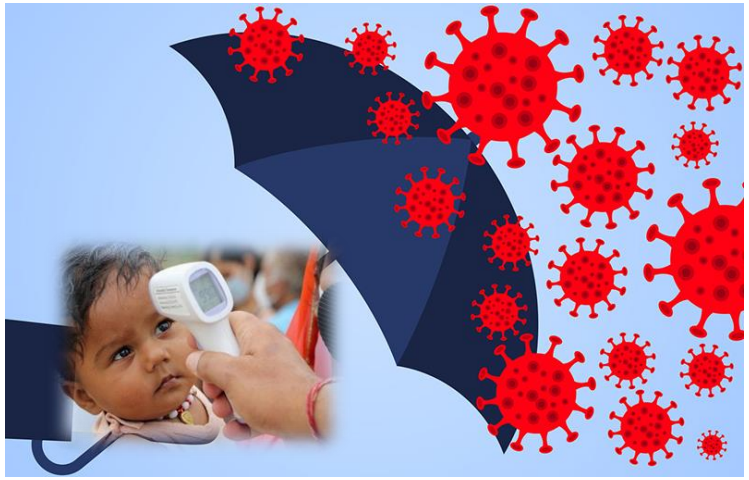
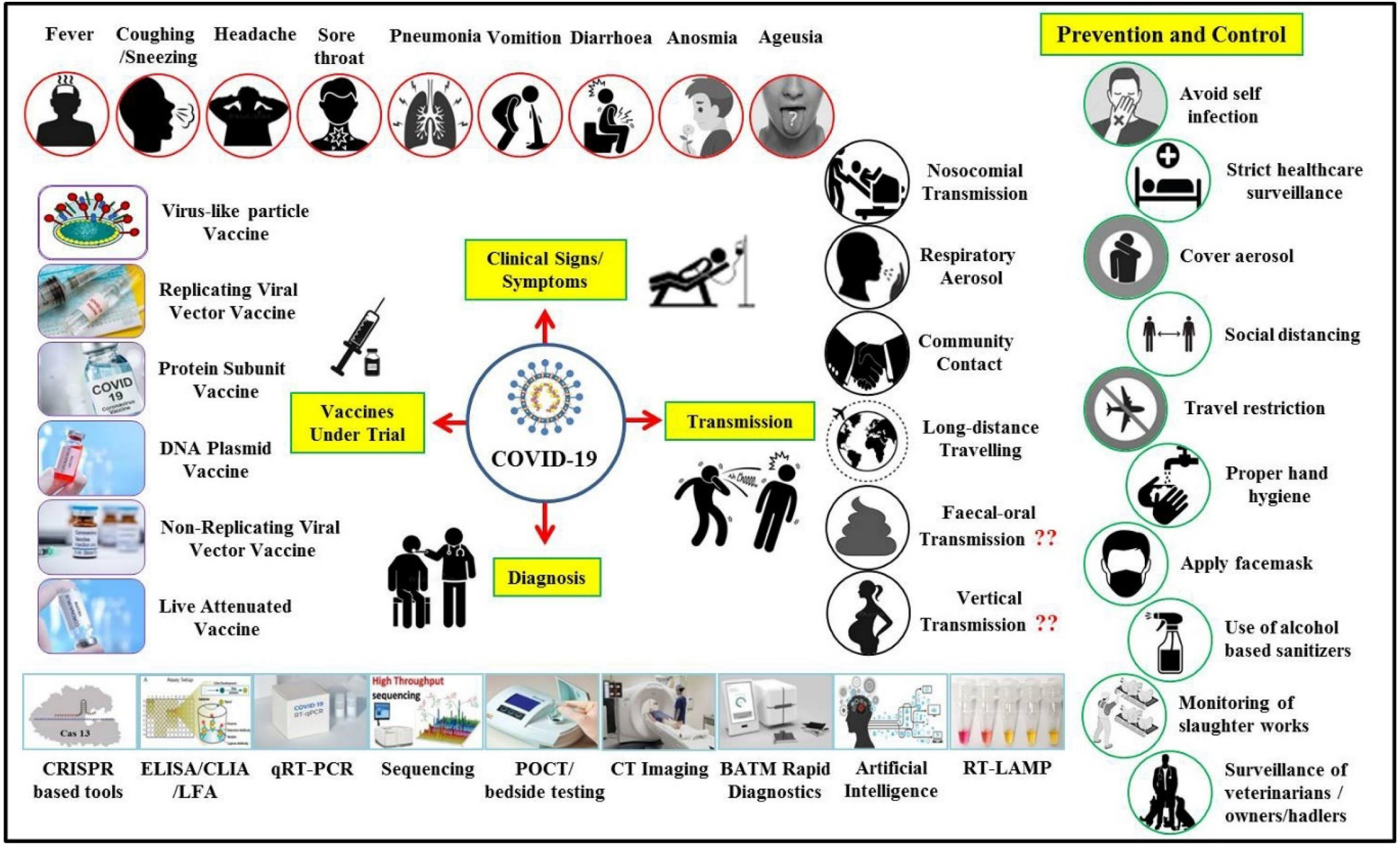


COVID-19 a gyermekkorban

Dr. Fekete Ferenc PhD

Heim Pál Országos Gyermekgyógyászati Intézet

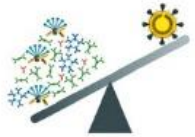

Fever
Coughing /Sneezing
Headache
Sore throat
Pneumonia
Vomition
Diarrhoea
Anosmia
Ageusia
Virus-like particle Vaccine
Replicating Viral Vector Vaccine
Protein Subunit Vaccine
DNA Plasmid Vaccine
Non-Replicating Viral Vector Vaccine
Live Attenuated Vaccine
Vaccines Under Trial
Clinical Signs/ Symptoms
COVID-19
Transmission
Diagnosis
Nosocomial Transmission
Respiratory Aerosol
Community Contact
Long-distance Travelling
Faecal-oral Transmission ??
Vertical Transmission ??
Prevention and Control
Avoid self infection
Strict healthcare surveillance
Cover aerosol
Social distancing
Travel restriction
Proper hand hygiene
Apply facemask
Use of alcohol based sanitizers
Monitoring of slaughter works
Surveillance of veterinarians / owners/hadlers
Cas 13
High Throughput sequencing
CRISPR based tools
ELISA/CLIA /LFA
qRT-PCR
Sequencing
POCT/ bedside testing
CT Imaging
BATM Rapid Diagnostics
Artificial Intelligence
RT-LAMP

Fertőződés rizikója

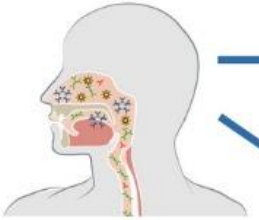
COVID-19 HOLISTIC MODEL

The cumulative dose of viral exposure from "donor" to "recipient" is a function of the viral load and shedding from the donor, the time and distance of the contact, and the number of contacts that the same recipient has with different donors.

SARS-CoV-2/nAbs low ratio



The balance of natural immunity (nIgM, nIgA, MBL) and the dose of viral exposure is relevant to decide if SARS-CoV-2 will penetrate the lower airways. Among children and young adults, normally innate immunity predominates.



Upper airways

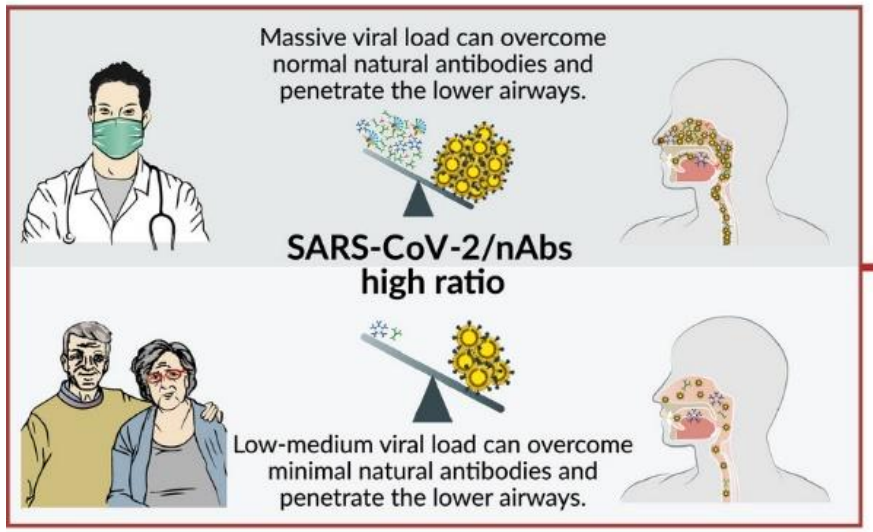
Natural antibodies and other components of the innate immunity in saliva and secretions can block the virus in the upper airways, especially if the dose of exposure is low.

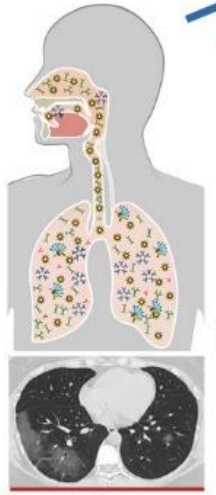
Physical activity, as usually practiced by non-professionals, at low-moderate workload, is recommended.

By contrast, extreme physical exercise, by inducing oral breathing with maximal hyperventilation, favors the deepest inhalation of the aerosol containing viral particles to the lower airways and alveoli.

During incubation and early paucisymptomatic stages of COVID-19, prolonged oral breathing with hyperventilation can cause viral particles contained in own exhaled aerosol to be re-inhaled and penetrate the lower airways and alveoli («viral auto-inhalation» mechanism»). This phenomenon causes early, hence severe pneumonia.

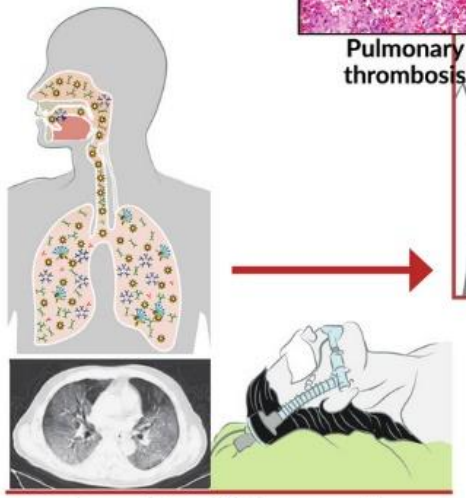
Healing



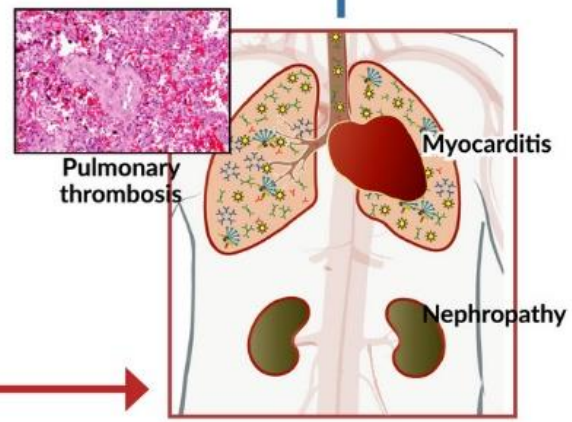


Interstitial pneumonia

Antibodies limit viral infectivity, but non-neutralizing antibodies may activate the complement system, the coagulation system and concur to cause the cytokine storm, by enhancing the infection ultimately leading to clinical complications.



Severe interstitial pneumonia



MBL and antibodies activate the complement system and the coagulation system, and the IL-6 driven cytokine storm, causing complications.

Death may be caused by several complications, including coinfections, kidney or heart failure, intravasal coagulation disseminated or limited to the lung.

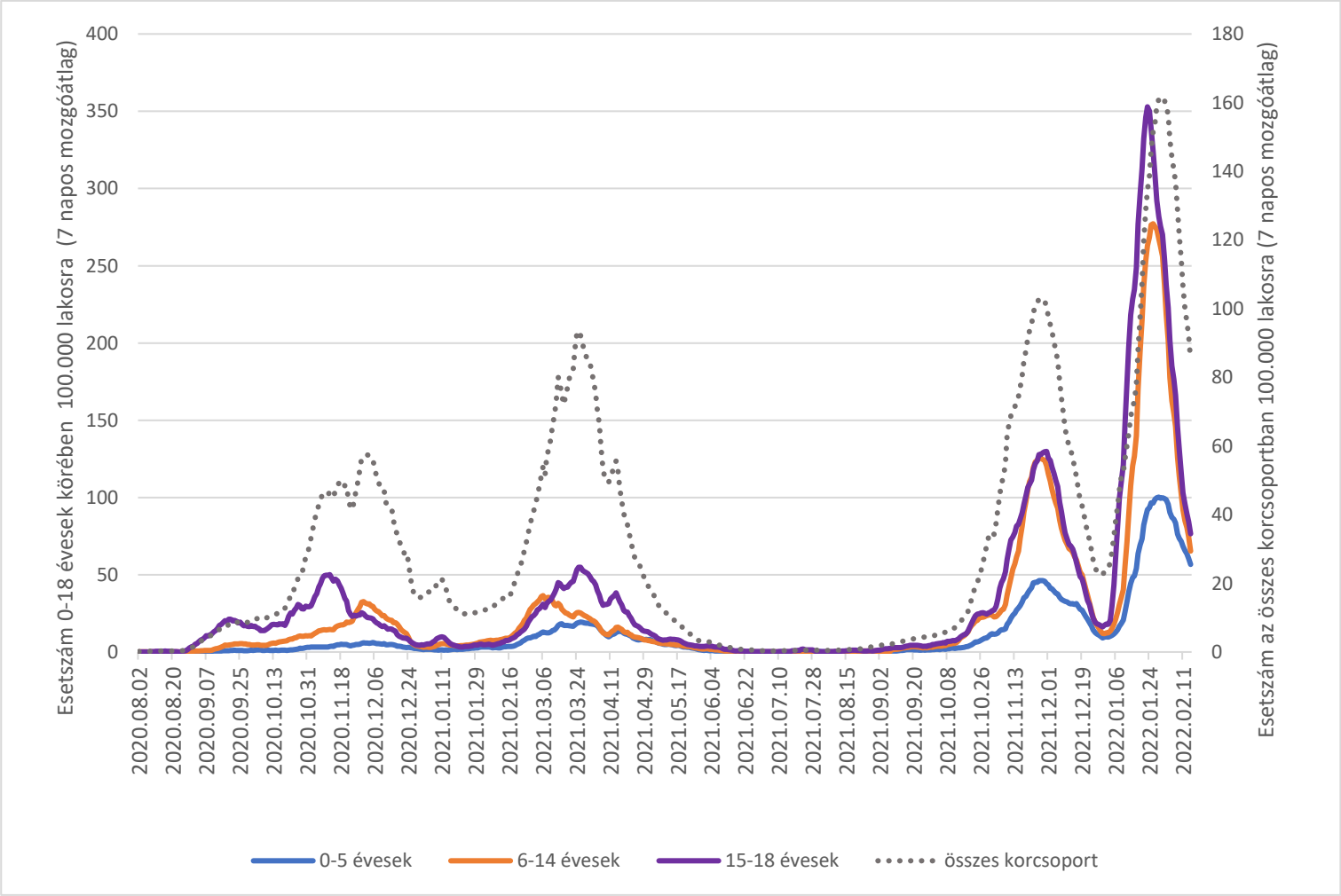
Pediatric Allergy and Immunology, Volume: 31, Issue: 5, Pages: 454-470, First published: 02 May 2020, DOI: (10.1111/pai.13271)

Igazolt 0-18 éves COVID-19 esetek száma, korspecifikus gyakorisága és kor szerinti megoszlása a 2. járványhullámtól, 2020. 06.20. és 2022. 02. 15. között

	II. hullám		III. hullám	
Korcsoport	**Megerősített COVID-19 esetek száma**	**Megerősített COVID-19 esetek részaránya**	**Megerősített COVID-19 esetek száma**	**Megerősített COVID-19 esetek részaránya**
0-18	**26 194**	**7,36%**	**32 577**	**7,27%**
19-X	**329 988**	**92,64%**	**415 377**	**92,73%**
Összesen	**356 182**		**447 954**	
	IV. hullám		**V. hullám (2022. 02. 15-ig)**	
Korcsoport	**Megerősített COVID-19 esetek száma**	**Megerősített COVID-19 esetek részaránya**	**Megerősített COVID-19 esetek száma**	**Megerősített COVID-19 esetek részaránya**
0-18	**68 386**	**15,65%**	**109 420**	**22,56%**
19-X	**368 663**	**84,35%**	**375 621**	**77,44%**
Összesen	**437 049**		**485 041**	

COVID-19 a gyermekek körében - mi az, amit jelenleg tudunk, és mi az, amit nem 2022. Népegészségügy in press

Korspecifikus megbetegedési arány 7 napos mozgóátlaga, 100.000 főre vetítve a fertőzés igazolásának dátuma szerint a II-V. járványhullámban 2020.08.01 – 2022.02.15 között.



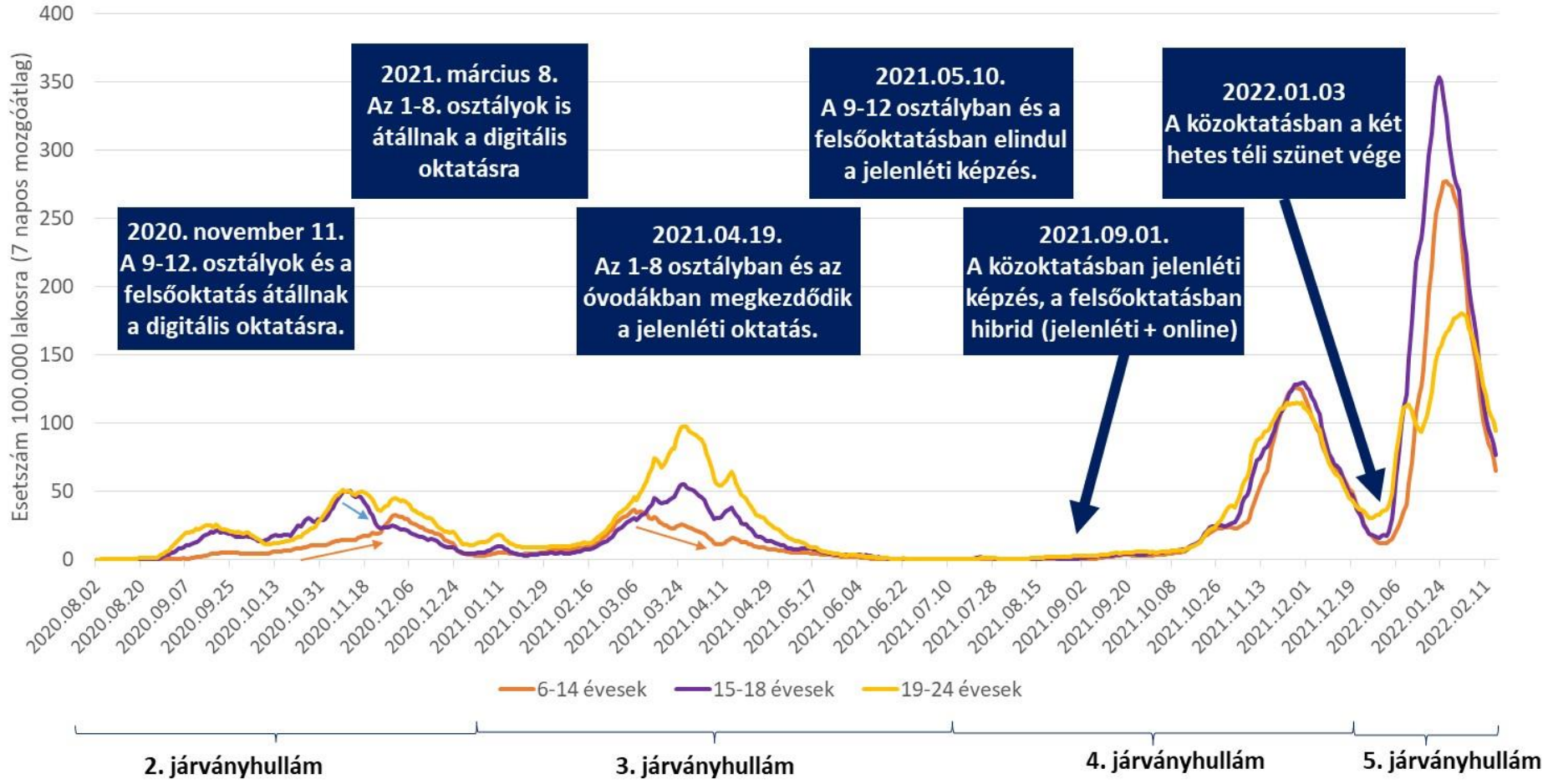
COVID-19 a gyermekek körében - mi az, amit jelenleg tudunk, és mi az, amit nem 2022. Népegészségügy in press

A COVID-19 világjárvány alapvető epidemiológiai mutatói 0-17 évesek körében a 2022. február 15-én rendelkezésre álló adatok alapján az Egyesült Államokban és Magyarországon

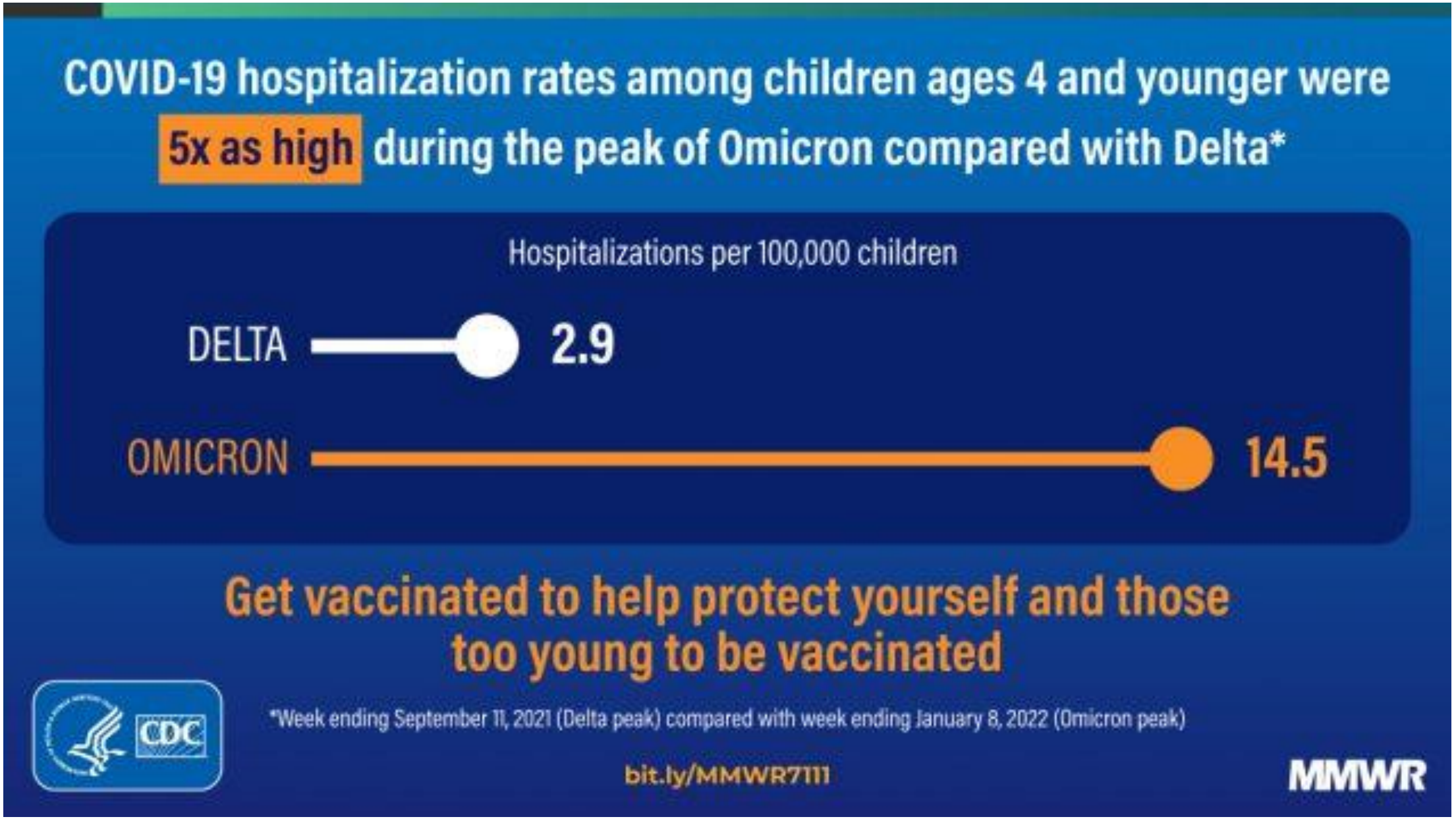
0-17 évesek	Egyesült Államok	Magyarország
Összes jelentett eset a pandémia kezdete óta (összes jelentett eset aránya, %)	**12 341 801 fő (19%)**	**217 879 fő (12,6%)**
Regisztrált összesített morbiditás	**16 397 eset 100 000 gyermekkorú lakosságra**	**12 624 eset 100,000 gyermekkorú lakosságra**
Átlagos hospitalizációs arány a regisztrált 0-17 éves eseteken belül	**0,1%-1,5%**	**0,27% (2021.07.05.-02.15.)**
Regisztrált letalitás	**0,00%-0,01%**	**0,01% alatt (17 elhunyt/217 879 regisztrált eset)**

COVID-19 a gyermekek körében - mi az, amit jelenleg tudunk, és mi az, amit nem 2022. Népegészségügy in press

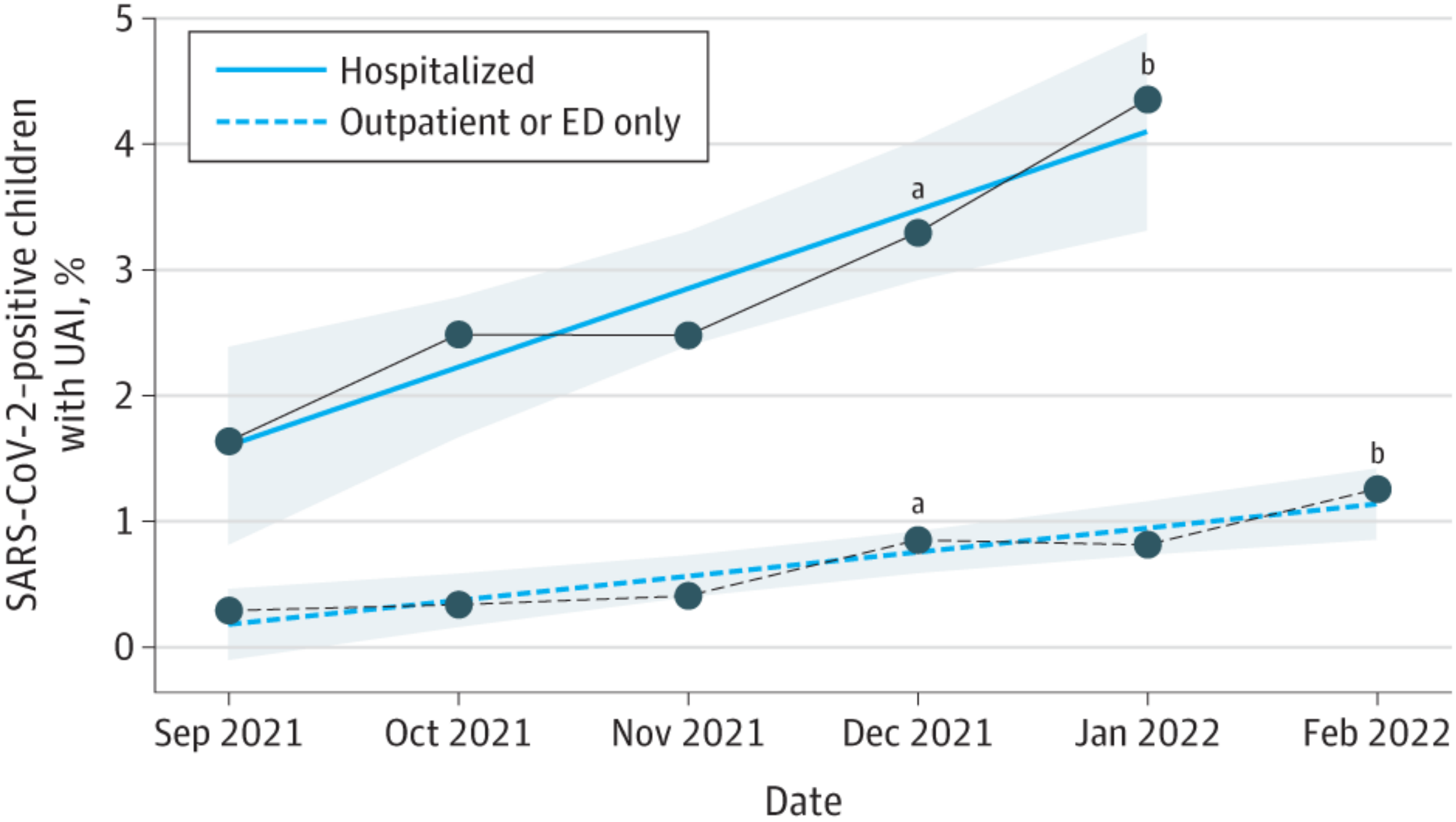
Korspecifikus COVID-19 megbetegedési arányok 7 napos mozgóátlaga a 2-5. járványhullám idején, és az iskolabezárások Magyarországon 2020.08.01 és 2022.02.15 között



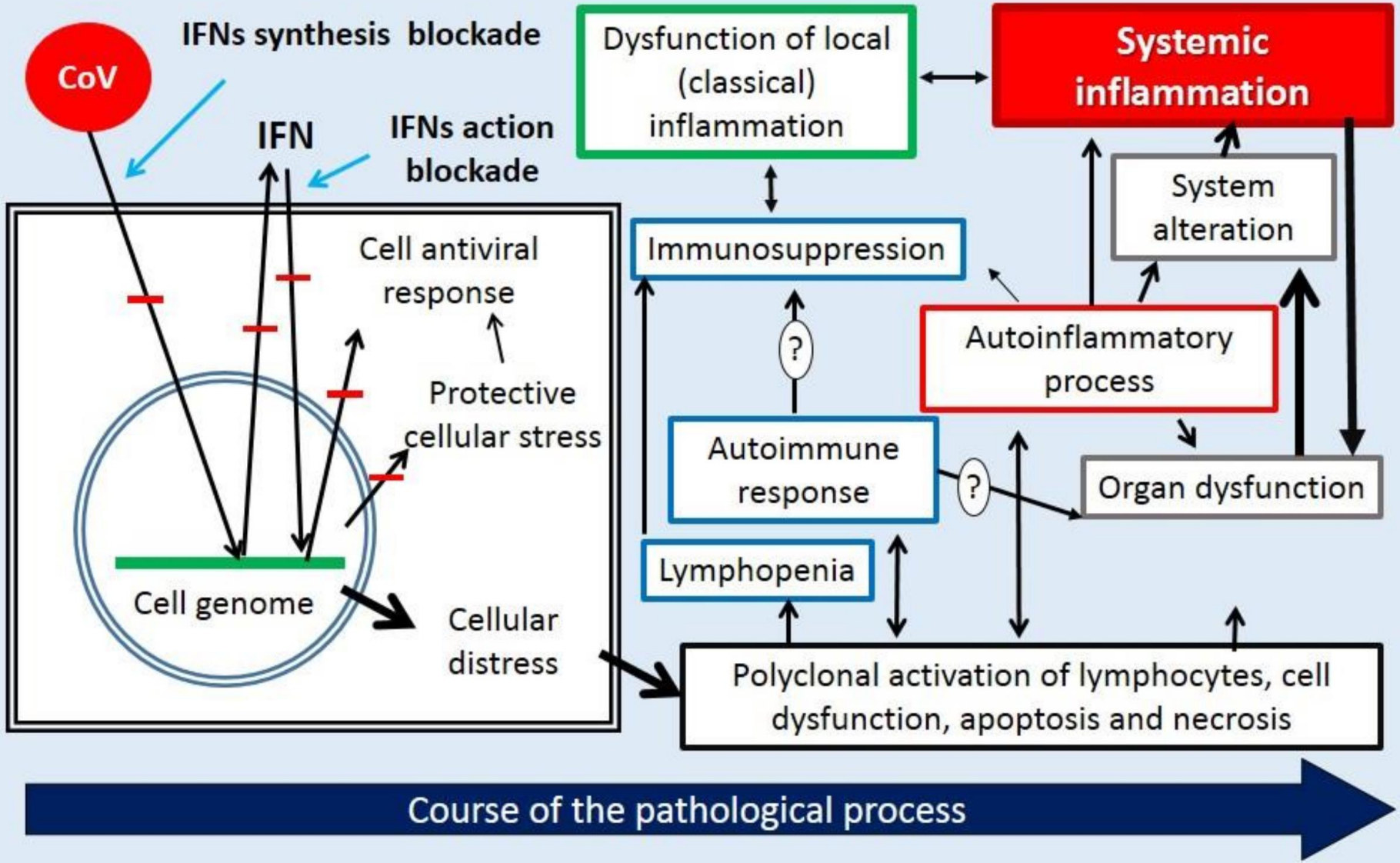
COVID-19 a gyermekek körében - mi az, amit jelenleg tudunk, és mi az, amit nem 2022. Népegészségügy in press



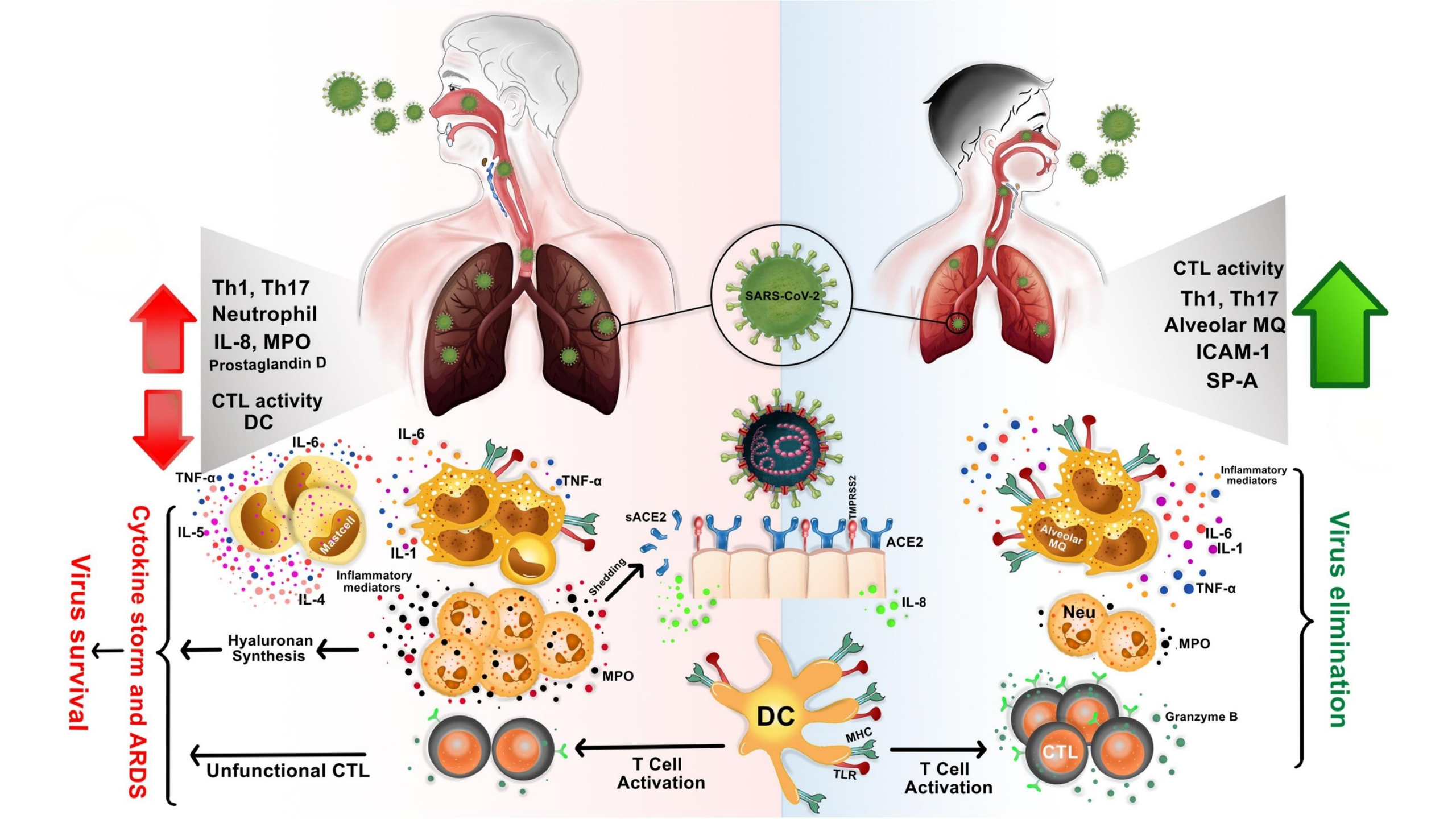
Marks KJ, Whitaker M, Agathis NT, et al. Hospitalization of Infants and Children Aged 0–4 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022. MMWR Morb Mortal Wkly Rep 2022;71:429–436. DOI: http://dx.doi.org/10.15585/mmwr.mm7111e2

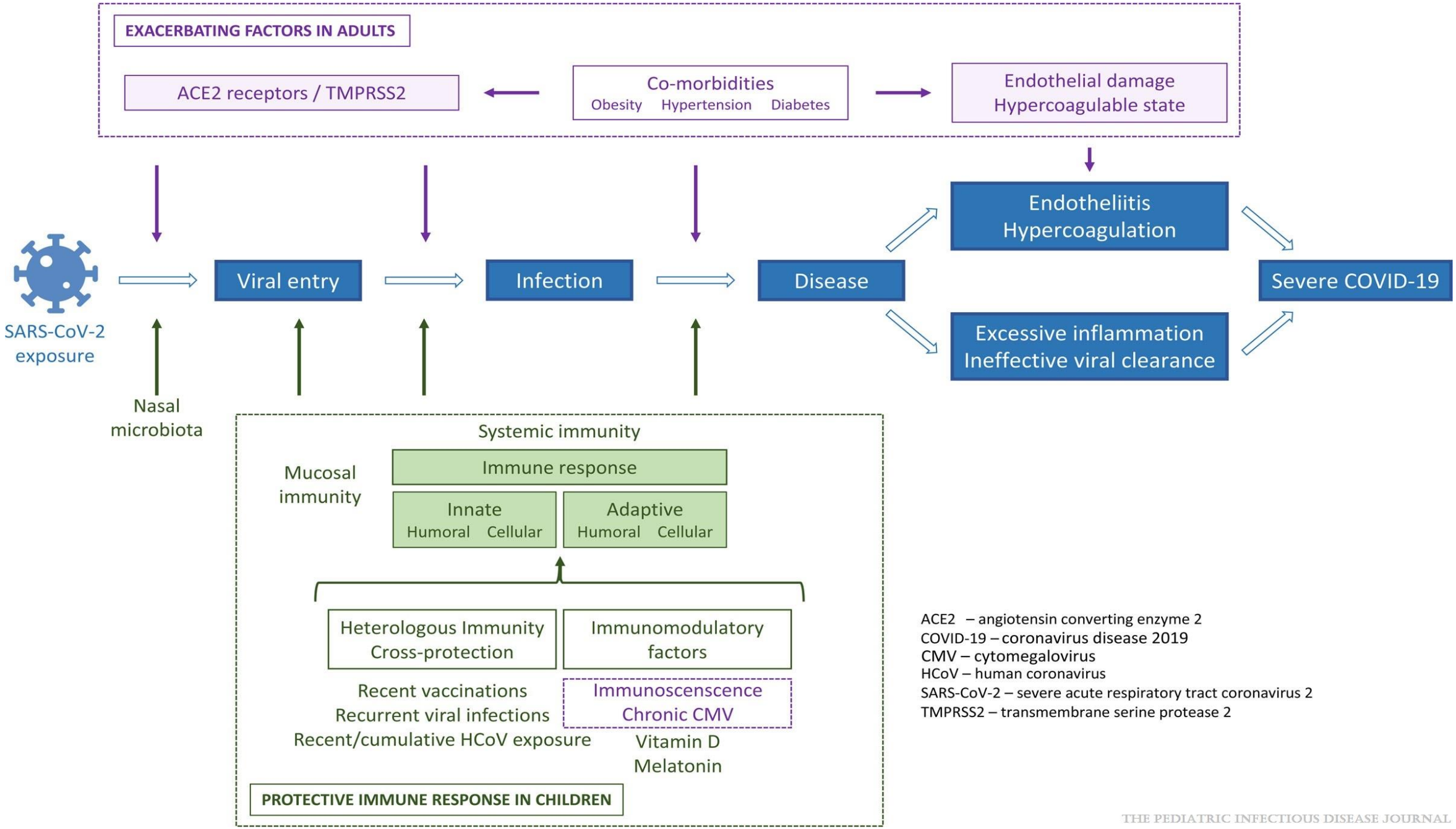


Martin Acute Upper Airway Disease in Children With the Omicron (B.1.1.529) Variant of SARS-CoV-2—A Report From the US National COVID Cohort Collaborative
JAMA Pediatr. Published online April 15, 2022. doi:10.1001/jamapediatrics.2022.1110



Gusev, E.; Sarapultsev, A.; Solomatina, L.; Cheresnev, V. SARS-CoV-2-specifikus immunválasz és a COVID-19 patogenezise. *Int. J. Mol. Sci.* **2022** , *23* , 1716. https://doi.org/10.3390/ijms23031716

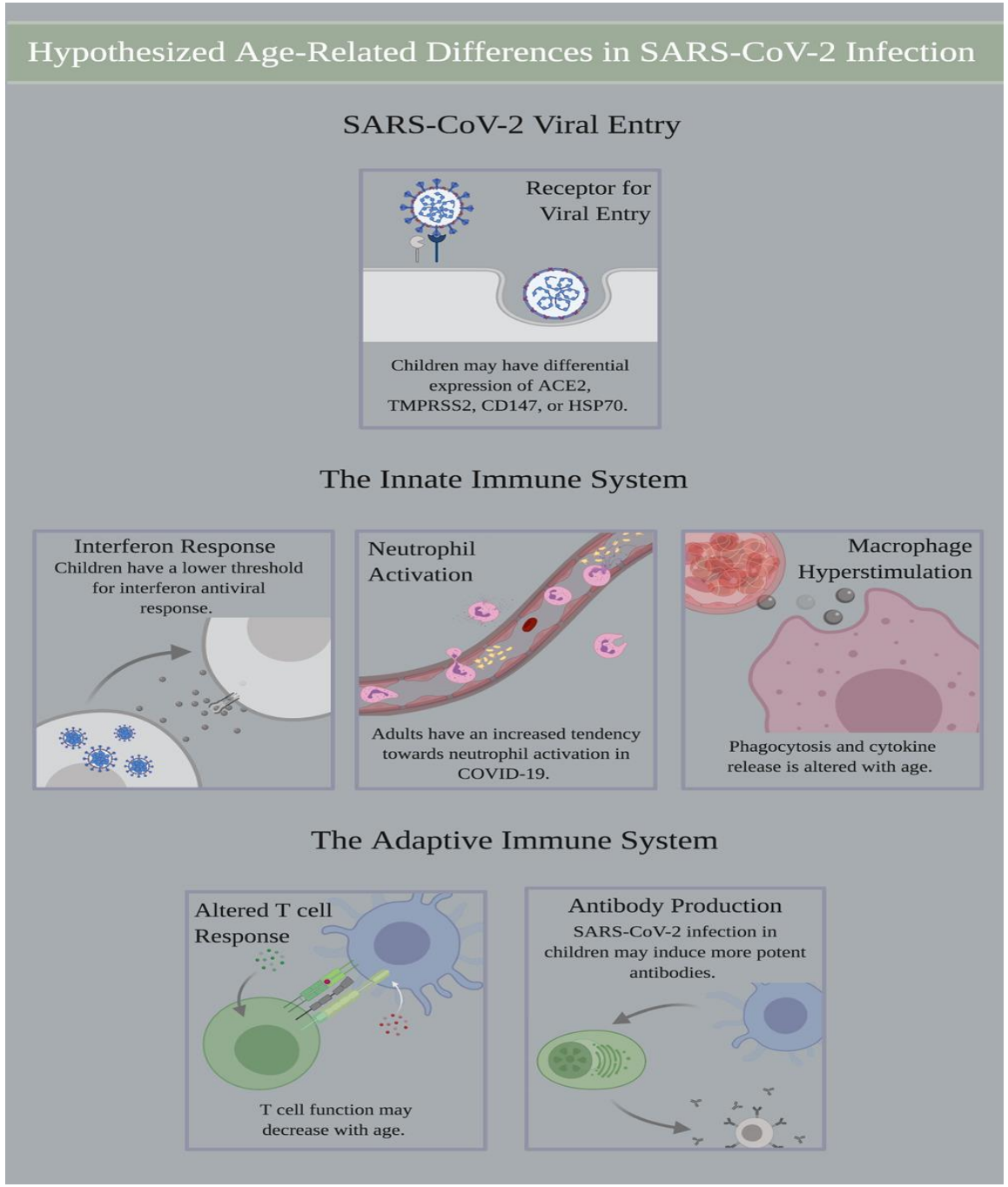

Th1, Th17
Neutrophil
IL-8, MPO
Prostaglandin D
CTL activity
DC
SARS-CoV-2
CTL activity
Th1, Th17
Alveolar MQ
ICAM-1
SP-A
IL-6
TNF-α
IL-5
Mastcell
IL-4
IL-6
TNF-α
IL-1
Inflammatory mediators
sACE2
Shedding
TMPRSS2
ACE2
IL-8
Inflammatory mediators
Alveolar MQ
IL-6
IL-1
TNF-α
Neu
MPO
Granzyme B
CTL
Virus survival
Cytokine storm and ARDS
Hyaluronan Synthesis
MPO
Unfunctional CTL
T Cell Activation
DC
MHC
TLR
T Cell Activation
Virus elimination



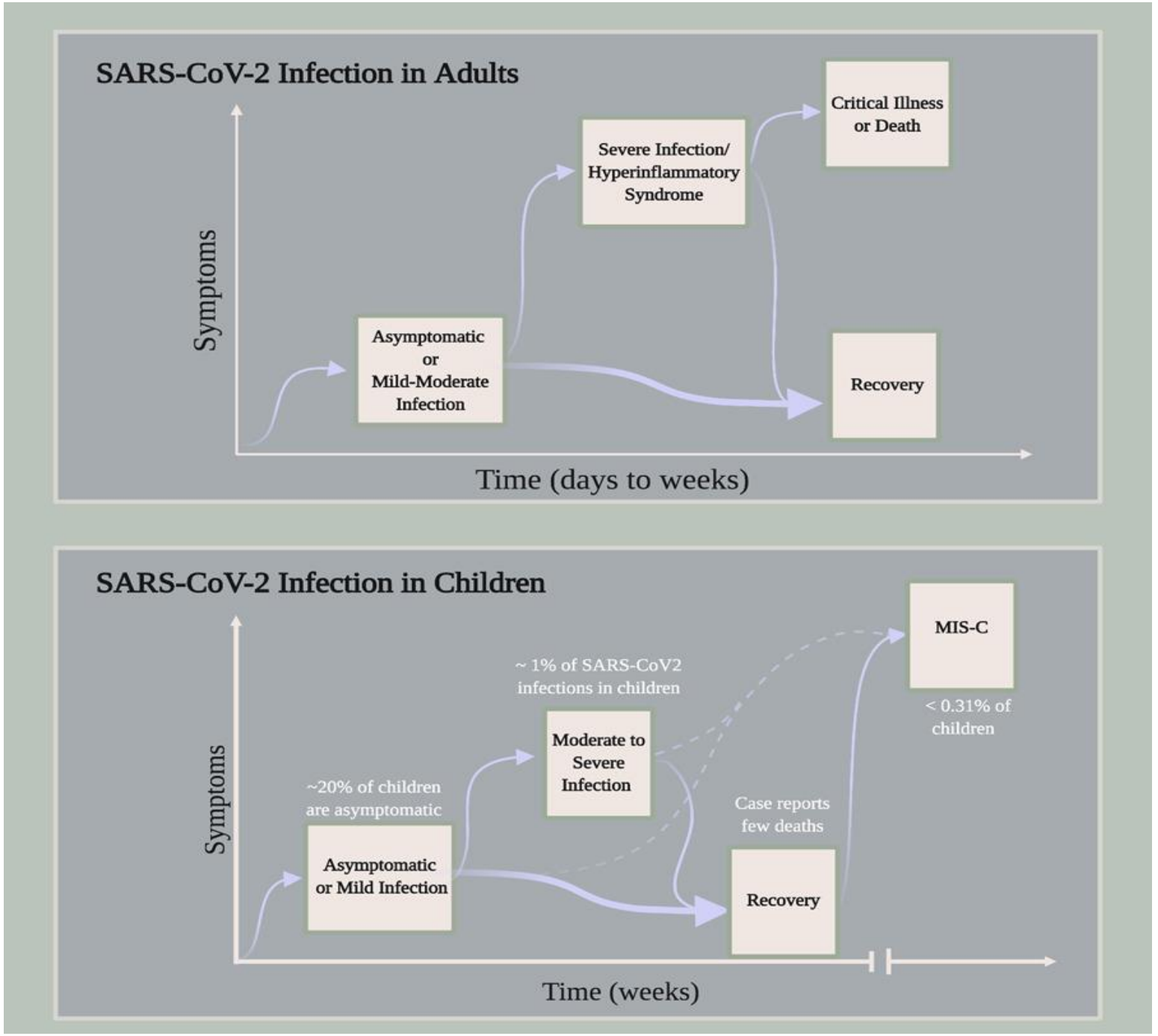
ACE2 – angiotensin converting enzyme 2
COVID-19 – coronavirus disease 2019
CMV – cytomegalovirus
HCoV – human coronavirus
SARS-CoV-2 – severe acute respiratory tract coronavirus 2
TMPRSS2 – transmembrane serine protease 2

THE PEDIATRIC INFECTIOUS DISEASE JOURNAL

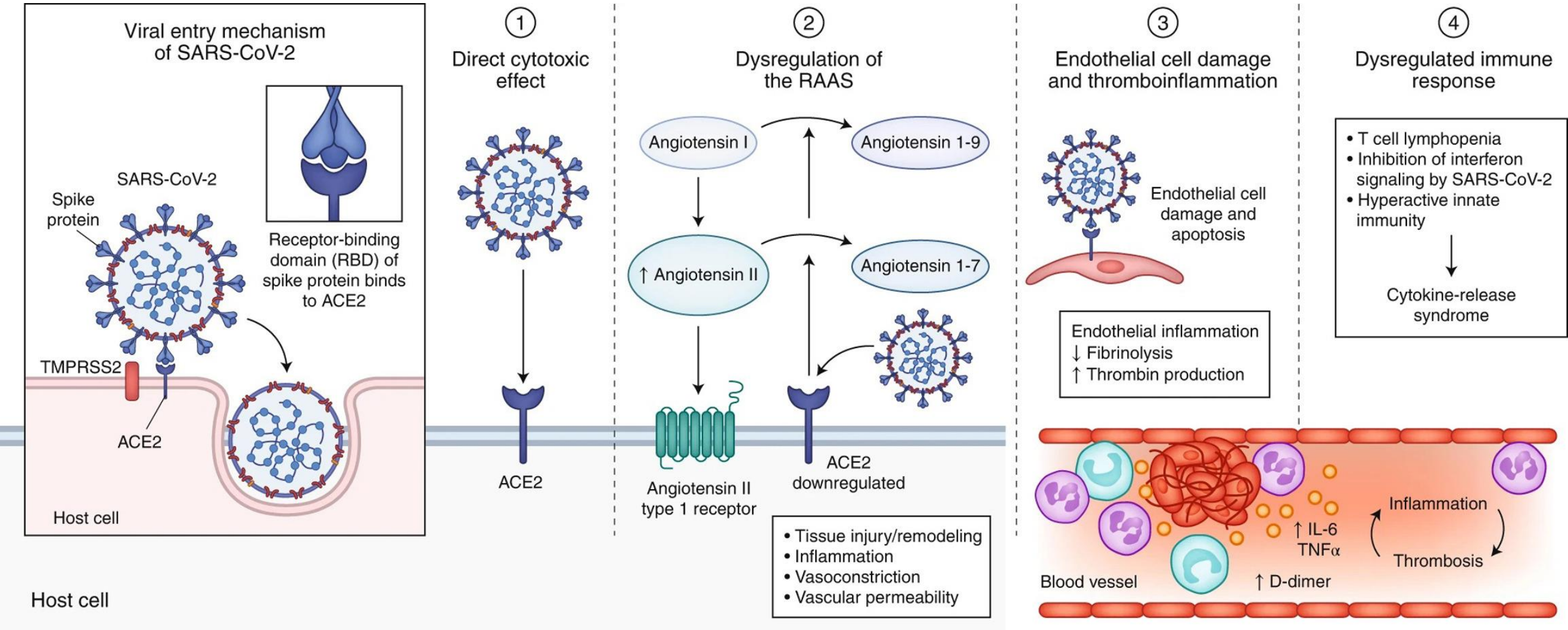
Zimmermann, Petra; Curtis, Nigel Why Does the Severity of COVID-19 Differ With Age?: Understanding the Mechanisms Underlying the Age Gradient in Outcome Following SARS-CoV-2 Infection
The Pediatric Infectious Disease Journal41(2):e36-e45, February 2022. doi: 10.1097/INF.0000000000003413



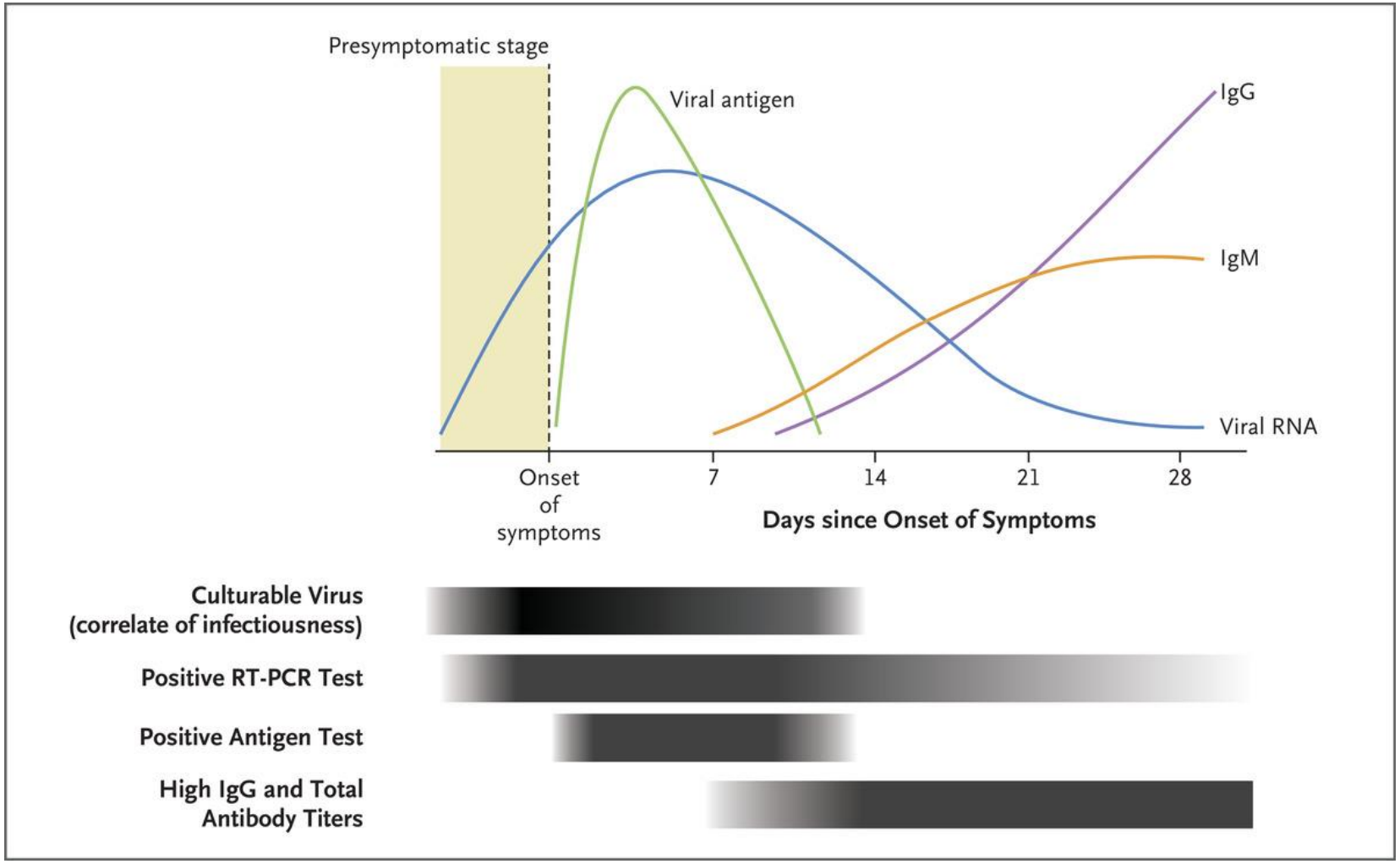
Pediatric Pulmonology, Volume: 55, Issue: 10, Pages: 2556-2564, First published: 25 July 2020, DOI: (10.1002/ppul.24981)



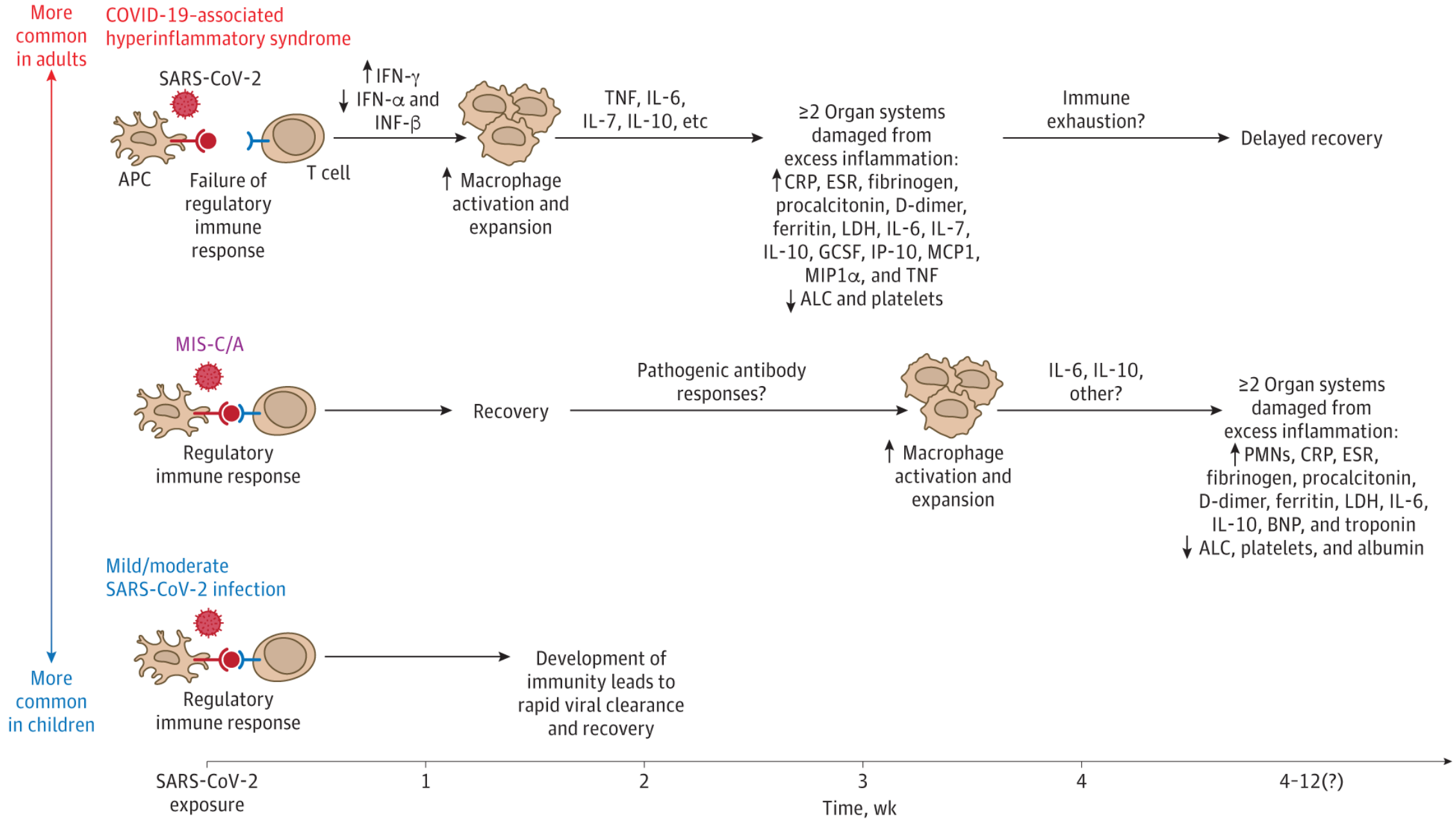
Pediatric Pulmonology, Volume: 55, Issue: 10, Pages: 2556-2564, First published: 25 July 2020, DOI: (10.1002/ppul.24981)


Viral entry mechanism of SARS-CoV-2
SARS-CoV-2
Spike protein
Receptor-binding domain (RBD) of spike protein binds to ACE2
TMPRSS2
ACE2
Host cell
1
Direct cytotoxic effect
ACE2
2
Dysregulation of the RAAS
Angiotensin I
Angiotensin 1-9
↑ Angiotensin II
Angiotensin 1-7
Angiotensin II type 1 receptor
ACE2 downregulated
• Tissue injury/remodeling
• Inflammation
• Vasoconstriction
• Vascular permeability
3
Endothelial cell damage and thromboinflammation
Endothelial cell damage and apoptosis
Endothelial inflammation
↓ Fibrinolysis
↑ Thrombin production
↑ IL-6
TNFα
↑ D-dimer
Blood vessel
Inflammation
Thrombosis
4
Dysregulated immune response
• T cell lymphopenia
• Inhibition of interferon signaling by SARS-CoV-2
• Hyperactive innate immunity
Cytokine-release syndrome
Host cell

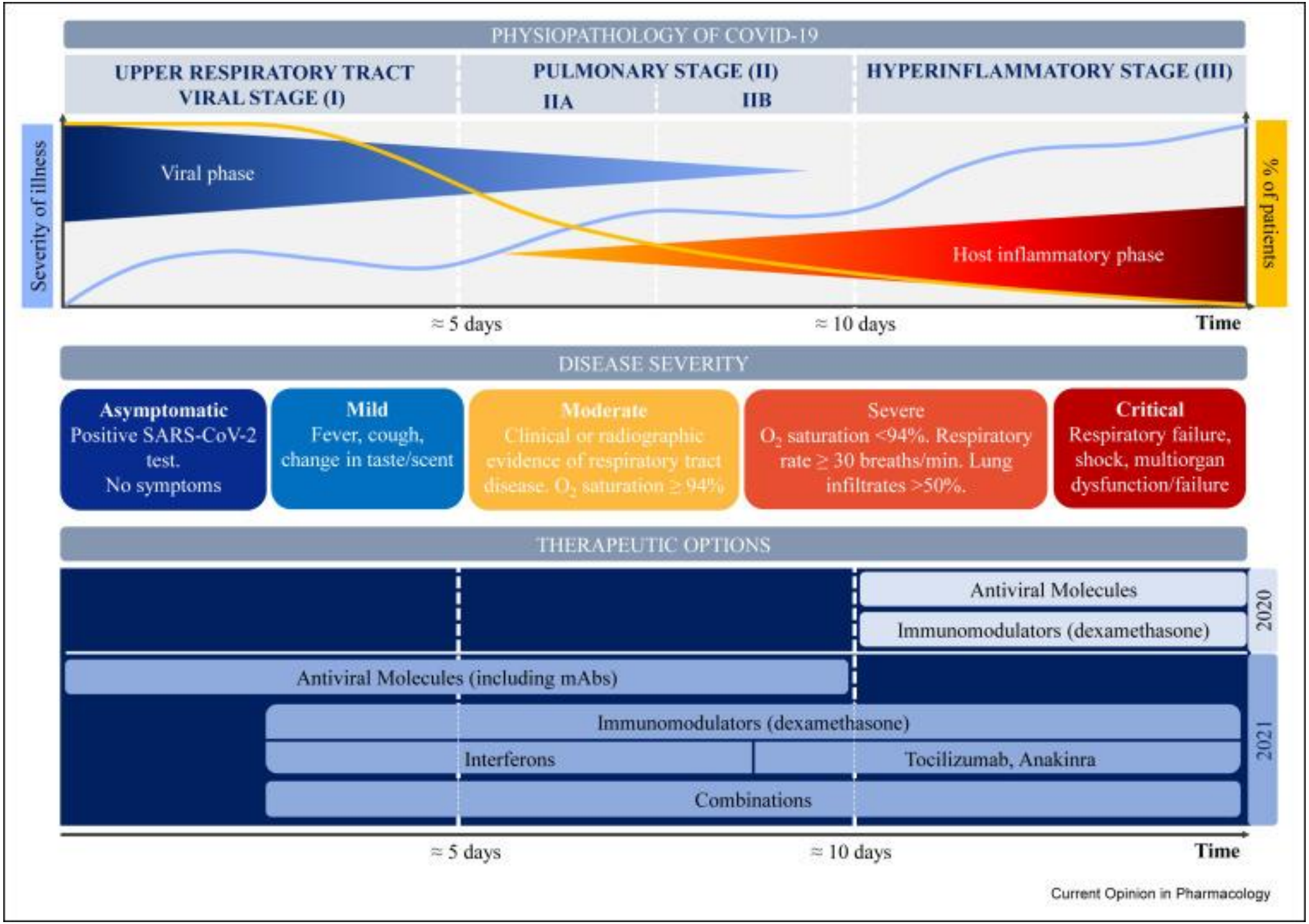
Pathophysiology and Timeline of Viremia, Antigenemia, and Immune Response during Acute SARS-CoV-2 Infection.



PK Drain. N Engl J Med 2022;386:264-272.



Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults: A Systematic Review
JAMA Netw Open. 2021;4(9):e2126456. doi:10.1001/jamanetworkopen.2021.26456


PHYSIOPATHOLOGY OF COVID-19
UPPER RESPIRATORY TRACT VIRAL STAGE (I)
PULMONARY STAGE (II)
IIA
IIB
HYPERINFLAMMATORY STAGE (III)
Severity of illness
Viral phase
Host inflammatory phase
% of patients
≈ 5 days
≈ 10 days
Time
DISEASE SEVERITY
Asymptomatic
Positive SARS-CoV-2 test.
No symptoms
Mild
Fever, cough, change in taste/scent
Moderate
Clinical or radiographic evidence of respiratory tract disease. O_2 saturation ≥ 94%
Severe
O_2 saturation <94%. Respiratory rate ≥ 30 breaths/min. Lung infiltrates >50%.
Critical
Respiratory failure, shock, multiorgan dysfunction/failure
THERAPEUTIC OPTIONS
Antiviral Molecules
Immunomodulators (dexamethasone)
2020
Antiviral Molecules (including mAbs)
Immunomodulators (dexamethasone)
Interferons
Tocilizumab, Anakinra
Combinations
2021
≈ 5 days
≈ 10 days
Time
Current Opinion in Pharmacology

Terápia

- Ezek a kezelések olyan betegek számára javasolt
  - **akiknél a legmagasabb a súlyos COVID-19 és a betegség progressziójának kockázata**
  - valamiért nem olthatók
  - alapbetegségük van
  - vagy immunszuppresszív kezelést kapnak
- Kevés gyermekspecifikus adat áll rendelkezésre a mAb-ek és az orális antivirális gyógyszerek biztonságosságára, hatékonyságára és farmakokinetikájára vonatkozóan minden gyermekkori korcsoportban
- A szerek jelentős része nem hozzáférhető

Management Strategies in Children and Adolescents with Mild to Moderate COVID-19
https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/outpatient-covid-19-management-strategies-in-children-and-adolescents/#Table1

	ANTIBODIES			ANTIVIRALS		
	Sotrovimab	**Bebtelovimab**	**Evusheld**	**Paxlovid**	**Remdesivir**	**Molnupiravir**
COVID-19 indication	Treatment	Treatment	Preexposure prophylaxis	Treatment	Treatment	Treatment
Approved age (y), weight (kg)	≥12 y	≥12 y	≥12 y	≥12 y	≥3.5 kg*	≥18 y
Route	IV	IV	IM	PO	IV	PO
Symptom onset, in days	≤10	≤7	n/a	≤5	≤7	≤5
Duration of therapy, in days	One time	One time	n/a	5	3	5
Other considerations	Requires IV infusion x1	Requires IV infusion x1	• Intramuscular administration at 2 sites (larger muscle groups preferred, ie, gluteal) • Little pediatric data	• Drug-drug interactions • Little pediatric data	• Requires IV infusion on 3 consecutive days and post-infusion monitoring • Operational and reimbursement challenges	• Not recommended in pregnancy and children • Lower efficacy, thus use only when other treatment agents cannot be used • Little pediatric data • Concerns for mutagenicity (low, based on animal studies)

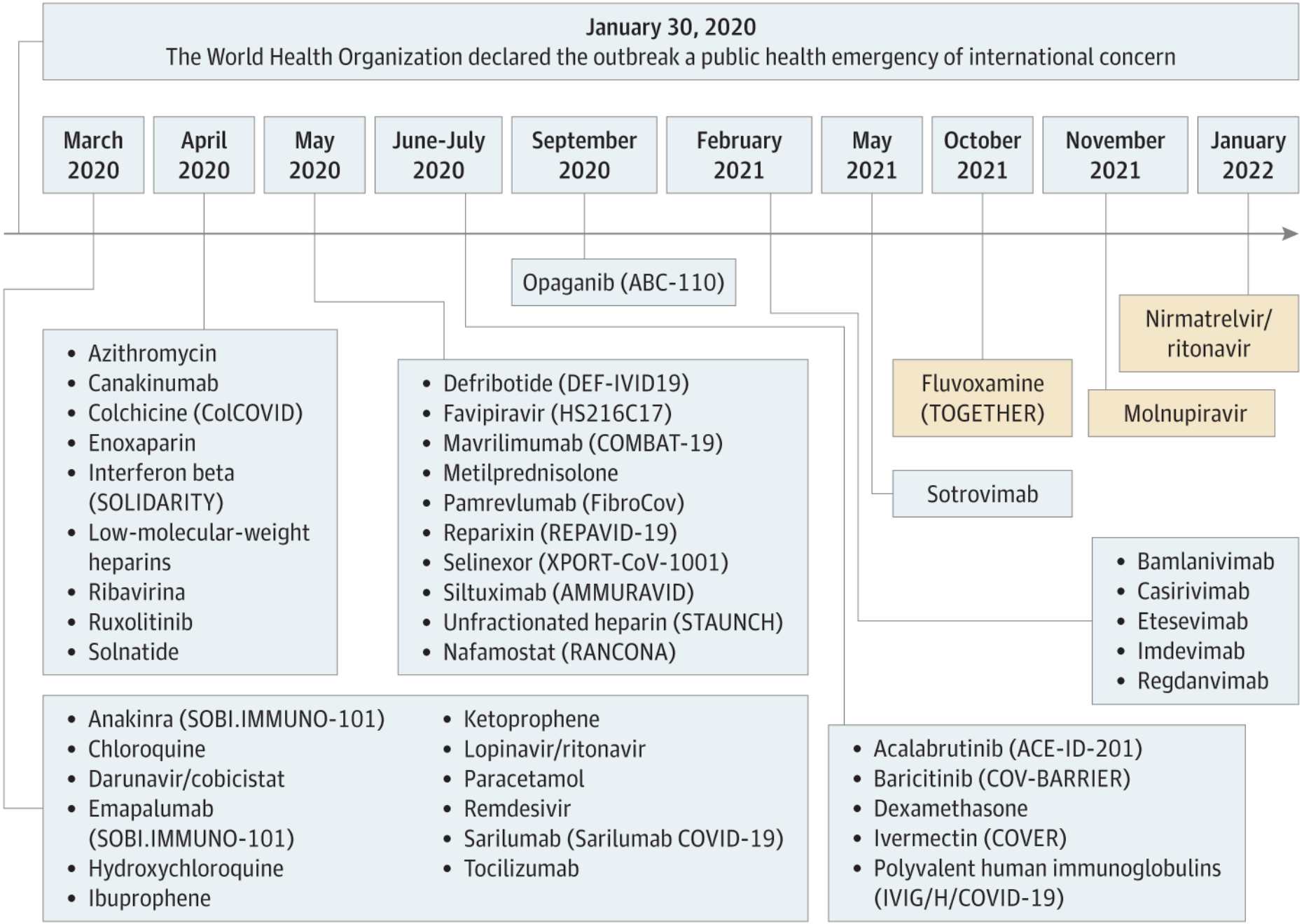
	Paxlovid	Molnupiravir
Date FDA EUA issued	12/22/21	12/23/21
Criteria	• High-risk adults and children ≥12 years of age and weighing ≥40 kg, **and** • with laboratory-confirmed SARS-CoV-2, **and** • are within 5 days of symptom onset, **and** • who are at high risk for progression to severe COVID-19	• High risk individuals ≥18 years of age, **and** • with laboratory-confirmed SARS-CoV-2, **and** • are within 5 days of symptom onset, **and** • who are at high risk for progression to severe COVID-19, **and** • for whom alternative, FDA-authorized COVID-19 treatment options are not accessible or clinically appropriate
Formulation	Nirmatrelvir 150 mg tablets, ritonavir 100 mg tablet	Molnupiravir 200 mg capsules
Dosage	Nirmatrelvir 300 mg (2 tablets) + ritonavir 100 mg BID (1 tablet) with a fatty food/meal; do not crush the tablets	Molnupiravir 800 mg (4 capsules) every 12 hours with or without food; do not open/crush the capsules
Duration	5 days	5 days
Health care provider fact sheet	www.fda.gov/media/155050/download	https://www.fda.gov/media/155054/download
Patient/family fact sheet, English and Spanish	https://www.fda.gov/media/155051/download https://www.fda.gov/media/155075/download	https://www.fda.gov/media/155055/download https://www.fda.gov/media/155055/download

Magas kockázat

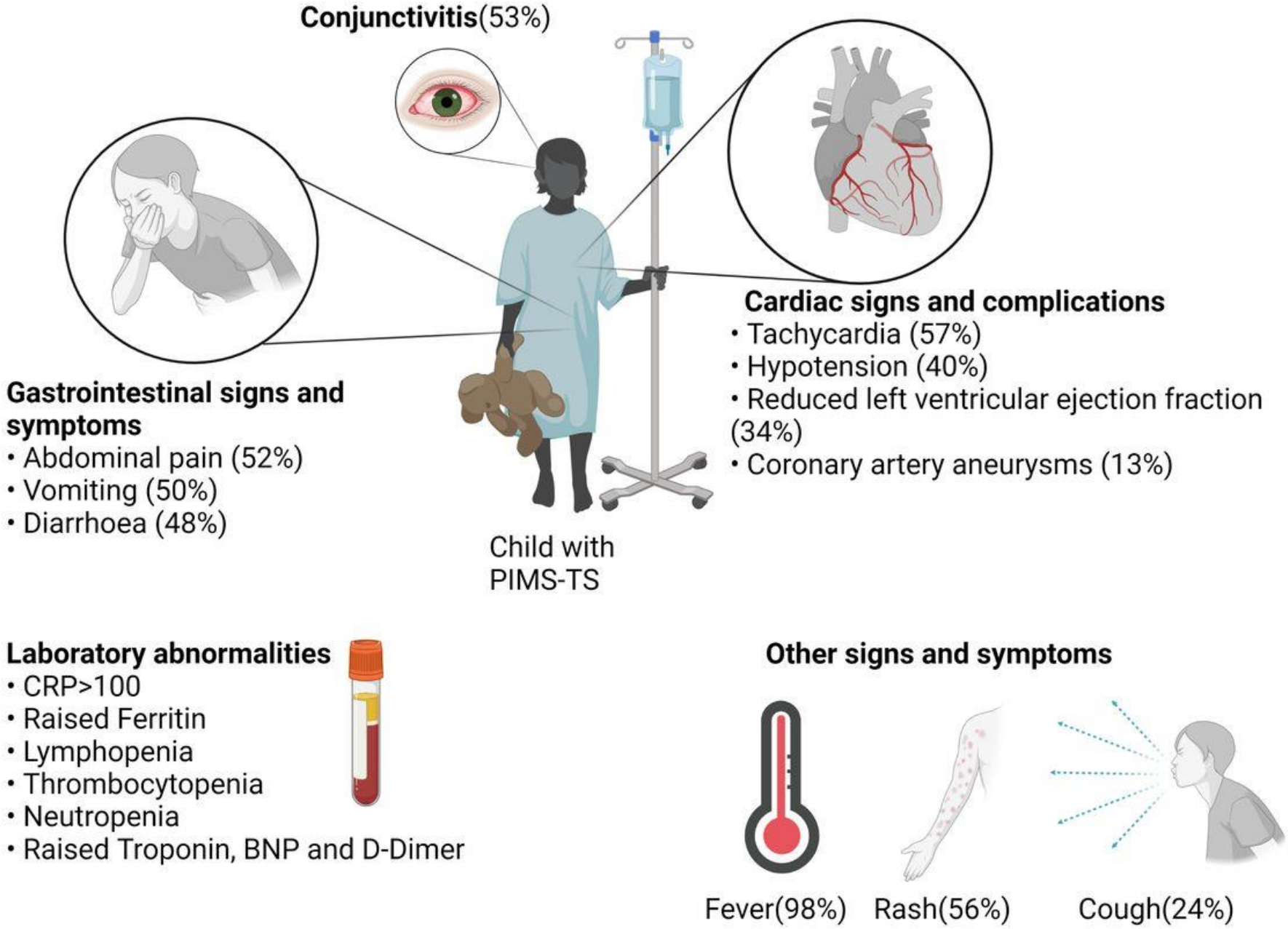
- Testtömegindex (BMI) ≥85. percentilis életkor és nem szerint
- Immunszuppresszív betegség vagy immunszuppresszív kezelésben részesült;
- Neurológiai fejlődési rendellenességek (pl. Cerebral paresis, 21-es triszómia);
- tracheostomia, pozitív nyomású lélegeztetés, gastrostomia;
- Veleszületett vagy szerzett szívbetegség;
- Krónikus betegségek
- Életkor <1 év
  - A csecsemők többsége enyhe betegséget produkál, de a probléma a 90 napnál fiatalabb, monoszimptomás lázas gyerekeknél van
  - A súlyos COVID-19 kockázati tényezője a koraszülöttség

Milyen gyógyszereket NEM szabad alkalmazni a COVID-19 kezelésére vagy megelőzésére gyermekeknél és serdülőknél?

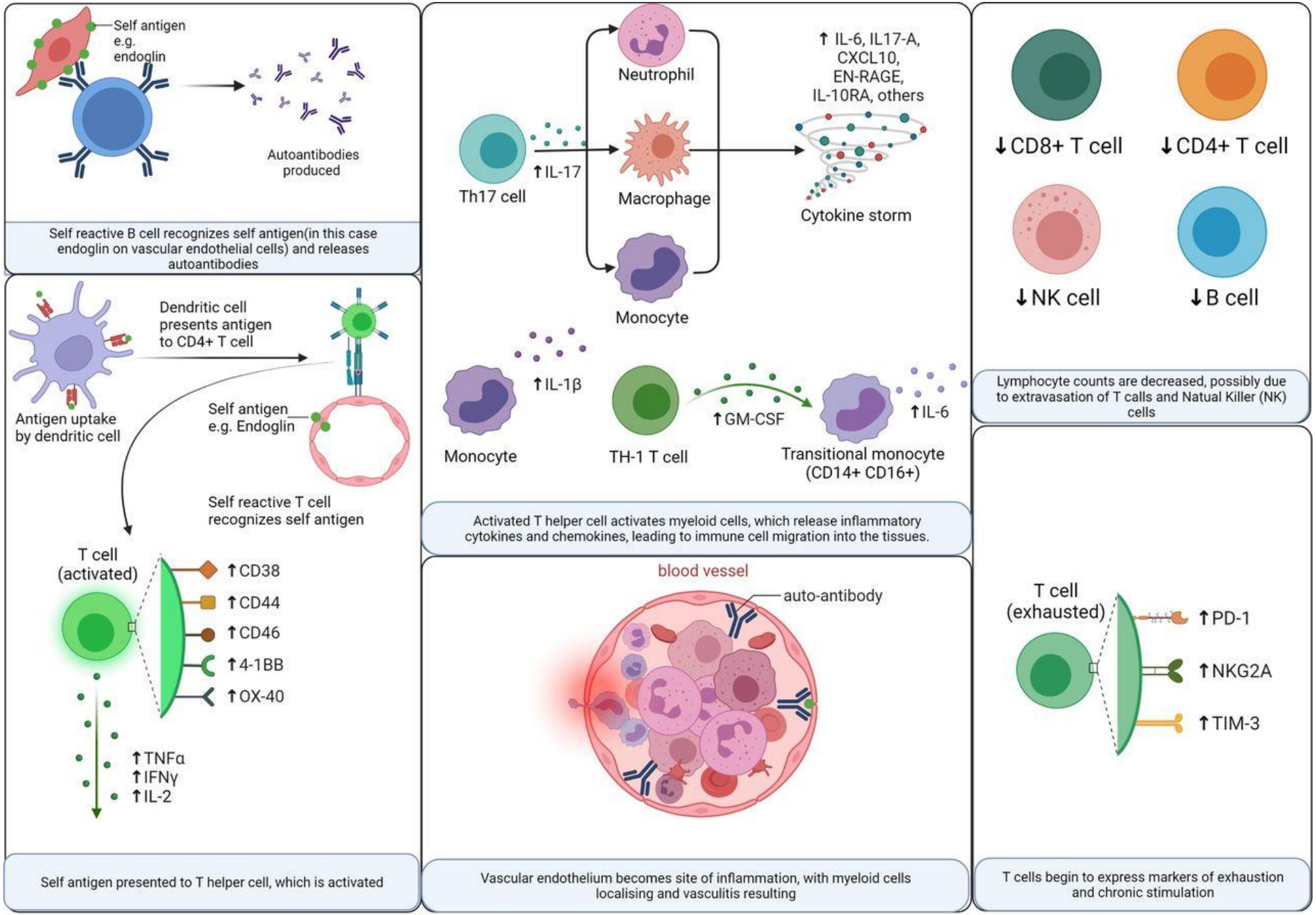
- Azythromycin
- Ivermectin
- Hydroxychloroquine/chloroquine



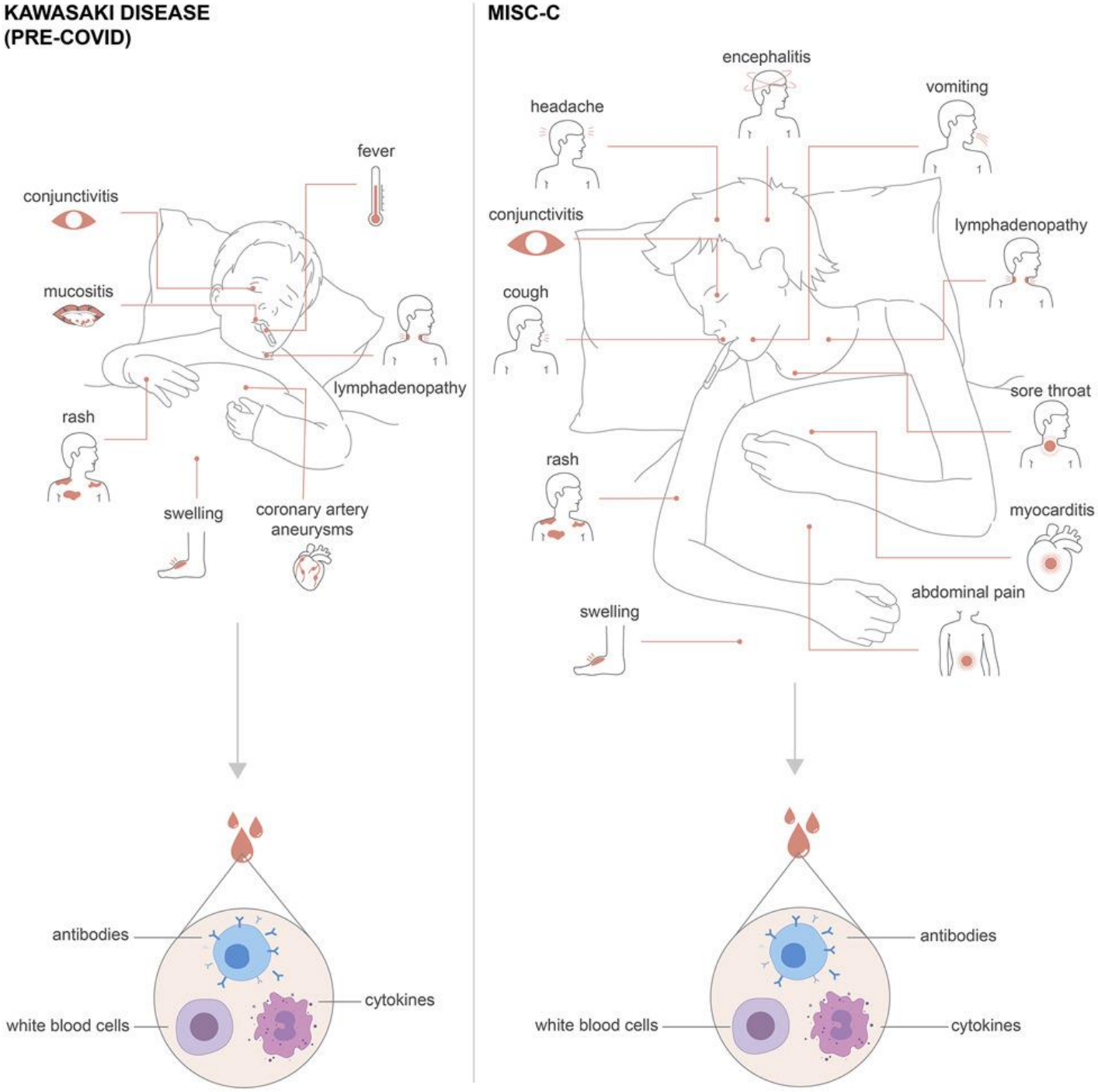
From: Identification of Drug Interaction Adverse Events in Patients With COVID-19: A Systematic Review JAMA Netw Open. 2022;5(4):e227970. doi:10.1001/jamanetworkopen.2022.7970



Cathal Roarty, and Thomas Waterfield Arch Dis Child doi:10.1136/archdischild-2021-323143



Cathal Roarty, and Thomas Waterfield Arch Dis Child doi:10.1136/archdischild-2021-323143



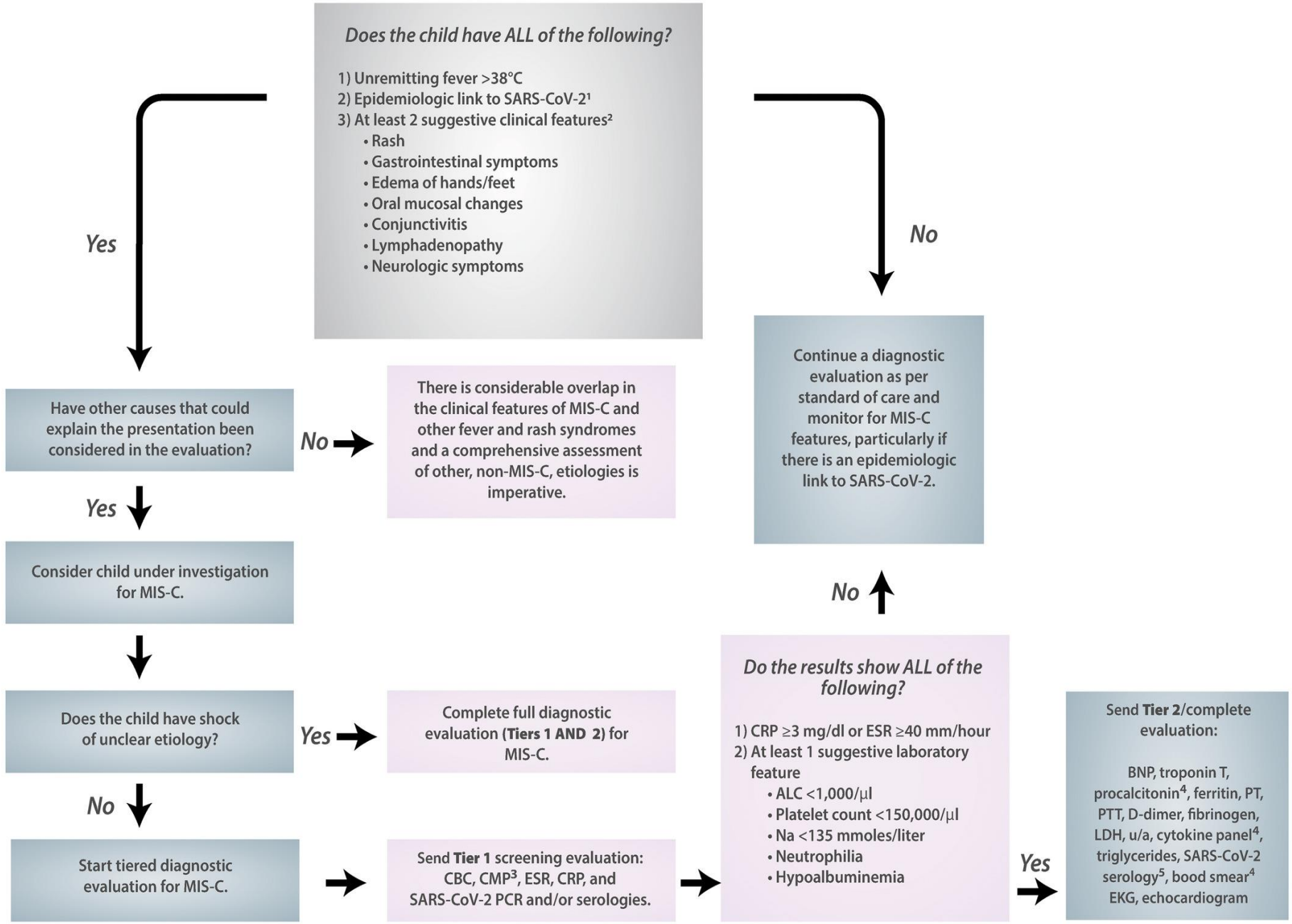
Camila RosatConsiglio et al.
The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19;
Volume 183, Issue 4, 12 November 2020, Pages 968-981.e7
https://doi.org/10.1016/j.cell.2020.09.016

MIS-C kritériumok

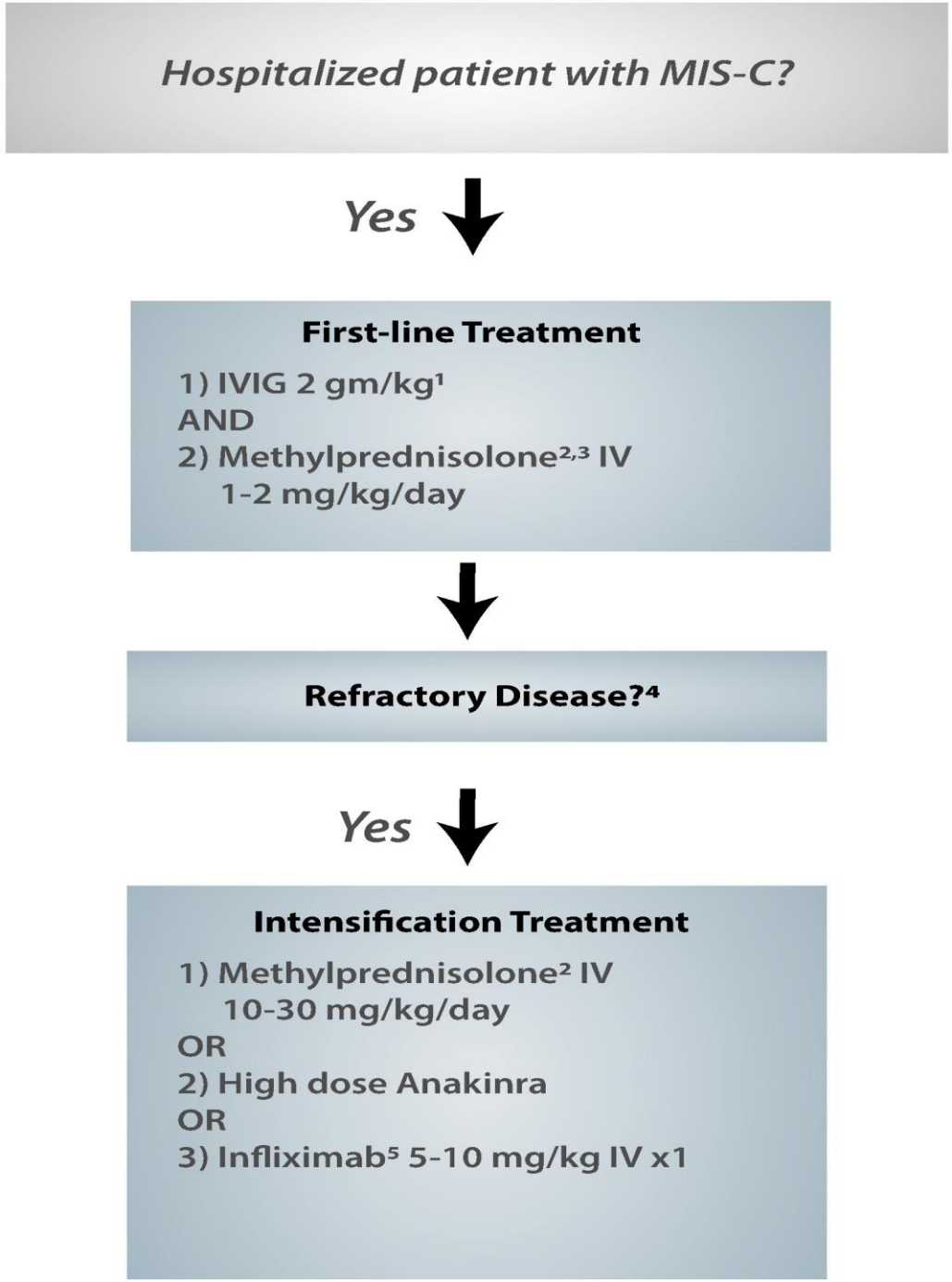
LÁZ	
Gyulladásos markerek	neutrofília, emelkedett WE, CRP, PCT és limfopénia, D-dimer, laktát)
Egy- vagy többszervi elégtelenség	Shock, szív-, légúti-, vese-, gyomor-bélrendszeri rendellenesség
Egyéb okok kizárása	Bakteriális szepszis, staphylococcus vagy streptococcus sokk szindróma, fertőző myocarditis/endocarditis
A SARS-CoV-2 fertőzés bizonyítéka	A polimeráz láncreakció (PCR) teszt pozitív vagy negatív lehet, de antitest van

Differenciál diagnózis

- Invazív bakteriális fertőzés, szepszis
- Toxikus sokk szindróma (TSS)
- Staphylococcus leforrázott bőr szindróma (SSSS)
- Kawasaki-kór (KD)
- Vírusos szívizomgyulladás/fertőzés (például EBV, CMV, adenovírus, enterovírus és más vírusok)
- Szérumbetegség
- Akut vakbélgyulladás/akut has
- Gastroenteritis
- Makrofág aktivációs szindróma (MAS) és hemophagocytás lymphohistiocytosis (HLH)
- Rosszindulatú betegségek, például akut leukémia.



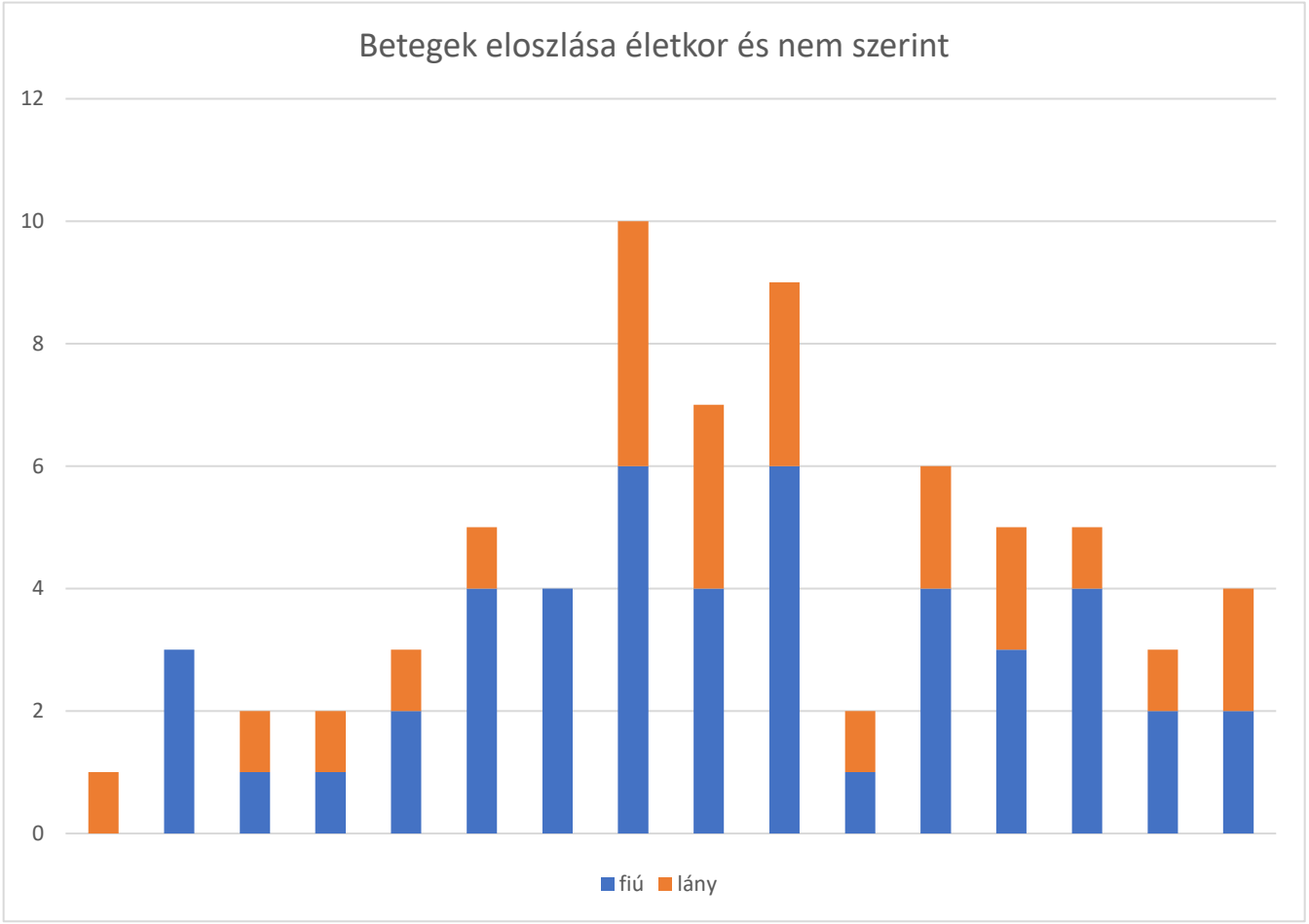
Arthritis & Rheumatology, Volume: 74, Issue: 4, Pages: e1-e20, First published: 03 February 2022, DOI: (10.1002/art.42062)



Arthritis & Rheumatology, Volume: 74, Issue: 4, Pages: e1-e20, First published: 03 February 2022, DOI: (10.1002/art.42062)

HOGYI – MIS-C

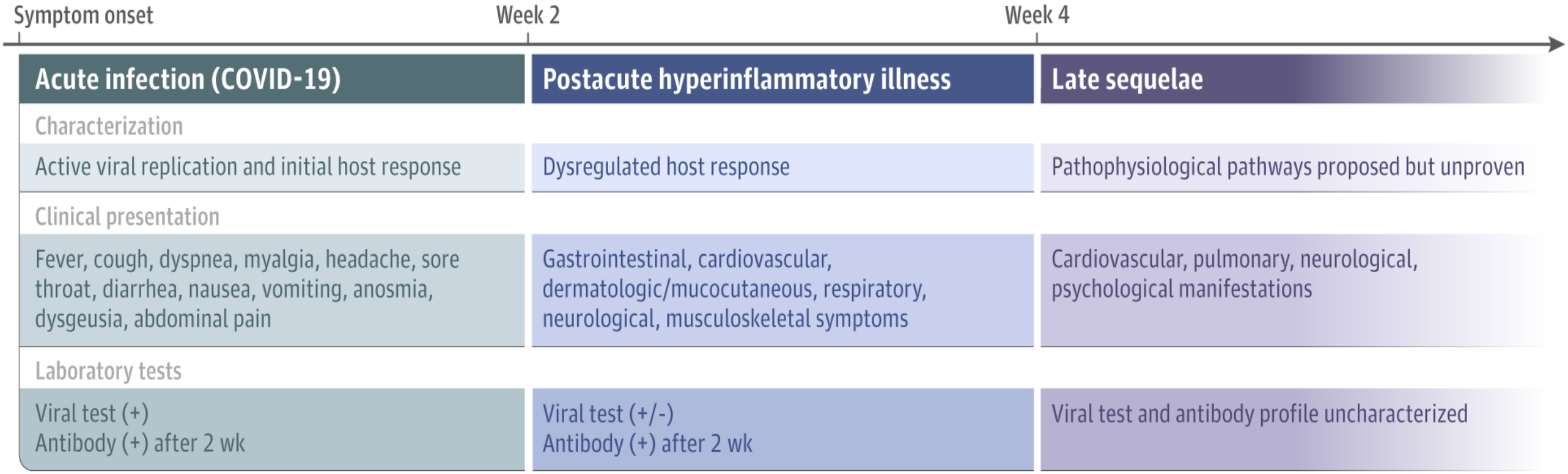
- Eddig 74 beteg
- 66% fiú
- 46% ITO – főképp keringés támogatás
- Mindenki hazament!



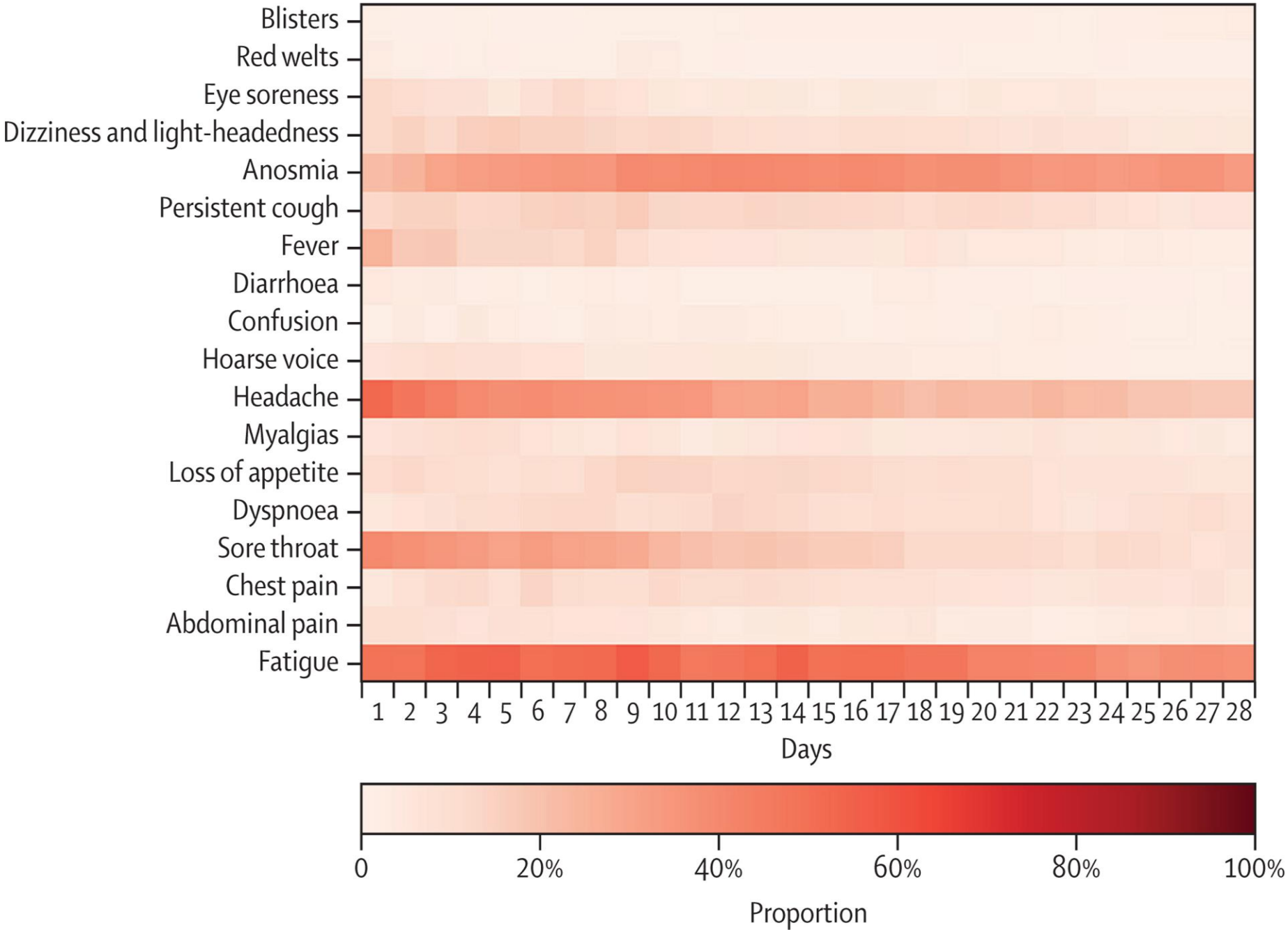
Figyelem!

- COVID időszakban ”mindenki COVID”
- A „poszt COVID” időszakban mindenki poszt COVID
- Pedig más betegségek is vannak!

Akut fertőzés és következményei



A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications
JAMA. Published online November 18, 2020. doi:10.1001/jama.2020.22717



Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2
The Lancet Child & Adolescent Health DOI: (10.1016/S2352-4642(21)00198-X)

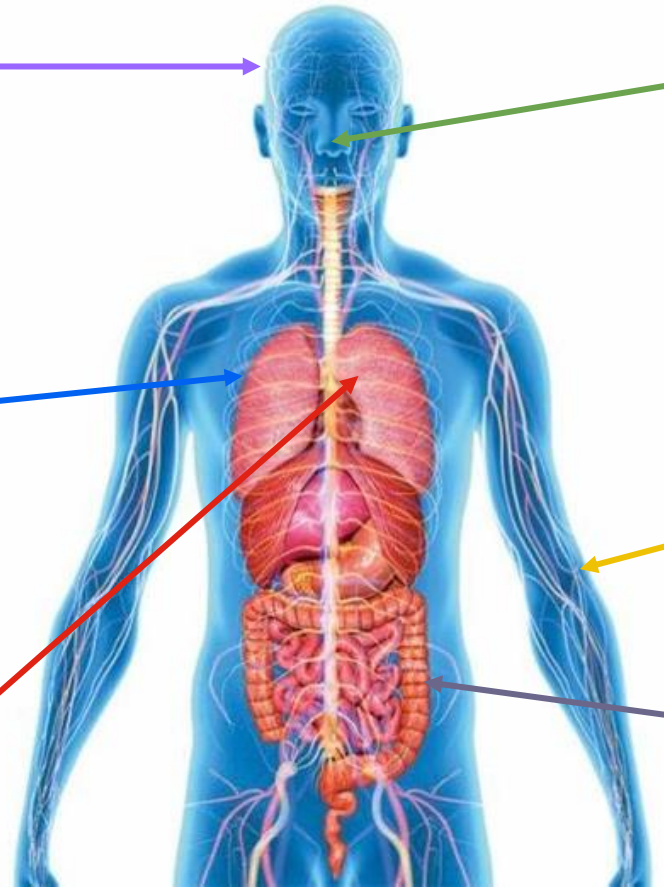
What are some of the symptoms?

Brain fog/Poor Memory
Headache
Sleep problems
Lightheadedness
Anxiety

Loss of Taste
Changes in Taste
Loss of Smell

Cough
Shortness of Breath

Muscle pain
Joint pain
Severe fatigue
Impaired function

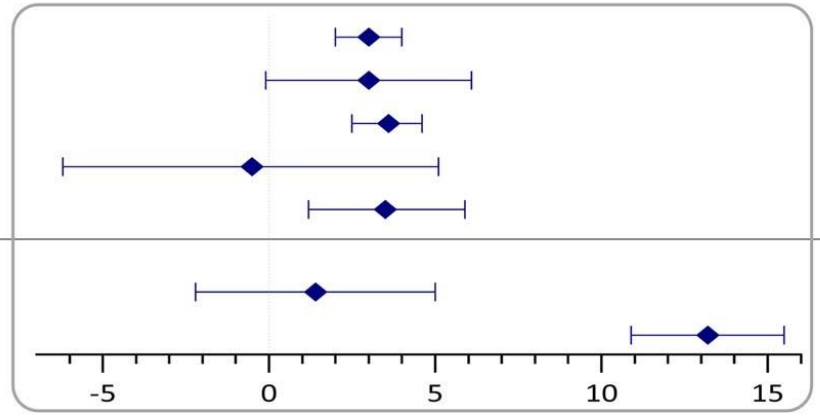


Chest pain
Palpitations

Poor appetite
Diarrhea

A long-Covid kihívásai gyermekkorban

First author	Age (y)[a]	Response rate	Proportion with persisting symptoms (95% CI) COVID-19 cases		Controls		Difference in prevalence (95% CI) between cases and controls (%)
Persisting >4 weeks							
Borch[5]	nr, <18	26.1%	3813/14883	25.6% (24.9 to 26.3)	3446/15234	22.6% (22.0 to 23.3)	3.0% (2.0 to 4.0)
Miller[19]	nr, ≤17	nr	8/174	4.6% (2.0 to 8.9)	72/4504	1.6% (1.3 to 2.0)	3.0% (-0.1 to 6.1)
Molteni[20]	median 13 (10-15)	33.5%	77/1734	4.4% (3.5 to 5.5)	15/1734	0.9% (0.5 to 1.4)	3.6% (2.5 to 4.6)
Radtke[21]	median 11 (nr)	75.3%	10/109	9.2% (4.5 to 16.2)	121/1246	9.7% (8.1 to 11.5)	-0.5% (-6.2 to 5.1)
Zavala[8]	range 2-16	35.0%	24/472	5.1% (3.3 to 7.5)	6/387	1.6% (0.6 to 3.3)	3.5% (1.2 to 5.9)
Persisting >12 weeks							
Radtke[21]	median 11 (nr)	75.3%	4/109	3.7% (1.0 to 9.1)	28/1246	2.2% (1.5 to 3.2)	1.4% (-2.2 to 5.0)
Stephenson[22]	range 11-17	13.4%	2038/3065	66.5% (64.8 to 68.2)	1993/3739	53.3% (51.7 to 54.9)	13.2% (10.9 to 15.5)

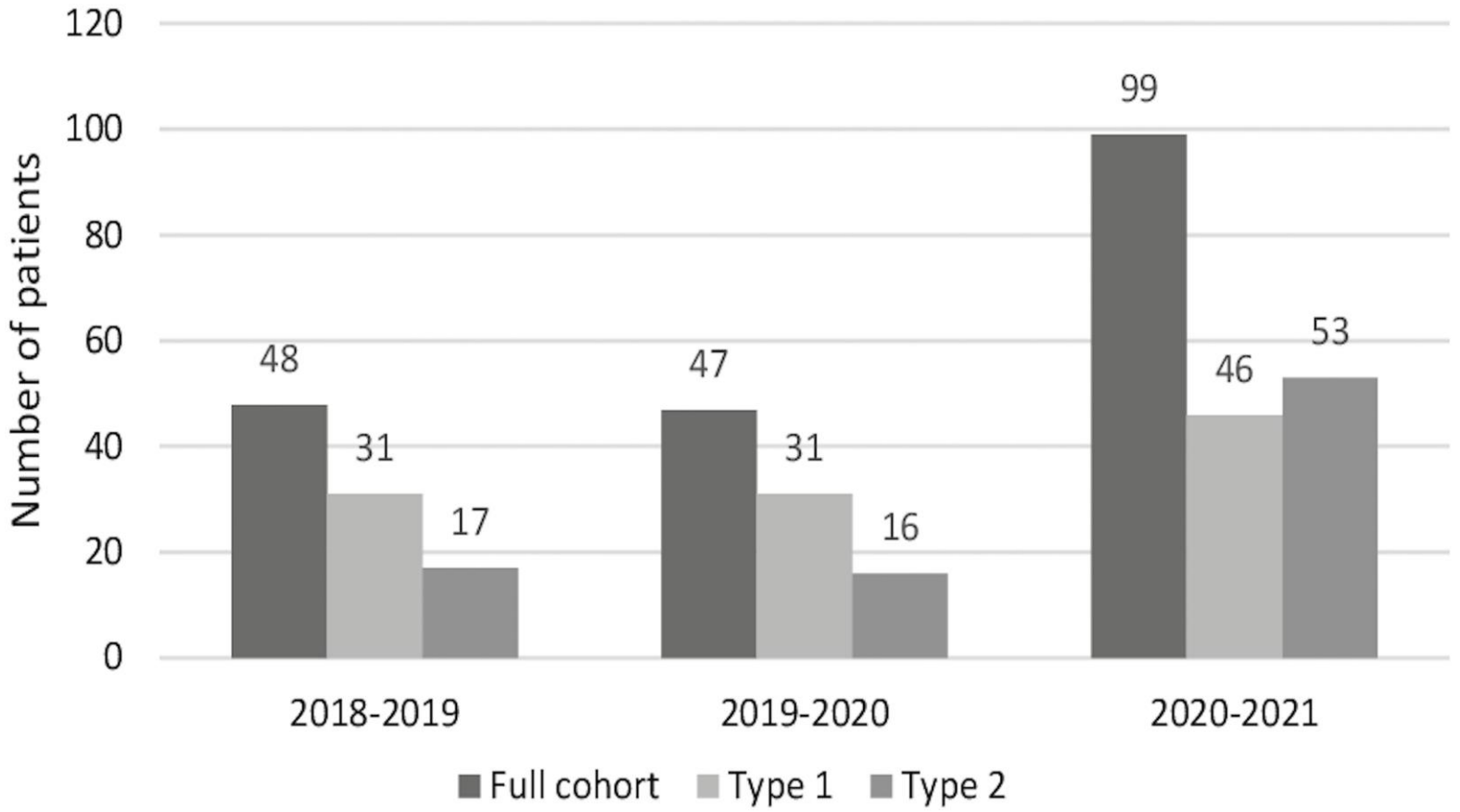


[a] mean (SD), median (interquartile range), or range; CI: confidence interval; nr: not reported.

THE PEDIATRIC INFECTIOUS DISEASE JOURNAL

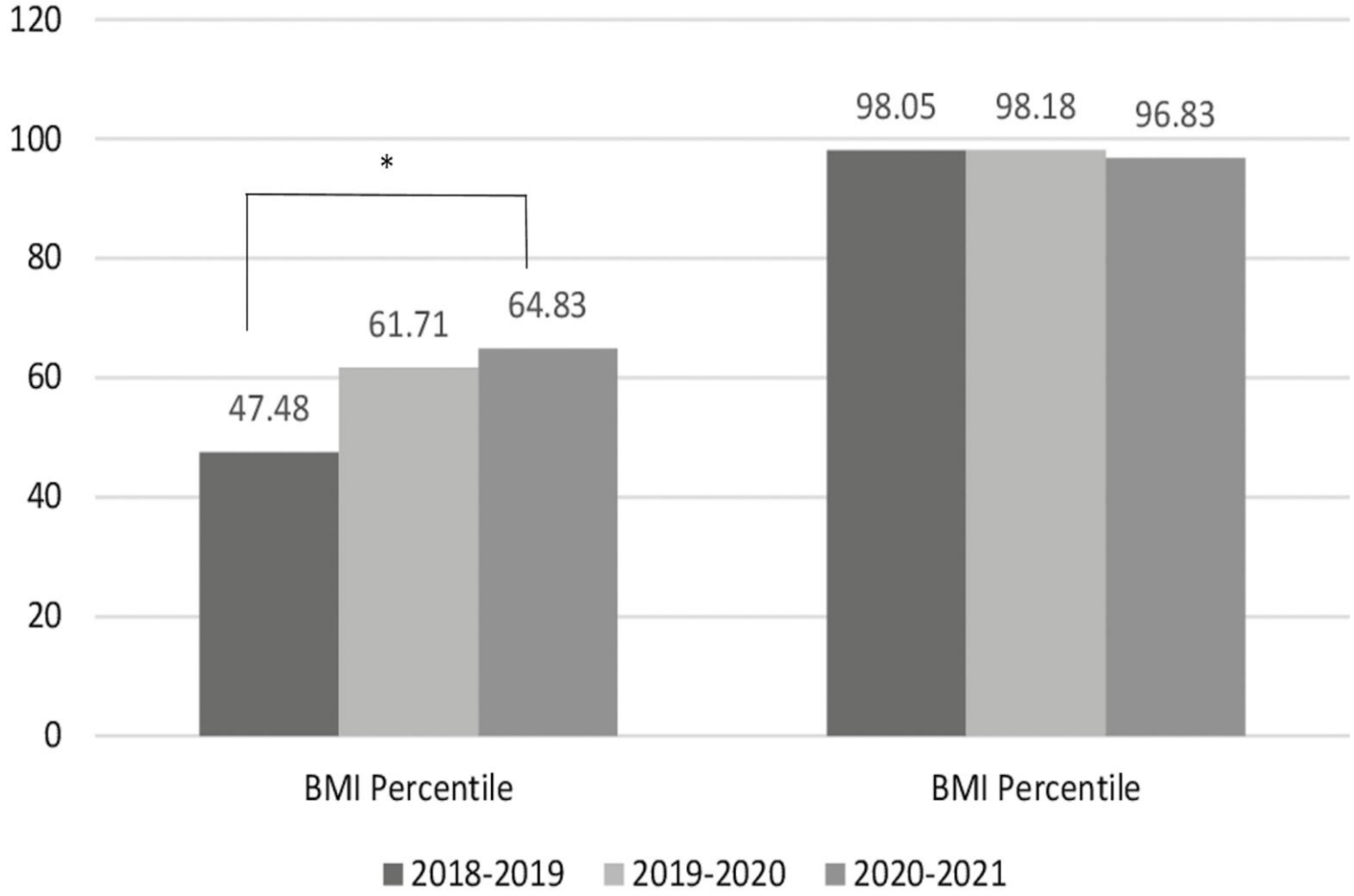
Zimmermann, Petra; Pittet, Laure F.; Curtis, Nigel The Challenge of Studying Long COVID: An Updated Review
The Pediatric Infectious Disease Journal41(5):424-426, May 2022. doi: 10.1097/INF.0000000000003502

Diabetes



Modarelli et al. **Pediatric Diabetes on the Rise: Trends in Incident Diabetes During the COVID-19 Pandemic**
J. Endocr. Soc., Volume 6, Issue 4, April 2022, bvac024, https://doi.org/10.1210/jendso/bvac024

BMI a diabetesesek körében



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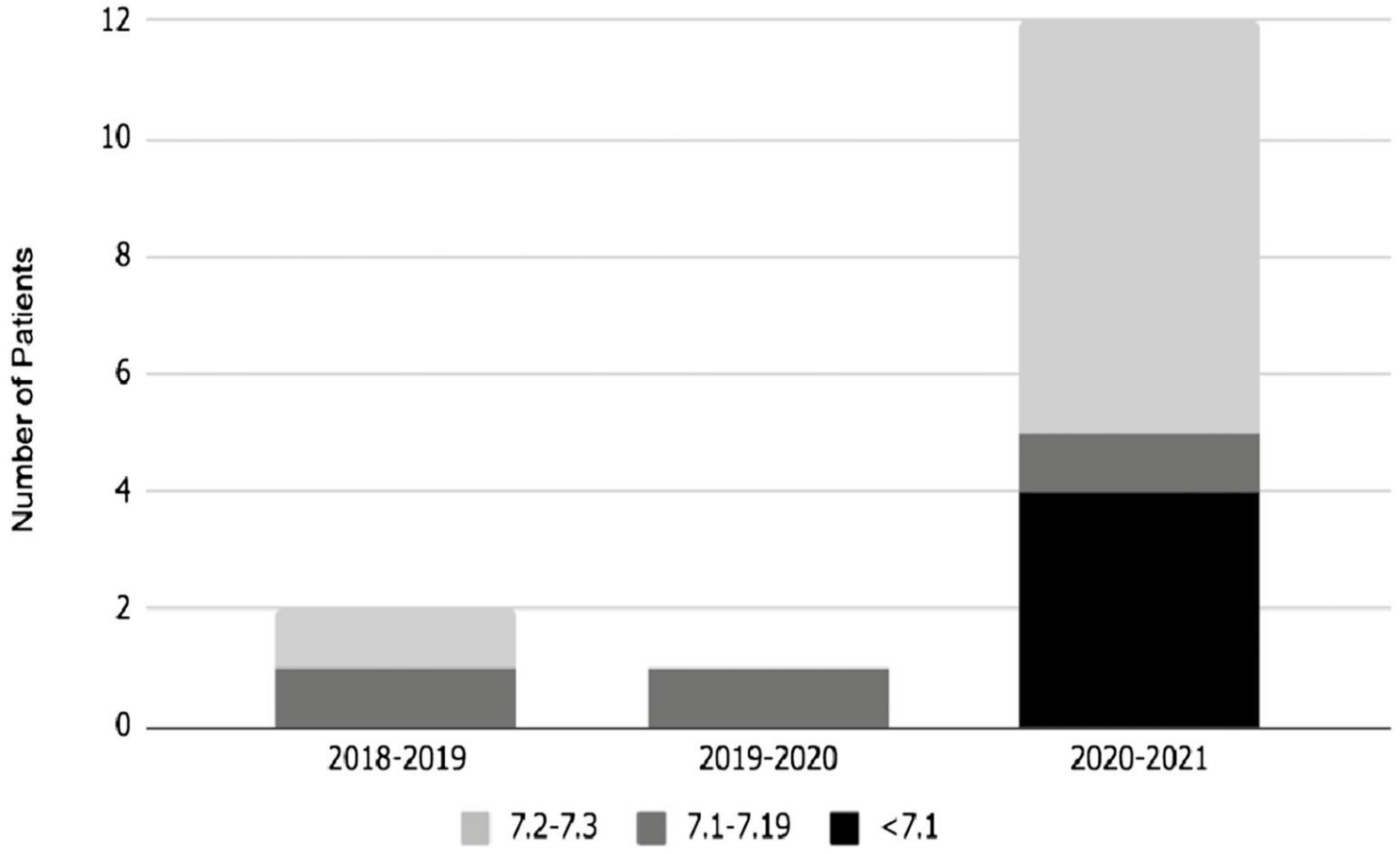
Ketoacidózis



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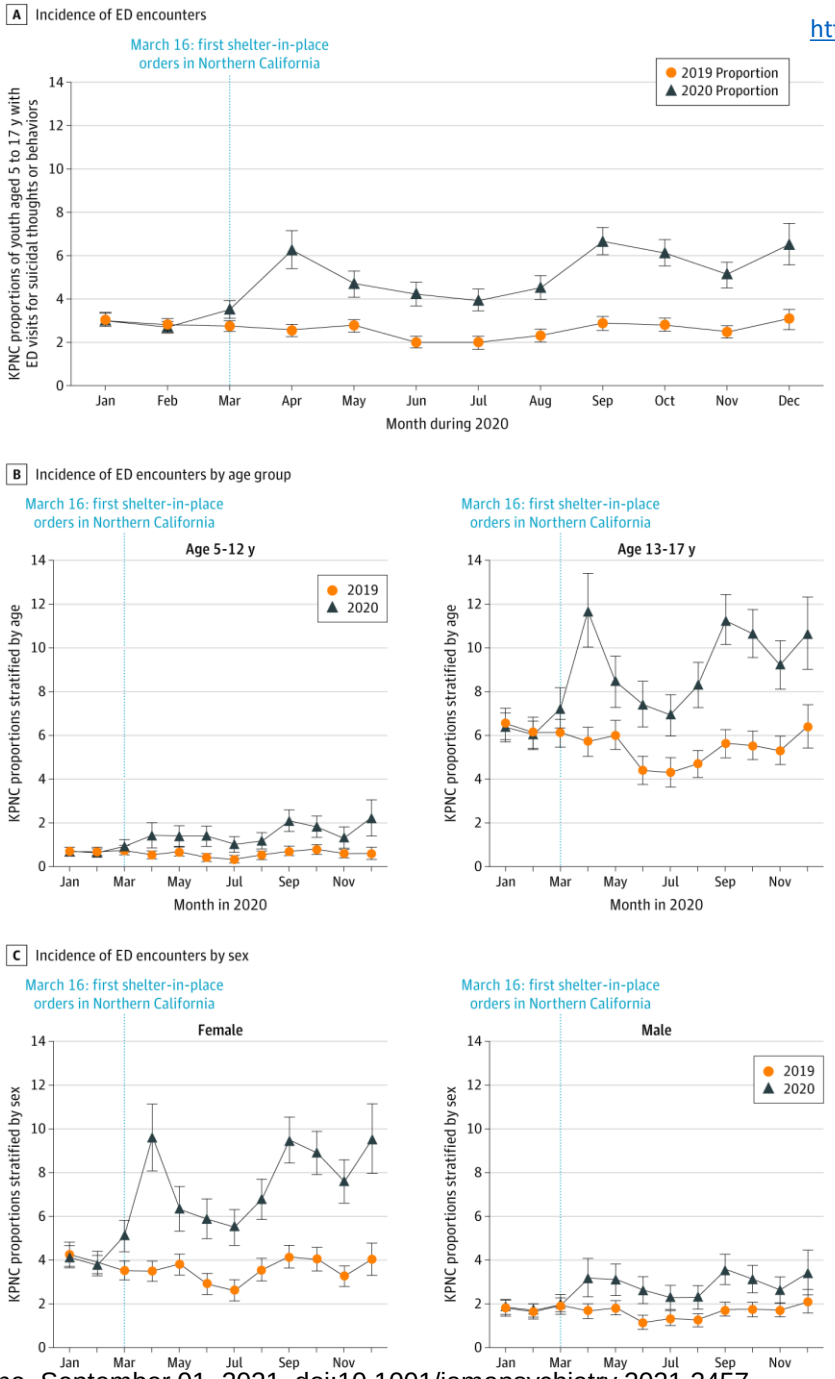
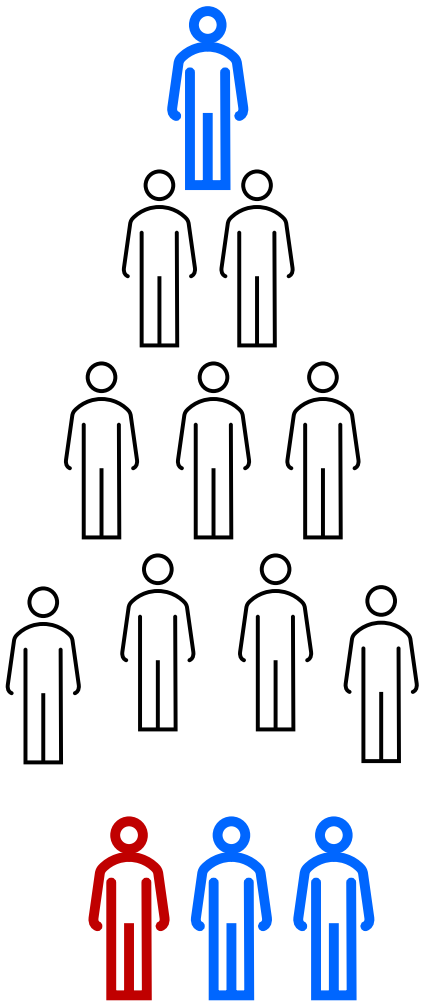
https://mhanational.org/sites/default/files/2021%20State%20of%20Mental%20Health%20in%20America_0.pdf

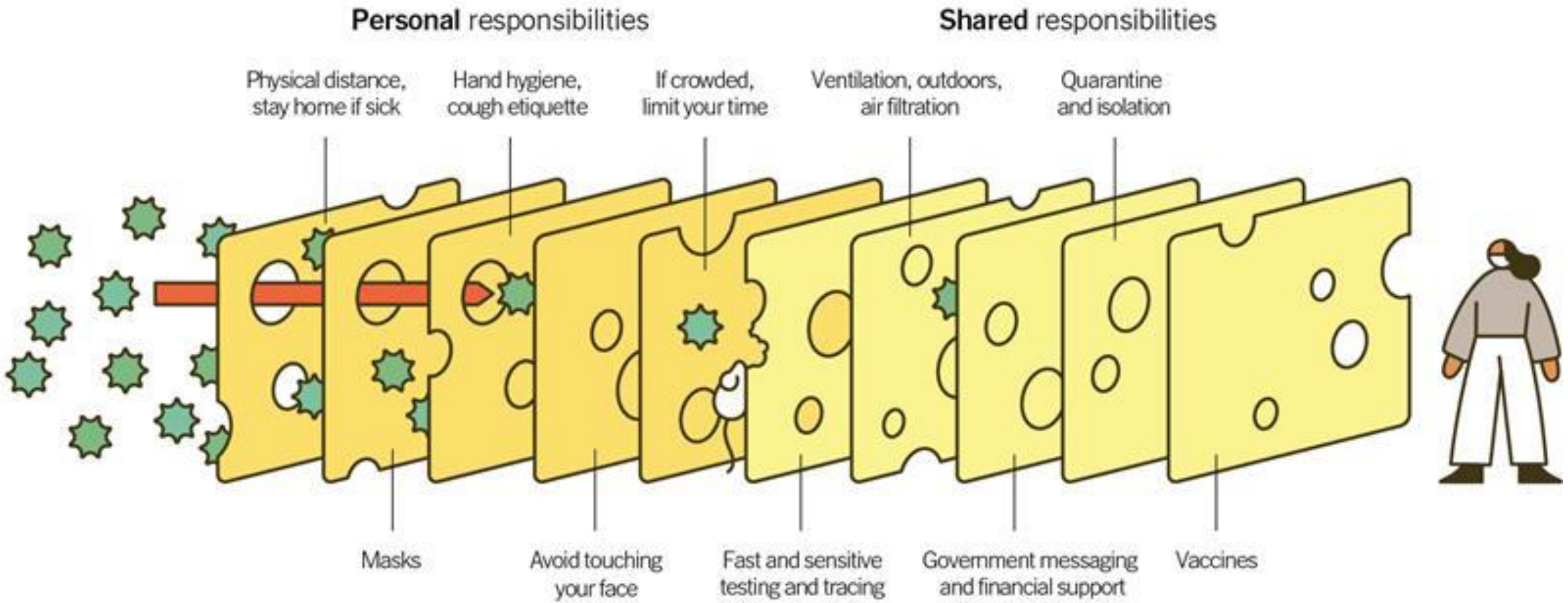




JAMA Psychiatry. Published online September 01, 2021. doi:10.1001/jamapsychiatry.2021.2457

Multiple Layers Improve Success

The Swiss Cheese Respiratory Pandemic Defense recognizes that no single intervention is perfect at preventing the spread of the coronavirus. Each intervention (layer) has holes.



Source: Adapted from Ian M. Mackay (virologydownunder.com) and James T. Reason. Illustration by Rose Wong