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be inFLUential

COVID-19 in Children – What do we know now?

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Disclosures

Former consultant for Sequiris

Objectives

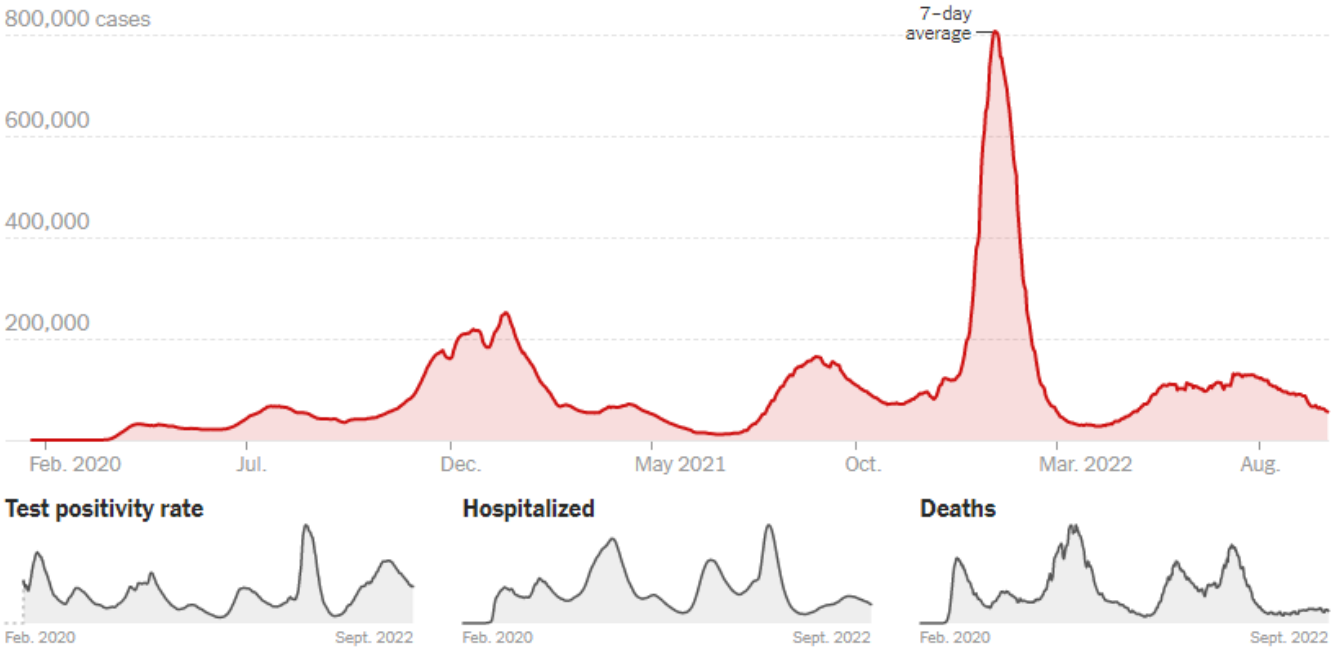
By the end of this talk you should be able to:

1. Discuss the current epidemiology of SARS-CoV-2 in children
2. Summarize testing and treatment guidelines
3. Review complications of COVID-19 including MIS-C and PASC
4. Understand current COVID-19 vaccination recommendations

The current state of the pandemic

“A marathon runner does not stop when the finish line comes into view. She runs harder, with all the energy she has left. So must we. We can see the finish line. We’re in a winning position. But ***now is the worst time to stop running****”*

COVID in the US

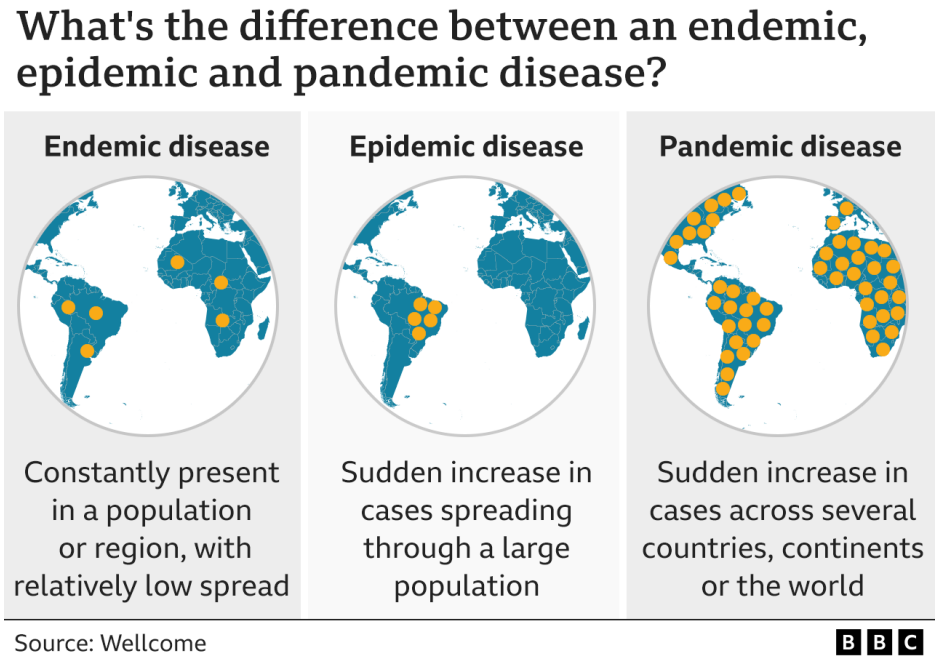


Likely to be a gross underestimate given more at home testing not reported to states

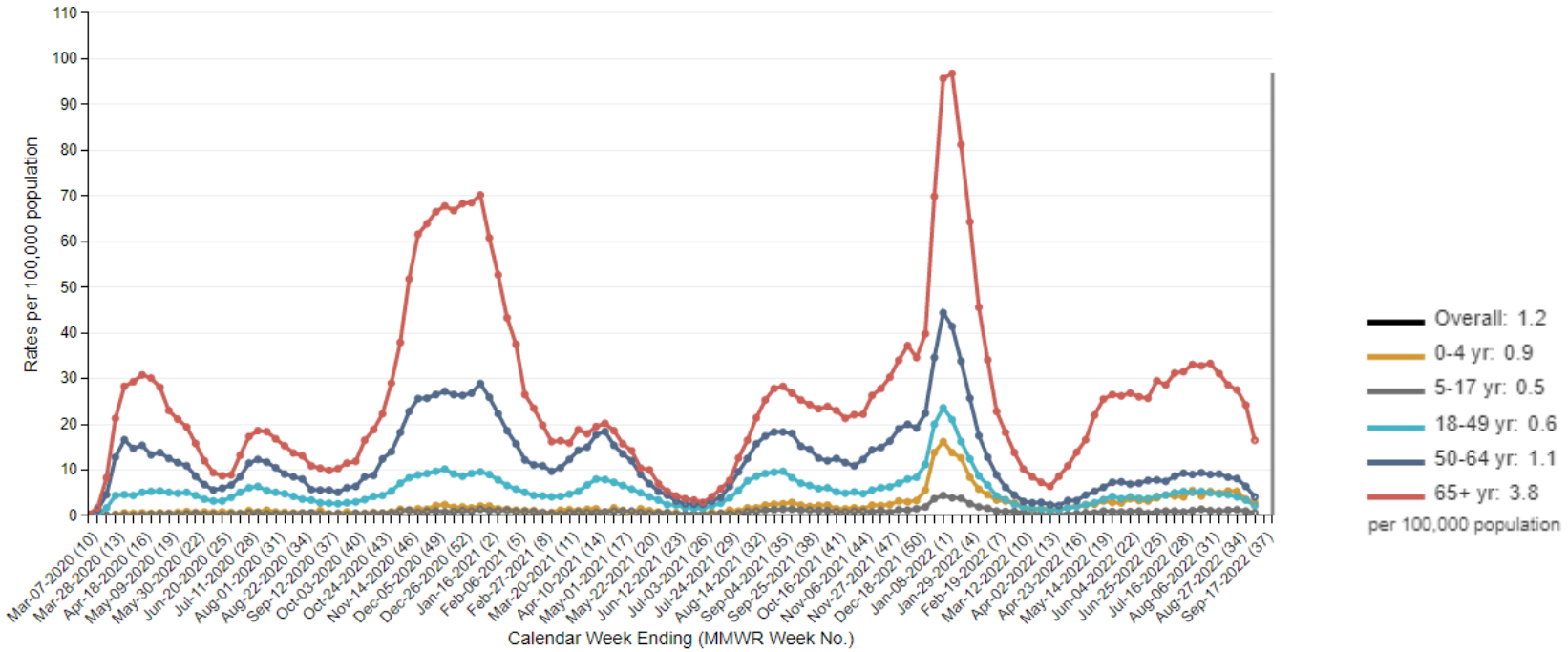
Source: New York Times Map and Case Count

What is the future of the pandemic?

- Early phase of the pandemic, experts considered end once herd immunity was reached
- Persisted due to rapidly evolving variants
- Rather than being eliminated, SARS-CoV-2 will become endemic
- Difficult to predict when this shift will happen



COVID-19 hospitalizations rates in the US



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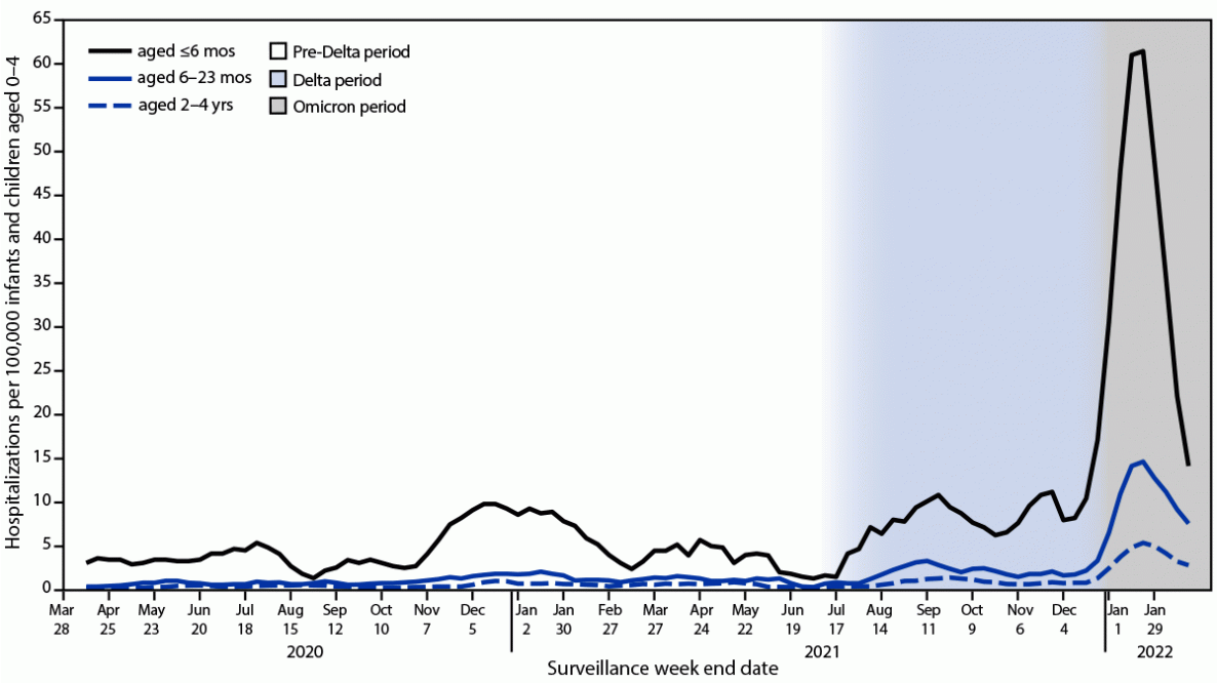
https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

Hospitalization rates in infants and children



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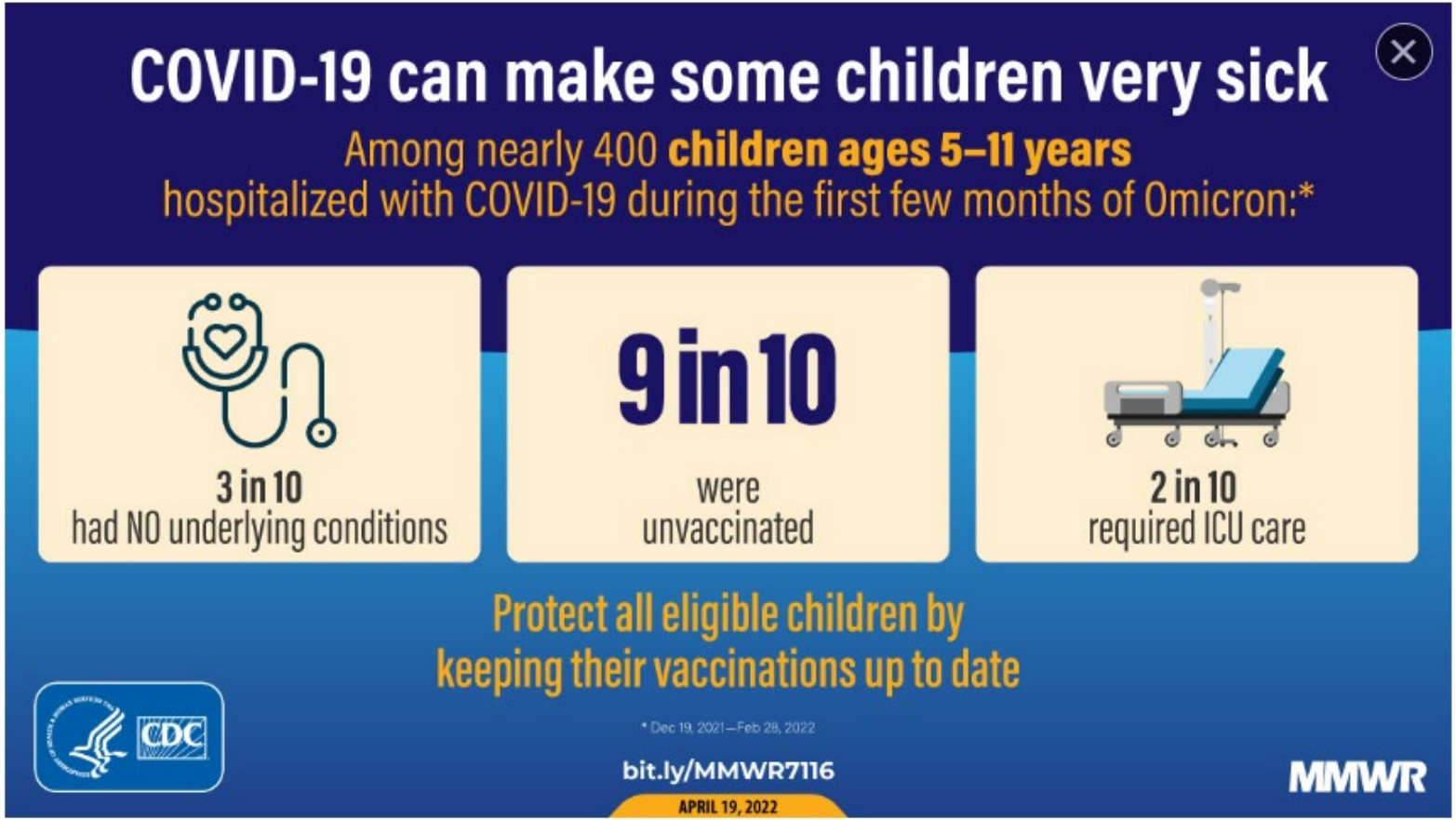
Marks, MMWR Morb Mortal Wkly Rep 2022;71:429–436



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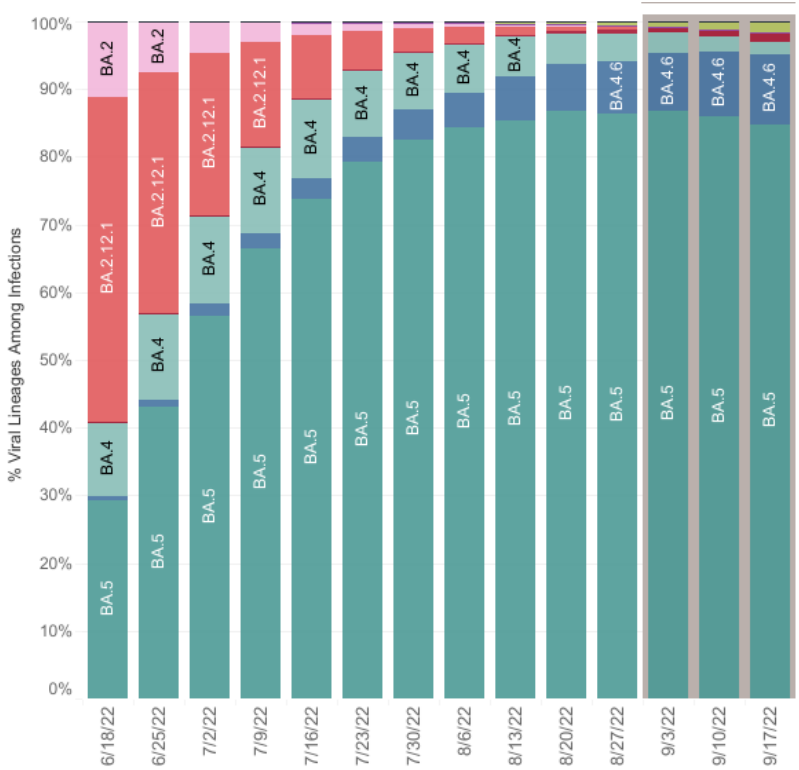
Shi et al. MMWR Morb Mortal Wkly Rep 2022;71:574-581

Current variants



- In US predominant variant BA.5
- BA.5 - growth and transmission advantage over BA.2.12.1 (additional spike mutation) and more severe disease in animal models
- BA.4/BA.5 4X more resistant to 3 vaccine doses, increasing risk of breakthrough infections
- BA.2.75 – first detected in India, more transmissible, greater concerns for immune escape (currently ~1.3%)

https://covid.cdc.gov/covid-data-tracker/#variant-proportions;
https://www.biorxiv.org/content/10.1101/2022.05.26.493539v1.full.pdf

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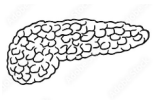
Clinical Characteristics

Who is at risk of severe COVID-19?

Age	**> 65 years**
	Asthma, ILD, PE, bronchiectasis, pulmonary hypertension, bronchiectasis, COPD, CF, TB
	e.g. heart failure, coronary artery disease, or cardiomyopathies
	Cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis, chronic kidney disease
	Diabetes type 1 and 2, **obesity**
	ADHD, CP, Congenital malformations, developmental disabilities, learning disabilities, spinal cord injuries, dementia, cerebrovascular disease
	**Primary immunodeficiencies**, **malignancy**, **SOT, HSCT HIV**, immunosuppressive medications
	Pregnancy and recent pregnancy

Source: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

Who is at risk of severe COVID-19?

Race/ethnicity	Black/African American, American Indian/Alaska Native, Hispanic/Latinx
Mental Health Disorders	Mood disorders including depression, schizophrenia spectrum disorders
Behavioral factors	Physical inactivity Smoking, current and former
Medical complexity	**Medical complexity with technology dependence**

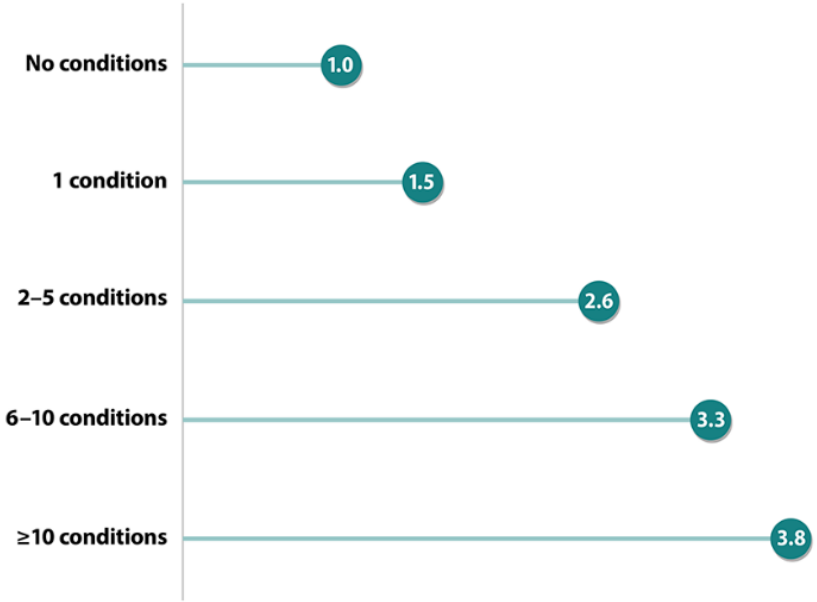
https://www.cdc.gov/flu/highrisk/index.htm
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

Risk for COVID-19 infection, hospitalization and death by race and ethnicity

Rate ratios compared to White, Non-Hispanic persons	American Indian or Alaska Native	Asian	Black or African American	Hispanic or Latinx persons
Cases	1.5x	0.8x	1.1x	1.5x
Hospitalization	3.0x	0.8x	2.3x	2.2x
Death	2.1x	0.8x	1.7x	1.8x

Source: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html

Death risk ratio for COVID-19 increases as number of comorbid conditions increases



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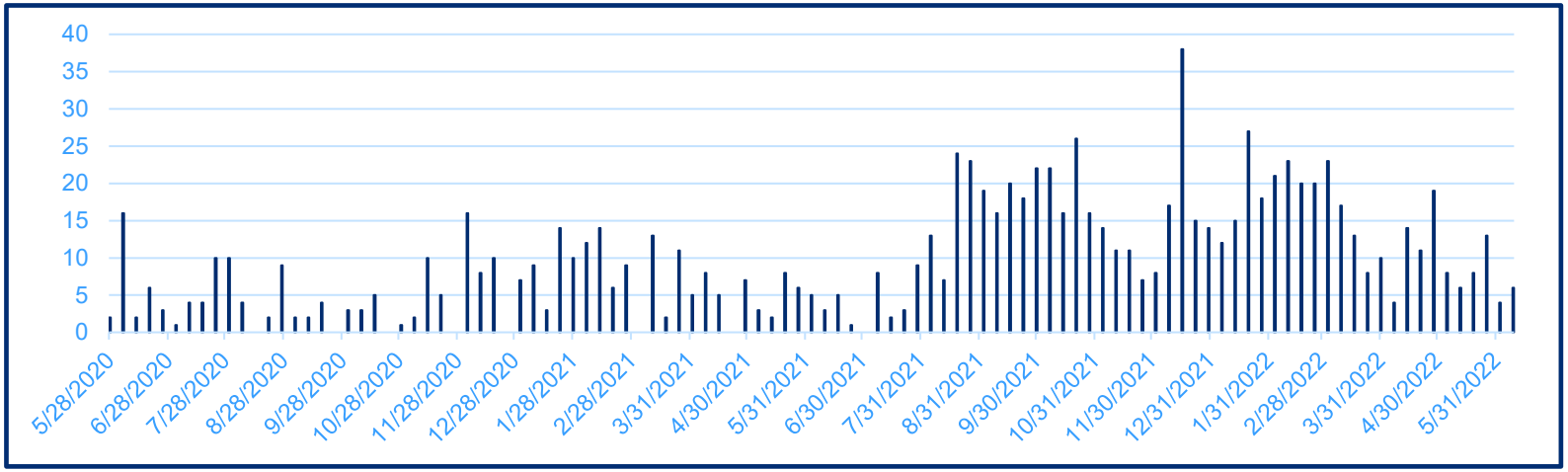
Kompaniyets L, Pennington AF, Goodman AB, Rosenblum HG, Belay B, Ko JY, et al. Underlying Medical Conditions and Severe Illness Among 540,667 Adults Hospitalized With COVID-19, March 2020–March 2021

COVID-19 deaths in children



https://downloads.aap.org/AAP/PDF/AAP%20and%20CHA%20-%20Children%20and%20COVID-19%20State%20Data%20Report%206.23.22%20FINAL.pdf?_ga=2.135341941.578427903.1656981628-255427512.1651171206

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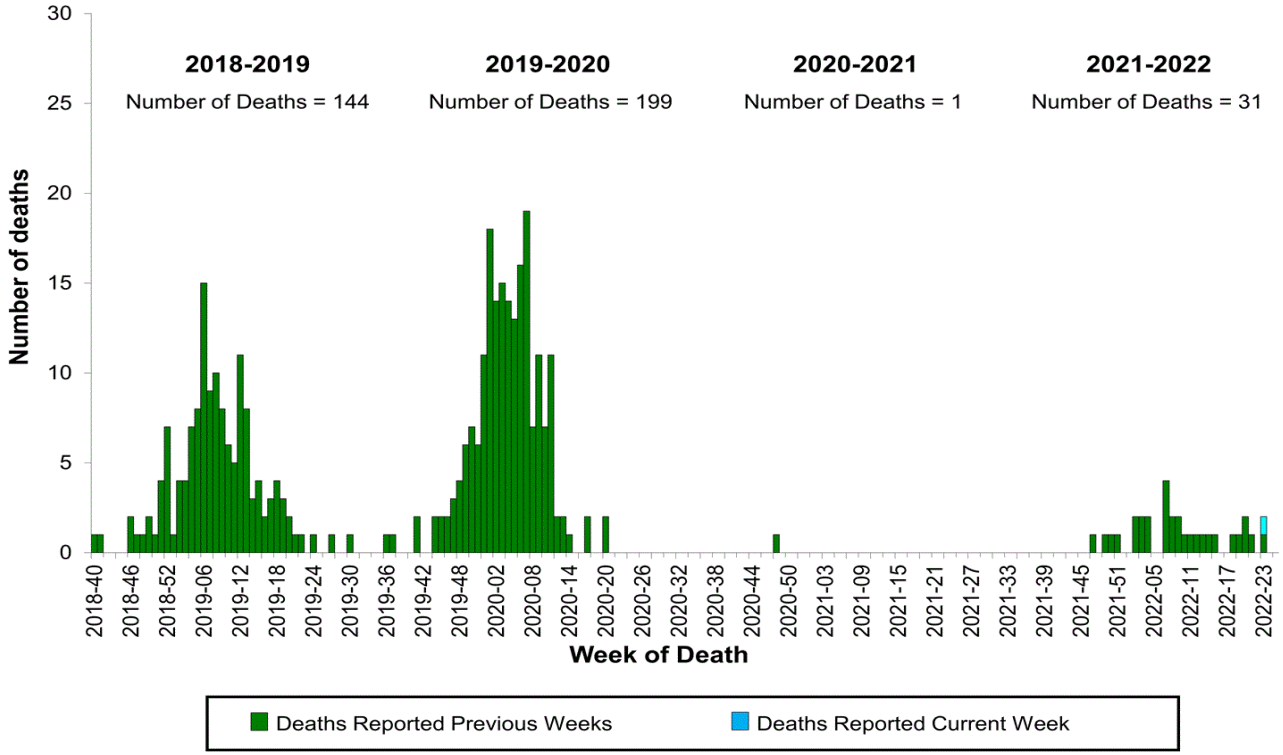
Influenza deaths in children



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https://www.cdc.gov/flu/weekly/index.htm

Limited distinctive clinical characteristics- influenza vs COVID-19

	COVID-19	Influenza
Common symptoms	Fever (50%), non-productive cough (38%) most common	Fever, cough, rhinorrhea most common
Other symptoms	Muscle aches, nasal congestion, headache, loss of appetite, shortness of breath	Muscle aches, nasal congestion, headache, loss of appetite, shortness of breath
Loss of taste and smell	Loss of smell/Loss of taste highly associated	Loss of smell reported in influenza
Gastrointestinal symptoms	Abdominal pain, diarrhea, vomiting more common than flu	Nausea, vomiting and diarrhea more common in pre-school aged children

Welge-Lussen, Adv Otorhinolaryngol 2006; CDC COVID-19 website; Song et al JAMA Network Open 2020 Sep 1;3(9):e2020495
Rao S et al. "Influenza" P, in: Kendig and Chernick's Disorders of the Respiratory Tract in Children, 9th Edition; AAP influenza Pedialink website

Complications of COVID-19 and influenza in children

Influenza	COVID-19
Cytokine storm, cardiorespiratory failure, ARDS	Inflammatory response, cardiorespiratory failure, ARDS
	MIS-C
Myocarditis (cardiac symptoms in 5-10% of adults, less frequent in children)	Cardiac dysfunction, myocarditis (12.6-17.6 cases per 100,000), arrhythmias
DIC (1% hospitalized patients)	Thromboembolic events (2.1% of hospitalized children)
AKI (lower incidence, 25-30% overall)	AKI 12% to 44% of hospitalized children
Reye's syndrome, febrile seizures, encephalitis, acute necrotizing encephalitis, encephalopathy	Neurologic involvement 30% to 40% of hospitalizations- severe encephalopathy, stroke, demyelinating conditions, cerebral edema, and Guillain-Barré syndrome,
Secondary bacterial infection	Less commonly seen than in influenza

Why is COVID-19 generally milder in children?

- Decreased susceptibility to infection?
- Cross-protection from other coronavirus infections?
- Different adaptive immune responses?
- Difference in ACE2 receptor expression?
- Different viral loads in upper respiratory tract?
- Different mucosal immune responses?

Why is COVID-19 generally milder in children?

- ~~Decreased susceptibility to infection?~~
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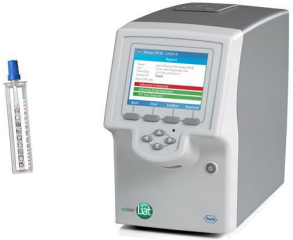
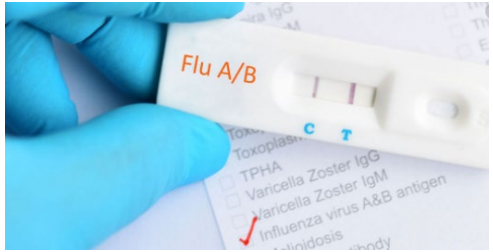
Testing

Testing





Point of care tests

PCR NAAT DIA RIDT

Decreasing sensitivity

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Source: Google images

Whom to test depends on how results will affect clinical management and public health considerations

- Turnaround time of tests
- Patient's illness severity
- Disease prevalence
- Availability of other ancillary test results
- Co-morbidities, risk factors
- Public health and infection control considerations
- Duration of symptoms
- Types of testing available

Hanson et al CID 2020
Rao S. Curr Opin Infect Dis. 2014 Aug;27(4):342-7

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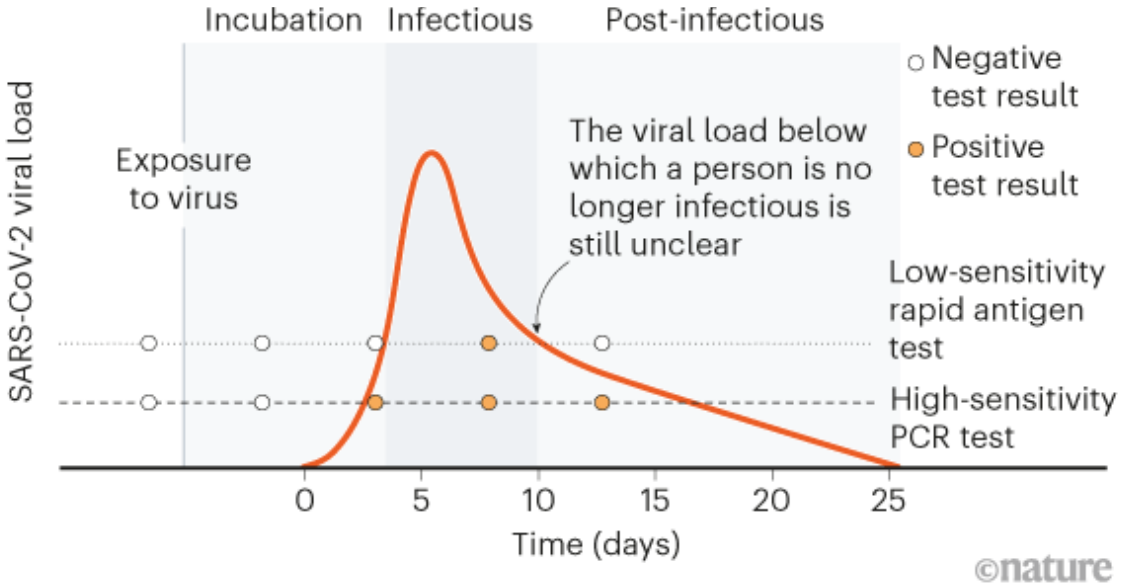
Hanson et al CID 2020
Rao S. Curr Opin Infect Dis. 2014 Aug;27(4):342-7

COVID-19 – Antigen testing

- Cochrane review
- 64 studies Europe and North America, 24,087 nose or throat samples
- 16 antigen tests and five molecular tests
- Antigen test- identified COVID-19 infection in an average of 72% symptomatic and 58% of asymptomatic people
- Most accurate - first week after symptoms first developed (78% detection)
- In test negative, antigen tests correctly ruled out infection in 99.5% of people with symptoms and 98.9% of people without symptoms

Dinnes J et al. Cochrane Database of Systematic Reviews 2021, Issue 3. Art. No.: CD013705.

COVID-19 – molecular testing vs antigen testing

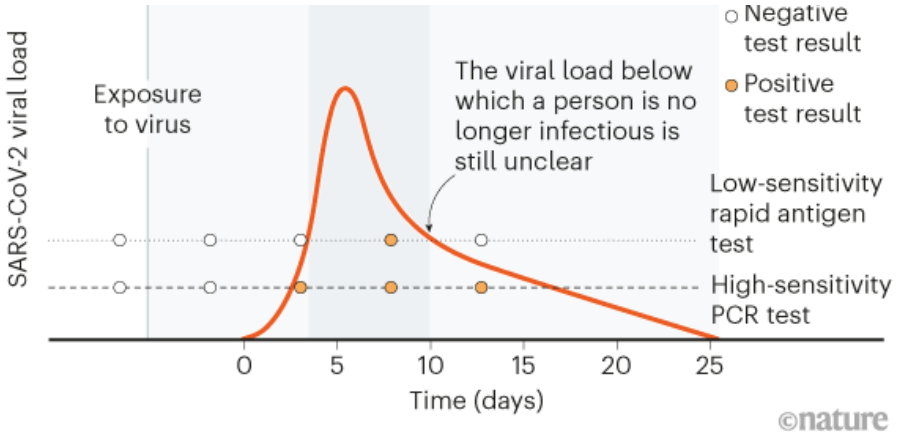


COVID-19 – molecular testing vs antigen testing

Serial testing 24-36 hrs apart preferred with rapid tests

Similar sensitivity when VL high, but more variable when VL is low

Test positive by PCR 1-2 days before antigen test



More likely to be contagious if positive antigen test

Under-reporting to state, one study showed that 1 in 3 reported results

Most research in controlled settings, need more real-world studies

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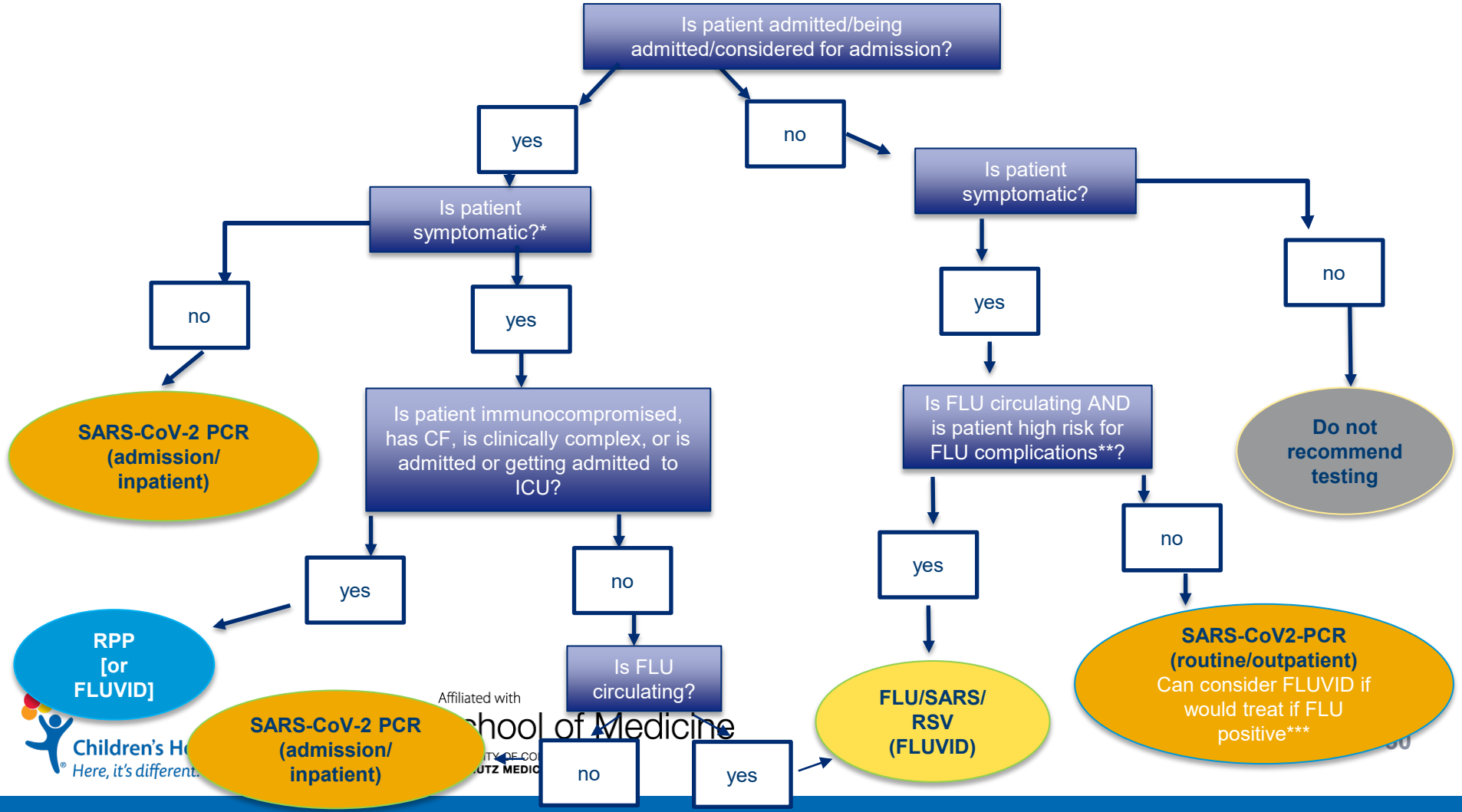
Is patient admitted/being admitted/considered for admission?
yes
no
Is patient symptomatic?*
no
yes
SARS-CoV-2 PCR (admission/ inpatient)
Is patient immunocompromised, has CF, is clinically complex, or is admitted or getting admitted to ICU?
yes
no
RPP [or FLUVID]
Is FLU circulating?
SARS-CoV-2 PCR (admission/ inpatient)
no
yes
Is patient symptomatic?
yes
no
Is FLU circulating AND is patient high risk for FLU complications**?
yes
no
FLU/SARS/ RSV (FLUVID)
Do not recommend testing
SARS-CoV2-PCR (routine/outpatient)
Can consider FLUVID if would treat if FLU positive***
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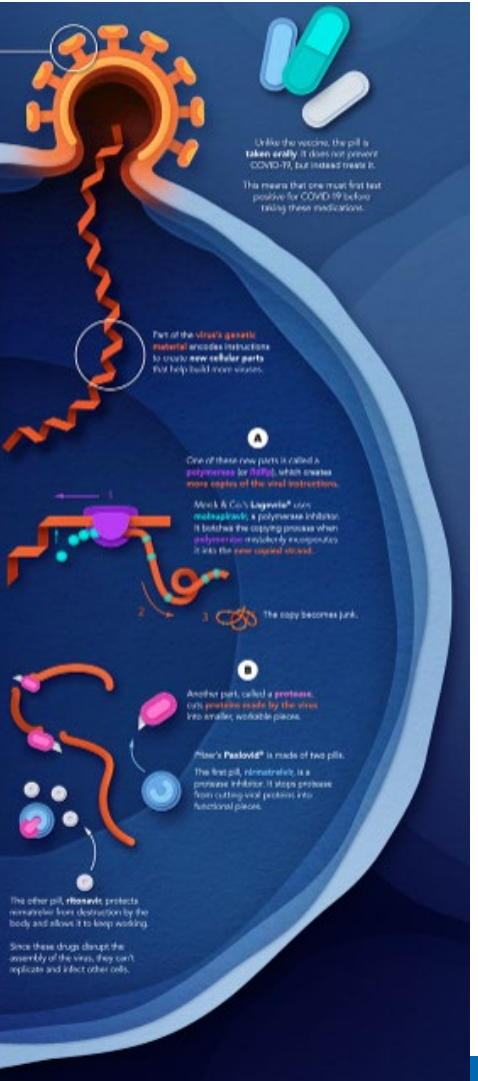
COVID-19 treatment



Antivirals and monoclonal antibodies against SARS-CoV-2

Monoclonal Antibodies e.g. bebtelovimab

Remdesivir

Molnupiravir

Nirmatrelvir/ritonavir (Paxlovid)

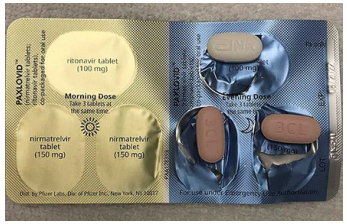
https://www.visualcapitalist.com/visualizing-how-covid-19-antiviral-pills-and-vaccines-work-at-the-cellular-level/

COVID-19 treatment

Not recommended | Recommended for certain patients | Recommended all patients

	Asymptomatic	Mild/Moderate	Severe	Critical
Definition	*No symptoms of acute COVID-19*	*No oxygen or baseline home oxygen*	*New or increased oxygen requirement*	*Rapidly worsening and/or new or increasing requirement for non-invasive/invasive ventilation, shock or multi-organ failure*
Antiviral Treatment	No treatment	Paxlovid first line for high risk Remdesivir 2nd line Molnupiravir if ≥ 18 yrs for high risk	Remdesivir	Remdesivir
Monoclonal antibodies	Not routinely recommended	Bebtelovimab for high risk as second line	Not authorized for IP use by EUA	Not authorized for IP use by EUA
Steroids	No treatment	Not recommended	Dexamethasone	Dexamethasone
Immuno-modulatory therapy	Not recommended	Not recommended	Not recommended	Tociluzimab, Anakinra, etc.

Nirmatrelvir/Ritonavir



- High risk, mild to moderate COVID, ≥ 12 years of age and weigh ≥ 40 kg
- IDSA guidelines suggest ≤ 5 days of symptom onset
- Dosing: 300 mg nirmatrelvir + 100 mg ritonavir bid X 5 days (3 tabs bid)
- Only available as oral tablets, crushing not recommended
- Drug interactions common – may require dose adjustment
- Contraindicated with drugs that are highly dependent on CYP3A for clearance and with drugs that are potent CYP3A inducers

Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

IDSA Infectious Diseases Society of America

IDSA COVID-19 TREATMENT AND MANAGEMENT GUIDELINE PANEL ON BEHALF OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID™

https://www.fda.gov/media/155050/download

Remdesivir- inpatient treatment

- Available for pts >3.5 kg
- Significant or rapidly increased oxygen requirement
- All critically ill patients with high-risk medical conditions, consider for critically ill patients without high-risk medical conditions
- Consider for those with high-risk medical conditions without significant or rapidly increasing oxygen requirement
- Most effective if started within 10 days of symptom onset, treatment for 5 days
- Side effects: transaminitis, nausea, increased PT, hypersensitivity reactions

https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/remdesivir/

Remdesivir – outpatient treatment

- Approved for use in infants ≥ 28 days and older and at least 3 kg
- 3-day treatment course
- Ideally start within 7 days
- Need to be monitored ~ 1 hour post infusion
- SE: elevated LFTs, hypersensitivity

https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/remdesivir/

Bebtelovimab (monoclonal antibody)

- High risk, mild to moderate COVID, ≥ 12 years of age and weigh ≥ 40 kg alternative COVID-19 treatment options not accessible
- Consider if unable to take pills, drug-drug interactions
- Ideally within 7 days of symptom onset
- Dosing: 175 mg IV once over at least 30 seconds, need to monitor for 1 hour post infusion
- Most common adverse reactions are infusion-related reactions (0.3%), pruritus (0.3%), and rash (0.8%)
- No drug interactions
- Infusion related reactions observed in clinical trials 24 hrs after injection (unclear if progression of COVID-19 or direct effect of infusion)

https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/summary-recommendations/

Steroids

RECOVERY trial – Open-Label RCT of Dexamethasone in Hospitalized Patients With COVID-19 in the United Kingdom

- Hospitalized adults, dexamethasone for 7 days
- All-cause mortality at 28 days: All patients: 23% in DEX arm vs. 26% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; *P* < 0.001)
- Greatest effect for those receiving mechanical ventilation
- No effect for those hospitalized who did not require oxygen.

CoDEX Trial- Open-Label RCT of Dexamethasone in Patients With Moderate or Severe ARDS and COVID-19 in Brazil

- Received MV within 48 hrs of ARDS, 20mg dexamethasone for 5 days then 10mg IV daily for 5 days or until ICU d/c
- Mean number of days alive and free from MV by Day 28: 7 in DEX arm vs. 4 in SOC arm (*P* = 0.04)

Improved clinical outcomes and ↓ mortality in hospitalized patients with COVID-19 on supplemental oxygen, not recommended if no supplemental oxygen

Antithrombotic therapy

- COVID-19 considered a risk factor for thrombosis
- Not recommended in non critically ill patients
- Insufficient evidence to recommend either for or against in critically ill patients with COVID-19
- Not recommended to continue VTE prophylaxis after hospital discharge
- Insufficient evidence to recommend either for or against continuing anticoagulation after hospital discharge unless another indication for VTE prophylaxis exists.

Tixagevimab plus cilgavimab- Evusheld

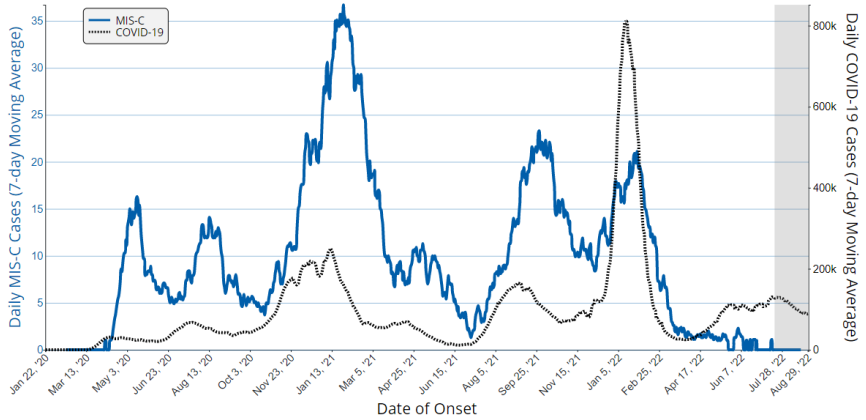
- EUA for tixagevimab with cilgavimab
- ≥ 12 years of age and ≥ 40 kilograms
- Pre-exposure prophylaxis if vaccine unlikely to work or if unable to get vaccinated
  - moderate to severely compromised immune systems and may not mount an adequate immune response to COVID-19 vaccination **or**
  - history of severe adverse reactions to a COVID-19 vaccine and/or component(s)
- 300 mg of tixagevimab and 300 mg of cilgavimab - two separate consecutive intramuscular (IM) injections every 6 months
- Higher dosing to overcome potential resistance to Omicron

MIS-C

MIS-C: multi-inflammatory syndrome in children

- <21 yrs, fever, inflammation, involvement of at least 2 organ systems requiring hospitalization (no alternative diagnosis, and evidence of infection/exposure)
- Coronary artery aneurysms occur in over 8% of patients
- Post-infectious syndrome occurring 3-6 weeks after mild or asymptomatic SARS-CoV-2 infection
- Children 6-12 years of age

- Estimates 3 in 10,000 children in the US <21y
- What triggers MIS-C in certain children remains unknown
- Cases of MIS-C decreasing over time (differences in inflammatory response a/w each variant, enhanced host immunity after infection and vaccination)



Source: https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance

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MIS-C evaluation

- CBC with differential (absolute lymphocyte count < 1000, platelets < 150,000)
- CRP (CRP >3 mg/dL)
- Complete metabolic profile (Na less than 130, Cr elevated for age or greater than 1.5X baseline, LFTs 2X upper limit of normal for age)
- ESR (greater than 40mm/hr)
- Rainbow draw

- pro-BNP, troponin
- SARS-CoV-2 serology, PCR
- Urinalysis
- Other labs based on severity and need to rule out other causes
- Echo

MIS-C management

- First line for all patients with HIGHLY SUSPECTED MIS-C is dual therapy with inFLIXimab followed by IVIG
- Pre-treat with acetaminophen and diphenhydramine

- Low dose aspirin

- Second line therapy- repeat dose of infliximab
- Corticosteroids (IV methylprednisolone)
- Anakinra

- Influenza vaccine prior to discharge, no live vaccines for 11 months

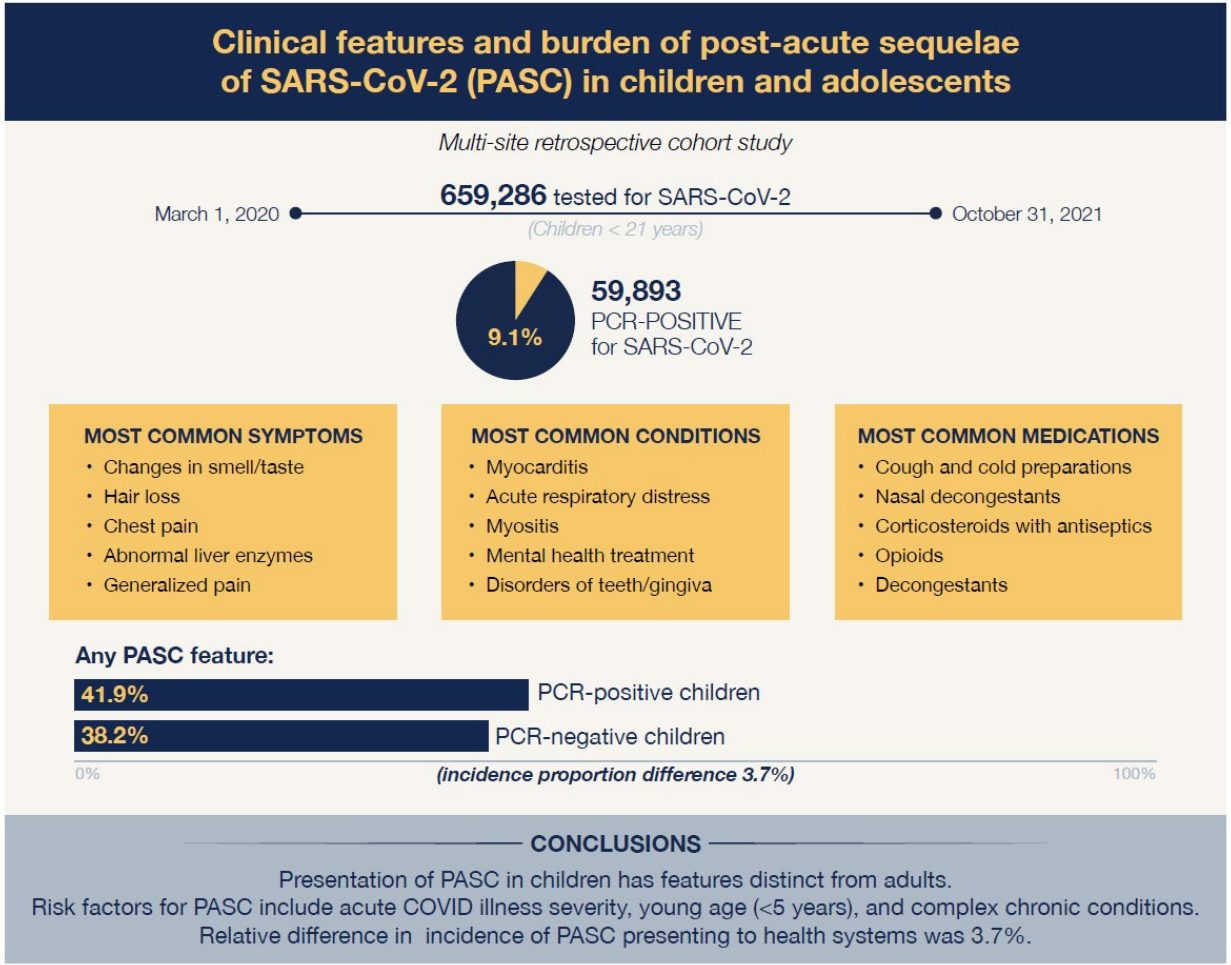
Post-acute sequelae of SARS-CoV-2

Post-acute sequelae of SARS-CoV-2 (PASC)

- Aka “long COVID”
- Ongoing, relapsing, or new symptoms or other health effects occurring after the acute phase of SARS-CoV-2 infection that is present 4 or more weeks after the acute infection
- **General symptoms:** Tiredness or fatigue, persistent fever
- **Respiratory and heart symptoms: d**ifficulty breathing or shortness of breath, cough, chest pain, palpitations
- **Neurological symptoms:** “brain fog”, headache, sleep problems, dizziness, paresthesias, change in smell or taste, depression or anxiety
- **GI symptoms:** Diarrhea, abdominal pain
- **Other symptoms:** joint or muscle pain, rash

How common is PASC?

Reference	What was examined?	The populations examined	Results/Comments
Radtke 2021, (Switzerland)	Symptoms > 4 weeks: Fatigue, difficulty concentrating, sleep issues, URI, stomachache	Children + SARS-CoV-2 Abs (N=109) Children - SARS-CoV-2 Abs (N=1246) (None were hospitalized)	4% 2%
Molteni, Sudre 2021 (UK)	Symptoms for at least 28 days, e.g., Fatigue, headache, anosmia	Symptomatic children + SARS-CoV-2 Abs (N=1734, 27 hospitalized) Symptomatic children - SARS-CoV-2 Abs (N=1734, 10 hospitalized)	4.4% 0.9% (greater number of symptoms in the seronegative group)
Chevinsky 2021 (US)	New diagnoses in the succeeding 4 months	305 matched pairs of children (+/- SARS-CoV-2 Abs)	No difference
Berg 2022 (UK)	Symptoms associated with COVID-19, school attendance, and health-related quality of life	24,315 adolescents with a positive SARS-CoV-2 test (case group) and 97,257 matched controls	61.9% case group 57.0% control group



Incidence, Features and Risk factors

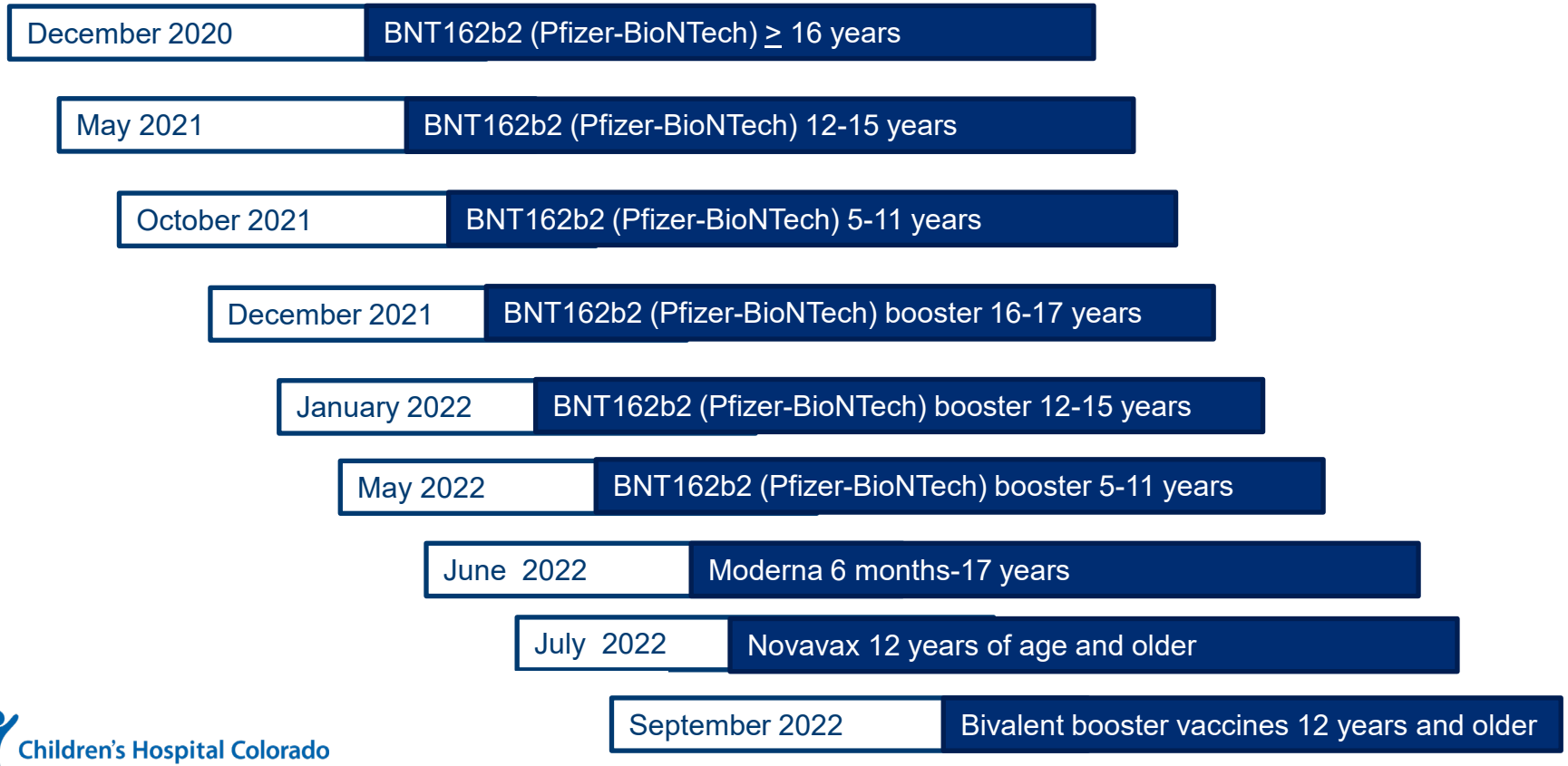
Ref: Rao et al. JAMA Pediatr. August 2022

How to help care for children with PASC

- Workup: if necessary to rule out other conditions
- Referrals: integrative medicine, rehab/PT, pulmonary, cardiology (POTS), counseling, ID, GI, PASC clinic if available
- Consider alternative therapies, integrative medicine
- Develop relationships, support through recovery
- Early data suggests that children recover faster than adults – better prognosis
- Routine follow-up appointments with patient to check in and measure progress, every 1-3 months
- Patient support sites
- Help support through school

Prevention – COVID-19 vaccination

Timeline of vaccination in children



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How well do vaccines work in children?

Pfizer's Covid-19 vaccine had 100% efficacy for 12-15 year olds, 88% efficacy in children 6-11 years of age, and 80.3% efficacy in children under 5 years old (3 doses)

Moderna vaccine efficacy for children between 6 months and 2 years of age was 43.7%, and 37.5% for 2-6 year olds (note 2 doses and during omicron wave)

Study in Singapore, VE was 65.3% against all PCR confirmed infection and 82.7% against hospitalizations

Study in US, VE was 68% against hospitalizations and 79% against critical illness during omicron

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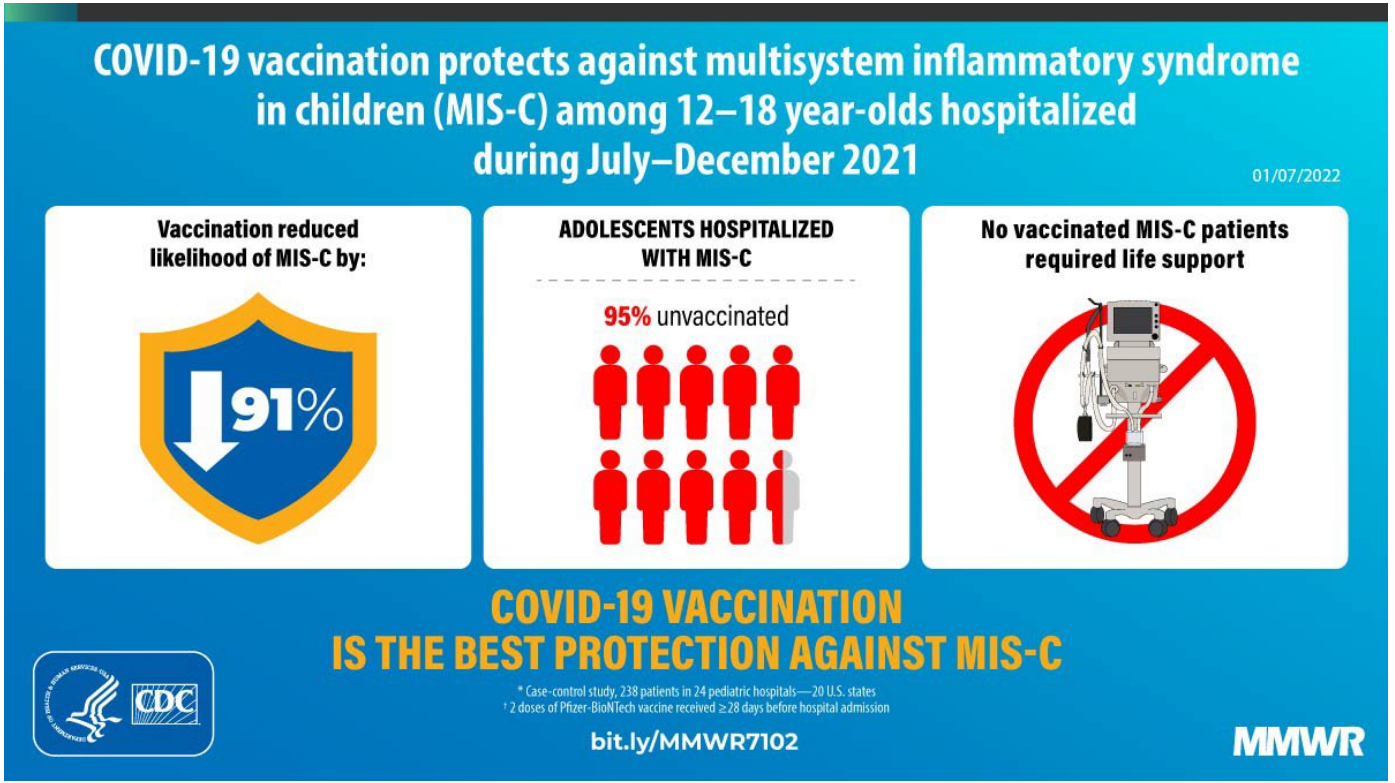
N Engl J Med 2022; 386:1899-1909;

Protection against MIS-C through vaccination



Vaccine recommendations

6 months to 4 years of age	1st dose (monovalent) 2nd dose 3-8 weeks after first dose (mono or biv) 3rd dose at least 8 weeks after second dose (mono or biv Pfizer only) Up to date – 2 weeks after third dose for Pfizer, 2 weeks after second dose for Moderna
5 to 11 years of age	1st dose (monovalent) 2nd dose 3-8 weeks after first dose (mono or biv) 3rd dose at least 5 months after second dose (mono or biv Pfizer only) Up to date – immediately after third dose for Pfizer, 2 weeks after second dose for Moderna

Vaccine recommendations

12-17 years of age	1st dose (monovalent) 2nd dose 3-8 weeks after first dose (mono or biv) 3rd dose at least 8 weeks after second dose or last booster, and can only be Pfizer-BioNTech biv Booster doses- can be different from primary series Up to date- after most recent booster recommendation

Vaccine information

Find Out When You Can Get Your Booster

Boosters are an important part of protecting yourself from getting seriously ill or dying from COVID-19. They are recommended for most people.

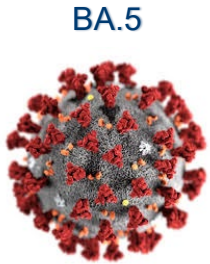
Use this tool to determine when or if you (or your child) can get one or more COVID-19 boosters.

Find Out When to Get a Booster >

This tool is intended to help you make decisions about getting COVID-19 vaccinations. It should not be used to diagnose or treat COVID-19.

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html?s_cid=11747:cdc%20up%20to%20date%20vaccine:sem.ga:p:RG:GM:gen:PTN:FY22

Take home points



Thank you