen COVID-19 vaccine, ACIP discussed the importance of optimizing vaccine-induced protection against SARS-CoV-2 in all recipients of primary vaccination because although VE against infection and hospitalization appears stable over time, VE estimates for Janssen vaccine are overall lower than those observed for mRNA vaccines.

ACIP also emphasized that achieving high and equitable coverage with a COVID-19 primary vaccination series remains the highest priority and is fundamental to reducing COVID-19–related morbidity and mortality. ACIP also stressed the importance of ensuring global equity in access to COVID-19 vaccines for the prevention of disease in vulnerable persons and mitigation of the emergence of SARS-CoV-2 variants.

Before vaccination, providers should provide the EUA Fact Sheet for the vaccine being administered and counsel vaccine recipients about expected systemic and local reactogenicity. Additional clinical education materials are available at https://www.cdc.gov/vaccines/covid-19/index.html, including additional clinical considerations at https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. The interim recommendations and clinical considerations are based on use of an additional or booster dose of COVID-19 vaccine under an EUA and might change as more evidence becomes available.

*** https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html
††† https://www.cdc.gov/media/releases/2021/p0924-booster-recommendations-.html

Reporting of Vaccine Adverse Events

FDA requires that immunization providers report vaccine administration errors, serious adverse events, cases of multisystem inflammatory syndrome, and cases of COVID-19 that result in hospitalization or death after administration of COVID-19 vaccine under an EUA (*2*). Adverse events that occur after receipt of any COVID-19 vaccine should be reported to the Vaccine Adverse Events Reporting System (VAERS, https://vaers.hhs.gov or 1-800-822-7967). Any person who administers or receives a COVID-19 vaccine is encouraged to report any clinically significant adverse event, whether or not it is clear that a vaccine caused the adverse event. In addition, CDC has developed a new, voluntary smartphone-based online tool (v-safe) that uses text messaging and online surveys to provide near real-time health check-ins after receipt of a COVID-19 vaccine (https://www.cdc.gov/vsafe).

Acknowledgments

Karen Broder, Amanda Cohn, Rachel Gorwitz, Anne Hause, Ruth Link-Gelles, Lauri Markowitz, Tom Shimabukuro, Rachel Slayton, John Su, Naomi Tepper, Erin Tromble, Melinda Wharton, CDC COVID-19 Response Team. Voting members of the Advisory Committee on Immunization Practices: Kevin A. Ault, University of Kansas Medical Center; Lynn Bahta, Minnesota Department of Health; Wilbur Chen, University of Maryland School of Medicine; Sybil Cineas, Warren Alpert Medical School of Brown University; James Loehr, Cayuga Family Medicine; Sarah Long, Drexel University College of Medicine; Veronica V. McNally, Franny Strong Foundation; Katherine A. Poehling, Wake Forest School of Medicine; Pablo J. Sánchez, The Research Institute at Nationwide Children's Hospital. Members of the Advisory Committee on Immunization Practices COVID-19 Vaccines Work Group: Edward Belongia, Center for Clinical Epidemiology & Population Health, Marshfield Clinic Research Institute; Henry Bernstein, Zucker School of Medicine at Hofstra/Northwell Cohen Children's Medical Center; Dayna Bowen Matthew, George Washington University Law School; Uzo Chukwuma, Indian Health Service; Marci Drees, Society for Healthcare Epidemiology of America; Jeffrey Duchin, Infectious Diseases Society of America; Kathy Kinlaw, Center for Ethics, Emory University; Doran Fink, Food and Drug Administration; Sandra Fryhofer, American Medical Association; Jason M. Goldman, American College of Physicians; Michael Hogue, American Pharmacists Association; Denise Jamieson, American College of Obstetricians and Gynecologists; Jeffery Kelman, Centers for Medicare & Medicaid; David Kim, U.S. Department of Health and Human Services; Susan Lett, Council of State and Territorial Epidemiologists; Kendra McMillan, American Nurses Association; Kathleen Neuzil, Center for Vaccine Development and Global

Health, University of Maryland School of Medicine; Sean O'Leary, American Academy of Pediatrics; Christine Oshansky, Biomedical Advanced Research and Development Authority; Stanley Perlman, Department of Microbiology and Immunology, University of Iowa; Marcus Plescia, Association of State and Territorial Health Officials; Chris Roberts, National Institutes of Health; José R. Romero, Arkansas Department of Health; William Schaffner, National Foundation for Infectious Diseases; Rob Schechter, Association of Immunization Managers; Kenneth Schmader, American Geriatrics Society; Bryan Schumacher, Department of Defense; Peter Szilagyi, University of California, Los Angeles; Jonathan Temte, American Academy of Family Physicians; Matthew Tunis, National Advisory Committee on Immunization Secretariat, Public Health Agency of Canada; Matt Zahn, National Association of County and City Health Officials; Rachel Zhang, Food and Drug Administration.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

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Effectiveness of 2-Dose Vaccination with mRNA COVID-19 Vaccines Against COVID-19–Associated Hospitalizations Among Immunocompromised Adults — Nine States, January–September 2021

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On November 2, 2021, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

Immunocompromised persons, defined as those with suppressed humoral or cellular immunity resulting from health conditions or medications, account for approximately 3% of the U.S. adult population (*1*). Immunocompromised adults are at increased risk for severe COVID-19 outcomes (*2*) and might not acquire the same level of protection from COVID-19 mRNA vaccines as do immunocompetent adults (*3*,*4*). To evaluate vaccine effectiveness (VE) among immunocompromised adults, data from the VISION Network* on hospitalizations among persons aged ≥18 years with COVID-19–like illness from 187 hospitals in nine states during January 17–September 5, 2021 were analyzed. Using selected discharge diagnoses,† VE against COVID-19–associated hospitalization conferred by completing a 2-dose series of an mRNA COVID-19 vaccine ≥14 days before the index hospitalization date§ (i.e., being fully vaccinated) was evaluated using a test-negative design comparing 20,101 immunocompromised adults (10,564 [53%] of whom were fully vaccinated) and 69,116 immunocompetent adults (29,456 [43%] of whom were fully vaccinated). VE of 2 doses of mRNA COVID-19 vaccine against COVID-19–associated hospitalization was lower among immunocompromised patients (77%; 95% confidence interval [CI] = 74%–80%) than among immunocompetent patients (90%; 95% CI = 89%–91%). This difference persisted irrespective of mRNA vaccine product, age group, and timing of hospitalization relative to SARS-CoV-2 (the virus that causes COVID-19) B.1.617.2 (Delta) variant predominance in the state of hospitalization. VE varied across immunocompromising condition subgroups, ranging from 59% (organ or stem cell transplant recipients) to 81% (persons with a rheumatologic or inflammatory disorder). Immunocompromised persons benefit from mRNA COVID-19 vaccination but are less protected from severe COVID-19 outcomes than are immunocompetent persons, and VE varies among immunocompromised subgroups. Immunocompromised persons receiving mRNA COVID-19 vaccines should receive 3 doses and a booster, consistent with CDC recommendations (*5*), practice nonpharmaceutical interventions, and, if infected, be monitored closely and considered early for proven therapies that can prevent severe outcomes.

Data came from the VISION Network, a collaboration between CDC and seven U.S. health care systems and research centers with integrated medical, laboratory, and vaccination records that was established to assess the effectiveness of COVID-19 vaccines (*6*). Eligible hospitalizations were defined as those among adults aged ≥18 years with SARS-CoV-2 molecular testing (from 14 days before through 72 hours after admission) and a COVID-19–like illness discharge diagnosis.¶ Encounters without molecular testing were excluded from

* Funded by CDC, the VISION Network includes Columbia University Irving Medical Center, New York, New York; HealthPartners Minnesota and Wisconsin; Intermountain Healthcare, Salt Lake City, Utah; Kaiser Permanente Northern California, Oakland, California; Kaiser Permanente Northwest, Portland, Oregon; Regenstrief Institute, Indianapolis, Indiana; and University of Colorado, Aurora, Colorado.

† Immunocompromised status was defined as the presence of at least one discharge diagnosis, using diagnosis codes from *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, Tenth Revision* (ICD-10), for solid malignancy (ICD-10 codes: C00–C80, C7A, C7B, D3A, Z51.0, and Z51.1), hematologic malignancy (ICD-10 codes: C81–C86, C88, C90–C96, D46, D61.0, D70.0, D61.2, D61.9, and D71), rheumatologic or inflammatory disorder (ICD-10 codes: D86, E85 [except E85.0], G35, J67.9, L40.54, L40.59, L93.0, L93.2, L94, M05–M08, M30, M31.3, M31.5, M32–M34, M35.3, M35.8, M35.9, M46, and T78.40), other intrinsic immune condition or immunodeficiency (ICD-10 codes: D27.9, D61.09, D72.89, D80, D81 [except D81.3], D82–D84, D89 [except D89.2], K70.3, K70.4, K72, K74.3–K74.6 [except K74.60 and K74.69], N04, and R18), or organ or stem cell transplant (ICD-10 codes: T86 [except T86.82–T86.84, T86.89, and T86.9], D47.Z1, Z48.2, Z94, and Z98.85).

§ Index date was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result before hospitalization or the hospitalization date if testing only occurred after admission.

¶ Hospitalizations with a discharge code consistent with COVID-19–like illness were included. COVID-19–like illness diagnoses included acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea) using diagnosis codes from ICD-9 and ICD-10.

this analysis. Immunocompromised patients were defined by the presence of at least one selected discharge diagnosis for immunocompromising conditions using the *International Classification of Diseases, Ninth Revision* and *International Classification of Diseases, Tenth Revision*. Diagnoses across five categories of immunocompromising conditions were derived from lists used in previous studies of large hospital-based or administrative databases and included the following conditions: 1) solid malignancies, 2) hematologic malignancies, 3) rheumatologic or inflammatory disorders, 4) other intrinsic immune conditions or immunodeficiencies, and 5) organ or stem cell transplants (*7*–*9*). Immunosuppressive medication use data were not available for these analyses. Vaccination status was documented in electronic health records or state immunization registries (*6*). Full vaccination was defined as receipt of the second in a 2-dose series of Moderna (mRNA-1273) or Pfizer-BioNTech (BNT162b2) vaccines ≥14 days before the index hospitalization date; unvaccinated patients had not received any COVID-19 vaccine doses and were considered the referent group. Patients who received 1) only 1 mRNA vaccine dose, 2) ≥3 mRNA vaccine doses, 3) the second dose <14 days before index hospitalization date, or 4) the Janssen (Johnson & Johnson [Ad26.COV2]) vaccine were excluded from the analysis.

VE was estimated using a test-negative design comparing the odds of a positive test result for SARS-CoV-2 between fully vaccinated and unvaccinated patients using multivariable logistic regression models. VE was adjusted for age, geographic region, calendar time (days from January 1 to hospitalization), and local virus circulation in the community where each partner site was located and weighted for inverse propensity to be vaccinated or unvaccinated (calculated separately for each VE estimate). Generalized boosted regression trees were used to estimate the propensity to be vaccinated based on sociodemographic characteristics, underlying medical conditions, known previous SARS-CoV-2 infection, and hospital characteristics. VE estimates were stratified by immunocompromised status, mRNA COVID-19 vaccine product received, age group, and network partner (representing different health care systems and geographic regions). Among immunocompromised patients, VE was also calculated separately among subgroups of patients with each of the five categories of immunocompromising diagnoses (subgroups that were not mutually exclusive). VE was also calculated separately for hospitalizations occurring before and after the period when the Delta variant accounted for ≥50% of sequenced isolates within each site's state (*10*). VE estimates with 95% CIs that did not overlap were considered statistically different, which is a conservative approach.This study was reviewed and approved by Westat, Inc. institutional review board.**

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

Among 69,116 immunocompetent adults and 20,101 immunocompromised adults hospitalized with COVID-19–like illness and with available molecular testing results for SARS-CoV-2, 29,456 (43%) and 10,564 (53%), respectively, were fully vaccinated (Table 1). The median ages of immunocompetent and immunocompromised patients were 68 years (interquartile range [IQR] = 52–79 years) and 70 years (IQR = 60–78 years), respectively. Among immunocompetent patients, 42% had received the Moderna vaccine and 58% had received the Pfizer-BioNTech vaccine, and among immunocompromised patients, 41% and 59% had received Moderna and Pfizer-BioNTech vaccines, respectively. Among immunocompetent patients, the median interval from receipt of the second vaccine dose to hospital admission was 89 days (IQR = 52–129 days) among Moderna vaccine recipients and 90 days (IQR = 52–131 days) among Pfizer-BioNTech vaccine recipients; among immunocompromised patients, the intervals were 89 days (IQR = 52–128 days) and 89 days (IQR = 53–128 days) for Moderna vaccine and Pfizer-BioNTech vaccine recipients, respectively.

Among immunocompetent patients, SARS-CoV-2 infection was laboratory-confirmed in 9,853 (24.8%) unvaccinated and 1,108 (3.8%) fully vaccinated persons, compared with 1,127 (11.8%) unvaccinated and 410 (3.9%) fully vaccinated immunocompromised patients (Table 2). VE of 2 doses of mRNA vaccine against COVID-19 hospitalization was lower among immunocompromised patients (77%) than among immunocompetent patients (90%). Differences persisted when analyzed among patients aged 18–64 years and aged ≥65 years, and among Moderna and Pfizer-BioNTech vaccine recipients. Among immunocompromised patients, VE was 81% for the Moderna vaccine and 71% for the Pfizer-BioNTech vaccine; however, CIs slightly overlapped between these two estimates. VE was similarly lower among immunocompromised than among immunocompetent patients both before the period of Delta variant predominance (76%; 95% CI = 69%–81% versus 91%; 95% CI = 90%–93%) and during the period of Delta variant predominance (79%; 95% CI = 74%–83% versus 90%; 95% CI = 89%–91%). Across network partners, VE point estimates varied more for immunocompromised patients (57–85%) than for immunocompetent patients (84%–94%).

Among immunocompromised patients, 8,887 (44%) had a solid malignancy, (range across network partners = 34%–47%), 2,790 (14%) a hematologic malignancy (range = 11%–19%), 5,024 (25%) a rheumatologic or inflammatory disorder (range = 22%–30%), 6,380 (32%) another intrinsic immune condition or immunodeficiency (range = 29%–37%), and 1,416 (7%) had received an organ or stem cell transplant (range = 4%–10%). VE point estimates ranged from 59% (organ or stem cell transplant patients) to 81% (patients with

TABLE 1. Characteristics of COVID-19–like illness hospitalizations* among immunocompetent and immunocompromised adults aged ≥18 years and proportions of 2-dose mRNA COVID-19 vaccine recipients with laboratory-confirmed SARS-CoV-2 infection — nine states,† January–September 2021

	Immunocompetent					Immunocompromised§				
	Total	Vaccinated¶		SARS-CoV-2–positive test result		Total	Vaccinated¶		SARS-CoV-2–positive test result	
Characteristic	No. (column %)	No. (row %)	SMD**	No. (row %)	SMD††	No. (column %)	No. (row %)	SMD**	No. (row %)	SMD††
All hospitalizations	**69,116 (100)**	**29,456 (43)**	—	**10,961 (16)**	—	**20,101 (100)**	**10,564 (53)**	—	**1,537 (8)**	—
Site										
Columbia University	**4,221 (6)**	1,338 (32)	0.70	673 (16)	0.39	**1,615 (8)**	645 (40)	0.86	149 (9)	0.50
HealthPartners	**1,695 (2)**	1,022 (60)		100 (6)		**721 (4)**	467 (65)		24 (3)	
Intermountain Healthcare	**6,937 (10)**	2,501 (36)		1,925 (28)		**1,479 (7)**	659 (45)		292 (20)	
Kaiser Permanente Northern California	**22,331 (32)**	14,222 (64)		3,253 (15)		**7,518 (37)**	5,707 (76)		461 (6)	
Kaiser Permanente Northwest	**3,531 (5)**	1,716 (49)		347 (10)		**1,117 (6)**	614 (55)		47 (4)	
Regenstrief Institute	**19,099 (28)**	6,188 (32)		3,562 (19)		**3,000 (15)**	1,121 (37)		320 (11)	
University of Colorado	**11,302 (16)**	2,469 (22)		1,101 (10)		**4,651 (23)**	1,351 (29)		244 (5)	
Age group, yrs										
18–49	**15,891 (23)**	3,469 (22)	0.62	3,542 (22)	0.43	**2,291 (11)**	709 (31)	0.47	241 (11)	0.21
50–64	**13,669 (20)**	4,597 (34)		2,989 (22)		**4,524 (23)**	1,874 (41)		411 (9)	
65–74	**15,715 (23)**	7,477 (48)		2,101 (13)		**6,149 (31)**	3,429 (56)		431 (7)	
75–84	**14,421 (21)**	8,270 (57)		1,491 (10)		**5,064 (25)**	3,201 (63)		341 (7)	
≥85	**9,420 (14)**	5,643 (60)		838 (9)		**2,073 (10)**	1,351 (65)		113 (5)	
Sex										
Men§§	**30,625 (44)**	13,106 (43)	–0.01	5,406 (18)	–0.12	**9,552 (48)**	5,082 (53)	–0.02	762 (8)	–0.04
Women	**38,491 (56)**	16,350 (42)		5,555 (14)		**10,549 (52)**	5,482 (52)		775 (7)	
Race, (regardless of ethnicity)										
White	**45,206 (65)**	20,094 (44)	0.28	6,512 (14)	0.20	**13,834 (69)**	7,344 (53)	0.23	985 (7)	0.16
Black	**7,204 (10)**	2,107 (29)		1,274 (18)		**1,821 (9)**	819 (45)		182 (10)	
Other	**5,382 (8)**	3,126 (58)		722 (13)		**1,725 (9)**	1,164 (67)		110 (6)	
Unknown	**11,324 (16)**	4,129 (36)		2,453 (22)		**2,721 (14)**	1,237 (45)		260 (10)	
Ethnicity										
Hispanic	**9,415 (14)**	3,464 (37)	0.10	2,069 (22)	0.26	**2,786 (14)**	1,366 (49)	0.09	271 (10)	0.14
Non-Hispanic	**48,146 (70)**	20,753 (43)		6,498 (13)		**14,448 (72)**	7,544 (52)		1,020 (7)	
Unknown	**11,555 (17)**	5,239 (45)		2,394 (21)		**2,867 (14)**	1,654 (58)		246 (9)	
Chronic respiratory condition¶¶										
Has chronic respiratory condition	**44,264 (64)**	19,788 (45)	0.11	6,891 (16)	–0.03	**13,652 (68)**	7,331 (54)	0.07	1,084 (8)	0.06
No chronic respiratory condition§§	**24,852 (36)**	9,668 (39)		4,070 (16)		**6,449 (32)**	3,233 (50)		453 (7)	
ICU admission										
Admitted to ICU	**10,939 (16)**	4,278 (39)	–0.06	1,700 (16)	–0.01	**4,285 (21)**	1,977 (46)	–0.13	361 (8)	0.06
Not admitted to ICU§§	**58,177 (84)**	25,178 (43)		9,261 (16)		**15,816 (79)**	8,587 (54)		1,176 (7)	
COVID-19 vaccination status										
Unvaccinated	**39,660 (57)**	0 (—)	—	9,853 (25)	0.94	**9,537 (47)**	0 (—)	—	1,127 (12)	0.60
Moderna (mRNA-1273)	**12,341 (18)**	12,341 (100)		357 (3)		**4,337 (22)**	4,337 (100)		138 (3)	
Pfizer-BioNTech (BNT162b2)	**17,115 (25)**	17,115 (100)		751 (4)		**6,227 (31)**	6,227 (100)		272 (4)	

Abbreviations: ICD-9 = *International Classification of Diseases, Ninth Revision*; ICD-10 = *International Classification of Diseases, Tenth Revision*; ICU = intensive care unit; SMD = standardized mean or proportion difference.

* Hospitalizations with a discharge code consistent with COVID-19–like illness were included, such as acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea), using diagnosis codes from ICD-9 and ICD-10. Clinician-ordered molecular assays (e.g., real-time reverse transcription–polymerase chain reaction test) for SARS-CoV-2 occurring ≤14 days before to <72 hours after hospital admission were included.

† Partners contributing data on hospitalizations were in California (range of earliest to latest hospitalization: March 1–September 5), Colorado (January 22–August 31), Indiana (January 22–September 5), Minnesota and Wisconsin (January 17–August 18), New York (January 22–September 5), Oregon and Washington (February 1–August 20), and Utah (February 1–September 5).

§ Immunocompromised status was presumed based on the presence of at least one discharge diagnosis, using ICD-9 and ICD-10 diagnosis codes for solid malignancy (ICD-10 codes: C00–C80, C7A, C7B, D3A, Z51.0, and Z51.1), hematologic malignancy (ICD-10 codes: C81–C86, C88, C90–C96, D46, D61.0, D70.0, D61.2, D61.9, and D71), rheumatologic or inflammatory disorder (ICD-10 codes: D86, E85 [except E85.0], G35, J67.9, L40.54, L40.59, L93.0, L93.2, L94, M05–M08, M30, M31.3, M31.5, M32–M34, M35.3, M35.8, M35.9, M46, and T78.40), other intrinsic immune condition or immunodeficiency (ICD-10 codes: D27.9, D61.09, D72.89, D80, D81 [except D81.3], D82–D84, D89 [except D89.2], K70.3, K70.4, K72, K74.3–K74.6 [except K74.60 and K74.69], N04, and R18), or organ or stem cell transplant (ICD-10 codes: T86 [except T86.82–T86.84, T86.89, and T86.9], D47.Z1, Z48.2, Z94, and Z98.85).

¶ Vaccination was defined as having received exactly 2 doses of an mRNA-based COVID-19 vaccine ≥14 days before the hospitalization index date, which was the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result before the hospitalization or the hospitalization date if testing only occurred after the admission.

** An absolute standardized mean or proportion difference ≥0.10 indicates a nonnegligible difference in variable distributions between hospitalizations for vaccinated versus unvaccinated patients.

†† An absolute standardized mean or proportion difference ≥0.10 indicates a nonnegligible difference in variable distributions between hospitalizations for SARS-CoV-2–positive versus SARS-CoV-2–negative patients.

§§ Indicates the reference group used for standardized mean or proportion difference calculations for dichotomous variables.

¶¶ Chronic respiratory condition was defined as the presence of discharge code for asthma, chronic obstructive pulmonary disease, or other lung disease using diagnosis codes from ICD-9 and ICD-10.

TABLE 2. Two-dose mRNA COVID-19 vaccine effectiveness* against laboratory-confirmed COVID-19–associated hospitalization† among immunocompetent and immunocompromised adults aged ≥18 years, by age group and vaccine — nine states,§ January–September 2021

Age group, yrs, vaccine	Total no. of adults	SARS-CoV-2–positive test result, no. (row %)	VE,¶ % (95% CI)
≥18, any mRNA COVID-19 vaccine			
Immunocompetent (n = 69,116)			
Unvaccinated	**39,660**	9,853 (24.8)	Ref
Vaccinated with 2 doses**	**29,456**	1,108 (3.8)	90 (89–91)
Immunocompromised†† (n = 20,101)			
Unvaccinated	**9,537**	1,127 (11.8)	Ref
Vaccinated with 2 doses**	**10,564**	410 (3.9)	77 (74–80)
18–64, any mRNA COVID-19 vaccine			
Immunocompetent (n = 29,560)			
Unvaccinated	**21,494**	6,243 (29.1)	Ref
Vaccinated with 2 doses**	**8,066**	288 (3.6)	93 (92–94)
Immunocompromised†† (n = 6,815)			
Unvaccinated	**4,232**	544 (12.8)	Ref
Vaccinated with 2 doses**	**2,583**	108 (4.2)	80 (74–84)
≥65, any mRNA COVID-19 vaccine			
Immunocompetent (n = 39,556)			
Unvaccinated	**18,166**	3,610 (19.9)	Ref
Vaccinated with 2 doses**	**21,390**	820 (3.8)	87 (86–88)
Immunocompromised†† (n = 13,286)			
Unvaccinated	**5,305**	583 (11)	Ref
Vaccinated with 2 doses**	**7,981**	302 (3.8)	75 (70–79)
≥18, Moderna (mRNA-1273) vaccine			
Immunocompetent (n = 52,001)			
Unvaccinated	**39,660**	9,853 (24.8)	Ref
Vaccinated with 2 doses**	**12,341**	357 (2.9)	93 (92–94)
Immunocompromised†† (n = 13,874)			
Unvaccinated	**9,537**	1,127 (11.8)	Ref
Vaccinated with 2 doses**	**4,337**	138 (3.2)	81 (76–85)
≥18, Pfizer-BioNTech (BNT162b2) vaccine			
Immunocompetent (n = 56,775)			
Unvaccinated	**39,660**	9,853 (24.8)	Ref
Vaccinated with 2 doses**	**17,115**	751 (4.4)	88 (86–89)
Immunocompromised†† (n = 15,764)			
Unvaccinated	**9,537**	1,127 (11.8)	Ref
Vaccinated with 2 doses**	**6,227**	272 (4.4)	71 (65–76)

Abbreviations: CI = confidence interval; ICD-9 = *International Classification of Diseases, Ninth Revision*; ICD-10 = *International Classification of Diseases, Tenth Revision*; Ref = referent group; VE = vaccine effectiveness.

* VE was estimated using a test-negative design, adjusted for age, geographic region, calendar time (days since January 1, 2021), and local virus circulation (percentage of SARS-CoV-2–positive results from testing within the counties surrounding the facility on the date of the hospitalization) and weighted for inverse propensity to be vaccinated or unvaccinated (calculated separately for each VE estimate) using sociodemographic characteristics, underlying medical conditions, known previous SARS-CoV-2 infection, and hospital characteristics, in addition to age, geographic region, calendar time, and local virus circulation.

† Hospitalizations with a discharge code consistent with COVID-19–like illness were included, such as acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea), using diagnosis codes from ICD-9 and ICD-10. Clinician-ordered molecular assays (e.g., real-time reverse transcription–polymerase chain reaction test) for SARS-CoV-2 occurring ≤14 days before to <72 hours after hospital admission were included.

§ Partners contributing data on hospitalizations were in California (range of earliest to latest hospitalization: March 1–September 5), Colorado (January 22–August 31), Indiana (January 22–September 5), Minnesota and Wisconsin (January 17–August 18), New York (January 22–September 5), Oregon and Washington (February 1–August 20), and Utah (February 1–September 5).

¶ VE was calculated as [1−odds ratio]x100%.

** Vaccination was defined as having received exactly 2 doses of an mRNA-based COVID-19 vaccine ≥14 days before the hospitalization index date, which was the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result before the hospitalization or the hospitalization date if testing only occurred after the admission.

†† Immunocompromised status was presumed based on the presence of at least one discharge diagnosis, using ICD-9 and ICD-10 diagnosis codes for solid malignancy (ICD-10 codes: C00–C80, C7A, C7B, D3A, Z51.0, and Z51.1), hematologic malignancy (ICD-10 codes: C81–C86, C88, C90–C96, D46, D61.0, D70.0, D61.2, D61.9, and D71), rheumatologic or inflammatory disorder (ICD-10 codes: D86, E85 [except E85.0], G35, J67.9, L40.54, L40.59, L93.0, L93.2, L94, M05–M08, M30, M31.3, M31.5, M32–M34, M35.3, M35.8, M35.9, M46, and T78.40), other intrinsic immune condition or immunodeficiency (ICD-10 codes: D27.9, D61.09, D72.89, D80, D81 [except D81.3], D82–D84, D89 [except D89.2], K70.3, K70.4, K72, K74.3–K74.6 [except K74.60 and K74.69], N04, and R18), or organ or stem cell transplant (ICD-10 codes: T86 [except T86.82–T86.84, T86.89, and T86.9], D47.Z1, Z48.2, Z94, and Z98.85).

a rheumatologic or inflammatory disorder) across these subgroups (Table 3). Subgroup VE point estimates were generally higher for the Moderna vaccine than for the Pfizer-BioNTech vaccine but were the same among patients with a rheumatologic or inflammatory disorder.

Discussion

In a multistate analysis of approximately 89,000 hospitalizations of adults with COVID-19–like illness during January 17–September 5, 2021, receipt of 2 doses of mRNA COVID-19 vaccine was effective in preventing laboratory-confirmed COVID-19 hospitalizations among patients who were immunocompromised (VE = 77%) and those who were immunocompetent (VE = 90%). Nonetheless, immunocompromised patients were significantly less protected from severe COVID-19 outcomes compared with immunocompetent patients, supporting the recommendation for administration of a third dose of mRNA vaccine to further enhance protection of moderately to severely immunocompromised persons against severe COVID-19 outcomes (*5*).

This study also found that VE was lower among certain subgroups of immunocompromised adults, such as solid organ or stem cell transplant recipients, than among others. These findings are consistent with other studies suggesting that certain immunocompromised persons experience an attenuated immune response to COVID-19 vaccines and make up a large proportion of hospitalizations for infections after vaccination (*3*,*4*). The prevalence of SARS-CoV-2 infection was approximately two times greater among unvaccinated immunocompetent patients compared with unvaccinated immunocompromised patients. Because the study sample was restricted to patients hospitalized with COVID-19–like illness, this difference might be related to a variation in the prevalence of other respiratory virus infections between the two groups, although this is unable to be confirmed. A strength of the test-negative design is that such a difference is not expected to influence the validity of VE estimates stratified by immunocompromised status.

The findings in this report are subject to at least six limitations. First, the use of selected discharge diagnoses as surrogates for presumed immunocompromised status and the absence of medication and other relevant data might have led to classification of persons as immunocompromised who were not; the opposite is also possible but is less likely. Second, selection bias might be possible if vaccination status influences the likelihood of receiving testing although a previous VISION Network study indicated that vaccination status did not affect receipt of testing (*6*). Third, despite the high specificity of COVID-19 vaccination status from these data sources, misclassification might be possible. Fourth, although inverse weights balanced unvaccinated and vaccinated hospitalized patients on sociodemographic and health characteristics, and further adjustments for age, geographic region, calendar time, and local virus circulation were made, unmeasured and residual confounding (e.g., mask-wearing and waning immunity) in this observational study might have biased these estimates. Fifth, the study only assessed mRNA COVID-19 vaccines and not the Janssen vaccine and included health care systems in only nine states, limiting the potential for the findings of this study to be extrapolated. Finally, immunocompromising conditions were not mutually exclusive, and sparse data in smaller immunocompromised subgroups reduced VE precision, so it was not possible to determine the independent effect of each subgroup on VE.

Immunocompromised persons benefit from and should receive COVID-19 vaccines. Given that VE is lower compared to immunocompetent patients, immunocompromised persons receiving mRNA vaccines should receive 3 doses and a booster 6 months after the third dose, consistent with CDC recommendations (*5*). In addition to vaccination, immunocompromised persons should implement nonpharmaceutical prevention strategies such as masking to help prevent SARS-CoV-2 infection, and, if infected with SARS-CoV-2, be monitored closely and considered early for proven therapies that might prevent progression to severe illness (e.g., monoclonal antibodies). Additional studies are needed to further characterize variation in VE among immunocompromised subpopulations and across geographic regions, determine the degree of improvements in VE conferred by additional COVID-19 vaccine doses in

Summary

What is already known about this topic?

Studies suggest that immunocompromised persons who receive COVID-19 vaccination might not develop high neutralizing antibody titers or be as protected against severe COVID-19 outcomes as are immunocompetent persons.

What is added by this report?

Effectiveness of mRNA vaccination against laboratory-confirmed COVID-19–associated hospitalization was lower (77%) among immunocompromised adults than among immunocompetent adults (90%). Vaccine effectiveness varied considerably among immunocompromised patient subgroups.

What are the implications for public health practice?

Immunocompromised persons benefit from COVID-19 mRNA vaccination but are less protected from severe COVID-19 outcomes than are immunocompetent persons. Immunocompromised persons receiving mRNA COVID-19 vaccines should receive 3 doses and a booster, consistent with CDC recommendations, practice nonpharmaceutical interventions, and, if infected, be monitored closely and considered early for proven therapies that can prevent severe outcomes.

TABLE 3. Two-dose mRNA COVID-19 vaccine effectiveness* against laboratory-confirmed COVID-19–associated hospitalization† among subgroups of adults aged ≥18 years with specific types of conditions and presumed to be immunocompromised (20,101)§ — nine states,¶ January–September 2021

Condition (no. of adults)	Total	SARS-CoV-2–positive tests, no. (row %)	VE,** % (95% CI)
Solid malignancy†† (8,887)			
Unvaccinated	**3,986**	304 (7.6)	Ref
Vaccinated with any 2 mRNA vaccine doses§§	**4,901**	106 (2.2)	79 (73–84)
Vaccinated with 2 Moderna (mRNA-1273) vaccine doses§§	**2,053**	30 (1.5)	85 (76–91)
Vaccinated with 2 Pfizer-BioNTech (BNT162b2) vaccine doses§§	**2,848**	76 (2.7)	72 (62–80)
Hematologic malignancy¶¶ (2,790)			
Unvaccinated	**1,156**	130 (11.2)	Ref
Vaccinated with any 2 mRNA vaccine doses§§	**1,634**	86 (5.3)	74 (62–83)
Vaccinated with 2 Moderna vaccine doses§§	**660**	26 (3.9)	85 (74–92)
Vaccinated with 2 Pfizer-BioNTech vaccine doses§§	**974**	60 (6.2)	62 (42–75)
Rheumatologic or inflammatory disorder* (5,024)**			
Unvaccinated	**2,380**	383 (16.1)	Ref
Vaccinated with any 2 mRNA vaccine doses§§	**2,644**	123 (4.6)	81 (75–86)
Vaccinated with 2 Moderna vaccine doses§§	**1,053**	48 (4.6)	78 (65–86)
Vaccinated with 2 Pfizer-BioNTech vaccine doses§§	**1,591**	75 (4.7)	78 (69–84)
Other intrinsic immune condition or immunodeficiency††† (6,380)			
Unvaccinated	**3,418**	429 (12.6)	Ref
Vaccinated with any 2 mRNA vaccine doses§§	**2,962**	137 (4.6)	73 (66–80)
Vaccinated with 2 Moderna vaccine doses§§	**1,199**	42 (3.5)	81 (71–87)
Vaccinated with 2 Pfizer-BioNTech vaccine doses§§	**1,763**	95 (5.4)	64 (50–74)
Organ or stem cell transplant§§§ (1,416)			
Unvaccinated	**607**	92 (15.2)	Ref
Vaccinated with any 2 mRNA vaccine doses§§	**809**	80 (9.9)	59 (38–73)
Vaccinated with 2 Moderna vaccine doses§§	**337**	31 (9.2)	70 (46–83)
Vaccinated with 2 Pfizer-BioNTech vaccine doses§§	**472**	49 (10.4)	45 (13–66)

Abbreviations: CI = confidence interval; "ICD-9 = *International Classification of Diseases, Ninth Revision*; ICD-10 = *International Classification of Diseases, Tenth Revision*; Ref = referent group; VE = vaccine effectiveness.

* VE was estimated using a test-negative design, adjusted for age, geographic region, calendar time (days since January 1, 2021), and local virus circulation (percentage of SARS-CoV-2–positive results from testing within the counties surrounding the facility on the date of the hospitalization) and weighted for inverse propensity to be vaccinated or unvaccinated (calculated separately for each VE estimate) using sociodemographic characteristics, underlying medical conditions, known previous SARS-CoV-2 infection, and hospital characteristics, in addition to age, geographic region, calendar time, and local virus circulation.

† Hospitalizations with a discharge code consistent with COVID-19–like illness were included, such as acute respiratory illness (e.g., COVID-19, respiratory failure, or pneumonia) or related signs or symptoms (cough, fever, dyspnea, vomiting, or diarrhea), using diagnosis codes from ICD-9 and ICD-10. Clinician-ordered molecular assays (e.g., real-time reverse transcription–polymerase chain reaction test) for SARS-CoV-2 occurring ≤14 days before to <72 hours after hospital admission were included.

§ Immunocompromising condition subgroups were not mutually exclusive, and patients could be represented in more than one of the five subgroups (i.e., solid malignancy, hematologic malignancy, rheumatologic or inflammatory disorder, other intrinsic immune condition or immunodeficiency, and organ or stem cell transplant).

¶ Partners contributing data on hospitalizations were in California (range of earliest to latest hospitalization: March 1–September 5), Colorado (January 22–August 31), Indiana (January 22–September 5), Minnesota and Wisconsin (January 17–August 18), New York (January 22–September 5), Oregon and Washington (February 1–August 20), and Utah (February 1–September 5).

** VE was calculated as [1−odds ratio]x100%.

†† Solid malignancy was defined as the presence of at least one discharge diagnosis using ICD-9 and ICD-10 diagnosis codes. ICD-10 codes included C00–C80, C7A, C7B, D3A, Z51.0, and Z51.1.

§§ Vaccination was defined as having received exactly 2 doses of an mRNA-based COVID-19 vaccine ≥14 days before the hospitalization index date, which was the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result before the hospitalization or the hospitalization date if testing only occurred after the admission.

¶¶ Hematologic malignancy was defined as the presence of at least one discharge diagnosis using ICD-9 and ICD-10 diagnosis codes. ICD-10 codes included C81–C86, C88, C90–C96, D46, D61.0, D70.0, D61.2, D61.9, and D71.

*** Rheumatologic or inflammatory disorder was defined as the presence of at least one discharge diagnosis using ICD-9 and ICD-10 diagnosis codes. ICD-10 codes included D86, E85 (except E85.0), G35, J67.9, L40.54, L40.59, L93.0, L93.2, L94, M05–M08, M30, M31.3, M31.5, M32–M34, M35.3, M35.8, M35.9, M46, and T78.40.

††† Other intrinsic immune condition or immunodeficiency was defined as the presence of at least one discharge diagnosis using ICD-9 and ICD-10 diagnosis codes. ICD-10 codes included D27.9, D61.09, D72.89, D80, D81 (except D81.3), D82–D84, D89 (except D89.2), K70.3, K70.4, K72, K74.3–K74.6 (except K74.60 and K74.69), N04, and R18.

§§§ Organ or stem cell transplant was defined as the presence of at least one discharge diagnosis using ICD-9 and ICD-10 diagnosis codes. ICD-10 codes included T86 (except T86.82–T86.84, T86.89, and T86.9), D47.Z1, Z48.2, Z94, and Z98.85.

immunocompromised populations, evaluate whether different approaches to vaccine administration might improve VE (e.g., dosage timing or temporarily withholding immunosuppressants), and further evaluate possible differences in VE between vaccine products.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Allison L. Naleway reports institutional support from Pfizer outside the submitted work. Anupam B. Kharbanda reports institutional support through HealthPartners to Children's Minnesota for VISION. Charlene McEvoy reports institutional support from AstraZeneca for the AZD1222 COVID-19 vaccine trial. Jill Ferdinands reports travel support from Institute for Influenza Epidemiology, funded in part by Sanofi Pasteur. Nicola P. Klein reports institutional support from Pfizer for COVID-19 vaccine clinical trials and institutional support from Pfizer, Merck, GlaxoSmithKline, Sanofi Pasteur, and Protein Sciences (now Sanofi Pasteur) outside the submitted work. Suchitra Rao reports grant support from GlaxoSmithKline and Biofire Diagnostics. No other potential conflicts of interest were disclosed.

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Erratum

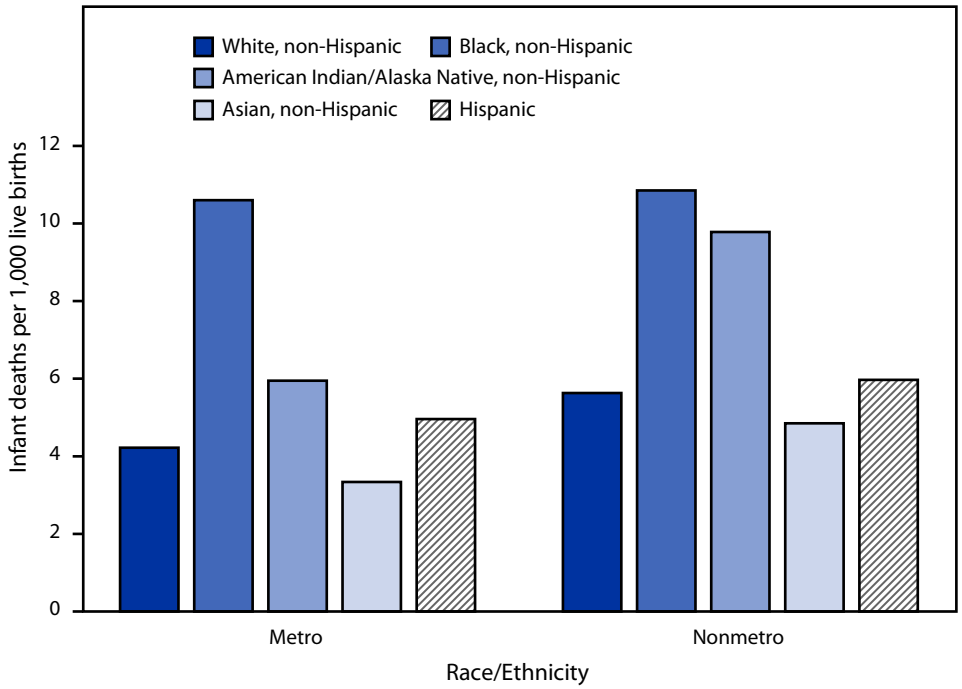
Vol 70, No. 42

In the report "*Mycobacterium porcinum* Skin and Soft Tissue Infections After Vaccinations — Indiana, Kentucky, and Ohio, September 2018–February 2019," on page 1474, in the second column, first continued paragraph, the sentence beginning on line 12 should have read, "Low or undetectable antigen levels in vaccine samples support the theory of a single diluent that might have been introduced during preparation, thereby reducing vaccine antigen levels found in tested predrawn syringes, though none of the four involved vaccines require reconstitution or dilution and company A **did not report** use of a diluent."

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Infant Mortality Rates for Metropolitan and Nonmetropolitan Counties,* by Single Race and Hispanic Origin — National Vital Statistics System, United States, 2019



* Urbanization level is based on maternal county of residence. Counties were classified according to their metropolitan status using the National Center for Health Statistics Urban-Rural Classification Scheme. https://www.cdc.gov/nchs/data_access/urban_rural.htm

In metropolitan counties, infant mortality rates were highest for infants of non-Hispanic Black mothers (10.60 infant deaths per 1,000 live births), followed by infants of non-Hispanic American Indian or Alaska Native (5.95), Hispanic (4.96), non-Hispanic White (4.22), and non-Hispanic Asian (3.34) mothers. In nonmetropolitan counties, the mortality rate was also highest for infants of non-Hispanic Black mothers (10.85), followed by infants of non-Hispanic American Indian or Alaska Native (9.78), Hispanic (5.97), non-Hispanic White (5.63), and non-Hispanic Asian (4.85) mothers. The infant mortality rate was significantly lower for infants of non-Hispanic White, non-Hispanic American Indian or Alaska Native, and Hispanic mothers in metropolitan counties compared with nonmetropolitan counties; differences in rates between metropolitan and nonmetropolitan counties for infants of non-Hispanic Black and non-Hispanic Asian mothers were not statistically significant.

Source: National Vital Statistics System. Linked Birth and Infant Death Data. https://www.cdc.gov/nchs/nvss/linked-birth.htm

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ISSN: 0149-2195 (Print)