# Pandemic lessons learned from the mitochondrial disease community

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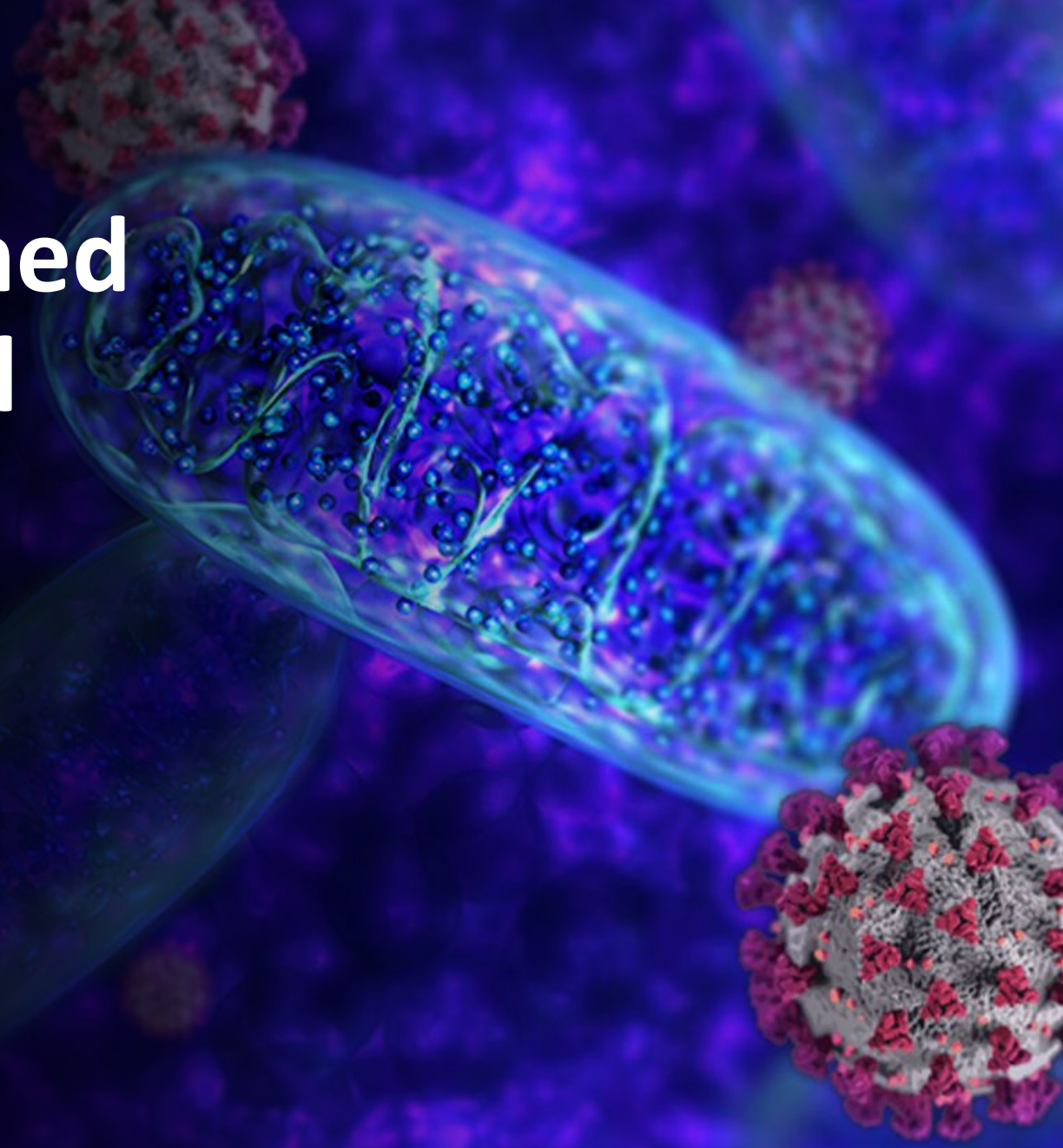
Head, Metabolism, Infection and Immunity Section

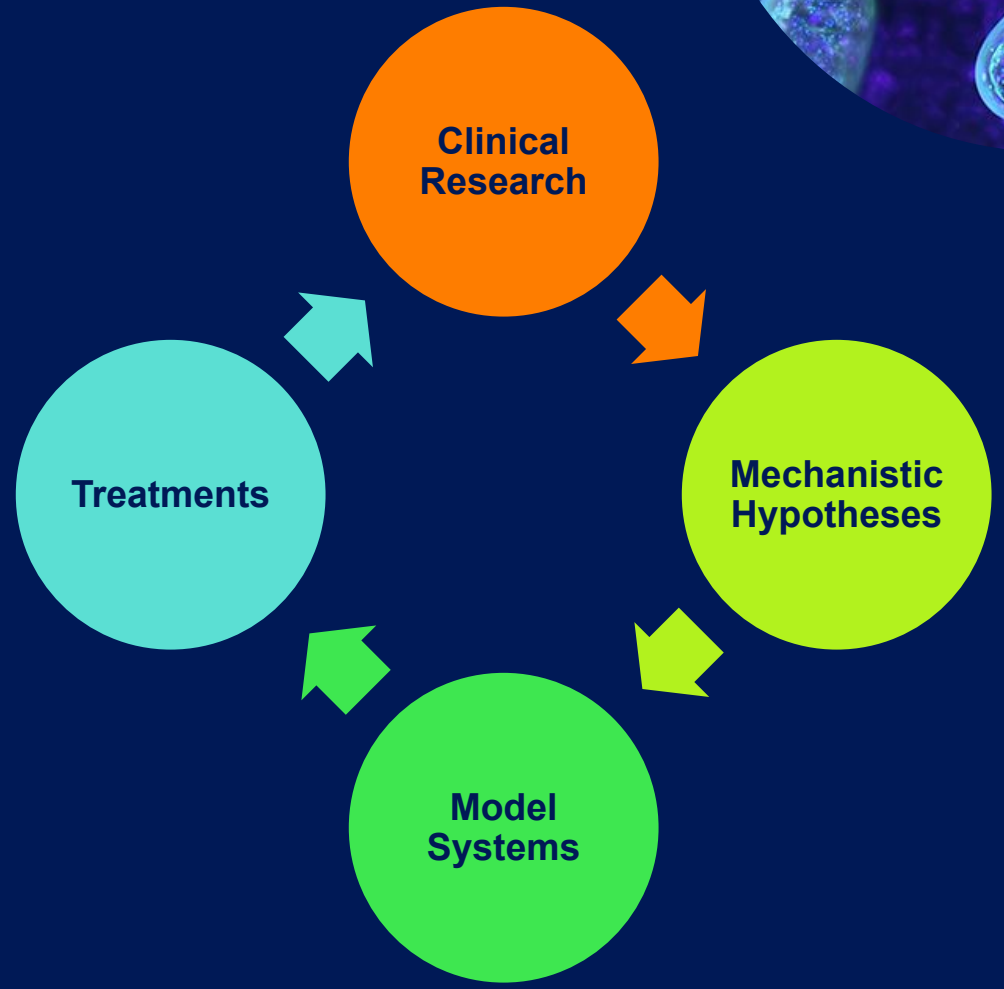
2022 MitoAction



NIH National Human Genome Research Institute

# MINI Section Mission

"The Metabolism, Infection and Immunity (MINI) Section aims to define the risk factors and mechanisms involved in infection-related clinical decline in children with mitochondrial disease."

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# Why do we care about infection and mitochondrial disease?

# Infection and mitochondrial disease (MD)

- Sepsis and pneumonia are two most common causes of death in children with MD (Eom et al., 2017).
- Sepsis is one of the top five admitting diagnoses for pediatric patients with MD (McCormack et al., 2017) .
- Up to 80% of children with MD experience recurrent infections, mostly respiratory (Tarasenko et al., 2017) .
- Intercurrent infection is a leading cause of episodic neurodegeneration in mitochondrial disease (Edmonds et al., 2002).
- COVID-19 pandemic represents a threat to patients with mitochondrial disease.

# Metabolic decompensation

- *In extremis* (life-threatening)
  - Bioenergetic failure
  - Lactic acidosis
  - Disease progression
  - Organ failure (e.g. liver failure)
  - Encephalopathy
  - Metabolic “stroke”
  - Sequelae
- Extensive ICU care
- Viral infections
- Treatment is limited

# Therefore, one of the goals of the MINI Section is to keep patients with mitochondrial disease healthy

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## Dec. 31, 2019

China alerts World Health Organization (WHO) to several cases of pneumonia with no known cause in Wuhan. The disease goes on to be named COVID-19.

## Jan. 7

WHO officials announce they have identified a new virus named SARS-CoV-2 that causes COVID-19. It belongs to the coronavirus family, which includes viruses that cause SARS, MERS and the common cold.

## Jan. 11

China announces the first death linked to COVID-19.

## Jan. 13

WHO reports the first case outside of China in Thailand.

## Feb. 26

National Institutes of Health (NIH) begin the first clinical trial in the U.S. for a potential COVID-19 treatment, remdesivir, an antiviral drug originally developed to treat Ebola.

## Feb. 29

The FDA took steps to expand novel coronavirus testing to hospital clinical microbiology laboratories.

## Mar. 11

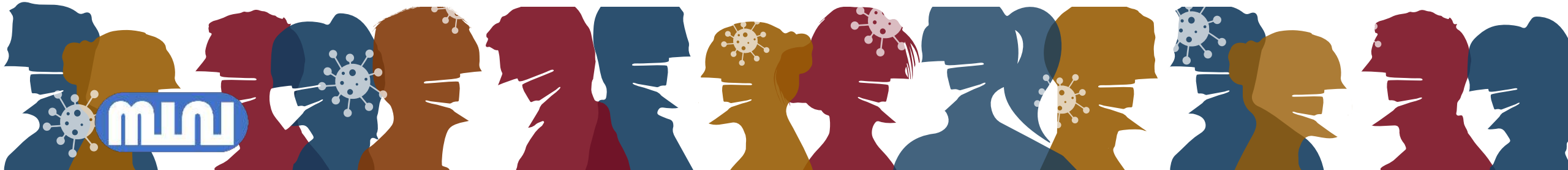
WHO declares COVID-19 a pandemic, with more than 100,000 cases and 4,000 deaths in 114 countries.

## Apr. 2

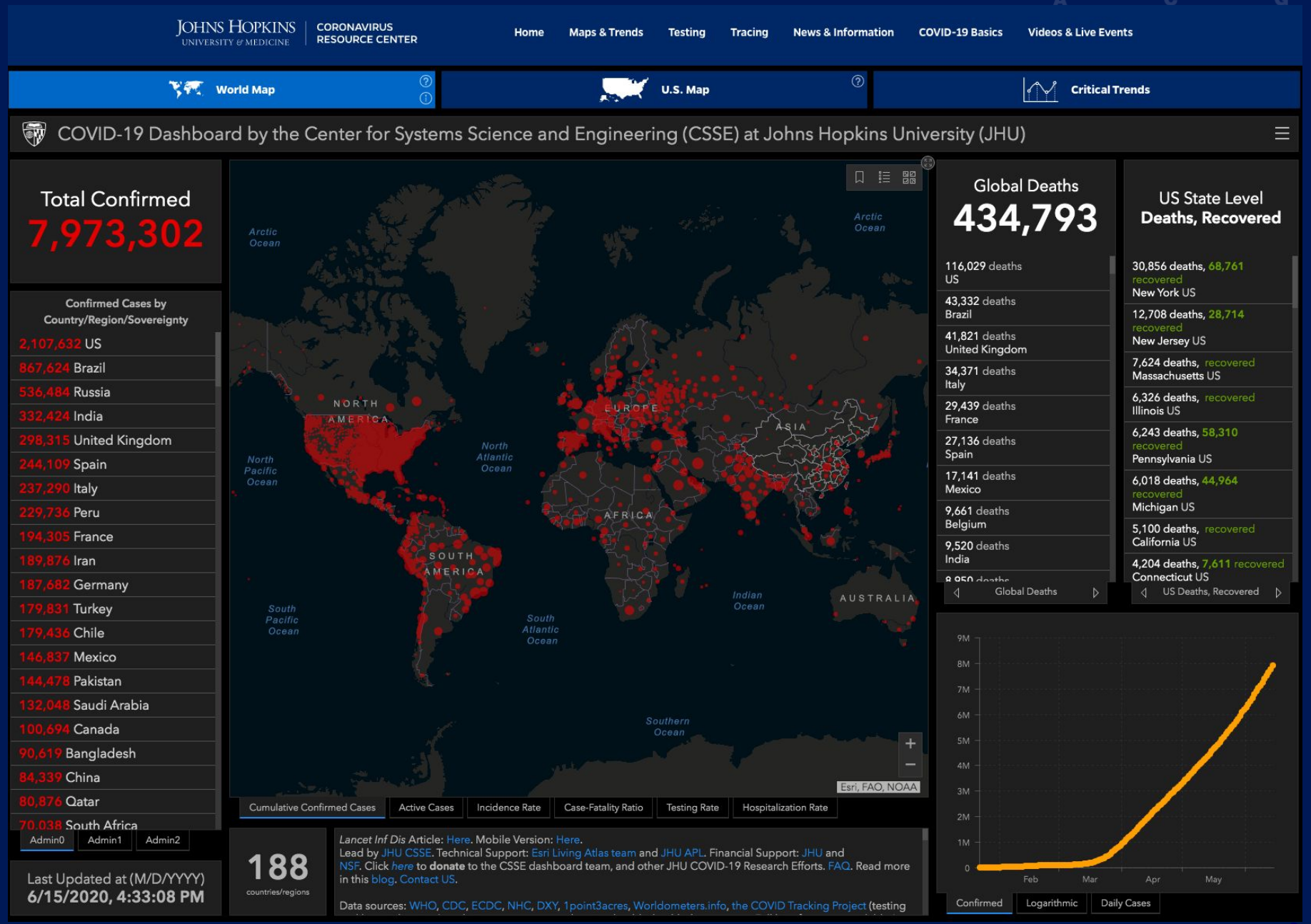
Confirmed cases of COVID-19 top 1 million worldwide.

## Apr. 10

Global deaths due to COVID-19 top 100,000.



**June 15, 2020**

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# April 4, 2022


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Home
Topics
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Tracking Home
Data Visualizations
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U.S. Map
Data in Motion
Tracking FAQ
COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)
Last Updated at (M/D/YYYY)
4/4/2022, 1:20 PM
Total Cases
491,804,269
Total Deaths
6,154,268
Total Vaccine Doses Administered
10,999,180,349
28-Day Cases
44,944,715
28-Day Deaths
157,411
28-Day Vaccine Doses Administered
415,484,770
Cases | Deaths by Country/Region/Sovereignty
Korea, South
28-Day: 9,334,429 | 8,357
Totals: 14,001,406 | 17,453
Germany
28-Day: 5,808,751 | 5,921
Totals: 21,706,329 | 130,052
Vietnam
28-Day: 5,383,628 | 1,787
Totals: 9,867,045 | 42,642
France
28-Day: 2,949,698 | 3,244
Totals: 26,186,606 | 143,540
United Kingdom
28-Day: 2,122,710 | 3,586
Totals: 21,522,352 | 166,378
Italy
28-Day: 1,819,703 | 3,897
Totals: 14,845,815 | 159,784
Australia
28-Day: 1,332,653 | 967
Totals: 4,722,185 | 6,392
Japan
28-Day: 1,305,494 | 3,339
Totals: 6,730,654 | 28,332
Netherlands
28-Day: 1,206,119 | 407
Totals: 8,098,269 | 22,642
Austria
28-Day: 1,019,595 | 977
Totals: 3,899,660 | 16,002
Brazil
28-Day: 946,260 | 7,972
Totals: 30,002,785 | 660,410
Russia
28-Day: 937,880 | 13,108
Arctic Ocean
NORTH AMERICA
EUROPE
ASIA
AFRICA
SOUTH AMERICA
AUSTRALIA
North Pacific Ocean
North Atlantic Ocean
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
Southern Ocean
Esri, FAO, NOAA
Powered by Esri
Admin0
Admin1
Admin2
28-Day
Totals
Incidence
Case-Fatality Ratio
Global Vaccinations
US Vaccinations
Terms of Use
Weekly Cases
Weekly Deaths
Weekly Doses Administered
Jul
2021
2022
Weekly
28-Day

# Addressing COVID19 and beyond

**Feb-Mar 2020**
UMDF
COVID19
Position Statement

**May 2020**
**Phase 2:** Acute Infection in Mitochondrial Disease: An Observational Prospective Natural History Study of Metabolism, Infection and Immunity During the COVID19 Pandemic
(Actively recruiting)

**Late Summer/Fall 2020**
**Phase 3:** SARS-CoV-2 Exposure in Children with Mitochondrial Disease

**2021-**
**Phase 5:** Viral History and Mitochondrial Disease


**NIH MINI Study:**
- **Study of infection and immunity in mitochondrial disease**
- **Instituted remote enrollment/samples for participants**
- **Invited to NIH Clinical Center at a later date**

**Apr 2020**
**Phase 1:** Understanding the Experience of the Mitochondrial Disease Community During the COVID19 Pandemic
(>450 participants)

**Late Apr 2020**
Ask the Mito Doc: COVID19

**June 2020**
**Phase 1:** Understanding the Experience of the Mitochondrial Disease Community During the COVID19 Pandemic
(Open now!)

**2021-2022**
**Phase 4:** SARS-CoV-2 Vaccination and Mitochondrial Disease

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# Metabolism, Infection and Immunity (MINI) Study

Understanding why people with mitochondrial disease decline during infection is the first critical step to improving their well-being.

Dr. Peter McGuire

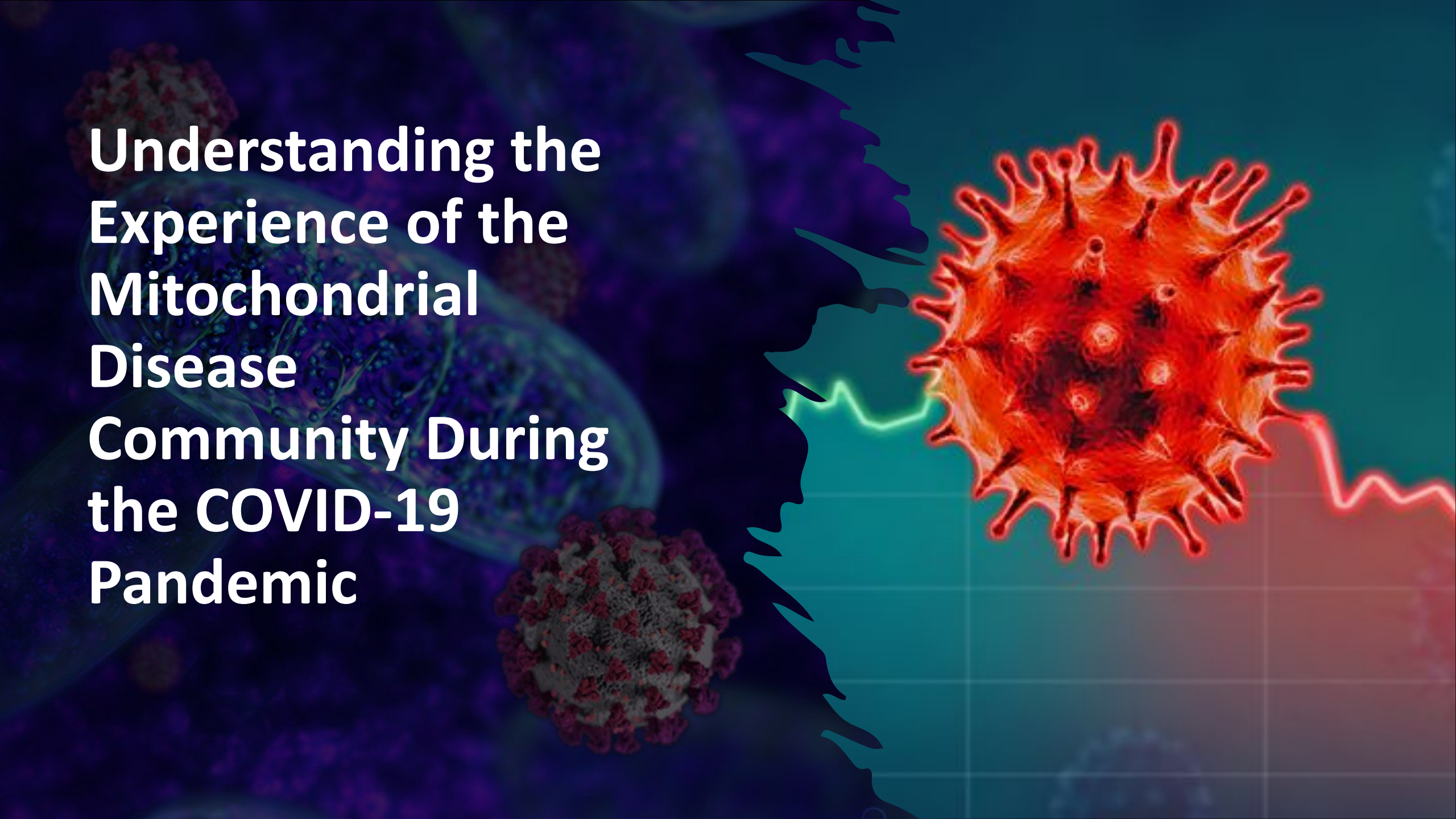
Dr. Eliza Gordon-Lipkin

Ms. Shannon Kruk

# NIH MINI Study: Metabolism, Infection and Immunity (NCT01780168)

- Natural history study of infection and immunity in children with MD
  - ✔ Infection history
  - ✔ Immune function
  - ✔ Disability

# Understanding the Experience of the Mitochondrial Disease Community During the COVID-19 Pandemic



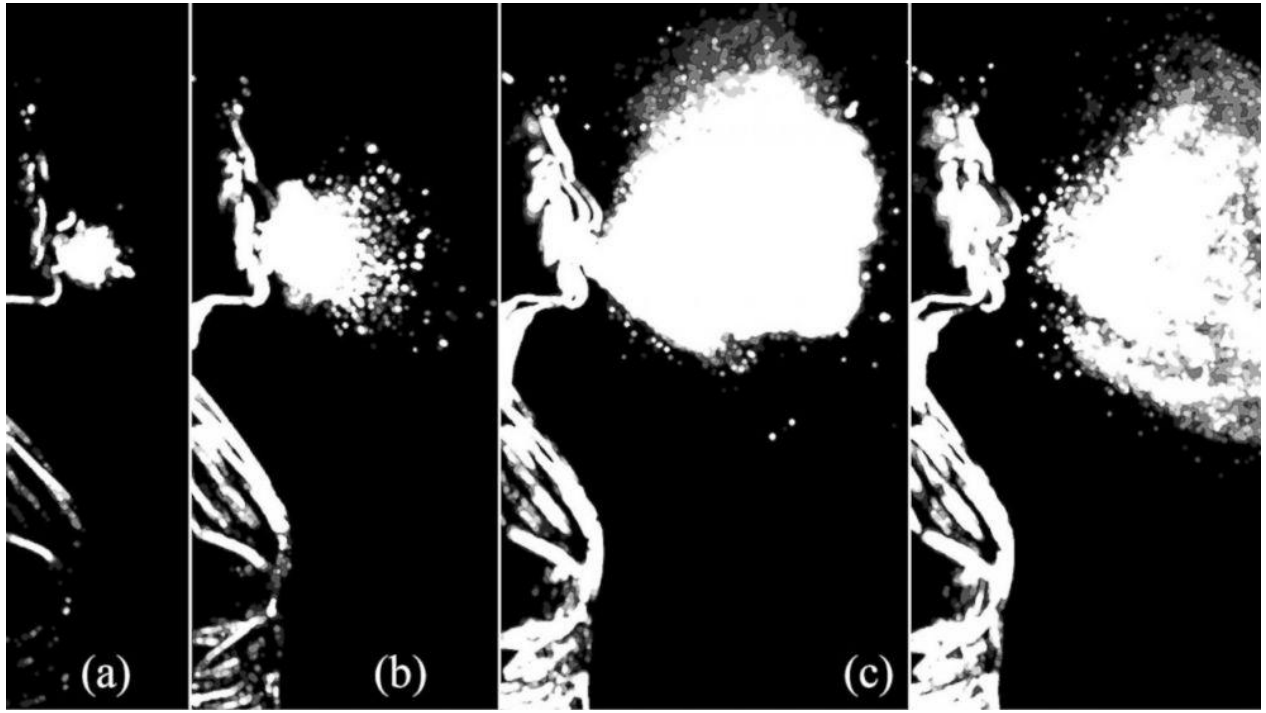
# Online surveys


- April 2020, June 2020
- 688 responses; 82% completion rate.
- 30% pediatric MD patients.
- Diagnoses: Mitochondrial Disease Not Otherwise Specified (33%), Mitochondrial Myopathy (28%) and Leigh Syndrome (11%).
- 62% known pathogenic variant
- 5 positive COVID-19 cases
- 68 requested a SARS-CoV-2 test, 14 (21%) were *unable* to receive testing.

## Symptoms That Overlap with COVID19

### Symptoms that overlap with COVID19 occurred frequently:

| | |
|---|---|
| Fever | 23% |
| New Cough | 15% |
| New Shortness of Breath | 14% |
| Pneumonia | 3% |



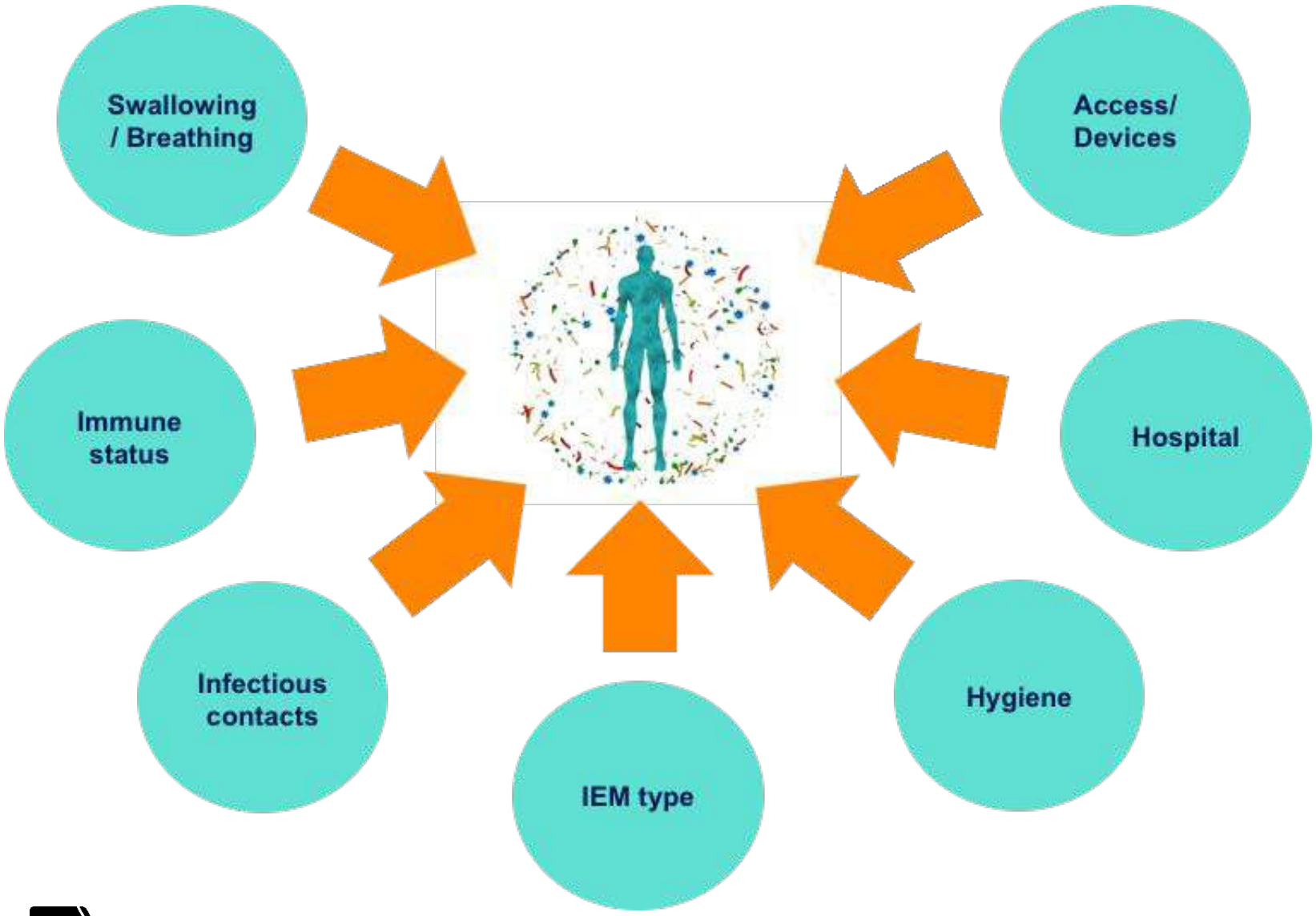

## Risk Factors for Exposure to SARS-COV2

### Exposure in Healthcare Settings

- **55% doctor's visit**
- 14% ER visit
- 12% hospitalized

### Public Contact During COVID19

- **38% have a household member who is an essential worker**
- 12% of adult patients are essential workers




## Risk Factors for Severe COVID19

**73% reported <u>at least one</u> condition recognized by CDC as risk factors for severe COVID19, including:**

35% Respiratory muscle weakness

31% Immuno-deficiency

25% Asthma



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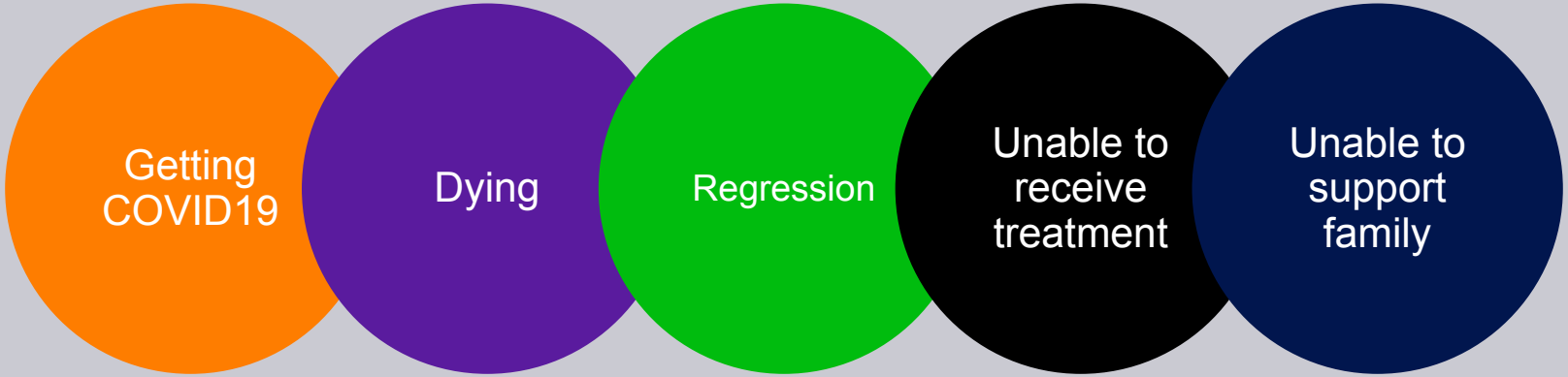
# “What is your greatest concern about COVID-19?”

*“[We are terrified of] our child with Leigh Syndrome contracting COVID19, or requiring hospitalization for some other reason, experiencing a metabolic crisis, losing developmental skills and [having our lives] changed forever.”*



# SLOW THE SPREAD OF COVID-19

cdc.gov/coronavirus

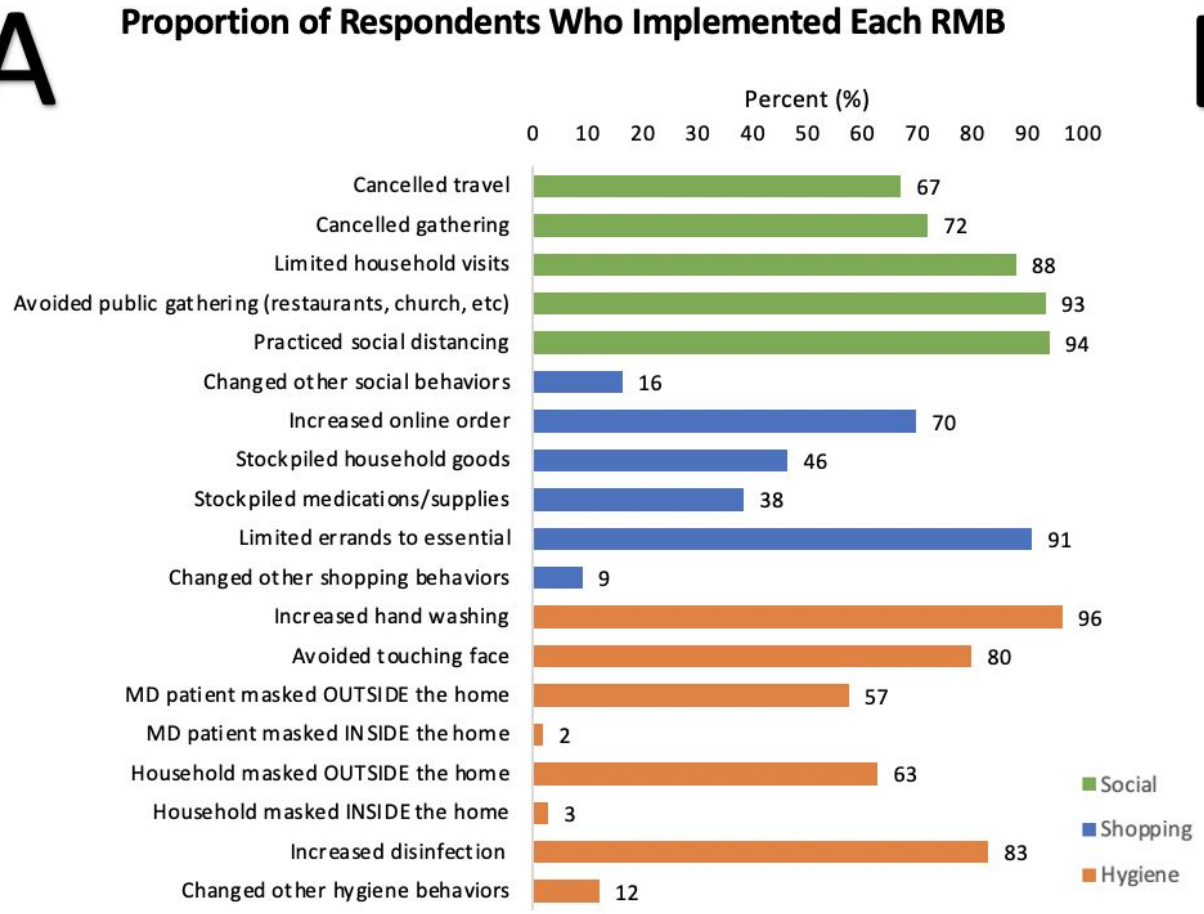
Wear a cloth face covering in public spaces

Stay at least 6 feet from other people

Frequently wash your hands

# Risk mitigation behaviors and mitochondrial disease

A

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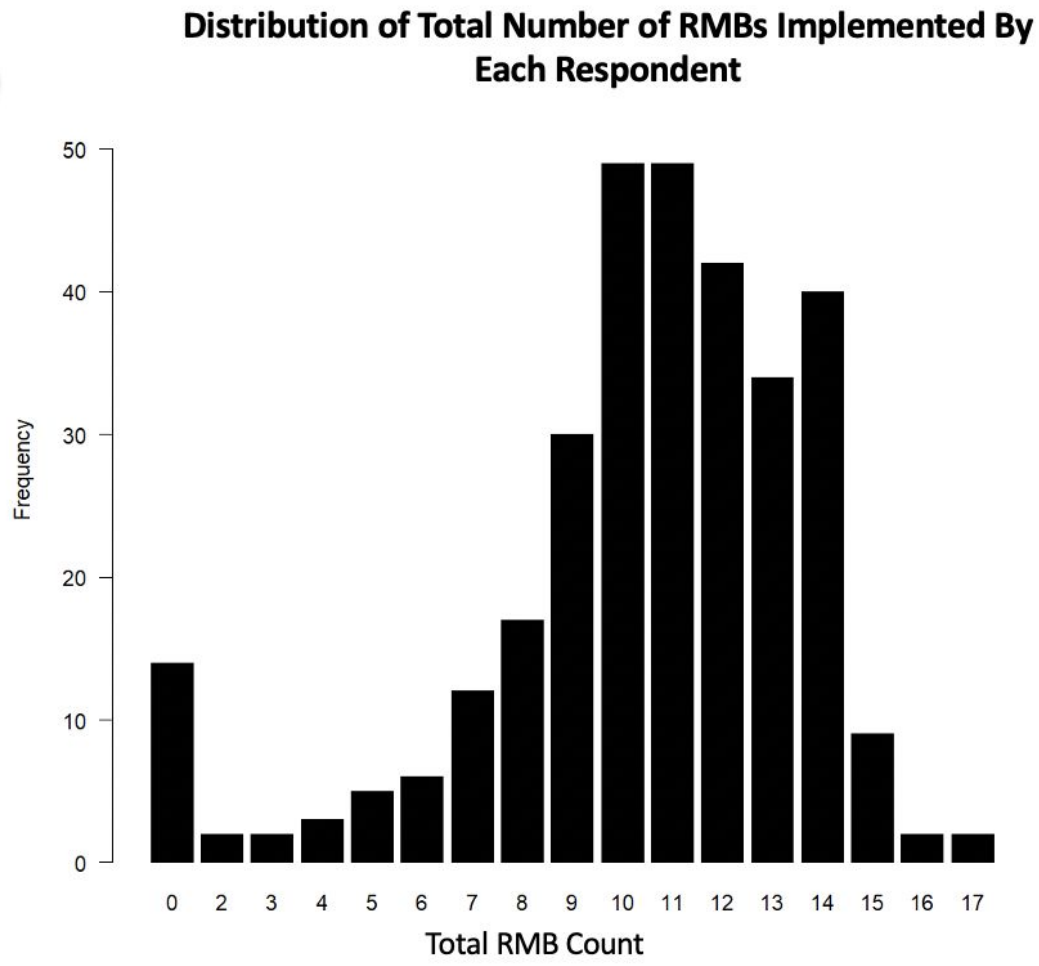



Gordon-Lipkin E, et al. Mol Genet Metab Rep. 2022 Mar;30:100837. doi: 10.1016/j.ymgmr.2021.100837. Epub 2021 Dec 18.

# Household Viral Exposure in Children with Mitochondrial Disease During COVID-19 Study

A study to learn more about the role of viral infection and biomarkers of immunity in mitochondrial disease using new technology with Neoteryx™ fingerstick at-home sampling.



# SARS-CoV-2 antibody status in households with children with mitochondrial disease

# Household members as risk factors for SARS-CoV-2 transmission to children with MtD

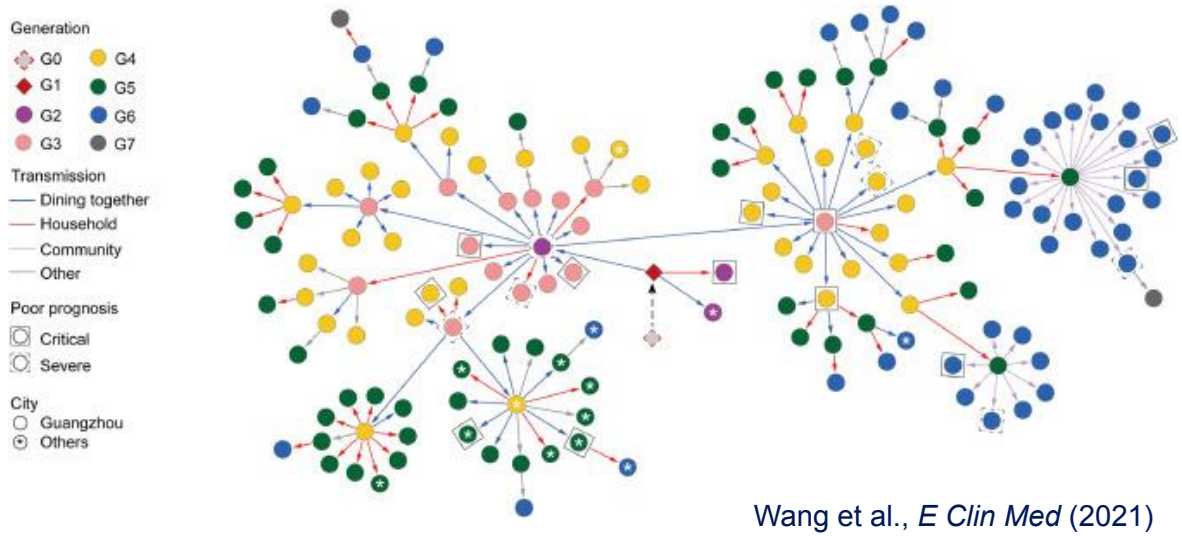
JAMA Network | Open

Original Investigation | Global Health

## Household Transmission of SARS-CoV-2
### A Systematic Review and Meta-analysis

Zachary J. Madewell, PhD; Yang Yang, PhD; Ira M. Longini Jr, PhD; M. Elizabeth Halloran, MD, DSc; Natalie E. Dean, PhD

- Meta-analysis: 54 studies, 77,258 participants
- Household secondary attack rate 16.6%




Wang et al., *E Clin Med* (2021)

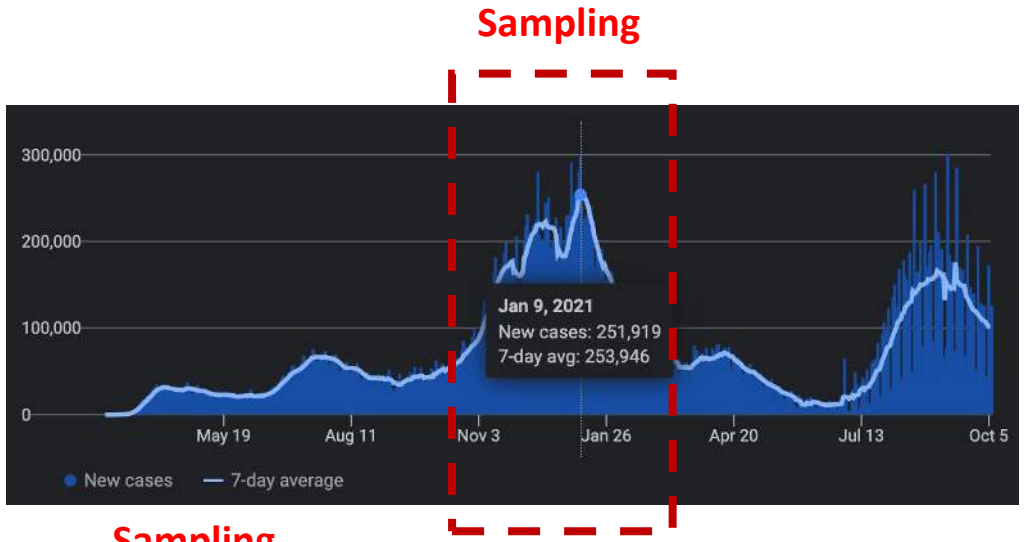
Chris Marcum, PhD

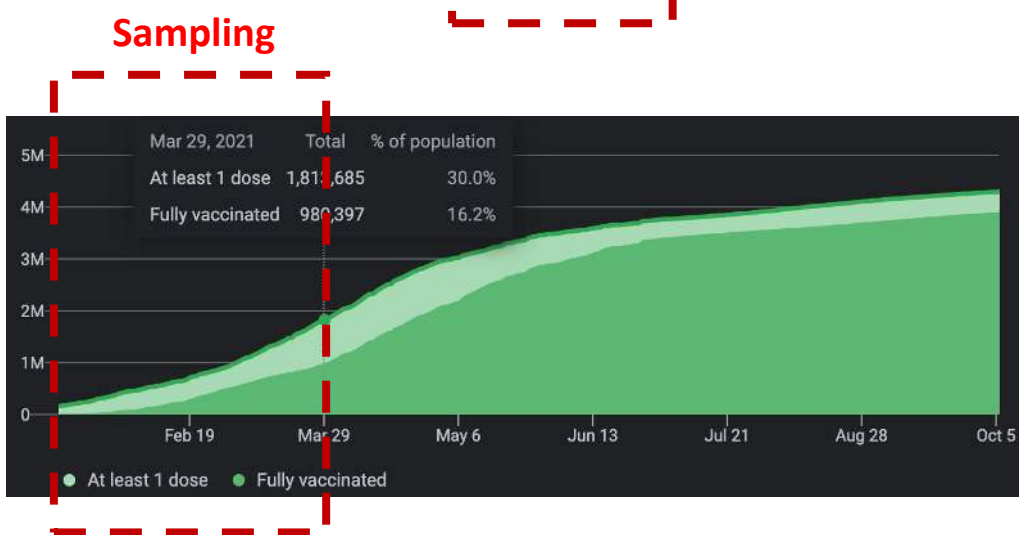
Neoteryx Mitra collection system

Risk determination using network scale up estimators

# Ongoing SARS-CoV-2 family studies:interim analysis

- Families with children with MtD
  - N=20 families
  - N=83 samples (~4 members/family)
  - Confirmed dx of MtD
- Remote sampling methods
  - October 2020 – March 2021
- SARS-CoV2 antibodies
  - Infection rate
  - Vaccination rate
- Other data collected
  - Network scale up estimators
  - Symptomatology
  - Local case count
- Post-vaccination surveillance

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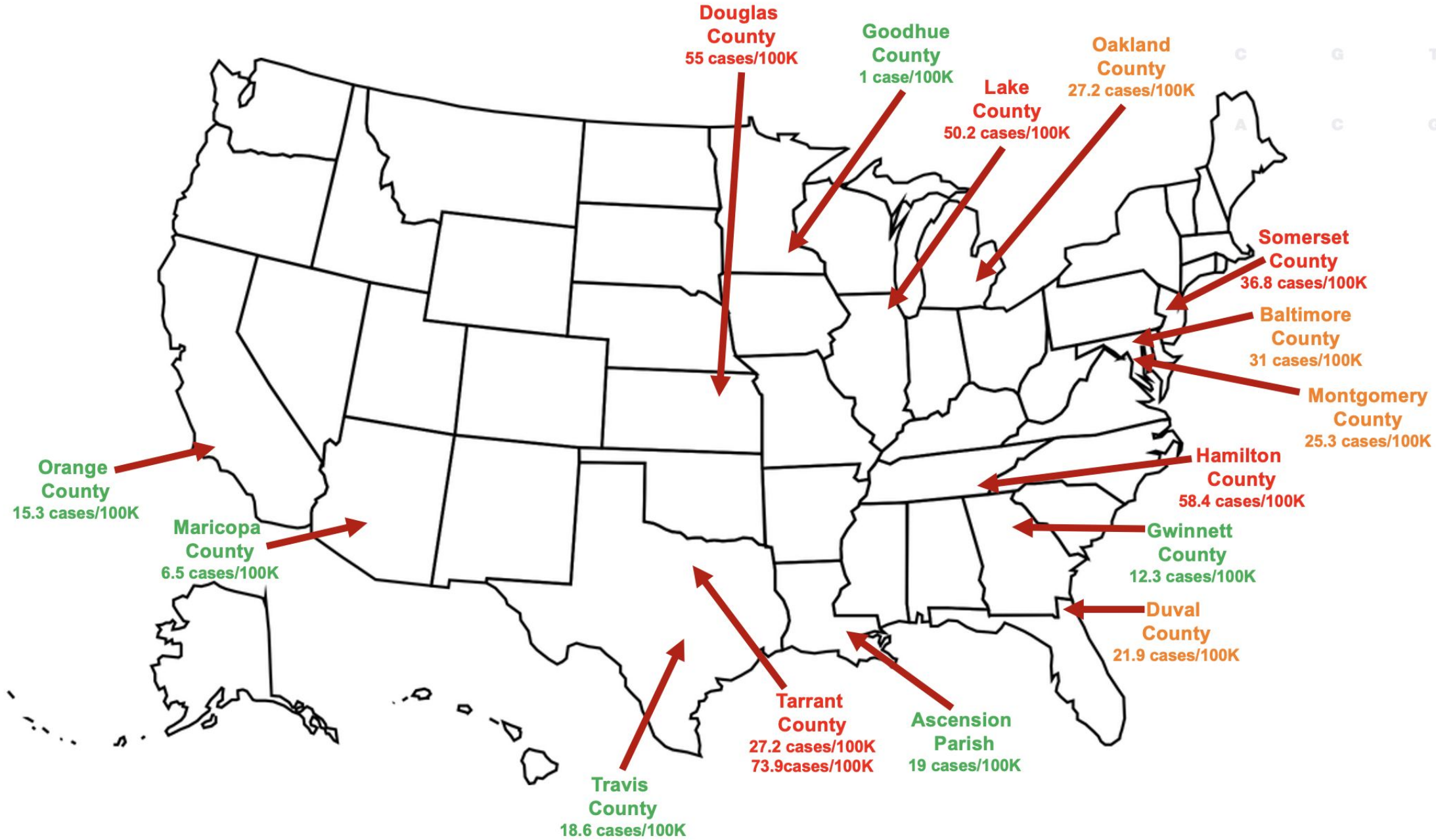
| Participants | MtD (N=22) | Household (> 16 y/o, N=49) |
|---|---|---|
| | Number/total (%/Std dev) | |
| **Mean age** | 8.8 (4.4) | 38.8 (11.2) |
| **Sex** | | |
| *Males* | 11/22 (50%) | 24/49 (49%) |
| *Females* | 11/22 (50%) | 25/49 (51%) |
| **Job/school setting** | | |
| *On site* | 2/22 (9.1%) | 8/49 (16.3%) |
| *Hybrid* | 2/22 (9.1%) | 9/49 (18.4%) |
| *Remote* | 18/22 (81.8%) | 23/49 (46.9%) |
| *Not applicable* | 0/22 (0.0%) | 9/49 (18.4%) |
| **COVID19 exposure/testing/diagnosis** | | |
| *Exposed* | 7/22 (31.8%) | 15/49 (30.6%) |
| *Tested* | 14/22 (63.6%) | 23/49 (46.9%) |
| *Diagnosed* | 1/22 (4.2%) | 1/49 (2.0%) |
| **COVID19 symptoms** | | |
| *Fever or chills* | 6/22 (27.2%) | 6/49 (12.2%) |
| *New or worsening cough* | 2/22 (8.3%) | 10/49 (20.4%) |
| *New or worsening shortness of breath* | 1/22 (4.2%) | 5/49 (10.2%) |
| *Pneumonia* | 2/22 (8.3%) | 1/49 (2.0%) |
| *Muscle or body aches* | 0/22 (0.0%) | 10/49 (20.4%) |
| *Vomiting or diarrhea* | 0/22 (0.0% | 5/49 (10.2%) |
| *Loss of taste or smell* | 0/22 (0.0%) | 1/49 (2.0%) |


Douglas County
55 cases/100K
Goodhue County
1 case/100K
Lake County
50.2 cases/100K
Oakland County
27.2 cases/100K
Somerset County
36.8 cases/100K
Baltimore County
31 cases/100K
Montgomery County
25.3 cases/100K
Hamilton County
58.4 cases/100K
Gwinnett County
12.3 cases/100K
Duval County
21.9 cases/100K
Orange County
15.3 cases/100K
Maricopa County
6.5 cases/100K
Tarrant County
27.2 cases/100K
73.9cases/100K
Ascension Parish
19 cases/100K
Travis County
18.6 cases/100K

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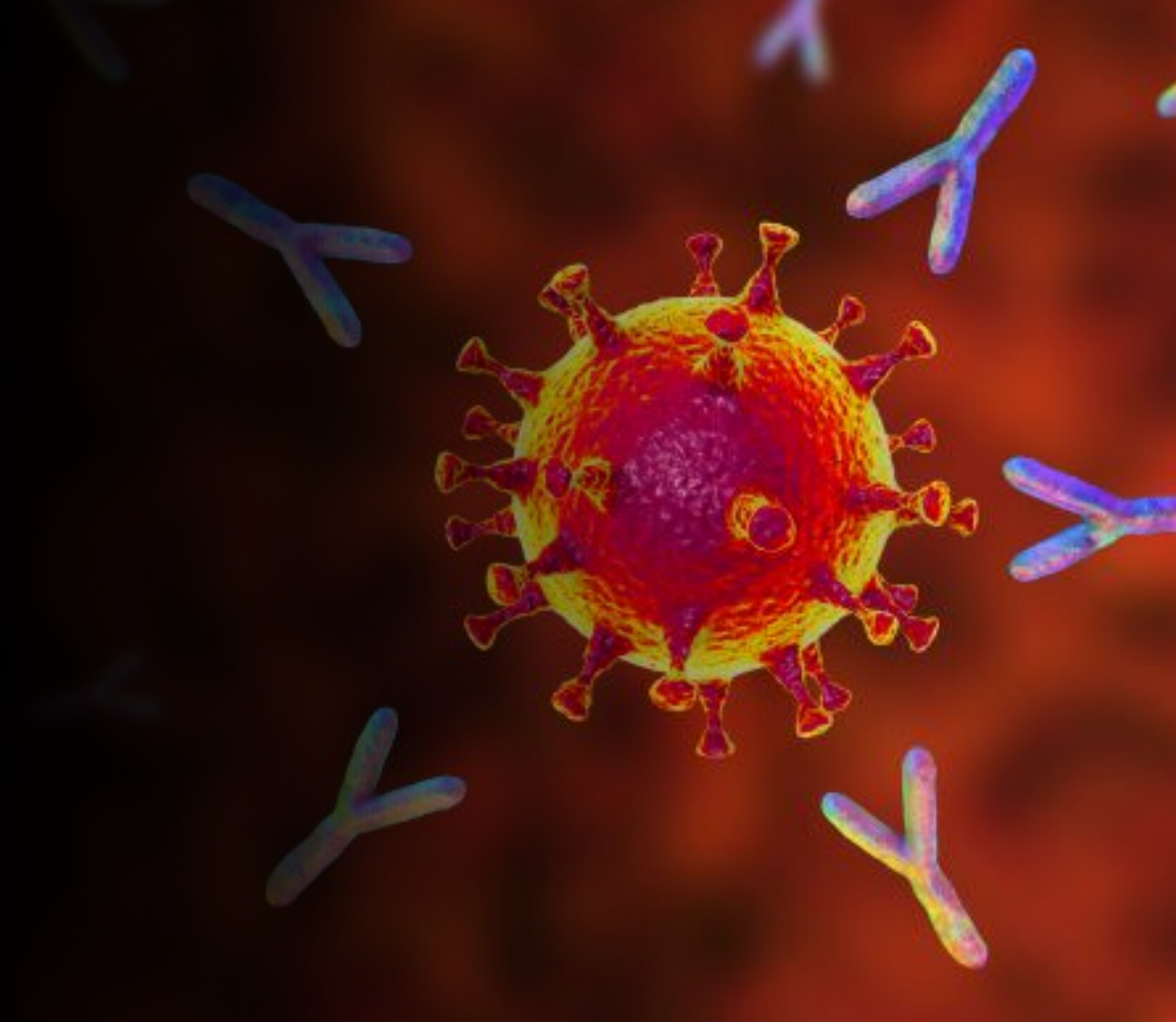
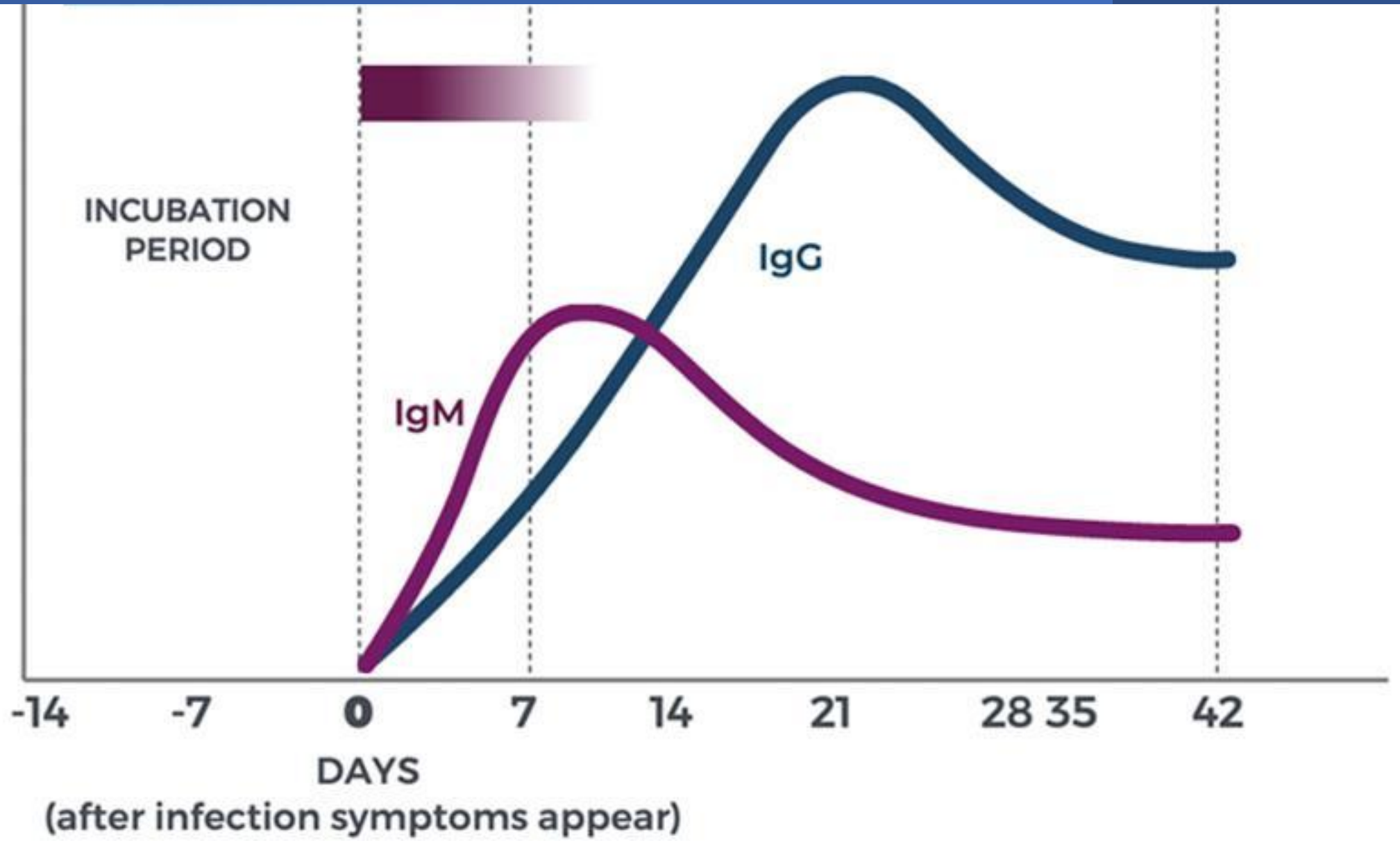
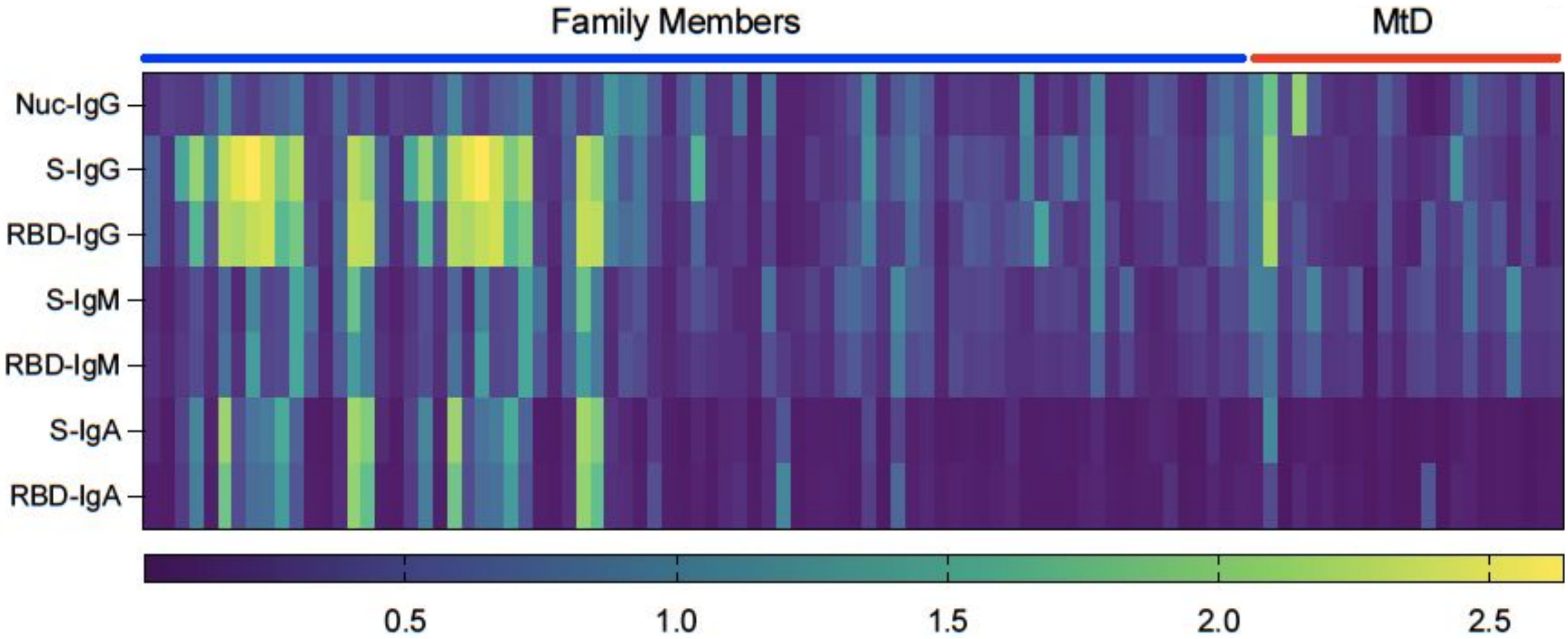
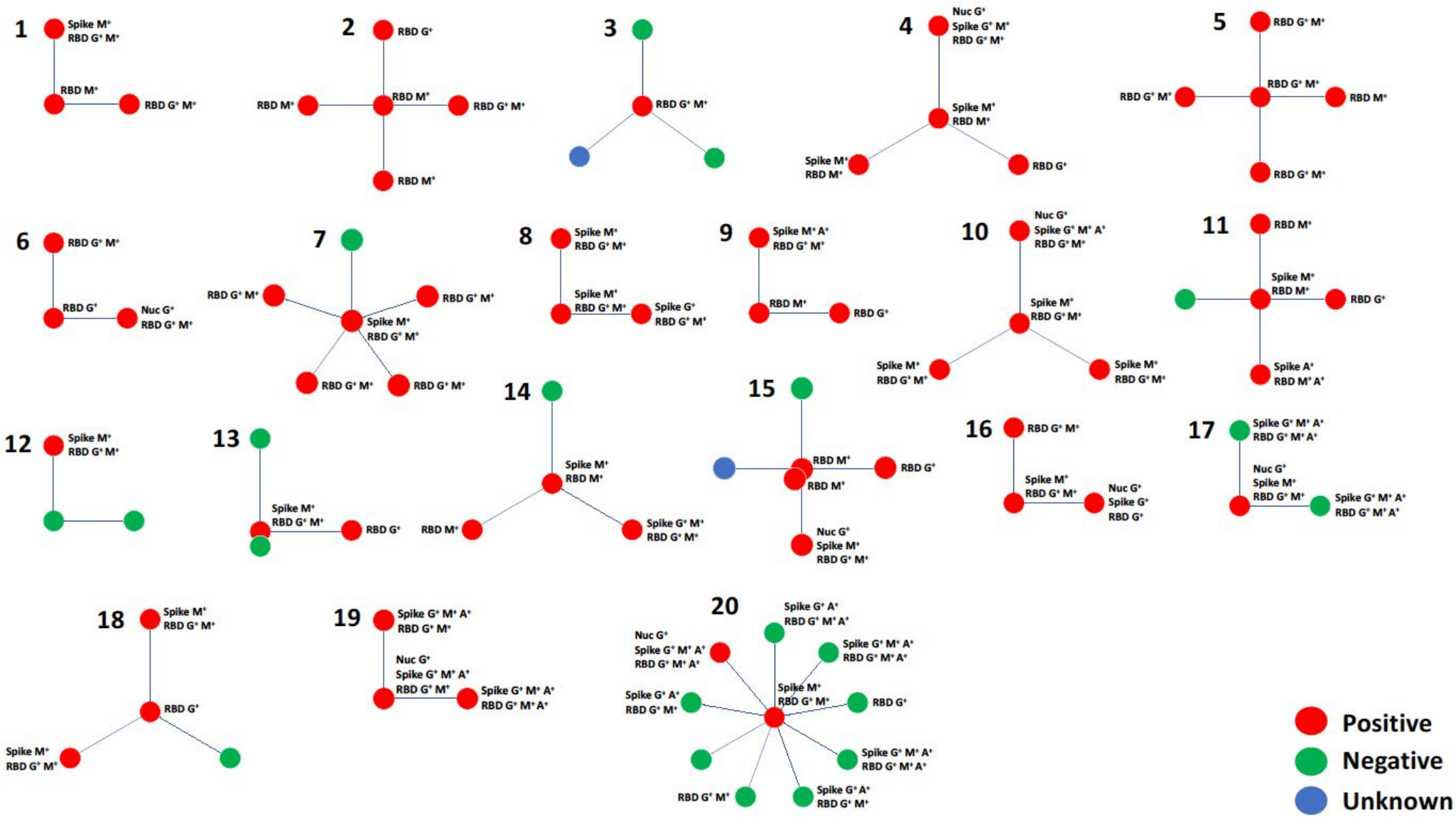
# Antibodies against SARS-CoV-2

- Nucleocapsid
- Spike protein
- Receptor binding domain




INCUBATION PERIOD
IgG
IgM
-14
-7
0
7
14
21
28 35
42
DAYS
(after infection symptoms appear)


Family Members
MtD
Nuc-IgG
S-IgG
RBD-IgG
S-IgM
RBD-IgM
S-IgA
RBD-IgA
0.5
1.0
1.5
2.0
2.5


1
Spike M+ RBD G+ M+
RBD M+
RBD G+ M+
2
RBD G+
RBD M+
RBD M+
RBD G+ M+
RBD M+
3
RBD G+ M+
4
Nuc G+ Spike G+ M+ RBD G+ M+
Spike M+ RBD M+
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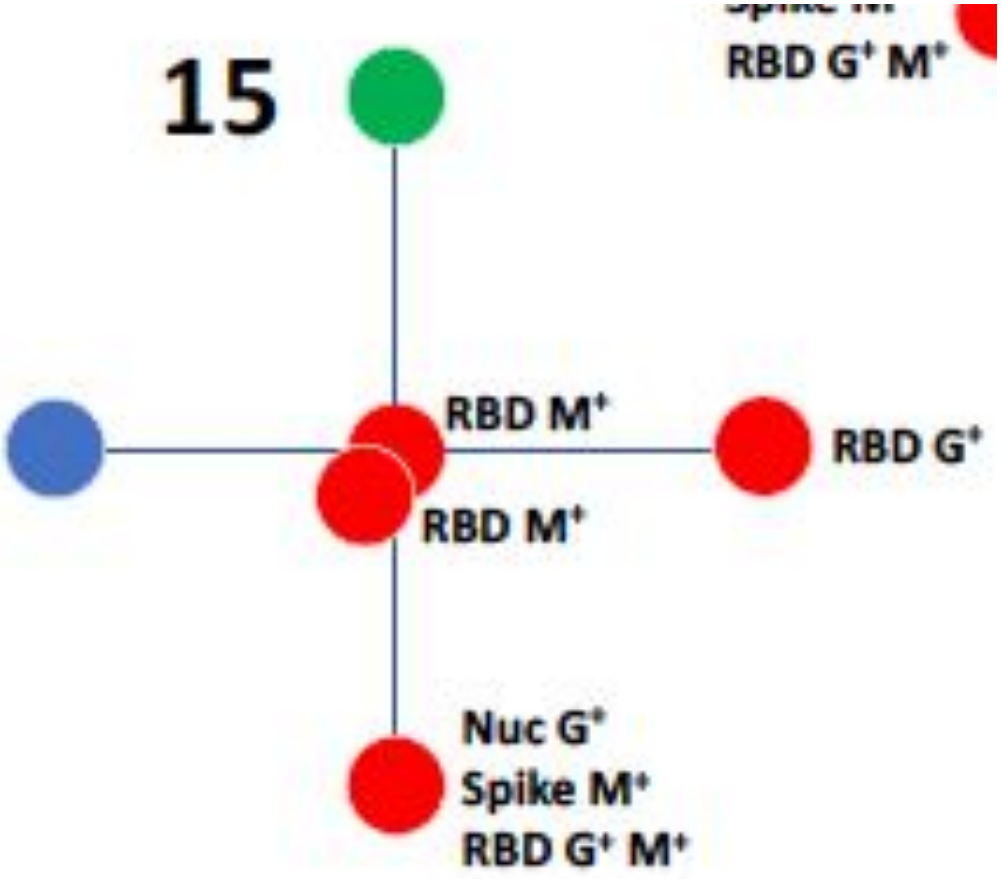
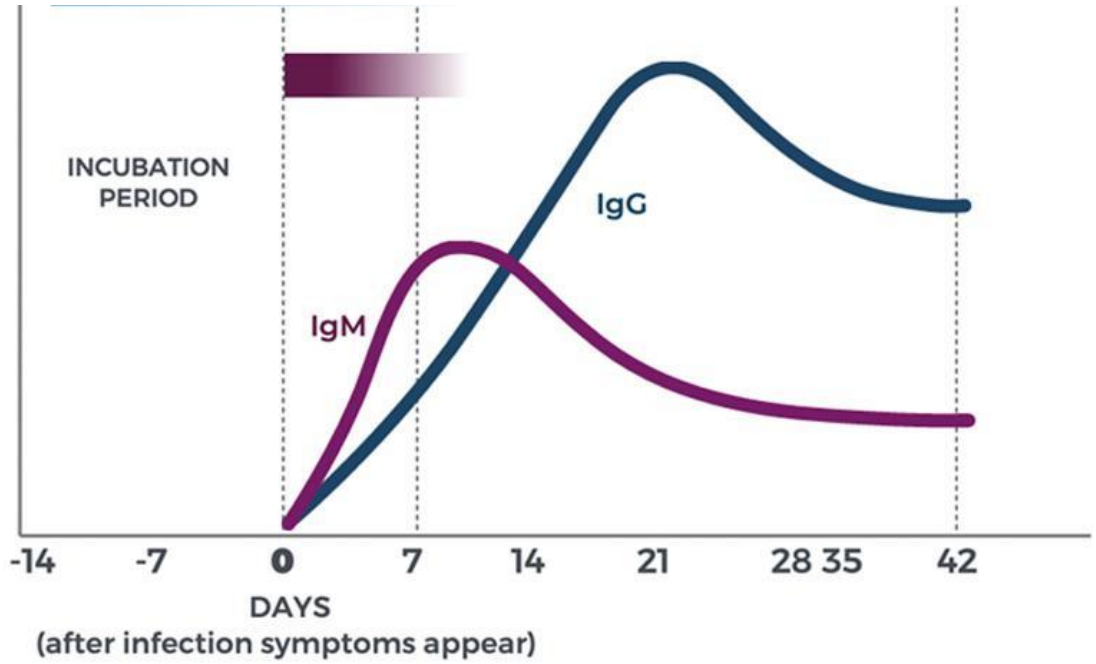
17
Spike G+ M+ A+ RBD G+ M+ A+
Nuc G+ Spike M+ RBD G+ M+
Spike G+ M+ A+ RBD G+ M+ A+
18
Spike M+ RBD G+ M+
RBD G+
Spike M+ RBD G+ M+
19
Spike G+ M+ A+ RBD G+ M+
Nuc G+ Spike G+ M+ A+ RBD G+ M+
Spike G+ M+ A+ RBD G+ M+ A+
20
Spike G+ A+ RBD G+ M+ A+
Nuc G+ Spike G+ M+ A+ RBD G+ M+ A+
Spike G+ M+ A+ RBD G+ M+ A+
Spike G+ A+ RBD G+ M+
Spike M+ RBD G+ M+
RBD G+
Spike G+ M+ A+ RBD G+ M+ A+
RBD G+ M+
Spike G+ A+ RBD G+ M+
Positive
Negative
Unknown

# Transmission from other household members?

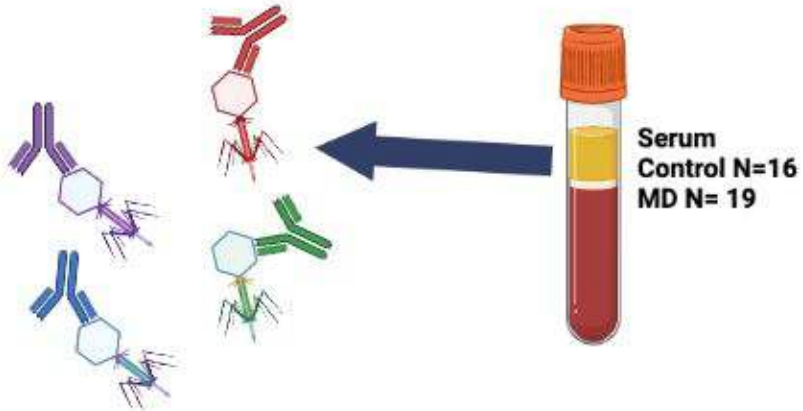


# Household Viral Exposure in Children with Mitochondrial Disease During COVID-19 Study

A study to learn more about the role of viral infection and biomarkers of immunity in mitochondrial disease using new technology with Neoteryx™ fingerstick at-home sampling.


# Can we assess the entire antiviral antibody repertoire?

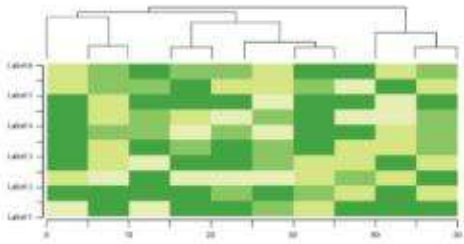



Serum
Control N=16
MD N= 19

>100,000 peptides

>9,000 proteins

>1,300 viral species



# VirScan articles

*RESEARCH*

RESEARCH ARTICLE

VIRAL IMMUNOLOGY

## Comprehensive serological profiling of human populations using a synthetic human virome

George J. Xu,[1,2,3,4]* Tomasz Kula,[3,4,5]* Qikai Xu,[3,4] Mamie Z. Li,[3,4] Suzanne D. Vernon,[6] Thumbi Ndung'u,[7,8,9,10] Kiat Ruxrungtham,[11] Jorge Sanchez,[12] Christian Brander,[13] Raymond T. Chung,[14] Kevin C. O'Connor,[15] Bruce Walker,[8,9] H. Benjamin Larman,[16] Stephen J. Elledge[3,4,6]†

PNAS

## Temporal virus serological profiling of kidney graft recipients using VirScan

Pierre Isnard[a,b,1], Tomasz Kula[c,d,1], Véronique Avettand Fenoel[e,f], Dany Anglicheau[a,b,f], Fabiola Terzi[a], Christophe Legendre[a,b,f], Stephen J. Elledge[c,d], and Guillaume Canaud[a,b,f,2]

[a]INSERM U1151, Institut Necker Enfants Malades, Hôpital Necker-Enfants Malades, 75015 Paris, France; [b]Service de Néphrologie Transplantation Adultes, Hôpital Necker-Enfants Malades, 75015 Paris, France; [c]Division of Genetics, Department of Medicine, Howard Hughes Medical Institute, Brigham and Women's Hospital, Boston, MA 02115; [d]Department of Genetics, Harvard University Medical School, Boston, MA 02115; [e]Laboratoire de Virologie, Hôpital Necker-Enfants Malades, 75015 Paris, France; and [f]Université Paris Descartes, Sorbonne Paris Cité, Hôpital Necker-Enfants Malades, 75006 Paris, France

VIRAL IMMUNOLOGY

## Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens

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LETTERS

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## The repertoire of maternal anti-viral antibodies in human newborns

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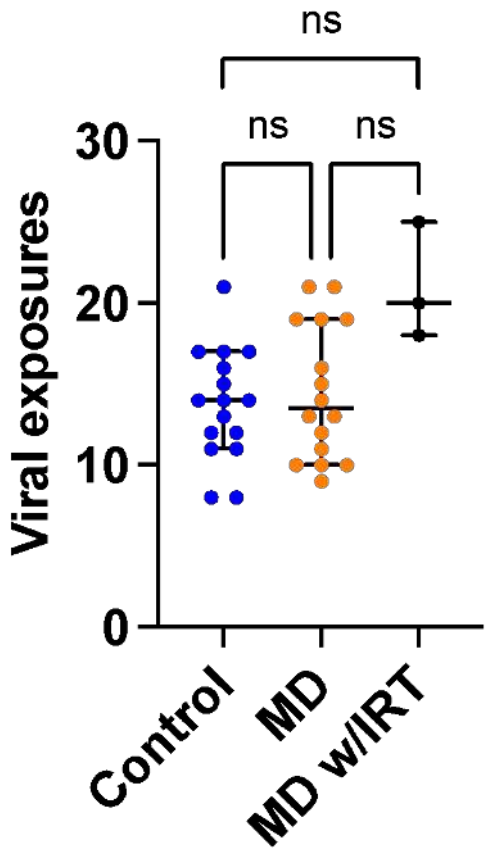
# Viral exposures via the AntiViral Antibody Response Deconvolution Algorithm (Monaco et al., bioRxiv, 2018)

- Disproportionate representation of viruses
- Antibody cross-reactivity for related viruses



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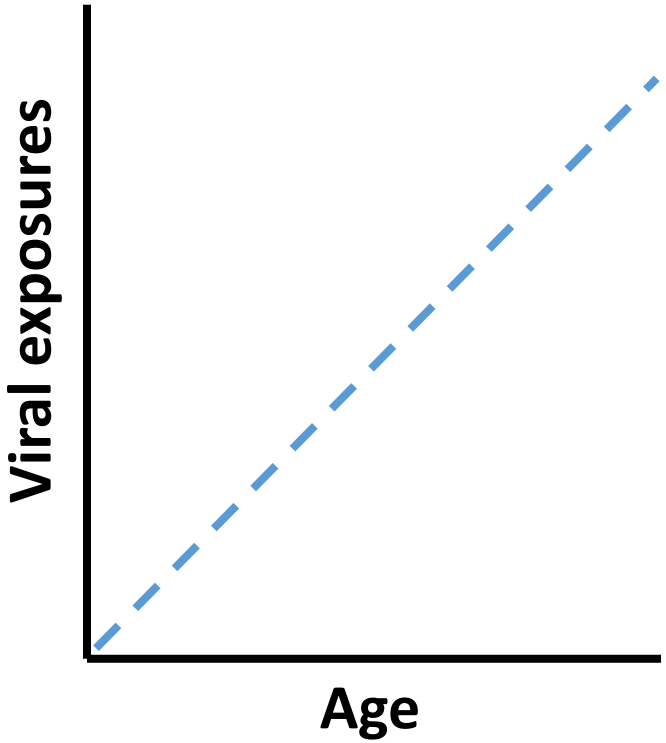


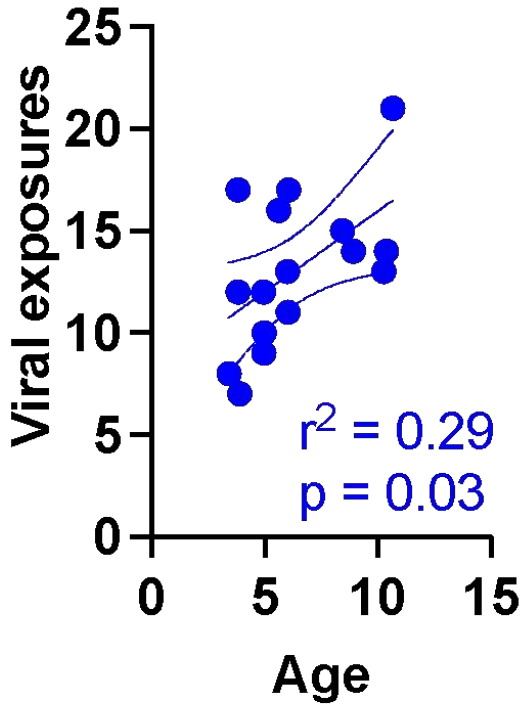


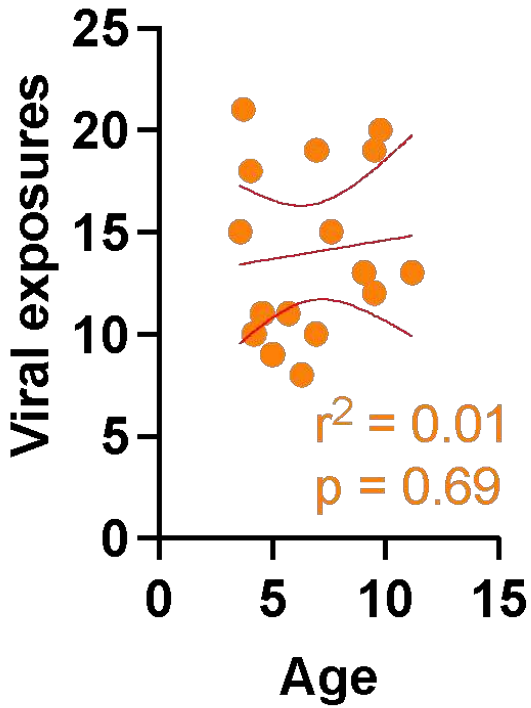

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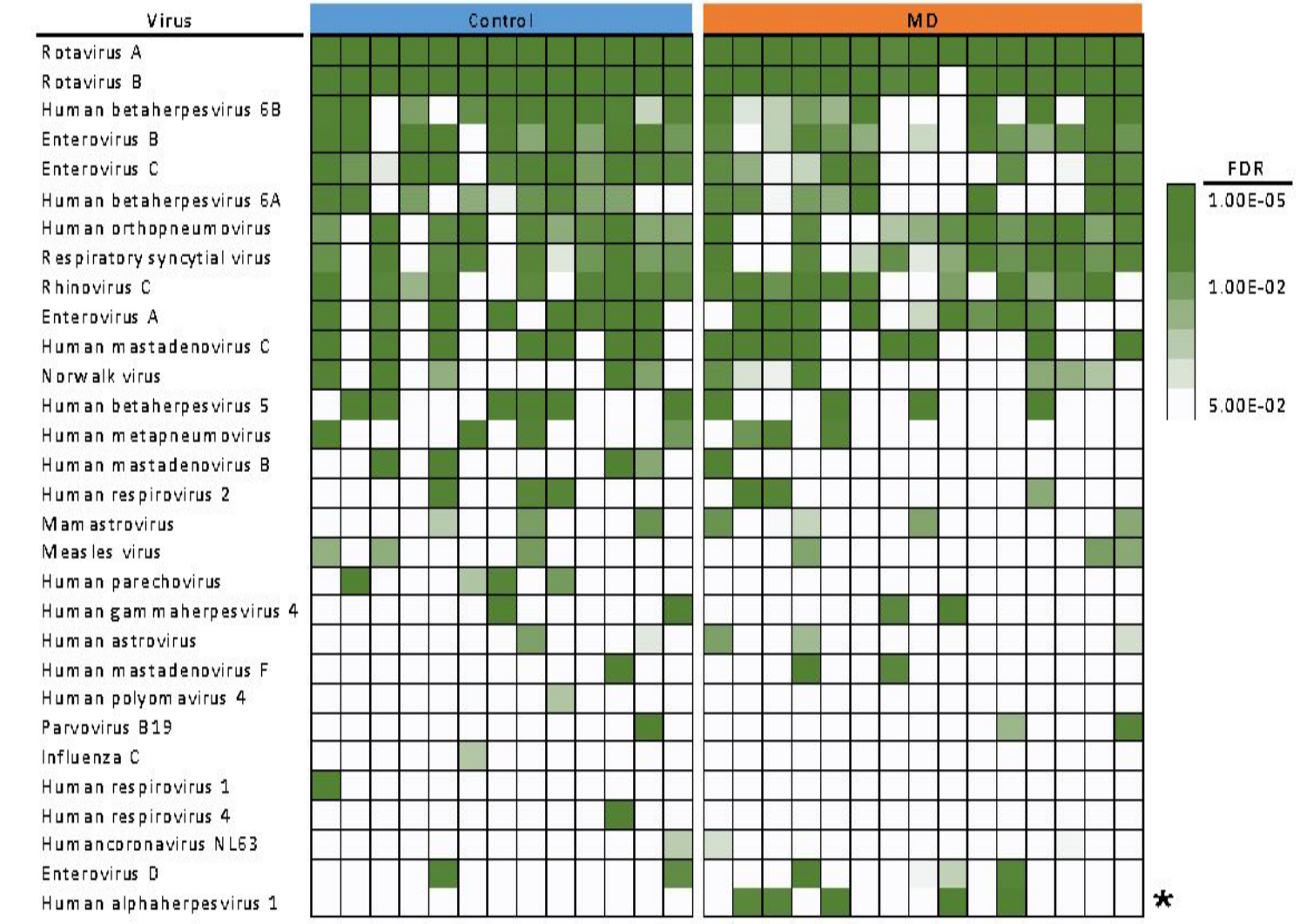
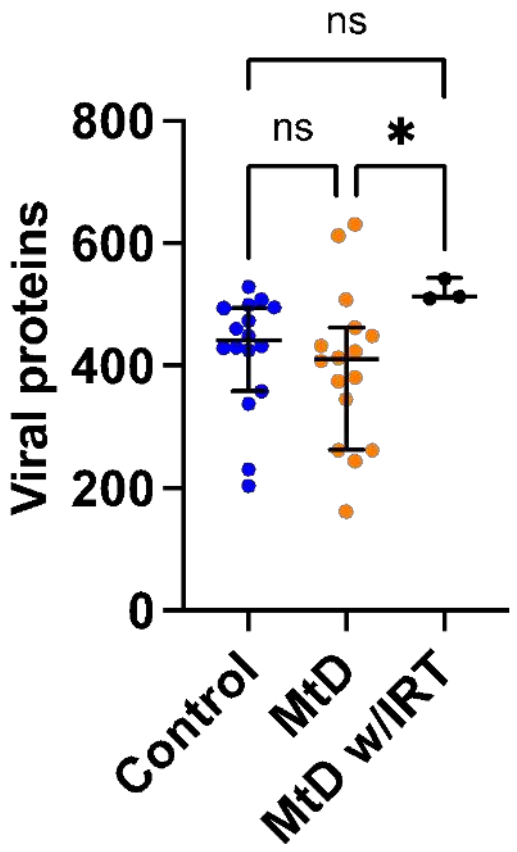


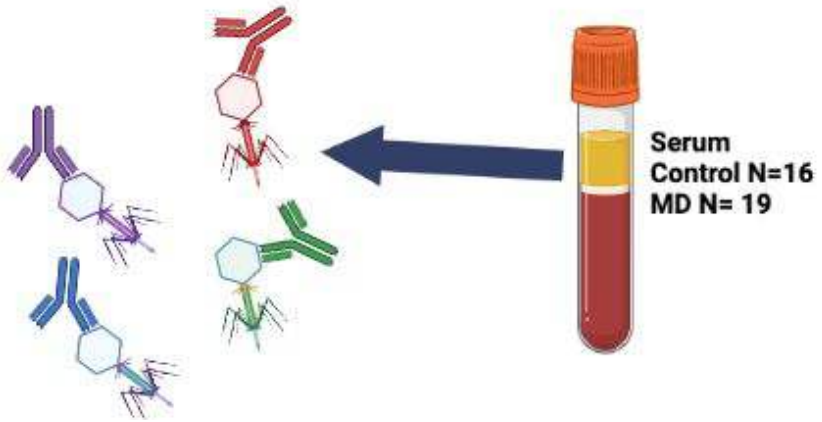
# Viral exposures via the AntiViral Antibody Response Deconvolution Algorithm (Monaco et al., bioRxiv, 2018)

| Control | |
|---|---|
| Virus | % positive |
| Rotavirus A | 100 |
| Rotavirus B | 100 |
| Enterovirus C | 92 |
| Human betaherpesvirus 6B | 85 |
| Enterovirus B | 85 |
| Respiratory syncytial virus | 77 |
| Human orthopneumovirus | 77 |
| Rhinovirus C | 69 |
| Human betaherpesvirus 6A | 69 |
| Enterovirus A | 62 |

| MD | |
|---|---|
| Virus | % positive |
| Rotavirus A | 100 |
| Rotavirus B | 93 |
| Human betaherpesvirus 6B | 80 |
| Enterovirus B | 80 |
| Respiratory syncytial virus | 80 |
| Human orthopneumovirus | 73 |
| Rhinovirus C | 73 |
| Enterovirus C | 67 |
| Human betaherpesvirus 6A | 60 |
| Enterovirus A | 60 |

# Number of viral proteins per individual

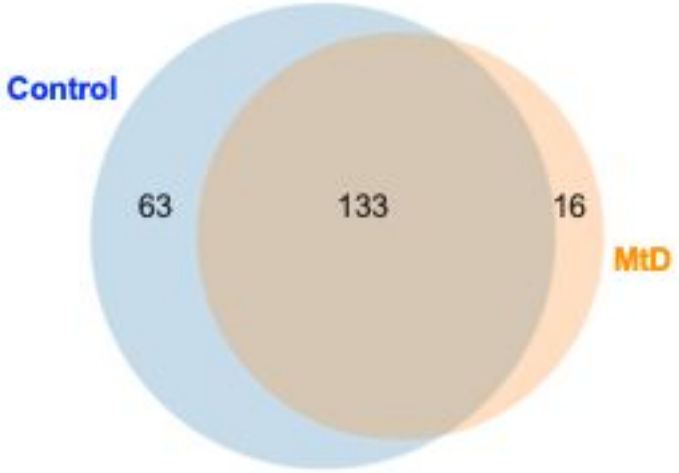


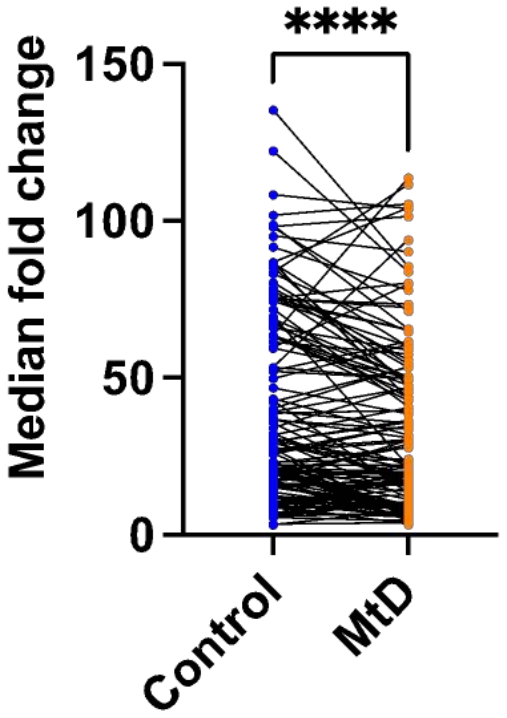




Controls mean age = 6.4 years old

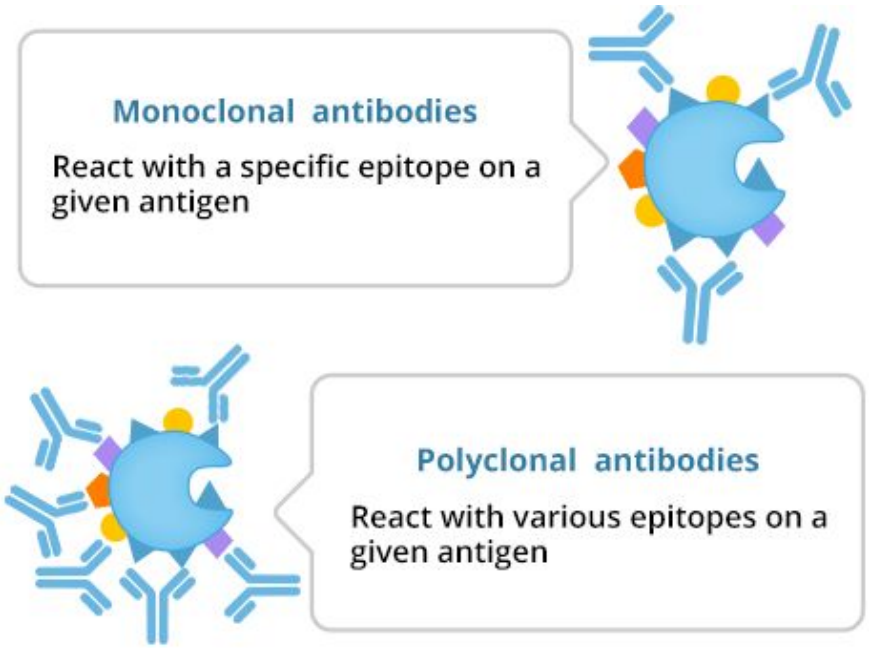
MtD mean age = 6.6 years old

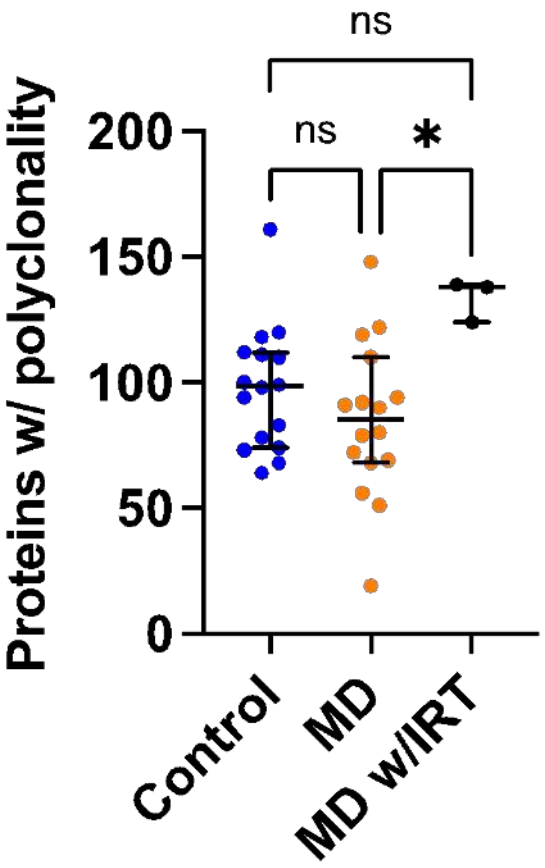
# Shared/unique proteins



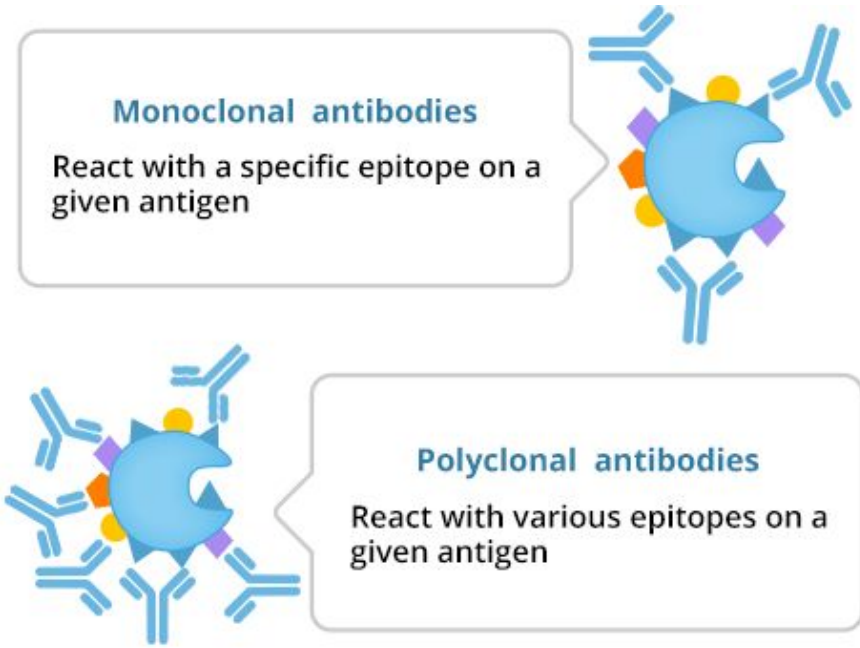



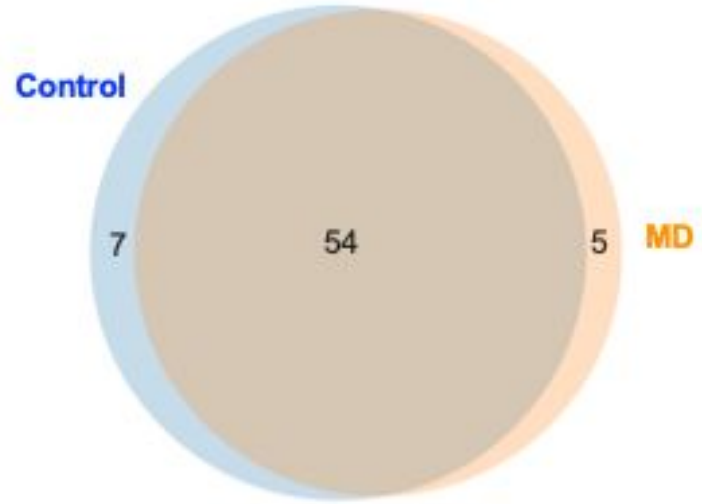
# Polyclonality for individuals

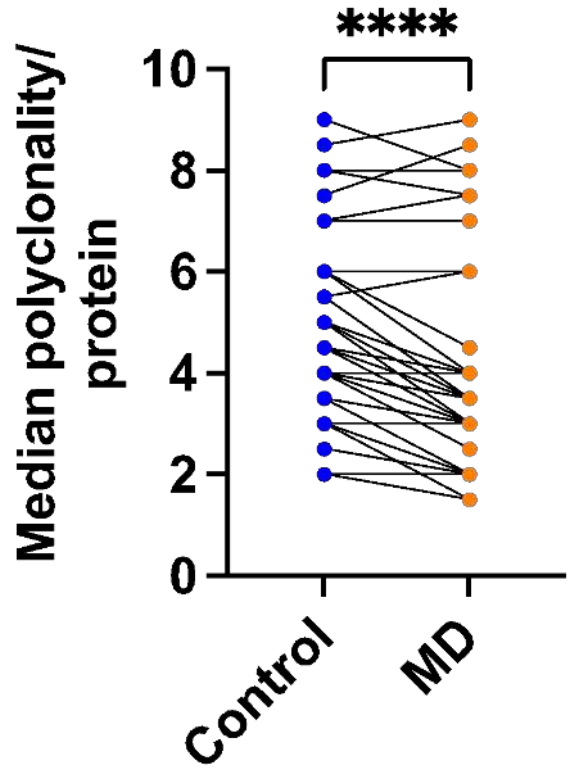


# Polyclonality for shared/unique proteins



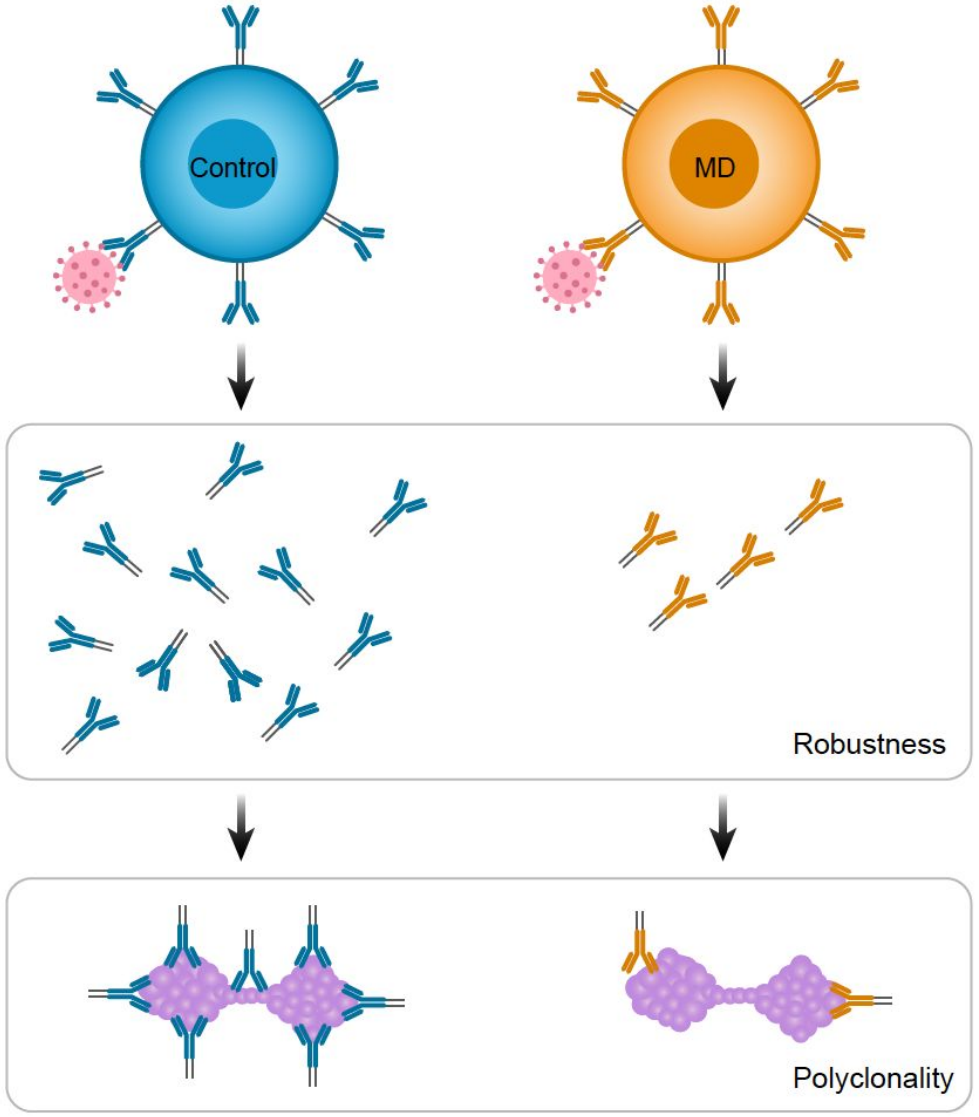



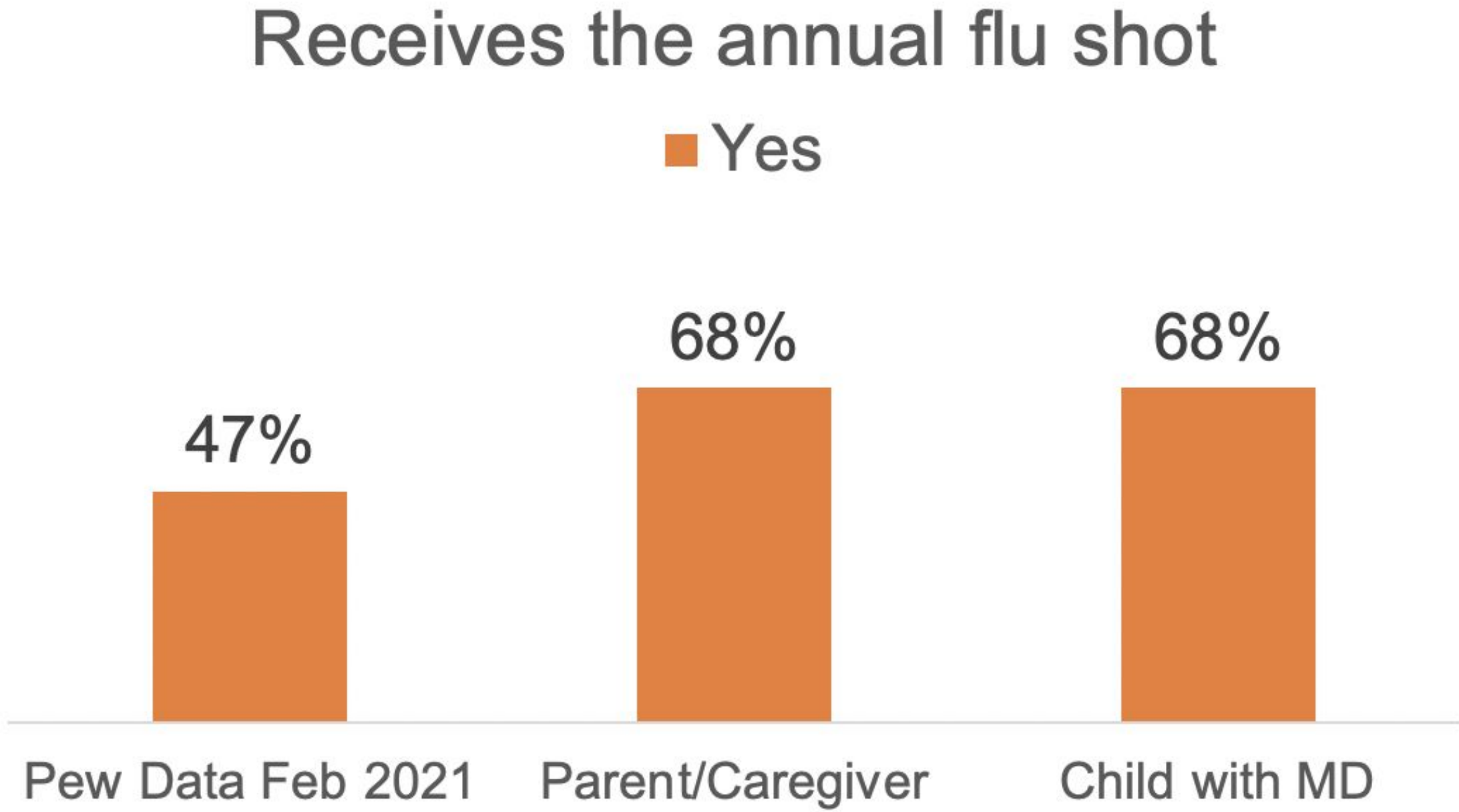
# Summary

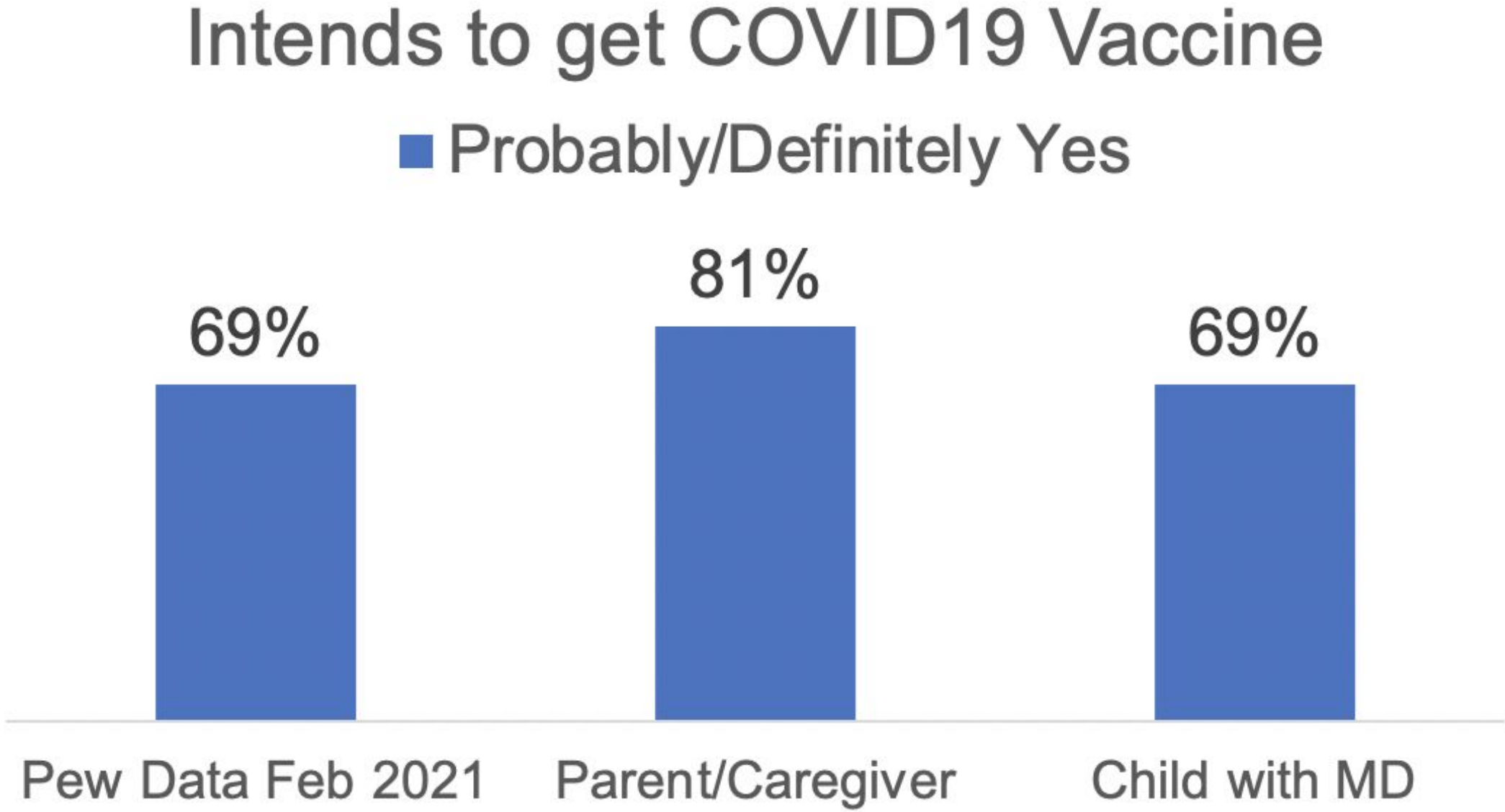
**Children with MtD:**

- Infection is inevitable
  - Viral exposure signatures are similar to healthy children
- Limitations in the antibody repertoire
- Asynchronous relationship with viral exposure
  - ↑↑ exposure at earlier age
- HSV-1 exposures earlier
  - ?natural host
  - Chronic neurodegeneration
- Necessary to start building a compendium of viral exposures in MtD

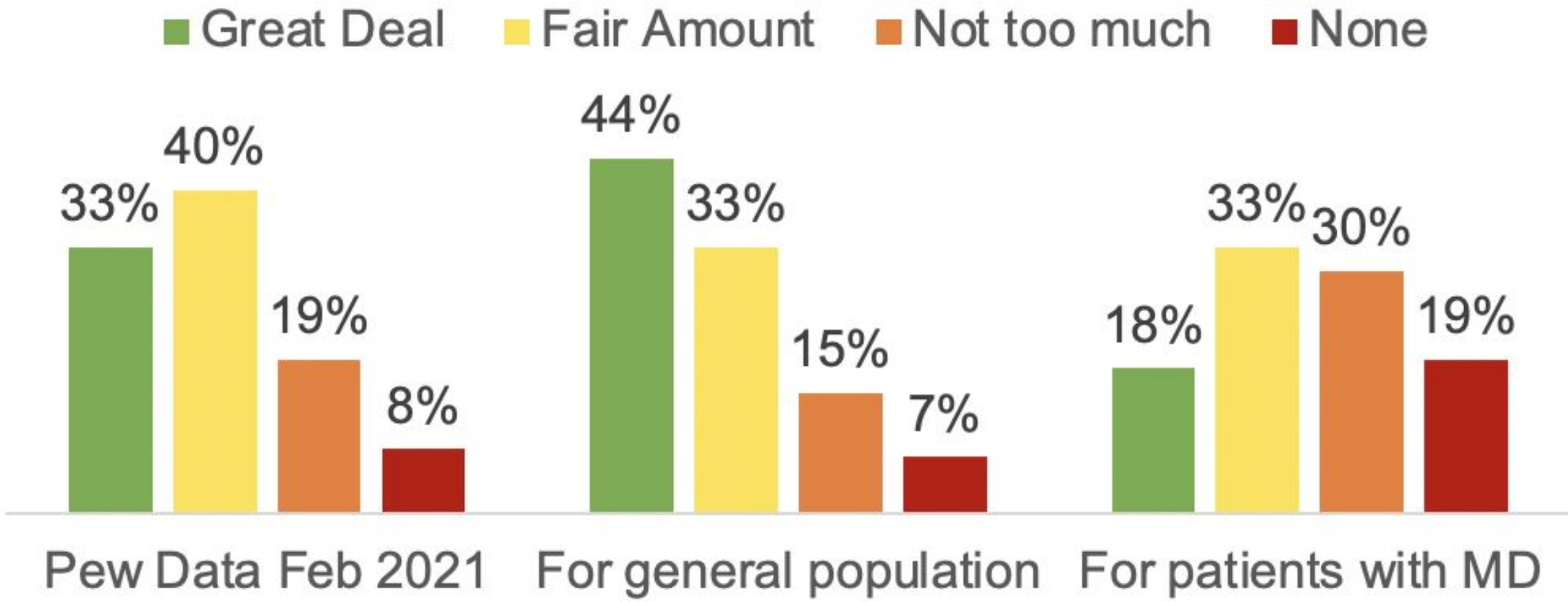


# Vaccine hesitancy and the COVID-19 vaccine

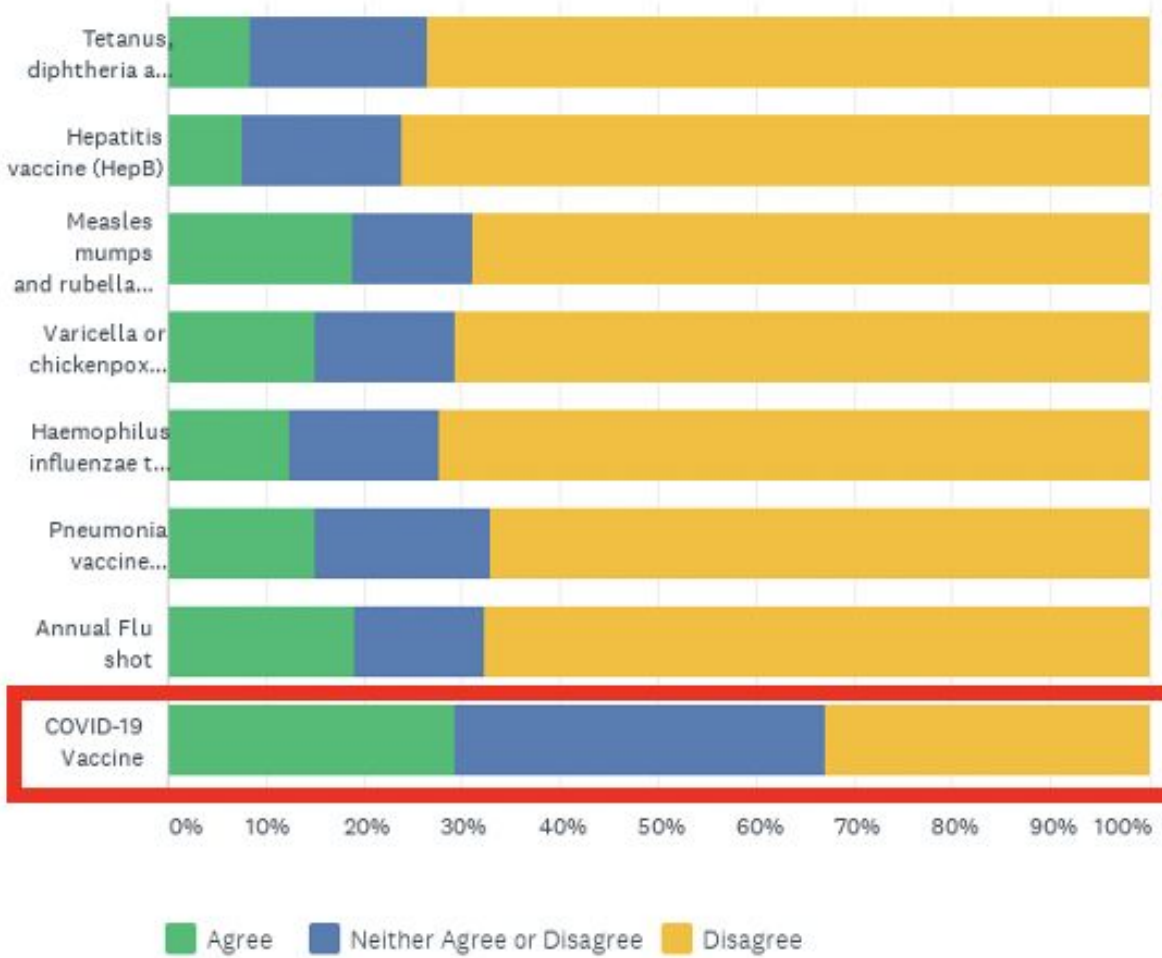

Receives the annual flu shot
Yes
47%
68%
68%
Pew Data Feb 2021
Parent/Caregiver
Child with MD


Intends to get COVID19 Vaccine
Probably/Definitely Yes
69%
81%
69%
Pew Data Feb 2021
Parent/Caregiver
Child with MD

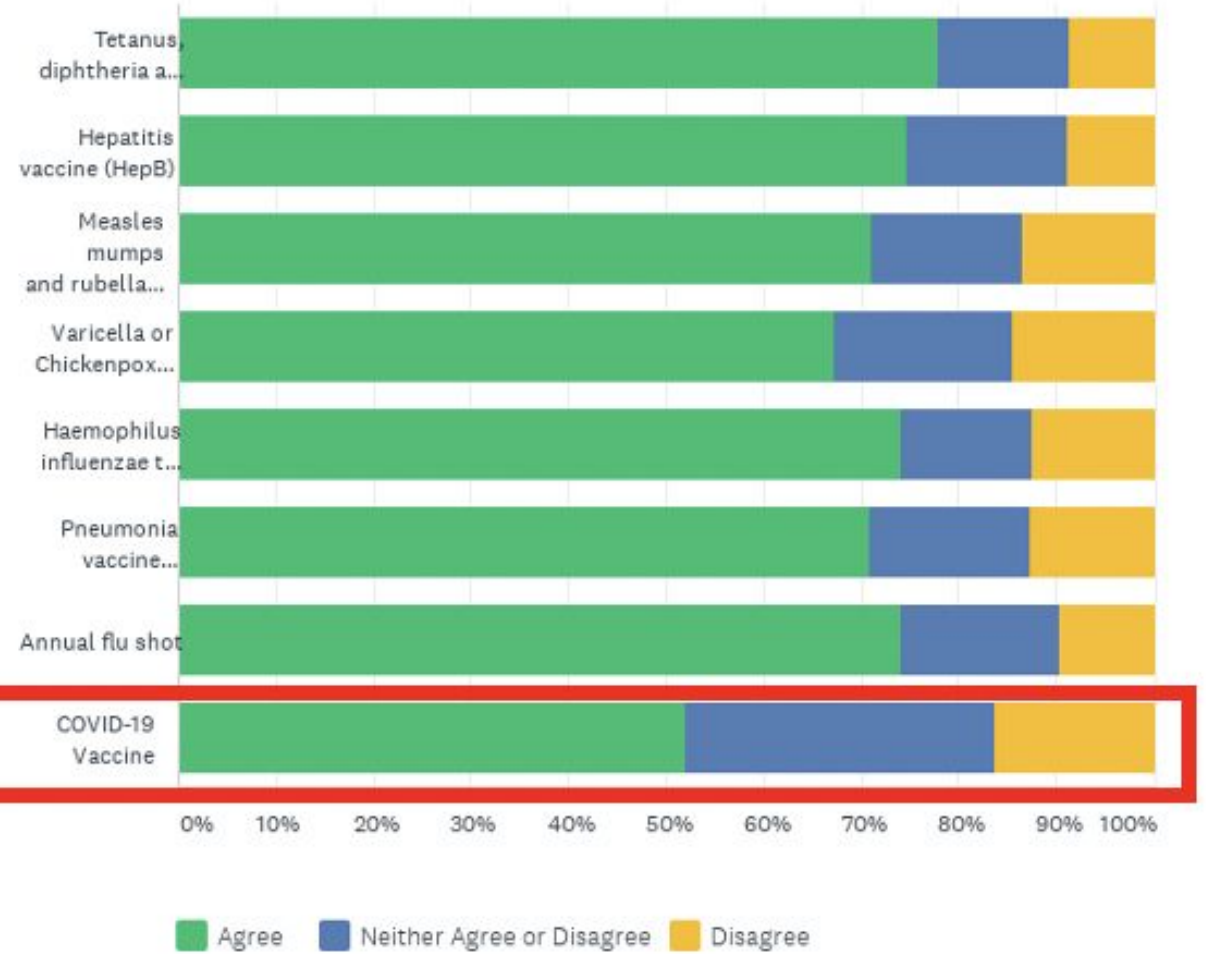
# Confidence in Safety/Efficacy of COVID19 Vaccine

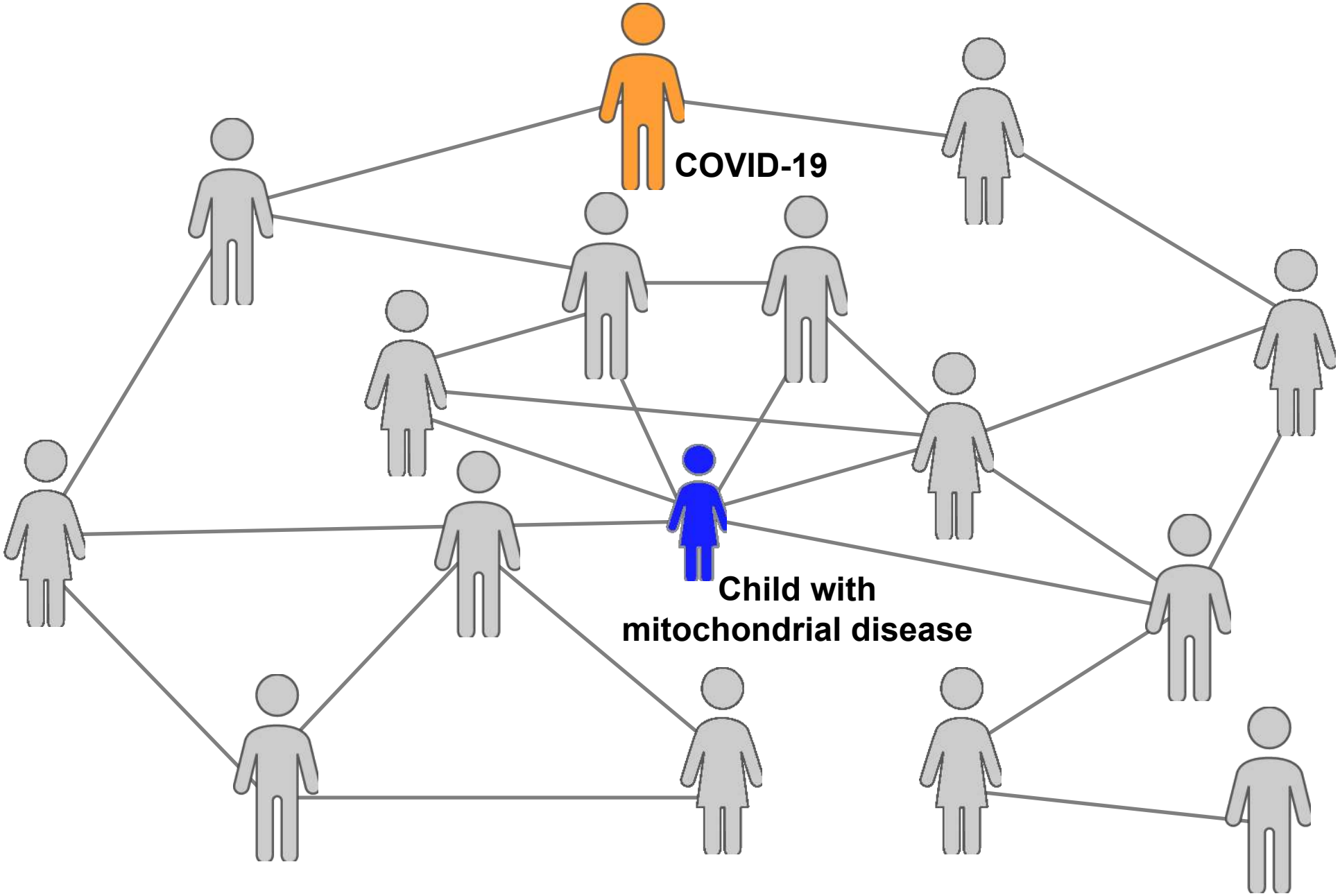


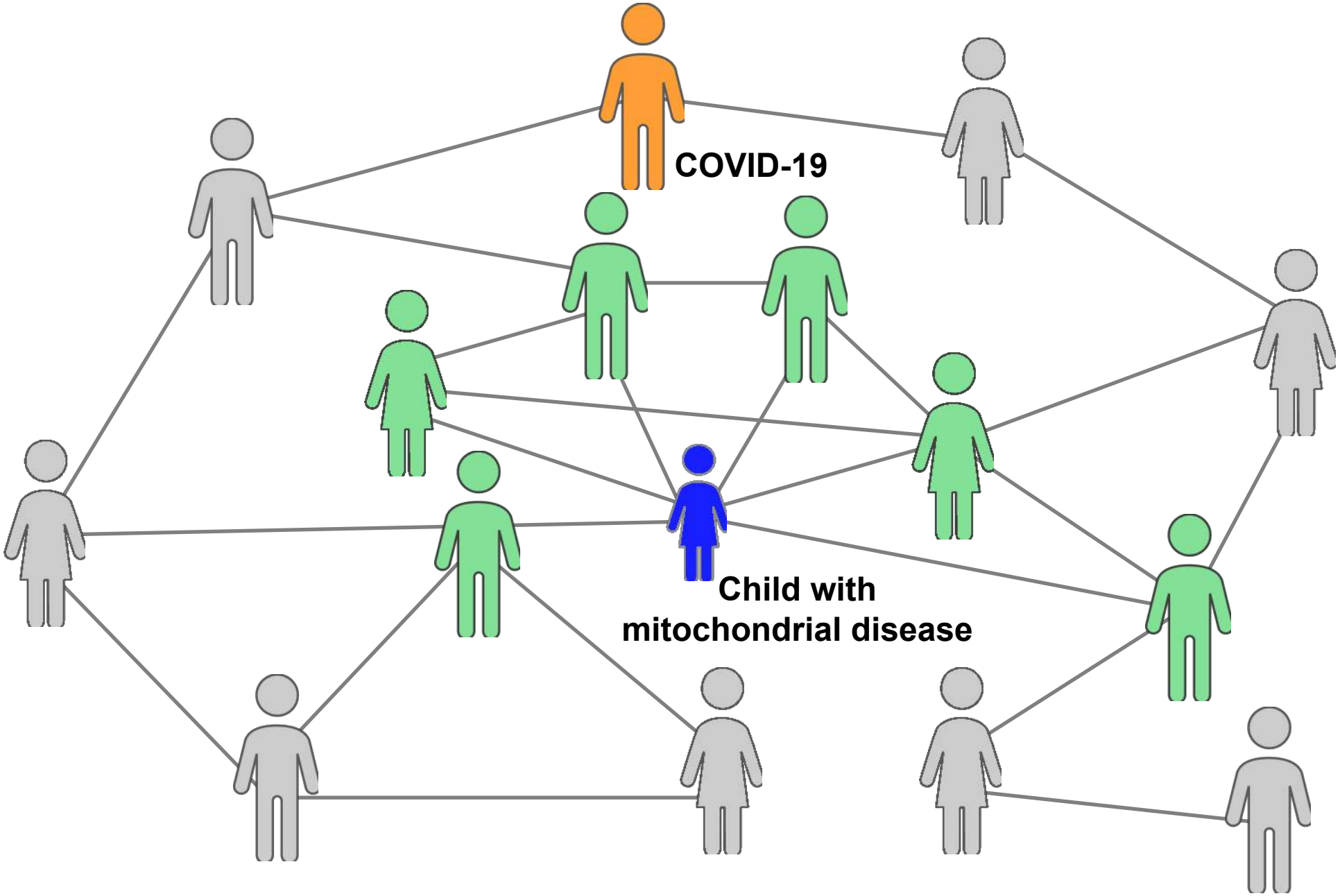
## "I am concerned that my child with MtD will become sick or deteriorate after the following vaccinations:"




## "The benefits of the following vaccines outweigh the risks in children with MtD."




COVID-19
Child with
mitochondrial disease


COVID-19
Child with
mitochondrial disease

# Post COVID-19 Vaccine Registry for Patients with Mitochondrial Disease

The NIH Metabolism, Infection and Immunity (MINI) Section invites people with mitochondrial disease who have already received the COVID-19 vaccine to participate in our new initiative: **the Post COVID-19 Vaccine Registry**.

# Interim data from registry

- 66 patients/caregivers
  - 14 children
- Diagnoses: MtD not otherwise specified (23%), mitochondrial myopathy (23%), and MELAS (13%).
- 20% immunodeficiency/immunocompromised
- 12% previous adverse reaction
- Side effects: injection site reaction (62%), fatigue (47%), aches (26%), headache (24%), weakness (18%), fever (10%), allergic reaction allergic reaction (1.5%), no symptoms (15%)

# Summary

- Individuals with MtD have risk factors for adverse outcomes with COVID-19
- Families with MtD are highly adherent to RMBs
- COVID-19 was widespread and underdiagnosed in MtD households
- RMBs may have worked
- Vaccine hesitancy occurs in the MtD community
- Ring vaccination is important
- Studies are ongoing: viral exposures, acute infection, vaccine registry

# Thank you



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