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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

- Majority of "Non-COVID-19 Vaccines in Patients with Chronic Liver Disease" and "Non-COVID-19 Vaccines in Immunosuppressed Patients" section moved to **Supplemental Materials**.
- "Assays to Detect Immunity to COVID-19" moved to **Supplemental Materials**.
- Majority of "Safety and Efficacy of FDA EUA mRNA COVID-19 Vaccines" moved to **Supplemental Materials**.
- New section: "**Safety and Efficacy of FDA EUA COVID-19 Vaccines**" with subheadings for mRNA and Adenoviral Vector Vaccines and data on Johnson & Johnson/Janssen vaccine.
- Clarification of recommendation to **defer COVID-19 vaccination for up to 90 days** after COVID-19 infection.
- "General Guidance for COVID-19 Vaccination" moved to **Supplemental Materials**.
- Clarification of recommendation to vaccinate **potential live liver donors and recipients of live donor livers** at least two weeks before transplantation when feasible.
- **Post-marketing data** on mRNA COVID-19 vaccination in SOT recipients.
- Updated **Table 1**, **Figure 2**, and **Figure 3**.
- "**Counseling Patients About COVID-19 Vaccination**" moved to a stand-alone document.

OVERVIEW AND RATIONALE

Coronavirus disease 2019 (COVID-19) is the illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Multiple studies demonstrate that older individuals and those with certain comorbidities, including chronic liver disease (CLD) (particularly cirrhosis), cardiac disease, obesity, and weakened immune systems from other diseases or medications, may be at higher risk of death from COVID-19. 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 March 2021, two mRNA-based vaccines given as two doses and a single-dose adenoviral vector vaccine 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. Given that persons with 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 (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.

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

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

Patients with CLD display innate and adaptive immune dysregulation that is associated with vaccine hyporesponsiveness[1] (**Supplemental Figure 1**). Given that subjects with CLD have an increased risk of complications after infection with influenza, *Streptococcus pneumoniae*, HAV, and HBV,[2,3] 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.[4,5] Immunosuppressed LT recipients are also known to have a lower response rate to many non-COVID-19 vaccines, particularly when given early after transplant. Therefore, it is generally recommended that vaccines be given before transplant whenever possible or waiting until 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.[6] See **Supplemental Text** for additional information regarding non-COVID-19 vaccines.

GUIDANCE FOR DOUBLE DOSING OF COVID-19 VACCINES

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

BACKGROUND ON COVID-19 VACCINES

Types of COVID-19 Vaccines in Development

Entry of SARS-CoV-2 requires binding of the viral spike glycoprotein to the angiotensin-converting enzyme 2 (ACE2) receptor on human epithelial cells.[7] 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 1 year.[8,9] Both Moderna and Pfizer-BioNTech developed a two-dose vaccine using synthetic nucleoside-modified mRNA that encodes the spike glycoprotein, while Johnson & Johnson/Janssen developed a vaccine using a modified adenoviral vector that contains DNA encoding the spike glycoprotein.[10–12] Other vaccines that are currently in development use DNA, protein subunits, inactivated SARS-CoV-2, viral vectors, and attenuated virus (**Table 1**, **Figure 1**). All of the vaccines described below are not live SARS-CoV-2 and cannot replicate, even in immunocompromised persons.

mRNA Vaccines

mRNA-based vaccines involve the delivery of noninfectious synthetic mRNA encoding one or more target antigens (e.g., SARS CoV-2 spike protein) that can be taken up by host cells including antigen presenting cells (e.g., dendritic cells) (**Figure 1**). Upon cytoplasmic entry, the delivered mRNA uses the host ribosomal translational machinery to make the target antigens that can be processed for cell surface expression via class I

and II major histocompatibility complex (MHC) or be secreted. This induces protective immunity against a future attack (e.g., from SARS-CoV-2) by priming antigen-specific cytotoxic CD8 T cells and helper T cells and a neutralizing antibody response from B cells.[13] 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.[14,15] Additionally, nucleoside modifications prevent innate immune activation and degradation. Nevertheless, the mRNA-based vaccines degrade within a few hours at room temperature and require very cold temperatures during manufacturing, transportation, and storage.

Adenoviral Vectors

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

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

Johnson & Johnson/Janssen's single shot adenoviral vector (Ad26) vaccine was recently authorized under EUA in the USA. Early safety data were favorable in the Phase 3 clinical trial of Oxford/AstraZeneca's AZD1222 adenovirus vectored COVID-19 vaccine,[18] leading to its authorization for emergency use in the UK on December 29, 2020.[19] 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).[20] Although these observations were not considered clinically significant, more data and experience with this and other replication defective adenovirus-based vaccines are needed. Replication defective adenovirus-based vaccines are not live or attenuated SARS-CoV-2 and are not expected to pose a risk to immunocompromised patients.

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).[21] The Novavax product is a recombinant spike protein subunit and adjuvant vaccine using nanoparticle technology that has started phase 3 trials in the USA. Novavax recently reported a vaccine efficacy (VE) of 89% in the UK and a VE of 49.4%

in South Africa, where the majority of COVID-19 cases are caused by an escape variant (B.1.351).[22] A Sanofi/GlaxoSmithKline protein subunit vaccine failed to generate adequate immune response in older adults and is being reengineered.

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

See **Supplemental Text** for background on assays to detect immunity to COVID-19.

Safety and Efficacy of FDA EUA COVID-19 Vaccines

mRNA COVID-19 Vaccines

In December 2020, the FDA granted EUA to two mRNA vaccines to prevent COVID-19: BNT162b2 manufactured by Pfizer-BioNTech and mRNA-1273 by Moderna, respectively (**Table 1**). Both vaccines are based on the SARS-CoV-2 spike glycoprotein antigen encoded by mRNA in lipid nanoparticles. The spike glycoprotein antigen mediates binding of the virus to the ACE2 receptor on host cells to enable viral entry and replication. In both vaccines, the mRNA encodes the spike glycoprotein antigen stabilized in its prefusion form, which more closely resembles the intact virus.[23]

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**). See **Supplemental Text** for additional information regarding these currently authorized mRNA vaccines.

Adenoviral Vector COVID-19 Vaccines

The Johnson & Johnson/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.[12] It is an intramuscular vaccine administered as a single dose containing 5×10^{10} viral particles (0.5 mL). The multiple-dose vials have a shelf life of 3 months when stored between 2 °C to 8 °C. Once the first dose is withdrawn, the vial must be used within 6 hours at 2 °C to 8 °C or within 2 hours at room temperature.

An EUA was granted by the FDA on February 27, 2021 based on median 2 months follow-up data from an ongoing registration Phase 3 randomized, double-blind, placebo-controlled trial (VAC31518COV3001). The Phase 3 trial enrolled adult participants ≥18 years stratified by age (younger, 18-59 years; older, ≥60 years) and comorbidities, including liver disease and solid organ transplantation (SOT). A 2-dose regimen of Ad26.COV2.S is the subject of an ongoing Phase 3 study and additional studies are planned in pregnant women.

In the Phase 3 Johnson & Johnson/Janssen trial, approximately 40,000 participants were randomized 1:1 to receive Ad26.COV2.S or placebo. Median age was 51.1 years and 55.5% were male. Most participants were White (62.1%), 17.2% Black, 3.5% Asian, 14% other racial groups, and 45.1% were Hispanic/Latino. There were

46.7% participants in the USA, 17.3% in Brazil, and 12.7% in South Africa. There were 40.8% of participants with one or more comorbidities, most commonly obesity and hypertension.

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

In analyses of secondary endpoints (central laboratory-confirmed and blind-adjudicated severe/critical COVID-19 occurring ≥14 days and ≥28 days after vaccination), VE was 76.7% (95% CI 54.6-89.1) and 85.4% (95% CI 54.2-96.9), respectively. This is the basis of the widely reported VE of 85% against severe COVID-19. There were no COVID-19 cases requiring hospitalization after 28 days post-vaccination compared to 5 cases in the placebo group. There were no COVID-19-related deaths in the vaccine group and 7 COVID-19-related deaths in the placebo group. Antibody titers generated by Ad26.COV2.S continue to increase up to at least day 56, after vaccination and there is evidence that protection against severe or critical COVID-19 may reach 95%.[24] The results suggest potential efficacy against asymptomatic infection after 29 days post-vaccination, but the numbers are small and follow-up time is still limited. It is unknown if Ad26.COV2.S prevents SARS-CoV-2 transmission by vaccinated individuals.

Safety data are available from 43,783 participants with a median of 2 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**).

A numerical imbalance was seen in thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, transverse sinus thrombosis, cerebral infarction, myocardial infarction, carotid artery occlusion) with 15 cases in the vaccine group and 10 in the placebo group. There were no reports of anaphylaxis immediately following vaccination; however, there were 5 cases of non-serious urticaria events in the vaccine group within 7 days of vaccination compared to 1 in the placebo group. At least one of these was likely a hypersensitivity reaction to the vaccine. There were 2 cases of facial paralysis (Bell's Palsy) in each of the study groups, and 1 report of Guillain-Barre Syndrome in each of the study groups. There were no deaths related to the vaccine.

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).[25] 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, 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 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).[26] Ninety percent of these occurred within 15 minutes of vaccination, 9 (90%) had a documented history of allergies or allergic reactions, and 100% were female. All patients were treated with epinephrine, 6 (60%) were hospitalized (including five in intensive care), and 17 (81%) were treated in an emergency department. No deaths from anaphylaxis were reported after receiving the Moderna COVID-19 vaccine.

A more recent report from the Centers for Disease Control and Prevention (CDC) summarized the safety reporting to VAERS from 13,749,904 mRNA vaccine doses given between December 14, 2020 to January 13, 2021.[27] The most frequent side effects were injection site pain (70.9%), fatigue (33.5%), and headache (29.5%) in a group of 1,602,065 individuals enrolled in the prospective V-Safe study wherein participants are asked to complete a web survey for 7 days after each vaccine dose. In addition, no unexpected patterns of reactions or safety concerns have been identified in that cohort thus far. 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.[25,26]

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 NOT receive either mRNA COVID-19 vaccine.**
- **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.**

SARS-CoV-2 Viral Variants

Rapidly spreading variants of SARS-CoV-2 originating from the UK (B.1.1.7),[28] South Africa (B.1.351),[29] and Brazil (P.1)[30] have been detected by genetic surveillance programs. These variants share the N501Y substitution in the viral spike protein receptor binding domain (RBD). B.1.351 and P.1 also share an E484K substitution in the RBD. All of these variants have been found in the USA[31–33] and are more transmissible.[28,34] The B.1.1.7 variant may be associated with higher morbidity and mortality.[31,35] Another variant, B.1.526, which also shares both N501Y and E484K, was first detected in New York City in November 2020.[36]

Early studies suggest that the E484K mutation impairs or abolishes the neutralizing effects of some of the available monoclonal antibodies with EUA and reduces the neutralizing activity of convalescent plasma and sera from persons vaccinated against COVID-19.[36] Despite reduced neutralization, particularly against B.1.351, preliminary studies suggest that both Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines likely provide protection against these variants.[37–39]

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GUIDANCE FOR VACCINATION IN SETTING 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**

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Pediatric Considerations in COVID-19 Vaccination

Only the Pfizer-BioNTech mRNA vaccine has been authorized for children aged <18 years (specifically ≥16 years). However, there are multiple vaccine trials underway for children ≥12 years. Although a small subset of children have had severe COVID-19 symptoms and/or developed complications such as multisystem inflammatory syndrome in children (MIS-C),[40] 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-LT have outcomes similar to the general pediatric population.[41] 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. Coadministration of different vaccines is usually safe; however, administration of the COVID-19 vaccine with other childhood immunizations has not yet been tested.

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GUIDANCE FOR ADMINSTRATION 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.**

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

Patients with Liver Disease in COVID-19 Vaccine Clinical Trials

Patients with stable chronic medical conditions such as compensated CLD, HIV, HBV, or HCV were eligible to participate in the Pfizer-BioNTech, Moderna, and Johnson & Johnson/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 Johnson & Johnson/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 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. Given that no participants with liver disease developed COVID-19, VE cannot be determined for this subgroup.

In the Johnson & Johnson/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 (7 in vaccine group and 3 in placebo group). Among participants with liver disease, 1 in the vaccine group and 2 in the

placebo group developed moderate to severe/critical COVID-19 ≥14-days after vaccination. Interpretation of these results is limited by the small sample size and low incidence of COVID-19. Data on the incidence of COVID-19 in the SOT subgroup have not yet been reported.

Prioritization During 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.[42] 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, and 2).[43] Health care 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.[44] Patients with underlying medical conditions, including liver disease (e.g., compensated and decompensated cirrhosis, liver cancer), SOT, and immunosuppression, are at risk for severe COVID-19 and are included in phase 1c.[45–49]

Because of the scarcity of COVID-19 vaccines and the observation that SARS-CoV-2 reinfection is uncommon within 90 days of first infection, the CDC recognizes that persons with recent SARS-CoV-2 infection may want to defer vaccination for up to 90 days. In addition, early work suggests that COVID-19 vaccine-related side effects may be more common in those with previous SARS-CoV-2 infection, particularly when vaccinated soon after infection.[50]

PRINCIPLES REGARDING PRIORITIZATION OF PATIENTS FOR COVID-19 VACCINATION

- **All health care 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).[51]**
- **For LT candidates, vaccination against COVID-19 should proceed even if LT is likely to occur before the second mRNA vaccine dose can be administered. The second dose of mRNA 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).[52–54]**
- **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, in the absence of contraindications (hypersensitivity to any vaccine components), all patients with CLD and SOT recipients should be encouraged to get vaccinated.**
- **Health care providers should be knowledgeable of the local criteria for vaccination, know where vaccine is available, and actively inform patients of this information.**
- **Vaccinated health care providers are encouraged to volunteer to assist with their local vaccination efforts.**
- **See Supplemental Text for additional guidance for COVID-19 vaccination.**

COVID-19 Vaccination in Patients with Chronic Liver Disease

Because of the increased morbidity and mortality with COVID-19 in adult CLD patients and particularly those with cirrhosis, it is recommended that these patients be prioritized for COVID-19 vaccination (phase 1c). 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 nor is efficacy expected to be lower than the general population; however, additional prospective studies are needed.

If the supply of COVID-19 vaccine is limited, it is reasonable to prioritize patients with higher Model for End-stage Liver Disease (MELD) or Child-Turcotte-Pugh scores for vaccination or those who are anticipated to undergo imminent LT, but all CLD patients should be vaccinated whenever possible.

The CDC recently recommended that fully vaccinated people can gather indoors without wearing a mask.[55] Although the CDC also recommend that vaccinated people can gather indoors with unvaccinated people from one other household without masks, it is important to understand that this does not apply to patients with CLD or SOT, who are at increased risk of severe COVID-19.[51]

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 are expected to have a favorable efficacy and safety profile in immunosuppressed patients and should be administered according to their standard dose and schedule.**
- **LT candidates with CLD should receive a COVID-19 vaccine prior to transplantation whenever possible to help ensure an adequate immune response.**
- **CLD patients receiving a 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.).**
- **See "Counseling Liver Disease Patients About COVID-19 Vaccination" for guidance on answering common questions from patients.**

COVID-19 Vaccination in Immunosuppressed Liver Transplant Recipients

Given that immunocompromised patients and SOT recipients were not included in the mRNA COVID-19 vaccine trials and only a small number were included in the adenoviral vector vaccine studies, there are limited data regarding the safety and efficacy of the available vaccines in this population. Johns Hopkins recently reported preliminary results of a study of invited SOT recipients in the USA who received early vaccination with

one of the mRNA COVID-19 vaccines.[56,57] In 187 SOT recipients, including 64% frontline health care workers and 19% liver transplant recipients, vaccine reactogenicity was mild and similar to rates reported in the non-transplant population.[56] There were no early reported episodes of acute cellular rejection (ACR), SARS-CoV-2 diagnoses, or major allergic reaction. Among 436 SOT recipients, including 78 LT recipients, only 17% developed antibodies to the SARS-CoV-2 spike protein at a median of 20 days after the first dose of mRNA COVID-19 vaccine.[57] This compares to spike antibody detection in 100% of participants in the clinical trials by day 15 (mRNA-1273) or day 21 (BNT162b2) following vaccination. SOT recipients on antimetabolite maintenance immunosuppression were less likely to develop an antibody response (37% vs. 63%), as were older recipients. For unclear reasons, those who received mRNA-1273 were more likely to develop an antibody response than those receiving BNT162b2 (69% vs. 31%).

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

Despite these uncertainties, the available COVID-19 vaccines do not contain live or attenuated virus and therefore are unlikely to pose a safety concern for immunosuppressed patients.[58] Given that replication defective or nonreplicating vaccines have not yet been tested in SOT recipients or other immunosuppressed patients, additional data are needed before use of these COVID-19 vaccines can be recommended in these patients.

GUIDANCE FOR COVID-19 VACCINATION IN LIVER TRANSPLANT RECIPIENTS
- **COVID-19 vaccination is recommended for all SOT recipients including LT recipients.**
- **The best time to administer the COVID-19 vaccine in liver LT is likely at least 3 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 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 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.**
- **Avoid COVID-19 vaccination in LT recipients with active ACR, those being treated for ACR, or those on high daily doses of corticosteroids until the episode is resolved and their baseline immunosuppression reestablished.**
- **In patients whose liver tests increase after vaccination and do not immediately return to baseline on repeat testing, a thorough evaluation should follow to exclude ACR or viral infection of the liver.**

- **Given the life-saving nature of LT, deceased donor transplantation should NOT be delayed in a patient who received a COVID-19 vaccine.**
- **If a patient is due for a second dose of an mRNA vaccine in the immediate posttransplant period, this may be delayed 6 weeks to elicit a better immune response.**
- **Potential live liver donors and recipients of live donor livers should be prioritized for COVID-19 vaccination and preferably vaccinated at least two weeks before transplantation when feasible. However, a lack of COVID-19 vaccination should NOT delay life-saving living donor LT.**
- **Family members and caregivers of LT recipients should be vaccinated against SARS-CoV-2 whenever possible.**

COVID-19 Vaccination Knowledge Gaps

Patients with advanced CLD have not been included in the COVID-19 vaccine studies and a small number of LT recipients were included in the Johnson & Johnson/Janssen studies. As such, data on effectiveness and safety are lacking in these populations. Postmarketing 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. Furthermore, there are known racial and ethnic differences in prevalence and incidence of various liver diseases.[59,60] 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.[60,61] Cirrhosis is inherently a state of qualitative and quantitative immune dysregulation,[1] whereas 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.[62,63] These large knowledge gaps related to liver disease and transplantation require special attention in further studies (**Table 2**).

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 adults over the age of 18 should receive the two-dose mRNA vaccines or single-dose adenoviral vector vaccine according to the manufacturers' recommendations to prevent future COVID-19. Prevaccination and postvaccination serological testing are not recommended because of the absence of studies regarding their impact on outcomes. Any currently authorized 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, immunosuppressed patients such as LT recipients, and living liver donors for COVID-19 vaccination based upon local health policies, protocols, and vaccine availability. The clinical impact of SARS-CoV-2 viral variants is rapidly evolving, and until further studies are available, COVID-19 vaccination should not be withheld or deferred in any patient because of efficacy or safety concerns 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. This document will be updated as additional data become available.

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Helpful Websites and Resources

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

TABLES

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

	Vaccine	Dosing	Efficacy	Safety issues	Storage issues
			Vaccines with FDA EUA		
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%[11] (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%[64]	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
Adenoviral vectors	Ad26.COV2.S (Johnson and Johnson/ Janssen)**	Single dose of 5x10^{10} viral particles (0.5 mL) EUA for ages 18 and older	66.9% after 14 days post-vaccination 85.4% for preventing severe/critical COVID-19 at least 28 days post-vaccination	Replication-defective adenovirus 26 vector (used in Ebola vaccine) Low seroprevalence of antibodies in N America	Stored at 2 °C to 8 °C for up to 3 months Once the first dose is withdrawn, the vial must be used within 6 hours at 2 °C to 8 °C or within 2 hours at room temperature

Vaccines in Phase 3 development				
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 2nd dose 62% standard dose (SD)/SD 90% low dose/SD[18] 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
	Ad5-NCoV (CanSino biologics)		96%-97% antibody induction at day 28[65]	Replication-defective adenovirus type 5 vector	
Recombinant protein	NCX-CoV2373 (Novavax)	2 IM doses 3 weeks apart	89.3% in UK study 49.4% in S Africa[22]	Recombinant spike protein nanoparticles Adjuvant of M-matrix which may be allergenic	2 °C to 8 °C
Inactivated virus	CoronaVac (Sinovac)		50.4% protection in Brazilian study[66]	Inactivated SARS-CoV-2 with alum hydroxide adjuvant	
	BBIBP-CorV Inactivated COVID-19 (Wuhan)		100% antibody induction at day 42[67]	Inactivated whole virion SARS-CoV-2	

PEG: polyethylene glycol

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

** Ingredients include citric acid, citrate dehydrate, ethanol, 2-hydroxypropyl-B-cyclodextrin, polysorbate 80, sodium chloride, sodium hydroxide, and hydrochloric acid

Table 2. COVID-19 Vaccination Knowledge Gaps

- Effectiveness and safety in patients with CLD based on liver disease etiology, comorbidities, CTP class, and MELD score
- Effectiveness and safety in immunocompromised/immunosuppressed individuals including transplant recipients
- Effectiveness and safety in 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 variants (e.g., B.1.1.7, B.1.351, P.1, B.1.526)
- Effectiveness against asymptomatic infection
- Effectiveness against SARS-CoV-2 transmission
- Effectiveness against long-term effects of COVID-19
- Effectiveness and safety in a diverse population including different racial and ethnic backgrounds
- Effectiveness and safety of vaccination with a different vaccine following a prior allergic/anaphylactic reaction to a COVID-19 vaccine
- Duration of protective immunity against SARS-CoV-2 infection
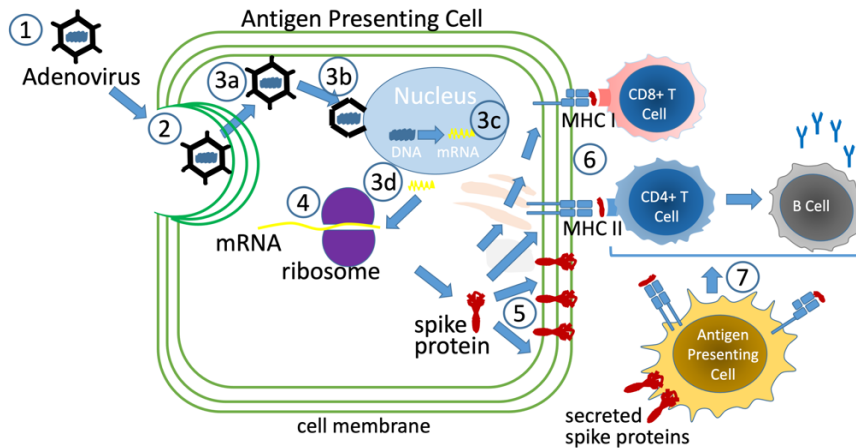- Mechanisms of vaccine failure

FIGURES
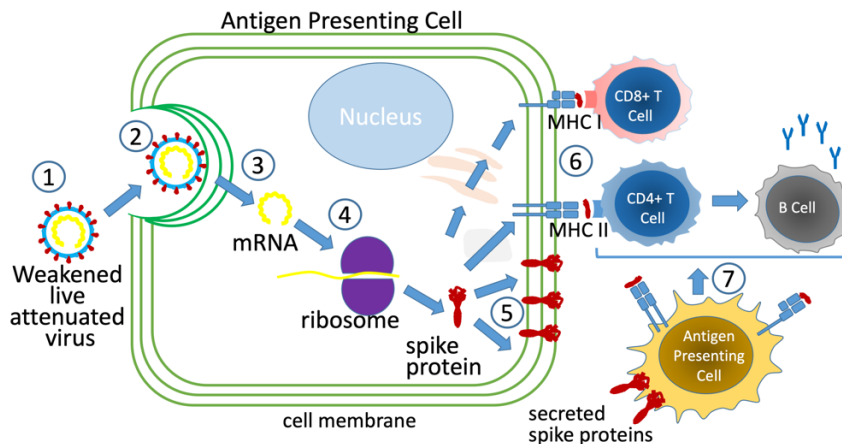
Figure 1. COVID-19 Vaccine Delivery Systems

1a.
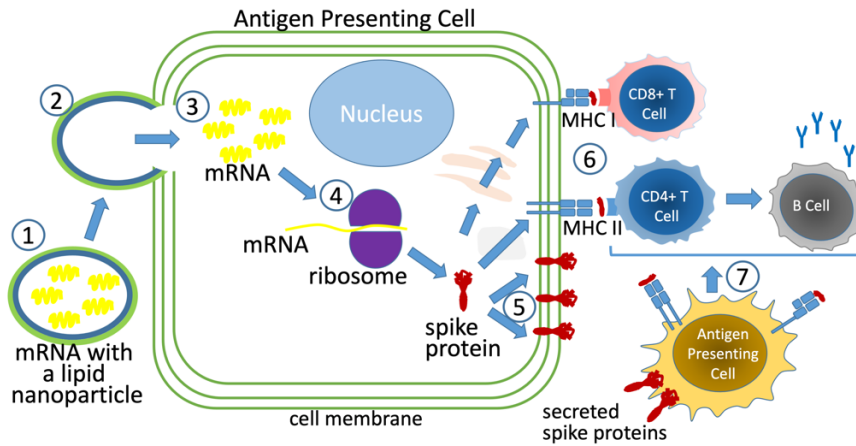
1b.

1c.

1a. mRNA Vaccines.
1. The mRNA is surrounded by a lipid nanoparticle
2. The lipid nanoparticle assists with cell entry
3. mRNA is released into the cytoplasm
4. Ribosomes and cellular proteins are used to translate the mRNA into the spike protein
5. The spike protein gets expressed on the cell surface and/or secreted into the serum
6. 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.

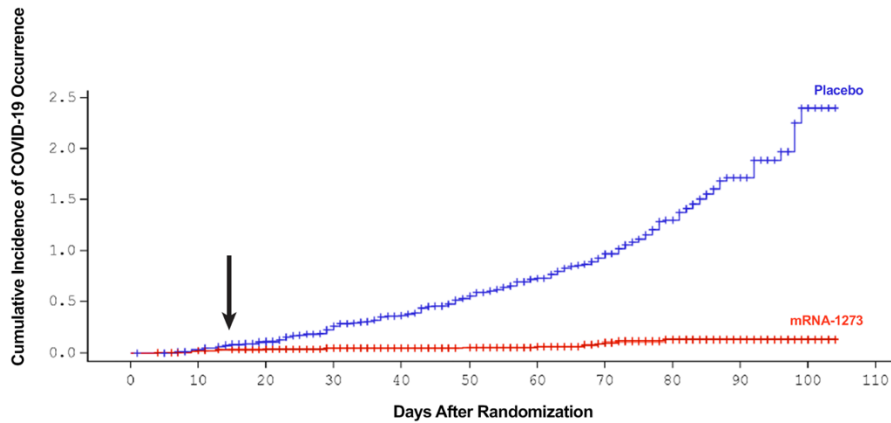ACE2, angiotensin-converting enzyme 2; MHC, major histocompatibility complex

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

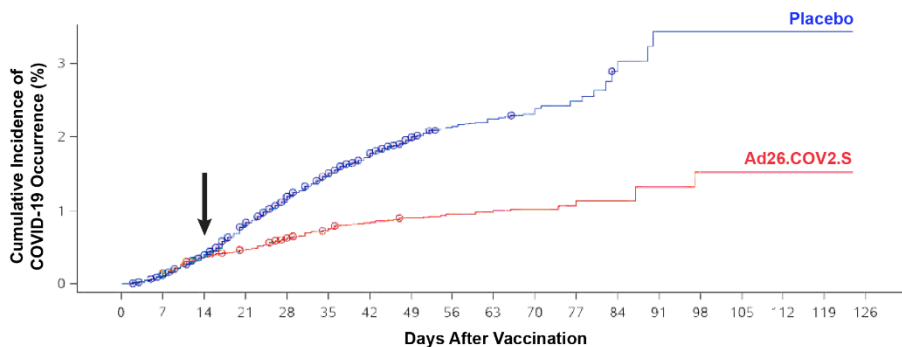Vaccine and placebo groups diverge at approximately 14 days after the first dose (arrow)

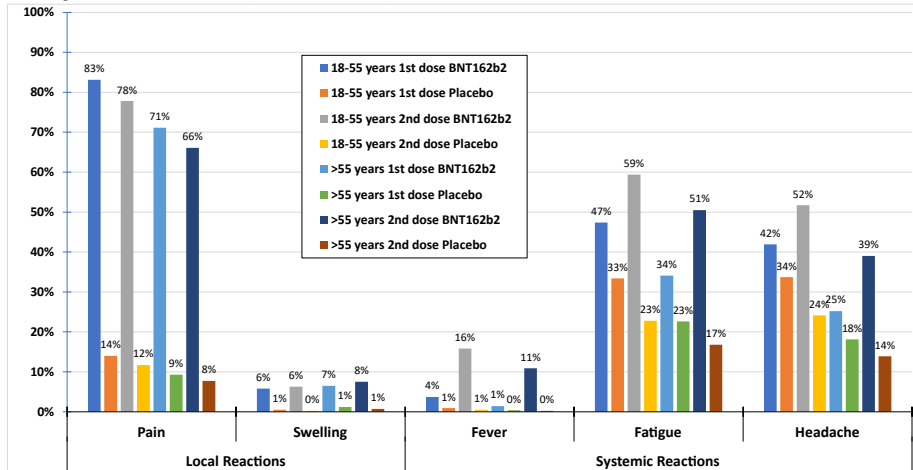### 2a. Pfizer-BioNTech (BNT162b2)
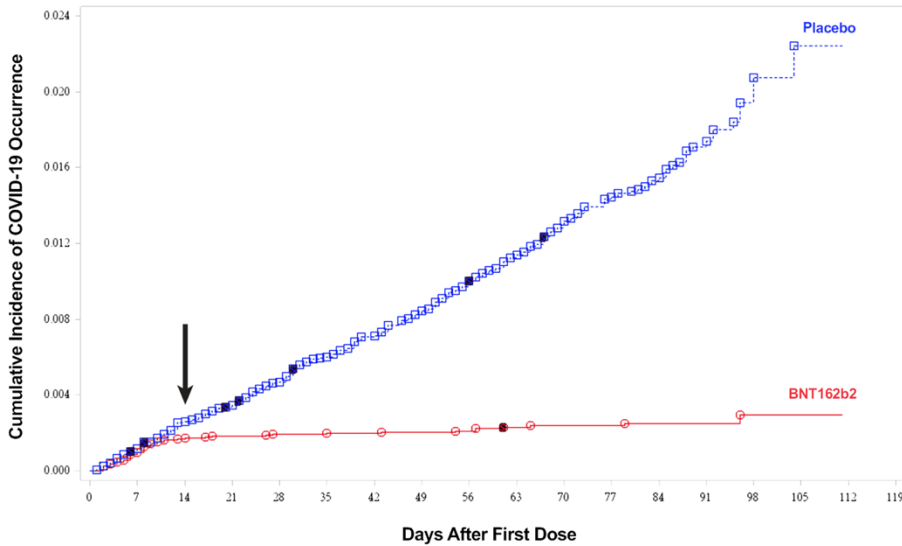
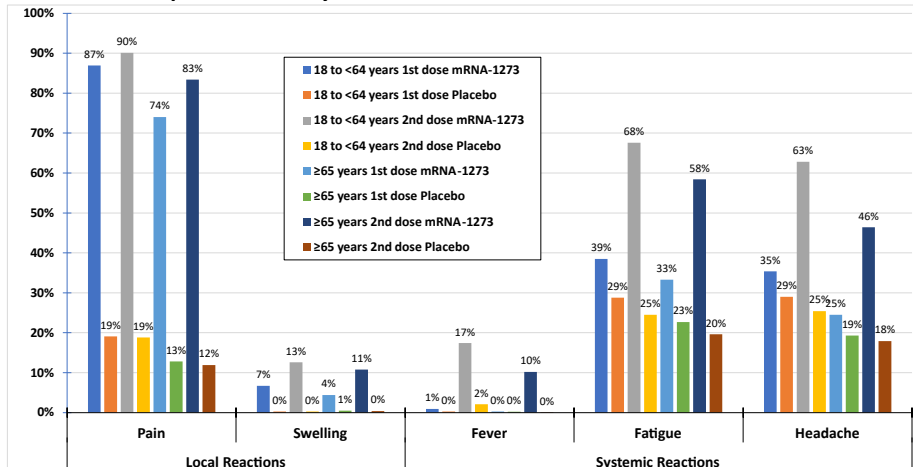### 2b. Moderna (mRNA-1273)

2c. Janssen (Ad26.COV2.S)

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

3a. Pfizer-BioNTech (BNT162b2)

3b. Moderna (mRNA-1273)

3c. Janssen (Ad26.COV2.S)