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# 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



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## Major Changes and Updates

- New <u>Table 1</u>: Summary of currently available COVID-19 vaccines for adults and children in the United States
- New section on Vaccine and Monoclonal Antibody Administration
- Revised section on <u>SARS-CoV-2 Viral Variants</u>
- Revised section on <u>Pediatric Considerations in COVID-19 Vaccination</u>
- New section on <u>Policies Requiring Vaccination of Liver Transplant Candidates</u>

*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, Mulitsystem inflammatory syndrome in children; SOT, solid organ transplantation; ACR, acute cellular rejection; TTS, thrombosis with thrombocytopenia.

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### **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, are at higher risk of hospitalization and death from COVID-19. As of December 5, 2021, the Pfizer-BioNTech mRNA-based vaccine given as two doses has full USA Food and Drug Administration (FDA) approval in those  $\geq$ 12 years of age, and as of January 31, 2022, the Moderna mRNA two-dose vaccine is approved for those ≥18 years of age. However, the Moderna two-dose vaccine and Johnson & Johnson (J&J)/Janssen single-dose adenoviral vector vaccine remain under Emergency Use Authorization (EUA) by the FDA for those 12-18 and ≥18 years of age, respectively. In addition, three doses of an mRNA vaccine, with the third dose given five months after the second dose, is recommended for all immunocompetent individuals ≥12 years of age. In addition, a booster dose of mRNA vaccine is recommended after the initial two doses of J&J vaccine (or J&J plus an mRNA vaccine as the initial series). As primary series, mRNA vaccines are preferred to the J&J vaccine. As of January 29, 2022, 449,354,046 doses of COVID-19 vaccines have been administered in the USA. In the USA population, 90.9% of those 65-74 years of age, 61.3% of those age 18-24 years, and 56.7%% of those 12-17 years of age are fully vaccinated, but the rates of vaccination and primary and breakthrough infection vary substantially by geographic region. Thus far, these vaccines appear to retain significant effectiveness against severe disease and hospitalization due to emerging SARS-CoV-2 Variants of Concern including the Delta and Omicron variants. Although there is concern that waning immunity could reduce protection against symptomatic disease caused by the Omicron variant, available data suggest COVID-19 vaccine efficacy (VE) might be reduced against symptomatic disease but protection against severe disease has been preserved.<sup>1</sup> The receipt of a booster dose of COVID-19 vaccine increases this protection from severe disease.<sup>2,3</sup> As of March 2022, severe cases in the fourth surge of COVID-19 are largely occurring in unvaccinated and immunocompromised individuals. While vaccinated individuals with breakthrough infection typically have mild to moderate disease, immunocompromised patients are more likely to develop severe breakthrough infection. The FDA modified the EUA for the COVID-19 mRNA vaccines on August 12, 2021 to authorize a three-dose primary series 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 February 5, 2022, the Advisory Committee on Immunization Practices (ACIP) recommended a booster dose to all immunocompromised individuals ≥18 years of age given at least three months after the third dose of an mRNA vaccine or two months after the primary series of the J&J/Janssen adenoviral vaccine.<sup>4</sup>

The goal of this document is to provide 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.



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

Patients with CLD display innate and adaptive immune dysregulation that is associated with vaccine hyporesponsiveness.<sup>5</sup> Given that subjects with CLD have an increased risk of complications after infection with influenza, *Streptococcus pneumoniae*, HAV, and HBV,<sup>6,7</sup> vaccination against these pathogens is recommended. Double dosing or booster dosing of the HBV vaccines can increase vaccine response rates in CLD patients.<sup>8,9</sup> 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 non-COVID-19 vaccines be given before transplant whenever possible or waiting until three to six months after transplant. The ACIP recommends avoiding live virus vaccines in those receiving high-dose corticosteroids and other immunosuppressed individuals because of concerns of uncontrolled viral replication, although emerging data suggests some live vaccine (e.g. varicella or MMR) may be safe in selected pediatric transplant recipients.<sup>10,11</sup> Of note, the CDC recommends that non-COVID-19 vaccines can and should be given while a patient is receiving COVID-19 vaccination.

## Types of COVID-19 Vaccines

Entry of SARS-CoV-2 requires binding of the viral spike glycoprotein to the angiotensin-converting enzyme 2 (ACE2) receptor on human epithelial cells.<sup>12</sup> 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.<sup>13,14</sup> Both Moderna and Pfizer-BioNTech developed a 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.<sup>15–17</sup> Other vaccines that are currently in development use DNA, protein subunits, inactivated SARS-CoV-2, viral vectors, and attenuated virus (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 overcome by using lipid nanoparticles that protect the mRNA from enzymatic degradation and enhance their



cellular uptake and biological half-life.<sup>18,19</sup> 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 may include different sequences of the SARS-CoV-2 RNA virus to ensure that vaccine resistance and escape mutations are minimized.

#### **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 tissue 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.<sup>20,21</sup>

J&J/Janssen's adenoviral vector (Ad26) vaccine is authorized under EUA in the USA.<sup>22</sup> Early safety data were favorable in the Phase 3 clinical trial of Oxford/AstraZeneca's AZD1222 adenovirus vectored COVID-19 vaccine,<sup>23</sup> leading to its authorization for emergency use in the UK on December 29, 2020.<sup>24</sup>

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 a VE of 91.6%,<sup>25</sup> although unpublished data suggests slightly lower efficacy. Its safety profile has been favorable with no reports of thrombotic disorders to date.<sup>26</sup> 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).<sup>27</sup> Although these observations were not considered clinically significant, more data and experience with this and other replication defective adenovirus-based vaccines are needed. Recent data suggest that a heterologous boost with an aerosolized adenovirus type-5 vector-based vaccine following two doses of inactivated COVID-19 vaccine (CoronaVac) may be useful, but these vaccines are not currently available in the USA.<sup>28</sup> Replication defective adenovirus-based vaccines are not live or attenuated SARS-CoV-2 and are not expected to pose a risk to immunocompromised patients.

#### **Other Vaccines**

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).<sup>29</sup> The Novavax COVID-19 vaccine is a recombinant spike protein subunit and adjuvant vaccine using nanoparticle technology that



recently completed phase 3 studies with a reported VE of 89% in the UK and 49.4% in South Africa.<sup>30</sup> The Novavax vaccine is currently available for use in 170 countries and is under review for EUA by the FDA as of February 12, 2022.<sup>31</sup>

# Assays to Detect Immune Response to SARS-CoV-2 and COVID-19 Vaccines Assays That Measure Spike and Nucleocapsid Antibodies

Currently, a large number of assays are authorized by the FDA to determine antibody responses to COVID-19.<sup>32</sup> 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. 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.<sup>33</sup> VE in clinical trials is typically defined by clinical events such as the number of infections, hospitalizations, severe cases, and deaths. The immunogenicity of COVID-19 vaccines can be determined by measuring anti-spike glycoprotein antibody levels as well as neutralizing antibody titers to test strains of the virus in cell culture systems. While good correlation between VE and neutralizing antibody titers has been observed across registration trials, precise correlates of immunity have not been determined for many of the different assays available and these assays are often qualitative.<sup>34</sup>

#### **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 *in vitro* response of host T cells to specific pathogens. Currently there are no T cell response assays that evaluate response to SARS-CoV-2 vaccine with FDA authorization for clinical use. However, there is a commercially available test to determine response to infection called the T-Detect COVID Test.<sup>35</sup>

## Safety and Efficacy of FDA EUA and Approved COVID-19 Vaccines

#### mRNA COVID-19 Vaccines

In clinical trials, 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 VE in multiple studies generally greater than 80% against SARS-CoV-2 infection and greater than 90% against symptomatic disease.<sup>36</sup> While reduction in neutralization titers have been observed against some variants, VE against severe disease and hospitalization has been largely preserved. However, there is concern that protection wanes with time from vaccination and that protection against the Omicron variant is less than that seen against prior variants.

#### **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.<sup>17</sup> It is an intramuscular vaccine administered as a single dose containing 5x10<sup>10</sup> viral particles (0.5 mL). The multiple-dose vials have a shelf life of three months when stored between 2 °C to 8 °C. Once the first dose is withdrawn, the vial must be used within six hours at 2 °C to 8 °C or within two hours at room temperature.

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  $\geq$ 14-day endpoint and 66.1% (95% CI 55.0-74.8) for the  $\geq$ 28-day endpoint (Figure 2). For the  $\geq$ 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  $\geq$ 28 days after vaccination. VE was lower in South Africa, where there was a predominance of the B.1.351 SARS-CoV-2 variant (52.0%, 95% CI 30.3-67.4 for  $\geq$ 14-day endpoint; 64.0%, 95% CI 41.2-78.7 for  $\geq$ 28-day endpoint) compared to the USA (74.4%, 95% CI 65.0-81.6 for  $\geq$ 14-day endpoint; 72.0%, 95% CI 58.2-81.7 for  $\geq$ 28-day endpoint). Similar VE was observed across subgroups defined by age, comorbidity, race, and ethnicity. VE was lower for older participants ( $\geq$ 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. There were no COVID-19 cases requiring hospitalization after 28 days post-vaccination compared to five cases in the placebo group. There were no COVID-19-related deaths in the vaccine group and seven 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%.<sup>37</sup> However, longer term follow-up revealed a decline in vaccine effectiveness, prompting a recommendation for administration of a second dose of vaccine (either the Ad26.COV2.2 or an mRNA vaccine at least two months following the initial dose).<sup>38</sup> It is unknown if Ad26.COV2.S prevents SARS-CoV-2 transmission by vaccinated individuals. In an unpublished study from South Africa, two doses of the J&J/Janssen vaccine demonstrated 85% protection against COVID-19-related hospitalizations during circulation of the Omicron variant.<sup>39</sup>

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). Because of rare but clinically significant adverse events, including Guillain-Barré Syndrome (GBS) and thrombosis with thrombocytopenia



syndrome, mRNA vaccines are preferred over the J&J/Janssen vaccine, whenever feasible.<sup>40,41</sup> As of February 5, 2022, the ACIP recommends that anyone who has received the first dose of the J&J/Janssen vaccine should receive a second dose of an mRNA vaccine at least 28 days later. In addition, a booster dose with an mRNA vaccine is recommended two months or more after the second dose for those  $\geq$ 18 years of age (Table 1).

## 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.<sup>42</sup> Similarly, among 338,700 V-Safe participants who received the J&J/Janssen (Ad26.COV2.S) vaccine, the most frequent side effects reported seven 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%).<sup>37,42</sup> 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 provider. See Table 2 for rare adverse events associated with COVID-19 vaccines.

#### 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).<sup>43</sup> 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).<sup>44</sup> Ninety percent of these occurred within 15 minutes of vaccination, nine (90%) had a documented history of allergies or allergic reactions, and 100% were female. All patients were treated with epinephrine, six (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.<sup>45</sup> 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.<sup>44–46</sup>



#### Anaphylactic Reactions to J&J/Janssen 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.<sup>47,48</sup> In contrast to the local injection site pain and swelling that is reported on average one day after vaccination, 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

On June 23, 2021, the ACIP reviewed instances of myocarditis and pericarditis in individuals receiving the Pfizer-BioNTech and Moderna mRNA vaccines.<sup>49</sup> 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 two doses and highest in younger individuals. In a recent population-based study of 2,292,924 vaccinated adults from California, 15 men had confirmed but self-limited myocarditis requiring hospitalization with an observed incidence of 0.8 cases per million first doses and 5.8 cases per million second doses. Another study from Hong Kong demonstrated an association of myocarditis with BNT162b2 vaccine after the second dose that also occurred in 10 per million vaccinated individuals, but there was no safety signal from the CoronaVac vaccine.<sup>50</sup> In an updated analysis from CDC and FDA VAERS database of over 192,000,000 individuals who received an mRNA COVID vaccine, there were 1626 cases of myocarditis with a median age of 21 years that occurred at a median of two days after vaccination. Males compromised 82% of the cases. The rates of myocarditis were highest in adolescent males ages 12-15 years at 70.7 per million doses of the BNT152b2 vaccine. 96% of the sample were hospitalized and the most common treatment was NSAIDs given to 87%.<sup>51</sup> 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.<sup>52</sup> 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) has 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.<sup>53,54</sup> 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. Because of the risk of TTS, the CDC currently recommends that the mRNA vaccines should be preferentially administered over the adenoviral vaccines when feasible.<sup>41</sup>

#### Guillain-Barré and Other Neurological Adverse Events with COVID-19 Vaccines

Acute inflammatory demyelinating syndrome (AIDP) or Guillain-Barré 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.<sup>55</sup> 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.

#### Immune-Mediated Hepatitis and Other Autoimmune Phenomena

Rare cases of immune-mediated hepatitis developing within several days to six weeks of subjects receiving COVID-19 vaccine have been reported.<sup>56–58</sup> In one multicenter study of 16 subjects, 81% had hepatocellular injury, 75% presented after the second dose, and six patients had a history of chronic liver disease including well-controlled autoimmune hepatitis in remission in four cases.<sup>59</sup> During follow-up, ten required hospitalization and six were treated with corticosteroids or azathioprine. Subjects had detectable serum autoantibodies and responded to corticosteroids; no deaths or liver transplants have been reported. Another recent study reported on five liver transplant recipients who developed acute cellular rejection after COVID-19 vaccination that responded to steroid therapy.<sup>60</sup> Similarly, case reports of other autoimmune phenomena such as hemolytic anemia and idiopathic thrombocytopenic purpura (ITP) have also been reported.<sup>61–63</sup> Due to their low incidence,



the CDC and VAERS have not been able to determine whether these rare events are causally related to the vaccine or coincidental.

#### **GUIDANCE FOR ADVERSE REACTIONS TO COVID-19 VACCINES**

- Anyone with a history of severe or immediate allergic reaction to any vaccine components, including polyethylene glycol, 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 in patients experiencing thromboembolic events.
- Rare instances of neurological adverse events have been reported including Guillain-Barré 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.
- mRNA vaccines are preferred over adenoviral COVID-19 vaccines for most populations whenever feasible due to rare reports of GBS and TTS with the adenoviral vaccines.
- 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 immune-mediated 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, mistakes may occur, and new nucleotides that are not lethal to the virus are evident in the progeny. Variants that share distinctive nucleotides reflecting a common ancestor are considered a lineage. 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. On June 1, 2021, the WHO began labeling major lineages with a Greek alphabetical system. Worldwide, public health agencies classify variants reflecting their own local epidemiology, and sometimes designations differ.

In the USA, variants are classified by the SARS-CoV-2 Interagency Group based on actual or projected public health impact. Starting on September 21, 2021, the USA system classified SARS-CoV-2 as: Variants Being



Monitored, Variants of Interest, Variants of Concern, and Variants of High Consequence. Those designations are based on multiple factors especially nucleotide mutations that alter fecundity, receptor binding, tropism for lower respiratory tract, diagnostic assay performance, and/or immunity. However, the most important factors differentiating the variants are the real-world experiences, especially how rapidly the variant overspreads a population, whether there appears to be greater pathogenicity (generally measured by the case fatality rate and hospitalization 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 Being Monitored might be reclassified as a Variant of Concern. Conversely, variants that once were of concern might be downgraded to Variants Being Monitored. As of December 13, 2021, there are no Variants of High Consequence and there are just two Variants of Concern: Delta and Omicron (Table 3). As Delta overspread the USA, some other variants like Alpha, Beta, and Gamma were downgraded on September 21, 2021 from Variants of Concern to Variants Being Monitored.

Because antibodies to the spike proteins are felt to represent and possibly mediate the protection produced by the SARS-CoV-2 vaccines, there is a lot of attention given to mutations in the spike glycoprotein genes. With Delta those mutations do not seem to affect the neutralizing potency of anti-spike antibodies, and nearly all the monoclonal antibodies with EUA are clinically active against Delta. Instead, Delta's sequence appears to allow increased replication and transmissibility, estimated twice that of the original SARS-CoV-2.<sup>64,65</sup> In addition, it appears that Delta causes more hospitalizations and mortality than Alpha or the original SARS-CoV-2.<sup>66</sup> However, vaccination still protects against severe COVID-19 and mortality, and probably reduces the number of days an infected person can transmit to others.<sup>65,67,68</sup>

Omicron has far more mutations than Delta, especially in the sequences that encode the spike protein. In fact, there are already three distinct lineages of Omicron, named BA.1, BA.2, and BA.3. BA.1 was the first to spread widely. A deletion at H69 and V70 in Omicron BA.1 causes one of the three targets of the Thermo Fisher TaqPath COVID-19 Combo Kit to fail. The finding of multiple tests positive by two of the three targets was one of the first expressions of Omicron. Most other diagnostic tests are not affected. While definitive studies are ongoing, it is anticipated that these Omicron mutations will reduce the potency of many of the EUA-approved monoclonal antibody preparations and convalescent plasma. In fact, on January 24, 2022, the FDA revoked the EUA for bamlanivimab and etesevimab combination monoclonal antibodies (Eli-Lilly) and casirivimab and imdevimab (Regeneron) because of their reduced efficacy against Omicron, which is estimated to account for more than 99% of cases in the USA. Sotrovimab appears to retain activity against BA.1 but may have reduced activity against BA.2. Since changes in SARS-CoV-2 continue and data are constantly updated, providers using monoclonal antibodies need to remain vigilant of the viruses circulating in their region and consult guidelines that are updated regularly.<sup>69</sup> The efficacy of vaccines may also be reduced against Omicron. As with Delta, it is hoped that boosting the quantity of circulating antibodies and preserved T cell responses will offset reductions in the potency of antibodies. Most of the research with Omicron is based on BA.1. By January 2022, very early data suggest that BA.2 may be more transmissible (and does not "fail" in one of three targets on the TaqPath Combo kit), but otherwise appears to have similar immune escape and pathogenicity as BA.1.



#### **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.
- COVID-19 vaccine boosting is recommended to offset reductions in vaccine efficacy conferred by the Delta and Omicron variants.

## Vaccine and Monoclonal Antibody Administration

### **Pre-Exposure Prophylaxis (Evusheld)**

Evusheld (Astra-Zeneca) is a monoclonal IgG1 antibody preparation consisting of tixagevimab/cilgavimab that received EUA for pre-exposure prophylaxis in immunocompromised individuals on December 12, 2021. In clinical trials of 4,220 nonvaccinated individuals >12 years of age and weighing at least 40 kg (PROVENT and STORM CHASER trials), IM injection of Evusheld led to a 77% reduction in SARS-CoV-2 infection compared to placebo at six months (0.2% vs 1.0%). Evusheld can be given to immunosuppressed individuals without known SARS-CoV-2 infection and who have a moderate to severe immunocompromised state at risk for severe SARS-CoV-2 infection, such as SOT recipients. Prior to administering Evusheld, patients should receive the patient care giver fact sheet and provide informed consent regarding the potential risks versus benefits.<sup>70</sup> Possible side effects of Evusheld include allergic reactions and rare but serious cardiac events including coronary ischemia, cardiac failure, and arrythmias (0.6% vs 0.2% in placebo-treated patients). Individuals with pre-existing heart disease were more likely to develop adverse cardiac events and therefore should be carefully screened. Evusheld should not be used as a treatment for COVID-19 or be used in place of vaccination. Evusheld should be delayed for two weeks after COVID-19 vaccine, but delays in vaccine administration after Evusheld is not required. Given that Evusheld has variable efficacy against Omicron, updating vaccines as per current recommended schedules should be considered for optimal prevention. In areas where the supply of Evusheld is limited, many transplant centers are allocating it based on the level of immunosuppression and prioritizing individuals within the first year of liver transplantation because of their higher level of immunosuppression or in those being treated for acute rejection. For current information regarding dosing of Evusheld see CDC<sup>71</sup> or FDA.<sup>72</sup>

### **Monoclonal Antibodies for Treatment or Secondary Prevention of COVID-19**

Monclonal antibodies (MAbs) are widely used to treat early COVID-19 or as secondary prevention after exposure to SARS-CoV-2 in high-risk patients. As different variants emerge, the effectiveness of specific MAbs may be affected and knowledge of local patterns of SARS-CoV-2 biology are required to appropriately select MAbs. No delay in vaccine administration is recommended before or after receiving MAbs, either for treatment of COVID-19 or secondary prevention.



GUIDANCE REGARDING THE USE OF EVUSHELD AND OTHER MONOCLONAL ANTIBODY PRODUCTS

- Evusheld should be delayed for two weeks after administration of COVID-19 vaccine.
- No delay of COVID-19 vaccine is recommended after receiving Evusheld.
- After receiving monoclonal antibodies for treatment or secondary prevention (after exposure) of COVID-19, no delay in vaccine administration is required.
- Evusheld should not be considered as a replacement for primary vaccination against COVID-19 but rather supplementary for high-risk individuals.
- The current EUA for Evusheld indicates that patients with decompensated liver disease are not eligible for administration. However, patients receiving active immunosuppression with equivalent of >20 mg of prednisone are eligible for Evusheld.
- Use of monoclonal antibodies and convalescent plasma for patients with COVID-19 should reflect product-specific, up-to-date information on SARS-CoV-2 variants prevalent in the community.

## Pediatric Considerations in COVID-19 Vaccination

The CDC recommends COVID-19 vaccination for everyone aged 5 years and older to help protect against COVID-19, community transmission, and potential severe complications, such as multisystem inflammatory syndrome in children (MIS-C).<sup>73</sup> The Pfizer-BioNTech mRNA vaccine was authorized for children aged ≥12 years on May 10, 2021 and then for children age 5-11 on October 29, 2021. In Phase 2-3 clinical trials in children ≥12 years, both Pfizer-BioNTech and Moderna mRNA vaccines demonstrated 100% efficacy after the two-dose series with no vaccine-related serious adverse events.<sup>74,75</sup> Similar high rates of efficacy were observed in children 5-11 years of age.<sup>76</sup> Systemic side effects of fever, fatigue, and muscle aches were substantially lower in both groups of children 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.<sup>77,78</sup>

Vaccination has been shown to be effective at protecting against MIS-C. In a CDC report of hospitalized patients aged 12-18 years at 24 pediatric hospitals in 20 states, two doses of Pfizer-BioNTech vaccine were shown to be 91% effective in preventing MIS-C in children between 12-18 years. Additionally, the severe MIS-C cases requiring life support were only observed in unvaccinated children.<sup>79,80</sup>

The COVID-19 vaccines may be co-administered with other 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, 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.<sup>81</sup>

## 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  $\geq$ 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 INCLUDING BOOSTER DOSES

- For LT candidates, vaccination against COVID-19 should proceed even if LT is likely to occur before the vaccine series is completed. The additional doses of mRNA vaccine should be given at the earliest appropriate interval after transplant (e.g., four weeks posttransplant).
- 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.

#### **PRIMARY SERIES**

- Immunocompromised adults require a three-dose primary series (mRNA vaccines) with the third dose given 28 days after the second dose. For those who received the J&J vaccine, a dose of an mRNA vaccine should be given 28 days after the J&J dose.
- For immunocompetent individuals who received the J&J vaccine for their primary series, a second dose of either J&J or an mRNA vaccine (preferred) is recommended 28 days after the first dose to complete the primary series. A booster (3<sup>rd</sup>) dose is recommended two months after the primary series.

#### BOOSTERS

- Booster mRNA doses are recommended for immunocompetent individuals age ≥12 years five months after completion of the two-dose primary series.
- For immunocompromised individuals who received an mRNA vaccine for their primary series, a fourth (booster) dose of mRNA vaccine is recommended three months after the third dose.
- For immunocompromised individuals who received the J&J vaccine, a booster dose is recommended with an mRNA vaccine at least two months after the primary vaccine series.
- Heterologous booster doses are acceptable but not preferred as part of the primary vaccine series for mRNA vaccines.



## 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 receive 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.<sup>82–86</sup>

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 cirrhosis patients from the Veterans Administration (VA) was recently studied to understand the impact of the Pfizer-BioNTech and Moderna mRNA vaccines compared with a propensitymatched control group of unvaccinated patients at similar risk of infection and severe COVID-19.87 Patients with CLD who received at least one dose of an mRNA 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.<sup>87</sup> 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-19.87 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-19related hospitalization or death after seven days. However, this study was conducted largely prior to the emergence of Delta or Omicron strains of COVID-19 in the USA and 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 cirrhosis patients and those with chronic non-cirrhotic liver disease.<sup>88</sup>

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.

## Policies Requiring Vaccination of Liver Transplant Candidates

A decision to require COVID-19 vaccination prior to listing for LT is at the discretion of the transplant center and can be ethically justified.<sup>89,90</sup> Data demonstrate the safety and efficacy of COVID-19 vaccination in patients with cirrhosis. Due to the greater seroconversion rate after vaccination in patients with cirrhosis compared to LT recipients, vaccination should occur prior to LT whenever possible. A prospective study of patients with cirrhosis and LT recipients demonstrated higher seroconversion rates after an mRNA COVID-19 vaccine in patients with cirrhosis (100%) compared to LT recipients (63%).<sup>91</sup>

A survey that included 770 patients, of which 304 had cirrhosis and 141 were LT recipients, reported that patients were more likely to follow their gastroenterologist's/hepatologist's recommendation (91.3%) than the government's recommendation (75.9%) regarding the COVID-19 vaccine.<sup>92</sup> Common concerns among SOT recipients included lack of longer-term data and inconsistent messaging from providers.<sup>93</sup> Outreach and discussion about these concerns between transplant clinicians and liver transplant recipients resulted in increased vaccination rates.



Data support recommending an mRNA vaccine to patients with cirrhosis and LT recipients to prevent hospitalization and death from COVID-19. Ideally, vaccination should occur prior to transplantation because seroconversion rates are higher in patients with cirrhosis than LT recipients. Furthermore, discussion between the hepatologist and patient is an important factor in increasing vaccination rates in this patient population.

CDC recommendations regarding the need to wear masks once fully vaccinated continue to evolve, with current recommendations hinging largely upon local disease transmission.<sup>94</sup> However, the CDC has acknowledged that immunocompromised hosts, including patients with liver disease on immunosuppression and SOT 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 have developed policies that require COVID-19 vaccination to be listed for SOT.
- 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 second dose
  of an mRNA COVID-19 vaccine in all immunosuppressed patients age ≥12, individuals with
  hepatocellular carcinoma and CLD patients receiving prednisone, anti-metabolites, or biological
  therapies with a booster three months after the third dose. For J&J recipients, a dose of mRNA
  vaccine is recommended 28 days after the J&J vaccine with a booster dose of mRNA vaccine two
  months later.
- 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.

## COVID-19 Vaccination in Immunosuppressed Liver Transplant Recipients

Important issues regarding COVID-19 vaccination of LT recipients include the humoral and cellular response to initial and repeated immunization against SARS-CoV-2 and the potential influence of immunosuppression on this response. Risk factors for lower serological response to immunization include older age, use of antimetabolite drugs, time from transplantation, and use of B cell-depleting therapies.<sup>95,96</sup> What remains uncertain is the actual impact of immunization on the frequency and severity of breakthrough infection.

Data support immunization against COVID-19 in LT patients, even in those with naturally-acquired immunity following recovery from COVID-19. When compared with immunocompetent patients, LT recipients show a



lower prevalence of adequate titer of anti-SARS-CoV-2 antibodies and more pronounced antibody level decline with time from infection.<sup>97</sup>

Early data on vaccination against COVID-19 from Johns Hopkins in SOT recipients in the USA included 78 (19%) LT recipients receiving early vaccination with one of the mRNA COVID-19 vaccines.<sup>98,99</sup> These data indicate that vaccine reactogenicity is mild and similar to rates reported in the non-transplant population.<sup>98</sup> There were no early reported episodes of acute cellular rejection (ACR), SARS-CoV-2 diagnoses, or major allergic reaction. However, only 17% developed antibodies to the SARS-CoV-2 spike protein at a median of 20 days after their first dose of mRNA COVID-19 vaccine.<sup>99</sup> This compares to spike antibody detection in 100% of participants in the initial clinical trials of non-transplant patients by day 15 (mRNA-1273) or day 21 (BNT162b2) following vaccination. This work hinted that SOT recipients on antimetabolite maintenance immunosuppression were less likely to develop an antibody response (37% vs. 63%), as were older recipients.

Like these early findings, Rabinowich et al. found that LT recipients developed substantially lower immunological response to mRNA-based vaccination against COVID-19.<sup>100</sup> LT recipients (n=80) and healthy volunteers (n=25) negative for SARS-CoV-2 nucleocapsid protein antibodies were compared for development of IgG antibodies directed against the S and N protein 10-20 days after receiving the second Pfizer-BioNTech vaccine. Immunogenicity among LT recipients was lower with positive serology observed in 38/80 (47.5%) compared to 100% of controls (p <0.001). Antibody titer was lower in LT recipients (mean 95.41 AU/ml vs. 200.5 AU/ml in controls, p <0.001). Predictors of negative response among LT recipients were older age, lower estimated glomerular filtration rate, and treatment with high dose steroids and mycophenolate mofetil. No serious adverse events from vaccination were reported in either group. A similar result was seen in a study by Boyarsky et al. that found an inadequate response in SOT recipients after the first and even second dose of both mRNA vaccines.<sup>101</sup> Inadequate responses were seen after both doses in 26 (20%), and after the first dose only with the second dose inducing a positive response in 62 (48%). Together these data support the need for additional immunization in the LT population.

Another prospective study included 62 LT patients and found that antibody responses to spike protein four weeks after the second dose of an mRNA vaccine or a single dose of the J&J vaccine were undetectable in 11 patients and suboptimal (median titer 17.6, range 0.47–212 U/ml) in 27 other patients.<sup>102</sup>

Similarly, in a prospective cohort study of 141 LT patients, patients with cirrhosis, and healthy controls, anti-SARS-CoV-2 spike-protein titers were determined before and 10-84 days after second vaccination.<sup>91</sup> This study included cellular response to virus by assessing the spike-specific T cell response using an interferon-gamma release assay (EUROIMMUN). They observed seroconversion in LT recipients after the second vaccination in 63% versus 100% of cirrhotic patients and controls using the anti-S trimer assay. Median anti-SARS-CoV-2 titers of responding LT recipients were also significantly lower compared with cirrhotic patients and controls (*P* < .001). With respect to cellular immune response, spike-specific T cell response rates were 36.6% in LT recipients, 65.4% in cirrhotic patients, and 100% in controls. Predictors of absent or low humoral response were age >65 years (OR 4.57; 95% CI 1.48-14.05) and arterial hypertension (OR 2.50; 95% CI 1.10-5.68). By contrast, failure was less likely with calcineurin inhibitor monotherapy than with other immunosuppressive regimens (OR 0.36; 95% CI 0.13-0.99). These additional data support the potential role for a third vaccination, especially in those with LT with low or absent responses.



#### **Breakthrough Infection After COVID-19 Vaccination**

New data from the SECURE-Liver and COVID-Hep registries identified 19 LT recipients who had at least one prior vaccination who developed laboratory-confirmed COVID-19.<sup>103</sup> In these patients, there were six hospitalizations (32%), including three (16%) resulting in mechanical ventilation and two (11%) resulting in death. All three cases of severe COVID-19 occurred in patients with a single vaccine dose within the prior 1-2 weeks, indicating more favorable outcomes for LT recipients with a completed series of vaccination. This contrasts starkly with what occurred in 77 unvaccinated LT recipients with laboratory-confirmed COVID-19 where 33 (43%) were hospitalized, seven (9%) were admitted to the ICU, nine (12%) required mechanical ventilation and six (8%) died from COVID-19 lung disease.

Another study showed a 64% decrease in COVID-19 infection, a 58% reduction in symptomatic infection, and an 87% reduction in death in 753 LT recipients who had received two mRNA vaccine doses compared to 753 matched controls that had not been vaccinated.<sup>104</sup>

#### Immunogenicity and Efficacy of the Three-Dose Regimen in Liver Transplant Recipients

VE is typically defined by clinical events such as the number of infections, hospitalizations, severe cases, and deaths in the treatment arm versus placebo control. The immunogenicity of COVID-19 vaccines can be determined by measuring anti-spike glycoprotein antibody levels as well as neutralizing antibody titers to test strains of the virus in cell culture systems. While good correlation between VE 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 qualitative.

Immunosuppressed individuals, including LT recipients, are less likely to demonstrate an immune response to vaccination; however, vaccine "failure" with respect to both immunogenicity and protection against COVID-19 is difficult to define and challenging to overcome. Development of antibody to SARS-CoV-2 proteins after vaccination is one serological definition of response. However, there are important distinctions in serum antibody testing as only "neutralizing antibodies" are true correlates to immunity in blocking viral infection, and this antibody function is not routinely measured by commercial assays. Serologic response was defined by an anti-receptor-binding domain (RBD) antibody level of at least 100 U per milliliter after a study in nonhuman primates found this to be protective (measured with Elecsys Anti-SARS-CoV-2 immunoassay [Roche]).<sup>105</sup> This threshold was then corroborated in clinical cohorts and thus is often used as a surrogate for response.<sup>106</sup>

Antibody production reflects only the humoral response; however, the cellular immune response (T cell mediated) to immunization likely provides additional protection against infection and severe disease. Making interpretation of immunogenicity even more complex was a recent study that found discordance between antibody production and T cell responses (assessed by semi-quantitative analysis of IFN-gamma release after spike-specific stimulation of T cells) in both LT recipients and patients with cirrhosis. Interestingly 27% (9/32) LT recipients without detectable antibody demonstrated a positive T cell response, and conversely 58% (29/50) of LT patients without a T cell response tested positive for antibody. It is also notable that 28% (23/82) of LT recipients had neither humoral nor T cell immune response despite two doses of an mRNA COVID-19 vaccine. Ultimately it will be important to determine the correlation of each of these categories of response with clinical efficacy and effectiveness.<sup>91</sup>



Although vaccine failure is not well-defined, those with no or very low titers of anti-spike glycoprotein antibody levels (<30 U/mL) after multiple immunizations are more likely true failures of vaccination and additional measures such as prophylactic monoclonal antibody administration may be considered.

As a result of suboptimal antibody responses after two doses of mRNA vaccines in transplant recipients, a third dose has been tested in a number of different cohorts. Overall, 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. For example, 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.<sup>107</sup> 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 prospective study from Canada, 120 SOT recipients who had received two doses of mRNA-1273 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.<sup>108</sup> The primary outcome was a serologic response at four months characterized by an anti-RBD antibody level of 100 U/mL 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.

As a result of these data, immunocompromised adults including transplant recipients are currently recommended to have a three-dose primary series (mRNA vaccines) with a third dose 28 days after the second dose. For patients who received the J&J vaccine, a second dose of the J&J or an mRNA vaccine should be given two months after the initial dose to complete the initial vaccine series. In addition, a fourth dose "booster" at least three months after a three-dose series is currently recommended for all severely immunosuppressed individuals, based upon small studies of immunocompromised patients demonstrating the immunogenicity of a fourth dose administered one to three months after the three-dose primary series.<sup>109–111</sup> It is not recommended to use antibody titers to determine the need for booster administration or pre-exposure prophylaxis with Evusheld.

Small subsets of LT recipients who received doses of both available mRNA vaccinations were described as having higher antibody responses.<sup>91</sup> It is unknown if this will be confirmed in larger cohorts and if this provides better protection from infection compared to homologous vaccination. As the impact of heterologous vaccination is currently not clear, routine heterologous vaccination is also not currently advised.



#### **GUIDANCE FOR COVID-19 VACCINATION IN LIVER TRANSPLANT RECIPIENTS**

- COVID-19 vaccination is recommended for all LT recipients including expanded primary series and an earlier booster dose than is recommended for immunocompetent persons (<u>Table 1</u>).
- 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 or third 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 preferably be vaccinated at least two weeks before transplantation when feasible. However, a lack of COVID-19 vaccination should NOT delay emergent living donor LT.
- Family members and caregivers of LT recipients should be vaccinated against SARS-CoV-2 whenever possible.
- LT recipients who recover from COVID-19 infection should still receive a complete series of COVID-19 vaccines.

## 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.<sup>112</sup> 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. The levels of neutralizing antibody and markers of innate immunity following vaccination that are predictive of protection from symptomatic SARS-CoV-2 infection are unknown. Data are needed regarding the effectiveness of the expanded vaccine schedule after exposure to the Omicron variant and the timing of additional doses for optimal protection from SARS-CoV-2 transmission, severe disease, and mortality. Studies of COVID-19 vaccination of patients with CLD are underway in other countries. Although these studies



involve vaccines not licensed in the USA, the findings will be informative for future policy development (ClinicalTrials.gov identifiers: NCT04775056, NCT05007665, NCT04794946) (Table 4).

## 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 age ≥5 years should be vaccinated for COVID-19. As of August 13, 2021, the CDC recommends an expanded primary series and earlier booster for immunocompromised persons including those receiving moderate doses of steroids, other immunosuppressants, or immunosuppressing biologics. Furthermore, due to waning immunity over time, all moderate to severely immunocompromised individuals such as LT recipients should receive a fourth booster dose of an mRNA vaccine at three months or more after their initial vaccine series. 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 Omicron) and potentially greater virulence in the USA and abroad, highlighting the urgency to vaccinate as many individuals as possible.

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 aside 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 as recommended by public health authorities.

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## Helpful Websites and Resources

- AASLD COVID-19 and the liver website
- AASLD expert panel consensus statement on COVID-19
- <u>Vaccine Adverse Event Reporting System (VAERS)</u>
- 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
- <u>CDC: Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the</u> <u>United States</u>
- <u>COVID-19 Real-Time Learning Network</u>
- <u>COVID-19 vaccines and pregnancy: conversation guide for clinicians (American College of Obstetricians</u> and Gynecologists)



## Tables

# Table 1. Summary of Currently Available COVID-19 Vaccines for Children and Adults in the United States

	Pfizer-BioNTech mRNA			Moderna mRNA	J&J/Janssen Adenoviral vector*
	Age 5-11	Age ≥12	Age ≥18	Age ≥18**	Age ≥18**
Primary series schedule (immunocompetent)	2 doses separated by 21 days			2 doses separated by 28 days	1 dose
Additional dose for moderate-severe immunocompromised	At least 28 days after 2 <sup>nd</sup> dose			At least 28 days after 2 <sup>nd</sup> dose	mRNA at least 28 days after J&J
Booster schedule	Not authorized for this age group	At least 3 months after primary series in moderate- severe immunocompromised At least 5 months after primary series in immunocompetent		At least 3 months after primary series in moderate-severe immunocompromised At least 5 months after primary series in immunocompetent	At least 2 months after primary series with mRNA vaccine

Table adapted from CDC COVID-19 Vaccine: Quick reference guide for healthcare professionals as of 2/16/22 at <u>https://www.cdc.gov/vaccines/covid-19/downloads/covid19-vaccine-quick-reference-guide-2pages.pdf</u> Please reference the website for latest recommendations

\*mRNA vaccine primary vaccine series preferred whenever possible

\*\*Heterologous mRNA vaccine booster dose allowed for individuals ≥18 years of age



## Table 2. Severe Adverse Events Associated with COVID-19 Vaccines

Adverse event	Vaccine association	Incidence (per million)	Time to onset	Management
Anaphylactic	mRNA	2-5 overall	Up to 1 hour	Immediate anti-
reaction	Adenoviral			histamine,
				epinephrine/
				steroids
				Hospitalize if severe
Guillain-Barré	Adenoviral	7.8 overall and up	Median 13 days	Hospitalize
Syndrome		to 15.6 in males 50-	(r: 0 to 75 days)	IVIG if progressive
		64 years	98% within 6-week	Intubation and
		100 cases reviewed	window	plasmapheresis if
				severe
Thrombosis and	Adenoviral	3.0 overall and 8.8	Within 15 days	Anti-PF4 antibodies
thrombocytopenia		in women 30-49		Avoid heparin
syndrome		years		
Myocarditis/	mRNA	10.6 overall	Median 2 days	Supportive care
pericarditis		and 70.7 in males		NSAIDs
		12-15 years		Steroids if severe



### Table 3. SARS-CoV-2 Variants of Concern

WHO name	Pango lineage	Initial association	Transmission	Mortality impact vs original	Response to monoclonal antibodies	Vaccination impact
Delta	B.1.617.2, AY.1, AY.2	India	Increased, not quantified	Possible increase	Reduced, but clinical impact unlikely	Some reduction in neutralization Preserved protection against severe disease
Omicron	B.1.1.529	South Africa	Increased, not quantified	Possible reduction	Predicted to be lower for most products	Reduced protection

As of December 13, 2021



## Table 4. COVID-19 Vaccination Knowledge Gaps

- Effectiveness, safety, and durability in patients with CLD based on liver disease etiology, comorbidities, CTP class, and MELD score
- Effectiveness, safety, and durability in immunocompromised/immunosuppressed individuals including transplant recipients
- Effectiveness, safety, and timing in individuals previously infected with SARS-CoV-2
- Effectiveness against SARS-CoV-2 Variants of Concern
- 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
- Mechanisms of vaccine failure
- Interpretation of serology and cell mediated immunity assays/clinical context



## Figures

## Figure 1. COVID-19 Vaccine Delivery Systems





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)













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

#### 3a. Pfizer-BioNTech (BNT162b2)



#### 3b. Moderna (mRNA-1273)



#### 3c. J&J/Janssen (Ad26.COV2.S)

