Clinical manifestations and diagnosis of coronavirus disease-19 in children

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Clinical manifestations of SARS-CoV-2 infection

- **Asymptomatic infection**
- Mild respiratory diseases
- Moderate-severe respiratory diseases:
  - Pneumonia, requiring oxygen supplementation
- Advanced diseases
  - Respiratory failure
  - **Multisystem inflammation syndrome**
  - Acute respiratory distress syndrome (ARDS)
  - Multiple organs failure
- **Extrapulmonary manifestations**
- Sequelae

Prevalence of **Asymptomatic** SARS-CoV-2 Infection

A Narrative Review (Oran DP & Topol EJ. Ann Intern Med 2020; doi:10.7326/M20-3012)

Table. Summary of SARS-CoV-2 Testing Studies

Cohort	Tested, *n*	SARS-CoV-2 Positive, *n* (%)	Positive but Asymptomatic, *n* (%)	Notes*
Iceland residents (6)	13 080	100 (0.8)	43 (43.0)	R
Vo', Italy, residents (7)	5155	102 (2.0)	43 (42.2)	R, L
Diamond Princess cruise ship passengers and crew (8)	3711	712 (19.2)	331 (46.5)	–
Boston homeless shelter occupants (9)	408	147 (36.0)	129 (87.8)	–
New York City obstetric patients (11)	214	33 (15.4)	29 (87.9)	L
U.S.S. *Theodore Roosevelt* aircraft carrier crew (12)	4954	856 (17.3)	~500 (58.4)	E
Japanese citizens evacuated from Wuhan, China (2)	565	13 (2.3)	4 (30.8)	L
Greek citizens evacuated from the United Kingdom, Spain, and Turkey (14)†	783	40 (5.1)	35 (87.5)	L
Charles de Gaulle aircraft carrier crew (13)	1760	1046 (59.4)	~500 (47.8)	E
Los Angeles homeless shelter occupants (10)	178	43 (24.2)	27 (62.8)	–
King County, Washington, nursing facility residents (15)	76	48 (63.2)	3 (6.3)	L
Arkansas, North Carolina, Ohio, and Virginia inmates (16)	4693	3277 (69.8)	3146 (96.0)	–
New Jersey university and hospital employees (17)	829	41 (4.9)	27 (65.9)	–
Indiana residents (18)	4611	78 (1.7)	35 (44.8)	R
Argentine cruise ship passengers and crew (19)	217	128 (59.0)	104 (81.3)	–
San Francisco residents (29)	4160	74 (1.8)	39 (52.7)	–

E = estimated from incomplete source data; L = longitudinal data collected; R = representative sample.
* A dash indicates that the study did not have a representative sample, collected no longitudinal data, and did not require estimation of missing data.
† Clarified via e-mail communication with coauthor.

Prevalence of Asymptomatic SARS-CoV-2 Infection

A Narrative Review (Oran DP & Topol EJ. Ann Intern Med 2020; doi:10.7326/M20-3012)

- Approximately **40% to 45%** of those infected with SARS-CoV-2 will remain **asymptomatic**
  - Suggests that the virus might have greater potential than previously estimated to spread silently and deeply through human populations
- Asymptomatic persons **can transmit** SARS-CoV-2 to others for an extended period, perhaps longer than 14 days
- The **absence** of COVID-19 **symptoms** in persons infected with SARS-CoV-2 might **not necessarily imply an absence of harm**
  - More research is needed to determine the significance of subclinical lung changes visible on computed tomography scans
- The focus of testing programs for SARS-CoV-2 should be substantially broadened to include persons who do not have symptoms of COVID-19

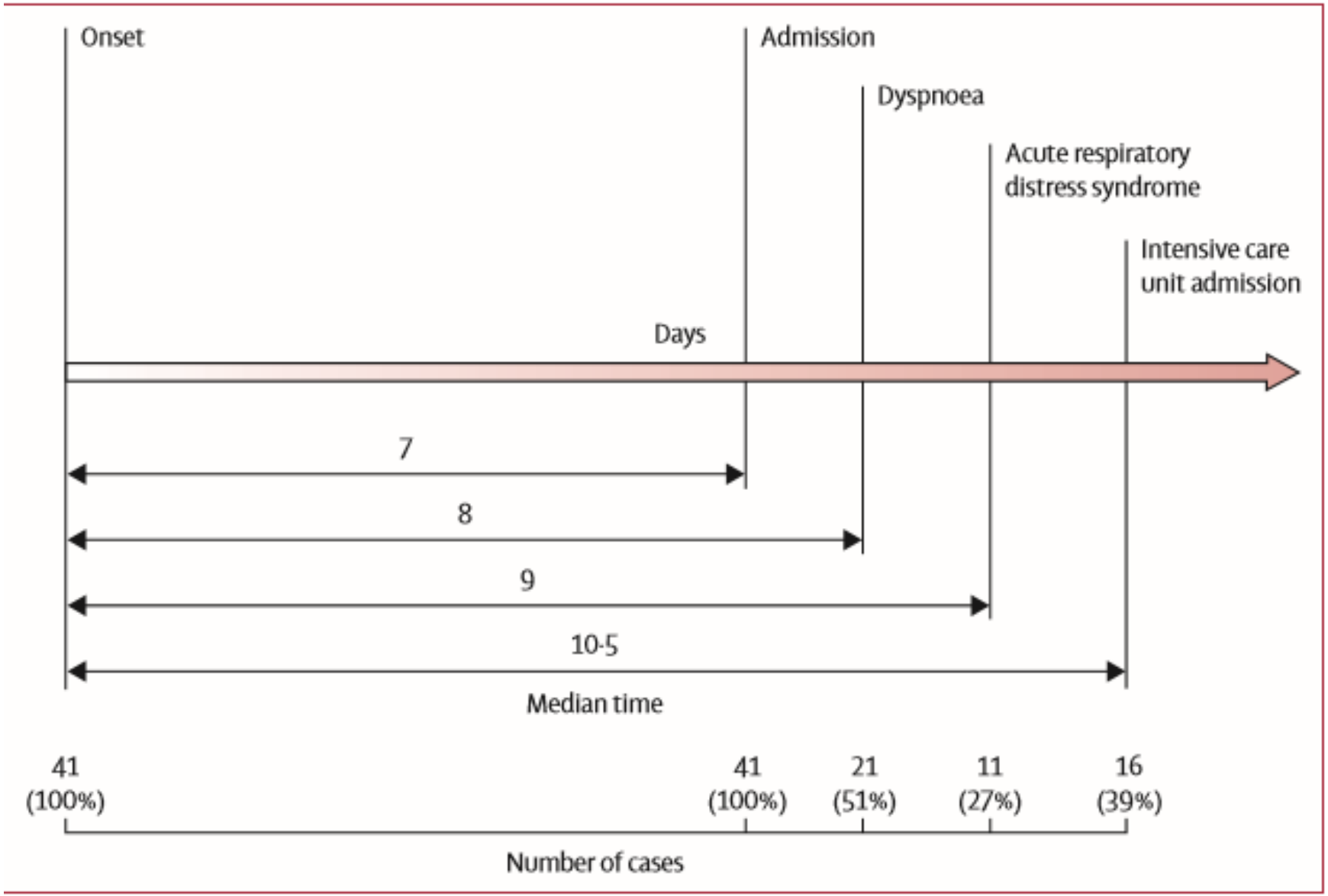


Figure 2: **Timeline of 2019-nCoV cases after onset of illness**

(Huang C et al Lancet 2020; 395: 497–506)

Characteristics of and Important Lessons From COVID-19 Outbreak in China: Summary of a Report of 72,314 Cases From the Chinese Center for Disease Control and Prevention

(Wu Z et al 2020 JAMA)

Box. Key Findings From the Chinese Center for Disease Control and Prevention Report

72 314 Cases (as of February 11, 2020)
- Confirmed cases: 44 672 (62%)
- Suspected cases: 16 186 (22%)
- Diagnosed cases: 10 567 (15%)
- Asymptomatic cases: 889 (1%)

Age distribution (N = 44 672)
- ≥80 years: 3% (1408 cases)
- 30-79 years: 87% (38 680 cases)
- 20-29 years: 8% (3619 cases)
- 10-19 years: 1% (549 cases)
- <10 years: 1% (416 cases)

Spectrum of disease (N = 44 415)
- Mild: 81% (36 160 cases)
- Severe: 14% (6168 cases)
- Critical: 5% (2087 cases)

Case-fatality rate
- 2.3% (1023 of 44 672 confirmed cases)
- 14.8% in patients aged ≥80 years (208 of 1408)
- 8.0% in patients aged 70-79 years (312 of 3918)
- 49.0% in critical cases (1023 of 2087)

Health care personnel infected
- 3.8% (1716 of 44 672)
- 63% in Wuhan (1080 of 1716)
- 14.8% cases classified as severe or critical (247 of 1668)
- 5 deaths

Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020 (Stokes EK et al MMWR 2020;69:759-65)

- Through May 30, 2020,
  - **COVID-19 pandemic resulted in 5,817,385 reported cases and 362,705 deaths worldwide**
  - 1,761,503 aggregated reported cases and 103,700 deaths in the United States
- Cumulative incidence, **403.6 cases per 100,000 persons**
  - similar among males (401.1) and females (406.0)
  - highest among persons aged ≥80 years (902.0)
- Among 287,320 (22%) cases with sufficient data on underlying health conditions
  - cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%)
- Overall, 184,673 (**14%**) patients were **hospitalized**, 29,837 (**2%**) admitted to an intensive care unit (**ICU**), and 71,116 (**5%**) **died**

TABLE 1. Reported laboratory-confirmed COVID-19 cases and estimated cumulative incidence,* by sex† and age group — United States, January 22–May 30, 2020

	Males		Females		Total	
Age group (yrs)	No. (%)	Cumulative incidence*	No. (%)	Cumulative incidence*	No. (%)	Cumulative incidence*
0–9	10,743 (1.7)	52.5	9,715 (1.4)	49.7	20,458 (1.5)	51.1
10–19	24,302 (3.8)	113.4	24,943 (3.7)	121.4	49,245 (3.7)	117.3
20–29	85,913 (13.3)	370.0	96,556 (14.3)	434.6	182,469 (13.8)	401.6
30–39	108,319 (16.8)	492.8	106,530 (15.8)	490.5	214,849 (16.3)	491.6
40–49	109,745 (17.0)	547.0	109,394 (16.2)	536.2	219,139 (16.6)	541.6
50–59	119,152 (18.4)	568.8	116,622 (17.3)	533.0	235,774 (17.9)	550.5
60–69	93,596 (14.5)	526.9	85,411 (12.7)	434.6	179,007 (13.6)	478.4
70–79	53,194 (8.2)	513.7	52,058 (7.7)	422.7	105,252 (8.0)	464.2
≥80	41,394 (6.4)	842.0	72,901 (10.8)	940.0	114,295 (8.7)	902.0
All ages	**646,358 (100.0)**	**401.1**	**674,130 (100.0)**	**406.0**	**1,320,488 (100.0)**	**403.6**

Abbreviation: COVID-19 = coronavirus disease 2019.

* Per 100,000 population.

† The analytic dataset excludes cases reported through case surveillance that were missing information on sex (n = 19,918) or age (n = 2,379).

(Stokes EK et al MMWR 2020;69:759-65)

TABLE 2. Reported underlying health conditions* and symptoms† among persons with laboratory-confirmed COVID-19, by sex and age group — United States, January 22–May 30, 2020

	No. (%)											
		Sex		Age group (yrs)								
Characteristic	Total	Male	Female	≤9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	≥80
Total population	**1,320,488**	**646,358**	**674,130**	**20,458**	**49,245**	**182,469**	**214,849**	**219,139**	**235,774**	**179,007**	**105,252**	**114,295**
Symptom§												
Known symptom status†	**373,883 (28.3)**	178,223 (27.6)	195,660 (29.0)	5,188 (25.4)	12,689 (25.8)	51,464 (28.2)	59,951 (27.9)	62,643 (28.6)	70,040 (29.7)	52,178 (29.1)	28,583 (27.2)	31,147 (27.3)
Fever, cough, or shortness of breath	**260,706 (69.7)**	125,768 (70.6)	134,938 (69.0)	3,278 (63.2)	7,584 (59.8)	35,072 (68.1)	42,016 (70.1)	45,361 (72.4)	51,283 (73.2)	37,701 (72.3)	19,583 (68.5)	18,828 (60.4)
Fever††	**161,071 (43.1)**	80,578 (45.2)	80,493 (41.1)	2,404 (46.3)	4,443 (35.0)	20,381 (39.6)	25,887 (43.2)	28,407 (45.3)	32,375 (46.2)	23,591 (45.2)	12,190 (42.6)	11,393 (36.6)
Cough	**187,953 (50.3)**	89,178 (50.0)	98,775 (50.5)	1,912 (36.9)	5,257 (41.4)	26,284 (51.1)	31,313 (52.2)	34,031 (54.3)	38,305 (54.7)	27,150 (52.0)	12,837 (44.9)	10,864 (34.9)
Shortness of breath	**106,387 (28.5)**	49,834 (28.0)	56,553 (28.9)	339 (6.5)	2,070 (16.3)	13,649 (26.5)	16,851 (28.1)	18,978 (30.3)	21,327 (30.4)	16,018 (30.7)	8,971 (31.4)	8,184 (26.3)
Myalgia	**135,026 (36.1)**	61,922 (34.7)	73,104 (37.4)	537 (10.4)	3,737 (29.5)	21,153 (41.1)	26,464 (44.1)	28,064 (44.8)	28,594 (40.8)	17,360 (33.3)	6,015 (21.0)	3,102 (10.0)
Runny nose	**22,710 (6.1)**	9,900 (5.6)	12,810 (6.5)	354 (6.8)	1,025 (8.1)	4,591 (8.9)	4,406 (7.3)	4,141 (6.6)	4,100 (5.9)	2,671 (5.1)	923 (3.2)	499 (1.6)
Sore throat	**74,840 (20.0)**	31,244 (17.5)	43,596 (22.3)	664 (12.8)	3,628 (28.6)	14,493 (28.2)	14,855 (24.8)	14,490 (23.1)	13,930 (19.9)	8,192 (15.7)	2,867 (10.0)	1,721 (5.5)
Headache	**128,560 (34.4)**	54,721 (30.7)	73,839 (37.7)	785 (15.1)	5,315 (41.9)	23,723 (46.1)	26,142 (43.6)	26,245 (41.9)	26,057 (37.2)	14,735 (28.2)	4,163 (14.6)	1,395 (4.5)
Nausea/Vomiting	**42,813 (11.5)**	16,549 (9.3)	26,264 (13.4)	506 (9.8)	1,314 (10.4)	6,648 (12.9)	7,661 (12.8)	8,091 (12.9)	8,737 (12.5)	5,953 (11.4)	2,380 (8.3)	1,523 (4.9)
Abdominal pain	**28,443 (7.6)**	11,553 (6.5)	16,890 (8.6)	349 (6.7)	978 (7.7)	4,211 (8.2)	5,150 (8.6)	5,531 (8.8)	6,134 (8.8)	3,809 (7.3)	1,449 (5.1)	832 (2.7)
Diarrhea	**72,039 (19.3)**	32,093 (18.0)	39,946 (20.4)	704 (13.6)	1,712 (13.5)	9,867 (19.2)	12,769 (21.3)	13,958 (22.3)	15,536 (22.2)	10,349 (19.8)	4,402 (15.4)	2,742 (8.8)
Loss of smell or taste	**31,191 (8.3)**	12,717 (7.1)	18,474 (9.4)	67 (1.3)	1,257 (9.9)	6,828 (13.3)	6,907 (11.5)	6,361 (10.2)	5,828 (8.3)	2,930 (5.6)	775 (2.7)	238 (0.8)

(Stokes EK et al MMWR 2020;69:759-65)

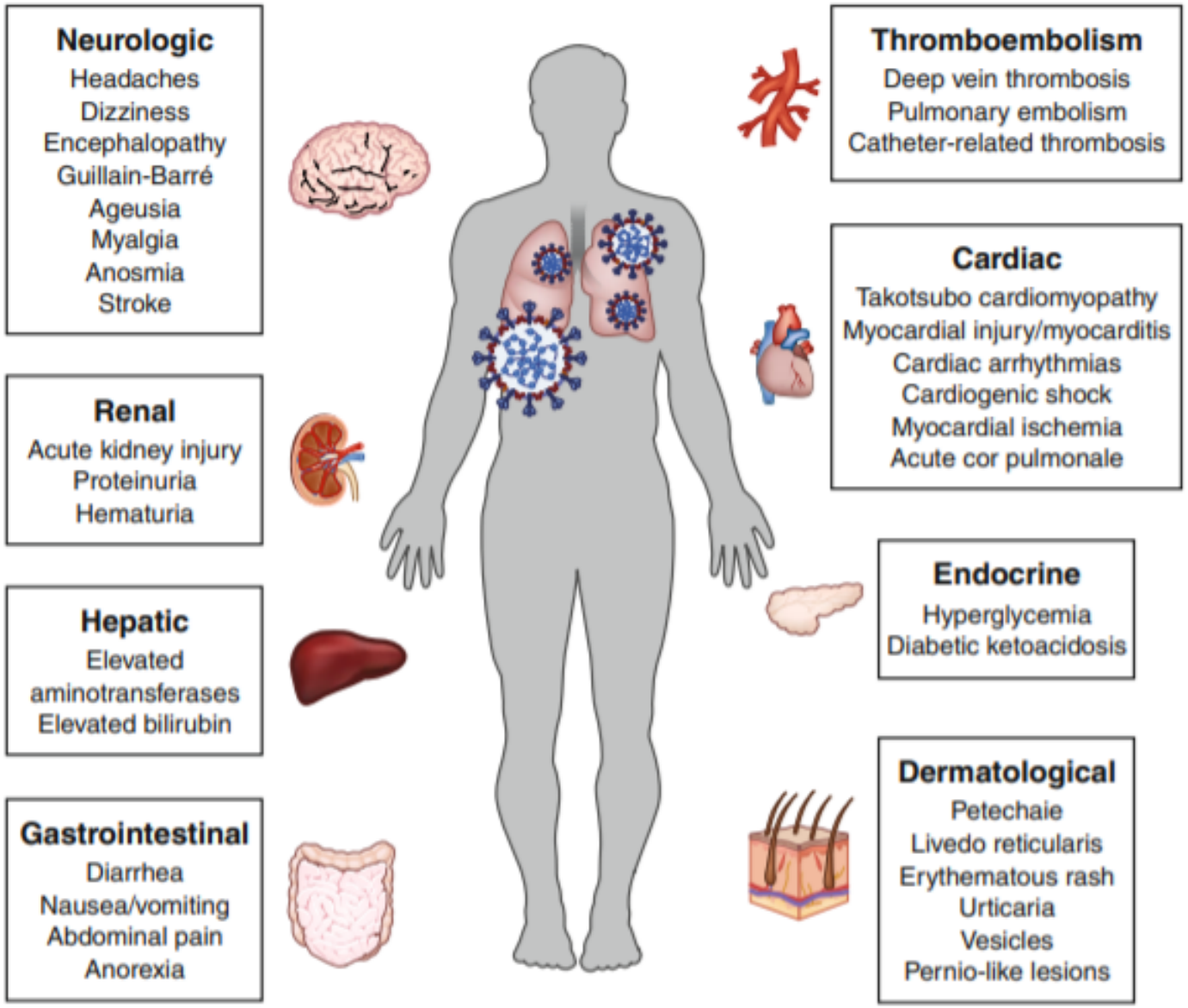
Extrapulmonary manifestations of COVID-19

(Gupta A et al Nat Med 2020;26:1017-32)

- While SARS-CoV-2 is known to cause substantial pulmonary disease, including pneumonia and acute respiratory distress syndrome (ARDS), clinicians have observed **many extrapulmonary manifestations** of COVID-19
  - Hematologic, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrinologic, neurologic, ophthalmologic, and dermatologic systems
- **ACE2**, the entry receptor for the causative coronavirus SARS-CoV-2, is expressed in **multiple extrapulmonary tissues**

Other respiratory viruses, such as influenza virus, adenovirus etc., also have many extrapulmonary manifestations

Extrapulmonary manifestations of COVID-19



(Gupta A et al Nat Med 2020;26:1017-32)

Hematologic and immune system–related manifestations of COVID-19 (Gupta A et al Nat Med 2020;26:1017-32)

- **Laboratory markers**
  - **Cell counts**: lymphopenia, leukocytosis, neutrophilia, thrombocytopenia
  - **Inflammatory markers**: elevations in erythrocyte sedimentation rate, C-reactive protein, ferritin, IL-6, lactate dehydrogenase
  - **Coagulation indices**: elevated D-dimer and fibrinogen; prolonged prothrombin time and partial thromboplastin time
- **Arterial thrombotic** complications: MI, ischemic stroke, acute limb, and mesenteric ischemia
- **Venous thrombotic** complications: deep vein thrombosis and pulmonary embolism
- **Catheter-related thrombosis**: thrombosis in arterial and venous catheters and extracorporeal circuits
- Cytokine-release syndrome: high-grade fevers, hypotension, multi-organ dysfunction

Neurological associations of COVID-19

(Ellul MA et al Lancet Neurol 2020; 19: 767–83)

- On the basis of knowledge of other coronaviruses, especially SARS and MERS, cases of CNS and peripheral nervous system disease caused by SARS-CoV-2 might be expected to be rare
- As of May 19, 2020, neurological manifestations described in **901 patients**
  - **Encephalopathy** reported for 93 patients in total, including
    - 16 (7%) of 214 hospitalised patients in Wuhan, China,
    - 40 (69%) of 58 patients in intensive care in France
  - **Encephalitis** described in eight patients
  - **Guillain-Barré syndrome** in 19 patients
  - SARS-CoV-2 detected in the CSF of some patients.
  - **Anosmia and ageusia** are common,
  - **Acute cerebrovascular disease** emerging as an important complication, with cohort studies reporting stroke in **2–6%** of patients hospitalised with COVID-19.
    - So far, 96 patients with **stroke** have been described

Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults

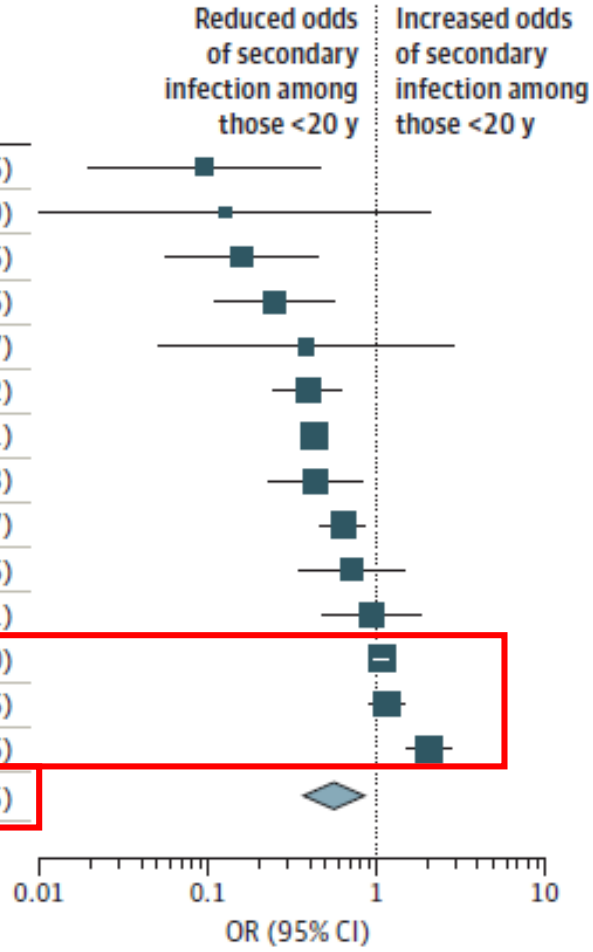
A Systematic Review and Meta-analysis (Viner RM et al JAMA Pediatr Published online September 25, 2020)

- The role of children and adolescents in transmission of SARS-CoV-2 is dependent on **susceptibility, symptoms, viral load**, **social contact patterns**, and **behavior**
- PubMed and medRxiv were searched from database inception **to July 28**, 2020, and a total of 13,926 studies were identified
- Studies that provided data on the prevalence of SARS-CoV-2 in children and adolescents (younger than 20 years) compared with adults (20 years and older) derived from **contact tracing or population screening** were included
- A total of **32 studies** comprising **41,640 children** and adolescents and **268,945 adults** met inclusion criteria, including **18 contact-tracing studies and 14 population screening studies**

Figure 2. Pooled Estimate of Odds of Being an Infected Contact Among Children and Adolescents Compared With Adults for All Contact-Tracing Studies

Source	Child		Adult		OR (95% CI)	Weight, %
	Positive	Negative	Positive	Negative		
Wang et al,[18] 2020	2	8	130	49	0.09 (0.02-0.46)	4.02
van der Hoek et al,[28] 2020	0	43	55	611	0.13 (0.01-2.09)	1.80
Li et al,[16] 2020	4	96	60	232	0.16 (0.06-0.46)	6.00
Wang et al,[20] 2020	13	23	64	28	0.25 (0.11-0.56)	7.03
Cheng et al,[17] 2020	1	280	21	2265	0.39 (0.05-2.87)	2.96
Rosenberg et al,[25] 2020	42	114	88	94	0.39 (0.25-0.62)	8.59
Dattner et al,[21] 2020	441	1297	432	546	0.43 (0.36-0.51)	9.45
Mizumoto et al,[19] 2020	10	165	284	2037	0.43 (0.23-0.83)	7.77
Zhang et al,[10] 2020	47	709	606	5831	0.64 (0.47-0.87)	9.12
Yousaf et al,[26] 2020	14	55	33	93	0.72 (0.35-1.46)	7.51
Chaw et al,[27] 2020	12	418	39	1278	0.94 (0.49-1.81)	7.75
Laxminarayan et al,[23] 2020	428	5647	2800	39 756	1.08 (0.97-1.20)	9.53
Liu et al,[24] 2020	93	1774	421	9292	1.16 (0.92-1.46)	9.32
Park et al,[12] 2020	50	644	2119	56 260	2.06 (1.54-2.76)	9.16
Overall					0.56 (0.37-0.85)	

Heterogeneity: $\tau^2 = 0.47$; $I^2 = 94.64\%$; $H^2 = 18.64$



Children and adolescents included those younger than 20 years, and adults included those 20 years and older. OR indicates odds ratio.

The pooled odds ratio of being an infected contact in children compared with adults was 0.56 (95% CI, 0.37-0.85), with substantial heterogeneity (I^2 = 94.6%)

Figure 3. Pooled Estimate of Odds of Being an Infected Contact Among Children and Among Adolescents Compared With Adults for Contact-Tracing Studies

Source	Child		Adult		OR (95% CI)	Weight, %
	Positive	Negative	Positive	Negative		
Children						
van der Hoek et al,[28] 2020 (<12 y)	0	31	55	611	0.17 (0.01-2.90)	1.92
Dattner et al,[21] 2020 (<9 y)	149	742	432	546	0.25 (0.20-0.32)	9.96
Rosenberg et al,[25] 2020 (<5 y)	5	20	88	94	0.27 (0.10-0.74)	6.50
Chaw et al,[27] 2020 (<9 y)	4	263	39	1278	0.50 (0.18-1.41)	6.43
Laxminarayan et al,[23] 2020 (<5 y)	40	1032	2800	39756	0.55 (0.40-0.76)	9.68
Park et al,[12] 2020 (<9 y)	5	232	2119	56260	0.57 (0.24-1.39)	7.14
Zhang et al,[10] 2020 (<14 y)	47	709	606	5831	0.64 (0.47-0.87)	9.72
Liu et al,[24] 2020 (<9 y)	60	988	421	9292	1.34 (1.01-1.77)	9.80
Heterogeneity: $\tau^2 = 0.31$; $I^2 = 88.05\%$; $H^2 = 8.37$					0.52 (0.33-0.82)	61.15
Adolescents						
van der Hoek et al,[28] 2020 (13-18 y)	0	12	55	611	0.44 (0.03-7.54)	1.89
Dattner et al,[21] 2020 (10-19 y)	291	555	432	546	0.66 (0.55-0.80)	10.02
Liu et al,[24] 2020 (10-19 y)	33	786	421	9292	0.93 (0.65-1.33)	9.54
Chaw et al,[27] 2020 (10-19 y)	8	155	39	1278	1.69 (0.78-3.68)	7.67
Park et al,[12] 2020 (10-19 y)	45	412	2119	56260	2.90 (2.13-3.96)	9.71
Heterogeneity: $\tau^2 = 0.41$; $I^2 = 91.59\%$; $H^2 = 11.90$					1.23 (0.64-2.36)	38.83
Overall					0.72 (0.46-1.10)	
Heterogeneity: $\tau^2 = 0.48$; $I^2 = 93.11\%$; $H^2 = 14.52$						

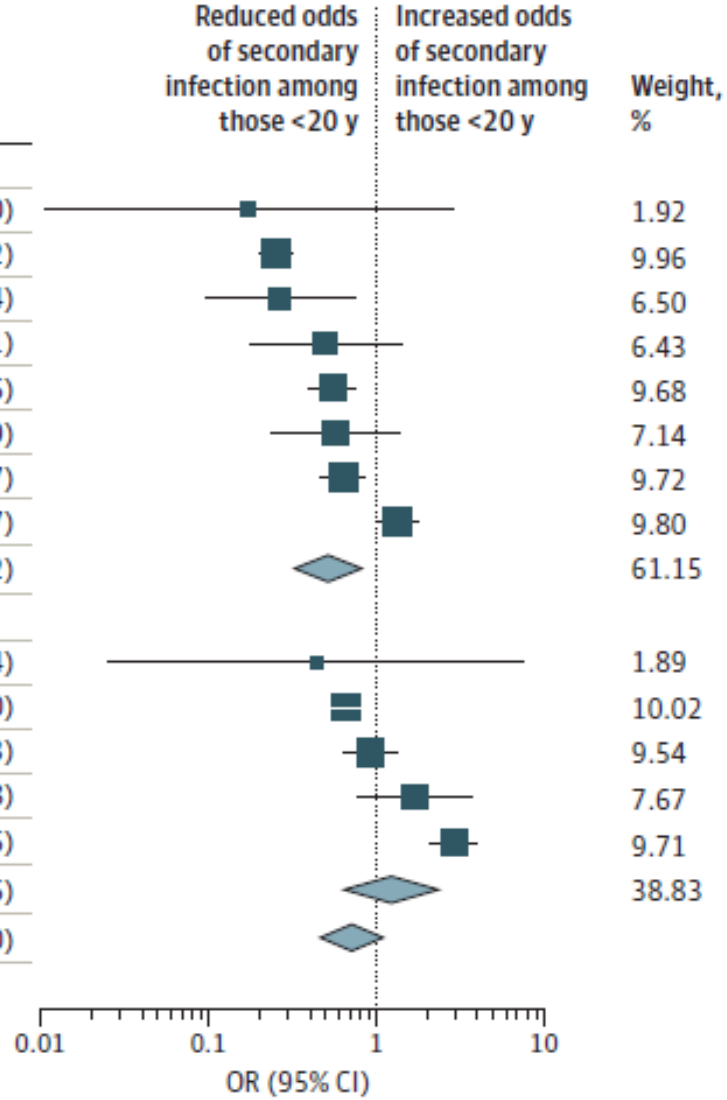
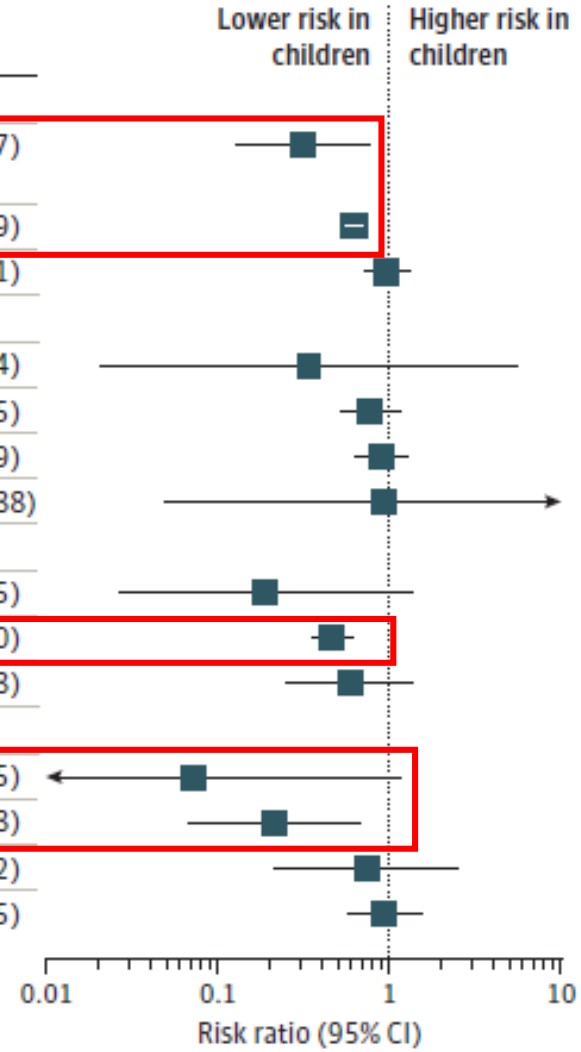


Figure 4. Ratios of the Prevalence of Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Children and Adolescents Compared With Adults in Population Screening Studies

Source	Child		Adult		Risk ratio (95% CI)
	Positive	Negative	Positive	Negative	
National seroprevalence					
National Institute for Public Health and the Environment,[7] 2020	5	581	69	2445	0.31 (0.13-0.77)
Pollán et al,[36] 2020	388	11034	2712	46941	0.62 (0.56-0.69)
Hallal et al,[38] 2020	46	3353	303	21294	0.97 (0.71-1.31)
Regional or municipal seroprevalence					
Biggs et al,[40] 2020	0	48	19	629	0.34 (0.02-5.54)
Shakiba et al,[39] 2020	24	110	97	320	0.77 (0.51-1.15)
Stringhini et al,[41] 2020	33	422	186	2125	0.90 (0.63-1.29)
Nawa et al,[42] 2020	0	98	3	641	0.93 (0.05-17.88)
Postoutbreak seroprevalence					
Weis et al,[44] 2020	1	57	51	511	0.19 (0.03-1.35)
Pagani et al,[43] 2020	52	423	866	2,802	0.46 (0.36-0.60)
Streeck et al,[45] 2020	5	50	132	725	0.59 (0.25-1.38)
Virus prevalence					
Gudbjartsson et al,[32] 2020	0	848	100	12132	0.07 (0.00-1.15)
Lavezzo et al,[33] 2020	3	464	70	2275	0.22 (0.07-0.68)
Public Health Agency of Sweden,[34] 2020	3	482	17	2069	0.73 (0.21-2.52)
Office for National Statistics,[35] 2020	18	5959	96	29728	0.94 (0.57-1.55)



Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults

A Systematic Review and Meta-analysis (Viner RM et al JAMA Pediatr Published online September 25, 2020)

Conclusions

- Preliminary evidence that **children and adolescents have lower susceptibility to SARS-CoV-2**, with an **odds ratio of 0.56** for **being an infected contact** compared with adults
- **Weak evidence** that **children and adolescents** play **a lesser role** than adults in **transmission** of SARS-CoV-2 at **a population level**
- This study provides **no information on the infectivity** of children

COVID-19 in children (Gupta A et al Nat Med 2020;26:1017-32)

- In a review of 72,314 patients with COVID-19 reported by the Chinese CDC, **less than 1%** of the patients were **younger than 10 years of age**
- In two retrospective studies from **China**, of >1,000 pediatric patients
  - The majority of the patients had mild or moderate disease,
  - **Only 1.8% required ICU admission**, **two deaths**
- A large group of **North American** pediatric ICUs, 38% of 48 critically ill children required **invasive ventilation**, with an in-hospital mortality rate of **4.2%**
- **Multisystem inflammation syndrome** in children
  - A person < 21 years of age presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (two or more) organ involvement in the setting of current or recent infection with SARS-CoV-2

Children and COVID-19: 10/15/20
Summary of State-Level Data Provided in this Report

Detail and links to state/local data sources provided in Appendix

Cumulative Number of Child COVID-19 Cases*

- 741,891 total child COVID-19 cases reported, and children represented 10.9% (741,891/6,837,527) of all cases
- Overall rate: 986 cases per 100,000 children in the population

Change in Child COVID-19 Cases, 10/1/20 – 10/15/20

- 84,319 new child cases reported from 10/1-10/15 (657,572 to 741,891), a 13% increase in child cases over 2 weeks

Testing (10 states reported)*

- Children made up between 5%-16.8% of total state tests, and between 3.5%-14.4% of children tested were tested positive

Hospitalizations (24 states and NYC reported)*

- Children were 1%-3.6% of total reported hospitalizations, and between 0.5%-7.2% of all child COVID-19 cases resulted in hospitalization

Mortality (42 states and NYC reported)*

- Children were 0%-0.27% of all COVID-19 deaths, and 14 states reported zero child deaths
- In states reporting, 0%-0.16% of all child COVID-19 cases resulted in death

See detail in Appendix: Data from 49 states, NYC, DC, PR, and GU; Analysis by American Academy of Pediatrics and Children's Hospital Association
** Note: Data represent cumulative counts since states began reporting; All data reported by state/local health departments are preliminary and subject to change*

Children and COVID-19: 11/12/20
Summary of State-Level Data Provided in this Report

Detail and links to state/local data sources provided in Appendix

Cumulative Number of Child COVID-19 Cases*

- 1,039,464 total child COVID-19 cases reported, and children represented 11.5% (1,039,464/9,037,991) of all cases
- Overall rate: 1,381 cases per 100,000 children in the population

Change in Child COVID-19 Cases*

- 111,946 new child COVID-19 cases were reported the past week from 11/5-11/12 (927,518 to 1,039,464)
- Over two weeks, 10/29-11/12, there was a 22% increase in child COVID-19 cases (185,829 new cases (853,635 to 1,039,464))

Testing (10 states reported)*

- Children made up between 5.0%-17.4% of total state tests, and between 3.9%-18.8% of children tested were tested positive

Hospitalizations (23 states and NYC reported)*

- Children were 1.2%-3.3% of total reported hospitalizations, and between 0.5%-6.1% of all child COVID-19 cases resulted in hospitalization

Mortality (42 states and NYC reported)*

- Children were 0.00%-0.21% of all COVID-19 deaths, and 16 states reported zero child deaths
- In states reporting, 0.00%-0.15% of all child COVID-19 cases resulted in death

See detail in Appendix: Data from 49 states, NYC, DC, PR, and GU; Analysis by American Academy of Pediatrics and Children's Hospital Association
** Note: Data represent cumulative counts since states began reporting; All data reported by state/local health departments are preliminary and subject to change*

Outcomes of **Maternal-Newborn Dyads** After Maternal SARS-CoV-2

(Verma S et al Pediatrics 2020; online)

- A multicenter, observational, descriptive cohort study collecting data from charts of maternal-newborn dyads that delivered at **four major New York City** metropolitan area hospitals between **March 1 and May 10**, 2020 with maternal SARS-CoV-2 infection
- A total of **149 mothers** with SARS-CoV-2 infection and **149 newborns** analyzed (3 sets of twins; **3 stillbirths**)
  - **40%** of these **mothers** were **asymptomatic**
  - Approximately **15%** of symptomatic mothers required some form of **respiratory support** and **8%** required **intubation**
  - Eighteen **newborns (12%) admitted to ICU**
  - 15 (**10%**) were born **preterm**, and five (3%) required mechanical ventilation.
  - **Symptomatic mothers** had more **premature deliveries** (16% vs 3%, P= 0.02) and **their newborns** were more likely to require **intensive care** (19% vs. 2%, P=0.001) than asymptomatic mothers
  - **One newborn tested positive** for SARS-CoV-2, considered a case of **horizontal postnatal transmission**

Outcomes of Maternal-Newborn Dyads After Maternal SARS-CoV-2

(Verma S et al Pediatrics 2020; online)

Conclusion:

- No distinct evidence of vertical transmission from mothers with SARS-CoV-2 to their newborns
- Observe **perinatal morbidities** among both mothers and newborns
- **Symptomatic mothers** more likely to experience **premature delivery** and their newborns to require intensive care

Detection of severe acute respiratory syndrome coronavirus 2 in placental and fetal membrane samples

TABLE

Summary of PCR results of placental or membrane samples from patients with COVID-19

Patient no.	Age, y	Gestational age	Interval from diagnosis of COVID-19 to delivery, d	Mode of delivery	PCR result of placental sample	PCR result of membrane sample	COVID-19 status	PCR results of infants				
								DOL1	DOL2	DOL3	DOL4	DOL5
1	37	36wk 6d	2	CD	N/A	Pos	Critical	—	Neg	—	Neg	—
2	36	26wk 5d	1	CD	N/A	Pos	Critical	Neg	—	—	—	Neg
3	38	38wk 3d	0	CD	N/A	Neg	Critical	Neg	—	Neg	—	—
4	40	34wk 2d	1	CD	Pos	N/A	Severe	Neg	—		Neg	Neg
5	26	37wk 6d	0	NSVD	N/A	Neg	Severe	Neg	—	Neg	—	—
6	34	37wk 1d	10	NSVD	N/A	Neg	Mild	—	—	Neg	Neg	—
7	23	41wk 3d	1	NSVD	N/A	Neg	Mild	—	Neg	—	—	—
8	23	40wk 5d	8	NSVD	N/A	Neg	Mild	—	Neg	—	—	—
9	35	39wk 6d	15	NSVD	N/A	Neg	Mild	Neg	—	—	—	—
10	34	40wk 0d	5	NSVD	N/A	Neg	Mild	Neg	—	—	—	—
11	22	41wk 0d	15	NSVD	N/A	Neg	Mild	—	Neg	—	—	—

CD, cesarean delivery; *COVID-19*, coronavirus disease 2019; *DOL*, day of life; *N/A*, not available; *Neg*, negative; *NSVD*, normal spontaneous vaginal delivery; *PCR*, polymerase chain reaction; *Pos*, positive.

Penfield. Detection of severe acute respiratory syndrome coronavirus 2 in placental and fetal membrane samples. AJOG MFM 2020.

ARTICLE

https://doi.org/10.1038/s41467-020-17436-6 OPEN

Transplacental transmission of SARS-CoV-2 infection

Alexandre J. Vivanti[1,8], Christelle Vauloup-Fellous[2,8], Sophie Prevot[3], Veronique Zupan[4], Cecile Suffee[5], Jeremy Do Cao[6], Alexandra Benachi[1] & Daniele De Luca[4,7]✉

(NATURE COMMUNICATIONS | (2020) 11:3572 | https://doi.org/10.1038/s41467-020-17436-6)

SARS-CoV-2 outbreak is the first pandemic of the century. SARS-CoV-2 infection is transmitted through droplets; other transmission routes are hypothesized but not confirmed. So far, it is unclear whether and how SARS-CoV-2 can be transmitted from the mother to the fetus. We demonstrate the transplacental transmission of SARS-CoV-2 in a neonate born to a mother infected in the last trimester and presenting with neurological compromise. The transmission is confirmed by comprehensive virological and pathological investigations. In detail, SARS-CoV-2 causes: (1) maternal viremia, (2) placental infection demonstrated by immunohistochemistry and very high viral load; placental inflammation, as shown by histological examination and immunohistochemistry, and (3) neonatal viremia following placental infection. The neonate is studied clinically, through imaging, and followed up. The neonate presented with neurological manifestations, similar to those described in adult patients.

COVID-19 in 7780 pediatric patients: A systematic review (Hoang A et al EClin Med 2020;24:100433)

- Searched four medical databases (PubMed, LitCovid, Scopus, WHO COVID-19 database) between December 1, 2019 **to May 14**, 2020
- Identified **131 studies** across **26 countries** comprising **7780 pediatric patients**
- **Fever (59.1%)** and **cough (55.9%)** the most frequent symptoms
- **19.3% of children asymptomatic**
- **Patchy lesions (21.0%)** and **ground-glass opacities (32.9%)** depicted lung radiograph and computed tomography findings, respectively

Patient characteristics, exp

Male gender
Mean age (years)
Exposure from family m
Travel to/lived-in high-ri
NP/throat SARS-CoV-2 d
Positive fecal viral shedd
Positive urine viral shed
Length of hospital stay (c
Intensive care unit admi

Underlying medical conditions and co-infection.

	# Studies	# Patients	N (%)
Underlying conditions	**20**	**655**	**233 (35.6)**
Co-infections	**35**	**1183**	**72 (5.6)**
Bacterial			
Mycoplasma pneumoniae			42 (58.3)
Enterobacter sepsis			2 (2.8)
Streptococcus pneumoniae			1 (1.4)
Viral			
Influenza virus A/B			8 (11.1)
Respiratory syncytial virus			7 (9.7)
Cytomegalovirus			3 (4.2)
Epstein-Barr virus			3 (4.2)
Adenovirus			2 (2.8)
Human metapneumovirus			2 (2.8)
Human parainfluenza virus			2 (2.8)

(Hoang A et al EClin Med 2020;24:100433)

Clinical symptoms and imaging

	# Studies	# Patients	N (%)
Clinical symptoms			
Asymptomatic	119	2367	456 (19.3)
Fever	119	2445	1446 (59.1)
Cough	119	2445	1367 (55.9)
Rhinorrhea, nasal congestion	119	2445	488 (20.0)
Myalgia, fatigue	119	2445	457 (18.7)
Sore throat	119	2445	446 (18.2)
Shortness of breath, dyspnea	119	2445	287 (11.7)
Abdominal pain, diarrhea	119	2445	159 (6.5)
Vomiting, nausea	119	2445	131 (5.4)
Headache, dizziness	119	2445	104 (4.3)
Pharyngeal erythema	119	2445	80 (3.3)
Decreased oral intake	119	2445	42 (1.7)
Rash	119	2445	6 (0.25)
Chest x-ray findings			
Normal	49	501	118 (23.6)
Patchy lesions	49	501	105 (21.0)
Ground-glass opacity	49	501	30 (6.0)
Consolidation	49	501	12 (2.4)
Computed Tomography (CT) findings			
Ground-glass opacity	67	1115	367 (32.9)
Normal	67	1115	211 (18.9)
Patchy lesions	67	1115	117 (10.5)
Consolidation	67	1115	72 (6.5)

(Hoang A et al EClin Med 2020;24:100433)

COVID-19 in 7780 pediatric patients: A systematic review (Hoang A et al EClin Med 2020;24:100433)

- **Immunocompromised children or those with respiratory/cardiac disease** comprised the largest subset of COVID-19 children with **underlying medical conditions** (152 of 233 individuals)
- **Coinfections** observed in **5.6%** of children
- Abnormal laboratory markers included serum D-dimer, procalcitonin, creatine kinase, and interleukin-6.
- Seven **deaths** reported (**0.09%**)
- 11 children (**0.14%**) met inclusion for **multisystem inflammatory syndrome** in children

SARS-CoV-2–Associated **Deaths** Among Persons **Aged < 21 Years** — United States, February 12–July 31, 2020

(Bixler D et al MMWR 2020;69 (37):1324-9)

- Persons **aged < 21 years** constitute **26%** of the **U.S. population**
- During the period, a total of 391,814 cases of COVID-19 and **MIS-C** (representing approximately **8% of all reported cases**) and **121 deaths** (approximately **0.08%** of all deaths) were identified among persons aged < 21 years
  - 63% in males, 10% of decedents aged < 1year, 20% aged 1–9 years, **70% aged 10–20 years**

FIGURE 2. Age at death among persons aged <21 years with SARS-CoV-2–associated deaths*,† — United States, February 12–July 31, 2020§

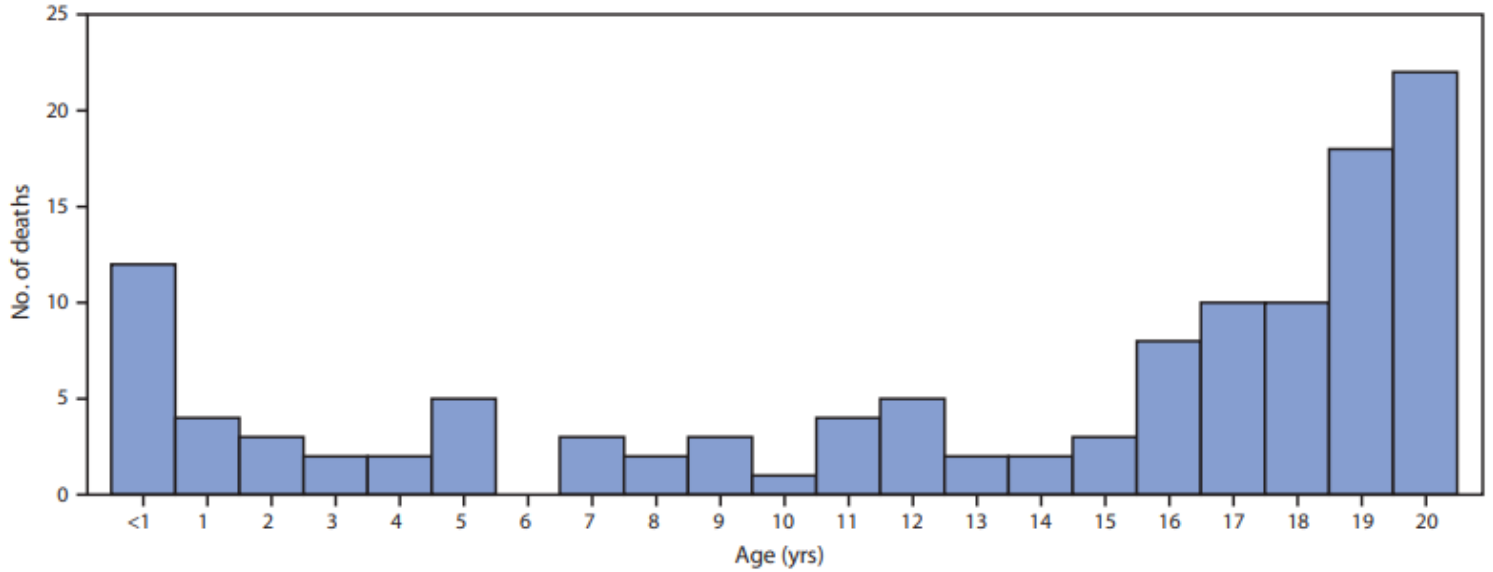
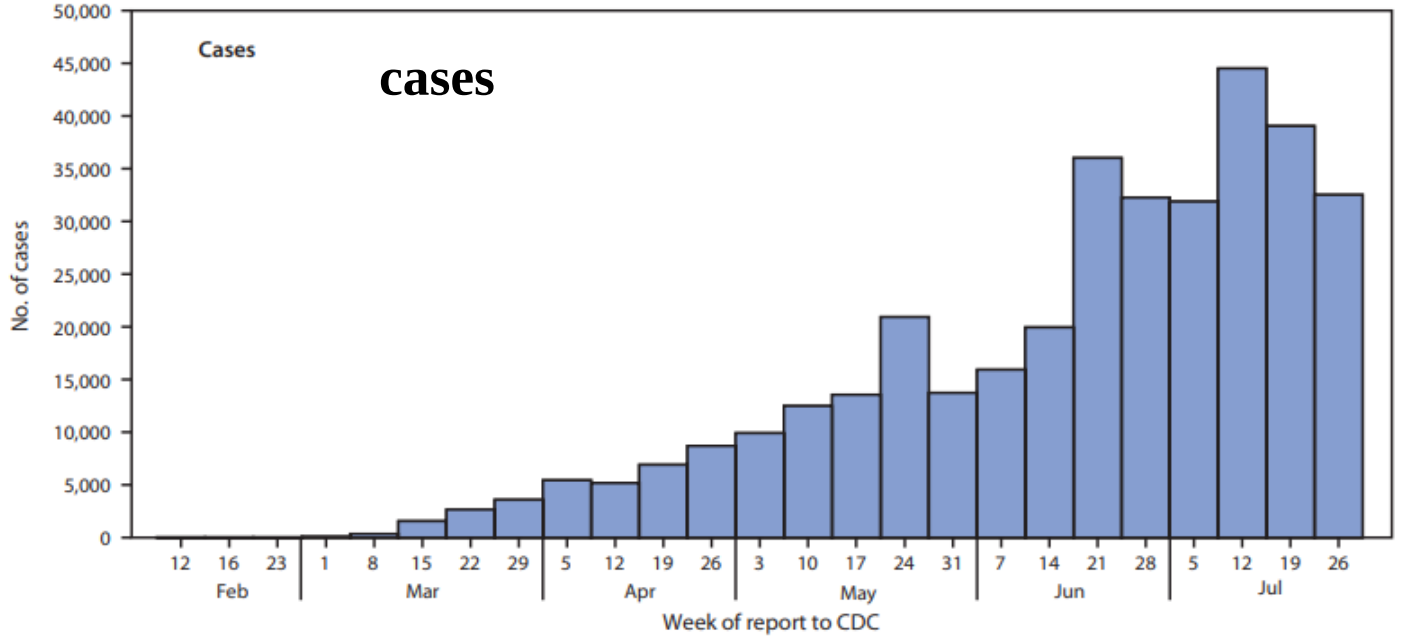
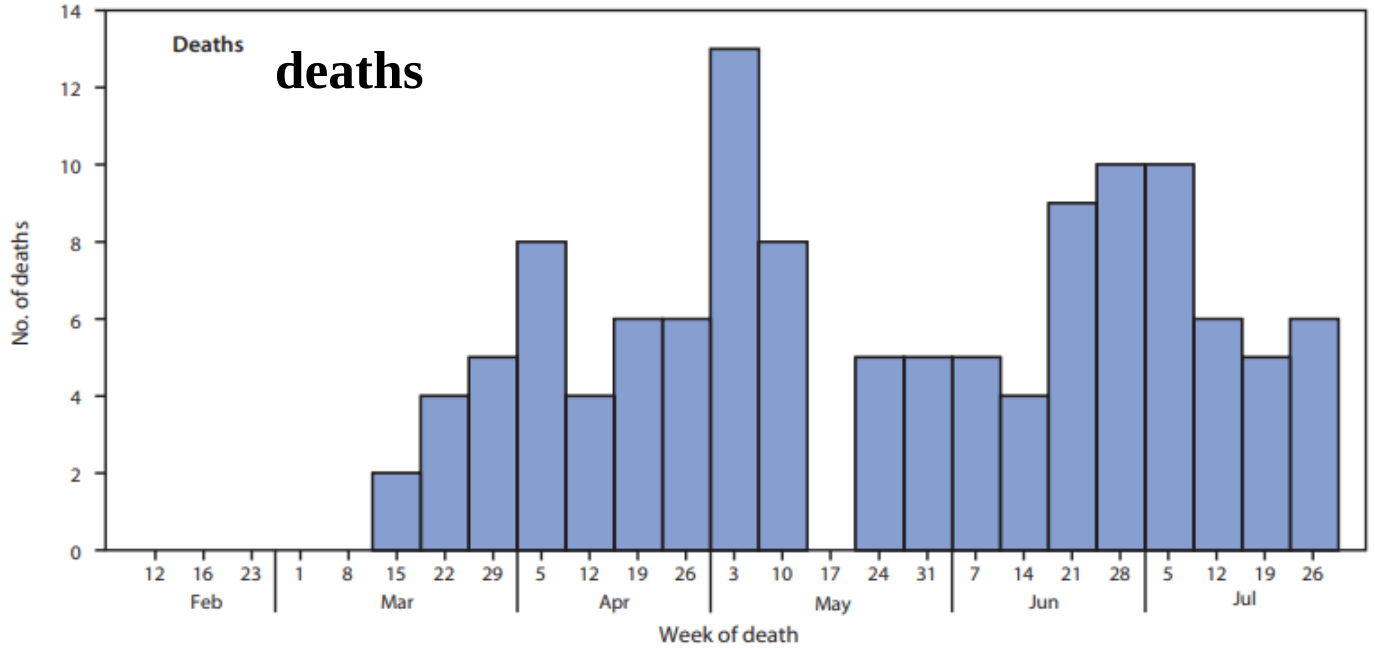


FIGURE 1. SARS-CoV-2–associated cases,*,† by week of case report to CDC, and deaths,§,¶ by week of death, among persons aged <21 years — United States, February 12–July 31, 2020**





(Bixler D et al MMWR 2020;69 (37):1324-9)

TABLE. Demographic and clinical characteristics of SAI associated deaths among persons aged <21 years — Unit February 12–July 31, 2020*

Characteristic	N
Total	121
Age group, yrs	
<1	1
1–4	1
5–9	13
10–13	1
14–17	23
18–20	50
Age, yrs, median (IQR)	16
Sex	
Female	45
Male	76
Race/Ethnicity	
Hispanic	54
American Indian/Alaska Native, non-Hispanic	
Asian or Pacific Islander, non-Hispanic	
Black, non-Hispanic	35
White, non-Hispanic	17
Multiple/Other†	
Missing/Unknown	
SARS-CoV-2–associated condition§	
COVID-19	120 (99.2)
MIS-C	15 (12.4)
Underlying medical condition¶	
No underlying condition	30 (24.8)
≥1 underlying condition	91 (75.2)
≥2 underlying conditions	54 (44.6)
Chronic lung disease**	34 (28.1)
Obesity††	33 (27.3)
Neurologic and developmental§§	26 (21.5)
Cardiovascular disease¶¶	22 (18.2)
Cancer or immunosuppressive condition***	17 (14.0)
Diabetes mellitus†††	11 (9.1)
Chronic kidney disease	5 (4.1)
Chronic liver disease	3 (2.5)
Other¶¶¶	37 (30.6)
Location of death	
Home	16 (13.2)
Emergency department	23 (19.0)
Hospital	79 (65.3)
Other/Unknown	3(2.5)
Median interval from symptom onset to hospital admission, days (IQR)****	3 (1–7)
Median interval from hospital admission to death, days (IQR)†††††	8 (4–21.5)
Median interval from symptom onset to death, days (IQR)§§§§	11 (6–24)

(Bixler D et al MMWR 2020;69 (37):1324-9)

SARS-CoV-2–Associated **Deaths** Among Persons **Aged < 21 Years** — United States, February 12–July 31, 2020

(Bixler D et al MMWR 2020;69 (37):1324-9)

Four important findings were identified

- Although **Hispanic, Black, and American Indian or Alaska Native** (AI/AN) persons represent **41%** of the **U.S. population** aged < 21 years, these groups accounted for approximately **75% of deaths** in persons aged < 21 years
- The possibility exists that **all deaths were not recognized or reported**, in part because of **incomplete testing**, **failure to update** vital status after death of a previously reported case of COVID-19 or MIS-C, or **delays in reporting** SARS-CoV-2–associated deaths because of the lengthy process for cause of death ascertainment
- Autopsy findings and death certificates were **not available to verify cause of death** for this report
  - **More detailed review** of available medical and death records is **currently underway** in collaboration with public health jurisdictions
- A **standard surveillance case definition** for **SARS-CoV-2–associated death** is **not in use** in the United States

An outbreak of sev epicentre of the SA cohort study

Lucio Verdoni, Angelo Mazza, Annalisa Gerva

Summary

Background The Bergamo provinc coronavirus 2 (SARS-CoV-2) epidem the past month we recorded an outb with Kawasaki-like disease diagnose

Methods All patients diagnosed with to symptomatic presentation before like presentations were managed a Kawasaki disease shock syndrome activation syndrome (MAS) by the previous infection was sought by rev and by serological qualitative test de

Findings Group 1 comprised 19 patie and Feb 17, 2020. Group 2 included Feb 18 and April 20, 2020; eight of incidence (group 1 *vs* group 2, 0·3 v six of ten), KDSS (zero of 19 *vs* five ((three of 19 *vs* eight of ten; all p<0·0

Interpretation In the past month we after the SARS-CoV-2 epidemic beg rate of cardiac involvement, and feat severe form of Kawasaki disease. A SARS-CoV-2 epidemic.

JAMA | Original Investigation

Clinical Characteristics of 58 (Multisystem Syndrome Temp

Elizabeth Whittaker, MD; Alasdair Bamford, MD; Julia Kenny Padmanabhan Ramnarayan, MD; Alain Fraisse, MD; Owen M Michael Carter, MD; Adriana Tremoulet, MD; Chisato Shimizu for the PIMS-TS Study Group and EUCLIDS and PERFORM C

IMPORTANCE In communities with high rates of c emerged of children with an unusual syndrome o

OBJECTIVES To describe the clinical and laborator who met criteria for the pediatric inflammatory m with severe acute respiratory syndrome coronavi these characteristics with other pediatric inflamm

DESIGN, SETTING, AND PARTICIPANTS Case series admitted between March 23 and May 16, 2020, w of inflammation meeting published definitions fo May 22, 2020. Clinical and laboratory characteris review, and were compared with clinical characte (KD) (n = 1132), KD shock syndrome (n = 45), and been admitted to hospitals in Europe and the US

EXPOSURES Signs and symptoms and laboratory definitional criteria for PIMS-TS from the UK, the

MAIN OUTCOMES AND MEASURES Clinical, laborat meeting definitional criteria for PIMS-TS, and com pediatric inflammatory disorders.

RESULTS Fifty-eight children (median age, 9 years [[34%]) were identified who met the criteria for PIM chain reaction tests were positive in 15 of 58 patien were positive in 40 of 46 (87%). In total, 45 of 58 p prior SARS-CoV-2 infection. All children presented including vomiting (26/58 [45%]), abdominal pain Rash was present in 30 of 58 (52%), and conjunctiv Laboratory evaluation was consistent with marked (229 mg/L [IQR, 156-338], assessed in 58 of 58) an in 53 of 58). Of the 58 children, 29 developed shoc dysfunction) and required inotropic support and flu received mechanical ventilation); 13 met the Americ had fever and inflammation without features of sho coronary artery dilatation or aneurysm. Comparison syndrome showed differences in clinical and labora age, 9 years [IQR, 5.7-14] vs 2.7 years [IQR, 1.4-4.7] greater elevation of inflammatory markers such as 156-338] vs 67 mg/L [IQR, 40-150 mg/L] and 193

CONCLUSIONS AND RELEVANCE In this case series PIMS-TS, there was a wide spectrum of presenting ranging from fever and inflammation to myocardia artery aneurysms. The comparison with patients w insights into this syndrome, and suggests this diso inflammatory entities.

JAMA. 2020;324(3):259-269. doi:10.1001/jama.2020.1036 Published online June 8, 2020. Corrected on June 30, 2020

Circulation

ORIGINAL RESEARCH

Acute Heart Inflammatory Context of G

Edit

BACKGROUND: Cardiac injury adults with coronavirus disease syndrome coronavirus 2 (SARS- minimally symptomatic. We re with acute heart failure potent and the multisystem inflammat US Centers for Disease Control

METHODS: Over a 2-month p pandemic in France and Switze biological, therapeutic, and ea admitted to pediatric intensive shock, left ventricular dysfunct

RESULTS: Thirty-five children v Median age at admission was were present in 28%, includin symptoms were prominent. Le in one-third; 80% required ino extracorporeal membrane oxyg suggestive of cytokine storm (i macrophage activation (D-dime (B-type natriuretic peptide) was patients (88%) tested positive chain reaction of nasopharyng intravenous immunoglobulin, one-third. Left ventricular funct discharged from the intensive treated with extracorporeal me weaned.

CONCLUSIONS: Children may decompensation caused by sev infection (multisystem inflamm with immunoglobulin appears ventricular systolic function.

Circulation. 2020;142:429–436. DOI: 10.1161/CI

Multisystem Inflammatory Syndrome in Children in New York State

Elizabeth M. Dufort, M.D., Emilia H. Koumans, M.D., M.P.H., Eric J. Chow, M.D., M.P.H., Elizabeth M. Rosenthal, M.P.H., Alison Muse, M.P.H., Jemma Rowlands, M.P.H., Meredith A. Barranco, M.P.H., Angela M. Maxted, D.V.M., Ph.D., Eli S. Rosenberg, Ph.D., Delia Easton, Ph.D., Tomoko Udo, Ph.D., Jessica Kumar, D.O., Wendy Pulver, M.S., Lou Smith, M.D., Brad Hutton, M.P.H., Debra Blog, M.D., M.P.H., and Howard Zucker, M.D., for the New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team*

ABSTRACT

BACKGROUND

A multisystem inflammatory syndrome in children (MIS-C) is associated with coronavirus disease 2019. The New York State Department of Health (NYSDOH) established active, statewide surveillance to describe hospitalized patients with the syndrome.

METHODS

Hospitals in New York State reported cases of Kawasaki's disease, toxic shock syndrome, myocarditis, and potential MIS-C in hospitalized patients younger than 21 years of age and sent medical records to the NYSDOH. We carried out descriptive analyses that summarized the clinical presentation, complications, and outcomes of patients who met the NYSDOH case definition for MIS-C between March 1 and May 10, 2020.

RESULTS

As of May 10, 2020, a total of 191 potential cases were reported to the NYSDOH. Of 95 patients with confirmed MIS-C (laboratory-confirmed acute or recent severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection) and 4 with suspected MIS-C (met clinical and epidemiologic criteria), 53 (54%) were male; 31 of 78 (40%) were black, and 31 of 85 (36%) were Hispanic. A total of 31 patients (31%) were 0 to 5 years of age, 42 (42%) were 6 to 12 years of age, and 26 (26%) were 13 to 20 years of age. All presented with subjective fever or chills; 97% had tachycardia, 80% had gastrointestinal symptoms, 60% had rash, 56% had conjunctival injection, and 27% had mucosal changes. Elevated levels of C-reactive protein, D-dimer, and troponin were found in 100%, 91%, and 71% of the patients, respectively; 62% received vasopressor support, 53% had evidence of myocarditis, 80% were admitted to an intensive care unit, and 2 died. The median length of hospital stay was 6 days.

CONCLUSIONS

The emergence of multisystem inflammatory syndrome in children in New York State coincided with widespread SARS-CoV-2 transmission; this hyperinflammatory syndrome with dermatologic, mucocutaneous, and gastrointestinal manifestations was associated with cardiac dysfunction.

From the New York State Department of Health, Albany (E.M.D., A.M., J.R., A.M.M., D.E., J.K., W.P., L.S., B.H., D.B., H.Z.); the Centers for Disease Control and Prevention (CDC) COVID-19 Response (E.H.K., E.J.C.) and the Epidemic Intelligence Service, Center for Surveillance, Epidemiology, and Laboratory Services (E.J.C.), CDC, Atlanta; and the University at Albany School of Public Health, State University of New York, Rensselaer (E.M.R., M.A.B., E.S.R., T.U.). Address reprint requests to Dr. Dufort at the New York State Department of Health, Empire State Plaza, Corning Tower, Rm. 503, Albany, NY 12237, or at elizabeth.dufort@health.ny.gov.

*The members of the investigation team are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Dufort, Koumans, and Chow, Ms. Rosenthal, and Ms. Muse contributed equally to this article.

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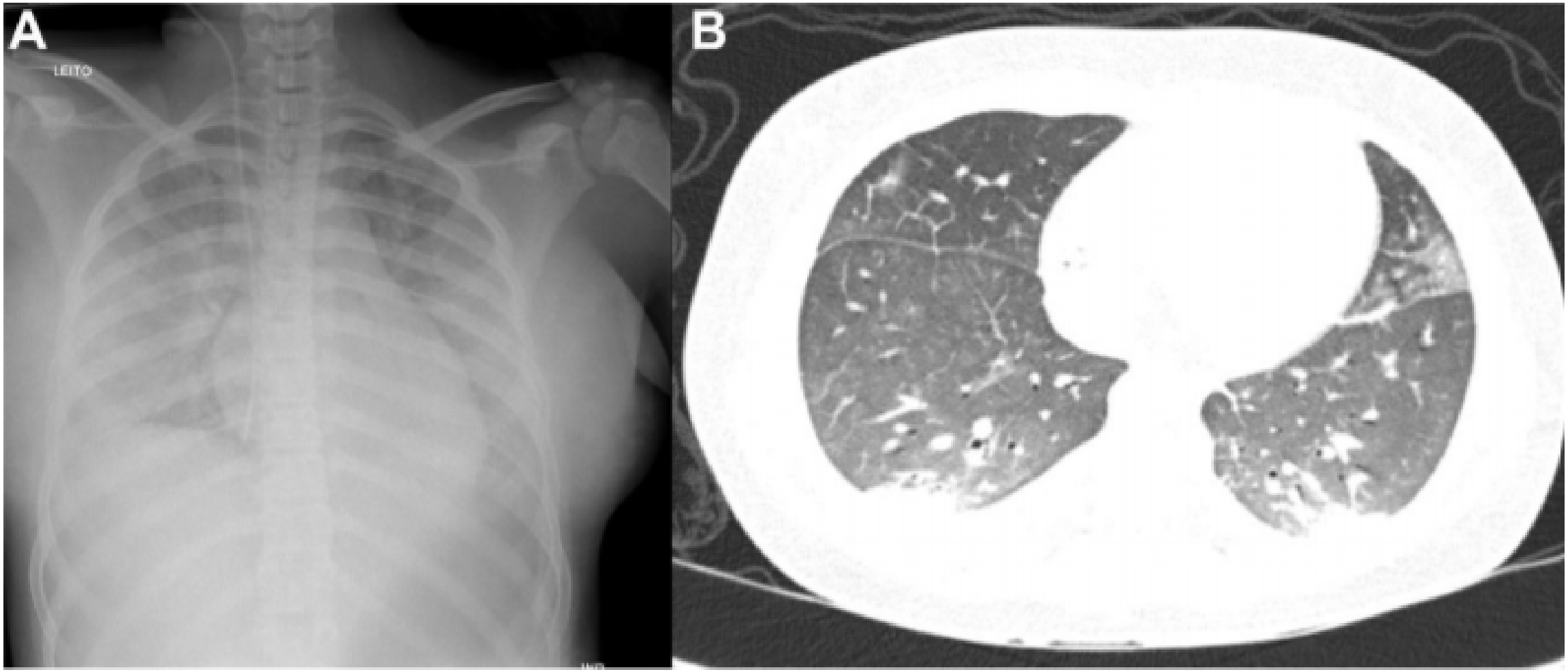
N Engl J Med 2020;383:347-58.
DOI: 10.1056/NEJMoa2021756

SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome (Dolhnikof M et al Lancet Child Adolesc Health August 20, 2020 https://doi.org/10.1016/ S2352-4642(20)30257-1)

- 11 y/o, otherwise healthy female of African descent
- **Fever for 7 days**, **odynophagia**, myalgia, and abdominal pain
- Admitted to **PICU** with **cardiovascular shock** and **persistent fever**
- On physical examination
  - Non-exudative **conjunctivitis** and **cracked lips**
  - Respiratory distress, **respiratory rate 70 breaths per min**, hypoxia
  - Signs of **congestive heart failure**, including jugular vein distention, crackles at the base of the lungs, displaced liver, **hypotension** (blood pressure 80/36 mm Hg), tachycardia (134 bpm), and **cold extremities** with filiform pulses



(A) Initial Chest X-ray showing **enlarged cardiac area and bilateral lung opacities**
(B) Chest computed tomography (CT) evidencing multiple **ground-glass pulmonary opacities**, associated with thickening of interlobular septa and sparse consolidation foci

(Dolhnikof M et al Lancet Child Adolesc Health August 20, 2020 https://doi.org/10.1016/ S2352-4642(20)30257-1)

Laboratory results at various timepoints after presentation

	0 h	7 h	14 h	17 h	24 h	Normal range
Haemoglobin, g/dL	10·0	11·8	12·1	11·4	11·0	12·7–14·7
Hematocrit, %	28·8%	34·3%	36·4%	34·3%	33·0%	38·0–44·0%
Platelets, ×10³ cells per µL	167	..	191	..	145	150–450
White blood cell count, ×10³ cells per mm³	25·73	24·28	35·90	40·30	38·22	4·50–14·40
Lymphocytes, %	1·03%	0·73%	0·36%	0·40%	3·44%	38·00–42·00%
Urea, mg/dL	67	73	78	78	93	11–38
Lactate, mg/dL	38·0	39·0	..	27·0	..	4·5–14·4
C-reactive protein, mg/dL	266·6	..	309·5	..	..	<500
Total protein, g/dL	5·0	..	..	..	..	6·0–8·0
Albumin, g/dL	2·6	..	..	..	..	3·8–5·4
Aspartate aminotransferase, U/L	61	..	67	..	..	13–35
Alanine aminotransferase, U/L	67	..	67	..	..	7–35
Oxygenation index	..	3·1	..	4·2	..	<4·0
International normalised ratio	..	..	1·4	..	..	0·9–1·2
Fibrinogen, mg/dL	..	..	513	..	..	200–393
Ferritin, ng/mL	..	..	..	1501	..	20–200
Triglycerides, mg/dL	..	..	..	162	..	<100

(Dolhnikof M et al Lancet Child Adolesc Health August 20, 2020 https://doi.org/10.1016/ S2352-4642(20)30257-1)

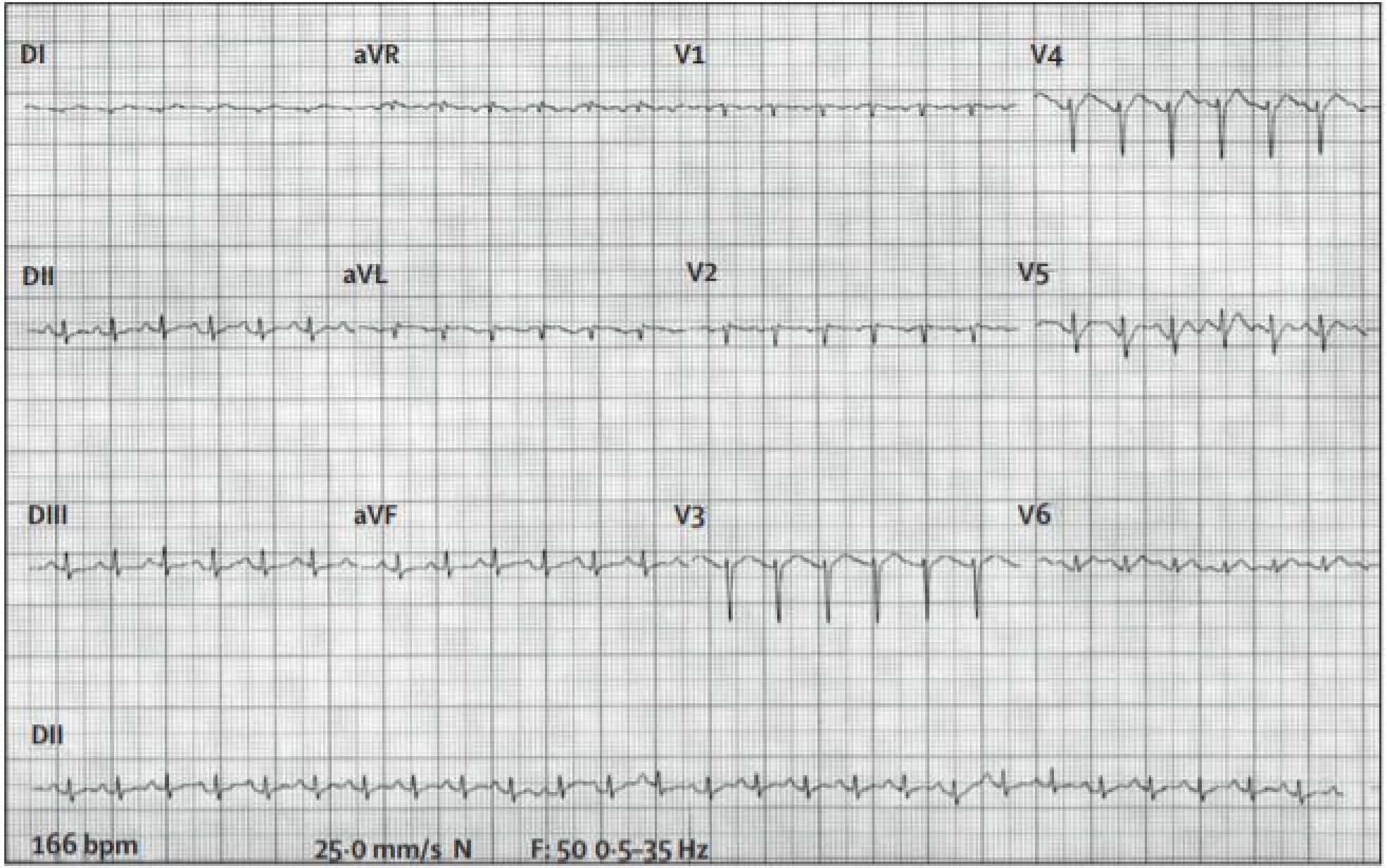


Figure 1: Electrocardiogram showing sinus tachycardia on admission

(Dolhnikof M et al Lancet Child Adolesc Health August 20, 2020 https://doi.org/10.1016/ S2352-4642(20)30257-1)

SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome (Dolhnikof M et al Lancet Child Adolesc Health August 20, 2020 https://doi.org/10.1016/ S2352-4642(20)30257-1)

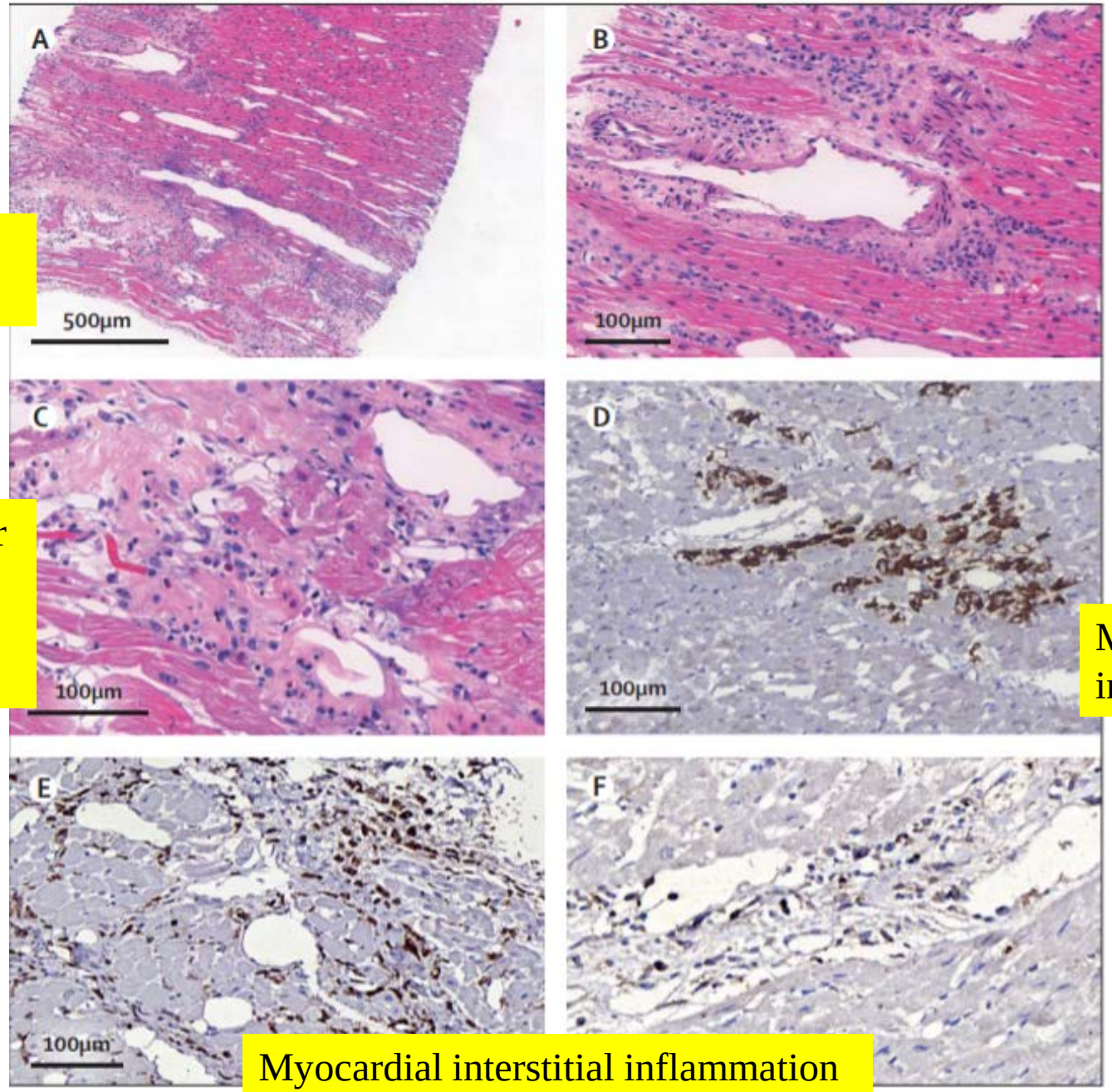
- Promptly **intubated**
- Antibiotic treatment with **ceftriaxone and azithromycin**
- **Peripheral epinephrine** was initiated in the emergency room
- A point-of-care **echocardiogram** showed **diffuse left ventricular hypokinesia** with no segmental wall motion abnormalities
- **Left-ventricular ejection fraction 31%,** no respiratory collapsibility of the inferior vena cava
- Received furosemide, and central line and invasive arterial monitoring were established
- The patient progressed to **hyperdynamic vasoplegic shock** refractory to volume resuscitation and vasoactive agents
- After **28 h of hospital admission**, she developed **ventricular fibrillation and died**

SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome (Dolhnikof M et al Lancet Child Adolesc Health August 20, 2020 https://doi.org/10.1016/ S2352-4642(20)30257-1)

- Post-mortem **CT angiography** did **not show any signs of coronary artery alterations**
- Post-mortem **ultrasound examination of the heart** showed a hyperechogenic and **diffusely thickened endocardium** (mean thickness 10 mm), a **thickened myocardium** (18 mm thick in the left ventricle), and a **small pericardial effusion**

Diffuse myocardial interstitial inflammation

Interstitial and perivascular myocardial inflammation , and foci of cardiomyocyte necrosis



Myocardial necrosis indicated by C4d staining

Myocardial interstitial inflammation containing CD68+ and CD45

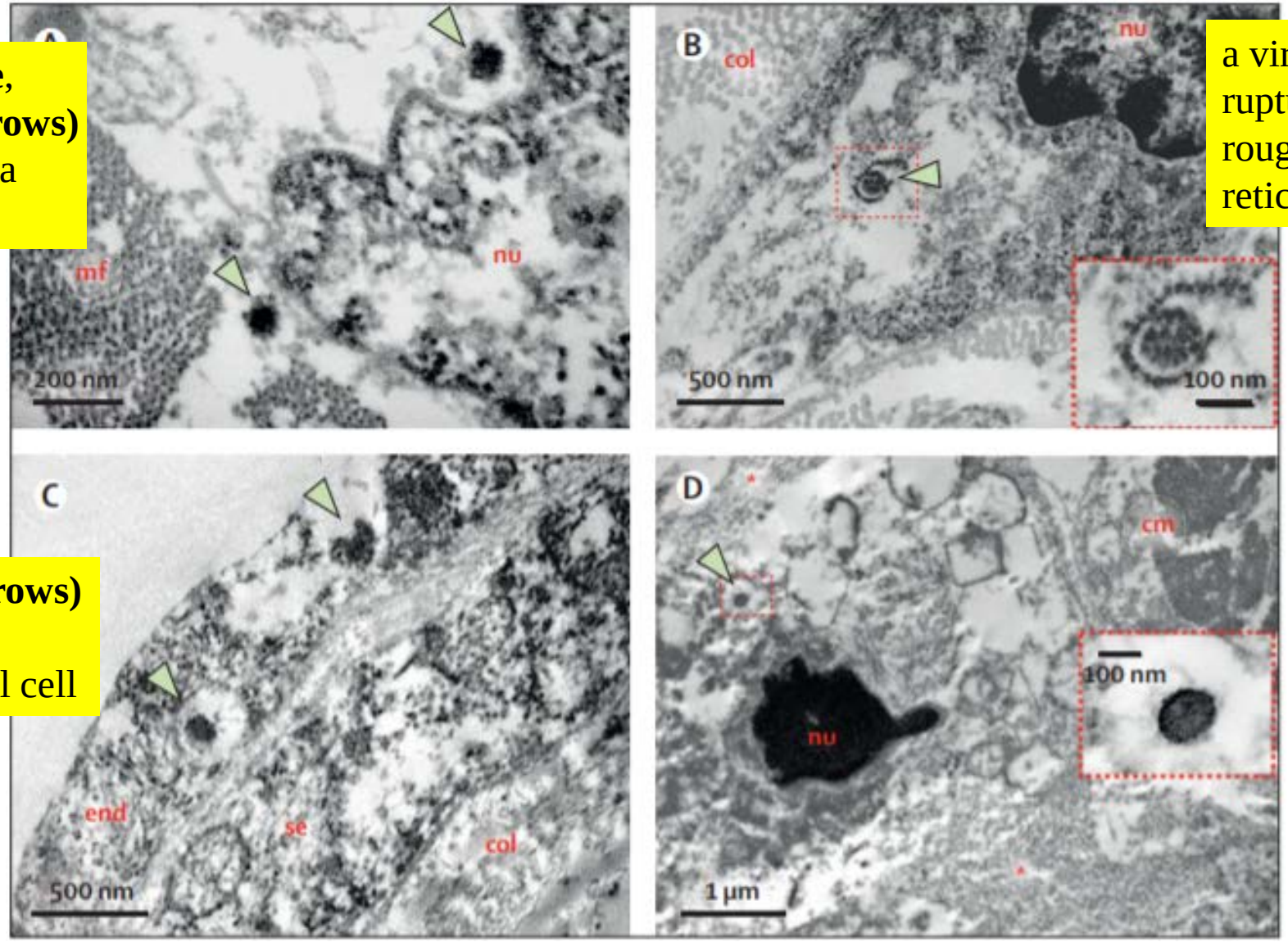
(Dolhnikof M et al Lancet Child A g/10.1016/ S2352-4642(20)30257-1)

Post-mortem electron microscopy findings

Part of a **cardiomyocyte**, with **viral particles (arrows)** within a cytoplasmic area close to the nucleus

a viral particle inside a ruptured fragment of the rough endoplasmic reticulum in a **fibroblast**

two **viral particles (arrows)** are present inside the **endocardial** endothelial cell



(Dolhnikof M et al Lancet Child Adolesc Health August 20, 2020 https://doi.org/10.1016/ S2352-4642(20)30257-1)

SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome (Dolhnikof M et al Lancet Child Adolesc Health August 20, 2020 https://doi.org/10.1016/ S2352-4642(20)30257-1)

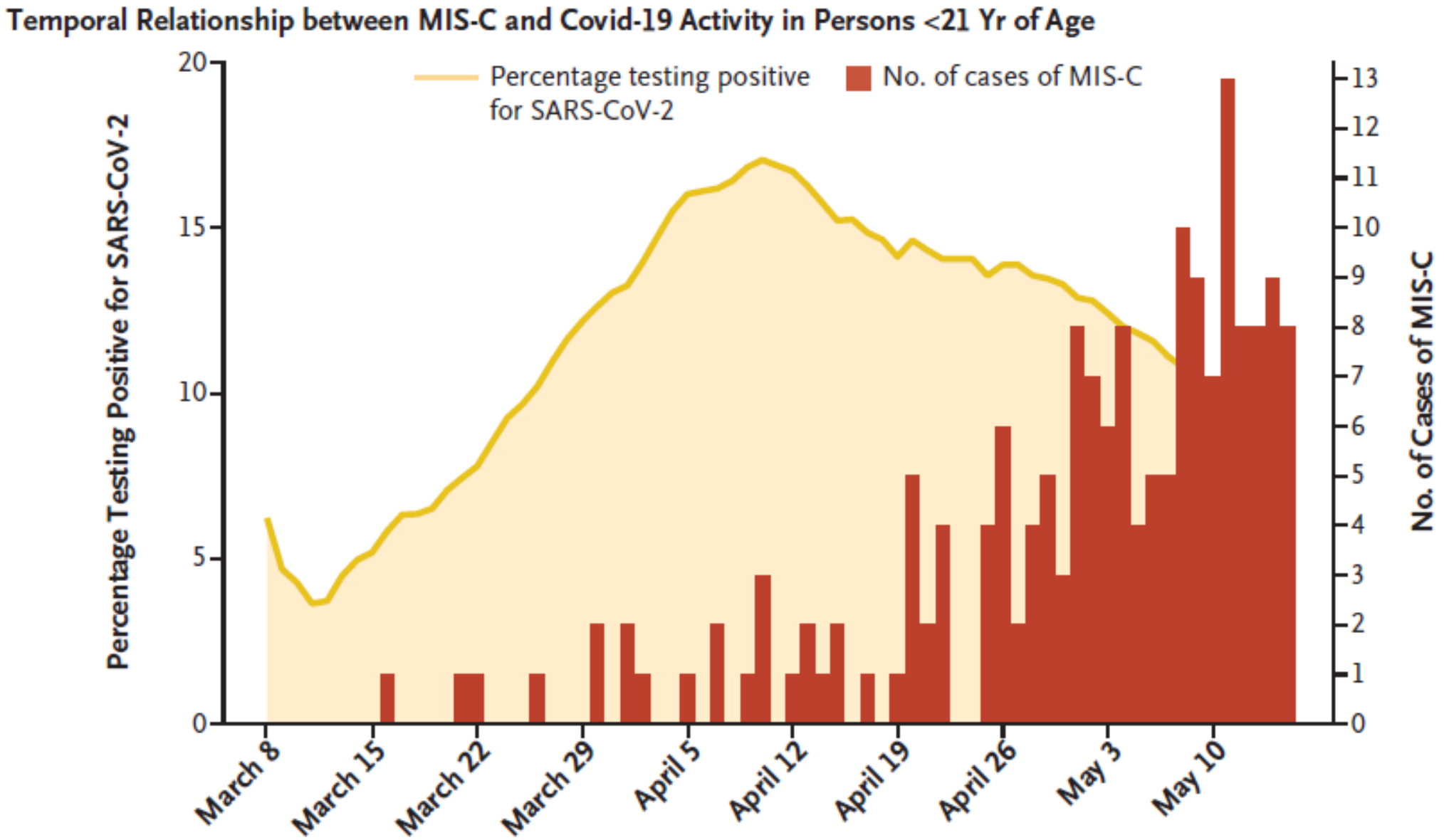
- **Microthrombi** in the pulmonary arterioles and renal glomerular capillaries
- SARS-CoV-2-associated **pneumonia was mild**, with patchy exudative changes in alveolar spaces and mild pneumocyte hyperplasia
- Lymphoid depletion and signs of **haemophagocytosis** were noted in the **spleen and lymph nodes**, indicating **secondary haemophagocytic lymphohistiocytosis** associated with systemic inflammation
- Acute tubular necrosis in the kidneys and hepatic centrilobular necrosis, secondary to shock, were also seen
- Brain tissue showed microglial reactivity

SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome (Dolhnikof M et al Lancet Child Adolesc Health August 20, 2020 https://doi.org/10.1016/ S2352-4642(20)30257-1)

- **SARS-CoV-2 RNA** was detected on a **post-mortem nasopharyngeal swab and in cardiac and pulmonary tissues** by **real time RT-PCR** using primers and probes set for E (envelope) gene
- **Cycle threshold** values for **lung and heart samples** were **35·6 and 36·0**, respectively, suggesting a **low viral load** in both organs
- To investigate a primary immunodeficiency, **whole exome sequencing** from genomic DNA extracted from whole blood was done, showing **No pathogenic**, likely pathogenic, or variant of unknown significance was found associated with inborn errors of immunity

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents (Feldstein LR et al NEJM 2020;383:334-46)

- The case definition included **six criteria**
  - Serious illness leading to **hospitalization**,
  - An age of **less than 21 years**,
  - **Fever** that lasted for **at least 24 hours**,
  - Laboratory evidence of **inflammation**,
  - **Multisystem organ** involvement,
  - Evidence of **infection with SARS-CoV-2** based on RT-PCR, **antibody testing**, or **exposure** to persons with Covid-19 in the past month



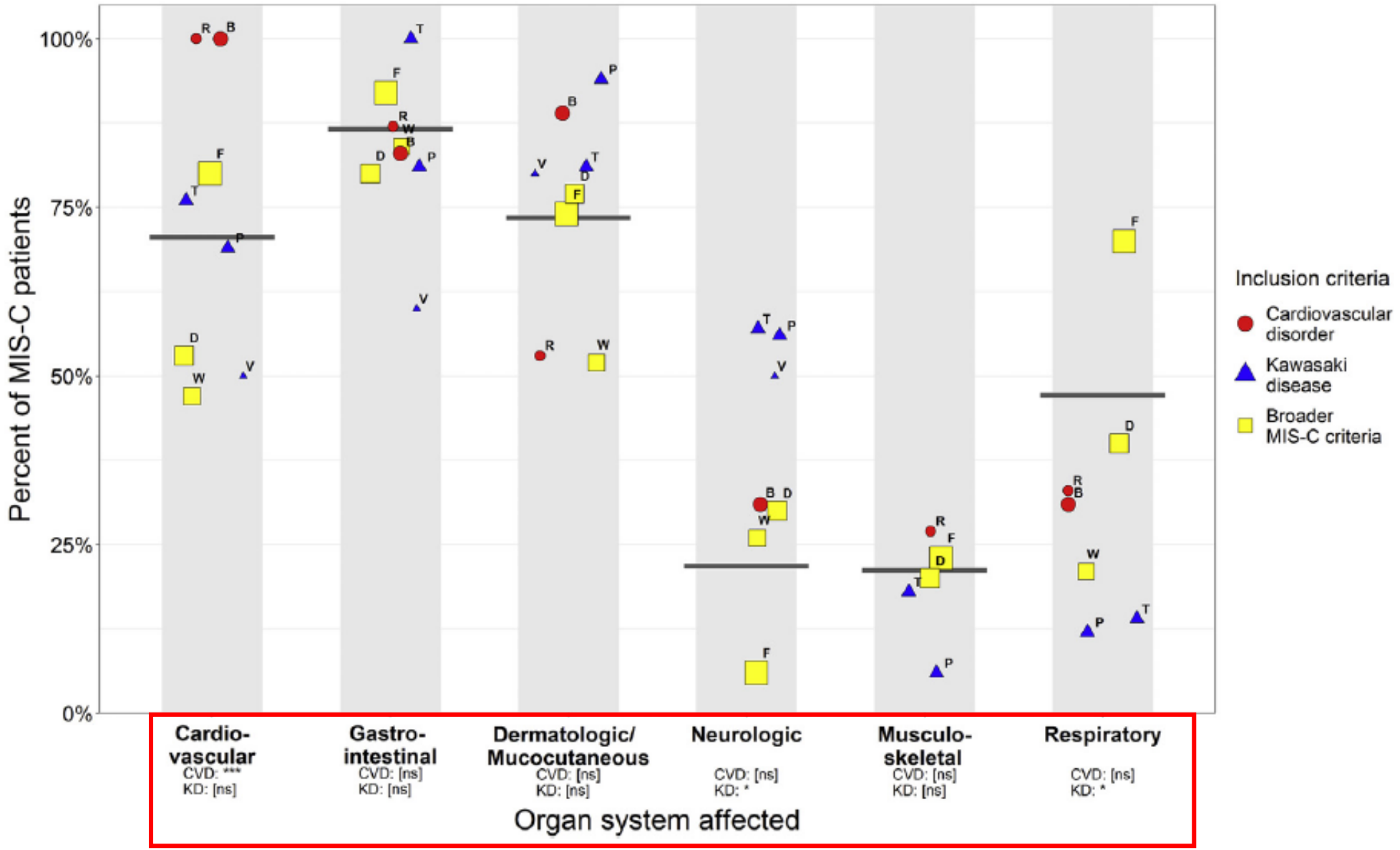
(Feldstein LR et al NEJM 2020;383:334-46)

Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2: A Systematic Review (Joseph Y et al J Ped 2020;226:45-54)

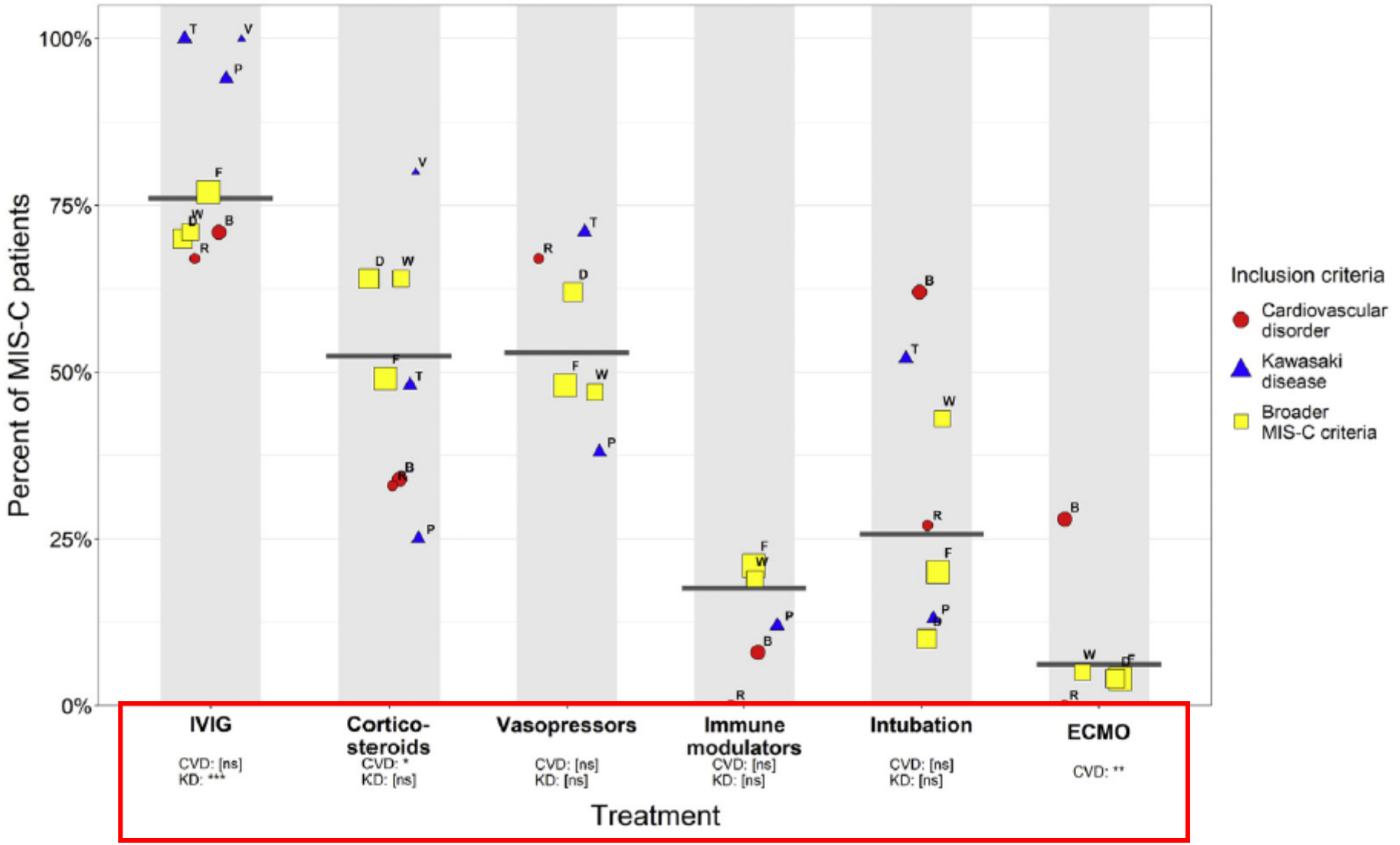
- Identify studies of MIS-C cases published from **April 25, 2020, through June 29, 2020**
- Inclusion criteria varied by study
  - 3 studies selected patients diagnosed with **Kawasaki disease**,
  - 2 required **cardiovascular involvement**,
  - 3 had **broader multisystem inclusion criteria**
- **Eight studies** were identified representing a total of **440 MIS-C cases**
  - **Median age** of patients by study ranged from **7.3 to 10 years**,
  - **59%** of patients **male**
  - Proportion of patients with positive results for SARS-CoV-2
    - For RT-PCR, ranged from 13% to 69%
    - **For serology, from 75% to 100%**

Studies	Ramcharan et al[29] 2020	Pouletty et al[28] 2020	Toubiana et al[9] 2020	Dufort et al[21] 2020	Feldstein et al[22] 2020
Location	Birmingham, England (Birmingham Children's Hospital)	5 hospitals in the Paris area	Paris, France (Necker-Enfants-Malades Hospital)	New York state, US	53 sites in 27 US states
N	15	16	21	99	186
Case hospitalization date range	April 10 to May 9	April 7 to April 30	April 27 to May 11	March 1 to May 10	March 15 to May 20
Other inclusion criteri	All patients referred for cardiovascular evaluation as confirmed PIMS-TS	<18 y, complete or incomplete Kawasaki disease, SARS-CoV-2 PCR+ or serology+ and/or close contact	Children ≤18 y who met criteria for Kawasaki disease (complete or incomplete)	New York state case definition: clinical and lab and/or epi criteria (includes positive SARS-CoV-2 test or reported exposure)[50]	CDC case definition: clinical and lab and/or epi criteria (includes positive SARS-CoV-2 test or reported exposure)
Median age, y (IQR)	8.8 (6.4-11.2)	10 (4.7-12.5)	7.9 (3.7-16.6)	NA	8.3 (3.3-12.5)
Sex (percent male)	73%	50%	43%	54%	62%
Race/ethnicity	40% Afro-Caribbean 40% South Asian 13% mixed 7% other	62% Afro-Caribbean 25% European 12% Middle Eastern	57% Afro-Caribbean 29% European 10% Asian 5% Middle Eastern	40% black 37% white 5% Asian 18% Other; 36% Hispanic*	39% Hispanic 31% black non-Hispanic 24% white non-Hispanic 6% other†
SARS-CoV-2 PCR, %	13%	69%	34%	51%	40%
SARS-CoV-2 serology, %	100%	100%	86%	99%	75%
Length of hospital sta median d (IQR)	12 (9 - 13)	NA	8	6 (4 - 9)	7 (4 - 10)
Died	0%	0%	0%	2%	2%

45-54)



(Joseph Y et al J Ped 2020;226:45-54)



(Joseph Y et al J Ped 2020;226:45-54)

Table II. Laboratory test results by study

Studies	Whittaker et al[31] 2020	Verdoni et al[10] 2020	Belhadjer et al[8] 2020	Toubiana et al[9] 2020	Dufort et al[21] 2020	Feldstein et al[22] 2020	Ramcharan et al[29] 2020	Pouletty et al[28] 2020
Erythrocyte sedimentation rate, mm/h								
Median	–	71	–	–	61.5	65	75	–
IQR	–	(52-94)	–	–	(43.0-77.5)	(42-91)	(45-90)	–
% Abnormal					77% (>40)	77% (>40)	75%-100%* (>9)	
Ferritin, ng/mL								
Median	610	893	–	–	522	639	558	1067
IQR	(359-1280)	(324-2000)	–	–	(305-820)	(333-1178)	(364-1325)	(272-1709)
% Abnormal	75%-100%* (>140)	56% (>684)	–	–	75% (>300)	61% (>500)	75%-100%* (>79)	50% (>500)
CRP, mg/L								
Median	229	241	241	253	219	178	154	207
IQR	(156-338)	(110-353)	(150-311)	(89-363)	(150-300)	(128-259)	(129-231)	(162-236)
% Abnormal	75%-100%* (>5)	80% (>100)	100% (>6)	–	87% (>100)	91% (>30)	75%-100%* (>10)	100%‡
Albumin, g/L								
Median	24	–	–	21	31	25	–	21
IQR	(21-27)	–	–	(16-37)	(25-36)	(20-29)	–	(19-23)
% Abnormal	75%-100%* (<35)	–	–	95% (<32)	48% (<30)	80% (<30)		43%‡
Interleukin-6, pg/mL								
Median	–	–	135	170	116.3	–	–	–
IQR	–	–	(87-175)	(4-1366)	(37.0-315.0)	–	–	–
% Abnormal		–	75%-100%* (>8.5)	–	97% (>5)	–		
Troponin, ng/L								
Median	45	111	347	282	–	–	396	58
IQR	(8-294)	(18-1879)	(186-1267)	(10-6900)	–	–	(100-1280)	(36-165)
% Abnormal	68% (>15)	56% (>53)	75-100%* (>26)	81% (>26)	71%‡	50%**	100% (>35)	
Fibrinogen, mg/dL								
Median	570	618	–	499	624	–	–	–
IQR	(440-700)	(483-759)	–	(78-838)	(506-764)	–	–	–
% Abnormal	75%-100%* (>409)	90% (>360)			86% (>400)	80% (>400)		
D-dimers, ng/mL								
Median	3578	–	5284	4025	2400	4090	2060	–
IQR	(2085-8235)	–	(4069-9095)	(350-19 330)	(1200-3700)	(2240-8405)	(1160-2610)	–
% Abnormal	75%-100%* (>560)	–	100% (>500)	95% (>500)	91% (>550)	67% (>3000)	75%-100%* (>300)	
BNP, pg/mL								
Median	–	–	5743	3354	–	1195	–	–
IQR	–	–	(2648-11 909)	(16-16 017)	–	(391-4833)	–	–
% Abnormal			100% (>100)	–	–	73% (>400)		
proBNP, ng/L								
Median	788	1236	41 484	–	–	–	24 470	–
IQR	(174-10 548)	(295-1921)	(35 811-52 475)	–	–	–	(17 212-26 655)	–
% Abnormal	83% (>100)	100% (>100)	100% (>100)	–	90%††	–	100% (>400)	

Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2: A Systematic Review (Joseph Y et al J Ped 2020;226:45-54)

- Patients with MIS-C had high prevalence of **gastrointestinal (87%), dermatologic/mucocutaneous (73%), and cardiovascular (71%)** symptoms
  - Prevalence of cardiovascular, neurologic, and respiratory system involvement **significantly differed by study inclusion criteria**
- All studies reported elevated **C-reactive protein, interleukin-6, and fibrinogen** levels **for at least 75%** of patients in each study

Conclusions

- **MIS-C cases** from **different studies across different countries** have **similar manifestations** with a strong temporal, geographic, and laboratory link with **SARS-CoV-2 infection**
- Clinical, laboratory, and epidemiologic characteristics of **MIS-C** appear to be **different from those of Kawasaki disease**

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 69
October 2, 2020

Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020

Sapna Bamrah Morris, MD[1]; Noah G. Schwartz, MD[1,2]; Pragna Patel, MD[1]; Lilian Abbo, MD[3]; Laura Beauchamps, MD[3]; Shuba Balan, MD[3]; Ellen H. Lee, MD[4]; Rachel Paneth-Pollak, MD[4]; Anita Geevarughese, MD[4]; Maura K. Lash, MPH[4]; Marie S. Dorsinville, MPH[4]; Vennus Ballen, MD[4]; Daniel P. Eiras, MD[4]; Christopher Newton-Cheh, MD[5,6]; Emer Smith, MPH[7,8]; Sara Robinson, MPH[7]; Patricia Stogsdill, MD[9]; Sarah Lim, MBBCh[10]; Sharon E. Fox, MD, PhD[11,12]; Gillian Richardson, MPH[13]; Julie Hand, MSPH[13]; Nora T. Oliver, MD[14]; Aaron Kofman, MD[15]; Bobbi Bryant, MPH[1,16]; Zachary Ende, PhD[1,16]; Deblina Datta, MD[1]; Ermias Belay, MD[1]; Shana Godfred-Cato, DO[1]

27 cases (3 fatal cases) were reported and identified

Genomewide Association Study of Severe Covid-19 with Respiratory Failure

RESULTS

We detected cross-replicating associations with rs11385942 at locus 3p21.31 and with rs657152 at locus 9q34.2, which were significant at the genomewide level ($P<5\times10^{-8}$) in the meta-analysis of the two case–control panels (odds ratio, 1.77; 95% confidence interval [CI], 1.48 to 2.11; $P=1.15\times10^{-10}$; and odds ratio, 1.32; 95% CI, 1.20 to 1.47; $P=4.95\times10^{-8}$, respectively). At locus 3p21.31, the association signal spanned the genes *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6* and *XCR1*. The association signal at locus 9q34.2 coincided with the *ABO* blood group locus; in this cohort, a blood-group–specific analysis showed a higher risk in blood group A than in other blood groups (odds ratio, 1.45; 95% CI, 1.20 to 1.75; $P=1.48\times10^{-4}$) and a protective effect in blood group O as compared with other blood groups (odds ratio, 0.65; 95% CI, 0.53 to 0.79; $P=1.06\times10^{-5}$).

CONCLUSIONS

We identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with Covid-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system. (Funded by Stein Erik Hagen and others.)

(NEJM 2020;383: 1522-34)

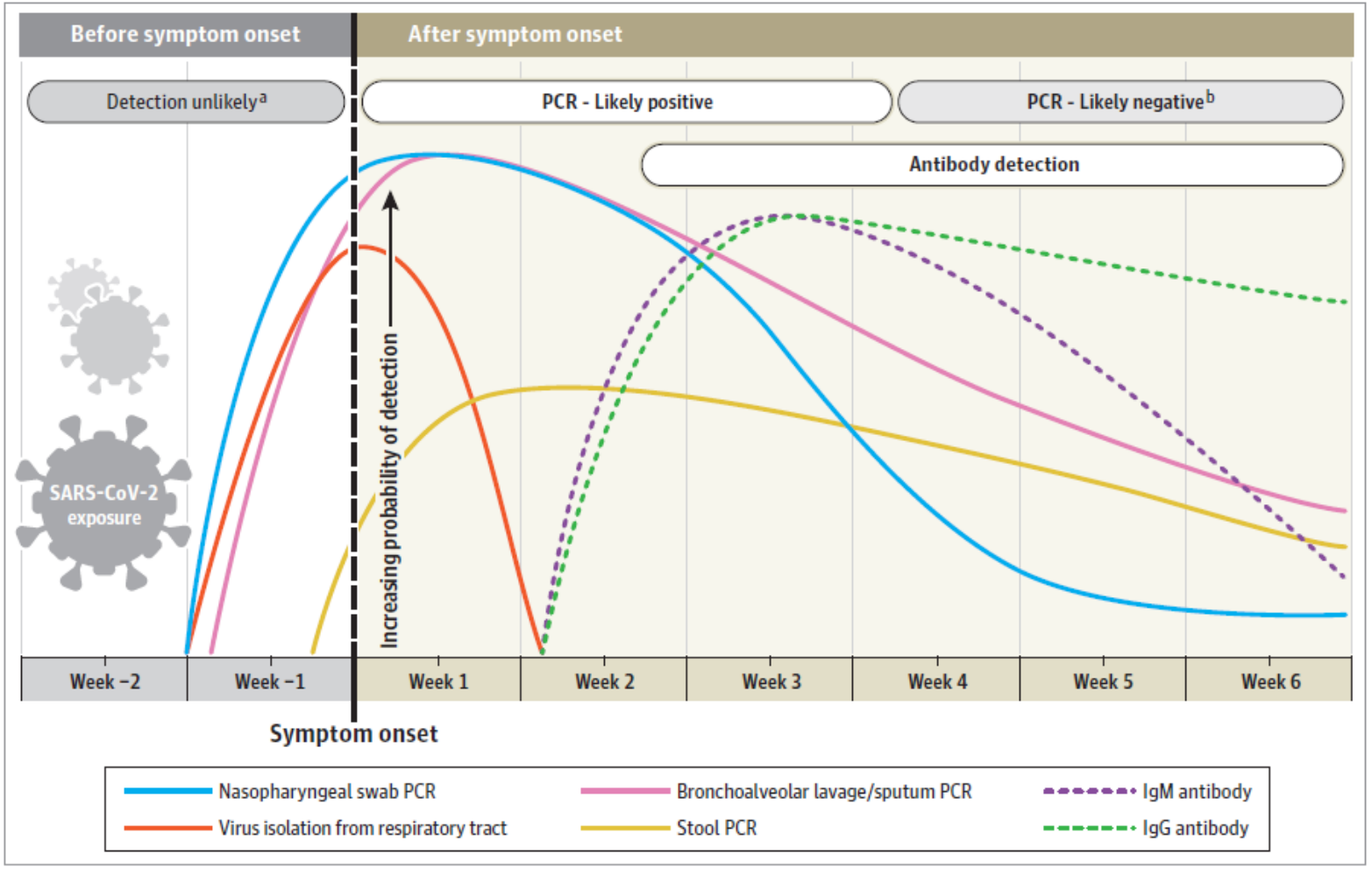

EXIT
緊急出口
黃玉成 常務理事
李秉穎 理事長
陳時中 部長
周志浩 署長
莊人祥 副署
葉彥伯 局長

Diagnosis of SARS-CoV-2 infection

- **Clinical diagnosis**
  - Symptoms & signs, lab data, image studies
- **Epidemiologic diagnosis**
  - Seasonality, local epidemics
  - Travel, Occupation, Cluster, Contact
- **Laboratory diagnosis**
  - **PCR-based**
  - Virus culture
  - Antigen detection
  - Serology: not timely

Interpreting Diagnostic Tests for SARS-CoV-2 (Sethuraman N et al JAMA 2020;May 6)

Figure. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset



Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

[a] Detection only occurs if patients are followed up proactively from the time of exposure.

[b] More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Laboratory diagnosis of SARS-CoV-2 infection

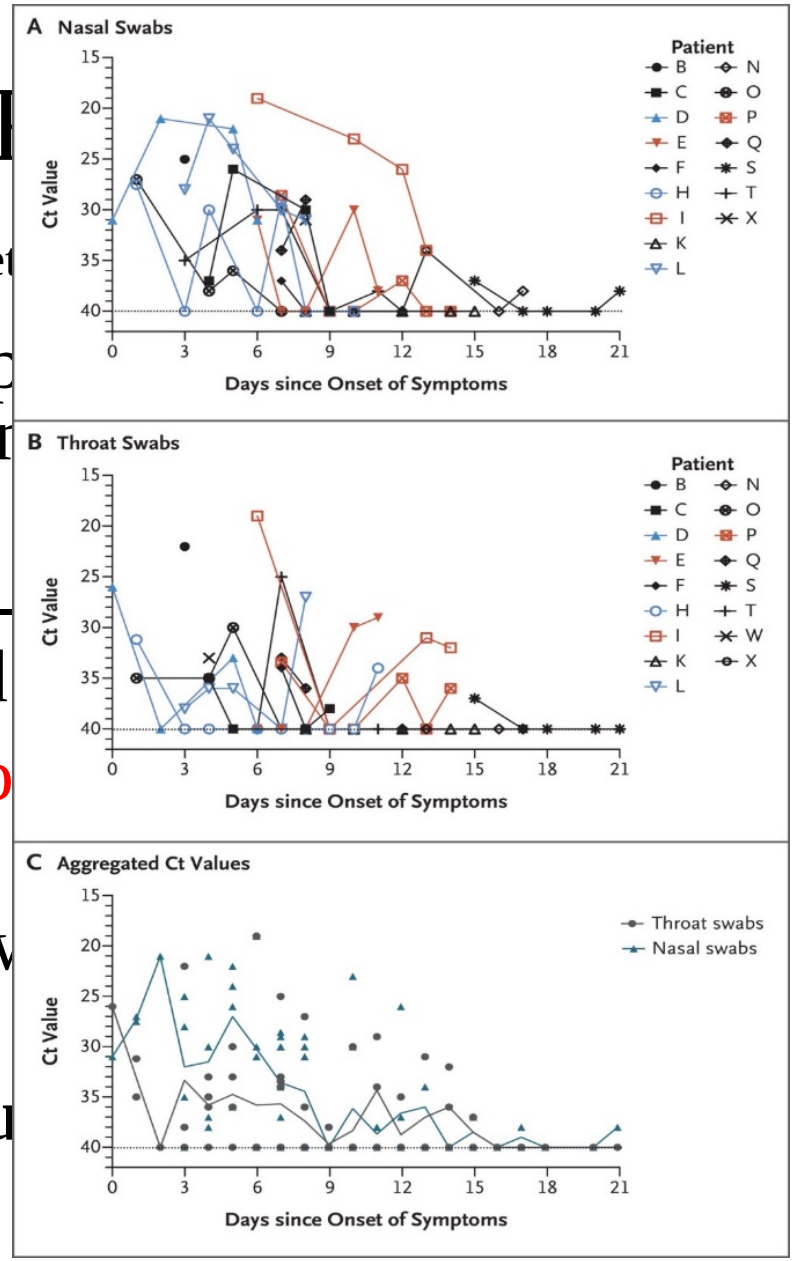
- **PCR-based**
  - Real time RT-PCR
  - Target genes: nucleocapsid gene, RdRP, envelope etc.
  - Specimens:
    - **Upper respiratory**: nasopharyngeal swab, throat swab, saliva, nasal swab
    - **Non-respiratory: stool**
- **Serologic tests**
  - Detect IgM and IgG may be reactive **as early as 4 days after symptom onset** and until **as late as 11–14 days** from the date of infection
  - May be **helpful** to **describe the epidemiology of SARS-CoV-2 retrospectively**, but population samples will be a key factor in interpreting the results
- **Interpretation of lab tests**
  - **Timing** of collection with respect to the illness course, **intermittent shedding**, **variability** of **sample collection**, **degradation** of viral **RNA** during shipping or storage of samples, the **specimen** acquisition **site**, and host and epidemiological factors must be considered in the interpretation of diagnostic test results

Laboratory Diagnosis of COVID-19: Current Issues and Challenges (Tang YW et al JCM 2020;58 (6):e00512-20)

- In the **pre-analytical stage**, collecting the **proper** respiratory tract **specimen** at the **right time** from the **right anatomic site** is essential for a prompt and accurate molecular diagnosis of COVID-19
- In the **analytic stage**, real-time **RT-PCR assays** remain the molecular **test of choice**, while **antibody-based** techniques are being introduced as **supplemental tools**
- In the **post-analytical stage**, testing results should be **carefully interpreted** using both molecular and serological findings
- Finally, random-access, integrated devices available at the **point of care** with scalable capacities will facilitate the rapid and accurate diagnosis and monitoring of SARS-CoV-2 infections

SARS-CoV-2 Viral Load in Upper R Specimens of Infected Patients (Zou L et

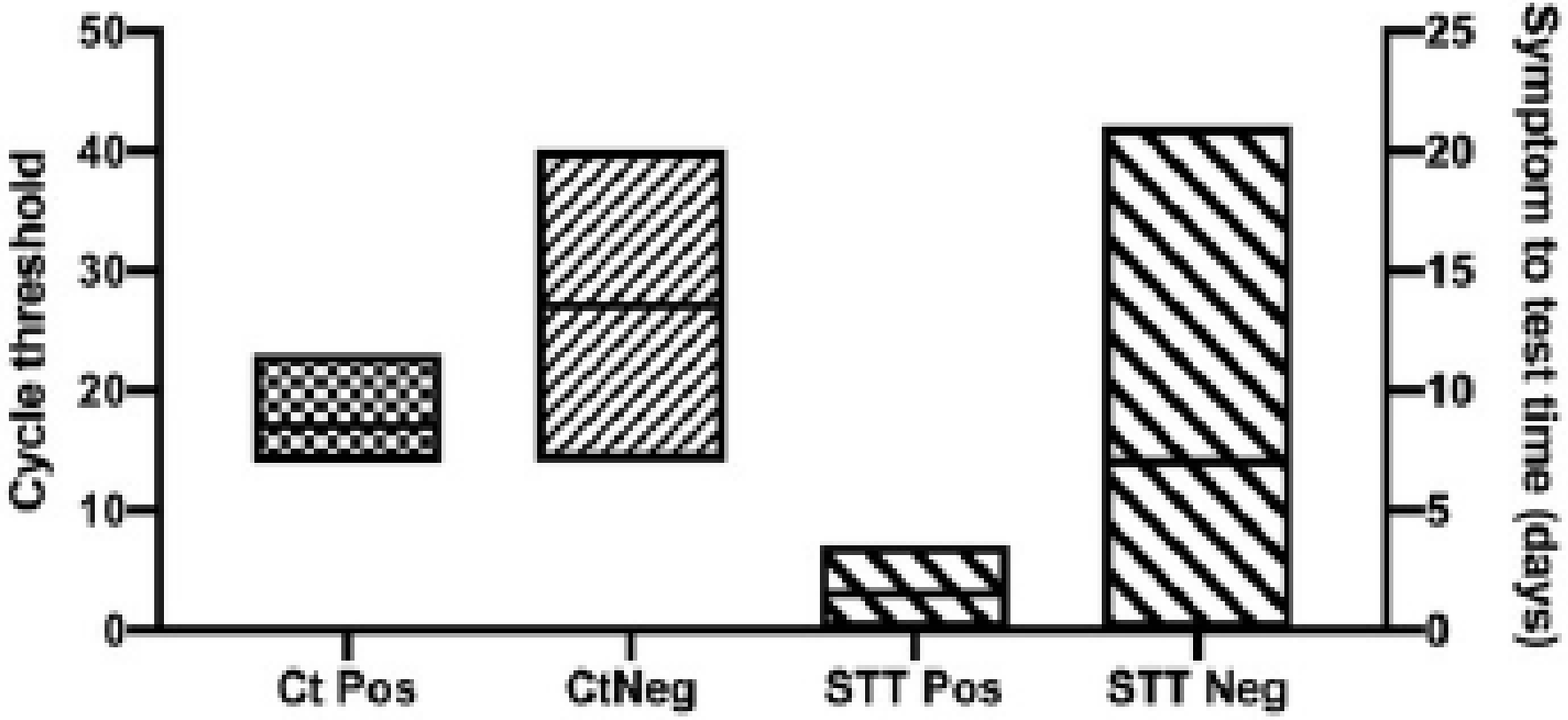
- Monitored SARS-CoV-2 viral loads in upper resp obtained from 18 patients (9 men and 9 women; r range, 26 to 76) in Zhuhai, Guangdong, China
- A total of 72 nasal swabs (sampled from the mid- nasopharynx) and 72 throat swabs were analyzed
- Higher viral loads detected soon after symptom o viral loads detected in the nose than in the throat
- **Viral load** detected in the asymptomatic patient v the symptomatic patients
- How SARS-CoV-2 **viral load correlates with cu** to be determined



Predicting infectious SARS-CoV-2 from diagnostic samples (Bullard J et al CID 2020;online)

- Retrospective cross-sectional study, we took SARS-CoV-2 RT-PCR confirmed positive samples and determined their ability to infect Vero cell lines
- 90 RT-PCR SARS-CoV-2 positive samples were incubated on **Vero cells**
  - Twenty-six samples (**28.9%**) demonstrated **viral growth**
  - Median TCID50/ml was 1780 (282-8511).
  - There was **no growth** in samples with a **Ct > 24** or **symptom onset to test (STT) > 8 days**
  - Multivariate logistic regression using positive viral culture as a binary predictor variable, STT and Ct demonstrated an odds ratio for positive viral culture of 0.64 (95% CI 0.49-0.84, p<0.001) for every one unit increase in Ct
  - Area under the receiver operating characteristic curve for Ct vs. positive culture was OR 0.91 (95% CI 0.85-0.97, p<0.001), with 97% specificity obtained at a Ct of >24

Figure 2



- Positive SARS-CoV-2 culture samples had a **significantly lower Ct** when compared to culture negative samples (17 [16-18] vs 27 [22-33], $p<0.001$).
- **Symptom to test time** was also **significantly lower** in culture positive vs. culture negative samples (3 [2-4] vs. 7 [4-11], $p<0.001$)

Predicting infectious SARS-CoV-2 from diagnostic samples (Bullard J et al CID 2020;online)

Conclusions

- SARS-CoV-2 **Vero cell infectivity** was **only observed for RT-PCR Ct < 24 and symptom onset to test < 8 days**
- Infectivity of patients with Ct >24 and duration of symptoms >8 days may be low

Spread of SARS-CoV-2 in the Icelandic Population

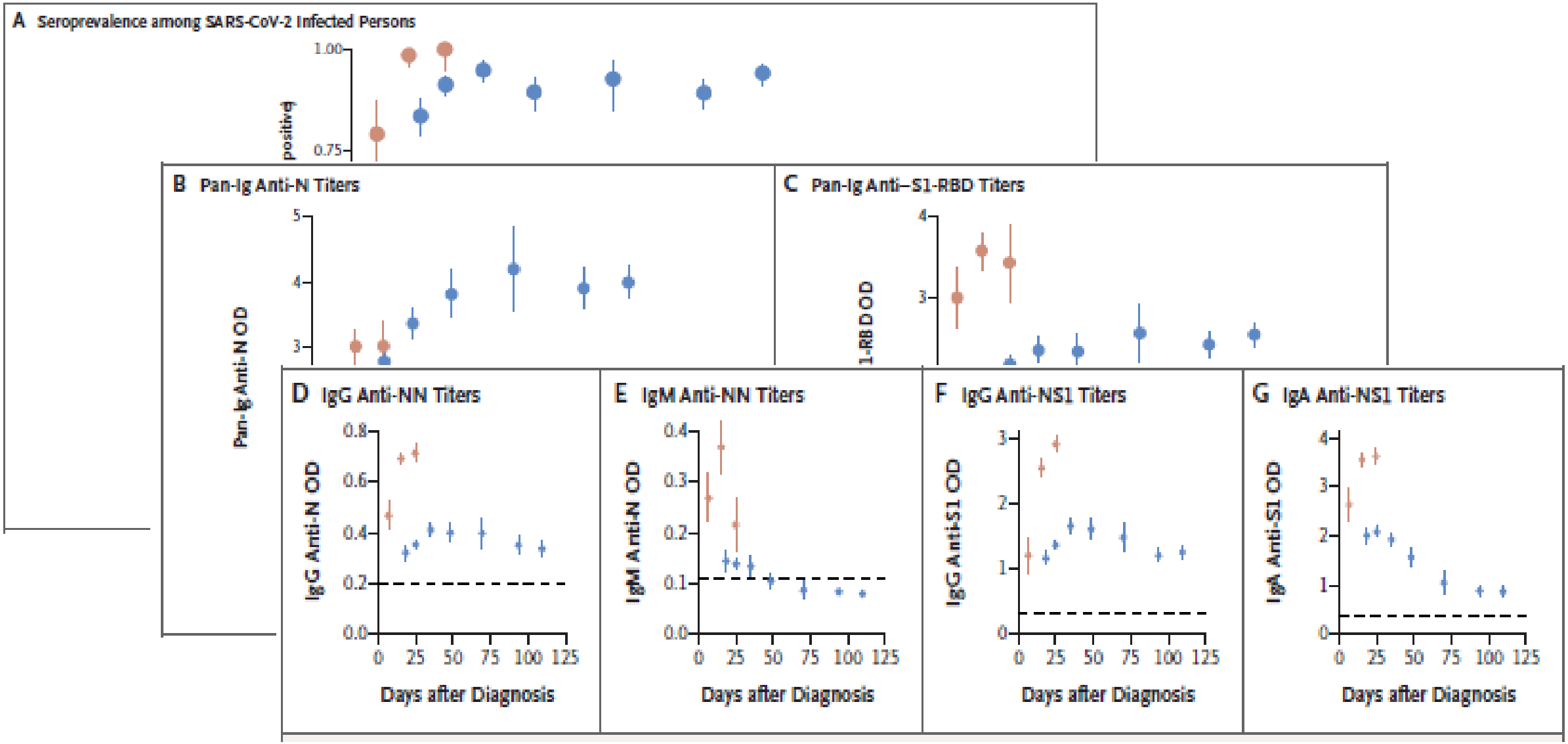
(Gudbjartsson DF et al NEJM 2020; 382:2302-2315)

- **Targeted testing** to persons living in Iceland who were at high **risk for infection** (mainly those who were symptomatic, had recently traveled to high-risk countries, or had contact with infected persons)
  - As of April 4, a total of **1221 of 9199 persons** (**13.3%**) **positive** results for infection with SARS-CoV-2
- Also carried out population screening using two strategies
  - Issuing an open invitation to 10,797 persons:
    - **87 (0.8%) positive**
  - Sending random invitations to 2283 persons
    - **13 (0.6%) positive**
- In total, 6% of the population was screened
- Sequenced SARS-CoV-2 from 643 samples
  - diverse and changed over time

Humoral Immune Response to SARS-CoV-2 in Iceland

(Gudbjartsson DF et al NEJM 2020; Sep 1, doi: 10.1056/NEJMoa2026116)

- Measured antibodies in serum samples from **30,576 persons** in Iceland, using six assays (including two pan-Ig assays), determined that the appropriate measure of seropositivity was a positive result with both pan-Ig assays
  - pan-immunoglobulin (pan-Ig: IgM, IgG, and IgA) antibodies against the **nucleoprotein (N)** (Roche)
  - pan-Ig antibodies against the receptor binding domain (**RBD**) in the S1 subunit of the spike protein (pan-Ig anti–S1-RBD) (Wantai);
  - **IgM and IgG** antibodies against **N** (IgM anti-N and IgG anti-N) (EDI/Eagle);
  - **IgG and IgA** against the **S1 subunit** of the **spike protein** (IgG anti-S1 and IgA anti-S1) (Euroimmun)
- Of the 1797 persons who had recovered from **SARS-CoV-2 infection**,
  - 1107 of the 1215 who were tested (**91.1%**) were **seropositive**;
  - antiviral **antibody titers** assayed by two pan-Ig assays **increased** during 2 months after diagnosis by qPCR and **remained on a plateau** for the remainder of the study
- Of 4222 **quarantined persons**, **2.3%** were seropositive
- Of 23452 persons with **unknown exposure**, **0.3%** were positive



Antibody Prevalence and Titers among qPCR-Positive Cases as a Function of Time since Diagnosis by qPCR

(Gudbjartsson DF et al NEJM 2020; Sep 1, doi: 10.1056/NEJMoa2026116)

Table 1. Prevalence of SARS

Sample Collection	No.

Table 2. Results of Repeated Pan-Ig Antibody Tests among Recovered qPCR-Diagnosed Persons.*

First Sample	Second Sample

Table 3. SARS-CoV-2 Infection among Quarantined Persons According to Exposure Type and Presence of Symptoms.*

Variable	No. of Persons	qPCR			Both Pan-Ig Antibody Assays		
		No. Tested	No. Positive (%)	OR (95% CI)†	No. Tested	No. Positive (%)	OR (95% CI)†
No household exposure	18,877	6839	689 (10.1)		3700	52 (1.4)	
Household exposure	1,889	1092	399 (36.5)	5.2 (4.5–6.1)	503	37 (7.4)	5.2 (3.3–8.0)
No reported symptoms	3,439	1421	142 (10.0)		1007	24 (2.4)	
Reported symptoms	1,639	1397	920 (65.9)	18.2 (14.8–22.4)	237	17 (7.2)	3.2 (1.7–6.2)

* Exposure data were available for 7931 persons who had been tested with qPCR and 4203 tested for antibodies. Symptom data were available for 2818 persons who had been tested with qPCR and 1244 tested for antibodies. The effects of household exposure and symptoms were tested separately among all persons who were tested by qPCR and the collected subset of non qPCR-positive persons tested for antibodies.
† The odds ratios (ORs) comparing exposed with nonexposed and symptomatic with nonsymptomatic were adjusted for sex, age, and age squared.

(Gudbjartsson DF et al NEJM 2020; Sep 1, doi: 10.1056/NEJMoa2026116)

Humoral Immune Response to SARS-CoV-2 in Iceland

(Gudbjartsson DF et al NEJM 2020; Sep 1, doi: 10.1056/NEJMoa2026116)

- Estimate that
  - **0.9%** of Icelanders were **infected with SARS-CoV-2**
  - the infection was **fatal in 0.3%**
  - **56%** of all SARS-CoV-2 infections in Iceland had been **diagnosed with qPCR**,
  - **14%** had occurred in **quarantined persons** who had **not been tested with qPCR** (or who had not received a positive result, if tested),
  - **30%** had occurred in persons **outside quarantine** and **not tested with qPCR**

Conclusions

- Results indicate that antiviral **antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis**
- Estimate that the **risk of death** from infection was **0.3%**, **44%** of **persons infected** with SARS-CoV-2 in Iceland were **not diagnosed by qPCR**


Thank you for your attention!!