The Strange and Varied Presentations of COVID-19 in the NICU

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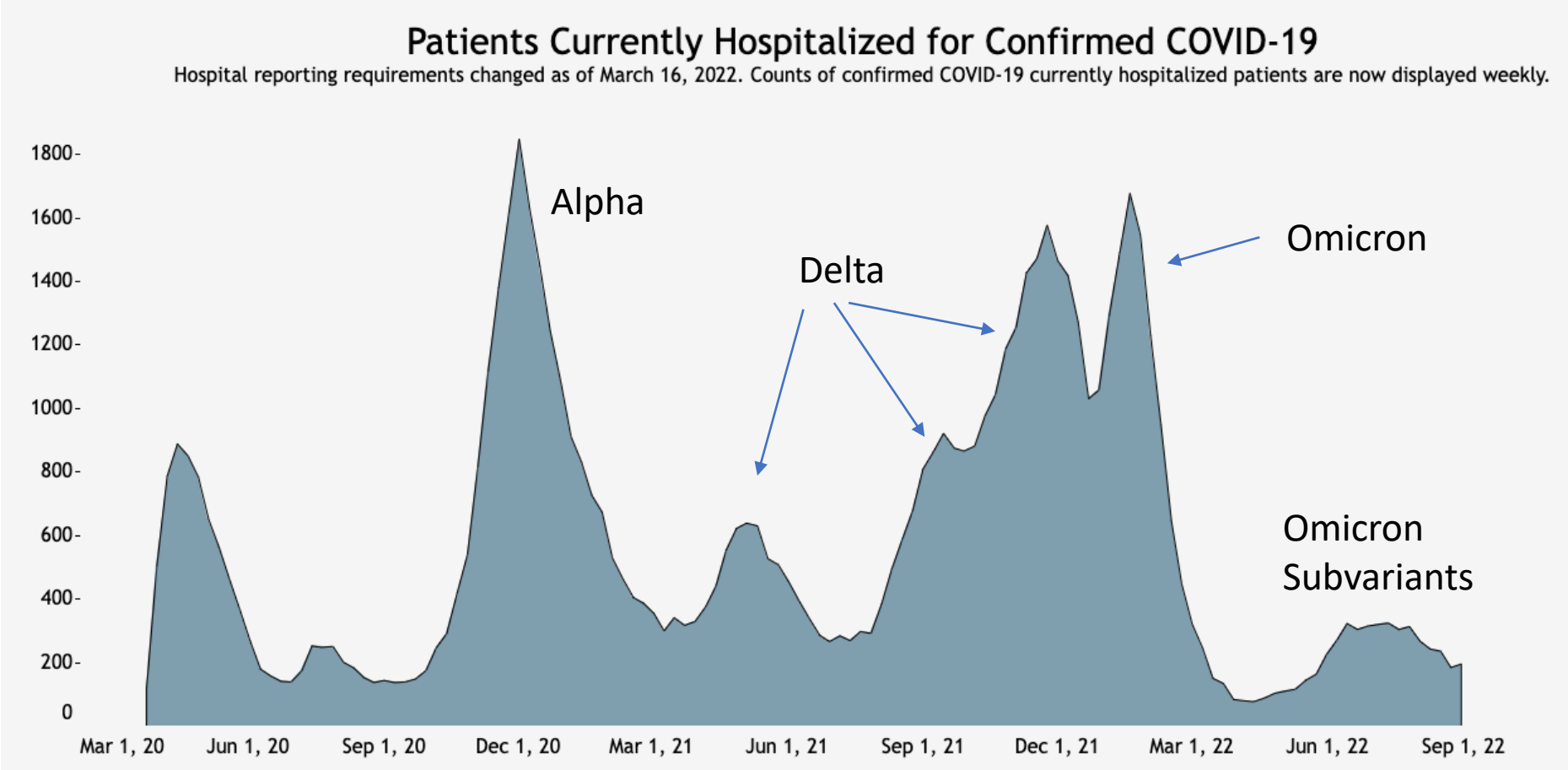
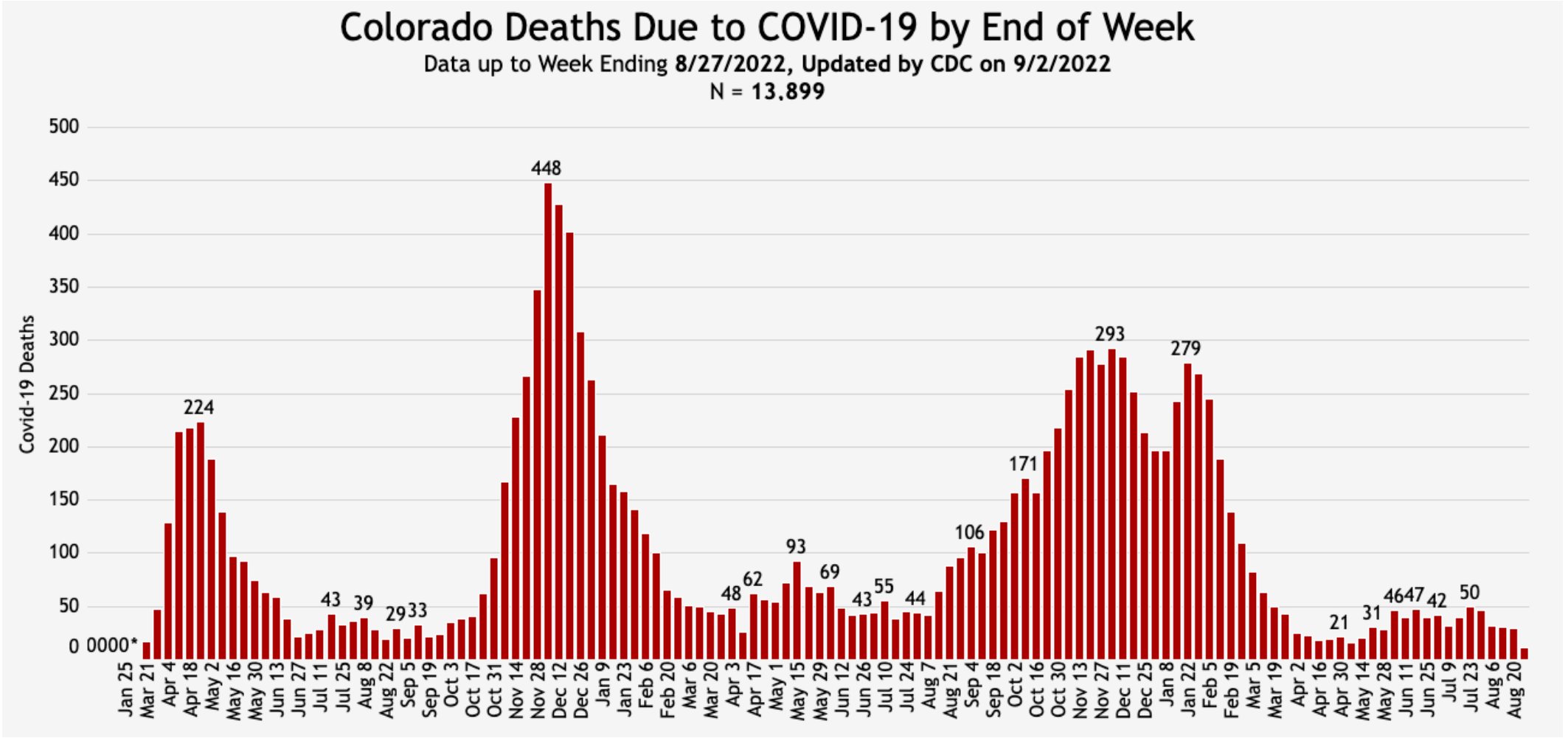
COVID-19 Basics

- Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- First case was identified in Wuhan, China in December 2019
- Infection is mediated via binding of the viral spike surface glycoprotein to angiotensin-converting enzyme 2 (ACE2) receptors on cells.
- First cases in Colorado were identified in March of 2020
- By now there have been 1.5 million COVID cases and almost 13,000 deaths in Colorado

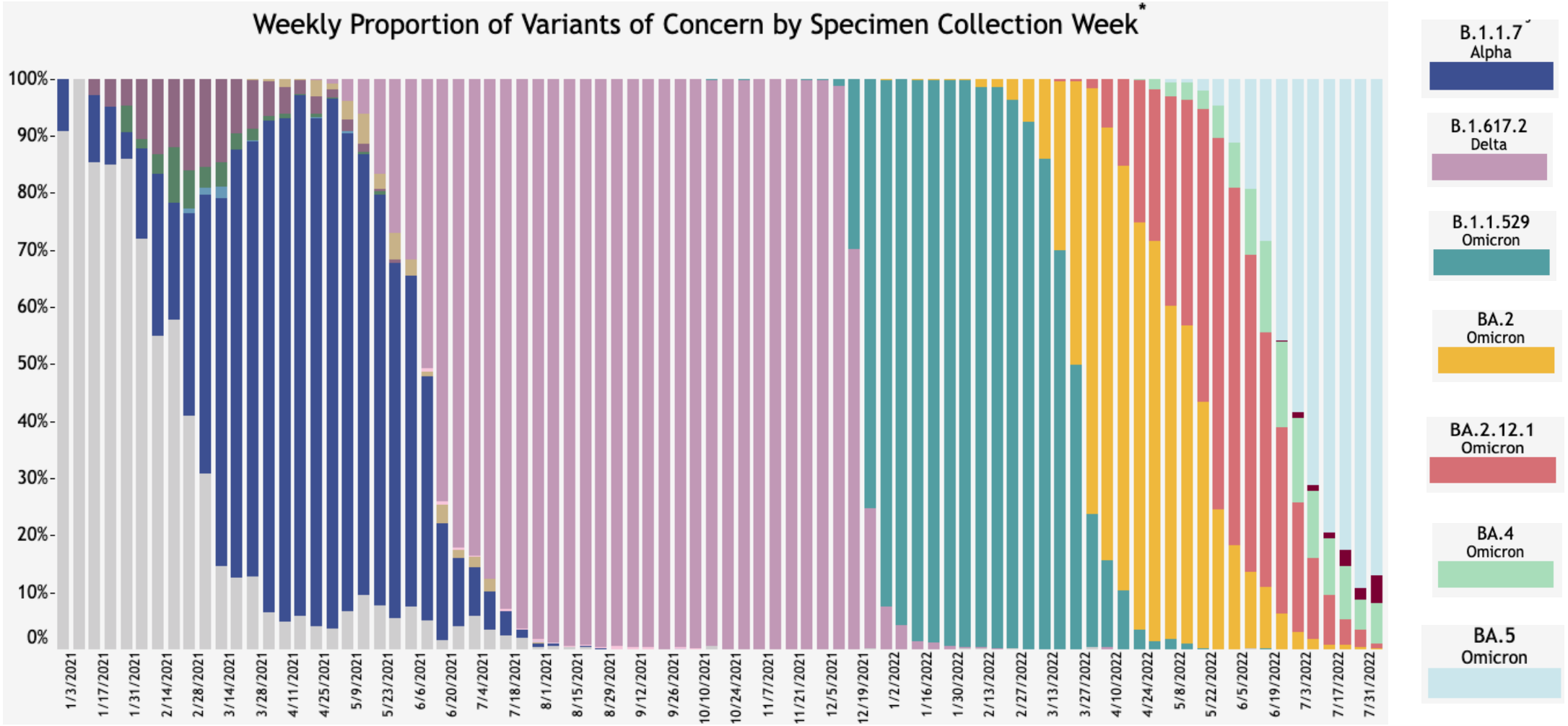
COVID Hospitalizations in Colorado



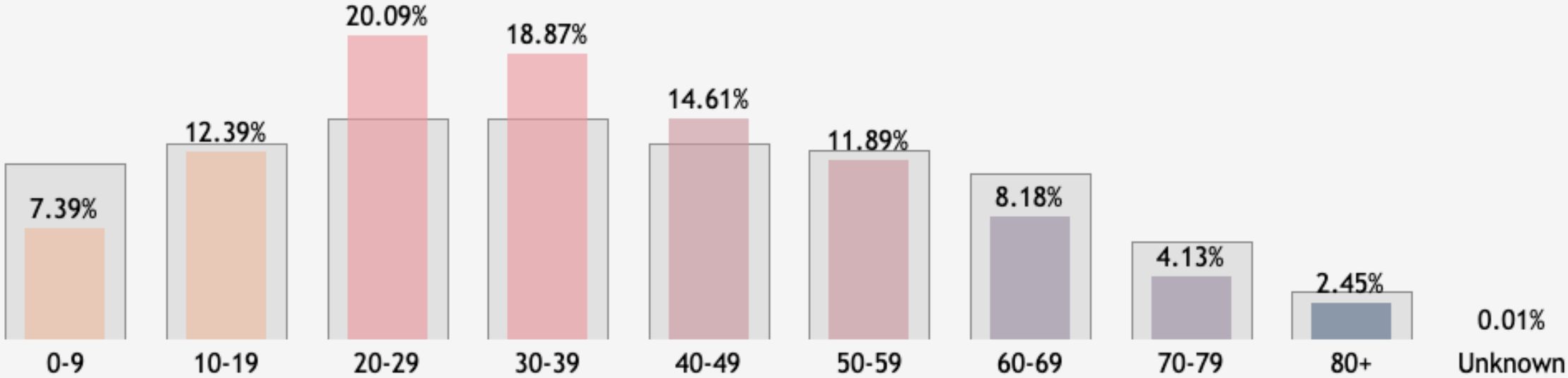
Colorado COVID Deaths



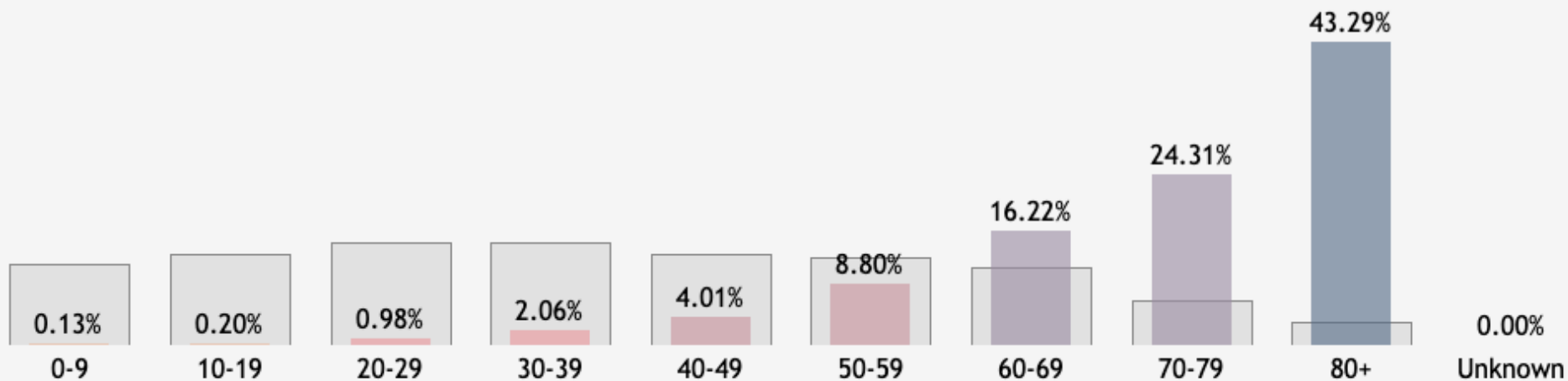
SARS-CoV-2 Variants by Week in Colorado



Percent of Cases by Age Group Compared to Colorado Population



Percent of Deaths Among COVID-19 Cases by Age Group Compared to Colorado Population*



Case #1: Maternal COVID

- Patient MR was a 25 2/7 weeks, 810g, female infant born via emergency C/S to a 36 y/o G4P2 COVID+ mother.
- Mother was admitted 4 days prior to delivery with COVID-19 pneumonia. Progressive hypoxia→intubation→ delivery.
- Infant had relatively uncomplicated course:
  - COVID negative x 2 tests
  - No IVH, no ROP
  - Discharged home on 1/16 LPM O2
- Mother with difficult course:
  - Pneumothoraces, tracheostomy, cardiomyopathy
  - Discharged to long-term care facility

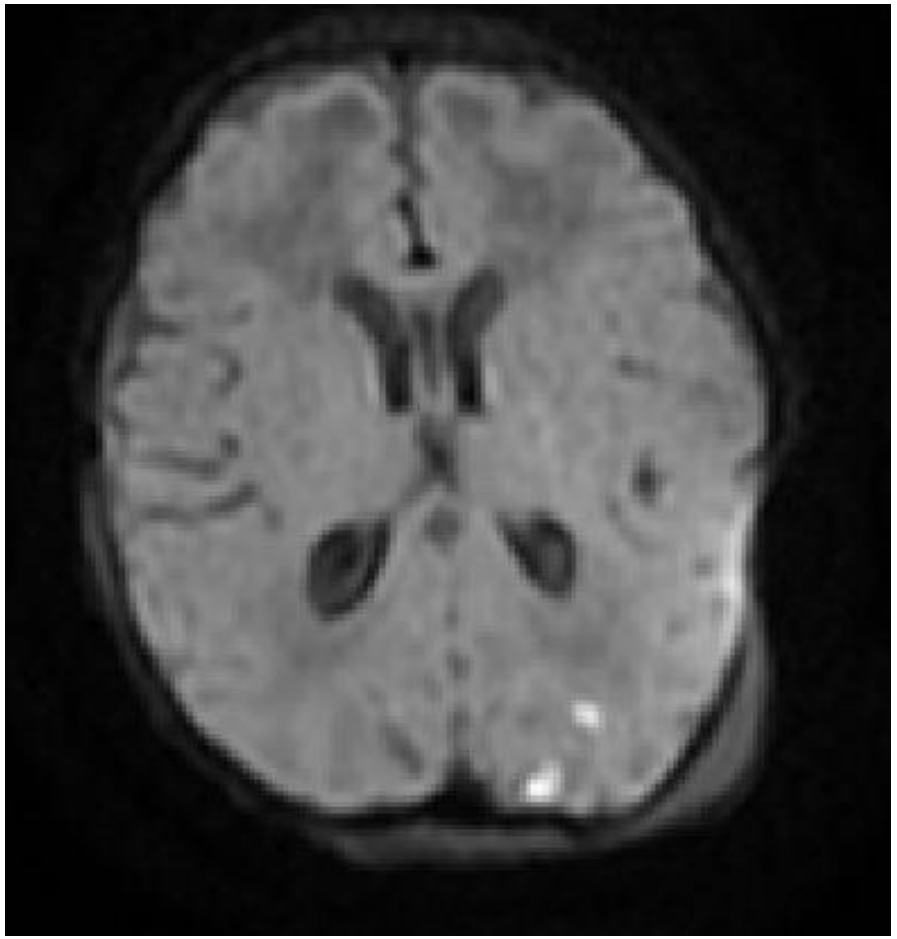
COVID and Pregnancy

- Pregnancy is a risk factor for severe disease
  - For ICU admission OR 2.13 (95% CI 1.53-2.95)
  - For intubation OR 2.59 (95% CI 2.28-2.94)
- COVID has been associated with preterm birth and preeclampsia, and associations are stronger with more severe COVID
  - Preterm birth OR 2.17 (95%CI 1.96-2.42; $p<0.001$)
  - Preeclampsia OR 1.55 (95% CI 1.29-1.85; $p<0.001$)

Case #2: COVID and the Placenta

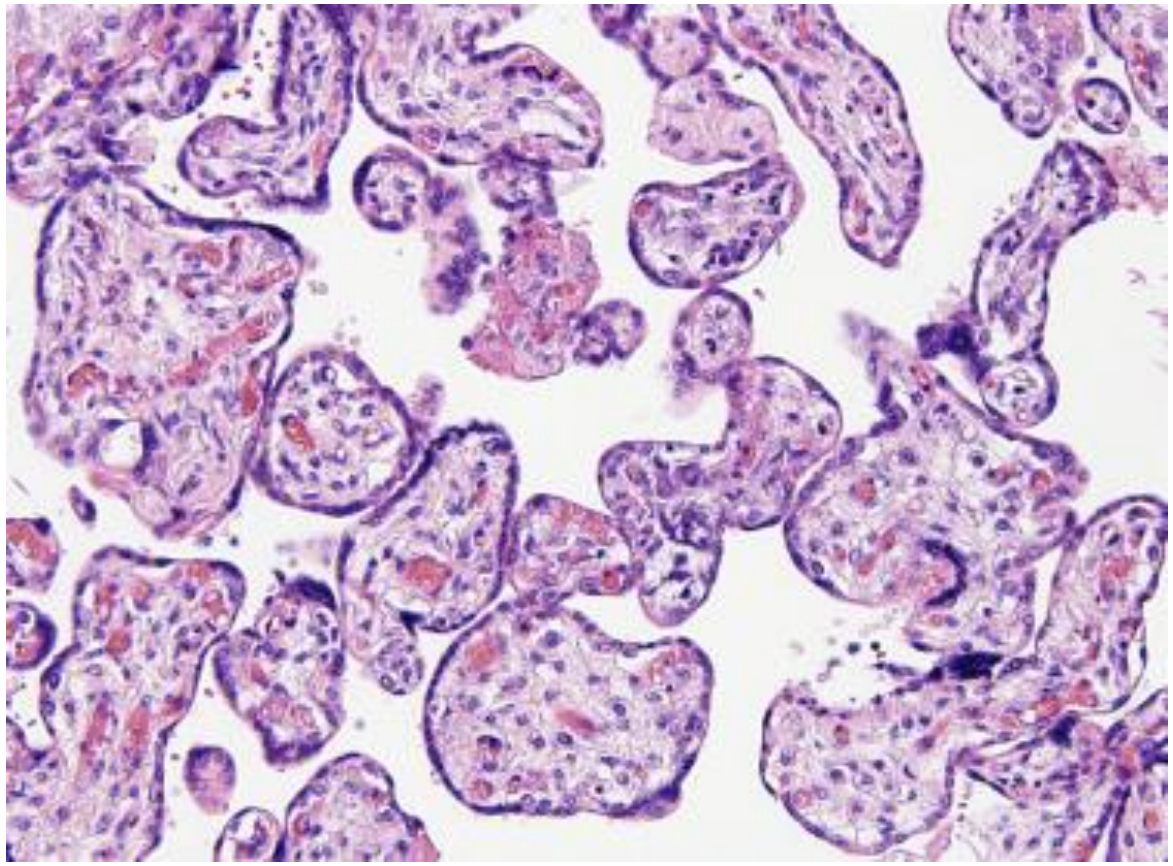
- Patient BB was a 36 3/7 weeks GA, 2910g, male infant born via urgent C/S.
- Pregnancy was unremarkable until 11 days prior to delivery when the mother developed fever, cough, and lost her sense of taste. Covid testing was positive.
- Apgars were 1, 4, and 6. Cord gases were 7.03/-19 and 6.94/-20.
- Infant was transferred to RMHC for therapeutic hypothermia.
- Infant COVID testing was negative x 2 tests
- Initial hospital course was complicated by a significant coagulopathy.
- He did not have seizures and completed 72 hours of cooling.

Case #2: COVID and the Placenta



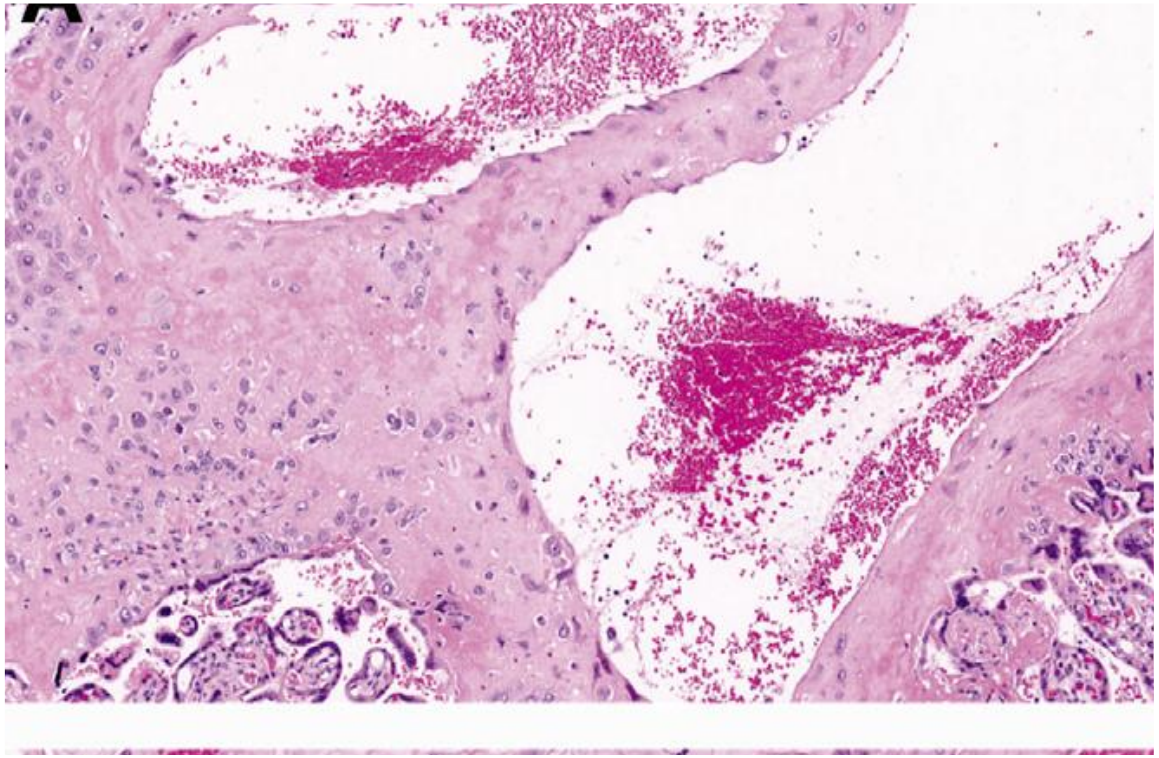
- An MRI after rewarming was essentially normal except for 4 small infarcts
- Extubated on DOL#5 and was discharged on DOL#18
- Placental pathology showed monocytic/histiocytic intervillositis with perivillous fibrin deposition.

Normal Placental Histology



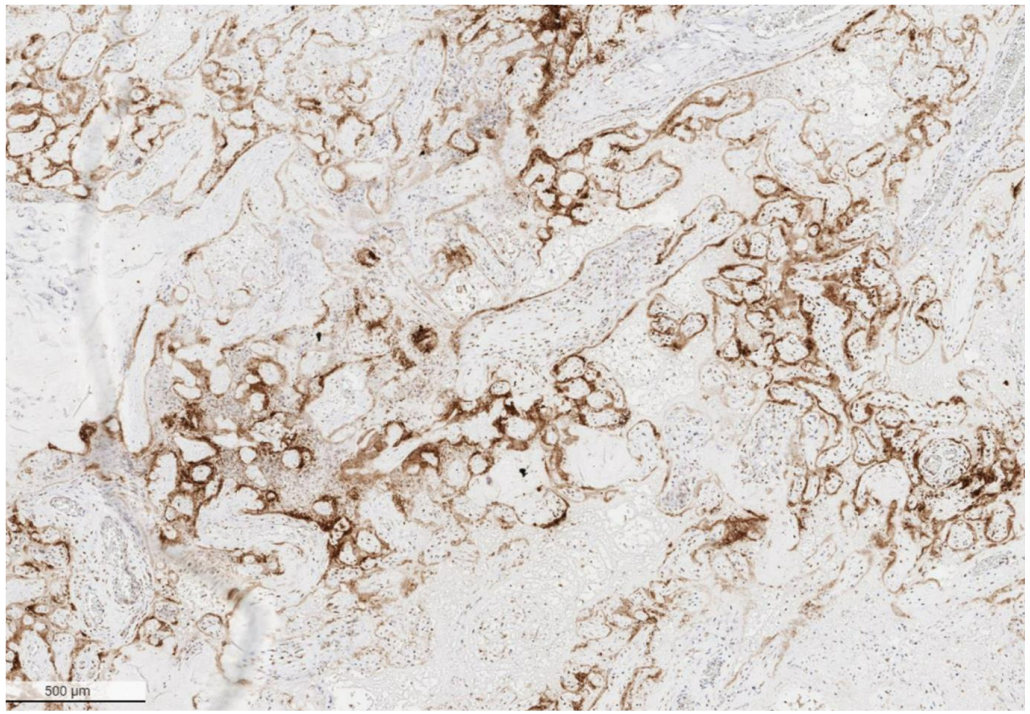
- Placental villi have thin-walled capillaries carrying fetal blood.
- Intervillous space is filled with maternal blood, but otherwise should be clear.
- Minimal inflammation.

Normal Placental Histology

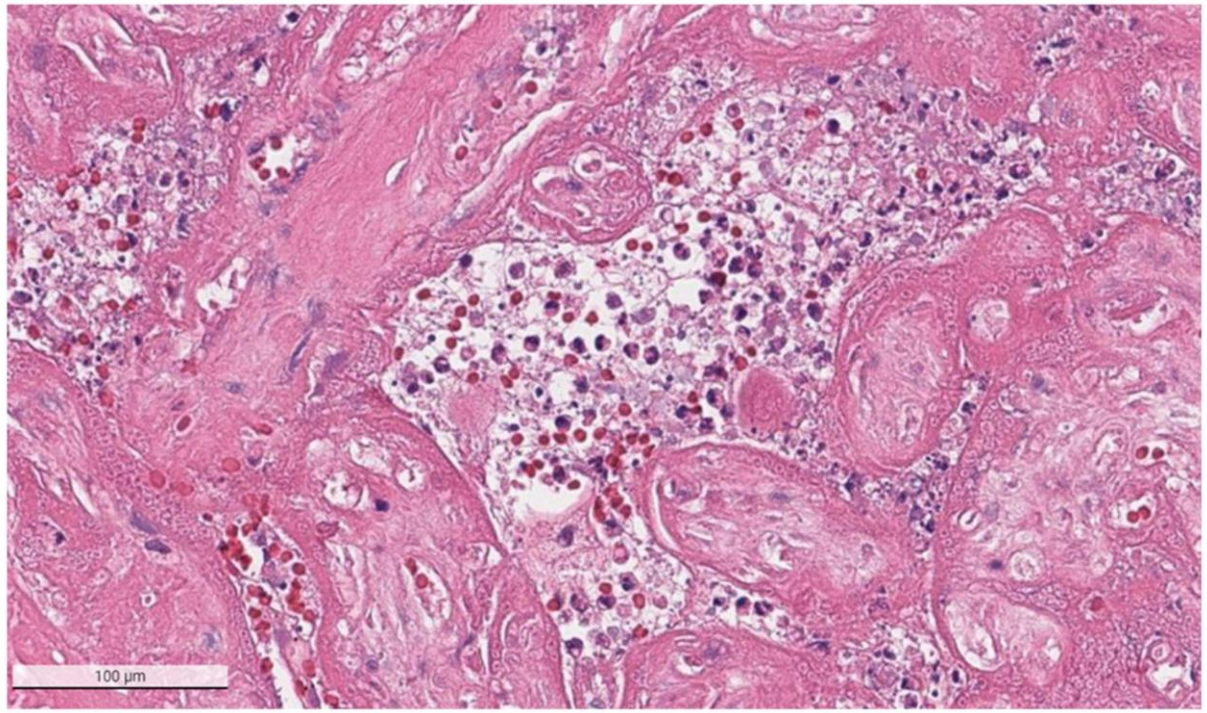


- Maternal arterioles in membranes and basal plate are thin walled with minimal muscularization.
- In maternal vascular malperfusion there are abnormalities in the maternal arteries supplying the placenta.
- For example, in preeclampsia maternal arterioles are muscularized.

COVID and the Placenta

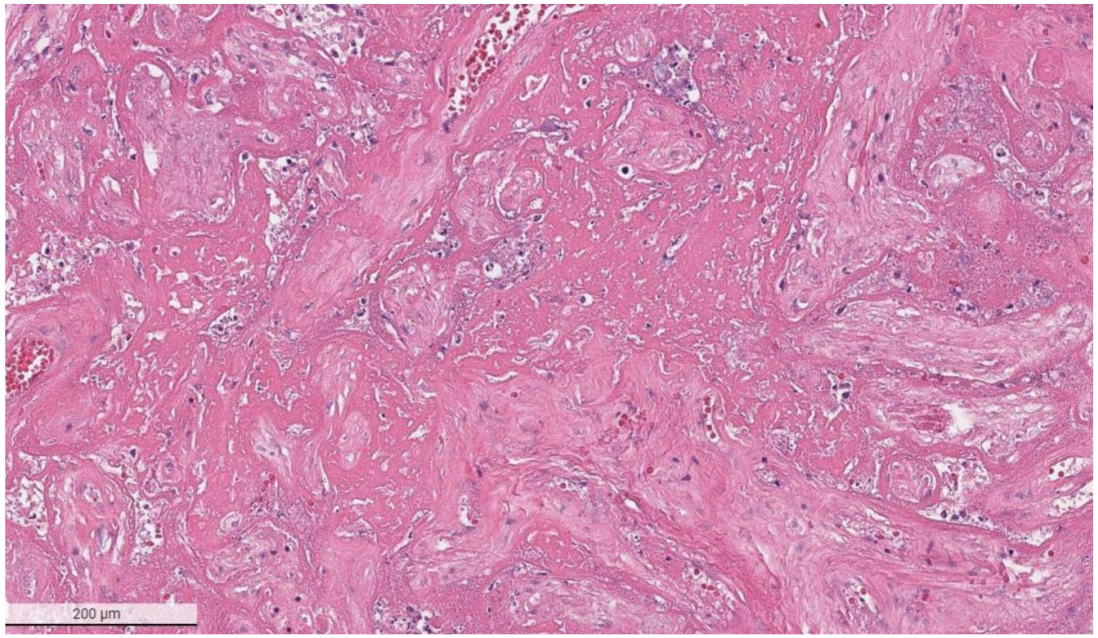


SARS-CoV-2 Spike Protein Staining in Placenta



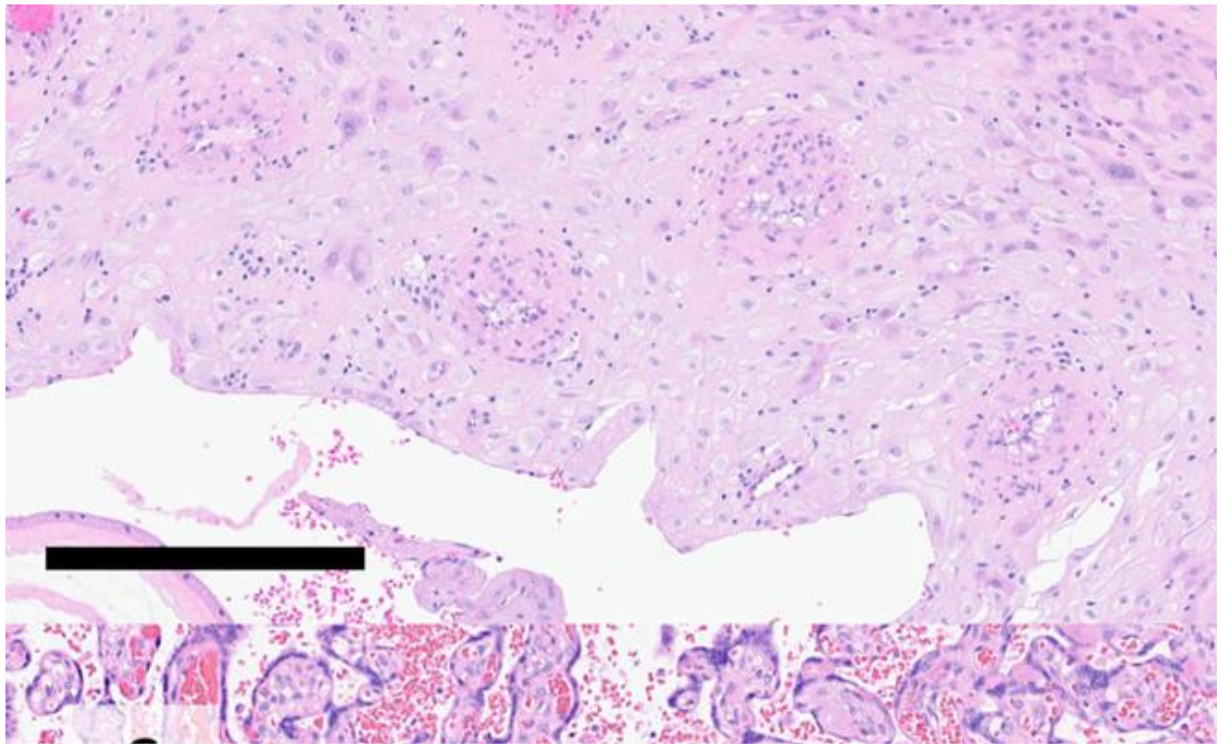
Chronic histiocytic intervillositis

COVID and the Placenta



- Inflammation in placenta can lead to perivillous fibrin deposition.
- Ischemic necrosis of the chorionic villi.
- Decreased oxygen transport to infant with fetal loss or hypoxic injury.

COVID and the Placenta



- Most common lesion associated with COVID is maternal vascular malperfusion.
- This can be seen even in mild cases of maternal COVID.

Perinatal COVID

- COVID virus transmitted from mother to infant transplacentally (rare) or in the perinatal period in 1.8-3.6% of cases
- Difficult to tell difference but cases where infant is positive in first 48 hours, especially if IgM positive are considered vertical transmission
- Most common presentation in the perinatal period is respiratory distress.

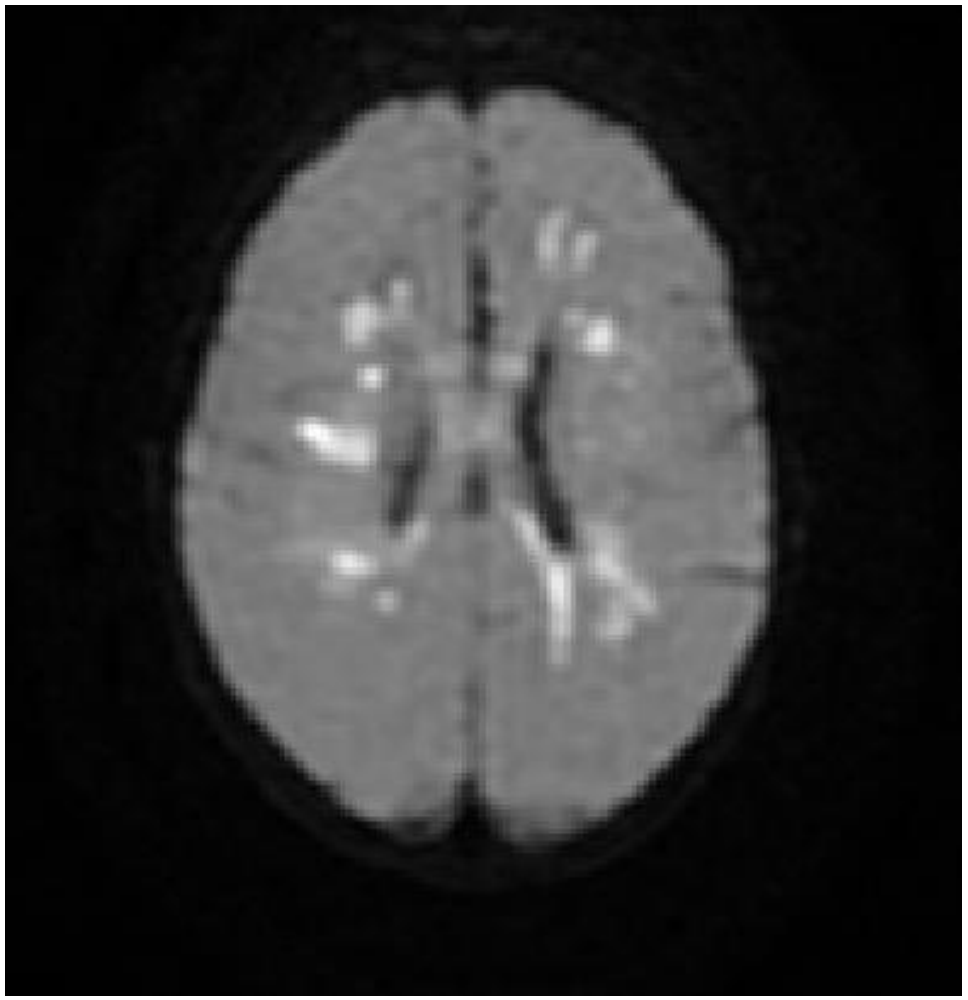
Case #3: CNS Manifestations of COVID

- Patient MM was a 38 week, 2828g male infant born via vaginal delivery to a 24 y/o G4P1 mother with no prenatal care
- There was no maternal fever, maternal GBS was negative, and there was no history of HSV.
- The mother had a history of THC, fentanyl, and methamphetamine use.
- Mother's COVID test was negative on admission
- Infant was monitored for neonatal abstinence. He did not have irritability or other signs of withdrawal, but began seizing on DOL#5

Case #3 (cont'd): CNS Manifestations of COVID

- Electrolytes were normal
- Ammonia was normal
- An LP was performed which showed 2 WBC and 9 RBC per field with 88% mono/macro.
- The infant was sent for an MRI

Case #3 (cont'd): CNS Manifestations of COVID



- Brain MRI with spectroscopy showed patchy diffusion changes in the optic radiations, bilateral thalami, and corpus collosum consistent with a viral encephalitis.
- CSF from the LP was sent for meningitis/encephalitis PCR testing and was negative for HSV and enteroviruses.
- A respiratory viral panel was negative
- COVID testing was sent which was positive.
- A repeat COVID test on the mother was also positive.
- Diagnosis= COVID encephalitis

COVID and the CNS

- Neurologic manifestations of COVID including stroke and encephalopathy are well documented in adults.
- In children, ~17% of patients have mild neurologic symptoms
- Only ~1% have severe complications such as encephalopathy or seizures.
- Neurologic complication rates are higher for patients hospitalized with MIS-C
- Encephalitis has been reported in infants

WHO Case-Definition of Multisystem Inflammatory Syndrome in Children (MIS-C)

- Age 0-19 y/o
- Fever >= 38.0 C for >= 72hours

AND 2 of the following:

- Rash or conjunctivitis
- Hypotension or shock
- Myocardial dysfunction, pericarditis, valvulitis, coronary abnormalities (including echo findings or elevated troponin/NT-proBNP)
- Lab evidence of coagulopathy
- GI symptoms

AND

- Elevated markers of inflammation such as ESR, CRP, or procalcitonin

AND

- No alternative plausible diagnosis
- Positive for current or recent SARS-CoV-2 infection

Characteristics of MIS-C

- Fever and GI symptoms are the most common presenting symptoms
- Cardiac symptoms can include ventricular dysfunction (~50%), pericardial effusions (~30%), coronary artery aneurysms (~10%).
- Pathogenesis involves “cytokine storm” with elevated IL-1, IL-6, IL-8, IL-17 and IFN-g
- Similar to Kawasaki disease but patients tend to be older and sicker
- Treatment includes IVIG, steroids, IL-1 antagonist (Anakinra), TNF-a blockade

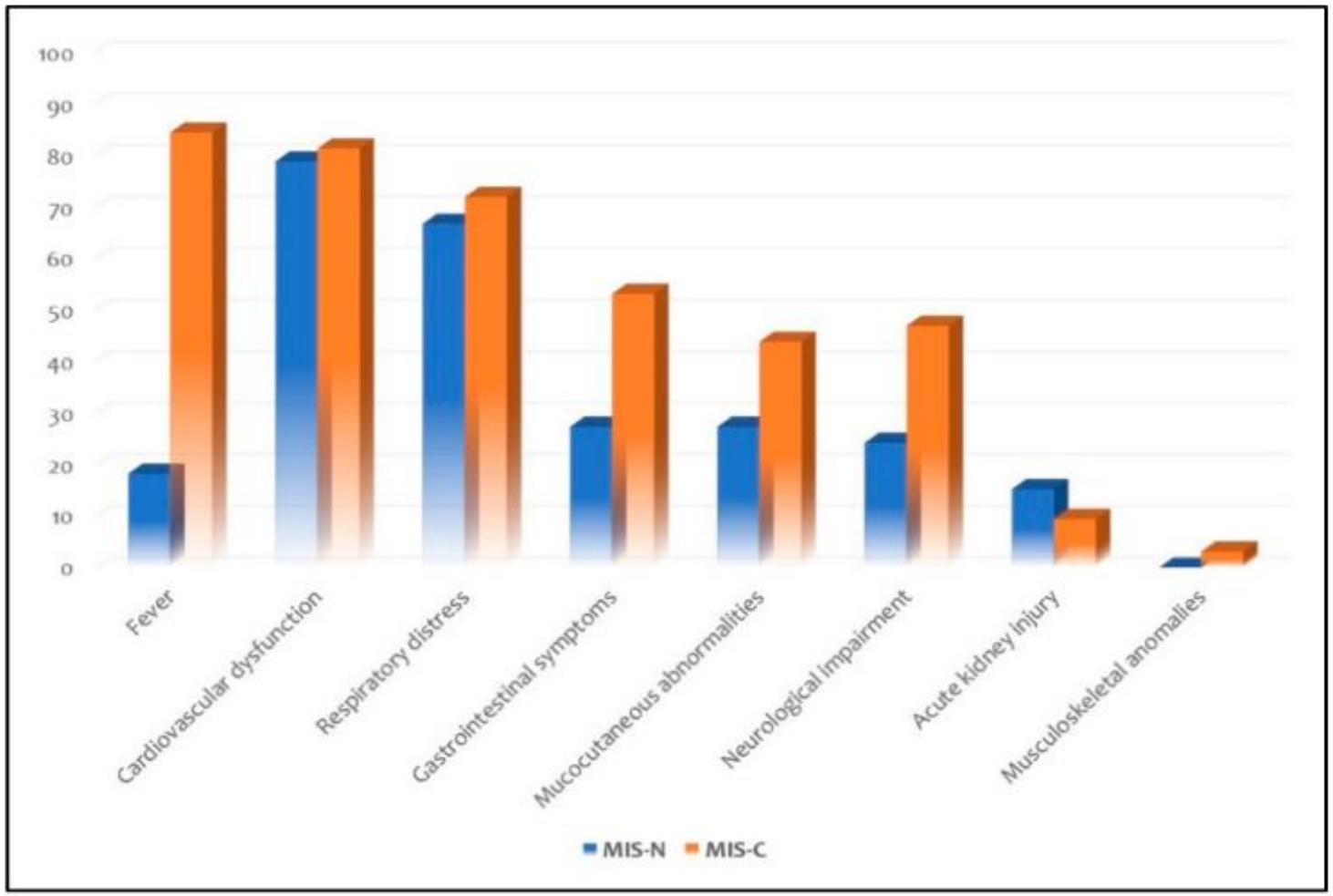
Case #4: COVID and MIS-C

- Patient KG was a 30 week GA, 1300g, female infant born via C/S delivery to a COVID+ mother. Mother also had a history of methamphetamine and cocaine use, but urine was negative for drugs.
- Infant was limp in DR with Apgars of 2, 6, and 7. The first infant gas was 7.13/-15. Infant was intubated in the delivery room, transported to RMHC, and placed on the ventilator.
- Initial labs showed Hct = 36, plts = 52, INR = 3.1
- COVID PCR testing was negative.

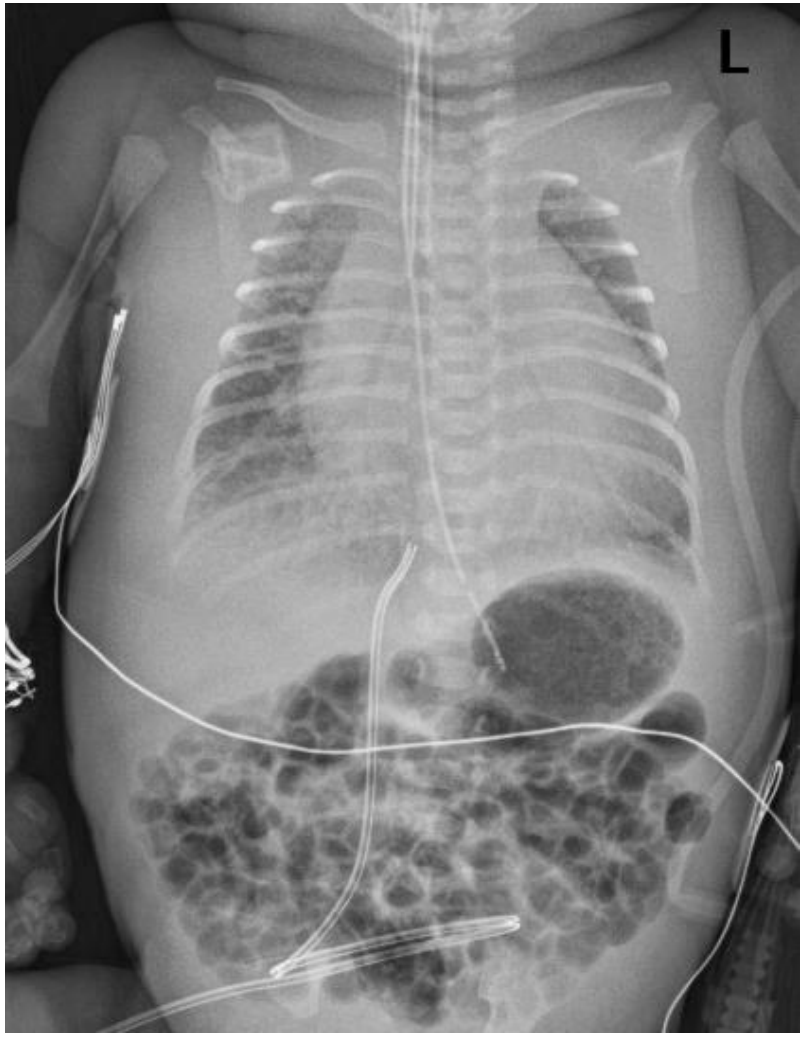
Case #4: COVID and MIS-C

- Moderate RDS on ventilator. Initial echocardiogram showed elevated pulmonary pressures with bidirectional shunt at the PDA. Otherwise initial echo was relatively normal.
- By 1 week of age, the infant began to show worsening respiratory distress with a large heart on Xray.
- A repeat echo showed diffusely dilated coronary arteries, dilated LA and LV with depressed function, and a small pericardial effusion. The BNP was elevated to >5000.
- A neonatal variation of COVID-associated MIS-C was suspected

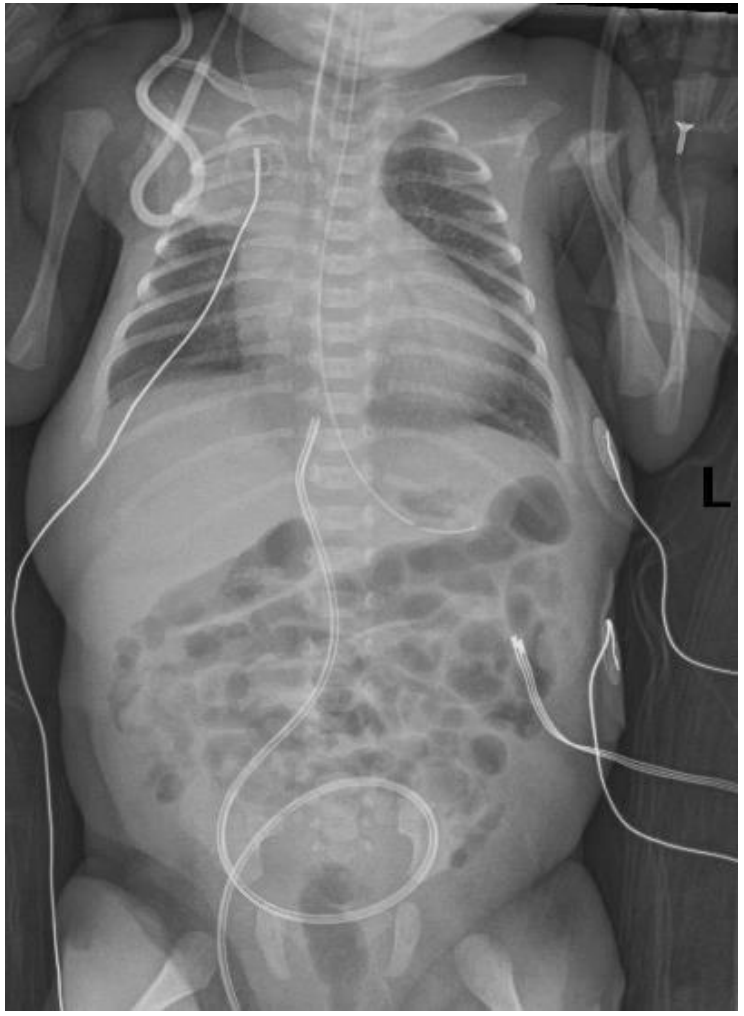
Multisystem Inflammatory Syndrome Presentation in Neonates vs. Children



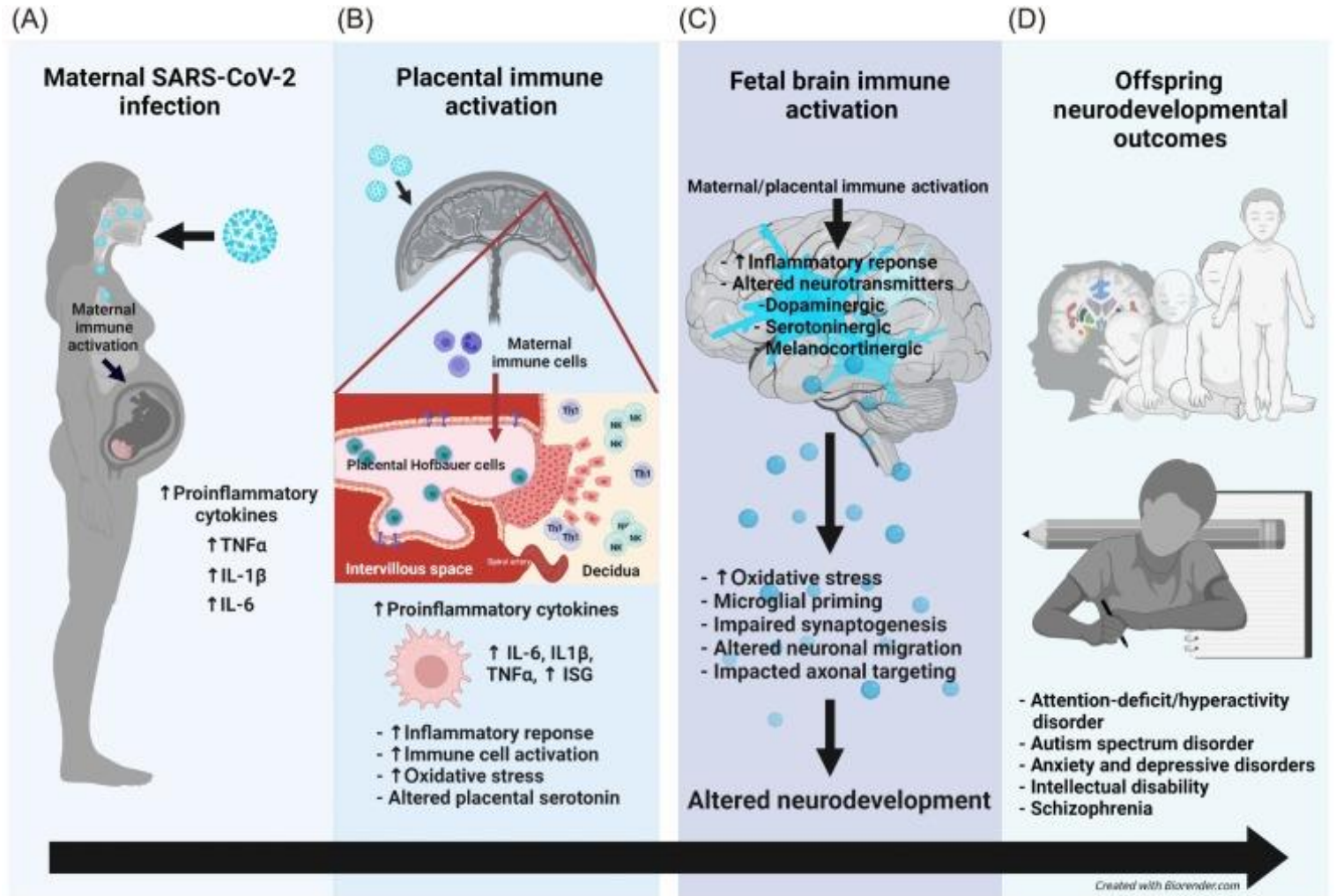
Case #4: COVID and MIS-C



IVIG



Is maternal COVID a risk factor for neurodevelopmental impairment?

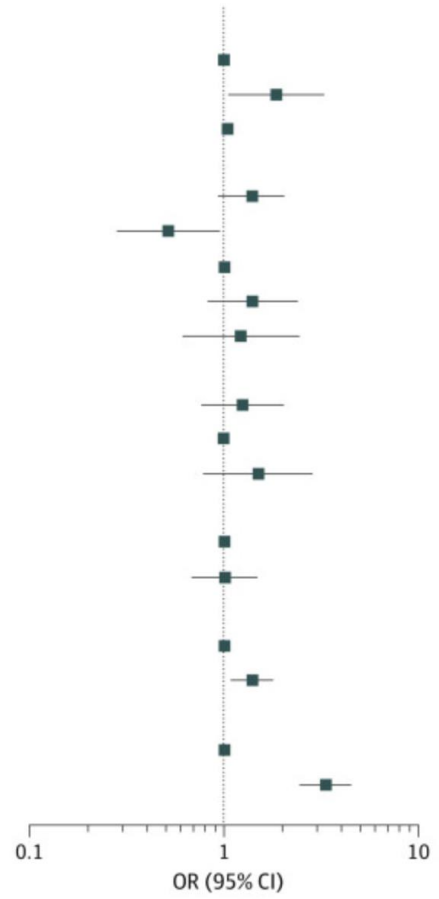


Trends in Molecular Medicine

Neurodevelopmental Impairment and COVID

- Edlow, et al used a health system data base to study rates of NDI ICD-10 code usage during the pandemic
- 7772 total infants, 222 COVID+ mothers
- Based on ICD-10 code usage, infants of COVID+ mothers were twice as likely to be seen later for concerns of NDI
- Higher NDI risk even after adjustment for prematurity

Variable	Patients, No.	OR (95% CI)	*P* value
Pregnancy SARS-CoV-2 status			
SARS-CoV-2 negative	7550	1 [Reference]	
SARS-CoV-2 positive	222	1.86 (1.03-3.36)	.04
Maternal age, y	7772	1.03 (1.00-1.06)	.05
Maternal race			
Asian	772	1.38 (0.92-2.07)	.11
Black or African American	656	0.51 (0.27-0.96)	.04
White	5363	1 [Reference]	
Other	733	1.40 (0.82-2.40)	.21
Unknown	248	1.22 (0.61-2.48)	.57
Maternal ethnicity			
Hispanic	1134	1.25 (0.76-2.06)	
Non-Hispanic	6378	1 [Reference]	.39
Unavailable	260	1.51 (0.78-2.92)	.22
Maternal public insurance			
No	6341	1 [Reference]	
Yes	1431	1.01 (0.68-1.50)	.97
Offspring sex			
Female	3819	1 [Reference]	
Male	3953	1.39 (1.07-1.81)	.01
Preterm birth			
No	7086	1 [Reference]	
Yes	686	3.39 (2.49-4.62)	<.001

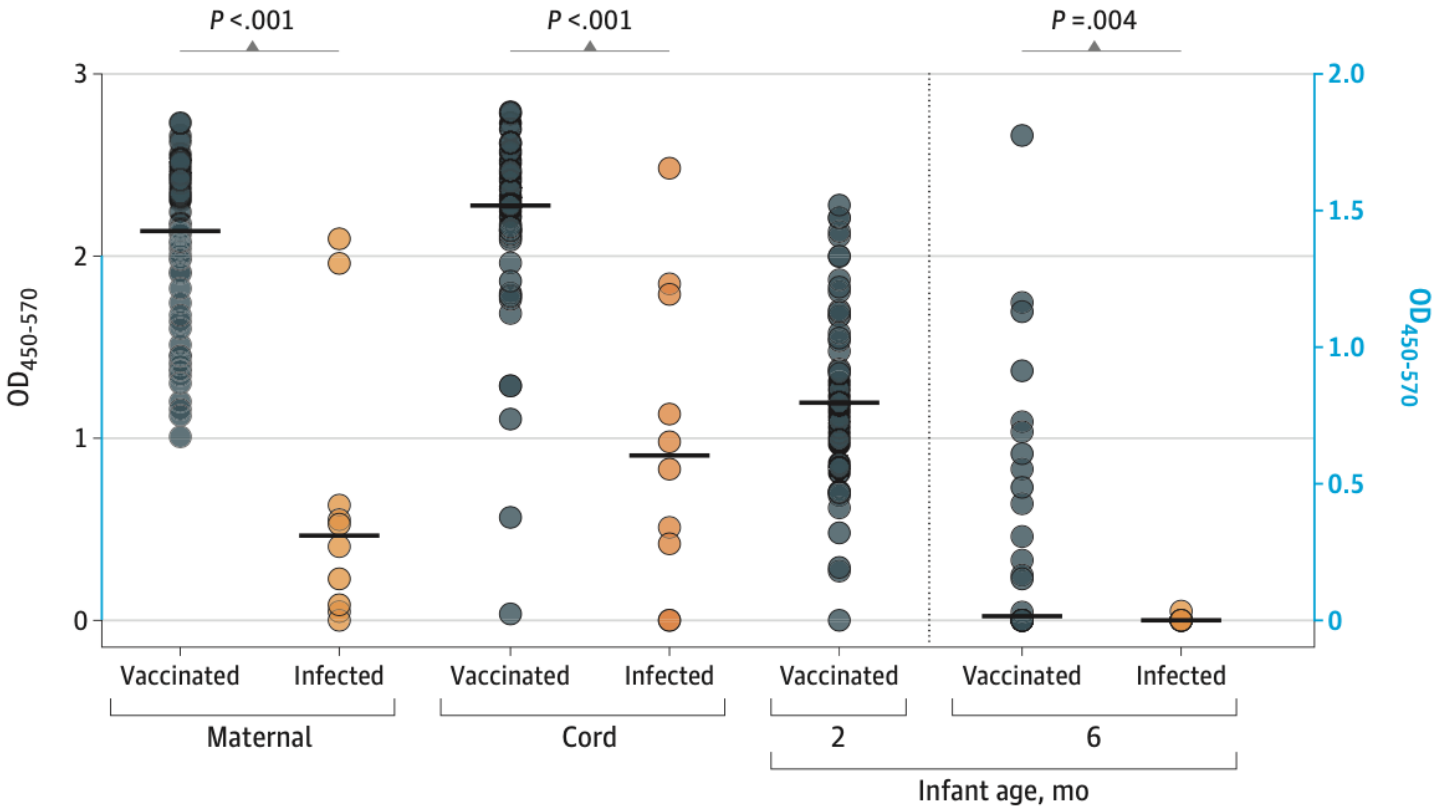


Can we protect babies from COVID?

- Protect the baby:
  - Maternal vaccines will likely work but only if they match the circulating virus strain
  - T cell immunity does not transfer
- Protect the mother:
  - Vaccines do work for mothers (antibodies and T cell immunity)
  - Herd immunity

Can we protect babies from COVID?

Figure. Persistence of Antibody in Infants After Maternal COVID-19 Vaccination or Infection



No. of serum samples	57	10	54	10	49	28	12

Summary

- COVID is rare in infants and tends to be milder than adults
- Presentations can vary widely:
  - Preterm delivery due to maternal illness
  - Preeclampsia or HIE due to placental involvement
  - Respiratory distress
  - Encephalitis
  - MIS-C
- Important to have COVID in your differential for any neonate with unusual respiratory distress, neurologic symptoms, or myocardial dysfunction
- It is plausible that COVID infection could affect neurodevelopmental outcomes, but it is too soon to tell
- Vaccines work but new variants may evade immunity

More questions to be answered:

- How will future variants will affect neonates?
  - Delta caused more severe placental infection
  - What about future variants?
- How will immunizations and history of previous infections affect neonates?
- Are neurodevelopmental impairment and psychiatric diseases a long-term risk?
- As more and more people gain immunity, will disease fade away?
- Does prior maternal infection protect babies?
- Do maternal vaccines protect babies?

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Thank you!

Questions?