Summary Recommendations

<table>
<thead>
<tr>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
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<th>Pre-Exposure Prophylaxis</th>
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<td>• The circulation of Omicron subvariants that are resistant to tixagevimab plus cilgavimab (Evusheld) has been increasing in the United States.</td>
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<td>• In the absence of an alternative option for PrEP, the Panel recommends the use of tixagevimab 300 mg plus cilgavimab 300 mg administered as 2 consecutive 3-mL intramuscular (IM) injections (BIIb) as SARS-CoV-2 PrEP for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, AND who:</td>
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<td>• Individuals who receive tixagevimab plus cilgavimab as PrEP should continue to take precautions to avoid infection. If they experience signs and symptoms consistent with COVID-19, they should be tested for SARS-CoV-2 and, if infected, promptly seek medical attention.</td>
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Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

General Prevention Measures

Transmission of SARS-CoV-2 is thought to occur primarily through exposure to respiratory droplets. Exposure can occur when someone inhales droplets or particles that contain the virus (with the greatest risk of transmission occurring within 6 feet of an infectious source) or touches their mucous membranes with hands that have been contaminated with the virus. Exhaled droplets or particles can also deposit the virus onto exposed mucous membranes.¹

Less commonly, airborne transmission of droplets and particles of SARS-CoV-2 to people farther than...
6 feet away can occur. In rare cases, people passing through a room that was previously occupied by an infectious person may become infected. SARS-CoV-2 infection via airborne transmission of small particles tends to occur after prolonged exposure (i.e., >15 minutes) to an infectious person who is in an enclosed space with poor ventilation.¹

The risk of SARS-CoV-2 transmission can be reduced by covering coughs and sneezes and maintaining a distance of at least 6 feet from others. When consistent distancing is not possible, face coverings may reduce the spread of infectious droplets from individuals with SARS-CoV-2 infection to others. Frequent handwashing also effectively reduces the risk of infection.² Health care providers should follow the Centers for Disease Control and Prevention (CDC) recommendations for infection control and the appropriate use of personal protective equipment.³

**Vaccines**

Vaccination is the most effective way to prevent SARS-CoV-2 infection. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible according to the CDC’s Advisory Committee on Immunization Practices (ACIP). Four vaccines are authorized or approved for use in the United States to prevent COVID-19. For primary and booster vaccinations, the mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) and the recombinant spike protein with matrix-M1 adjuvant vaccine NVX-CoV2373 (Novavax) are preferable to the adenovirus vector vaccine Ad26.COV2.S (Johnson & Johnson/Janssen) due to its risk of serious adverse events.⁴

A primary series of COVID-19 vaccinations is recommended for everyone aged ≥6 months in the United States. The Food and Drug Administration (FDA) Emergency Use Authorization (EUA) fact sheet and the product label for each vaccine provide detailed information on the vaccination schedule and doses approved or authorized for that vaccine. Bivalent mRNA vaccines that protect against the original SARS-CoV-2 virus strain and Omicron subvariants BA.4 and BA.5 are now recommended for individuals at least 2 months after receiving the primary vaccine series or a booster dose. The type and dose of vaccine and the timing of these additional doses depend on the recipient’s age and underlying medical conditions. The CDC regularly updates the clinical considerations for use of the COVID-19 vaccines currently approved by the FDA or authorized for use in the United States.⁵

**Adverse Events**

COVID-19 vaccines are safe and effective. Local and systemic adverse events are relatively common with these vaccines. Most of the adverse events that occurred during vaccine trials were mild or moderate in severity (i.e., they did not prevent vaccinated people from engaging in daily activities) and resolved after 1 or 2 days. There have been a few reports of severe allergic reactions following COVID-19 vaccination, including rare reports of patients who experienced anaphylaxis after receiving an mRNA vaccine.⁶,⁷

Reports have suggested that there is an increased risk of thrombosis with thrombocytopenia syndrome (TTS) in adults who received the Johnson & Johnson/Janssen vaccine⁷ and, rarely, the Moderna vaccine.⁸ TTS is a rare but serious condition that causes blood clots in large blood vessels and low platelet levels. Women aged 30 to 49 years should be aware of the increased risk of TTS. The American Society of Hematology and the American Heart Association/American Stroke Association Stroke Council leadership have published considerations relevant to the diagnosis and treatment of TTS that occurs in people who receive the Johnson & Johnson/Janssen vaccine.⁹,¹⁰ These considerations include information on administering a nonheparin anticoagulant and intravenous immunoglobulin to these patients. Given the rarity of this syndrome and the unique treatment required, consultation with a
hematologist should be considered for patients with TTS.

Myocarditis and pericarditis after COVID-19 vaccination are rare, and most of the reported cases were very mild and self-limiting.11 These conditions have occurred most often in male adolescents, young adults, and people who have received mRNA vaccines.

Guillain-Barré syndrome (GBS) in people who received the Johnson & Johnson/Janssen vaccine is rare.11 GBS is a neurologic disorder that causes muscle weakness and sometimes paralysis. Most people with GBS fully recover, but some have permanent nerve damage. Onset typically occurs about 2 weeks after vaccination. GBS has mostly been reported in men aged ≥50 years.

The CDC provides regular updates on selected adverse events of COVID-19 vaccines on its website.

Vaccination in Pregnant or Lactating People

Pregnant and lactating individuals were not included in the initial COVID-19 vaccine trials. However, the CDC, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine recommend vaccination for pregnant and lactating people based on the accumulated safety and efficacy data on the use of these vaccines in pregnant people, as well as the increased risk of severe disease in pregnant individuals with COVID-19.12-17 These organizations also recommend vaccination for people who are trying to become pregnant or who may become pregnant in the future. The ACOG publication includes a guide for clinicians on counseling pregnant patients about COVID-19 vaccination.18

Pre-Exposure Prophylaxis

Anti-SARS-CoV-2 Monoclonal Antibodies

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. However, some individuals cannot or may not mount an adequate protective response to COVID-19 vaccines. Others may not have been fully vaccinated because they have a history of severe adverse reactions to a COVID-19 vaccine or its components.

On the basis of results from PROVENT, a large randomized controlled trial conducted when the major circulating SARS-CoV-2 variants were Alpha, Beta, Delta, and Epsilon,19 the FDA issued an EUA for the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld).20 The EUA allows these anti-SARS-CoV-2 mAbs to be used as pre-exposure prophylaxis (PrEP) for certain individuals who are immunocompromised and therefore may have inadequate responses to COVID-19 vaccines or are unable to be fully vaccinated due to a history of severe adverse reactions to a COVID-19 vaccine. A modification in the fragment crystallizable (Fc) region gives these anti-SARS-CoV-2 mAbs prolonged half-lives, resulting in potential protection from SARS-CoV-2 infection for up to 6 months, depending on the variant.

The PROVENT trial used tixagevimab 150 mg plus cilgavimab 150 mg, which was the dose initially authorized by the FDA. However, in vitro data indicated that the Omicron subvariants BA.4 and BA.5 had decreased susceptibility to tixagevimab plus cilgavimab. Because of these findings, in February 2022, the FDA revised the EUA to authorize the use of an increased dose of tixagevimab 300 mg plus cilgavimab 300 mg.20-23 For individuals who only received tixagevimab 150 mg plus cilgavimab 150 mg, a tixagevimab 300 mg plus cilgavimab 300 mg dose should be administered as soon as possible. On June 30, 2022, the FDA further revised the EUA to authorize repeated doses of tixagevimab 300 mg plus cilgavimab 300 mg to be administered every 6 months.

The prevalence of certain Omicron subvariants (i.e., BA.4.6, BA.2.75.2, BA.5.2.6, BF.7, BQ.1,
BQ.1.1) that are resistant to tixagevimab plus cilgavimab is rapidly increasing. However, tixagevimab plus cilgavimab is the only agent authorized by the FDA for use as SARS-CoV-2 PrEP in people who are not expected to mount an adequate immune response to COVID-19 vaccination or those with contraindications for COVID-19 vaccines. Therefore, the Panel recommends the use of **tixagevimab plus cilgavimab** as PrEP for eligible individuals (BIIb).

When prescribing tixagevimab plus cilgavimab for SARS-CoV-2 PrEP, clinicians should be aware of the following:

- Tixagevimab plus cilgavimab is authorized for use as PrEP in a population that was not well represented in the PROVENT trial (i.e., a very small proportion of the participants were immunocompromised).
- There are no clinical trial efficacy data on the tixagevimab 300 mg plus cilgavimab 300 mg dose administered for the prevention of symptomatic COVID-19, and there are no data for any repeated dose at any defined interval. This dose and the strategy of repeating the dose every 6 months are based on pharmacokinetic/pharmacodynamic (PK/PD) modeling data. Substantial uncertainty in the PK/PD model remains.
- Safety data on the use of tixagevimab 300 mg plus cilgavimab 300 mg primarily come from TACKLE, a Phase 3 clinical trial that evaluated single doses of tixagevimab plus cilgavimab for the treatment of patients with mild to moderate COVID-19.

**Recommendations**

Factoring in the limitations outlined above:

- The Panel recommends the use of **tixagevimab 300 mg plus cilgavimab 300 mg** administered as 2 consecutive 3-mL intramuscular (IM) injections (BIIb) as SARS-CoV-2 PrEP for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, AND who:
  - Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; or
  - Are not able to be fully vaccinated with any available COVID-19 vaccines due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components.
- For individuals who only received tixagevimab 150 mg plus cilgavimab 150 mg, a tixagevimab 300 mg plus cilgavimab 300 mg dose should be administered as soon as possible.
- Given the increasing prevalence of resistant SARS-CoV-2 subvariants, the decision to administer tixagevimab plus cilgavimab should be based on the regional prevalence of the resistant subvariants, the individual patient’s risks, the available resources, and logistics. The Panel’s recommendations for the use of tixagevimab plus cilgavimab may change if the prevalence of resistant subvariants increases.
- Individuals who receive tixagevimab plus cilgavimab as PrEP should continue to take precautions to avoid infection. If they experience signs and symptoms consistent with COVID-19, they should be tested for SARS-CoV-2 and, if infected, promptly seek medical attention.
- The Panel recommends repeat dosing of **tixagevimab 300 mg plus cilgavimab 300 mg** administered as IM injections every 6 months (BIIb). Repeat doses should be timed from the most recent dose of tixagevimab plus cilgavimab.
- **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended.**
Additional Considerations

- Evusheld contains the ingredient polysorbate 80, which is structurally related to polyethylene glycol. COVID-19 vaccines approved or authorized by the FDA contain either polysorbate 80 or polyethylene glycol. There is a theoretical risk of cross-hypersensitivity between Evusheld and COVID-19 vaccines. Before administering Evusheld to individuals with a history of severe hypersensitivity reactions to a COVID-19 vaccine, consultation with an allergist/immunologist should be considered.

- Individuals who qualify as having moderate to severe immunocompromising conditions under the FDA EUA for tixagevimab plus cilgavimab include, but are not limited to, those who:
  - Are receiving active treatment for solid tumors and hematologic malignancies.
  - Have a hematologic malignancy (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia) that has been associated with poor response to COVID-19 vaccines, regardless of the patient’s current treatment.
  - Received a solid organ or islet transplant and are receiving immunosuppressive therapy.
  - Received chimeric antigen receptor T cell therapy or a hematopoietic cell transplant (and are within 2 years of transplantation or are receiving immunosuppressive therapy).
  - Have a moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
  - Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte cell counts <200 cells/mm³, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).
  - Are receiving active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or immunosuppressive or immunomodulatory biologic agents (e.g., B cell-depleting agents).
  - The strength of the Panel’s current recommendation for tixagevimab 300 mg plus cilgavimab 300 mg is based partly on PK/PD modeling for the Omicron BA.1 and BA.1.1 subvariants and partly on the BA.2 subvariant’s near-full susceptibility to tixagevimab plus cilgavimab shown in vitro. The Panel’s recommendation may change if subvariants with reduced susceptibility to tixagevimab plus cilgavimab become more prevalent.
  - If supplies of tixagevimab plus cilgavimab are limited, priority for use as PrEP should be given to those who are at the highest risk for severe COVID-19.
  - If a person has received a COVID-19 vaccine, tixagevimab plus cilgavimab should be administered at least 2 weeks after vaccination.

Clinical Trial Data for Tixagevimab Plus Cilgavimab

PROVENT is an ongoing, Phase 3, double-blind, randomized, placebo-controlled trial that evaluated the use of tixagevimab plus cilgavimab for SARS-CoV-2 PrEP. The study enrolled adults aged ≥18 years who had not received a COVID-19 vaccine and who were at increased risk of severe SARS-CoV-2 infection (e.g., those aged ≥60 years or those who had a prespecified comorbidity) or who had an increased risk of acquiring SARS-CoV-2 infection due to their occupation or living situation. The study excluded those with a history of confirmed SARS-CoV-2 infection or who had a positive SARS-CoV-2 antibody result at screening.

The analyzed population included participants who received a negative reverse transcription polymerase
chain reaction (RT-PCR) result at baseline. Participants received either tixagevimab 150 mg plus cilgavimab 150 mg (administered as 2 consecutive IM injections; n = 3,460) or placebo (administered as 2 IM injections; n = 1,737). The primary endpoint was symptomatic SARS-CoV-2 infection and a positive RT-PCR result during the 183 days of follow-up.

Once COVID-19 vaccines became available, participants could choose to be unblinded and receive the vaccine during the study. Only the primary endpoints that occurred prior to unblinding or vaccine receipt were included in the analysis, resulting in a median follow-up of 83 days. Baseline characteristics were well balanced between the arms. Prior to unblinding or vaccination, RT-PCR-confirmed symptomatic SARS-CoV-2 infection was reported for 8 participants (0.2%) in the tixagevimab plus cilgavimab arm and 17 participants (1.0%) in the placebo arm, representing a 77% reduction in the incidence of infection in the tixagevimab plus cilgavimab arm (95% CI, 46% to 90%; P < 0.001). A post hoc analysis after a median follow-up period of 6 months showed a relative risk reduction of 82.8% (95% CI, 65.8% to 91.4%) for symptomatic infection in the tixagevimab plus cilgavimab arm. Five cases of COVID-19 were considered to be severe or critical, and 2 COVID-19-related deaths were reported. All of these events occurred in participants who received placebo.

Adverse events were reported for 35.3% of participants in the tixagevimab plus cilgavimab arm and 34.2% of participants in the placebo arm. Serious adverse events were reported for 1% of participants in each arm; 1 participant in the tixagevimab plus cilgavimab arm had an anaphylactic reaction that was resolved with epinephrine therapy. The incidence of adverse events was similar in both study arms; most events were mild (62%) or moderate (32%). Rare, serious cardiac adverse events occurred in 0.7% of participants in the tixagevimab plus cilgavimab arm and in 0.3% of participants in the placebo arm. All participants who experienced a cardiac event had cardiac risk factors or a history of cardiac disease at baseline. There was no clear temporal pattern between these serious cardiac adverse events and administration of the anti-SARS-CoV-2 mAbs.20

TACKLE was a Phase 3 trial that evaluated the use of tixagevimab plus cilgavimab for the treatment of nonhospitalized patients with mild to moderate COVID-19. In this study, 452 high-risk adults aged ≥18 years received a single IM dose of tixagevimab 300 mg plus cilgavimab 300 mg and had a follow-up visit within 183 days (the median follow-up period was 84 days). Adverse events were reported for 29% of patients in the tixagevimab plus cilgavimab arm and for 36% of patients in the placebo arm; the majority of events were mild to moderate in severity. Serious cardiac adverse events were reported for 4 patients; 3 had received tixagevimab plus cilgavimab and 1 had received placebo. All events occurred in patients who had cardiac risk factors or a history of cardiovascular disease.20

**Other Drugs for Pre-Exposure Prophylaxis**

- The Panel recommends against the use of any oral drugs for SARS-CoV-2 PrEP, except in a clinical trial (AIII).

Clinical trials are investigating several agents, including emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate; hydroxychloroquine; ivermectin; and supplements such as zinc, vitamin C, and vitamin D.

Hydroxychloroquine, given at different doses and durations, has been studied in randomized controlled trials to assess whether it could prevent SARS-CoV-2 infection in those at risk of being exposed to infected individuals, such as health care workers. One study reported no evidence of a benefit of hydroxychloroquine, and it was ultimately halted due to futility before it reached its target enrollment.27 In another hydroxychloroquine study, which also did not meet its target enrollment and was stopped early, the majority of the potential transmission events were not confirmed by virologic testing.28 Neither
study demonstrated any evidence of a reduction in the rate of acquiring infection. Both studies reported an increased frequency of mild adverse events in the treatment group.

Post-Exposure Prophylaxis

Anti-SARS-CoV-2 Monoclonal Antibodies

• The Panel recommends against the use of bamlanivimab plus etesevimab and casirivimab plus imdevimab for post-exposure prophylaxis (PEP), as the Omicron variant and its subvariants, which are not susceptible to these agents, are currently the dominant SARS-CoV-2 variants circulating in the United States (AIII).

Vaccination remains a highly effective way to prevent SARS-CoV-2 infection. However, despite the widespread availability of COVID-19 vaccines, some individuals are not fully vaccinated or cannot mount an adequate response to the vaccine. Some of these individuals, if infected, are at high risk of progressing to serious COVID-19. Bamlanivimab plus etesevimab and casirivimab plus imdevimab have previously received FDA EUAs for PEP; however, the Omicron variant and its subvariants are currently the dominant SARS-CoV-2 variants circulating in the United States. The Panel recommends against the use of these anti-SARS-CoV-2 mAbs because the Omicron variant and its subvariants are not susceptible to them (AIII).

Chloroquine and Hydroxychloroquine

• The Panel recommends against the use of hydroxychloroquine for SARS-CoV-2 PEP (A1).

Both chloroquine and hydroxychloroquine have in vitro activity against SARS-CoV and SARS-CoV-2. A small cohort study without a control group suggested that hydroxychloroquine might reduce the risk of SARS-CoV-2 transmission to close contacts. There have been several large trials to determine whether hydroxychloroquine can reduce the risk of infection after exposure to individuals infected with SARS-CoV-2. These studies used different dose schedules and targeted different at-risk populations. In addition, some studies were unable to confirm infection using molecular or antigen tests. None of these studies demonstrated any evidence of efficacy for hydroxychloroquine, and all showed a higher risk of generally mild adverse events in those who received the drug.

Other Drugs for Post-Exposure Prophylaxis

• The Panel recommends against the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial (AIII).

A number of other agents (e.g., ivermectin, hyperimmune gamma globulin, COVID-19 convalescent plasma, interferons, tenofovir with or without emtricitabine, vitamin D) have been studied for SARS-CoV-2 PEP. The Panel recommends against their use as SARS-CoV-2 PEP because the studies of these agents have not demonstrated sufficient benefit.

References


25. Food and Drug Administration. Emergency use authorization (EUA) for Evusheld. 2022. Available at: https://www.fda.gov/media/156674/download.


