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## AASLD EXPERT PANEL CONSENSUS STATEMENT: VACCINES TO PREVENT COVID-19 INFECTION 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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### **List of Abbreviations**

AE	adverse event	Ig	immunoglobulin
BNT162b2	Pfizer-BioNTech mRNA vaccine	mRNA-1273	Moderna mRNA vaccine
CDC	Centers for Disease Control and Prevention	PEG	polyethylene glycol
CLD	chronic liver disease	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
COVID-19	coronavirus disease 2019	SOT	solid organ transplant
EUA	emergency use authorization	VAERS	Vaccine Adverse Event Reporting System
FDA	Food and Drug Administration		

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## OVERVIEW & 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 (particularly cirrhosis), cardiac disease, obesity, and weakened immune systems from other diseases or medications may be at higher risk of death from COVID-19. Over the past year, over 60 vaccine candidates have been identified and are under development as a means to prevent COVID-19. As of the beginning of February 2021, two mRNA-based vaccines have received Emergency Use Authorization (EUA) from the US Food and Drug Administration (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. Since persons with chronic liver disease (CLD) and immunosuppressed transplant recipients are frequently hyporesponsive to licensed vaccines, additional studies regarding the safety and efficacy of COVID-19 vaccines are urgently needed in these patient subgroups. The goal of this document is to provide concise safety and efficacy data regarding the commercially available COVID-19 vaccines and their use in CLD patients and liver transplant recipients. Our intent is to provide clinically useful information for hepatologists, liver transplant care providers, and their patients. This online document will be updated regularly as more data become available and additional vaccines are authorized for use.

## BACKGROUND ON NON-COVID-19 VACCINES IN PATIENTS WITH CHRONIC LIVER DISEASE AND IMMUNOSUPPRESSION

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

Patients with CLD display innate and adaptive immune dysregulation that is associated with vaccine hyporesponsiveness.<sup>1</sup> ([Supplemental Figure 1](#)) Since subjects with CLD have an increased risk of complications after infection with influenza, *S. pneumoniae*, hepatitis A virus (HAV), and hepatitis B virus (HBV),<sup>2,3</sup> vaccination against these pathogens is recommended. ([Supplemental Table 1](#)) Double dosing or booster dosing of the HAV and HBV vaccines can increase vaccine response rates in CLD patients.<sup>4,5</sup> Immunosuppressed liver transplant 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 prior to transplant whenever possible or waiting until 3 to 6 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.<sup>6</sup>

Innate immunity provides the first line of defense through a system of cell surface and intracellular pattern recognition receptors that recognize pathogen- and danger-associated molecular patterns (PAMPs or DAMPs). Adaptive immunity, mediated by B- and T-cells, is required for effective and durable pathogen-specific protective immunity that forms the basis for vaccination. Recent reviews have highlighted the range of immune dysfunction observed in the setting of cirrhosis.<sup>7,8</sup> ([Supplemental Figure 1](#)) In addition, lack of T-cell help has been associated with nonalcoholic fatty liver disease,<sup>9</sup> altered B-cell function has been reported in hepatitis C virus (HCV)-related cirrhosis, and chronic HBV has been associated with global and virus-specific B- and T-cell dysfunction.<sup>10–12</sup> Although the degree of immune dysregulation is higher in patients with more severe or decompensated liver disease compared to those with compensated liver disease, this has not been precisely quantified.<sup>13</sup>

The available evidence suggests that, while influenza virus does not directly target the liver, it contributes to collateral liver damage<sup>14</sup> and promotes hepatic decompensation.<sup>15,16</sup> In several studies, patients with CLD had a significantly increased risk of hospitalization and death related to influenza infection.<sup>2,17</sup> The available evidence suggests that, while influenza vaccine may not protect against all-cause mortality, it triggers an effective antibody response and may reduce the risk of all-cause hospitalization in patients with CLD.<sup>2</sup> Therefore, the Centers for Disease Control and Prevention (CDC) and others recommend routine annual vaccination in CLD patients.

Guidelines from the CDC and AASLD also recommend vaccination against HAV and HBV in patients with CLD.<sup>18,19</sup> ([Supplemental Figure 1](#)) Furthermore, while HBV vaccination is associated with >95% response among young, healthy subjects,<sup>20</sup> a recent review of HBV vaccination in cirrhotic patients highlighted a weaker immune response of 47% on average, with slightly greater responses noted in higher dose compared to standard dose vaccination (53% vs 38%).<sup>21</sup> Lower immunogenicity has been associated with more advanced liver disease as measured by model for end-stage liver disease (MELD) or Child-Turcotte-Pugh (CTP) score, as well as age and genetic factors.<sup>4,22</sup> Although improved responses have been noted with double-dose vaccination and booster vaccination,<sup>4,5</sup> such measures were met with low rates of response among patients with end-stage liver disease.<sup>23</sup> A small, non-randomized clinical trial of cirrhotic patients showed a slightly greater overall HBV vaccine response rate for high dose accelerated compared to standard vaccine regimens (78.6% vs 67.4%,  $P=0.19$ ).<sup>24</sup> In the same study, however, the overall vaccine response to HAV was 100% for high dose accelerated versus 94.3% for standard dose, suggesting that cirrhotic patients can indeed mount an effective vaccine response. More recently, a novel adjuvanted HBV vaccine (HepB-CpG with 20 µg antigen) has been found to be more immunogenic in patients with CLD, with response rates that were 2.7 times that of patients receiving standard recombinant HBV vaccine.<sup>25</sup>

#### GUIDANCE FOR DOUBLE DOSING OF COVID-19 VACCINES

- **While double dosing is recommended for some non-COVID-19 vaccines in CLD patients, this approach is NOT recommended with COVID-19 vaccines.**

### Non-COVID-19 Vaccines in Immunosuppressed Patients

The immunosuppression used in solid organ transplant (SOT) recipients including corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus), and purine synthesis inhibitors (mycophenolate mofetil) acts to inhibit the immune response via various mechanisms that culminate in a net inhibition in T- and B-cell function and adaptive immunity. This raises concerns about the efficacy of vaccination in SOT and other immunosuppressed patients compared to age- and sex-matched population controls.<sup>26</sup> Additionally, hypogammaglobulinemia has been described post-SOT. An immunoglobulin (Ig) G level <600 mg/dL is associated with insufficient antibody production in 15%-30% of patients depending on the inoculant.<sup>27</sup> One of the strategies to augment posttransplant antibody response sufficient to provide protection includes vaccination prior to transplant and preferably prior to the onset of end stage organ failure when immunity is lower and immune dysregulation higher.<sup>28</sup> Vaccination within 6 months after transplantation is associated with the lowest response rate because of high levels of immunosuppression during this period. Therefore, vaccinations should ideally be administered

at the time of diagnosis of CLD long before transplantation may be needed and preferably before the onset of more advanced liver disease.

The American Society of Transplantation,<sup>29</sup> ACIP,<sup>6</sup> and CDC all recommend that SOT recipients should receive various vaccinations preferably prior to transplantation and periodically after SOT (pneumovax, HAV, HBV, influenza, Haemophilus influenza type b, and tetanus-diphtheria-pertussis). ([Supplemental Table 1](#)) Such FDA-licensed vaccines are safe with little risk for inducing graft rejection.<sup>15</sup>

There is significant concern for administering live vaccines to SOT recipients because of the risk of uncontrolled replication of the live virus in the host. The ACIP recommends avoiding live vaccines in those receiving high-dose corticosteroids, defined as  $\geq 2$  mg/kg of body weight or  $\geq 20$  mg/day of prednisone or equivalent for  $\geq 14$  consecutive days.<sup>6</sup> Administration of a live vaccine should be delayed by a minimum of one month after stopping high-dose steroids. A similar waiting period of one month is also recommended to initiate high-dose steroids after receiving a live vaccine. Although research suggests that certain live virus vaccines (varicella, and measles, mumps, and rubella) can be administered safely to selected pediatric liver transplant recipients, live viral vaccines are currently not recommended in most circumstances following transplantation.<sup>29,30</sup>

## BACKGROUND ON COVID-19 VACCINES

### Types of COVID-19 Vaccines in Development

Entry of the SARS-CoV-2 requires binding of the viral spike glycoprotein to the angiotensin-converting enzyme 2 (ACE2) receptor on human epithelial cells.<sup>31</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 and vectors. The release of the 29,903-nucleotide sequence of the SARS-CoV-2 genome on January 10, 2020<sup>32</sup> led to diagnostic testing and the development of Operation Warp Speed in the US with the goal of developing safe and effective vaccines within one year.<sup>33</sup> Both Moderna and Pfizer-BioNTech developed a vaccine using synthetic nucleoside-modified mRNA that encodes the spike glycoprotein.<sup>34,35</sup> 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 non-infectious 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) for antigen expression and immune activation. ([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.<sup>36</sup> 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.<sup>37,38</sup> Additionally, nucleoside modifications prevent innate immune activation and degradation. Nevertheless, the mRNA-based vaccines degrade within a few days at room temperature and require very cold temperatures during manufacturing and storage.

### ***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 and do not require very low temperature storage. Prior 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>39,40</sup>

Early safety data were favorable in the Phase 3 clinical trial of Oxford/AstraZeneca's AZD1222 adenovirus vectored COVID-19 vaccine,<sup>41</sup> leading to its authorization for emergency use in the United Kingdom (UK) on December 29, 2020.<sup>42</sup> Phase 3 clinical trials from Johnson & Johnson demonstrate vaccine efficacy (VE) rates of 57%-72% following a single dose.<sup>43</sup> Early clinical trials with CanSino's non-replicating adenovirus (Ad5) vectored COVID-19 vaccine showed mild to moderate increases in total bilirubin (8% of recipients) and alanine aminotransferase (9% of recipients).<sup>44</sup> While these observations were not considered clinically significant, more data and experience with this and other replication defective adenovirus-based vaccines are needed before their widespread use can be recommended in patients with CLD. Replication defective adenovirus-based vaccines are not live or attenuated SARS-CoV-2 and are not expected to pose a risk to immunocompromised patients, but further guidance from regulatory and public health authorities is expected once these vaccines are granted EUA by the FDA.

### ***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. The 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).<sup>45</sup> The Novavax product is a recombinant spike protein subunit and adjuvant vaccine using nanoparticle technology that has started phase 3 trials in the US. Novavax recently reported a 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).<sup>46</sup> A Sanofi/GlaxoSmithKline

protein subunit vaccine, also based on recombinant technology similar to an approved influenza 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 such as vesicular stomatitis virus (VSV), where VSV genes are replaced with the SARS-CoV-2 spike protein gene to generate a host anti-spike glycoprotein response. An effective Ebola virus vaccine using VSV in this manner has been approved in the US. While 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 due to concerns of excessive viral replication.

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

Effective vaccine strategies provide durable protective immune responses to prevent infection and limit disease onset and severity. Some vaccines such as MMR provide long-lasting immunity over decades while others like pneumococcal vaccines provide immunity for 3-5 years, and influenza for 1-2 years. The duration and durability of a vaccine response may also be driven by the rate of viral escape mutations in the population. Protective immunity to viral pathogens involves the adaptive immune components including: 1) B-cells producing neutralizing antibodies; 2) CD4 T-cells that help to regulate an efficient adaptive immune response; 3) CD8 effector T-cells that can recognize, kill, and/or cure infected cells. While neutralizing antibody responses have provided correlates of vaccine efficacy and protection for both DNA (e.g., HBV and papillomavirus) and RNA viruses (e.g., HAV and poliovirus), SARS-CoV-2 vaccine strategies using mRNA and adenoviral vectors can also induce potent CD8 T-cell responses.

### ***Antibodies that bind SARS-CoV-2***

Currently, over 60 assays are commercially available to detect IgG and/or IgM antibodies to SARS-CoV-2 spike glycoprotein and/or nucleoprotein under EUA.<sup>47</sup> Most of these assays have a high sensitivity, specificity, and negative predictive value (median 97%-100%), but variable positive predictive value (median 87%, range 50%-100%) for detecting prior exposure to SARS-CoV-2. These serological assays can be used to monitor antibody responses in blood during and after acute infection. Importantly, while these assays represent viral exposure, they do not necessarily reflect protective immunity. Furthermore, the durability of antibody response to SARS CoV-2 is not well established at this time, although antiviral IgM and IgG titers may wane over 6 months of initial infection, particularly among asymptomatic subjects.<sup>48-50</sup> Because the currently authorized vaccination strategy is focused on the spike protein on the surface of SARS-CoV-2, immune response to spike protein (e.g., antibody and/or T-cell response) may be detected after natural infection as well as successful vaccination.<sup>26</sup> By contrast, immune response to nucleoprotein or other viral proteins will be detected after natural infection but not after vaccination with current mRNA approaches.

### ***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.<sup>51</sup>

### ***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 commercially available T-cell response assays that evaluate response to SARS-CoV-2 vaccine or infection.

#### **GUIDANCE FOR ANTIBODY TESTING AGAINST SARS-COV-2**

- **Serum antibody testing against SARS-CoV-2 is NOT recommended pre- or post-vaccination to confirm immunity.**

### **Safety and Efficacy of FDA EUA mRNA COVID-19 Vaccines**

In December 2020, the FDA granted EUA to two mRNA vaccines to prevent COVID-19: the first developed by Pfizer and BioNTech, and the second by Moderna. ([Table 1](#)) 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 pre-fusion form, which more closely resembles the intact virus.<sup>52</sup>

#### ***Pfizer-BioNTech vaccine***

The Pfizer-BioNTech vaccine (BNT162b2) is an intramuscular vaccine administered as a series of two 30 µg doses (0.3 mL each) given three weeks apart.<sup>53</sup> The multiple-dose vials must be stored between -80 °C to -60 °C. Once thawed and diluted, the multiple-dose vials must be used within 6 hours.

An [EUA](#) was granted by the FDA on December 11, 2020 based on median 60-day follow-up data from an ongoing registration Phase 1/2/3 randomized, observer-blind, placebo-controlled trial (C4591001).<sup>35</sup> The Phase 2/3 trial enrolled adult participants stratified by age (younger, 18-55 years of age; older, >55 years of age); adolescents (older, 16-17 years of age; younger, 12-15 years of age) were added later. Inclusion criteria included medical conditions or exposure that conferred a higher risk for acquiring COVID-19, including CLD, stable chronic HBV or HCV, and autoimmune disease. Exclusion criteria included treatment with immunosuppressive therapy, diagnosis of an immunocompromising condition, or prior known COVID-19. The phase 3 study is ongoing and being conducted in the US and several other countries. Additional studies are planned to evaluate BNT162b2 in pregnant women, children younger than 12 years of age, and immunocompromised persons.

In the Phase 2/3 Pfizer-BioNTech trial, participants were randomized 1:1 to receive BNT162b2 (n=21,720) or placebo (n=21,728).<sup>35</sup> Median age was 52 years and 50.6% were male. Most participants were White (82.9%), 9.4% Black, 4.3% Asian, <3% other racial groups. There were 28% Hispanic/Latino participants. About 35% were obese (BMI ≥30.0 kg/m<sup>2</sup>) and 21% had at least one coexisting condition.

VE for the 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% (95% confidence interval, 90.3-97.6). ([Figure 2](#)) There were 8 COVID-19 cases in the BNT162b2 group and 162 COVID-19 cases in the placebo group. There was evidence for some efficacy after the first dose with a VE of 52.4% between the first and second doses. Host immunity from vaccination is not immediate and full protection may take one to two weeks from the second dose. There was also evidence that BNT162b2 was protective against severe COVID-19, with only 1 case of severe COVID-19 in the BNT162b2 group and 9 cases in the placebo group. Similar VE was observed across subgroups defined by age, sex, race, ethnicity, BMI, and the presence of coexisting conditions, including participants  $\geq 65$  years of age (94.7%). Serial PCR testing was not performed; therefore, the efficacy of the vaccine in potentially preventing spread of SARS-CoV-2 could not be determined.

Safety data are available from 43,448 participants, including 37,706 participants with a median of 2 months of follow-up after the second dose. Reactogenicity and adverse events (AEs) were generally milder and less frequent in the older than the younger group. ([Figure 3](#)) Local reactions including pain at the injection site, redness and swelling were most frequently observed, mostly mild to moderate in severity, and generally similar in frequency after the first and second doses. Systemic events (fatigue, headache, muscle pain, chills, joint pain, fever, vomiting, diarrhea) were more frequent and more severe in the younger age group compared with the older age group. Frequencies and severity of systemic events generally increased with the number of doses (except vomiting and diarrhea). Systemic events were generally reported less frequently in the placebo group than in the BNT162b2 group. In vaccine recipients, the most commonly reported systemic events were fatigue and headache (39%-59% depending on age group and dose number). Fever after the second dose was reported by 16% of younger vaccine recipients and 11% of older recipients. Of particular interest were AEs of lymphadenopathy, reported in 64 participants (0.3%) in the BNT162b2 group and 6 participants (<0.1%) in the placebo group, usually in the arm or neck region within 2 to 4 days after vaccination.

Hypersensitivity adverse events (2 in BNT162b2 group and 1 in the placebo group) were assessed as unrelated to the vaccine. Serious autoimmune disorders were considered when reporting adverse events of clinical interest. Four participants in the vaccine group developed Bell's palsy.<sup>53</sup> The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population according to the FDA. The incidence of serious adverse events and deaths was low and comparable for BNT162b2 and placebo, and no deaths were considered to be related to the vaccine or placebo.

### **Moderna Vaccine**

The Moderna vaccine (mRNA-1273) is an intramuscular vaccine administered as a series of two 100  $\mu$ g doses (0.5 mL each) given 1 month apart.<sup>54</sup> The multiple-dose vials must be stored between -25 °C to -15 °C. Once thawed, vials can be stored between 2 °C to 8 °C for up to 30 days or between 8 °C to 25 °C for up to 12 hours. Once the first dose is withdrawn, the vial must be used within 6 hours.

An [EUA](#) was granted by the FDA on December 18, 2020 based on an ongoing Phase 3 randomized, observer-blind, placebo-controlled trial (mRNA-1273-P301).<sup>55</sup> Participants were stratified into three groups: 18 to <65 years of age and not at risk for progression to severe COVID-19 (58.6%), 18 to <65 years of age and at risk for progression to severe COVID-19 (16.7%), and  $\geq 65$  years of age (24.8%). Underlying comorbidities that conferred a risk for progression to severe COVID-19 included diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, CLD, or HIV infection. The study was conducted in the US. Moderna is conducting a clinical trial to evaluate safety and effectiveness of mRNA-1273 in healthy adolescents 12 to <18 years old.<sup>56</sup>

In the Phase 3 Moderna trial, participants were randomized 1:1 to receive mRNA-1273 (n=15,181) or placebo (n=15,170). Median age was 52 years and 52.6% were male. Most participants were White (79.4%), 9.7% Black, 4.7% Asian, <3% other racial groups. There were 20% Hispanic/Latino participants.

VE for the primary endpoint (protocol-defined 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%, with 11 COVID-19 cases in the mRNA-1273 group and 185 COVID-19 cases in the placebo group. ([Figure 2](#)) The primary efficacy endpoint was clinical disease and asymptomatic infection was not assessed. VE was lower in participants  $\geq 65$  years of age compared to those 18 to <65 years of age (86.4% vs 95.6%). Similar to the Pfizer-BioNTech Phase 3 trial, there was evidence for some efficacy after one dose of mRNA-1273. There was also similar evidence for a protective effect of mRNA-1273 on preventing severe COVID-19, with 0 cases of severe COVID-19 in the mRNA-1273 group and 30 cases in the placebo group.

Safety data are available for 30,350 participants with a median follow-up of 9 weeks after the second dose. The most common AEs were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). ([Figure 3](#)) Similar to the Pfizer-BioNTech vaccine, lymphadenopathy was reported in 173 participants (1.1%) in the mRNA-1273 group and 95 participants (0.63%) in the placebo group. There were more hypersensitivity AEs in the mRNA-1273 group (1.5%) compared to the placebo group (1.1%), but no anaphylactic or severe hypersensitivity reactions. There were 3 reports of Bell's palsy in the mRNA-1273 group and 1 case in the placebo group. The incidence of serious adverse events was low but more frequent after the second dose than after the first dose and generally less frequent in older ( $\geq 65$  years of age) compared to younger participants. The safety profile of mRNA-1273 was generally similar across subgroups, including participants with medical comorbidities, except for more frequent and generally mild to moderate reactogenicity in the younger age group. Safety conclusions could not be made about pediatric populations, pregnant and lactating individuals, and immunocompromised individuals because of insufficient data.

## Post-Marketing Reports of Anaphylactic Reactions to mRNA COVID-19 Vaccines

During December 14-23, 2020, monitoring by the Vaccine Adverse Event Reporting System ([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>57</sup> 71% 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, 4 (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-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>58</sup> 90% 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 10 (100%) were treated in an emergency department. No deaths from anaphylaxis were reported after receiving the Moderna COVID-19 vaccine.

It is unclear why the vast majority of cases of anaphylaxis occurred in women; however, this observation could be confounded by the fact that more women than men received the first doses of the Pfizer-BioNTech and Moderna COVID-19 vaccines during the analytic period.<sup>57,58</sup>

The incidence of anaphylaxis associated with the Pfizer-BioNTech vaccine may be 10 times as high (1 in 100,000) as the incidence reported with previously approved vaccines (1 in 1,000,000).<sup>59</sup> 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.

Vaccination locations must screen for potential contraindications or precautions, ensure that necessary supplies are available to manage anaphylaxis (e.g., epinephrine), implement recommended postvaccination observation periods (15 or 30 minutes depending on patient's history of allergic reactions), and ensure health care providers can recognize the signs and symptoms of anaphylaxis and immediately treat suspected anaphylaxis with intramuscular epinephrine.<sup>57,58</sup>

#### **GUIDANCE FOR ALLERGIC REACTIONS TO mRNA COVID-19 VACCINES**

- **Anyone with a history of severe or immediate allergic reaction to any vaccine components, including PEG, should be EXCLUDED from receiving either mRNA COVID-19 vaccine.**
- **Anyone with an immediate allergic reaction to the first dose of an mRNA COVID-19 vaccine should NOT receive additional doses of either mRNA COVID-19 vaccine.**

### **SARS-CoV-2 Viral Variants**

Rapidly spreading variants of SARS-CoV-2 have been described from the UK (B.1.1.7)<sup>60</sup> and South Africa (501Y.V2 or B.1.351)<sup>61</sup> that share the spike N501Y substitution located in the viral spike protein receptor binding domain for cell entry. Another variant from Brazil (P.1) also contains mutations in the receptor binding domain of the spike protein.<sup>62</sup> All of these variants have been found in the US,<sup>63</sup> are more transmissible,<sup>60</sup> and may be associated with higher morbidity and mortality.<sup>63,64</sup> Non-peer reviewed studies suggest that both Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines may provide protection against the UK B.1.1.7 and South African B.1.351 variants.<sup>65–67</sup>

#### **GUIDANCE FOR VACCINATION IN SETTING OF SARS-COV-2 VIRAL VARIANTS**

- **Withholding COVID-19 vaccination due to concerns about current or future SARS-CoV-2 viral variants is NOT recommended**

### **Pediatric Considerations in COVID-19 Vaccination**

Only the Pfizer-BioNTech mRNA vaccine has been authorized for ages <18 years (specifically ≥16 years). However, there are multiple vaccine trials underway for children ≥12 years. While a small subset of children have had severe COVID-19 symptoms and/or developed complications such as multisystem inflammatory syndrome in children (MIS-C),<sup>68</sup> the vast majority of children with COVID-19 have had mild illness. Data from a North American [pediatric registry](#) suggest that children with liver disease and those post-liver transplant have

outcomes similar to the general pediatric population.<sup>69</sup> The differences in COVID-19 presentations and disease course from adults underscores the importance of continued pediatric clinical trials to establish vaccine efficacy, dosing, and safety in children. It is also possible that protection from COVID-19 through vaccination will also protect against its complications, including MIS-C, but more data and long-term follow-up studies are needed. Co-administration of different vaccines is usually safe; however, administration of the COVID-19 vaccine with other childhood immunizations has not yet been tested.

#### GUIDANCE FOR ADMINISTRATION INTERVAL OF COVID-19 AND OTHER VACCINES

- The CDC recommends that COVID-19 vaccines be administered alone with a minimum interval of 14 days before or after administration of other vaccines.

## 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 both the Pfizer-BioNTech and Moderna Phase 3 trials. However, those on immunosuppressive therapy were excluded.

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 patients 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 yet 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. Since no participants with liver disease developed COVID-19, VE cannot be determined for this subgroup.

### Prioritization of the Limited Supply of COVID-19 Vaccines

The COVID-19 vaccines are currently a limited resource that requires rational selection of the highest risk candidates for priority access. Providers must administer COVID-19 vaccines in accordance with prioritization groups determined by appropriate [public health authorities](#).<sup>70</sup> The CDC has published a [dynamic document](#) that ranks groups at high risk for exposure or poor outcome from COVID-19 (Phases 1a, 1b, 1c, 2).<sup>71</sup> Healthcare workers are prioritized by the CDC (Phase 1a) to receive the COVID-19 vaccines because of their high risk of exposure to SARS-CoV-2, the need to protect patients from infection, and the need to preserve the capacity to care for patients.<sup>72</sup> Patients with underlying medical conditions, including liver disease (e.g., compensated and decompensated cirrhosis, liver cancer) and immunosuppression, are at risk for severe COVID-19 and are included in Phase 1c.<sup>73–77</sup>

#### PRINCIPLES REGARDING PRIORITIZATION OF PATIENTS FOR COVID-19 VACCINATION

- All healthcare workers should be prioritized for the COVID-19 vaccine (Phase 1a).
- Patients with comorbidities identified as high risk by the CDC, including CLD, should be prioritized for vaccination (Phase 1c).<sup>78</sup>
- For liver transplant candidates, vaccination against COVID-19 should proceed even if liver transplant is likely to occur before the second dose can be administered. The second dose of vaccine should be given at the earliest appropriate interval after transplant (e.g., 6 weeks posttransplant).
- Data are insufficient to determine the risk of severe COVID-19 in patients with immune-mediated liver disease on chronic immunosuppression and posttransplant patients relative to patients with cirrhosis; therefore, they should be prioritized for vaccination (Phase 1c).<sup>79–81</sup>
- Data are lacking to determine if a prior diagnosis of COVID-19 or the presence of antibodies to SARS-CoV-2 should be used to determine the need for vaccination; therefore, all patients with CLD and SOT recipients should be encouraged to get vaccinated.
- Healthcare providers should be knowledgeable of the local criteria for vaccination, know where vaccine is available, and actively inform patients of this information.
- Vaccinated healthcare providers are encouraged to volunteer to assist with their local vaccination efforts.
- Regardless of vaccination eligibility or status, everyone should continue to mitigate their risk of SARS-CoV-2 exposure by avoiding large groups, masking, social distancing, etc.

### COVID-19 Vaccination in Patients with Chronic Liver Disease

Due to the increased mortality with COVID-19 infection in adult CLD patients and particularly those with cirrhosis, it is recommended that these patients be prioritized for COVID-19 vaccination (Phase 1c). Although safety and efficacy data with the two available mRNA vaccines in CLD patients are limited, adverse events are not anticipated to be more frequent nor is efficacy expected to be lower than the general population; however, additional prospective studies are needed. Although studies of patients with alcohol-associated liver disease suggest they may have worse outcomes with COVID-19,<sup>82</sup> it is unknown if vaccination safety or efficacy will differ compared to other CLD patients.

If the supply of COVID-19 vaccine is limited, it is reasonable to prioritize patients with higher MELD or CTP scores for vaccination or those who are anticipated to undergo imminent liver transplantation, but all CLD patients should be vaccinated whenever possible.

#### GENERAL GUIDANCE FOR COVID-19 VACCINATION

- Persons  $\geq 16$  years (Pfizer-BioNTech) or  $\geq 18$  years (Moderna) with CLD are recommended to receive a COVID-19 vaccine (Phase 1c).
- The FDA and CDC recommend that all COVID-19 vaccine recipients should receive two doses of the mRNA vaccines as close to the recommended interval as possible.



- The second dose of the mRNA COVID-19 vaccines may be given up to 6 weeks after the first dose if necessary; however, the vaccine series should not be restarted if there is a longer delay before the second dose.<sup>83</sup>
- Each vaccine series should be completed with the same vaccine used initially. However, in exceptional situations, any available mRNA COVID-19 vaccine may be given at least 28 days after the first dose.<sup>83</sup>
- The FDA and CDC DO NOT RECOMMEND testing for serum IgM or IgG antibodies to the SARS-CoV-2 spike glycoprotein before or after COVID-19 vaccination.
- Administration of the COVID-19 vaccines should be at least 14 days after administration of other elective vaccines to minimize the likelihood of reduced efficacy and adverse events.
- The CDC recommends that persons with a known history of prior COVID-19 infection should wait a minimum of 90 days before receiving a COVID-19 vaccine because of concerns of an overly exuberant immune response. However, there may be special circumstances in which earlier vaccination may be recommended.
- The CDC recommends that people with a history of severe allergic reactions to medications or foods, and those with a history of Guillain-Barre syndrome, should receive an mRNA COVID-19 vaccine.
- **CONTRAINDICATION:** Individuals with an immediate allergic reaction of any severity (including hives) to a previous dose of an mRNA COVID-19 vaccine, to any of its components, or to polysorbate (with which there can be cross-reactive hypersensitivity to PEG) should NOT receive an mRNA COVID-19 vaccine unless they have been evaluated by an allergy expert who determines that it can be given safely.
- All patients who receive a COVID-19 vaccine should be monitored for a minimum of 15 minutes after the injection for an allergic reaction. Individuals with a history of an anaphylactic or anaphylactoid reaction to any prior drug or vaccine should be monitored for a minimum of 30 minutes.
- COVID-19 vaccines should be administered in an area and facility where immediate allergic reactions can be managed appropriately.
- To facilitate ongoing safety evaluation, vaccine providers should report vaccine administration errors, serious adverse events associated with vaccination, cases of multisystem inflammatory syndrome, and cases of COVID-19 that result in hospitalization or death through the [VAERS](#).
- Safety of the COVID-19 vaccines has not yet been established in children or pregnant women. However, pregnancy is NOT a contraindication to COVID-19 vaccine administration and should be discussed with the patient's obstetrician.

#### 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 COVID-19 vaccines are expected to have a favorable efficacy and safety profile in immunosuppressed patients available and should be administered according to their standard dose and schedule.
- Liver transplant candidates with CLD should receive the mRNA COVID-19 vaccine prior to transplantation whenever possible to help ensure an adequate immune response.
- Healthy living liver donors should receive an mRNA COVID-19 vaccine electively and preferably prior to donation and admission to the hospital.
- CLD patients receiving the mRNA COVID-19 vaccine may have local and systemic reactions (fever, myalgias, headache) in the first 48 hours after vaccination. However, respiratory symptoms or systemic symptoms may be indicative of COVID-19 and warrant further investigation.
- 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.

### COVID-19 Vaccination in Immunosuppressed Liver Transplant Recipients

As immunocompromised patients and SOT recipients were not included in the clinical trials of vaccines against SARS-CoV-2, there is a lack of data regarding the safety and efficacy of the available vaccines in this population. Furthermore, because COVID-19 vaccines employ novel technology, including an mRNA platform and adenovirus vectors, the efficacy and safety of these vaccines in the liver transplant population are not known. Other unknowns regarding vaccination of liver transplant recipients include:

1. Efficacy of the immune response to the vaccine to prevent SARS-CoV-2 infection 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 acute cellular rejection (ACR) reduces VE
4. The best timing 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 mRNA COVID-19 vaccines do not contain live or attenuated virus and therefore are unlikely to pose a safety concern for immunosuppressed patients.<sup>84</sup> Since replication defective or non-replicating vaccines have also 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 liver transplant recipients.
- The best time to administer the COVID-19 vaccine in liver transplant recipients is likely at least 3 months post liver transplantation 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 given as early as 6 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 liver transplant recipients solely to elicit an immune response to immunization against SARS-CoV-2 as there is a risk of ACR with lower immunosuppression.
- Avoid COVID-19 vaccination in liver transplant 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 re-established.
- 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 liver transplantation, deceased donor transplantation should **NOT** be delayed in a patient who received a COVID-19 vaccine.
- If the patient is due for a second dose of vaccine in the immediate posttransplant period, this may be delayed 6 weeks to elicit a better immune response.
- Potential live liver donors and recipients of live donor livers should receive the second dose of the COVID-19 vaccine at least two weeks before transplantation.
- Family members and caregivers of liver transplant recipients should be vaccinated against SARS-CoV-2 whenever possible.
- The American Society of Transplantation's [COVID-19 FAQ sheet](#) provides updated information for transplant professionals.

## COVID-19 Vaccination Knowledge Gaps

Patients with advanced CLD and liver transplant recipients have not been included in the mRNA vaccine studies and as such data on effectiveness and safety are lacking in these populations. [Post-marketing research](#) is being conducted on antibody response to COVID-19 vaccines in patients with chronic conditions, including cirrhosis and autoimmune diseases. Acute and chronic liver diseases encompass a wide spectrum of etiologies and severity of disease and thus represent a heterogeneous population. Further, there are known racial and ethnic differences in prevalence and incidence of various liver diseases.<sup>85,86</sup> 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.<sup>86,87</sup> Cirrhosis is inherently a state of qualitative and quantitative immune dysregulation,<sup>1</sup> while some patients may be further immunosuppressed with medications such as transplant recipients and those with autoimmune hepatitis. Increasing liver disease severity has been associated with lower non-COVID-19 vaccine responsiveness.<sup>88,89</sup> Thus, there are large knowledge gaps in various areas related to liver disease and transplantation that require special attention in further studies. ([Table 2](#))

## Counseling Liver Disease Patients About COVID-19 Vaccination

Many questions will arise related to the use, safety, and efficacy of COVID-19 vaccination in patients with CLD and SOT recipients. However, vaccination is rarely contraindicated because of comorbidities or pre-existing allergies or intolerances. Few people are at risk who should defer vaccination. It is important to counsel patients about the overall safety, efficacy, and clinical benefit of mRNA COVID-19 vaccines compared to the risk of

becoming ill with COVID-19. The following are summarized recommendations to address patient-specific concerns. The CDC has developed a more extensive [guide](#) for patient counseling concerns.<sup>83</sup>

### ***Preferred COVID-19 vaccines for patients with liver disease***

At this time, there are insufficient data to recommend one mRNA COVID-19 vaccine (e.g., Pfizer-BioNTech or Moderna) over another. While there are differences between vaccines, the currently authorized mRNA vaccines are nearly equivalent in terms of efficacy, each demonstrating a 95% VE. One notable difference is the minimum age authorized to receive vaccination (Moderna  $\geq 18$  years, Pfizer-BioNTech  $\geq 16$  years).

### ***Pre-vaccination serological testing***

We do not recommend pre-vaccination testing for SARS-CoV-2 IgG or IgM antibodies. Multiple commercially available assays under EUA measure antibodies to various SARS-CoV-2 proteins. They are primarily used to monitor antibody response during and after COVID-19. Notably, while they may confirm prior exposure, they may not represent protective immunity. Furthermore, limited data exist describing the durability of these antibodies. Given the lack of evidence in demonstrating protective immunity, we do not recommend serological testing prior to COVID-19 vaccination.

### ***Post-vaccination serological testing***

We do not recommend post-vaccination testing for SARS-CoV-2 IgG or IgM antibodies until new and validated studies show detection of an effective immune response that correlates with disease prevention or amelioration. Commercially available antibody assays are directed toward SARS-CoV-2 spike glycoprotein and/or nucleoproteins. Current vaccines stimulate an immune response to spike proteins detectable after both vaccination and natural infection. In contrast, assays directed toward other non-spike proteins will be detected only after natural infection. Data related to the utility of post-vaccination serological testing are lacking and such testing is not currently recommended.

### ***Administration and timing of vaccination***

We recommend completing both mRNA COVID-19 vaccine doses in the timeline recommended. The CDC currently recommends administration of the second dose of the Pfizer-BioNTech mRNA vaccine at 3 weeks (21 days) and the Moderna mRNA vaccine at 4 weeks (28 days). The second dose can be given up to 4 days early (i.e., 17 and 24 days, respectively). If patients are unable to receive the second dose at this recommended interval, the CDC recommends administration no later than 6 weeks after the first dose; however, the vaccine series should not be restarted if there is a longer delay before the second dose.<sup>83</sup> Vaccine administration errors and side effects should be reported to the [VAERS](#). There are no convincing data to support a single-dose vaccination schedule.

### ***Vaccination in patients with autoimmune hepatitis or other autoimmune diseases***

We recommend administration of the vaccine to patients with autoimmune hepatitis and/or CLD patients with autoimmune diseases. The Pfizer-BioNTech and Moderna clinical trials included participants with

autoimmune disease; however, participants on immunosuppressive medications were excluded. In both studies, neither side effects nor efficacy were provided for these subgroups. The exclusion of immunosuppressed participants in these trials precludes conclusions on VE in this population. There are no data to support delaying or holding immunosuppression prior to administration of the COVID-19 vaccine.

### ***Use of antipyretics as pre-vaccination prophylaxis or post-vaccination treatment***

We do not recommend antipyretics or NSAIDs pre-vaccination as prophylaxis for local or systemic reactions because of the absence of data on the impact of these medications on vaccine immunogenicity.

We support the use of antipyretics or NSAIDs post-vaccination to treat local or systemic reactions as needed. Neither Pfizer-BioNTech nor Moderna study protocol advised for or against use of antipyretics following vaccination. Neither protocol mandated use of these agents as a protocol violation or addressed timing of participants' baseline medication use relative to vaccination. There is no evidence to suggest that use of antipyretics or NSAIDs following vaccination will affect safety or efficacy of the COVID-19 vaccination.

### ***Concurrent medication timing or use***

We do not recommend withholding baseline medications before or after vaccine administration. Neither the Pfizer-BioNTech nor Moderna study protocol addressed concurrent medication use or timing in relationship to the vaccination.

Consistent with CDC guidance, patients who received monoclonal antibodies or convalescent plasma for the treatment of COVID-19 should wait to be vaccinated at least 90 days from the time of dosing of these medications. If monoclonal antibodies or convalescent plasma for COVID-19 are administered after receiving the initial vaccine dose, the second dose should be delayed for 90 days following this therapy. Other monoclonal antibody therapies (i.e., non-COVID-19 therapies) do not require a delay in COVID-19 vaccination.

### ***COVID-19 vaccination of inpatients versus outpatients***

All of the participants in the mRNA vaccine trials were stable outpatients at the time of enrollment. Therefore, there are no data to guide the use of COVID-19 vaccination in individuals who are currently hospitalized. A review of overall risk versus benefit and potential for adverse events should be considered on a case-by-case basis.

### ***History of anaphylaxis***

We recommend vaccination in all patients unless there is a history of prior anaphylaxis to the mRNA COVID-19 vaccine or any of its components. ([Supplemental Table 2](#)) Prior anaphylaxis to any other allergen (including venom, food, and medication) does not preclude the use of mRNA COVID-19 vaccination, but those individuals should be observed for adverse events for a minimum of 30 minutes after vaccination compared to the standard 15-minute observation period. Vaccine side effects should be reported to the [VAERS](#).

The CDC has provided a table that may be helpful to clinicians in counseling patients. ([Supplemental Table 2](#)) The individual components of each vaccine are available from the CDC.<sup>83</sup> Neither vaccine contains eggs, gelatin, latex, or preservatives. The common anaphylaxis-inducing allergens of insect venom, milk, eggs, animal

dander, and oral medications are not a contraindication or precautions with use of the Pfizer-BioNTech or Moderna mRNA COVID-19 vaccines.

### ***Post-vaccination continuation of behaviors to avoid exposure to SARS-CoV-2***

We recommend that everyone continue behaviors to mitigate the risk of SARS-CoV-2 exposure (e.g., masking, hand hygiene, social distancing, etc.) regardless of vaccination status. The onset of protective immunity post-vaccination is not clear and infection occurred in vaccinated participants in the clinical trials even after the second dose.

### ***Common side effects of COVID-19 vaccination and distinguishing these from true infection***

Injection site pain is the most common complaint, with “severe pain” occurring in 1% of recipients within 12-24 hours. Fever, myalgia, and headache are also commonly reported. Younger patients may experience symptoms more commonly than older recipients. ([Figure 3](#))

Distinguishing COVID-19 from vaccination reaction can be challenging given the nonspecific symptoms associated with both conditions. High fevers and respiratory symptoms (e.g., cough or shortness of breath) are uncommon after vaccination. If observed, clinicians should consider testing for SARS-CoV-2 or another infectious etiology. As most side effects of vaccination should subside within 1-2 days, additional testing should be considered in patients with symptoms persisting beyond this time frame. It should be noted that mRNA vaccines do not cause positive nucleic acid (PCR) or antigen-based tests for SARS-CoV-2. A positive test after vaccination should be considered a true SARS-CoV-2 infection.

## **CONCLUSION**

Since the identification of the SARS-CoV-2 genome in January 2020, remarkable progress has been made in the development of two highly effective and generally safe mRNA vaccines for COVID-19. The CDC currently recommends that all adults over the age of 18 should receive these 2-dose vaccines according to the manufacturers’ recommendations to prevent future COVID-19. Pre- and post-vaccination serological testing is not recommended due to the absence of studies regarding their impact on outcomes. Due to their mechanism of action, both mRNA COVID-19 vaccines are recommended for all patients with CLD (compensated or decompensated) and immunosuppressed SOT recipients. The AASLD recommends that providers advocate for prioritizing patients with compensated or decompensated cirrhosis or liver cancer, patients receiving immunosuppression such as SOT 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 a rapidly evolving area, and until further studies are available, COVID-19 vaccination should not be withheld or deferred in any patient because of efficacy or safety concerns. All COVID-19 vaccine recipients are recommended to continue social distancing, masking, frequent hand washing, and follow other exposure-mitigating behaviors.



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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](#)

## TABLES

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

	Vaccine	Dosing	Efficacy	Safety issues	Storage issues
	<b>Vaccines with FDA EUA</b>				
mRNA vaccines	mRNA BNT162b2 (Pfizer- BioNTech)	30 µg (0.3 mL) IM x 2 doses 21 days apart  EUA for ages 16 and older	95% <sup>35</sup> (95.3% in those with comorbidities including CLD)	Synthetic lipid nanoparticle Contraindicated if history of severe or immediate allergic reaction to any vaccine components, including PEG*	Store between -80 °C to -60 °C Once thawed and diluted, multi- dose vials must be stored between 2 °C to 25 °C and used within 6 hours
	mRNA-1273 (Moderna)	100 µg (0.5 mL) IM x 2 doses 28 days apart  EUA for ages 18 and older	94.1% <sup>55</sup> (Unknown in CLD patients because no vaccine or placebo pts developed COVID-19 in clinical trials)	Synthetic lipid nanoparticle Contraindicated if history of severe or immediate allergic reaction to any vaccine components, including PEG*	Store between -25 °C to -15 °C Thawed vials stored at 2 °C to 8 °C for up to 30 days or between 8 °C to 25 °C for up to 12 hours Once first dose is withdrawn, vial must be used within 6 hours
	<b>Vaccines in Phase 3 development</b>				
Adenoviral vectors	AZD1222 (AstraZeneca)	1 or 2 IM doses 28 day apart  EUA in UK, Europe, and South America for ages ≥18 years	70.4% (pooled) after the 2 <sup>nd</sup> dose 62% standard dose (SD)/SD 90% low dose/SD <sup>41</sup> Unknown in CLD patients	Replication- defective chimpanzee adenovirus vector  2 cases of transverse myelitis reported	Stored and distributed at 2 °C to 8 °C for up to 6 months  Easier to scale up production vs mRNA
	Ad26.COVS.2 (Johnson and Johnson/ Janssen)	1 or 2 IM doses are being tested	72% in US with single dose 66% in Latin America 57% in S Africa <sup>90</sup>	Replication- defective adenovirus 26 vector (used in Ebola vaccine)	Stored at 2 °C to 8 °C for up to 3 months

				Low seroprevalence of antibodies in N America	
	Ad5-NCoV (CanSino biologics)		96%-97% antibody induction at day 28 <sup>91</sup>	Replication-defective adenovirus type 5 vector	
<b>Recombinant protein</b>	NCX-CoV2373 (Novavax)	2 IM doses 3 weeks apart	89.3% in UK study 49.4% in S Africa <sup>46</sup>	Recombinant spike protein nanoparticles  Adjuvant of M-matrix which may be allergenic	2 °C to 8 °C
<b>Inactivated virus</b>	CoronaVac (Sinovac)		50.4% protection in Brazilian study <sup>92</sup>	Inactivated SARS-CoV-2 with alum hydroxide adjuvant	
	BBIBP-CorV Inactivated COVID-19 (Wuhan)		100% antibody induction at day 42 <sup>93</sup>	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

**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 pediatric populations (adolescents and children)
- Effectiveness and safety in pregnant and lactating women
- Effectiveness and safety in individuals previously infected with SARS-CoV-2
- Effectiveness against SARS-CoV-2 viral variants (e.g., B.1.1.7, B.1.351, P.1)
- 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 an mRNA COVID-19 vaccine
- Duration of protective immunity against SARS-CoV-2 infection
- Mechanisms of vaccine failure

## FIGURES

### Figure 1. COVID-19 Vaccine Delivery Systems

#### 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. The spike proteins expressed on the cell surface by the MHC receptors can activate T-cells, which can activate the immune system, for 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. The spike proteins expressed on the cell surface by the MHC receptors can activate T-cells, which can activate the immune system, for 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.

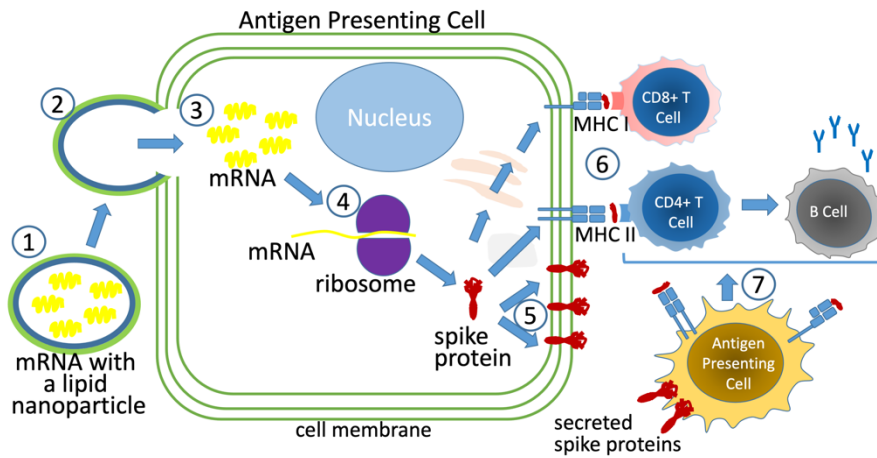
#### 1c. Weakened Live Attenuated Virus Vaccines.

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. The spike proteins expressed on the cell surface by the MHC receptors can activate T-cells, which can activate the immune system, for 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.

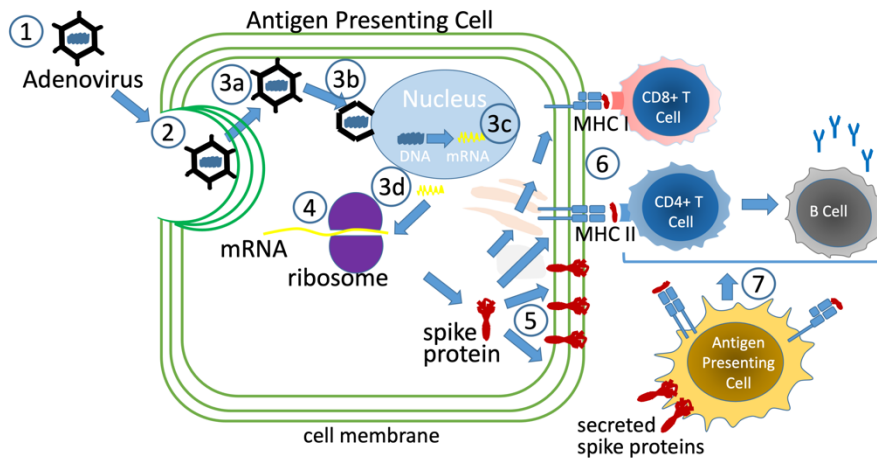
*ACE2, angiotensin-converting enzyme 2; MHC, major histocompatibility complex*



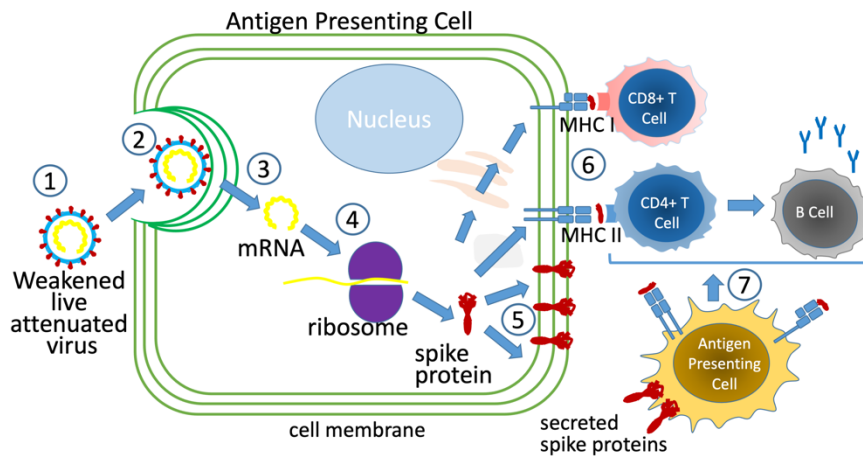
1a.



1b.



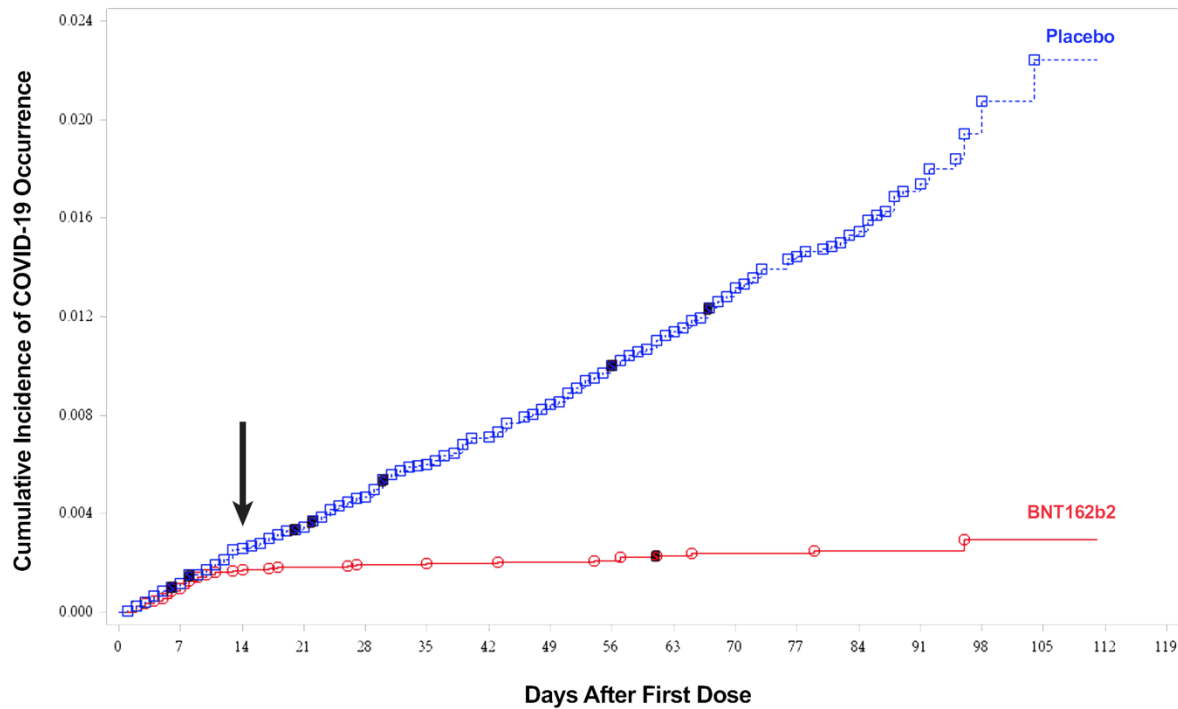
1c.



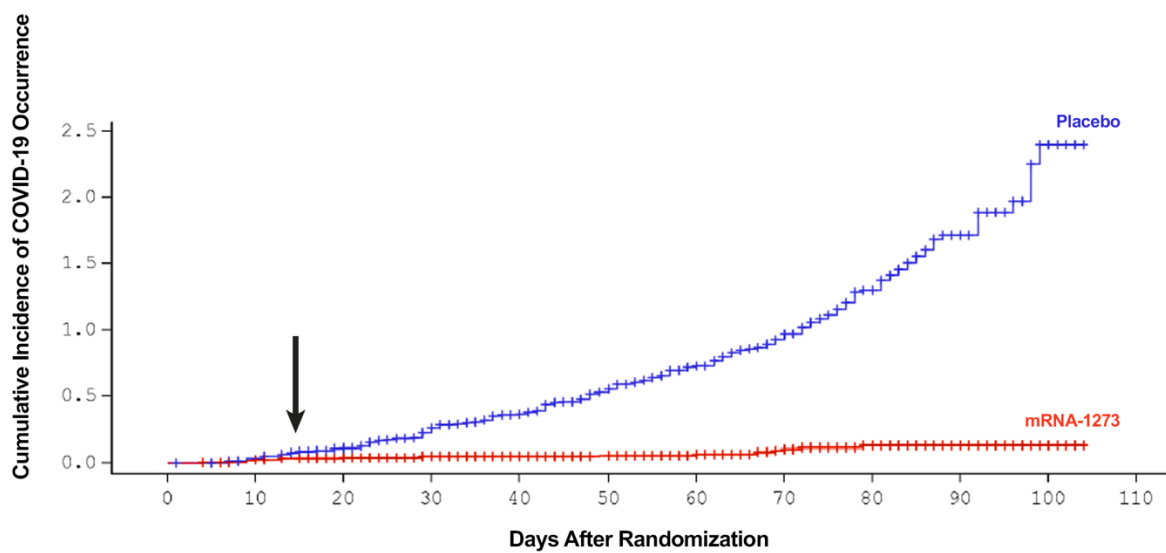
## Figure 2. Cumulative Incidence of First COVID-19 Occurrence in Phase 3 Clinical Trials

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

### 2a. Pfizer-BioNTech (BNT162b2)

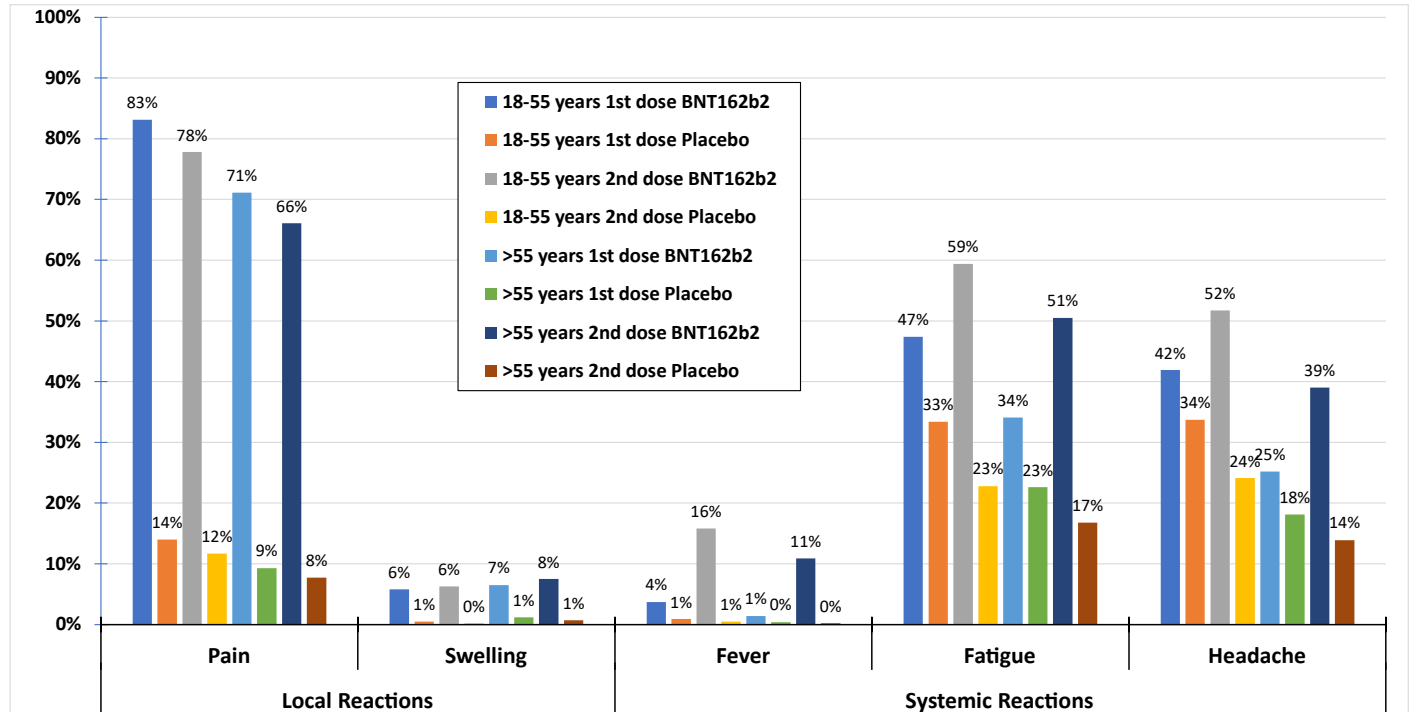


### 2b. Moderna (mRNA-1273)

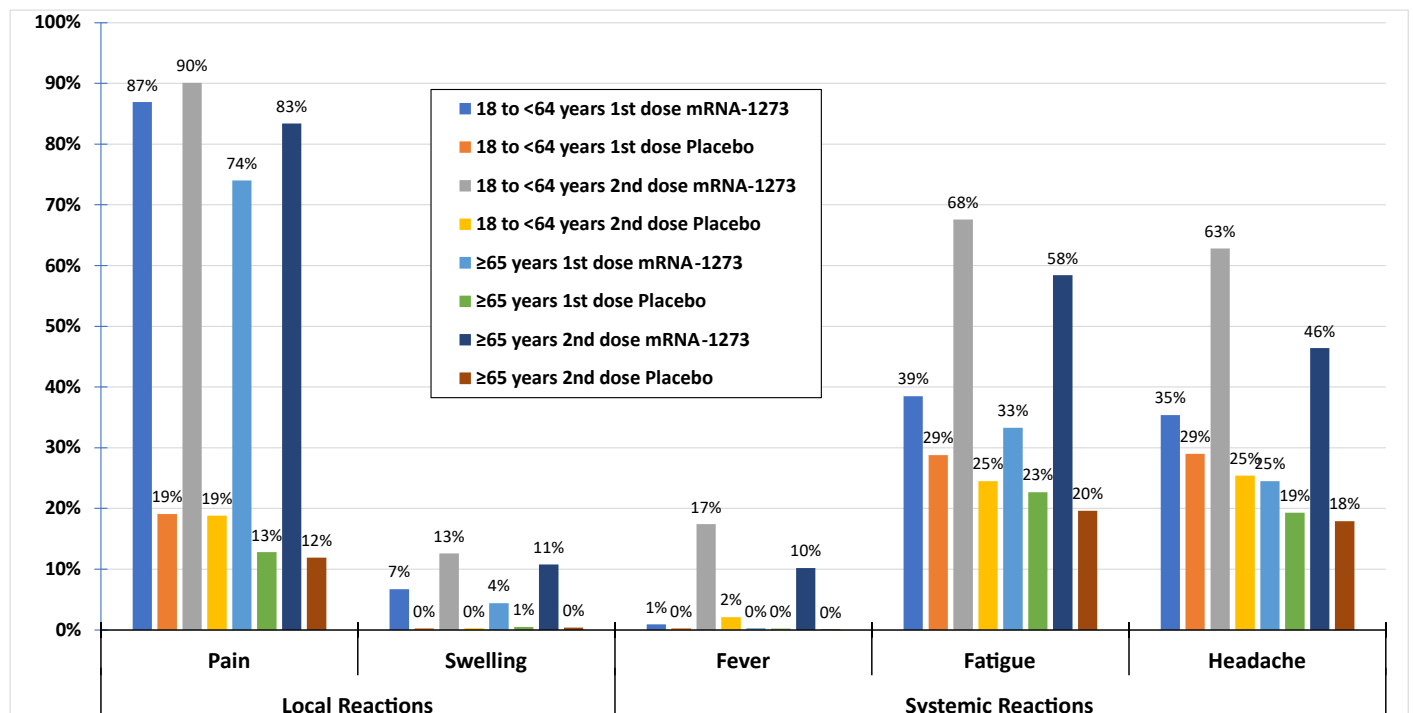


**Figure 3. Frequency of Adverse Events of FDA EUA mRNA Vaccines Compared to Placebo**

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



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



## SUPPLEMENTAL TABLES

**Supplemental Table 1. Recommended Vaccines in Adults with CLD and SOT Recipients**

Vaccine	Dosing	CLD	SOT recipients	Comments
Influenza	1 dose (yearly)	Inactivated Recombinant Live intranasal*	Inactivated Recombinant Live contraindicated	Live intranasal contraindicated in SOT recipients and those >50 years
Tdap (tetanus, diphtheria, pertussis)	1 dose (10 years)			
Pneumococcal 13	1 dose			
Pneumococcal polysaccharide (23)	1, 2, or 3 doses (3-5 years)			
Hepatitis B (Engerix, Recombivax HB)	0, 1, and 6 months	Increased immunogenicity		
(Hepalisav B)	0 and 1 month			
Hepatitis A	0 and 6 months			
Zoster (Shingrix)		≥50 years	>1 year post SOT (not studied)	
Human papillomavirus (HPV)	2 or 3 doses depending on age, condition			Adults up to age 25 and some 27-45 years
Measles, mumps, and rubella (MMR)	1 or 2 doses at 0 and 6 months		Contraindicated	If born after 1957 or no prior immunity
Varicella	2 doses		Contraindicated	
Meningococcus	1-3 doses			
H. Influenzae	1 dose			

\*only if age <50 years

Adapted from the CDC<sup>18</sup> and MMWR 2020; 69

CLD, chronic liver disease; SOT, solid organ transplant

**Supplemental Table 2. Triage of Persons Presenting for mRNA COVID-19 Vaccination**

	May Proceed with Vaccination	Precaution to Vaccination	Contraindication to Vaccination
<b>CONDITIONS</b>	<b>Conditions</b> <ul style="list-style-type: none"> <li>Immunocompromising conditions</li> <li>Pregnancy</li> <li>Lactation</li> </ul> <b>Actions</b> <ul style="list-style-type: none"> <li>Additional information provided</li> <li>15 minute observation period</li> </ul>	<b>Conditions</b> <ul style="list-style-type: none"> <li>Moderate/severe acute illness</li> </ul> <b>Actions</b> <ul style="list-style-type: none"> <li>Risk assessment</li> <li>Potential deferral of vaccination</li> <li>15-minute observation period if vaccinated</li> </ul>	<b>Conditions</b> <ul style="list-style-type: none"> <li>None</li> </ul> <b>Actions</b> <ul style="list-style-type: none"> <li>N/A</li> </ul>
<b>ALLERGIES</b>	<b>Allergies</b> <p>History of allergies that are unrelated to components of an mRNA COVID-19 vaccine*, other vaccines, injectable therapies, or polysorbate, such as:</p> <ul style="list-style-type: none"> <li>Allergy to oral medications (including the oral equivalent of an injectable medication)</li> <li>History of food, pet, insect, venom, environmental, latex, etc., allergies</li> <li>Family history of allergies</li> </ul> <b>Actions</b> <ul style="list-style-type: none"> <li>30-minute observation period: Persons with a history of anaphylaxis (due to any cause)</li> <li>15-minute observation period: All other persons</li> </ul>	<b>Allergies</b> <ul style="list-style-type: none"> <li>History of any immediate allergic reaction to vaccines or injectable therapies (except those related to component of mRNA COVID-19 vaccines* or polysorbate, as these are contraindicated)</li> </ul> <b>Actions</b> <ul style="list-style-type: none"> <li>Risk assessment</li> <li>Consider deferral of vaccination and/or referral to allergist-immunologist</li> <li>30-minute observation period if vaccinated</li> </ul>	<b>Allergies</b> <p>History of the following are contraindications to receiving either of the mRNA COVID-19 vaccines*:</p> <ul style="list-style-type: none"> <li>Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components</li> <li>Immediate allergic reaction<sup>†</sup> of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components<sup>^</sup> (including polyethylene glycol)</li> <li>Immediate allergic reaction of any severity to polysorbate</li> </ul> <b>Actions</b> <ul style="list-style-type: none"> <li>Do not vaccinate**</li> <li>Consider referral to allergist-immunologist</li> </ul>

\*Refers only to mRNA COVID-19 vaccines currently authorized in the United States (i.e., Pfizer-BioNTech, Moderna COVID-19 vaccines)

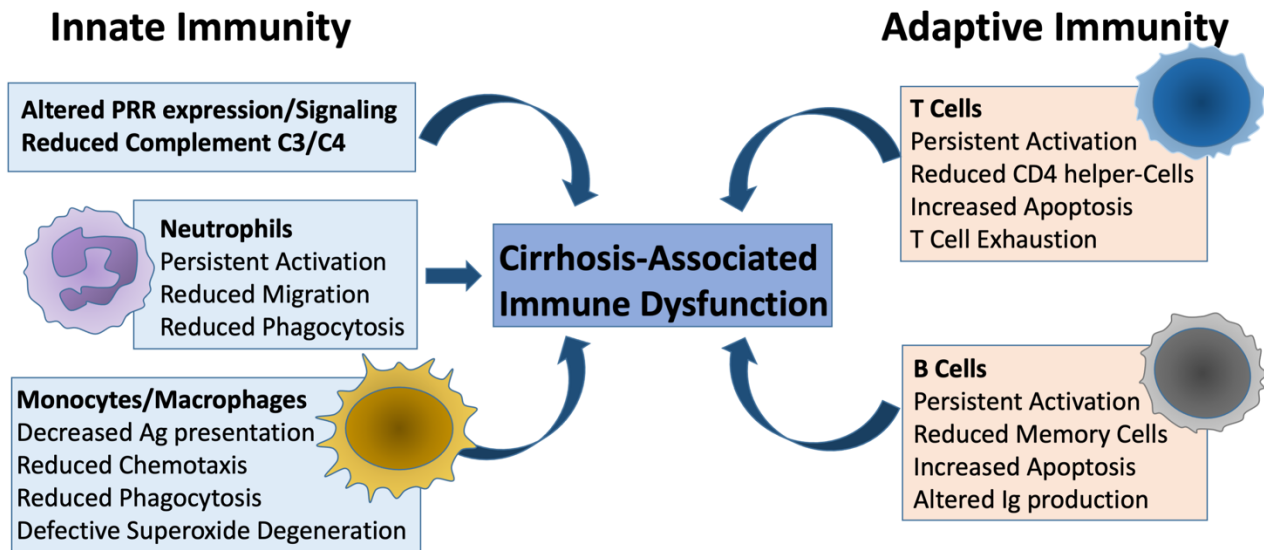
\*\*These persons should not receive mRNA COVID-19 vaccination at this time unless they have been evaluated by an allergist-immunologist and it is determined that the person can safely receive the vaccine (e.g., under observation, in a setting with advanced medical care available)

Adapted from the CDC<sup>83</sup>

## SUPPLEMENTAL FIGURES

### Supplemental Figure 1. Immune Dysfunction in Cirrhosis

Alterations in innate and adaptive immune function occur in cirrhosis which may contribute to vaccine hyporesponsiveness in this population.



Adapted from Noor and Manoria 2017<sup>8</sup>