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Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022

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In 2021, 20-valent pneumococcal conjugate vaccine (PCV) (PCV20) (Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc.) and 15-valent PCV (PCV15) (Merck Sharp & Dohme Corp.) were licensed by the Food and Drug Administration for adults aged ≥18 years, based on studies that compared antibody responses to PCV20 and PCV15 with those to 13-valent PCV (PCV13) (Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc.). Antibody responses to two additional serotypes included in PCV15 were compared to corresponding responses after PCV13 vaccination, and antibody responses to seven additional serotypes included in PCV20 were compared with those to the 23-valent pneumococcal polysaccharide vaccine (PPSV23) (Merck Sharp & Dohme Corp.). On October 20, 2021, the Advisory Committee on Immunization Practices (ACIP) recommended use of either PCV20 alone or PCV15 in series with PPSV23 for all adults aged ≥65 years, and for adults aged 19–64 years with certain underlying medical conditions or other risk factors* who have not previously received a PCV or whose previous vaccination history is unknown. ACIP employed the Evidence to Recommendation (EtR) framework,† using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)§ approach to guide its deliberations regarding use of these vaccines. Before this, PCV13 and PPSV23 were recommended for use for U.S. adults

* Alcoholism; chronic heart, liver, or lung disease; chronic renal failure; cigarette smoking; cochlear implant; congenital or acquired asplenia; cerebrospinal fluid leak; diabetes mellitus; generalized malignancy; HIV; Hodgkin disease; immunodeficiency; iatrogenic immunosuppression; leukemia, lymphoma, or multiple myeloma; nephrotic syndrome; solid organ transplant; sickle cell disease; or other hemoglobinopathies.

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

§ https://www.cdc.gov/vaccines/acip/recs/grade/about-grade.html

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and the recommendations varied by age and risk groups. This was simplified in the new recommendations.

PPSV23 has been recommended for use in the United States since the 1980s for adults aged ≥65 years and for younger adults with underlying conditions that increase their risk for pneumococcal disease (*1*). PCV13 was first recommended for use in U.S. children in 2010, and indirect effects from its use in children reduced PCV13-type pneumococcal disease incidence in all adult groups (Figure). In 2012, ACIP recommended administration of PCV13 in series with PPSV23 for adults with immunocompromising conditions,[¶] cerebrospinal fluid leaks, or cochlear implants (*2*), and in 2014, the recommendation was extended to all adults aged ≥65 years (*3*). On the basis of review of accrued evidence, the PCV13 recommendation was changed in 2019 to shared clinical decision-making for adults aged ≥65 years without an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant. The recommended pneumococcal vaccine doses and intervals between doses differ by age and underlying conditions, making adult pneumococcal vaccine recommendations complicated.

Recent systematic reviews continue to support the effectiveness of PCV13 against invasive pneumococcal disease (IPD)[**] and pneumococcal pneumonia among adults (*4*,*5*). Whereas effectiveness of PPSV23 against IPD has been demonstrated, data on effectiveness against pneumococcal pneumonia were considered to be inconsistent (*3*); recent observational studies reported 21%–46% effectiveness against PPSV23-type pneumococcal pneumonia when PPSV23 was given <5 years before illness onset (*6*–*8*). Nevertheless, older adults and adults with chronic medical conditions[††] or immunocompromising conditions, cerebrospinal fluid leaks, or cochlear implants (certain underlying conditions) remain at increased risk for pneumococcal disease, accounting for >90% of adult IPD cases in 2019 (Active Bacterial Core surveillance, unpublished data, 2021).

During February–October 2021, ACIP reviewed the epidemiology of pneumococcal disease and considerations for use of PCV15 and PCV20 in adults. The ACIP Pneumococcal

[¶] Immunocompromising conditions are defined as chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, HIV, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplant, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies.

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

[††] Alcoholism; chronic heart, liver, or lung disease; cigarette smoking; or diabetes mellitus.

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Vaccines Work Group (Work Group) evaluated the quality of evidence for PCV15 and PCV20 immunogenicity and safety using the GRADE approach.[§§] Using the EtR framework,[¶¶] the Work Group reviewed relevant scientific evidence regarding the benefits and harms of PCV15 and PCV20 use among adults aged ≥65 years and younger adults with certain underlying conditions. Within the EtR framework, ACIP considered the importance of the public health problem, benefits and harms, target populations' values and preferences, resource use, equity, acceptability, and feasibility for PCV15 or PCV20 use. After a systematic review of the literature, the Work Group defined critical outcomes and used GRADE to assess certainty of evidence rated on a scale of 1 (high certainty) to 4 (very low certainty) (*9*).

[§§] https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV20-risk-based.html; https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV15-PPSV23-risk-based.html; https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV20-age-based.html; https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV15-PPSV23-age-based.html

[¶¶] https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV20-risk-based-etr.html; https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV20-age-based-etr.html; https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV15-PPSV23-risk-based-etr.html; https://www.cdc.gov/vaccines/acip/recs/grade/pneumo-PCV15-PPSV23-age-based-etr.html

Evidence

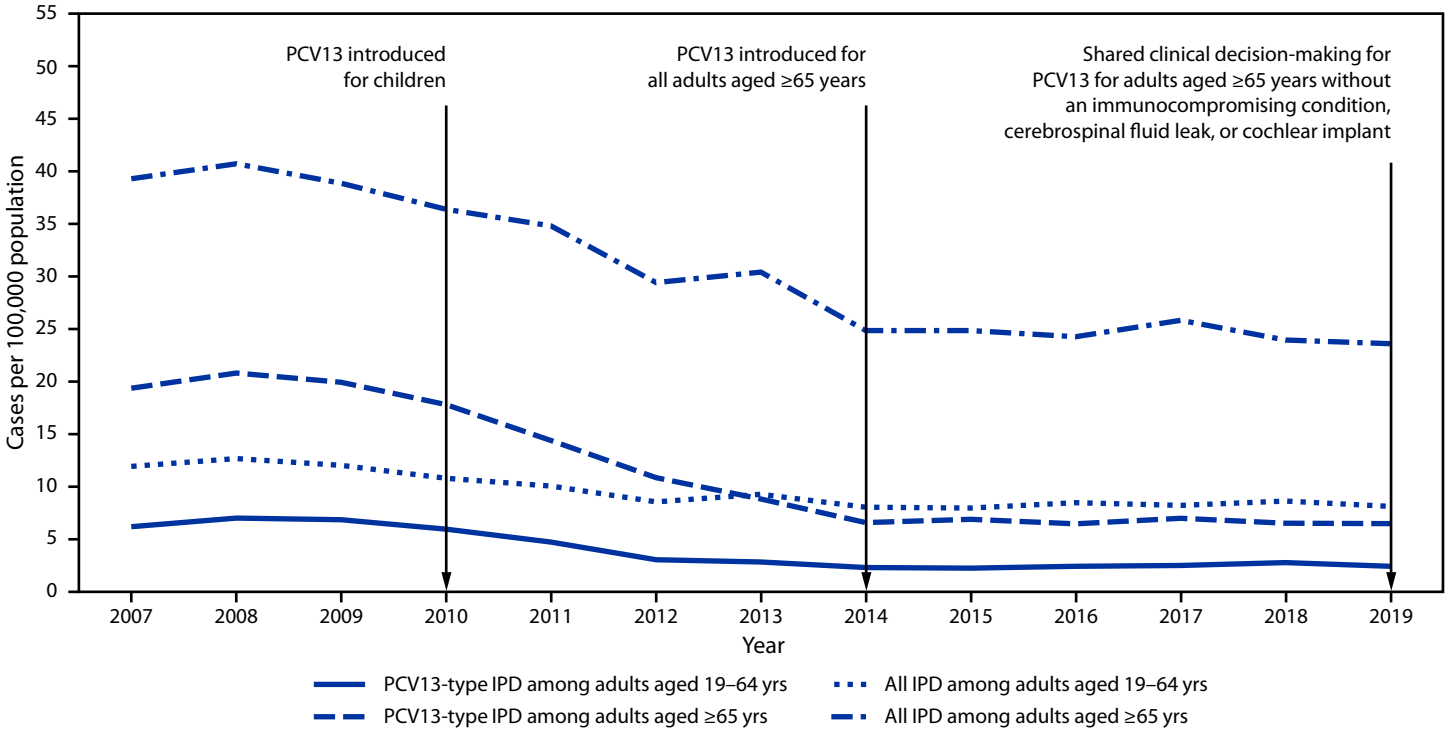
Pneumococcal disease incidence in adults. During 2018–2019, the incidence of all IPD in adults aged ≥65 years was 24 per 100,000 population (Figure), and PCV13 serotypes accounted for 27% of cases; additional serotypes unique to PCV15,[***] PCV20,[†††] and PPSV23[§§§] caused 15%, 27%, and 35% of IPD, respectively. In adults aged 19–64 years with certain underlying conditions, PCV13 serotypes accounted for 30% of IPD; serotypes unique to PCV15, PCV20, and PPSV23 caused 13%, 28%, and 43% of IPD, respectively. Estimates of pneumococcal pneumonia incidence are more variable. Annual incidence among U.S. adults aged <65 and ≥65 years hospitalized with community-acquired pneumonia was estimated at 126–422 and 847–3,365 per 100,000, respectively, during 2010–2016 (*10*). In a multisite study of adults hospitalized with community-acquired pneumonia, 4.6% of cases were caused by PCV13 serotypes, and 1.4% and 3.3% were caused by additional serotypes included in PCV15 and PCV20, respectively (*11*).

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

[†††] Serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F, in addition to PCV13 serotypes.

[§§§] Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F, in addition to PCV13 serotypes.

FIGURE. Incidence of all invasive pneumococcal disease and 13-valent pneumococcal conjugate vaccine-type* invasive pneumococcal disease among adults aged ≥19 years, by invasive pneumococcal disease type and age group — United States, 2007–2019†



Abbreviations: IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine.

* Includes serotype 6C, which shows cross-protection from 6A antigen in PCV13 and was grouped with PCV13 serotypes for IPD incidence.

† Active Bacterial Core surveillance, 2021.

PCV15 immunogenicity. PCV15 contains pneumococcal polysaccharide serotypes 22F and 33F in addition to the PCV13 serotypes, conjugated to CRM197 (genetically detoxified diphtheria toxin) (*9*). Phase II and III randomized controlled trials (RCTs) evaluated the immunogenicity and safety of a dose of PCV15 compared with a dose of PCV13 in healthy adults aged ≥50 years (*12–14*), adults aged 18–49 years who are Native American (a population with higher rates of IPD than the general U.S. population) (*15*) or with ≥1 risk condition for pneumococcal disease (*16*), and adults aged ≥18 years with HIV infection (*17*). Serotype-specific functional antibody responses were measured 1 month after vaccination using an opsonophagocytic activity (OPA) assay. Correlates of protection have not been established for adults. In one phase III RCT among adults aged ≥50 years, PCV15 met the noninferiority criteria[¶¶¶] compared with PCV13 for the 13 shared serotypes and had statistically significantly greater response[****] for shared serotype 3 and PCV15-unique serotypes 22F and 33F (*14*). In studies that evaluated the immunogenicity of PCV15 or PCV13 followed by PPSV23 2–12 months later (*16–18*), persons who received PCV15 had numerically similar or higher OPA geometric mean antibody titers (GMTs) for 9–13[††††] shared PCV13 serotypes and a higher percentage of seroresponders[§§§§] for 5–11 shared serotypes compared with persons who received PCV13 when measured 1 month after receipt of PPSV23.

PCV15 safety. Safety of PCV15 was assessed in seven RCTs with 5,630 participants aged ≥18 years who received 1 dose of PCV15. Most participants were immunocompetent; however, one study included 302 adults with HIV infection. Participants included those vaccinated with PPSV23 ≥1 year before receiving PCV15, those who received PCV15 followed by PPSV23, and those who received PCV15 concomitantly with a seasonal inactivated quadrivalent influenza vaccine (QIV). The most frequently reported adverse reactions were injection site pain, fatigue, and myalgia. The rates of serious adverse events (SAEs) within 6 months of vaccination were 2.5% among PCV15 recipients and 2.4% among PCV13 recipients. No SAEs or deaths were considered to be related to the study vaccines (*9*,*19*).

PCV20 immunogenicity. PCV20 contains pneumococcal polysaccharide serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F, in addition to PCV13 serotypes, conjugated to CRM197 (*20*). A phase II study among adults aged 60–64 years and two phase III RCTs among adults aged ≥18 years evaluated immunogenicity and safety of PCV20 compared with PCV13 and with PPSV23 for the seven additional serotypes included in PCV20 (*21–23*). These studies included adults with stable medical conditions, but none included adults with immunocompromising conditions. Compared with PCV13 recipients, PCV20 recipients elicited responses that met noninferiority criteria[¶¶¶¶] for all 13 serotypes in a phase III trial among adults aged ≥60 years (*21*); however, PCV20 recipients appeared to have lower GMTs and included a lower percentage of seroresponders to 12–13 of the 13 PCV13-shared serotypes (*21*,*22*). Compared with PPSV23 recipients, PCV20 recipients had numerically higher GMTs and a higher percentage of seroresponders to six of seven (excluding serotype 8) shared non-PCV13 serotypes (*21*,*23*); noninferiority criteria were met for those six serotypes (*21*).

PCV20 safety. Safety of PCV20 was assessed in six trials among immunocompetent adults aged ≥18 years that included a total of 4,552 participants who received PCV20. Participants included those who were naïve to pneumococcal vaccination and those who had previously received pneumococcal vaccination. The most frequently reported adverse reactions were injection site pain, muscle pain, fatigue, headache, and joint pain. SAEs reported within 6 months after vaccination occurred among 1.5% of PCV20 recipients and 1.8% among controls. No SAEs or deaths were considered to be related to study vaccines (*20*,*24*).

Intervals between PCV and PPSV23. Findings from eight immunogenicity studies that evaluated the immune response after a sequence of 7-valent PCV, PCV13, or PCV15 followed by PPSV23 administered at intervals of 2, 6, or 12 months or 3–4 years were reviewed (*16–18*,*25–29*). Three studies comparing intervals ranging from 2 to 6 months between administration of PCV and PPSV23 found no significant difference in immunogenicity measured after PPSV23 receipt, although reactogenicity tended to be higher with shorter intervals (*25–29*). In a study that compared antibody responses to 1 dose of PCV13 with responses to PCV13 followed by PPSV23 1 year apart, the immune responses following PPSV23 were significantly lower compared with the responses after a dose of PCV13 for eight of 12 common serotypes (*27*). In another study that compared antibody response to 1 dose of PCV13 with responses to PCV13 followed by PPSV23 approximately 4 years apart, the immune responses following PPSV23 were significantly higher for seven of 12 common serotypes (*26*).

[¶¶¶] Lower bound of the two-sided 95% CI of the OPA GMT ratio (PCV15 / PCV13) to be >0.5.

[****] For PCV15-unique serotypes 22F and 33F, defined as the lower bound of the two-sided 95% CI of the OPA GMT ratio (V114 / PCV13) to be >2.0 and the lower bound of the two-sided 95% CI of the differences (V114 – PCV13) between the percentages of participants with a fourfold rise to be >0.1. For serotype 3, defined as the lower bound of the two-sided 95% CI of the OPA GMT ratio (V114 / PCV13) to be >1.2 and the lower bound of the two-sided 95% CI of the differences (V114 – PCV13) between the percentages of participants with a fourfold rise to be >0.

[††††] Range reflects the difference in results across studies.

[§§§§] Subjects with a fourfold or larger rise in OPA GMT titer postvaccination compared with prevaccination.

[¶¶¶¶] Defined as the lower bound of the two-sided 95% CI of the ratio (PCV20 / PCV13) of opsonophagocytic geometric mean titers being >0.5.

These findings suggested that longer intervals between administration of PCV and PPSV23 might improve immunogenicity in immunocompetent adults, although a direct comparison between a 1- versus 4-year interval was not made.

Cost-effectiveness. Economic models assessed cost-effectiveness of the new policy options compared with existing recommendations (*30*). Three economic models assessed PCV20 alone for all adults aged ≥65 years; cost-effectiveness estimates ranged from cost-saving[*****] to $39,000 per quality-adjusted life-year (QALY) gained. Two economic models assessed use of PCV15 in series with PPSV23 for all adults aged ≥65 years; estimates ranged from cost-saving to $282,000 per QALY gained. The CDC model found cost savings in all scenarios for use of either PCV20 alone or PCV15 in series with PPSV23 for all adults aged ≥65 years. Cost estimates of policy options for adults aged 19–64 years with certain underlying medical conditions ranged from $11,000 to $292,000 per QALY gained for PCV20 and from $250,000 to $656,000 for PCV15 in series with PPSV23.

Summary. Use of PCV20 alone or PCV15 in series with PPSV23 is expected to reduce pneumococcal disease incidence in adults aged ≥65 years and in those aged 19–64 years with certain underlying conditions. Findings from studies suggested that the immunogenicity and safety of PCV20 alone or PCV15 in series with PPSV23 were comparable to PCV13 alone or PCV13 in series with PPSV23. Cost-effectiveness studies demonstrated that use of PCV20 alone or PCV15 in series with PPSV23 for adults at age 65 years was cost-saving. The new policy simplifies adult pneumococcal vaccine recommendations (Table 1) and is expected to improve vaccine coverage among adults and prevent more pneumococcal disease. An amendment to recommend PCV20 for all adults aged ≥50 years instead of age ≥65 years was considered but rejected (Table 2). A summary of Work Group deliberations on use of either PCV20 alone or PCV15 in series with PPSV23 for all

[*****] Lower cost and improved health outcomes compared with previous recommendations.

TABLE 1. Recommendations for use of 15-valent pneumococcal conjugate vaccine in series with 23-valent pneumococcal polysaccharide vaccine or 20-valent pneumococcal conjugate vaccine in pneumococcal conjugate vaccine-naïve adults aged ≥19 years — United States, 2022

Medical indication group	Specific underlying medical condition	Age group, yrs	
		19–64	≥65
None	None	None	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later*
Underlying medical conditions or other risk factors	Alcoholism Chronic heart disease† Chronic liver disease Chronic lung disease¶ Cigarette smoking Diabetes mellitus Cochlear implant CSF leak Congenital or acquired asplenia** Sickle cell disease or other hemoglobinopathies** Chronic renal failure** Congenital or acquired immunodeficiencies**,†† Generalized malignancy** HIV infection** Hodgkin disease** Iatrogenic immunosuppression**,§§ Leukemia** Lymphoma** Multiple myeloma** Nephrotic syndrome** Solid organ transplant**	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later§	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later*

Abbreviations: CSF = cerebrospinal fluid; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

* Adults with immunocompromising conditions, cochlear implant, or CSF leak might benefit from shorter intervals such as ≥8 weeks. These vaccine doses do not need to be repeated if given before age 65 years.
† Includes congestive heart failure and cardiomyopathies.
§ Adults with immunocompromising conditions, cochlear implant, or CSF leak might benefit from shorter intervals such as ≥8 weeks.
¶ Includes chronic obstructive pulmonary disease, emphysema, and asthma.
** Indicates immunocompromising conditions.
†† Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).
§§ Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.

adults aged ≥65 years or adults aged 19–64 years with certain underlying conditions is available in the EtR tables.

New Pneumococcal Vaccine Recommendations

Adults aged ≥65 years. Adults aged ≥65 years who have not previously received PCV or whose previous vaccination history is unknown should receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23 (Table 1).

Adults aged 19–64 years with certain underlying medical conditions or other risk factors. Adults aged 19–64 years with certain underlying medical conditions or other risk factors who have not previously received PCV or whose previous vaccination history is unknown should receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23.

Clinical Guidance

Dosing schedule. When PCV15 is used, the recommended interval between administration of PCV15 and PPSV23 is ≥1 year. A minimum interval of 8 weeks can be considered for adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak to minimize the risk for IPD caused by serotypes unique to PPSV23 in these vulnerable groups (*31*).

Adults with previous PPSV23 only. Adults who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose. When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23.

Adults with previous PCV13. The incremental public health benefits of providing PCV15 or PCV20 to adults who have received PCV13 only or both PCV13 and PPSV23 have not been evaluated. These adults should complete the previously recommended PPSV23[†††††] series (*2*,*30*).

Coadministration with other vaccines. PCV15, PCV20, or PPSV23 can be coadministered with QIV in an adult immunization program, as concomitant administration (PCV15 or PPSV23 and QIV [Fluarix], PCV20 and adjuvanted QIV [Fluad]) has been demonstrated to be immunogenic and safe. However, slightly lower pneumococcal serotype-specific OPA GMTs or geometric mean concentrations were reported when pneumococcal vaccines were coadministered with QIV compared with when pneumococcal vaccines were given alone (*9*,*19*,*32*,*33*). Currently, no data are available on coadministration with other vaccines (e.g., tetanus, diphtheria, acellular pertussis vaccine, hepatitis B, or zoster vaccine) among adults. Evaluation of coadministration of PCV15, PCV20, or PPSV23 with COVID-19 vaccines is ongoing (*34*,*35*).

Future Research and Monitoring Priorities

CDC and ACIP will continue to assess safety of PCV15 and PCV20 vaccines, monitor the impact of implementation of new recommendations, and assess postimplementation vaccine effectiveness and update pneumococcal vaccination recommendations as appropriate.

[†††††] For adults who have received PCV13 but have not completed their recommended pneumococcal vaccine series with PPSV23, one dose of PCV20 may be used if PPSV23 is not available.

TABLE 2. Age-based policy options for use of 15-valent pneumococcal conjugate vaccine or 20-valent pneumococcal conjugate vaccine in adults presented for a vote and considerations by the Advisory Committee on Immunization Practices — United States, October 2021

Proposed policy	Considerations raised during October 2021 ACIP meeting in favor of the option	Outcome (votes in favor: against)
Adults aged ≥50 years who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either PCV20 or PCV15). If PCV15 is used, this should be followed by a dose of PPSV23.	Might reduce existing pneumococcal disease disparity in adults aged 50–64 years. Age-based recommendation is easier to implement than risk-based recommendation. Might provide more opportunities to vaccinate adults before underlying conditions develop.	Rejected (4:11)
Adults aged ≥65 years who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either PCV20 or PCV15). If PCV15 is used, this should be followed by a dose of PPSV23.	Potential for waning vaccine-induced immunity makes it favorable to vaccinate later in life when risk for disease is higher. Consistently cost saving in cost-effectiveness analyses. Still provides an opportunity for higher PCV coverage in adults compared with current recommendations. No evidence that lowering the age-based recommendation will reduce disparity in vaccine-preventable disease compared with risk-based recommendations.	Affirmed (15:0)

Abbreviations: ACIP = Advisory Committee on Immunization Practices; PCV = pneumococcal conjugate vaccine; PCV15 = 15-valent PCV; PCV20 = 20-valent PCV; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

Summary

What is already known about this topic?

Currently, the 13-valent pneumococcal conjugate vaccine (PCV) (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) are recommended for U.S. adults. Recommendations vary by age and risk groups.

What is added by this report?

On October 20, 2021, the Advisory Committee on Immunization Practices recommended 15-valent PCV (PCV15) or 20-valent PCV (PCV20) for PCV–naïve adults who are either aged ≥65 years or aged 19–64 years with certain underlying conditions. When PCV15 is used, it should be followed by a dose of PPSV23, typically ≥1 year later.

What are the implications for public health practice?

Pneumococcal vaccination recommendations were simplified across age and risk group. Eligible adults may receive either PCV15 in series with PPSV23 or PCV20 alone.

Before administering PCV20, PCV15, or PPSV23, health care providers should consult relevant package inserts (*9*,*20*,*36*) regarding precautions and contraindications. Adverse events occurring after administration of any vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted to VAERS online, by fax, or by mail. Additional information about VAERS is available at https://vaers.hhs.gov/.

Acknowledgments

Members of the Advisory Committee on Immunization Practices (member roster for August 24, 2021–June 20, 2022, is available at https://www.cdc.gov/vaccines/acip/members/index.html).

ACIP Pneumococcal Vaccines Work Group

Chair: Katherine A. Poehling, Wake Forest School of Medicine; ACIP members: Sarah S. Long, Drexel University College of Medicine; H. Keipp Talbot, Vanderbilt University Medical Center. Ex officio members: Jeffrey Kelman, Centers for Medicare & Medicaid Services; Lucia Lee, Tina Mongeau, Food and Drug Administration; Thomas Weiser, Uzo Chukwuma, Indian Health Service; Kristina Lu, Mamodikoe Makhene, National Institutes of Health; Liaison representatives: Lynn Fisher, American Academy of Family Physicians; Mark Sawyer, American Academy of Pediatrics/ Committee on Infectious Diseases; Jason Goldman, American College of Physicians; David Nace, American Geriatrics Society/ The Society for Post-Acute and LTC Medicine; Emily Messerli, Association of Immunization Managers; Elissa Abrams, Oliver Baclic, Canadian National Advisory Committee on Immunization; Carol Baker, Infectious Diseases Society of America; William Schaffner, National Foundation for Infectious Diseases; Virginia Cane, National Medical Association; Consultants: Doug Campos-Outcalt, University of Arizona; Monica M. Farley, Atlanta Veterans Affairs Medical Center/Emory University; Keith Klugman, Bill & Melinda Gates Foundation; Rebecca L. Morgan, McMaster University; Arthur Reingold, University of California, Berkeley; Lorry Rubin, Cohen Children's Medical Center of Northwell Health; Cynthia Whitney, Emory University; Richard K. Zimmerman, University of Pittsburgh. Marc Fischer, Penina Haber, Pedro Moro, Sarah Schillie, CDC.

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Effectiveness of a Third Dose of Pfizer-BioNTech and Moderna Vaccines in Preventing COVID-19 Hospitalization Among Immunocompetent and Immunocompromised Adults — United States, August–December 2021

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COVID-19 mRNA vaccines (BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna]) provide protection against infection with SARS-CoV-2, the virus that causes COVID-19, and are highly effective against COVID-19–associated hospitalization among eligible persons who receive 2 doses (*1*,*2*). However, vaccine effectiveness (VE) among persons with immunocompromising conditions* is lower than that among immunocompetent persons (*2*), and VE declines after several months among all persons (*3*). On August 12, 2021, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for a third mRNA vaccine dose as part of a primary series ≥28 days after dose 2 for persons aged ≥12 years with immunocompromising conditions, and, on November 19, 2021, as a booster dose for all adults aged ≥18 years at least 6 months after dose 2, changed to ≥5 months after dose 2 on January 3, 2022 (*4*,*5*,*6*). Among 2,952 adults (including 1,385 COVID-19 case-patients and 1,567 COVID-19–negative controls) hospitalized at 21 U.S. hospitals during August 19–December 15, 2021, effectiveness of mRNA vaccines against COVID-19–associated hospitalization was compared between adults eligible for but who had not received a third vaccine dose (1,251) and vaccine-eligible adults who received a third dose ≥7 days before illness onset (312). Among 1,875 adults without immunocompromising conditions (including 1,065 [57%] unvaccinated, 679 [36%] 2-dose recipients, and 131 [7%] 3-dose [booster] recipients), VE against COVID-19 hospitalization was higher among those who received a booster dose (97%; 95% CI = 95%–99%) compared with that among 2-dose recipients (82%; 95% CI = 77%–86%) (p <0.001). Among 1,077 adults with immunocompromising conditions (including 324 [30%] unvaccinated, 572 [53%] 2-dose recipients, and 181 [17%] 3-dose recipients), VE was higher among those who received a third dose to complete a primary series (88%; 95% CI = 81%–93%) compared with 2-dose recipients (69%; 95% CI = 57%–78%) (p <0.001). Administration of a third COVID-19 mRNA vaccine dose as part of a primary series among immunocompromised adults, or as a booster dose among immunocompetent adults, provides improved protection against COVID-19–associated hospitalization.

During August 19–December 15, 2021, a period in which the SARS-CoV-2 B.1.617.2 (Delta) variant was predominant, adults admitted to 21 hospitals in 18 states within the Influenza or Other Viruses in the Acutely Ill Network (IVY Network) who received testing for SARS-CoV-2 were included in a VE analysis. The analysis start date of August 19, 2021, was one week after the EUA of a third dose for persons with immunocompromising conditions. VE against COVID-19 hospitalization was compared between two groups: 1) adults who had completed a 2-dose mRNA vaccination series and were eligible for but had not received a third dose†; and 2) adults who were eligible for and had received a third dose ≥7 days before illness onset. VE was calculated for 2-dose and 3-dose recipients by comparing odds of antecedent vaccination between COVID-19 case-patients and control patients who

* Persons with immunocompromising conditions defined by the IVY Network included those with one or more of the following: active solid organ cancer (active cancer was defined as treatment for the cancer or newly diagnosed cancer in the past 6 months); active hematologic cancer (such as leukemia, lymphoma, or myeloma); HIV infection without AIDS; AIDS; congenital immunodeficiency syndrome; previous splenectomy; prior solid organ, stem cell, or bone marrow transplant; use of immunosuppressive medication; systemic lupus erythematosus; rheumatoid arthritis; psoriasis; scleroderma; or inflammatory bowel disease, including Crohn's disease or ulcerative colitis.

† During the surveillance period, third doses were recommended ≥28 days after dose 2 if the patient had an immunocompromising condition to complete a primary series or at least 6 months after dose 2 as a booster dose if the patient did not have an immunocompromising condition. The booster dose for Moderna (0.25 mL) is one half the dose used for the primary series (0.5 mL). The third dose to complete a primary series in persons with immunocompromising conditions is the same as the first 2 doses (0.5 mL).

did not have COVID-19. Case-patients had COVID-19–like illness[§] and received positive SARS-CoV-2 test results by a nucleic acid amplification test (NAAT) or antigen test within 10 days of illness onset. Control patients were hospitalized with or without COVID-19–like illness and received negative SARS-CoV-2 test results by NAAT.

Patients or their proxies were interviewed regarding patient demographic and clinical characteristics, and medical record searches were completed to collect information about chronic medical conditions. Information about receipt of prior COVID-19 vaccination doses, including dates, locations, and vaccine product received, was obtained through self-report and review of source documentation (including state vaccination registries, medical records, and vaccination cards). A patient was considered to be vaccinated if vaccination could be verified through source documentation or by self-report, including dates and location. Three vaccination groups were considered: 1) unvaccinated patients, who had received no COVID-19 vaccine doses before illness onset; 2) 2-dose mRNA vaccine recipients, who were eligible for but had not received a third vaccine dose or had received a third dose <7 days before illness onset; and 3) 3-dose mRNA vaccine recipients, who received a third dose ≥7 days before illness onset. Patients were excluded if they were admitted to the hospital ≤7 days after EUA authorization of a third dose, received one or more vaccine doses but did not qualify for inclusion in the 2-dose or 3-dose vaccine group,[¶] received a non-mRNA vaccine (e.g., Ad26.COV2.S [Janssen (Johnson & Johnson)]), or if verification of vaccination was pending.

VE against COVID-19–associated hospitalization was estimated using logistic regression, comparing the odds of being vaccinated versus being unvaccinated among case-patients and controls using the equation VE = 100 × (1 − adjusted odds ratio). The regression model included case-patient or control status as the outcome variable and an indicator vari¬able for vaccination group (unvaccinated, 2-dose recipient, or 3-dose recipient), and was adjusted for admission date, region of hospital (U.S. Department of Health and Human Services or U.S. Census Bureau), age group (18–49, 50–64, or ≥65 years), sex, and self-reported race and ethnicity. Separate models were generated for immunocompetent adults and adults with immunocompromising conditions. To compare VE among 2-dose versus 3-dose mRNA vaccine recipients, post hoc comparisons were performed with the pwcompare function in Stata with a two-sided significance threshold of $p<0.05$. Analyses were conducted using Stata software (version 16.0; StataCorp). This activity was determined to be public health surveillance by each participating site and CDC and was conducted consistent with applicable federal law and CDC policy.[**]

During August 19–December 15, 2021, the IVY Network enrolled 4,094 adults aged ≥18 years. After excluding 1,142 patients (619 because they did not belong to an included vaccination group, 386 because the patients had received a non-mRNA vaccine or vaccination verification was incomplete, and 137 because they met other exclusion criteria), 2,952 hospitalized patients were included (1,385 case-patients and 1,567 non–COVID-19 controls). Among all participants, median age was 62 years, 49% of patients were female, 58% were non-Hispanic White, and 36% had an immunocompromising condition. Among the 1,385 case-patients, 931 (67%), 408 (29%), and 46 (3%) had received 0, 2, and 3 mRNA vaccine doses, respectively. Among 1,567 non–COVID-19 controls, 458 (29%), 843 (54%), and 266 (17%) had received 0, 2, and 3 mRNA vaccine doses, respectively. Among patients without immunocompromising conditions (Table 1), 2- and 3-dose recipients were similar in terms of age (median = 69 and 72 years, respectively) but differed in self-reported race/ethnicity distribution (a higher percentage of non-Hispanic White persons were among 3-dose recipients; $p = 0.008$) and U.S. Census Bureau region of the admitting hospital ($p = 0.030$). Two-dose recipients were less likely to report working in health care settings (5%) than were 3-dose recipients (10%) ($p = 0.023$) and were more likely to be enrolled as a COVID-19 case-patient (31%) than were 3-dose recipients (8%) ($p<0.001$). Among patients with immunocompromising conditions (Table 2), 2-dose recipients were more likely to be enrolled as a case-patient (34%) than were 3-dose recipients (20%) ($p<0.001$). VE against COVID-19 hospitalization among adults without immunocompromising conditions was 82% (95% CI = 77%–86%) for 2 doses and 97% (95% CI = 95%–99%) for 3 doses ($p<0.001$) (Table 3). VE against COVID-19 hospitalization among adults with immunocompromising conditions was 69% (95% CI = 57%–78%) for 2 doses and 88% (95% CI = 81%–93%) for 3 doses

[§] COVID-19–like illness was defined as having one or more of the following: fever, cough, shortness of breath, loss of taste, loss of smell, use of respiratory support for the acute illness, or new pulmonary findings on chest imaging consistent with pneumonia.

[¶] Patients were excluded if they received a third COVID-19 mRNA vaccine dose before the FDA EUA (before August 12, 2021 for patients with immunocompromising conditions or before September 22, 2021 for patients without immunocompromising conditions [when a single booster dose of the Pfizer-BioNTech vaccine was authorized]), were admitted to the hospital before ≤7 days had elapsed since EUA authorization (before August 19, 2021 for patients with immunocompromising conditions or before September 29, 2021 for patients without immunocompromising conditions) or received a third dose before recommended during the surveillance period (<28 days after dose 2 for patients with immunocompromising conditions or <180 days after dose 2 for patients without immunocompromising conditions).

[**] 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.

TABLE 1. Characteristics of vaccine effectiveness analysis participants without immunocompromising conditions, including case-patients hospitalized with COVID-19 and controls hospitalized without COVID-19, by mRNA vaccination group — 21 hospitals,* 18 U.S. states, August–December 2021

Characteristic	Vaccination group, no./Total no. (%)†			P-value for comparison of 2-dose versus 3-dose group¶
	Unvaccinated (n = 1,065)	2 mRNA vaccine doses (n = 679)†	3 mRNA vaccine doses§ (n = 131)	
COVID-19 case-patients	744/1,065 (70)	212/679 (31)	10/131 (8)	<0.001
Age group, yrs				
18–49	454/1,065 (43)	64/679 (9)	9/131 (7)	0.31
50–64	327/1,065 (31)	179/679 (26)	29/131 (22)	
≥65	284/1,065 (27)	436/679 (64)	93/131 (71)	
Female sex	486/1,065 (46)	329/679 (48)	67/131 (51)	0.57
Race/Ethnicity**				
White, non-Hispanic	566/1,065 (53)	409/679 (60)	100/131 (76)	0.008
Black, non-Hispanic	220/1,065 (21)	134/679 (20)	16/131 (12)	
Any race, Hispanic	195/1,065 (18)	85/679 (13)	10/131 (8)	
Non-Hispanic, all other races	57/1,065 (5)	37/679 (5)	2/131 (2)	
Unknown	27/1,065 (3)	14/679 (2)	3/131 (2)	
U.S. Census region				
Northeast	176/1,065 (17)	160/679 (24)	20/131 (15)	0.030
Midwest	215/1,065 (20)	151/679 (22)	32/131 (24)	
South	391/1,065 (37)	210/679 (31)	35/131 (27)	
West	283/1,065 (27)	158/679 (23)	44/131 (34)	
LTCF resident††	25/1,004 (2)	71/663 (11)	17/120 (14)	0.27
Employed	343/813 (42)	104/556 (19)	23/96 (24)	0.23
Health care worker	21/813 (3)	26/556 (5)	10/96 (10)	0.023
Reported ≥1 previous hospitalization in the last year	267/947 (28)	298/598 (50)	50/119 (42)	0.12
No. of chronic medical condition types (IQR)	1 (0–2)	2 (1–3)	2 (1–3)	0.10
Self-reported previous laboratory-confirmed SARS-CoV-2 infection	68/1,063 (6)	36/679 (5)	7/131 (5)	0.98
Vaccine product received				
Pfizer-BioNTech	NA	386/679 (57)	93/131 (71)	0.001
Moderna	NA	288/679 (42)	35/131 (27)	
Both products	NA	5/679 (0.7)	3/131 (2)	
Interval between second vaccine dose and illness onset, days, median, (IQR)	NA	225 (203–248)	257 (240–276)	<0.001
Interval between second and third vaccine dose, days, median (IQR)	NA	NA	230 (211–248)	NA
Interval between third vaccine dose and illness onset, days, median (IQR)	NA	NA	25 (13–36)	NA

Abbreviations: LTCF = long-term care facility; NA = not applicable.

* Hospitals by U.S. Census region included *Northeast*: Baystate Medical Center (Springfield, Massachusetts), Beth Israel Deaconess Medical Center (Boston, Massachusetts), Montefiore Medical Center (New York City borough of the Bronx, New York); *Midwest*: University of Iowa Hospitals & Clinics (Iowa City, Iowa), University of Michigan Hospital (Ann Arbor, Michigan), Hennepin County Medical Center (Minneapolis, Minnesota), Barnes-Jewish Hospital (St. Louis, Missouri), Cleveland Clinic (Cleveland, Ohio), The Ohio State University Wexner Medical Center (Columbus, Ohio); *South*: Vanderbilt University Medical Center (Nashville, Tennessee), University of Miami Medical Center (Miami, Florida), Emory University Hospital (Atlanta, Georgia), The Johns Hopkins Hospital (Baltimore, Maryland), Atrium Health Wake Forest Baptist Medical Center (Winston-Salem, North Carolina), Baylor Scott & White Medical Center (Temple, Texas); *West*: Stanford University Medical Center (Palo Alto, California), Ronald Reagan UCLA Medical Center (Los Angeles, California), UCHealth University of Colorado Hospital (Aurora, Colorado), Oregon Health & Science University Hospital (Portland, Oregon), Intermountain Medical Center (Murray, Utah), University of Washington Medical Center (Seattle, Washington).

† Three vaccination groups were included; unvaccinated patients received no COVID-19 vaccine doses before the date of current illness onset; 2-dose recipients received 2 doses of an mRNA COVID-19 vaccine with the second dose received ≥180 days before the date of illness onset; 3-dose recipients received a third (booster) dose of vaccine with ≥180 days between the second and third dose and ≥7 days between the date of dose 3 receipt and illness onset. Among those who received a third dose with mRNA-1273 from Moderna, one half a dose (0.25 mL) was recommended for the third dose.

§ Dose 3 received ≥6 months after dose 2.

¶ Comparisons were made between 2-dose (primary series only) and 3-dose recipients (booster) groups using Pearson's chi-square testing for categorical variables and the non-parametric Wilcoxon rank-sum test for continuous variables.

** Race and ethnic groups self-reported.

†† LTCFs included residence in a nursing home, assisted living home, or rehab hospital or other subacute or chronic facility before the hospital admission.

TABLE 2. Characteristics of vaccine effectiveness analysis participants with immunocompromising conditions,* including case-patients hospitalized with COVID-19 and controls hospitalized without COVID-19, by mRNA vaccination group — 21 hospitals,† 18 U.S. states, August–December 2021

Characteristic	Vaccination group, no./Total no. (%)§			P-value for comparison of 2-dose versus 3-dose group**
	Unvaccinated (n = 324)	mRNA vaccine, 2 doses (n = 572)†	mRNA vaccine, 3 doses¶; (n = 181)	
COVID-19 case patients	187/324 (58)	196/572 (34)	36/181 (20)	<0.001
Age group, yrs				
18–49	100/324 (31)	84/572 (15)	20/181 (11)	0.17
50–64	131/324 (40)	197/572 (34)	55/181 (30)	
≥65	93/324 (29)	291/572 (51)	106/181 (59)	
Female sex	168/324 (52)	303/572 (53)	81/181 (45)	0.054
Race/Ethnicity††				
White, non-Hispanic	176/324 (54)	329/572 (58)	133/181 (73)	0.001
Black, non-Hispanic	82/324 (25)	113/572 (20)	24/181 (13)	
Any race, Hispanic	55/324 (17)	97/572 (17)	14/181 (8)	
Non-Hispanic, all other races	8/324 (2)	25/572 (4)	9/181 (5)	
Unknown	3/324 (0.9)	8/572 (1)	1/181 (0.6)	
U.S. Census region				
Northeast	48/324 (15)	94/572 (16)	24/181 (13)	0.56
Midwest	72/324 (22)	131/572 (23)	48/181 (27)	
South	145/324 (45)	206/572 (36)	61/181 (34)	
West	59/324 (18)	141/572 (25)	48/181 (27)	
LTCF resident§§	8/316 (3)	18/558 (3)	3/178 (2)	0.28
Employed	62/258 (24)	108/497 (22)	34/159 (21)	0.93
Health care worker	9/258 (3)	13/497 (3)	5/159 (3)	0.72
Reported ≥1 previous hospitalization in the last year	153/307 (50)	317/540 (59)	96/164 (59)	0.97
No. of chronic medical condition types (IQR)	3 (2–4)	3 (2–4)	3 (3–4)	0.88
Self-reported previous laboratory-confirmed SARS-CoV-2 infection	33/324 (10)	38/572 (7)	12/181 (7)	1.00
Vaccine product received				
Pfizer-BioNTech	NA	334/572 (58)	120/181 (66)	<0.001
Moderna	NA	238/572 (42)	57/181 (31)	
Both products	NA	0/572 (—)	4/181 (2)	
Interval between second vaccine dose and illness onset, days, median (IQR)	NA	178 (142.5–213)	226 (199–251)	<0.001
Interval between second and third vaccine dose, days, median (IQR)	NA	NA	178 (148–202)	NA
Interval between third vaccine dose and illness onset, days, median (IQR)	NA	NA	40 (21–68)	NA

Abbreviations: LTCF = long-term care facility; NA = not applicable.

* Immunocompromising conditions included having one or more of the following: active solid organ cancer (active cancer defined as treatment for the cancer or newly diagnosed cancer in the past 6 months); active hematologic cancer (such as leukemia, lymphoma, or myeloma); HIV infection without AIDS; AIDS; congenital immunodeficiency syndrome; prior splenectomy; prior solid organ, stem cell, or bone marrow transplant; immunosuppressive medication; systemic lupus erythematosus; rheumatoid arthritis; psoriasis; scleroderma; or inflammatory bowel disease, including Crohn's disease or ulcerative colitis. Among 2-dose vaccine recipients with immunocompromising conditions (572), 274 (48%) had active cancer, 156 (27%) were on immunosuppressive medications, 118 (21%) had a history of solid organ transplant, and 146 (26%) had another immunocompromising condition; among 3-dose vaccine recipients with immunocompromising conditions (181), 88 (49%) had active cancer, 74 (41%) were on immunosuppressive medications, 65 (36%) had a history of solid organ transplant, and 20 (11%) had another immunocompromising condition.

† Hospitals by U.S. Census region included *Northeast*: Baystate Medical Center (Springfield, Massachusetts), Beth Israel Deaconess Medical Center (Boston, Massachusetts), Montefiore Medical Center (New York City borough of the Bronx, New York); *Midwest*: University of Iowa Hospitals & Clinics (Iowa City, Iowa), University of Michigan Hospital (Ann Arbor, Michigan), Hennepin County Medical Center (Minneapolis, Minnesota), Barnes-Jewish Hospital (St. Louis, Missouri), Cleveland Clinic (Cleveland, Ohio), The Ohio State University Wexner Medical Center (Columbus, Ohio); *South*: Vanderbilt University Medical Center (Nashville, Tennessee), University of Miami Medical Center (Miami, Florida), Emory University Hospital (Atlanta, Georgia), The Johns Hopkins Hospital (Baltimore, Maryland), Atrium Health Wake Forest Baptist Medical Center (Winston-Salem, North Carolina), Baylor Scott & White Medical Center (Temple, Texas); *West*: Stanford University Medical Center (Palo Alto, California), Ronald Reagan UCLA Medical Center (Los Angeles, California), UCHealth University of Colorado Hospital (Aurora, Colorado), Oregon Health & Science University Hospital (Portland, Oregon), Intermountain Medical Center (Murray, Utah), University of Washington Medical Center (Seattle, Washington).

§ Three vaccination groups were included; unvaccinated patients received no COVID-19 vaccine doses before the date of current illness onset; 2-dose recipients received 2 doses of an mRNA COVID-19 vaccine with the second dose received ≥28 days before the date of illness onset; 3-dose recipients received 3 doses of vaccine to complete a primary vaccine series with ≥28 days between the second and third dose and ≥7 days between the date of dose 3 receipt and illness onset.

¶ Dose 3 received ≥28 days after dose 2.

** Comparisons were made between 2-dose and 3-dose recipient groups using Pearson's chi-square testing for categorical variables and the nonparametric Wilcoxon rank-sum test for continuous variables.

†† Race and ethnic groups self-reported.

§§ LTCFs included residence in a nursing home, assisted living home, or rehab hospital or other subacute or chronic facility before the hospital admission.

(p<0.001). In a sensitivity analysis among patients with moderately to severely immunocompromising conditions defined by CDC†† (*7*), VE was 65% (95% CI = 49%–76%) for receipt of 2 doses, and 87% (95% CI = 78%–92%) for receipt of 3 doses (p<0.001).

Discussion

In a multistate network, adults vaccinated with 2 or 3 doses of a COVID-19 mRNA vaccine were protected against COVID-19–associated hospitalization. Significantly higher VE was observed in adults who received a third mRNA vaccine dose either as part of a primary vaccine series (immunocompromised persons) or as a booster dose (immunocompetent persons) compared with those who had received 2 doses. These findings underscore the importance of immunocompromised adults obtaining a third mRNA vaccine dose ≥28 days after the second vaccine dose and of immunocompetent adults receiving a third (booster) dose currently recommended ≥5 months after the second dose.§§

This study was conducted during a period of SARS-CoV-2 Delta variant predominance (*8*). VE against the B.1.1.529 (Omicron) variant of SARS-CoV-2 might be lower than for other variants that have circulated widely, possibly because of immune evasion. Early evidence suggests that a third mRNA vaccine dose elicits markedly stronger neutralizing antibody responses to the Omicron variant compared with responses to 2 vaccine doses (*9*), and increases VE against severe disease following infection with the Omicron variant (*10*). The effectiveness of 3 doses of COVID-19 mRNA vaccines against a range of disease severity associated with the Omicron variant needs to be carefully evaluated in different populations.

The findings in this report are subject to at least six limitations. First, 2-dose and 3-dose vaccine recipients were similar in terms of most demographic and clinical characteristics but might have differed with respect to exposure risk for SARS-CoV-2 infection or risk factors for severe COVID-19. Therefore, residual or unmeasured confounding was possible. Second, VE associated with newly emergent variants, including Omicron, was not assessed. Third, VE was not assessed against SARS-CoV-2 infection or mild illness. Fourth, most 3-dose mRNA vaccine recipients were vaccinated within several weeks of enrollment and durability of protection will require future analysis. Fifth, VE associated with a fourth mRNA vaccine dose, recommended as a booster dose in immunocompromised individuals ≥5 months after dose 3, was not assessed. Finally, although medical centers in 18 states were included in the

†† The definition adapted from CDC definitions of moderately to severely immunocompromising conditions included having one or more of the following: active solid organ cancer (active cancer defined as treatment for the cancer or newly diagnosed cancer in the past 6 months), active hematologic cancer (such as leukemia, lymphoma, or myeloma), AIDS, congenital immunodeficiency syndrome, previous solid organ, stem cell, or bone marrow transplant, or active immunosuppressive medication use.

§§ https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

TABLE 3. Effectiveness of 2-dose and 3-dose regimens of COVID-19 mRNA vaccines against COVID-19 hospitalization among adults with and without immunocompromising conditions — 21 hospitals, 18 U.S. states,*,† August–December 2021

Subgroup	Vaccinated versus unvaccinated, 2 doses		Vaccinated versus unvaccinated, 3 doses		P-value for VE comparison for 2-dose versus 3-dose recipients§
	No. vaccinated/ Total no. (%)	VE (95% CI)*	No. vaccinated/ Total no. (%)	VE (95% CI)*	
Patients without immunocompromising conditions					
COVID-19 case-patients	212/956 (22)	82 (77–86)	10/754 (1)	97 (95–99)	<0.001
Control patients	467/788 (59)		121/442 (27)		
Patients with immunocompromising conditions					
COVID-19 case-patients	196/383 (51)	69 (57–78)	36/223 (16)	88 (81–93)	<0.001
Control patients	376/513 (73)		145/282 (51)		

Abbreviation: VE = vaccine effectiveness.

* VE was estimated using logistic regression, comparing the odds of being vaccinated with the Moderna or Pfizer-BioNTech COVID-19 vaccine product versus being unvaccinated among case-patients and controls using the equation VE = 100 × (1 − adjusted odds ratio). The regression model included three categories for vaccination status: unvaccinated, vaccinated with 2 doses of an mRNA vaccine, or vaccinated with 3 doses of an mRNA vaccine. VE was calculated separately comparing 2-dose recipients to unvaccinated controls and 3-dose recipients to unvaccinated controls. Models were adjusted for date of hospital admission (biweekly intervals), U.S. Department of Health and Human Services region of hospital, age group (18–49, 50–64, or ≥65 years), sex, and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic of any race, non-Hispanic Other, or unknown).

† Hospitals by U.S. Department of Health and Human Services region included: *Region 1*: Baystate Medical Center (Springfield, Massachusetts), Beth Israel Deaconess Medical Center (Boston, Massachusetts); *Region 2*: Montefiore Medical Center (New York City borough of the Bronx, New York); *Region 3*: The Johns Hopkins Hospital (Baltimore, Maryland); *Region 4*: Vanderbilt University Medical Center (Nashville, Tennessee), University of Miami Medical Center (Miami, Florida), Emory University Hospital (Atlanta, Georgia), Atrium Health Wake Forest Baptist Medical Center (Winston-Salem, North Carolina); *Region 5*: University of Michigan Hospital (Ann Arbor, Michigan), Hennepin County Medical Center (Minneapolis, Minnesota), Cleveland Clinic (Cleveland, Ohio), The Ohio State University Wexner Medical Center (Columbus, Ohio); *Region 6*: Baylor Scott & White Medical Center (Temple, Texas); *Region 7*: University of Iowa Hospitals & Clinics (Iowa City, Iowa), Barnes-Jewish Hospital (St. Louis, Missouri); *Region 8*: UCHealth University of Colorado Hospital (Aurora, Colorado), Intermountain Medical Center (Murray, Utah); *Region 9*: Stanford University Medical Center (Palo Alto, California), Ronald Reagan UCLA Medical Center (Los Angeles, California); *Region 10*: Oregon Health & Sciences University Hospital (Portland, Oregon), University of Washington Medical Center (Seattle, Washington).

§ Post-hoc pairwise comparisons of VE for 2-dose versus 3-dose vaccine recipients was evaluated using the pwcompare function in Stata software (version 16; StataCorp); a two sided p-value <0.05 indicated a significant difference in VE between groups.

Summary

What is already known about this topic?

For adults aged ≥18 years who received 2 doses of an mRNA COVID-19 vaccine, third doses are recommended. However, the associated benefits in preventing COVID-19 hospitalization are incompletely understood.

What is added by this report?

In a study of hospitalized adults, compared with receipt of 2 mRNA COVID-19 vaccine doses, receipt of a third dose increased vaccine effectiveness against hospitalization among adults without and with immunocompromising conditions, from 82% to 97% and from 69% to 88%, respectively.

What are the implications for public health practice?

Administration of a third COVID-19 mRNA vaccine dose as part of a primary series among immunocompromised adults, or as a booster dose among immunocompetent adults, provides improved protection against COVID-19–associated hospitalization.

analysis, patients might not be representative of the general U.S. population.

Among adults with and without immunocompromising conditions who were eligible to receive a third dose of COVID-19 mRNA vaccine, third doses were found to increase protection beyond that of a 2-dose vaccination series for the prevention of COVID-19 hospitalization. Administration of a third COVID-19 mRNA vaccine dose as part of a primary series among immunocompromised adults, or as a booster dose among immunocompetent adults, provides improved protection against COVID-19 hospitalization.

IVY Network

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COVID-19 Cases and Hospitalizations by COVID-19 Vaccination Status and Previous COVID-19 Diagnosis — California and New York, May–November 2021

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By November 30, 2021, approximately 130,781 COVID-19–associated deaths, one in six of all U.S. deaths from COVID-19, had occurred in California and New York.* COVID-19 vaccination protects against infection with SARS-CoV-2 (the virus that causes COVID-19), associated severe illness, and death (*1*,*2*); among those who survive, previous SARS-CoV-2 infection also confers protection against severe outcomes in the event of reinfection (*3*,*4*). The relative magnitude and duration of infection- and vaccine-derived protection, alone and together, can guide public health planning and epidemic forecasting. To examine the impact of primary COVID-19 vaccination and previous SARS-CoV-2 infection on COVID-19 incidence and hospitalization rates, statewide testing, surveillance, and COVID-19 immunization data from California and New York (which account for 18% of the U.S. population) were analyzed. Four cohorts of adults aged ≥18 years were considered: persons who were 1) unvaccinated with no previous laboratory-confirmed COVID-19 diagnosis, 2) vaccinated (14 days after completion of a primary COVID-19 vaccination series) with no previous COVID-19 diagnosis, 3) unvaccinated with a previous COVID-19 diagnosis, and 4) vaccinated with a previous COVID-19 diagnosis. Age-adjusted hazard rates of incident laboratory-confirmed COVID-19 cases in both states were compared among cohorts, and in California, hospitalizations during May 30–November 20, 2021, were also compared. During the study period, COVID-19 incidence in both states was highest among unvaccinated persons without a previous COVID-19 diagnosis compared with that among the other three groups. During the week beginning May 30, 2021, compared with COVID-19 case rates among unvaccinated persons without a previous COVID-19 diagnosis, COVID-19 case rates were 19.9-fold (California) and 18.4-fold (New York) lower among vaccinated persons without a previous diagnosis; 7.2-fold (California) and 9.9-fold lower (New York) among unvaccinated persons with a previous COVID-19 diagnosis; and 9.6-fold (California) and 8.5-fold lower (New York) among vaccinated persons with a previous COVID-19 diagnosis. During the same period, compared with hospitalization rates among unvaccinated persons without a previous COVID-19 diagnosis, hospitalization rates in California followed a similar pattern. These relationships changed after the SARS-CoV-2 Delta variant became predominant (i.e., accounted for >50% of sequenced isolates) in late June and July. By the week beginning October 3, compared with COVID-19 cases rates among unvaccinated persons without a previous COVID-19 diagnosis, case rates among vaccinated persons without a previous COVID-19 diagnosis were 6.2-fold (California) and 4.5-fold (New York) lower; rates were substantially lower among both groups with previous COVID-19 diagnoses, including 29.0-fold (California) and 14.7-fold lower (New York) among unvaccinated persons with a previous diagnosis, and 32.5-fold (California) and 19.8-fold lower (New York) among vaccinated persons with a previous diagnosis of COVID-19. During the same period, compared with hospitalization rates among unvaccinated persons without a previous COVID-19 diagnosis, hospitalization rates in California followed a similar pattern. These results demonstrate that vaccination protects against COVID-19 and related hospitalization, and that surviving a previous infection protects against a reinfection and related hospitalization. Importantly, infection-derived protection was higher after the Delta variant became predominant, a time when vaccine-induced immunity for many persons declined because of immune evasion and immunologic waning (*2*,*5*,*6*). Similar cohort data accounting for booster doses needs to be assessed, as new variants, including Omicron, circulate. Although the epidemiology of COVID-19 might change with the emergence of new variants, vaccination remains the safest strategy to prevent SARS-CoV-2 infections and associated complications; all eligible persons should be up to date with COVID-19 vaccination. Additional recommendations for vaccine doses might be warranted in the future as the virus and immunity levels change.

Four cohorts of persons aged ≥18 years were assembled via linkages of records from electronic laboratory reporting databases and state-specific immunization information systems.†

* https://covid.cdc.gov/covid-data-tracker/#cases_deathsper100klast7days

† Statewide immunization databases in California are the California Immunization Registry, Regional Immunization Data Exchange, and San Diego Immunization Registry; the laboratory system is the California COVID Reporting System (CCRS). In New York, immunization information systems include Citywide Immunization Registry and the New York State Immunization Information System; the laboratory system is the Electronic Clinical Laboratory Reporting System (ECLRS). California data were matched between the immunization and case registries using a probabilistic algorithm with exact match for zip code and date of birth and fuzzy match on first name and last name. New York data were matched to the ECLRS with the use of a deterministic algorithm based on first name, last name, and date of birth. In California, person-level hospitalization data from CCRS and supplementary hospitalization reports were used to identify COVID-19–associated hospitalizations.

Persons were classified based on whether they had had a laboratory-confirmed SARS-CoV-2 infection by March 1, 2021 (i.e., previous COVID-19 diagnosis)[§]; had received at least the primary COVID-19 vaccination series[¶] by May 16, 2021; had a previous COVID-19 diagnosis and were fully vaccinated[**]; or had neither received a previous COVID-19 diagnosis by March 1 nor received a first COVID-19 vaccine dose by the end of the analysis period. The size of the unvaccinated group without a previous diagnosis was derived by subtracting the observed groups from U.S. Census estimates.[††] To maintain each defined cohort, persons who received a COVID-19 diagnosis during March 1–May 30, 2021, or who died before May 30, 2021, were excluded (to maintain eligibility for incident cases for all cohorts on May 30, 2021),[§§] as were persons who received a first vaccine dose during May 30–November 20, 2021. During May 30–November 20, 2021, incident cases were defined using a positive nucleic acid amplification test (NAAT) result from the California COVID-19 Reporting System (CCRS) or a positive NAAT or antigen test result from the New York Electronic Clinical Laboratory Reporting System. In California, person-level hospitalization data from CCRS and supplementary hospitalization reports were used to identify COVID-19–associated hospitalizations. A lifetable method was used to calculate hazard rates (average daily cases during a 7-day interval or hospitalizations over a 14-day interval), hazard ratios, and 95% CIs for each cohort. Rates were age-adjusted to 2000 U.S. Census data using direct standardization.[¶¶] Supplementary analyses stratified case rates by timing of previous diagnoses and primary series vaccine product. SAS (version 9.4; SAS Institute) and R (version 4.0.4; The R Foundation) were used to conduct all analyses. Institutional review boards (IRBs) in both states determined this surveillance activity to be necessary for public health work, and therefore, it did not require IRB review.

Approximately three quarters of adults from California (71.2%) and New York (72.2%) included in this analysis were vaccinated and did not have a previous COVID-19 diagnosis; however, 18.0% of California residents and 18.4% of New York residents were unvaccinated with no previous COVID-19 diagnosis (Table 1). In both states, 4.5% of persons were vaccinated and had a previous COVID-19 diagnosis; 6.3% in California and 4.9% in New York were unvaccinated with a previous diagnosis. Among 1,108,600 incident COVID-19 cases in these cohorts (752,781 in California and 355,819 in New York), the median intervals from vaccination or previous COVID-19 diagnosis to incident diagnosis were slightly shorter in California (138–150 days) than in New York (162–171 days).

Before the Delta variant became predominant in each state's U.S. Department of Health and Human Services region (June 26 in Region 9 [California] and July 3 in Region 2 [New York]),[***] the highest incidence was among unvaccinated persons without a previous COVID-19 diagnosis; during this time, case rates were relatively low among the three groups with either previous infection or vaccination and were lowest among vaccinated persons without a previous COVID-19 diagnosis (Supplementary Figure 1, https://stacks.cdc.gov/view/cdc/113253) (Supplementary Figure 2, https://stacks.cdc.gov/view/cdc/113253). During the week beginning May 30, 2021, compared with COVID-19 case rates among unvaccinated persons without a previous COVID-19 diagnosis, COVID-19 case rates were 19.9-fold (California) and 18.4-fold (New York) lower among vaccinated persons without a previous diagnosis; rates were 7.2-fold (California) and 9.9-fold (New York) lower among unvaccinated persons with a previous COVID-19 diagnosis and 9.6-fold (California) and 8.5-fold (New York) lower among vaccinated persons with a previous COVID-19 diagnosis (Table 2).

As the Delta variant prevalence increased to >95% (97% in Region 9 and 98% in Region 2 on August 1), rates increased more rapidly among the vaccinated group with no previous COVID-19 diagnosis than among both the vaccinated and unvaccinated groups with a previous COVID-19 diagnosis (Supplementary Figure 1, https://stacks.cdc.gov/view/cdc/113253) (Supplementary Figure 2, https://stacks.cdc.gov/view/cdc/113253). For example, during the week of

[§] For both classification into cohorts of persons with previous COVID-19 diagnoses and for measuring incident cases, laboratory-confirmed infection was defined as the receipt of a new positive SARS-CoV-2 nucleic acid amplification test (NAAT) or antigen test (both for New York and NAAT only for California) result, but not within 90 days of a previous positive result.

[¶] Fully vaccinated with the primary vaccination series is defined as receipt of a second dose of an mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) or 1 dose of the Janssen (Johnson & Johnson) vaccine ≥14 days before May 30, 2021.

[**] Because of the timing of full vaccination, the cohort definitions, and analysis timeframe, this cohort consisted nearly exclusively of persons who had previously received a laboratory-confirmed diagnosis of COVID-19 and later were fully vaccinated (California: 99.9%, New York: 99.7%), as opposed to the reverse order.

[††] Whereas vaccinated cohorts were directly observed in the immunization information system databases, unvaccinated persons without a previous COVID-19 diagnosis were defined using U.S. Census population estimates minus the number of persons partially or fully vaccinated by December 11, 2021, and unvaccinated persons with a previous laboratory-confirmed infection before May 30, 2021. In California, the California Department of Finance population estimates were used for 2020, and the 2018 CDC National Center for Health Statistics Bridged Race file for U.S. Census population estimates were used in New York, consistent with other COVID-19 surveillance reporting.

[§§] In California, a person-level match was performed to exclude deaths in each cohort before May 30, 2021. In New York, COVID-19 deaths were removed in aggregate from the starting number of unvaccinated persons with a previous COVID-19 diagnosis on May 30, 2021.

[¶¶] https://www.cdc.gov/nchs/data/statnt/statnt20.pdf

[***] https://covid.cdc.gov/covid-data-tracker/#variant-proportions

TABLE 1. Cohort sizes and cohort-specific incident laboratory-confirmed COVID-19 cases in California (N = 752,781) and New York (N = 355,819) and hospitalizations in California (N = 56,177) — May 30–November 20, 2021

State/Vaccination and diagnosis status*,†	No. of persons in each cohort (%)	Incident laboratory-confirmed COVID-19 cases			Incident COVID-19 hospitalizations**
		No. (cumulative incidence)§,¶	Median (IQR) interval from vaccination to positive test, days	Median (IQR) interval from previous diagnosis to positive test, days	No. (cumulative incidence)§,¶
California					
Vaccinated					
Previous COVID-19 diagnosis	968,167 (4.5)	3,471 (3.6)	138 (95–181)	262 (218–322)	273 (0.3)
No previous diagnosis	15,484,235 (71.2)	240,045 (15.5)	150 (112–189)	NA	10,737 (0.7)
Unvaccinated					
Previous COVID-19 diagnosis	1,370,782 (6.3)	6,805 (5.0)	NA	277 (229–356)	378 (0.3)
No previous diagnosis	3,911,146 (18.0)	502,460 (128.5)	NA	NA	44,789 (11.5)
New York					
Vaccinated					
Previous COVID-19 diagnosis	485,649 (4.5)	2,355 (4.9)	162 (118–201)	276 (227–348)	NA
No previous diagnosis	7,809,968 (72.2)	142,388 (18.2)	171 (133–203)	NA	NA
Unvaccinated					
Previous COVID-19 diagnosis	527,140 (4.9)	3,250 (6.2)	NA	295 (242–427)	NA
No previous diagnosis	1,993,709 (18.4)	207,826 (104.2)	NA	NA	NA

Abbreviations: NA = not applicable; NAAT = nucleic acid amplification test.

* Statewide immunization databases in California are the California Immunization Registry, Regional Immunization Data Exchange, and San Diego Immunization Registry, and the laboratory system is the California COVID Reporting System; in New York, Immunization Information Systems include Citywide Immunization Registry and the New York State Immunization Information System; the laboratory system is the Electronic Clinical Laboratory Reporting System. California data were matched between the immunization and case registries using a probabilistic algorithm with exact match for zip code and date of birth and fuzzy match on first name and last name. New York data were matched to the Electronic Clinical Laboratory Reporting System with the use of a deterministic algorithm based on first name, last name, and date of birth. In California, person-level hospitalization data from the California COVID Reporting System and supplemental hospitalization reports were used to identify COVID-19-associated hospitalizations.

† For both classification into cohorts of persons with previous COVID-19 diagnoses and for measuring incident cases, laboratory-confirmed infection was defined as the receipt of a new positive SARS-CoV-2 NAAT or antigen test (both for New York and NAAT only for California) result, but not within 90 days of a previous positive result. Fully vaccinated is defined as having received a second dose of an mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) or 1 dose of the Janssen (Johnson & Johnson) vaccine ≥14 days before May 30, 2021. Whereas vaccinated cohorts were directly observed in the immunization information system databases, unvaccinated persons without a previous COVID-19 diagnosis were defined using U.S. Census population estimates minus persons partially or fully vaccinated by December 11, 2021, and unvaccinated persons with a previous laboratory-confirmed infection before May 30, 2021. In California, the California Department of Finance population estimates were used for 2020, and the 2018 CDC National Center for Health Statistics Bridged Race file for census population estimates were used in New York, consistent with other COVID-19 surveillance reporting.

§ Cumulative cases per 1,000 persons.

¶ These summaries of cumulative incidence are estimated across a period of variability in the epidemic for all cohorts.

** Hospitalization data for New York are not included in this analysis.

October 3, compared with rates among unvaccinated persons without a previous COVID-19 diagnosis, rates among vaccinated persons without a previous diagnosis were 6.2-fold lower (95% CI = 6.0–6.4) in California and 4.5-fold lower (95% CI = 4.3–4.7) in New York (Table 2). Further, rates among unvaccinated persons with a previous COVID-19 diagnosis were 29-fold lower (95% CI = 25.0–33.1) than rates among unvaccinated persons without a previous COVID-19 diagnosis in California and 14.7-fold lower (95% CI = 12.6–16.9) in New York. Rates among vaccinated persons who had had COVID-19 were 32.5-fold lower (95% CI = 27.5–37.6) than rates among unvaccinated persons without a previous COVID-19 diagnosis in California and 19.8-fold lower (95% CI = 16.2–23.5) in New York. Rates among vaccinated persons without a previous COVID-19 diagnosis were consistently higher than rates among unvaccinated persons with a history of COVID-19 (3.1-fold higher [95% CI = 2.6–3.7] in California and 1.9-fold higher [95% CI = 1.5–2.3] in New York) and rates among vaccinated persons with a history of COVID-19 (3.6-fold higher [95% CI = 2.9–4.3] in California and 2.8-fold higher [95% CI = 2.1–3.4] in New York).

COVID-19 hospitalization rates in California were always highest among unvaccinated persons without a previous COVID-19 diagnosis (Table 2) (Figure). In the pre-Delta period during June 13–June 26, for example, compared with hospitalization rates among unvaccinated persons without a previous COVID-19 diagnosis, hospitalization rates were 27.7-fold lower (95% CI = 22.4–33.0) among vaccinated persons without a previous COVID-19 diagnosis, 6.0-fold lower (95% CI = 3.3–8.7) among unvaccinated persons with a previous COVID-19 diagnosis, and 7.1-fold lower (95% CI = 4.0–10.3) among vaccinated persons with a previous COVID-19 diagnosis. However, this pattern also shifted as the Delta variant became predominant. During October 3–16, compared with hospitalization rates among unvaccinated persons without a previous COVID-19 diagnosis, hospitalization rates were 19.8-fold lower (95% CI = 18.2–21.4) among vaccinated persons without a previous COVID-19 diagnosis, 55.3-fold lower (95% CI = 27.3–83.3) among unvaccinated

TABLE 2. Hazard ratios for incident laboratory-confirmed COVID-19 cases — New York and California and hospitalizations* — California, May 30–November 20, 2021

State and date range	Hazard ratio (95% CI)†				
	Unvaccinated, no previous COVID-19 diagnosis versus			Vaccinated, no previous COVID-19 diagnosis versus	
	Vaccinated, no previous COVID-19 diagnosis	Unvaccinated, previous COVID-19 diagnosis	Vaccinated, previous COVID-19 diagnosis	Unvaccinated, previous COVID-19 diagnosis	Vaccinated, previous COVID-19 diagnosis
Cases, California					
May 30–Jun 5	20.9 (18.9–22.9)	8.2 (6.6–9.9)	10.6 (8.1–13.2)	0.4 (0.3–0.5)	0.5 (0.4–0.6)
Jun 6–12	17.9 (16.2–19.5)	8.6 (6.8–10.4)	10.5 (7.9–13.0)	0.5 (0.4–0.6)	0.6 (0.4–0.7)
Jun 13–19	16.0 (14.7–17.4)	10.8 (8.5–13.2)	10.6 (8.2–13.1)	0.7 (0.5–0.8)	0.7 (0.5–0.8)
Jun 20–26	12.3 (11.4–13.1)	14.5 (11.2–17.8)	17.3 (12.8–21.8)	1.2 (0.9–1.5)	1.4 (1.0–1.8)
Jun 27–Jul 3	9.7 (9.2–10.2)	16.6 (13.5–19.7)	20.9 (16.0–25.8)	1.7 (1.4–2.0)	2.2 (1.6–2.7)
Jul 4–10	8.7 (8.4–9.0)	24.0 (20.1–28.0)	29.3 (23.1–35.6)	2.8 (2.3–3.2)	3.4 (2.6–4.1)
Jul 11–17	7.8 (7.5–8.0)	29.0 (25.0–32.9)	33.4 (27.3–39.4)	3.7 (3.2–4.2)	4.3 (3.5–5.1)
Jul 18–24	7.4 (7.2–7.6)	31.8 (28.1–35.6)	35.2 (29.8–40.6)	4.3 (3.8–4.8)	4.7 (4.0–5.5)
Jul 25–31	7.5 (7.4–7.7)	26.5 (24.1–29.0)	38.6 (33.3–43.9)	3.5 (3.2–3.8)	5.1 (4.4–5.8)
Aug 1–7	7.8 (7.6–7.9)	32.6 (29.5–35.6)	42.2 (36.7–47.7)	4.2 (3.8–4.6)	5.4 (4.7–6.1)
Aug 8–14	8.1 (7.9–8.2)	33.4 (30.4–36.5)	43.1 (37.6–48.6)	4.1 (3.8–4.5)	5.3 (4.7–6.0)
Aug 15–21	8.4 (8.3–8.6)	31.3 (28.5–34.1)	42.0 (36.7–47.3)	3.7 (3.4–4.0)	5.0 (4.3–5.6)
Aug 22–28	8.4 (8.3–8.6)	31.3 (28.4–34.3)	41.0 (35.5–46.5)	3.7 (3.4–4.1)	4.9 (4.2–5.5)
Aug 29–Sep 4	8.5 (8.3–8.6)	31.2 (28.1–34.3)	42.0 (36.1–48.0)	3.7 (3.3–4.1)	5.0 (4.3–5.7)
Sep 5–11	8.3 (8.1–8.5)	35.0 (31.0–39.0)	48.0 (40.2–55.9)	4.2 (3.7–4.7)	5.8 (4.8–6.7)
Sep 12–18	8.4 (8.2–8.6)	33.8 (29.9–37.8)	48.0 (39.8–56.2)	4.0 (3.6–4.5)	5.7 (4.7–6.7)
Sep 19–25	8.0 (7.8–8.2)	27.0 (23.8–30.1)	37.8 (31.5–44.1)	3.4 (3.0–3.8)	4.7 (4.0–5.5)
Sep 26–Oct 2	7.7 (7.5–7.9)	28.6 (24.9–32.2)	34.8 (28.9–40.7)	3.7 (3.2–4.2)	4.5 (3.7–5.3)
Oct 3–9	7.2 (7.0–7.4)	30.0 (26.0–34.1)	33.5 (28.5–38.6)	4.1 (3.6–4.7)	4.6 (3.9–5.3)
Oct 10–16	7.2 (7.0–7.4)	31.2 (26.8–35.7)	33.9 (27.8–40.0)	4.3 (3.7–5.0)	4.7 (3.9–5.5)
Oct 17–23	7.1 (7.0–7.3)	31.9 (27.6–36.1)	40.7 (33.3–48.1)	4.5 (3.9–5.0)	5.7 (4.7–6.7)
Oct 24–30	7.1 (6.9–7.3)	26.6 (23.3–29.9)	40.1 (32.9–47.3)	3.7 (3.3–4.2)	5.6 (4.6–6.6)
Oct 31–Nov 6	6.8 (6.6–7.0)	33.1 (28.7–37.6)	37.9 (31.0–44.7)	4.9 (4.2–5.5)	5.5 (4.5–6.6)
Nov 7–13	7.1 (6.9–7.3)	30.6 (26.3–35.0)	41.2 (33.0–49.5)	4.3 (3.7–4.9)	5.8 (4.6–7.0)
Nov 14–20	7.3 (7.0–7.5)	25.4 (21.4–29.3)	32.5 (25.5–39.5)	3.5 (2.9–4.0)	4.5 (3.5–5.5)
Cases, New York					
May 30–Jun 5	19.4 (16.9–21.8)	10.9 (7.5–14.3)	9.5 (6.7–12.4)	0.6 (0.4–0.7)	0.5 (0.3–0.7)
Jun 6–12	15.2 (13.2–17.2)	8.0 (5.5–10.6)	10.4 (6.6–14.3)	0.5 (0.4–0.7)	0.7 (0.4–0.9)
Jun 13–19	12.8 (11–14.5)	8.2 (5.3–11.2)	5.4 (3.7–7.0)	0.6 (0.4–0.9)	0.4 (0.3–0.6)
Jun 20–26	10.1 (8.8–11.4)	7.9 (5.1–10.7)	6.0 (4.0–8.0)	0.8 (0.5–1.1)	0.6 (0.4–0.8)
Jun 27–Jul 3	7.3 (6.5–8.1)	8.8 (5.8–11.8)	11.2 (6.7–15.7)	1.2 (0.8–1.6)	1.5 (0.9–2.2)
Jul 4–10	6.1 (5.6–6.7)	17.8 (10.6–25.0)	11.5 (7.5–15.6)	2.9 (1.7–4.1)	1.9 (1.2–2.6)
Jul 11–17	4.5 (4.2–4.8)	11.7 (8.5–15.0)	14.7 (9.9–19.6)	2.6 (1.9–3.3)	3.2 (2.2–4.3)
Jul 18–24	4.7 (4.5–5.0)	21.7 (15.6–27.8)	14.1 (10.5–17.7)	4.6 (3.3–5.9)	3.0 (2.2–3.8)
Jul 25–31	5.1 (4.9–5.3)	16.1 (13.1–19.2)	18.3 (14.1–22.6)	3.2 (2.6–3.8)	3.6 (2.8–4.4)
Aug 1–7	5.3 (5.2–5.5)	19.2 (15.9–22.6)	18.3 (14.7–21.9)	3.6 (3.0–4.2)	3.4 (2.7–4.1)
Aug 8–14	5.3 (5.2–5.5)	16.2 (13.8–18.6)	19.2 (15.6–22.7)	3.0 (2.6–3.5)	3.6 (2.9–4.3)
Aug 15–21	5.5 (5.3–5.7)	19.5 (16.5–22.6)	22.7 (18.4–26.9)	3.6 (3.0–4.1)	4.1 (3.4–4.9)
Aug 22–28	5.4 (5.2–5.6)	19.2 (16.4–22.1)	26.5 (21.2–31.8)	3.6 (3.0–4.1)	4.9 (3.9–5.9)
Aug 29–Sep 4	5.5 (5.3–5.6)	17.9 (15.3–20.5)	20.9 (17.2–24.6)	3.3 (2.8–3.8)	3.8 (3.1–4.5)
Sep 5–11	5.4 (5.2–5.5)	18.9 (16.1–21.6)	22.3 (18.3–26.4)	3.5 (3.0–4.0)	4.2 (3.4–4.9)
Sep 12–18	5.8 (5.6–5.9)	15.0 (13.1–16.9)	23.2 (19.1–27.4)	2.6 (2.3–2.9)	4.0 (3.3–4.8)
Sep 19–25	5.6 (5.4–5.7)	15.4 (13.3–17.5)	23.8 (19.3–28.3)	2.8 (2.4–3.1)	4.3 (3.5–5.1)
Sep 26–Oct 2	5.4 (5.2–5.5)	18.4 (15.5–21.2)	24.2 (19.3–29.1)	3.4 (2.9–4.0)	4.5 (3.6–5.4)
Oct 3–9	5.5 (5.3–5.7)	15.7 (13.6–17.9)	20.8 (17.2–24.5)	2.9 (2.5–3.3)	3.8 (3.1–4.4)
Oct 10–16	5.5 (5.3–5.6)	17.2 (14.7–19.8)	25.9 (20.6–31.1)	3.2 (2.7–3.6)	4.7 (3.8–5.7)
Oct 17–23	5.4 (5.2–5.6)	18.9 (15.7–22.1)	27.6 (21.2–34.0)	3.5 (2.9–4.1)	5.1 (3.9–6.3)
Oct 24–30	5.2 (5.0–5.4)	21.0 (17.2–24.7)	25.9 (20.2–31.6)	4.0 (3.3–4.7)	5.0 (3.9–6.1)
Oct 31–Nov 6	4.8 (4.6–4.9)	17.3 (14.7–20.0)	20.1 (16.3–23.8)	3.6 (3.1–4.2)	4.2 (3.4–5.0)
Nov 7–13	4.8 (4.7–4.9)	23.9 (20.1–27.6)	24.5 (20.1–28.9)	5.0 (4.2–5.8)	5.1 (4.2–6.1)
Nov 14–20	4.8 (4.6–4.9)	22.6 (19.4–25.7)	23.0 (19.3–26.6)	4.7 (4.1–5.4)	4.8 (4.1–5.6)

See table footnotes on the next page.

persons with a previous COVID-19 diagnosis, and 57.5-fold lower (95% CI = 29.2–85.8) among vaccinated persons with a previous COVID-19 diagnosis.

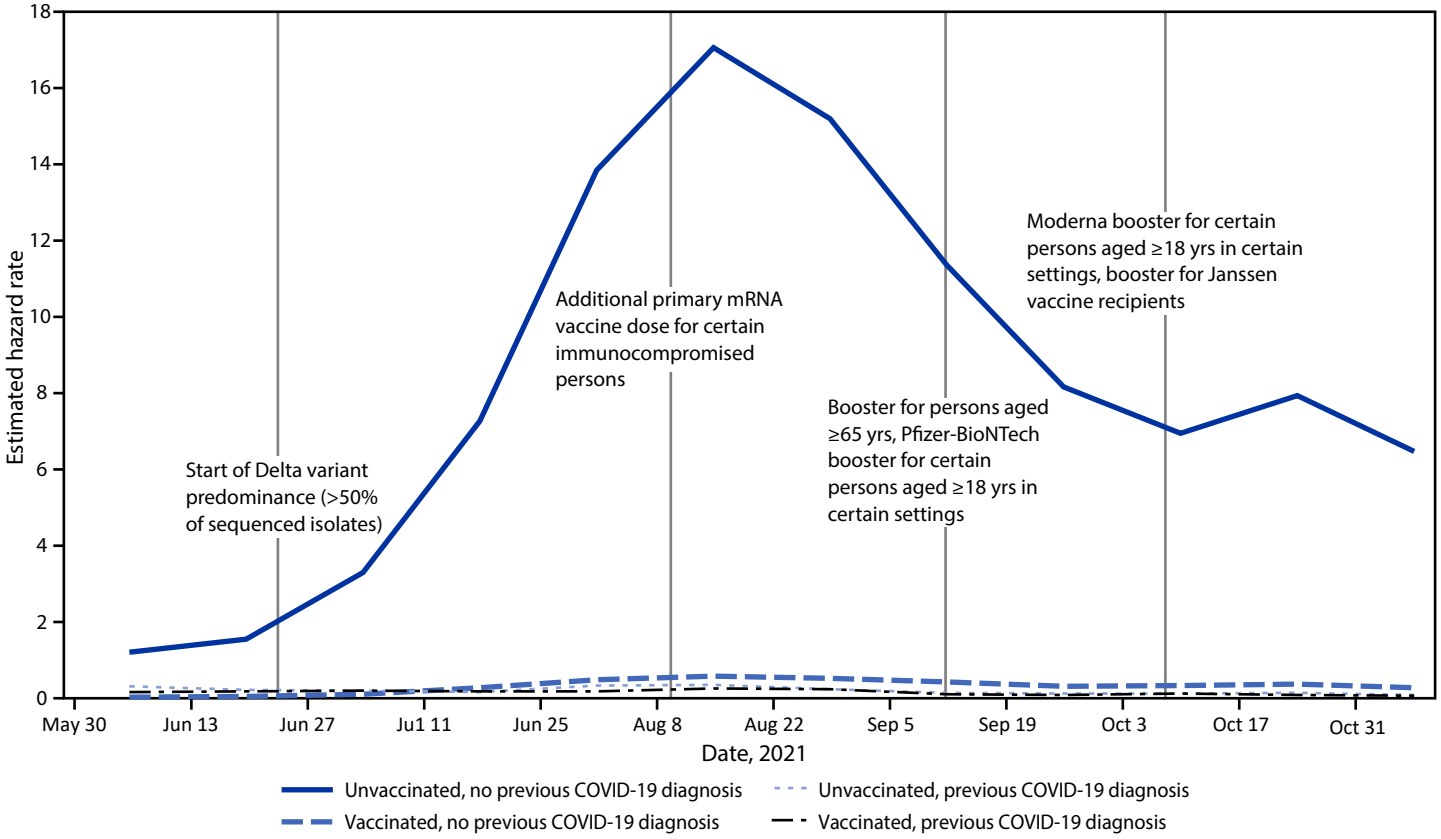
Among the two cohorts with a previous COVID-19 diagnosis, no consistent incidence gradient by time since the previous diagnosis was observed (Supplementary Figure 3, https://stacks.cdc.gov/view/cdc/113253). When the vaccinated cohorts were stratified by the vaccine product received, among vaccinated persons without a previous COVID-19 diagnosis, the highest incidences were observed among persons receiving the Janssen (Johnson & Johnson), followed by Pfizer-BioNTech, then Moderna vaccines (Supplementary Figure 4, https://stacks.cdc.gov/view/cdc/113253). No pattern by product was observed among vaccinated persons with a previous COVID-19 diagnosis.

TABLE 2. (*Continued*) Hazard ratios for incident laboratory-confirmed COVID-19 cases — New York and California and hospitalizations* — California, May 30–November 20, 2021

State and date range	Hazard ratio (95% CI)†				
	Unvaccinated, no previous COVID-19 diagnosis versus			Vaccinated, no previous COVID-19 diagnosis versus	
	Vaccinated, no previous COVID-19 diagnosis	Unvaccinated, previous COVID-19 diagnosis	Vaccinated, previous COVID-19 diagnosis	Unvaccinated, previous COVID-19 diagnosis	Vaccinated, previous COVID-19 diagnosis
Hospitalizations, California					
May 30–Jun 12	29.8 (23.5–36.1)	3.7 (2.5–5.0)	7.2 (4.2–10.1)	0.1 (0.1–0.2)	0.2 (0.1–0.3)
Jun 13–26	28.7 (23.4–34.0)	7.0 (4.3–9.7)	8.1 (5.0–11.3)	0.2 (0.1–0.3)	0.3 (0.2–0.4)
Jun 27–10	30.1 (26.1–34.0)	16.4 (10.0–22.8)	16.0 (10.0–22.1)	0.5 (0.3–0.8)	0.5 (0.3–0.7)
Jul 11–24	25.8 (23.7–28.0)	45.0 (27.6–62.4)	41.5 (25.2–57.8)	1.7 (1.1–2.4)	1.6 (1.0–2.2)
Jul 25–Aug 7	28.8 (27.1–30.6)	41.7 (29.2–54.1)	72.9 (44.4–101.4)	1.4 (1.0–1.9)	2.5 (1.5–3.5)
Aug 8–21	29.7 (28.0–31.4)	49.0 (35.0–62.9)	64.0 (43.0–85.1)	1.6 (1.2–2.1)	2.2 (1.4–2.9)
Aug 22–Sep 4	29.1 (27.4–30.8)	62.4 (41.4–83.3)	63.9 (42.2–85.5)	2.1 (1.4–2.9)	2.2 (1.4–2.9)
Sep 5–18	26.3 (24.6–28.1)	74.4 (40.9–107.9)	96.4 (48.3–144.4)	2.8 (1.5–4.1)	3.7 (1.8–5.5)
Sep 19–Oct 2	25.0 (23.1–26.9)	61.9 (34.5–89.3)	99.4 (43.8–155.0)	2.5 (1.4–3.6)	4.0 (1.7–6.2)
Oct 3–16	20.8 (19.2–22.4)	56.3 (28.3–84.3)	58.5 (30.2–86.8)	2.7 (1.4–4.1)	2.8 (1.4–4.2)
Oct 17–30	21.5 (19.9–23.0)	56.5 (31.5–81.5)	92.1 (39.1–145.1)	2.6 (1.5–3.8)	4.3 (1.8–6.8)
Oct 31–Nov 13	22.7 (20.8–24.6)	70.7 (32.0–109.4)	86.1 (34.2–138.1)	3.1 (1.4–4.8)	3.8 (1.5–6.1)

* Life tables estimated at 7-day intervals for cases and 14-day intervals for hospitalizations.
† Hazard ratios and 95% CIs reported in this table differ numerically from presentation of corresponding results in the text as "X-fold lower" rates (i.e., a hazard rate of 1.0 is zero-fold lower). For example, a hazard ratio of 20.9 (95% CI = 18.9–22.9) for those "Unvaccinated–no previous COVID-19 diagnosis" versus "Vaccinated, no previous COVID-19 diagnosis" is equivalent to a 19.9-fold lower (95% CI = 17.9–21.9) rate for those "Vaccinated, no previous COVID-19 diagnosis" relative to those "Unvaccinated, no previous COVID-19 diagnosis."

FIGURE. Incident laboratory-confirmed COVID-19–associated hospitalizations among immunologic cohorts defined by vaccination and previous diagnosis histories — California, May 30–November 13, 2021*,†



* The SARS-CoV-2 Delta variant exceeded 50% of sequences in U.S. Department of Health and Human Services Region 9 (containing California) during the week of June 26. https://covid.cdc.gov/covid-data-tracker/#variant-proportions
† Estimated hazard rate is laboratory-confirmed COVID-19-associated hospitalizations per 100,000 person-days visualized at midpoint of each reporting interval.

Summary

What is already known about this topic?

Data are limited regarding the risks for SARS-CoV-2 infection and hospitalization after COVID-19 vaccination and previous infection.

What is added by this report?

During May–November 2021, case and hospitalization rates were highest among persons who were unvaccinated without a previous diagnosis. Before Delta became the predominant variant in June, case rates were higher among persons who survived a previous infection than persons who were vaccinated alone. By early October, persons who survived a previous infection had lower case rates than persons who were vaccinated alone.

What are the implications for public health practice?

Although the epidemiology of COVID-19 might change as new variants emerge, vaccination remains the safest strategy for averting future SARS-CoV-2 infections, hospitalizations, long-term sequelae, and death. Primary vaccination, additional doses, and booster doses are recommended for all eligible persons. Additional future recommendations for vaccine doses might be warranted as the virus and immunity levels change.

Discussion

This analysis integrated laboratory testing, hospitalization surveillance, and immunization registry data in two large states during May–November 2021, before widespread circulation of the SARS-CoV-2 Omicron variant and before most persons had received additional or booster COVID-19 vaccine doses to protect against waning immunity. Rate estimates from the analysis describe different experiences stratified by COVID-19 vaccination status and previous COVID-19 diagnosis and during times when different SARS-CoV-2 variants predominated. Case rates were initially lowest among vaccinated persons without a previous COVID-19 diagnosis; however, after emergence of the Delta variant and over the course of time, incidence increased sharply in this group, but only slightly among both vaccinated and unvaccinated persons with previously diagnosed COVID-19 (*6*). Across the entire study period, persons with vaccine- and infection-derived immunity had much lower rates of hospitalization compared with those in unvaccinated persons. These results suggest that vaccination protects against COVID-19 and related hospitalization and that surviving a previous infection protects against a reinfection. Importantly, infection-derived protection was greater after the highly transmissible Delta variant became predominant, coinciding with early declining of vaccine-induced immunity in many persons (*5*). Similar data accounting for booster doses and as new variants, including Omicron, circulate will need to be assessed.

The understanding and epidemiology of COVID-19 has shifted substantially over time with the emergence and circulation of new SARS-CoV-2 variants, introduction of vaccines, and changing immunity as a result. Similar to the early period of this study, two previous U.S. studies found more protection from vaccination than from previous infection during periods before Delta predominance (*3*,*7*). As was observed in the present study after July, recent international studies have also demonstrated increased protection in persons with previous infection, with or without vaccination, relative to vaccination alone[†††, §§§] (*4*). This might be due to differential stimulation of the immune response by either exposure type.[¶¶¶] Whereas French and Israeli population-based studies noted waning protection from previous infection, this was not apparent in the results from this or other large U.K. and U.S. studies[****] (*4*,*8*). Further studies are needed to establish duration of protection from previous infection by variant type, severity, and symptomatology, including for the Omicron variant.

The findings in this report are subject to at least seven limitations. First, analyses were not stratified by time since vaccine receipt, but only by time since previous diagnosis, although earlier studies have examined waning of vaccine-induced immunity (Supplementary Figure 3, https://stacks.cdc.gov/view/cdc/113253) (*2*). Second, persons with undiagnosed infection are misclassified as having no previous COVID-19 diagnosis; however, this misclassification likely results in a conservative bias (i.e., the magnitude of difference in rates would be even larger if misclassified persons were not included among unvaccinated persons without a previous COVID-19 diagnosis). California seroprevalence data during this period indicate that the ratio of actual (presumptive) infections to diagnosed cases among adults was 2.6 (95% CI = 2.2–2.9).[††††] Further, California only included NAAT results, whereas New York included both NAAT and antigen test results. However, antigen testing made up a smaller percentage of overall testing volume reported in California (7% of cases) compared with New York (25% of cases) during the study period. Neither state included self-tests, which are not easily reportable to public health. State-specific hazard ratios were generally comparable, although differences in rates among unvaccinated persons with a previous COVID-19 diagnosis were noteworthy. Third, potential exists for bias related to unmeasured confounding (e.g., behavioral or geographic differences in exposure risk) and uncertainty in the population size of the unvaccinated group without a previous COVID-19 diagnosis. Persons might be more or less likely to receive testing based on previous diagnosis or vaccination status; however, different trajectories between vaccinated persons with and without a previous COVID-19 diagnosis, and similar findings for cases and hospitalizations, suggest that these biases were minimal. Fourth, this analysis did not include information on the severity of

[†††] https://www.medrxiv.org/content/10.1101/2021.09.12.21263461v1
[§§§] https://www.medrxiv.org/content/10.1101/2021.11.29.21267006v1
[¶¶¶] https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/vaccine-induced-immunity.html#anchor_1635540449320
[****] https://www.medrxiv.org/content/10.1101/2021.12.04.21267114v1
[††††] https://www.medrxiv.org/content/10.1101/2021.12.09.21267565v1

initial infection and does not account for the full range of morbidity and mortality represented by the groups with previous infections. Fifth, this analysis did not ascertain receipt of additional or booster COVID-19 vaccine doses and was conducted before many persons were eligible or had received additional or booster vaccine doses, which have been shown to confer additional protection.[§§§§] Sixth, some estimates lacked precision because of sample size limitations. Finally, this analysis was conducted before the emergence of the Omicron variant, for which vaccine or infection-derived immunity might be diminished.[¶¶¶¶] This study offers a surveillance data framework to help evaluate both infections in vaccinated persons and reinfections as new variants continue to emerge.

Vaccination protected against COVID-19 and related hospitalization, and surviving a previous infection protected against a reinfection and related hospitalization during periods of predominantly Alpha and Delta variant transmission, before the emergence of Omicron; evidence suggests decreased protection from both vaccine- and infection-induced immunity against Omicron infections, although additional protection with widespread receipt of booster COVID-19 vaccine doses is expected. Initial infection among unvaccinated persons increases risk for serious illness, hospitalization, long-term sequelae, and death; by November 30, 2021, approximately 130,781 residents of California and New York had died from COVID-19. Thus, vaccination remains the safest and primary strategy to prevent SARS-CoV-2 infections, associated complications, and onward transmission. Primary COVID-19 vaccination, additional doses, and booster doses are recommended by CDC's Advisory Committee on Immunization Practices to ensure that all eligible persons are up to date with COVID-19 vaccination, which provides the most robust protection against initial infection, severe illness, hospitalization, long-term sequelae, and death.[*****] Additional recommendations for vaccine doses might be warranted in the future as the virus and immunity levels change.

[§§§§] https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status
[¶¶¶¶] https://www.medrxiv.org/content/10.1101/2021.12.30.21268565v1; https://www.medrxiv.org/content/10.1101/2022.01.07.22268919v1
[*****] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

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COVID-19 Incidence and Death Rates Among Unvaccinated and Fully Vaccinated Adults with and Without Booster Doses During Periods of Delta and Omicron Variant Emergence — 25 U.S. Jurisdictions, April 4–December 25, 2021

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Previous reports of COVID-19 case, hospitalization, and death rates by vaccination status† indicate that vaccine protection against infection, as well as serious COVID-19 illness for some groups, declined with the emergence of the B.1.617.2 (Delta) variant of SARS-CoV-2, the virus that causes COVID-19, and waning of vaccine-induced immunity (*1*–*4*). During August–November 2021, CDC recommended§ additional primary COVID-19 vaccine doses among immunocompromised persons and booster doses among persons aged ≥18 years (*5*). The SARS-CoV-2 B.1.1.529 (Omicron) variant emerged in the United States during December 2021 (*6*) and by December 25 accounted for 72% of sequenced lineages (*7*). To assess the impact of full vaccination with additional and booster doses (booster doses),¶ case and death rates and incidence rate ratios (IRRs) were estimated among unvaccinated and fully vaccinated adults by receipt of booster doses during pre-Delta (April–May 2021), Delta emergence (June 2021), Delta predominance (July–November 2021), and Omicron emergence (December 2021) periods in the United States. During 2021, averaged weekly, age-standardized case IRRs among unvaccinated persons compared with fully vaccinated persons decreased from 13.9 pre-Delta to 8.7 as Delta emerged, and to 5.1 during the period of Delta predominance. During October–November, unvaccinated persons had 13.9 and 53.2 times the risks for infection and COVID-19–associated death, respectively, compared with fully vaccinated persons who received booster doses, and 4.0 and 12.7 times the risks

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† A COVID-19 case in a fully vaccinated person occurred when SARS-CoV-2 RNA or antigen was detected in a respiratory specimen collected ≥14 days after completing the primary series of a COVID-19 vaccine with Food and Drug Administration (FDA) approval or emergency use authorization. The COVID-19 case definition, including criteria to distinguish a new case from an existing case, is per the July 2021 update to the national standardized surveillance case definition and national notification for 2019 novel coronavirus disease (COVID-19) (21-ID-01) (https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2021/). Fully vaccinated persons were those with a completed primary series of 2 doses of the Pfizer-BioNTech or Moderna mRNA vaccine or a single dose of the Janssen vaccine (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html). A COVID-19 case in an unvaccinated person occurred when the person did not receive any FDA-authorized COVID-19 vaccine doses before the specimen collection date. Cases were excluded in partially vaccinated persons who received at least one FDA-authorized or approved vaccine dose but did not complete a primary series ≥14 days before collection of a respiratory specimen with SARS-CoV-2 RNA or antigen detected. Ascertaining vaccination status for COVID-19 patients through active linkage of case surveillance and immunization information systems typically assumes that cases among persons who are unmatched to the registry are unvaccinated. This analysis represents the combined impact of the Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines, which had different clinical efficacies against confirmed infection. Information on different FDA-authorized and approved COVID-19 vaccine products, including clinical efficacy, is available online. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html

§ On August 13, 2021, CDC recommended an additional Pfizer-BioNTech or Moderna primary series dose for persons moderately or severely immunocompromised (https://www.cdc.gov/media/releases/2021/s0813-additional-mRNA-mrna-dose.html). On September 24, 2021, CDC recommended a Pfizer-BioNTech booster dose for certain Pfizer-BioNTech primary series recipients, including all adults aged ≥65 years and persons aged ≥18 years in certain populations and high risk occupational and institutional settings (https://www.cdc.gov/media/releases/2021/p0924-booster-recommendations-.html). On October 21, 2021, CDC recommended a booster dose for adults aged ≥18 years who had received the Janssen vaccine and for Pfizer-BioNTech or Moderna primary series vaccine recipients, including all adults aged ≥65 years and persons aged ≥18 years in certain populations and high risk occupational and institutional settings (https://www.cdc.gov/media/releases/2021/p1021-covid-booster.html). On November 19, 2021, and November 29, 2021, CDC expanded recommendations for booster doses to include all adults aged ≥18 years (https://www.cdc.gov/media/releases/2021/s1119-booster-shots.html, https://www.cdc.gov/media/releases/2021/s1129-booster-recommendations.html).

¶ A COVID-19 case in a fully vaccinated person with a booster dose occurred when a person had SARS-CoV-2 RNA or antigen detected on a respiratory specimen collected ≥14 days after receipt of at least 1 additional or booster dose of any COVID-19 vaccine on or after August 13, 2021 (this definition does not distinguish between vaccine recipients who are immunocompromised and are receiving an additional dose versus those who are not immunocompromised and receiving a booster dose).

compared with fully vaccinated persons without booster doses. When the Omicron variant emerged during December 2021, case IRRs decreased to 4.9 for fully vaccinated persons with booster doses and 2.8 for those without booster doses, relative to October–November 2021. The highest impact of booster doses against infection and death compared with full vaccination without booster doses was recorded among persons aged 50–64 and ≥65 years. Eligible persons should stay up to date with COVID-19 vaccinations.

Weekly COVID-19 cases (April 4–December 25, 2021) and associated deaths (April 4–December 4, 2021) by vaccination status, including additional and booster doses starting October 3, were reported from 25 state and local health departments that routinely link case surveillance to vaccination data from immunization registries; 2- and 5-week reporting lag times for cases and deaths, respectively, allowed for more complete reporting, data linkage, and mortality ascertainment. Standardized definitions were used for COVID-19 cases in fully vaccinated or unvaccinated persons, COVID-19 cases in fully vaccinated persons with booster doses, and COVID-19–associated deaths,** with specimen collection dates used as time points. Partially vaccinated persons were excluded; reinfections occurring after >90 days were counted as new cases, per current guidance. Analysis periods were determined based on variant proportion estimates in the United States.†† Age-specific vaccine administration data were used for incidence rate denominators; numbers of unvaccinated persons were estimated by subtracting the numbers of fully and partially vaccinated persons from 2019 U.S. intercensal population estimates.§§ A continuity correction assumed at ≥5% of each age group and jurisdiction would always be unvaccinated (i.e., fully vaccinated coverage ≤95%). Average weekly incidences were calculated by age group (18–49, 50–64, and ≥65 years), vaccination status, and primary series vaccine product (Ad.26.COV2.S [Janssen {Johnson & Johnson}], BNT162b2 [Pfizer-BioNTech], and mRNA-1273 [Moderna]) during each period; rates overall and by vaccine product were age-standardized using the 2000 U.S. Census standard population.¶¶ IRRs were calculated by dividing incidence among unvaccinated persons by incidence among fully vaccinated persons (overall and by receipt of booster doses); after detrending the underlying linear changes in incidence, 95% CIs were calculated based on the remaining variation in observed weekly rates (*8*,*9*). To interpret IRR changes, age-standardized crude vaccine effectiveness (VE) was estimated as (1 – [incidence in vaccinated / incidence in unvaccinated]). SAS (version 9.4; SAS Institute) and R (version 4.1.0; R Foundation) were used to conduct all analyses. This activity was conducted consistent with applicable federal law and CDC policy.***

During April 4–December 25, 2021, a total of 6,812,040 COVID-19 cases among unvaccinated persons and 2,866,517 cases among fully vaccinated persons were reported among persons aged ≥18 years in 25 U.S. jurisdictions; 94,640 and 22,567 COVID-19–associated deaths among unvaccinated and fully vaccinated persons, respectively, were reported by December 4 (Table 1). Average weekly, age-standardized rates of cases and deaths (events per 100,000 population) were higher during periods of Delta predominance and Omicron emergence than during pre-Delta and Delta emergence periods and were consistently higher in all periods among unvaccinated persons (range = 64.0–725.6 [cases] and 1.5–11.4 [deaths]) than among fully vaccinated persons (range = 7.4–230.9 and 0.1–0.7).

The age-standardized IRR for cases in unvaccinated versus fully vaccinated persons was 13.9 during April–May and progressively declined to 8.7 during June, 5.1 during July–November, and 3.1 during December, coinciding with the periods of Delta emergence, Delta predominance, and Omicron emergence, respectively. This decline suggests a change in crude VE for infection from 93% during April–May, to 89% during June, 80% during July–November, and to 68% during December. Age-standardized IRRs for deaths among unvaccinated versus fully vaccinated persons were relatively stable; crude VE for deaths was 95% during April–May, 94% during June, and 94% during July–November.

Rates of COVID-19 cases were lowest among fully vaccinated persons with a booster dose, compared with fully vaccinated persons without a booster dose, and much lower than rates among unvaccinated persons during October–November (25.0, 87.7, and 347.8 per 100,000 population, respectively) and December 2021 (148.6, 254.8, and 725.6 per 100,000 population, respectively) (Table 2). Similar trends

** A COVID-19–associated death occurred in a person with a documented COVID-19 diagnosis who died, and whose report local health authorities reviewed (e.g., using vital records, public health investigation, or other data sources) to make that determination. Per national guidance, this group should include persons whose death certificate lists COVID-19 disease or SARS-CoV-2 as an underlying cause of death or as a significant condition contributing to death (https://cdn.ymaws.com/www.cste.org/resource/resmgr/pdfs/pdfs2/20211222_interim-guidance.pdf). Rates of COVID-19 deaths by vaccination status are reported based on when the patient was tested for COVID-19, not the date the patient died.

†† National weighted estimates of the proportions of infections attributed to SARS-CoV-2 variants by week are based on analyses of whole-genome sequencing results submitted to or performed by CDC (https://covid.cdc.gov/covid-data-tracker/#variant-proportions). Analysis periods were categorized as April 4–May 29, 2021 (pre-Delta: 0.1%–7% proportion range), May 30–July 3, 2021 (Delta emergence: 14%–69%), July 4–November 27, 2021 (Delta predominance: 81%–99%), and November 28–December 25, 2021, (Omicron emergence: 1%–72%). Other lineages in the analysis period before the Delta transition included Alpha (>50%), Gamma, Epsilon, Iota, Mu, and other lineages.

§§ https://www.census.gov/programs-surveys/popest/data/tables.2019.html

¶¶ https://www.cdc.gov/nchs/data/statnt/statnt20.pdf

*** 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.0 Sect.552a; 44 U.S.C. Sect. 3501 et seq.

were noted for differences in the mortality rates among these three groups (0.1, 0.6, and 7.8 per 100,000 population, respectively) during October–November. Age-standardized case IRRs among unvaccinated persons compared with fully vaccinated persons with a booster dose declined from 13.9 during October–November to 4.9 during December, representing potential decreases in crude VE for infection from 93% to 80%, respectively. Comparing unvaccinated persons with fully vaccinated persons without a booster dose, age-standardized case IRRs during October–November and December were 4.0 and 2.8 respectively, representing decreases in VE from 75% to 64%. During October–November, age-standardized IRRs for deaths among unvaccinated persons were 53.2 compared with those in fully vaccinated persons with a booster dose and 12.7 compared with persons without a booster dose; these results represented crude VE against death of 98% and 92%, respectively. Protection improved among persons who received a booster dose compared with not receiving a booster, regardless of primary series vaccine product type. Booster doses provided the largest gains in protection among persons aged ≥65 years followed by persons aged 50–64 years when compared with those aged 18–49 years.

Peaks in age-standardized case and death rates occurred during August (>95% of infections attributed to the Delta variant); case rates also peaked during the 2 weeks ending December 18 and 25 (39% and 72% infections attributed to the Omicron variant, respectively) (Figure). IRRs during the pre-Delta period and period of Delta predominance periods were relatively stable, followed by declines corresponding to transitions in variant prevalence (Supplementary Figure, https://stacks.cdc.gov/view/cdc/113543). Differences in case rates between fully vaccinated persons with and without a booster dose decreased over time; however, more protection was afforded from booster doses, even during Omicron emergence.

TABLE 1. Average weekly age-standardized incidence of COVID-19 cases (April 4–December 25, 2021) and associated deaths (April 4–December 4, 2021) and incidence rate ratios* for unvaccinated and fully vaccinated persons,† by period§ — 25 U.S. jurisdictions,¶ April–December 2021

Event/Variant emergence/ Predominance period§	Unvaccinated persons		Fully vaccinated persons		
	Total no.	Average weekly incidence*	Total no.	Average weekly incidence*	Average weekly IRR (95% CI)**
COVID-19 cases					
Pre-Delta (April–May 2021)	**1,006,686**	163.8	**48,111**	11.8	13.9 (12.4–15.5)
Delta emergence (June 2021)	**196,988**	64.0	**30,317**	7.4	8.7 (6.1–12.4)
Delta predominance (July–November 2021)	**4,546,682**	460.1	**1,862,090**	90.9	5.1 (4.3–6.0)
Omicron emergence (December 2021)	**1,061,684**	725.6	**925,999**	230.9	3.1 (1.7–5.8)
Total	**6,812,040**	—	**2,866,517**	—	—
COVID-19–associated deaths					
Pre-Delta (April–May 2021)	**11,047**	2.7	**1,016**	0.1	21.9 (17.8–26.8)
Delta emergence (June 2021)	**3,107**	1.5	**556**	0.1	16.4 (13.2–20.4)
Delta predominance (July–November 2021)	**78,256**	11.4	**20,313**	0.7	16.3 (13.8–19.3)
Omicron emergence (first week in December 2021)††	**2,230**	9.7	**682**	0.5	NC
Total	**94,640**	—	**22,567**	—	—

Abbreviations: FDA = Food and Drug Administration; IRR = incidence rate ratio; NC = not calculated for the single reported week of deaths in December 2021.

* Events per 100,000 population. Average weekly incidences and rate ratios are provided by age group, primary series vaccine type, and overall; overall and vaccine-specific rates were standardized by age, according to the enumerated 2000 U.S. Census age distribution. IRRs were calculated by dividing incidence among unvaccinated persons by incidence among fully vaccinated persons overall.

† A COVID-19 case in a fully vaccinated person occurred when SARS-CoV-2 RNA or antigen was detected in a respiratory specimen collected ≥14 days after completing the primary series of a COVID-19 vaccine with FDA approval or emergency use authorization. A COVID-19 case in an unvaccinated person occurred when the person did not receive any FDA-authorized COVID-19 vaccine doses before the specimen collection date. Excluded were partially vaccinated persons who had received at least one FDA-authorized or approved vaccine dose but did not complete a primary series ≥14 days before collection of a specimen with SARS-CoV-2 RNA or antigen detected. This analysis represents the combined impact of BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Ad.26.COV2.S (Janssen [Johnson & Johnson]) COVID-19 vaccines, which had different clinical efficacies against confirmed infection; fully vaccinated persons also include those persons who received additional primary doses and booster doses starting in mid-August. A COVID-19–associated death occurred in a person with a documented COVID-19 diagnosis who died, and whose report local health authorities reviewed (e.g., using vital records, public health investigation, or other data sources) to make that determination. Per national guidance, this should include persons whose death certificate lists COVID-19 disease or SARS-CoV-2 as an underlying cause of death or as a significant condition contributing to death. Rates of COVID-19 deaths by vaccination status are reported based on when the patient was tested for COVID-19, not the date they died.

§ Four analysis periods were designated based on the threshold week when the weighted proportions of lineages from whole-genome sequencing results submitted to or performed by CDC: pre-Delta (April 4–May 29, 2021: 0.1%–7% proportion range), Delta emergence (May 30–July 3, 2021: 14%–69%), Delta predominance (July 4–November 27, 2021: 81%–99%), and Omicron emergence (November 28–December 25, 2021: 1%–72%).

¶ Alabama, Arkansas, California, Colorado, District of Columbia, Florida, Georgia, Idaho, Indiana, Kansas, Louisiana, Massachusetts, Michigan, Minnesota, Nebraska, New Jersey, New Mexico, New York, New York City (New York), Rhode Island, Seattle/King County (Washington), Tennessee, Texas, Utah, and Wisconsin.

** 95% CIs were calculated after detrending underlying linear changes in weekly incidence rates using piecewise linear regression. Each CI represents the remaining variation in observed weekly incidence rates and resulting incidence rate ratios. The number of observations informing each CI reflects the number of weeks per period: April–May (7), June (5), July–November (21), and December (4).

†† For deaths, a single week (November 28–December 4, 2021) of data was reported during the December 2021 period of Omicron emergence, but the proportion of Omicron variant during that first week was approximately 1%.

Discussion

COVID-19 vaccines reduced risks for SARS-CoV-2 infection and COVID-19–associated death during periods of Delta variant predominance and infection risk during Omicron variant emergence. Because of reporting lags, the influence of the Omicron variant on COVID-19–associated deaths by vaccination status in December could not be evaluated. Substantial case rate increases were recorded among unvaccinated and vaccinated persons when Omicron became the predominant variant in December, resulting in decreased IRRs and declining crude VE estimates (*7*). IRRs and VE were higher among persons who were fully vaccinated and had received a booster dose than among fully vaccinated persons who had not received a booster dose for cases and deaths during the period of Delta predominance and for cases during the period of Omicron emergence in December. The added benefits of booster doses were especially prominent among persons aged 50–64 and ≥65 years.

The findings in this report are subject to at least five limitations. First, booster doses could not be distinguished from additional primary doses administered to immunocompromised persons, which could result in reduced IRRs because of lower VE in this population. Second, this ecological study lacked multivariable adjustments, and causality could not be determined. Possible differences in testing, infection-derived immunity, waning of vaccine-derived immunity, or prevention behaviors by age and vaccination status might partly explain differences in rates between groups; trends are likely affected by temporal changes in testing or reporting. Third, national variant prevalence estimates

TABLE 2. Average weekly incidence* of cases and deaths and incidence rate ratios† for unvaccinated compared with fully vaccinated persons§ with and without booster doses,¶ by age, vaccine type, and period†† — 25 U.S. jurisdictions§§ October 3–December 25, 2021**

	COVID-19 vaccination status							
	Unvaccinated		Fully vaccinated (no booster dose)			Fully vaccinated (with booster dose)		
Event/Time/ Characteristic	Total no.	Average weekly incidence*	Total no.	Average weekly incidence*	Average weekly IRR (95% CI)¶¶	Total no.	Average weekly incidence*	Average weekly IRR (95% CI)¶¶
COVID-19 cases								
October–November								
Overall (age-standardized)	**1,108,298**	347.8	**650,820**	87.7	4.0 (3.6–4.4)	**19,954**	25.0	13.9 (12.2–15.9)
Age group, yrs								
18–49	**760,042**	330.3	**343,602**	89.9	3.6 (3.2–4.3)	**6,265**	27.4	12.0 (10.0–14.5)
50–64	**225,290**	355.3	**174,071**	86.5	4.1 (3.5–4.8)	**4,911**	23.2	15.3 (12.8–18.3)
≥65	**122,966**	403.6	**133,147**	80.7	5.0 (4.4–5.6)	**8,778**	18.1	22.3 (19.0–26.1)
Vaccine product								
Moderna	**NR**	NR	**219,623**	75.0	4.6 (4.2–5.1)	**4,911**	20.0	17.4 (14.5–21.1)
Pfizer-BioNTech	**NR**	NR	**358,933**	93.9	3.7 (3.4–4.1)	**14,292**	27.1	12.9 (11.4–14.5)
Janssen (Johnson & Johnson)	**NR**	NR	**71,897**	107.5	3.2 (2.9–3.6)	**745**	26.0	13.4 (10.6–16.9)
December								
Overall (age-standardized)	**1,061,684**	725.6	**800,940**	254.8	2.8 (1.6–5.2)	**125,059**	148.6	4.9 (2.7–8.9)
Age group, yrs								
18–49	**781,969**	745.6	**547,733**	302.5	2.5 (1.1–5.6)	**65,710**	191.7	3.9 (1.8–8.6)
50–64	**189,789**	680.8	**176,639**	208.8	3.3 (1.7–6.4)	**31,753**	97.0	7.0 (3.0–16.3)
≥65	**89,926**	704.9	**76,568**	133.5	5.3 (3.3–8.4)	**27,596**	50.4	14.0 (6.4–30.6)
Vaccine								
Moderna	**NR**	NR	**251,784**	221.6	3.3 (1.7–6.1)	**39,813**	130.4	5.6 (3.1–10.1)
Pfizer-BioNTech	**NR**	NR	**473,115**	280.1	2.6 (1.4–4.7)	**77,844**	162.6	4.5 (2.4–8.3)
Janssen (Johnson & Johnson)	**NR**	NR	**75,903**	246.6	2.9 (1.8–4.8)	**7,377**	132.7	5.5 (3.2–9.4)
COVID-19–associated deaths								
October–November								
Overall (age-standardized)	**16,527**	7.8	**5,493**	0.6	12.7 (11.6–13.8)	**285**	0.1	53.2 (37.5–75.4)
Age, yrs								
18–49	**2,094**	1.0	**124**	0.0	27.6 (16.3–46.5)	**5**	0.0	NC***
50–64	**4,427**	7.3	**659**	0.4	21.0 (18.9–23.2)	**38**	0.2	38.0 (17.1–78.9)
≥65	**10,006**	33.4	**4,710**	3.1	11.0 (9.8–12.2)	**242**	0.5	61.4 (47.8–78.9)
Vaccine								
Moderna	**NR**	NR	**2,379**	0.5	14.6 (13.0–16.4)	**96**	0.2	40.1 (19.5–82.5)
Pfizer–BioNTech	**NR**	NR	**2,550**	0.7	11.8 (10.8–12.9)	**187**	0.1	58.7 (36.8–93.9)
Janssen (Johnson & Johnson)	**NR**	NR	**560**	1.0	7.9 (6.0–10.3)	**2**	0.1	NC***

See table footnotes on the next page.

TABLE 2. (*Continued*) Average weekly incidence* of cases and deaths and incidence rate ratios† for unvaccinated compared with fully vaccinated persons§ with and without booster doses,¶ by age, vaccine type, and period†† — 25 U.S. jurisdictions§§ October 3–December 25, 2021**

Abbreviations: FDA = Food and Drug Administration; IRR = incidence rate ratio; NC = not calculated for categories with counts <20; NR = not relevant for individual vaccine types because the comparison being made is to overall unvaccinated counts and age-adjusted rates.

* Events per 100,000 population.

† Average weekly incidence rates and rate ratios are provided by age group, primary series vaccine type, and overall; overall and vaccine-specific rates were standardized by age, according to the enumerated 2000 U.S. Census age distribution. IRRs were calculated by dividing incidence among unvaccinated persons by incidence among fully vaccinated persons (overall and by receipt of booster doses).

§ A COVID-19 case in a fully vaccinated person occurred when SARS-CoV-2 RNA or antigen was detected in a respiratory specimen collected ≥14 days after completing the primary series of a COVID-19 vaccine with FDA approval or emergency use authorization. A COVID-19 case in an unvaccinated person occurred when the person did not receive any FDA-authorized COVID-19 vaccine doses before the specimen collection date. Excluded were partially vaccinated persons who had received at least one FDA-authorized or approved vaccine dose but did not complete a primary series ≥14 days before collection of a specimen with SARS-CoV-2 RNA or antigen detected. This analysis represents the combined impact of BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Ad.26.COV2.S (Janssen [Johnson & Johnson]) COVID-19 vaccines, which had different clinical efficacies against confirmed infection; fully vaccinated persons also include those persons who received additional primary doses and booster doses starting in mid-August. A COVID-19–associated death occurred in a person with a documented COVID-19 diagnosis who died, and whose report local health authorities reviewed (e.g., using vital records, public health investigation, or other data sources) to make that determination. Per national guidance, this should include persons whose death certificate lists COVID-19 disease or SARS-CoV-2 as an underlying cause of death or as a significant condition contributing to death. Rates of COVID-19 deaths by vaccination status are reported based on when the patient was tested for COVID-19, not the date they died.

¶ A COVID-19 case in a fully vaccinated person with a booster dose occurred when a person had SARS-CoV-2 RNA or antigen detected on a respiratory specimen collected ≥14 days after receipt of at least one additional or booster dose of any COVID-19 vaccine on or after August 13, 2021. On August 13, 2021, CDC recommended an additional Pfizer-BioNTech or Moderna primary series dose for persons with moderately or severely immunocompromise. On September 24, 2021, CDC recommended a Pfizer-BioNTech booster dose for certain Pfizer-BioNTech primary series recipients, including all adults aged ≥65 years and persons aged ≥18 years in certain populations and high risk occupational and institutional settings. On October 21, 2021, CDC recommended a booster dose for adults aged ≥18 years who received the Janssen vaccine and for Pfizer-BioNTech or Moderna primary series recipients, including all adults aged ≥65 years and persons aged ≥18 years in certain populations and high risk occupational and institutional settings. On November 19, 2021, and November 29, 2021, CDC expanded recommendations for booster doses to include all adults aged ≥18 years.

** Reporting is by primary series vaccine type rather than additional or booster dose vaccine type. The booster dose vaccine type may be different than the primary series vaccine type. For primary mRNA vaccination series, the vaccine product of the second dose was used to determine primary series product type. If the Janssen vaccine was either the first dose or the second dose, the series type was called Janssen. The overall fully vaccinated group includes FDA-approved vaccinations of unknown vaccine type.

†† Analysis periods for this table were designated based on robust reporting of cases among persons with booster doses from October 2021 and the threshold week when the weighted proportions of lineages from whole-genome sequencing results submitted to or performed by CDC: October 3–November 27, 2021 (Delta predominance: 99%), and November 28–December 25, 2021 (Omicron emergence: 1%–72%).

§§ Alabama, Arkansas, California, Colorado, District of Columbia, Florida, Georgia, Idaho, Indiana, Kansas, Louisiana, Massachusetts, Michigan, Minnesota, Nebraska, New Jersey, New Mexico, New York, New York City (New York), Rhode Island, Seattle/King County (Washington), Tennessee, Texas, Utah, and Wisconsin.

¶¶ 95% CIs were calculated after detrending underlying linear changes in weekly incidence rates using piecewise linear regression. Each CI represents the remaining variation in observed weekly incidence rates and resulting incidence rate ratios. The number of observations informing each CI reflects the number of weeks per period: October–November (7), and December (4).

*** https://www.cdc.gov/nchs/data/statnt/statnt24.pdf

were used, but prevalence differed by jurisdiction over time. Fourth, variable data linkage completeness might have resulted in misclassifications (e.g., booster doses not being linked to primary series) that could influence IRR estimates (*5*). Finally, these data represent 62% of the overall U.S. population, and therefore might not be generalizable.

Early analysis of surveillance data provided crude signals of VE that were consistent with other studies reporting decreased VE against Omicron infection compared with Delta and increased protection from booster doses compared with a primary series of COVID-19 vaccination alone††† (*10*). Ongoing analyses will help monitor the impact of the Omicron variant and other emerging variants on VE against COVID-19 cases and associated deaths; rates by vaccination status will be updated monthly on CDC's COVID Data Tracker website (*3*). All eligible persons should stay up to date with primary series, additional, and booster doses of COVID-19 vaccine.

Summary

What is already known about this topic?

Although COVID-19 vaccine effectiveness decreased with emergence of the Delta variant and waning of vaccine-induced immunity, protection against hospitalization and death has remained high.

What is added by this report?

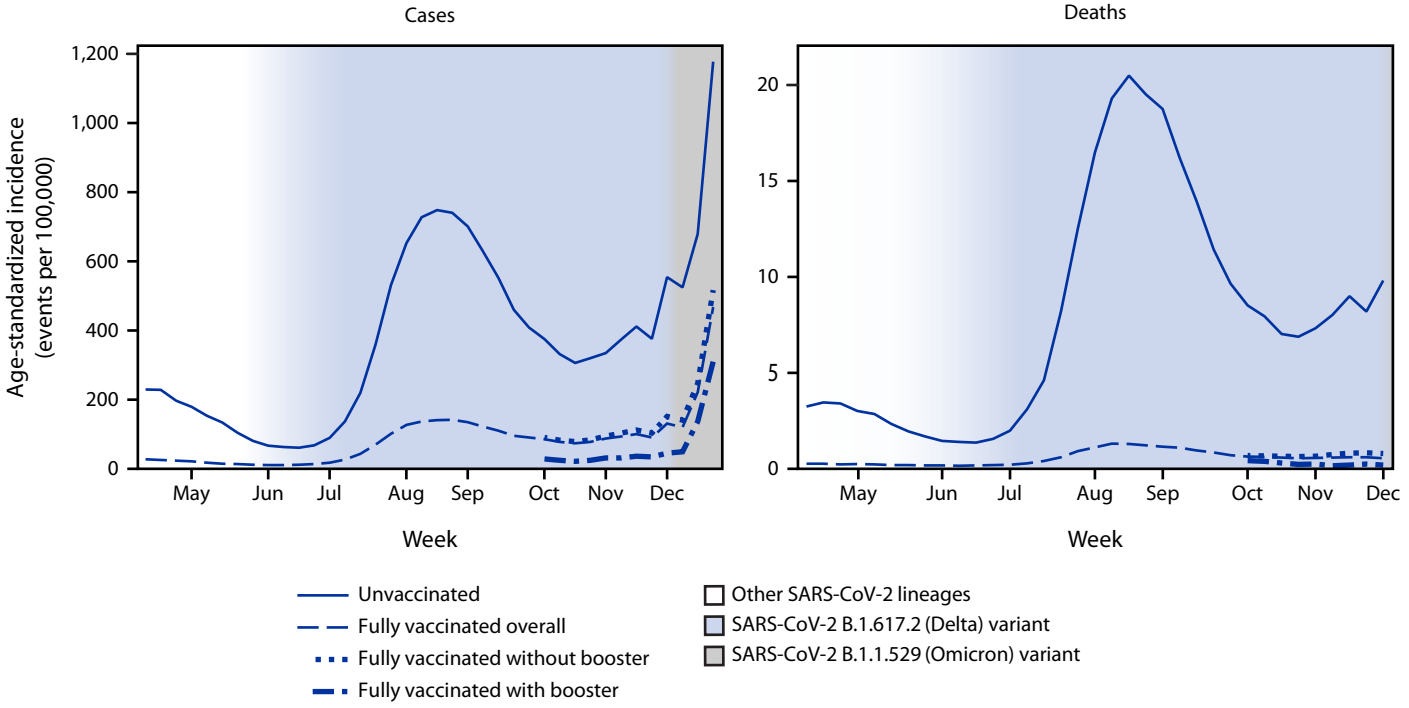
In 25 U.S. jurisdictions, decreases in case incidence rate ratios for unvaccinated versus fully vaccinated persons with and without booster vaccine doses were observed when the Omicron variant emerged in December 2021. Protection against infection and death during the Delta-predominant period and against infection during Omicron emergence were higher among booster vaccine dose recipients, especially among persons aged 50–64 and ≥65 years.

What are the implications for public health practice?

COVID-19 vaccination protected against SARS-CoV-2 infection, even as the Omicron variant became predominant. All eligible persons should stay up to date with COVID-19 vaccination.

††† https://www.medrxiv.org/content/10.1101/2022.01.07.22268919v1.full; https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4011905

FIGURE. Weekly trends in age-standardized incidence of COVID-19 cases (April 4–December 25, 2021) and deaths (April 4–December 4, 2021) for unvaccinated compared with fully vaccinated persons,* overall and by receipt of booster doses† and national weighted estimates of variant proportions§ — 25 U.S. jurisdictions¶



Abbreviation: FDA = Food and Drug Administration.

* A COVID-19 case in a fully vaccinated person occurred when SARS-CoV-2 RNA or antigen was detected in a respiratory specimen collected ≥14 days after completing the primary series of a COVID-19 vaccine with FDA approval or emergency use authorization. A COVID-19 case in an unvaccinated person occurred when the person did not receive any FDA–authorized COVID-19 vaccine doses before the specimen collection date. Excluded were partially vaccinated persons who had received at least one FDA–authorized or approved vaccine dose but did not complete a primary series ≥14 days before collection of a specimen with SARS-CoV-2 RNA or antigen detected. This analysis represents the combined impact of the BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Ad.26.COV2.S (Janssen [Johnson & Johnson]) COVID-19 vaccines, which had different clinical efficacies against confirmed infection. A COVID-19–associated death occurred in a person with a documented COVID-19 diagnosis who died, and whose report local health authorities reviewed (e.g., using vital records, public health investigation, or other data sources) to make that determination. Per national guidance, this should include persons whose death certificate lists COVID-19 disease or SARS-CoV-2 as an underlying cause of death or as a significant condition contributing to death. Rates of COVID-19 deaths by vaccination status are reported based on when the patient was tested for COVID-19, not the date they died.

† A COVID-19 case in a fully vaccinated person with a booster dose occurred when a person had SARS-CoV-2 RNA or antigen detected on a respiratory specimen collected ≥14 days after receipt of at least one additional or booster dose of any COVID-19 vaccine on or after August 13, 2021. On August 13, 2021, CDC recommended an additional Pfizer-BioNTech or Moderna primary series dose for persons with moderately or severely immunocompromise. On September 24, 2021, CDC recommended a Pfizer-BioNTech booster dose for certain Pfizer-BioNTech primary series recipients, including all adults aged ≥65 years and persons aged ≥18 years in certain populations and high risk occupational and institutional settings. On October 21, 2021, CDC recommended a booster dose for adults aged ≥18 years who received the Janssen vaccine and for Pfizer-BioNTech or Moderna primary series recipients, including all adults aged ≥65 years and persons aged ≥18 years in certain populations and high risk occupational and institutional settings. On November 19, 2021, and November 29, 2021, CDC expanded recommendations for booster doses to include all adults aged ≥18 years.

§ National weighted estimates of the proportions of infections attributed to SARS-CoV-2 variants by week are based on whole-genome sequencing results submitted to or performed by CDC (https://covid.cdc.gov/covid-data-tracker/#variant-proportions). Other lineages prior to the Delta transition included Alpha (>50%), Gamma, Epsilon, Iota, Mu, and other lineages.

¶ Alabama, Arkansas, California, Colorado, District of Columbia, Florida, Georgia, Idaho, Indiana, Kansas, Louisiana, Massachusetts, Michigan, Minnesota, Nebraska, New Jersey, New Mexico, New York, New York City (New York), Rhode Island, Seattle/King County (Washington), Tennessee, Texas, Utah, and Wisconsin.

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Effectiveness of a Third Dose of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022

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Estimates of COVID-19 mRNA vaccine effectiveness (VE) have declined in recent months (*1*,*2*) because of waning vaccine induced immunity over time,* possible increased immune evasion by SARS-CoV-2 variants (*3*), or a combination of these and other factors. CDC recommends that all persons aged ≥12 years receive a third dose (booster) of an mRNA vaccine ≥5 months after receipt of the second mRNA vaccine dose and that immunocompromised individuals receive a third primary dose.† A third dose of BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine increases neutralizing antibody levels (*4*), and three recent studies from Israel have shown improved effectiveness of a third dose in preventing COVID-19 associated with infections with the SARS-CoV-2 B.1.617.2 (Delta) variant (*5*–*7*). Yet, data are limited on the real-world effectiveness of third doses of COVID-19 mRNA vaccine in the United States, especially since the SARS-CoV-2 B.1.1.529 (Omicron) variant became predominant in mid-December 2021. The VISION Network§ examined VE by analyzing 222,772 encounters from 383 emergency departments (EDs) and urgent care (UC) clinics and 87,904 hospitalizations from 259 hospitals among adults aged ≥18 years across 10 states from August 26, 2021¶ to January 5, 2022. Analyses were stratified by the period before and after the Omicron variant became the predominant strain (>50% of sequenced viruses) at each study site. During the period of Delta predominance across study sites in the United States (August–mid-December 2021), VE against laboratory-confirmed COVID-19–associated ED and UC encounters was 86% 14–179 days after dose 2, 76% ≥180 days after dose 2, and 94% ≥14 days after dose 3. Estimates of VE for the same intervals after vaccination during Omicron variant predominance were 52%, 38%, and 82%, respectively. During the period of Delta variant predominance, VE against laboratory-confirmed COVID-19–associated hospitalizations was 90% 14–179 days after dose 2, 81% ≥180 days after dose 2, and 94% ≥14 days after dose 3. During Omicron variant predominance, VE estimates for the same intervals after vaccination were 81%, 57%, and 90%, respectively. The highest estimates of VE against COVID-19–associated ED and UC encounters or hospitalizations during both Delta- and Omicron-predominant periods were among adults who received a third dose of mRNA vaccine. All unvaccinated persons should get vaccinated as soon as possible. All adults who have received mRNA vaccines during their primary COVID-19 vaccination series should receive a third dose when eligible, and eligible persons should stay up to date with COVID-19 vaccinations.

VISION Network methods have been previously published (*1*,*8*,*9*). In brief, eligible medical encounters were defined as those among adults aged ≥18 years with a COVID-19–like illness diagnosis** who had received molecular testing (primarily reverse transcription–polymerase chain reaction assay) for

* https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3961378

† CDC initially recommended a third dose of mRNA vaccine for all adults 6 months after receipt of the second mRNA COVID-19 vaccine dose. On January 4, 2022, CDC amended the interval to 5 months after receipt of the second dose for recipients of the BNT162b2 (Pfizer-BioNTech) vaccine. On January 7, 2022, CDC amended the interval to 5 months for recipients of the mRNA-1273 (Moderna) vaccine. CDC recommends the Pfizer-BioNTech booster at 5 months, and an additional primary dose for certain immunocompromised persons aged ≥5 years (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html). CDC recommends the Moderna booster at 5 months. https://www.cdc.gov/media/releases/2022/s0107-moderna-booster.html

§ Funded by CDC, the VISION Network includes Baylor Scott & White Health (Texas), 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).

¶ The study period at Baylor Scott & White Health began on September 11, 2021.

** 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*.

SARS-CoV-2 (the virus that causes COVID-19) within 14 days before or 72 hours after the admission or encounter. The study period began on August 26, 2021, 14 days after the first U.S. recommendation for a third mRNA COVID-19 primary vaccine dose in immunocompromised persons.[††] The date when the Omicron variant became predominant was determined for each study site based on state and national surveillance data. Recipients of Ad26.COV2 (Janssen [Johnson & Johnson]), 1 or >3 doses of an mRNA vaccine, and those for whom 1–13 days had elapsed since receipt of any dose were excluded. Immunocompromised patients were identified by previously published diagnosis codes[§§] (*9*).

VE was estimated using a test-negative design, comparing the odds of a positive SARS-CoV-2 test result between vaccinated and unvaccinated patients using multivariable logistic regression models, as previously described[¶¶] (*1*,*8*,*9*). Vaccination status was categorized based on the number of vaccine doses received and number of days from vaccination to the index medical encounter date.[***] Potential effect modification by vaccine product, age group (aged 18–64 years versus ≥65 years), and immunocompromised status (for whom a third dose is the last dose in their primary series) was assessed by adding interaction terms for vaccination by these covariates to the regression model. Effect modification was only examined for medical encounters during the Delta period of predominance, given relatively sparse data during the Omicron period. A statistically significant difference was indicated by a p-value <0.01 for an interaction term, 95% CI that did not overlap, or standardized mean or proportion differences ≥0.2 indicating nonnegligible difference in distributions of vaccination or infection status (*9*). This study was reviewed and approved by the institutional review boards at participating sites or under a reliance agreement with the Westat, Inc. institutional review board.[†††]

Among 222,772 eligible ED or UC encounters, 204,745 (92%) and 18,027 (8%) occurred during the Delta- and Omicron-predominant periods, respectively (Table 1). A higher percentage of Hispanic, non-Hispanic Black, persons of unknown race/ethnicity, and adults aged <65 years were unvaccinated or had not received a third COVID-19 vaccine dose; adults aged <65 years were more likely to have received a positive SARS-CoV-2 test result. Among persons with COVID-19–like illness seeking care at ED or UC facilities who had received the second dose <180 days earlier and ≥180 days earlier, the median interval since receipt of the second dose was 137 days and 223 days, respectively. Among those who had received the third dose ≥14 days earlier, the median interval since receipt of that dose was 44 days. During the Delta-predominant period, VE against laboratory-confirmed COVID-19–associated ED and UC encounters was significantly lower among patients who had received the second vaccine dose ≥180 days earlier (76%) than it was among those who had received the dose 14–179 days earlier (86%); VE among those who had received the third mRNA COVID-19 vaccine dose was 94% (Table 2). VE after receipt of the third dose was lower among the 4% of patients with immunocompromised status (74%; 95% CI = 65%–80%) versus those without (95%; 95% CI = 94%–95%) (p<0.001) (CDC, unpublished data, 2022). During the period of Omicron predominance, the pattern was similar, although all VE estimates were significantly lower. VE against COVID-19–associated ED and UC encounters 14–179 days after receipt of dose 2 was 52%, and at ≥180 days after dose 2 was 38%. VE after receipt of 3 vaccine doses among all adults was 82%.

Among 87,904 eligible hospitalizations, 86,327 (98%) and 1,577 (2%) occurred during the Delta- and Omicron-predominant periods, respectively (Table 3). Hospitalized adults aged <65 years or who were Hispanic, non-Hispanic Black, unknown race/ethnicity, or who did not have chronic nonrespiratory medical conditions were more likely to be unvaccinated or, if vaccinated, less likely to have received a third vaccine dose. In addition, adults aged <65 years and those without chronic nonrespiratory conditions were more likely to have received a positive SARS-CoV-2 test result. Among persons hospitalized with COVID-19–like illness who had received the second mRNA COVID-19 vaccine dose <180 days earlier and ≥180 days earlier, the median interval since receipt of the second dose was 144 days and 222 days, respectively. Among those who had received the third dose ≥14 days earlier, the median interval since receipt of that dose was 41 days. During Delta predominance, VE against laboratory-confirmed COVID-19–associated hospitalization was 90% among persons who had received the second dose 14–179 days earlier, 81% among those who had received it ≥180 days earlier, and

[††] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised

[§§] 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.

[¶¶] With a test-negative design, vaccine performance is assessed by comparing the odds of antecedent vaccination among case-patients with acute laboratory-confirmed COVID-19 and control-patients without acute COVID-19. This odds ratio was adjusted for age, geographic region, calendar time (days from August 26, 2021), and local virus circulation in the community and weighted for inverse propensity to be vaccinated or unvaccinated (calculated separately for each vaccine exposure group).

[***] 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.

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

94% among persons who had received a third dose ≥14 days earlier (Table 2). VE after receipt of the third dose was lower among the 21% of patients with immunocompromised status (83%; 95% CI = 78%–87%) versus among those without (96%; 95% CI = 95%–97%) (p = 0.001) (CDC, unpublished data, 2022). During Omicron predominance, VE against COVID-19–associated hospitalization was 81% among 2-dose recipients who had received the second dose 14–179 days earlier, 57% among those who had received it ≥180 days earlier, and 90% at ≥14 days after receipt of a third dose. VE estimates for patients who received dose 2 ≥180 days earlier significantly declined during Omicron predominance compared with estimates during Delta predominance.

Discussion

In a multistate analysis of 222,772 ED and UC encounters and 87,904 hospitalizations among adults with COVID-19–like illness during August 26, 2021–January 5, 2022, estimates of VE against laboratory-confirmed COVID-19 declined during the Omicron-predominant period compared with VE during the Delta-predominant period. During both periods, VE was significantly lower among patients who received their second mRNA COVID-19 vaccine dose ≥180 days before the medical

TABLE 1. Characteristics of emergency department and urgent care encounters among adults with COVID-19–like illness,* by mRNA COVID-19 vaccination status† and SARS-CoV-2 test result — 10 states, August 2021–January 2022§

Characteristic	Total no. (column %)	mRNA COVID-19 vaccination status, no. (row %)				SMD**	Positive SARS-CoV-2 test result, no. (row %)	SMD**
		Unvaccinated	2 doses (<180 days earlier)	2 doses (≥180 days earlier)	3 doses¶			
All ED/UC events	**222,772 (100)**	**105,083 (47)**	**41,375 (19)**	**57,915 (26)**	**18,399 (8)**	—	**53,719 (24)**	—
Variant predominance period								
B.1.617.2 (Delta)	**204,745 (92)**	98,087 (48)	39,629 (19)	52,506 (26)	14,523 (7)	0.10	47,173 (23)	0.18
B.1.1.529 (Omicron)	**18,027 (8)**	6,996 (39)	1,746 (10)	5,409 (30)	3,876 (22)		6,546 (36)	
Sites								
Baylor Scott & White Health	**34,143 (15)**	19,787 (58)	4,476 (13)	8,179 (24)	1,701 (5)	0.57	7,854 (23)	0.27
Columbia University	**4,608 (2)**	2,500 (54)	921 (20)	1,031 (22)	156 (3)		803 (17)	
HealthPartners	**5,347 (2)**	1,536 (29)	1,832 (34)	1,689 (32)	290 (5)		873 (16)	
Intermountain Healthcare	**62,740 (28)**	28,837 (46)	12,210 (19)	16,615 (26)	5,078 (8)		15,593 (25)	
Kaiser Permanente Northern California	**42,919 (19)**	11,027 (26)	9,418 (22)	15,341 (36)	7,133 (17)		8,564 (20)	
Kaiser Permanente Northwest	**15,813 (7)**	6,028 (38)	4,168 (26)	4,075 (26)	1,542 (10)		2,958 (19)	
Regenstrief Institute	**35,233 (16)**	23,110 (66)	4,986 (14)	5,895 (17)	1,242 (4)		12,174 (35)	
University of Colorado	**21,969 (10)**	12,258 (56)	3,364 (15)	5,090 (23)	1,257 (6)		4,900 (22)	
Age group, yrs								
18–49	**117,000 (53)**	68,469 (59)	23,268 (20)	21,492 (18)	3,771 (3)	0.56	29,494 (25)	0.20
50–64	**45,056 (20)**	19,966 (44)	9,671 (21)	12,118 (27)	3,301 (7)		12,435 (28)	
65–74	**28,858 (13)**	9,187 (32)	4,625 (16)	10,140 (35)	4,906 (17)		6,492 (22)	
75–84	**21,175 (10)**	5,103 (24)	2,699 (13)	9,033 (43)	4,340 (20)		3,723 (18)	
≥85	**10,683 (5)**	2,358 (22)	1,112 (10)	5,132 (48)	2,081 (19)		1,575 (15)	
Sex								
Male††	**90,372 (41)**	44,951 (50)	15,490 (17)	22,252 (25)	7,679 (8)	0.09	24,497 (27)	–0.13
Female	**132,400 (59)**	60,132 (45)	25,885 (20)	35,663 (27)	10,720 (8)		29,222 (22)	
Race/Ethnicity								
White, non-Hispanic	**140,967 (63)**	63,794 (45)	25,190 (18)	38,952 (28)	13,031 (9)	0.25	33,054 (23)	0.10
Black, non-Hispanic	**21,020 (9)**	12,294 (58)	3,864 (18)	3,853 (18)	1,009 (5)		5,241 (25)	
Hispanic	**34,791 (16)**	17,426 (50)	7,147 (21)	8,130 (23)	2,088 (6)		8,765 (25)	
Other, non-Hispanic§§	**13,469 (6)**	4,266 (32)	3,041 (23)	4425 (33)	1,737 (13)		2,790 (21)	
Unknown	**12,525 (6)**	7,303 (58)	2,133 (17)	2,555 (20)	534 (4)		3,869 (31)	
Chronic respiratory condition¶¶								
Yes††	**42,449 (19)**	19,111 (45)	7,333 (17)	11,875 (28)	4,130 (10)	–0.04	8,110 (19)	0.14
No	**180,323 (81)**	85,972 (48)	34,042 (19)	46,040 (26)	14,269 (8)		45,609 (25)	
Chronic nonrespiratory condition* **								
Yes††	**59,223 (27)**	25,123 (42)	10,380 (18)	17,654 (30)	6,066 (10)	–0.12	12,232 (21)	0.12
No	**163,549 (73)**	79,960 (49)	30,995 (19)	40,261 (25)	12,333 (8)		41,487 (25)	
Vaccine product								
Moderna	**44,287 (38)**	—	14,227 (32)	24,489 (55)	5,571 (13)	—	4,464 (10)	0.14
Pfizer-BioNTech	**72,307 (61)**	—	27,045 (37)	33,344 (46)	11,918 (16)		9,244 (13)	
Combination of mRNA products	**1,095 (1)**	—	103 (9)	82 (7)	910 (83)		71 (6)	

See table footnotes on the next page.

TABLE 1. (*Continued*) Characteristics of emergency department and urgent care encounters among adults with COVID-19–like illness,* by mRNA COVID-19 vaccination status† and SARS-CoV-2 test result — 10 states, August 2021–January 2022§

Abbreviations: ED = emergency department; SMD = standardized mean or proportion difference; UC = urgent care.

* 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 the encounter date were included. Recipients of Janssen, 1 or >3 doses of an mRNA vaccine, and those for whom 1–13 days had elapsed since receipt of any dose were excluded.

† Vaccination was defined as having received the listed number of doses of an mRNA-based COVID-19 vaccine ≥14 days before the medical event 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 medical event or the admission date if testing only occurred after the admission.

§ Partners contributing data on medical events and estimated dates of Omicron predominance were in California (December 21), Colorado (December 19), Indiana (December 26), Minnesota and Wisconsin (December 25), New York (December 18), Oregon (December 24), Texas (December 16), Utah (December 24), and Washington (December 24). The study period began in September 2021 for partners located in Texas.

¶ The "3 doses" category includes persons who have received a third dose in their primary series or have received an additional dose following their 2-dose primary series; this includes the reduced-dosage Moderna booster.

** An absolute standardized mean or proportion difference ≥0.20 indicates a nonnegligible difference in variable distributions between medical events for vaccinated versus unvaccinated patients; single SMD calculated by averaging pairwise comparisons of each vaccinated category versus unvaccinated and separately for patients with SARS-CoV-2–positive versus SARS-CoV-2–negative test results. For example, the age SMD calculation comparing unvaccinated versus different vaccinated categories was generated by averaging the pairwise SMD calculations for unvaccinated and 2 doses (<180 days earlier), unvaccinated and 2 doses (≥180 days earlier), and unvaccinated and 3 doses.

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

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

¶¶ 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 the *International Classification of Diseases, Ninth Revision* and the *International Classification of Diseases, Tenth Revision.*

*** Chronic nonrespiratory condition was defined as the presence of discharge code for heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes type I or II, other diabetes, metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, immunosuppression, organ transplant, cancer, dementia, neurologic disorder, musculoskeletal disorder, or Down syndrome using diagnosis codes from the *International Classification of Diseases, Ninth Revision* and the *International Classification of Diseases, Tenth Revision*.

encounters compared with those vaccinated more recently. VE increased following a third dose and was highly effective during both the Delta- and Omicron-predominant periods at preventing COVID-19–associated ED and UC encounters (94% and 82%, respectively) and preventing COVID-19–associated hospitalizations (94% and 90%, respectively).

Estimates of VE for 2 doses of an mRNA vaccine were higher against COVID-19–associated hospitalizations than against COVID-19–associated ED or UC encounters, especially during the Omicron period, which is consistent with possible vaccine attenuation of severity of COVID-19 disease but was not observed in this network previously (*1*,*8*). This study also found that immunocompromised adults had lower third dose VE against COVID-19–associated ED and UC encounters and hospitalization, which is consistent with trends observed for VE following a second dose (*9*) and is consistent with recommendations for a booster dose for this group 5 months after the additional primary dose.§§§

The findings in this report are subject to at least seven limitations. First, VE estimates from this study do not include COVID-19-associated outpatient visits or non-medically attended COVID-19. Second, the median interval from receipt of dose 3 to medical encounters was 41–44 days; thus, the observed performance of dose 3 is limited to a relatively short period after vaccination. Third, the reasons for the decline in VE during the Omicron period are unclear; however, the drop in VE during a short period suggests increased immune evasion by the variant. Fourth, limited data during the Omicron period reduced the precision of the VE estimates and precluded tests for effect modification. Fifth, despite adjustments to balance the differences between unvaccinated and vaccinated adults, unmeasured and residual confounding (e.g., wearing a mask and close contact with persons with COVID-19) in this observational study might have biased the estimates. Sixth, genetic characterization of patients' viruses was not available, and analyses therefore relied on dates when the Omicron variant became predominant based on surveillance data. The Omicron period of predominance in this study likely includes medical encounters associated with the Delta variant. If VE is reduced against medical care associated with Omicron variant, this study likely overestimated VE. Finally, although the facilities in this study serve heterogeneous populations in 10 states, the findings might not be generalizable to the U.S. population.

These findings underscore the importance of receiving a third dose of mRNA COVID-19 vaccine to prevent both moderately severe and severe COVID-19, especially while the Omicron variant is the predominant circulating variant and when the effectiveness of 2 doses of mRNA vaccines is significantly reduced against this variant. All unvaccinated persons should get vaccinated as soon as possible. All adults who have received mRNA vaccines during their primary COVID-19 vaccination series should receive a third dose when eligible, and eligible persons should stay up to date with COVID-19 vaccinations.

§§§ CDC recommends that all immunocompromised persons receive a booster dose of either Pfizer-BioNTech or Moderna COVID-19 vaccines 5 months after completing their 3-dose primary series. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html

TABLE 2. mRNA COVID-19 vaccine effectiveness* against laboratory-confirmed COVID-19–associated† emergency department and urgent care encounters and hospitalizations among adults aged ≥18 years, by number and timing of vaccine doses§ and vaccine product received — VISION Network, 10 states, August 2021–January 2022¶

Encounter/Predominant variant period/Vaccination status	Total	SARS-CoV-2 positive test result, no. (%)	VE, %* (95% CI)
ED or UC encounters			
Delta predominant			
Unvaccinated (Ref)	**98,087**	36,542 (37.2)	—
Any mRNA vaccine			
2 doses (14–179 days earlier)	**39,629**	3,269 (8.2)	86 (85–87)
2 doses (≥180 days earlier)	**52,506**	6,893 (13.1)	76 (75–77)
3 doses	**14,523**	469 (3.2)	94 (93–94)
Omicron predominant			
Unvaccinated (Ref)	**6,996**	3,398 (48.6)	—
Any mRNA vaccine			
2 doses (14–179 days earlier)	**1,746**	591 (33.9)	52 (46–58)
2 doses (≥180 days earlier)	**5,409**	2,037 (37.7)	38 (32–43)
3 doses	**3,876**	520 (13.4)	82 (79–84)
Hospitalizations			
Delta predominant			
Unvaccinated (Ref)	**37,400**	14,272 (38.2)	—
Any mRNA vaccine			
2 doses (14–179 days earlier)	**14,645**	895 (6.1)	90 (89–90)
2 doses (≥180 days earlier)	**26,190**	2,563 (9.8)	81 (80–82)
3 doses	**8,092**	209 (2.6)	94 (93–95)
Omicron predominant			
Unvaccinated (Ref)	**460**	174 (37.8)	—
Any mRNA vaccine			
2 doses (14–179 days earlier)	**115**	14 (12.2)	81 (65–90)
2 doses (≥180 days earlier)	**488**	86 (17.6)	57 (39–70)
3 doses	**514**	24 (4.7)	90 (80–94)

Abbreviations: ED = emergency department; Ref = reference group; UC = urgent care; VE = vaccine effectiveness.

* VE was calculated as ([1−odds ratio] x 100%), estimated using a test-negative design, adjusted for age, geographic region, calendar time (days since August 26, 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 encounter) 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, and facility characteristics.

† 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 admission were included. Recipients of Janssen, 1 or >3 doses of an mRNA vaccine, and those for whom 1–13 days had elapsed since receipt of any dose were excluded.

§ Vaccination status was documented in electronic health records and immunization registries and was defined as having received the listed number of doses of an mRNA-based COVID-19 vaccine ≥14 days before the medical event index date. 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 the medical event or the admission date if testing only occurred after the admission. Three-dose recipients include persons who received a third dose in their primary series or received an additional (booster) dose after their 2-dose primary series; this includes the reduced-dosage Moderna booster.

¶ Partners contributing data on medical events and estimated dates of Omicron predominance were in California (December 21), Colorado (December 19), Indiana (December 26), Minnesota and Wisconsin (December 25), New York (December 18), Oregon (December 24), Texas (December 16), Utah (December 24), and Washington (December 24). The study period began in September 2021 for partners located in Texas.

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TABLE 3. Characteristics of hospitalizations with COVID-19–like illness,* by mRNA COVID-19 vaccination status† and SARS-CoV-2 test result — 10 states, August 2021–January 2022§

Characteristic	Total, no. (column %)	mRNA COVID-19 vaccination status, no. (row %)				SMD**	Positive SARS-CoV-2 test result, no. (row %)	SMD**
		Unvaccinated	2 doses (<180 days earlier)	2 doses (≥180 days earlier)	3 doses¶			
All hospitalizations	**87,904 (100)**	**37,860 (43)**	**14,760 (17)**	**26,678 (30)**	**8,606 (10)**	—	**18,237 (21)**	—
Variant predominance period								
B.1.617.2 (Delta)	**86,327 (98)**	37,400 (43)	14,645 (17)	26,190 (30)	8,092 (9)	0.08	17,939 (21)	−0.02
B.1.1.529 (Omicron)	**1,577 (2)**	460 (29)	115 (7)	488 (31)	514 (33)		298 (19)	
Sites								
Baylor Scott & White Health	**15,226 (17)**	7,730 (51)	2,180 (14)	4,372 (29)	944 (6)	0.56	2,462 (16)	0.51
Columbia University	**3,254 (4)**	1,372 (42)	696 (21)	975 (30)	211 (6)		331 (10)	
HealthPartners	**1,159 (1)**	265 (23)	374 (32)	450 (39)	70 (6)		133 (11)	
Intermountain Healthcare	**8435 (10)**	4283 (51)	1158 (14)	2201 (26)	793 (9)		3117 (37)	
Kaiser Permanente Northern California	**22,181 (25)**	4,891 (22)	4,691 (21)	8,591 (39)	4,008 (18)		2,716 (12)	
Kaiser Permanente Northwest	**3,879 (4)**	1,628 (42)	927 (24)	961 (25)	363 (9)		740 (19)	
Regenstrief Institute	**23,370 (27)**	12,641 (54)	3,134 (13)	6,274 (27)	1,321 (6)		6,686 (29)	
University of Colorado	**10,400 (12)**	5,050 (49)	1,600 (15)	2,854 (27)	896 (9)		2,052 (20)	
Age group, yrs								
18–49	**21,128 (24)**	13,609 (64)	3,980 (19)	2,780 (13)	759 (4)	0.63	5,523 (26)	0.31
50–64	**20,193 (23)**	10,204 (51)	4,407 (22)	4,407 (22)	1,175 (6)		5,132 (25)	
65–74	**19,798 (23)**	6,952 (35)	3,283 (17)	7,052 (36)	2,511 (13)		3,684 (19)	
75–84	**17,052 (19)**	4,647 (27)	2,122 (12)	7,609 (45)	2,674 (16)		2,626 (15)	
≥85	**9,733 (11)**	2,448 (25)	968 (10)	4,830 (50)	1,487 (15)		1,272 (13)	
Sex								
Male††	**39,602 (45)**	17,468 (44)	6,131 (15)	11,969 (30)	4,034 (10)	0.04	9,252 (23)	−0.14
Female	**48,302 (55)**	20,392 (42)	8,629 (18)	14,709 (30)	4,572 (9)		8,985 (19)	
Race/Ethnicity								
White, non-Hispanic	**56,669 (64)**	23,297 (41)	8,855 (16)	18,333 (32)	6,184 (11)	0.25	11,743 (21)	0.17
Black, non-Hispanic	**9,628 (11)**	5,026 (52)	1835 (19)	2,240 (23)	527 (5)		1,707 (18)	
Hispanic	**11,304 (13)**	5,337 (47)	2,171 (19)	2,955 (26)	841 (7)		2,585 (23)	
Other, non-Hispanic§§	**5,488 (6)**	1,524 (28)	1,232 (22)	1,940 (35)	792 (14)		808 (15)	
Unknown	**4,815 (5)**	2,676 (56)	667 (14)	1,210 (25)	262 (5)		1,394 (29)	

See table footnotes on the next page.

Summary

What is already known about this topic?

COVID-19 mRNA vaccine effectiveness (VE) in preventing COVID-19 might decline because of waning of vaccine-induced immunity or variant immune evasion.

What is added by this report?

VE was significantly higher among patients who received their second mRNA COVID-19 vaccine dose <180 days before medical encounters compared with those vaccinated ≥180 days earlier. During both Delta- and Omicron-predominant periods, receipt of a third vaccine dose was highly effective at preventing COVID-19–associated emergency department and urgent care encounters (94% and 82%, respectively) and preventing COVID-19–associated hospitalizations (94% and 90%, respectively).

What are the implications for public health practice?

All unvaccinated persons should start vaccination as soon as possible. All adults who have received mRNA vaccines during their primary COVID-19 vaccination series should receive a third dose when eligible, and eligible persons should stay up to date with COVID-19 vaccinations.

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TABLE 3. (Continued) Characteristics of hospitalizations with COVID-19–like illness,* by mRNA COVID-19 vaccination status† and SARS-CoV-2 test result — 10 states, August 2021–January 2022§

Characteristic	Total, no. (column %)	mRNA COVID-19 vaccination status, no. (row %)				SMD**	Positive SARS-CoV-2 test result, no. (row %)	SMD**
		Unvaccinated	2 doses (<180 days earlier)	2 doses (≥180 days earlier)	3 doses¶			
Chronic respiratory condition¶¶								
Yes††	**57,225 (65)**	24,037 (42)	9,549 (17)	17,693 (31)	5,946 (10)	–0.06	11,648 (20)	0.03
No	**30,679 (35)**	13,823 (45)	5,211 (17)	8,985 (29)	2,660 (9)		6,589 (21)	
Chronic nonrespiratory condition* **								
Yes††	**74,943 (85)**	29,810 (40)	12,787 (17)	24,270 (32)	8,076 (11)	–0.32	13,924 (19)	0.30
No	**12,961 (15)**	8,050 (62)	1,973 (15)	2,408 (19)	530 (4)		4,313 (33)	
Vaccine product								
Moderna	**20,236 (40)**	—	5,690 (28)	11,903 (59)	2,643 (13)	—	1,294 (6)	0.15
Pfizer-BioNTech	**29,418 (59)**	—	9,023 (31)	14,740 (50)	5,655 (19)		2,480 (8)	
Combination of mRNA products	**390 (1)**	—	47 (12)	35 (9)	308 (79)		17 (4)	

Abbreviations: ED = emergency department; SMD = standardized mean or proportion difference; UC = urgent care.

* 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 admission were included. Recipients of Janssen, 1 or >3 dose of an mRNA vaccine, and those for whom 1–13 days had elapsed since receipt of any dose were excluded.

† Vaccination was defined as having received the listed number of doses of an mRNA-based COVID-19 vaccine ≥14 days before the medical event 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 medical event or the admission date if testing only occurred after the admission.

§ Partners contributing data on medical events and estimated dates of Omicron predominance were in California (December 21), Colorado (December 19), Indiana (December 26), Minnesota and Wisconsin (December 25), New York (December 18), Oregon (December 24), Texas (December 16), Utah (December 24), and Washington (December 24). The study period began in September 2021 for partners located in Texas.

¶ The "3 doses" category includes persons who have received a third dose in their primary series or received an additional dose following their 2-dose primary series; this includes the reduced-dosage Moderna booster.

** An absolute standardized mean or proportion difference ≥0.20 indicates a nonnegligible difference in variable distributions between medical events for vaccinated versus unvaccinated patients. First, a single SMD was calculated by averaging pairwise comparisons of each vaccinated category versus unvaccinated, and then, a second SMD was calculated separately for SARS-CoV-2–positive versus SARS-CoV-2–negative patients. For example, the age SMD calculation comparing unvaccinated versus different vaccinated categories was generated by averaging the pairwise SMD calculations for unvaccinated and 2 doses (<180 days earlier), unvaccinated and 2 doses (≥180 days earlier), and unvaccinated and 3 doses.

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

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

¶¶ 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 the *International Classification of Diseases, Ninth Revision* and the *International Classification of Diseases, Tenth Revision*.

*** Chronic nonrespiratory condition was defined as the presence of discharge code for heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes type I or II, other diabetes, metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, immunosuppression, organ transplant, cancer, dementia, neurologic disorder, musculoskeletal disorder, or Down syndrome using diagnosis codes from the *International Classification of Diseases, Ninth Revision* and the *International Classification of Diseases, Tenth Revision*.

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Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods — United States, December 2020–January 2022

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The B.1.1.529 (Omicron) variant of SARS-CoV-2, the virus that causes COVID-19, was first clinically identified in the United States on December 1, 2021, and spread rapidly. By late December, it became the predominant strain, and by January 15, 2022, it represented 99.5% of sequenced specimens in the United States* (*1*). The Omicron variant has been shown to be more transmissible and less virulent than previously circulating variants (*2*,*3*). To better understand the severity of disease and health care utilization associated with the emergence of the Omicron variant in the United States, CDC examined data from three surveillance systems and a large health care database to assess multiple indicators across three high–COVID-19 transmission periods: December 1, 2020–February 28, 2021 (winter 2020–21); July 15–October 31, 2021 (SARS-CoV-2 B.1.617.2 [Delta] predominance); and December 19, 2021–January 15, 2022 (Omicron predominance). The highest daily 7-day moving average to date of cases (798,976 daily cases during January 9–15, 2022), emergency department (ED) visits (48,238), and admissions (21,586) were reported during the Omicron period, however, the highest daily 7-day moving average of deaths (1,854) was lower than during previous periods. During the Omicron period, a maximum of 20.6% of staffed inpatient beds were in use for COVID-19 patients, 3.4 and 7.2 percentage points higher than during the winter 2020–21 and Delta periods, respectively. However, intensive care unit (ICU) bed use did not increase to the same degree: 30.4% of staffed ICU beds were in use for COVID-19 patients during the Omicron period, 0.5 percentage points lower than during the winter 2020–21 period and 1.2 percentage points higher than during the Delta period. The ratio of peak ED visits to cases (event-to-case ratios) (87 per 1,000 cases), hospital admissions (27 per 1,000 cases), and deaths (nine per 1,000 cases [lagged by 3 weeks]) during the Omicron period were lower than those observed during the winter 2020–21 (92, 68, and 16 respectively) and Delta (167, 78, and 13, respectively) periods. Further, among hospitalized COVID-19 patients from 199 U.S. hospitals, the mean length of stay and percentages who were admitted to an ICU, received invasive mechanical ventilation (IMV), and died while in the hospital were lower during the Omicron period than during previous periods. COVID-19 disease severity appears to be lower during the Omicron period than during previous periods of high transmission, likely related to higher vaccination coverage,† which reduces disease severity (*4*), lower virulence of the Omicron variant (*3*,*5*,*6*), and infection-acquired immunity (*3*,*7*). Although disease severity appears lower with the Omicron variant, the high volume of ED visits and hospitalizations can strain local health care systems in the United States, and the average daily number of deaths remains substantial.§ This underscores the importance of national emergency preparedness, specifically, hospital surge capacity and the ability to adequately staff local health care systems. In addition, being up to date on vaccination and following other recommended prevention strategies are critical to preventing infections, severe illness, or death from COVID-19.

CDC used data from three surveillance systems to assess U.S. disease related to COVID-19 during December 1, 2020–January 15, 2022. COVID-19 aggregate cases and deaths reported to CDC by state and territorial health departments¶ were tabulated by report date.** ED visits with COVID-19 diagnosis codes were obtained from the National Syndromic

* Predominance defined as >50% of specimens sequenced. Proportion that was Omicron variant during the week ending December 18: 39.4%; December 25: 71.6%; January 1: 92.3%; January 8: 98.3%; and January 15: 99.5%. https://covid.cdc.gov/covid-data-tracker/#variant-proportions

† https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total (Accessed January 15, 2022).

§ https://covid.cdc.gov/covid-data-tracker/#trends_dailydeaths (Accessed January 15, 2022).

¶ CDC official counts of COVID-19 cases and deaths, released daily (https://covid.cdc.gov/covid-data-tracker), are aggregate counts from reporting jurisdictions. A COVID-19 case is defined by detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person with a confirmed or probable case of COVID-19 according to the Council of State and Territorial Epidemiologists' updated case definition. https://cdn.ymaws.com/www.cste.org/resource/resmgr/ps/ps2021/21-ID-01_COVID-19.pdf

** Date of report is used for consistency because most jurisdictions are not reporting case by onset or test date. The same applies to deaths, where there might be an even larger lag between date of death and date of report of death.

Surveillance Program (NSSP).[††] Hospital admissions and inpatient and ICU bed use among patients with laboratory-confirmed COVID-19 were obtained from the Unified Hospital Data Surveillance System.[§§] ED visits and hospital admissions were tabulated by admission date and stratified by the following age groups: 0–17, 18–49, and ≥50 years.

The maximum 7-day moving averages of the daily number of COVID-19 cases, ED visits, hospital admissions, and deaths during the Omicron period were compared with the peak 7-day moving averages for the winter 2020–21 and Delta periods. The maximum percentages of inpatient and ICU bed use overall and by COVID-19 patients were compared between periods. For each period analyzed, ratios of ED visits, hospital admissions, and deaths per 1,000 COVID-19 cases were calculated.[¶¶]

CDC used the BD Insights Research Database (BD), a U.S. health care facility database,[***] to assess hospitalized COVID-19 patients as a percentage of total hospital admissions: the percentage of hospitalized COVID-19 patients who were admitted to an ICU, received IMV, or died while in the hospital; and the mean and median length of hospital stay.[†††] Indicators were tabulated based on discharge date and stratified by age group: 0–17, 18–50, and >50 years.[§§§] Three-week windows were analyzed during each period to stabilize estimates.[¶¶¶] Statistical differences between the Omicron and winter 2020–21 and Delta periods were assessed using z-tests for proportions and t-tests for mean length of stay; statistical significance criterion was $p<0.05$.

Analyses were carried out in Python (version 3.8.6, Python Software Foundation) and Kotlin (version 1.4, Kotlin Foundation).[****] This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.[††††]

The daily 7-day moving average of COVID-19 cases, ED visits, and hospital admissions rapidly increased during the Omicron period (Figure). However, during the week ending January 15, 2022, ED visits appeared to be decreasing and the rapid increase in cases and hospital admissions appeared to be slowing. As of January 15, 2022, the maximum daily 7-day moving average number of cases (798,976), ED visits (48,238), admissions (21,586), and deaths (1,854) observed during the Omicron period reflects changes of 219%, 137%, 31%, and

[††] NSSP collects electronic health data, including ED visits with COVID-19 diagnoses, from a subset of hospitals in 49 states and the District of Columbia (71% of nonfederal EDs in the United States). ED visits for COVID-19 are defined as ED visits with any of the following: *International Classification of Diseases, Tenth Revision* codes U07.1 or J12.82 or Systematized Nomenclature of Medicine codes 840539006, 840544004, or 840533007. https://www.cdc.gov/nssp/overview.html

[§§] The U.S. Department of Health and Human Services (HHS) Unified Hospital Data Surveillance System includes data from all U.S. hospitals registered with the Centers for Medicare & Medicaid Services (CMS) as of June 1, 2020, and from hospitals not CMS–registered but reporting COVID-19 data through this system since July 1, 2020. Data, including counts of new hospital admissions of patients with confirmed COVID-19 by age group, are reported to HHS either directly from facilities or via a state health department submission; on January 11, 2022, 96% of hospitals reported data. This analysis includes children's, short-term acute care, long-term acute care, critical access, Veterans Administration, Defense Health Agency, and Indian Health Services hospitals and excludes psychiatric, rehabilitation, and religious nonmedical hospitals. Reporting guidelines are published in the HHS COVID-19 Guidance for Hospital Reporting and FAQs document. https://www.hhs.gov/sites/default/files/covid-19-faqs-hospitals-hospital-laboratory-acute-care-facility-data-reporting.pdf

[¶¶] Ratios of ED visits and hospital admissions per 1,000 COVID-19 cases were calculated as peak daily 7-day moving averages of ED visits or hospital admissions divided by the corresponding daily 7-day moving average of COVID-19 cases observed when peak ED visits and hospital admissions occurred. The ratio of deaths per 1,000 COVID-19 cases was calculated with a 3-week lag in cases from the date when peak daily 7-day moving averages of deaths occurred to account for the time between case ascertainment, occurrence of death, and reporting.

[***] BD is a large U.S. health care facility database that includes patient-level electronically captured laboratory results; pharmacy orders; and admission, discharge, and transfer data from 267 hospitals. CDC receives aggregate BD data via a surveillance dashboard that is updated every Tuesday with data for the previous week (Sunday through Saturday) (release date January 18, 2022; access date January 18, 2022). This analysis used data from 199 hospitals that reported data during all three periods; of these hospitals, 135 (68%) had information for IMV, and 148 (74%) had information on in-hospital deaths. Geographically, hospital distribution is uneven; hospitals are overrepresented in the South (53%) and Northeast (17%) U.S. Census regions and underrepresented in the West (9%) and Midwest (21%) regions. Monthly trends in disease severity indicators from BD and two other data sources are available on CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#hospitalizations-severity

[†††] Hospitalized COVID-19 patients were identified by the presence of a positive SARS-CoV-2 polymerase chain reaction or antigen test result during the 14 days before or 14 days after date of admission; 43% of all admissions did not have a SARS-CoV-2 test result available (January 2021–January 2022). To identify patients admitted to an ICU, care settings were classified using the CDC National Healthcare Safety Network classification and then further classified as ICU (critical care) or non-ICU (inpatient adult wards, specialty care areas, and step-down wards); https://academic.oup.com/ofid/article/5/10/ofy241/5104818. Because of lack of timely device data to identify ventilator use, the following surrogate definition for IMV use was used: a) the patient was started on intravenous/intravenous push (IV/IVP) sedation medications (propofol, lorazepam, midazolam, dexmedetomidine, or ketamine) or IV/IVP opioids (fentanyl, remifentanil, sufentanil, or hydromorphone) with a duration ≥24 hours, and b) at least two arterial blood gas results were collected at least 24 hours apart (on the first day of sedation medication and a subsequent result 24 hours later) (https://academic.oup.com/ofid/article/8/6/ofab232/6285220). In-hospital death was defined by a designation of death, mortality, or presence in morgue in the admission, discharge, and transfer data feeds. A validity check of this method had been previously performed by randomly selecting 50 mortality cases and evaluating encounter-level data for clinical signs of mortality (e.g., uncorrected severe metabolic acidosis determined by pH from arterial blood gases and uncorrected electrolyte changes incompatible with life). https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2778237

[§§§] Age groups for patients are preestablished on the BD surveillance dashboard and do not align exactly with older age grouping (i.e., aged <50 years versus ≥50 years) available in the surveillance data.

[¶¶¶] The 7-day daily average peak in the case surveillance data was used as the central day of the 3-week window for the winter 2020–21 (January 1–January 21, 2021) and Delta (August 22–September 11, 2021) periods; the most recent 3 weeks of available data were used for the Omicron period (December 26, 2021–January 15, 2022). Date ranges are based on date of hospital discharge.

[****] Surveillance data cleaning, processing, and calculation of peak rates were conducted using Python and Kotlin.

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

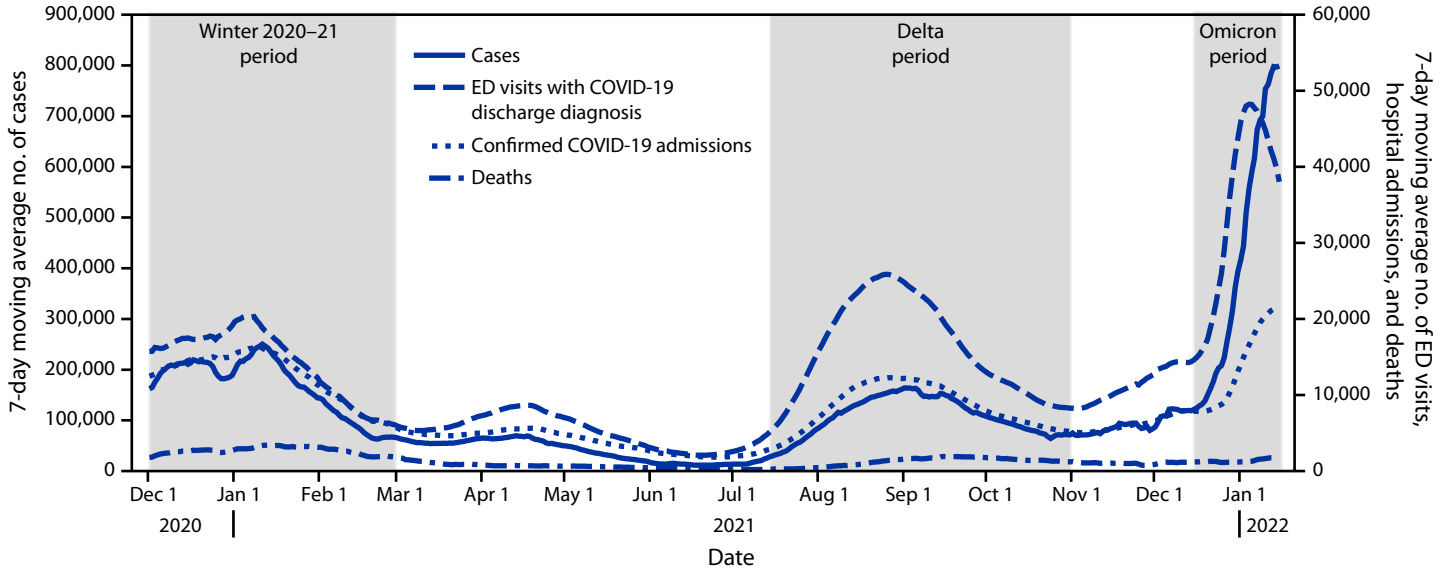
–46%, respectively, compared with those during the winter 2020–21 period, and 386%, 86%, 76%, and –4%, respectively, compared with those during the Delta period (Table 1). The largest relative differences in ED visits and admissions were observed among children and adolescents aged 0–17 years during the Omicron period; however, this age group represented only 14.5% of COVID-19 ED visits and 4.2% of COVID-19 admissions. During the Omicron period, a maximum of 20.6% of staffed inpatient beds were in use for COVID-19 patients, 3.4 and 7.2 percentage points higher than during the winter 2020–21 and Delta periods, respectively. However, ICU bed use did not increase to the same degree: 30.4% of staffed ICU beds were in use for COVID-19 patients during the Omicron period, 0.5 percentage points lower than during the winter 2020–21 period and 1.2 percentage points higher than during the Delta period. When comparing the indicators at their peaks during the Omicron period, event-to-case ratios for ED visits (87 visits per 1,000 cases), hospitalizations (27 hospitalizations per 1,000 cases), and deaths (nine deaths per 1,000 cases [lagged by 3 weeks]) were lower than those observed during the peak winter 2020–21 (92, 68, and 16, respectively) and Delta (167, 78, and 13, respectively) periods (Supplementary Figure, https://stacks.cdc.gov/view/cdc/113628).

In BD, hospitalized COVID-19 patients represented 12.0%, 9.4%, and 12.9% of all admissions during the winter 2020–21, Delta, and Omicron periods, respectively. Disease severity among hospitalized COVID-19 patients was associated with increasing age; IMV and in-hospital deaths were rare among patients aged 0–17 years, therefore, differences between periods were not assessed. The percentage of hospitalized COVID-19 patients admitted to an ICU during Omicron (13.0%) was 28.8% lower than during the winter 2020–21 (18.2%) and 25.9% lower than during Delta (17.5%) periods overall, and for all three age groups ($p<0.05$) (Table 2). The percentage of hospitalized COVID-19 patients who received IMV (3.5%) or died while in the hospital (7.1%) during Omicron was lower than during the winter 2020–21 (IMV = 7.5%; deaths = 12.9%) and Delta (IMV = 6.6%; deaths = 12.3%) periods overall, and for both adult age groups ($p<0.001$). Mean length of hospital stay during Omicron (5.5 days) was 31.0% lower than during the winter 2020–21 (8.0 days) and 26.8% lower than during Delta (7.6 days) periods overall, and for both adult age groups ($p<0.001$).

Discussion

Emergence of the Omicron variant in December 2021 led to a substantial increase in COVID-19 cases in the United States. Although the rapid rise in cases has resulted in the highest number of COVID-19–associated ED visits and hospital admissions since the beginning of the pandemic, straining the health care system, disease severity appears to be lower than compared with previous high disease-transmission periods. In addition to

FIGURE. Seven-day moving average number of COVID-19 cases, emergency department visits, hospital admissions, and deaths — United States,* December 1, 2020–January 15, 2022



Sources: CDC state-reported data (cases and deaths), Unified Hospital dataset (admissions), and National Syndromic Surveillance Program (ED visits with COVID-19 discharge diagnoses).
Abbreviation: ED = emergency department.
* COVID-19 hospital admissions include admissions for COVID-19 as well as patients who receive a positive SARS-CoV-2 test result after being admitted for other reasons. National Syndromic Surveillance Program represents approximately 70% of all U.S. ED visits.

TABLE 1. COVID-19 disease, hospital, and death indicators during the Omicron period compared with the winter 2020–21 and Delta periods* — United States, December 2020–January 2022†

	Winter 2020–21 period		Delta period		Omicron period		Comparison of Omicron with winter 2020–21 period		Comparison of Omicron with Delta period	
Indicator/ Age group, yrs	Peak value date range	Peak value (7-day moving average)	Peak value date range	Peak value (7-day moving average)	Date of maximum assessed value§	Maximum 7-day moving average	Number or percentage point difference¶	Relative % difference**	Number or percentage point difference¶	Relative % difference**
Disease (cases, ED visits)										
COVID-19 cases, N	Jan 4–11, 2021	250,335	Aug 25–Sep 1, 2021	164,249	Jan 15, 2022	798,976	548,641	219.2	634,727	386.4
COVID-19 ED visits, by age group, N (% of total)	Dec 29, 2020–Jan 5, 2021	20,372	Aug 19–26, 2021	25,873	Jan 4, 2022	48,238	27,866	136.8	22,365	86.4
0–17		901 (4.4)		3,177 (12.3)		6,990 (14.5)	6,089 (10.1)	676.1	3,813 (2.2)	120.0
18–49		6,872 (33.7)		11,853 (45.8)		23,372 (48.5)	16,500 (14.7)	240.1	11,519 (2.6)	97.2
≥50		12,406 (60.9)		10,546 (40.8)		17,471 (36.2)	5,066 (−24.7)	40.8	6,926 (−4.5)	65.7
Hospital (admissions)										
COVID-19 admissions, by age group, N (% of total)	Jan 2–9, 2021	16,497	Aug 20–27, 2021	12,285	Jan 15, 2022	21,586	5,089	30.8	9,301	75.7
0–17		207 (1.3)		319 (2.6)		914 (4.2)	707 (3.0)	341.9	595 (1.6)	186.5
18–49		2,761 (16.7)		3,559 (29.0)		5,218 (24.2)	2,457 (7.4)	89.0	1,659 (−4.8)	46.6
≥50		12,840 (77.8)		7,828 (63.7)		14,773 (68.4)	1,933 (−9.4)	15.1	6,945 (4.7)	88.7
Inpatient beds in use for COVID-19, N	Jan 4–11, 2021	125,100	Aug 28–Sep 4, 2021	94,503	Jan 15, 2022	142,687	17,587	14.1	48,184	51.0
Staffed beds in use for COVID-19, %		17.2		13.4		20.6	3.4	20.0	7.2	53.7
Staffed beds in use, %		74.1		76.8		79.2	5.1	6.9	2.4	3.1
ICU beds in use for COVID-19, N	Jan 9–16, 2021	27,958	Sep 6–13, 2021	24,774	Jan 15, 2022	24,776	−3,182	−11.4	2	0.0
Staffed ICU beds in use for COVID-19, %		30.9		29.2		30.4	−0.5	−1.7	1.2	4.2
Staffed ICU beds in use, %		78.2		79.6		82.2	4.0	5.1	2.6	3.2
Deaths										
COVID-19 deaths, N	Jan 6–13, 2021	3,422	Sep 9–15, 2021	1,924	Jan 15, 2022	1,854	−1,568	−45.8	−70	−3.6

Sources: CDC state-reported data (case and death totals), CDC case line-level data (cases by age), Unified Hospital data set (hospital admissions, inpatient, and ICU), and National Syndromic Surveillance Program (ED visits with COVID-19 discharge diagnoses).

Abbreviations: ED = emergency department; ICU = intensive care unit; N = no. of hospital admissions.

* COVID-19 hospital admissions include admissions for COVID-19 as well as patients who receive a positive test result for COVID-19 after being admitted for other reasons. National Syndromic Surveillance Program data are not inclusive of all ED visits, representing approximately 71% of all visits. The peak value and associated date are calculated independently for each indicator as the highest 7-day moving average value during Dec 1, 2020–Jan 31, 2021 (winter 2020–21 period), Aug 1–Sep 30, 2021 (Delta period), or Dec 19, 2021–Jan 15, 2022 (Omicron period). The date and value of peaks might change slightly if data are backfilled.

† Data were pulled on January 20, 2022.

§ Maximum value date for the Omicron period was assessed for December 19, 2021–January 15, 2022. This date is defined as the maximum value for each of the severity indicators at the time that the data were pulled for this report on January 20, 2022. The date of the maximum value might be different at the time of publication.

¶ Total difference is presented for the number of cases, ED visits, hospital admissions, deaths, and inpatient and ICU beds in use. Percentage point difference is presented for the percentage of ED visits and hospital admissions by age groups and for the percentages of inpatient and ICU beds in use for COVID-19 patients.

** Relative percent difference is calculated as the value for cases, ED visits, hospital admissions, inpatient bed use, ICU bed use, and deaths from the Omicron period minus the same indicator value from the comparison period (winter 2020–21 or Delta period) divided by the same indicator value from the comparison period.

lower ratios of ED visits, hospitalizations, and deaths to cases observed during the Omicron period, disease severity indicators were also lower among hospitalized COVID-19 patients, including ICU admission, receipt of IMV, length of stay, and in-hospital death. This apparent decrease in disease severity is likely related to multiple factors, most notably increases in vaccination coverage among eligible persons (*4*,*8*), and the use of vaccine boosters among recommended subgroups[§§§§] (*9*). For example, during the Omicron period, 207 million persons were fully vaccinated compared with 178 million persons and 1.5 million persons during the Delta and the winter 2020–21 periods, respectively (*8*). Further, during the Omicron period, 78 million persons had received vaccine boosters compared

[§§§§] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html

TABLE 2. Total hospitalizations, hospitalized COVID-19 patients, and indicators of disease severity among hospitalized COVID-19 patients during the Omicron period compared with the winter 2020–21 and Delta periods,* by age group, 199 hospitals—United States, January 2021–January 2022

Indicator/ Age group, yrs	No. (%) Winter 2020–21 period Jan 1–21, 2021	Delta period Aug 22–Sep 11, 2021	Omicron period Dec 26, 2021–Jan 15, 2022	Comparison of Omicron with winter 2020–21 period: Percentage point or mean difference	Comparison of Omicron with winter 2020–21 period: Relative % difference	Comparison of Omicron with Delta period: Percentage point or mean difference	Comparison of Omicron with Delta period: Relative % difference
Total hospitalizations							
All	108,360	110,950	98,920	—	—	—	—
0–17	11,504	13,946	11,517	—	—	—	—
18–50	31,070	34,537	28,040	—	—	—	—
>50	65,786	62,467	59,363	—	—	—	—
Hospitalized COVID-19 patients as a percentage of total hospitalizations							
All	12,963 (12.0)	10,440 (9.4)	12,800 (12.9)	–1.0†	8.2	3.5†	37.5
0–17	147 (1.3)	272 (2.0)	405 (3.5)	2.2†	175.2	1.6†	80.3
18–50	2,474 (8.0)	3,304 (9.6)	3,988 (14.2)	6.3†	78.6	4.7†	48.7
>50	10,342 (15.7)	6,864 (11.0)	8,407 (14.2)	–1.6†	–9.9	3.2†	28.9
ICU admission among hospitalized COVID-19 patients							
All	2,359 (18.2)	1,824 (17.5)	1,658 (13.0)	–5.2†	–28.8	–4.5†	–25.9
0–17	25 (17.0)	50 (18.4)	42 (10.4)	–6.6§	–39.0	–8.0§	–43.6
18–50	346 (14.0)	438 (13.3)	377 (9.5)	–4.5†	–32.4	–3.8†	–28.7
>50	1,988 (19.2)	1,336 (19.5)	1,239 (14.7)	–4.5†	–23.3	–4.7†	–24.3
IMV among hospitalized COVID-19 patients¶							
All	764 (7.5)	503 (6.6)	358 (3.5)	–4.0†	–53.4	–3.1†	–46.5
0–17	1 (0.8)	1 (0.4)	0 (—)	NC	NC	NC	NC
18–50	122 (6.2)	118 (4.9)	73 (2.3)	–3.9†	–63.2	–2.6†	–53.2
>50	641 (8.0)	384 (7.7)	285 (4.3)	–3.7†	–46.2	–3.4†	–44.3
In-hospital death among hospitalized COVID-19 patients**							
All	976 (12.9)	803 (12.3)	533 (7.1)	–5.8†	–44.9	–5.2†	–42.3
0–17	1 (1.1)	0 (—)	0 (—)	NC	NC	NC	NC
18–50	57 (4.0)	110 (5.4)	38 (1.7)	–2.3†	–58.3	–3.7†	–69.2
>50	918 (15.2)	693 (16.0)	495 (10.0)	–5.2†	–34.2	–6.0†	–37.5
Length of stay among hospitalized COVID-19 patients, by age group, yrs							
Median							
All	5	5	3	—	—	—	—
0–17	2	2	2	—	—	—	—
18–50	3	4	2	—	—	—	—
>50	5	6	4	—	—	—	—
Mean (SD)							
All	8.0 (15.6)	7.6 (10.6)	5.5 (13.1)	–2.5†	–31.0	–2.0†	–26.8
0–17	4.4 (10.1)	3.9 (5.3)	3.5 (9.7)	–0.9	–20.3	–0.4	–9.5
18–50	5.8 (7.8)	6.1 (6.9)	4.3 (7.4)	–1.5†	–25.6	–1.8†	–29.9
>50	8.6 (17.0)	8.4 (12.0)	6.2 (15.1)	–2.4†	–27.7	–2.2†	–25.8

Source: BD Insights Research Database.
Abbreviations: ICU = intensive care unit; IMV = invasive mechanical ventilation; NC = not calculated.
* The winter period was defined as January 1–21, 2021, the Delta period was defined as August 22–September 11, 2021, and the Omicron period was defined as December 26, 2021–January 15, 2022 for BD analysis.
† p<0.001.
§ p<0.05.
¶ Data on IMV were available from a subset of 135 hospitals. The denominators of hospitalized COVID-19 patients for IMV percentages were as follows for each period and age group: winter 2020–21 (0–17 years [132]; 18–50 years [1,964]; and >50 years [8,039]); Delta (0–17 years [258]; 18–50 years [2,415]; and >50 years [4,988]); and Omicron (0–17 years [355]; 18–50 years [3,189]; and >50 years [6,646]).
** Data on in-hospital deaths were available from a subset of 148 hospitals. The denominators of hospitalized COVID-19 patients for in-hospital death percentages were as follows for each period and age group: winter 2020–21 (0–17 years [87]; 18–50 years [1,437]; and >50 years [6,048]); Delta (0–17 years [142]; 18–50 years [2,045]; and >50 years [4,333]); and Omicron (0–17 years [250]; 18–50 years [2,297]; and >50 years [4,954]).

with 1.6 million persons during the Delta period; boosters were not available during winter 2020–21 (*8*). Other key factors for lower disease severity include infection-acquired immunity (*3,7*), and potential lower virulence of the Omicron variant (*3,5,6*).

These findings are consistent with reports from South Africa (*2*), England (*10*), and Scotland,¶¶¶¶ as well as from health

¶¶¶¶ https://www.pure.ed.ac.uk/ws/portalfiles/portal/245818096/Severity_of_Omicron_variant_of_concern_and_vaccin%20e_effectiveness_against_symptomatic_disease.pdf%2012

systems in California (*3*) and Texas,***** where the Omicron variant was not associated with an increase in hospital or disease severity indicators among patients with Omicron infections compared with those with Delta infections. Death and in-hospital severity indicators, including in the context of vaccination status, should continue to be monitored for changes or differential effects among subpopulations throughout the Omicron period.

Among children aged <18 years, in-hospital severity indicators, including length of stay and ICU admission, were similar to and lower, respectively, during the Omicron period compared with those during previous high-transmission periods. However, high relative increases in ED visits and hospitalizations were observed among children during the Omicron period, which might be related to lower vaccination rates in children compared with those in adults, especially among children aged 0–4 years who are currently not eligible for vaccination. Children's susceptibility to the Omicron variant and the impact of changes in exposure on severity risk require additional study. Among adults aged ≥18 years, all in-hospital severity indicators assessed were lower during the Omicron period, which might be related to increased population immunity against SARS-CoV-2 because of higher vaccination coverage and booster rates and previous infection providing protection (*3*,*4*,*7*,*9*). Receipt of a third mRNA vaccine dose was found to be highly effective at preventing urgent care encounters, ED visits, and hospital admissions during both Delta and Omicron periods (*9*). Booster doses were also found to be effective at preventing infection during the early Omicron period, particularly among persons aged ≥50 years (*4*).

The findings in this report are subject to at least seven limitations. First, BD is not nationally representative and NSSP does not capture all ED visits across the United States; therefore, geographic and demographic differences in disease transmission and severity might bias findings. Second, the variation in vaccination coverage during the three periods assessed was not taken into account when comparing severity indicators. This limitation is most relevant when comparing the Omicron period to the winter 2020-21 period, when vaccines were just becoming available in the United States. Third, person-level vaccination status was not available to compare severity indicators based on being up to date on vaccinations. Fourth, the hospital data do not exclude incidental SARS-CoV-2 infections, which might be higher during the Omicron period because of increased transmissibility of the Omicron variant; inclusion of incidental infections could inflate hospitalization-to-case ratios and have an unknown effect on in-hospital severity indicators. Fifth, changes in testing and reporting behaviors, including the likely increase in self-administered tests, might bias comparisons; specifically, reported case counts during the Omicron period might be biased downward because of self-administered test use compared with counts during other periods.††††† Sixth, co-circulation of the Omicron and Delta variants might affect the magnitude of the severity indicators during the beginning of the Omicron period, particularly for in-hospital severity indicators based on date of hospital discharge. Finally, the findings reflect an ecologic analysis of event-based indicators; findings should not be misinterpreted as person-level indicators (e.g., case-fatality ratios).

Emergence of the Omicron variant has resulted in a rapid increase in COVID-19 cases. Concurrent increases in ED visits and hospital admissions appear to be driven by high case counts and not by increased disease severity following acute infection. Although patients hospitalized during the Omicron period have shorter stays and less frequent ICU admissions, the high volume of hospitalizations resulting from high transmission rates during a short period can strain local health care systems

Summary

What is already known about this topic?

The SARS-CoV-2 B.1.1.529 (Omicron) variant became predominant in the United States by late December 2021, leading to a surge in COVID-19 cases and associated ED visits and hospitalizations.

What is added by this report?

Despite Omicron seeing the highest reported numbers of COVID-19 cases and hospitalizations during the pandemic, disease severity indicators, including length of stay, ICU admission, and death, were lower than during previous pandemic peaks.

What are the implications for public health practice?

Although disease severity appears lower with the Omicron variant, the high volume of hospitalizations can strain local health care systems and the average daily number of deaths remains substantial. This underscores the importance of national emergency preparedness, specifically, hospital surge capacity and the ability to adequately staff local health care systems. In addition, being up to date on vaccinations and following other recommended prevention strategies are critical to preventing infections, severe illness, or death from COVID-19.

***** https://www.medrxiv.org/content/10.1101/2021.12.30.21268560v2

††††† Case data in this report are based on data reported by states. Some states report both confirmed and probable cases, and some states report only confirmed cases. For states that include probable cases, a case based on antigen test results with symptoms might meet the case definition and be included in the probable case count. However, positive self-administered tests alone (which are also antigen tests) might not be reported to public health authorities, and do not meet the current Council of State and Territorial Epidemiologists' case definition criteria, and thus, will likely not be included by states in probable case counts reported to CDC.

in the United States, and the average daily number of deaths remains substantial. This underscores the importance of national emergency preparedness, specifically, hospital surge capacity and the ability to adequately staff local health care systems when critical care needs arise and before the system is overwhelmed. Previous studies have identified increased risk for severe outcomes among unvaccinated persons (*4*,*9*). Thus, being up to date with COVID-19 vaccinations and following other recommended prevention strategies are critical to prevent infections, severe illness, or death from COVID-19.

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Notes from the Field

Increased Incidence of Fentanyl-Related Deaths Involving *Para*-fluorofentanyl or Metonitazene — Knox County, Tennessee, November 2020–August 2021

Jordan Trecki, PhD[1]; Roy R. Gerona, PhD[2]; Ross Ellison[2]; Chris Thomas[3]; Darinka Mileusnic-Polchan, MD, PhD[3]

Data from the National Center for Health Statistics indicate that drug overdose deaths in the United States have increased by 28.5% during 2020–2021, from 78,056 during a 12-month period ending in April 2020 to 100,306 during the same period in 2021 (*1*). Approximately 75% of drug overdose deaths during 2020 involved opioids. With illicitly manufactured fentanyl continuing to supplant the heroin market, and increasing illicit use of counterfeit pills containing either fentanyl, various fentanyl-related compounds, or other opioids, the risk for drug overdose deaths remains high (*2*). Recently, *para*-fluorofentanyl, a substance from research efforts in the 1960s and referred to as "China-white" before it was classified as a schedule I substance in 1986, has begun to reemerge on the illicit drug market.* It is found in heroin packets, counterfeit pills, and is reported in autopsy findings and supporting toxicology results.† More recently, another class of compounds known as benzimidazole-opioids have begun appearing in cities across the country as adulterants in the heroin supply, adding a new threat to public health (*3*). Discovered through research for new opioid analgesics in the late 1950s, this class of opioid receptor agonists did not receive market authorization for therapeutic use. Based on law enforcement seizure data from the National Forensic Laboratory Information System (NFLIS)§ and medical examiner reports as described below, metonitazene, a benzimidazole-opioid, and *para*-fluorofentanyl (both in combination with fentanyl), are being encountered more often in the United States.

The Knox County Regional Forensic Center (KCRFC) in Knoxville, Tennessee is the medical examiner for Knox and Anderson counties, and also conducts autopsies when requested from 21 surrounding counties. KCRFC first identified *para*-fluorofentanyl in toxicology results of victims of drug overdoses in November 2020, and metonitazene, either alone or in combination with fentanyl and *para*-fluorofentanyl, in January 2021. During November 2020–August 2021, KCRFC reported 770 total unintentional drug overdose deaths. Among these deaths, 562 (73.0%) cases received postmortem positive test results for fentanyl (Table), including 192 fentanyl-positive cases reported in the absence of other substances (i.e., fentanyl only), 188 that involved fentanyl and methamphetamine, 48 that involved *para*-fluorofentanyl, and 26 that involved metonitazene.

These findings demonstrate the contribution of both *para*-fluorofentanyl and the benzimidazole-opioid metonitazene to unintentional overdose deaths in eastern Tennessee. NFLIS data indicate a sharp increase in law enforcement encounters with *para*-fluorofentanyl and metonitazene from 2020 to 2021; reporting from late 2021 is in process. Although the percentage of law enforcement encounters with these substances in Tennessee decreased relative to the national total percentage within this time frame, the increase in encounters both within Tennessee and nationally reflect an increased distribution of *para*-fluorofentanyl and metonitazene throughout the United States. With *para*-fluorofentanyl and metonitazene each alone being capable of producing respiratory depression leading to death, the various combinations of these substances, in addition to possible other opioids including fentanyl-related compounds or adulterants included in each drug exhibit that could cause or exacerbate serious adverse effects, pose an even greater potential harm to the patient than that previously observed. Naloxone still serves as an effective drug to reverse opioid overdose; however, additional doses of naloxone might be required when stronger opioids like fentanyl, *para*-fluorofentanyl, metonitazene, or other benzimidazoles are involved or combined (*4*).

Physicians, medical examiners, and toxicology laboratories should be aware of the increased presence of *para*-fluorofentanyl and the benzimidazole class of opioids¶ when treating patients in the emergency department or identifying these substances postmortem. Increasing public awareness regarding the fatal consequences after the ingestion of fentanyl, *para*-fluorofentanyl, metonitazene, and other opioids in addition to expanded naloxone availability should be prioritized to reduce opioid-related deaths both in Tennessee and throughout the United States.

* https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf (Accessed January 21, 2022).

† https://www.dea.gov/sites/default/files/2020-06/Synthetic%20Opioids-2020.pdf

§ The National Forensic Laboratory Information System (NFLIS) is an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle approximately 98% of an estimated 1.5 million distinct annual federal, state, and local drug analysis cases. NFLIS-Drug includes drug chemistry results from completed analyses only. https://www.nflis.deadiversion.usdoj.gov/

¶ https://www.deadiversion.usdoj.gov/drug_chem_info/benzimidazole-opioids.pdf

TABLE. Demographic characteristics, circumstances, and co-occurring substances among overdose decedents with fentanyl, *para*-fluorofentanyl, or metonitazene detected in postmortem toxicology — Knoxville, Tennessee and surrounding counties,* November 2020–August 2021

Characteristic	No. (%)
Total postmortem cases with fentanyl, *para*-fluorofentanyl, or metonitazene present, alone or in combination	572† (100)
Sex	
Male	388 (68.5)
Female	184 (31.5)
Race/Ethnicity	
White, non-Hispanic	515 (90.0)
Black, non-Hispanic	44 (7.7)
Hispanic or Latino	11 (2.0)
Other, non-Hispanic§	2 (0.3)
Age group, yrs	
<25	30 (5.2)
25–34	153 (26.7)
35–44	160 (28.0)
45–54	128 (22.4)
≥55	101 (17.7)
Route of administration¶	
Injection	75 (13.1)
Ingestion	52 (9.1)
Snorting	27 (4.7)
Smoking	0 (—)
Unknown	418 (73.1)
Occurrence of substances**	
Fentanyl, total	562 (98.3)
Para-fluorofentanyl, total	48 (8.4)
Metonitazene, total	26 (4.6)
Fentanyl only	192 (33.6)
Fentanyl and cocaine only	24 (4.2)
Fentanyl, cocaine and other opioids††	4 (0.7)
Fentanyl and methamphetamine only	188 (32.9)
Fentanyl, methamphetamine, and cocaine	12 (2.1)
Fentanyl, methamphetamine, and other opioids§§	32 (5.6)
Fentanyl and other stimulants¶¶	2 (0.3)
Fentanyl, methamphetamine, and other stimulants¶¶	6 (1.0)
Fentanyl and other opioids***	39 (6.8)
Para-fluorofentanyl only	3 (0.5)
Fentanyl and *para*-fluorofentanyl only	17 (3.0)
Fentanyl, *para*-fluorofentanyl, and metonitazene only	2 (0.3)
Fentanyl, *para*-fluorofentanyl and other opioids†††	4 (0.7)
Fentanyl, *para*-fluorofentanyl and other stimulants§§§	1 (0.2)
Fentanyl, *para*-fluorofentanyl and methamphetamine	15 (2.6)
Fentanyl, *para*-fluorofentanyl and cocaine	4 (0.7)
Fentanyl and metonitazene only	4 (0.7)
Fentanyl, *para*-fluorofentanyl and methamphetamine, and cocaine	1 (0.2)
Fentanyl, *para*-fluorofentanyl and methamphetamine, and metonitazene	1 (0.2)
Fentanyl, metonitazene, and cocaine	1 (0.2)
Fentanyl, metonitazene, and methamphetamine	12 (2.1)
Fentanyl, metonitazene, and other opioids¶¶¶	1 (0.2)
Metonitazene only	2 (0.3)
Metonitazene and methamphetamine	3 (0.5)
Fentanyl and other benzimidazole-opioids****	2 (0.3)
Location	
Knox County	304 (53.1)
Anderson County	45 (7.9)
Blount County	53 (9.3)
Sevier County	40 (7.0)
Monroe County	10 (1.7)
Other counties††††	120 (21.0)
NFLIS-Drug, Tennessee reports/Total U.S. reports (%) (2015–2021)§§§§	
***Para*-fluorofentanyl**	
2015–2019	0/19 (—)
2020	19/133 (14.3)
2021	186/2,561 (7.3)
Metonitazene	
2015–2019	0/0 (—)
2020	46/109 (42.2)
2021	101/439 (23.0)

Abbreviations: MDA = 3,4-methylenedioxyamphetamine; MDMA = 3,4-methylenedioxymethamphetamine; NFLIS = National Forensic Laboratory Information System.

* The drug deaths listed in the table are not comprehensive of the actual drug related death totals for counties other than Knox and Anderson because medical examiners from these counties did not refer every drug overdose case to the Knox County Regional Forensic Center.

† Includes eight cases in which *para*-fluorofentanyl or metonitazine were identified in the absence of fentanyl.

§ Asian , American Indian or Alaska Native, or Native Hawaiian or Other Pacific Islander.

¶ Based on drug paraphernalia present at the scene.

** Values will sum to >100% to account for various combinations.

†† Other opioids include 6-monoacetylmorphine, dihydrocodeine, hydrocodone, hydromorphone, methadone, mitragynine, morphine, oxycodone, and oxymorphone.

§§ Other opioids include morphine, oxycodone, and oxymorphone.

¶¶ Other stimulants included amphetamine, MDA, and MDMA.

*** Other opioids include acetyl fentanyl, buprenorphine, codeine, hydrocodone, hydromorphone, methadone, mitragynine, oxycodone, oxymorphone, and tramadol.

††† Other opioids include 6-monoacetylmorphine, acetyl fentanyl, buprenorphine, dihydrocodeine, hydrocodone, methadone, morphine, oxycodone, oxymorphone, and tramadol.

§§§ Other stimulants include amphetamine.

¶¶¶ Other opioids include dihydrocodeine and hydrocodone.

**** Isotonitazene or protonitazene, other benzimidazole-opioids, were identified in two cases.

†††† Number of detections in other counties served by the Knox County Regional Forensic Center: Bradley = five; Campbell = 11; Cocke = 12; Fentress = two; Grainger = six; Hamblen = 10; Jefferson = 12; Loudon = 12; McMinn = nine; Meigs = one; Morgan = nine; Polk = two; Rhea = six; Roane = 17; Union = six.

§§§§ Data were queried on January 21, 2022; data reporting for 2021 is ongoing.

Acknowledgments

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Errata

Vol. 71, No. 1

In the report "Alcohol Consumption and Binge Drinking During Pregnancy Among Adults Aged 18–49 Years — United States, 2018–2020," in the figure on page 12, for Region 8, the values listed should have been 10.8% (**7.3%**–14.3%).

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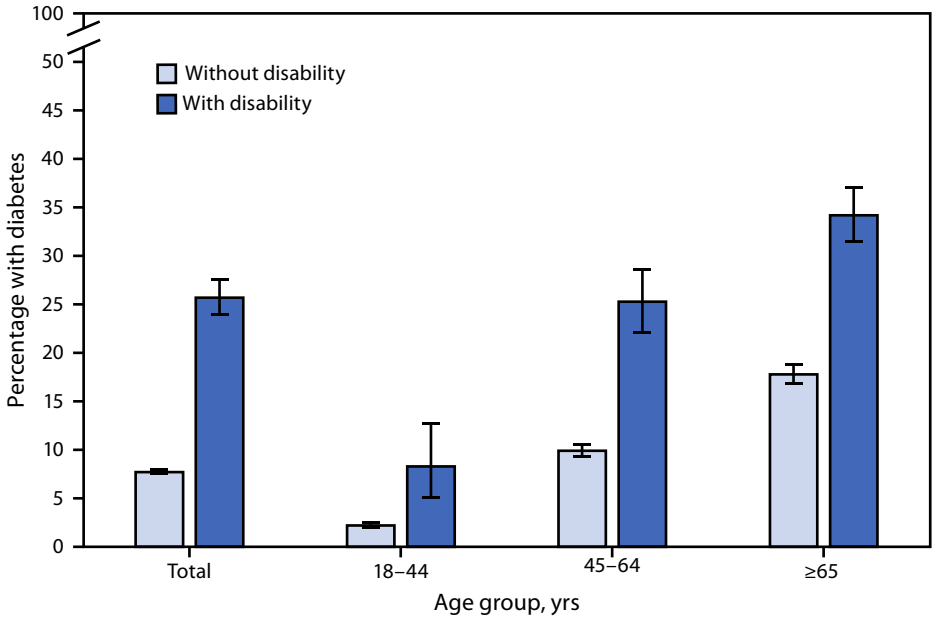
In the report "Trends in Breast Cancer Incidence, by Race, Ethnicity, and Age Among Women Aged ≥20 Years — United States, 1999–2018," on page 47, in the Summary box, the second sentence in the "What is added by this report?" section should have read, "Incidence increased among non-Hispanic **Asian or** Pacific Islander women and women aged 20–39 years but decreased among non-Hispanic White women and women aged 50–64 and ≥75 years."

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage* of Adults Aged ≥18 Years with Diagnosed Diabetes,† by Disability Status§ and Age Group — National Health Interview Survey,¶ United States, 2020



* With 95% CIs indicated with error bars.
† Based on a positive response to the survey question, "Has a doctor or other health professional ever told you that you had diabetes?" Respondents were asked not to include prediabetes or gestational diabetes.
§ Disability was defined by the reported level of difficulty to questions about six domains of functioning: "Do you have any difficulty… seeing, even if wearing glasses; hearing, even if wearing hearing aids; walking or climbing stairs; communicating, for example understanding or being understood; remembering or concentrating; and self-care, such as washing all over or dressing." Response categories were "no difficulty," "some difficulty," "a lot of difficulty," or "cannot do at all." Adults who responded "a lot of difficulty" or "cannot do at all" to at least one domain were classified with disability.
¶ Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population.

In 2020, 25.7% of adults aged ≥18 years with disability had diagnosed diabetes compared with 7.7% of those without disability. For each age group, those with disability were more likely to have diabetes: adults aged 18–44 years (8.3% versus 2.2%), 45–64 years (25.3% versus 9.9%), and ≥65 years (34.2% versus 17.8%). Regardless of disability status, the percentage of adults with diagnosed diabetes increased with age.

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

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For more information on this topic, CDC recommends the following link:
https://www.cdc.gov/ncbddd/disabilityandhealth/features/disability-and-diabetes-prevention.html

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format. To receive an electronic copy each week, visit *MMWR* at *https://www.cdc.gov/mmwr/index.html*.

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