COVID-19 Vaccination in Patients with Liver Disease

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

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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Webinar Moderator

Kyong-Mi Chang, MD, FAASLD

- Professor of Medicine (GI) – University of Pennsylvania Perelman School of Medicine
- Associate Chief of Staff and Associate Dean for Research at the affiliated Corporal Michael J. Crescenz VA Medical Center in Philadelphia

Webinar Moderator

Gregory A. Poland, MD

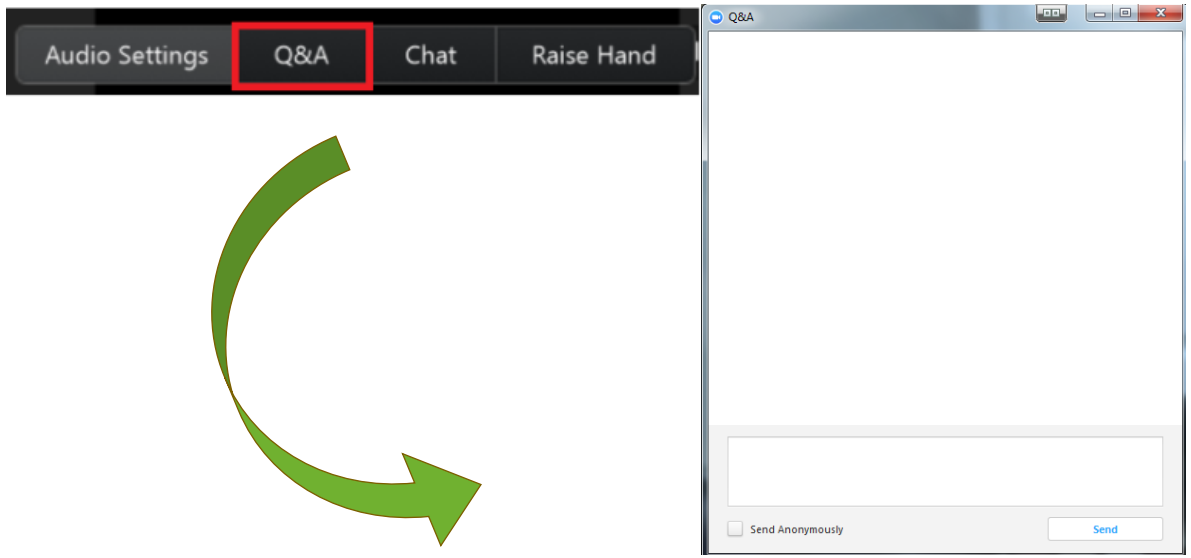
- Mary Lowell Leary Professor of Medicine at the Mayo Clinic in Rochester, Minnesota
- Director of the Mayo Clinic's Vaccine Research Group

Webinar Agenda

Talks	Speakers
Webinar and Presenter Introductions	Dr. Chang & Poland
"Safety and efficacy of conventional vaccination in patients with liver disease”	Dr. Hugo Rosen
“Safety of vaccines with adenoviral vectors in liver disease patients”	Prof. Eleanor Barnes
“Safety of RNA vaccines in liver disease patients” - Moderna	Dr. Drew Weissman
“Safety of RNA vaccines in liver disease patients” - Pfizer	Dr. Onyema Ogbuagu
Panel Discussion / Q&A	All

Webinar Q&A

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

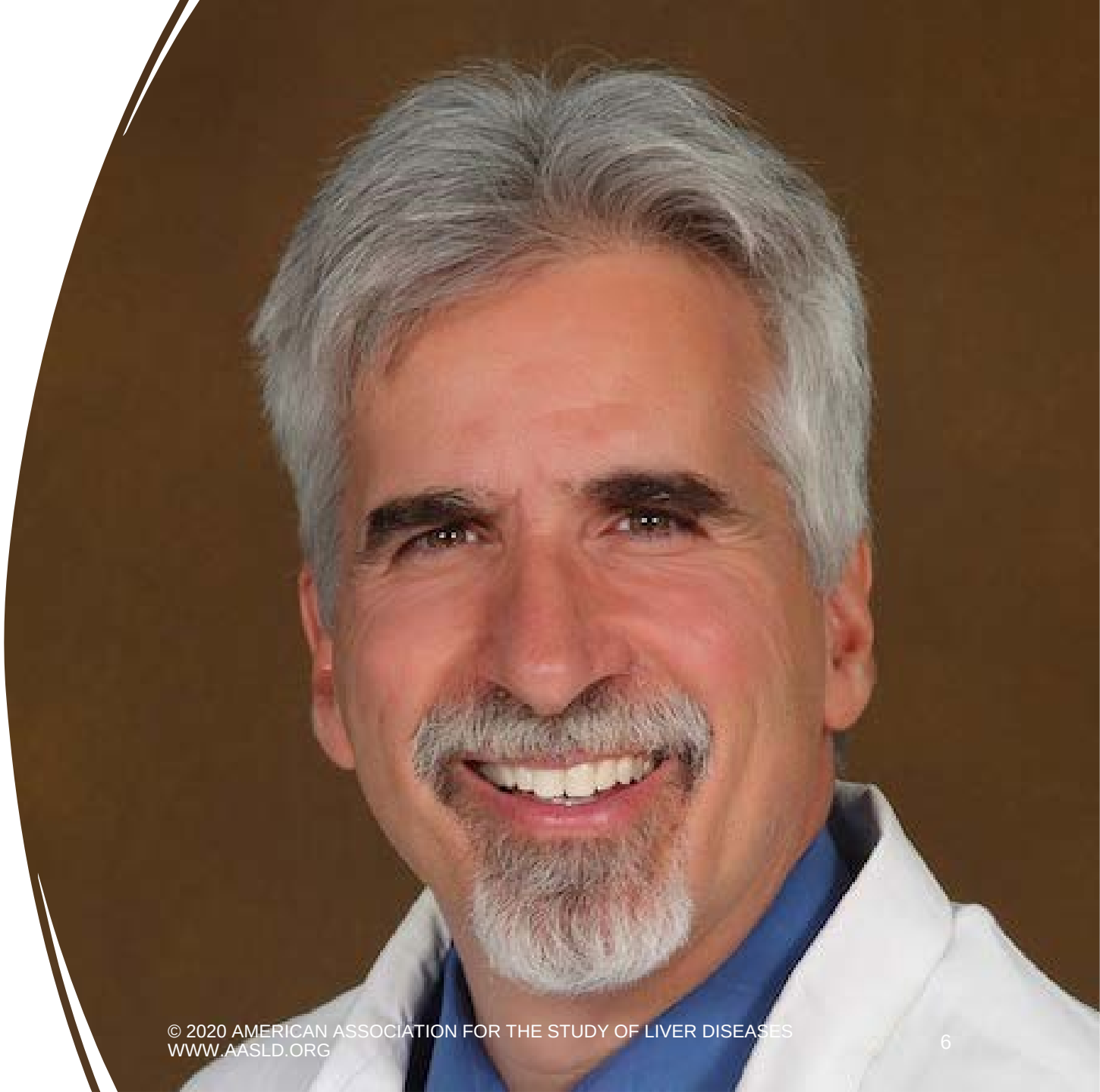


- Questions will be answered at the end of the presentations.

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



Webinar Presenter

Eleanor Barnes

- Professor of Hepatology and Experimental Medicine
- University of Oxford

Webinar Presenter

Drew Weissman, M.D., Ph.D.

- Professor of Medicine
- Perelman School of Medicine – University of Pennsylvania

Webinar Presenter

Onyema Ogbuagu, MBBCh, FACP, FIDSA

- Associate Professor of Medicine
- Director of the HIV Clinical Trials program of the Yale AIDS Program
- Section of Infectious Diseases of the Yale School of Medicine

AASLD's COVID-19 Clinical Oversight & Education Subcommittee

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- 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
Chairman of Medicine, University of Southern California
Program Director, Research Center for Liver Diseases
Professor of Medicine, Molecular Microbiology, and Immunology
hugo.rosen@usc.edu

No disclosures

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:

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

- Influenza vaccine each year to protect against seasonal flu — Inactivated Influenza A and B
- Tdap vaccine to protect against tetanus, diphtheria, and whooping cough
- Pneumococcal polysaccharide vaccine to protect against serious pneumococcal diseases — PV-13 once as adult; PPSV23 Up to 3 lifetime doses
- 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 — Shingrix recommended, better immunogenicity
- 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.) — Gardisil-9 for adult men and women up to 45 years old
- 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 — If MMR IgG antibodies not detected, provide one dose
- 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 — If VZV IgG is negative→ two doses separated by ≥ 4 weeks

Immune Dysregulation in CLD

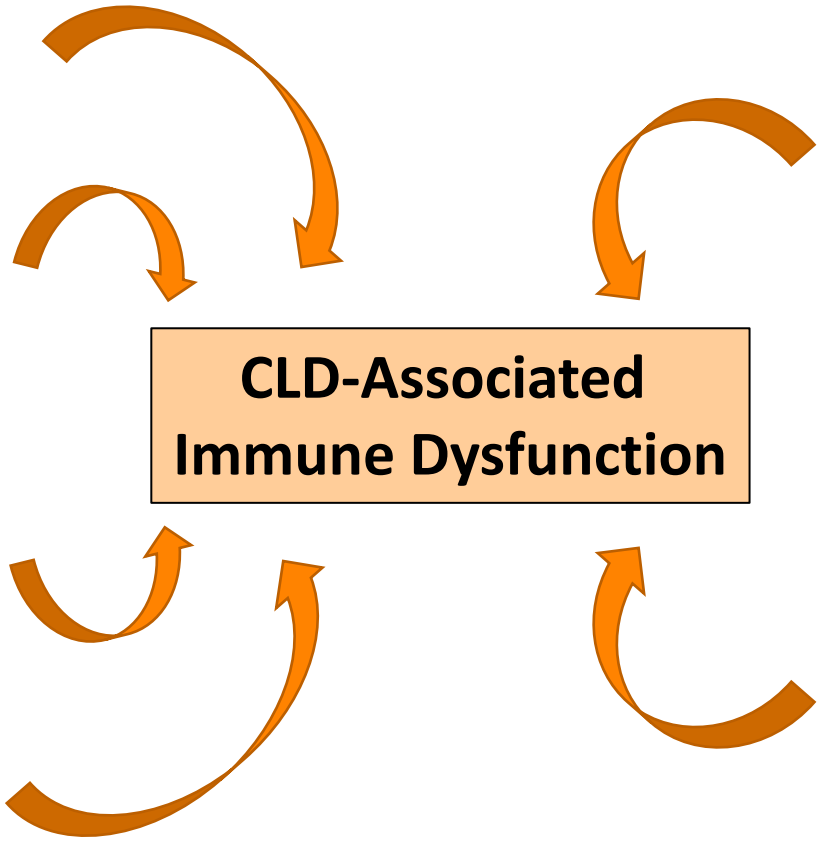
Innate Immunity

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
Bonnel/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

Rhee Y, Sha BE, Santos CAQ; CLD 2020; 15: 2

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

Wigg AJ, Clin Gastro Hepatology 2019; 17: 1210-1212

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

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
Wigg, AJ, Clin Gastro Hepatology 2019; 17: 1210-1212
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

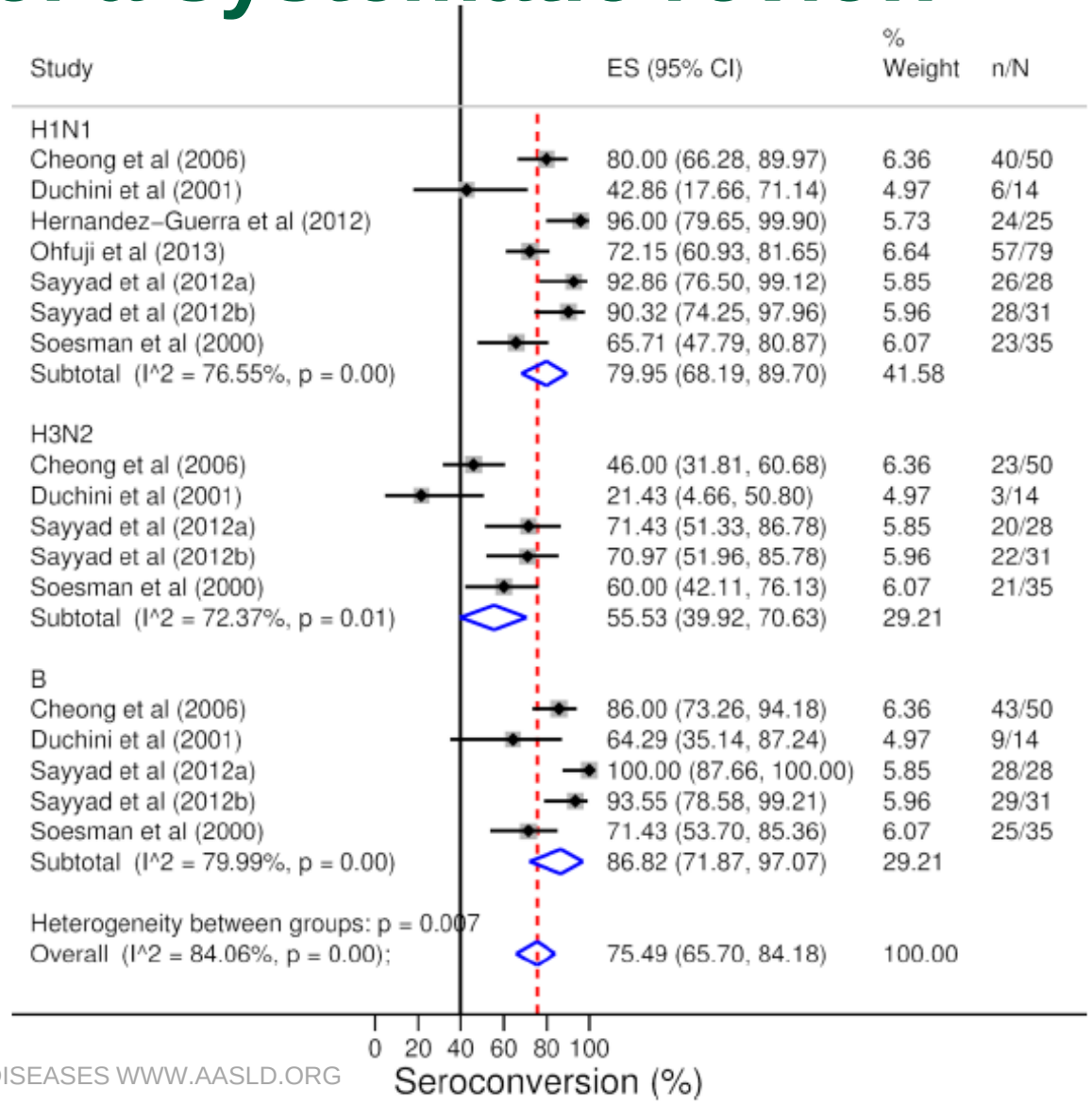
- Influenza infection can worsen liver disease
  - Contributes to collateral liver damage *(Polakos et al., Am J Pathol 2006)*
  - Promotes hepatic decompensation *(Duchini et al., Arch intern Med 2000)*

- 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

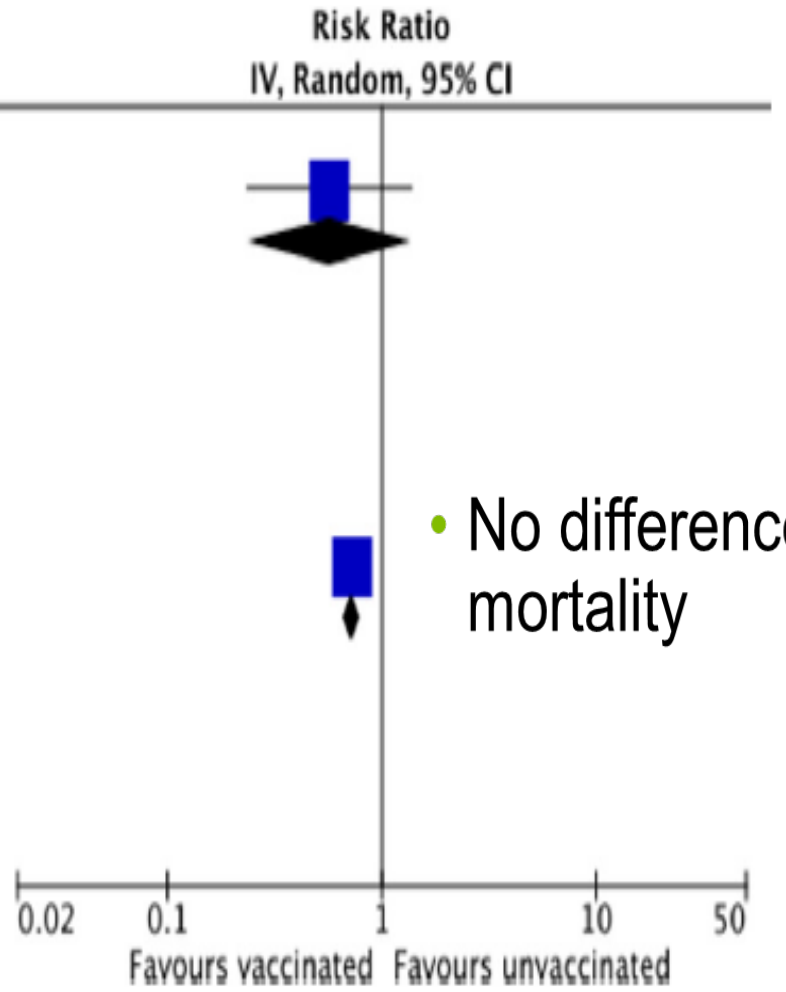
- 12 studies included
- HI antibody levels in patients with CLD increased in response to vaccination
- Seroprotection rate > 70% reference level in most studies

***Härmälä** S, Parisinos C, BMJ Open. 2019*



All-cause hospitalizations in CLD decreased with influenza vaccination

Study or Subgroup	Vaccinated Events	Total	Unvaccinated Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Influenza season						
Ohfuji et al (2014)	6	132	22	276	100.0%	0.57 [0.24, 1.37]
Subtotal (95% CI)		**132**		**276**	**100.0%**	**0.57 [0.24, 1.37]**
Total events	6		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
2.1.2 All year						
Su et al (2016)	661	4434	748	3646	100.0%	0.73 [0.66, 0.80]
Subtotal (95% CI)		**4434**		**3646**	**100.0%**	**0.73 [0.66, 0.80]**
Total events	661		748			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.59 (P < 0.00001)						



- No difference in all-cause mortality

***Härmälä** S, Parisinos C, BMJ Open. 2019*

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

hugo.rosen@usc.edu

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

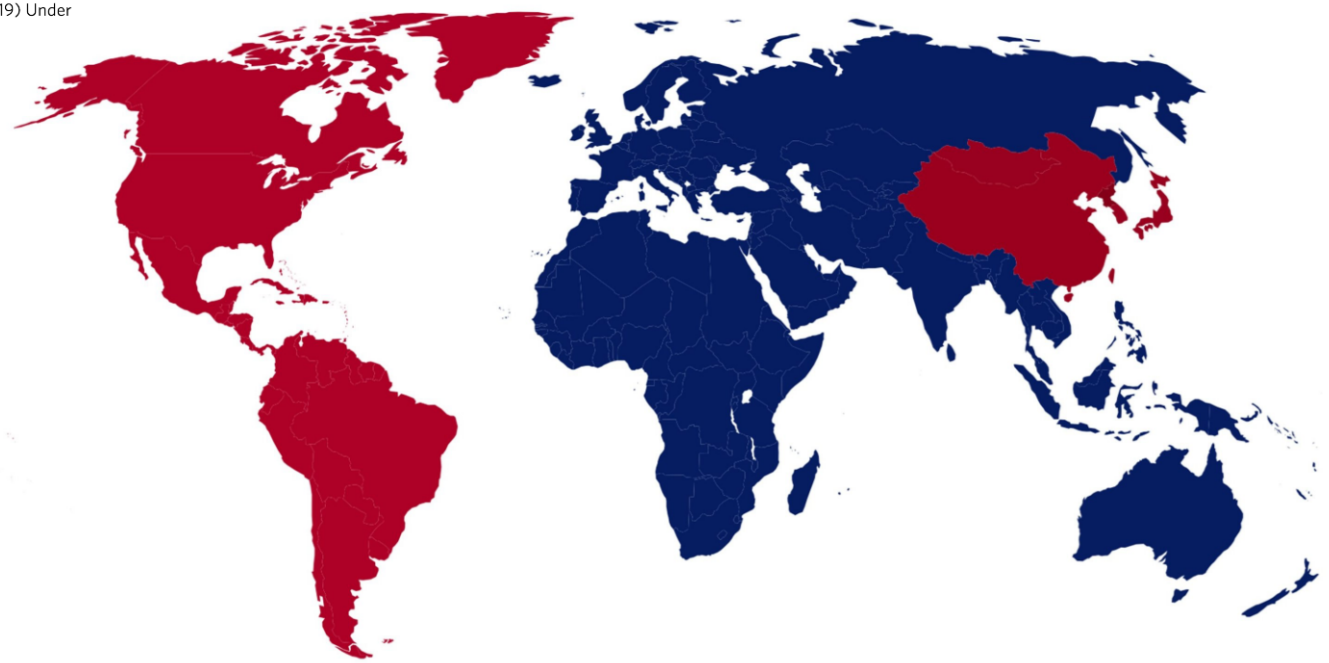
- The need for SARS-CoV-2 vaccines in patients with liver disease
- Published data on Adenoviral vectored (Ad) vaccines
  - Immunogenicity of Oxford/Az vaccine (ChAdOx1nCoV-19)
  - ChAd vaccines in given liver patients
- Future plans for assessing safety and efficacy of ChAdOx1nCoV-19 in liver patients

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

International registry assessing outcomes of COVID-19 in liver patients

SECURE-Cirrhosis REGISTRY
Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion

EASL™ | COVID-HEP REGISTRY
COVID-19 in Patients with Liver Disease or Transplantation



UNIVERSITY OF NORTH CAROLINA CHAPEL HILL

Andrew M Moon
A Sidney Barritt IV

UNIVERSITY OF OXFORD

Tom Marjot
Gwilym J Webb
Eleanor Barnes

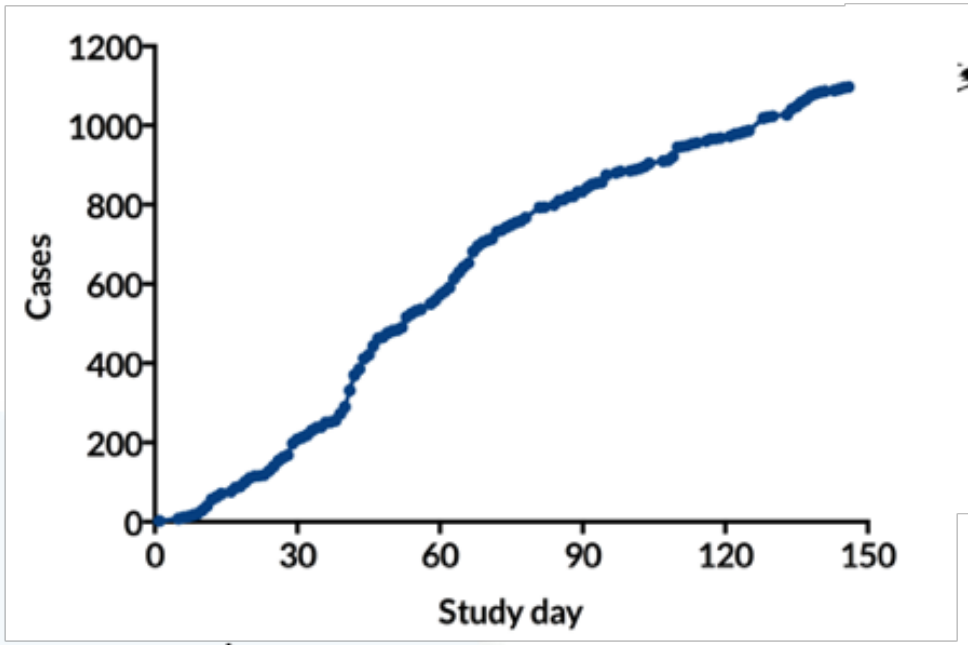
https://www.covid-hep.net/

>1200 liver patients in 35 countries now recruited

EASL™ The Home of Hepatology | COVID-HEP REGISTRY
COVID-19 in Patients with Liver Disease or Transplantation

SECURE-Cirrhosis REGISTRY
Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion

Registry recruitment over time



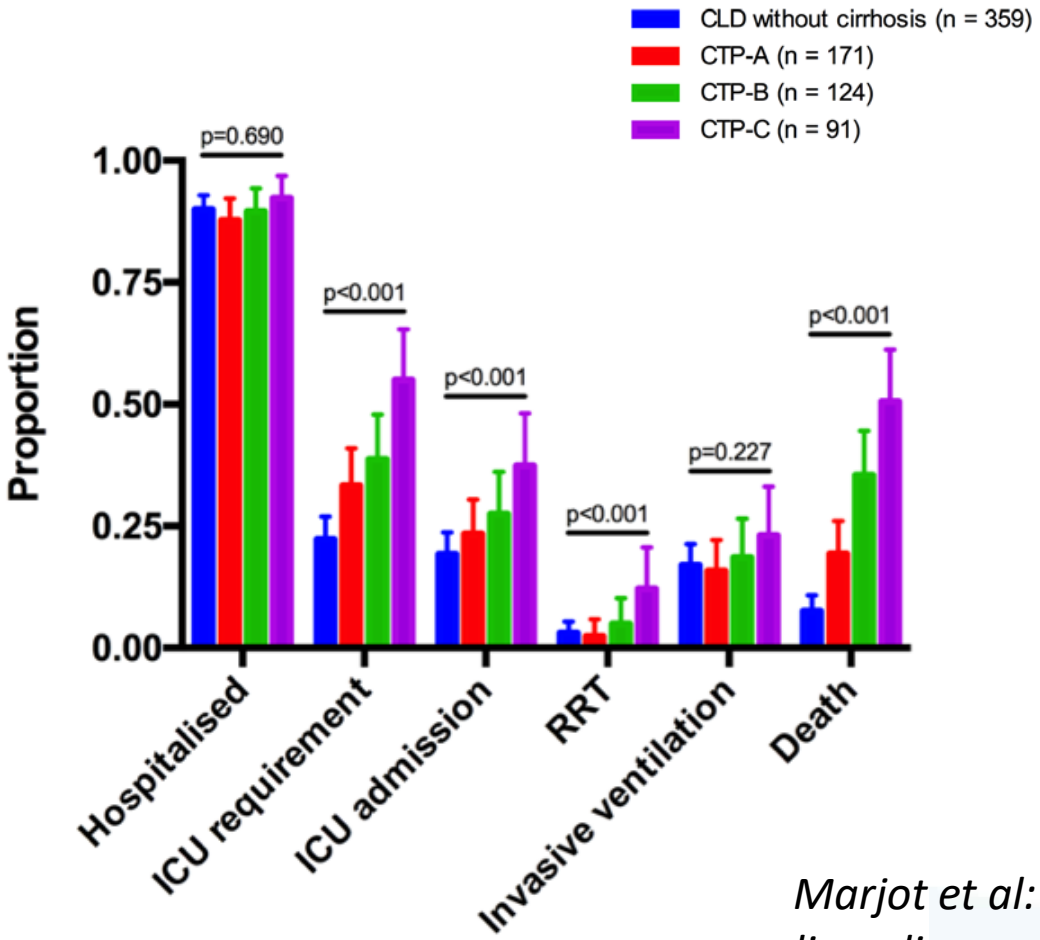
Submissions from 35 countries

Thanks to all those contributing to the registries

As of 14th August

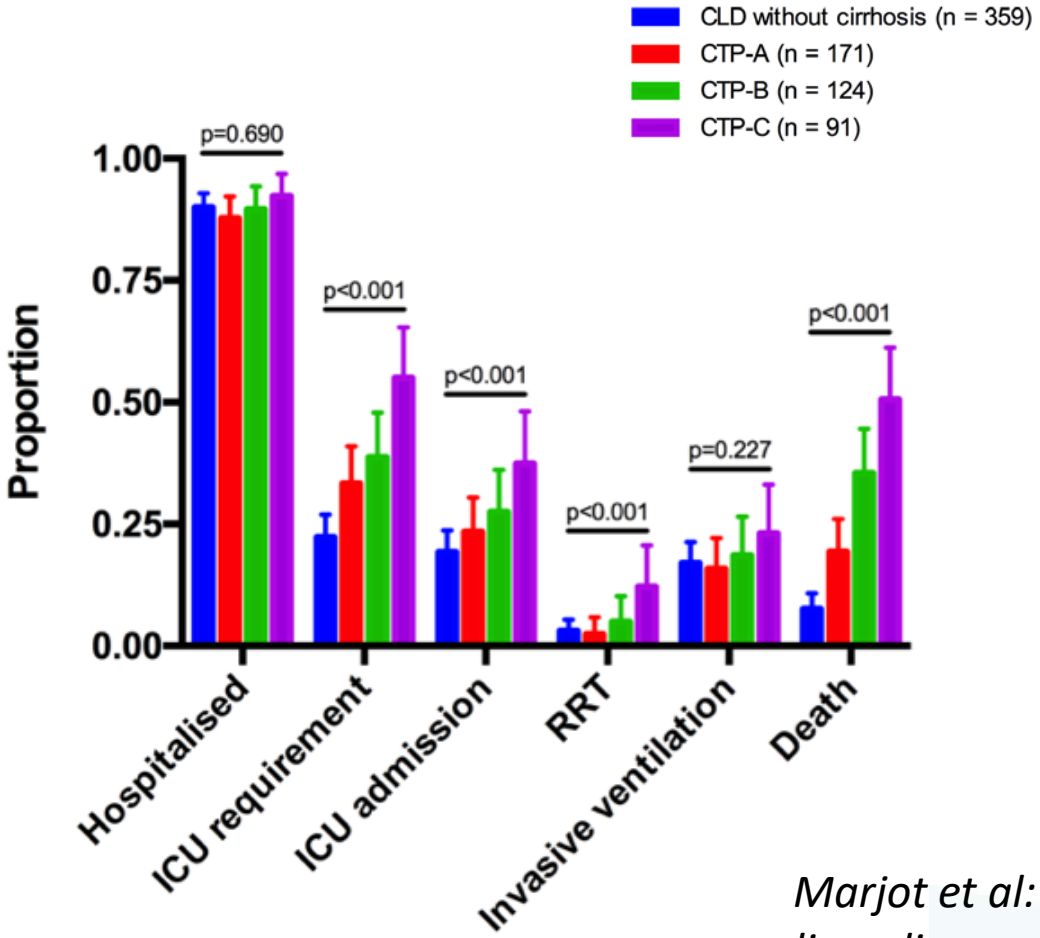
n=1097 total cases	n=424 CLD without cirrhosis	n=506 cirrhosis	n=167 LT recipients

Outcomes in liver disease patients



Marjot et al: Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study: J Hep Oct 2020: PMID: 33035628

Outcomes in liver disease patients

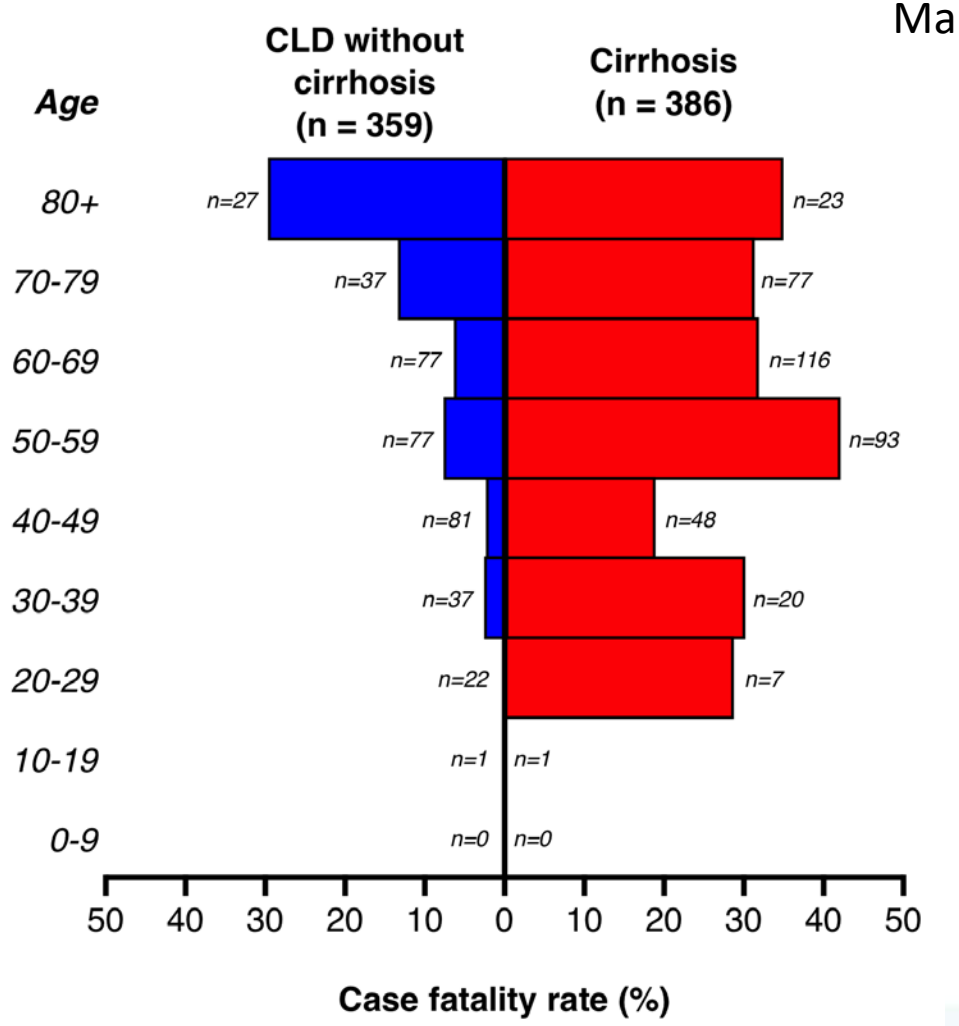


	Case fatality rate		
	Once hospitalised	Once admitted to ICU	Once receiving Invasive ventilation
CLD without cirrhosis	8%	20%	21%
CTP-A	22%	40%	52%
CTP-B	39%	62%	74%
CTP-C	54%	79%	90%

Marjot et al: Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study: J Hep Oct 2020: PMID: 33035628

Patients with cirrhosis die younger with SARS-CoV-2

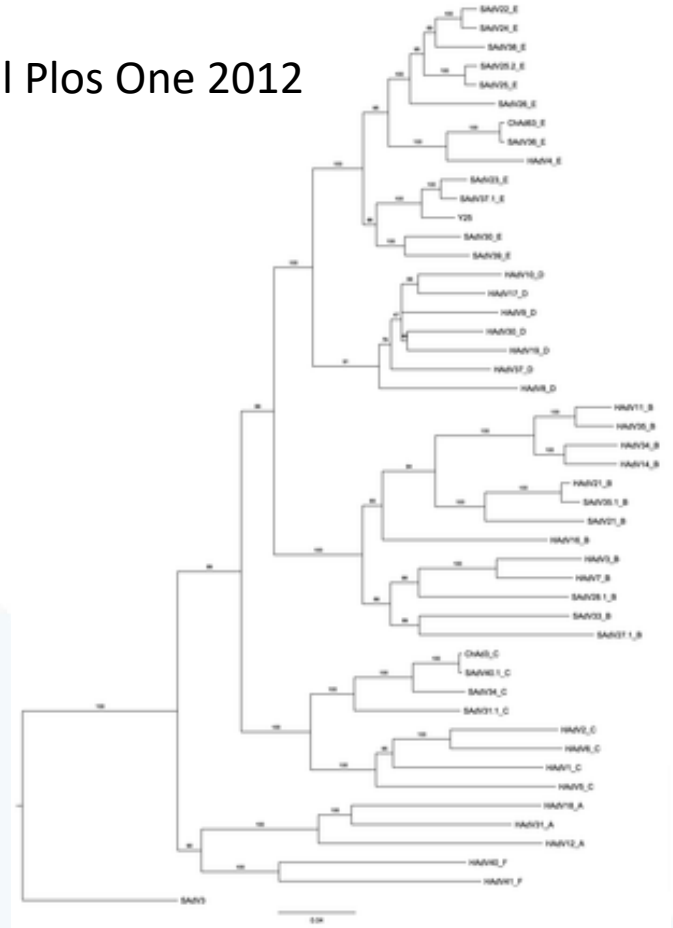
Marjot et al J Hep Oct 2020: PMID: 33035628

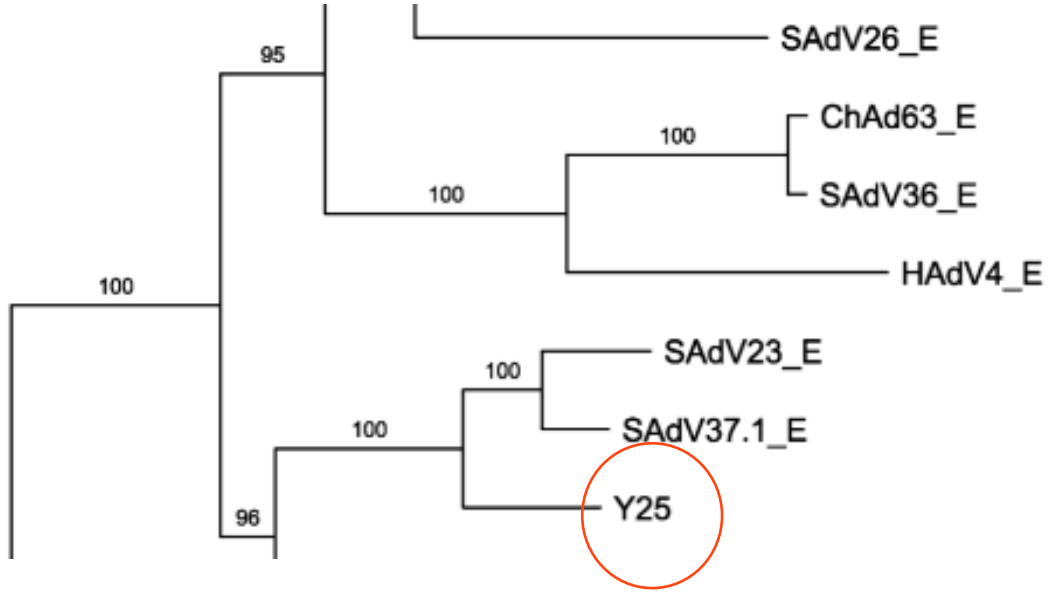


ChAd viral vectored vaccines in liver disease

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

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ChAd Ox1nCoV-19 from immunogenicity to efficacy

- Overall efficacy approx 70%
- Much higher for severe disease

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

July 2020

Pedro M Folegatti*, Katie J Ewer*, Parvinder K Aley, Brian Angus, Stephan Becker, Sandra Belij-Rammerstorfer, Duncan Bellamy, Sagida Bibi, Mustapha Bittaye, Elizabeth A Clutterbuck, Christina Dold, Saul N Faust, Adam Finn, Amy L Flaxman, Bassam Hallis, Paul Heath, Daniel Jenkin, Rajeka Lazarus, Rebecca Makinson, Angela M Minassian, Katrina M Pollock, Maheshi Ramasamy, Hannah Robinson, Matthew Snape, Richard Tarrant, Merryn Voysey, Catherine Green*, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard*, on behalf of the Oxford COVID Vaccine Trial Group†

Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial

Nov 2020

Maheshi N Ramasamy*, Angela M Minassian*, Katie J Ewer*, Amy L Flaxman*, Pedro M Folegatti*, Daniel R Owens*, Merryn Voysey*, Parvinder K Aley, Brian Angus, Gavin Babbage, Sandra Belij-Rammerstorfer, Lisa Berry, Sagida Bibi, Mustapha Bittaye, Katrina Cathie, Harry Chappell, Sue Charlton, Paola Cicconi, Elizabeth A Clutterbuck, Rachel Colin-Jones, Christina Dold, Katherine R W Emary, Sofiyah Fedosyuk, Michelle Fuskova, Diane Gbesemete, Catherine Green, Bassam Hallis, Mimi M Hou, Daniel Jenkin, Carina C D Joe, Elizabeth J Kelly, Simon Kerridge, Alison M Lawrie, Alice Lelliott, May N Lwin, Rebecca Makinson, Natalie G Marchevsky, Yama Mujadidi, Alasdair P S Munro, Mihaela Pacurar, Emma Plested, Jade Rand, Thomas Rawlinson, Sarah Rhead, Hannah Robinson, Adam J Ritchie, Amy L Ross-Russell, Stephen Saich, Nisha Singh, Catherine C Smith, Matthew D Snape, Rinn Song, Richard Tarrant, Yrene Themistocleous, Kelly M Thomas, Tonya L Villafana, Sarah C Warren, Marion E E Watson, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Saul N Faust*, Andrew J Pollard*, and the Oxford COVID Vaccine Trial Group

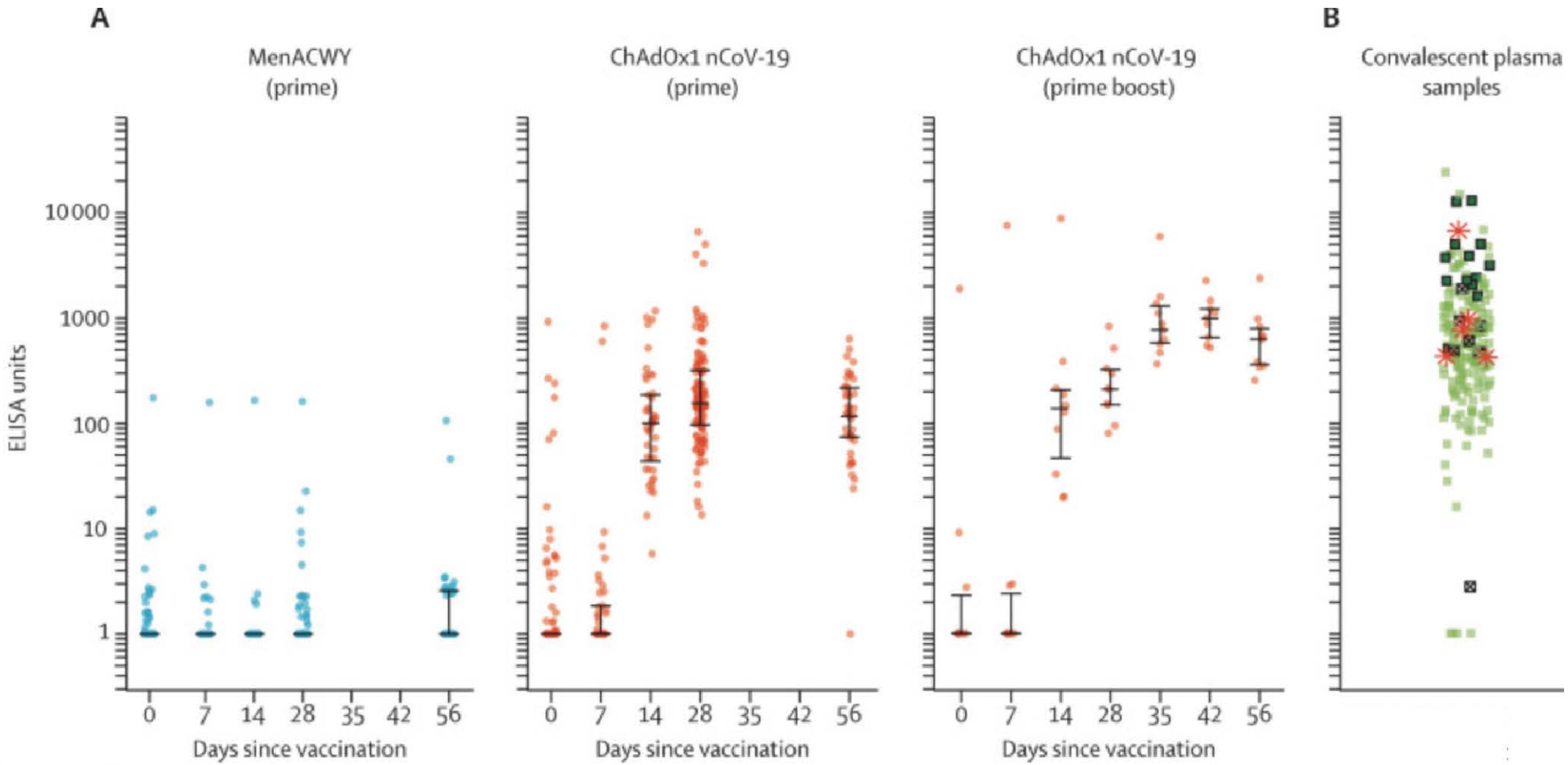
THE LANCET

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

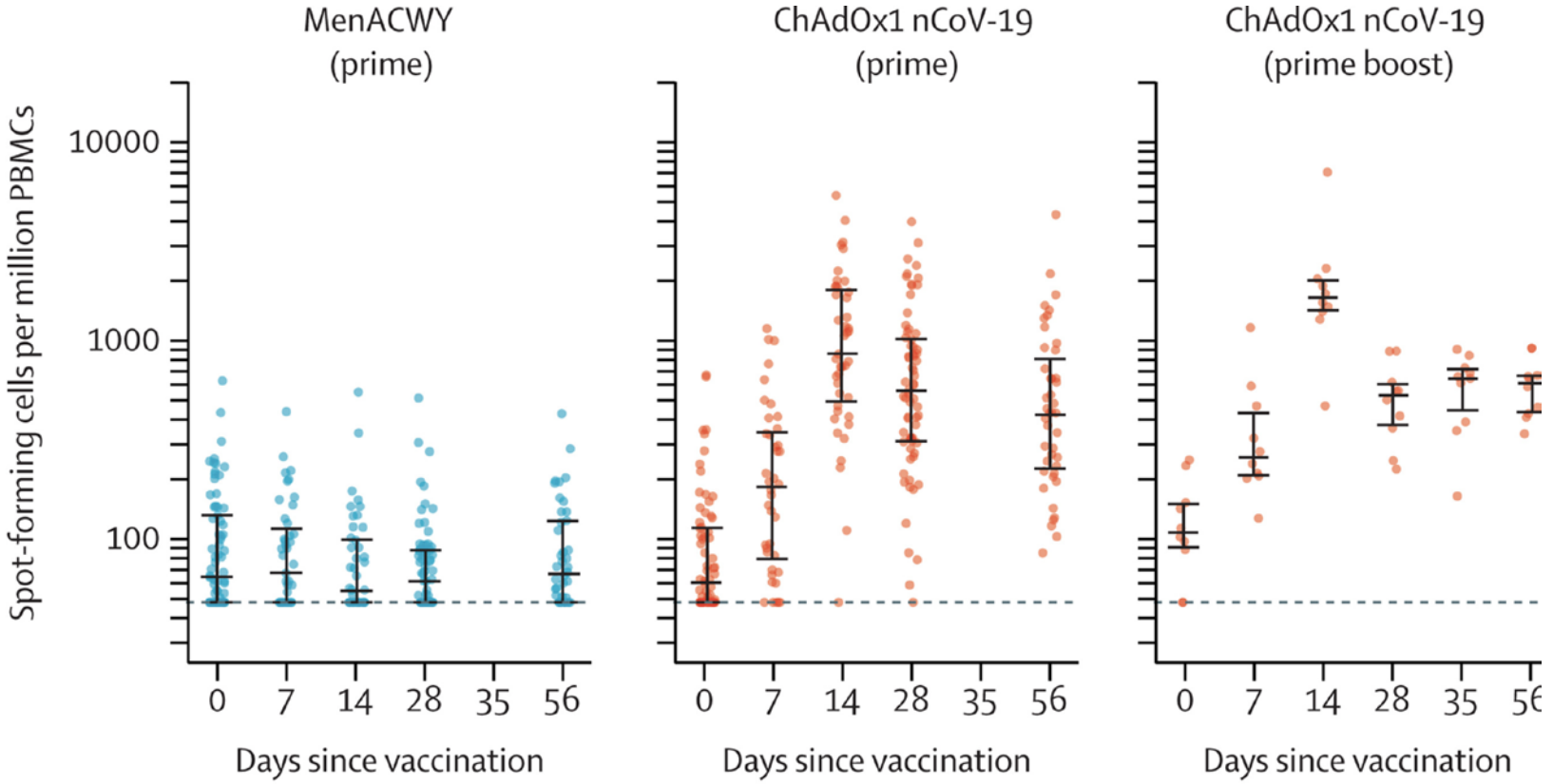
Dec 2020

Merryn Voysey*, Sue Ann Costa Clemens*, Shabir A Madhi*, Lily Y Weckx*, Pedro M Folegatti*, Parvinder K Aley, Brian Angus, Vicky L Baillie, Shaun L Barnabas, Qasim E Bhorat, Sagida Bibi, Carmen Briner, Paola Cicconi, Andrea M Collins, Rachel Colin-Jones, Clare L Cutland, Thomas C Darton, Keertan Dheda, Christopher J A Duncan, Katherine R W Emary, Katie J Ewer, Lee Fairlie, Saul N Faust, Shuo Feng, Daniela M Ferreira, Adam Finn, Anna L Goodman, Catherine M Green, Christopher A Green, Paul T Heath, Catherine Hill, Helen Hill, Ian Hirsch, Susanne H C Hodgson, Alane Izu, Susan Jackson, Daniel Jenkin, Carina C D Joe, Simon Kerridge, Anthonet Koen, Gaurav Kwatra, Rajeka Lazarus, Alison M Lawrie, Alice Lelliott, Vincenzo Libri, Patrick J Lillie, Raburn Mallory, Ana V A Mendes, Eveline P Milan, Angela M Minassian, Alastair McGregor, Hazel Morrison, Yama F Mujadidi, Anusha Nana, Peter J O'Reilly, Sherman D Padayachee, Ana Pittella, Emma Plested, Katrina M Pollock, Maheshi N Ramasamy, Sarah Rhead, Alexandre V Schwarzbold, Nisha Singh, Andrew Smith, Rinn Song, Matthew D Snape, Eduardo Sprinz, Rebecca K Sutherland, Richard Tarrant, Emma C Thomson, M Estée Török, Mark Toshner, David P J Turner, Johan Vekemans, Tonya L Villafana, Marion E E Watson, Christopher J Williams, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard* on behalf of the Oxford COVID Vaccine Trial Group†

High titres of SARS-CoV-2 Abs with ChAdOx1nCoV-19 vaccines

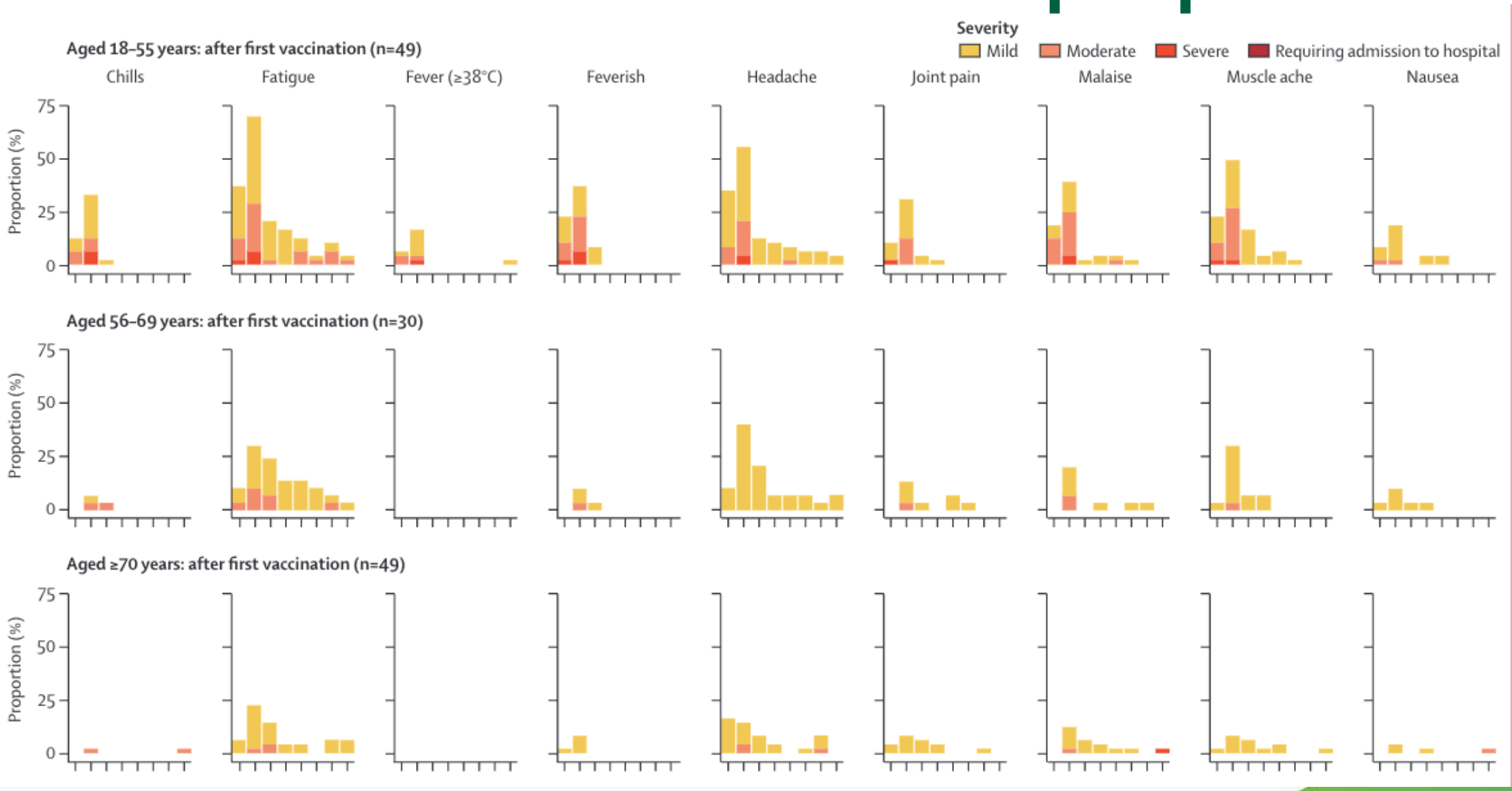


High magnitude SARS-CoV-2 specific T cells



T cell IFN-ɣ ELISpot-cultured with spike antigens

Less side effects in older people



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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!

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Nucleoside-modified mRNA-LNP vaccines.

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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.

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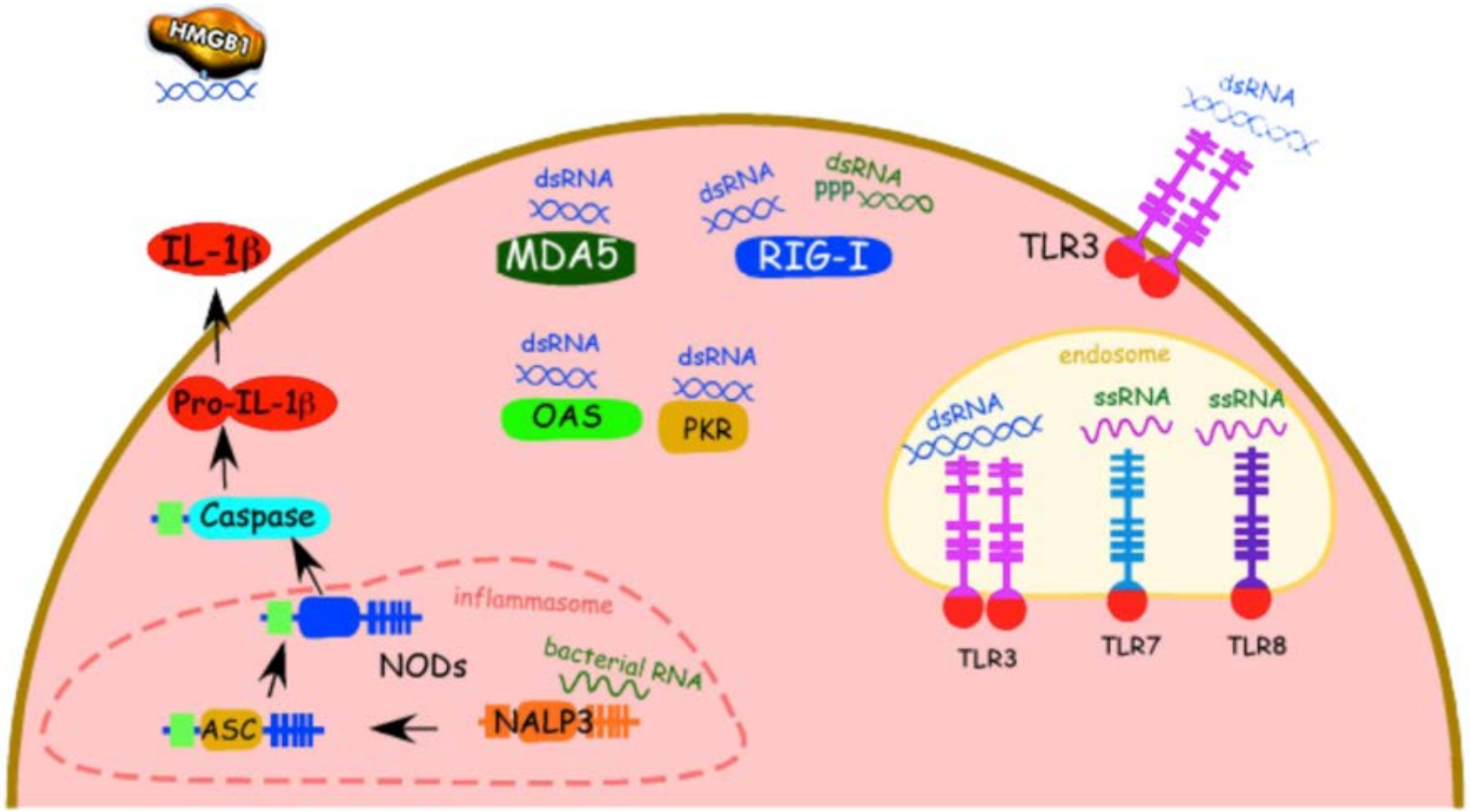
Intra- and extracellular mammalian RNA sensors



IFIT-2, DDX60, DHX9, DDX3, the DDX1-DDX21-DHX36 complex, RNaseL, and LRRFIP1

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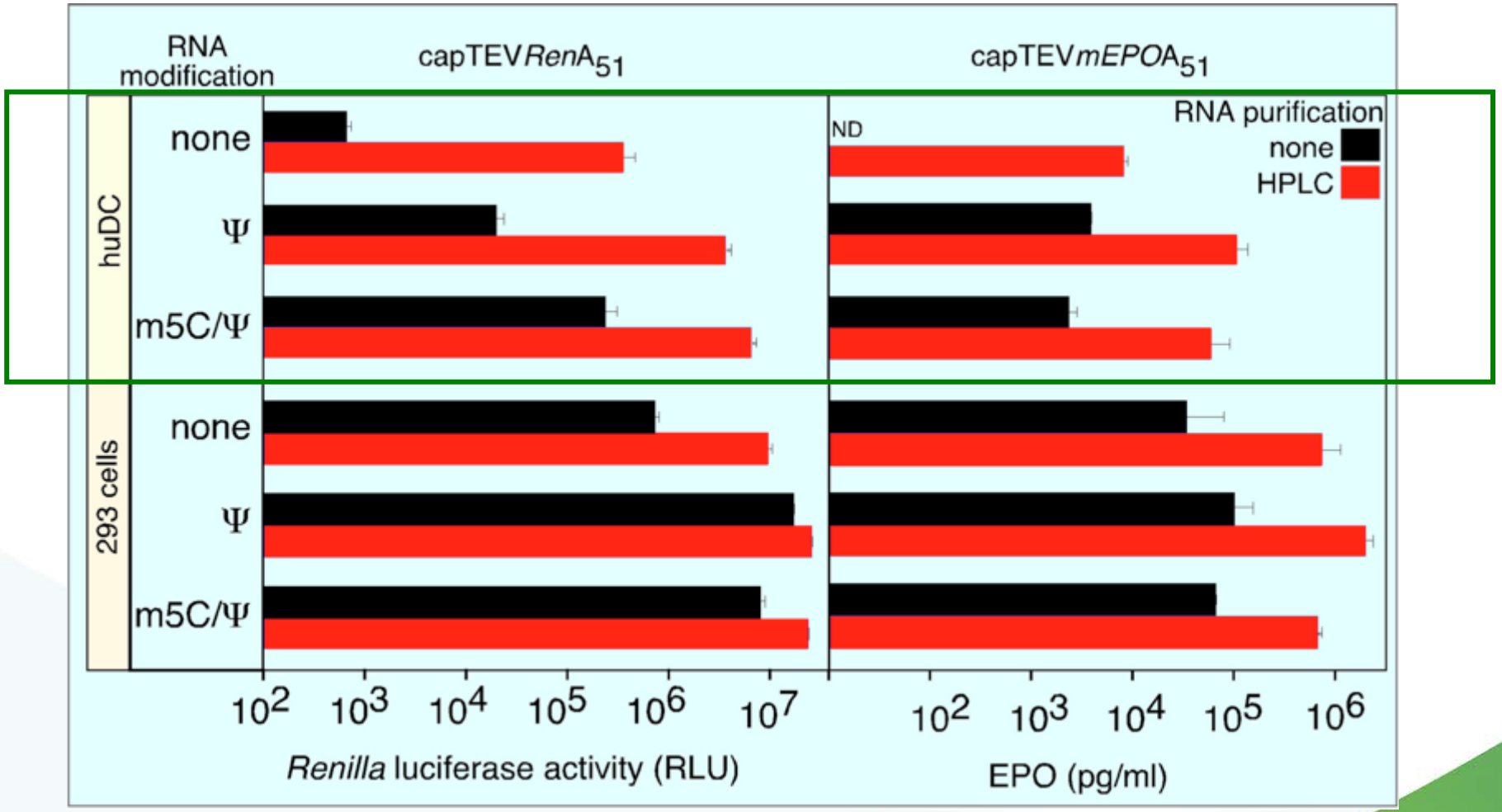
Purification and nucleoside modification increase translation of in vitro transcribed mRNA



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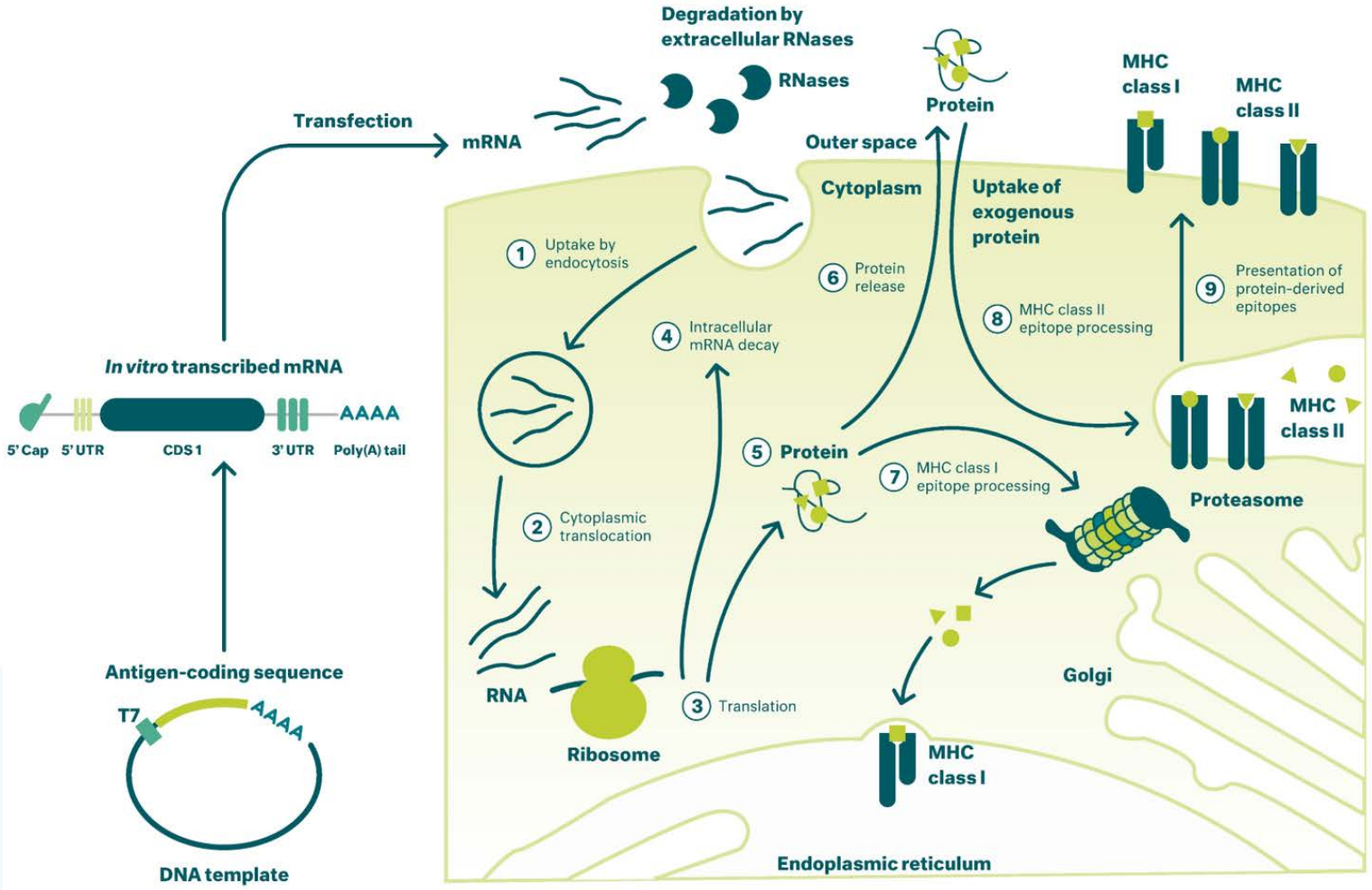
Nucleic Acids Res. 2011,39:e142

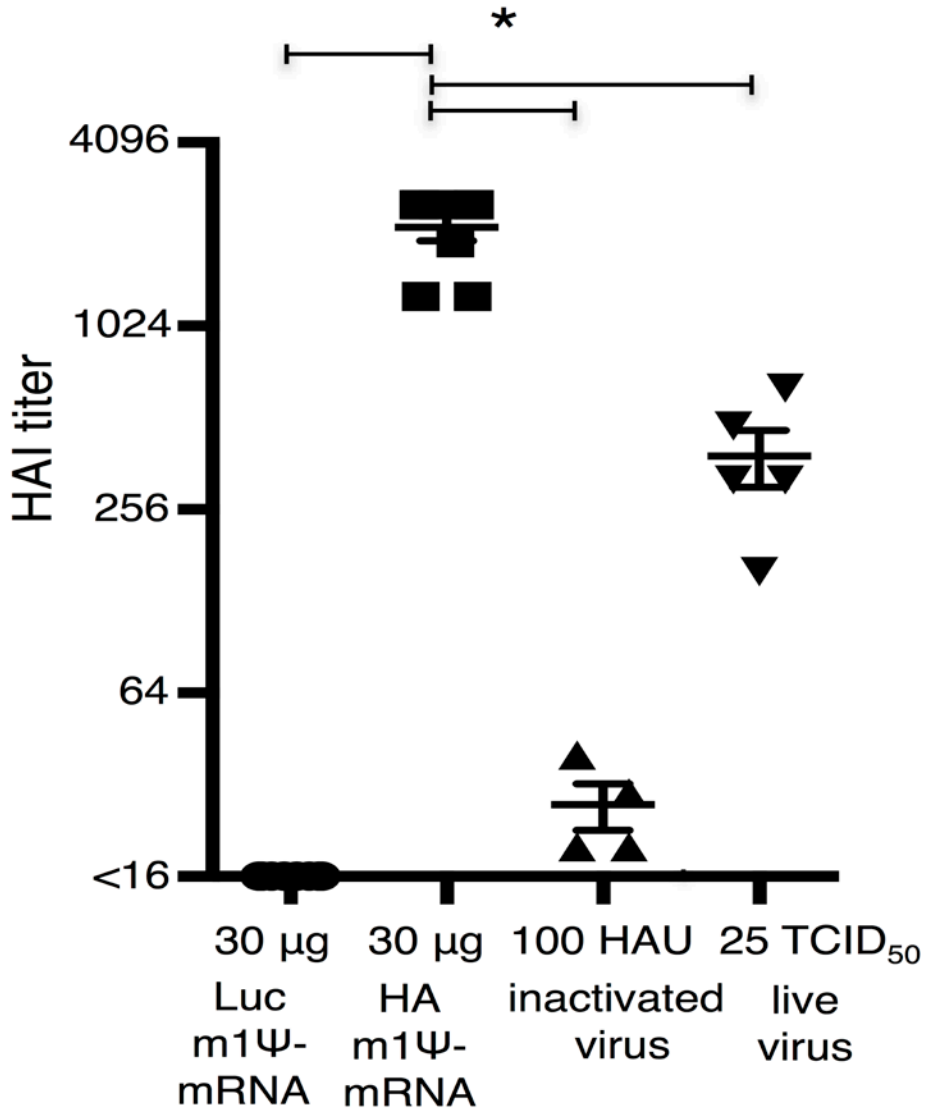
Nucleoside modified mRNA-LNP vaccine platform for emerging and pandemic viruses

mRNA Vaccine Formulation and Pharmacology[1–3]



1. BioNTech Pre-effective Amendment No. 1 to Form-F1 Registration Statement under the Securities Act of 1993. Filed with the Securities and Exchange Commission (SEC) on July 23, 2020. 2. Armbruster N, Jasny E, Petsch B. Vaccines 2019; 7(132). 3. Siegrist C, Vaccine Immunology. In: Plotkin SA, Orenstein WA, Offit PA, editors. Plotkin's Vaccines. 7th edition. Philadelphia, PA: Elsevier; 2017. Available from WHO website: https://www.who.int/immunization/documents/Elsevier_Vaccine_immunology.pdf. Accessed November 27, 2020.

Acute infection with PR8 influenza induces lower levels of neutralization than modified mRNA-LNP vaccination



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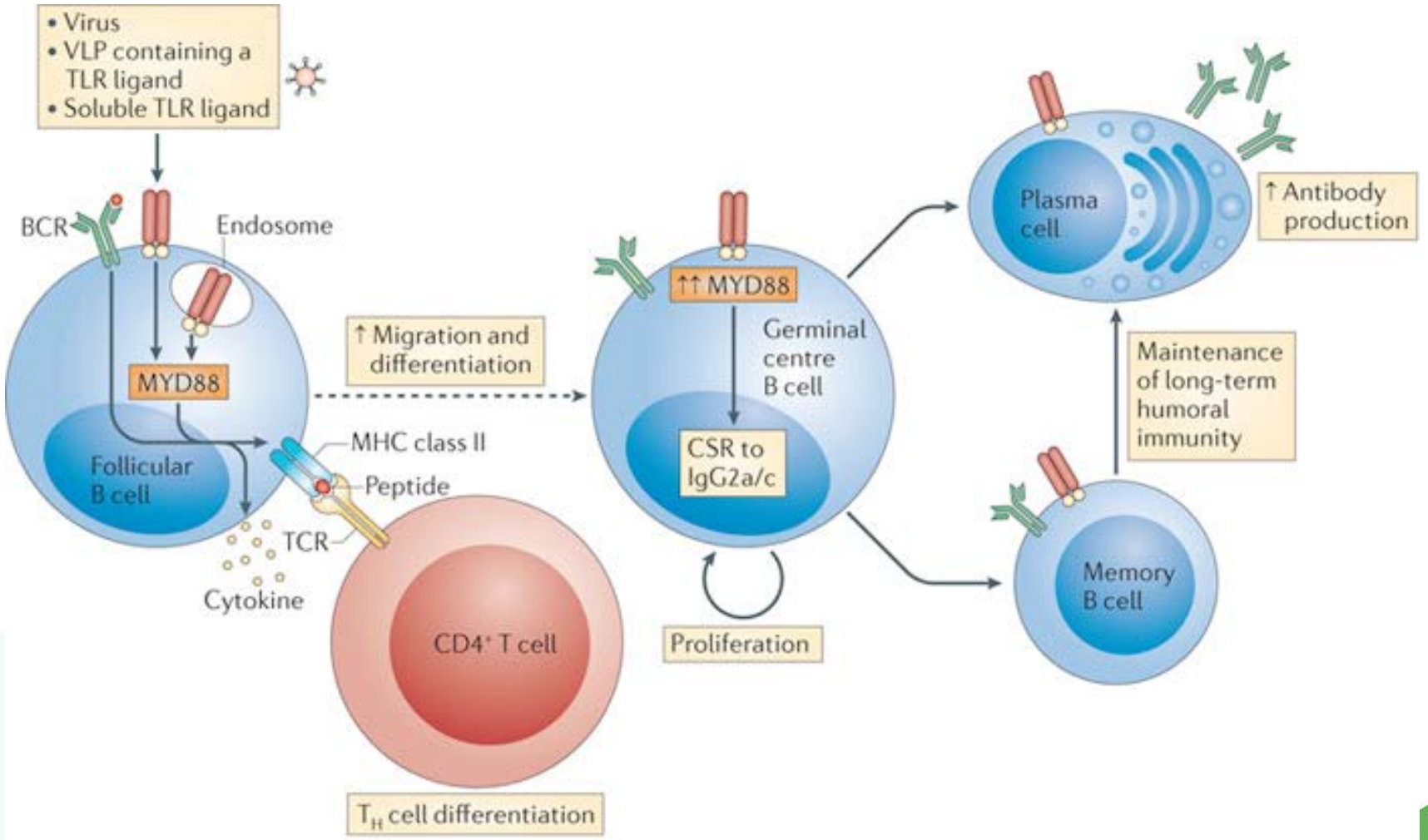
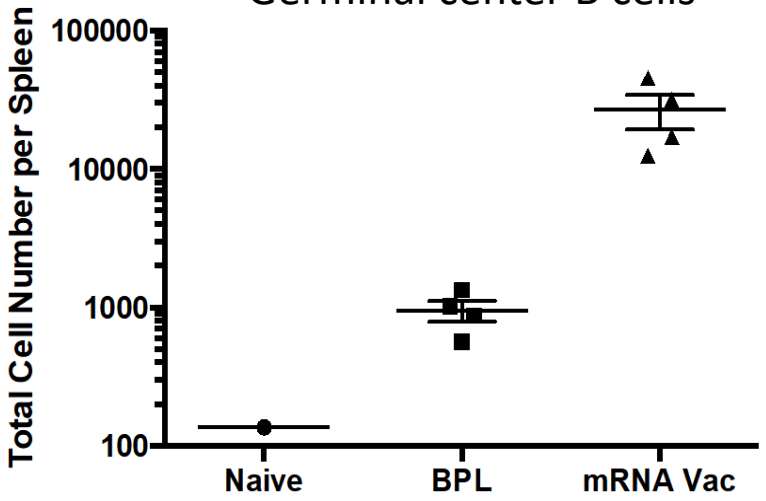
B cell response



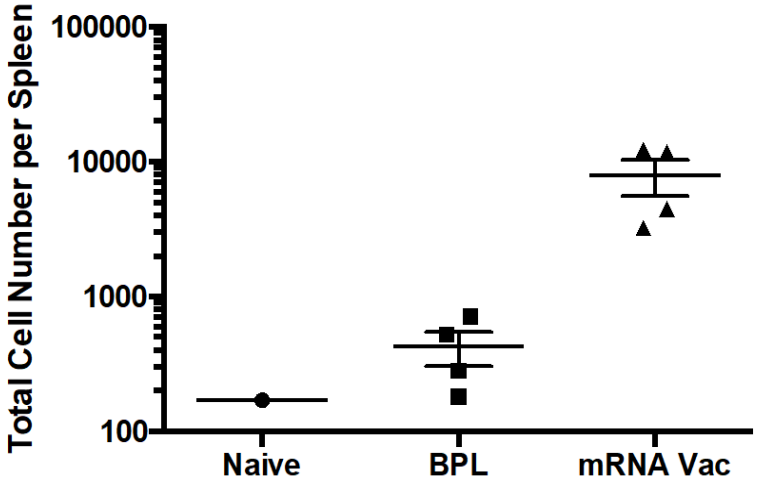
Nature Reviews | Immunology

A single immunization of PR8 HA encoding mRNA-LNPs produces HA-specific germinal center, memory, and long-lived plasma cells

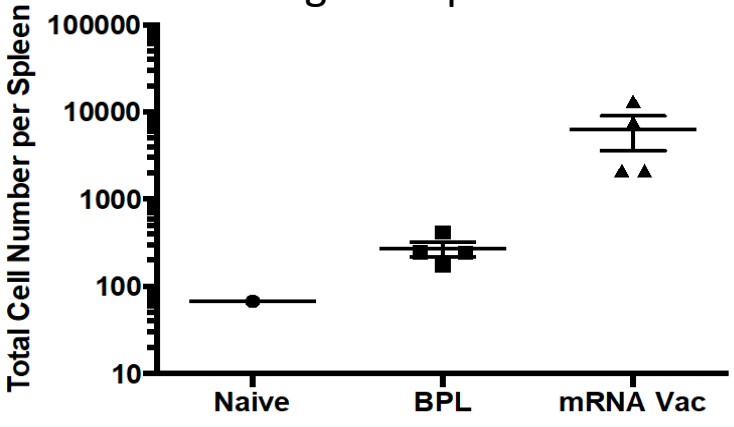
Germinal center B cells



Memory B cells



Long-lived plasma cells



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4 weeks after a single immunization with HA mRNA-LNPs

mRNA1273, Moderna modified mRNA-LNP vaccine

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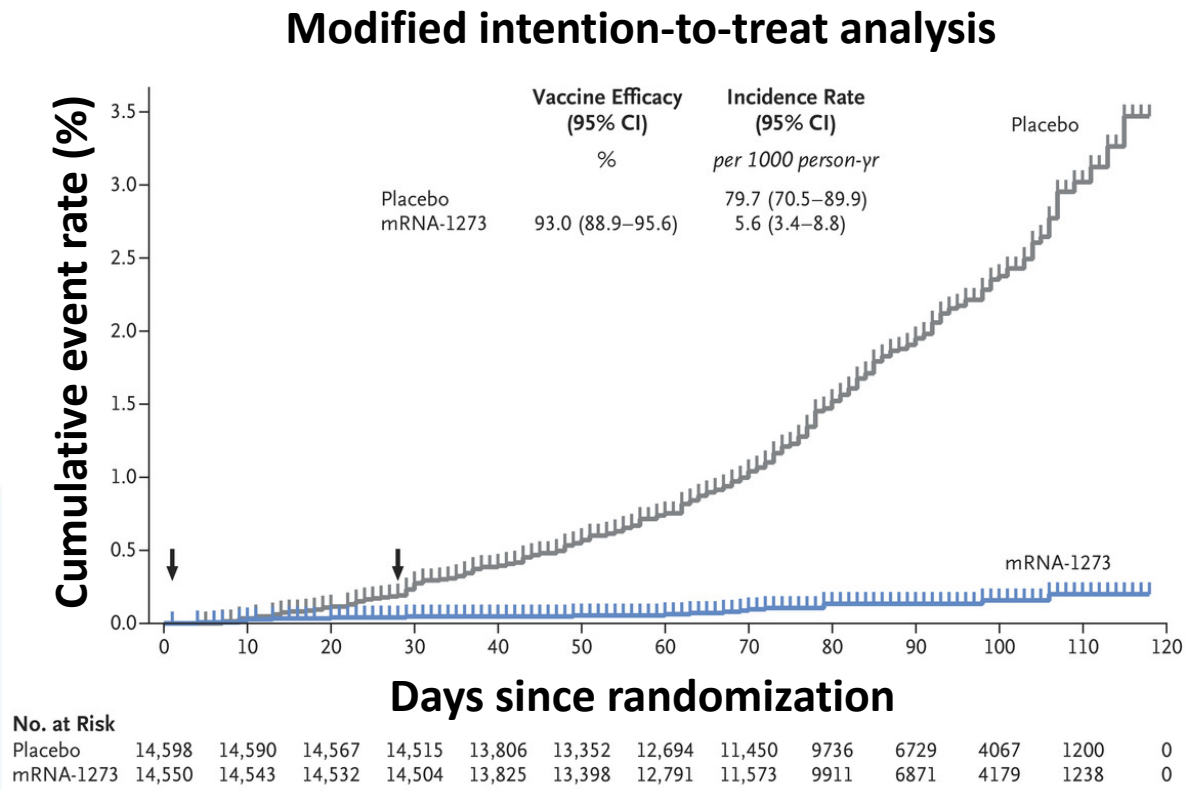
mRNA-1273: reduced COVID-19 with 94.1% efficacy

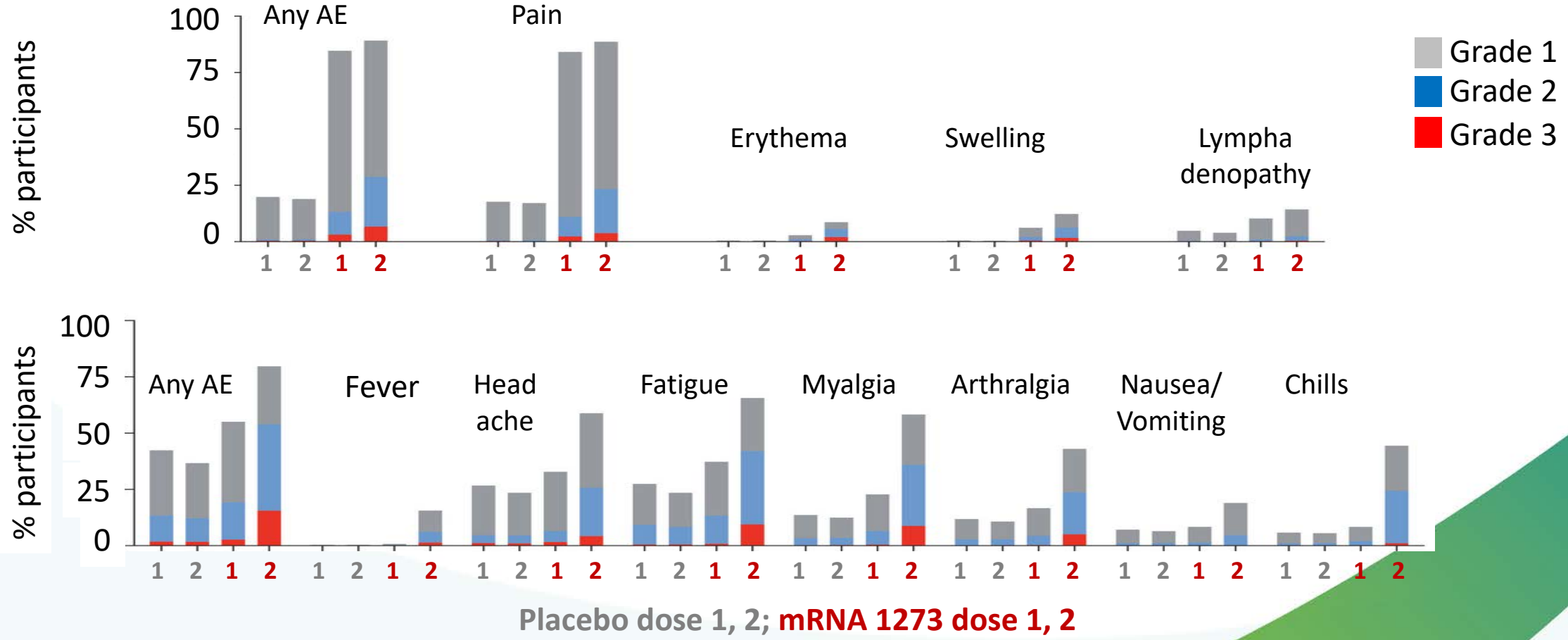


94.1% efficacy at preventing COVID-19 illness including severe disease

COVID-19 Onset	# COVID-19+ post-dose Placebo N=14,598	mRNA-1273 N=14,550
Up to 14d post dose 1	11	5
14d to dose 2	35	2
dose 2-14d pd2	19	0
After 14d pd2	204	12
Total	**269**	**19**

LR Baden et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2035389

mRNA 1273 Trial: Local and systemic adverse events



LR Baden et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2035389

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

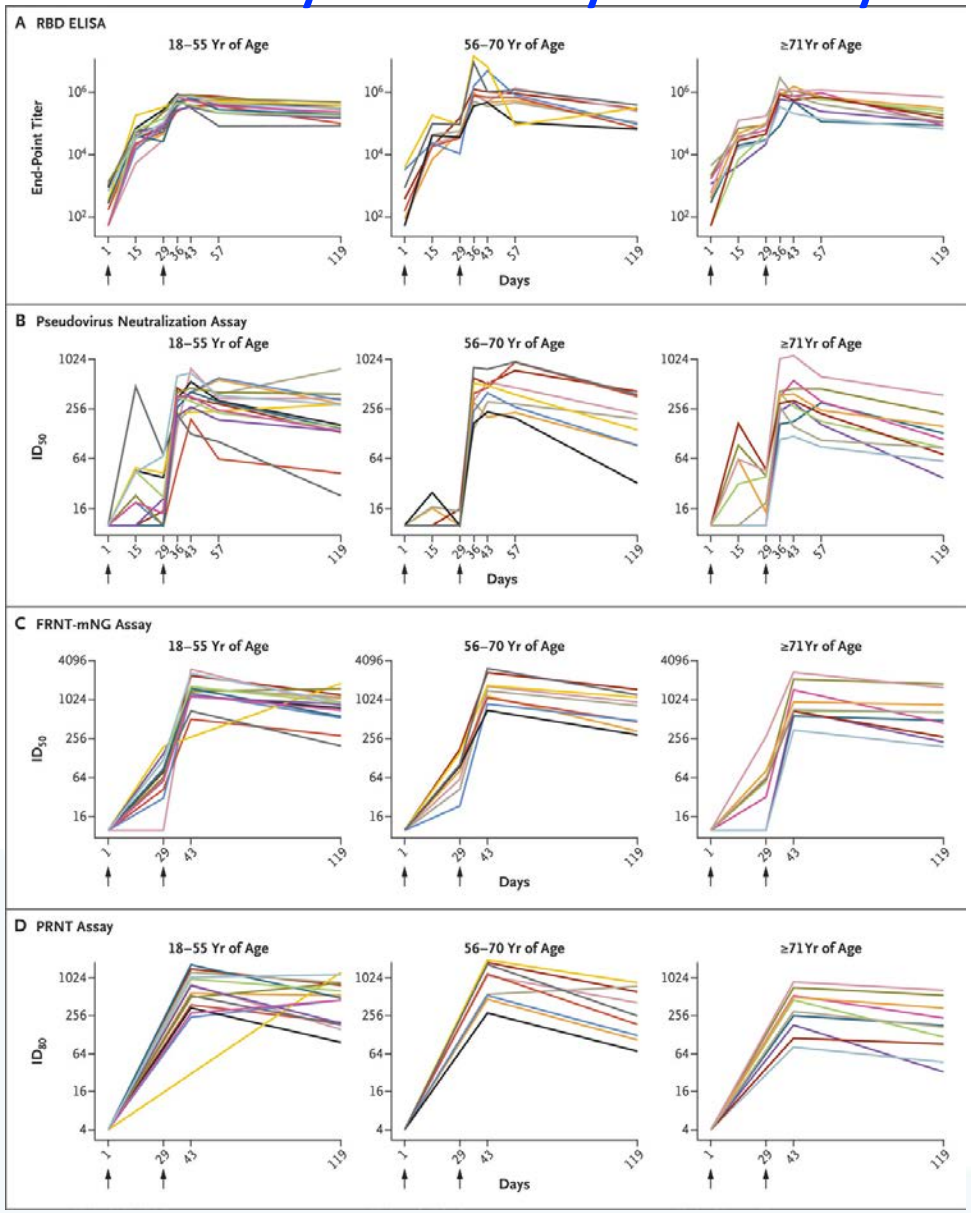
18-55y 56-70y >71y

RBD Elisa

Pseudovirus Neutralization Assay

Focus Reduction neutralization Assay

Plaque reduction neutralizing Assay



AT Widge et al. N Engl J Med 2021;384:80-82.

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.

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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

Disclosures / COI

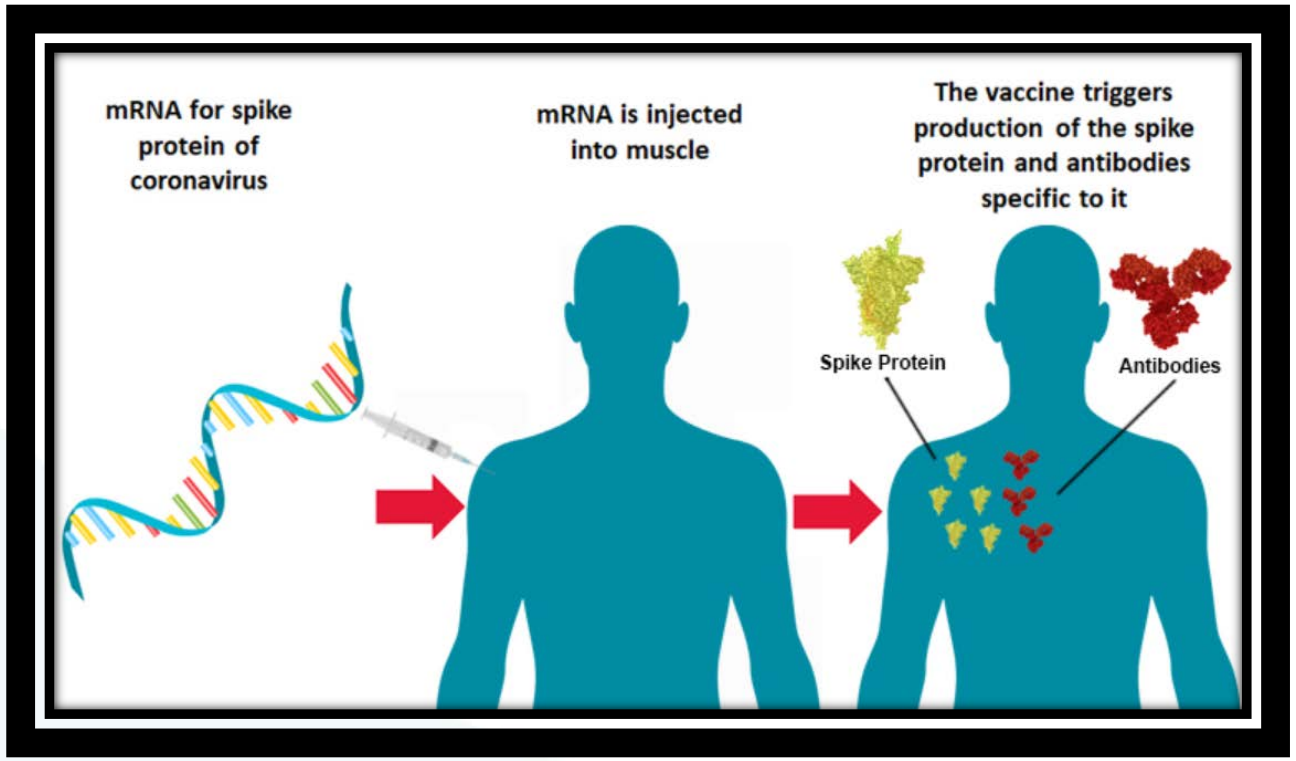
- None related to this presentation

BNT162b2 mRNA vaccine

Vaccine approach	Manufacturer / Sponsor	Advantages	Limitations / concerns
mRNA	BioNTech / Pfizer	Easy to mass produce Easy to adjust for emerging strains	mRNA unstable cold chain requirement 2 dose requirement

Vaccine Component	Role
mRNA	Encodes for prefusion stabilized membrane anchored full length viral spike protein
lipids - (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	Protects mRNA from degradation and facilitate cellular uptake *may be responsible for allergic reactions
Buffer solution and others potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.	Maintains pH of vaccine at desired range Sucrose is a cryoprotectant Includes diluent Note: no preservative

mRNA vaccines- how they work and what they don't do!



Source: NIH.gov

- 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"

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Study Design (patient eligibility)

Pfizer Phase 2/3 RCT study populations– who was in and left out

Who was in

- >=Age 16

Who was added on

- HIV (well controlled, CD4>200)
- HBV (HBeAg-, HBeAb+, DNA<2K, normal ALT/AST, biopsy – necroinflammation)
- HCV (cured or cleared)
- Age 12-15

Who is left out (for now)

- Kids Age 11 and below
- Pregnant and breastfeeding women
- Immunosuppressive therapy

*Ultimately, 214 patients with mild liver disease and 3 patients with moderate to severe liver disease were included in the study

Study Results (immunogenicity)

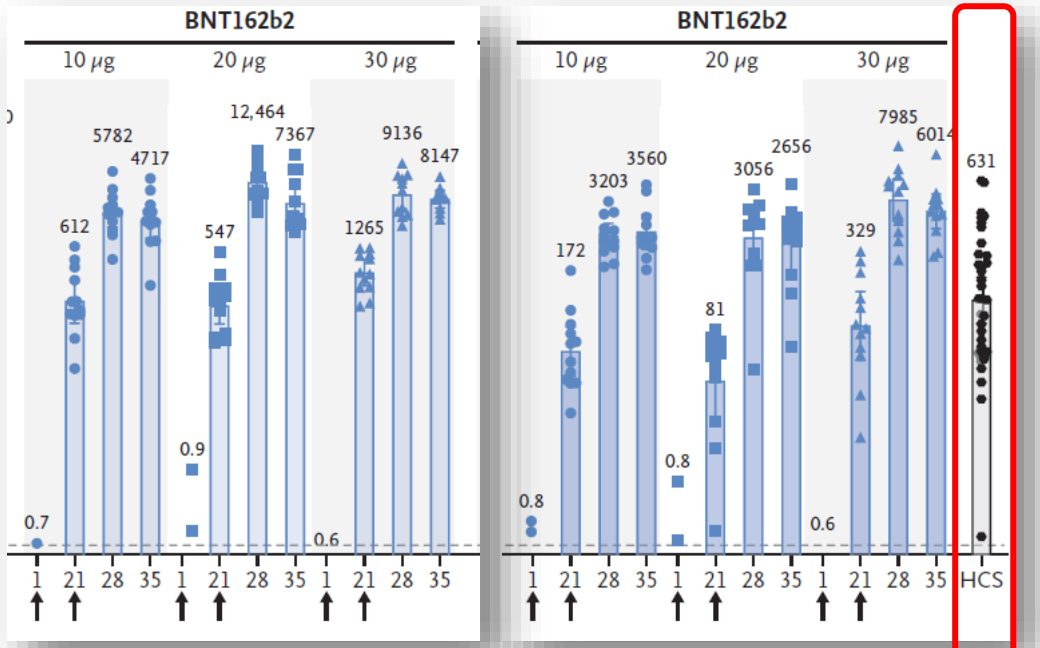
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

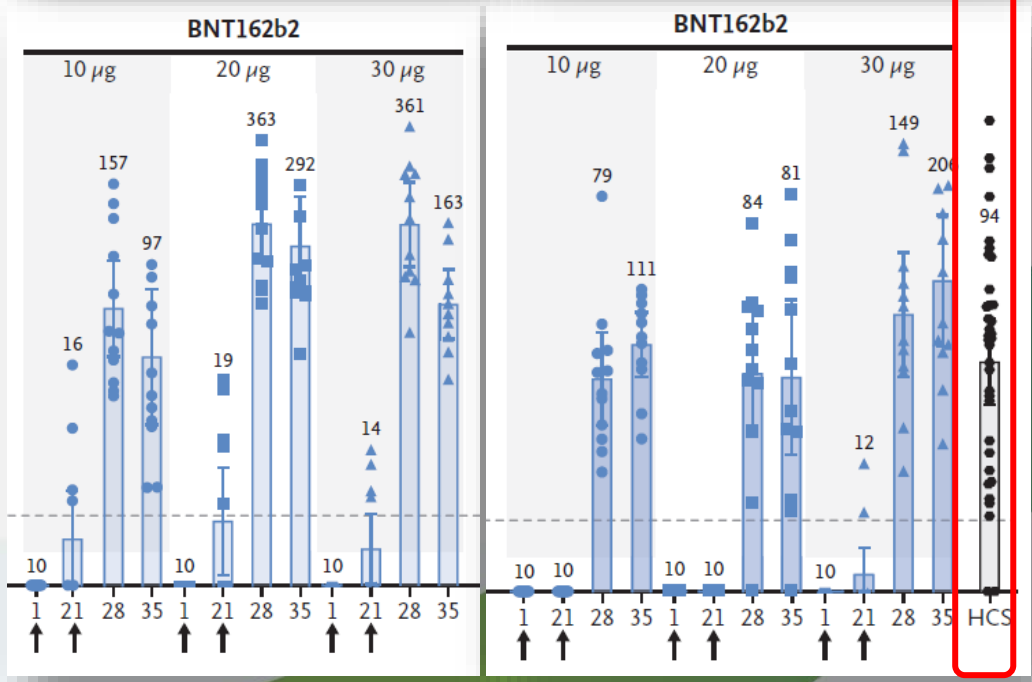
Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates

Edward E. Walsh, M.D., Robert W. Frenck, Jr., M.D., Ann R. Falsey, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., Kathleen Neuzil, M.D., Mark J. Mulligan, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Ping Li, Ph.D., Kenneth Koury, Ph.D., Warren Kalina, Ph.D., David Cooper, Ph.D., Camila Fontes-Garfias, B.Sc., Pei-Yong Shi, Ph.D., Özlem Türeci, M.D., Kristin R. Tompkins, B.Sc., Kirsten E. Lyke, M.D., Vanessa Raabe, M.D., Philip R. Dormitzer, M.D., Kathrin U. Jansen, Ph.D., Uğur Şahin, M.D., and William C. Gruber, M.D.

S1-binding IgG (u/mL) in 18-55yrs (left) and 65-85 years (right)



50% neutralization titers 18-55yrs (left) and 65-85 years (right)



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

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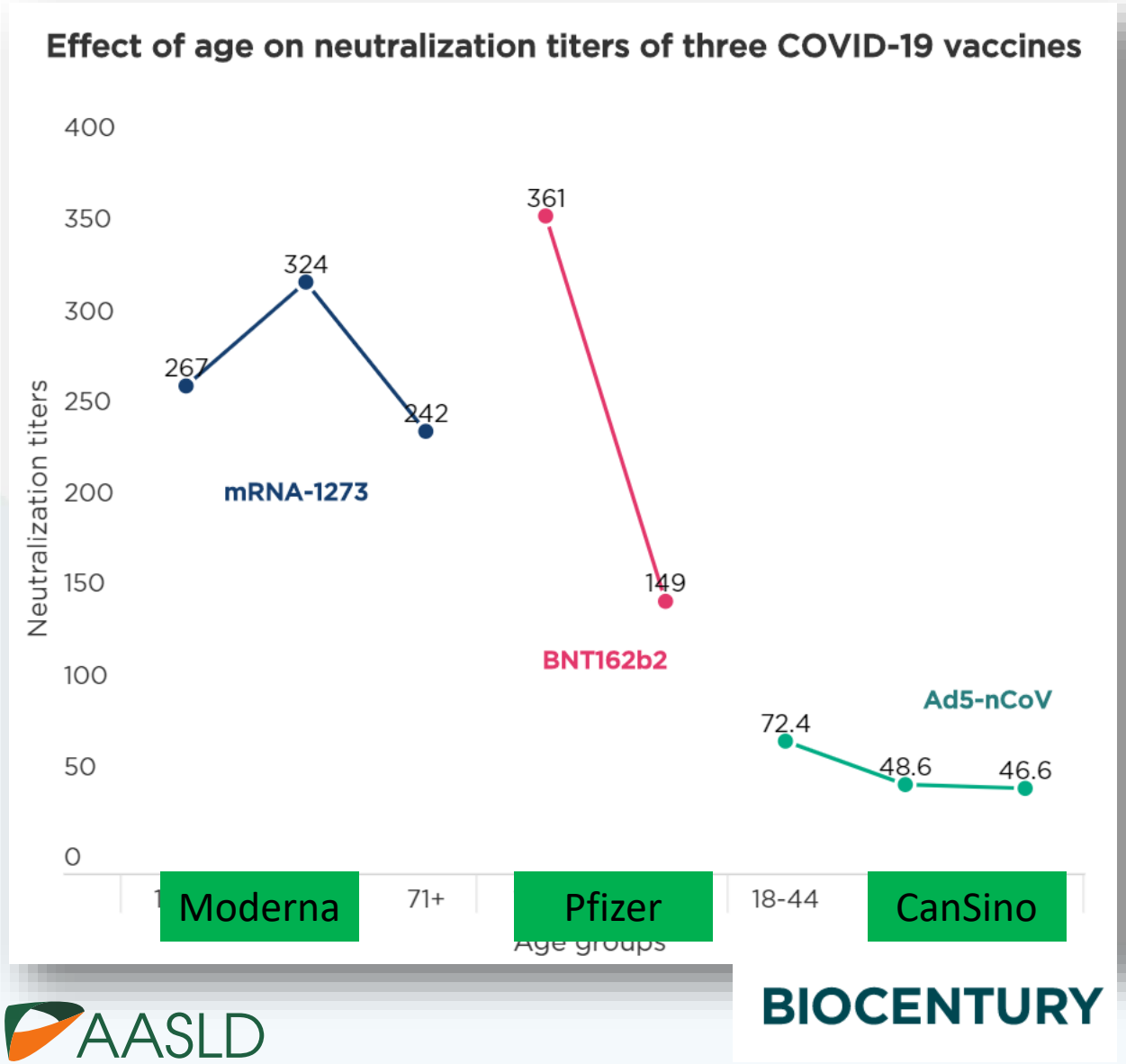
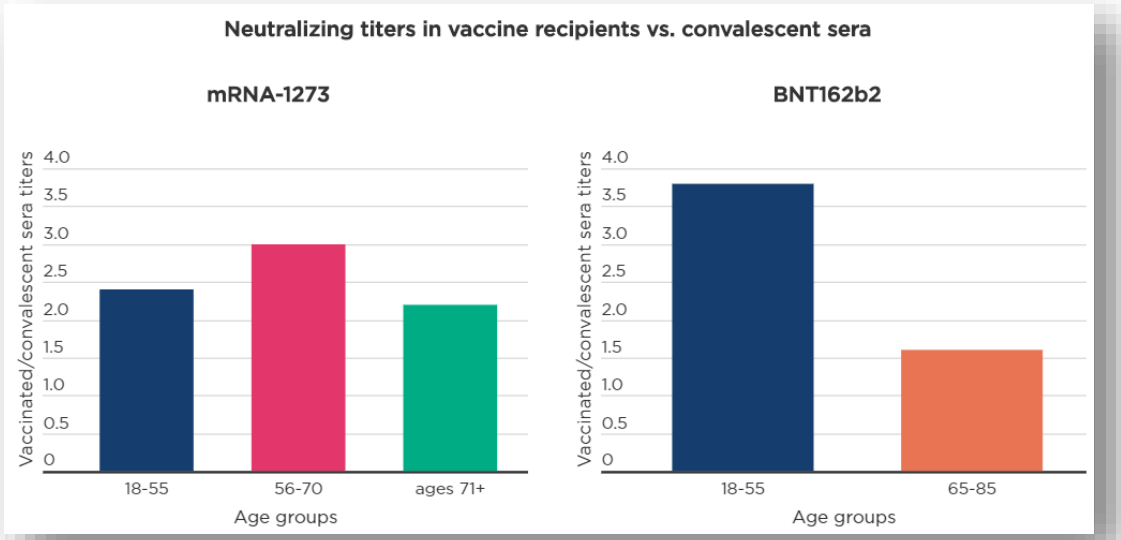
How are older folk doing in early phase trials?





Caveat: Different neutralization assays used

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

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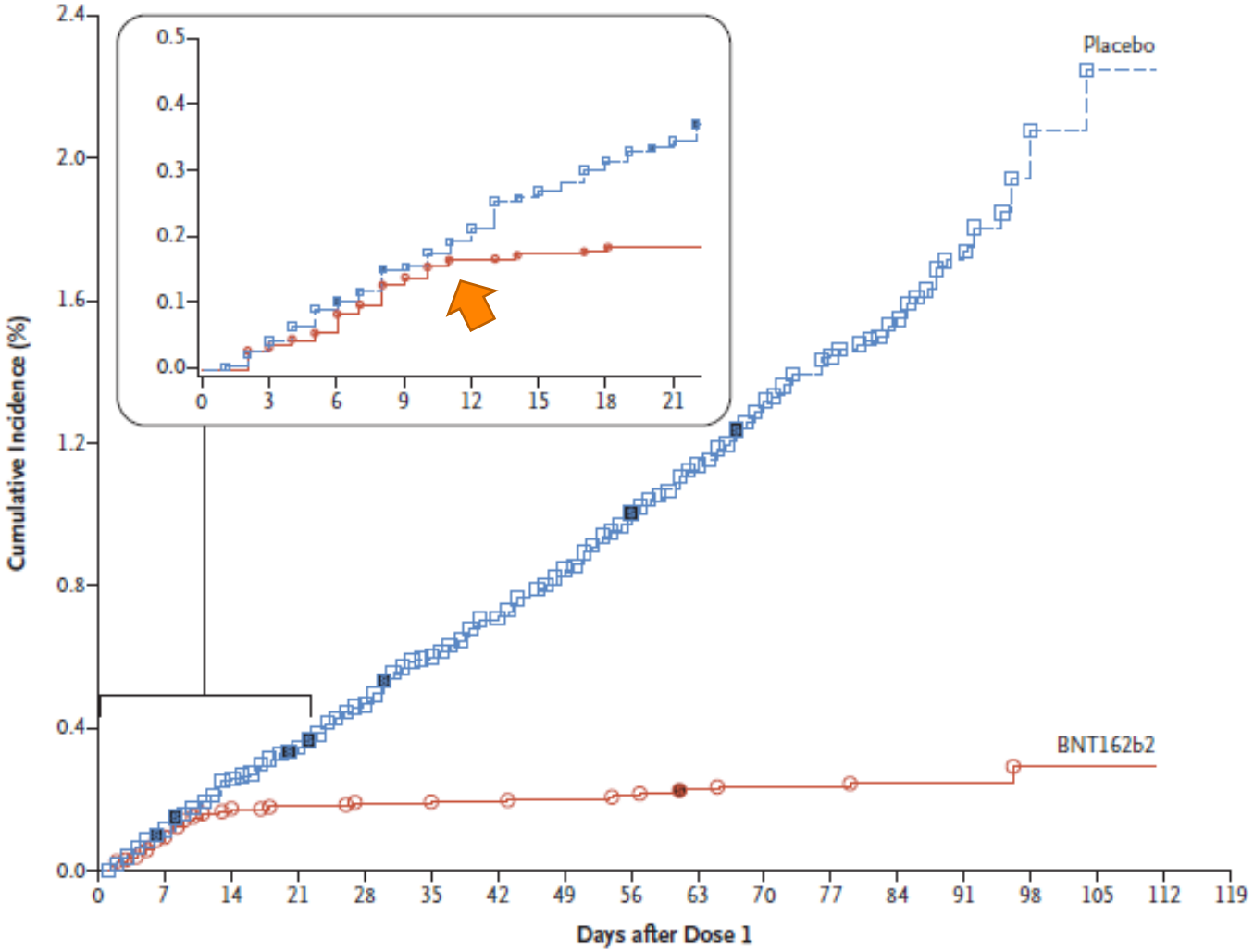
BIOCENTURY

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



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	BNT162b2, 30 μg (N=21,669) Surveillance time *person-yr (no. at risk)*	Placebo (N=21,686) No. of participants	Placebo (N=21,686) Surveillance time *person-yr (no. at risk)*	VE (95% CI) *percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

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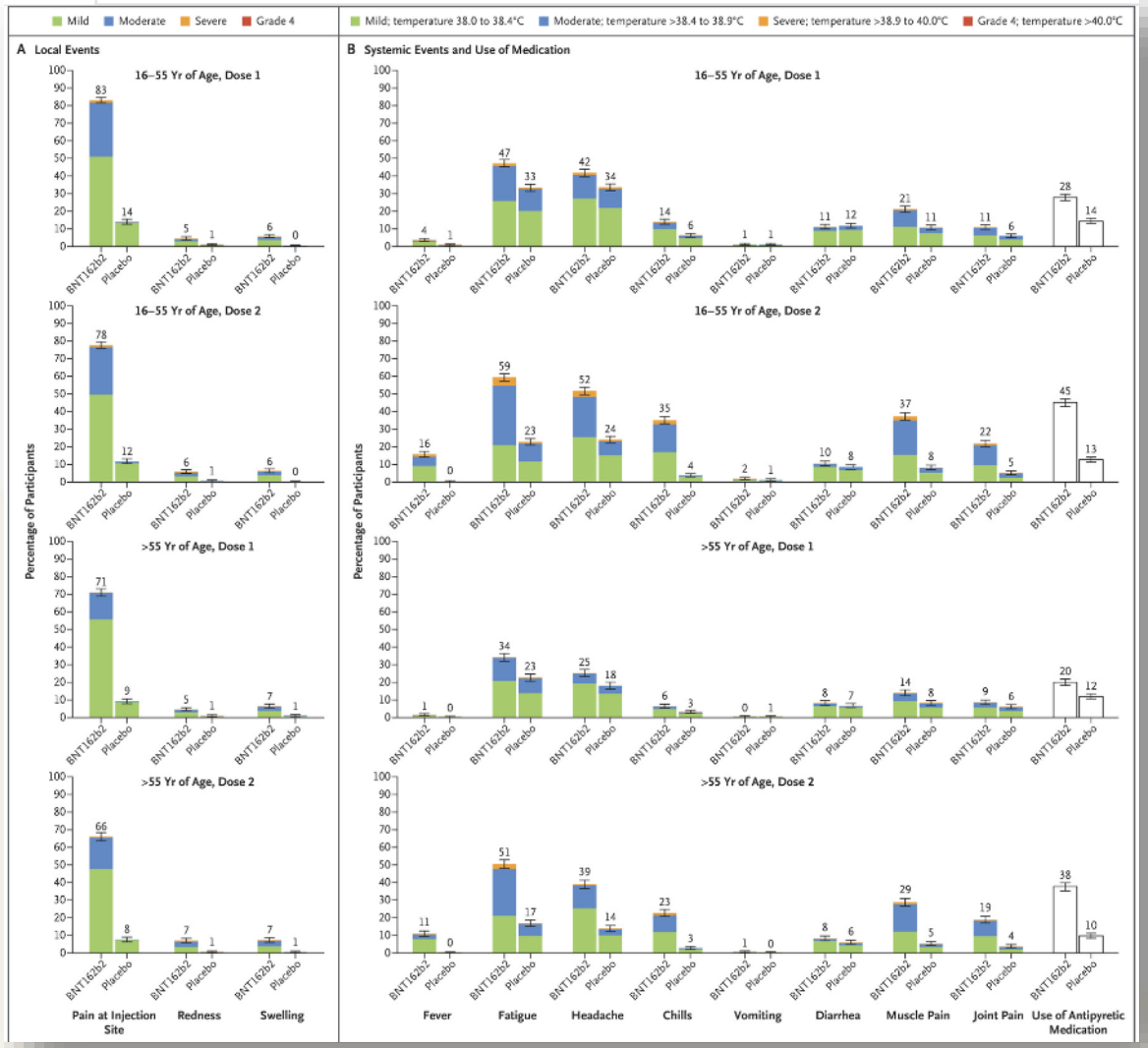
BNT162b2 safety

Safety summary – Phase 2/3 studies



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%).

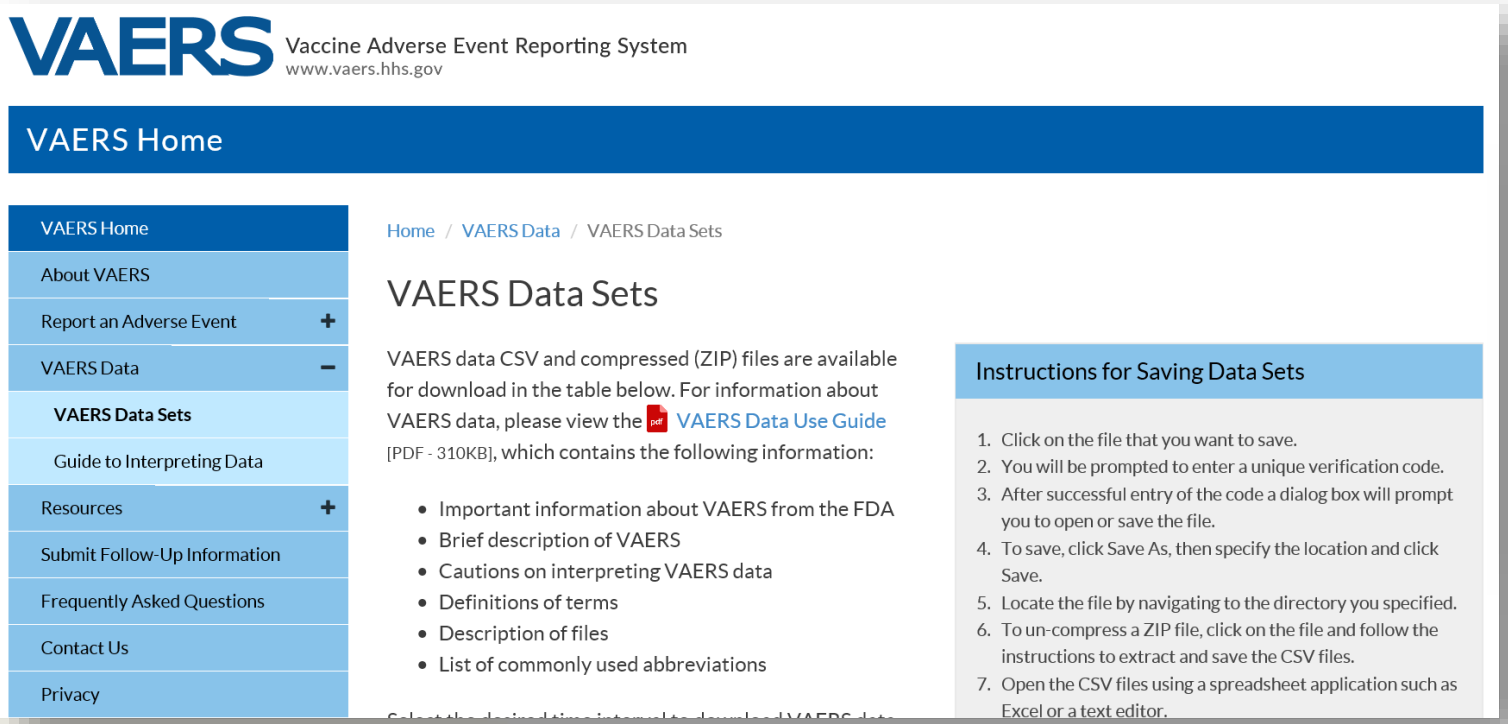
SAFETY SUMMARY

- 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?



These results are for 9 total events.
Rows with zero Events Reported are hidden. Use Quick Options above to show zero rows.

Symptoms	Vaccine Type	Vaccine Manufacturer	Events Reported
JAUNDICE	COVID19 VACCINE (COVID19)	PFIZER\BIONTECH	2
		Total	2
	Total		2
LIVER FUNCTION TEST	COVID19 VACCINE (COVID19)	PFIZER\BIONTECH	4
		Total	4
	Total		4
LIVER FUNCTION TEST INCREASED	COVID19 VACCINE (COVID19)	PFIZER\BIONTECH	3
		Total	3
	Total		3
TRANSAMINASES INCREASED	COVID19 VACCINE (COVID19)	PFIZER\BIONTECH	1
		Total	1
	Total		1
Total			10

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.

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