AASLD EXPERT PANEL CONSENSUS STATEMENT:
vaccines to prevent COVID-19 in patients with liver disease

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This is a “living” document that will be updated as new information becomes available.

More AASLD resources for COVID-19 and the Liver:
https://www.aasld.org/about-aasld/covid-19-and-liver
Major Changes and Updates

- New GUIDANCE statements on adverse reactions to COVID-19 vaccines
- New GUIDANCE statements on who and how to administer an additional third dose of mRNA COVID-19 vaccines: general principles, immunosuppressed chronic liver disease patients, and liver transplant recipients
- New Table 3: Overview of Adverse Events Associated with COVID-19 Vaccines
- New Table 4: SARS-CoV-2 Variants of Concern
- New Table 5: SARS-CoV-2 Variants of Interest
- New Table 6: Conditions and Treatments Associated with Moderate to Severe Immune Compromise Based on CDC Criteria
- New Table 7: Recommendations for Additional COVID-19 mRNA Vaccine Doses in Moderately to Severely Immunocompromised Individuals
- Revised section on SARS-CoV-2 Viral Variants
- Revised section on Post-Marketing Reports of Adverse Events to COVID-19 Vaccines
- Revised section on COVID-19 Vaccination in Patients with Chronic Liver Disease
- Revised section on COVID-19 Vaccination in Immunosuppressed Liver Transplant Recipients
- Revised section on Pediatric Considerations in COVID-19 Vaccination
- Updated tables, figures, and references throughout
OVERVIEW AND RATIONALE

Coronavirus disease 2019 (COVID-19) is the illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Multiple studies demonstrate that older individuals and those with certain comorbidities, including chronic liver disease (CLD) (particularly cirrhosis), cardiac disease, obesity, and weakened immune systems from other diseases or medications, may be at higher risk of death from COVID-19. As of August 23, 2021, the Pfizer-BioNTech mRNA-based vaccine given as two doses has full USA Food and Drug Administration (FDA) approval in those 16 years of age and older while the Moderna mRNA two-dose vaccine and the Johnson & Johnson (J&J)/Janssen single-dose adenoviral vector vaccine have received Emergency Use Authorization (EUA) from the FDA. An EUA is a legal means for the FDA to provide preliminary authorization of new drugs, vaccines, or devices during a declared national emergency until a full review of the complete safety and efficacy data has been completed. As of August 11, 2021, 353,205,544 doses of COVID-19 vaccines have been administered in the USA. The percent of the USA population who is fully vaccinated includes 80.5% of those ≥65 years of age, 61.3% of those ≥18 years of age, and 58.9% of those ≥12 years of age, but the rate of vaccination and primary and breakthrough infection varies substantially by geographic region in the USA. Thus far, these vaccines appear to be effective against severe disease and hospitalization due to emerging SARS-CoV-2 variants of concern including the highly transmissible Delta strain, although there is concern that waning immunity could reduce protection against symptomatic disease. As of August 2021, the fourth surge of COVID-19 is largely occurring in unvaccinated individuals, while the minority of vaccinated individuals with breakthrough infection typically have mild to moderate disease, although immunocompromised patients are more likely to develop severe breakthrough infection. As a result, the FDA modified the EUA for the COVID-19 mRNA vaccines on August 12, 2021 to authorize a third dose of an mRNA vaccine to be given to the estimated 7.8 million Americans who are moderately to severely immunosuppressed. The third dose should be given at least 28 days after the second dose of an mRNA vaccine to all immunocompromised individuals including solid organ transplant (SOT) recipients, patients with actively treated cancer, and patients receiving immunosuppressive drugs. In addition, on August 18, 2021, the Department of Health and Human Services stated that they plan to implement booster doses of the COVID-19 vaccines to be given at least eight months following COVID-19 vaccination to all previously vaccinated individuals in the general population in a phased manner starting in late September 2021.1

The goal of this document is to provide concise safety and efficacy data regarding the commercially available COVID-19 vaccines and their recommended use in CLD patients and liver transplant (LT) recipients. Our intent is to provide clinically useful information for all health care providers involved in the care of patients with liver disease, including hepatologists and liver transplant care providers, and their patients.

List of Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy syndrome; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CLD, chronic liver disease; EUA, emergency use authorization; FDA, Food and Drug Administration; GBS, Guillain-Barre Syndrome; VE, vaccine efficacy; BNT162b2, Pfizer-BioNTech mRNA vaccine; mRNA-1273, Moderna mRNA vaccine; AD26.COV2.S, Johnson & Johnson/Janssen vaccine; VAERS, Vaccine Adverse Event Reporting System; CDC, Centers for Disease Control and Prevention; MIS-C, Multisystem inflammatory syndrome in children; SOT, solid organ transplantation; ACR, acute cellular rejection; TTS, thrombosis with thrombocytopenia.
BACKGROUND ON NON-COVID-19 VACCINES IN PATIENTS WITH CHRONIC LIVER DISEASE AND IMMUNOSUPPRESSION

Non-COVID-19 Vaccines in Patients with Chronic Liver Disease and in Immunosuppressed Patients

Patients with CLD display innate and adaptive immune dysregulation that is associated with vaccine hyporesponsiveness (Supplemental Figure 1). Given that subjects with CLD have an increased risk of complications after infection with influenza, Streptococcus pneumoniae, HAV, and HBV, vaccination against these pathogens is recommended (Supplemental Table 1). Double dosing or booster dosing of the HBV vaccines can increase vaccine response rates in CLD patients. Immunosuppressed LT recipients are also known to have a lower response rate to many non-COVID-19 vaccines, particularly when given early after transplant. Therefore, it is generally recommended that vaccines be given before transplant whenever possible or waiting until three to six months after transplant. The Advisory Committee on Immunization Practices (ACIP) recommends avoiding live virus vaccines in those receiving high-dose corticosteroids and other immunosuppressed individuals because of concerns of uncontrolled viral replication. Of note, the CDC recommends that non-COVID-19 vaccines can and should be given while a patient is receiving COVID-19 vaccination. See Supplemental Text for additional information regarding non-COVID-19 vaccines.

BACKGROUND ON COVID-19 VACCINES

Types of COVID-19 Vaccines in Development

Entry of SARS-CoV-2 requires binding of the viral spike glycoprotein to the angiotensin-converting enzyme 2 (ACE2) receptor on human epithelial cells. As a result, researchers have targeted the viral spike glycoprotein to induce vaccine-mediated immune response against SARS-CoV-2 using various delivery systems. The release of the 29,903-nucleotide sequence of the SARS-CoV-2 genome on January 10, 2020 led to diagnostic testing and the development of Operation Warp Speed in the USA with the goal of developing safe and effective vaccines within one year. Both Moderna and Pfizer-BioNTech developed a two-dose vaccine using synthetic nucleoside-modified mRNA that encodes the spike glycoprotein, while J&J/Janssen developed a vaccine using a modified adenoviral vector that contains DNA encoding the spike glycoprotein. Other vaccines that are currently in development use DNA, protein subunits, inactivated SARS-CoV-2, viral vectors, and attenuated virus (Table 1, Figure 1). All of the vaccines described below are not live SARS-CoV-2 and cannot replicate, even in immunocompromised persons.

**mRNA Vaccines**

mRNA-based vaccines involve the delivery of noninfectious synthetic mRNA encoding one or more target antigens (e.g., SARS-CoV-2 spike protein) that can be taken up by host cells including antigen presenting cells (e.g., dendritic cells) (Figure 1). Upon cytoplasmic entry, the delivered mRNA uses the host ribosomal translational machinery to make the target antigens that can be processed for cell surface expression via class I and II major histocompatibility complex (MHC) or be secreted. This induces protective immunity against a future attack (e.g., from SARS-CoV-2) by priming antigen-specific cytotoxic CD8 T cells and helper T cells and a neutralizing antibody response from B cells. A key challenge to the mRNA vaccine platform is its stability and
efficiency, which is related to its susceptibility to enzymatic degradation, limited cellular uptake, and capacity for innate immune activation that can inhibit mRNA translation. In recent years, these challenges have been addressed by using lipid nanoparticles that protect the mRNA from enzymatic degradation and enhance their cellular uptake and biological half-life.\textsuperscript{14,15} Additionally, nucleoside modifications prevent innate immune activation and degradation. Nevertheless, the mRNA-based vaccines degrade within a few hours at room temperature and require very cold temperatures during manufacturing, transportation, and storage. Future iterations of the mRNA COVID-19 vaccines will likely include different sequences of the SARS-CoV-2 RNA virus to ensure that vaccine resistance and escape mutations are minimized.

\textbf{Adenoviral Vectors}

Adenovirus-based vaccines use a harmless, genetically modified exogenous virus as the carrier to bring DNA that encodes the SARS-CoV-2 spike protein into the recipient's cells. Once the adenovirus enters a cell, it delivers the DNA for the SARS-CoV-2 spike protein into the nucleus and the corresponding mRNA is transcribed. Using the host cellular machinery, the mRNA is then translated into SARS-CoV-2 spike protein, which triggers the host immune response after being expressed on cell surface membranes or secreted into the serum.

There are hundreds of known adenoviruses and most do not cause disease in humans, while others cause a range of symptoms depending on the tropism of the strains. The adenovirus vector is modified to prevent it from replicating in host cells. Adenovirus-vector vaccines are stable at room temperature for prolonged periods. Earlier studies have shown that replication defective chimp adenoviral vector vaccines can effectively deliver viral genes to the liver, induce a host immune response, and are safe to use in both healthy volunteers and patients with CLD.\textsuperscript{16,17}

J&J/Janssen's single shot adenoviral vector (Ad26) vaccine is authorized under \textit{EUA} in the USA. Early safety data were favorable in the Phase 3 clinical trial of Oxford/AstraZeneca's AZD1222 adenovirus vectored COVID-19 vaccine,\textsuperscript{18} leading to its authorization for emergency use in the UK on December 29, 2020.\textsuperscript{19} Sputnik V (Gam-COVID-Vac) was the first vaccine to be registered for use, despite an absence of data preceding this registration. As an adenovirus-based vaccine, it is unique in its use of different adenovirus vectors for the first and second doses of the two-dose series. Despite initially very limited data and significant controversy over its deployment, Sputnik V has been distributed throughout the world, with use in 70 countries. A phase 3 trial revealed an efficacy of 91.6%,\textsuperscript{20} although unpublished data suggests slightly lower efficacy. Safety profile has been favorable with no reports of thrombotic disorders to date.\textsuperscript{21} Nevertheless, Sputnik V has yet to receive approval for use from the World Health Organization (WHO) or USA FDA.

Early clinical trials with CanSino's nonreplicating adenovirus (Ad5) vectored COVID-19 vaccine showed mild to moderate increases in total bilirubin (8% of recipients) and serum alanine aminotransferase levels (9% of recipients).\textsuperscript{22} Although these observations were not considered clinically significant, more data and experience with this and other replication defective adenovirus-based vaccines are needed. Replication defective adenovirus-based vaccines are not live or attenuated SARS-CoV-2 and are not expected to pose a risk to immunocompromised patients.

\textbf{Other Vaccines}

Inactivated whole virus vaccines are made by treating the virus with heat and/or chemicals (usually formalin) to prevent its capacity to replicate but are typically given in multiple doses to induce a more robust host immune response. This technology has been used for vaccines against rabies, polio, and HAV.
inactivated whole virus Sinovac vaccine against SARS-CoV-2 has completed small phase 3 trials with mixed efficacy.

Protein subunit vaccines (e.g., herpes zoster vaccine) isolate immunogenic portions of the pathogen of interest that are often combined with an adjuvant (e.g., Alum, MF59, AS01, AS03, AS04).\textsuperscript{23} The Novavax product is a recombinant spike protein subunit and adjuvant vaccine using nanoparticle technology that has started phase 3 trials in the USA. Novavax recently reported a vaccine efficacy (VE) of 89\% in the UK and a VE of 49.4\% in South Africa, where the majority of COVID-19 cases are caused by an escape variant (B.1.351).\textsuperscript{24} A Sanofi/GlaxoSmithKline protein subunit vaccine failed to generate adequate immune response in older adults and is being reengineered.

Live-attenuated viral vaccines are also being developed for COVID-19. One of these uses a virus of limited pathogenicity in humans, vesicular stomatitis virus (VSV), where VSV genes are replaced with the SARS-CoV-2 spike protein gene to generate a host antispcape glycoprotein response. An effective Ebola virus vaccine using VSV in this manner has been approved in the USA. Although there are no live-attenuated virus COVID-19 vaccines nearing FDA authorization, in general, live-attenuated vaccines are not recommended for use in immunocompromised patients because of concerns of excessive viral replication.

**Assays to Detect Immunity to COVID-19**

See Supplemental Text for background on assays to detect immunity to COVID-19. Currently, a large number of assays are authorized by the FDA to determine antibody responses to COVID-19.\textsuperscript{25} These assays may detect response to the spike (S) protein or to the nucleocapsid (N) protein. Successful COVID-19 vaccination result in S but not N protein responses. Precise correlates of immunity have not been defined, and at this time the FDA recommends against using antibody testing to the spike glycoprotein to assess immunity after COVID-19 vaccination or to guide decisions regarding the need to administer additional doses.\textsuperscript{26} While good correlation between vaccine efficacy and neutralizing antibody titers has been observed across registration trials, precise correlates of immunity have not been determined for the many different assays available and these assays are often quantitative.\textsuperscript{27}

**Assays That Measure Virus Neutralizing Antibodies**

Currently, there is no FDA-authorized commercial assay to measure neutralizing antibody response to SARS-CoV-2. However, neutralizing activity can be measured in research laboratories by incubating live virus or pseudovirus with patient serum or plasma (containing antibodies) before inoculating permissive cells in laboratories approved for biosafety level 3 or 2 work. Such antibody assays are being used in COVID-19 vaccine development programs to determine levels that define protective immunity against SARS-CoV-2.

**Assays to Measure T cell Responses**

Various assays can measure the frequency, phenotype, and function of host immune cells, such as the gamma-interferon release (tuberculosis) and intracellular cytokine staining (cytomegalovirus) that detect \textit{in vitro} response of host T cells to specific pathogens. Currently there are no commercially available T cell response assays that evaluate response to SARS-CoV-2 vaccine or infection.
Safety and Efficacy of FDA EUA and Approved COVID-19 Vaccines

**mRNA COVID-19 Vaccines**

In December 2020, the FDA granted EUA to two mRNA vaccines to prevent COVID-19: BNT162b2 manufactured by Pfizer-BioNTech and mRNA-1273 by Moderna, respectively (Table 1). In addition, the Pfizer-BioNTech received full FDA approval on August 23, 2021 as a two dose series for those 16 years of age and older. Both vaccines are based on the SARS-CoV-2 spike glycoprotein antigen encoded by mRNA in lipid nanoparticles. The spike glycoprotein antigen mediates binding of the virus to the ACE2 receptor on host cells to enable viral entry and replication. In both vaccines, the mRNA encodes the spike glycoprotein antigen stabilized in its prefusion form, which more closely resembles the intact virus.

VE for the Pfizer-BioNTech primary endpoint (confirmed COVID-19 occurring at least 7 days after the second dose in participants without serological or virological evidence of past SARS-CoV-2 infection) was 95.0%, while VE for the Moderna primary endpoint (COVID-19 occurring at least 14 days after the second dose in participants who were negative for SARS-CoV-2 at baseline) was 94.1% (Figure 2). In both vaccines, reactogenicity and adverse events were generally milder and less frequent in older than in younger participants and more frequent and more severe after the second dose (Figure 3). Real world data has confirmed clinical trial results with vaccine efficacy in multiple studies generally greater than 80% against SARS-CoV-2 infection and greater than 90% against symptomatic disease. While reduction in neutralization titers have been observed against some variants, VE against severe disease and hospitalization has been largely preserved, although there is concern that protection may wane with time from vaccination. See Supplemental Text for additional information regarding these currently authorized/approved mRNA vaccines.

**Adenoviral Vector COVID-19 Vaccines**

The J&J/Janssen vaccine (Ad26.COV2.S) is a replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding a variant of the SARS-CoV-2 spike protein in a stabilized conformation. It is an intramuscular vaccine administered as a single dose containing 5x10¹⁰ viral particles (0.5 mL). The multiple-dose vials have a shelf life of 3 months when stored between 2 °C to 8 °C. Once the first dose is withdrawn, the vial must be used within 6 hours at 2 °C to 8 °C or within 2 hours at room temperature.

An EUA was granted by the FDA on February 27, 2021 based on median two months follow-up data from an ongoing registration Phase 3 randomized, double-blind, placebo-controlled trial (VAC31518COV3001). The Phase 3 trial enrolled adult participants ≥18 years stratified by age (younger, 18-59 years; older, ≥60 years) and comorbidities, including liver disease and SOT. A two-dose regimen of Ad26.COV2.S is the subject of an ongoing Phase 3 study and additional studies are planned in pregnant women.

In the Phase 3 J&J/Janssen trial, approximately 40,000 participants were randomized 1:1 to receive Ad26.COV2.S or placebo. Median age was 51.1 years and 55.5% were male. Most participants were White (62.1%), 17.2% Black, 3.5% Asian, 14% other racial groups, and 45.1% were Hispanic/Latino. There were 46.7% participants in the USA, 17.3% in Brazil, and 12.7% in South Africa. There were 40.8% of participants with one or more comorbidities, most commonly obesity and hypertension.

VE for the primary endpoints (co-primary efficacy endpoints of molecularly confirmed, moderate to severe/critical COVID-19 occurring at least 14 and 28 days after vaccination in participants without evidence of SARS-CoV-2 infection before vaccination) was 66.9% (95% CI 59.0-73.4) for the ≥14-day endpoint and 66.1% (95% CI 55.0-74.8) for the ≥28-day endpoint (Figure 2). For the ≥14-day endpoint, there were 116 COVID-19 cases in the vaccine group and 348 COVID-19 cases in the placebo group, and 66 and 193 cases, respectively,
that occurred ≥28 days after vaccination. VE was lower in South Africa, where there is a predominance of the B.1.351 SARS-CoV-2 variant (52.0%, 95% CI 30.3-67.4 for ≥14-day endpoint; 64.0%, 95% CI 41.2-78.7 for ≥28-day endpoint) compared to the USA (74.4%, 95% CI 65.0-81.6 for ≥14-day endpoint; 72.0%, 95% CI 58.2-81.7 for ≥28-day endpoint). Similar VE was observed across subgroups defined by age, comorbidity, race, and ethnicity. VE was lower for older participants (≥60 years) with comorbidities (42.3%, 95% CI -13.1-71.6) compared with the overall population.

In analyses of secondary endpoints (central laboratory-confirmed and blind-adjudicated severe/critical COVID-19 occurring ≥14 days and ≥28 days after vaccination), VE was 76.7% (95% CI 54.6-89.1) and 85.4% (95% CI 54.2-96.9), respectively. This is the basis of the widely reported VE of 85% against severe COVID-19. There were no COVID-19 cases requiring hospitalization after 28 days post-vaccination compared to 5 cases in the placebo group. There were no COVID-19-related deaths in the vaccine group and 7 COVID-19-related deaths in the placebo group. Antibody titers generated by Ad26.COV2.S continue to increase up to at least day 56, after vaccination and there is evidence that protection against severe or critical COVID-19 may reach 95%. The results suggest potential efficacy against asymptomatic infection after 29 days post-vaccination, but the numbers are small and follow-up time is still limited. It is unknown if Ad26.COV2.S prevents SARS-CoV-2 transmission by vaccinated individuals.

Safety data are available from 43,783 participants with a median of two months of follow-up. Similar to the mRNA COVID-19 vaccines, the most common adverse reactions were mild/moderate and included injection site pain (48.6%), headache (38.9%), fatigue (38.2%), and myalgia (33.2%). Also similar to the mRNA vaccines, reactogenicity was less frequent in the older than the younger group (Figure 3).

Post-Marketing Reports of Adverse Events to COVID-19 Vaccines

**Common Side Effects**

The most frequent side effects reported to the Vaccine Adverse Event Reporting System (VAERS) from 13,749,904 mRNA doses given between December 14, 2020 and January 13, 2021 were injection site pain (70.9%), fatigue (33.5%), and headache (29.5%) in 1,602,065 individuals enrolled in the prospective V-Safe study. In addition, no unexpected patterns of reactions or safety concerns have been identified in that cohort thus far.31 Similarly, among 338,700 V-Safe participants who received the J&J/Janssen (Ad26.COV2.S) vaccine, the most frequent side effects reported 7 days after vaccination were fatigue (59.1%), injection site pain (57.9%), headache (52.2%), myalgia (47.8%), fever (34.7%), and chills (34.2%).30,31 The safety of additional doses of a COVID-19 vaccine in those with a previous severe systemic reaction is not known and, therefore, we recommend that those patients should discuss the risk versus benefit of additional doses with their local physician.

**Anaphylactic Reactions to mRNA COVID-19 Vaccines**

During December 14-23, 2020, monitoring by VAERS detected 21 cases of anaphylaxis after administration of a reported 1,893,360 first doses of the Pfizer-BioNTech mRNA COVID-19 vaccine (11.1 cases per million doses).32 Seventy-one percent of these occurred within 15 minutes of vaccination, 17 (81%) had a documented history of allergies or allergic reactions, and 90% were female. Nineteen (90%) were treated with epinephrine, four (19%) were hospitalized (including three in intensive care), and 17 (81%) were treated in an emergency department. No deaths from anaphylaxis were reported after receiving the Pfizer-BioNTech COVID-19 vaccine.
Similarly, during December 21, 2020 to January 10, 2021, monitoring by VAERS detected 10 cases of anaphylaxis after administration of a reported 4,041,396 first doses of the Moderna mRNA COVID-19 vaccine (2.5 cases per million doses). Ninety percent of these occurred within 15 minutes of vaccination, 9 (90%) had a documented history of allergies or allergic reactions, and 100% were female. All patients were treated with epinephrine, 6 (60%) were hospitalized (including five in intensive care), and 17 (81%) were treated in an emergency department. No deaths from anaphylaxis were reported after receiving the Moderna COVID-19 vaccine.

A more recent report from the CDC summarized the safety reporting to VAERS from 13,749,904 mRNA vaccine doses given between December 14, 2020 and January 13, 2021. The overall incidence of anaphylaxis was 4.5 cases per million doses administered and is comparable to the rate seen with inactivated influenza vaccine (1.4 per million), pneumococcal vaccine (2.5 per million), and live attenuated herpes zoster vaccine (9.6 per million). Polyethylene glycol (PEG), used to stabilize the lipid nanoparticles and prolong their half-life in both mRNA vaccines, has been implicated as a potential cause for anaphylaxis.

It is unclear why the vast majority of cases of anaphylaxis occurred in women; however, more women than men received the first doses of the mRNA COVID-19 vaccines during the analytic period.

**Anaphylactic Reactions to J&J Adenoviral Vaccine**

As of April 21, 2021, 7.98 million doses of the J&J/Janssen (Ad26.COV2.S) vaccine had been administered, 50% were administered to women. Seventy-nine cases of suspected anaphylaxis after vaccination were reported to VAERS during this time, among which four were confirmed to be anaphylaxis (<0.5 cases per million) and four remained under review.

**Delayed Localized Cutaneous Reactions to mRNA Vaccines**

Delayed localized cutaneous reactions, also known as “COVID arm” have been reported with the Moderna and Pfizer-BioNTech vaccines. In contrast to the local injection site pain and swelling that is reported on average one day after vaccination and lasts a median two-three days, onset of COVID arm is typically seven days after injection with median duration of five days. Histologic findings are consistent with a delayed-type dermal hypersensitivity reaction and may represent a T cell mediated response to a vaccine component. Importantly, this reaction is distinct from immediate hypersensitivity reactions such as anaphylaxis and urticaria. The delayed localized cutaneous reaction is self-limited and is not a contraindication to subsequent vaccination; however, patients should be counseled that it may recur and may develop sooner after the second vaccine dose.

**Myocarditis and Pericarditis with mRNA COVID-19 Vaccines**

Myocarditis is inflammation of the heart muscle and, when accompanied by pericarditis, is referred to as myopericarditis. Idiopathic myocarditis most commonly occurs in males more than females in the general population and its incidence is highest in infants, adolescents, and young adults. On June 23, 2021, the ACIP reviewed instances of myocarditis and pericarditis in individuals receiving the Pfizer-BioNTech and Moderna mRNA vaccines. A total of 1226 events were reviewed. The majority of individuals were young with a median age of 26 years and the median time to symptom onset was three days after vaccination with 76% of the cases occurring after the second dose. There was a preponderance of males (76%) in this series. Among the 323 patients under the age of 30 who had full data available for review, 96% were hospitalized but none had died. A
clinical syndrome of troponin elevation with or without EKG changes was noted. There were also rare instances of new onset biventricular cardiomyopathy.

The overall incidence of myopericarditis was 10.6 per million individuals receiving 2 doses and highest in younger individuals. Recommended management of myopericarditis includes bedrest for two to three weeks, NSAIDs in mild to moderate cases, corticosteroids for moderate to severe hospitalized patients, and inpatient monitoring for patients with symptomatic arrhythmias or evidence of cardiomyopathy. The ACIP recommends that overall benefit exceeds risk and that practitioners should continue to support this vaccine. The EUA fact information was modified to include information regarding the signs, symptoms, and incidence of myopericarditis.

**Thrombosis with Thrombocytopenia (TTS) Events with Adenoviral Vector COVID-19 Vaccines**

Thrombosis with thrombocytopenia syndrome (TTS) had been reported with both the Ad.26.COV2.S (J&J) and with the AstraZeneca adenoviral vectored vaccine resulting in a temporary pause in April 2021 in the use of the J&J vaccine in the USA. This rare syndrome with an estimated incidence of three per million receiving the J&J vaccine is caused by the rapid development of PF4 antibodies similar to those generated in some individuals by heparin. Middle aged women (30-49 years) had the highest incidence at 8.8 cases per million doses. The most common sites of thromboses were cavernous sinus followed by splanchnic thromboses and deep venous thromboses of the legs. The 34 thrombotic events all occurred within 15 days of vaccine administration. Coincident clotting and bleeding in the setting of thrombocytopenia may occur, and heparin use should be avoided. PF4 antibody testing is utilized as part of the diagnostic algorithm, and in suspected cases hematology consultation is advised. The CDC and FDA analysis determined that the J&J vaccine should continue to be used in all groups and that benefits outweigh the risks of this rare syndrome.

**Guillain-Barre and Other Neurological Adverse Events with COVID-19 Vaccines**

Acute inflammatory demyelinating syndrome (AIDP) or Guillain-Barre Syndrome (GBS) is an acquired autoimmune condition involving injury to myelinated cells on spinal roots and peripheral and cranial nerves. It classically presents with monophasic progression of symmetric, ascending weakness, sensory loss, and areflexia over two to four weeks. On July 22, 2021, the ACIP reviewed 100 spontaneous reports of GBS following COVID-19 vaccination that occurred within six weeks of the J&J vaccine, with 95% requiring hospitalization but only one death. The median patient age was 57 years (range: 24 to 76) with 83% of the cases in adults aged 18 to 64 and 16% in those over the age of 65 years. The incidence of GBS was 7.8 cases per million individuals vaccinated and five times higher than the background rate. The highest rate was in males aged 50 to 64 years with 15.6 cases per million. In July 2021, the package information of the EUA of the J&J vaccine was modified to include GBS as a potential side effect. However, overall benefit of J&J vaccine is felt to exceed risk. The incidence of GBS following mRNA vaccines has been within the expected range.

**Autoimmune Hepatitis and Other Autoimmune Phenomena**

Rare cases of autoimmune hepatitis developing within several days to weeks of subjects receiving COVID-19 vaccine have been reported. Subjects had detectable serum autoantibodies and responded to corticosteroids; no deaths or liver transplants have been reported. Similarly, case reports of other autoimmune phenomena such as hemolytic anemia and idiopathic thrombocytopenic purpura (ITP) have also been
GUIDANCE FOR ADVERSE REACTIONS TO COVID-19 VACCINES

- Anyone with a history of severe or immediate allergic reaction to any vaccine components, including PEG, should NOT receive either mRNA COVID-19 vaccine without consultation with an allergist.
- Anyone with a severe or immediate allergic reaction to the first dose of an mRNA COVID-19 vaccine should NOT receive additional doses of either mRNA COVID-19 vaccine without consultation with an allergist.
- Rare instances of thromboembolic events have been reported following use of adenoviral COVID-19 vaccines. In addition to hematology consultation, diagnostic testing for anti-PF4 antibody is recommended and heparin should be avoided.
- Rare instances of neurological adverse events have been reported including Guillain-Barre Syndrome (GBS) within six weeks of the J&J vaccine at a higher rate than seen in the general population. Hospitalization and possible use of IVIG and plasmapheresis are recommended under the guidance of a neurology consultant.
- Rare instances of cardiac adverse events including myocarditis and pericarditis have been reported within three to seven days following the mRNA vaccines. Affected individuals are generally younger and male with most cases being mild and self-limited. Recommended management includes supportive care, NSAIDs, and corticosteroids in moderate to severe cases that are hospitalized under the care of a cardiologist.
- Rare cases of autoimmune hepatitis, ITP, hemolytic anemia, and other autoimmune phenomena have been reported with COVID-19 vaccines. Causality versus coincidence in these circumstances has not been established due to the small numbers of cases reported.
- Consultation with a local expert and review of the VAERS database is recommended to find the latest information on the incidence and clinical presentation of COVID-19 vaccine-associated adverse events.

SARS-CoV-2 Viral Variants

When SARS-CoV-2 replicates, the RNA sequences are copied and, because they share the same sequences, the parent and progeny can be identified and are considered a lineage. Mistakes occur when copying the nucleotides and those new nucleotides are also passed down. When enough genomes are identified that share a new nucleotide change (for example, recovered from at least five people), those are considered a new lineage of variants. In some naming systems, a lineage is given a designation like B.1 and subsequent lineages further denoted as B.1.1 and B.1.1.7 to show both the distinct family and the ancestral relationship. Variants were initially characterized by the geographic location where they were first identified, such as in the UK, South Africa, Brazil, India, or New York variants. Despite being convenient, that geographic nomenclature was misleading and was replaced on June 1, 2021 by the WHO with a Greek alphabetical system (Table 4 and Table 5).

Variants are classified into groups to reflect escalating actual or projected public health impact beginning with local or regional observations, which are called variants of interest (Table 5), to those having global impact,
which are called variants of concern (Table 4). The USA CDC also has another category called variants of high consequence to refer to variants that have been shown to significantly reduce preventive or therapeutic countermeasures. Multiple factors affect those designations. Improved understanding of the mechanisms of SARS-CoV-2 pathogenesis and medical countermeasures has focused special attention on nucleotide mutations that alter key amino acids that might increase fecundity, increase binding to receptors or tropism for cells in the lower respiratory tract, reduce detection by diagnostic assays, and/or diminish the ability of antibodies to block virus entry. When such mutations are recognized, the variants are denoted as being “of interest” and monitored closely. However, the most important factors differentiating the level of interest or concern are how rapidly the variant overspreads a population (as an indication that it has increased transmissibility), whether there appears to be greater pathogenicity (generally measured by the case fatality rate), and how well antibodies produced by SARS-CoV-2 vaccination neutralize those variants (often measured using plasma from a vaccinated person to neutralize infection in cell culture). When these features are observed, a variant of interest may be reclassified as a variant of concern. Note that the naming hierarchy assumes an accumulation of properties such that a variant of concern has all the attributes of a variant of interest and more.

Although there are no variants of high consequence as of July 15, 2021, there are at least 4 important examples of variants of concern (Table 4): Alpha, originally referred to as B.1.1.7 and associated with spread in the UK;48 Beta, originally referred to as B.1.351 and associated with spread in South Africa;49 Gamma, originally referred to as P.1 and associated with spread in Brazil;50 and Delta, originally referred to as B.1.617.2 and associated with spread in India.51 Compared to the original SARS-CoV-2 sequence, all these variants of concern have mutations in the sequences that encode the key spike protein that mediates cell entry. All of these variants have been found in the USA52–54 and are more transmissible than the original SARS-CoV-2.48,55 The Alpha variant may be associated with higher morbidity and mortality.52,56 These mutations can impair or abolish the neutralizing effects of some of the available monoclonal antibodies. For example, the EUA initially granted on November 9, 2020 for bamlanivimab was revoked on April 16, 2021 as the proportion of SARS-CoV-2 in the USA that was not effectively neutralized by the antibody rose,57 and the combination product (bamlanivimab/etesevimab) was revoked on June 25, 2021.58 Despite some evidence in vitro of reduced neutralization, studies suggest that both Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines likely provide some protection against these variants of concern.59–61 The AstraZeneca vaccine and the single dose J&J vaccine have been shown to have reduced effectiveness against the Beta variant and single doses of the two-dose series of mRNA vaccines or AstraZeneca vaccine have reduced effectiveness against the Delta variant highlighting the importance of completing a vaccine series to maximize protection.62 As of August 2021, the Delta variant has overspread the USA and many other regions of the world, accounting for over 95% of newly reported cases. Delta appears to be considerably more transmissible than other variants, even than other variants of concern. In one study, Delta virus quantities in respiratory secretions were 1000-fold higher than those from persons infected early in the epidemic with viruses from the A/B lineage.

There are also notable variants of interest (Table 5). For example, the WHO-named Iota variant (also called B.1.526), has notable mutations N501Y and E484K. Iota was first detected in New York City in November 2020 and has reduced susceptibility to bamlanivimab and etesevimab.63 However, Iota has not overspread the USA suggesting its transmissibility is not substantially increased, or at least is lower than other variants like Delta. Epsilon, also named B.1.429, was first identified in California and appeared to have increased transmissibility and reduced susceptibility to bamlanivimab and etesevimab. However, Epsilon did not spread widely nor
markedly reduce the effectiveness of vaccination, and on June 29, 2021, Epsilon was de-escalated from a variant of concern to a variant of interest.

GUIDANCE REGARDING THE CLINICAL IMPACT OF SARS-COV-2 VIRAL VARIANTS

- Withholding or delaying COVID-19 vaccination because of concerns about current or future SARS-CoV-2 viral variants is NOT recommended
- Use of monoclonal antibodies and convalescent plasma for patients with COVID-19 infection or to prevent primary infection should reflect up-to-date information on SARS-CoV-2 variants prevalent in the community.
- Testing for SARS-CoV-2 viral variants is not commercially available and not recommended for medical decision making on an individual patient basis.

Pediatric Considerations in COVID-19 Vaccination

The CDC recommends COVID-19 vaccination for everyone aged 12 years and older to help protect against COVID-19, community transmission, and potential severe complications, such as multisystem inflammatory syndrome in children (MIS-C). The Pfizer-BioNTech mRNA vaccine was authorized for children aged ≥12 years on May 10, 2021. In Phase 2-3 clinical trials in children 12 years and older, both Pfizer-BioNTech and Moderna mRNA vaccines demonstrated 100% efficacy after the two-dose series with no vaccine-related serious adverse events. In addition, systemic side effects of fever, fatigue, and muscle aches were substantially lower compared to adults receiving the same vaccine. There have been reports of myocarditis and pericarditis occurring after mRNA COVID-19 vaccination, particularly after receiving the second dose and in male adolescents and young adults >16 years of age.

There is no longer any minimum duration between COVID-19 vaccination and other vaccines. The COVID-19 vaccines may be co-administered with other childhood vaccines. If multiple vaccines are given at a single visit, the CDC recommends that each injection be in a different site within the deltoid muscle for adolescents.

With regards to return to school, since most school-aged children are not eligible for the COVID-19 vaccine, the CDC has recommended universal indoor masking and physical distancing as key prevention strategies, but formal guidance about vaccine requirements and masking is dictated by individual locales.

COVID-19 VACCINES IN PATIENTS WITH CHRONIC LIVER DISEASE AND IMMUNOSUPPRESSION

Patients with Liver Disease in COVID-19 Vaccine Clinical Trials

Patients with stable chronic medical conditions such as compensated CLD, HIV, HBV, or HCV were eligible to participate in the Pfizer-BioNTech, Moderna, and J&J/Janssen phase 3 trials. Those on immunosuppressive therapy were excluded from the Pfizer-BioNTech and Moderna trials, while a small number of SOT recipients were included in the J&J/Janssen trial.
In the Pfizer-BioNTech phase 2/3 trial, 20.5% of study participants had a comorbidity defined by the Charlson Comorbidity Index categories, which include liver disease (8030 with a comorbidity received BNT162b2 and 8029 received placebo). VE was 95.3% in participants with comorbidities and was similar to that seen in participants without comorbidities (94.7%). Among the 214 participants (0.6%) with liver disease, 124 received BNT162b2 and 90 received placebo, but safety and efficacy data in this subgroup have not been reported.

In the Moderna phase 3 trial, at least one high-risk condition was present in 22.3% of the participants. Among the 196 (0.6%) participants with liver disease, 100 received mRNA-1273 and 96 received placebo. Given that no participants with liver disease developed COVID-19, VE cannot be determined for this subgroup.

In the J&J/Janssen phase 3 trial, 40.8% of participants had one or more comorbidities, including liver disease and SOT. Among the 206 (0.5%) participants with liver disease, 103 received Ad26.COV2.S and 103 received placebo. There were 10 immunocompromised participants who were recipients of SOT (seven in vaccine group and three in placebo group). Among participants with liver disease, one in the vaccine group and two in the placebo group developed moderate to severe/critical COVID-19 ≥14-days after vaccination. Interpretation of these results is limited by the small sample size and low incidence of COVID-19. Data on the incidence of COVID-19 in the SOT subgroup have not been reported.

### PRINCIPLES REGARDING COVID-19 VACCINATION AND THE NEED FOR ADDITIONAL DOSES

- **For LT candidates,** vaccination against COVID-19 should proceed even if LT is likely to occur before the second or third mRNA vaccine dose can be administered. The second dose of mRNA vaccine should be given at the earliest appropriate interval after transplant (e.g., four weeks posttransplant).
- **Health care providers** should be knowledgeable of the local criteria for vaccination, know where vaccine is available, and actively inform patients of this information.
- **Routine non-COVID-19 vaccines** should be given as scheduled while a patient is receiving their COVID-19 vaccines with no need to delay or alter their administration.
- **A third dose of an mRNA vaccine** is authorized and recommended for all moderate to severely immunocompromised adults who have received a prior two-shot series of an mRNA vaccine because of their lower rate of response and increased risk for breakthrough infections.
- **The third dose of the mRNA vaccine** should be given at least 28 days after the last dose of the mRNA vaccine and should be the same (homologous) mRNA vaccine whenever possible, but the alternative (heterologous) mRNA vaccine can be used if necessary.
- **Given the hyporesponsiveness** of immunocompromised patients to COVID-19 vaccines, there is a compelling rationale to consider additional vaccine doses in recipients of the J&J vaccine, but this is currently not authorized by the FDA. The decision to administer an additional dose to a recipient of the J&J vaccine should be done via consultation with the patient’s local physician regarding the potential risk versus benefit of additional COVID-19 vaccine doses.
- **In some states,** administration of COVID-19 vaccine doses is registered in statewide vaccine registries. Clinicians should familiarize themselves with the location of vaccine administration information in the electronic medical record of their institution to assist eligible patients seeking an additional dose of an mRNA vaccine.
- **See Supplemental Text** for additional guidance for COVID-19 vaccination.
COVID-19 Vaccination in Patients with Chronic Liver Disease

Because of the increased morbidity and mortality with COVID-19 in adult CLD patients and particularly those with cirrhosis, we strongly recommend that these patients be prioritized for COVID-19 vaccination. Although safety and efficacy data with the three available COVID-19 vaccines in CLD patients are limited, adverse events are not anticipated to be more frequent, but it remains unclear if efficacy of the standard doses may be lower than in the general population.\(^\text{69–73}\)

While there are not yet robust data regarding antibody and cellular immune responses to these vaccines among patients with cirrhosis and different forms of CLD, some clinical efficacy data are emerging in real world datasets. A large cohort of patients with cirrhosis from the Veterans Administration (VA) was recently studied to understand the impact of the Pfizer-BioNTech and Moderna mRNA vaccines in patients with cirrhosis compared with a propensity-matched control group of unvaccinated patients at similar risk of infection and severe COVID-19.\(^\text{74}\) Patients with CLD who received at least one dose of the vaccine \(n=20,037\) were propensity matched with 20,037 controls to assess the association between vaccination and new SARS-CoV-2 infection and COVID-19 hospitalization and death. By 28 days after the initial dose, receipt of one dose of an mRNA vaccine was associated with a 64.8% reduction in SARS-CoV-2 infections and 100% protection against hospitalization or death because of COVID-19. The association of reduced SARS-CoV-2 infections after the first dose was lower among patients with decompensated (50.3%) compared with compensated cirrhosis (66.8%). Receipt of a second dose was associated with a 78.6% reduction in SARS-CoV-2 infections and 100% reduction in COVID-19-related hospitalization or death after seven days. However, this study was conducted largely prior to the emergence of Delta strains of COVID-19 in the USA and that the number of clinical outcomes reported was very small in both groups of patients. Therefore, additional real-world data are needed to confirm safety and efficacy in this population and those with chronic non-cirrhotic liver disease.\(^\text{75}\)

If the supply of COVID-19 vaccine is limited, it is reasonable to prioritize patients with higher Model for End-stage Liver Disease (MELD) or Child-Turcotte-Pugh scores for vaccination or those who are anticipated to undergo imminent LT, but all CLD patients should be vaccinated whenever possible. In the USA, where vaccines are widely available, there remains some vaccine hesitancy among patients with cirrhosis despite the increased risk of hospitalization and death. Recent data from the VA identified that those who are under-vaccinated were likely to be younger, White, a current or former smoker, resident of the Southeast, and resident of a rural area. These data could be used to steer vaccine education in this high-risk population. Debate remains regarding the ethical implications of requiring vaccination among transplant candidates specifically.\(^\text{76}\)

CDC recommendations regarding the need to wear masks once fully vaccinated continue to evolve, with current recommendations hinging largely upon local disease transmission.\(^\text{77}\) However, the CDC has acknowledged that immunocompromised hosts, including patients with liver disease on immunosuppression and transplant recipients, should continue to wear masks indoors and practice social distancing despite vaccination.

GUIDANCE FOR COVID-19 VACCINATION IN PATIENTS WITH CLD

- Patients with CLD who are receiving antiviral therapy for HBV or HCV or medical therapy for primary biliary cholangitis or autoimmune hepatitis should NOT withhold their medications while receiving the COVID-19 vaccines.
• Patients with hepatocellular carcinoma undergoing locoregional or systemic therapy should also be considered for vaccination without interruption of their treatment. However, patients with recent infections or fever should NOT receive the COVID-19 vaccine until they are medically stable.
• mRNA and adenoviral vector COVID-19 vaccines have a favorable efficacy and safety profile in patients with CLD in post-marketing studies and should be administered according to their standard dose and schedule.
• LT candidates should receive a COVID-19 vaccine prior to transplantation whenever possible to help ensure an adequate immune response. Some transplant centers are developing policies that require COVID-19 vaccination prior to living donor or deceased donor transplantation.
• All patients with CLD, including vaccine recipients, should continue to mitigate their risk of SARS-CoV-2 exposure (e.g., masking, social distancing, hand washing, etc.).
• An additional third dose of an mRNA vaccine is recommended at least 28 days after the last dose of an mRNA COVID-19 vaccine in all patients with hepatocellular carcinoma and CLD patients receiving prednisone, anti-metabolites, or biological therapies.
• It is not recommended to withhold immunosuppression prior to or after COVID-19 vaccine administration for the purposes of increasing the likelihood of vaccine efficacy.
• Due to their known hyporesponsiveness to vaccines in general and potentially severe outcome with SARS-CoV-2 infection, patients with cirrhosis, particularly decompensated cirrhosis, should be considered and prioritized for an additional mRNA vaccine dose after completing a two-dose vaccine series. However, additional data and formal authorization from the CDC and FDA are awaited to routinely administer a third mRNA dose in patients with CLD.
• See “Counseling Liver Disease Patients About COVID-19 Vaccination” for guidance on answering common questions from patients.

COVID-19 Vaccination in Immunosuppressed Liver Transplant Recipients

Immunocompromised people comprise nearly 2.7% of USA adults including patients with solid tumor and hematological malignancies, recipients of SOT, persons with HIV infection, and subjects receiving immunosuppressive medications. These individuals have been shown to be at increased risk for adverse outcomes with SARS-CoV-2 infection. Given that immunocompromised patients and SOT recipients were not included in the mRNA COVID-19 vaccine trials and only a small number were included in the adenoviral vector vaccine studies, there are limited data regarding the safety and efficacy of the available vaccines in this population. Johns Hopkins recently reported preliminary results of a study of SOT recipients in the USA who received early vaccination with one of the mRNA COVID-19 vaccines. In 187 SOT recipients, including 64% frontline health care workers and 19% LT recipients, vaccine reactogenicity was mild and similar to rates reported in the non-transplant population. There were no early reported episodes of acute cellular rejection (ACR), SARS-CoV-2 diagnoses, or major allergic reaction. Among 436 SOT recipients, including 78 LT recipients, only 17% developed antibodies to the SARS-CoV-2 spike protein at a median of 20 days after the first dose of mRNA COVID-19 vaccine. This compares to spike antibody detection in 100% of participants in the clinical trials by day 15 (mRNA-1273) or day 21 (BNT162b2) following vaccination. SOT recipients on antimetabolite maintenance immunosuppression were less likely to develop an antibody response (37% vs. 63%), as were older recipients. For unclear reasons, those who received mRNA-1273 were more likely to develop an antibody
response than those receiving BNT162b2 (69% vs. 31%). In multiple other studies in transplant recipients, VE after two mRNA doses in SOT recipients has not exceeded 60%. As seen with other vaccines, antibody responses may not predict cellular responses in SOT recipients and thus it may be difficult to estimate the overall level of protection based solely on antibody responses. In case series, LT recipients may have a better serological response, but it is unclear if there is a lower risk of infection compared to other SOT recipients (not on anti-metabolites). Risk factors for lower serological response include older recipient age, use of anti-metabolite drugs, time from transplantation, and B cell-depleting therapies.

**Additional Doses of COVID-19 mRNA Vaccines in Immunocompromised Patients**

Numerous studies have shown reduced serological and cellular immune responses to COVID-19 vaccines in immunosuppressed populations including SOT recipients. The majority of studies have focused on kidney transplant recipients with more limited data in LT recipients and patients with CLD. This mirrors the reduced responses observed in immunosuppressed populations to other vaccines and has raised the question regarding protection from hospitalization or severe COVID-19 in SOT recipients. It is difficult to determine effectiveness given that most reports do not include comprehensive denominator data. In one study of immunocompromised patients including SOT recipients in Israel, mRNA vaccines were 71% effective against SARS-CoV-2 infection. In a preprint of the IVY hospital consortium in the USA, full vaccination with an mRNA vaccine was 50%-60% effective against hospitalization among immunocompromised individuals, significantly lower than the protection observed among immunocompetent individuals. Another recently published report of COVID-19 vaccine effectiveness in a kidney transplant cohort showed a much higher level of protection with respect to the development of symptomatic disease. However, breakthrough infections, particularly with the Delta variant, appear to be more common in immunosuppressed transplant recipients than in non-immunosuppressed individuals.

Limited information is available regarding the benefit of a third dose of mRNA COVID-19 vaccines in immunocompromised individuals. Among those who had no detectable antibody response to an initial two-dose mRNA vaccine series, 33%-50% developed an antibody response to an additional dose.

In a study from France of 101 patients with SOT, 40 patients (40%) had no detectable antibody response to an initial Pfizer-BioNTech mRNA vaccine series. The first two doses were given one month apart, and the third dose was administered 61 ± 1 days after the second dose. In patients who were seronegative after the second dose, antibody response was seen in 26 patients (44%) after the third dose. No serious adverse events were reported after administration of the third dose and the were no episodes of ACR. Patients who did not have an antibody response were older, had a higher degree of immunosuppression, and had a lower estimated glomerular filtration rate than patients who had an antibody response.

In a recent study from Canada, 120 SOT recipients who had received two doses of mRNA-1273 (Moderna) were randomly assigned in a 1:1 ratio to receive either a third dose or placebo two months after the second dose of mRNA-1273. The primary outcome was a serologic response at four months characterized by an anti-receptor-binding domain (RBD) antibody level. An anti-RBD antibody level of 100 U per milliliter has been found to correlate with 50% in vitro virus neutralization. At month four, an anti-RBD antibody response was present in 33 of 60 patients (55%) in the mRNA-1273 group and only in 10 of 57 patients (18%) in the placebo group. The third dose also significantly increased neutralizing antibody and cellular immune response to SARS-CoV-2 compared to placebo. Local and systemic events were slightly more common after the third dose of mRNA-1273 than after the placebo but no grade 3 or 4 events, hospitalizations, and no cases of ACR were reported. Overall,
despite limited studies, current data suggest a benefit of a third vaccine dose, at least with the mRNA-1273 vaccine, and that it appears to be safe.

Growing data suggest that immunocompromised individuals are more likely to become severely ill from COVID-19 and are at higher risk for prolonged infection, which contributes to transmission. They are also at increased risk for breakthrough infection after vaccination, with 44% of hospitalized breakthrough cases in the USA occurring in this population. Despite limited data, on August 12, 2021, the FDA modified the EUAs for COVID-19 vaccines to allow for administration of an additional dose (i.e., a third dose) of an mRNA COVID-19 vaccine after an initial two-dose primary mRNA COVID-19 vaccine series for selected moderate to severely immunocompromised people (Table 6). This group includes SOT recipients and others diagnosed with conditions that are considered to have an equivalent level of immunocompromise. On August 13, 2021, ACIP also made an interim recommendation for use of an additional dose of Pfizer-BioNTech COVID-19 vaccine (for persons aged ≥12 years) or Moderna COVID-19 vaccine (for persons aged ≥18 years) at least 28 days after an initial two-dose mRNA COVID-19 vaccine series for moderately to severely immunocompromised people. There is currently no authorization for additional vaccine doses for individuals who received the J&J/Janssen vaccine.

It is also well recognized that different medical conditions and treatments can result in widely varying degrees of immunosuppression. Although the CDC does not explicitly specify patients with cirrhosis or portal hypertension with leukopenia, these patients do have known immune deficits and hyporesponsiveness to multiple vaccines. In addition, the rapid spread of the highly transmissible Delta variant worldwide with associated hospitalizations further increases the potential for breakthrough infection in these hyporesponsive patients. Therefore, we believe that patients with cirrhosis should be prioritized for additional mRNA COVID-19 vaccine doses but await additional data and formal authorization and recommendations from the CDC and FDA.

Other unknowns regarding vaccination of LT recipients include:
1. Efficacy of the immune response to the vaccine to prevent SARS-CoV-2 infection and moderate/severe COVID-19 in SOT recipients.
2. Whether the duration of vaccine-conferred immunity differs from immunocompetent hosts.
3. Whether intensified immunosuppression in the immediate posttransplant period and following treatment of ACR reduces VE.
4. The best timing, dosing regimen, and safety of vaccine administration for patients who had COVID-19.
5. The frequency of elevation of liver tests or ACR following vaccination.
6. The best choice of vaccine in this population.

Despite these uncertainties, the available COVID-19 vaccines do not contain live or attenuated virus and therefore are unlikely to pose a safety concern for immunosuppressed patients. Given that replication defective or nonreplicating vaccines have not yet been tested in SOT recipients or other immunosuppressed patients, additional data are needed before use of these COVID-19 vaccines can be recommended in these patients.

GUIDANCE FOR COVID-19 VACCINATION IN LIVER TRANSPLANT RECIPIENTS
- COVID-19 vaccination is recommended for all SOT recipients including LT recipients.
- If a COVID-19 vaccine is not administered prior to transplantation, the optimal time to administer the COVID-19 vaccine is likely at least three months post-LT when immunosuppression is lower and other
prophylactic medications are stopped or minimized. However, given the ongoing community spread of SARS-CoV-2, immunization may be initiated as early as four weeks posttransplant, especially for the highest-risk individuals with other comorbid factors associated with severe COVID-19.

- A reduction in immunosuppression is NOT RECOMMENDED in LT recipients solely to elicit an immune response to immunization against SARS-CoV-2 because there is a risk of acute cellular rejection (ACR) with lower immunosuppression.
- In order to optimize response, COVID-19 vaccination should be avoided in LT recipients with active ACR, those being treated for ACR, or those on high daily doses of corticosteroids, until the episode is resolved and their baseline immunosuppression reestablished.
- In patients whose liver tests increase after vaccination and do not immediately return to baseline on repeat testing, a thorough evaluation should follow to exclude ACR or viral infection of the liver.
- Given the life-saving nature of LT, deceased donor transplantation should NOT be delayed in a patient who received a COVID-19 vaccine.
- If a patient is due for a second dose of an mRNA vaccine in the immediate posttransplant period, this may be delayed at least four weeks to elicit a better immune response.
- Some programs are developing policies to require COVID-19 vaccination in living liver donors and recipients. We recommend that potential live liver donors and recipients of live donor livers should be prioritized for COVID-19 vaccination and preferably vaccinated at least two weeks before transplantation when feasible. However, a lack of COVID-19 vaccination should NOT delay life-saving living donor LT.
- Family members and caregivers of LT recipients should be vaccinated against SARS-CoV-2 whenever possible.
- An additional mRNA vaccine dose using an homologous vaccine is currently recommended for moderate to severely immunosuppressed individuals in the USA including all SOT recipients.
- The additional third mRNA COVID-19 vaccine dose should be administered at least 28 days after the completion of the initial two-dose mRNA COVID-19 vaccine series.
- See Table 7 for additional recommendations regarding additional COVID-19 mRNA vaccine doses in moderate to severely immunocompromised individuals.

COVID-19 Vaccination Knowledge Gaps

Only a small number of patients with advanced CLD were included in the COVID-19 vaccine clinical trials and a small number of LT recipients were included in the J&j/Janssen studies. As such, scant data on effectiveness and safety are available for these populations. Post-marketing research of vaccines currently authorized/approved in the USA is needed regarding the antibody response to COVID-19 vaccines in patients with chronic conditions, including cirrhosis and autoimmune diseases, and the duration of protection from acute and long COVID-19. Based on limited data, the FDA and CDC recently recommended persons who are moderately to severely immunocompromised should receive an additional dose of mRNA COVID-19 vaccine after the initial two doses. Recipients of SOT are recommended to receive the three-dose vaccine schedule. Studies of the effectiveness of a three-dose schedule are in progress. Studies of COVID-19 vaccination of patients with CLD are underway in other countries. Although these studies involve vaccines not yet licensed in
the USA, the findings will be informative for future policy development (ClinicalTrials.gov identifiers: NCT04775056, NCT05007665, NCT04794946). Acute and chronic liver diseases encompass a wide spectrum of etiologies and severity of disease and thus represent a heterogeneous population. Furthermore, there are known racial and ethnic differences in prevalence and incidence of various liver diseases. Several confounders, such as obesity, diabetes mellitus, hypertension, and alcohol use, may impact immune regulation, liver disease progression, and severity that are relevant in the context of vaccination. Cirrhosis is inherently a state of qualitative and quantitative immune dysregulation. Increasing liver disease severity has been associated with lower non-COVID-19 vaccine responsiveness. These large knowledge gaps related to liver disease and transplantation require special attention in further studies.

CONCLUSION

Since the identification of the SARS-CoV-2 genome in January 2020, remarkable progress has been made in the development of highly effective and generally safe vaccines for COVID-19. The CDC currently recommends that all individuals over the age of 12 years should receive the two-dose mRNA vaccines or single-dose adenoviral vector vaccine (age ≥18 years) according to the manufacturers’ recommendations to prevent future COVID-19. As of August 13, 2021, the CDC recommends that all moderately to severely immunocompromised patients including SOT recipients should receive a third dose of an mRNA vaccine at least 28 days after completion of the initial two-dose COVID-19 vaccine series. Due to their known hyporesponsiveness to vaccines and risk for severe COVID-19, all patients receiving moderate doses of steroids, other immunosuppressants, or immunosuppressing biologics are also authorized and recommended to receive an additional dose of the mRNA COVID-19 vaccine. Pre-vaccination and post-vaccination serological testing are not recommended because of the absence of studies regarding their impact on outcomes. SARS-CoV-2 variants of concern have been detected that have increased transmissibility (e.g., Delta) and potentially greater virulence in the USA and abroad, highlighting the urgency to vaccinate as many individuals as possible. Routine testing for SARS-CoV-2 variants of concern and variants of interest is not recommended for clinical care but rather for epidemiological studies. Any currently authorized COVID-19 vaccines are recommended for all patients with CLD (compensated or decompensated) and immunosuppressed SOT recipients. Although there is a low rate of breakthrough infection in vaccinated individuals, immunocompromised and older individuals are at greater risk of breakthrough infection.

The AASLD recommends that providers advocate for prioritizing patients with compensated or decompensated cirrhosis or liver cancer, immunosuppressed patients such as LT recipients, and living liver donors for COVID-19 vaccination based upon local health policies, protocols, and vaccine availability. The clinical impact of SARS-CoV-2 viral variants is rapidly evolving, and until further studies are available, COVID-19 vaccination should not be withheld or deferred in any patient because of efficacy or safety concerns outside from severe allergic reaction to any vaccine components. All COVID-19 vaccine recipients with CLD or SOT are recommended to continue social distancing, masking, and frequent hand washing, and follow other exposure-mitigating behaviors. Due to their known hyporesponsiveness to vaccines and potentially severe outcomes with COVID-19 infection, the AASLD believes that patients with cirrhosis, particularly those with decompensated cirrhosis, should be prioritized for additional mRNA COVID-19 vaccine doses after completing a two-dose mRNA vaccine series; however, additional data and formal authorization from the CDC and FDA are needed before widespread recommendation can be made for a third dose in patients with CLD.
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Helpful Websites and Resources

- AASLD COVID-19 and the liver website
- AASLD expert panel consensus statement on COVID-19
- Vaccine Adverse Event Reporting System (VAERS)
- Johns Hopkins Vaccine Tracker
- American Society of Transplantation COVID-19 Vaccine FAQ
- NIH COVID-19 Vaccines
- Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccine Recommendations
- Johns Hopkins COVID-19 Vaccine Research Study
- CDC: Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States
- COVID-19 Real-Time Learning Network
- COVID-19 vaccines and pregnancy: conversation guide for clinicians (American College of Obstetricians and Gynecologists)
### TABLES

#### Table 1. Summary of Currently Available COVID-19 Vaccines and Those in Phase 3 Trials Worldwide

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<td>mRNA BNT162b2 (Pfizer-BioNTech)</td>
<td>30 µg (0.3 mL) IM x 2 doses 21 days apart</td>
<td>95%\textsuperscript{12} (95.3% in those with comorbidities including CLD)</td>
<td>Synthetic lipid nanoparticle Contraindicated if history of severe or immediate allergic reaction to any vaccine components, including PEG*</td>
<td>Store between -80 °C to -60 °C to expiration date. Frozen -25° C to -15° C for up to 2 weeks. Refrigerated 2°C to 8°C for up to 5 days.</td>
</tr>
<tr>
<td>mRNA-1273 (Moderna)</td>
<td>100 µg (0.5 mL) IM x 2 doses 28 days apart</td>
<td>94.1%\textsuperscript{95}</td>
<td>Synthetic lipid nanoparticle Contraindicated if history of severe or immediate allergic reaction to any vaccine components, including PEG*</td>
<td>Frozen: -25 to -15°C to expiration date. Refrigerated: 2°C to 8°C for up to 30 days</td>
</tr>
<tr>
<td><strong>Adenoviral vectors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad26.COV2.S (Johnson and Johnson/Janssen)**</td>
<td>Single dose of 5x10\textsuperscript{10} viral particles (0.5 mL)</td>
<td>66.9% after 14 days post-vaccination</td>
<td>Replication-defective adenovirus 26 vector (used in Ebola vaccine)</td>
<td>Refrigerated: 2°C to 8°C until expiration date</td>
</tr>
<tr>
<td></td>
<td>EUA for ages 18 and older</td>
<td>85.4% for preventing severe/critical COVID-19 at least 28 days post-vaccination</td>
<td>Low seroprevalence of antibodies in N America</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccines in Phase 3 development</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoviral vectors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD1222 (AstraZeneca)</td>
<td>1 or 2 IM doses 28 day apart</td>
<td>70.4% (pooled) after the second dose</td>
<td>Replication-defective chimpanzee</td>
<td>Stored and distributed at 2 to 8°C for</td>
</tr>
</tbody>
</table>

\textsuperscript{12} CLD = chronic liver disease

\textsuperscript{95} PEG = polyethylene glycol

\textsuperscript{95} Ebola vaccine

\textsuperscript{95} Low seroprevalence of antibodies

\textsuperscript{95} N America
| Vaccine Type          | EUA in UK, Europe, and South America for ages ≥18 years | 62% standard dose (SD)/SD 90% low dose/SD\(^1^8\) Unknown in CLD patients | adenovirus vector 2 cases of transverse myelitis reported | up to 6 months |
|----------------------|--------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------|
| Ad5-NCoV (CanSino biologics) | 96%-97% antibody induction at day 28\(^2^2\) Replication-defective adenovirus type 5 vector | 2 to 8°C |
| Recombinant protein | NCX-CoV2373 (Novavax) 2 IM doses 3 weeks apart | 89.3% in UK study 49.4% in S Africa\(^2^4\) Recombinant spike protein nanoparticles Adjuvant of M-matrix which may be allergenic | 2 to 8°C |
| Inactivated virus   | CoronaVac (Sinovac) 50.4% protection in Brazilian study\(^2^6\) | Inactivated SARS-CoV-2 with alum hydroxide adjuvant | 2 to 8°C |
|                     | BBIBP-CorV Inactivated COVID-19 (Wuhan) 100% antibody induction at day 42\(^2^7\) | Inactivated whole virion SARS-CoV-2 | |

PEG: polyethylene glycol

* Ingredients include mRNA, lipids, polyethylene glycol, cholesterol, potassium chloride, potassium phosphate, sodium chloride, sodium phosphate, sucrose

** Ingredients include citric acid, citrate dehydrate, ethanol, 2-hydroxypropyl-B-cyclodextrin, polysorbate 80, sodium chloride, sodium hydroxide, and hydrochloric acid
Table 2. COVID-19 Vaccination Knowledge Gaps

- Effectiveness and safety in patients with CLD based on liver disease etiology, comorbidities, CTP class, and MELD score
- Effectiveness and safety in immunocompromised/immunosuppressed individuals including transplant recipients
- Effectiveness and safety in children < 12 years of age
- Effectiveness and safety in pregnant and lactating women
- Effectiveness and safety in individuals previously infected with SARS-CoV-2
- Effectiveness against SARS-CoV-2 variants of concern
- Effectiveness against asymptomatic infection
- Effectiveness against SARS-CoV-2 transmission
- Effectiveness against long-term effects of COVID-19
- Effectiveness and safety in a diverse population including different racial and ethnic backgrounds
- Effectiveness and safety of vaccination with a different vaccine following a prior allergic/anaphylactic reaction to a COVID-19 vaccine
- Duration of protective immunity against SARS-CoV-2 infection
- Mechanisms of vaccine failure
- Effectiveness of a three dose vaccine series for patients with CLD and SOT recipients
- Interpretation of serology and cell mediated immunity assays/clinical context
Table 3. Overview of Adverse Events Associated with COVID-19 Vaccines

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Vaccine association</th>
<th>Incidence (per million)</th>
<th>Time to onset</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic reaction</td>
<td>mRNA Adenoviral</td>
<td>2-5</td>
<td>Up to 1 hour</td>
<td>Immediate anti-histamine; epinephrine/steroids hospitalize if severe</td>
</tr>
<tr>
<td>Guillain-Barre Syndrome</td>
<td>Adenoviral</td>
<td>7.8 overall and up to 15.6 in males 50-64 years 100 cases reviewed</td>
<td>Median 13 days (r: 0 to 75 days) 98% within 6 week window</td>
<td>Hospitalize; IVIG if progressive; intubation and plasmapheresis if severe</td>
</tr>
<tr>
<td>Thromboses and thrombocytopenia syndrome</td>
<td>Adenoviral</td>
<td>3.0 overall and 8.8 in women 30-49 years</td>
<td>Within 15 days</td>
<td>Anti-PF4 antibodies Avoid heparin</td>
</tr>
<tr>
<td>Myocarditis/pericarditis</td>
<td>mRNA</td>
<td>10.6</td>
<td>Median 3 days</td>
<td>Supportive care NSAIDs/steroids if severe</td>
</tr>
<tr>
<td>WHO name</td>
<td>Pango lineage</td>
<td>Initial association</td>
<td>Transmission increase</td>
<td>Mortality increase</td>
</tr>
<tr>
<td>----------</td>
<td>---------------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Alpha</td>
<td>B.1.1.7</td>
<td>UK</td>
<td>~50%</td>
<td>Possible</td>
</tr>
<tr>
<td>Beta</td>
<td>B.1.351</td>
<td>South Africa</td>
<td>~50%</td>
<td>Minimal/none</td>
</tr>
<tr>
<td>Gamma</td>
<td>P.1</td>
<td>Brazil/Japan</td>
<td>Minimal/none</td>
<td>Reduced bamlanivimab and etesevimab</td>
</tr>
<tr>
<td>Delta</td>
<td>B.1.617.2, AY.1, AY.2</td>
<td>India</td>
<td>Increase clear but not quantified</td>
<td>Possible</td>
</tr>
</tbody>
</table>

As of July 15, 2021
Table 5. SARS-CoV-2 Variants of Interest

<table>
<thead>
<tr>
<th>WHO Label</th>
<th>Pango Lineages</th>
<th>GISAID Clade</th>
<th>Nextstrain Clade</th>
<th>Earliest Documented Samples</th>
<th>Date of Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eta</td>
<td>B.1.525</td>
<td>G/484K.V3</td>
<td>21D</td>
<td>Multiple countries, Dec 2020</td>
<td>March 17, 2021</td>
</tr>
<tr>
<td>Iota</td>
<td>B.1.526</td>
<td>GH/253G.V1</td>
<td>21F</td>
<td>USA, Nov 2020</td>
<td>March 24, 2021</td>
</tr>
<tr>
<td>Kappa</td>
<td>B.1.617.1</td>
<td>G/452R.V3</td>
<td>21B</td>
<td>India, Oct 2020</td>
<td>April 4, 2021</td>
</tr>
<tr>
<td>Lambda</td>
<td>C.37</td>
<td>GR/452Q.V1</td>
<td>21G</td>
<td>Peru, Dec 2020</td>
<td>June 14, 2021</td>
</tr>
</tbody>
</table>

As of July 15, 2021

Table reproduced from https://www.who.int/en/activities/tracking-SARS-CoV-2-variants
Table 6. Conditions and Treatments Associated with Moderate to Severe Immune Compromise Based on CDC Criteria

- Active or recent treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ or recent hematopoietic stem cell transplant
- Severe primary immunodeficiency
- Advanced or untreated HIV infection
- Treatment with immunosuppressive medications such as cancer chemotherapeutic agents, TNF blockers, certain biologic agents (e.g., rituximab), and high-dose corticosteroids

Table 7. Recommendations for Additional COVID-19 mRNA Vaccine Doses in Moderately to Severely Immunocompromised Individuals

- A third dose of Pfizer-BioNTech COVID-19 vaccine (≥12 years) or Moderna COVID-19 vaccine (≥18 years) is recommended after an initial 2-dose primary mRNA COVID-19 vaccine series for moderately to severely immunocompromised people including SOT recipients.
- Ideally, the third dose should be the same mRNA vaccine as the original series, but substitution is permissible when needed.
- The third dose should be administered at least 28 days after the completion of the initial two-dose mRNA COVID-19 vaccine series.
- The clinical benefit of an additional mRNA vaccine dose after an initial two-dose primary mRNA COVID-19 vaccine series for immunocompromised people is not precisely known. However, with the potential to increase immune response, acceptable safety profile with no increased risk of rejection, the CDC recommends a third mRNA vaccine dose after an initial two-dose primary mRNA COVID-19 vaccine series.
- Serologic (antibody) testing or cellular immune testing in immunocompromised people following COVID-19 vaccination outside of the context of research studies is not recommended in the USA at this time.
- Evidence is needed regarding the safety and immunogenicity of using a mixed-dose approach for J&J/Janssen + mRNA vaccine in immunocompromised people. Since an additional mRNA vaccine dose is not currently authorized after adenoviral vector vaccines, patients should speak with their physician regarding risks versus benefits.
- Immunocompromised people should be counseled about the potential for reduced immune responses to COVID-19 vaccination and the need to follow prevention measures because these patients may still have a poor response despite three doses of an mRNA vaccine.
- All close contacts of immunocompromised people, especially household contacts, should be encouraged to be vaccinated against COVID-19.
- There is no recommendation for any alteration of immunosuppression in anticipation of additional doses of an mRNA COVID-19 vaccine.
FIGURES

Figure 1. COVID-19 Vaccine Delivery Systems

1a.

1b.

1c.
1a. mRNA Vaccines.
1. The mRNA is surrounded by a lipid nanoparticle
2. The lipid nanoparticle assists with cell entry
3. mRNA is released into the cytoplasm
4. Ribosomes and cellular proteins are used to translate the mRNA into the spike protein
5. The spike protein gets expressed on the cell surface and/or secreted into the serum
6. Spike proteins are processed into antigenic peptides that are bound by class I MHC molecules and expressed on the cell surface to activate CD8 T cells. In professional antigen presenting cells, antigenic peptides derived from spike may be cross-presented by class II MHC molecules and expressed on cell surface to activate CD4 T cells which can activate additional T cells, B cells and the production of antibodies against the spike protein.
7. Antigen-presenting cells can engulf secreted spike proteins, which can also activate the immune system.

1b. Adenoviral Vector Vaccines.
1. The adenovirus contains DNA, which includes genetic material to produce the spike protein
2. The adenovirus is taken up by the human cell
3. 
   a. The adenovirus enters the cytoplasm
   b. The adenovirus releases its DNA into the nucleus
   c. Transcription of the DNA to mRNA occurs in the nucleus
   d. mRNA is transferred into the cytoplasm
4. Ribosomes and cellular proteins are used to translate the mRNA into the spike protein
5. The spike protein gets expressed on the cell surface and/or secreted into the serum
6. Spike proteins are processed into antigenic peptides that are bound by class I MHC molecules and expressed on the cell surface to activate CD8 T cells. In professional antigen presenting cells, antigenic peptides derived from spike may be cross-presented by class II MHC molecules and expressed on cell surface to activate CD4 T cells which can activate additional T cells, B cells, and the production of antibodies against the spike protein.
7. Antigen-presenting cells can engulf secreted spiked proteins, which can also activate the immune system.

1c. Weakened Live Attenuated Virus Vaccines.
1. Weakened live attenuated virus containing the mRNA of the spike protein
2. The attenuated virus binds to the ACE2 for cell entry
3. mRNA is released into the cytoplasm
4. Ribosomes and cellular proteins are used to translate the mRNA into the spiked protein
5. The spike protein gets expressed on the cell surface and/or secreted into the serum
6. Spike proteins are processed into antigenic peptides that are bound by class I MHC molecules and expressed on the cell surface to activate CD8 T cells. In professional antigen presenting cells, antigenic peptides derived from spike may be cross-presented by class II MHC molecules and expressed on cell surface to activate CD4 T cells which can activate additional T cells, B cells, and the production of antibodies against the spike protein.
7. Antigen-presenting cells can engulf secreted spiked proteins, which can also activate the immune system.

1d Recombinant spike glycoprotein vaccines.
1. The recombinant protein is taken up by the antigen presenting cell.
2. Proteins are degraded into antigenic peptides by proteases in the endocytic pathway.
3. Class II MHC molecules are assembled in the endoplasmic reticulum and transported through the Golgi into the MHC class II compartment (MIIC) or late endosome where they are uploaded with antigenic peptides.
4. Peptide-loaded MHC class II molecules are transported to cell surface to activate CD4 T cells which can activate additional T cells, B cells, and the production of antibodies against the spike protein.

ACE2, angiotensin-converting enzyme 2; MHC, major histocompatibility complex
Figure 2. Cumulative Incidence of First COVID-19 Occurrence in Phase 3 Clinical Trials

Vaccine and placebo groups diverge at approximately 14 days after the first dose (arrow)

2a. Pfizer-BioNTech (BNT162b2)

2b. Moderna (mRNA-1273)

Figure 3. Frequency of Adverse Events of FDA EUA Vaccines Compared to Placebo

3a. Pfizer-BioNTech (BNT162b2)

3b. Moderna (mRNA-1273)