COVID-19 Vaccination in Patients with Liver Disease

Moderated By: Kyong-Mi Chang, MD, FAASLD & Gregory A. Poland, MD
Webinar Moderator

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Webinar Moderator

Gregory A. Poland, MD

• Mary Lowell Leary Professor of Medicine at the Mayo Clinic in Rochester, Minnesota
• Director of the Mayo Clinic's Vaccine Research Group
Webinar Agenda

Talks

Webinar and Presenter Introductions

"Safety and efficacy of conventional vaccination in patients with liver disease"

“Safety of vaccines with adenoviral vectors in liver disease patients”

“Safety of RNA vaccines in liver disease patients” - Moderna

“Safety of RNA vaccines in liver disease patients” - Pfizer

Panel Discussion / Q&A

Speakers

Dr. Chang & Poland

Dr. Hugo Rosen

Prof. Eleanor Barnes

Dr. Drew Weissman

Dr. Onyema Ogbuagu

All
Webinar Q&A

• Submit your questions anytime during the webinar in the Q&A box at the top or bottom of your screen.

• Questions will be answered at the end of the presentations.
Webinar Presenter

Hugo R. Rosen, MD, FAASLD

- Professor and Chair, Department of Medicine
- Kenneth T. Norris, Jr., Chair in Medicine
- Keck School of Medicine of USC

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Webinar Presenter

Eleanor Barnes
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• University of Oxford
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AASLD’s COVID-19 Clinical Oversight & Education Subcommittee

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- Brendan M. McGuire, MD, University of Alabama (Alabama)
- Mark W. Russo, MD, MPH, FAASLD, Carolinas Medical Center (North Carolina)
- Michael Schilsky, MD, FAASLD, Yale University (Connecticut)
- Andrew Reynolds, (Patient Advocate)
- Raymond Chung, Massachusetts General Hospital (Massachusetts) (ex-officio)
- K. Rajender Reddy, University of Pennsylvania Medical Center (Pennsylvania) (ex-officio)
- Elizabeth C. Verna, MD, MS, Columbia University (New York) (ex-officio)
Safety and efficacy of conventional vaccination in patients with liver disease

Hugo R. Rosen, MD
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Program Director, Research Center for Liver Diseases
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Overview/Themes

• Recommended vaccinations in patients with chronic liver disease (CLD)
  • HAV/HBV and non-hepatotropic infections

• Putative factors influencing vaccine ineffectiveness
  • Immune dysregulation in liver disease
  • Inverse responsiveness with severity of liver disease

• Suboptimal vaccination rates in patients with liver disease
  • Despite recommendations from AASLD, CDC, EASL, NIH, IDSA, AST

• Post-liver transplant recommendations

• COVID-19 in patients with CLD
Liver Disease and Adult Vaccination

Vaccines are especially critical for people with health conditions such as liver disease.

If you have chronic liver disease, talk with your doctor about:

- **Influenza vaccine** each year to protect against seasonal flu
- **Tdap vaccine** to protect against tetanus, diphtheria, and whooping cough
- **Pneumococcal polysaccharide vaccine** to protect against serious pneumococcal diseases
- **Hepatitis B vaccine** series to protect against hepatitis B
- **Hepatitis A vaccine** series to protect against hepatitis A
- **Zoster vaccine** to protect against shingles if you are 60 years and older
- **HPV vaccine** to protect against cancers and genital warts caused by human papillomavirus if you are an adult through age 26 years (HPV vaccine is not recommended for everyone older than age 26 years, but some adults age 27 through 45 years who are not already vaccinated may decide to get HPV vaccine after speaking with their doctor about their risk for new HPV infections and the possible benefits of vaccination. HPV vaccination in this age range provides less benefit, as more people have already been exposed to HPV.)
- **MMR vaccine** to protect against measles, mumps, and rubella if you were born in 1957 or after and have not gotten this vaccine or do not have immunity to these diseases
- **Varicella vaccine** to protect against chickenpox if you were born in 1980 or after and have not gotten two doses of this vaccine or do not have immunity to this disease

**Inactivated Influenza A and B**

- PV-13 once as adult; PPSV23 Up to 3 lifetime doses

**Shingrix recommended, better immunogenicity**

- Gardasil-9 for adult men and women up to 45 years old

If MMR IgG antibodies not detected, provide one dose

If VZV IgG is negative → two doses separated by ≥ 4 weeks
Immune Dysregulation in CLD

**Innate Immunity**
- Altered PRR Expression/Signaling
  - Reduced Complement C3/C4
- Neutrophils
  - Persistent Activation
  - Reduced Migration
  - Reduced Phagocytosis
- Monocytes/Macrophages
  - Decreased Antigen Presentation
  - Reduced Migration
  - Reduced Phagocytosis
  - Defective Superoxide Degeneration
- NK Cells
  - Decreased Levels
  - Decreased Activation
  - Altered Function (↓ IFN-γ)
  - Reduced Anti-Fibrotic activity
  - Reduced Tumor Surveillance

**Adaptive Immunity**
- T Cells
  - Persistent Activation
  - Reduced CD4 helper-cells
  - Increased Apoptosis
  - T Cell Exhaustion (PD-1, TIM-3)
  - Decreased Anti-Viral Cytokines
- B Cells
  - Persistent Activation
  - Reduced Memory Cells
  - Increased Apoptosis
  - Altered Ig Production

Collectively contribute to vaccine hyporesponsiveness

Adapted from Noor and Manoria 2017
Bonnell/Reddy CGH 2011
General guidelines for vaccination in patients with liver disease

- Clinicians should actively vaccinate patients with LD and post-liver transplant (LT) to reduce vaccine-preventable illnesses
- Early vaccination prior to progression of LD and pre-LT provide the best chance of optimal vaccine response
- Vaccines are safe; however,
  - Live vaccines should be avoided in immunosuppressed patients (risk of secondary disseminated disease)
  - LT candidates should not receive live vaccines within 4 weeks of anticipated LT
Hepatitis A vaccination in CLD

- Current AASLD guidelines recommend HAV vaccination in all patients with chronic hepatitis B and C
- Low rates of vaccination (12-40%) in patients with CLD
  - Patients > 65 y old consistently under-vaccinated
- Seroconversion rates (post-Havrix vaccine)
  - ~71% after primary dose and 98% after booster dose in Child-Pugh class A
  - vs. 37% and 66% in patients with Child-Pugh B/C

Rhee Y, Clinical Liver Disease 2020
Leise, MD, Talwalkar JA Curr Gastroenterol Rep 2013
Arguedas MR, Hepatology 2001; 34: 28-31
Yue X, Vaccine 2018; 1183-1189
Younossi ZM, Hepatology 2011
Increased Efficacy of High-Dose, Rapid HAV Vaccination in patients with Cirrhosis

• Single Center Australian Study (n =134), nonrandomized
• Standard dose HAV schedule Twinrix 720 µg at 0, 1, 6 months or Havrix 1440 µg at 0 and 6 months
  • For patients failing to seroconvert, a single Havrix 1440 µg booster was given
• High-dose HAV schedule Havrix 1440 µg at 0, 1, and 2 months, with a single 720-µg booster for patients failing to seroconvert

• Initial response: 79.5% in standard dose vs. 94.3% high-dose
  • Boosting→ successful 67% (8 of 12) in standard dose and 100% (1 of 1) in high-dose

HBV vaccination success in health and ineffectiveness in liver disease

• HBV vaccination is effective and protective in healthy adults, with a seroconversion rate >95% (3-dose vaccination)

• Factors associated with decreased protective antibody responses
  • Increasing age, male gender, race, obesity, smoking, genetic factors (HLA haplotype), liver disease (related to MELD, Child-Pugh Score)

• HBV vaccination is safe and well-tolerated in cirrhosis
  • ~38-47% immune response

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Aggeletopoulou, I, Rev in Med Virology, 2017; 27: 6
Gutierrez Domingo, Transpl Proc 2012; 44: 1499
Roni, Adv Virol. 2013
Strategies to improve HBV immunogenicity in CLD

- Increased dose (40μg) → slightly increases immunogenicity (53% vs. 38%; p = NS); 7 studies
- Accelerating dose schedule (0, 7, 21 days)-similar responses
- Revaccination- small series, inconclusive
- High dose accelerated Twinrix or Engerix-B 40μg at 0, 1, and 2 months, with the schedule repeated as a booster if non-immune
  - (78.6% in the high-dose boosted group, p = NS)
- Two-dose Heplisav-B (TLR9 adjuvant; 0 and 1 month) achieves significantly higher rates of seroconversion vs. three-dose Engerix-B in patients with CLD (aOR: 2.74)

Aggeletopoulou, I, Rev in Med Virology, 2017; 27: 6
Amjad, W; Dig Dis Sciences 2020
Influenza Infection in Chronic Liver Disease

- Randomized trials on vaccine effectiveness in patients with liver disease lacking
  - Withholding vaccine may place risk to patients’ safety and health
  - Uncertainty whether influenza vaccines are able to trigger an appropriate antibody response in patients with liver disease

- Influenza infection can worsen liver disease
  - Contributes to collateral liver damage *(Polakos et al., Am J Pathol 2006)*
  - Promotes hepatic decompensation *(Duchini et al., Arch intern Med 2000)*

- Liver disease patients have worse outcomes than non-liver disease patients
  - 5-fold increased risk of influenza-related hospitalization and
  - 17-fold increased risk of death *(Van Kerkhove et al., PLoS Med 2011)*
Effectiveness of influenza vaccines in adults with chronic liver disease: a systematic review and meta-analysis

- 12 studies included
- HI antibody levels in patients with CLD increased in response to vaccination
- Seroprotection rate > 70% reference level in most studies

Härmälä S, Parisinos C, BMJ Open. 2019
All-cause hospitalizations in CLD decreased with influenza vaccination

Härmälä S, Parisinos C, BMJ Open. 2019

- No difference in all-cause mortality
Post-liver transplant vaccinations- High Yield Points

- CDC recommends all solid-organ transplant (SOT) recipients receive vaccinations before and periodically post
  - pneumovax, HAV, HBV, influenza A/B, and tetanus-diphtheria-pertussis
- Vaccination within 6 months post-LT has lower response rates
- In most circumstances, live replicating vaccinations should be avoided in immunosuppressed patients

Kaul D, Blumberg E, Kulik L- AASLD expert panel consensus (in press)
COVID-19 and Liver Disease

- Elevated LFTs noted in more than 20% of patients with COVID-19
- Abnormal LFTs at COVID-19 presentation associated with >2-fold risk of ICU admission
- Higher mortality in patients with pre-existing liver disease who develop COVID-19 (RR 2.8), especially in those with cirrhosis (RR 4.6)

Singh, S, Khan A, Gastroenterology 2020; 159: 769
Cai Q, J Hepatology 2020
Marjot et. Al, J Hepatology 2020
Summary-Conventional Vaccination in Patients with Chronic Liver Disease-1

- CLD is a state of immune dysregulation- innate, adaptive, regulatory- that likely reduces adequate vaccination responses
- Every effort should be made to immunize early in liver disease
  - Recommendations from expert societies are non-uniform
  - Heplisav-B (with TLR9 adjuvant) more effective than accelerated/higher dosing for HBV
  - Use of vaccines post-LT should be guided/timed according to immunosuppression
Summary-Conventional Vaccination in Patients with Chronic Liver Disease-2

• Unknown how well CLD patients will be protected by COVID vaccinations
  • There may be differences based on approaches
  • Warrants further examination

Thank you for listening
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Safety of Adenoviral Vectored Vaccines in Liver Disease Patients

Ellie.barnes@ndm.ox.ac.uk
Professor of hepatology and Experimental Medicine
University of Oxford, UK
Presentation structure

- The need for SARS-CoV-2 vaccines in patients with liver disease

- Published data on Adenoviral vectored (Ad) vaccines
  - Immunogenicity of Oxford/Az vaccine (ChAdOx1nCoV-19)
  - ChAd vaccines in given liver patients

- Future plans for assessing safety and efficacy of ChAdOx1nCoV-19 in liver patients
The need for SARS-CoV-2 vaccines in liver patients
International registry assessing outcomes of COVID-19 in liver patients

Andrew M Moon
A Sidney Barritt IV

Tom Marjot
Gwilym J Webb
Eleanor Barnes

https://www.covid-hep.net/
>1200 liver patients in 35 countries now recruited

Registry recruitment over time

Submissions from 35 countries

As of 14th August

<table>
<thead>
<tr>
<th>Cases</th>
<th>Study day</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>0</td>
<td>60</td>
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<tr>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>0</td>
<td>150</td>
</tr>
</tbody>
</table>

- n=1097 total cases
- n=424 CLD without cirrhosis
- n=506 cirrhosis
- n=167 LT recipients

Thanks to all those contributing to the registries
Outcomes in liver disease patients

Outcomes in liver disease patients

Patients with cirrhosis die younger with SARS-CoV-2

Marjot et al J Hep Oct 2020: PMID: 33035628
ChAd viral vectored vaccines in liver disease
What is ChAd Ox1nCoV-19?

Dick et al Plos One 2012

Phylogenetic trees based on alignment of nucleotide sequences of the hexon protein
What is ChAd Ox1nCoV-19?

- Chimpanzee Ad vector
  - lack of pre-existing immunity that may limit vaccine efficacy
- E1-E3 deleted
  - Replication incompetent
  - Cannot replicate even in immune compromised patients
- Encodes full length spike antigen from SARS-CoV-2
- No additional adjuvants
ChAd Ox1nCoV-19 from immunogenicity to efficacy

- Overall efficacy approx 70%
- Much higher for severe disease
High titres of SARS-CoV-2 Abs with ChAdOx1nCoV-19 vaccines
High magnitude SARS-CoV-2 specific T cells

T cell IFN-Ɣ ELISpot cultured with spike antigens
Less side effects in older people
COVID-19 Vaccines in Liver Patients

- 100,000 people in Covid-19 vaccine trials
- ChAdOx1nCoV-19 vaccine trials-liver patients excluded
- Pfizer vaccine trials - 37,706, liver disease in 217 (0.6%)
  - three (<0.1%) had moderate to severe liver disease
- Moderna vaccine trials - 30,351, liver disease 196 (0.6%)
- The criteria used to classify liver disease unclear.
- 2 trials ChAd3 HCV vaccines in patients with HCV-well tolerated (cirrhosis excluded)
  - Kelly et al Hepatology 2016, Swadling et al Vaccines 2016
- All trials listed systemic immunosuppression as exclusion criterion
- Likely to be safe-but efficacy unknown

Marjot et al. Lancet Gastro Hep PMID: 33444545
Future plans

• Launch a new international registry “COVID-Hep 2.0” to assess SARS-CoV-2 infection rate following vaccination in patients with liver disease
• Deep phenotype immune responses in a subset of patients chronic liver disease (n=150)
  • OCTAVE: Observational patient Cohort study of T cells, Abs and Vaccine Efficacy
  • UK wide-liver, IBD, rheumatology, cancer and renal disease
  • Vaccine study of secondary immunodeficiency

Provide urgently needed data on vaccine immunogenicity, efficacy in liver disease

Thanks for listening!
Nucleoside-modified mRNA-LNP vaccines.

Drew Weissman
University of Pennsylvania
Philadelphia, USA
Conflicts of Interest

- Dr. Weissman has been issued multiple patents and has more in the process of submission covering nucleoside modified mRNA as a therapeutic, mRNA-LNP vaccines, modified mRNA delivery of cas9 gene editing systems, LNP delivery systems and other therapeutic applications of modified mRNA and LNPs.
Therapeutic mRNA background

- mRNA and DNA encoding a protein were first injected into an animal in 1990. Since then, a single report of therapeutic mRNA injection into the brain was made in 1992, until recently.
- mRNA was studied as a vaccine with both ex vivo dendritic cell pulsing and in vivo injection.
- The reason why RNA was not studied is due to its complex activation of many innate immune sensors.
Intra- and extracellular mammalian RNA sensors

IFIT-2, DDX60, DHX9, DDX3, the DDX1-DDX21-DHX36 complex, RNaseL, and LRRFIP1
Purification and nucleoside modification increase translation of in vitro transcribed mRNA
Nucleoside modified mRNA-LNP vaccine platform for emerging and pandemic viruses
mRNA Vaccine Formulation and Pharmacology

Acute infection with PR8 influenza induces lower levels of neutralization than modified mRNA-LNP vaccination.
B cell response
A single immunization of PR8 HA encoding mRNA-LNPs produces HA-specific germinal center, memory, and long-lived plasma cells.
mRNA1273, Moderna modified mRNA-LNP vaccine
mRNA-1273: reduced COVID-19 with 94.1% efficacy

94.1% efficacy at preventing COVID-19 illness including severe disease

Modified intention-to-treat analysis

<table>
<thead>
<tr>
<th>Vaccine Efficacy (95% CI)</th>
<th>Incidence Rate (95% CI) per 1000 person-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>79.7 (70.3–89.9)</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>5.6 (3.4–8.8)</td>
</tr>
</tbody>
</table>

Cumulative event rate (%)

No. at Risk
Placebo 14,598 14,590 14,567 14,515 13,806 13,352 12,694 11,450 9736 6729 4067 1200 0
mRNA-1273 14,550 14,543 14,532 14,504 13,825 13,398 12,791 11,573 9911 6871 4179 1238 0

# COVID-19+ post-dose

<table>
<thead>
<tr>
<th>COVID-19 Onset</th>
<th>Placebo</th>
<th>mRNA-1273</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>N=14,598</td>
<td>N=14,550</td>
</tr>
<tr>
<td>Up to 14d post dose 1</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>14d to dose 2</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>dose 2-14d pd2</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>After 14d pd2</td>
<td>204</td>
<td>12</td>
</tr>
</tbody>
</table>

mRNA 1273 Trial: Local and systemic adverse events

Any AE: Fever, Headache, Fatigue, Myalgia, Arthralgia, Nausea/Vomiting, Chills

Pain: Erythema, Swelling, Lymphadenopathy

Grade 1, Grade 2, Grade 3

% participants

Placebo dose 1, 2; mRNA 1273 dose 1, 2

Durability of SARS-CoV-2 binding and neutralizing antibody response after mRNA-1273 vaccination and age

Conclusions

• The modified mRNA-LNP SARS-CoV-2 vaccines have very high efficacy, >94.5%, in all races, populations, and ages.
• Moderate local adverse events are observed, as well as systemic, fever, fatigue, flu-like symptoms in about 20%.
• These adverse events demonstrate the vaccine is working, they are due to activation of the immune system.
• The only unexpected adverse event, so far, is an anaphylactoid reaction in about 1:100,000 subjects.
BNT162b2 mRNA vaccine: safety in Liver disease patients

Onyema Ogbuagu, MD FIDSA
Associate Professor of Medicine & Director, HIV clinical trials
Section of Infectious Diseases
Yale School of Medicine

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Disclosures / COI

• None related to this presentation
# BNT162b2 mRNA vaccine

<table>
<thead>
<tr>
<th>Vaccine approach</th>
<th>Manufacturer / Sponsor</th>
<th>Advantages</th>
<th>Limitations / concerns</th>
</tr>
</thead>
</table>
| mRNA             | BioNTech / Pfizer       | Easy to mass produce 
Easy to adjust for emerging strains | mRNA unstable 
cold chain requirement 
2 dose requirement |

<table>
<thead>
<tr>
<th>Vaccine Component</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA</td>
<td>Encodes for prefusion stabilized membrane anchored full length viral spike protein</td>
</tr>
</tbody>
</table>
| lipids            | Protects mRNA from degradation and facilitate cellular uptake 
*may be responsible for allergic reactions |
| Buffer solution and others | Maintains pH of vaccine at desired range 
Sucrose is a cryoprotectant 
Includes diluent 
Note: no preservative |

- (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) 
- 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide 
- 1,2-Distearoyl-sn-glycero-3-phosphocholine, and - cholesterol
mRNA vaccines - how they work and what they don’t do!

- They don’t alter DNA
- They don’t involve parts of the virus and can’t make you develop COVID
- No evidence of antibody enhanced disease for “breakthrough cases”

Source: NIH.gov
Study Design
(patient eligibility)
Pfizer Phase 2/3 RCT study populations—who was in and left out

<table>
<thead>
<tr>
<th>Who was in</th>
<th>Who was added on</th>
<th>Who is left out (for now)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &gt;=Age 16</td>
<td>• HIV (well controlled, CD4&gt;200)</td>
<td>• Kids Age 11 and below</td>
</tr>
<tr>
<td></td>
<td>• HBV (HBeAg-, HBeAb+, DNA&lt;2K, normal ALT/AST, biopsy – necroinflammation)</td>
<td>• Pregnant and breastfeeding women</td>
</tr>
<tr>
<td></td>
<td>• HCV (cured or cleared)</td>
<td>• Immunosuppressive therapy</td>
</tr>
<tr>
<td></td>
<td>• Age 12-15</td>
<td></td>
</tr>
</tbody>
</table>

*Ultimately, 214 patients with mild liver disease and 3 patients with moderate to severe liver disease were included in the study*
Study Results (immunogenicity)
Key points

• Lower antibody and neutralizing titers in elderly compared to younger individuals
• However, elderly patient responses exceeded that of healthy convalescent sera
• Second dose important to exceed target range
How are older folk doing in early phase trials?

Caveat: Different neutralization assays used

Levels of neutralization titers do not always correlate to degree of immunity against disease
BNT162b2 efficacy
Efficacy

Key points:

• “protection” signal noted 10 days after dose 1
• 52% efficacy btw dose 1 & 2
• Max efficacy 7 days after dose 2
• Same efficacy in those without and (composite of with and without) prior asymptomatic SARS CoV-2 infection
• Vaccine efficacy among subgroups defined by gender, age, race/ethnicity, obesity and presence of a coexisting condition similar to that observed in the overall population
• Mitigated disease severity
BNT162b2 safety
Overall, participants 16 years of age and older experienced pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%).

SAFETY SUMMARY

- Side effects occur but are mostly mild and tolerable (LIKE ANY OTHER VACCINE AND CORRELATE WITH DEVELOPMENT OF IMMUNITY)
- For Pfizer vaccine, side effects more after second dose
- Older individuals tend to have less side effects
Unique considerations for liver disease patients

- Patients with untreated (HCV) and advanced liver disease (HBV and HCV) not included in BNT162b2 trials (data gap)
- Liver transplant candidates not included as well (data gap)
- No registered clinical trials addressing above gaps YET
- Immune responses expected to / may be diminished in patients with liver disease (FDA EUA document)
- Sub-group analyses will be helpful to assess safety, efficacy in liver disease patients enrolled
VAERS (public database for vaccine AEs): Do SARS CoV-2 vaccines cause liver injury?

Available at https://vaers.hhs.gov/data.html
Managed by US CDC and FDA

*LIMITATIONS: It is a Passive reporting system, many search terms, denominator is unknown
Panel Discussion

Please submit your questions to the Q&A Chat now.