



COVID Pediatric Update

Pediatric Grand Rounds

July 15-23, 2021

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Pediatric Infectious Disease

Providence St Vincent



Conflicts of interest

- The Planning Committee and Faculty have no relevant financial relationships with commercial interests to disclose.
- The Speaker receives a grant from Gilead Foundation for hepatitis C research.

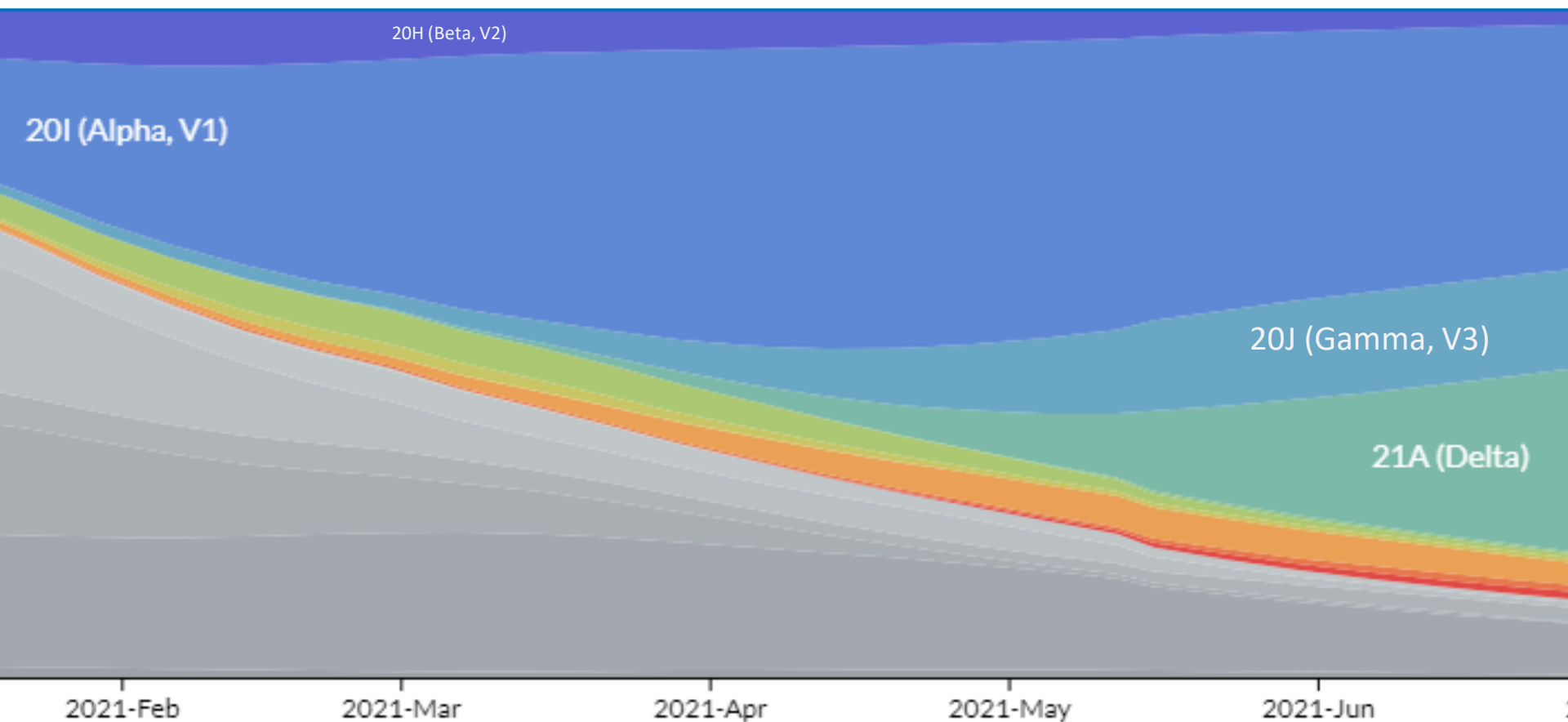


Vaccine & Variants



Variants

North America



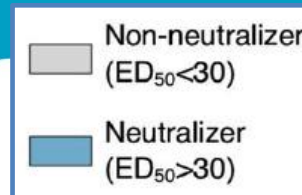


Vaccines work, even against variants*

Efficacy = % ↓ disease in controlled trial

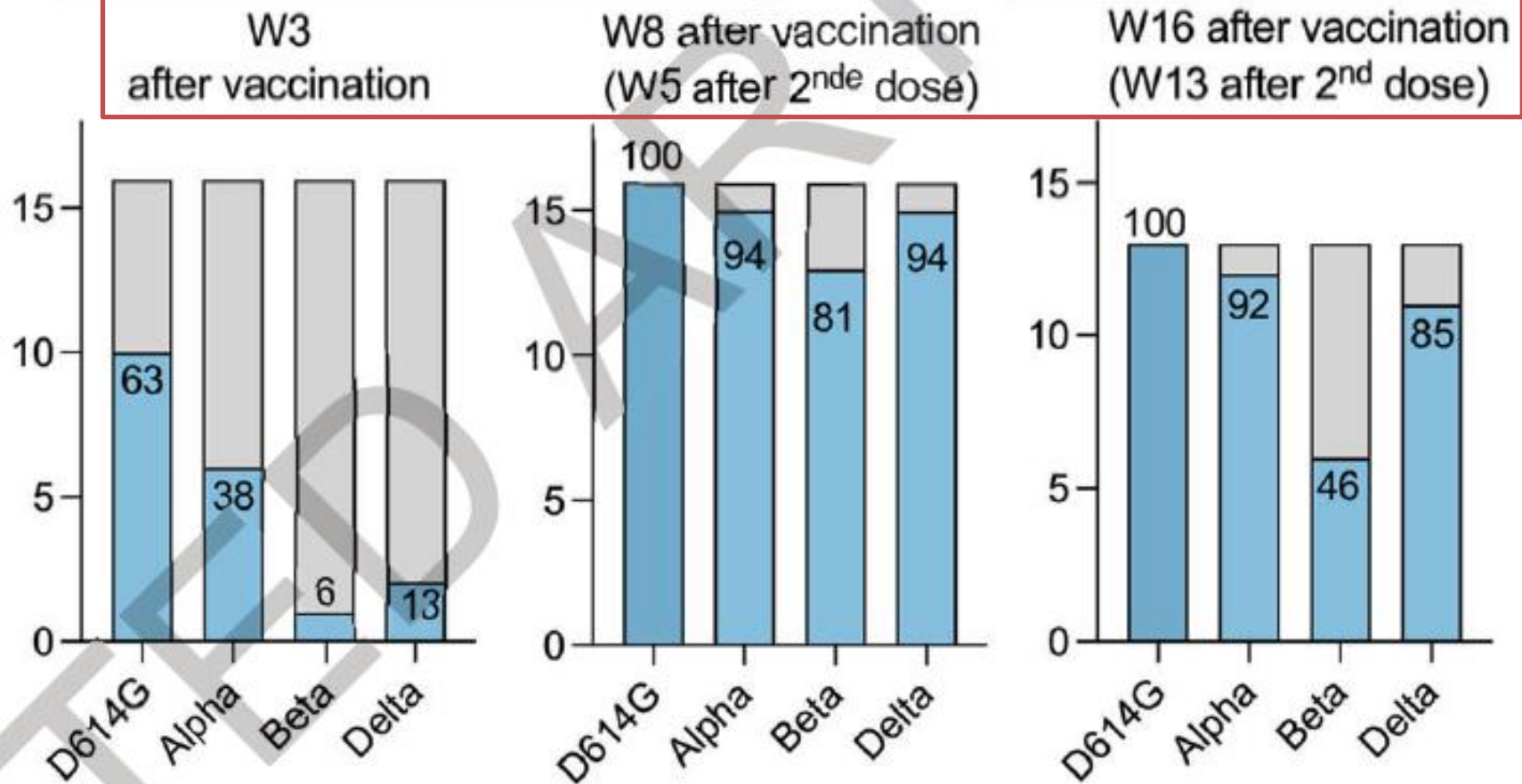
- mRNA vaccines, J&J
 - Vs. severe disease
 - Decreased vs Beta (B.1.351)
- Neutralization titers
 - Some lower v variants, but unclear if meaningful (Jongeneelen 2021)

Effectiveness = % ↓ disease in real world



d

Pfizer



Beta (B.1.351) might be harder to neutralize than Delta (B.1.617.2); BUT sera from 2-dose vaccinated persons neutralized all.



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Effectiveness = % ↓ disease in real world

- Effective in HCW studies
- Un- or under-vaccinated persons are:
 - >90% of current COVID-19 cases
 - >95% of current hospitalized cases
 - >98% of recent deaths a/w COVID-19
- Vaccines do not have to have a high effectiveness to be useful
- Breakthrough cases
 - Under-vaccinated
 - Immunocompromised patients
 - Other comorbidities



Certain percentage of breakthrough expected

When 70% of your population is vaccinated & vaccine efficacy is 95%, 10% of new disease cases will have been vaccinated, but total case number decreases.

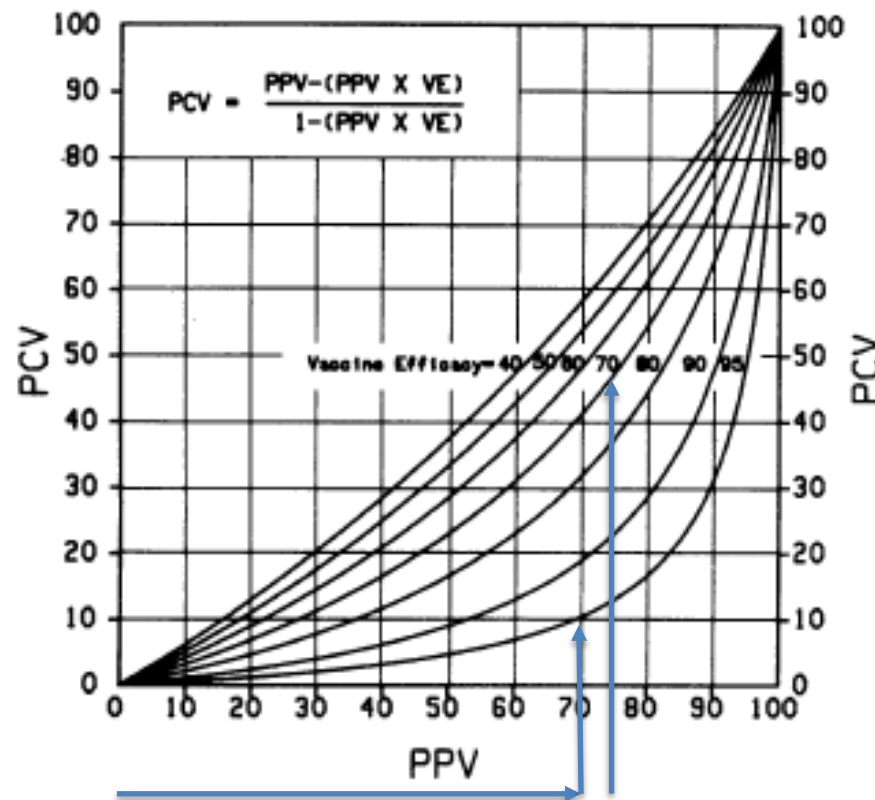


Fig. 1. The relationship between the percentage of cases vaccinated (PCV) and the percentage of the population vaccinated (PPV) for seven different percentage values of vaccine efficacy (VE).

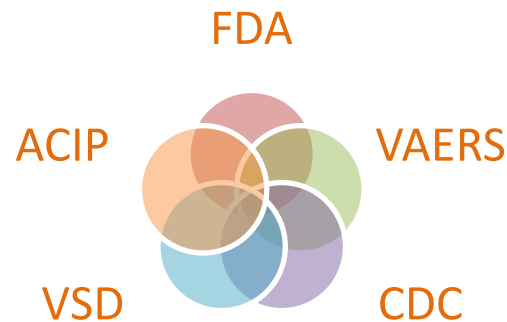


Pediatric vaccine studies

- **Pfizer** (mRNA)
 - Phase 1, 2/3: age 5-12y; 2-5y; 6m-2y: RECRUITING
 - Start Mar 2021, primary completion Mar 2022; study completion Sep 2023
 - Pregnant women: RECRUITING
- **Moderna** (mRNA)
 - Phase 2/3 age 12-18y, ENROLLMENT COMPLETE
 - Phase 2/3 age 6m-12y: RECRUITING
 - Start Mar 2021, completion June 2023
- **Novavax** (Nanoparticle + Spike Ag + saponin-based adjuvant)
 - Phase 3 $\geq 18y$ with expansion to 12-17y: RECRUITING
 - Start Dec 2020, completion June 2023
- **Overcoming2**: vaccine effectiveness against COVID-19 or MIS-C



Vaccine adverse effects: closely monitored



- Common
 - Malaise, fever, chills, headache
 - More frequent mRNA, Moderna in trials
 - Self-limited 1-3 days
 - Lack of side effects NOT associated w/protection



Most commonly reported adverse events to VAERS after Pfizer-BioNTech COVID-19 vaccination* (data thru Jun 11, 2021)

12–15 years old* (N= 2,540)

Adverse event [‡]	n (%)
Dizziness	618 (24.3)
Syncope	446 (17.6)
Nausea	308 (12.1)
Headache	281 (11.1)
Vomiting	221 (8.7)
Pallor	218 (8.6)
Loss of consciousness	217 (8.5)
Pyrexia (fever)	215 (8.5)
Hyperhidrosis	211 (8.3)
Fatigue	182 (7.2)

16–25 years old[†] (N= 12,759)
(for comparison)

Adverse event [‡]	n (%)
Dizziness	2,832 (22.2)
Headache	2,197 (17.2)
Nausea	1,955 (15.3)
Pyrexia (fever)	1,948 (15.3)
Fatigue	1,689 (13.2)
Chills	1,609 (12.6)
Pain	1,560 (12.2)
Syncope	1,257 (9.9)
Hyperhidrosis	946 (7.4)
Vomiting	918 (7.2)

- 12–15 years old: ~6.0 million doses administered (May 10 thru Jun 11, 2021)
- 16–25 years old: ~21.6 million doses administered (December 14, 2020, thru Jun 11, 2021)

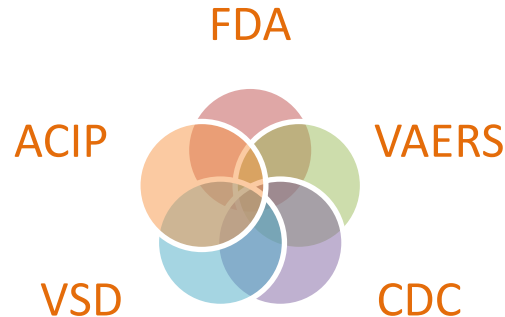
* Data as of June 14, 2021, for reports with vaccination date and receipt date May 10 through June 11, 2021

[†] Data as of June 14, 2021, for reports with vaccination date and receipt date December 14, 2020, through June 11, 2021

[‡] Adverse events are not mutually exclusive



Vaccine adverse effects: closely monitored



- Rare
 - Anaphylaxis
 - Range: 3.7 (FDA) to 7.9 (panel) to 250 per million vaccinations (Blumenthal 2021)
 - Vaccine-induced thrombocytopenic thrombosis
 - 9-12 per million Janssen COVID-19 doses in VAERS; NONE in VSD (~160K doses)
 - Myocarditis or pericarditis
 - Highest expected among males aged 12–29 yrs (39-47 per million second mRNA doses); balance with COVID-19 cases and deaths prevented AND risk of myocarditis from primary infection or MIS-C (Gargano 2021)



Benefit-risk

COVID disease

- COVID-19 cardiac involvement
 - 1 case clinical myocarditis per 177 COVID-19 PCR+ college athletes (Daniels 2021)



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- Thrombosis
 - 2–7% COVID-19 pediatric hospitalizations; 6.5–8% with MIS-C
 - CSVT w/i 2 weeks of COVID-19 (hospitalized): 1 per 25,640 (39 per million) SARS-CoV-2



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- Secondary infections from glucocorticoids
 - Unknown incidence: Aspergillus, mucormycosis, TB, etc



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- Secondary infections from glucocorticoids
 - Unknown incidence: Aspergillus, mucormycosis, TB, etc
- Long COVID: Sx >4 weeks after COVID-19 infection
 - Unknown incidence in children
 - N = 129 PCR+ surveyed:
 - 50% ≥1 symptom 120d later
 - 42% of these affected daily activities
 - 3 MISC, 2 myocarditis (Buonsenso, 2021, preprint)



Long COVID

Commonly reported symptoms include dyspnea, fatigue, post-exertional malaise, and brain fog

Common Post-COVID Symptoms

- | | |
|---|---|
| • Dyspnea or increased respiratory effort | • Abdominal pain |
| • Fatigue | • Diarrhea |
| • Post-exertional malaise | • Insomnia and other sleep difficulties |
| • "Brain fog," cognitive impairment | • Fever |
| • Cough | • Lightheadedness |
| • Chest pain | • Impaired daily function and mobility |
| • Headache | • Pain |
| • Palpitations and/or tachycardia | • Rash (e.g., urticaria) |
| • Arthralgia | • Mood changes |
| • Myalgia | • Anosmia or dysgeusia |
| • Paresthesia | • Menstrual cycle irregularities |





Benefit-risk

Post-Vaccine

- Local and systemic symptoms of immune response
 - common, self-limited
- Myocarditis post-vaccine
 - 1 per 79,365 second dose (12.6 cases per million) among persons aged 12–39 yr (N=26 in 3.4 million doses)
 - Rapid recovery. No deaths, transplants, no multi-system involvement
- Vaccine-induced thrombocytopenic thrombosis
 - UK: 1 per 126,582 vaccinated (7.9 per million) (Astra-Zeneca)
 - US Females aged 18-49y: 1 per 142,857 vaccinated (7 per million) (J&J)
- Guillaume-Barré
 - Imbalance in mRNA vaccine studies, not borne out in post-EUA vaccination
 - J&J: 100 VAERS reports only; 12.5 million doses (1 per 125,000 doses)

<https://www.cdc.gov/mis/cases/index.html>. Accessed 9 Jul 2021

<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/05-COVID-Wallace-508.pdf>. Accessed 11 Jul 2021

<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf>. Accessed 10 Jul 2021



Benefit – Risk Stadium

COVID disease: 100,000 susceptible persons aged 12–29 years

1100 infections
56 hospitalizations
2 thrombotic events
1 death
6-25 cases myocarditis
<1 case MIS-C
doses of steroids, abx
long COVID

Post-vaccine: 100,000 vaccinated persons (2-dose) aged 12–29 years

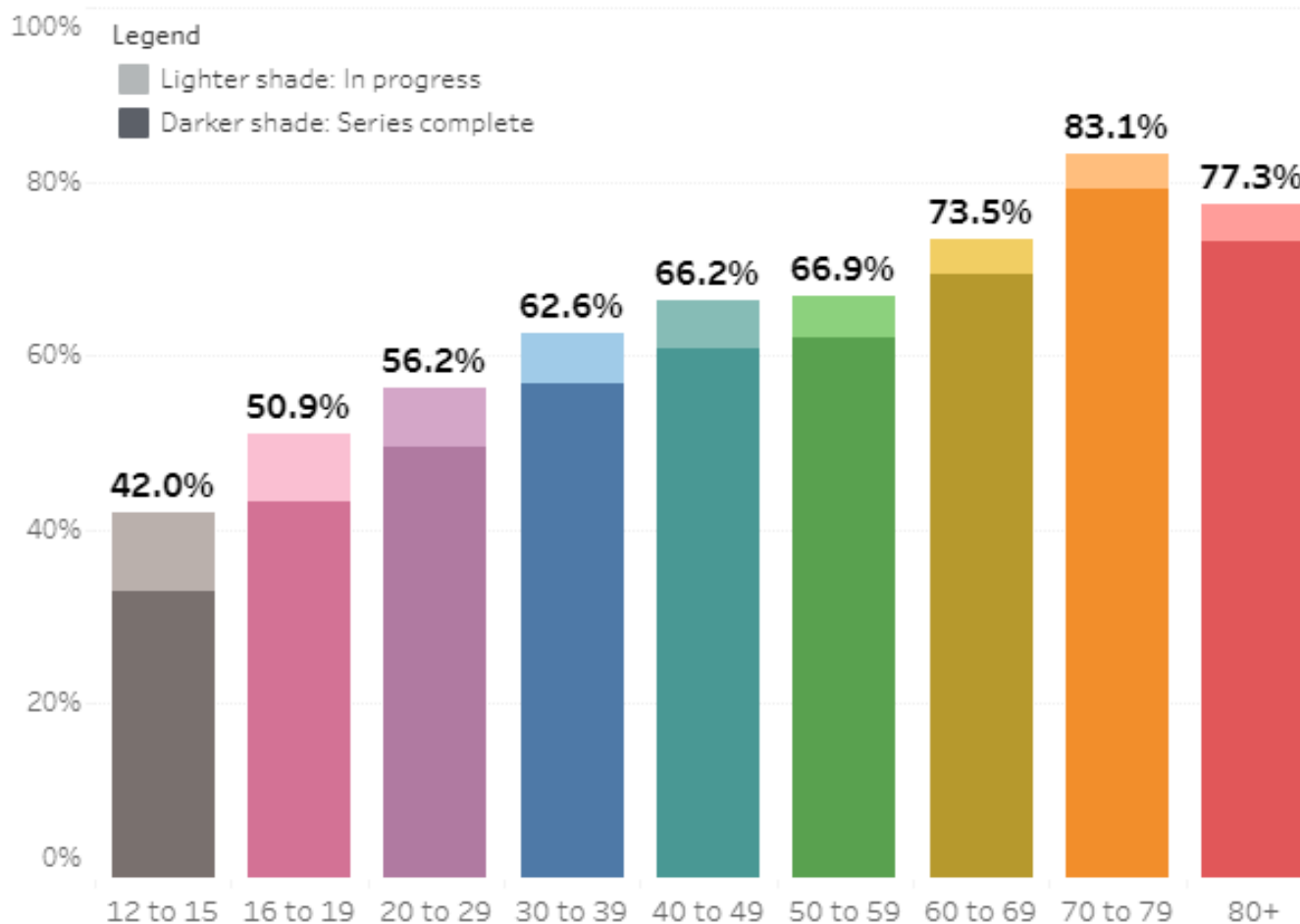
77 infections*
<1 hospitalization
0 deaths
1 post-COVID myocarditis
0 MIS-C, long COVID?
4 post-vaccine myocarditis
<1 VITT, <1 GBS

As of July 19, 2021: 3.4 million pediatric cases (age 0-17yrs); 491 deaths



Current vaccination rates by age

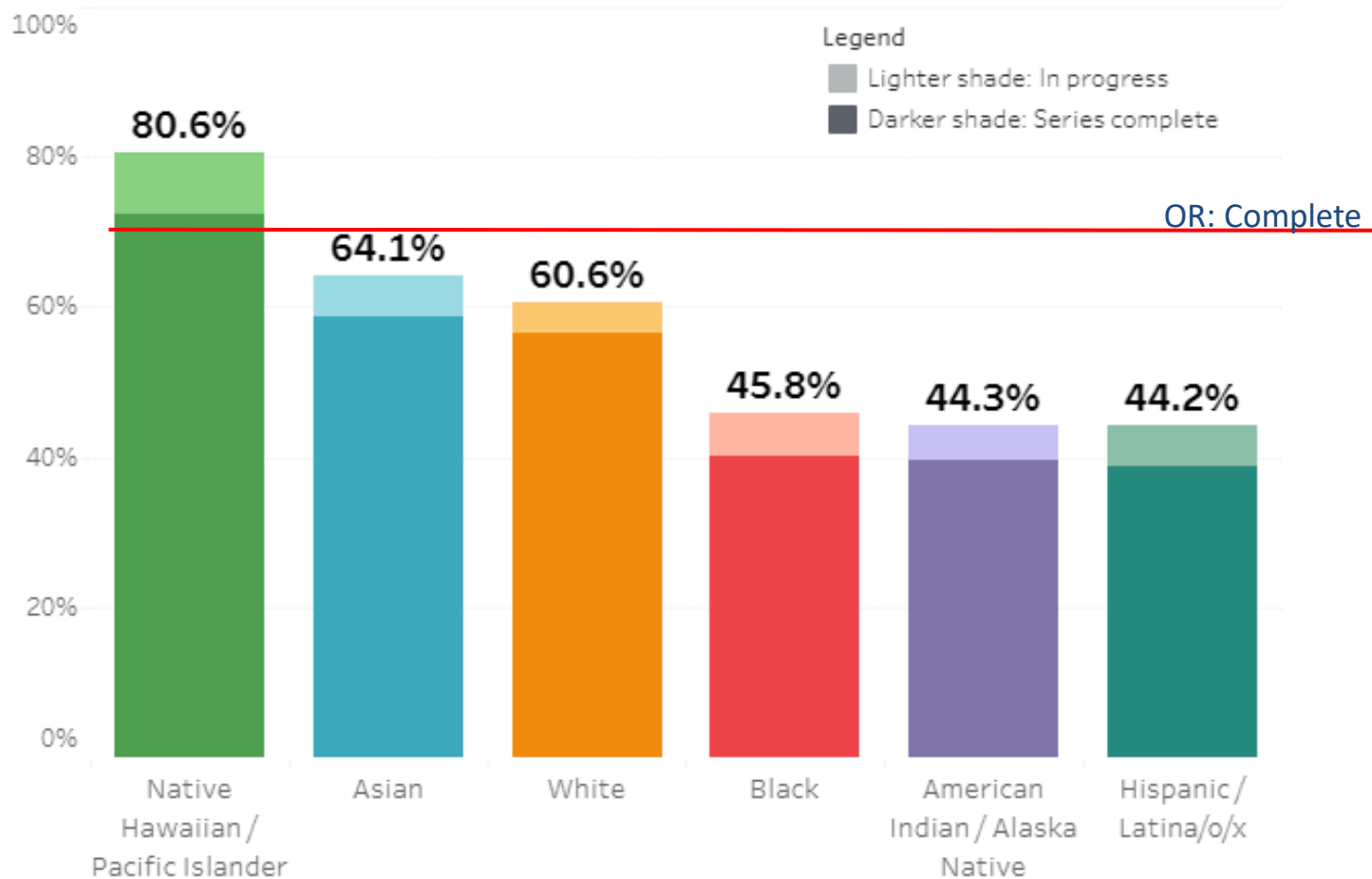
Labeled with % people vaccinated with at least one dose





Current vaccination rates by rarest race and ethnicity

Labeled with % people vaccinated with at least one dose





Opportunity for variants

Red cluster dots: Counties with lower vaccination coverage than expected





Let's talk about confidence

- Most people are confident about vaccines
 - Local successes: Native Hawaiian/ Pacific Islander and Asian communities in Oregon by established outreach and grass-roots
- Natural disease vs vaccine side effects
- More pharmacies, physician offices
- Motivational interviewing, keep door open
- CATCH UP on OTHER DELAYED VACCINATIONS!!!



Case



Summer: Fever, sore throat, rash

- 17y male
- Day 5 of fatigue, Day 3 neck pain, headache, sore throat, fever 102°F
- Came to ED for dehydration:
 - BP 96/56
 - Pulse 93
 - Temp 37.1°C
 - Resp 16
 - SpO2 100%
- Dry mucous membranes
- 1 L NS x 2, labs
- Conjunctivitis and rash noted on admit



Rash on Day 3 of illness



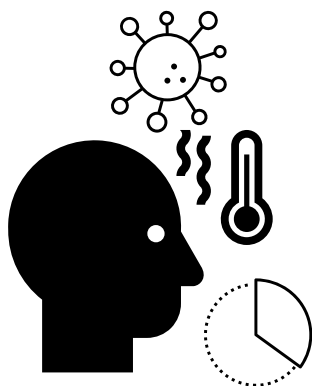
Left lateral
neck



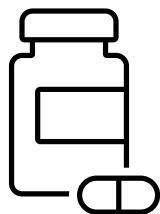
Chest



History



COVID DISEASE 4 MONTHS
AGO



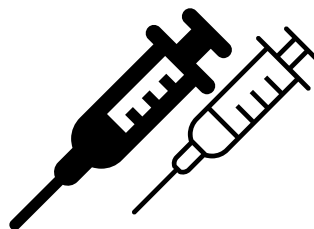
ISORETINOIN



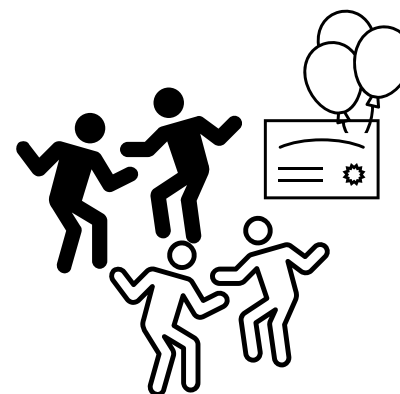
SPORTS



INJURY



MENINGOCOCCAL





Differential Pre-COVID

- Toxic shock syndrome: streptococcal, staphylococcal
- Infection with rash: meningococcal, CMV/EBV, enterovirus, Mycoplasma, HIV
- Drug hypersensitivity reaction (Steven Johnson Syndrome/Toxic Epidermal Necrolysis/Drug Reaction with Eosinophilia and Skin Syndrome)
- Septic thrombophlebitis or Lemierre's syndrome (*Fusobacterium necrophorum*)
- Kawasaki Disease (mucocutaneous lymph node vasculitis)
- Auto-immune vasculitis, systemic Juvenile Rheumatoid Arthritis, Hemophagocytic
- Vectorborne: RMSF, leptospirosis, ehrlichia/anaplasmosis, Lyme disease
- Malignancy with secondary opportunistic infection



Labs, pertinent: fever + rash + neck pain

- Blood culture x 2
- Heme
- Organ systems
- Inflammatory markers
- Coagulation
- Infection
- Imaging
- Antibiotics, coverage toxic shock
- Fluids



Laboratory

- WBC 5.3, 88% neutrophils, 10-20% bands
- Hgb 14.3
- Platelets 46
- Na 140, Cr 1.07
- ALT 112, AST 83, Albumin 3.2
- CRP 12.4
- ESR 37
- D-dimer 3.8, INR 1.5, fibrinogen 475
- Blood culture no growth 24h; throat cx negative for GAS
- CT scan: small fluid collection skull base to C5 (2.7x0.9cm) retropharyngeal space, no extension to mediastinum. No septic thrombosis.
- Ceftriaxone + clindamycin



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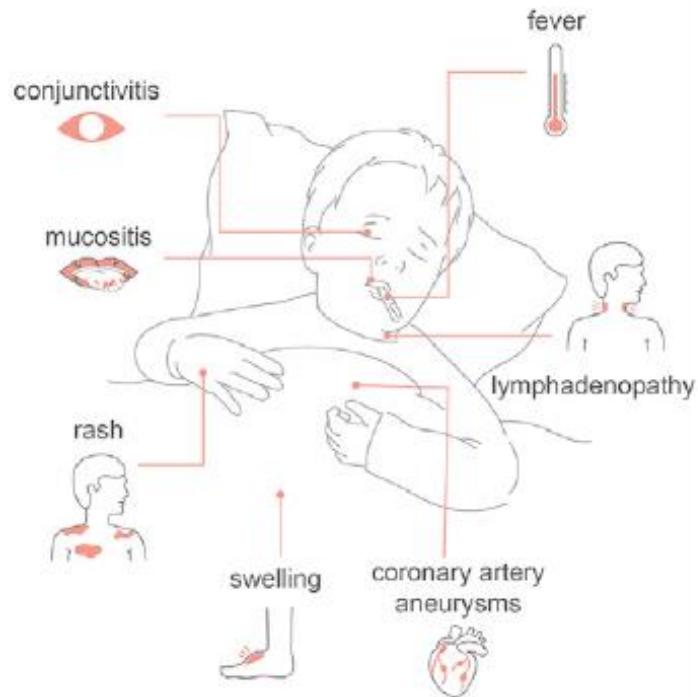


Post-COVID: Multi-system inflammatory syndrome

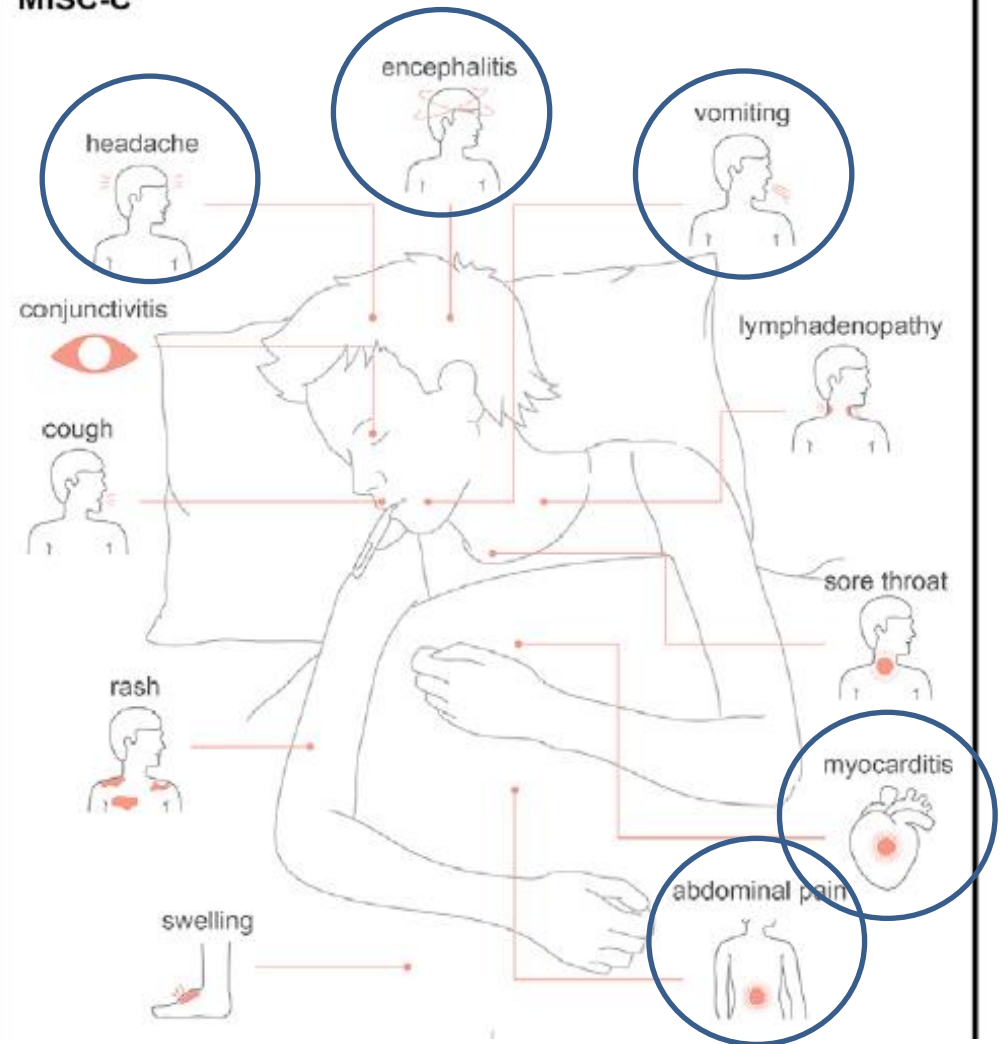
- **Inflammation:** elevated CRP, ESR, D-dimer, hepatitis, retropharyngeal edema
- **CNS:** Headache
- **Skin:** Rash
- **Cardiac:**
 - Troponin 260 → peak 294 (≤ 45 ng/L)
 - Echo normal function, no coronary artery anomalies, no effusion
- **Gastroenteritis:**
 - Started having more abdominal pain and diarrhea
- **Treatment for inflammatory syndrome:**
 - IVIG 100g
 - methylprednisolone 1mg/kg BID x 4 days + 2.5wk taper
 - ceftriaxone + clindamycin x 48h; amp-sulbactam x 72h
 - ASA 81mg daily
 - Famotidine



KAWASAKI DISEASE (PRE-COVID)

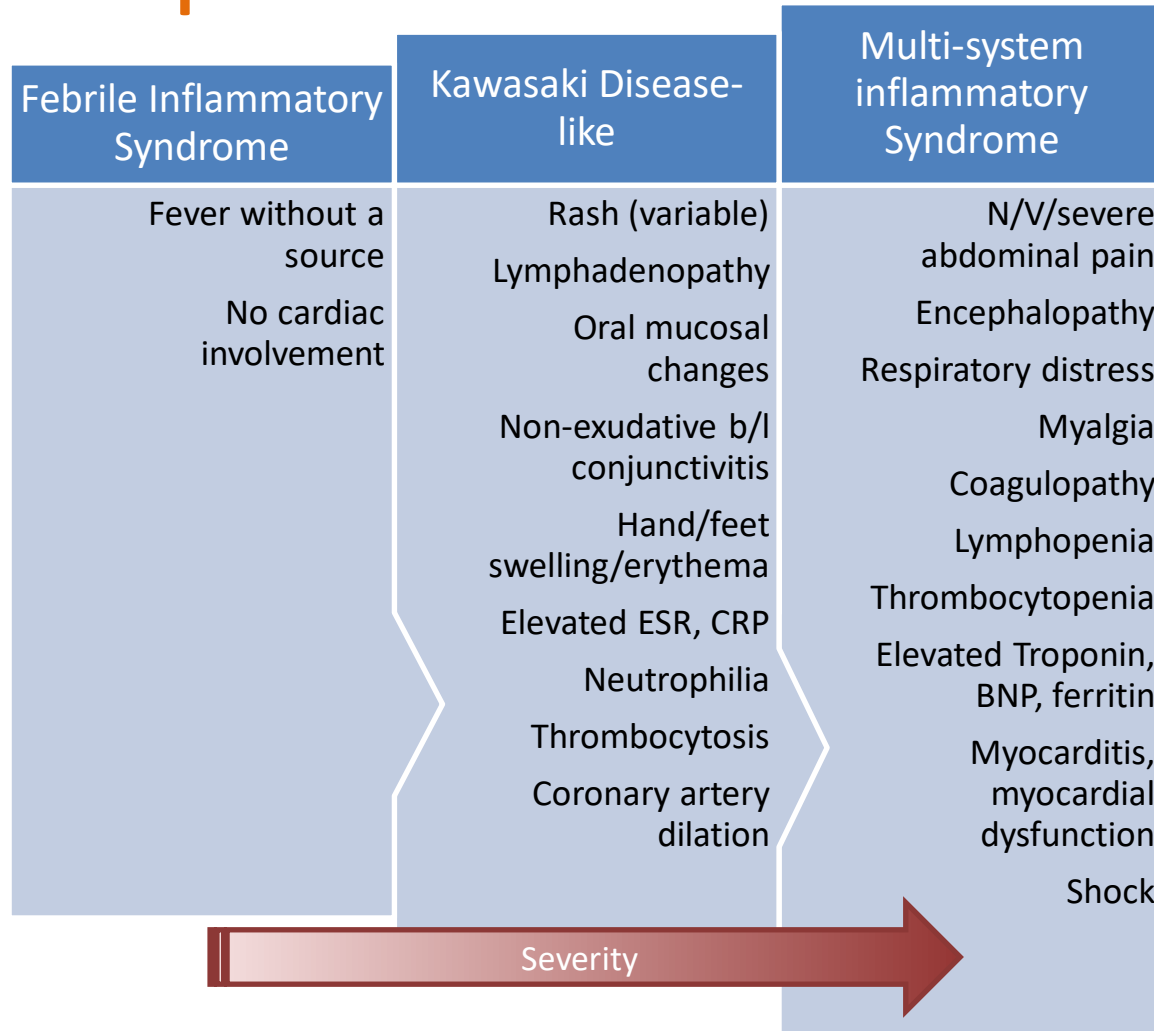


MISC-C





Spectrum of MIS-C





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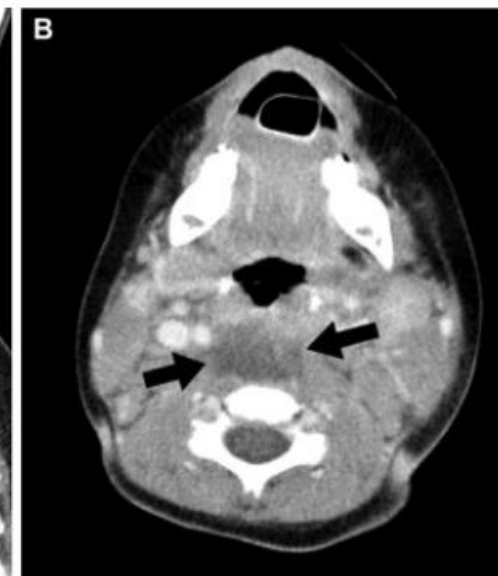
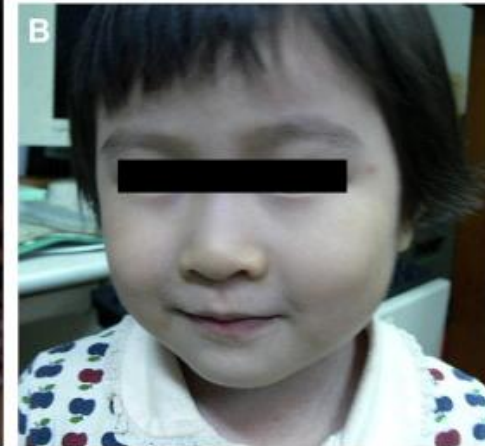
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Retropharyngeal inflammation in Kawasaki

- Hypodense lesion of posterior pharyngeal space
- Delays KD diagnosis until other stigmata & no improvement on abx
- Improves with IVIG, steroids
- Do get coronary artery dilation





When to consider MIS-C?

- Fever $\geq 38.0^{\circ}\text{C}$ for ≥ 3 days AND ≥ 2 organ system involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological consistent with MIS-C); OR
- Fever $\geq 38.0^{\circ}\text{C}$ for < 3 days AND evidence of myocardial dysfunction, hypotension, vasopressor support; OR
- Fever ≥ 5 days without an identified source
- Complete or incomplete Kawasaki disease or Toxic Shock Syndrome

Neutrophilia

Lymphopenia (<1000)

Thrombocytopenia (<150)

Hyponatremia

Hypoalbuminemia

$\uparrow\uparrow\uparrow$ CRP, $\uparrow\uparrow\uparrow$ procalcitonin

\uparrow troponin, BNP, D-dimer



Evaluation: sepsis PLUS

Tier 1

- CBC + diff, CMP, ESR, CRP, Urinalysis + micro (culture if indicated), blood cultures
- CXR
- Respiratory PCR panel with SARS CoV-2, SARS CoV-2 antibodies
- PLUS any other specific labs based on clinical picture or concern: i.e., CXR (if respiratory symptoms present), etc.

Tier 2

- Procalcitonin, LDH, ferritin
- Troponin, BNP, lactic acid
- D-dimer, INR/PT/PTT, fibrinogen
- Rapid strep, ASO
- EKG & STAT Echocardiogram to assess for myocardial dysfunction
- Quantitative immunoglobulins (IgG, IgA, IgM) prior to IVIG
- Specimen storage, red and lavender tube (freeze) prior to IVIG
- IGRA testing for tuberculosis exposure prior to steroids
- Other tests, as indicated by history / exam



Total Cases

208K

Deaths

2,760

Hospitalizations

11,654

Positive Tests

301K

Negative Tests

5.1M

Total Tests

5.4M

Oregon's Epi Curve

COVID-19 Testing by County

COVID-19 Testing Over Time

Data current as of 12:01am 6/24/2021

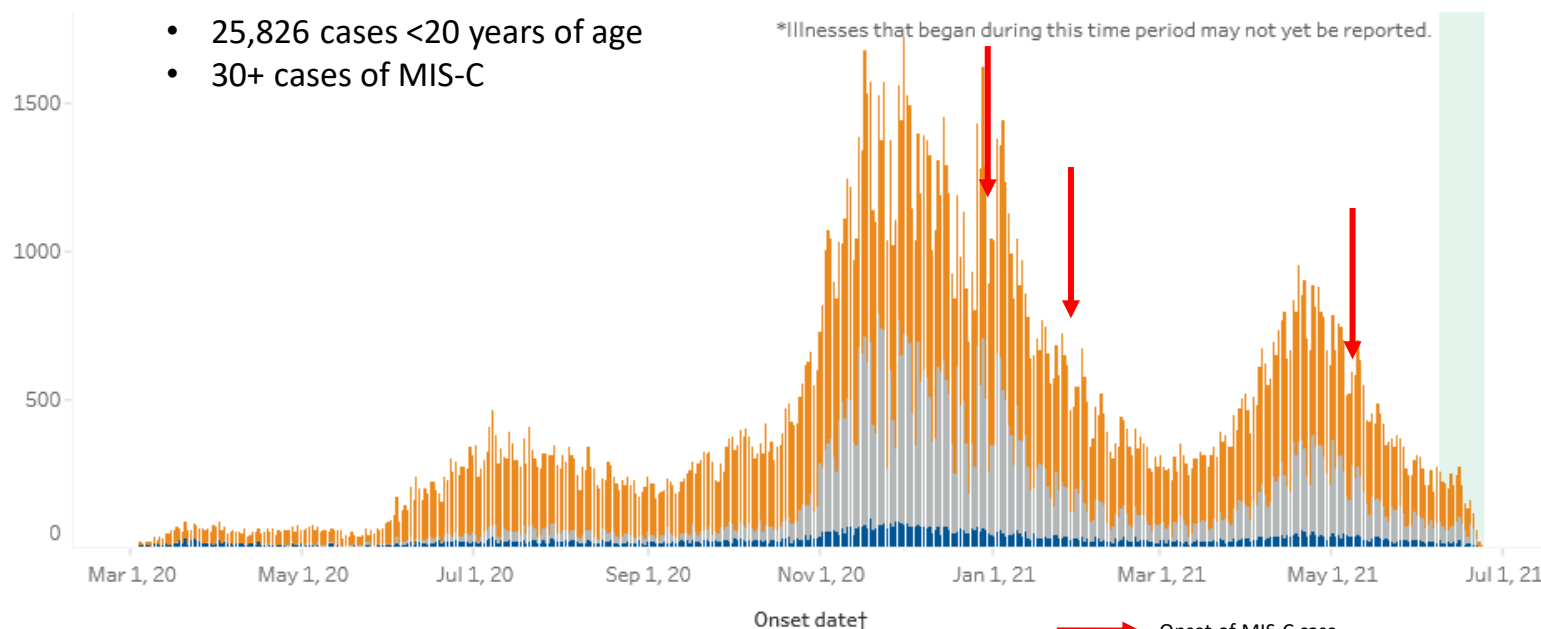
Oregon's Epi Curve: COVID-19 cases

This chart shows the number of Oregonians who have been identified as COVID-19 cases and whether they were ever hospitalized for their illness.†

Total Cases	Hospitalized	Not Hospitalized	Hospitalization Status Unknown
207,558	11,654	139,280	56,624

- 25,826 cases <20 years of age
- 30+ cases of MIS-C

*Illnesses that began during this time period may not yet be reported.



When people say we want to “flatten the curve,” this is the curve they are talking about.

We want to slow the number of new cases of COVID-19 so our healthcare system isn't overwhelmed and can provide care to everyone who needs it. Staying home except for essential needs and practicing social distancing are important ways we can flatten the curve.

Please note: The light blue shaded area shows the past 17 days, and not all people who got sick during this time period have been reported yet to OHA.

Enter or drag the cursors to change the onset date range.

March 4, 2020

June 23, 2021

Not Hospitalized

Hospitalized

Hospitalization Status Unknown

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MIS-C Kids Are:

- Older
- Male
- Obesity
- BNH
- More abdominal and neurologic complaints
- More toxic appearing
..than KD

MIS-C Kids Have:

- Lower WBC
- Lower Lymphs
- Lower PLT
- Higher CRP
- Lower ESR
- Higher ferritin
- Lower albumin
- More shock
- More myocardial dysfunction
- More arrhythmias
- Fewer coronary aneurysms
- Slower recovery ...than KD



Clinical course, N=539

Clinical

- Pericardial effusion 25%
- Ejection fraction <45% 16%
- Coronary artery aneurysm 13.4% (93% mild)
- Arrhythmia 8%
- Fatal 1.9%
 - vs 1.5% COVID-19

Treatment

- IVIG 77%
- Systemic steroids 70%
- Immune modulatory therapy 24%*
- Vent 18%
- ECMO 3.3%



Therapy Pearls

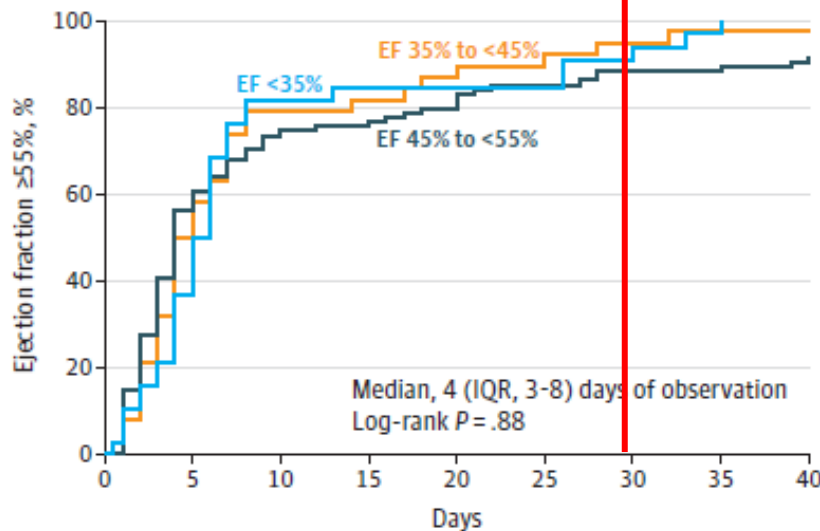
- Avoid excess fluid resuscitation
- Halt inflammatory cascade: **IVIg + steroids > either alone?**
 - IVIG
 - Steroids
 - Targeted cytokine antagonism: anakinra (IL-1 receptor antagonist)
- Cardiac & shock support
- Anti-thrombotic
- Gastric protection
- Parenteral nutrition



Resolution of left ventricular function

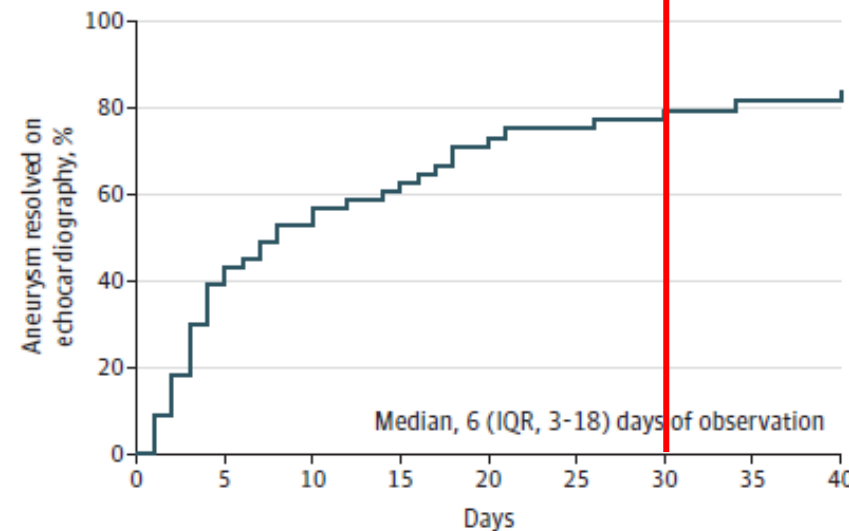
Figure 4. Cardiovascular Outcomes of Patients With MIS-C^a

A Resolution of decreased left ventricular ejection fraction



No. at risk									
EF 45% to <55%	95	41	25	23	19	14	11	11	9
EF 35% to <45%	39	19	8	7	5	4	2	1	1
EF <35%	38	24	6	5	5	5	3	1	0

B Resolution of coronary artery aneurysms



No. at risk	57	31	24	20	14	12	11	8	8
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Why?

- Is MIS-C more diffuse inflammatory process than Kawasaki Disease
 - KD auto-antibodies more specific to vascular proteins (EDIL3)
 - Myocarditis & severe abdominal pain rare in KD; common in MIS-C
- Related to age-differences in immune system?
- Related to prior viral experience?
- Super-antigen polyclonal T-cell expansion?

Cytokine profiles MIS-C v. KD v. Adult COVID

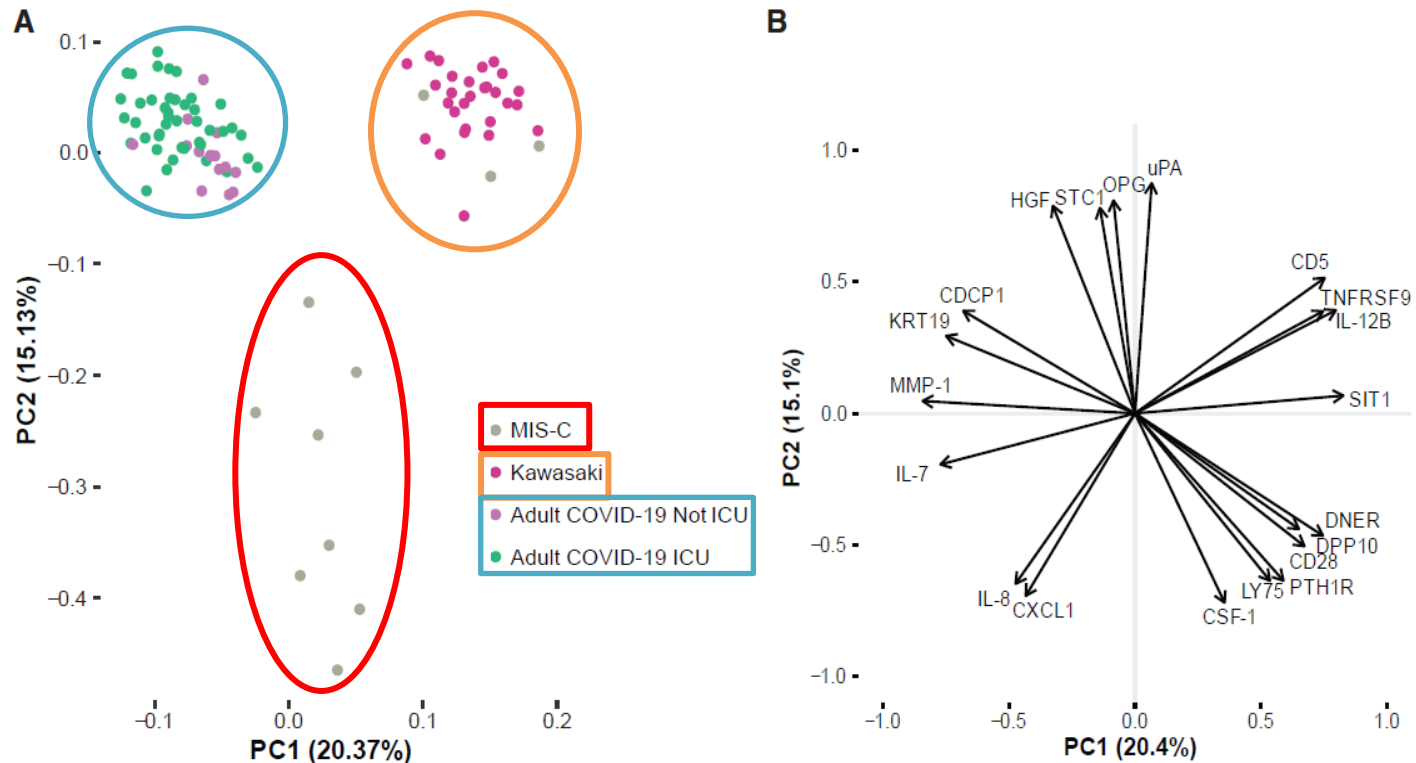


Figure 2. MIS-C Hyperinflammation Differs from Severe Acute COVID-19 Hyperinflammation

(A) Principal components 1 and 2 show variation in cytokine profiles among adult COVID-19 patients with severe disease treated in intensive care units (ICU) or not, and children with MIS-C or Kawasaki disease. $n = 97$ samples included, and 112 unique proteins included in the analysis.

(B) Top 20 proteins mostly contributing to the PCs 1–2.

See also [Table S1](#).



Conclusions

- Benefit of efficacious vaccines outweighs rare side effects
- Prevention of COVID prevents sequelae of COVID infection
- Keep a broad differential in febrile child with rash
- Reach out if questions: we are learning together
- IDSA Real-time Learning Network:
- <https://www.idsociety.org/covid-19-real-time-learning-network/>





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When to Refer

- Unclear infectious disease presentation or treatment
- Except pediatric HIV infection



Questions?

- Phone number: 503-216-6050
- Fax: 971-282-0102
- Epic code for internal referrals: REF76B
- Include: Relevant history and clinical question



Extra



Pregnancy and vaccination



- Observational study: Dec 17, 2020–Mar 2, 2021
- Vaccinated women had much higher titers than natural infection
- Breastmilk:
 - Boost in IgG, not IgA or IgM in vaccinated; elevated IgA after natural infection.
- Cord blood:
 - Spike- and RBD-specific IgG detectable 10 of 10 samples; more later from 2nd dose
- Prospective studies
 - OHSU study enrolling: <https://news.ohsu.edu/2021/04/15/ohsu-studies-impacts-of-covid-19-infection-vaccination-on-immune-system-during-pregnancy-lactation>
 - MOMI-VAX (NIAIS/NIH) enrolling: <https://idcrc.org/concept/studies.html>



Benefit – risk discussion

COVID disease

- COVID-19 cardiac involvement
 - 1 case clinical myocarditis per 177 COVID-19 PCR+ college athletes;
 - 1 per 43 with any evidence of myocarditis (2.3% of 1,597) (Daniels, 2021)
 - N=37: 9 clinical myocarditis, 8 probable subclinical myocarditis; 20 possible
- MIS-C U.S.
 - 1 case MIS-C per 3200 SARS-CoV-2 infections <21 y (316 per million) (Payne, 2021)
 - N=4,196: 60% male; 62% Hisp/BlackNH; 9y (IQR 5–13y)
 - 37 deaths
 - High-dose steroids, IVIG, immune modulators (anakinra), immune suppression, long-term follow-up with cardiology, stress test, neurologic? Long-term?
- Thrombosis
 - 2–7% with COVID-19; 6.5–8% with MIS-C
 - CSVT w/i 2 weeks of COVID-19 (hospitalized): 1 per 25,640 (39 per million)
- Secondary infections from glucocorticoids:
 - Unknown incidence: Aspergillus, mucormycosis, TB, etc
- Long COVID: Sx >4 weeks after COVID-19 infection
 - Unknown incidence in children
 - N = 129 PCR+ surveyed: 50% ≥1 symptom 120d later; 42% of these affected daily activities; 3 MISC, 2 myocarditis (Buonsenso, 2021, preprint)
 - Fatigue, muscle/joint pain, headache, insomnia, respiratory problems, palpitations

Post-vaccine

- Local and systemic symptoms of immune response: self-limited
- Myocarditis post-vaccine
 - 1 per 79,365 second dose (12.6 cases per million) among persons aged 12–39 yr (N=26 in 3.4 million doses)
 - Rapid recovery. No deaths, transplants, no multi-system involvement
- Vaccine-induced thrombocytopenic thrombosis
 - UK: 1 per 126,582 vaccinated (7.9 per million) (Astra-Zeneca)
 - US Females aged 18-49y: 1 per 142,857 vaccinated (7 per million) (J&J)
- Guillaume-Barré
 - Imbalance in mRNA vaccine studies, not borne out in post-EUA vaccination
 - J&J: 100 VAERS reports only; 12.5 million doses (1 per 125,000 doses)

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Benefit-Harm analysis mRNA vaccine & myocarditis*

TABLE 2. Individual-level estimated number of COVID-19 cases and COVID-19-associated hospitalizations, intensive care unit admissions, and deaths prevented after use of 2-dose mRNA COVID-19 vaccine for 120 days and number of myocarditis cases expected per million second mRNA vaccine doses administered, by sex and age group* — United States, 2021

Sex/Benefits and harms from mRNA vaccination	No. per million vaccine doses administered in each age group (yrs) [†]				
	12–29	12–17	18–24	25–29	≥30
Male					
Benefit					
COVID-19 cases prevented [§]	11,000	5,700	12,100	15,200	15,300
Hospitalizations prevented	560	215	530	936	4,598
ICU admissions prevented	138	71	127	215	1,242
Deaths prevented	6	2	3	13	700
Harms					
Myocarditis cases expected [¶]	39–47	56–69	45–56	15–18	3–4
Female					
Benefit					
COVID-19 cases prevented [§]	12,500	8,500	14,300	14,700	14,900
Hospitalizations prevented	922	183	1,127	1,459	3,484
ICU admissions prevented	73	38	93	87	707
Deaths prevented	6	1	13	4	347
Harm					
Myocarditis cases expected [¶]	4–5	8–10	4–5	2	1

Abbreviations: ICU = intensive care unit; VAERS = Vaccine Adverse Event Reporting System.

* This analysis evaluated direct benefits and harms, per million second doses of mRNA COVID-19 vaccine given in each age group, over 120 days. The numbers of events per million persons aged 12–29 years are the averages of numbers per million persons aged 12–17 years, 18–24 years, and 25–29 years.

[†] Receipt of 2 doses of mRNA COVID-19 vaccine, compared with no vaccination.

[§] Case numbers have been rounded to the nearest hundred.

[¶] Ranges calculated as $\pm 10\%$ of crude VAERS reporting rates. Estimates include cases of myocarditis, pericarditis, and myopericarditis.

*myocarditis = myocarditis, pericarditis, myopericarditis

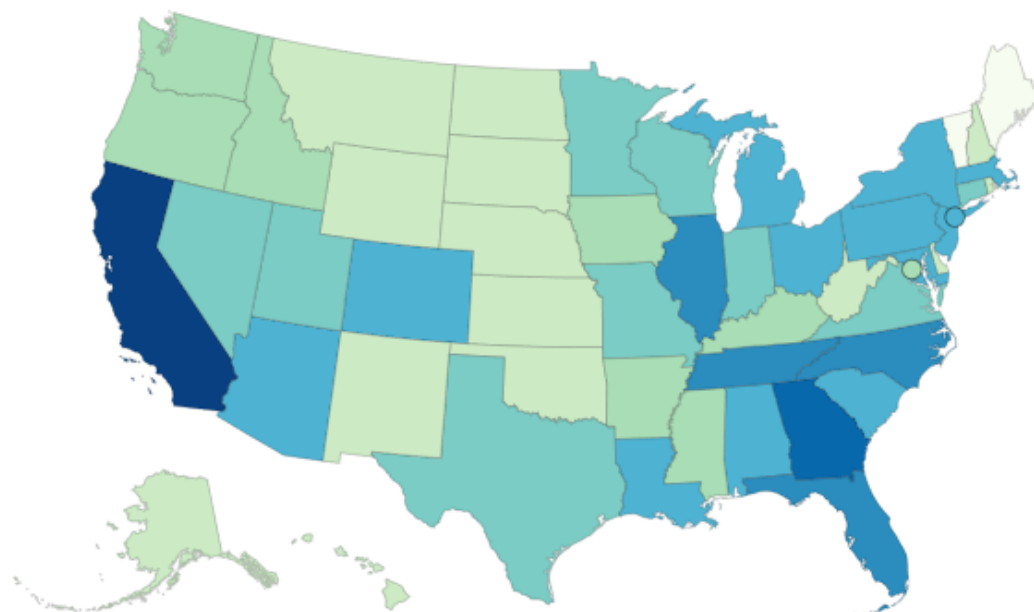


Epidemiology of MIS-C

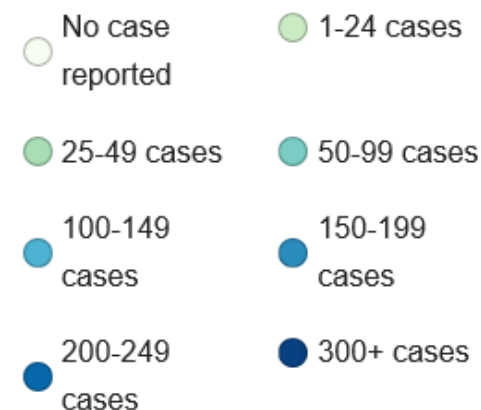
Reported MIS-C Case Ranges by Jurisdiction, on or before June 2, 2021*

TOTAL MIS-C PATIENTS MEETING CASE
DEFINITION*
4018

TOTAL MIS-C DEATHS MEETING CASE
DEFINITION
36



Reported MIS-C Cases



Territories **AS** **GU** **MH** **FM** **PW** **PR** **VI**



<https://www.cdc.gov/mis-c/cases/index.html>