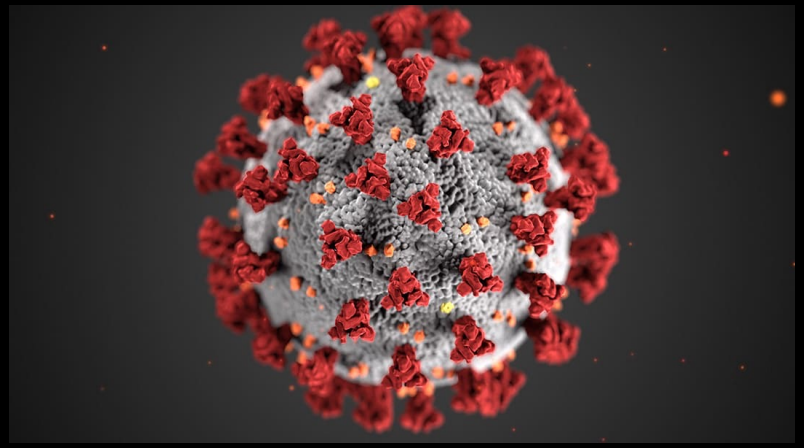
Are We Post-Pandemic? What's Next in COVID Management and Prevention



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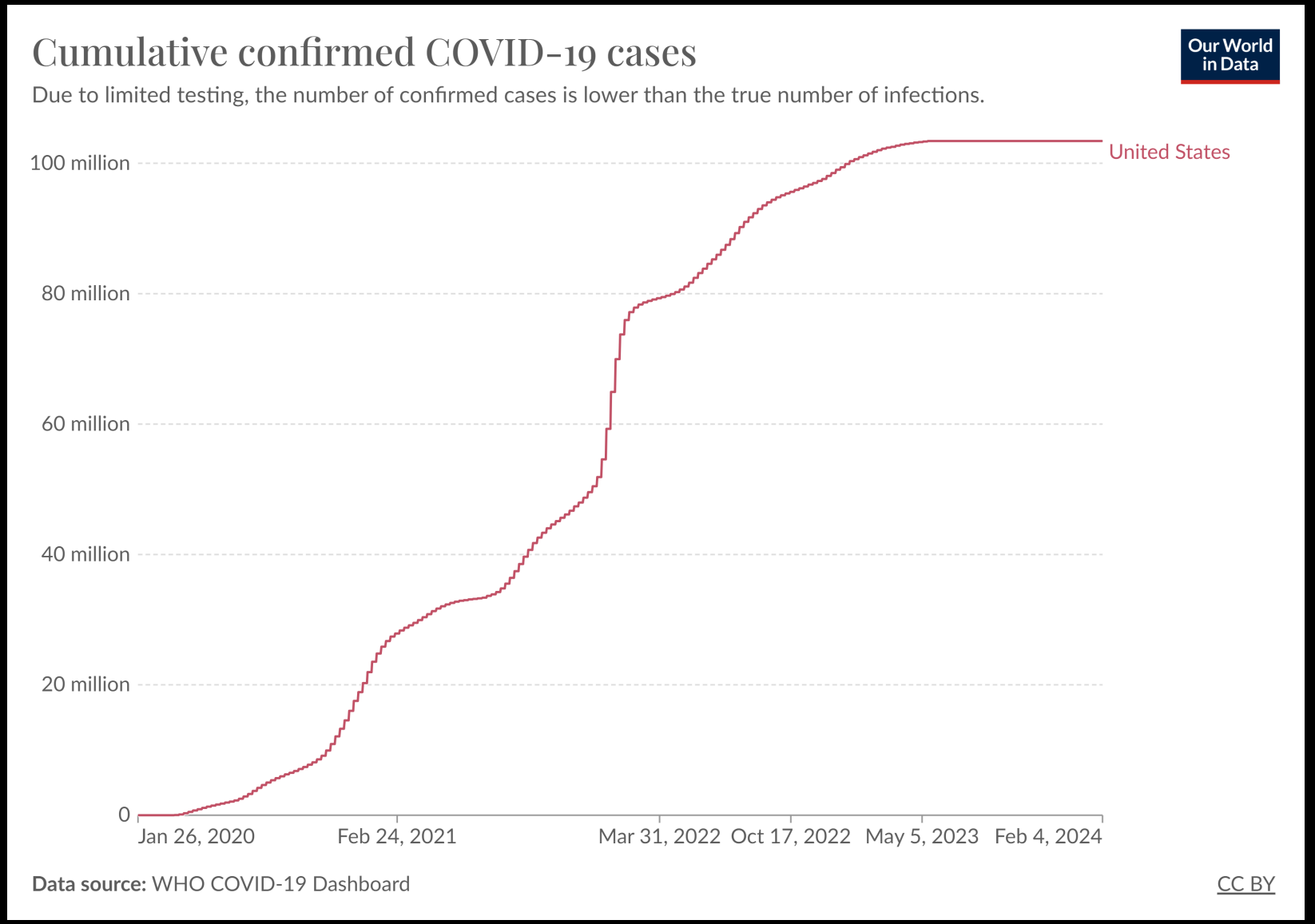
Disclosures

- Participated in Medical Advisory Board for Pfizer COVID-19 vaccination in pregnancy trial
- Site PI for a Pfizer COVID-19 vaccination in pregnancy Phase 2/3 trial
- Site PI for a Pfizer RSV vaccination in pregnancy trial
- Site PI for a Pfizer pharmacokinetics of Paxlovid in pregnancy study

Learning Objectives

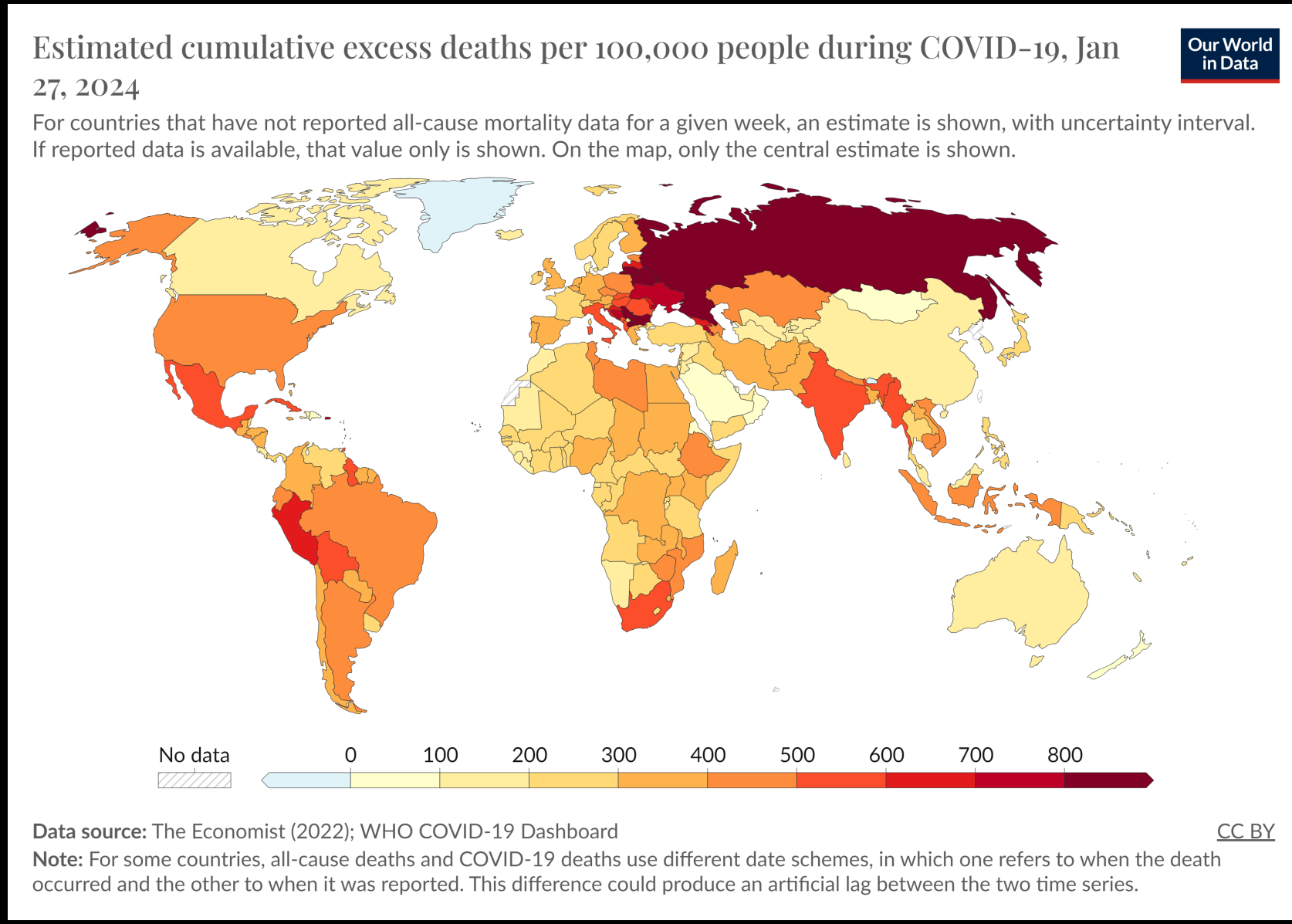
- Describe anticipated outcomes for individuals with SARS-CoV-2 during pregnancy or postpartum
- Describe efficacy and outcomes associated with SARS-CoV-2 vaccination in pregnancy
- Describe current treatments for COVID in pregnancy
- Discuss long COVID or Post Acute Sequelae of SARS-CoV-2

The COVID-19 Pandemic

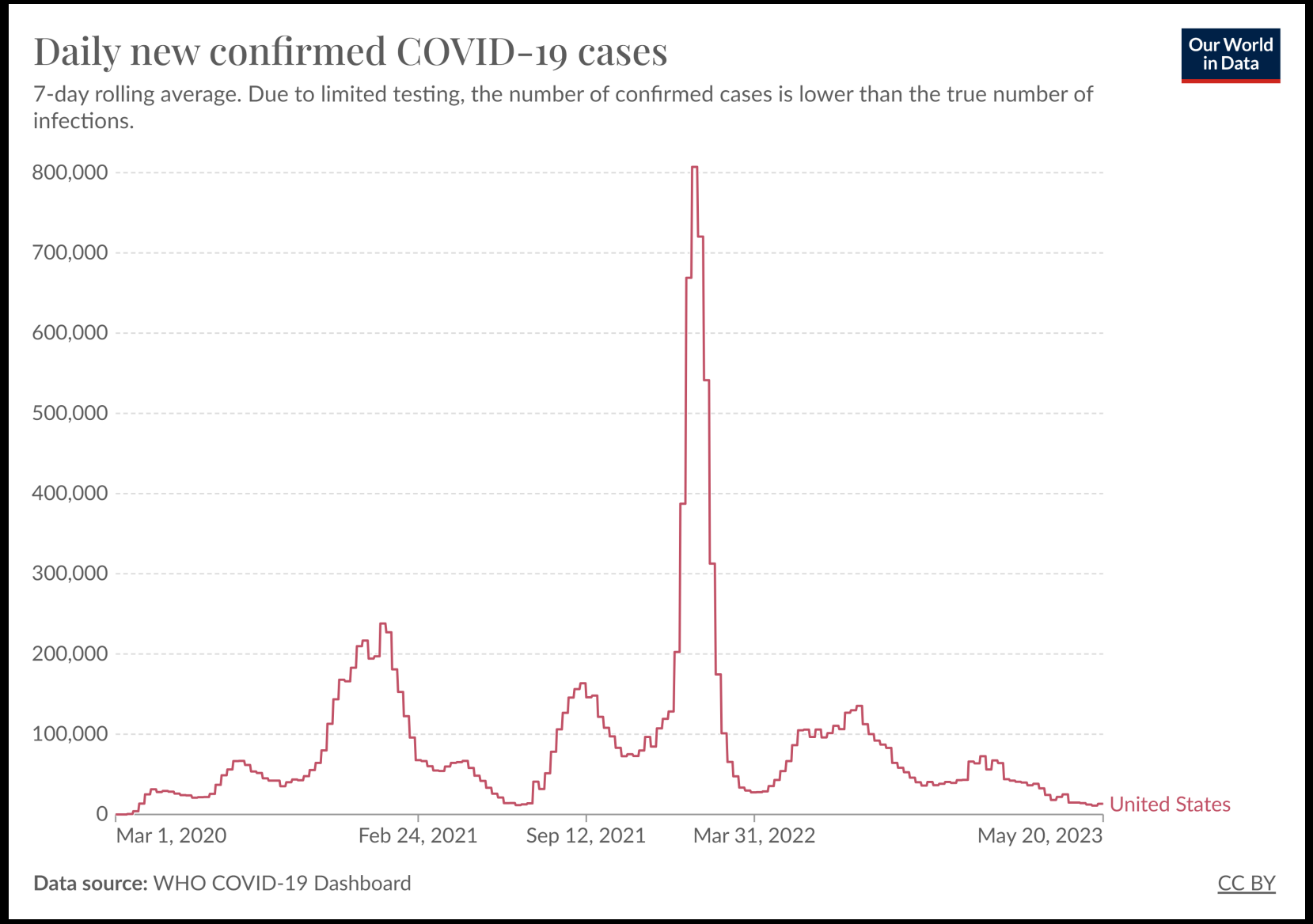


https://ourworldindata.org/covid-cases?country=~USA#select-countries-to-show-in-all-charts

Excess Deaths During Pandemic



Is the pandemic over?



Pregnant Compared with Non-Pregnant

- MMWR report of cases submitted to the CDC from Jan 22 to October 3, 2020
  - **N= 1,300,938 females of reproductive age** who tested positive for SARS-CoV-2
  - Data on pregnancy status available for 35.5% of these individuals (461,825)
    - 88.7% were symptomatic
  - Among symptomatic people, 5.7% (23,434) were pregnant

MMWR Weekly Report (Nov 2, 2020)

Pregnant Compared with Non-Pregnant

- **After adjustment for age, comorbidities and race/ethnicity, pregnant individuals were at increased risk of**
  - **ICU admission: 10.5 vs 3.9 per 1,000 cases**(aRR 3.0, 95% CI=2.6-3.4)
  - **Mechanical ventilation: 0.5% vs 0.3%** (aRR 1.7, 95% CI 1.2-2.4)
  - **Risk of death: 1.5 vs 1.2 per 1,000 cases** (aRR 1.7, 95% CI 1.2-2.4)
- **Disparities were prevalent**
  - Individuals who identified as Black represent 14% of cohort, but 37% of deaths overall and 27% of deaths among pregnant people

MMWR Weekly Report (Nov 2, 2020)

SARS-CoV-2 in Pregnancy

- Retrospective cohort of all deliveries from April-Nov
  - All-payer database encompassing 20% of U.S. population
  - Identified participants with billing codes
- N=406,446 patients hospitalized for childbirth
  - 6,380 (1.6%) COVID-19 diagnostic code

Jering KS et al, JAMA Int Med

Outcome	No COVID N=400,066	With COVID N=6,380	Unadjusted OR	Adjusted OR
Cesarean	27.5%	28.9%	1.08 (1.02-1.14)	**1.07 (1.02-1.13)**
PTL	4.0%	5.2%	1.31 (1.17-1.46)	**1.19 (1.06-1.33)**
PTB	5.8%	7.2%	1.26 (1.14-1.38)	**1.17 (1.06-1.29)**
Stillbirth	0.3%	0.5%	1.66 (1.18-2.33)	1.23 (0.87-1.75)
PreE	6.8%	8.8%	1.36 (1.22-1.46)	**1.21 (1.11-1.33)**
Eclampsia	0.1%	0.1%	1.74 (0.86-3.52)	1.56 (0.77-3.16)
HELLP	0.2%	0.5%	2.10 (1.48-2.97)	**1.96 (1.36-2.81)**
VTE	0.1%	0.2%	3.52 (2.09-5.92)	**3.43 (2.01-5.82)**
ICU	0.4%	3.3%	7.84 (6.78-9.06)	**6.47 (5.55-7.55)**
Vent	0.1%	1.3%	25.77 (20.03-33.15)	**23.70 (17.95-31.29)**

Jering KS et al, JAMA Int Med

NICHD MFMU GRAVID

NICHD MFMU GRAVID Study

- Retrospective cohort study 17 U.S. hospitals participating in the NICHD Maternal-Fetal Medicine Units Network
- 14,104 pregnant or postpartum patients
- Delivered March-Dec 2020

Metz et al JAMA 2022

NICHD MFMU GRAVID

- 2,352 patients had SARS-CoV-2 infection
- Compared with those without SARS-CoV-2 who delivered on randomly selected dates (n=11,752)
- Primary Outcome
  - Maternal death or serious morbidity from common pregnancy complications including hypertensive disorders of pregnancy, postpartum hemorrhage, and infections other than SARS-CoV-2

Metz et al JAMA 2022

Serious Maternal Morbidity

Outcome	SARS-CoV-2 N=2352	No SARS-CoV-2 n=11,752	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
Composite death or serious morbidity	13.4%	9.2%	1.45 (1.29-1.64)	1.41 (1.23-1.61)
Death	0.2%	0%	-	-
Hypertensive disorders of pregnancy	10.1%	6.5%	1.56 (1.35-1.79)	1.53 (1.31-1.79)
Postpartum hemorrhage	2.6%	2.4%	1.06 (0.81-1.40)	1.13 (0.83-1.53)
Infection other than SARS-CoV-2	2.3%	0.9%	2.61 (1.88-3.63)	2.08 (1.41-3.05)

Stratified by Infection Severity

- Adverse outcomes among those with moderate or higher disease severity (except HDP)
  - Need to prevent progression to higher disease severity
  - Vaccines and treatments for COVID-19

Metz et al JAMA 2022

Vaccine Efficacy

- Population-based data from Scotland (Dec 2020-Oct 2021)
- Vaccine coverage lower for pregnant (32.3%) compared with non-pregnant females (77.4%)
- Compared SARS-CoV-2 infection outcomes vaccinated vs unvaccinated pregnant people

Stock et al Nature Medicine 2022

Vaccine Efficacy

- 77.4% of SARS-CoV-2 infections were in unvaccinated individuals
  - 11.5% partially vaccinated
  - 11.1% fully vaccinated
- 91% of SARS-CoV-2 infections associated with hospitalization
- 98% of SARS-CoV-2 infections associated with critical care admissions were in unvaccinated individuals

Stock et al Nature Medicine 2022

Vaccine Efficacy

- Of 2,364 total births, 11 stillbirths and 8 livebirths resulted in neonatal deaths
- All perinatal deaths occurred in unvaccinated individuals

Stock et al Nature Medicine 2022

Vaccine Efficacy

- Retrospective cohort 15,865 pregnant patients
- Vaccinated (at least 2 doses of mRNA vaccine) compared with unvaccinated
  - n=2,069 vaccinated group and 13,796 unvaccinated
- Lower rates of adverse perinatal outcomes with vaccination
  - Perinatal death (0.5% vs 0.8%, aOR 0.20, 95% CI 0.05-0.88)
  - Preterm delivery (aOR 0.63, 95% CI 0.48-0.82)
  - Very low birth weight (aOR 0.35, 95% CI 0.15-0.84)
  - NICU admission (aOR 0.66, 95% CI 0.52-0.85)

Morgan JA et al, Obstet Gynecol 2023

Vaccine Efficacy

- Systematic review and meta of 23 studies including 117,552 COVID-19 vaccinated pregnant people
- Effectiveness 89.5% (95% CI 69.0-96.4%) against SARS-CoV-2 infection 7 days after 2nd dose
- Risk of stillbirth lower in vaccinated (pOR 0.85, 0.73-0.99)
- No evidence of higher risk of miscarriage, earlier gestational age at delivery, abruption, pulmonary embolism, PPH, maternal death, ICU admission, lower birthweight, NICU

Prasad et al Nat Commun 2022

Vaccine Efficacy Against Neonatal Disease

- Case-control study
- 537 case infants hospitalized for COVID under 6 months of age (181 Delta, 356 Omicron)
- 16% case infants and 29% control infants born to unvaccinated mothers
- Effectiveness of maternal vaccination against neonatal hospitalization for COVID was 52% overall
  - 69% efficacy when administered after 20 weeks' gestation

Halasa NB et al New Eng J Med 2022

Vaccine Boosters

- Prospective cohort
- 31 pregnant, 12 lactating, 20 nonpregnant age-matched controls
- 15 dyads with cord blood
- Increased IgG levels against Omicron spike with booster
- Levels in pregnant and lactating similar to nonpregnant controls
- Spike-specific IgG levels in cord increased with time since vaccination

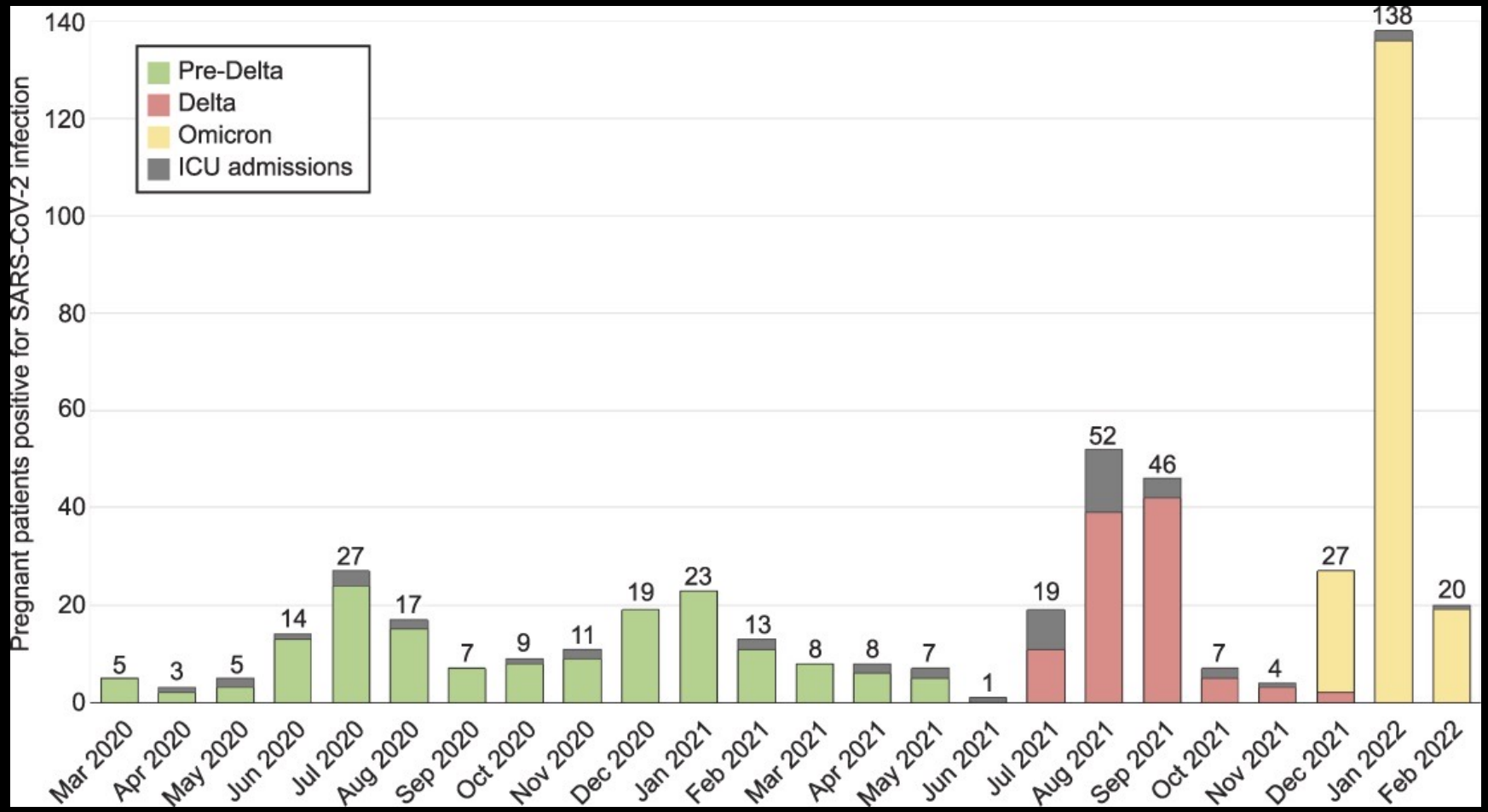
Atyeo et al Am J Obstet Gynecol 2022

Vaccine Boosters

- Annual booster along with flu vaccination
- Primarily for maternal benefit (similar to flu)
- In contrast to seasonal RSV vaccination aimed solely to produce antibodies for neonatal transfer

Variant Matters

- Severe-critical disease: 1.8% Omicron, 13.3% pre-Delta, 24.1% Delta



Seasely et al Obstet Gynecol 2022

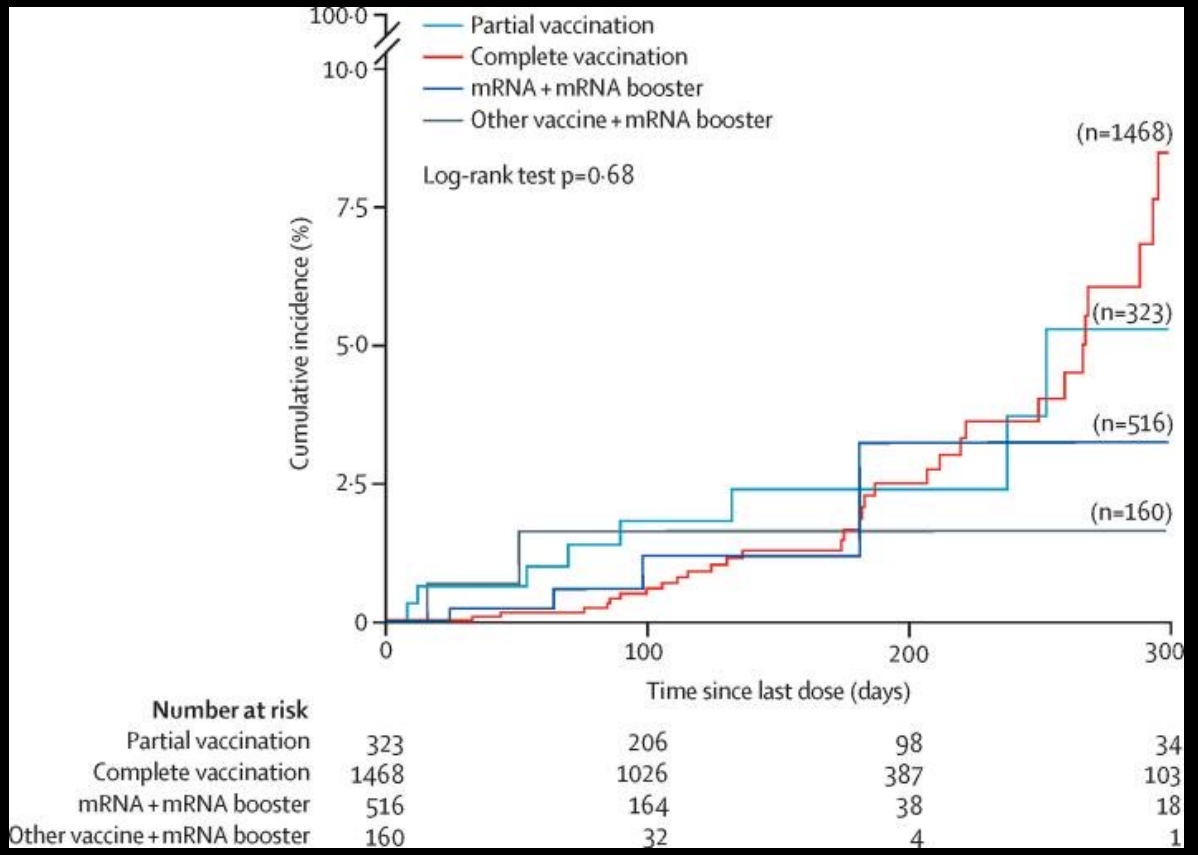
SARS-CoV-2 Variant

- CDC MMWR
  - Increased risk of stillbirth with SARS-CoV-2 infection
    - March 2020-Sept 2021, aRR 1.90 (95% CI 1.69-2.15)
    - During period with Delta variant, aRR 4.04 (95% CI 3.28-4.97)

CDC MMWR 2021

Omicron Variant INTERCOVID Data

- 4618 pregnant people with SARS-CoV-2 during Omicron dominance
  - n=1545 with COVID
- Those with COVID higher rates of maternal morbidity and mortality
- Unvaccinated experienced higher rates of maternal morbidity
- Booster protective



Villar et al Lancet 2023

Omicron Variant INTERCOVID Data

- For pregnant people with COVID-19, vaccine highly effective in preventing severe disease
- Vaccine effectiveness for those with complete regimen 76%
- Vaccine effectiveness for those with a booster 91%

Villar et al Lancet 2023

Omicron Variant CDC Data

- Premier Healthcare Database
- Evaluated pre-Delta, Delta, Omicron
- Exposure to COVID-19 identified by diagnostic code for COVID-19 during delivery hospitalization
- During Omicron period, COVID-19 remained associated with sepsis, ARDS, shock, renal failure, ICU, mechanical ventilation, death

Carlson J et al Obstet Gynecol 2024

Antenatal Surveillance

- During early and Delta variant predominance performed growth ultrasounds
- Non-stress tests for abnormal growth
- Fetal deaths from massive perivillous fibrin deposition and placental insufficiency
- No longer conducting antenatal surveillance for SARS-CoV-2 infection alone

COVID-19 Treatment in Pregnancy

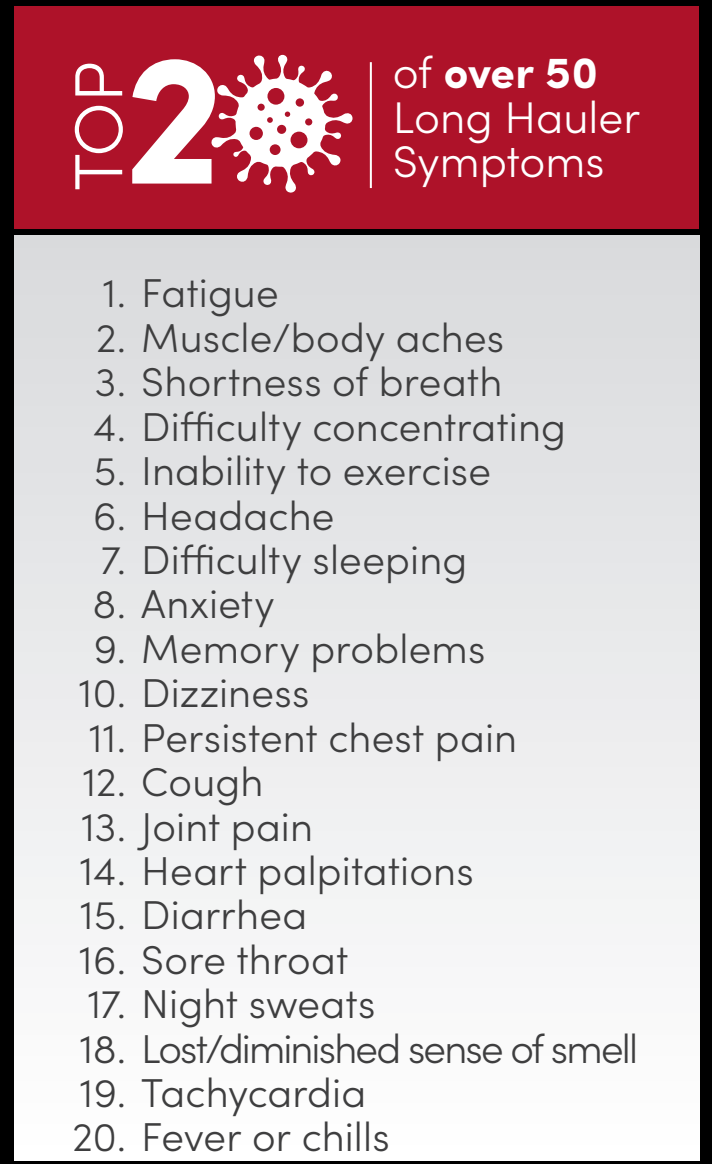
- Treatment in pregnant individuals similar to non-pregnant high risk populations
- Paxlovid for mild to moderate COVID (outpatient) to prevent progression to severe disease
- Dexamethasone and remdesivir if requiring oxygen
- Molnupiravir should be avoided
- Insufficient evidence for or against UFH/LMWH

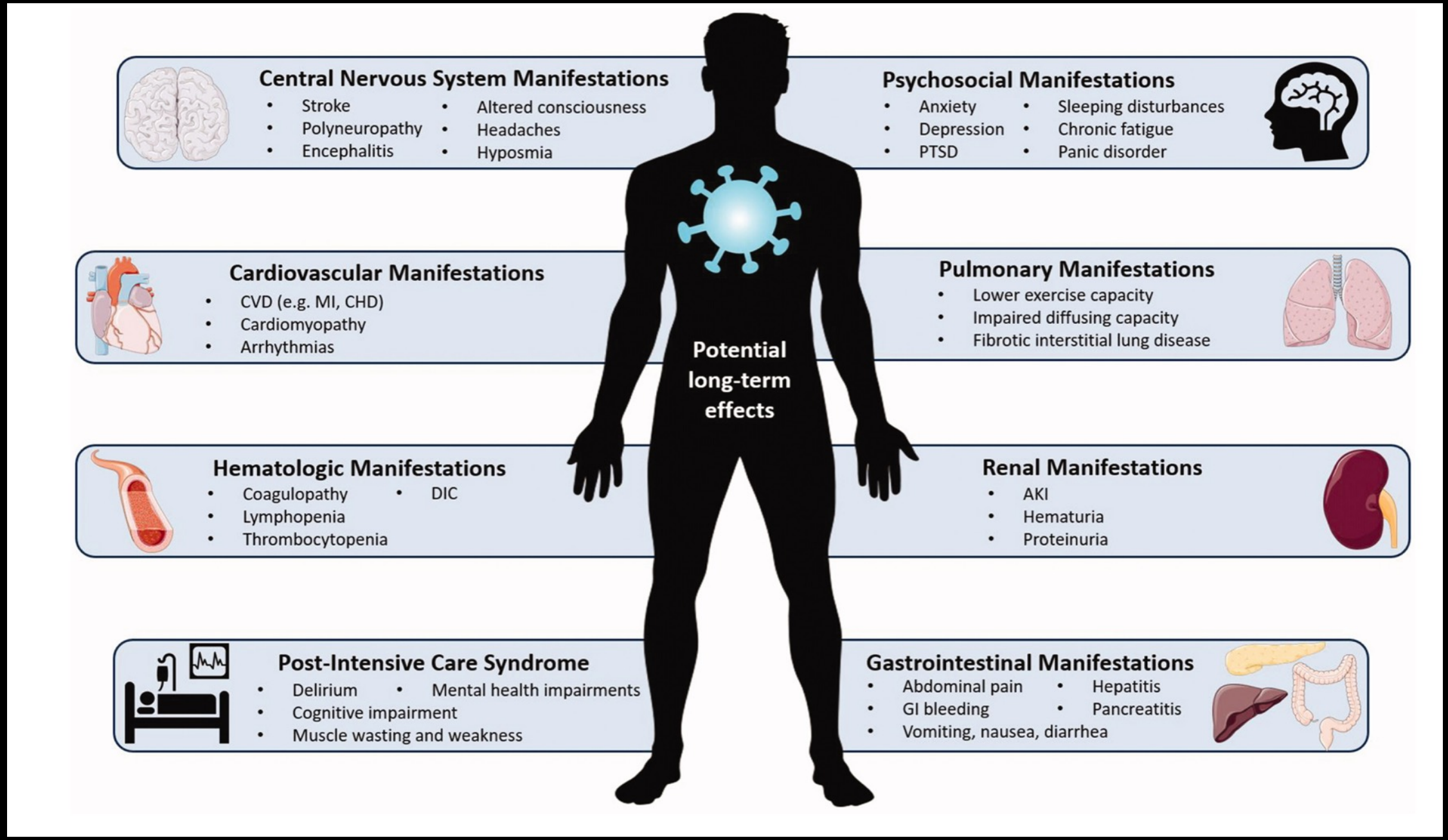
https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

What’s Next?

Long COVID or PASC

- Long COVID or Post-Acute Sequelae of COVID (PASC)
- Occurs in 10-25% of people who acquire SARS-CoV-2
- Possibly resulting from inflammatory response, viral reservoirs
- Public health crisis





Victoria Higgins, Dorsa Sohaei, Eleftherios P. Diamandis & Ioannis Prassas (2021) COVID-19: from an acute to chronic disease? Potential long-term health consequences, Critical Reviews in Clinical Laboratory Sciences, 58:5,297-310, DOI: 10.1080/10408363.2020.1860895

NIH RECOVER-Pregnancy Cohort

- Remains unclear how pregnancy affects PASC
- NIH RECOVER Cohort designed to understand prevalence and pathophysiology of PASC
- Established RECOVER-Pregnancy Cohort to follow people with SARS-CoV-2 during pregnancy
  - May observe differential prevalence or risk factors

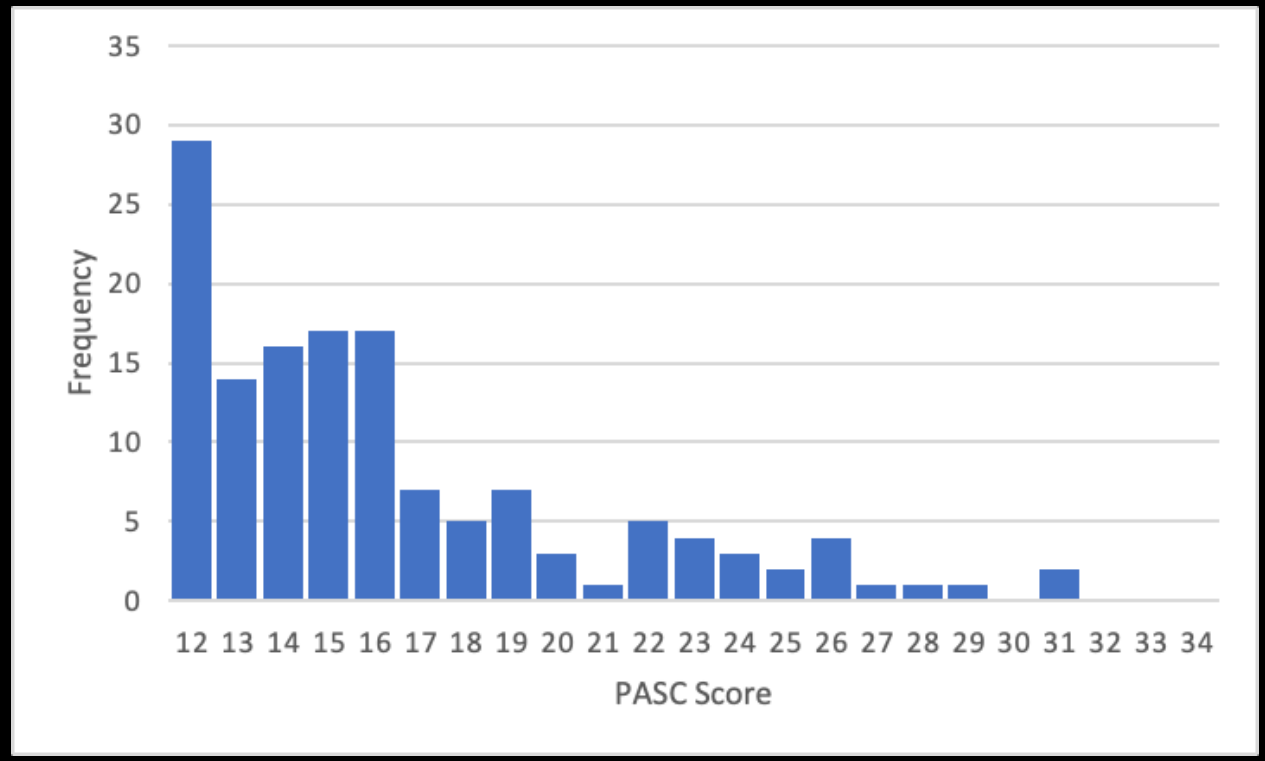
NIH RECOVER Initiative

RECOVER
Researching COVID to Enhance Recovery

- To estimate the prevalence of Post-Acute Sequelae of SARS-CoV-2 infection (PASC or long COVID) after infection with SARS-CoV-2 during pregnancy in the RECOVER- Pregnancy Cohort and characterize associated risk factors

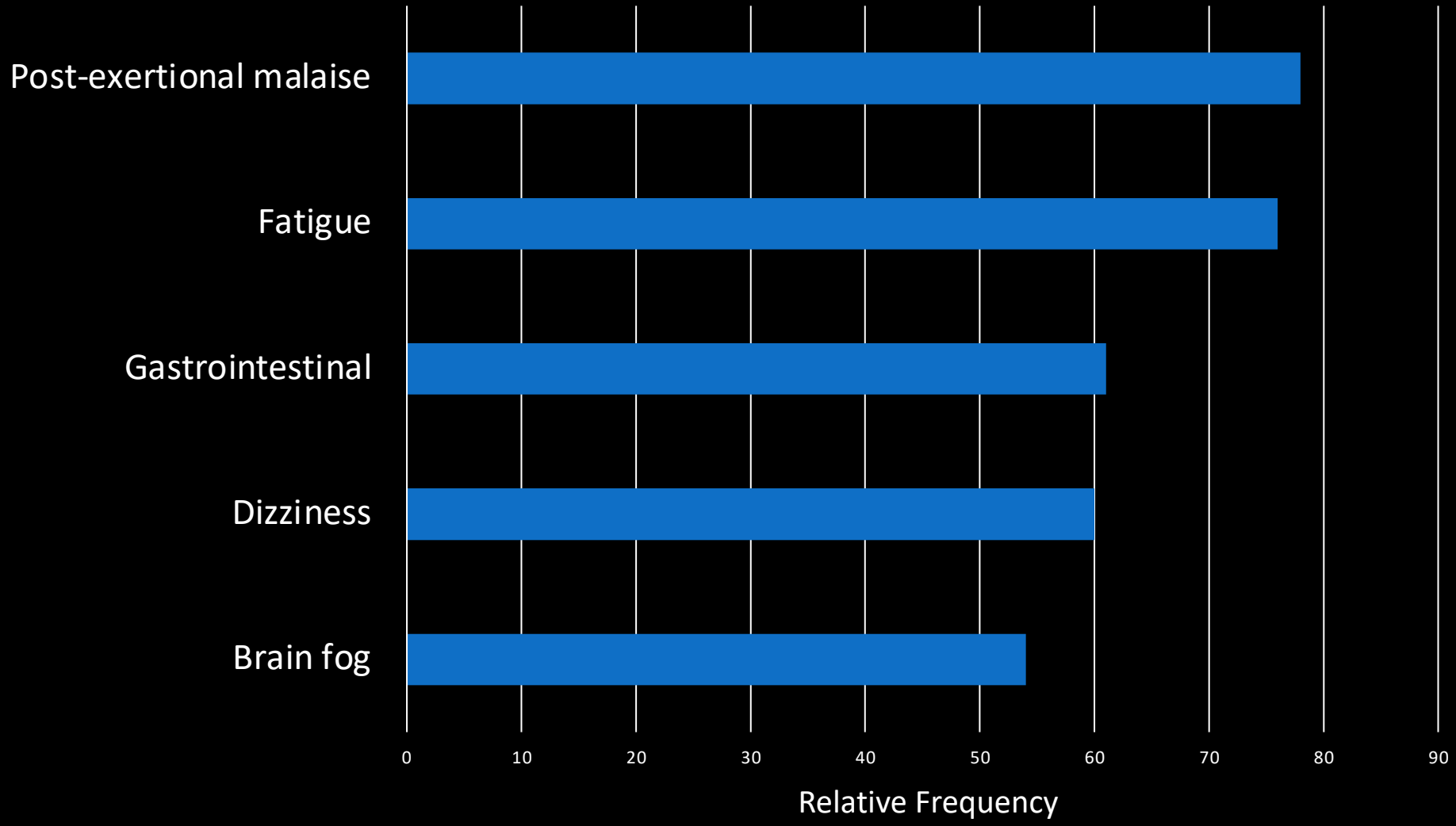
Pregnancy and PASC

- 9.3% (95% CI 7.9-10.9%) met criteria for PASC
- Median time from index date to PASC-defining study visit 10.3 months (IQR 6.1-21.5)



Thaweethai et al JAMA 2023

PASC Symptoms



Risk Factors for PASC

Characteristic	PASC Positive n=139	PASC Indeterminate n=1363	Odds Ratio	Adjusted Odds Ratio
Covering expenses difficult	57%	41%	1.93 (1.36, 2.75)	1.57 (1.05, 2.34)
Obesity	38%	22%	2.19 (1.51, 3.16)	1.65 (1.12, 2.43)
Depression or anxiety	59%	35%	2.61 (1.82, 3.74)	2.64 (1.79, 3.88)
Oxygen for acute infection	12%	6%	2.34 (1.34, 4.09)	1.86 (1.00, 3.44)

Multivariable logistic regression model also adjusted for age, era of infection, insurance status, discrimination index, vaccination, tobacco use, other medical comorbidities, number prior pregnancies, trimester of infection

RECOVER-Pregnancy Cohort

- 1 in 10 individuals with SARS-CoV-2 during pregnancy will develop PASC
- Symptoms include post-exertional malaise, fatigue and GI symptoms
- Socioeconomic and clinical characteristics associated with development of PASC
- Rates of PASC among pregnant populations may be lower than non-pregnant adults with estimates ranging from 10-25%

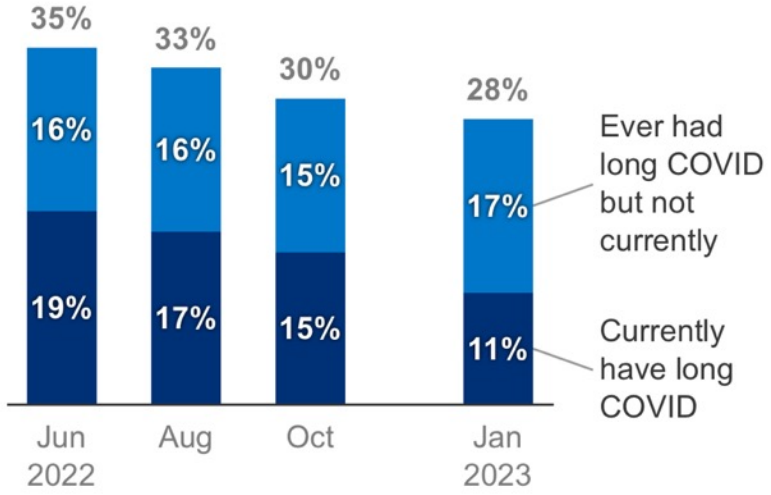
Symptom Duration

- Unclear duration and trajectory
- BMJ study (2021) most patients recovered at 1 year
- UK statistics- 30% of patients with PASC having symptoms for ≥ 2 years
- Follow RECOVER participants for 4 years

Figure 1

Among People Who Have Had COVID, the Percentage who Currently Have Long COVID is Declining

Percentage of people reporting that they currently have or ever had long COVID among those who have had COVID as of January 16, 2023



NOTE: The Pulse Survey, an experimental survey conducted by the Census Bureau and National Center for Health Statistics, asked respondents whether they had any symptoms of COVID that had lasted longer than 3 months. This figure reports the findings as of 6/13/2022, 8/8/2022, 10/17/2022, and 1/16/2023.

SOURCE: National Center for Health Statistics. Post-COVID Conditions. Data accessed Jan 26, 2023. Available from: https://data.cdc.gov/d/gsea-w83j. • PNG

KFF

LONG COVID CONTINUES TO IMPACT UTAHN'S HEALTH AND PRODUCTIVITY

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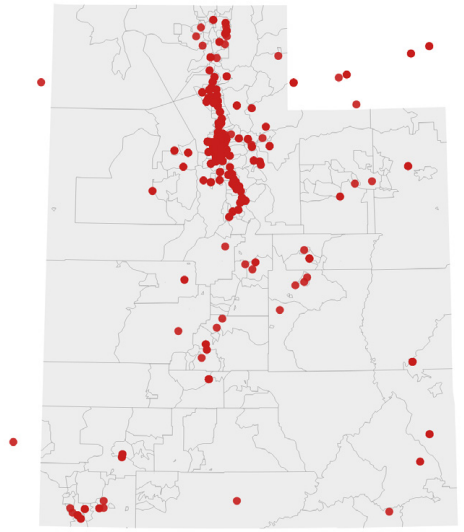
Many people who had COVID-19 continue to experience ongoing health problems even after they recovered from the initial infection. These problems can include **respiratory issues, cardiovascular problems, and neurological issues**, among others. **Long-term COVID clinics can provide specialized care and support** to these individuals to help them manage their ongoing health issues.

>1800
PATIENTS SINCE
JULY 2021

U of U Health's Comprehensive COVID Clinic Reach



Map data: © Esri, TomTom North America, Inc., United States Postal Service

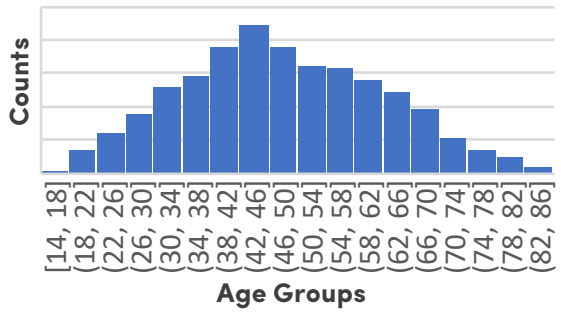
Long COVID affects 1 in 5 adults[1]

- Since July 2021, U of U Health's Comprehensive COVID Clinic cared for **>1,800 patients**
- **67% of patients were female,** 32% were male
- **49% of patients are from rural and underserved areas** with low health equity
- Majority of patients are **between 26 and 62**

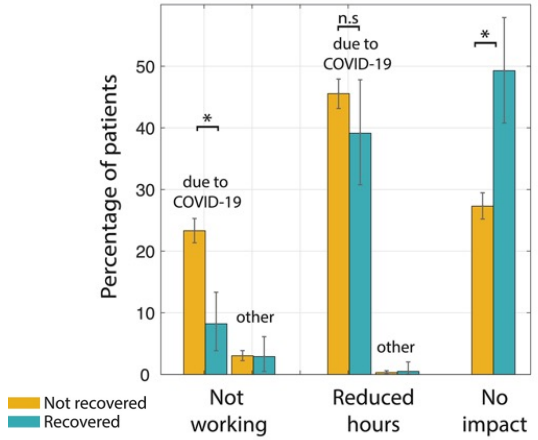
Patients with long COVID:

- Are **less able to work** and **may lose health insurance**
  - **40%** working reduced hours
  - **20%** not able to work
- **Struggle to care for children** and elderly family members

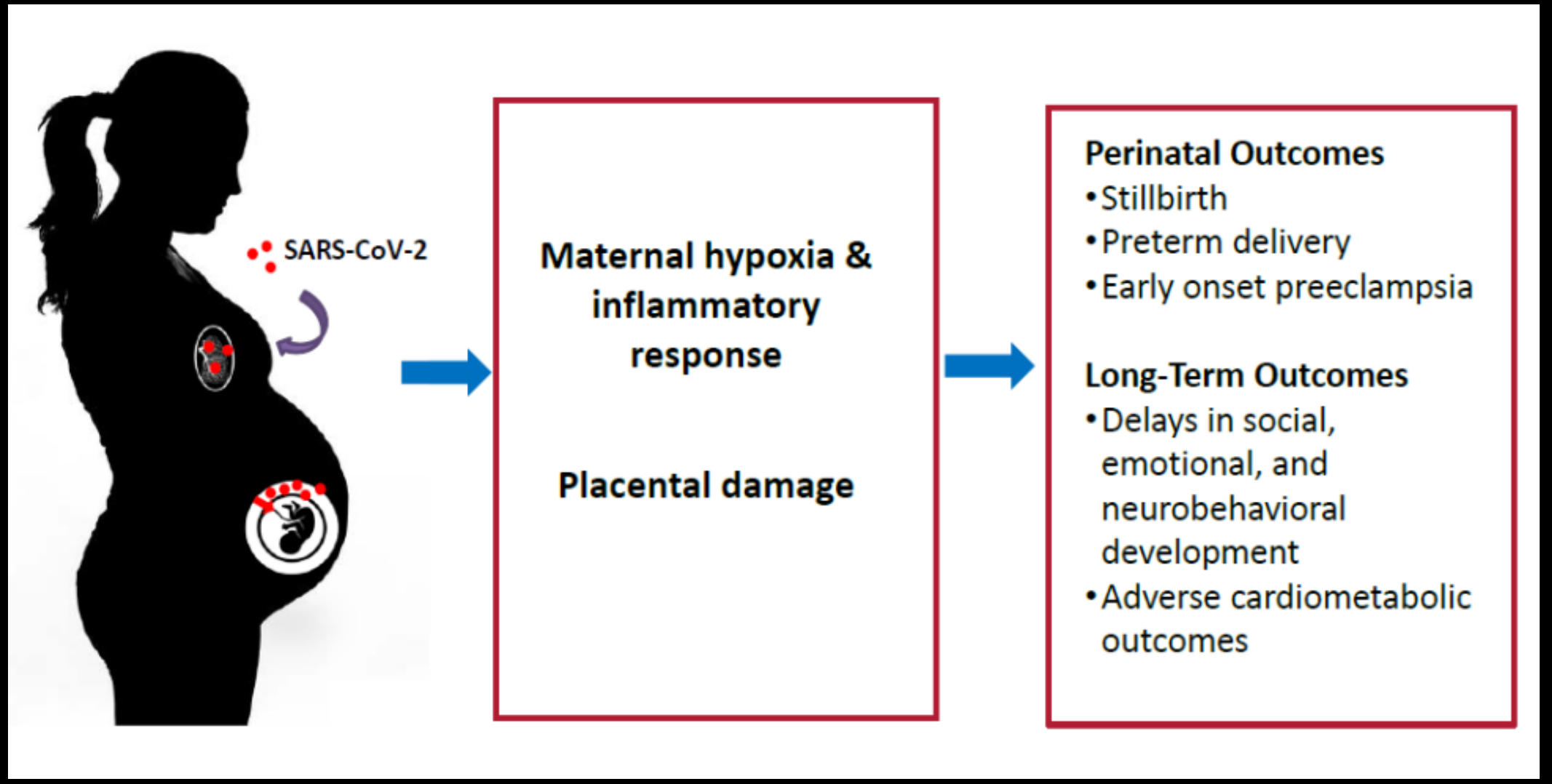
Distribution of ages



d. Long COVID impact on work



Are offspring affected?



Offspring Neurodevelopment

- Prospective cohort N=255
  - 114 exposed to SARS-Cov-2 and 141 unexposed
  - 62 historical cohort pre-pandemic
- Performed ASQ-3 at 6 months
- Birth during pandemic but not in utero exposure associated with difference in ND at 6 months

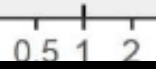
Shuffrey et al JAMA Peds 2022

Offspring Neurodevelopment

- Retrospective cohort N=7772 live births
  - 222 births to SARS-CoV-2 positive mothers
- Queried diagnosis codes and labs for 8 hospitals in the northeast (March- Dec 2020)

Edlow et al JAMA Open 2022

Variable		N	Odds ratio	p
Pregnancy COVID status	COVID negative	7550	Reference	
	COVID positive	222	1.86 (1.03, 3.36)	0.04
Maternal age (years)		7772	1.03 (1.00, 1.06)	0.05
Maternal race	White	5363	Reference	
	Asian	772	1.38 (0.92, 2.07)	0.11
	Black or African American	656	0.51 (0.27, 0.96)	0.04
	Other	733	1.40 (0.82, 2.40)	0.21
	Unknown	248	1.22 (0.61, 2.48)	0.57
Maternal ethnicity	Not Hispanic	6378	Reference	
	Hispanic	1134	1.25 (0.76, 2.06)	0.39
	Unavailable	260	1.51 (0.78, 2.92)	0.22
Maternal public insurance	No	6341	Reference	
	Yes	1431	1.01 (0.68, 1.50)	0.97
Offspring sex	Female	3819	Reference	
	Male	3953	1.39 (1.07, 1.81)	0.01
Pre-term birth	No	7086	Reference	
	Yes	686	3.39 (2.49, 4.62)	<0.001



Remaining Offspring Questions

- Is it exposure to the pandemic and societal changes of the pandemic or the exposure itself?
- Do the findings persist when compared with controls who are unexposed evaluated in the same way?
- Does initial COVID-19 severity matter?

Summary

- COVID-19 had a huge, ongoing societal impact
- Continue to observe excess deaths
- Perinatal morbidity and mortality remain higher with Omicron
- Boosters effective against severe disease
- Vaccines offer neonatal protection
- PASC public health crisis warrants ongoing attention

Research in Pregnant Individuals

"Protection by exclusion of pregnant women from drug development and clinical therapeutic trials, even during epidemics and pandemics, is not unprecedented. Moreover, it is both misguided and not justifiable and may have excluded them from potentially beneficial interventions…pregnant women should be given the opportunity to be included in clinical trials for COVID-19 based on the concepts of justice, equity, autonomy and informed consent."

Costantine et al Obstet Gynecol 2020

Thank you!

- Jeanette Brown, MD
  Medical Director U of Utah Long COVID Clinic

- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development for funding the MFMU GRAVID study

- National Heart, Lung and Blood Institute for funding the RECOVER study