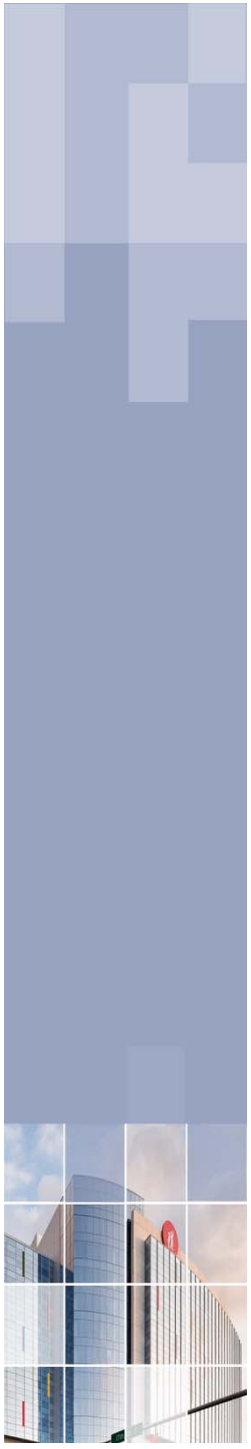


COVID-19 Updates for the Primary Care Doctor

Robert Pass, MD
William Britt, MD
David Kimberlin, MD
Randy Cron, MD, PhD
Swetha Pinninti, MD

UAB MEDICINE PEDIATRICS

Children's of Alabama

Children's of Alabama

UAB MEDICINE
PEDIATRICS

Practical Day of Pediatrics

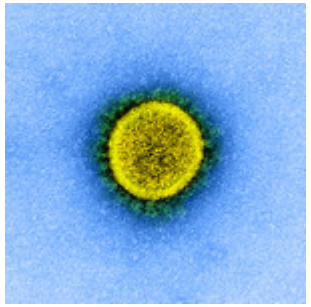
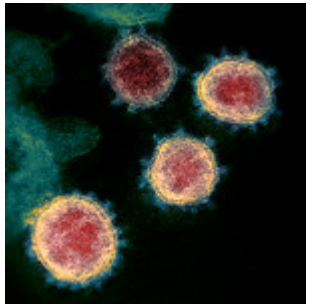
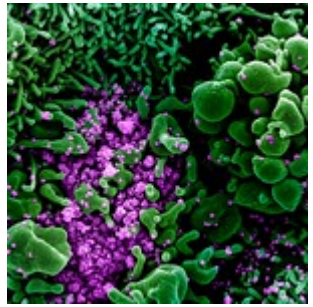
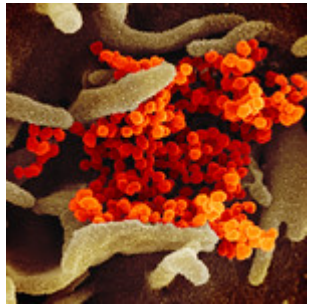
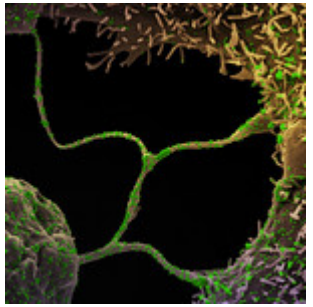
February 6, 2021

Please note: Robert Pass, MD

- Does not intend to discuss commercial products or services.
- Does not intend to discuss non-FDA approved uses of products/providers of services.
- Discloses a financial relationship with:

  Moderna, Inc. – Scientific Advisory Board; Consultant related to cytomegalovirus vaccine development

  Astra Zeneca – Stock ownership

Serious Acute Respiratory Syndrome Coronavirus 2

SARS-CoV-2, Know the enemy.

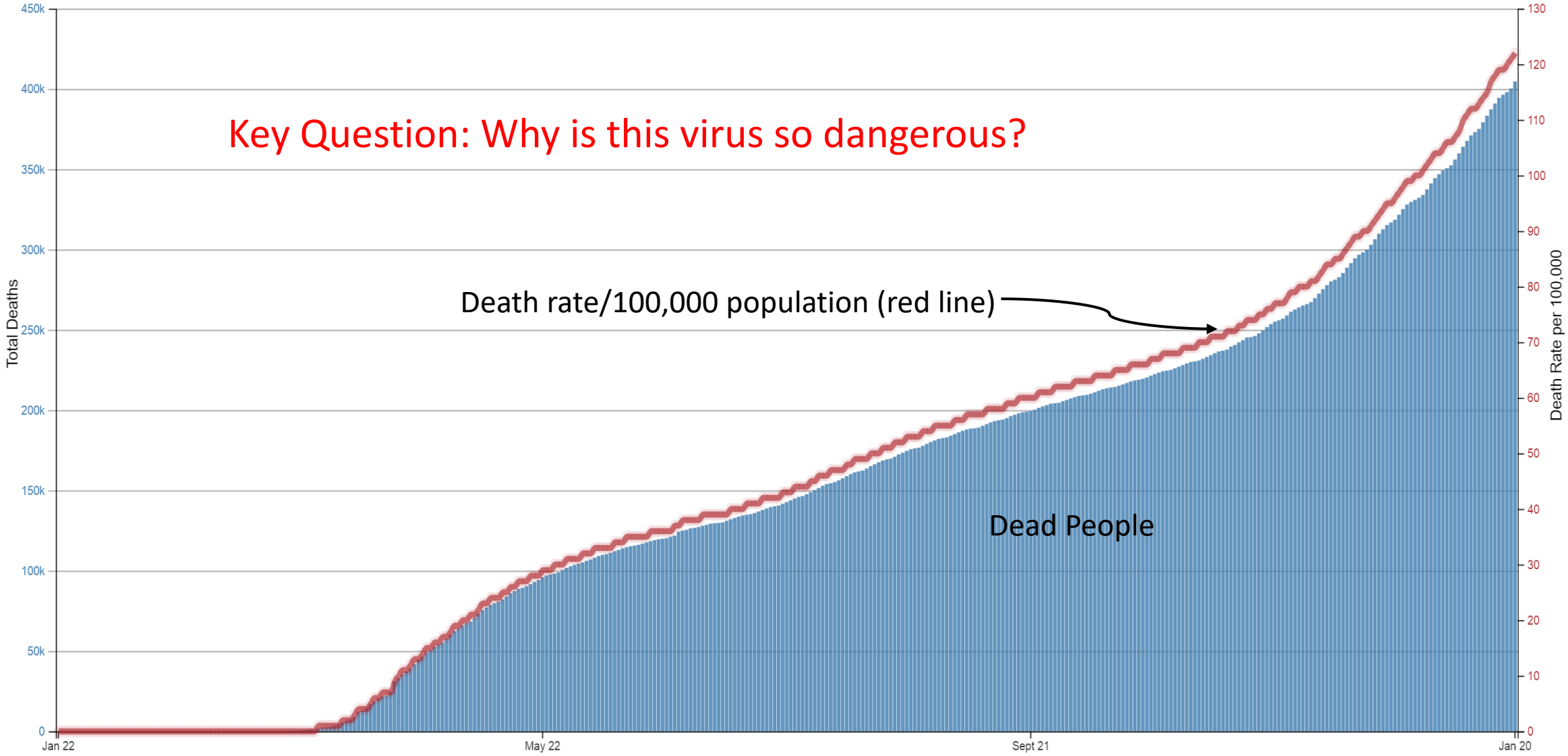
Robert Pass, MD

UAB Department of Pediatrics

Practical Day of Pediatrics, February 6, 2021

Images available from NIAID,
https://www.flickr.com/photos/niaid/albums/72157712914621487/with/50748458672/

Covid 19 is now the 3rd leading cause of death in the U.S.



Children's of Alabama

UAB MEDICINE PEDIATRICS

How does SARS-CoV-2 cause disease and why is it more dangerous than other coronaviruses that infect humans?

WE WILL CONSIDER 4 LIKELY FACTORS

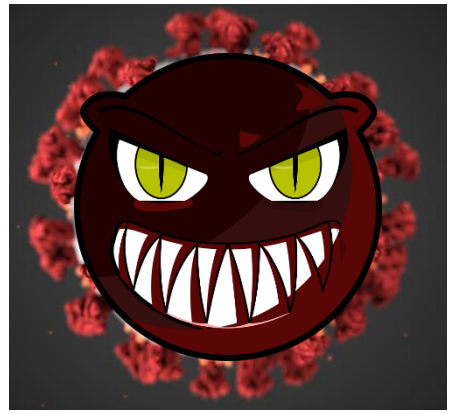
1. Viral replication
2. Lack of adaptive immunity (no immunologic memory)
3. Physiological consequences of interaction with its receptor, angiotensin converting enzyme 2 (ACE-2)
4. Virus and host genetic variability

What is a coronavirus?

It is a very small biological machine that invades mammalian cells to make millions of copies of itself.

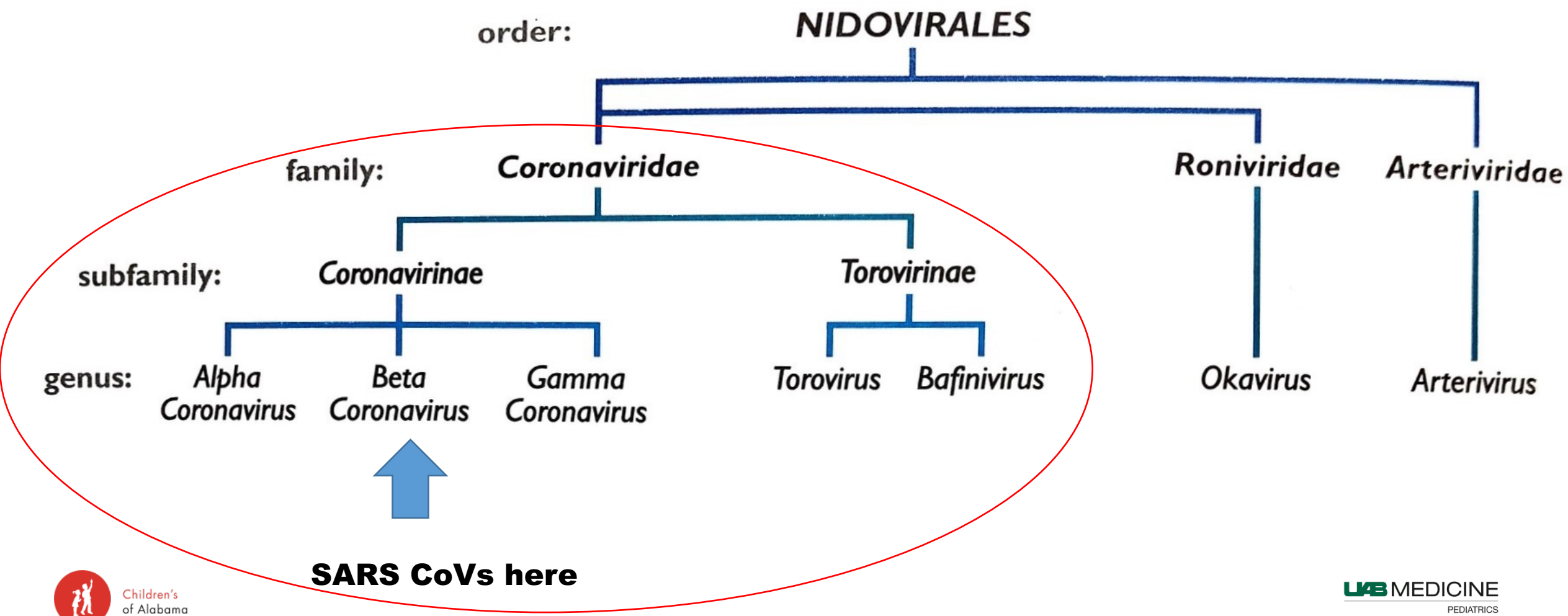
Enveloped single stranded RNA virus

- 100 -160 nanometer diameter
- + sense RNA (like mRNA)
- Nucleoprotein core
- Lipoprotein envelope
- Spike (S) glycoprotein on surface



SARS-CoV-2

There are lots of different coronaviruses



A few of the many coronaviruses

Adapted from Masters & Perlman, Coronaviridae in Fields Virology 6th Edition (Eds: Knipe and Howlery), Lippincott Williams & Wilkins, 2013

Alpha Coronaviruses

- Feline infectious peritonitis virus
- Transmissible gastroenteritis virus
- Porcine endemic diarrhea virus
- Human coronavirus 229E (HCoV-229E)*
- Human coronavirus NL63 (HCoV-NL63)*

Beta Coronaviruses

- Porcine hemagglutinating encephalomyelitis virus
- Mouse hepatitis virus
- Human coronavirus OC 43 (HCoV-OC43)*
- Human coronavirus HKU1 (HCoV-HKU1)*
- Human severe acute respiratory syndrome coronavirus (SARS-CoV* & SARS-CoV-2*)
- Middle eastern respiratory syndrome coronavirus (MERS-CoV)*

Gamma Coronaviruses

- Infectious bronchitis virus (IBV)
- Turkey coronavirus (TuCoV)
- Beluga whale coronavirus

*Human pathogens

1

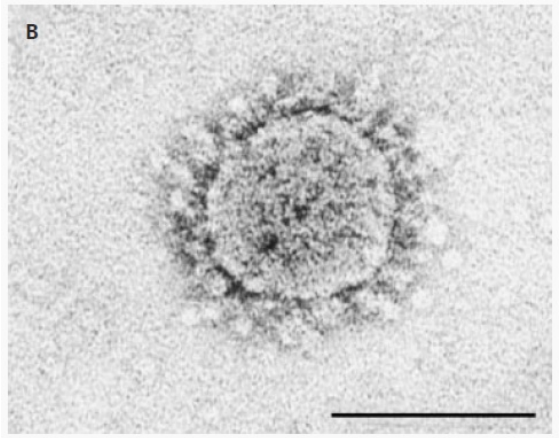
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 15, 2003 VOL. 348 NO. 20

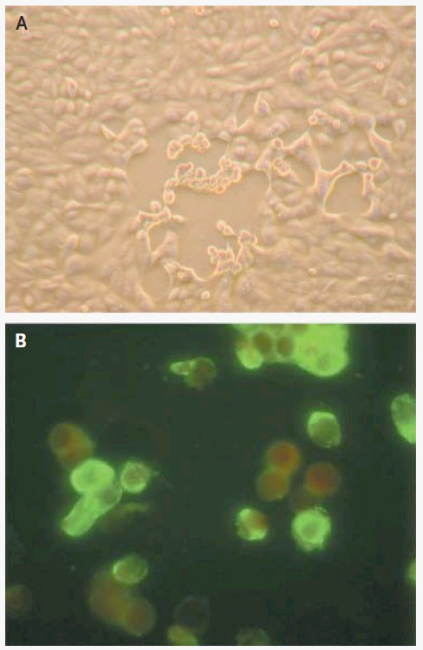
A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome

Thomas G. Ksiazek, D.V.M., Ph.D., Dean Erdman, Dr.P.H., Cynthia S. Goldsmith, M.S., Sherif R. Zaki, M.D., Ph.D., Teresa Peret, Ph.D., Shannon Emery, B.S., Suxiang Tong, Ph.D., Carlo Urbani, M.D.,* James A. Comer, Ph.D., M.P.H., Wilina Lim, M.D., Pierre E. Rollin, M.D., Scott F. Dowell, M.D., M.P.H., Ai-Ee Ling, M.D., Charles D. Humphrey, Ph.D., Wun-Ju Shieh, M.D., Ph.D., Jeannette Guarner, M.D., Christopher D. Paddock, M.D., M.P.H.T.M., Paul Rota, Ph.D., Barry Fields, Ph.D., Joseph DeRisi, Ph.D., Jyh-Yuan Yang, Ph.D., Nancy Cox, Ph.D., James M. Hughes, M.D., James W. LeDuc, Ph.D., William J. Bellini, Ph.D., Larry J. Anderson, M.D., and the SARS Working Group†

What is this?



Where did it come from?
When?



cell culture with SARS-CoV CPE

Serum from SARS-CoV patient binds to infected cells

- Established a novel coronavirus as etiology of SARS
- By sequence analysis determined that it was distinct from previously known human CoVs
- Linked multiple cases to point source outbreak by viral gene sequencing
- Demonstrated immune response to the virus by SARS patients

"Those who cannot remember the past are condemned to repeat it."

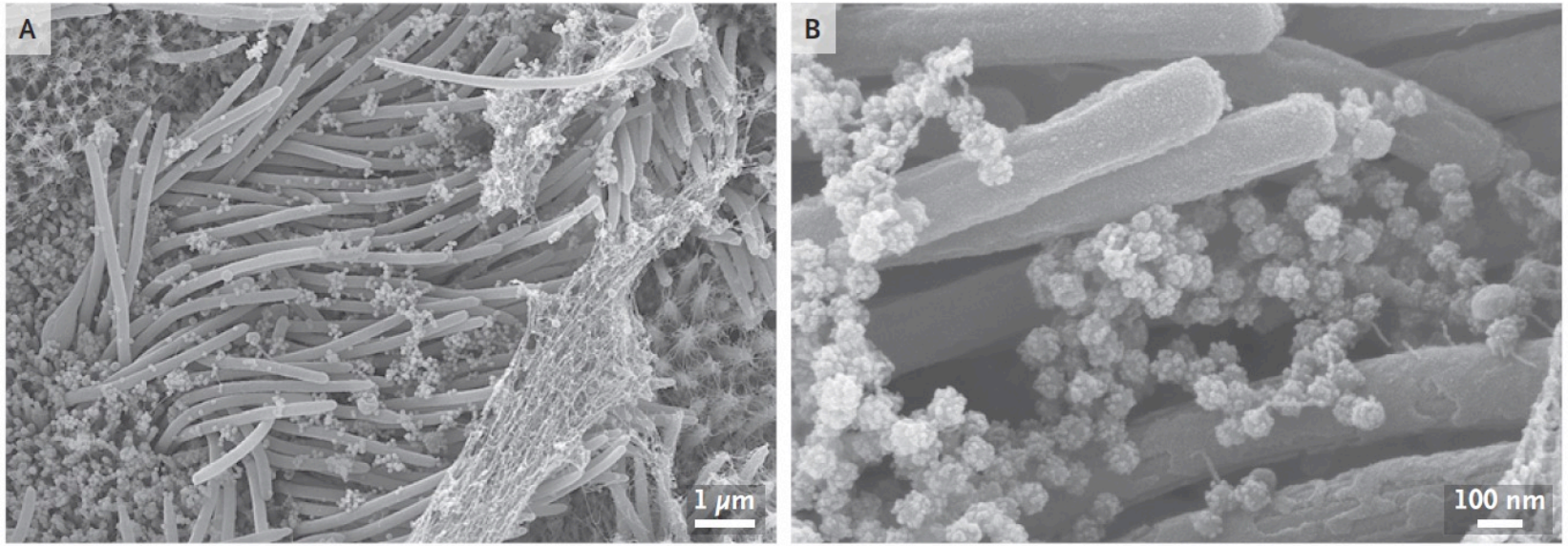
SARS-CoV-2 infection: sequence of events

1. Exposure → inoculum
2. Virus reaches cells in upper respiratory tract
   - Airborne transmission could lead directly to lung infection
   - Oral ingestion could lead directly to intestinal infection
3. Virus attaches to its receptor, angiotensin converting enzyme 2 (ACE2), on the surface of cells
   - Virus enters cell
   - Viral RNA translated → viral proteins
   - New virions assembled and leave cell
   - Excess spike protein S enters extracellular space
   - Cell dies
4. Virus spreads throughout the body to other cells with ACE2
5. Viral shedding from respiratory tract and GI tract and onset of symptoms

Apologies for this gross over simplification!

1

Extent of viral replication



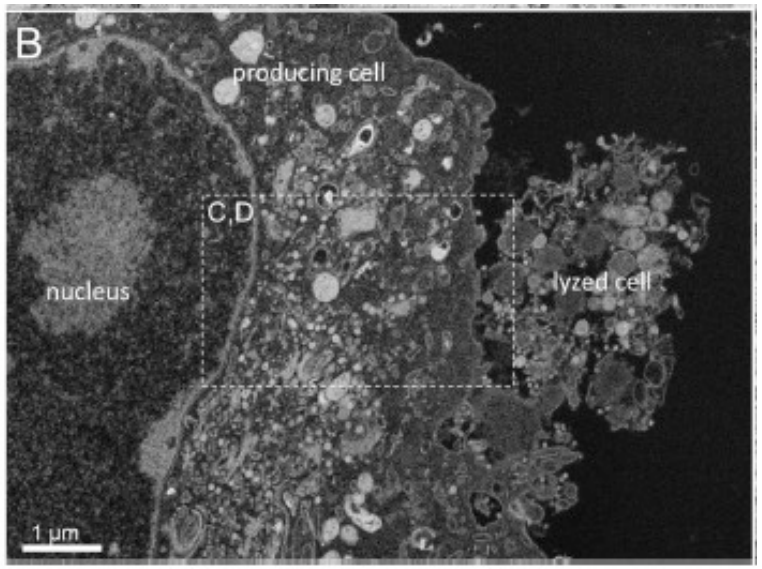
Photos from Ehre, SARS-CoV-2 Infection of Airway Cells, *New Engl J Med*, Sept 3, 2020

- Human bronchial epithelial cell culture
- Multiplicity of input, 3:1 (3 virions per each cell)
- Photos are 96 hours post infection, scanning electron microscope
- 3 million virions per cell culture, by virus culture! (not PCR)

Respiratory cultures from infected persons can peak at 10^8 to 10^9 copies per ml

SARS-CoV-2 infection causes host cell lysis

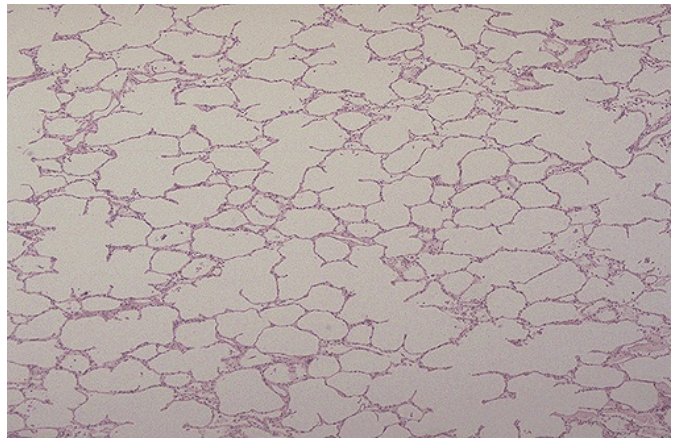
In vitro, 12 hours post-inoculum



From Belhaouari et al, Scanning electron microscopy in deciphering SARS-CoV-2 infectious cycle, *Front Microbiol*, Aug 2020

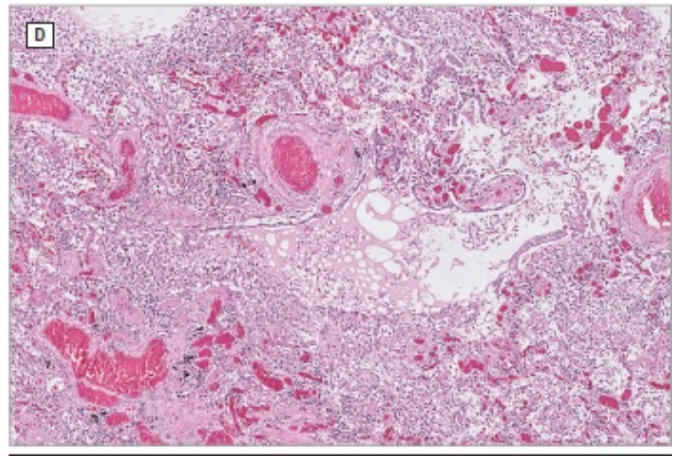
HUMAN LUNG

Normal



https://webpath.med.utah.edu/HISTHTML/NORMAL/NORM030.html

COVID-19, ARDS



Wiersinga et al, Pathophysiology, transmission, diagnosis, & treatment of COVID-19, *JAMA*, July 2020

1

Consequences of exuberant viral replication

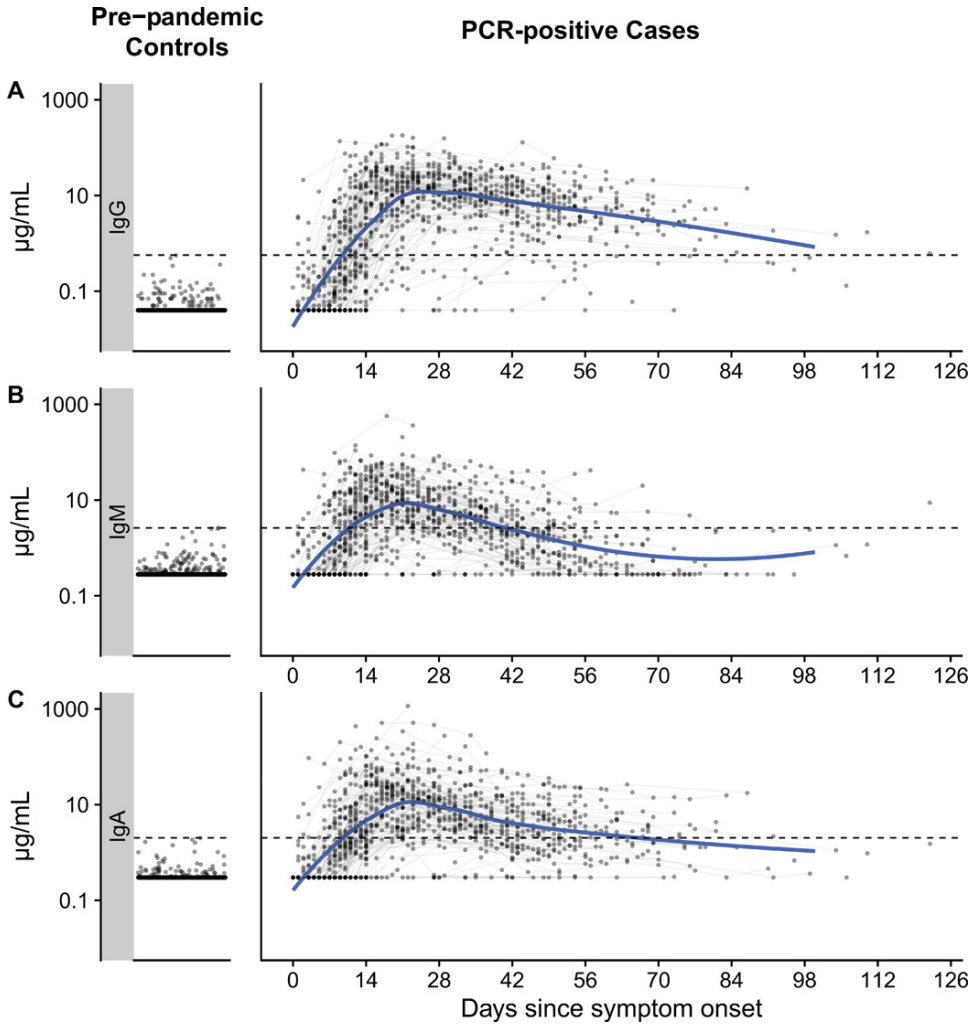
- Rapid spread to multiple tissues in the host
- More cells infected = more cells destroyed
- High levels of virus in body fluids → increased transmissibility
- Higher inoculum at time of infection = ↑ chance of disease

What do we know about adaptive immunity to SARS-CoV-2?

- Provides antibody in body fluids that will neutralize virus.
  - Decreases amount virus that gets past mucosal barriers.
  - Decreases spread of virus from initial site of infection.
- Decreases amount of virus shed in body fluids →↓transmissibility.
- Provides immunologic memory → rapid (days) multi-faceted attack on the virus.

PRIOR TO INFECTION OR VACCINE WE HUMANS DID NOT HAVE ADAPTIVE IMMUNITY IMMUNITY TO SARS-COV-2

2 *No adaptive immunity: the clock is ticking*



- Antibody to RBD correlates with protection
- Prior to infection – no antibody to RBD
- Typical kinetics of antibody response post-infection in this study of patients (93% hospitalized)
- ~10-14 days post onset of symptoms to have circulating antibody to virus

Antibody to receptor binding domain (RBD) of spike protein

From Iyer et al, *Sci. Immunol.* 10.1126/sciimmunol.abe0367 (2020)

2 *We have proof that adaptive immunity provides protection -*

- Results of clinical trials with vaccines
  - BNT162b2 vaccine 95% effective preventing Covid-19 [Polack, NEJM, Dec, 2020]
  - mRNA 1273 vaccine 94% effective preventing Covid-19 [Baden, NEJM, Dec, 2020]
- Healthcare workers followed for 31 weeks, [Lumley, NEJM, Dec 23, 2020]
  - 11,364 ab neg→223 became PCR +ve (123/223 symptomatic)
  - 1,265 ab +ve → 2 became PCR +ve (0 symptomatic)
  - Rates per 10,000 days at risk: 1.09 vs 0.13
- Passive immunization (plasma or monoclonal antibody) provides only one component of adaptive immunity – antibody
  - But it works if given early
  - Decreases disease severity
  - Might even decrease viral shedding

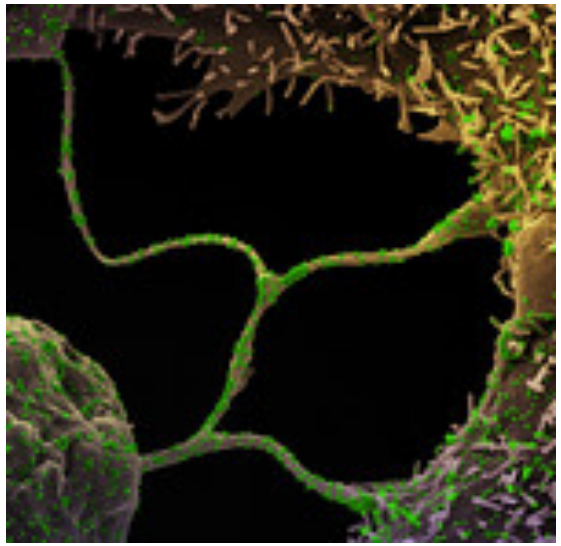
3 what about ACE2?

Human coronavirus receptors

	Virus	Receptor	Receptor Function
	HCoV-229E	Human aminopeptidase N	Enterocytes, digestion of peptides; cell adhesion, cell mobility
√	HCoV-NL63	Angiotensin converting enzyme 2	Control of renin angiotensin system (RAS)
	HCoV-OC43	N-acetyl-9-*O*-acetylneuraminic acid	Ubiquitous sialic acid; cellular adhesion, proliferation, apoptosis, immune cell interactions
	HCoV-HKU1	N-acetyl-9-*O*-acetylneuraminic acid	Ditto
	MERS	Dipeptidyl peptidase 4	DDP4 AKA CD26: T cell activation; glucose metabolism
√	SARS-CoV	Angiotensin converting enzyme 2	Control of renin angiotensin system (RAS)
√	SARS-CoV-2	Angiotensin converting enzyme 2	Control of renin angiotensin system (RAS)

Which lung cells have ACE2 - can be infected by SARS-CoV-2?

Cell type	Function	SARS-CoV-2 Infected?
Ciliated bronchial epithelium	Move mucus, foreign material	√
Type I pneumocytes	Gas exchange, cover 95% of air sacs	√
Type II pneumocytes	Surfactant, protection of air sacs	√
Blood vessels, alveolar capillaries	Gas exchange, deliver oxygen	√
macrophages	Host defense	√



Exp Physiol 93.5 pp 543–548, 2008
Experimental Physiology – ***Review Article***

The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice

Yumiko Imai[1,3], Keiji Kuba[2] and Josef M. Penninger[3]
[1]*The Global Center of Excellence program, Akita University Graduate School of Medicine, Akita 010-8543, Japan*
[2]*Medical Top Track Program, Medical Research Institute, Tokyo Medical and Dental University, Tokyo 101-0062, Japan*
[3]*Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Dr. Bohr-gasse 3, Vienna, A-1030, Austria*

- ACE-2 protects mouse lungs from injury due to chemical or infectious insults
- SARS-CoV infection reduces ACE-2 expression
- The S spike protein of SARS-CoV alone reduces ACE-2 expression
- “injection of SARS-CoV spike into mice worsens acute lung failure *in vivo*, which can be attenuated by blocking the renin–angiotensin pathway…”

The renin angiotensin system

from Vaajanen et al, Graefes Arch Clin Exp Ophthalmol, 253;1053-59, 2015

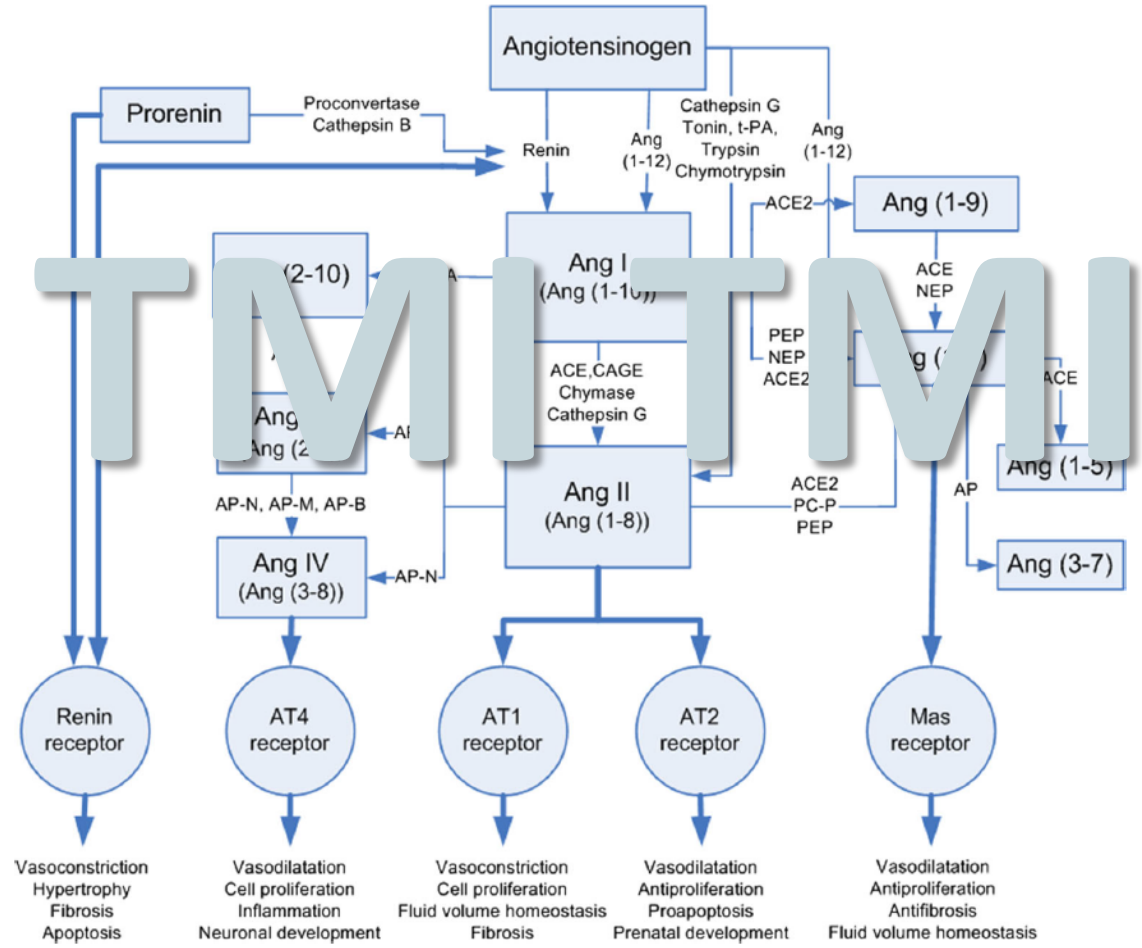
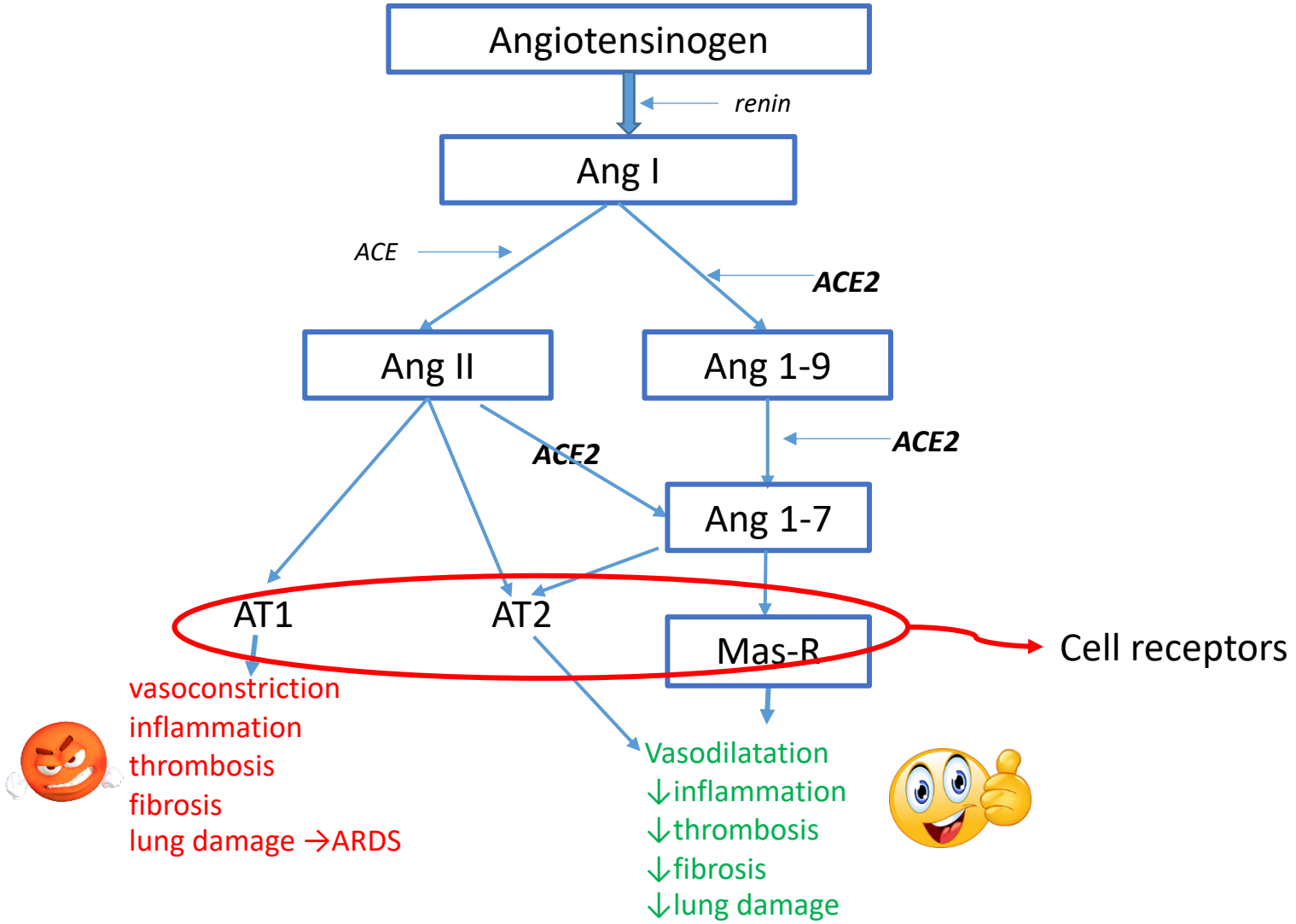


Fig. 1 A RAS cascade. *ACE*=angiotensin-converting enzyme, *ACE2*=angiotensin-converting enzyme-related carboxypeptidase, *Ang I,II,III,IV*=angiotensin I,II,III,IV, *Ang (1–10)*=angiotensin (1–10), *Ang (1–8)*=angiotensin (1–8), *Ang (2–8)*=angiotensin (2–8), *Ang (3–8)*=angiotensin (3–8), *Ang (1–9)*=angiotensin (1–9), *Ang (1–7)*=angiotensin (1–7), *Ang (1–5)*=angiotensin (1–5), *Ang (3–7)*=angiotensin (3–7), *AT1*=angiotensin II type 1 receptor, *AT2*=angiotensin II type 2 receptor, *AT4*=angiotensin II type 4 receptor, *AP*=aminopeptidase (−A,-N,-M,-B), *CAGE*=chymostatin-sensitive Ang II-generating enzyme, *Mas-receptor*=Ang (1–7) receptor type, *Nep*=neprilysin, *PEP*=prolyl endopeptidase, *PC-P* = prolylcarboxy-peptidase, *tPA*=tissue-type plasminogen activator. (Vaajanen et al. 2008a, a modified version)

3 *Angiotensin converting enzyme2, a counter-balance to RAS*

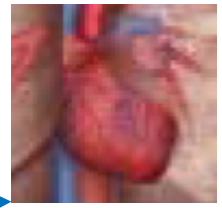


Potential effects of decreased ACE2

adapted from Gheblawi et al, Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system, *Circ Res*, May 2020 (Figure 6)

SARS-CoV-2
↓
↓ACE 2
↓
↓Ang (1-7)

Heart

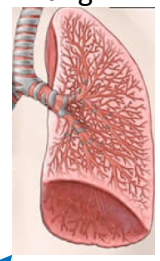


Inflammation
Myocarditis
CHF
Arrythmia
Thrombosis
MI

Vascular sys

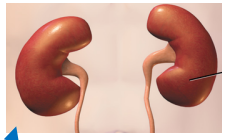
Inflammation
↑ Resistance
↑ BP
thrombosis

Lung



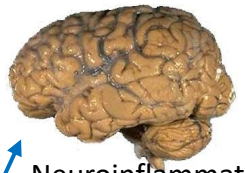
Inflammation
Thrombosis
Fibrosis

Kidney



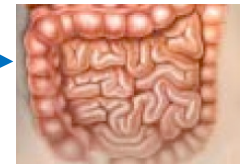
Inflammation
Hypertrophy
AKI

Brain



Neuroinflammation
Encephalopathy
Hypertension

Intestine

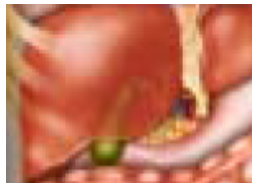


Inflammation
Appendicitis?

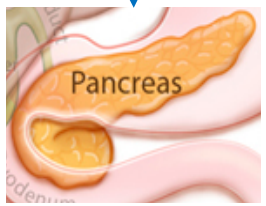
Adipocytes

↓Insulin sensitivity
↑ glucose uptake

Liver



↓Insulin sensitivity
Fibrosis

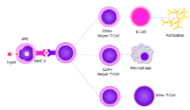


↓Insulin secretion
Pancreatitis

Muscle

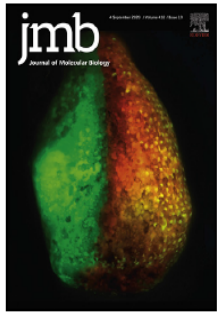
↓ Insulin sensitivity

Immune sys



Immune dysreg
↑IL-6, ↑TNF-α

4 virus & host genetics



Mutations Strengthened SARS-CoV-2 Infectivity

Jiahui Chen[1], Rui Wang[1], Menglun Wang[1] and Guo-Wei Wei[1,2,3]

1 - Department of Mathematics, Michigan State University, MI 48824, USA
2 - Department of Electrical and Computer Engineering, Michigan State University, MI 48824, USA
3 - Department of Biochemistry and Molecular Biology, Michigan State University, MI 48824, USA

Published on-line, July and in print Sept 2020

- Studied over 15,000 viral genomes from 17 countries, collected Jan-June, 2020
- Identified mutations in the spike protein compared with origin sequence from Wuhan, published Jan 5, 2020
- Examined effect of mutations on binding of spike to ACE2
- Found 89 mutations on the receptor binding domain of spike protein
- 52 of these were in the region that is in direct contact with ACE2
- Conclusion: "mutations have made all clusters of SARS-CoV-2 more infectious"

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

pubs.acs.org/jcim

Decoding SARS-CoV-2 Transmission and Evolution and Ramifications for COVID-19 Diagnosis, Vaccine, and Medicine

Rui Wang, Yuta Hozumi, Changchuan Yin,* and Guo-Wei Wei*

- Examined mutation frequency for viral proteins
- Conclusion: potential for impacting antibody testing, PCR detection, vaccine efficacy and antiviral treatment

Children's of Alabama

UAB MEDICINE PEDIATRICS

Does genetic variability in humans affect susceptibility to SARS-CoV-2 or severity of disease? Maybe.

- Sequence variability in human genes for proteins essential for SARS-CoV-2 infection have been identified.
  - ACE2: receptor where S1 portion of surface spike attaches
  - TMPRSS-2: a transmembrane serine protease acts on S2 portion of spike after attachment, necessary processing to allow entry of viral genome
- To date, no convincing association between a specific human mutation and susceptibility to or outcome of SARS-CoV-2 infection.
- Other genetic variabilities in humans (blood type, toll like receptors, HLA types, natural killer cells, interferons, …) could affect outcome of Covid-19.

SARS-CoV-2 infection is dangerous because -

1. We have no prior experience, no adaptive immunity
2. The virus is really good at replication in humans
   - Outpaces the immune system and disseminates in the host
   - Large quantities of virus are shed by asymptomatic persons →transmission
3. It kills the cells it infects producing extensive tissue damage
4. The virus uses a receptor that has an important role in homeostasis and is widely distributed in human organs and tissues – angiotensin converting enzyme 2 (ACE 2)
5. The virus decreases availability of ACE 2 leading to increased vascular resistance, proinflammatory state, thrombosis, disruption of homeostatic mechanisms and damage to multiple organs.
6. SARS-CoV-2 has a high frequency of mutations; mutations that increase its ability to attach to and enter human cells are rapidly appearing

References

1. Trends in Number of COVID-19 Cases and Deaths in the US Reported to CDC, by State/Territory: https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#trends_totalandratedeaths
2. Ksiazek et al, A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med*; 348:1953-66, 2003.
3. Ehre C, SARS-CoV-2 infection of airway cells. *N Engl J Med*; 383:969, 2020.
4. Belhaouari et al, The strengths of scanning electron microscopy in deciphering SARS-CoV-2 infectious cycle. *Front Microbiol*; 11: Aug 2020, doi.org/10.3389/fmicb.2020.02014.
5. Wiersinga et al, Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. *JAMA*; 324:782-93, 2020.
6. Iyer et al, Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. *Sci Immunol*; 10.1126/sciimmunol.abe0367, 2020.
7. Polack et al, Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med;* 383:2603-15, 2020.
8. Baden et al, Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*; DOI: 10.1056/NEJMoa2035389, 2020.
9. Imai et al, The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. *Exp Physiol*; 93.5:543-8, 2008.
10. Vaajanen et al, The expression of Mas-receptor of the renin–angiotensin system in the human eye. *Graefes Arch Clin Exp Ophthalmol*; 253:1053-59, 2015.
11. Gheblawi et al, Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system, celebrating the 20th anniversary of the discovery of ACE2. *Circ Res*; 126:1456-74, 2020.
12. Chen et al, Mutations strengthened SARSCoV-2 infectivity. *J Mol Biol*; 432:5212-26, 2020.
13. Wang et al, Decoding SARS-CoV-2 Transmission and evolution and ramifications for COVID-19 diagnosis, vaccine, and medicine. *J Chem Inf Model*; doi.org/10.1021/acs.jcim.0c00501, 2020.

Diagnostic Testing for SARS-CoV-2 Infection

William Britt, MD
Dept of Pediatrics
Division of Infectious Diseases
UAB

Current Approaches for Detection of SARS-CoV-2 Infection

1) Viral Isolation (culture)

2) Molecular testing (nucleic acid amplification testing (NAAT))

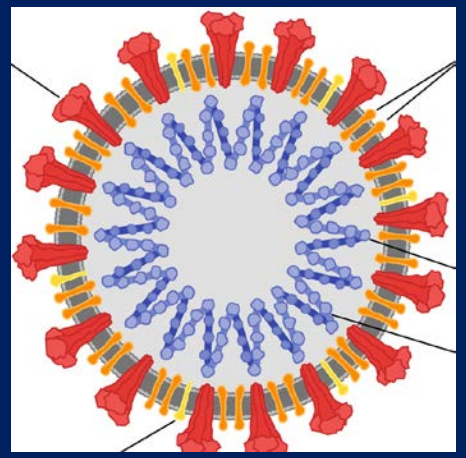
3) Antigen Detection

4) Serological Testing

Nucleic Acid Amplification Testing

1) Real Time-quantitative polymerase chain reaction (RT-qPCR)

(A)Sample Collection (B)Nucleic Acid Extraction (C)Enzymatic Amplification



Viral RNA +Reverse Transcriptase → cDNA

Forward Primer →

ATG CCG TTC AGG CCG.....GTA CCT GGA CCA AAG

TAV GGC AAG TCC GGC……. CAT GGA CCT GGT TTC

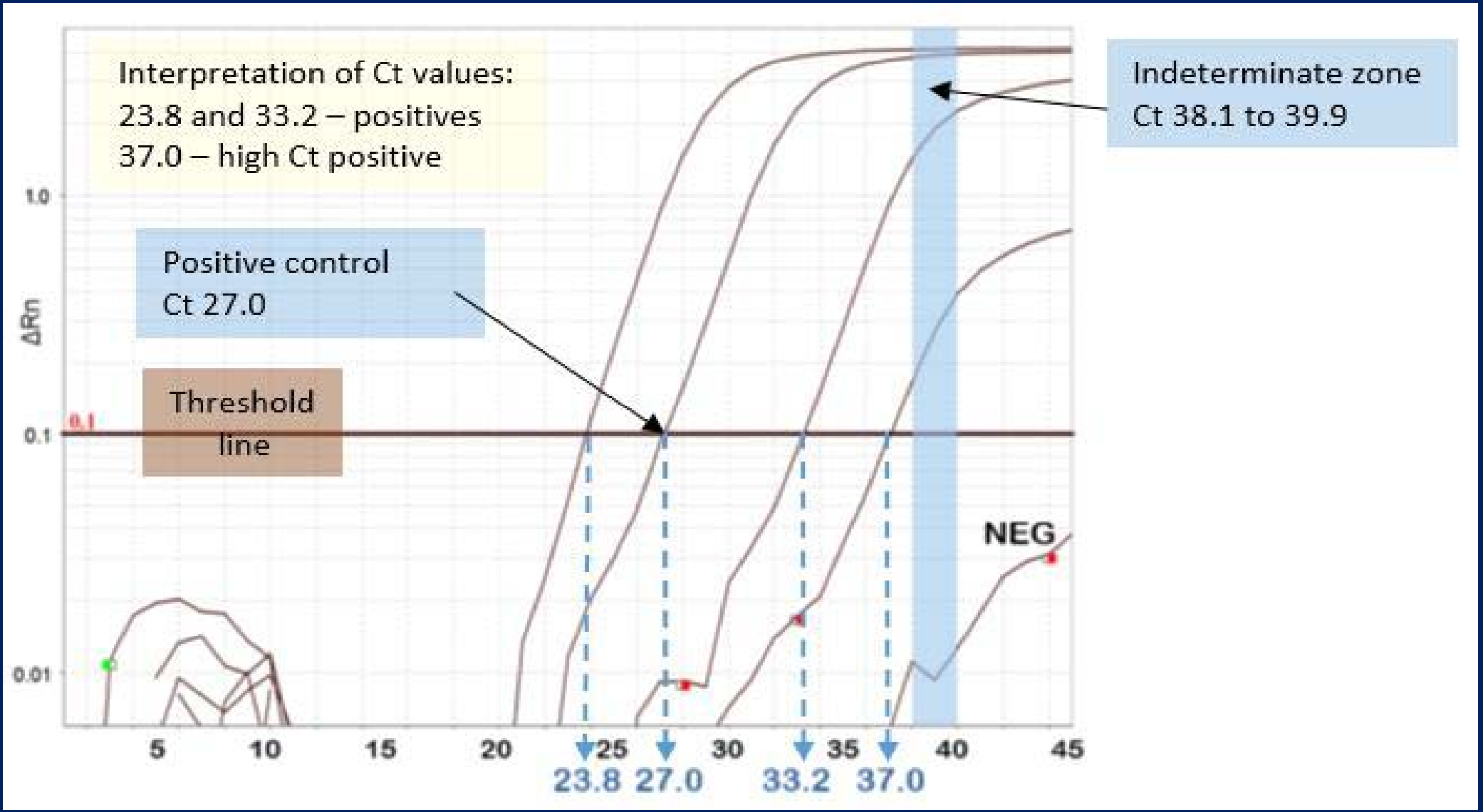
← Reverse Primer

Polymerase Chain Reaction (PCR)

2^N copies (N= cycles of denaturation/annealing/polymerization.

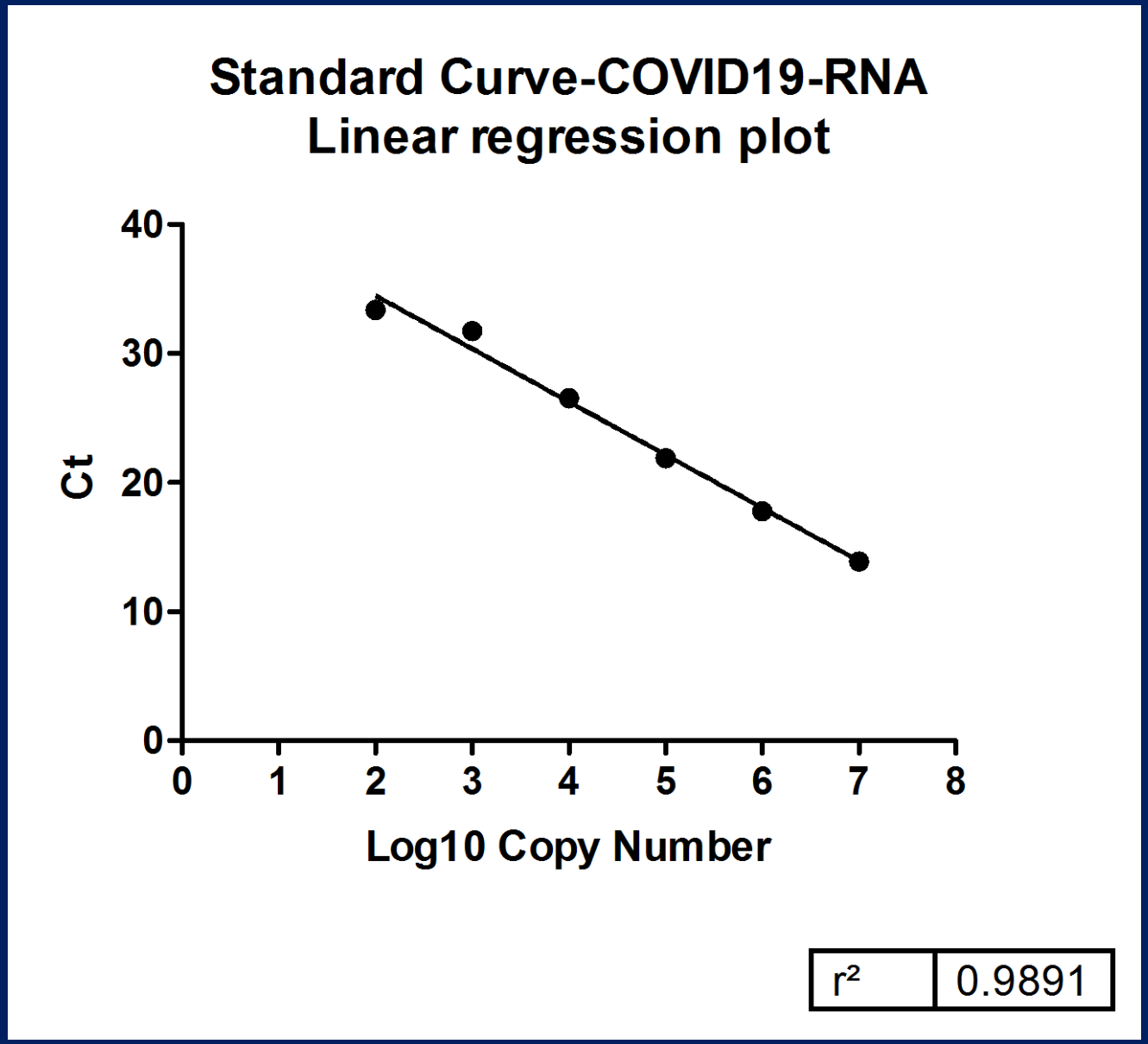
Cycle number where signal detected is estimate of quantity (copy number of input RNA template)

Example of Typical Data from q-PCR Testing



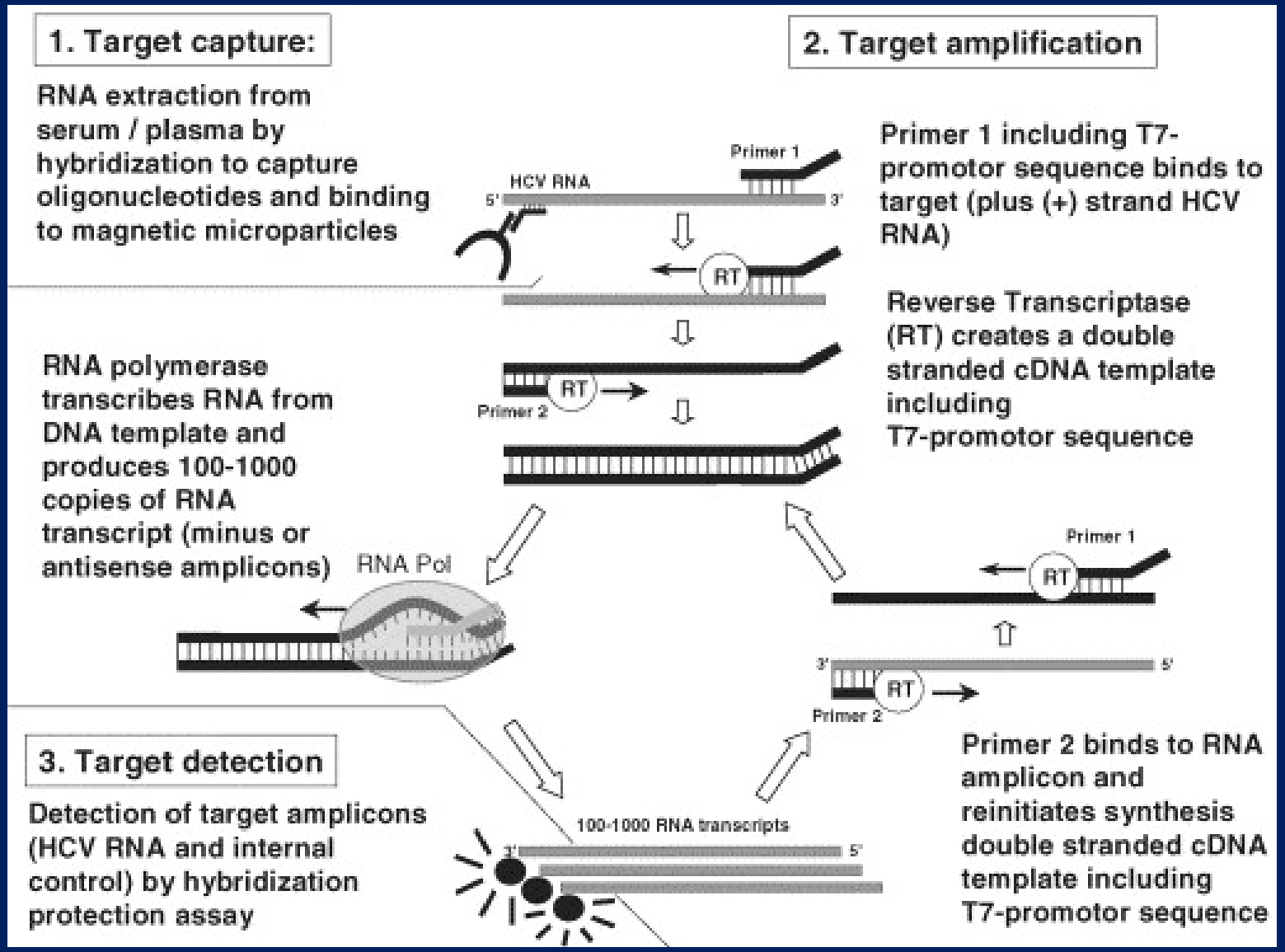
Ontario Agency for Health Protection and Promotion, 2020

RT-qPCR Testing Allows Quantitation of Amount of Viral RNA in Patient Specimen



Nucleic Acid Amplification Testing

2) Transcription Mediated Amplification (Hologics Aptima System)



Advantages: Sensitivity; Work Flow

Disadvantages: Semi-Quantitative

Relative Sensitivity of Transcription Mediated Amplification vs. q-PCR

copies/mL*	TMA** reactivity	Taqpath RT-PCR reactivity†	CDC RT-PCR††
5.5 × 10e5	5/5 (100 %)	5/5 (100 %)	5/5 (100 %)
5.5 × 10e4	5/5 (100 %)	5/5*** (100%)	2/5 (40 %)
5.5 × 10e3	5/5 (100 %)	0/5 (0%)	0/5 (0%)
5.5 × 10e2	1/5 (20 %)	0/5 (0%)	0/5 (0%)
5.5 × 10e1	0/5 (0%)	0/5 (0%)	0/5 (0%)
5.5 × 10e0	0/5 (0%)	0/5 (0%)	0/5 (0%)

Gorzalski, A Journal of Clinical Virology, 2020

NAAT: Rapid Testing (<1 hr) or Point of Care Testing

1) Cepheid GenXpert

2) Abbott ID Now

Advantages: Rapid Turnaround, Point of Care Testing

Disadvantages: Sensitivity (Abbott)

Detection of SARS-CoV-2 Clinical Specimens: Cepheid GenXpert vs Abbott ID NOW Testing

1) FDA reported Limit of Detections: GenXpert 5400 units/ml
   Abbott ID NOW 30,000 units/ml

	Positive GenXpert
Positive ID NOW	17
Negative ID NOW	14
Total	31

Abbott Sensitivity 17/31 (54.8%)

Basu, et.al. Journal Clinical Microbiology, 2020

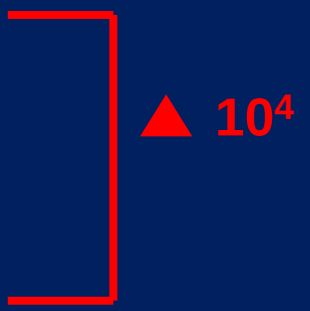
NAAT: Determination of Sensitivity (Limit of Detection of Viral RNA)

1) Limit of Detection Determined by use of synthetic RNAs or with inactivated SARS-CoV-2

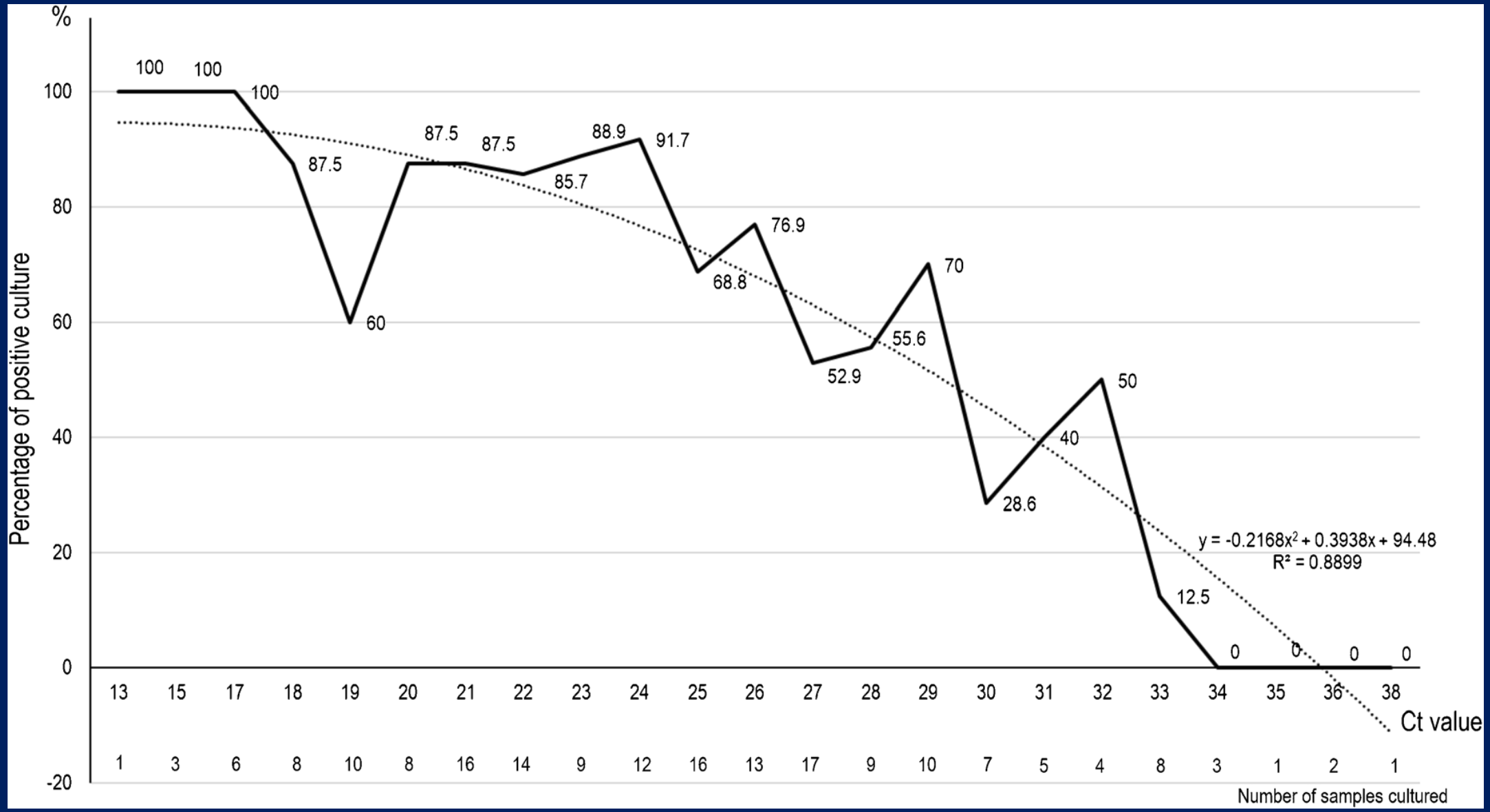
2) Generally reported as either copies of viral RNA/ml or RNA detected in inactivated virus

3) Examples of Sensitivity of Several NAAT (values derived from inactivated virus):

COA RT-qpCR	1800 units/ml	
Roche Cobas	1800 units/ml	
Quest Diagnostics	1800 units/ml	
Abbott Real Time Sars2	2700 units/ml	
Hologics Aptima	600 units/ml	(0.01 Infectious units/ml)
Hologics Fusion	600 units/ml	
BioFire	5400 units/ml	
Cepheid	5400 units/ml	
Abbott ID Now	30,000 units/ml	(100 infectious units/ml)



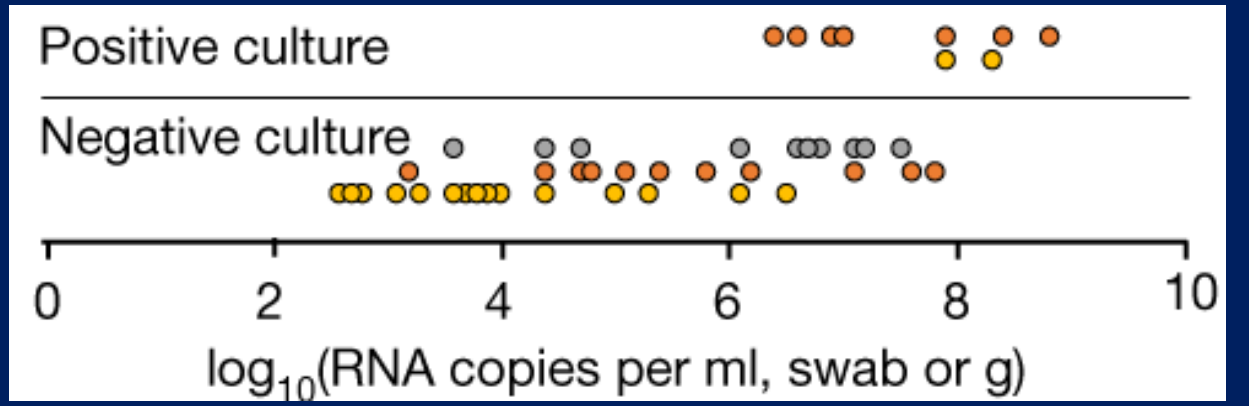
Recovery of Infectious SARS-CoV-2 from NP Swabs as Function of Viral Load



La Scola, Eur J Clin Microbiology and Infect Dis, 2020

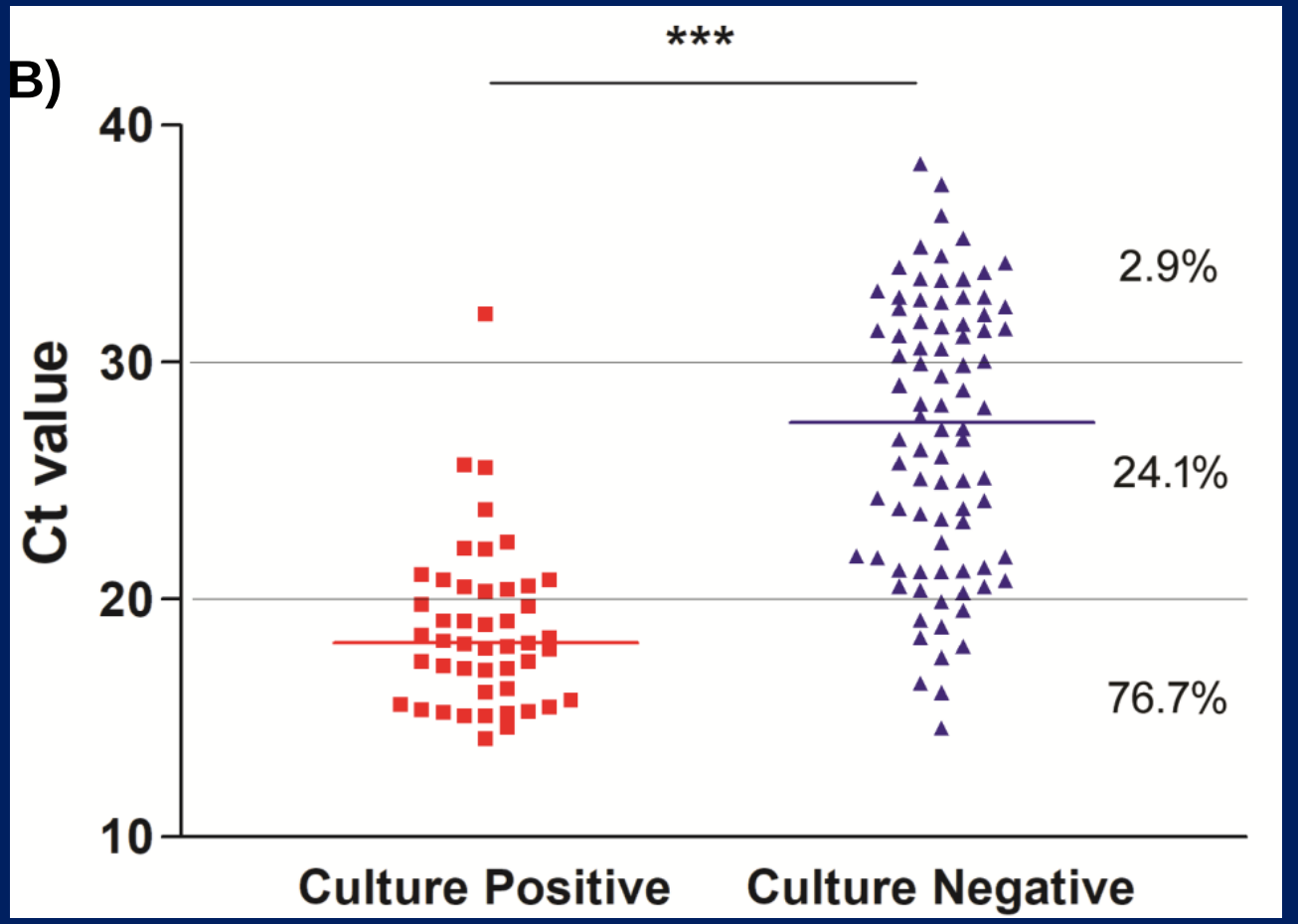
Isolation of Infectious Virus as Function of Viral Load (q-PCR)

A)



Wolfel, Nature, 2020

B)



Gniazdowski, Clin Inf Dis; 2020

Antigen Detection for Diagnosis of SARS-CoV-2 Infections

1) Lateral Flow Immunoassays for Detection of SARS-CoV-2 Proteins in Respiratory Specimens
2) Simple, Rapid Methodology with High Sensitivity for Detection of SARS-CoV-2 (Symptomatic Pts)
3) High False Negative Rate in Asymptomatic Patients, Requires Follow-Up NAAT
4) False Positives reported

Test	Analytical Sensitivity
Abbott BianxNOW	100 infectious units (40,000 copies or estimated Ct of 29)
Quidel Sofia SARS2	100-800 infectious units

Sensitivity and Specificity of Rapid Antigen Testing (BianxNow and Sofia SARS2)

Asymptomatic Patients (871)

	PCR Positive	PCR Negative	Total
Antigen Positive	7	14	21
Antigen Negative	10	840	850
Sensitivity	41.2%		
Specificity	98.4%		

Symptomatic Patients (227)

	PCR Positive	PCR Negative	Total
Antigen Positive	32	2	34
Antigen Negative	8	185	193
Sensitivity	80%		
Specificity	98.9%		

Pray, MMWR Jan1,2021

Asymptomatic Patients (2592)

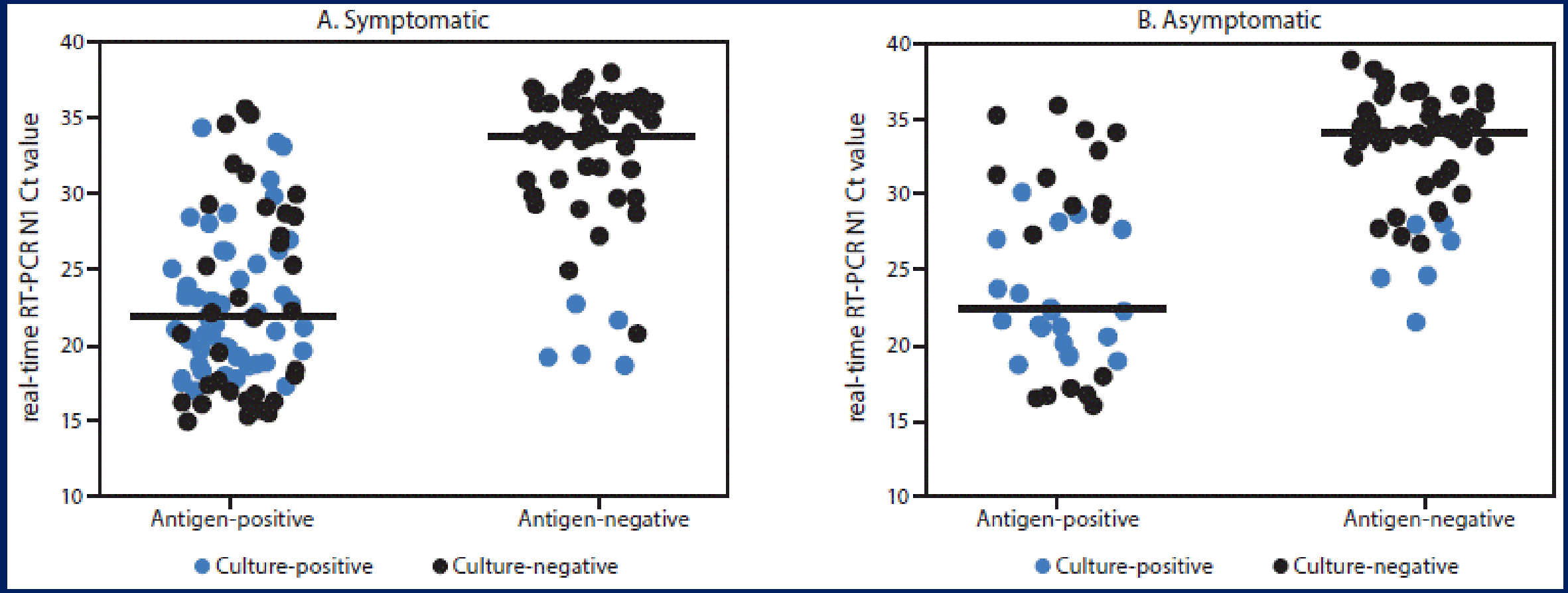
	PCR Positive	PCR Negative	Total
Antigen Positive	44	4	48
Antigen Negative	79	2469	2544
Sensitivity	35.8%		
Specificity	99.8%		

Symptomatic Patients (827)

	PCR Positive	PCR Negative	Total
Antigen Positive	113	0	113
Antigen Negative	63	651	714
Sensitivity	64%		
Specificity	100%		

Prince-Guerra, MMWR Jan19,2021

Recovery of Infectious SARS-CoV-2 from Respiratory Tract Specimens



Prince-Guerra, MMWR Jan19,2021

Summary:

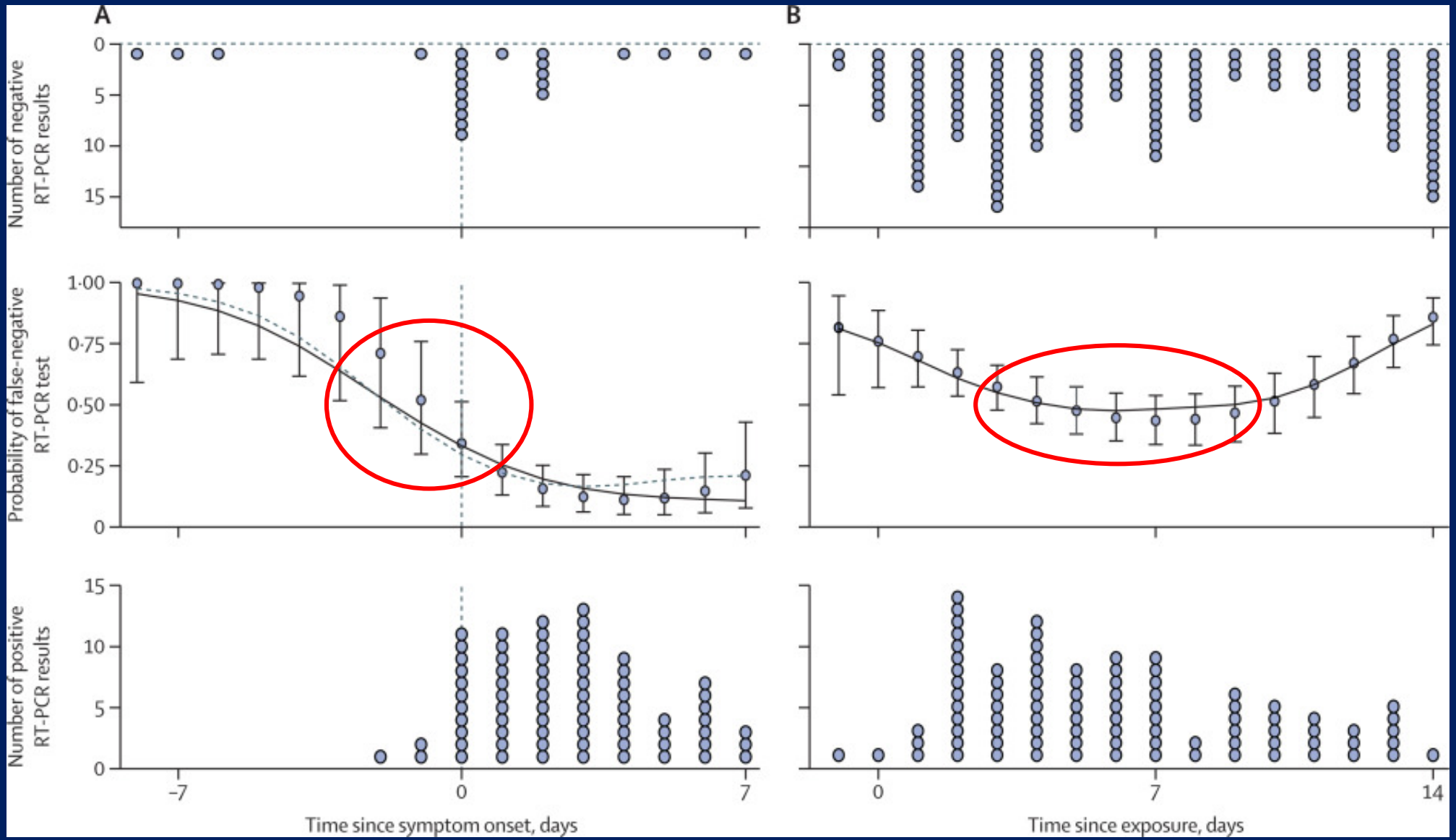
1) NAAT tests remain “gold standard” for diagnosis of SARS-CoV-2 infection

2) Rapid point care testing has value in identifying symptomatic infections but limit in sensitivity reduce value for screening

3) Selection of testing formats dictated by goals of for testing program, i.e. hospitalized patients vs public health screening

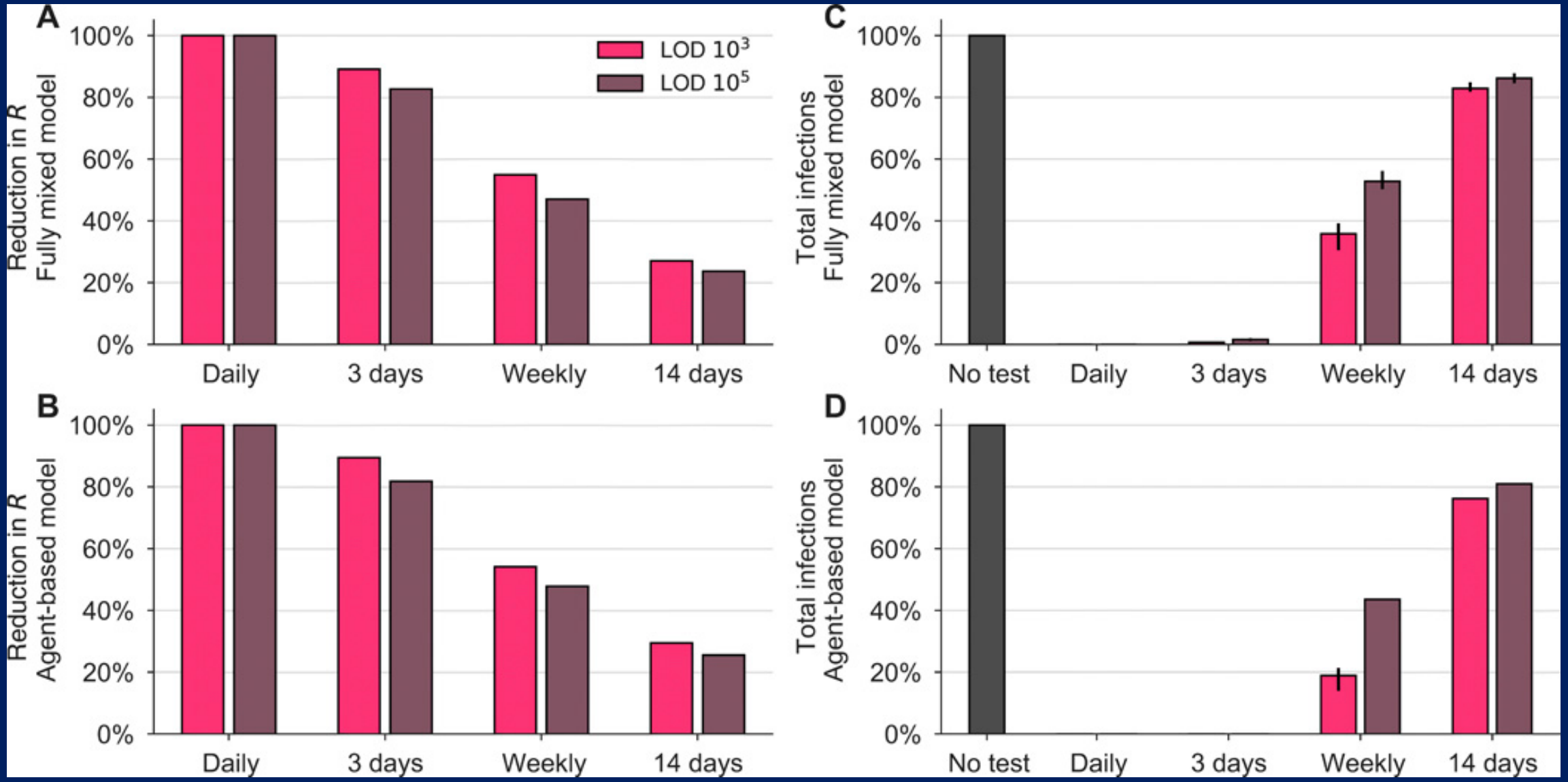
4) Current modeling argues that frequent testing in population is most effective approach for limiting community spread

Modeling of the Likelihood of Positive PCR Test Result as Function of Time From Symptoms or Exposure



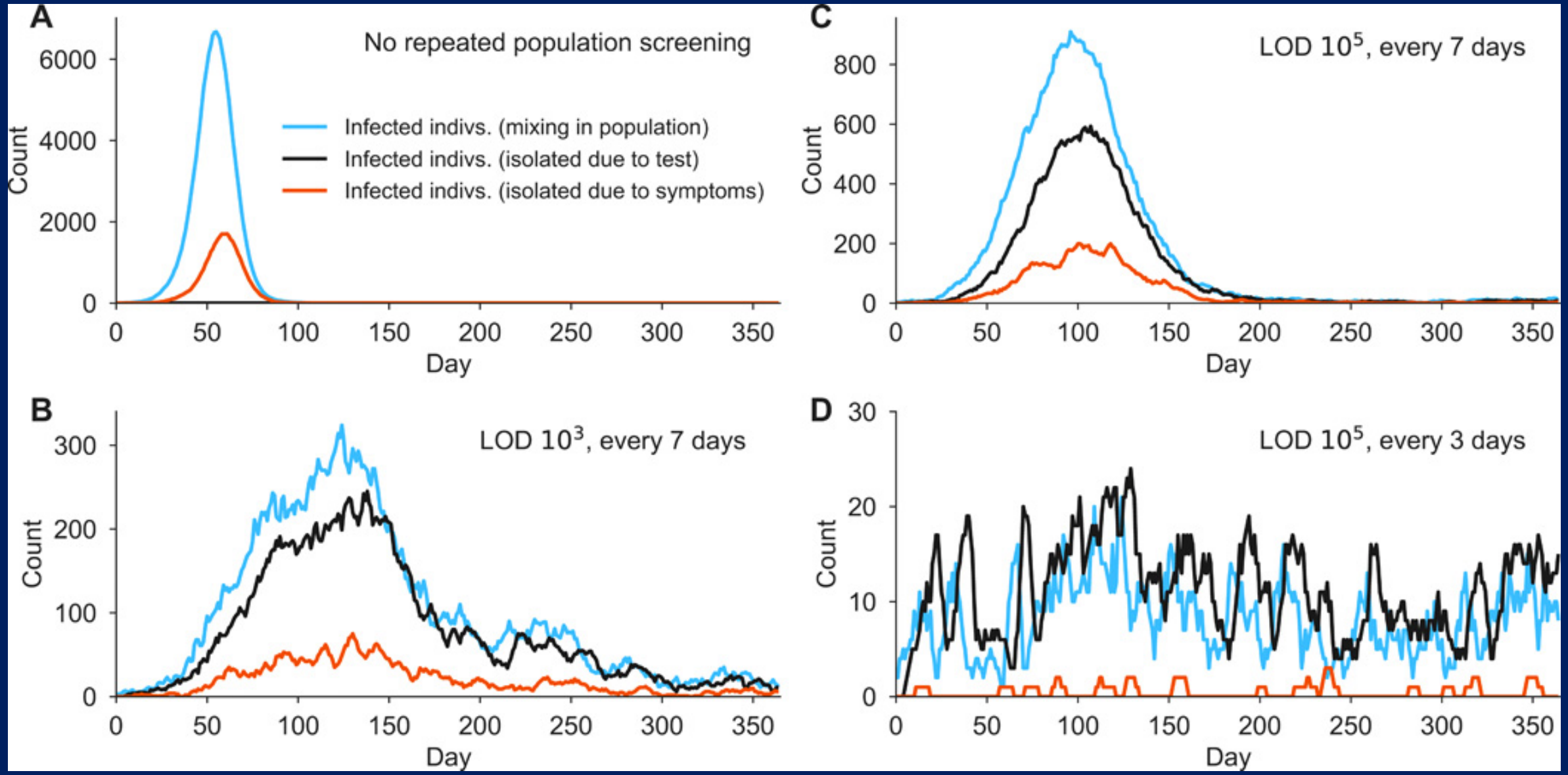
Zhang, Lancet Microbe, 2021

Impact of Test Sensitivity and Frequency of Testing on Spread



Larremore, Science Advance 2021

Testing Frequency not Sensitivity Reduce SARS-CoV-2 Spread in Population



Larremore, Science Advance 2021

Acknowledgments:

1) Suresh Boppana MD (Dept of Pediatrics, UAB)
2) Swetha Pinninti MD (Dept of Pediatrics, UAB)
3) Celia Hutto MD (Dept of Pediatrics, UAB)
4) Members of Diagnostic Virology Laboratory (Dept of Pediatrics, UAB)

Funding:
1) NCI

COVID-19 Vaccine Update

David W. Kimberlin, M.D.

University of Alabama at Birmingham

UAB MEDICINE
PEDIATRICS

Children's of Alabama

Faculty Disclosure

- I do intend to discuss use of commercial products/services – diagnostic tests and antiviral therapies.
- I do intend to discuss non-FDA approved uses of products/services – antiviral therapies, vaccines.
- I do have a relevant financial relationship with the manufacturers of commercial products and/or providers of commercial services discussed in this CME activity.
  - Site PI on Gilead PK/PD study of remdesivir in pediatric population
  - All monies go directly to my university and not to me.

COVID-19 Vaccines in Human Clinical Trials – United States*

Candidate	Manufacturer	Type	Phase	Schedule	Age	Size	Trial #	Recruiting
mRNA-1273	Moderna	mRNA	III	2 doses (0, 28d)	≥18 years	30,000 participants	NCT04470427	Enrollment complete
mRNA-BNT162	Pfizer, Inc./ BioNTech	mRNA	III	2 doses (0, 21d)	12-85 years	44,000 participants	NCT04368728	✓
AZD1222	U of Oxford/ AstraZeneca	Viral vector (Non-replicating)	III	2 doses (0, 28d)	≥18 years	40,000 participants	NCT04516746	✓
Ad26COVS1	Janssen	Viral vector (Non-replicating)	III	1 dose	≥18 years	30,000 participants	NCT04614948	✓
NVX-CoV2373	Novavax	Protein Subunit	III	2 doses (0, 21d)	≥18 years	30,000 participants	NCT04611802	✓

*As of Jan 9, 2021

Modified from ACIP Meeting, November 23, 2020

Sources:https://milkeninstitute.org/covid-19-tracker; https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines; https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/ ; https://clinicaltrials.gov/;https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

COVID-19 Vaccines in Human Clinical Trials – United States*

Candidate	Manufacturer	Type	Phase	Schedule	Age	Size	Trial #	Recruiting
NVX-CoV2373	Novavax	Protein Subunit	I/II	2 doses (0, 21d)	18-84 years	1400 participants	NCT04368988	Enrollment complete
--	Sanofi/GSK	Protein Subunit	I/II	1 dose or 2 doses (0, 21d)	≥18 years	440 participants	NCT04537208	Active, not recruiting
VXA-CoV2-1	Vaxart	Viral vector (Non-replicating)	I	2 doses (1, 29d) *Oral	18-54 years	48 participants	NCT04563702	Active, not recruiting
INO-4800	Inovio	DNA plasmid	I	2 doses (0, 4w) *Electroporation	≥18 years	120 participants	NCT04336410	Active, not recruiting
AV-COVID-19	Aivita	AuDendritic cell	I/II	1 dose	≥18 years	180 participants	NCT04386252	Not yet recruiting

*As of Jan 9, 2021

Modified from ACIP Meeting, November 23, 2020

Sources:https://milkeninstitute.org/covid-19-tracker; https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines; https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/ ; https://clinicaltrials.gov/;https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

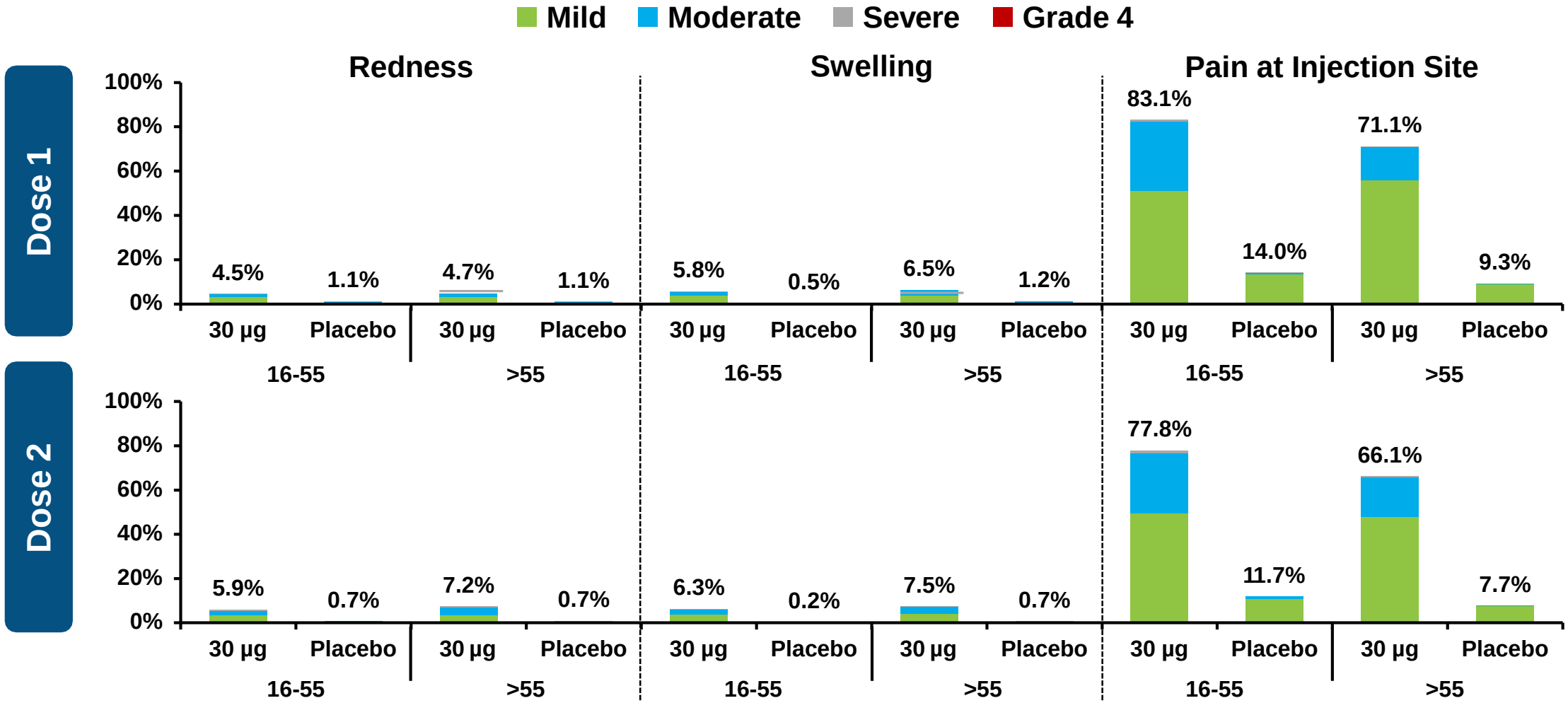
Pfizer / BioNTech Vaccine

Demographic Characteristics

Phase 2/3 (N=43,448)

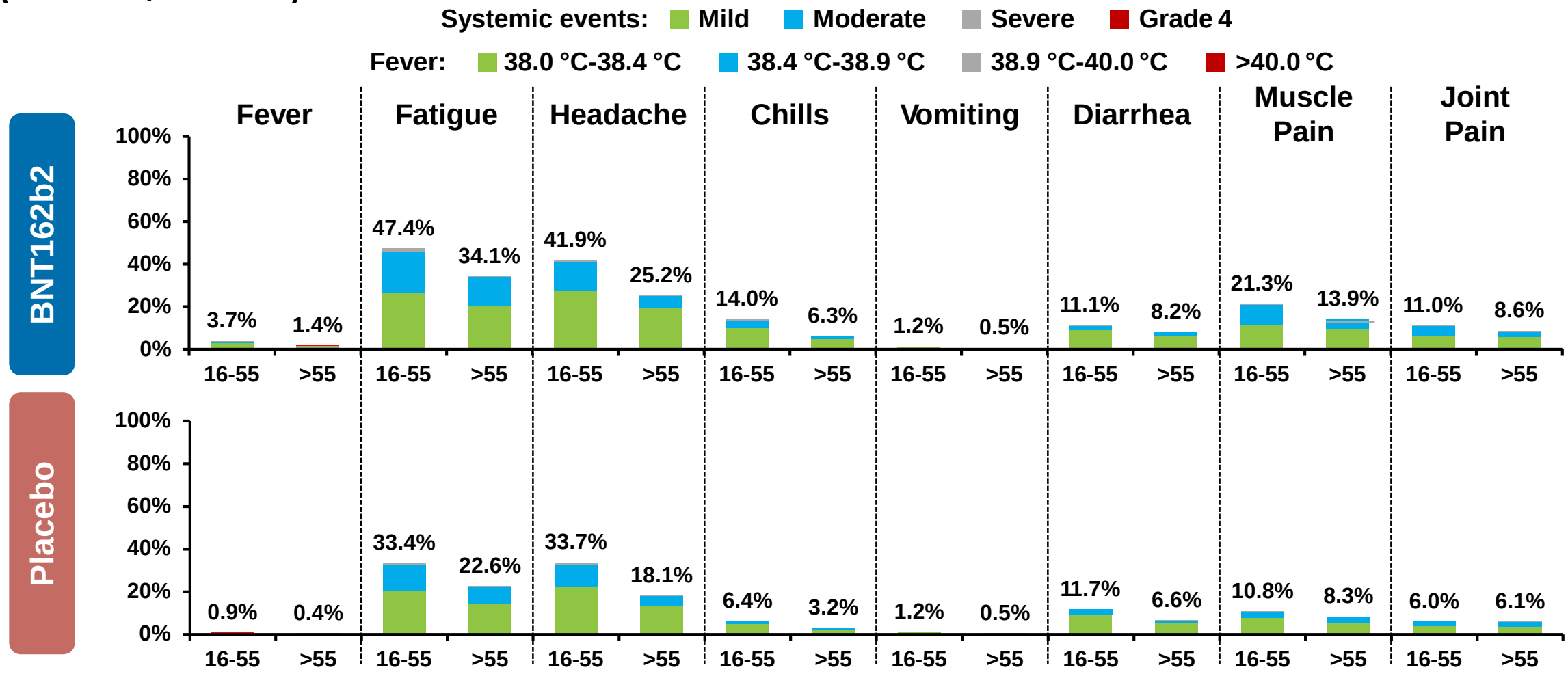
		BNT162b2 (30 µg) N=21,720 n (%)	Placebo N=21,728 N (%)	Total N=43,448 n (%)
Sex	Male	11,183 (51.5)	10,942 (50.4)	22,125 (50.9)
	Female	10,537 (48.5)	10,786 (49.6)	21,323 (49.1)
Race	White	17,839 (82.1)	17,857 (82.2)	35,696 (82.2)
	Black or African American	2,091 (9.6)	2,107 (9.7)	4,198 (9.7)
	All others	1,790 (8.2)	1,764 (8.1)	3,554 (8.2)
Ethnicity	Hispanic/Latino	5,672 (26.1)	5,668 (26.1)	11,340 (26.1)
	Non-Hispanic/non-Latino	15,928 (73.3)	15,940 (73.4)	31,868 (73.3)
	Not reported	120 (0.6)	120 (0.6)	240 (0.6)
Age	16-55 Years	12,780 (58.8)	12,822 (59.0)	25,602 (58.9)
	>55 Years	8,940 (41.2)	8,906 (41.0)	17,846 (41.1)
	16-64 Years	17,176 (79.1)	17,190 (79.1)	34,366 (79.1)
	65-74 Years	3,620 (16.7)	3,646 (16.8)	7,266 (16.7)
	≥75 Years	924 (4.3)	892 (4.1)	1,816 (4.2)

Local Events Within 7 Days From Dose 1 and 2 (N=8,183)



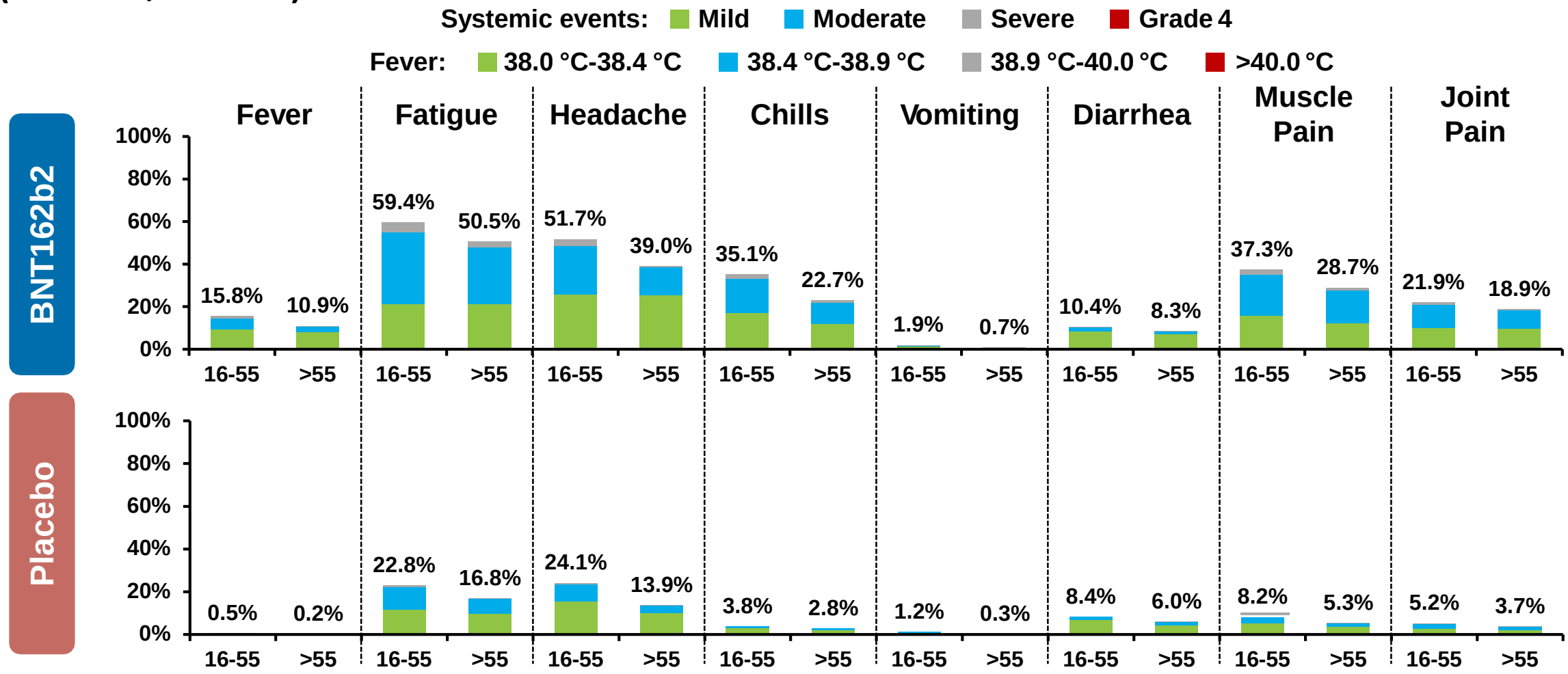
Redness and sweeling severity definition: Mild= >2-5cm, Moderate= >5-10 cm; Severe= >10 cm; Grade 4= necrosis
Pain at injection site severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Dose 1: 16-55 yrs N=4589; >55 yrs N=3594 Dose 2: 16-55 yrs N=4201 >55 yrs N=3306

Systemic Events Within 7 Days From Dose 1 (N=8,183)



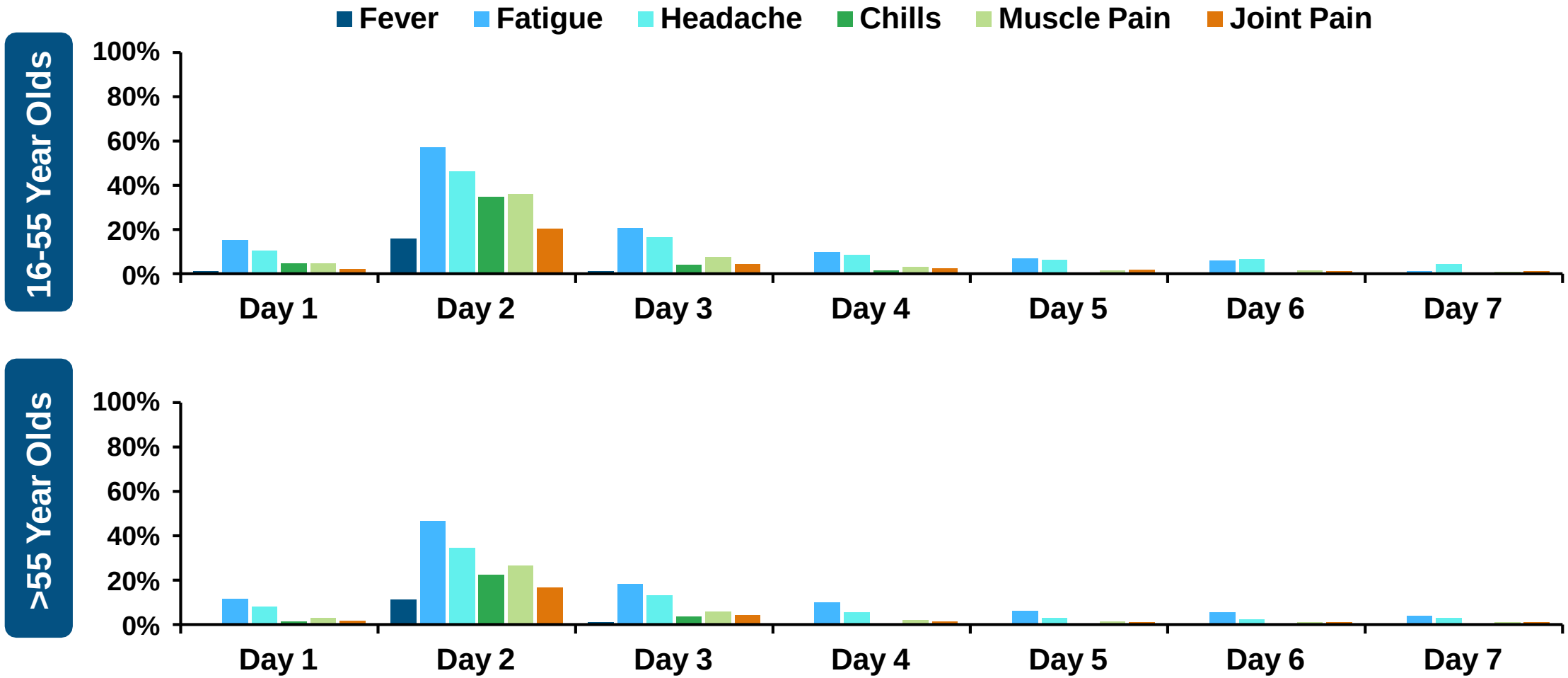
Fatigue, headache, chills, muscle pain, joint pain severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Vomiting severity definition: Mild=1-2 time in 24h; Moderate=>2times in 24h; Severe=Requires IV hydration; Grade 4=ER visit or hospitalization
Diarrhea severity definition: Mild=2-3 times in 24h; Moderate=4-5 times in 24h; Severe=6 or more times in 24h; Grade 4=ER visit or hospitalization
Dose 1: 18-55 yrs N=3529; 56-85 yrs N=3027 Dose 2: 18-55 yrs N=3345; 56-85 yrs N=2899

Systemic Events Within 7 Days From Dose 2 (N=8,183)



Fatigue, headache, chills, muscle pain, joint pain severity definition: Mild=no interference; Moderate=some interference; Severe=prevents daily activity; Grade 4=ER visit or hospitalization
Vomiting severity definition: Mild=1-2 time in 24h; Moderate=>2times in 24h; Severe=Requires IV hydration; Grade 4=ER visit or hospitalization
Diarrhea severity definition: Mild=2-3 times in 24h; Moderate=4-5 times in 24h; Severe=6 or more times in 24h; Grade 4=ER visit or hospitalization
Dose 1: 18-55 yrs N=3529; 56-85 yrs N=3027 Dose 2: 18-55 yrs N=3345; 56-85 yrs N=2899

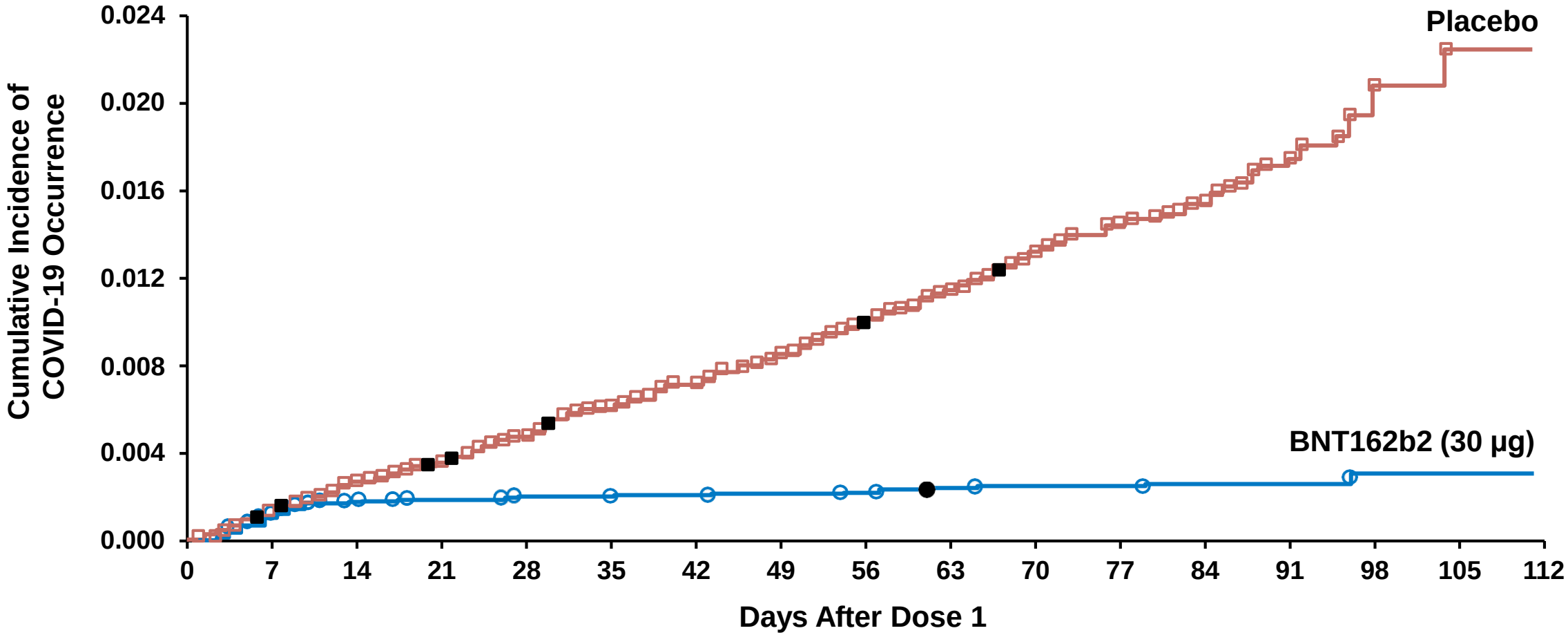
Systemic Events Each Day From Dose 2 (N=8,183) BNT162b2



Severe/Grade 3 Local Reactions Within 7 Days after each dose (N=8,183)

		BNT162b2 (30 µg) n (%)	Placebo N (%)
Dose 1	Pain at the injection site	28/4093 (0.7)	2/4090 (0.0)
	Redness	9/4093 (0.2)	6/4090 (0.1)
	Swelling	7/4093 (0.2)	3/4090 (0.1)
Dose 2	Pain at the injection site	33/3758 (0.9)	0/3749 (0.0)
	Redness	18/3758 (0.5)	1/3749 (0.0)
	Swelling	10/3758 (0.3)	1/3749 (0.0)

Cumulative Incidence of COVID-19 After Dose 1



Solid fill marker indicates subjects with severe COVID-19

First COVID-19 Occurrence From 7 Days After Dose 2

Phase 2/3 Efficacy – Final Analysis

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

Efficacy Endpoint	BNT162b2 (30 µg) N=18,198		Placebo N=18,325				
	n	Surveillance Time (n)	n	Surveillance Time (n)	VE (%)	(95% CI)	Pr (VE >30%)
First COVID-19 occurrence ≥7 days after Dose 2	8	2.214 (17,411)	162	2.222 (17,511)	95.0	(90.3, 97.6)	>0.9999

Total surveillance time: 1000 person-years for all subjects within each group at risk for the endpoint..
Pr=Posterior probability

First COVID-19 Occurrence From 7 Days After Dose 2

Phase 2/3 Efficacy – Final Analysis: Subgroups

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

		BNT162b2 N=18,198 n	Placebo N=18,325 n	VE (%)	(95% CI)
Overall		**8**	**162**	**95.0**	**(90.0, 97.9)**
Age	**18-64 years**	**7**	**143**	**95.1**	**(89.6, 98.1)**
	65-74 years	**1**	**14**	**92.9**	**(53.1, 99.8)**
	≥75 years	**0**	**5**	**100.0**	**(-13.1, 100.0)**
Sex	**Male**	**3**	**81**	**96.4**	**(88.9, 99.3)**
	Female	**5**	**81**	**93.7**	**(84.7, 98.0)**
Race	**White**	**7**	**146**	**95.2**	**(89.8, 98.1)**
	Black or African American	**0**	**7**	**100.0**	**(31.2, 100.0)**
	All Others	**1**	**9**	**89.3**	**(22.6, 99.8)**
Ethnicity	**Hispanic/Latino**	**3**	**53**	**94.4**	**(82.7, 98.9)**
	Non-Hispanic/Non-Latino	**5**	**109**	**95.4**	**(88.9, 98.5)**
Country	**Argentina**	**1**	**35**	**97.2**	**(83.3, 99.9)**
	Brazil	**1**	**8**	**87.7**	**(8.1, 99.7)**
	USA	**6**	**119**	**94.9**	**(88.6, 98.2)**

First COVID-19 Occurrence From 7 Days After Dose 2

Phase 2/3 Efficacy – Final Analysis: Risk Factor Subgroups

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

		BNT162b2 N=18,198 n	Placebo N=18,325 n	VE (%)	(95% CI)
Overall		**8**	**162**	**95.0**	**(90.0, 97.9)**
At risk[1]	**Yes**	**4**	**86**	**95.3**	**(87.7, 98.8)**
	No	**4**	**76**	**94.7**	**(85.9, 98.6)**
Age group at risk	**16-64 and not at risk**	**4**	**69**	**94.2**	**(84.4, 98.5)**
	16-64 and at risk	**3**	**74**	**95.9**	**(87.6, 99.2)**
	≥65 and not at risk	**0**	**7**	**100.0**	**(29.0, 100.0)**
	≥65 and at risk	**1**	**12**	**91.7**	**(44.2, 99.8)**
Obese[2]	**Yes**	**3**	**67**	**95.4**	**(86.0, 99.1)**
	No	**5**	**95**	**94.8**	**(87.4, 98.3)**
Age group and obese	**16-64 and not obese**	**4**	**83**	**95.2**	**(87.3, 98.7)**
	16-64 and obese	**3**	**60**	**94.9**	**(84.4, 99.0)**
	≥65 and not at obese	**1**	**12**	**91.8**	**(44.5, 99.8)**
	≥65 and obese	**0**	**7**	**100.0**	**(27.1, 100.0)**

[1] At least one of Charlson Comorbidity index or obesity
[2] Obesity: BMI ≥ 30 kg/m^2

First COVID-19 Occurrence From 7 Days After Dose 2

Phase 2/3 Efficacy – Final Analysis

Subjects WITH or WITHOUT Evidence of Infection Prior to 7 days after Dose 2

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) N=19,965		Placebo N=20,172				
Efficacy Endpoint	n	Surveillance Time (n)	n	Surveillance Time (n)	VE (%)	(95% CI)	Pr (VE >30%)
First COVID-19 occurrence ≥7 days after Dose 2	9	2.332 (18,559)	169	2.345 (18,708)	94.6	(89.9, 97.3)	>0.9999

Total surveillance time: 1000 person-years for all subjects within each group at risk for the endpoint..
Pr=Posterior probability

BNT162b2 Protects Against Severe Disease

Phase 2/3 Efficacy – Final Analysis (CDC definition)

Severe Disease Severe illness - CDC definition: hospitalization, admission to the ICU, intubation or mechanical ventilation, or death

	BNT162b2 (30 µg) N=18,198		Placebo N=18,325				
Efficacy Endpoint	**n**	**Surveillance Time (n)**	**n**	**Surveillance Time (n)**	**VE (%)**	**(95% CI)**	
First Severe COVID-19 occurrence >7 days after Dose 2	**0**	**2.215 (17,399)**	**5**	**2.229 (17,495)**	**100**	**(-9.9, 100)**	

	BNT162b2 (30 µg) N=21,669		Placebo N=21,686				
Efficacy Endpoint	**n**	**Surveillance Time (n)**	**n**	**Surveillance Time (n)**	**VE (%)**	**(95% CI)**	
First Severe COVID-19 occurrence after Dose 1	**1**	**4.018 (21,299)**	**14**	**4.001 (21,238)**	**92.9**	**(53.2, 99.8)**	

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Total surveillance time: 1000 person-years for all subjects within each group at risk for the endpoint..

First COVID-19 Occurrence After Dose 1

	BNT162b2 (30 µg) N=21,669 n	Placebo N=21,686 n	VE (%)	(95% CI)
COVID-19 occurrence after Dose 1	**50**	**275**	**82.0**	**(75.6, 86.9)**
After Dose 1 and before Dose 2	**39**	**82**	**52.4**	**(29.5, 68.4)**
Dose 2 to 7 days after Dose 2	**2**	**21**	**90.5**	**(61.0, 98.9)**
≥7 days after Dose 2	**9**	**172**	**94.8**	**(89.8, 97.6)**

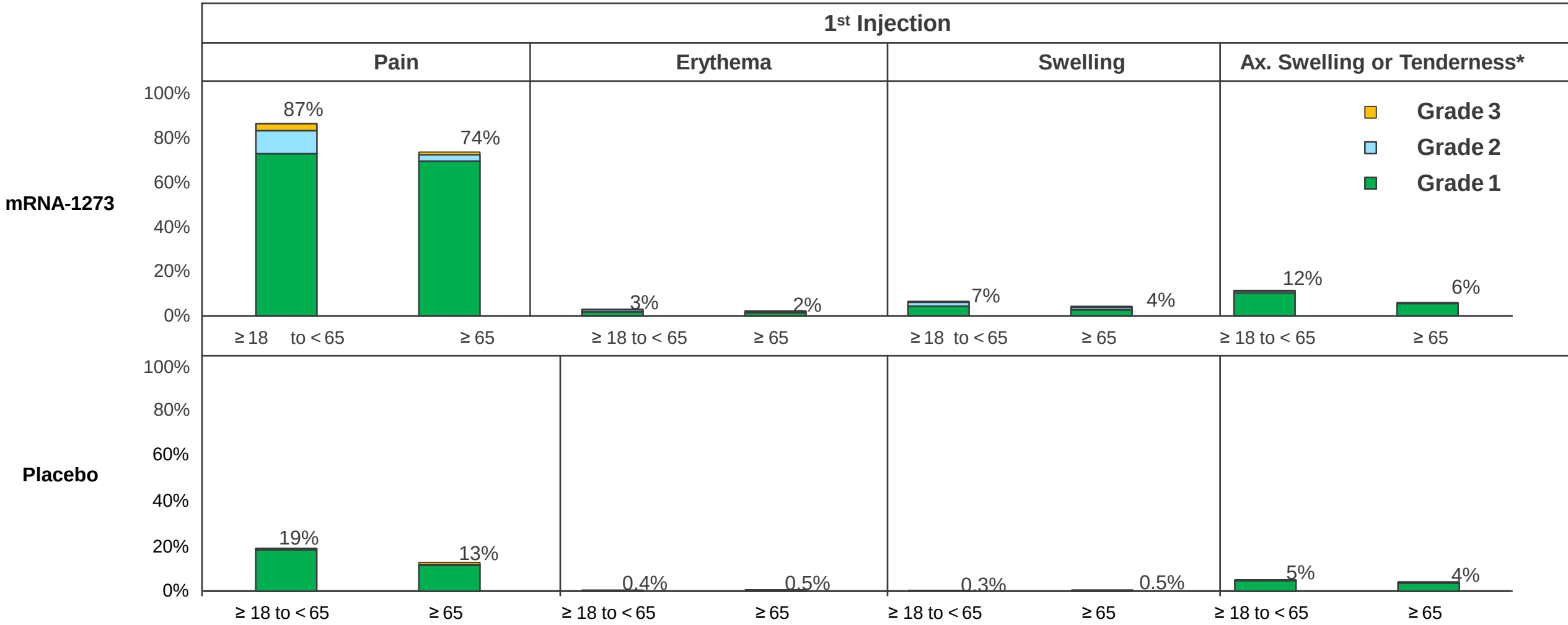
Moderna Vaccine

Race/Ethnicity Enrollment Distribution Compared With US Population
Full Analysis Set

	Study 301 (N=30,351)	US Population
Race	**%**	**%**
White	**79.2%**	**75.0%**
Black or African American	**10.2%**	**14.2%**
Asian	**4.6%**	**6.8%**
More than one race	**2.1%**	**3.4%**
American Indian or Alaska Native	**0.8%**	**1.7%**
Hawaiian or other Pacific Islander	**0.2%**	**0.4%**
Other	**2.1%**	**5.5%**
Not reported or unknown	**0.9%**	**0%**
Ethnicity		
Hispanic or Latino	**20.5%**	**18.4%**

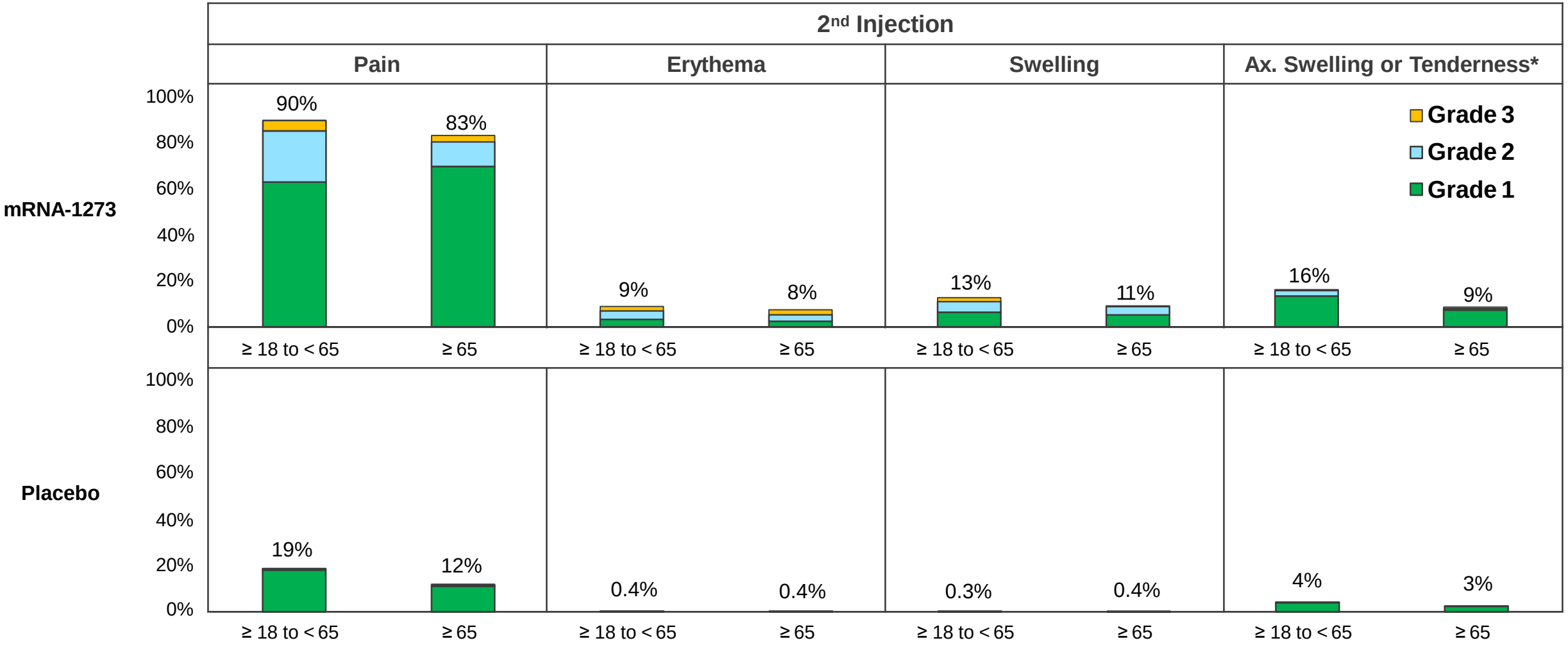
EDC, US Census Bureau: ACS Demographic Estimate

Solicited Local Adverse Reactions (Dose 1)
Safety Set, 9-Week Median Follow-up



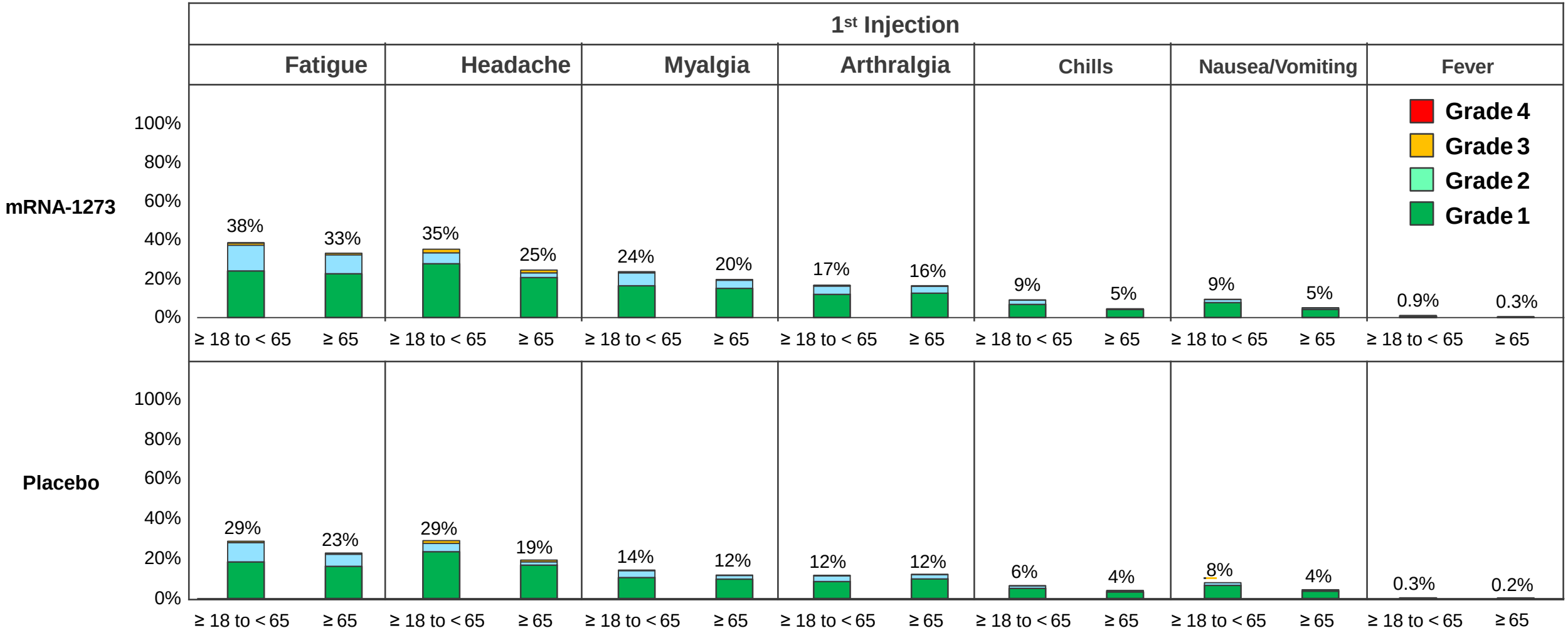
Includes reports within 7 days of injection. *Localized axillary swelling or tenderness ipsilateral to the vaccination arm.

Solicited Local Adverse Reactions (Dose 2)
Safety Set, 9-Week Median Follow-up



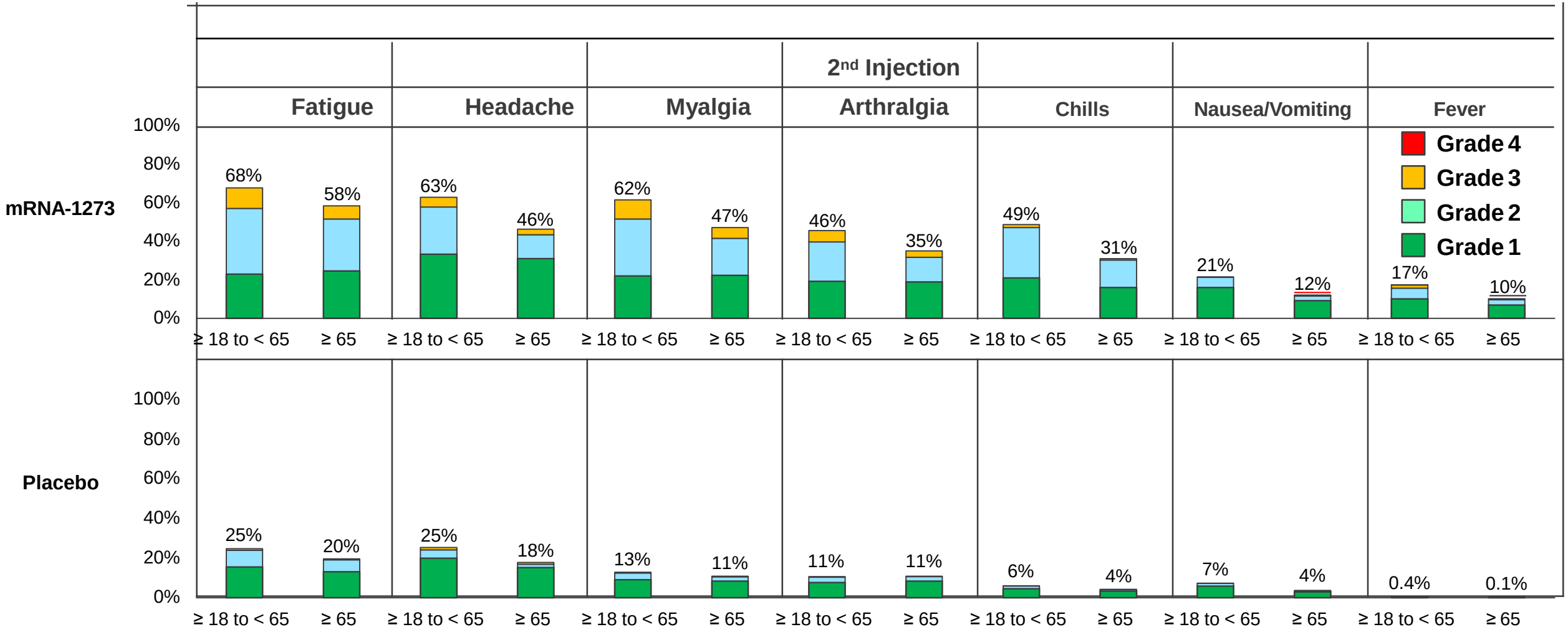
Includes reports within 7 days of injection. *Localized axillary swelling or tenderness ipsilateral to the vaccination arm.

Solicited Systemic Adverse Reactions (Dose 1)
Safety Set, 9-Week Median Follow-up



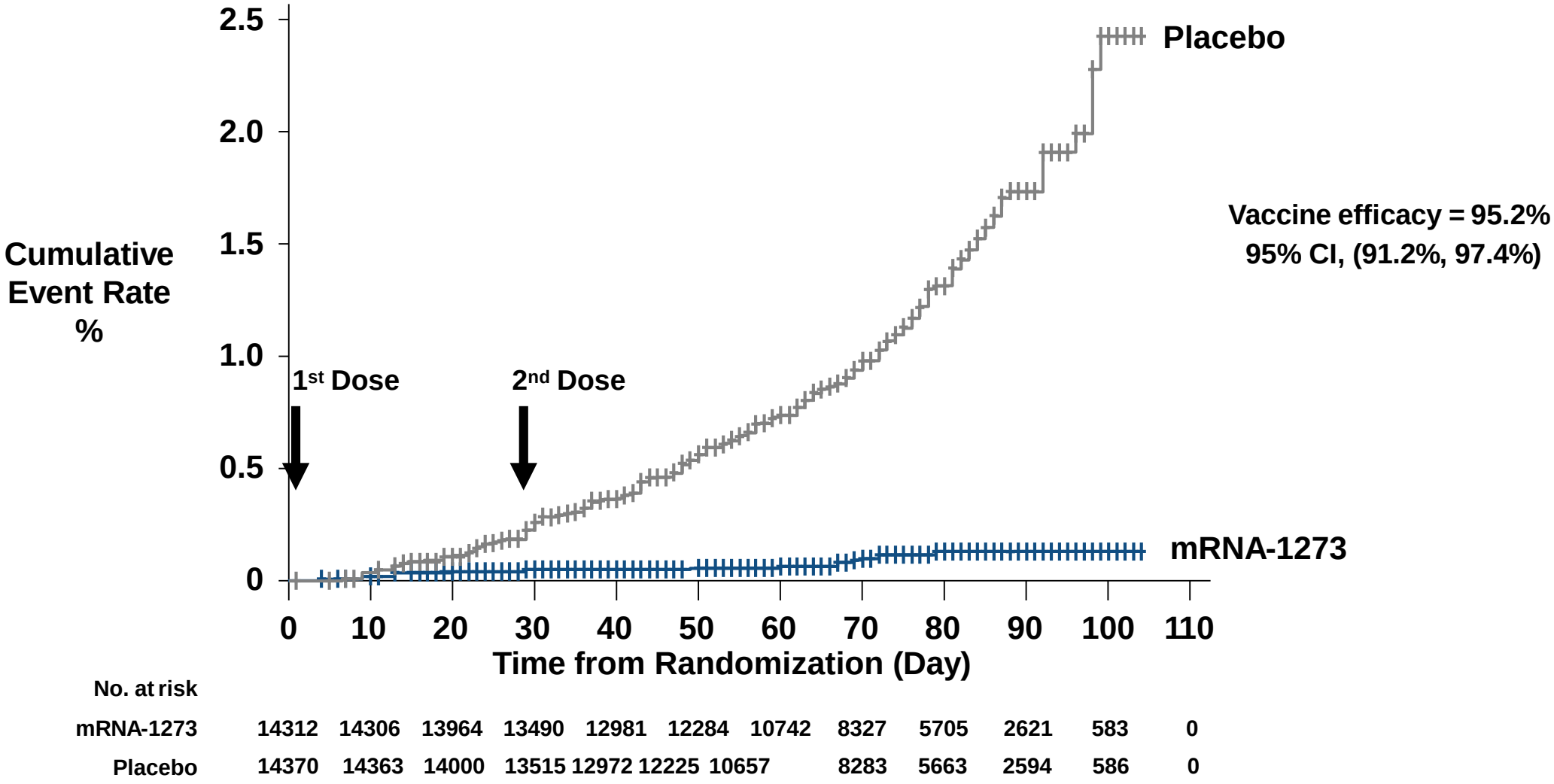
Solicited Systemic ARs include reports within 7 days of injection

Solicited Systemic Adverse Reactions (Dose 2)
Safety Set, 9-Week Median Follow-up



Solicited Systemic ARs include reports within 7 days of injection

Cumulative Incidence of COVID-19 After Dose 1



Primary Efficacy Analysis

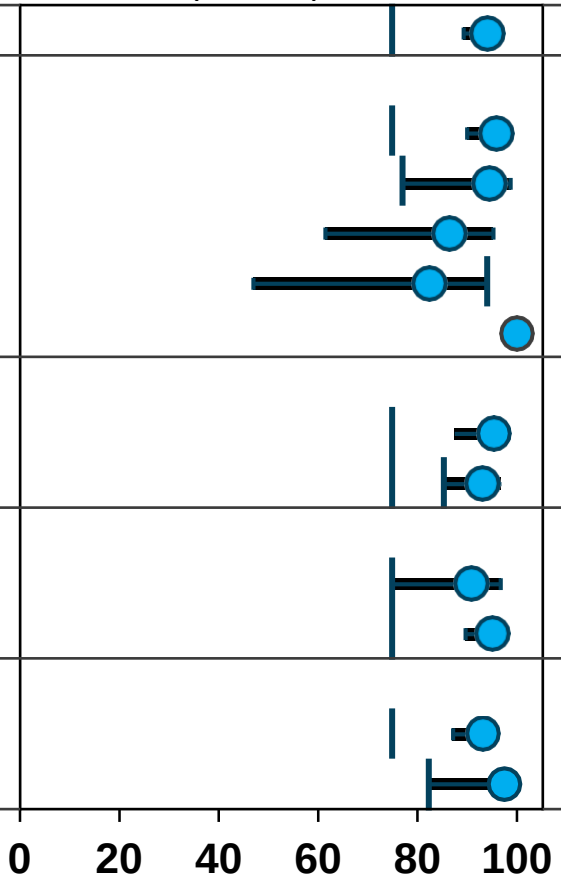
Per Protocol

	Primary Efficacy Analysis	
Confirmed, Symptomatic COVID-19 Cases	**mRNA-1273 N=14,134**	**Placebo N=14,073**
Number of cases, n (%)	**11 (< 0.1%)**	**185 (1.3%)**
Vaccine efficacy based on hazard ratio (95% CI)	**94.1% (89.3%, 96.8%)**	
p-value	**< 0.0001**	
Incidence rate per 1000 person-years	**3.3**	**56.5**

Subgroup Efficacy Analysis

Per Protocol

Subgroup	# Events / N mRNA-1273 N=14,134	# Events / N Placebo N=14,073	Vaccine Efficacy (95% CI)	Vaccine Efficacy (95% CI)
Overall	**11 / 14,134**	**185 / 14,073**		**94.1%** (89.3%, 96.8%)
Age and risk				
18 to < 65 without comorbidities	**5 / 8,396**	**121 / 8,403**		**95.9%** (90.0%, 98.3%)
18 to < 65 with comorbidities	**2 / 2,155**	**35 / 2,118**		**94.4%** (76.9%, 98.7%)
≥ 65 with or without comorbidities	**4 / 3,583**	**29 / 3,552**		**86.4%** (61.4%, 95.2%)
65 to < 70 with or without comorbidities	**4 / 2,953**	**22 / 2,864**		**82.4%** (46.9%, 93.9%)
≥ 70 with or without comorbidities	**0 / 630**	**7 / 688**		**100%** (NE, 100)
Sex				
Male	**4 / 7,366**	**87 / 7,462**		**95.4%** (87.4%, 98.3%)
Female	**7 / 6,768**	**98 / 6,611**		**93.1%** (85.2%, 96.8%)
Participants with comorbidities (all ages)				
Yes	**4 / 3,206**	**43 / 3,167**		**90.9%** (74.7%, 96.7%)
No	**7 / 10,928**	**142 / 10,906**		**95.1%** (89.6%, 97.7%)
Race and Ethnicity				
Non-Hispanic White	**10 / 9,023**	**144 / 8,916**		**93.2%** (87.1%, 96.4%)
Communities of Color	**1 / 5,088**	**41 / 5,132**		**97.5%** (82.2%, 99.7%)



NE: not estimable

Secondary Efficacy Endpoint: Severe COVID-19 Cases

Per Protocol

Confirmed, Severe COVID-19 Cases	Primary Efficacy Analysis mRNA-1273 N=14,134	 Placebo N=14,073
Number of cases, n (%)	**0 (0%)**	**30 (0.2%)**
Vaccine efficacy based on hazard ratio (95% CI)	**100%** (NE, 100%)	
Incidence rate per 1000 person-years	**0**	**9.1**

- **One participant death due to COVID-19 in the placebo group**
- **Given the high efficacy against severe disease, no evidence for vaccine-associated enhanced disease was observed**

One potential case of severe disease was reported in the mRNA-1273 group after data cut-off for the primary efficacy analysis, this case has yet to be adjudicated.

NE: not estimable

Asymptomatic SARS-CoV-2 Infections as Measured by Scheduled NP Swabs Prior to Dose 2

Per Protocol – Primary Efficacy Analysis

RT-PCR NP Swab Results	mRNA-1273 N=14,134 n	%	Placebo N=14,073 N	%	Relative Risk (95% CI)
No documented COVID-19 symptoms between 1st dose and 2nd dose	**14**	**0.1%**	**38**	**0.3%**	**0.37 (0.20, 0.68)**

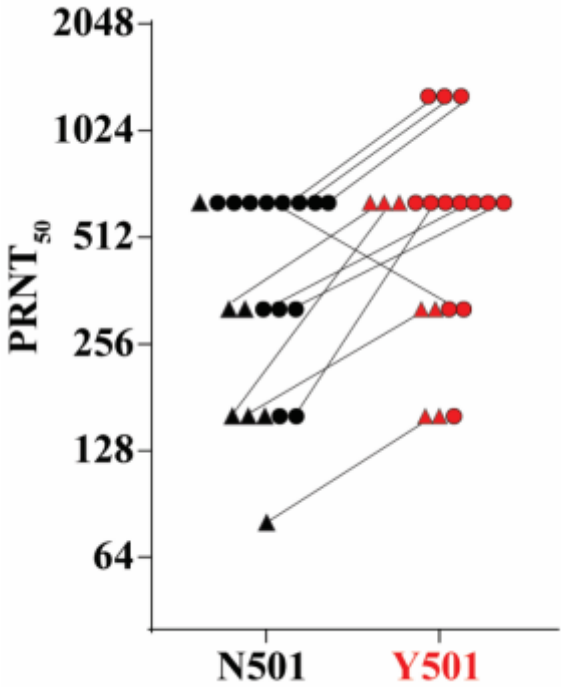
Summary Comparisons

	Pfizer (16-55 y, > 55 y)	**Moderna (18-64, > 64 y)**
Pain	78-83% , 66-71%	87-90% , 74-83%
Fatigue	47% , 34%	38-68% , 33-58%
Headache	42% , 25%	35-63% , 25-46%
Muscle Pain	21% , 14%	24-62% , 20-47%
Joint Pain	11% , 9%	17-46% , 16-35%
Chills	14% , 6%	9-49% , 5-31%
Fever	4% , 1%	1-17% , 0-10%
Efficacy > 7 days after Dose 2		
All infection	95%	94%
Severe disease	100%	100%
Efficacy after Dose 1		
All infection	82%	90%
Severe disease	93%	

Pediatric Vaccine Studies

- Pfizer enrollment of 12 through 17 year olds completed
- Moderna enrolling 12 through 17 year olds
- Both then are planning age de-escalation studies following this
- Both companies plan to do immunobridging
- Data from 12 through 17 year olds may be available in late Spring

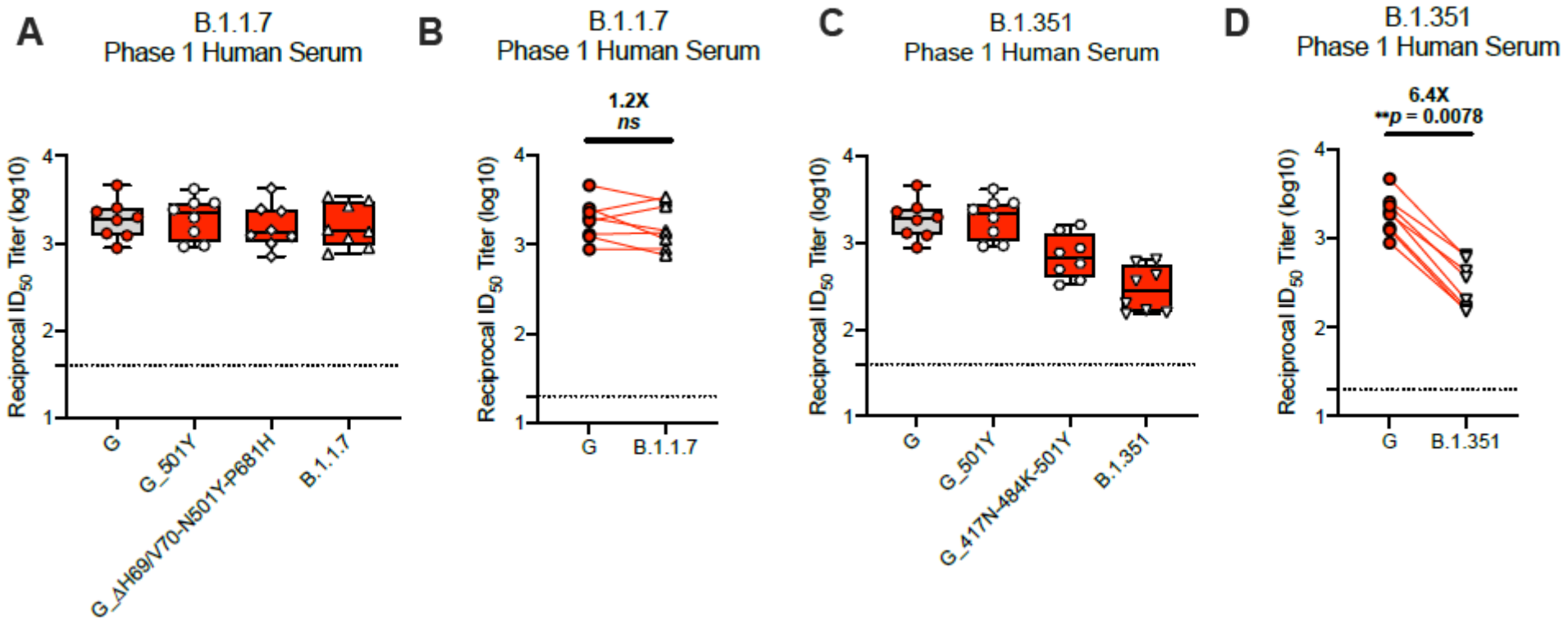
Pfizer Vaccine Efficacy Against Novel Variants



20 sera from BNT162b2 vaccine recipients against N501 and Y501 SARS-CoV-2
Seven sera (indicated by triangles) were drawn 2 weeks after the second dose of vaccine
13 sera (indicated by circles) were drawn 4 weeks after the second dose

bioRxiv preprint doi: https://doi.org/10.1101/2021.01.07.425740
Posted January 7, 2021

Moderna Vaccine Efficacy Against Novel Variants



Neutralization of B.1.1.7 and B.1.351 SARS-CoV-2 pseudoviruses by serum from mRNA-1273-immunized Phase 1 participants.

bioRxiv preprint doi: https://doi.org/10.1101/2021.01.25.427948
Posted January 25, 2021


17th St S

Who Would Have Predicted MIS-C?

Randy Q. Cron, MD, PhD

University of Alabama at Birmingham

February 6, 2021

Children's of Alabama

Practical Day of Pediatrics

Children's of Alabama

UAB MEDICINE

DEPARTMENT OF PEDIATRICS

Disclosures

Randy Q. Cron, M.D., Ph.D.

SOBI – investigator initiated clinical trial of anakinra to treat MAS

SOBI – advisory board for MAS therapy

SOBI – paid speaker/moderator for MEDSCAPE/WebMD

Novartis – consultant on switching therapy

Pfizer – clinical trial MAS adjudication committee chair

Sironax – consultant on RIP1 inhibitor

UAB MEDICINE
DEPARTMENT OF PEDIATRICS

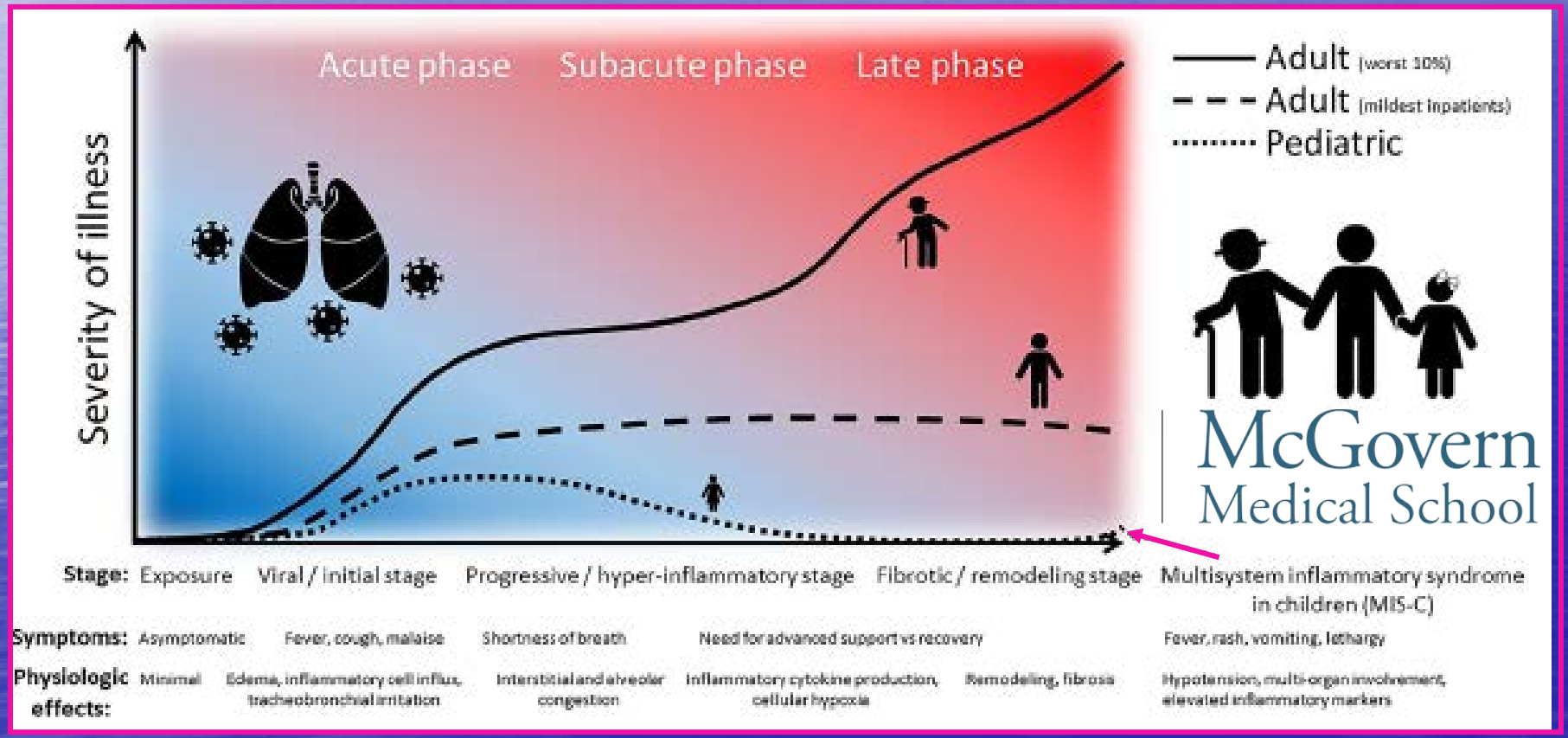
Children's of Alabama

Understanding the age divide in COVID-19: why are children overwhelmingly spared?

Am J Physiol Lung Cell Mol Physiol 319: L39–L44, 2020.

K. Lingappan,[1] H. Karmouty-Quintana,[2] J. Davies,[1] B. Akkanti,[3] and M. T. Harting[4]

Hartling



Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

Sistema Sanitario Regione Lombardia

MIS-C/PIMS-TS

D'Antiga

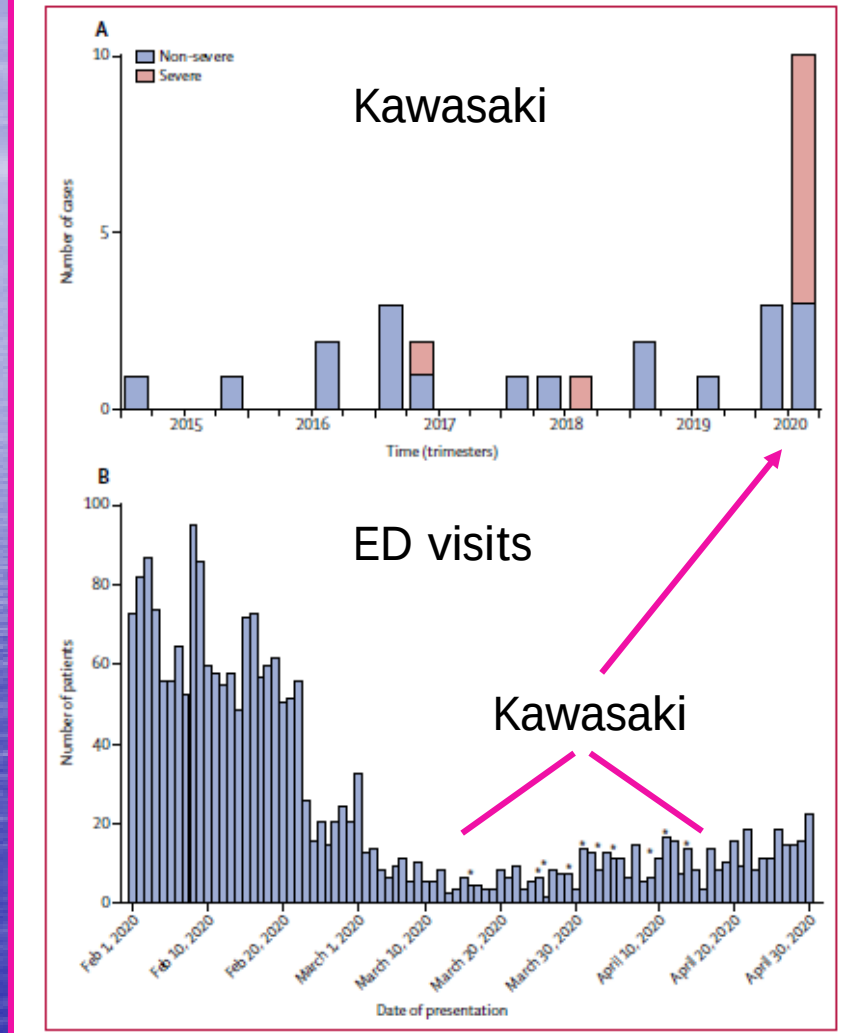


Figure: Incidence of Kawasaki disease in the study period and in the past 5 years
(A) Frequency of Kawasaki disease at the paediatric emergency department of Hospital Papa Giovanni XXIII of Bergamo, Italy, in the past 5 years, by case severity. (B) Number of patients presenting to the paediatric emergency department during the severe acute respiratory syndrome coronavirus 2 epidemic, and date of presentation of ten patients with Kawasaki-like disease (indicated by asterisks).

An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study

Lancet 2020 Jun 6;395(10239):1771-1778

Lucio Verdoni, Angelo Mazza, Annalisa Gervasoni, Laura Martelli, Maurizio Ruggeri, Matteo Ciuffreda, Ezio Bonanomi, Lorenzo D'Antiga

Research in context

Evidence before this study
Kawasaki disease is an acute self-limiting vasculitis with specific predilection for the coronary arteries that affects previously healthy young infants and children. Despite half a century having passed since Kawasaki disease was first reported in Japan, the cause of this condition remains unknown. We did a PubMed database search to identify studies investigating the cause and pathogenesis of Kawasaki disease using the terms "Kawasaki disease", "etiology", "pathogenesis", "intravenous immunoglobulin", "corticosteroids", "macrophage activation syndrome (MAS)", and "KD shock syndrome". All relevant articles were evaluated. The most accepted pathogenetic hypothesis supports an aberrant response of the immune system to one or more unidentified pathogens in genetically predisposed subjects. An infectious trigger, however, has not been identified.

Added value of this study
Shortly after the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to our region (Bergamo, Italy), we found a 30-fold increased incidence of Kawasaki disease. Children diagnosed after the SARS-CoV-2 epidemic began showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, and features of MAS. We therefore showed that SARS-CoV-2 might cause a severe form of Kawasaki-like disease.

Implications of all the available evidence
Outbreaks of Kawasaki-like disease might occur in countries affected by the SARS-CoV-2 pandemic, and might present outside the classic Kawasaki disease phenotype. This condition might be serious and requires prompt and more aggressive management. Future research on the cause of Kawasaki disease and similar syndromes should focus on immune responses to viral triggers.

Italy

Burns

JAMA | Original Investigation

JAMA 2020;324:259-269

Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

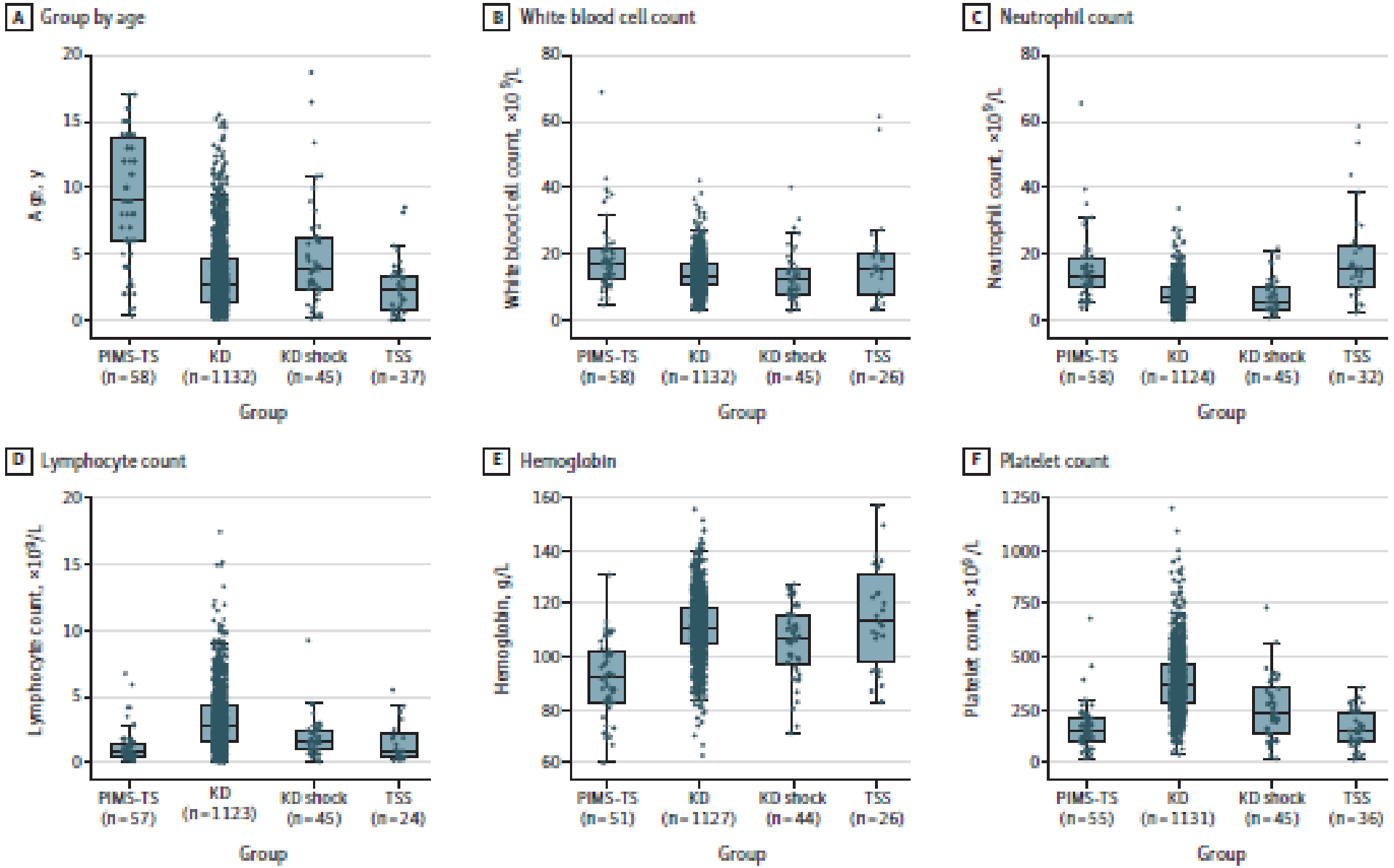
Elizabeth Whittaker, MD; Alasdair Bamford, MD; Julia Kenny, MD; Myrsini Kaforou, PhD; Christine E. Jones, MD; Priyen Shah, MD; Padmanabhan Ramnarayan, MD; Alain Fraisse, MD; Owen Miller, MD; Patrick Davies, MD; Filip Kucera, MD; Joe Brierley, MD; Marilyn McDougall, MD; Michael Carter, MD; Adriana Tremoulet, MD; Chisato Shimizu, MD; Jethro Herberg, MD; Jane C. Burns, MD; Hermione Lyall, MD; Michael Levin, MD; for the PIMS-TS Study Group and EUCLIDS and PERFORM Consortia

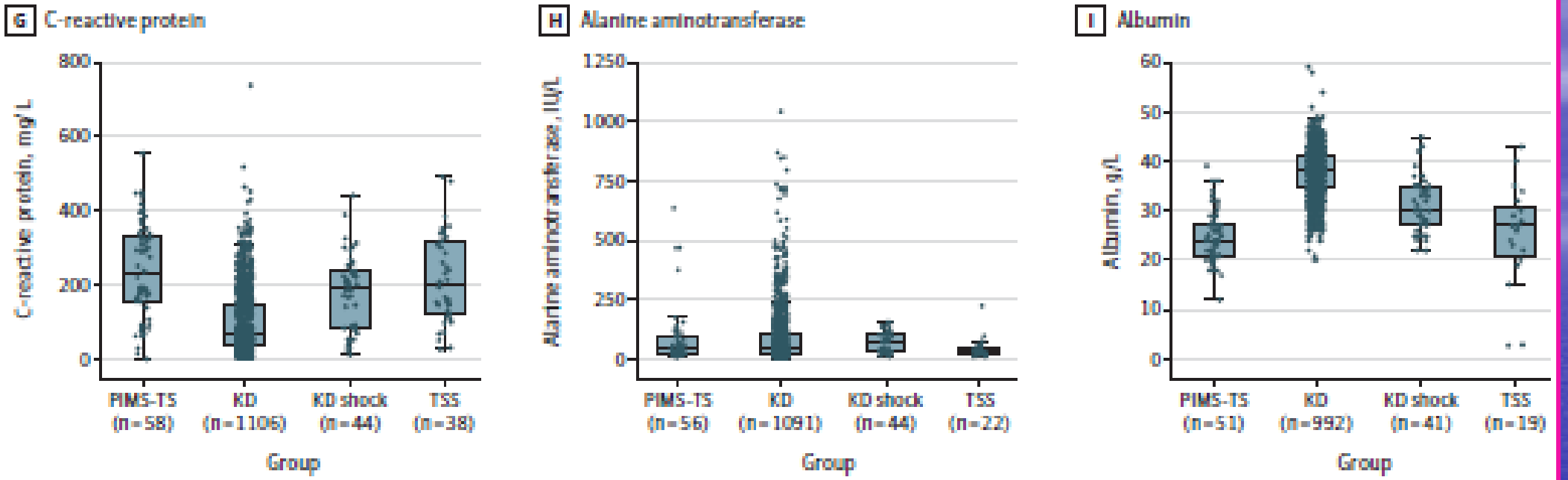
Levin

Table 1. Case Definitions for Emerging Inflammatory Condition During COVID-19 Pandemic From the World Health Organization, Royal College of Paediatrics and Child Health, and Centers for Disease Control and Prevention

World Health Organization[8]	Royal College of Paediatrics and Child Health (United Kingdom)[7]	Centers for Disease Control and Prevention (United States)[9]
Children and adolescents 0-19 y of age with fever >3 d AND 2 of the following: 1. Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP) 4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers) 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome	A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features (see listed in eAppendix in Supplement 2). This may include children fulfilling full or partial criteria for Kawasaki disease[a] Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice) SARS-CoV-2 PCR test results may be positive or negative	An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 wk prior to the onset of symptoms Additional comments Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

Figure. Comparison of Age and Laboratory Results In 4 Different Patient Groups




G C-reactive protein
C-reactive protein, mg/L
800
600
400
200
0
PIMS-TS (n=58)
KD (n=1106)
KD shock (n=44)
TSS (n=38)
Group
H Alanine aminotransferase
Alanine aminotransferase, IU/L
1250
1000
750
500
250
0
PIMS-TS (n=56)
KD (n=1091)
KD shock (n=44)
TSS (n=22)
Group
I Albumin
Albumin, g/L
60
50
40
30
20
10
0
PIMS-TS (n=51)
KD (n=992)
KD shock (n=41)
TSS (n=19)
Group
J Ferritin
Ferritin, µ/L
6000
5000
4000
3000
2000
1000
0
PIMS-TS (n=52)
KD (n=22)
KD shock (n=5)
Group
K Troponin
Troponin, ng/mL
1000
750
500
250
0
PIMS-TS (n=50)
KD (n=13)
KD shock (n=13)
Group
L D-dimer
D-dimer, ng/mL
30000
20000
10000
0
PIMS-TS (n=53)
KD (n=61)
KD shock (n=13)
Group

The NEW ENGLAND JOURNAL of MEDICINE

Boston

Dufort

Multisystem Inflammatory Syndrome in Children in New York State

N Engl J Med. 2020;383:347-358

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*

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

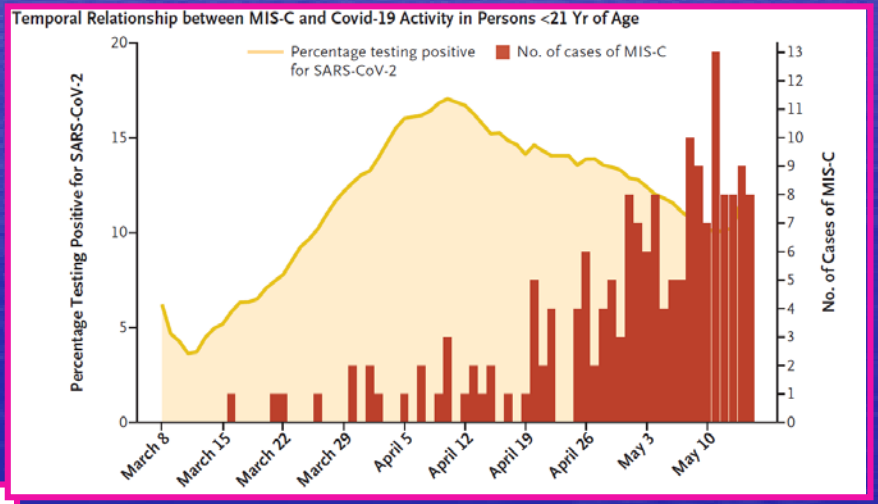
L.R. Feldstein, E.B. Rose, S.M. Horwitz, J.P. Collins, M.M. Newhams, M.B.F. Son, J.W. Newburger, L.C. Kleinman, S.M. Heidemann, A.A. Martin, A.R. Singh, S. Li, K.M. Tarquinio, P. Jaggi, M.E. Oster, S.P. Zackai, J. Gillen, A.J. Ratner, R.F. Walsh, J.C. Fitzgerald, M.A. Keenaghan, H. Alharash, S. Doymaz, K.N. Clouser, J.S. Giuliano, Jr., A. Gupta, R.M. Parker, A.B. Maddux, V. Havalad, S. Ramsingh, H. Bukulmez, T.T. Bradford, L.S. Smith, M.W. Tenforde, C.L. Carroll, B.J. Riggs, S.J. Gertz, A. Daube, A. Lansell, A. Coronado Munoz, C.V. Hobbs, K.L. Marohn, N.B. Halasa, M.M. Patel, and A.G. Randolph, for the Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team*

Randolph

Symptom Category	0–5 Years (N=31)	6–12 Years (N=42)	13–20 Years (N=26)
Dermatologic or mucocutaneous	87.1	78.6	61.5
Gastrointestinal	74.2	83.3	80.8
KD or atypical KD	48.4	42.9	11.5
Myocarditis	38.7	50.0	73.1
Neurologic	12.9	38.1	38.5

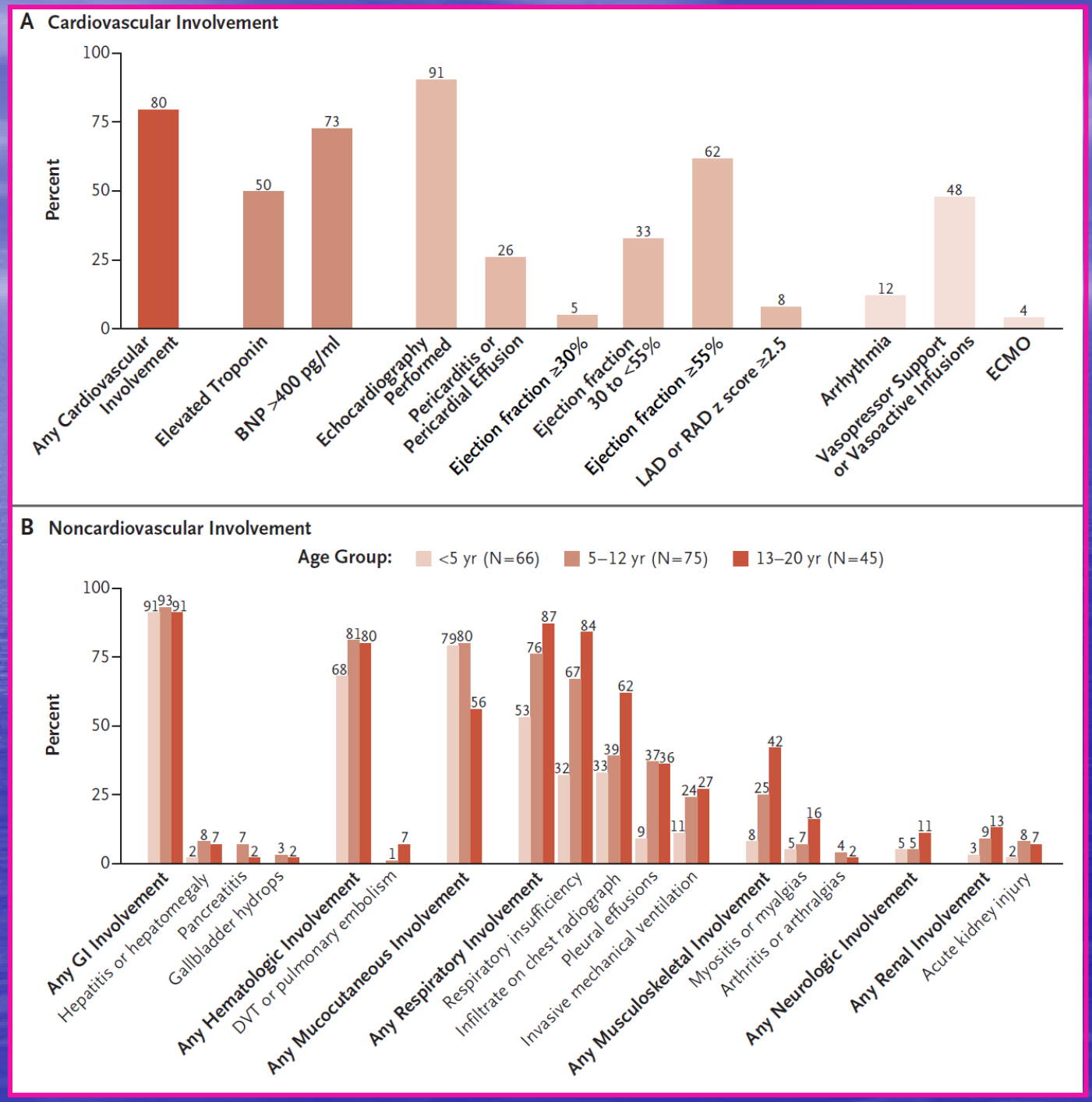
Percent of Patients

0 to 38.4 | 38.5 to 46.2 | 46.3 to 66.1 | 66.2 to 79.0 | 79.1 to 100



Variable	Overall (N=99)	0–5 Years (N=31)	6–12 Years (N=42)	13–20 Years (N=26)
Diagnoses — no. (%)‡				
Kawasaki's disease or atypical Kawasaki's disease	36 (36)	15 (48)	18 (43)	3 (12)
Myocarditis	52 (53)	12 (39)	21 (50)	19 (73)
Shock	10 (10)	4 (13)	5 (12)	1 (4)
Coronary-artery aneurysm	9 (9)	4 (13)	4 (10)	1 (4)
Acute kidney injury	10 (10)	3 (10)	4 (10)	3 (12)
Death — no. (%)	2 (2)	1 (3)	1 (2)	0

N Engl J Med. 2020;383:334-346


A Cardiovascular Involvement
Percent
100
75
50
25
0
80
50
73
91
26
5
33
62
8
12
48
4
Any Cardiovascular Involvement
Elevated Troponin
BNP >400 pg/ml
Echocardiography Performed
Pericarditis or Pericardial Effusion
Ejection fraction ≥30%
Ejection fraction 30 to <55%
Ejection fraction ≥55%
LAD or RAD z score ≥2.5
Arrhythmia
Vasopressor Support or Vasoactive Infusions
ECMO
B Noncardiovascular Involvement
Age Group: <5 yr (N=66) 5–12 yr (N=75) 13–20 yr (N=45)
Percent
100
75
50
25
0
Any GI Involvement
Hepatitis or hepatomegaly
Pancreatitis
Gallbladder hydrops
Any Hematologic Involvement
DVT or pulmonary embolism
Any Mucocutaneous Involvement
Any Respiratory Involvement
Respiratory insufficiency
Infiltrate on chest radiograph
Pleural effusions
Invasive mechanical ventilation
Any Musculoskeletal Involvement
Myositis or myalgias
Arthritis or arthralgias
Any Neurologic Involvement
Any Renal Involvement
Acute kidney injury

Esper

BRIEF REPORT

J Infect Dis 2005;191:499-502

Association between a Novel Human Coronavirus and Kawasaki Disease

Frank Esper,[1] Eugene D. Shapiro,[1,2,3] Carla Weibel,[1] David Ferguson,[4] Marie L. Landry,[4] and Jeffrey S. Kahn[1,3]

[1]Department of Pediatrics, Division of Infectious Diseases, [2]Department of Pediatrics, Division of General Pediatrics, and Departments of [3]Epidemiology and Public Health and [4]Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut

the mouth or pharynx, strawberry tongue, or stomatitis; (3) polymorphous rash; (4) erythema or edema of the hands or feet; and (5) nonsuppurative cervical lymphadenopathy—or meet at least 3 of these criteria and have evidence of coronary artery abnormalities [2]. Incomplete or atypical Kawasaki disease, in which these criteria are not met, can occur and can also result in aneurysms of the coronary arteries [3]. The etiology of Kawasaki disease is unknown. Laboratory findings are nonspecific, and there are no diagnostic tests for Kawasaki disease.

Table 1. Clinical and laboratory features of children with Kawasaki disease.

Case subject[a] (sex)	Age (month/year of diagnosis), months	Interval,[b] days	Bilateral conjunctivitis	Erythema of the mouth or pharynx	Polymorphous rash	Erythema or edema of the hands or feet	Lymphadenopathy[c]	No. of criteria[d]	Echocardiographic result[e]	HCoV-NH by PCR
1 (M)[f]	6 (2/02)	4	+	+	+	+	−	4	CA-D	+
2 (M)	8 (1/04)	6	+	−	+	−	+	3	CA-D	+
3 (M)	12 (4/03)	5	+	+	+	+	−	4	Normal	+
4 (M)	15 (1/04)	4	+	+	+	−	−	3	CA-D	+
5 (F)	21 (3/04)	5	+	+	+	−	+	4	Normal	+
6 (F)	27 (2/04)	10	+	+	+	+	−	4	Normal	+
7 (M)	60 (4/04)	5	+	+	+	−	+	4	Normal[g]	+
8 (M)	67 (3/04)	9	+	+	+	−	−	3	CA-abnl	+
9 (M)	2 (11/02)	5	−	+	+	−	+	3	CA-abnl	−
10 (M)	15 (1/03)	13	+	−	+	+	−	3	Normal	−
11 (M)	34 (12/02)	7	+	+	+	−	+	4	Normal	−

Note. −, negative; +, positive; CAabnl, abnormal echogenicity of the coronary arteries without evidence of dilation; CAD, abnormal echogenicity of the coronary arteries with evidence of dilation; F, female; HCoV-NH, New Haven coronavirus; M, male; PCR, polymerase chain reaction.

[a] All case subjects had fever for >5 days.
[b] Between onset of fever and the date the specimen was collected.
[c] Cervical lymph node enlargement with at least 1 node >1.5 cm.
[d] No. of diagnostic criteria met (in addition to fever).
[e] Echocardiograms were obtained at the time of diagnosis of Kawasaki disease.
[f] First case identified.
[g] Subsequent echocardiogram revealed dilation of the origin of the left coronary artery

KD is not a disease, but a syndrome

Ravelli

Editorial

Kawasaki disease or Kawasaki syndrome?

Angelo Ravelli [1,2,3] Alberto Martini [4]

In the first months of COVID-19 pandemic, paediatricians were not much involved in the management of the illness. Reports from China had shown that relatively few children and adolescents were affected, and that most of those who were infected had experienced milder disease compared with adults.[1 2] The same trend was initially seen after the spread of COVID-19 to Western countries.[3 4]

However, between April and May 2020, a rise in the number of children and adolescents with an acute multisystem hyperinflammatory state fulfilling full or partial criteria for Kawasaki disease (KD),[5] although frequently accompanied by unusual or less common symptoms, such as abdominal pain, diarrhoea and myocardial failure, was noticed in European and North American countries or regions mostly hit by the COVID-19 pandemic.[6–9] A number of these children needed urgent intensive care treatment due to the development of toxic shock syndrome, leading to multiorgan failure and circulatory shock, usually of myocardial origin, and some of them had signs of macrophage activation syndrome (MAS). Markers of inflammation were elevated, with neutrophilia, prominently increased C-reactive protein, interleukin (IL)-6, D-dimer and ferritin levels, and hypoalbuminaemia. Lymphopenia and relative thrombocytopenia were often present. Management was based on the administration of anti-inflammatory treatment, which included intravenous immunoglobulin (IVIG) and glucocorticoids. In some instances, IL-1, IL-6 or tumour necrosis factor inhibitors were given. Some, but not all, of these patients tested positive on swabs or serology for SARS-CoV-2 or were exposed to potential contact with a household member affected with COVID-19.

Alerts have been issued by national health authorities and paediatric scientific societies to raise awareness of this emerging syndrome in the medical community.[10–14] This condition, which has been named 'Paediatric inflammatory multisystem syndrome temporarily associated to SARS-CoV-2 infection' (PIMS-TS) in the UK, 'Multisystem inflammatory syndrome in children' in the USA and 'Multisystem inflammatory syndrome in children and adolescents with COVID-19' by the WHO, has encountered an increasing interest within the media. National and international collaborative efforts are currently ongoing, with the aim to characterise its features and risk factors, to understand causality and to examine treatment interventions, clinical presentations, severity, outcomes and epidemiology.

The suspicion of a possible association between COVID-19 and KD was first put forward by Jones *et al*,[15] who reported in Hospital Pediatrics on 7 April 2020 that a girl aged 6 months diagnosed and treated for classic KD tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR). One month later, Riphagen *et al*[6] described the features of eight children with the aforementioned hyperinflammatory syndrome, which presented with clinical manifestations similar to atypical KD, together with prominent gastrointestinal symptoms, and progressed towards multiorgan involvement and severe shock, requiring admission to the Intensive Care Unit (ICU) and haemodynamic support. All children were given IVIG and four of them received methylprednisolone. One patient developed a giant coronary aneurysm. Despite family exposure to COVID-19 in four children, all tested negative for SARS-CoV-2 on bronchoalveolar lavage or nasopharyngeal aspirates. Six out of eight children were of Afro-Caribbean descent and one of them died.

Shortly afterwards, the characteristics of 10 children diagnosed with a KD-like disease (five with classic KD and five with incomplete features) seen in Bergamo, Italy were detailed by Verdoni *et al*.[7] These patients were aged 2.9 to 16 years (mean 7.5) and eight of them tested positive for SARS-CoV-2 either by nasal swab or serology. Five exhibited evidence of MAS and five of KD shock syndrome. Ten were administered IVIG and eight methylprednisolone. All 10 patients recovered without sequelae, although coronary aneurysms >4 mm were detected in two patients. The monthly incidence of these KD-like cases was at least 30 times greater than that observed for KD in the same region across the previous 5 years. As compared with 19 children with KD diagnosed before the start of COVID-19 epidemic, these patients were older and had higher rates of cardiac involvement, and features of MAS.

After these earlier experiences, several other case series with similar characteristics seen in various countries have been published.[8 9 16–18] The larger sample was reported by Whittaker *et al*,[17] who described the features of 58 children (median age 9 years, 69% of black or Asian race) meeting the criteria for PIMS-TS admitted in eight UK hospitals between 23 March and 16 May 2020. In total, 78% of the patients had evidence of prior or current SARS-CoV-2 infection. Three clinical patterns were identified by examining the clinical course: (1) 23 children had persistent fever and elevated acute phase reactants, but no signs of organ failure or features suggestive of KD or toxic shock syndrome; (2) 29 children developed shock, often associated with clinical, echocardiographic and laboratory evidence of myocardial injury; (3) seven children fulfilled the American Heart Association (AHA) diagnostic criteria for KD[5]; one of them progressed to shock. When coronary artery aneurysms were considered, a total of 13 children met the criteria for KD. Treatment included IVIG in 71% of the patients, glucocorticoids in 64% and inotropic support in 47%. Eight patients received infliximab and three anakinra; 22% of the patients recovered with supportive care alone. Comparison of patients with PIMS-TS to pre-COVID-19 patients with KD and KD shock syndrome revealed differences in clinical and laboratory features, namely older age, greater elevation of inflammatory parameters and lower lymphocyte counts and haemoglobin.

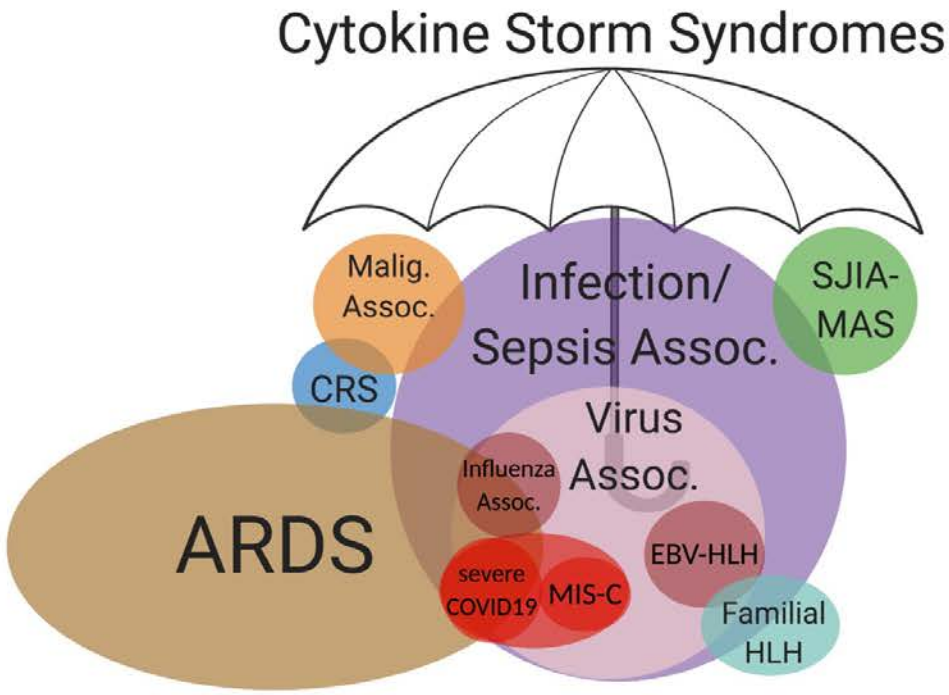
In this issue of the journal, Pouletty *et al*[19] describe the features of a further cluster of 16 patients seen in the Paris area between March and April 2020. Ten (71%) patients met the AHA criteria for complete KD,[5] 13 (81%) had gastrointestinal symptoms,

[1]Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[2]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOGMI), Università degli Studi di Genova, Genoa, Italy
[3]Sechenov First Moscow State Medical University, Moscow, Russian Federation
[4]Professor Emeritus, Università degli Studi di Genova, Genoa, Italy

Correspondence to Dr Angelo Ravelli, Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, Via G. Gaslini 5, Genova 16147, Italy; angeloravelli@gaslini.org

Martini

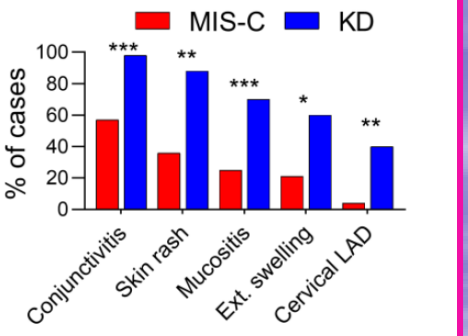
Ann Rheum Dis. 2020 Aug;79(8):993-995

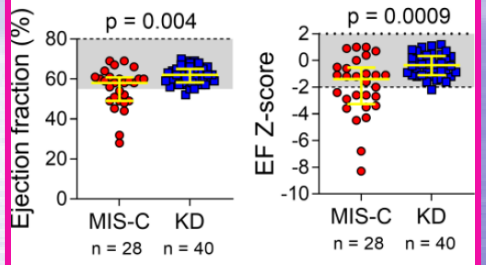


Canna

Henderson, L.A., Canna, S.C., Schulert, G.S., Volpi, S., Lee, P.Y., Kernan, K.F., Hazen, M.M., Halyabar, O., Hoyt, K.J., Han, J., Grom, A.A., Gattorno, M., Ravelli, A., de Benedetti, F., Behrens, E.M., Cron, R.Q., and Nigrovic, P.A. 2020. On the alert for cytokine storm: immunopathology in COVID-19. *Arthrritis Rheumatol*. 72:1059-1063

Figure generated by Dr. Scott Canna, Univ. Pittsburgh





JCI The Journal of Clinical Investigation

Distinct clinical and immunological features of SARS-COV-2-induced multisystem inflammatory syndrome in children

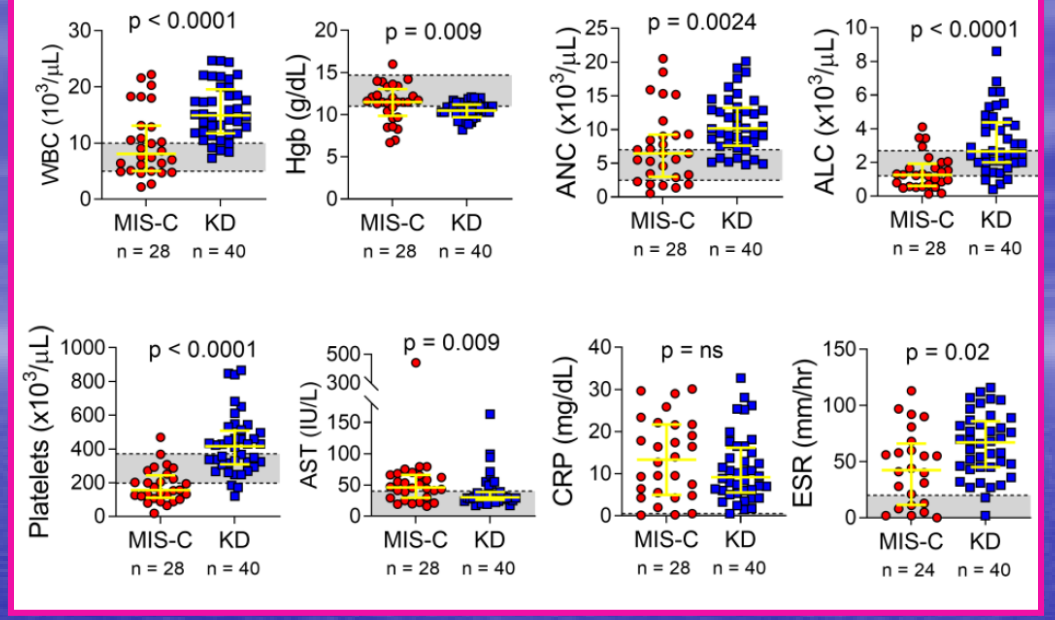
Pui Y. Lee, … , Jane W. Newburger, Mary Beth F. Son

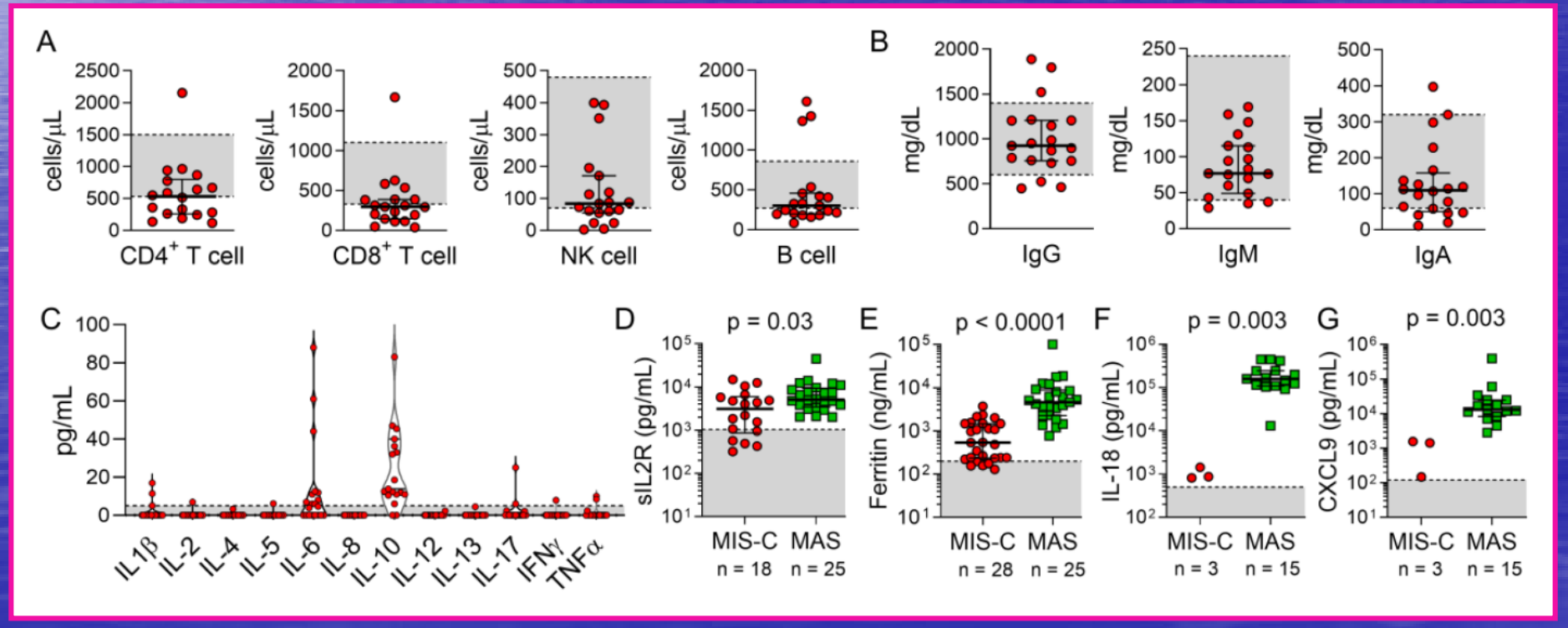
Boston Children's

J Clin Invest. 2020. https://doi.org/10.1172/JCI141113.

130:5942-5950

Lee





Penn Medicine

JCI The Journal of Clinical Investigation

Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2

Children's Hospital of Philadelphia

Caroline Diorio, … , David T. Teachey, Hamid Bassiri

J Clin Invest. 2020. https://doi.org/10.1172/JCI140970. 130:5967-5975

Bassiri

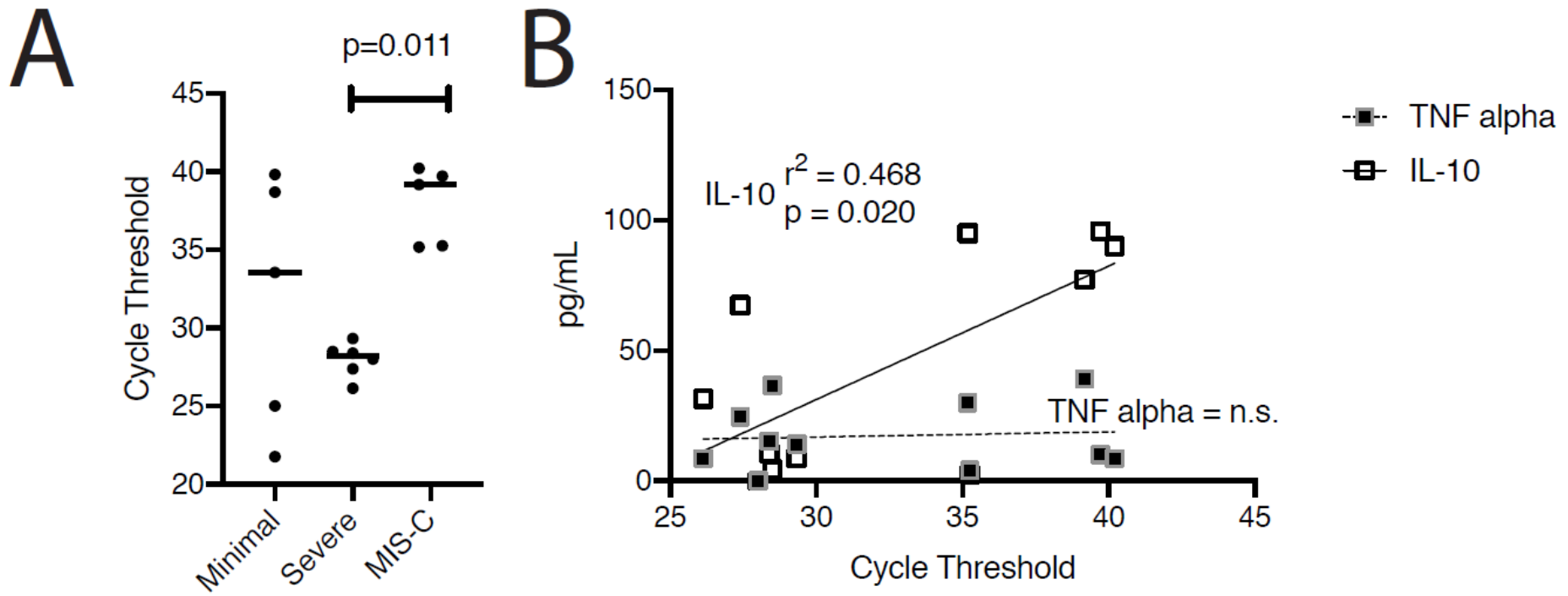
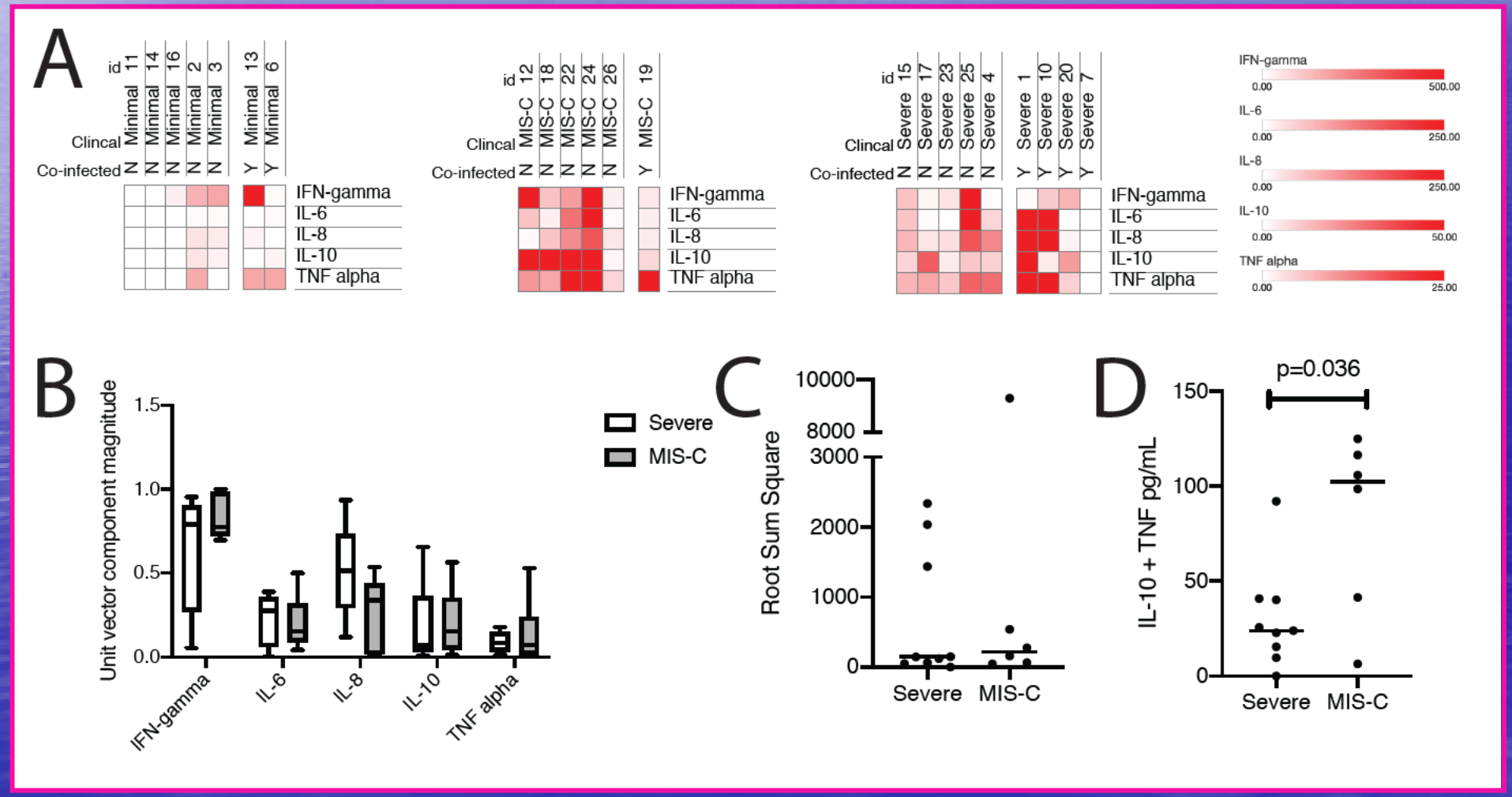


Figure 1. Cytokine architecture associated with SARS-CoV-2 infections in children. A) Heat map of the 5 most differentially present cytokines in the plasma of pediatric SARS-CoV-2 infections. Comparison of patients with and without co-infections for each of the three clinical phenotypes of pediatric SARS-CoV-2 infection (N=20). Patient IDs are listed above each column for reference. B) Cytokine profiles for each patient (N=15) were treated as a 5-dimensional vector and converted into unit vectors by dividing each component by the root sum square of the vector. Box and whisker plot of each unit vector with median values of each for MIS-C versus severe COVID-19 presentations (line). Whiskers represent maximum and minimum and boxes the 25th to 75th percentile. Differences between phenotypes or



Treating the MIS-C Cytokine Storm Syndrome

Children's of Alabama

UAB MEDICINE

DEPARTMENT OF PEDIATRICS

JAMA | Original Investigation

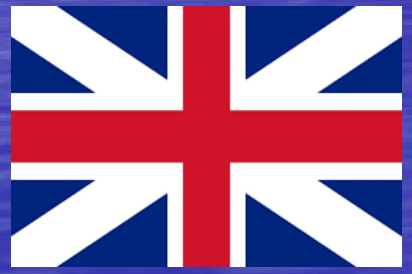
JAMA 2020;324:259-269

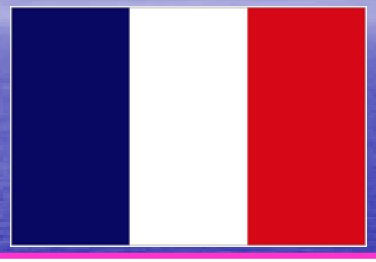
Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

Elizabeth Whittaker, MD; Alasdair Bamford, MD; Julia Kenny, MD; Myrsini Kaforou, PhD; Christine E. Jones, MD; Priyen Shah, MD; Padmanabhan Ramnarayan, MD; Alain Fraisse, MD; Owen Miller, MD; Patrick Davies, MD; Filip Kucera, MD; Joe Brierley, MD; Marilyn McDougall, MD; Michael Carter, MD; Adriana Tremoulet, MD; Chisato Shimizu, MD; Jethro Herberg, MD; Jane C. Burns, MD; Hermione Lyall, MD; Michael Levin, MD; for the PIMS-TS Study Group and EUCLIDS and PERFORM Consortia

Characteristic	All PIMS-TS cases (n = 58)[b]
Pharmacotherapy	
Intravenous immunoglobulin	41 (71)
Corticosteroids	37 (64)
Anakinra (IL-1 receptor antagonist)	3 (5)
Infliximab (TNF-α antagonist)	8 (14)

Whittaker





Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort *Ann Rheum Dis* 79:999-1006

Marie Pouletty,[1,2] Charlotte Borocco,[3,4] Naim Ouldali,[1,5] Marion Caseris,[1,6] Romain Basmaci,[7,8] Noémie Lachaume,[7,8] Philippe Bensaid,[9] Samia Pichard,[9] Hanane Kouider,[10] Guillaume Morelle,[11] Irina Craiu,[12] Corinne Pondarre,[13] Anna Deho,[14] Arielle Maroni,[14] Mehdi Oualha,[15] Zahir Amoura,[16,17] Julien Haroche,[16,17] Juliette Chommeloux,[18] Fanny Bajolle,[19] Constance Beyler,[20] Stéphane Bonacorsi,[6,8] Guislaine Carcelain,[21] Isabelle Koné-Paut,[3,4] Brigitte Bader-Meunier,[22,23] Albert Faye,[1,2,5] Ulrich Meinzer,[1,2,24,25] Caroline Galeotti,[3] Isabelle Melki[1,22,26]

Table 1 Clinical and biological features of the Kawa-COVID-19 cohort

Clinical and biological results	Kawa-COVID-19 cohort
Treatment:	
Intravenous immunoglobulin	15 (93%)
Single infusion	10 (67%)
Second infusion	5 (33%)
Steroids	4 (25%)
Anti-IL-1 treatment	1 (6%)
Anti-IL-6 treatment	1 (6%)
Hydroxychloroquine	1 (6%)

JCI The Journal of Clinical Investigation

Distinct clinical and immunological features of SARS-COV-2-induced multisystem inflammatory syndrome in children

Pui Y. Lee, … , Jane W. Newburger, Mary Beth F. Son

J Clin Invest. 2020. https://doi.org/10.1172/JCI141113.

Boston Children's

130:5942-5950

Son

	Total (n = 28)	ICU (n = 17)	Non-ICU (n = 11)
Duration of hospitalization (days, median)	8.0	9.5	4.0
Discharge from hospital (%)	100%	-	-
Death	0%	-	-
Immunomodulatory therapy [A], n (%)			
None	6 (21%)	3 (18%)	3 (27%)
IVIG only	4 (14%)	0 (0%)	4 (36%)
Methylprednisolone only	1 (4%)	1 (6%)	0 (0%)
Anakinra only	1 (4%)	0 (0%)	1 (9%)
IVIG + Methylprednisolone	12 (43%)	9 (53%)	3 (27%)
IVIG + Methylprednisolone + Anakinra	4 (14%)	4 (24%)	0 (0%)
Anti-microbial therapy, n (%)			
Remdesivir	7 (25%)	6 (35%)	1 (9%)
Antibiotics	15 (54%)	12 (71%)	3 (27%)
Anticoagulation therapy [B], n (%)			
None	4 (14%)	2 (12%)	2 (18%)
Aspirin	19 (68%)	13 (76%)	6 (55%)
Enoxaparin	18 (64%)	13 (76%)	5 (45%)

Carter

nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-1054-6

2020;26:1701-1707

Check for updates

Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection

Michael J. Carter[1,2,7], Matthew Fish[3,4,5,7], Aislinn Jennings[3,4,7], Katie J. Doores[4], Paul Wellman[2], Jeffrey Seow[4], Sam Acors[4], Carl Graham[4], Emma Timms[5], Julia Kenny[1,2], Stuart Neil[4], Michael H. Malim[4], Shane M. Tibby[2]✉ and Manu Shankar-Hari[3,4,6]✉

[1]Department of Women and Children's Health, King's College London, London, UK. [2]Paediatric Intensive Care Unit, Evelina London Children's Hospital, London, UK. [3]Department of Intensive Care Medicine, Guy's and St Thomas' NHS Foundation Trust, London, UK. [4]Department of Infectious Diseases, School of Immunology and Microbial Sciences, King's College London, London, UK. [5]Peter Gorer Department of Immunobiology, School of Immunology and Microbial Sciences, King's College London, London, UK. [6]Present address: School of Immunology and Microbial Sciences, King's College London,

Table 1 | Characteristics of the study cohort

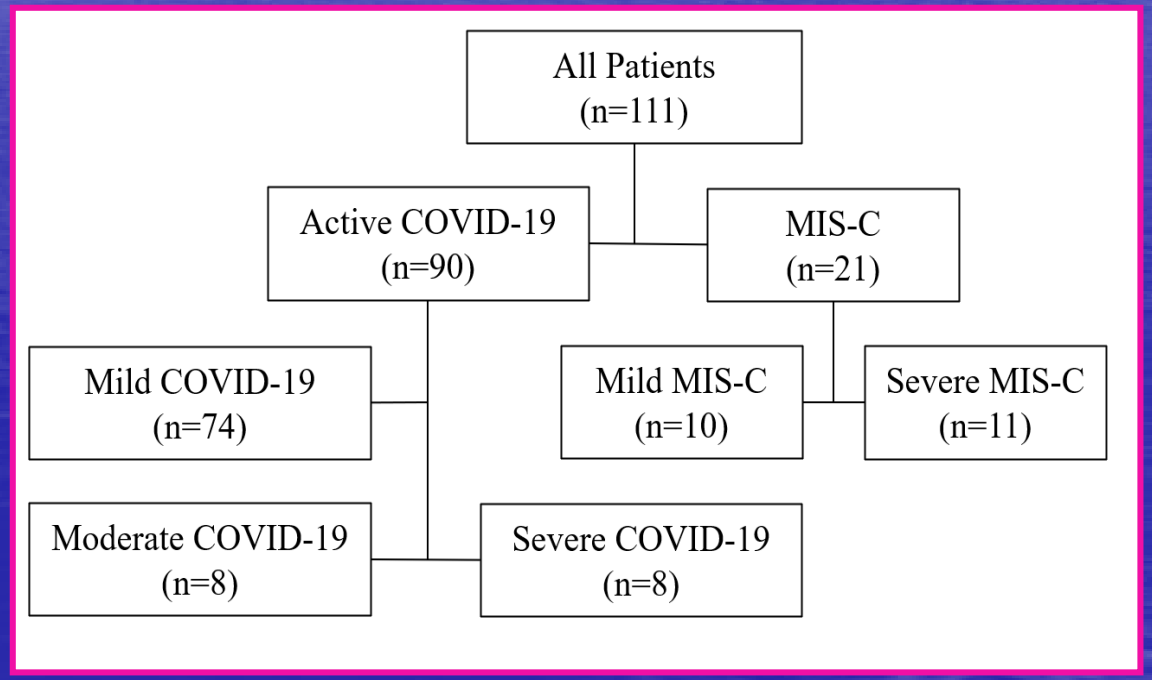
Characteristics	All patients ($n = 25$)	SARS-CoV-2 serology	
		Negative ($n = 8$)	Positive ($n = 17$)
Treatments during admission			
Mechanical ventilation (n (%))	2 (8%)	1 (13%)	1 (6%)
Vasoactive infusion (n (%))	12 (48%)	2 (25%)	10 (59%)
High-dose corticosteroids (n (%))	20 (80%)	4 (50%)	16 (94%)
Intravenous immunoglobulin (n (%))	23 (92%)	7 (88%)	16 (94%)
Biologic immunomodulation (n (%))[e]	14 (56%)	1 (13%)	13 (76%)

1-anakinra
4-infliximab
10-tocilizumab

Patients

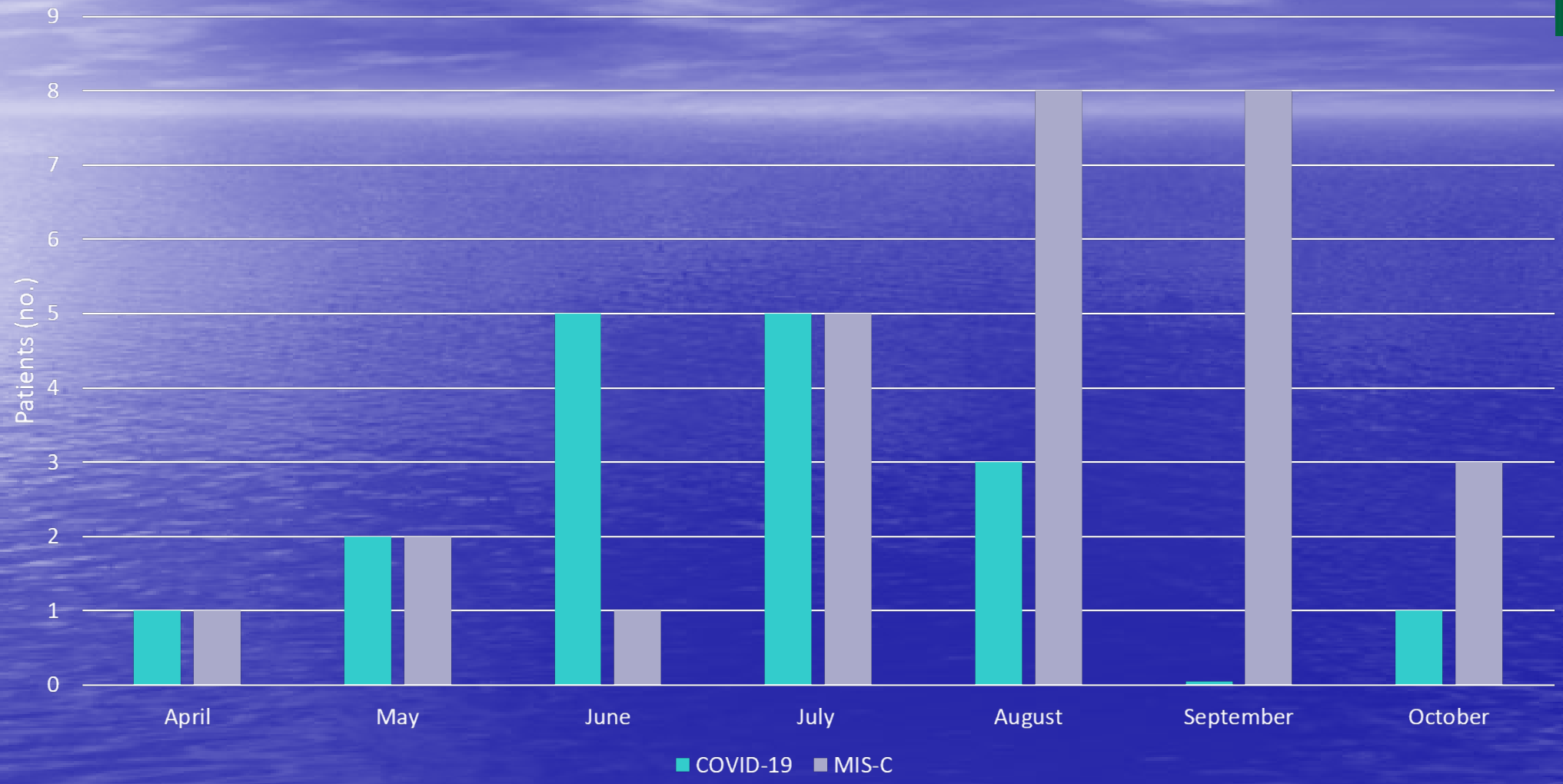
- 10 mild MIS-C patients
  - Low respiratory support
  - Nasal cannula or high-flow nasal cannula to max 2 L/min
- 11 severe MIS-C patients
  - Positive pressure ventilation and/or vasopressor support

Reiff



Reiff D, Mannion ML, Samuy N, Scalici P, Cron RQ. Distinguishing active pediatric COVID-19 from MIS-C. *Pediatr. Rheumatol. Online J., in press*.

Patients admitted to Children's of Alabama

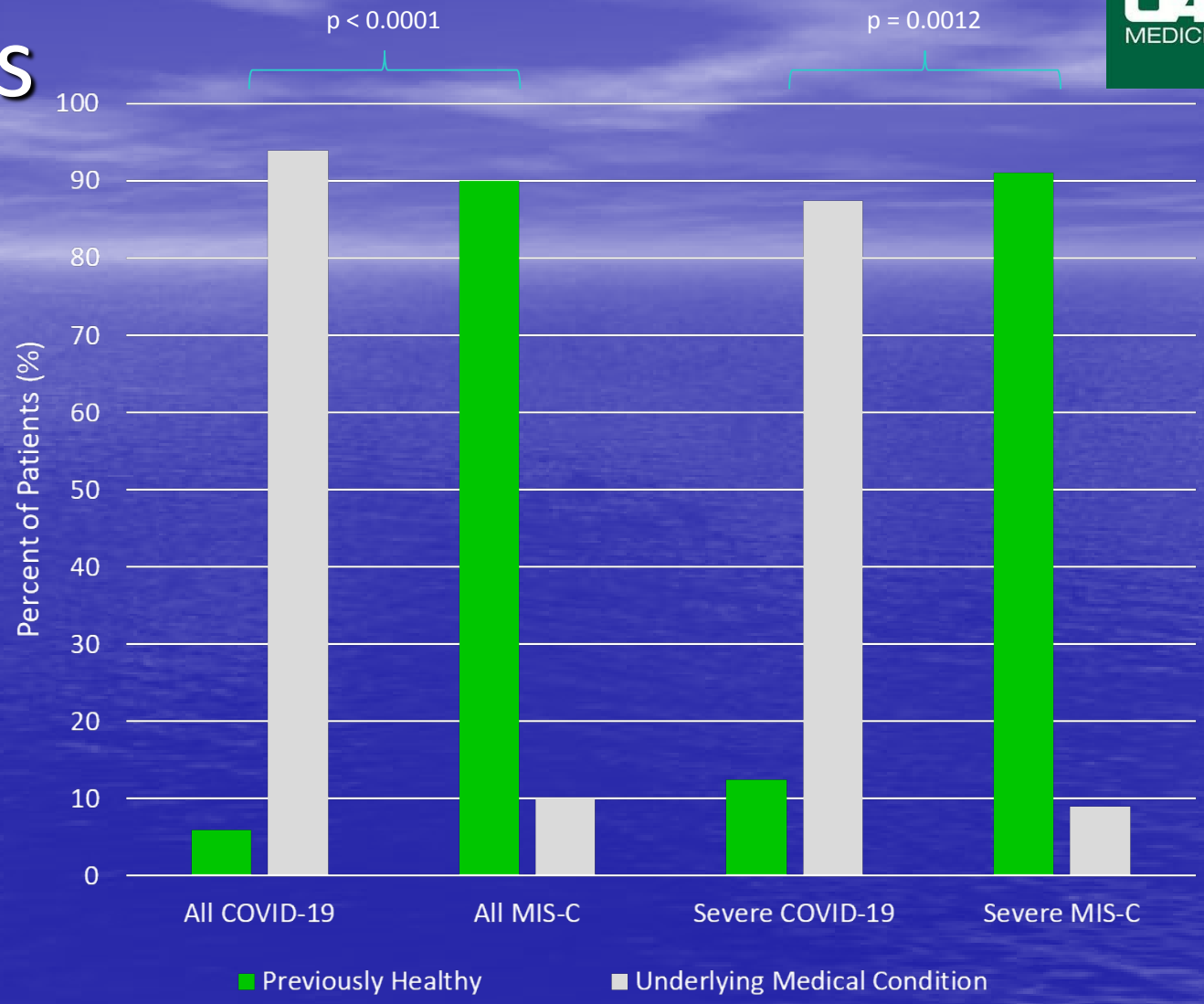


Serologies

- Symptomatic COVID-19
  - All 17 patients (100%) SARS-CoV-2 PCR positive on admission
- MIS-C
  - 9/28 patients (32%) SARS-CoV-2 PCR positive on admission
  - 22/24 patients (92%) SARS-CoV-2 IgG antibody positive on admission

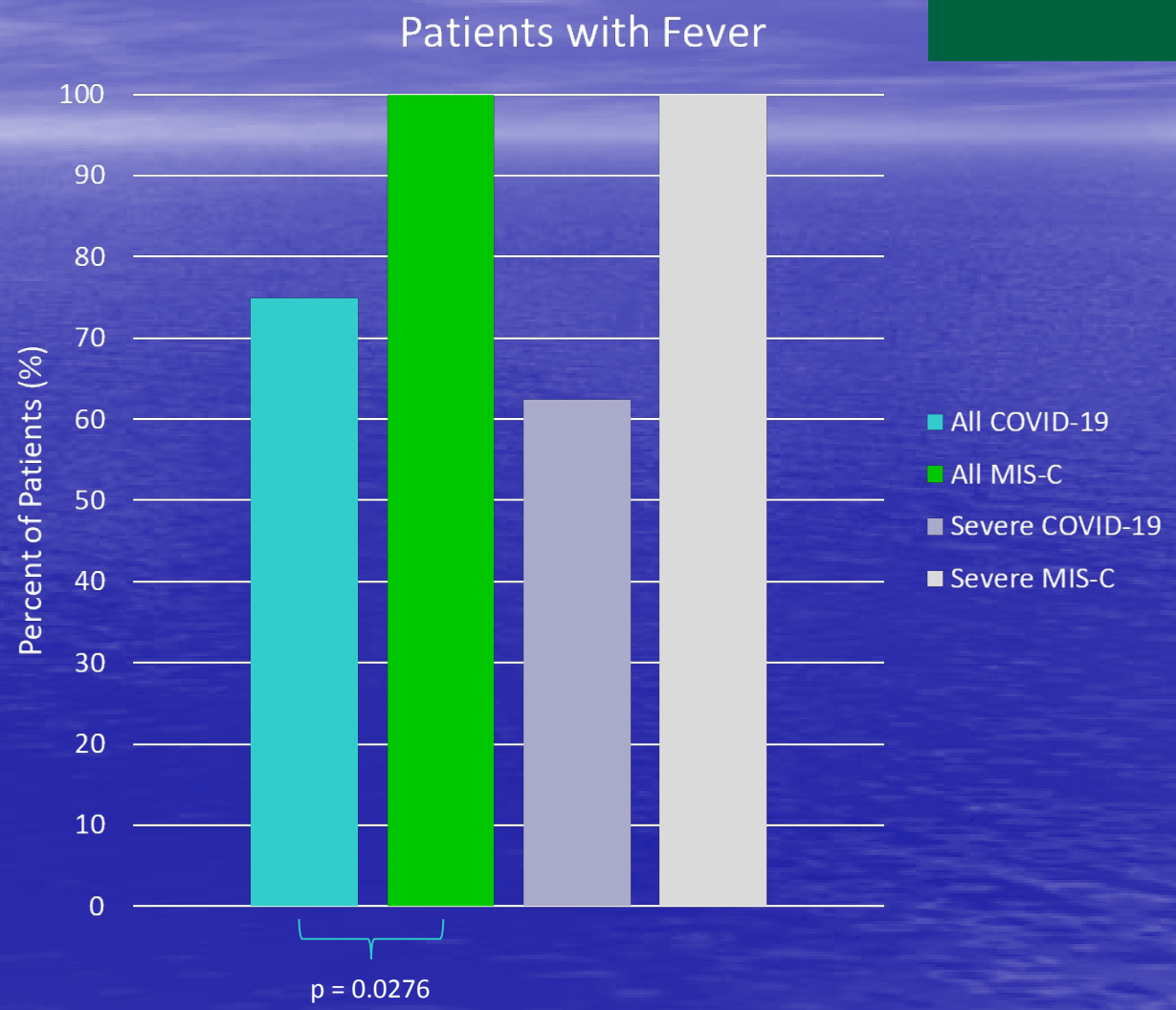
Underlying Conditions

- COVID-19 patients
  - Obesity, asthma, chronic lung disease, cancer, autoimmune disease, diabetes, CHD, neurodevelopmental disorder
- MIS-C patients
  - Asthma



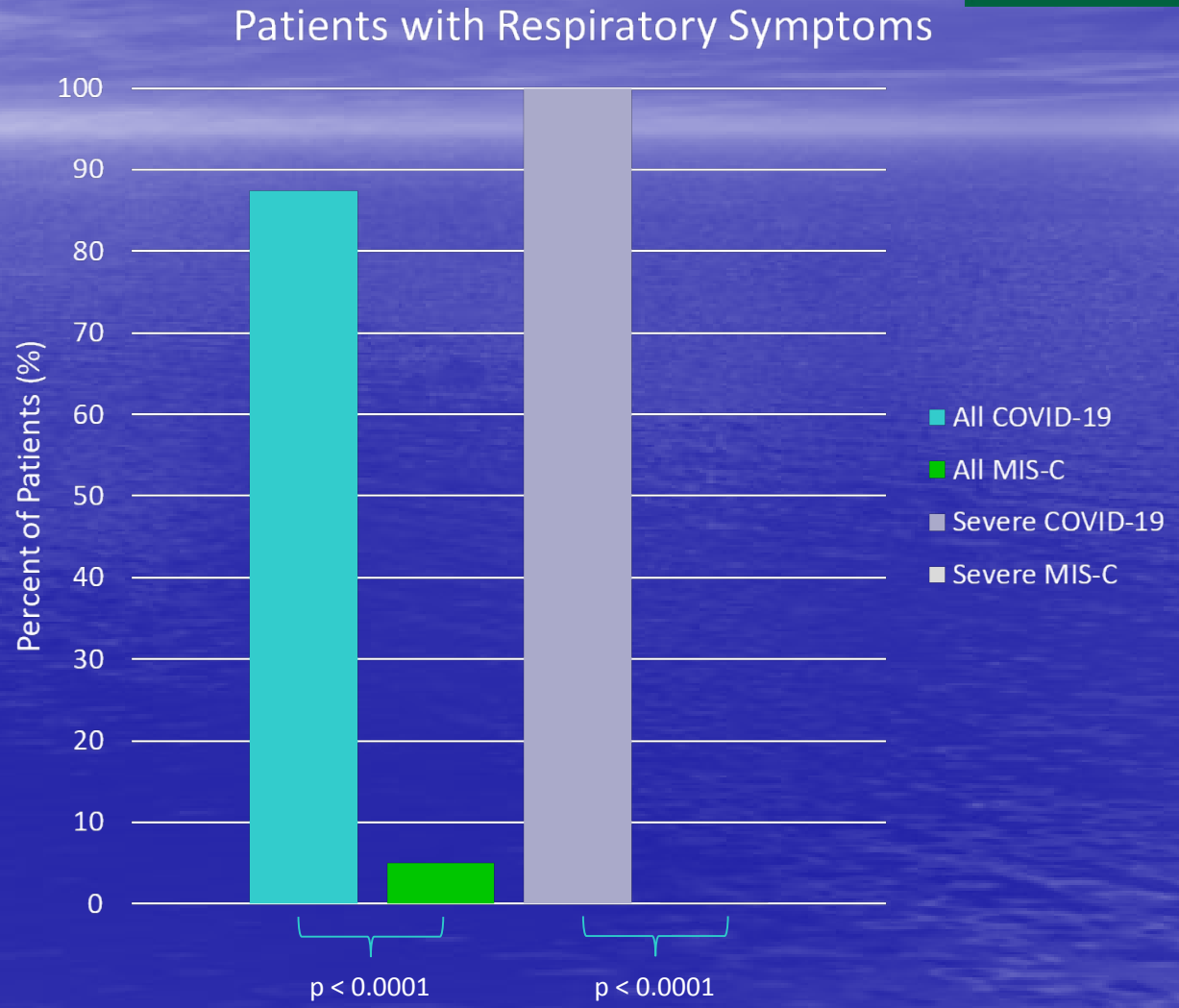
Presenting Symptoms

- Fever – more common in MIS-C patients, but no difference between severe categories



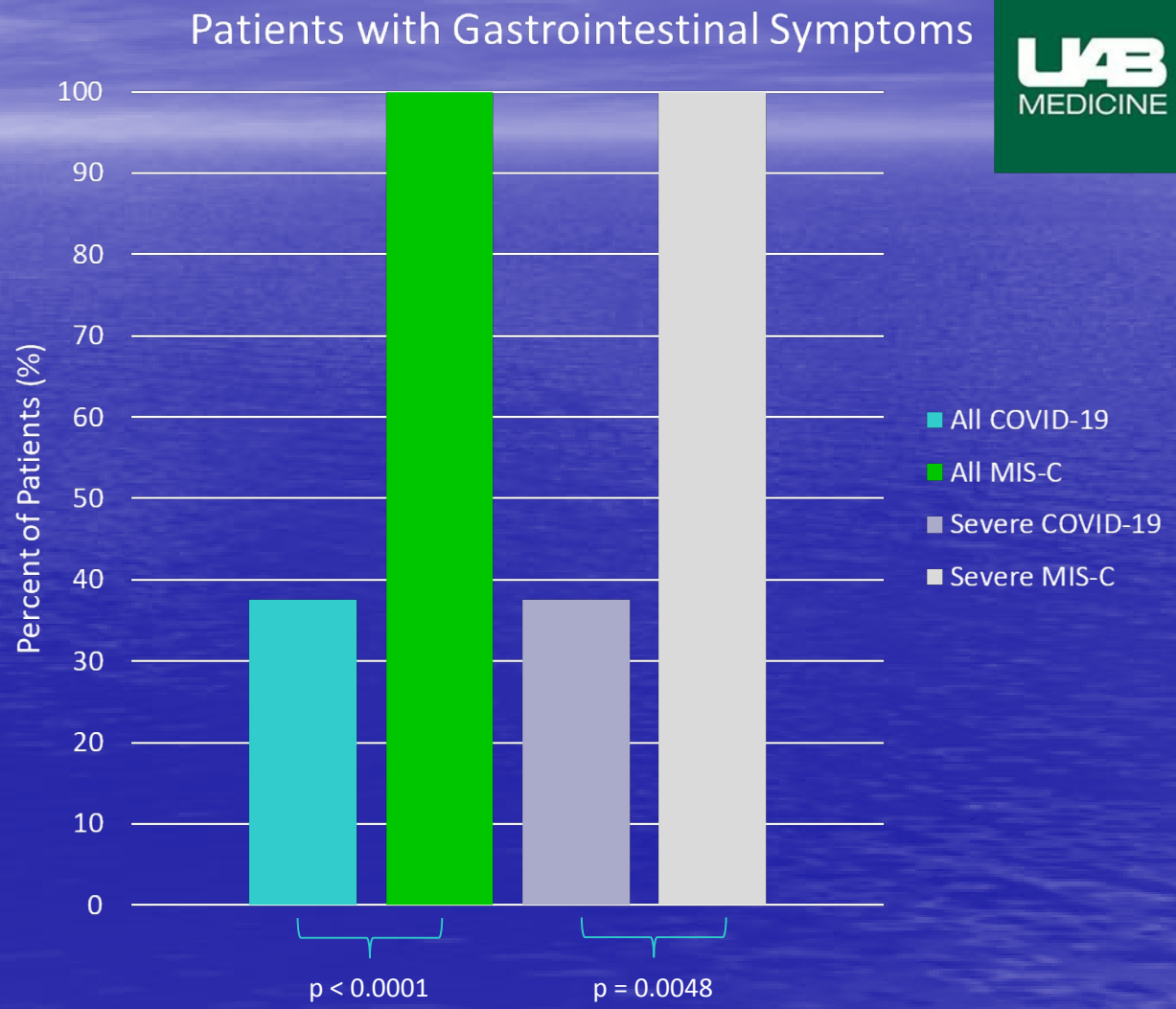
Presenting Symptoms

- Fever – more common in MIS-C patients, but no difference between severe categories
- Respiratory symptoms – significantly more common in COVID-19 groups
  - Hypoxia, cough, shortness of breath
  - Severe COVID-19 – more likely to need positive pressure ventilation (p = 0.0445)



Presenting Symptoms

- Fever – more common in MIS-C patients, but no difference between severe categories
- Respiratory symptoms – significantly more common in COVID-19 groups
- Gastrointestinal symptoms – significantly more common in MIS-C groups
  - Nausea/Vomiting, diarrhea, abdominal pain



Distinguishing Pediatric COVID-19 and MIS-C

- COVID-19 patients more likely to:
  - Have chronic underlying medical conditions
  - Present with primary respiratory symptoms
  - Have higher LDH on admission

- MIS-C patients more likely to:
  - Be previously healthy
  - Present with fever, GI symptoms, rash, and conjunctivitis
  - Have longer duration between known exposure and symptoms
  - Have lower sodium, higher inflammatory markers, and higher d-dimer on admission

Reiff D, Mannion ML, Samuy N, Scalici P, Cron RQ. Distinguishing active pediatric COVID-19 from MIS-C. *Pediatr. Rheumatol. Online J., in press*.

Treatment Strategies

- Active COVID-19
  - Management per PICU
  - Dexamethasone + Remdesivir
  - Rheumatology involved in cases with cytokine storm/MAS
  - Anakinra – goal 10 mg/kg/day with long taper
- MIS-C
  - Mild cases
    - IVIG 2g/kg + aspirin tx
    - If continued symptoms, will add steroid equivalent of methylpred 1-2 mg/kg/day with 2-3 week taper
  - Severe cases +/- coronary changes
    - IVIG 2 g/kg + methylpred 10 mg/kg BID
    - Aspirin vs lovenox per PICU
    - Add anakinra if concern for CSS
    - Taper steroids over 2-3 week course and transition to aspirin as outpatient

Treatment Strategies and Outcomes

- Active COVID-19
  - 13/17 (76%) received steroids – all June 1st and later
  - 12/17 (71%) received Remdesivir
  - 6/17 (35%) received anakinra for concurrent cytokine storm syndrome
  - One patient received tocilizumab
  - Two patients received convalescent plasma
- Median LOS
  - All COVID-19: 14 days (IQR 6.75-28.25)
  - Severe COVID-19: 29.5 days (IQR 21.75-47)
- 2 patient remains admitted, other 15 patients discharged to home

- MIS-C
  - 27/28 (96%) received IVIG
  - 18/28 (64%) received steroids
    - 6 required 10-20 mg/kg/day max
    - 12 required 1-2 mg/kg/day max
  - 2 patients required anakinra
  - 25/28 (89%) received aspirin
  - 9/28 (32%) received anticoagulation
- Median LOS
  - All MIS-C: 5 days (IQR 3-8)
  - Severe MIS-C: 7 days (IQR 5.5-10)

American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1

Arthritis & Rheumatology
Vol. 0, No. 0, Month 2020, pp 1–15
DOI 10.1002/art.41454

Lauren A. Henderson,[1] Scott W. Canna,[2] Kevin G. Friedman,[1] Mark Gorelik,[3] Sivia K. Lapidus,[4] Hamid Bassiri,[5] Edward M. Behrens,[5] Anne Ferris,[6] Kate F. Kernan,[7] Grant S. Schulert,[8] Philip Seo,[9] Mary Beth F. Son,[1] Adriana H. Tremoulet,[10] Rae S. M. Yeung,[11] Amy S. Mudano,[12] Amy S. Turner,[13] David R. Karp,[14] and Jay J. Mehta[5]

Henderson

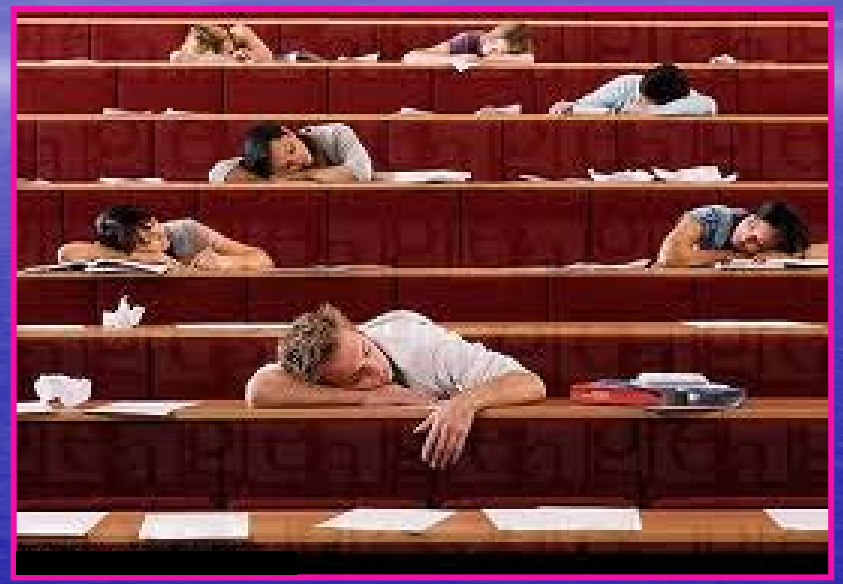
Boston Children's Hospital

Table 5. Immunomodulatory treatment in MIS-C*

Guidance statement	Level of consensus
Patients "under investigation" for MIS-C without life-threatening manifestations should undergo diagnostic evaluation for MIS-C, as well as other possible infections and non–infection-related conditions, before immunomodulatory treatment is initiated.	Moderate
Patients "under investigation" for MIS-C with life-threatening manifestations may require immunomodulatory treatment for MIS-C before the full diagnostic evaluation can be completed.	High
After evaluation by specialists with expertise in MIS-C, some patients with mild symptoms may only require close monitoring without immunomodulatory treatment. The panel noted uncertainty around the empiric use of IVIG to prevent CAAs in this setting.	Moderate
A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with IVIG and/or glucocorticoids considered as first-tier treatments.	Moderate to high
High-dose IVIG (typically 1–2 gm/kg) may be considered for treatment of MIS-C. Cardiac function and fluid status should be assessed in MIS-C patients with shock before IVIG treatment is provided, and IVIG should be administered when cardiac function is restored.	Moderate to high
Low-to-moderate doses of glucocorticoids may be considered for treatment of MIS-C. High-dose IV pulse glucocorticoids may be considered to treat patients with life-threatening complications, such as shock, and specifically, if a patient requires high-dose or multiple inotropes and/or vasopressors.	Moderate to high
Anakinra (IV or SC) may be considered for treatment of MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to these treatments.	Moderate to high
Serial laboratory testing and cardiac assessment should guide the immunomodulatory treatment response and tapering. Patients will often require a 2–3-week taper of immunomodulatory medications.	High

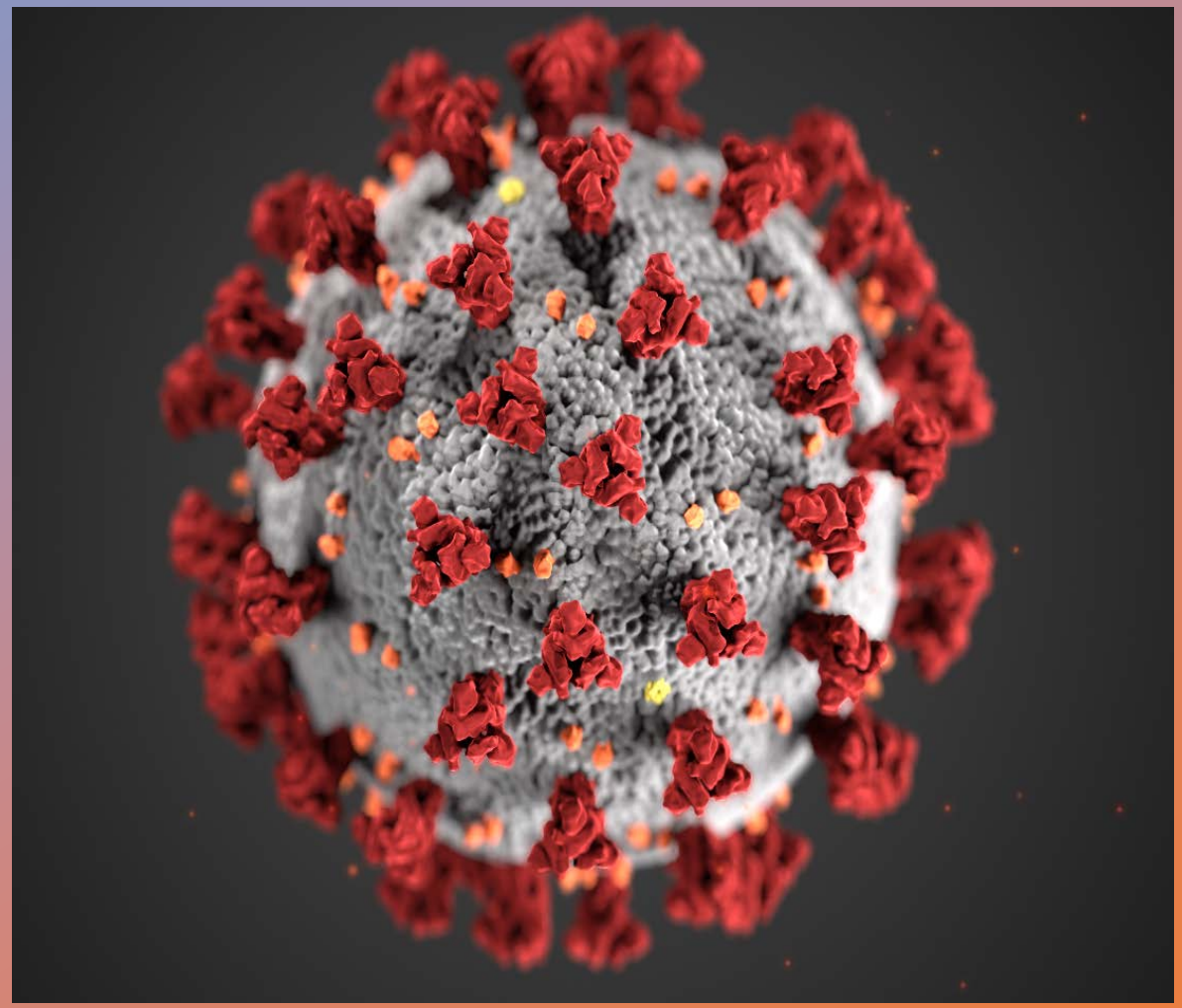
American College of Rheumatology

Questions?? rcron@peds.uab.edu



WWW.PEDS.UAB.EDU

COVID-19/MIS-C Follow up



Swetha Pinninti, MD
Pediatric Infectious Diseases

UAB MEDICINE
PEDIATRICS

Children's of Alabama

I have no conflicts of Interest

Short-term and Long-term follow-up

- Long-term outcomes unknown
-
- Cardiac
- Pulmonary
- Rheumatological/Immunological
- Neurological
- Neuropsychiatric
- ? Renal/GI
- Metabolic

Post-Hospitalization Follow-up

- Rheumatology
  - 2 weeks
  - MIS-C discharged home on steroids/Immunomodulators
  - repeat inflammatory markers – telehealth visit

- COVID ID Clinic
  - 4 – 6 weeks
  - All hospitalized COVID-19/MIS-C and outpatient referrals
  - Repeat inflammatory markers
  - ECHO/ EKG/ CXR
  - BASC3 questionnaire

Clinic Information

- Visits: 1, 6 months and 12 months
- Clinic 7 – x1/week - Friday

- Contact:

-Cathy Seripin cathy.seripin@childrensal.org

-Swetha Pinninti (spinninti@peds.uab.edu)

-Suresh Boppana (sboppana@peds.uab.edu)

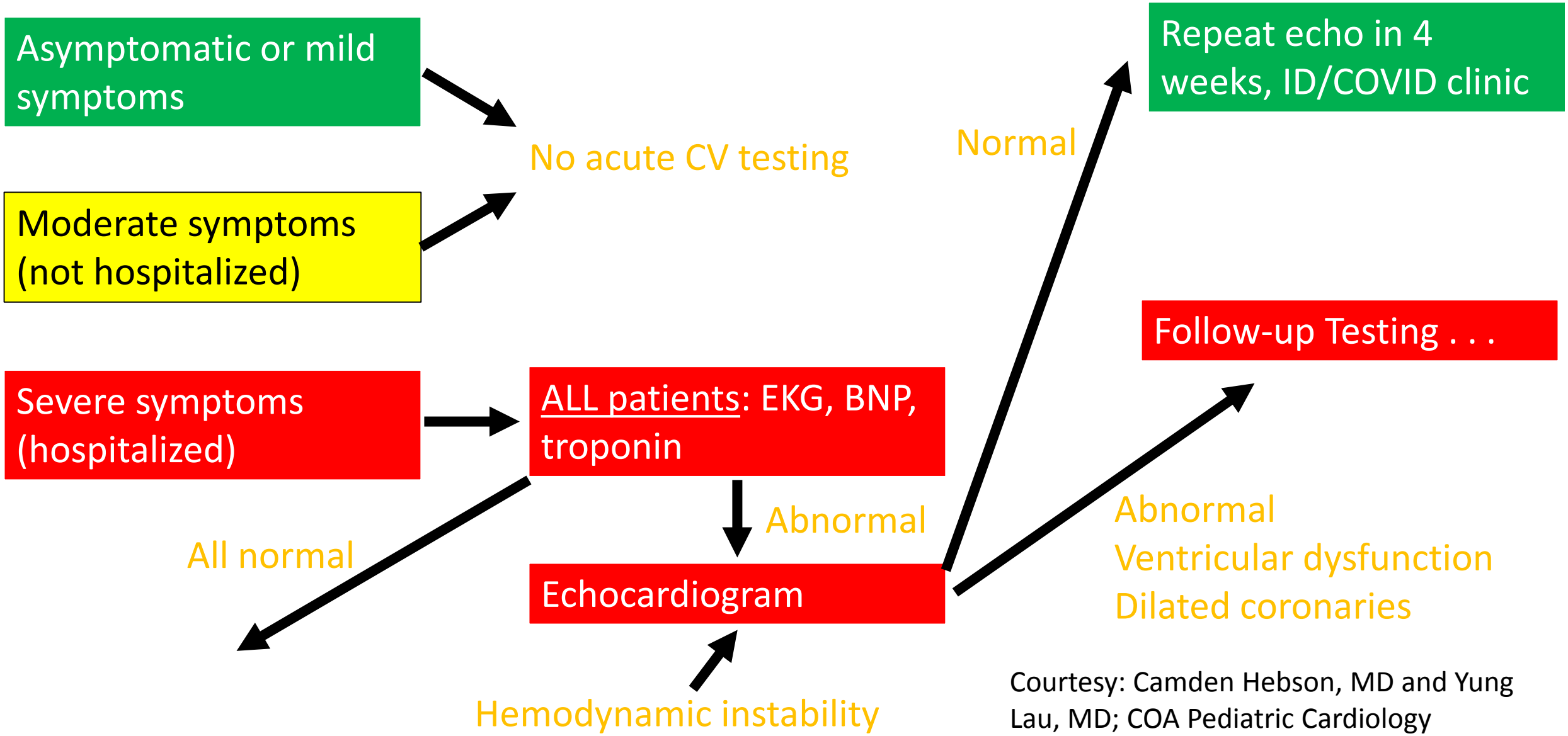
Post- Hospitalization

- Rheumatology – 2 weeks
  - repeat inflammatory markers

- ID COVID Clinic
  - 4-6 weeks
  - Repeat inflammatory markers
  - ECHO/ EKG/ CXR
  - Cardiology –
  - Pulmonary – PFT’s

CV Follow up

Acute COVID-19/MIS-C Evaluation



Courtesy: Camden Hebson, MD and Yung Lau, MD; COA Pediatric Cardiology

Echo - Points of Emphasis

- In-patient – ventricular function, coronary size/presence of aneurysms, pericardial effusion, valve regurgitation

- Follow-up - ventricular function (qualitative and quantitative), diastolic function, global strain, valve function, pericardial effusion, coronary assessment

Acute Follow-up CV Testing

- abnormal BNP (>100 ng/mL), troponin (>0.04 ng/mL), and/or EKG → repeat weekly while inpatient
- If coronaries dilated on the initial echo (Z > 2.5) → repeat Echo weekly until discharge and coronaries stable
- Discharge → repeat at 4 week follow up
- ventricular dysfunction → Echoonce a week (or prior to discharge) during the acute illness, + as clinically indicated, and repeated in 4 wks in ID clinic

Long-term Follow-up CV Testing for Severe/Hospitalized Patients

- BNP, troponin, and EKG → repeat again at 4 weeks, 6 months, and 1 year (in ID clinic)

- Repeat ECHO - 4 weeks, 6 months, and 1 year (ID clinic)

- ventricular dysfunction, myocarditis, and/or significant coronary dilation → cMRI at ~2-6 months

  - extent of coronary dilation, as well as edema, fibrosis, and scar by delayed enhancement.

- abnormal findings on initial cMRI → repeat MRI at 6 months and 1 year

- cMRI → clinical information vs sedation risk

Cardiac Indications for Anticoagulation

- acute COVID presentation or with MIS-C
- dilated coronaries (Z > 2.5)
- meeting criteria for Kawasaki disease
- moderate to severe LV dysfunction, would prescribe low dose aspirin.
- Dose: ~5 mg/kg/dose once a day (1/4, 1/2, or full 81 mg tablet)
- Wean when - coronaries normalize, ventricular fxn improves, or per KD guidelines based on follow-up echocardiograms (ID/COVID clinic or cardiology clinic)
- Would recommend further anticoagulation (clopidogrel, enoxaparin, warfarin) only for those with true coronary aneurysms, as determined by the consulting cardiologist

Clearance for sports/PE for Athletes

- Pulmonary
- Hematology-oncology
- Neurology
- Neuropsych screening

Data from 1 month follow-up

- Patients seen in clinic to-date:
- ECHO’s performed
-
- % normal laboratory data
- % normal ECHO’s
- Further follow up