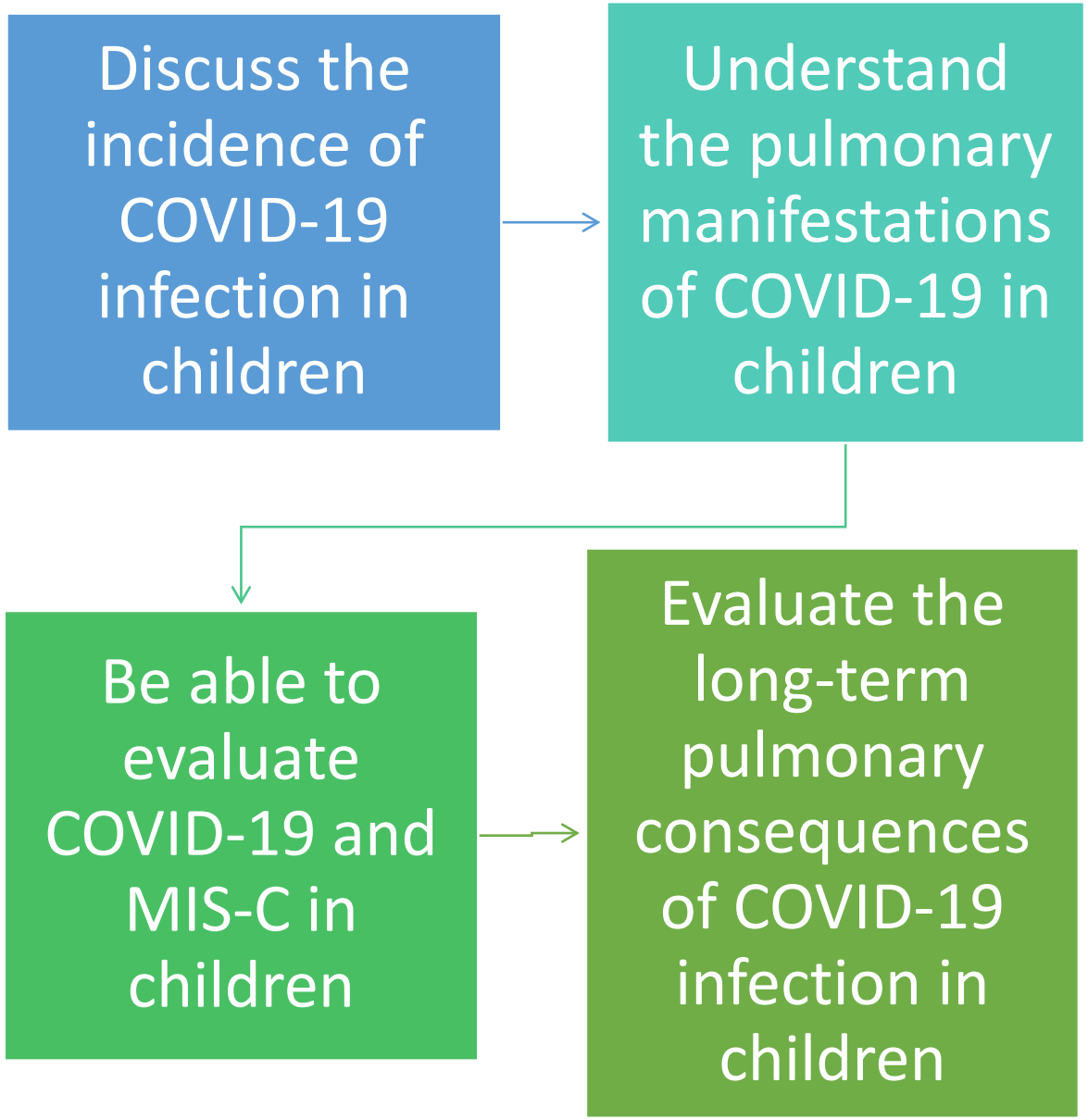
Pediatric Lungs and COVID-19

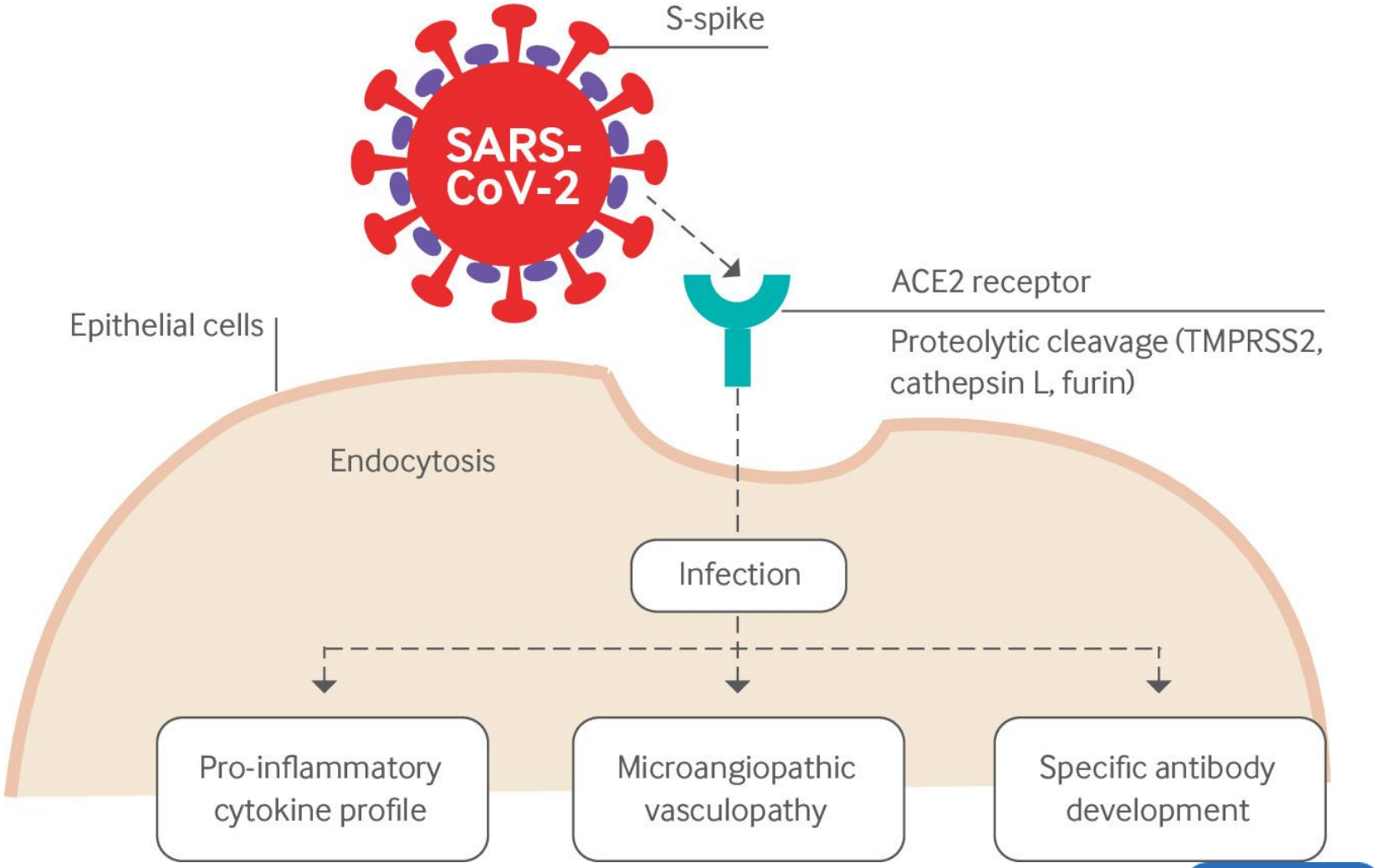
- Cori Daines, MD
- Pediatric Pulmonary and Sleep Medicine
- University of Arizona

- August 17, 2021

Objectives

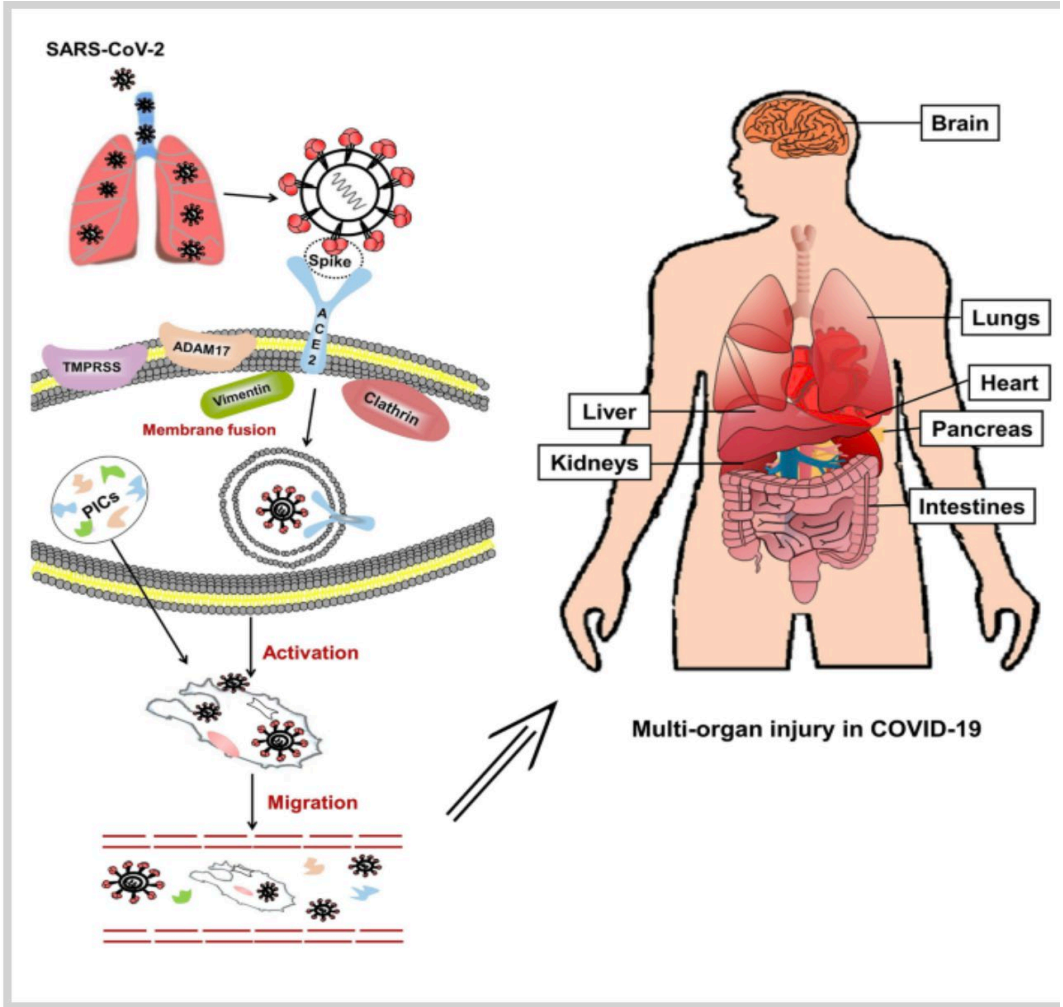

Discuss the incidence of COVID-19 infection in children
Understand the pulmonary manifestations of COVID-19 in children
Be able to evaluate COVID-19 and MIS-C in children
Evaluate the long-term pulmonary consequences of COVID-19 infection in children

SARS-CoV-2 S spike protein binds to the ACE2 receptor, which leads to proteolytic cleavage by TMPRSS2, cathepsin L, and furin in the epithelial cell of the respiratory tract.



Amy H Attaway et al. BMJ 2021;372:bmj.n436

Pathogenesis

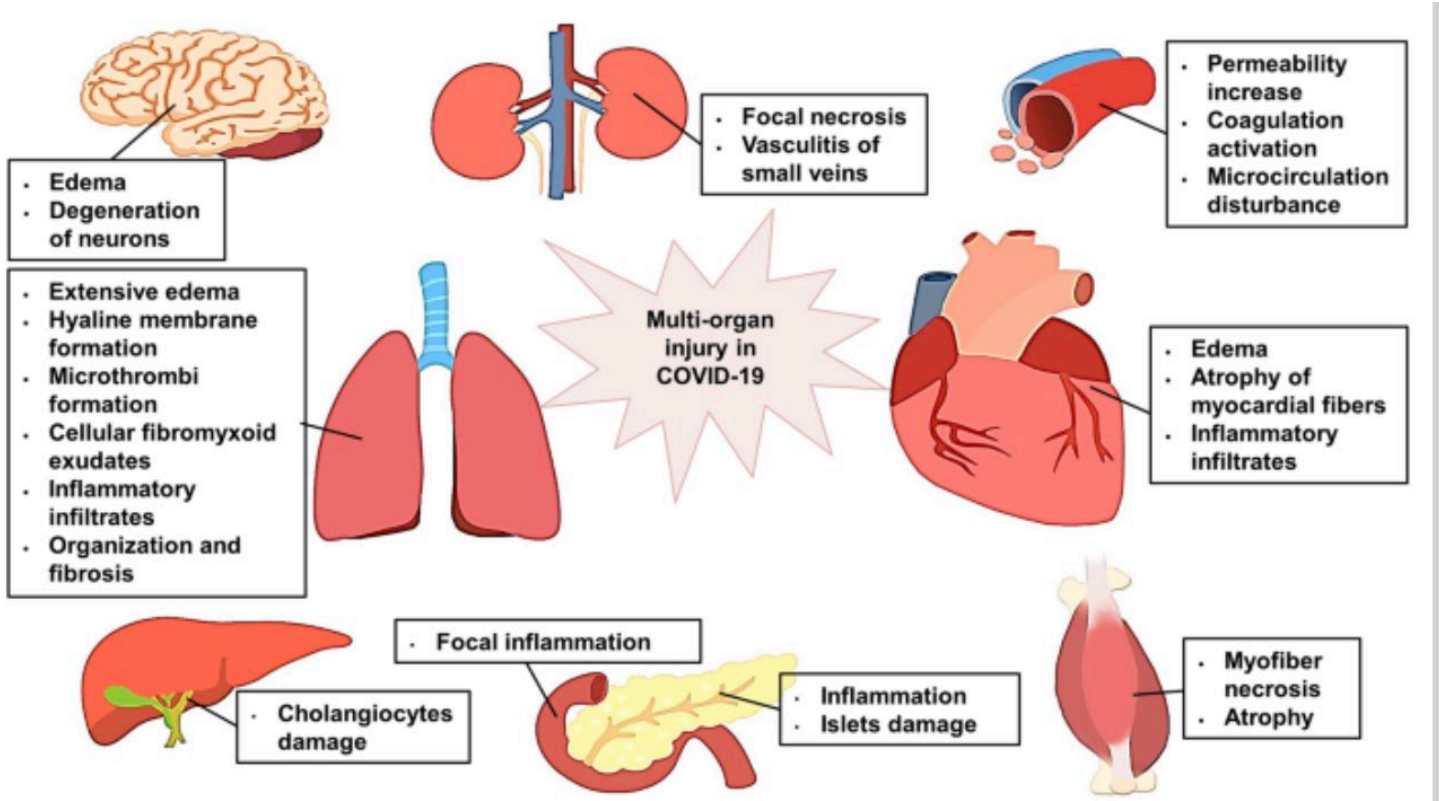


Ni W, et al Crit Care 2020

- ACE2 receptors are found in large quantities on the surfaces of these organs.

- ACE2 receptors are up-regulated in diabetes, obesity, male sex, advancing age, smokers. Theses same risk factors associate with impaired immune response.

Pathogenesis



Main organs involved in COVID-19

Ni W, et al Crit Care 2020

COVID-19 Weekly Cases per 100,000 Population by Age Group, United States

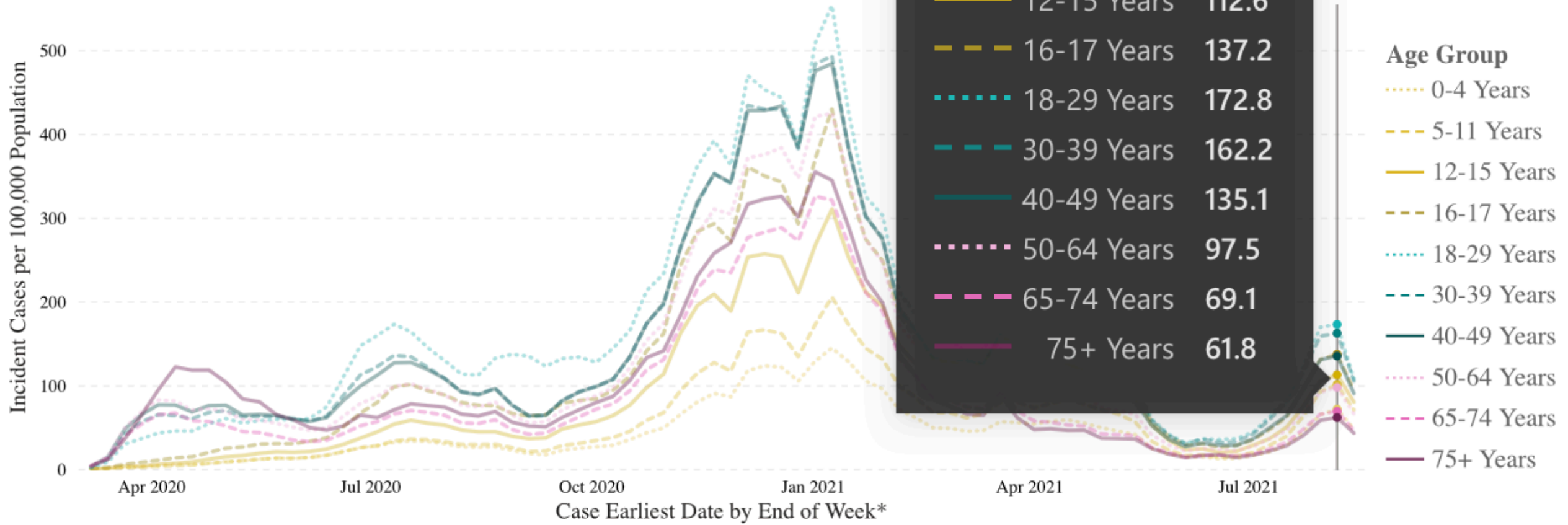
Jurisdiction: US

3/7/2020 – 8/14/2021

August 01, 2021 - August 07, 2021*

Cases | Deaths

Sex | Age | Race/Ethnicity



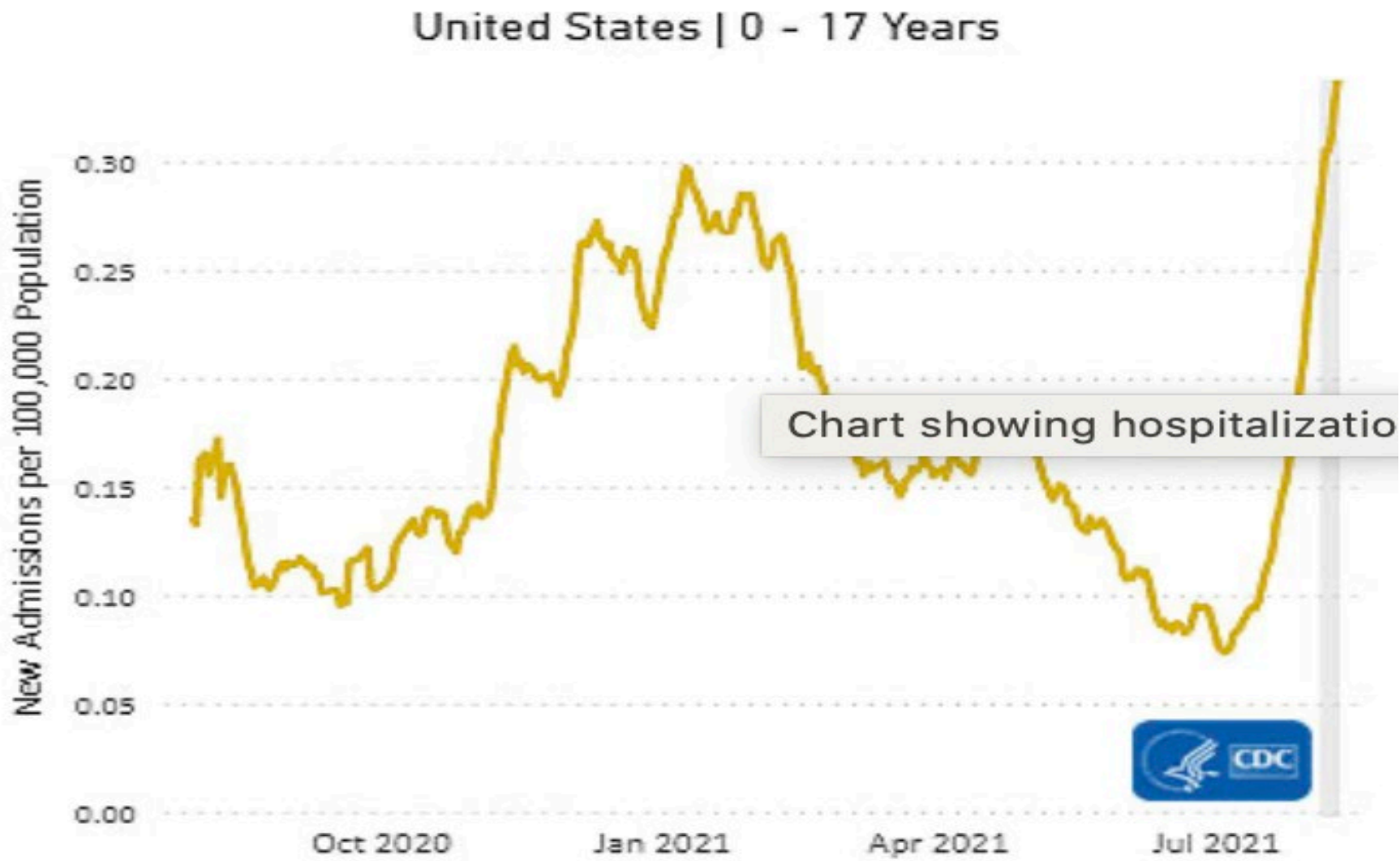
US: The most recent line level case record was reported during the week ending on Aug 14, 2021. Percentage of cases reporting age by date - 98.89%

US territories are included in case and death counts but not in population counts. Potential two-week delay in case reporting to CDC denoted by gray bars.

**Case Earliest Date is the earliest of the clinical date (related to illness or specimen collection and chosen by a defined hierarchy) and the Date Received by CDC.*

Last Updated: Aug 16, 2021

Source: CDC COVID-19 Case Line-Level Data, 2019 US Census, HHS Protect; Visualization: Data, Analytics & Visualization Task Force and CDC CPR DEO Situational Awareness Public


United States | 0 - 17 Years
New Admissions per 100,000 Population
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Oct 2020
Jan 2021
Apr 2021
Jul 2021
Chart showing hospitalizatio
CDC

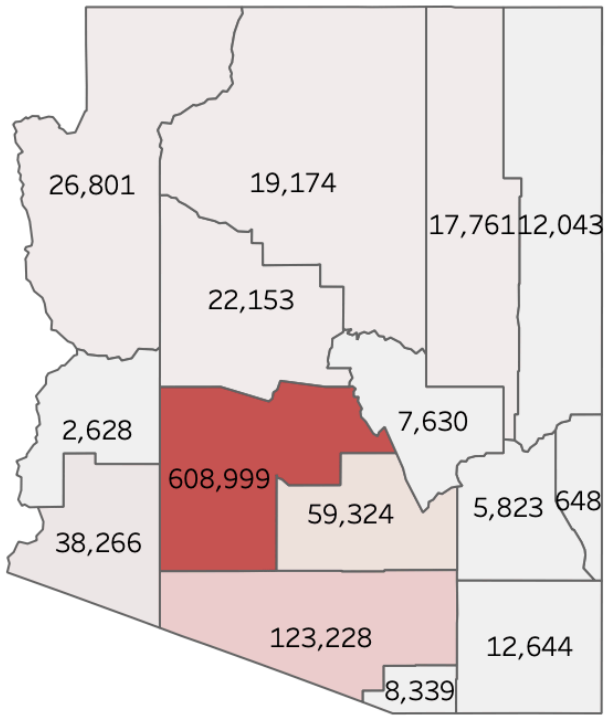
Demographics

Number of Cases
965,462

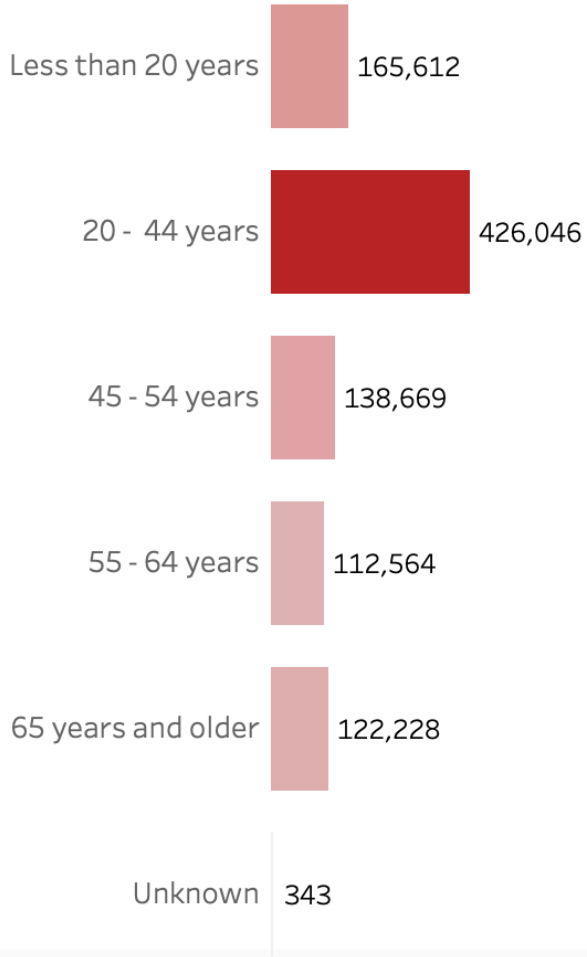
Hover over the icon to get more information on the data in this dashboard.

Select a county to filter the other graphs.

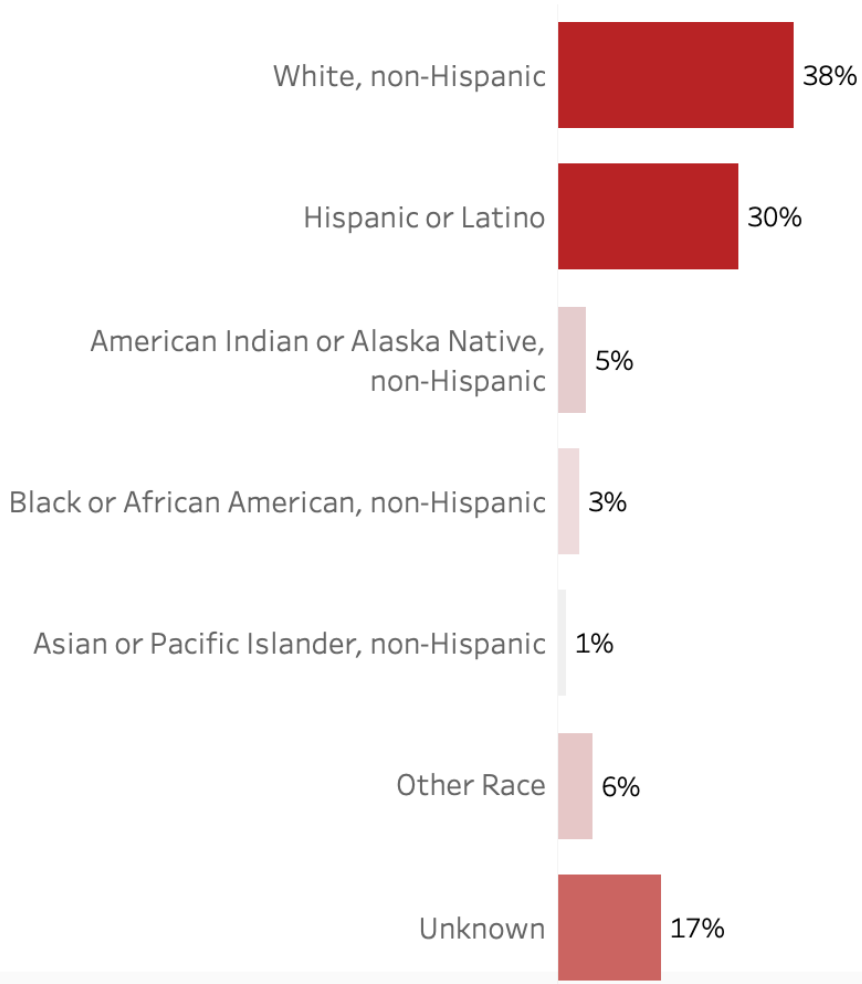
Graphs will not be displayed for counties with fewer than 10 cases.



COVID-19 Cases by Age Group



COVID-19 Cases by Race/Ethnicity



AZ Dept of Health Website

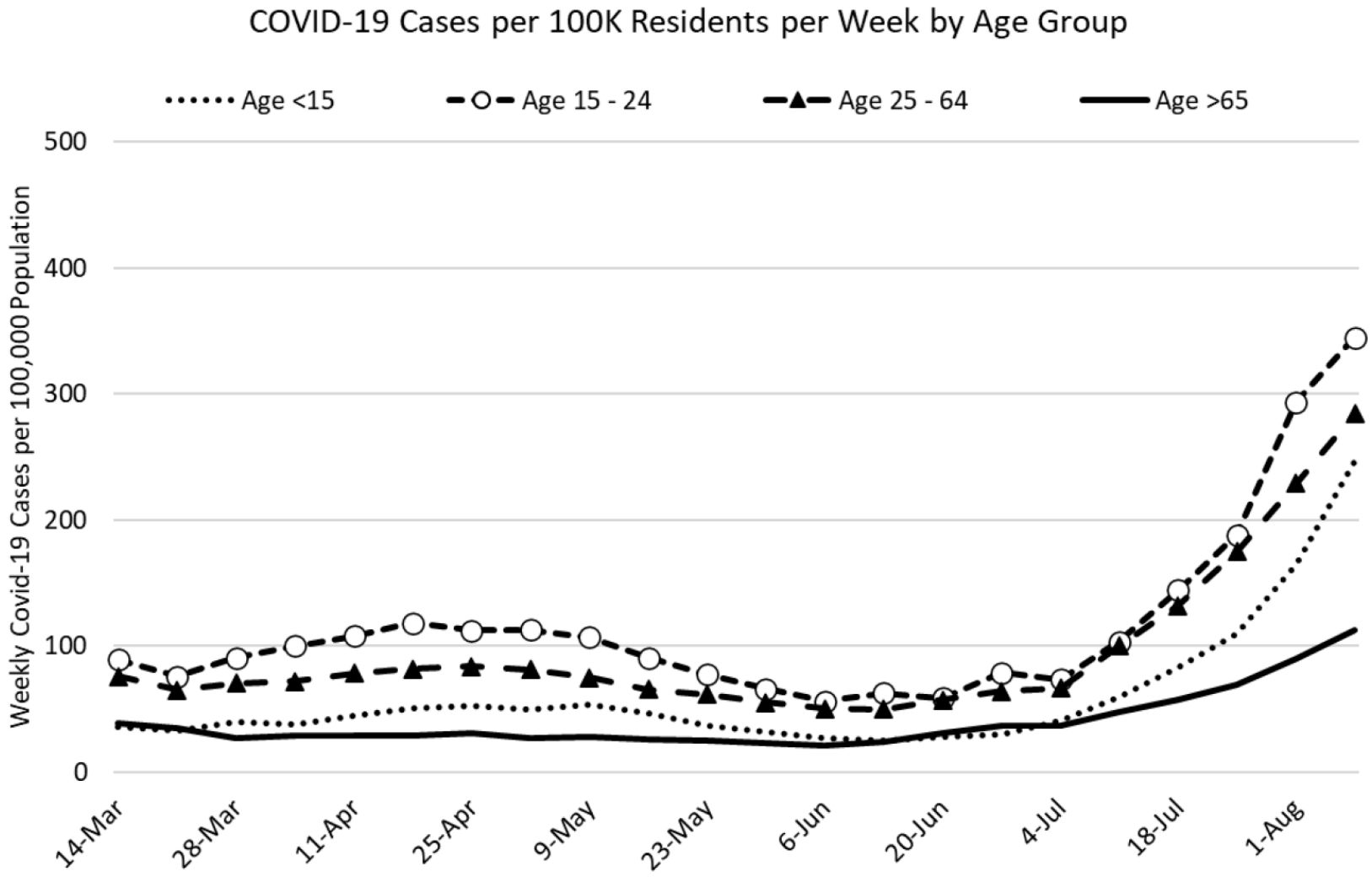


Figure 2a. Newly Diagnosed Covid-19 Cases in Arizona by Age Group March 7 – August 8, 2021.

While difficult to appreciate, Figure 2a shows a new reversal of relative position between children (dotted) and older adults (solid). Historically, children 15 – 19 years of age have had rates approximating those of adults while prepubertal children have had meaningfully lower rates; however, rates among those age 5 – 9 years resemble those of their older counterparts in the presence of the Delta variant and the absence of effective non-pharmacologic measures (see CDC and the American Academy of Pediatrics recommendations; Figure 2b).

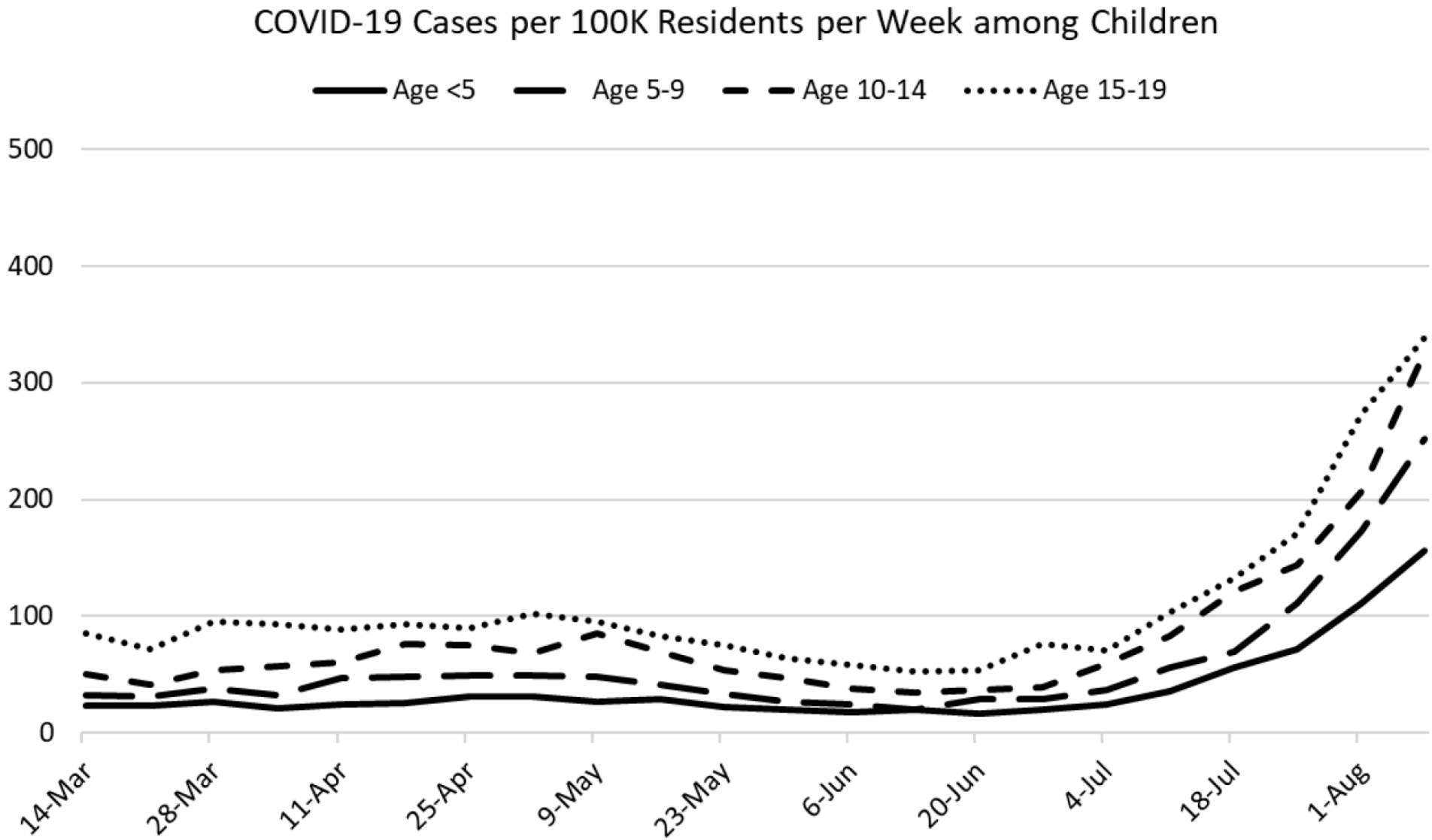


Figure 2b. Newly Diagnosed Covid-19 Cases in Arizona by Age Group March 7 – August 8, 2021.

Created by: Joe K. Gerald, MD, PhD (Associate Professor, Zuckerman College of Public Health, geraldj@email.arizona.edu) with assistance from Patrick Wightman, PhD from the UA Center for Population Health Sciences.

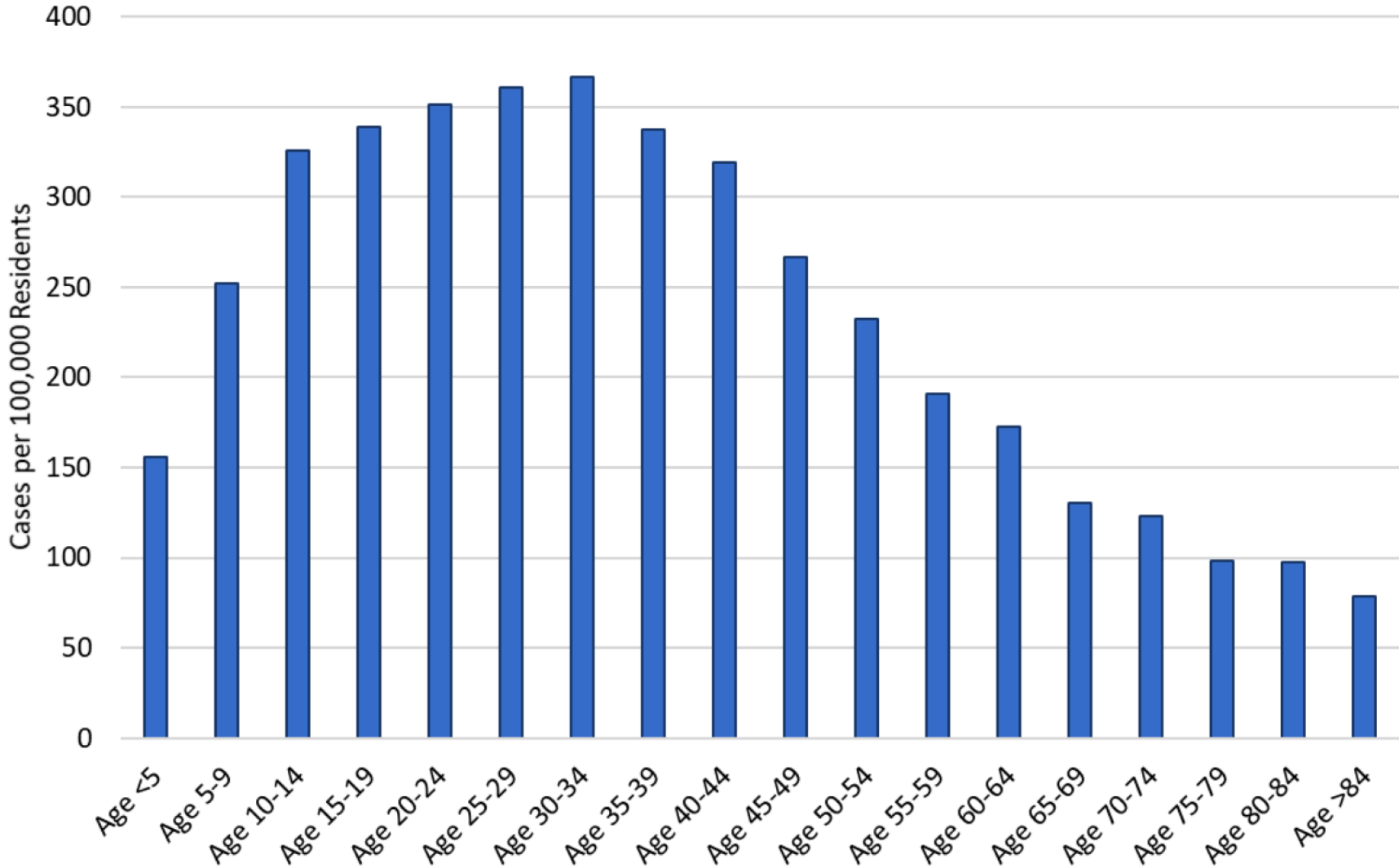


Figure 2c. Weekly COVID-19 Incidence by Age Group August 1 - 8, 2021.

Vaccination has only modestly shifted the age distribution of cases with children “switching” relative position with older adults (Figure 2d). Children now represent about 18% of cases, up from 10% during the winter 2020 outbreak, while older adults now represent about 8% of cases, down from 15% during the winter 2020 outbreak.

Symptoms in Children

- Begin 2-14 days after exposure
- Fever and chills
- Cough
- Shortness of breath or difficulty breathing
- Headache
- Sore throat
- New loss of taste or smell
- Congestion or runny nose
- Diarrhea

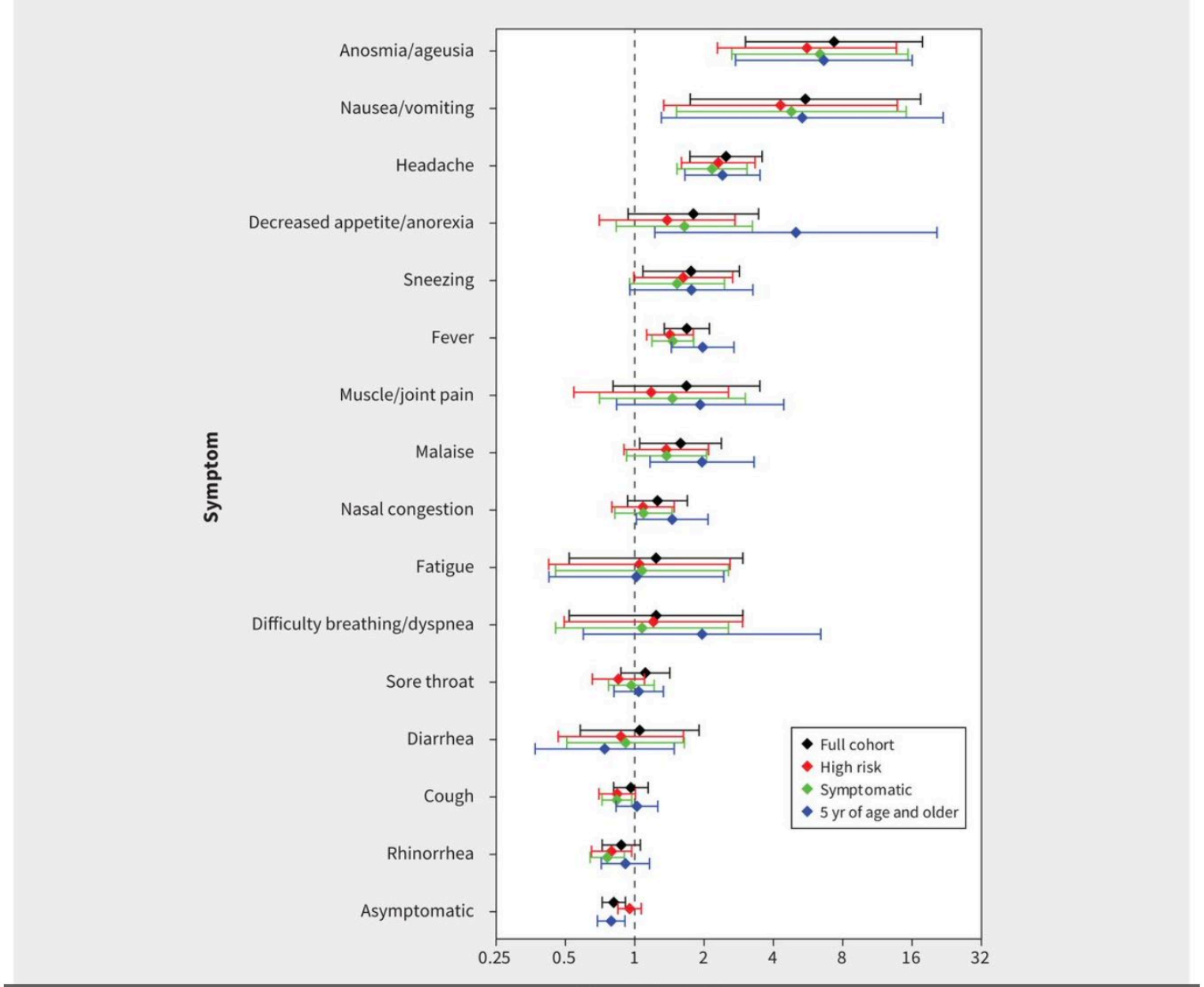
Symptoms with Positive Swab

Variable	No. (%) in patients with positive SARS-CoV-2 swab* $n = 1987$	No. (%) in patients with negative SARS-CoV-2 swab* $n = 476$	Unadjusted OR (95% CI)	Unadjusted positive LR for SARS-CoV-2 infection (95% CI)
Demographic characteristic				
Age, yr; mean ± SD	9.3 ± 5.2	8.5 ± 5.3	NA	NA
Age 0–4 yr	458 (23.0)	143 (30.0)	0.70 (0.56–0.87)	0.77 (0.65–0.90)
Age 5–12 yr	849 (42.7)	199 (41.8)	1.04 (0.85–1.27)	1.02 (0.91–1.15)
Age 13–17 yr	680 (34.2)	134 (28.2)	1.33 (1.07–1.65)	1.22 (1.04–1.42)
Male sex	989 (49.8)	254 (53.4)	0.87 (0.71–1.06)	0.93 (0.85–1.03)
Symptom				

King JA et al CMAJ 2021

Symptom	+swab	-swab		
Anosmia/ageusia	153 (7.7)	5 (1.1)	7.86 (3.21–19.26)	7.33 (3.03–17.76)
Nausea/vomiting	69 (3.5)	Suppressed as count < 5	5.67 (1.78–18.10)	5.51 (1.74–17.43)
Headache	312 (15.7)	30 (6.3)	2.77 (1.88–4.09)	2.49 (1.74–3.57)
Decreased appetite/anorexia	75 (3.8)	10 (2.1)	1.83 (0.94–3.56)	1.80 (0.94–3.45)
Sneezing	132 (6.6)	18 (3.8)	1.81 (1.09–2.99)	1.76 (1.08–2.85)
Fever or feverish chills	506 (25.5)	72 (15.1)	1.92 (1.46–2.51)	1.68 (1.34–2.11)
Muscle/joint pain (myalgia, arthralgia, muscular or joint pain)	56 (2.8)	8 (1.7)	1.70 (0.80–3.58)	1.68 (0.80–3.49)
Malaise	165 (8.3)	25 (5.3)	1.63 (1.06–2.52)	1.58 (1.05–2.38)
Nasal congestion	241 (12.1)	46 (9.7)	1.29 (0.93–1.80)	1.26 (0.93–1.69)
Fatigue	31 (1.6)	6 (1.3)	1.24 (0.51–2.99)	1.24 (0.52–2.95)
Difficulty breathing/dyspnea	31 (1.6)	6 (1.3)	1.24 (0.51–2.99)	1.24 (0.52–2.95)
Sore throat	311 (15.7)	67 (14.1)	1.13 (0.85–1.51)	1.11 (0.87–1.42)
Diarrhea	57 (2.9)	13 (2.7)	1.05 (0.57–1.94)	1.05 (0.58–1.90)
Cough	486 (24.5)	121 (25.4)	0.95 (0.75–1.20)	0.96 (0.81–1.14)
Rhinorrhea	383 (19.3)	105 (22.1)	0.84 (0.66–1.08)	0.87 (0.72–1.06)
Chest pain	15 (0.8)	Suppressed as count < 5	NA	NA
Conjunctivitis	11 (0.6)	Suppressed as count < 5	NA	NA
Asymptomatic	714 (35.9)	211 (44.3)	0.70 (0.58–0.86)	0.81 (0.72–0.91)

King JA et al CMAJ 2021



Positive likelihood ratios (LRs) for symptoms associated with positive results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) swabs in children in Alberta. Estimates of positive LRs and associated 95% confidence intervals (CIs) are shown for the full cohort (black), those children identified as having a high risk of exposure through contact tracing (red), those with at least 1 symptom (green) and those aged 5 years or older (blue).

King JA et al CMAJ 2021

TABLE 4. - Signs and Symptoms of Children With COVID-19, Greece, February 26 to June 30, 2020

Signs/symptoms	N (%)
	N = 92
Fever	42 (45.6)
Low-grade fever	26 (28.3)
Runny nose	25 (27.5)
Cough	24 (26.1)
Headache	17 (18.5)
Sore throat	11 (12)
Diarrhea	10 (10.9)
Loss of taste and/or smell	9 (9.8)
Weakness	9 (9.8)
Myalgia	8 (8.8)
Dyspnea	7 (7.6)
Nausea/vomiting	5 (5.4)
Arthralgia	4 (4.3)
Abdominal pain	2 (2.2)
Restlessness/irritation	1 (1.1)

Maltezou HC et al
Pediatr Infect Dis 2020

Multisystem Inflammatory Syndrome in Children (MIS-C) Criteria

- <21 years
- Fever >/= 38.0 degrees C for >/= 24 hours
- Evidence of inflammation: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH or IL-6 or low lymphocytes or albumin
- Multisystem involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurologic)
- No alternative diagnosis
- Positive SARS-CoV-2 infection or exposure to confirmed COVID-19 case within the 4 weeks prior to symptom onset

cdc.gov

MIS-C Phenotypes

Three groupings:

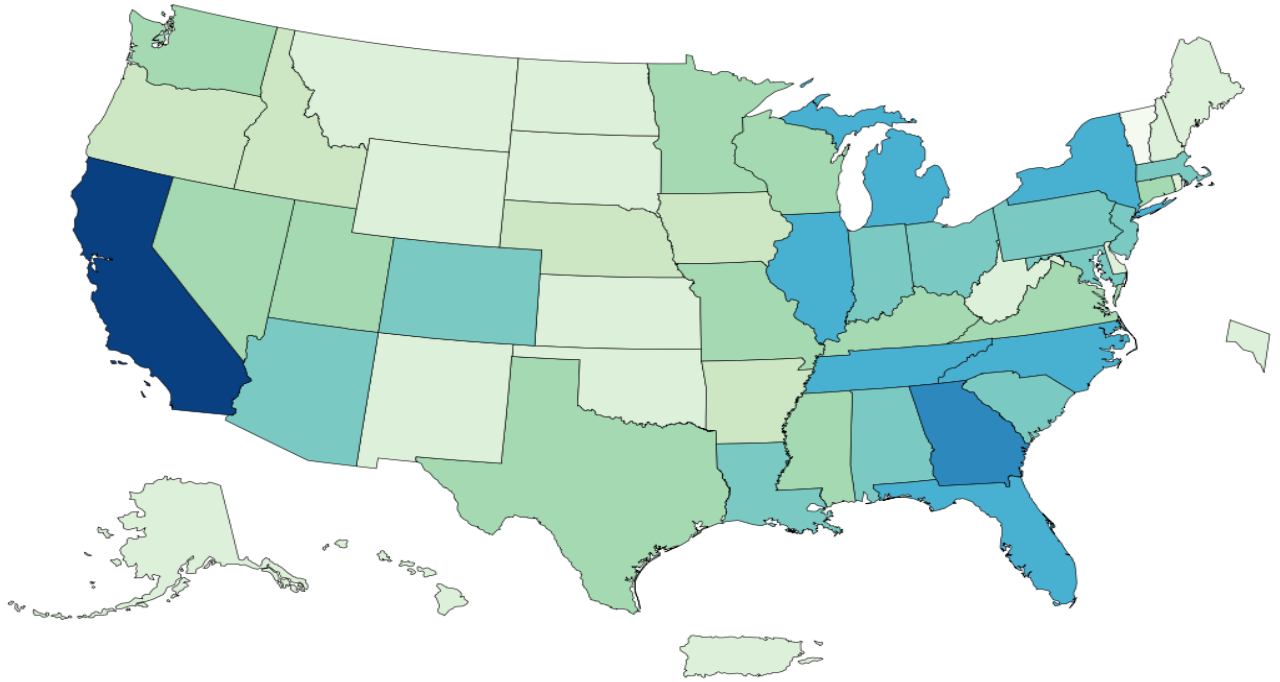
Type 1—multisystem involvement with cardiovascular and gastrointestinal involvement and higher prevalence of abdominal pain, shock, myocarditis, lymphopenia and inflammatory markers

Type 2—respiratory system involvement with cough, shortness of breath, pneumonia and ARDS and case fatality rate over 5%

Type 3– younger, more like Kawasaki with rash, mucosal lesions, lowest prevalence of complications and lower inflammatory markers

Godfred-Cato S et al MMWR Morb Mortal Wkly Rep 2020

Reported MIS-C Case Ranges by Jurisdiction, on or before July 30, 2021*



AS FSM GU MP PW RMI VI

Reported MIS-C Cases

- No case reported
- 1-24 cases
- 25-49 cases
- 50-99 cases
- 100-149 cases
- 150-199 cases
- 200-249 cases
- 250-299 cases
- 300+ cases

Total cases: 4404
Total deaths: 37

cdc.gov

Confounders—the ACE2 Receptor

ACE2 is a receptor protein on epithelial cells

Breaks down large protein angiotensin II which causes inflammation and bronchoconstriction

In smokers and likely vapers, ACE2 is upregulated—more receptors

ACE2 is also the target of the SARS-CoV-2 virus, so more ACE2 means more sites for virus to bind

Rates of ICU hospitalization and ventilator need in COVID-19 are 2 times higher in smokers

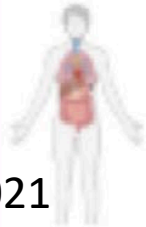
Effects of electonic cigarette use on the respiratory system

increased mucosal permeability, impaired muco-ciliary clearance, peri-bronchial inflammation and fibrosis

upregulation of ACE2 receptors on the lung epithelium

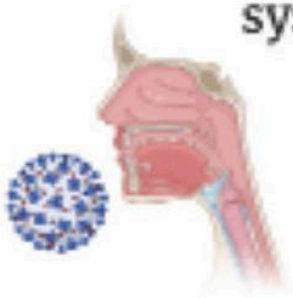
compromised neutrophil trafficking, NET formation, humoral and cell-mediated immune responses

upregulation of pro-inflammatory biomarkers, such as IL-6, TNF-a



cytokine storm leading to multi-organ inflammation, damage and ultimately failure

Effects of SARS-CoV-2 (COVID-19) on the respiratory system



pathogen entry into host via respiratory droplets or aerosols

binding of the S2 domain on the coronavirus to the ACE2 receptor on lung epithelium

compromised neutrophil trafficking, NET formation, humoral and cell-mediated immune responses

upregulation of pro-inflammatory biomarkers, such

cytokine storm resulting in pneumonia, as well as multi-organ inflammation, damage and ultimately failure (MIS-C)

Brar E et al Front Pediatr 2021

	Ever-use of inhaled tobacco and…			Past 30-day use of inhaled tobacco and…		
	COVID-19–related symptoms (n = 4,043)	COVID-19 test (n = 4,048)	COVID-19–positive diagnosis (n = 4,048)	COVID-19–related symptoms (n = 4,043)	COVID-19 test (n = 4,048)	COVID-19–positive diagnosis (n = 4,048)
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Inhaled tobacco products						
Cigarettes only	1.40 (.83, 2.38)	**3.94 (1.43, 10.86)**	2.32 (.34, 15.86)	1.15 (.58, 2.27)	1.16 (.64, 2.12)	1.53 (.29, 8.14)
E-cigarettes only	1.18 (.80, 1.73)	**3.25 (1.77, 5.94)**	**5.05 (1.82, 13.96)**	1.43 (.84, 2.43)	**2.55 (1.33, 4.87)**	1.91 (.77, 4.73)
Dual use	1.36 (.90, 2.04)	**3.58 (1.96, 6.54)**	**6.97 (1.98, 24.55)**	**4.69 (3.07, 7.16)**	**9.16 (5.43, 15.47)**	**6.84 (2.40, 19.55)**
Never used	Ref	Ref	Ref	Ref	Ref	Ref

Children and youth 13-24 yrs

More common symptoms if smoked and vaped – cough, fever, fatigue, difficulty breathing

And more likely to get a COVID-19 test

But even more likely to have a POSITIVE COVID-19 test

HELP YOUR ADOLESCENTS STOP VAPING

Giaha SM, et al *J Adol Health* 2020

Long-term Symptoms in Adults

- Symptom report in the Netherlands during infection and 79 days later—2001 people not hospitalized, 112 hospitalized

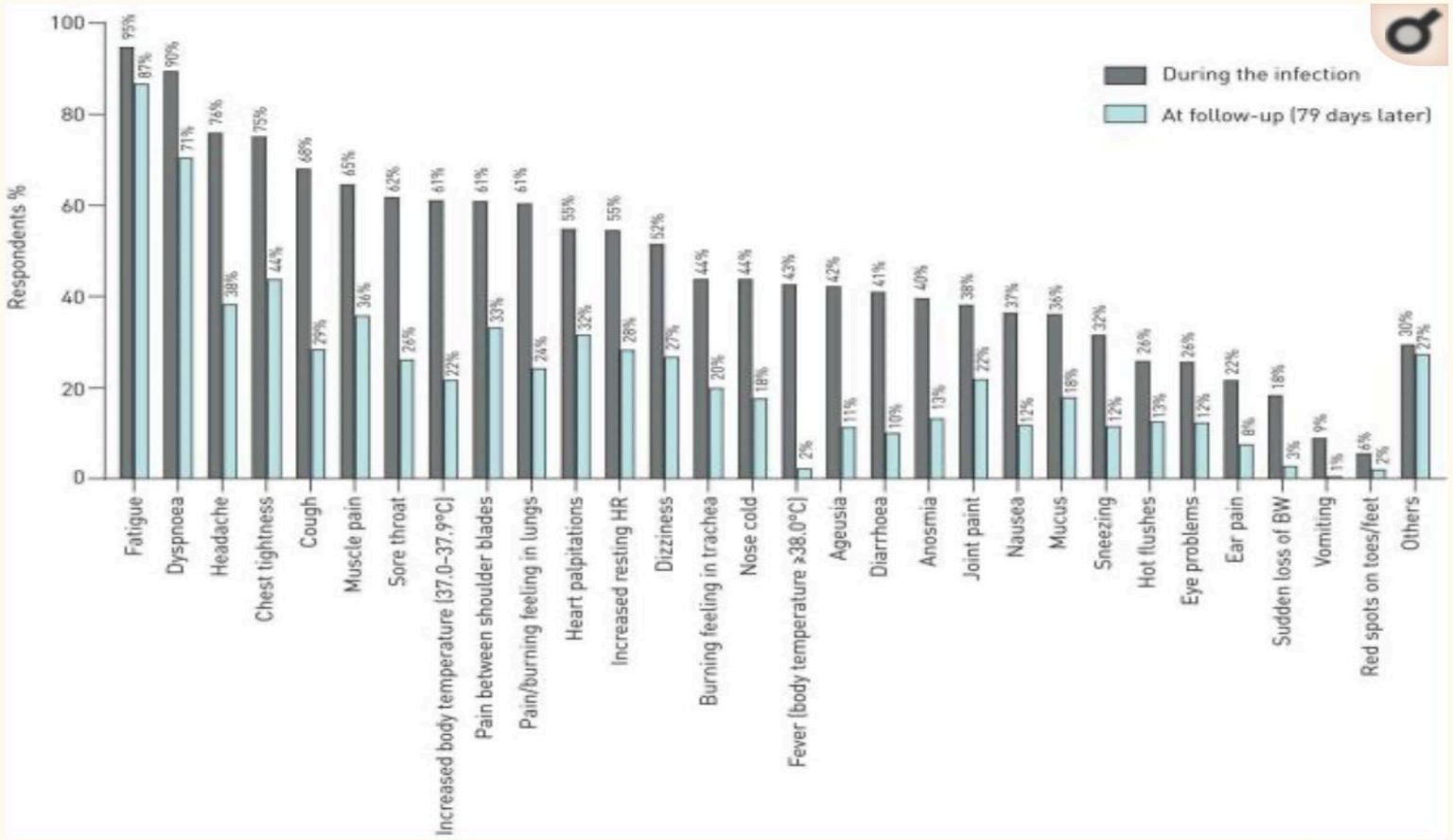


FIGURE 2

Prevalence of symptoms during the infection and at follow-up (79 days later). BW: body weight; HR: heart rate.

Goetz D, et al ERJ Open Res 2020

Long COVID (Adults and Children)

Characteristic	All	0–15 years	16–30 years	31–45 years	46–60 years	Over 60 years
	% (*n*/*N*)	% (*n*)	% (*n*)	% (*n*)	% (*n*)	% (*n*)
	N = 247	*N* = 16	*N* = 61	*N* = 58	*N* = 67	*N* = 45
Age, median (IQR)	43 (27–55)	8 (6–12)	24(22–27)	37 (34–41)	53 (49–55)	67 (63–73)
Female gender	53% (131/247)	56% (9)	54% (33)	52% (30)	52% (35)	53% (24)
Status at 6 months						
Any symptoms	55% (136/247)	13% (2)*	52% (32)	59% (34)	61% (41)	60% (27)
Fever	2% (4/247)	0% (0)	0% (0)	5% (3)	1% (1)	0% (0)
Cough	6% (15/247)	0% (0)	0% (0)	9% (5)	4% (3)	16% (7)
Dyspnea	15% (38/247)	0% (0)	13% (8)	17% (10)	18% (12)	18% (8)
Palpitations	6% (15/247)	0% (0)	3% (2)	7% (4)	9% (6)	7% (3)
Stomach upset	6% (15/247)	6% (1)	5% (3)	7% (4)	6% (4)	7% (3)
Disturbed taste/smell	27% (67/247)	13% (2)	28% (17)	34% (20)	28% (19)	20% (9)
Fatigue	30% (69/231)	- [a]	21% (13)	31% (18)	33% (22)	36% (16)
Concentration problems	19% (44/231)	- [a]	13% (8)	19% (11)	21% (14)	24% (11)
Memory problems	18% (42/231)	- [a]	11% (7)	16% (9)	22% (15)	24% (11)
Sleep problems	5% (13/247)	0% (0)	5% (3)	7% (4)	4% (3)	7% (3)
Headache	11% (28/247)	0% (0)	11% (7)	14% (8)	9% (6)	16% (7)
Dizziness	10% (24/247)	0% (0)	7% (4)	10% (6)	10% (7)	16% (7)
Tingling in fingers	4% (9/247)	0% (0)	0% (0)	2% (1)	4% (3)	11% (5)

Bloomberg B et al Nat Med 2021

Italian Study of Persistent Symptoms In Children

	All
Persisting symptoms	***N* 129**
Fatigue (compared to before COVID−19 diagno	
Less	1 (0.8%)
A bit less	16 (12.4%)
Same	98 (75.9%)
A bit more	13 (10.1%)
More	1 (0.8%)
Insomnia	24 (18.6%)
Nasal congestion/ rhinorrhoea	16 (12.4%)
Persistent muscle pain	13 (10.1%)
Headache	13 (10.1%)
Lack of concentration	13 (10.1%)
Weight loss	10 (7.7%)
Joint pain or swelling	9 (6.9%)
Skin rashes	9 (6.9%)
Chest tightness	8 (6.2%)
Constipation	8 (6.2%)
Persistent cough	7 (5.4%)
Altered smell	6 (4.6%)
Palpitations	5 (3.8%)
Chest pain	4 (3.1%)
Altered taste	4 (3.1%)
Hypersomnia	4 (3.1%)
Stomach/abdominal pain	3 (2.3%)
Diarrhoea	2 (1.5%)
Menstruation	2 (1.5%)
other: yes	3 (2.3%)
Any persisting symptoms	
None	54 (41.9%)
1–2	46 (35.6%)

Buonsenso D et al
Acta Paediatr 2021

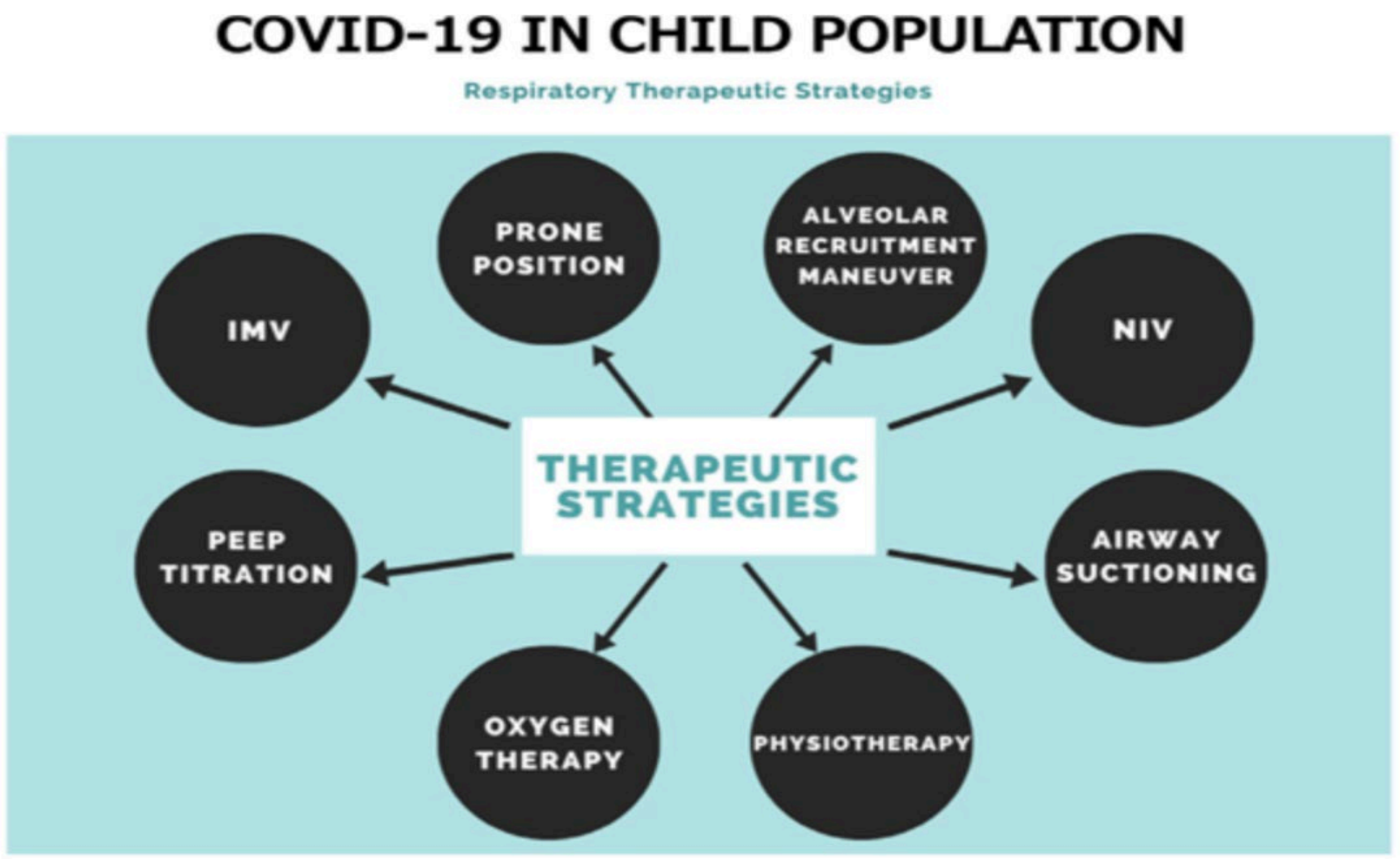
Possible Treatments for Hospitalized Children

Table 2 Therapeutic considerations for acute covid-19 by clinical syndrome/disease severity

Clinical scenario	Pharmacologic interventions
Hospitalized for mild to moderate covid-19 (not hypoxemic)	• Supportive care • No clear benefit for remdesivir or convalescent plasma • Steroids have no demonstrated benefit and may cause harm
Hospitalized for severe covid-19, but not critical (hypoxemic needing low flow supplemental oxygen)	• Supportive care • Corticosteroids (dexamethasone 6 mg/day × 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone) • May consider remdesivir • May benefit from use of tocilizumab.
Hospitalized for covid-19 and critically ill (needing HFNC, NIV, IMV, or ECMO)	• Supportive care • Corticosteroids (dexamethasone 6 mg/day × 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone) • May consider remdesivir • May benefit from use of tocilizumab.

Attaway AH, at al BMJ 2021

Pulmonary Acute Therapy Potential



NlH Treatment Guidelines in Children

- No RCT’s to reference
- COVID 19 is generally milder in children and requires no specific therapies
- Children with special health care needs and risk factors may be at more risk for severe disease
- Most mild COVID are managed w/ supportive care alone

Remdesivir in Children

- Hospitalized children >/= 12 y.o. w/ severe risk factors for severe disease or increasing O2 need
- Hospitalized children >/= 16 y.o. w/ increasing O2 need
- Consult ID for use in younger hospitalized children

Dexamethasone in Children

- Hospitalized children with HFNC O2/NIV/INV Ventilation/ECMO

Convalescent Plasma

- Against use in hospitalized children not requiring ventilation

Persistent Symptoms Post-COVID in Children

UK data—500,000 infections in children

12.9% of children 2-11 y.o. still have symptoms 5 weeks after infection

14.5% of children 12-16 y.o. still have symptoms 5 weeks after infection

Symptoms include fatigue, muscle and joint pain, headache, insomnia, respiratory problems, heart problems, gastrointestinal problems, nausea, dizziness, seizures, hallucinations, testicular pain

Thomson H et al New Scientist 2021

Respiratory Sequelae in Adults

- Adults 3 months post severe COVID-19 infections -- PFTs

	FEV1 (%)	89.4 ± 15.7
	FVC (L)	3.38 ± 0.81
	FVC (%)	83.64 ± 16.9
	FEV1/FCV	0.86 ± 0.06
	DLCO (%)	80.7 ± 14.3
PFT interpretation	Normal	n = 10
	Restrictive pattern	n = 2
	Restrictive + altered diffusion	n = 4
	Altered diffusion	n = 6
6MWDT, n = 20 (mean ± SD)	Distance (m)	514.4 ± 93.1
	Distance (%)	73.5 ± 12.3
	Distance < 80%	n = 13
	Desaturation	n = 6

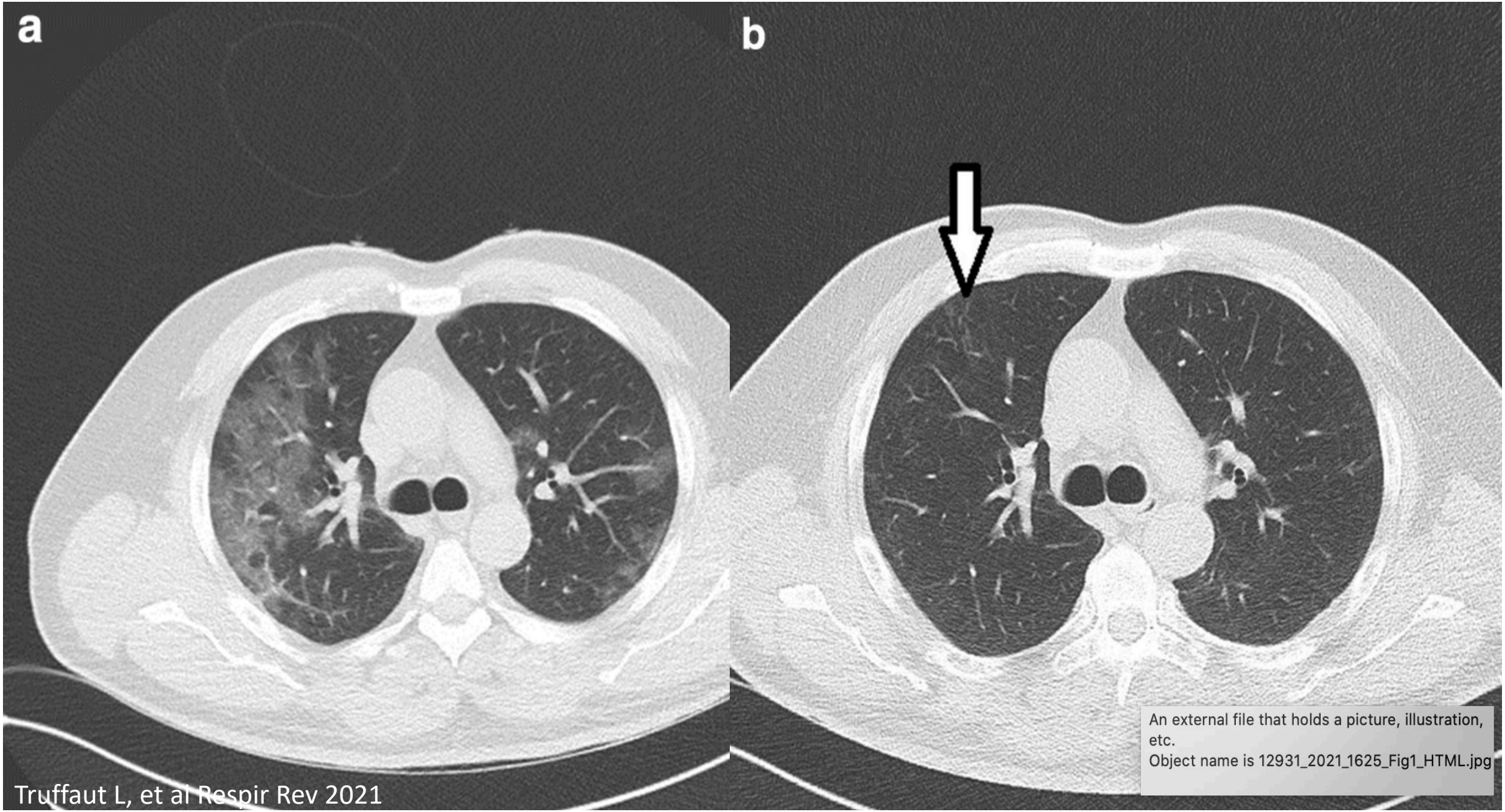
Truffaut L, et al Respir Rev 2021

Respiratory Sequelae in Adults

- Adults 3 months post severe COVID-19 infections—CT findings

Chest CT Scan, n = 22	*Baseline*	*3-months*
Normal	n = 0	n = 3
Number of affected segments in both lungs (mean ± SD), score/20	17.2 ± 19	8.1 ± 10.1
Predominant abnormalities		
Ground glass opacities	n = 22	n = 0
Consolidation	n = 16	n = 2
Fibrosis	n = 9	n = 19
Abnormalities distribution		
Peripheral location	n = 8	n = 7
Diffuse location	n = 14	n = 12
Lower lobes predominant involvement	n = 12	n = 11

Truffaut L, et al Respir Rev 2021



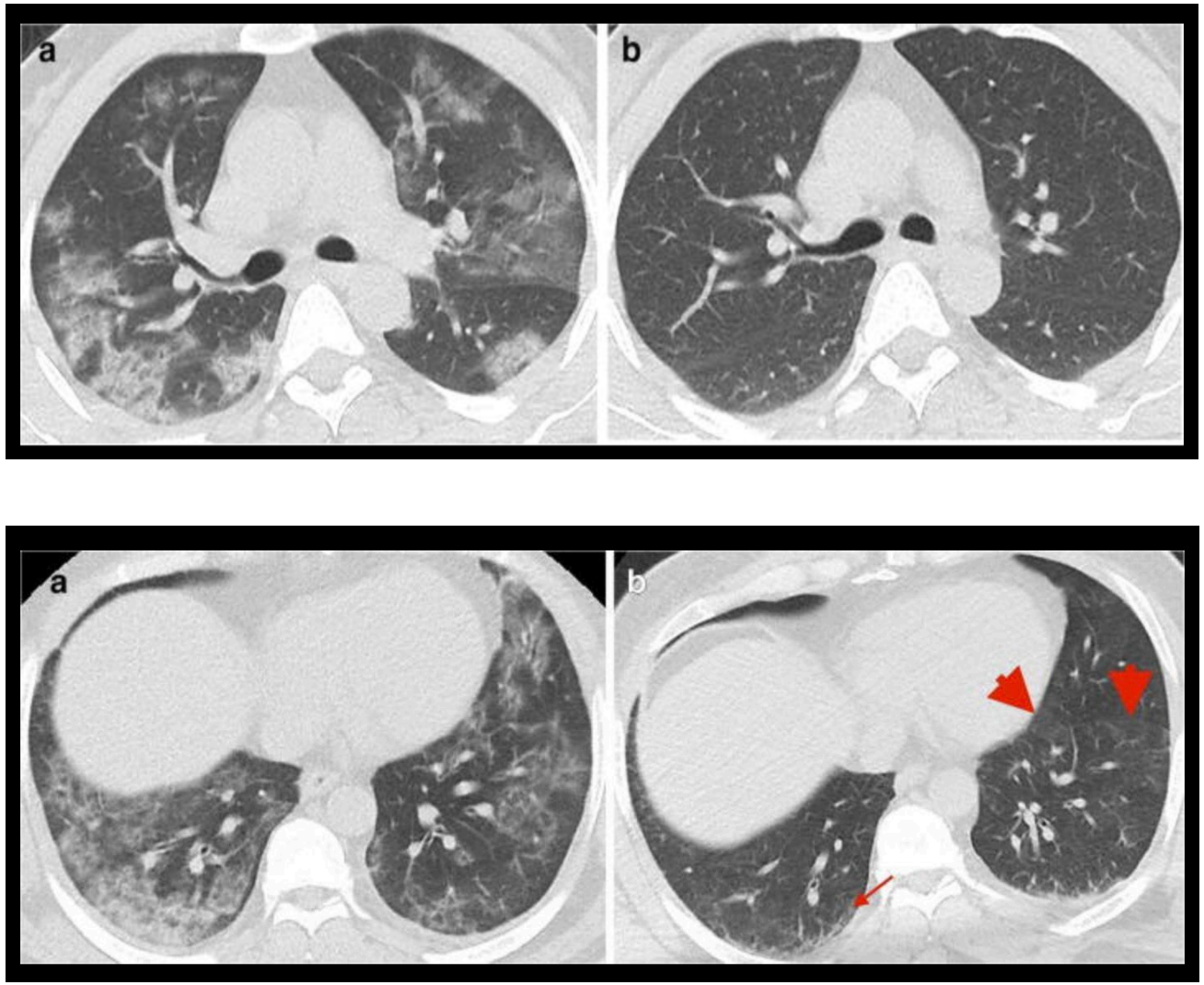
Truffaut L, et al Respir Rev 2021

Adults with COVID-19 Pneumonia

Minimum 3 month follow up

57.7% with full resolution (top)

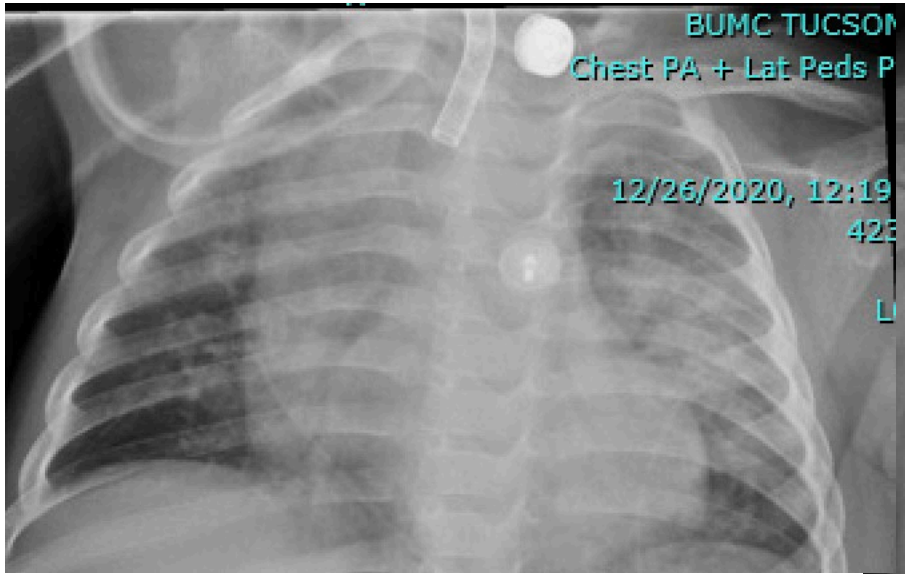
42.3% with residual disease (bottom)



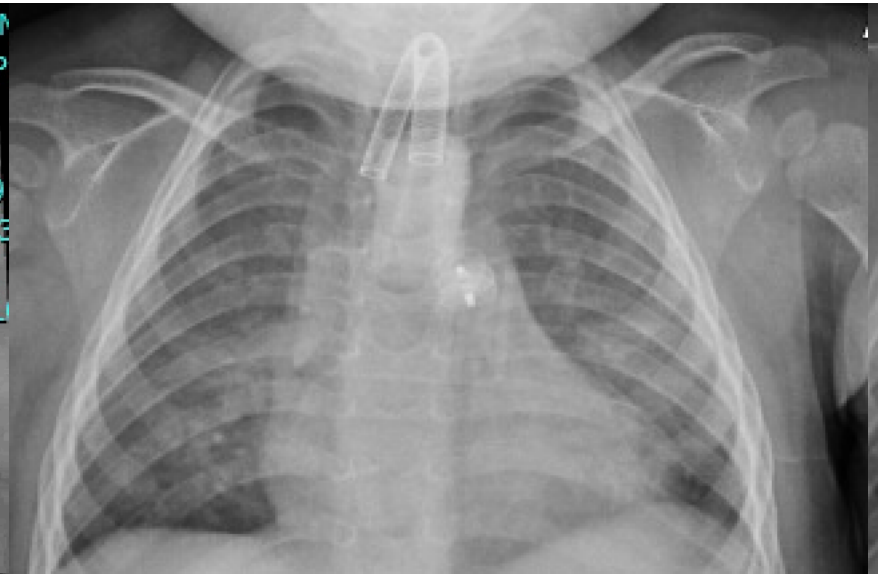
Tabatabaei SMH, et al Emerg Radiol 2020

Pulmonary Sequelae in Children

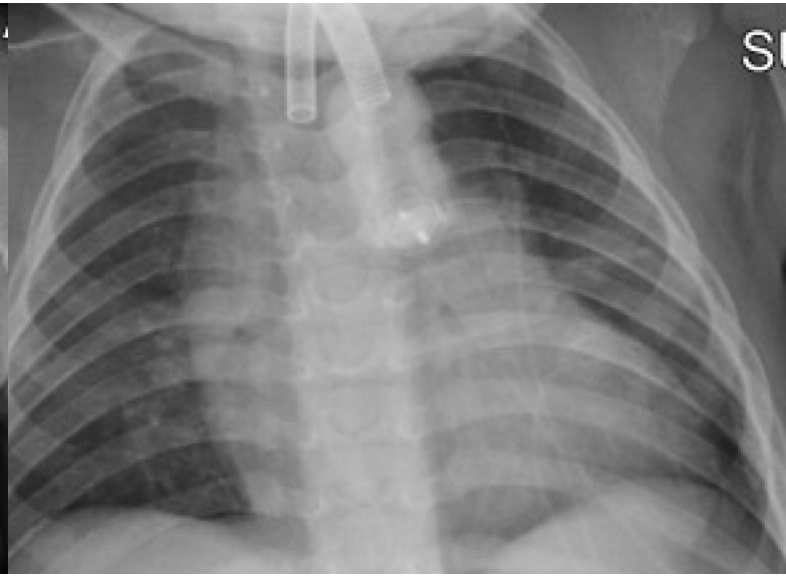
- No data
- Symptoms clearly persist in some children
- Children are at risk for MIS-C
- Data from adults suggest we should be watchful, especially if underlying conditions



December



January



April

American Academy of Pediatrics Recommendations

- All patients who test positive for SARS CoV-2 infection need at least one follow up with primary care—after quarantine is over and before returning to physical activities
- If moderate to severe symptoms, should follow up in person. If mild symptoms, follow up virtually is o.k.
- Encourage vaccination
- Facilitate return to learning and activity with plan for extra supports and time as necessary. Educational make-up plans, communication

More Recommendations

- If a child had moderate to severe COVID, should have a screening EKG, American Heart Association screening or cardiology evaluation
- Watchfulness for MIS-C as typically this does not occur until 2 to 4 weeks after infection
- Monitor for ongoing symptoms:

Respiratory: chest pain, cough, exercise induced dyspnea

- If ongoing for 3 months, get a CXR
- If 6 years or older, refer for pulmonary function testing
- Consider cardiopulmonary evaluation, thromboembolic evaluation

What Else--Control in Schools

- Frequent cleaning of surfaces
- Good ventilation
- Hand hygiene
- Face mask use
- Exclusion of sick children
- Vaccines

Ismail SA, Lancet Inf Dis 2021

References

- cdc.gov
- COCA presentations (many of the slides)
- State health offices
- aap.org