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American Association for the Study of Liver Diseases Expert Panel Consensus Statement: Vaccines to Prevent Coronavirus Disease 2019 Infection in Patients With Liver Disease

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The aim of this document is to provide a concise scientific review of the currently available COVID-19 vaccines and those in development, including mRNA, adenoviral vectors, and recombinant protein approaches. The anticipated use of COVID-19 vaccines in patients with chronic liver disease (CLD) and liver transplant (LT) recipients is reviewed and practical guidance is provided for health care providers involved in the care of patients with liver disease and LT about vaccine prioritization and administration. The Pfizer and Moderna mRNA COVID-19 vaccines are associated with a 94%-95% vaccine efficacy compared to placebo against COVID-19. Local site reactions of pain and tenderness were reported in 70%-90% of clinical trial participants, and systemic reactions of fever and fatigue were reported in 40%-70% of participants, but these reactions were generally mild and self-limited and occurred more frequently in younger persons. Severe hypersensitivity reactions related to the mRNA COVID-19 vaccines are rare and more commonly observed in women and persons with a history of previous drug reactions for unclear reasons. Because patients with advanced liver disease and immunosuppressed patients were excluded from the vaccine licensing trials, additional data regarding the safety and efficacy of COVID-19 vaccines are eagerly awaited in these and other subgroups. Remarkably safe and highly effective mRNA COVID-19 vaccines are now available for widespread use and should be given to all adult patients with CLD and LT recipients. The online companion document located at https://www.aasld.org/about-aasld/covid-19-resources will be updated as additional data become available regarding the safety and efficacy of other COVID-19 vaccines in development. (Hepatology 2021;74:1049-1064).

An earlier version of this document was first posted online on February 2, 2021 at https://www.aasld.org/about-aasld/covid-19-resources *and will continue to be updated.*

Coronavirus disease 2019 (COVID-19) is the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Multiple studies

Abbreviations: ASLD, American Association for the Study of Liver Diseases; ACE2, angiotensin-converting enzyme 2; ACR, acute cellular rejection; BNT162b2, Pfizer-BioNTech mRNA vaccine; CDC, Centers for Disease Control and Prevention; CLD, chronic liver disease; COVID-19, coronavirus disease 2019; EUA, Emergency Use Authorization; FDA, U. S. Food and Drug Administration; LT, liver transplant; MHC, Moderna mRNA vaccine; mRNA-1273, Moderna mRNA vaccine; PEC, polyethylene glycol; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant; VE, vaccine efficacy; VSV, vesicular stomatitis virus.

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demonstrate that older persons 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, >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 U.S. 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 LT care providers, and their patients.

Background on Non-COVID-19 Vaccines in Patients with CLD and Immunosuppression

Patients with CLD display innate and adaptive immune dysregulation that is associated with vaccine

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hyporesponsiveness[1] (Supporting Fig. S1). 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 (Supporting Table S1). 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 3-6 months after transplant. The Advisory Committee on Immunization Practices recommends avoiding live virus vaccines in those receiving high-dose corticosteroids and other immunosuppressed persons because of concerns of uncontrolled viral replication.[6] See the Supporting Information 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 vaccine using synthetic nucleoside-modified mRNA that encodes the spike glycoprotein.[10,11] Other vaccines that are currently in development use DNA, protein subunits, inactivated SARS-CoV-2, viral vectors, and attenuated virus (Table 1; Fig. 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; Fig. 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 by 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.[12] 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.[13,14] 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.

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	30 μg (0.3 mL) IM × two doses 21 days apart	95% (11)	Synthetic lipid nanoparticle	Store between
	BNT162b2		(95.3% in those with comorbidities, including CLD)	Contraindicated if history of severe or immediate allergic reaction to any vaccine components, including PEG*	–80°C and –60°C
	(Pfizer-BioNTech)	EUA for ages ≥16 years			Once thawed and diluted, multidose vials must be stored between 2°C and 25°C and used within 6 hours
	mRNA-1273	100 μg (0.5 mL) IM × two doses 28 days apart	94.1%(57)	Synthetic lipid nanoparticle	Store between
	(Moderna)		(Unknown in CLD patients because no vaccine or placebo pts developed COVID-19 in clinical trials)	Contraindicated if history of severe or immediate allergic reaction to any vaccine components, including PEG*	–25°C and –15°C
		EUA for ages ≥18 years			Thawed vials stored at 2°C-8°C for up to 30 days or between 8°C and 25°C for up to 12 hours
					Once first dose is withdrawn, vial must be used within 6 hours
	Vaccines in phase 3 development				
Adenoviral vectors	AZD1222	One or two IM doses 28 day apart	70.4% (pooled) after the second dose	Replication-defective chimpanzee adenovirus vector	Stored and distributed at 2°C-8°C for up to 6 months
	(AstraZeneca)		62% standard dose (SD)/SD		
		EUA in UK, Europe, and South America for ages ≥18 years	90% low dose/SD (17)	Two cases of transverse myelitis reported	Easier to scale up production vs. mRNA
			Unknown in CLD patients		
	Ad26.COV2.S	One or two IM doses are being tested	72% in USA with single dose	Replication-defective adenovirus 26 vector (used in Ebola vaccine)	Stored at 2°C-8°C for up to 3 months
	(Johnson & Johnson/ Janssen)		66% in Latin America		
			57% in S Africa (58)	Low seroprevalence of antibodies in North America	
	Ad5-NCoV		96%-97% antibody induction at day 28 (59)	Replication-defective adenovirus type 5 vector	
	(CanSino biologics)				

TABLE 1. *Continued*

	Vaccine	Dosing	Efficacy	Safety Issues	Storage Issues
Recombinant protein	NCX-CoV2373 (Novavax)	Two IM doses 3 weeks apart	89.3% in UK study 49.4% in South Africa (22)	Recombinant spike protein nanoparticles Adjuvant of M-matrix, which may be allergenic	2°C-8°C
Inactivated virus	CoronaVac (Sinovac)		50.4% protection in Brazilian study (60)	Inactivated SARS-CoV-2 with alum hydroxide adjuvant	
	BBIBP-CorV		100% antibody induction at day 42 (61)	Inactivated whole virion SARS-CoV-2	
	Inactivated COVID-19 (Wuhan)				

*Ingredients include mRNA, lipids, polyethylene glycol, cholesterol, potassium chloride, potassium phosphate, sodium chloride, sodium phosphate, and sucrose.
Abbreviations: IM, intramuscular; pts, patients.

There are hundreds of known adenoviruses and most do not cause disease in humans, whereas 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.[15,16]

Early safety data were favorable in the phase 3 clinical trial of Oxford/AstraZeneca's AZD1222 adenovirus vectored COVID-19 vaccine,[17] leading to its authorization for emergency use in the UK on December 29, 2020.[18] Phase 3 clinical trials from Johnson & Johnson (Ad26) demonstrate vaccine efficacy (VE) rates of 57%-72% following a single dose.[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 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. Further guidance from regulatory and public health authorities is eagerly awaited following their authorization, and further information regarding any elevations in liver function tests (although not in patients with advanced liver disease) will be available from ongoing or recently completed large phase 3 trials.

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

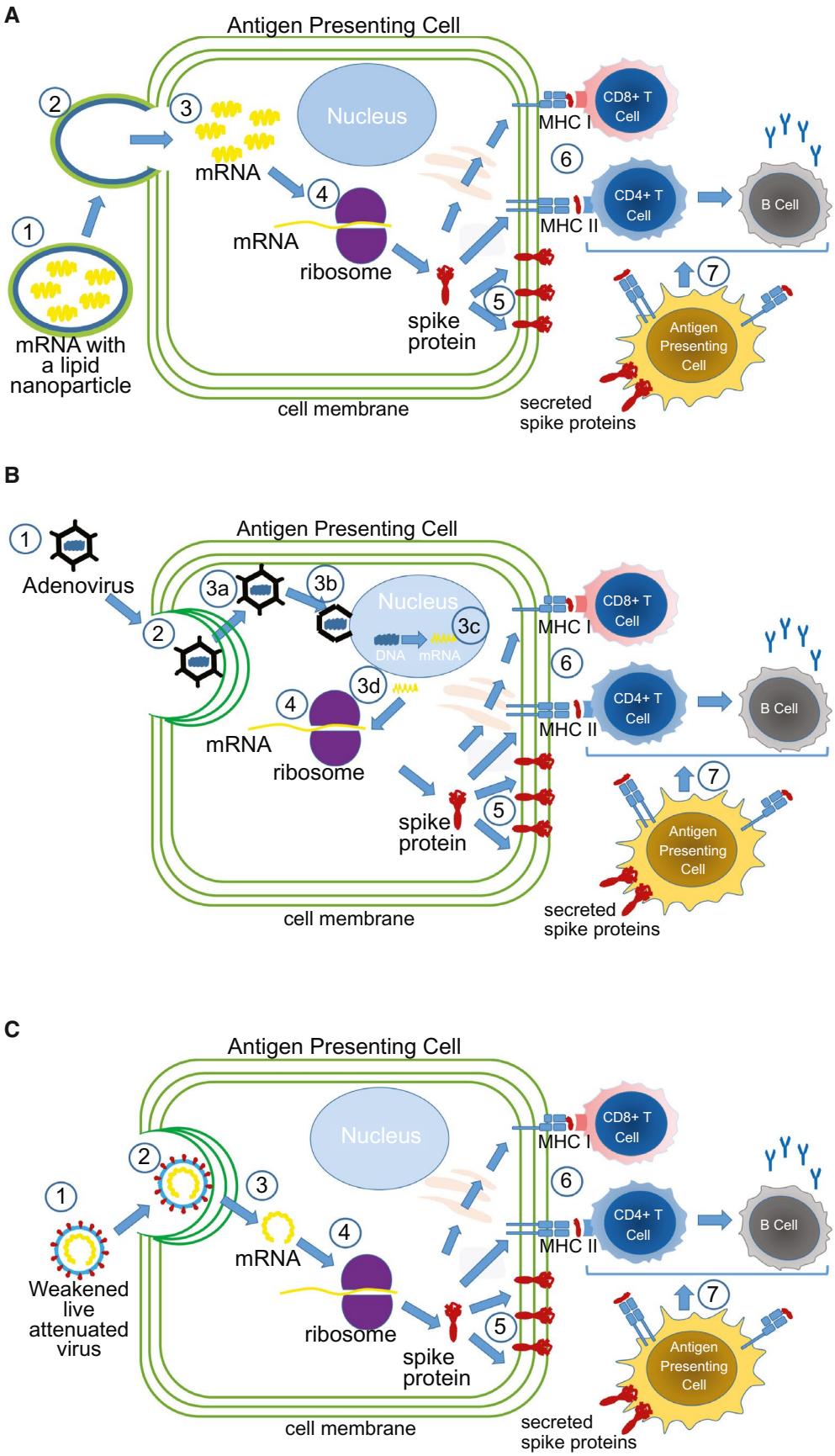
A
Antigen Presenting Cell
Nucleus
mRNA
mRNA
ribosome
spike protein
mRNA with a lipid nanoparticle
cell membrane
MHC I
MHC II
CD8+ T Cell
CD4+ T Cell
B Cell
Antigen Presenting Cell
secreted spike proteins
B
Antigen Presenting Cell
Adenovirus
Nucleus
DNA
mRNA
mRNA
ribosome
spike protein
cell membrane
MHC I
MHC II
CD8+ T Cell
CD4+ T Cell
B Cell
Antigen Presenting Cell
secreted spike proteins
C
Antigen Presenting Cell
Nucleus
mRNA
ribosome
spike protein
Weakened live attenuated virus
cell membrane
MHC I
MHC II
CD8+ T Cell
CD4+ T Cell
B Cell
Antigen Presenting Cell
secreted spike proteins

FIG. 1. COVID-19 vaccine delivery systems.
(A) 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.
(B) 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.
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.
3. Ribosomes and cellular proteins are used to translate the mRNA into the spike protein.
4. The spike protein gets expressed on the cell surface and/or secreted into the serum.
5. 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.
6. Antigen-presenting cells can engulf secreted spiked proteins, which can also activate the immune system.
(C) 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.

of interest that are often combined with an adjuvant (e.g., Alum, MF59, AS01, AS03, or 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 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 the Supporting Information Text for background on assays to detect immunity to COVID-19.

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: 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%, whereas 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% (Fig. 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 (Fig. 3). See the Supporting Information Text for additional information regarding these currently authorized vaccines. At the time of writing, Johnson & Johnson/Janssen have submitted an application to the FDA for EUA of their single-shot COVID-19 vaccine candidate.[24]

POSTMARKETING REPORTS OF ANAPHYLACTIC REACTIONS TO mRNA COVID-19 VACCINES

During December 14-23, 2020, monitoring by the Vaccine Adverse Event Reporting System (VAERS)

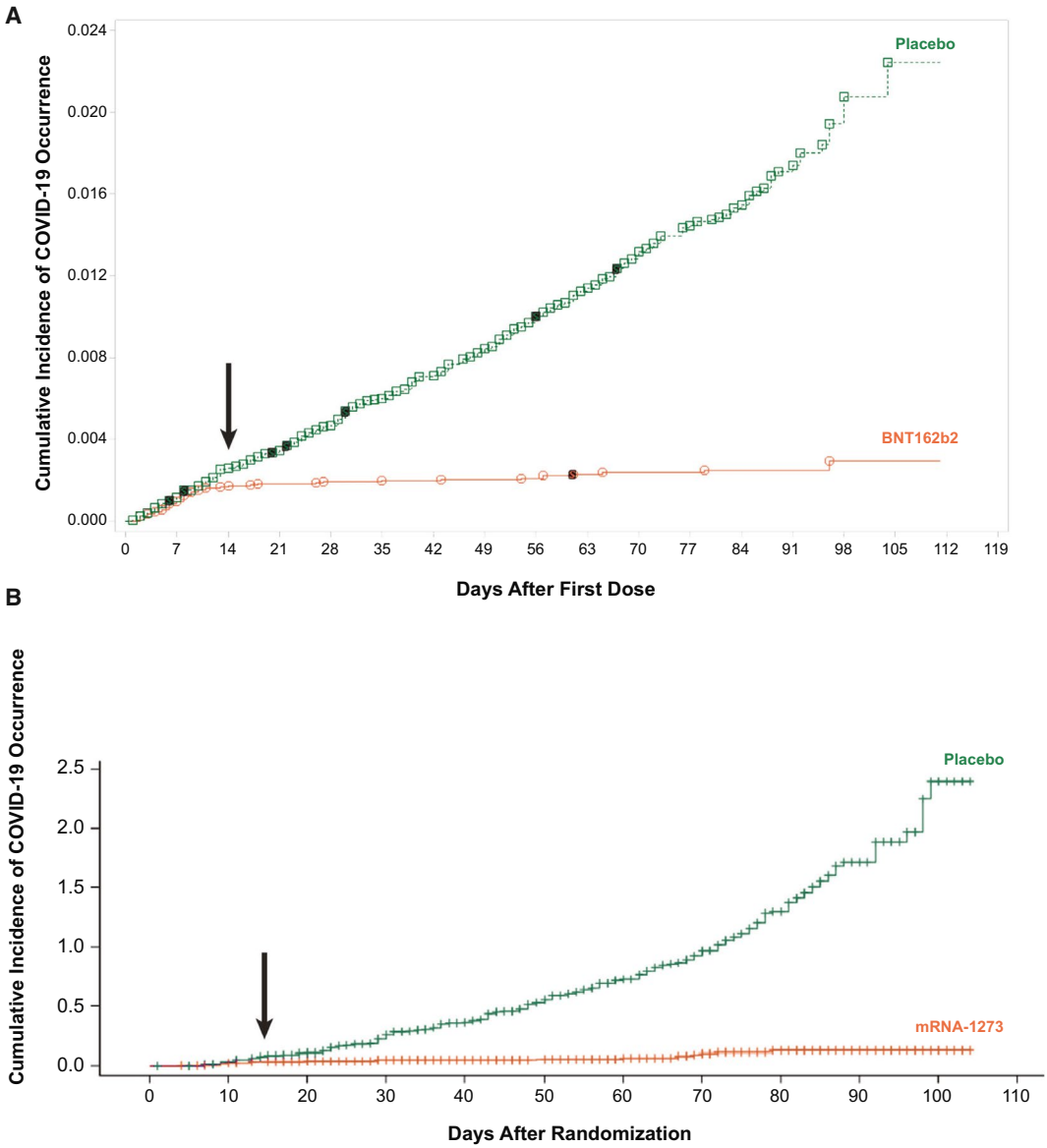

FIG. 2. Cumulative incidence of first COVID-19 occurrence in phase 3 clinical trials. Vaccine and placebo groups diverge at approximately 14 days after the first dose (arrow). (A) Pfizer-BioNTech (BNT162b2). (B) Moderna (mRNA-1273).

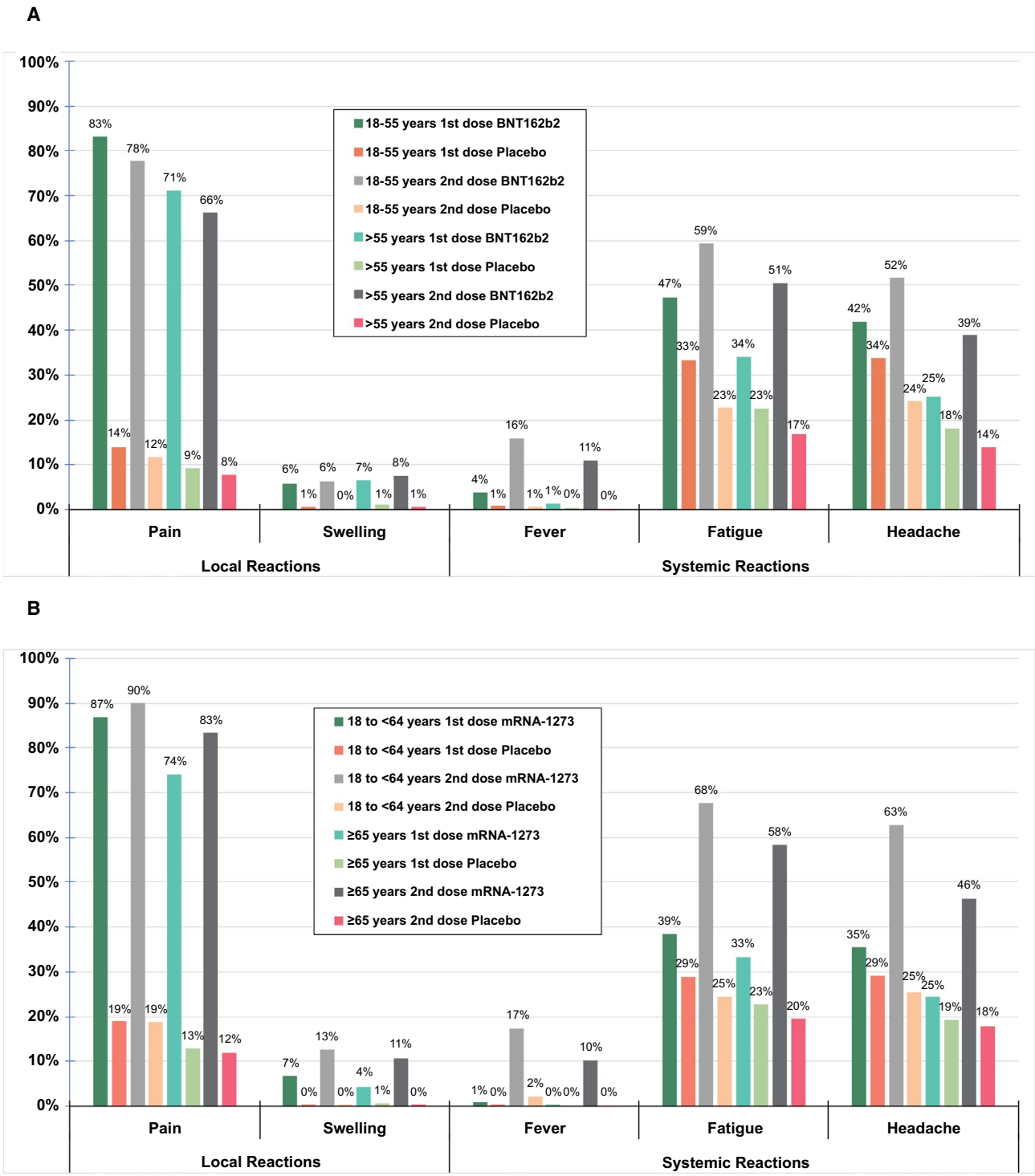

FIG. 3. Frequency of adverse events of FDA EUA mRNA vaccines compared to placebo. (A) Pfizer-BioNTech (BNT162b2). (B) Moderna (mRNA-1273).

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 3 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 5 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.

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 analytical period.[25,26]

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).[27] 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.

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 have been described from the UK (B.1.1.7)[28] and South Africa (501Y.V2 or B.1.351)[29] 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.[30] All of these variants have been found in the USA,[31] are more transmissible,[28] and may be associated with higher morbidity and mortality.[31,32] 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.[33-35]

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

- Withholding COVID-19 vaccination because of 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 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,[36] 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.[37] The differences in COVID-19 presentations and disease course from adults underscore 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.

GUIDANCE FOR ADMINSTRATION INTERVAL OF COVID-19 AND OTHER VACCINES

- The Centers for Disease Control and Prevention (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 CLD 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 (8,030 with a comorbidity received BNT162b2 and 8,029 received placebo). VE was 95.3% in participants with comorbidities and was similar to that observed 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. Given that no participants with liver disease developed COVID-19, VE cannot be determined for this subgroup.

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.[38] 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).[39] 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.[40] Patients with underlying medical conditions, including liver disease (e.g., compensated and decompensated cirrhosis, liver cancer), solid organ transplantation (SOT), and immunosuppression, are at risk for severe COVID-19 and are included in phase 1c.[41-45]

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.[46]

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).[47]
- For LT candidates, vaccination against COVID-19 should proceed even if LT 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).[48-50]
- Data are lacking to determine whether a previous 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 the Supporting Information Text for additional guidance for COVID-19 vaccination.

COVID-19 Vaccination in Patients With CLD

Because of 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.

If the supply of COVID-19 vaccine is limited, it is reasonable to prioritize patients with higher Model for End-Stage Liver Disease 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.

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 HCC 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 and should be administered according to their standard dose and schedule.
- LT candidates with CLD should receive the mRNA COVID-19 vaccine before transplantation whenever possible to help ensure an adequate immune response.
- CLD patients receiving the mRNA COVID-19 vaccine may have local and systemic reactions (fever, myalgias, and 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 LT RECIPIENTS

Given that 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. Other unknowns regarding vaccination of LT 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.[51] Given that replication defective or nonreplicating 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 LT RECIPIENTS

- COVID-19 vaccination is recommended for all SOT recipients, including LT recipients.
- The best time to administer the COVID-19 vaccine in LT recipients 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 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 LT recipients solely to elicit an immune response to immunization against SARS-CoV-2 given that there is a risk of 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 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 be prioritized for COVID-19 vaccination and preferably receive the second dose of the COVID-19 vaccine at least 2 weeks before transplantation when feasible based upon vaccine availability. 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.

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 persons, including transplant recipients
- Effectiveness and safety in pediatric populations (adolescents and children)
- Effectiveness and safety in pregnant and lactating women
- Effectiveness and safety in persons previously infected with SARS-CoV-2
- Effectiveness against SARS-CoV-2 viral variants (e.g., B.1.1.7, B.1.351, and 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 previous allergic/anaphylactic reaction to an mRNA COVID-19 vaccine
- Duration of protective immunity against SARS-CoV-2 infection
- Mechanisms of vaccine failure

Abbreviation: CTP, Child-Turcotte-Pugh.

COVID-19 Vaccination Knowledge Gaps

Patients with advanced CLD and LT recipients have not been included in the mRNA vaccine studies, and 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.[52,53] 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.[53,54] 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.[55,56] 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 mRNA vaccines for COVID-19. The CDC currently recommends that all adults over the age of 18 should receive the two-dose mRNA vaccines 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. Both mRNA COVID-19 vaccines are recommended for all patients with CLD (compensated or decompensated) and immunosuppressed SOT recipients. The American Association for the Study of Liver Diseases (AASLD) recommends that providers advocate for prioritizing patients with compensated or decompensated cirrhosis or liver cancer, immunosuppressed patients 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 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 are recommended to continue social distancing, masking, and frequent hand washing and follow other exposure-mitigating behaviors. The online companion document located at https://www.aasld.org/about-aasld/covid-19-resources will be updated as additional data become available regarding the safety and efficacy of other COVID-19 vaccines in development.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31751/suppinfo.