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ICTR COVID-19 Clinical Research Center Town Hall

Wednesday March 10, 2021

ICTR COVID-19 Clinical Research Center

https://ictr.johnshopkins.edu/covid-research-center

COVID-19 Steering Committee

- Capital Region Research @ Sibley, Suburban, and HCGH
- Recruitment Innovation Unit
- Research Coordinator Support Service

COVID-19 Outpatient Clinical Research Units

COVID-19 Clinical Research Coordinating Committee

COVID-19 And Data Research Evaluation Committee (CADRE)

COVID-19 Biospecimen Repository Committee

Agenda Part 1- Children and COVID-19

- **Introduction: Kelly Dooley**
- **Part I: Children and COVID-19**
- **Overview of SARS-CoV-2 Infection in Children**
- Anna Sick Samuels, MD, MPH; Assistant Professor of Pediatrics
- **Overview of Studies in Children at JHU**
- Deborah Persaud, MD; Professor, Department of Pediatrics, Interim Chief, Division of Infectious Diseases
- **CCPSEI Cohort Study**
- Nadine Peart, MD; Senior Fellow, Pediatric Infectious Diseases
- **Remdesivir PK Study in Children**
- Allison Agwu, MD, ScM; Associate Professor, Pediatrics, Division of Infectious Diseases
- **Convalescent Plasma in Children**
- Oren Gordon, MD; Senior Fellow, Pediatric Infectious Diseases
- **Studies at All Children's Hospital**
- Neil Goldenberg, MD; Ph.D.; Professor and Director of Research
- Raquel Hernandez, MD; Assistant Professor, Pediatrics
- **SARS-Co-V-2 Vaccines and Children**
- Kawsar Talaat, MD, Assistant Professor, Johns Hopkins Bloomberg School of Public Health
- **Emergency Pediatrics During the COVID-19 Pandemic**
- Kemi Badaki-Makun, MD, Assistant Professor, Pediatric Emergency Medicine
- **Cardiac Complications of SARS-CoV-2**
- Cedric Manlhiot, Assistant Professor, Pediatric Cardiology

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Agenda Part 2- Pregnant Women and COVID

- **Part 2: Pregnant Women and COVID**
- **COVID-19 in Pregnancy, an Overview plus Remdesivir in Pregnancy, A Clinical Trial**
- Ahizechukwu Eke, MD, PhD, Assistant Professor, Maternal-Fetal Medicine, Department of Obstetrics and Gynecology
- **Convalescent Plasma in Pregnancy**
- Jeanne Sheffield, Professor of Obstetrics and Gynecology, Division Director, Maternal-Fetal Medicine
- **Immune Responses to SARS-CoV-2 Infection in Pregnant Women**
- Irina Burd, MD, PhD, Professor of Obstetrics and Gynecology; Director, Integrated Research Center for Fetal Medicine

- **Discussion & Q&A**

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Overview of SAR-CoV2 Infection in Children

Anna Sick-Samuels, MD, MPH

Assistant Professor of Pediatrics, Division of Pediatric Infectious Diseases

Associate Hospital Epidemiologist, Johns Hopkins Hospital

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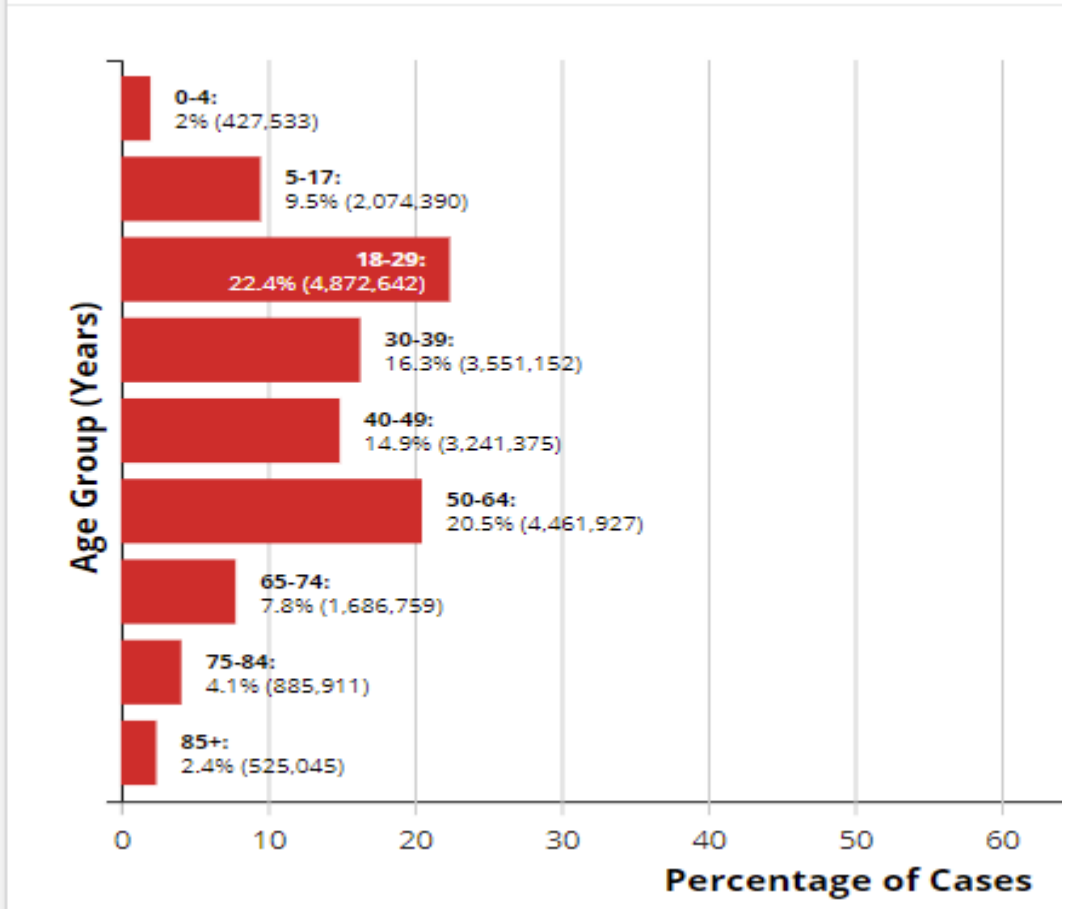
Epidemiology of SARS-COV-2 in Children



https://covid.cdc.gov/covid-data-tracker/#demographics

BMJ 2021; 372 doi: https://doi.org/10.1136/bmj.n385

Symptom	Range
Asymptomatic	**16-19%**
Fever	48-59%
Cough	39-56%
Rhinorrhea, nasal congestion	7-20%
Myalgia	14-19%
Sore throat	14-18%
Headache	3-13%
Tachypnea, dyspnea	8-12%
Diarrhea	7-10%
Nausea, vomiting	2-9%
Abdominal pain	6-7%
Fatigue	5-8%
Rash	<1%

Remaining Questions

- Are children at lower risk for getting infected if exposed?
    - More asymptomatic/unrecognized infections?
    - Just under-tested?
    - Biologic reason? (eg, decreased viral entry)
    - Protective immunity?
- Why do children have more mild manifestation?
- Are children less likely to transmit to others? Is this age or interaction dependent?

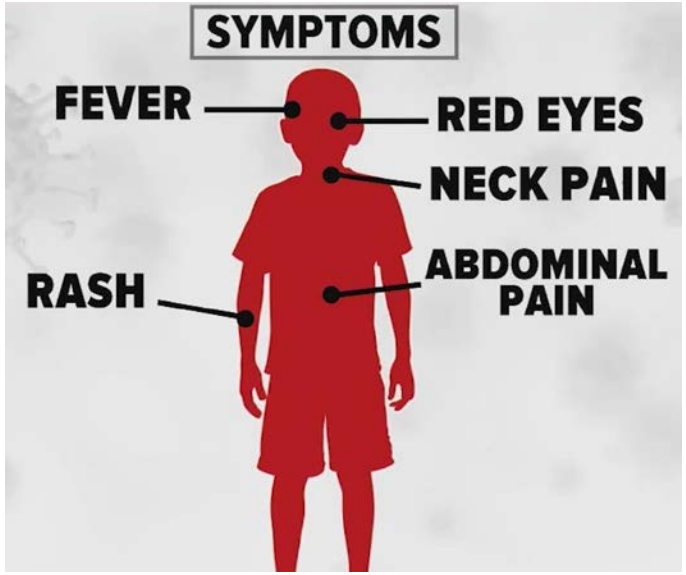
Multisystem Inflammatory Syndrome in Children (MISC)

TOTAL MIS-C CASES MEETING CASE DEFINITION*

2617

TOTAL MIS-C DEATHS MEETING CASE DEFINITION

33



- Post-infectious inflammatory illness ~4 weeks after infection
- Can rapidly progress to cardiac failure/hypotension
- 2/3 go to ICU
- 2-4% death
- Previously healthy, median age 8-9 years
- 2/3 among Hispanic or Black children

BMJ 2021; 372 doi: https://doi.org/10.1136/bmj.n385
https://www.cdc.gov/mis-c/cases/index.html
https://media.kvue.com/assets/KVUE/images/af3afd57-9bd8-4622-bfa1-8de86e3b08a4/af3afd57-9bd8-4622-bfa1-8de86e3b08a4_1920x1080.jpg

Unanswered questions

- What is the pathophysiology of MIS-C?
  - —Different than Kawasaki's disease?
  - —Inform treatment options and timing
  - —Long-term sequelae
- What are the risk factors for MIS-C?
  - —Biologic risk factors
  - —Protective immunity
- Can SARS-COV-2 infection lead to other aberrant immune responses or autoimmune conditions?

Overview of Studies of SARS-CoV-2 in Children at Johns Hopkins

Deborah Persaud, MD, Professor of Pediatrics, Division of Pediatric Infectious Diseases

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Rationale for Pediatric Studies

- **Epidemiology of coronavirus disease 2019 (COVID-19) in children is challenging to establish**
  - —High prevalence of asymptomatic infection
- **Lower secondary attack rates in children compared to adults in household studies**
  - —may reflect lower testing in children and overall reduced exposure
  - —may not reflect differences in biological susceptibility
- **Shorter periods of shedding of infectious virus in children and less broad antibody responses than in adults**
  - —make diagnosis challenging
  - —raise concerns for vaccine efficacy

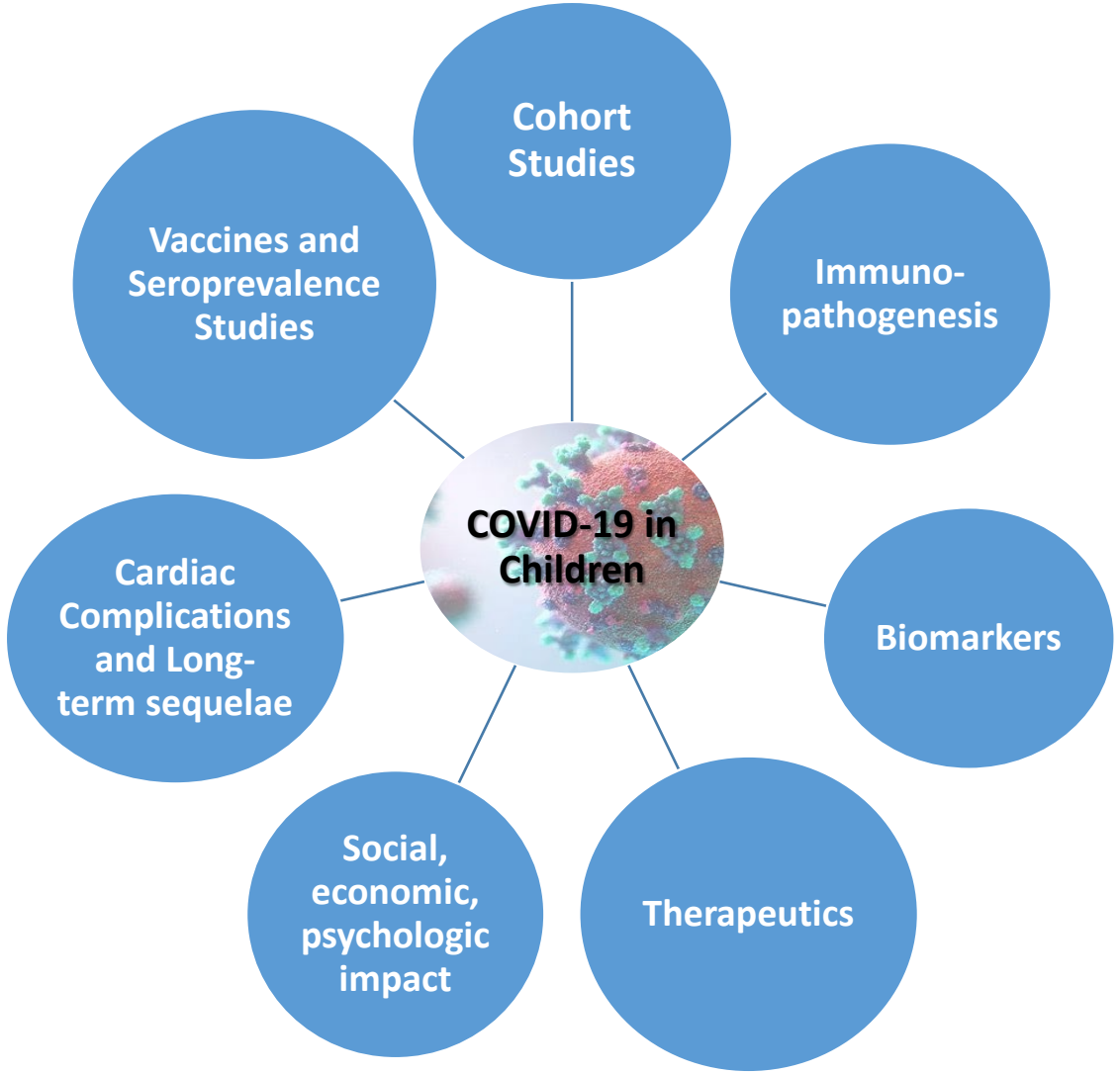
Hyde Z, Differences in SARS-CoV-2 attack rates between children and adults may reflect bias CID 2021: in press

Lower disease prevalence and low mortality raises ethical considerations for vaccine studies in children, especially with newer mRNA platforms

- concerns around enhanced disease, such as MIS-C
- long-term effects, and efficacy unknown

<u>Knowledge gaps in:</u>

- Epidemiology
- Immunopathogenesis
- Optimal therapies
- Immune responses
- Long-term consequences
- Risk-benefit assessment of mRNA SARS vaccine platform in children



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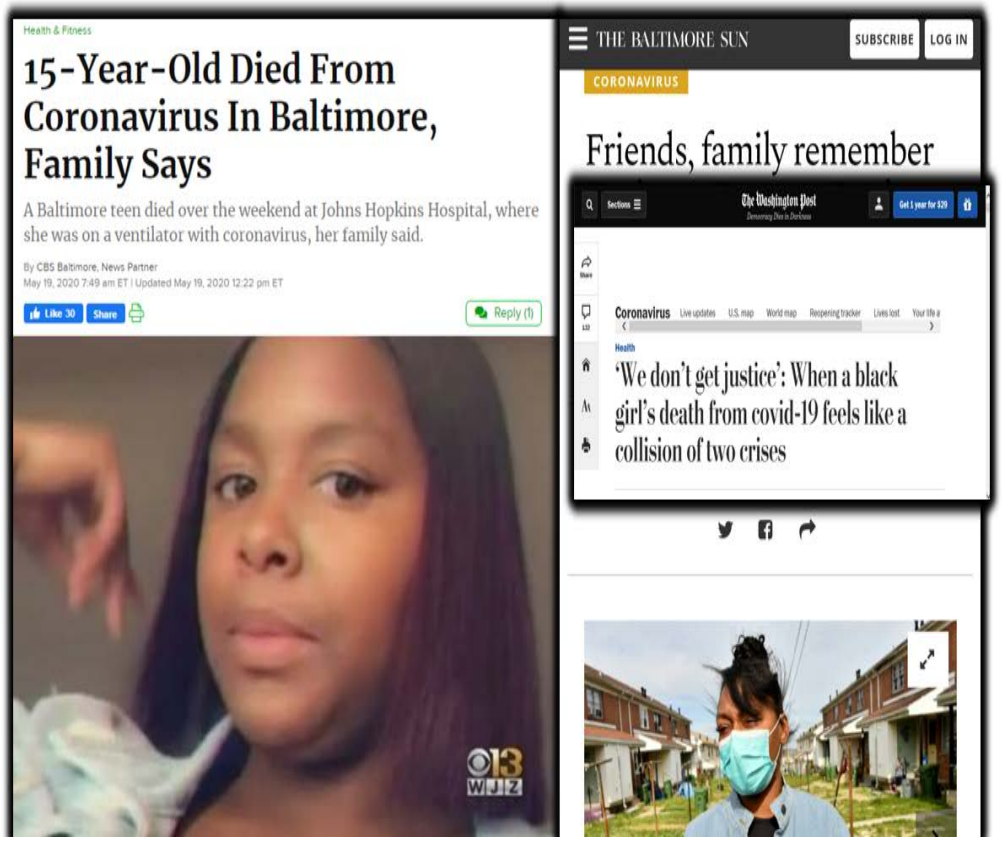
Johns Hopkins Children's Center SENTINEL EVENT (May 2020)

- 15 y/o previously healthy adolescent girl (Dar'yana Dyson) who died within 4 days of presentation (Day 11 of an illness)
- Presented with one wk of epigastric pain, and anorexia, and two days of nasal congestion and rhinorrhea
- No sore throat, dyspnea, or cough
- Concern for intraabdominal process--transferred to JHU; COVID PCR test negative x 2
- Over the next 4 days, she developed worsening abdominal pain, fever, diffuse myalgias, and pleuritic chest pain→ hypotension, increased work of breathing→ hypoxemic respiratory failure → death over <12 hours.
  - Pro-BNP 8328 pg/mL
  - IL-6 239 CRP 30.9 ESR 118 WBC 37.5 B28% ALC 750 PLT 280K
- SARS-CoV-2 IgG and IgA positive; 3rd COVID-19 PCR positive
- Diagnosis: Multisystem Inflammatory Syndrome Related to SARS-CoV-2

"Please say her name and share her story. Teach others. I don't want my baby to have died in vain."



Slide courtesy of Allison Agwu, MD

Beaudry, J et al. PIDJ 2021; 40(2): e72-76

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CCPSEI Cohort Study

Nadine Peart, MD and Deborah Persaud, MD;
Division of Pediatric Infectious Diseases

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Background

- Immune dysregulation in adult patients with COVID-19 has been studied extensively in comparison to children; we are still understanding this disease in children
- Although SARS-CoV-2 in children is most often mild, the Multisystem Inflammatory syndrome in Children (MIS-C), associated with COVID-19 represents a severe phenotype in pediatric patients
- Better understanding of the immune dysregulation in this severe phenotype may inform risk stratification of those susceptible to severe disease and lead to earlier initiation and development of therapeutics to improve outcomes

Liu, J., et al. (2020). EBioMedicine doi: 10.1016/j.ebiom.2020.102763
Dong, et al (2020) Pediatrics doi: 10.1542/peds.2020-0702
Xu, Z.-S., et al. (2020). Signal Transduction and Targeted Therapy doi: 10.1038/s41392-020-0211-1
Satış, H., et al. (2021). Cytokine 137: 155302. https://doi.org/10.1016/j.cyto.2020.155302
Wilson, J. G., et al. (2020). JCI Insight 5(17). 10.1172/jci.insight.140289
Feldstein, L. R., et al. (2020). New England Journal of Medicine 10.1056/NEJMoa2021680

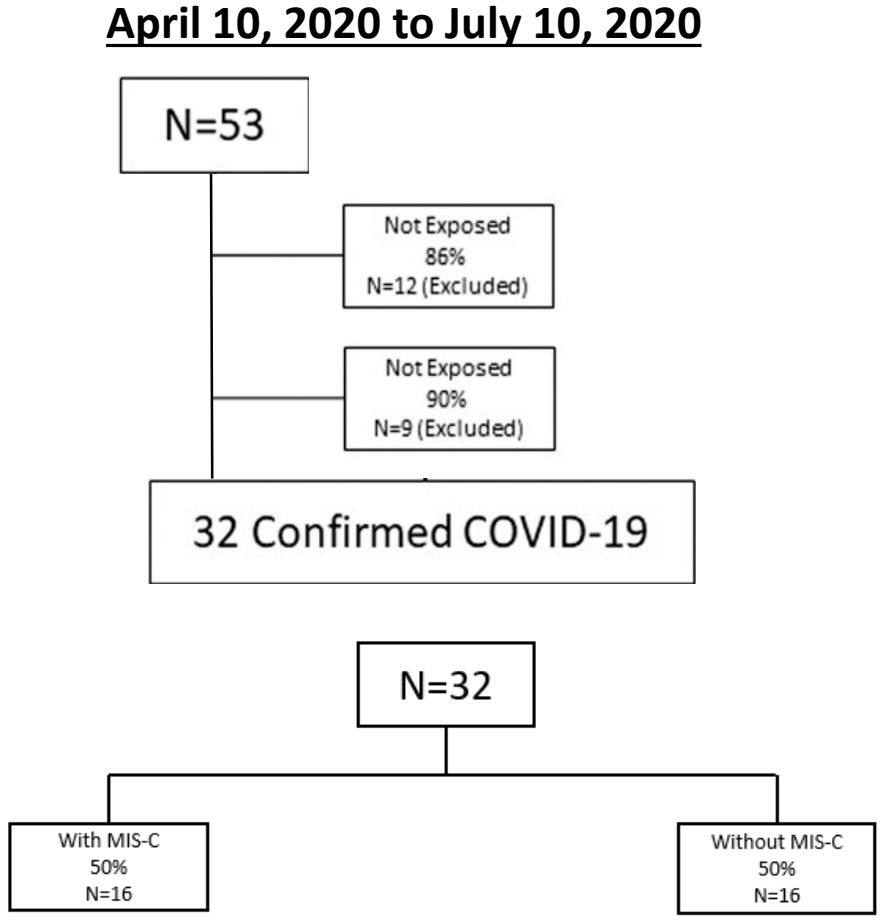
JHU CCPSEI Cohort Study (Insttution Supported) Principal Investigators: Lauren Sauer, MS; Paul Blair, MD (Adult Study); Deborah Persaud, MD (Pediatric Study)

Study Design

- Prospective cohort study nested within an adult study entitled **"Clinical Characterization Protocol for Severe Emerging Infections"**

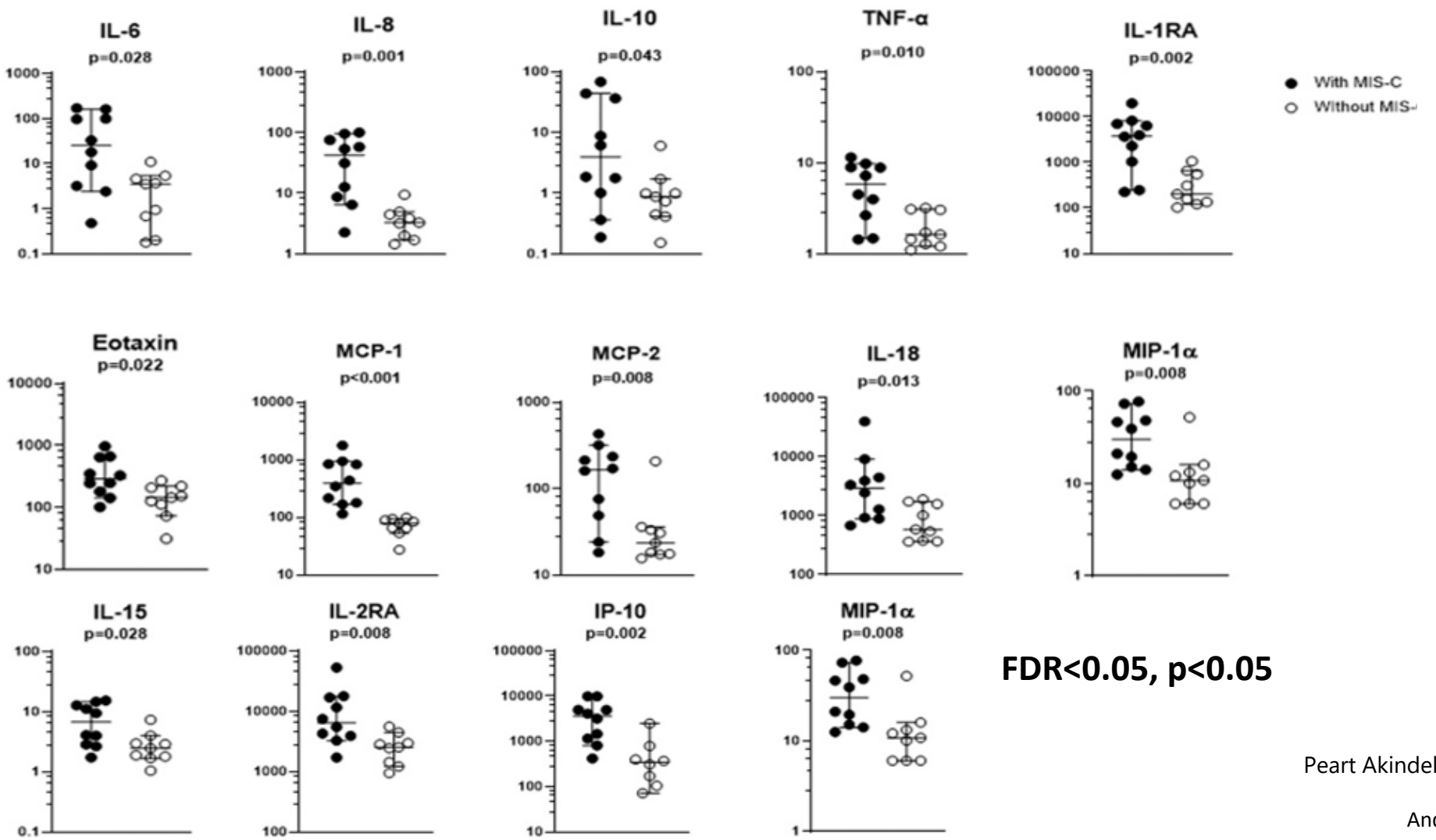
- **Interventions:**
  - ❖ Prospective and/or retrospective sample collection
  - ❖ Medical chart review for clinical, demographic and laboratory data
  - ❖ Cytokine/chemokine profiles
  - ❖ Quantitative viral RNA loads

- **Outcomes/Measures:** Differences between those with and without MIS-C

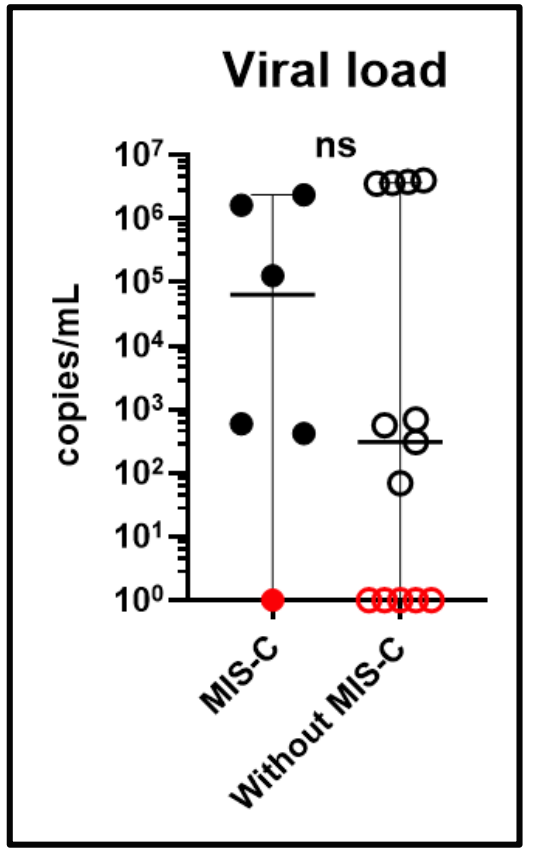


As of March 8, 2021, there are 83 pediatric patients enrolled into the cohort

Results

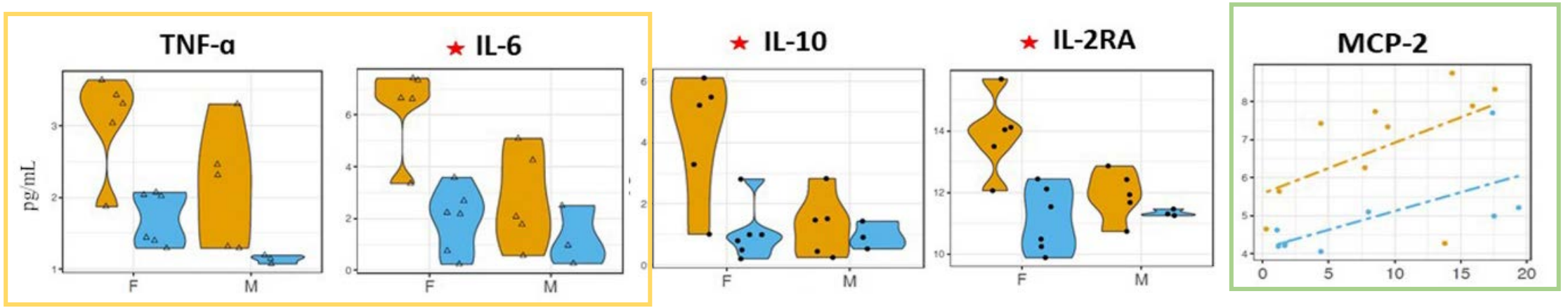


FDR<0.05, p<0.05



Peart Akindele et al,; unpublished data, under review; 2021
Cytokine/chemokine Profiling:
Andrew Karaba, MD, PhD, and Andrea Cox, MD, PhD

Results



- Regardless of age or MIS-C status, **2 cytokines** correlated with female sex, FDR <0.25, p<0.05
- There were **3 cytokines (★)** that also showed a trend of being higher in female patients with MIS-C, FDR <0.25, p<0.05
- Regardless of sex or MIS-C status, **1 cytokine** correlated with age, FDR <0.025, p<0.05

Peart Akindele et al,; unpublished data, under review; 2021

CONCLUSIONS

SARS-CoV-2-infection in children leads to a distinct pattern of heightened cytokine/chemokine dysregulation with MIS-C compared to acute COVID-19, irrespective of age or sex

Remdesivir PK study in Children

Allison Agwu, MD ScM (Site PI)
Aleisha Collinson-Streng, RN (Senior Nurse Study Coordinator)

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A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants from Birth to < 18 Years of Age with COVID-19

- Remdesivir (RDV) in vitro activity against SARS-CoV-2
- Mechanism of action: nucleotide prodrug intracellularly metabolized into analog of adenoside triphosphate inhibiting viral RNA polymerases; has broad activity against CoVs, and other viruses (filoviruses, paramyxoviruses)
- Adult data: RCT showed superior to placebo in shortening time to recovery in adults hospitalized with COVID-19 and lower respiratory tract disease; shorter time to recovery (9-10 days vs. 15 days)
- Overall safe in adults– up to 10 daily infusions
- No data in children (potential for different PK among children)
- Study considerations: While overall children do better with SARS-CoV-2, some may have significant disease and could benefit from administration
- Therefore, higher risk children (hospitalized and needing intervention) selected as the target study population

(Sponsor: Gilead Sciences, Inc)(NCT04431453)

Biegel JH, et al. Remdesivir for the Treatment of COVID-19- Final Report. NEJM 2020: 383: 1813-1826

Primary objective:
Safety, Tolerability (Incidence of SAE)
Secondary objectives:
Efficacy, antiviral activity, change from baseline in oxygenation use, mechanical ventilation or ECMO, clinical improvement, use of medications other than RDV

Exploratory: correlation between reduction in viral shedding and timing and magnitude of immunoglobulin response, emergence of viral resistance to RDV, safety, efficacy, and PK of RDV in participants with laboratory-confirmed COVID-19 with body mass index (BMI) for age ≥ 95th percentile as defined by the CDC

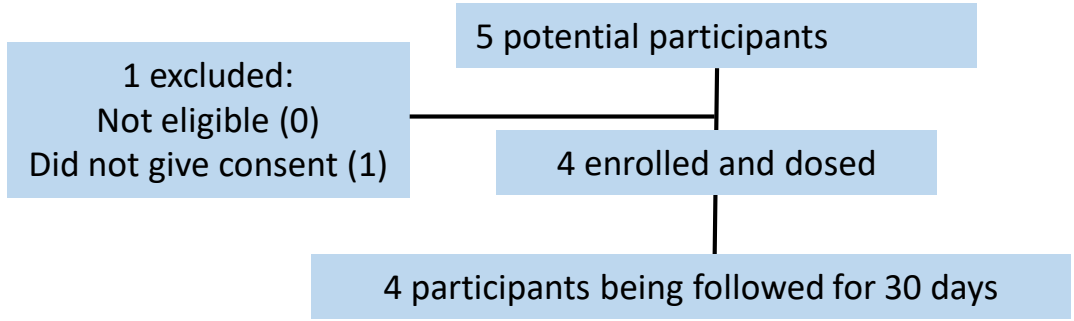
- First prospective pediatric study on RDV among children 0-18 years
- Parenteral administration
- 52 centers (US, UK, Italy, Spain)
- Coordination between HIV Clinical Research Team, Peds ID, Critical Care, Pharmacy, and Pediatric Services
    - Significant off hours commitment

Preliminary results: JHU

- Number of participants: 4 (1 male, 3 females)
- Median age 5.5 years (4 months – 15 years)
- Comorbidities: immunodeficiency, chronic lung disease, genetic/chromosomal anomaly, muscular atrophy
- Median time from presentation to RDV: 2.5 days
- Duration of treatment: average 5 days
- Concomitant meds: 3/4 also received convalescent plasma, all received dexamethasone
- Overall study: 49/52 enrolled

Safety outcomes

- There were no SAEs (JHU); overall data unavailable



At least 52 participants aged 0 days to < 18 years will be enrolled as described in the table below.

Cohort	Description
1	≥ 12 years to < 18 years and weight ≥ 40 kg
2	≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg
3	≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg
4	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg
5	≥ 14 days to < 28 days of age, gestational age > 37 weeks and weight at Screening ≥ 2.5 kg
6	0 days to < 14 days of age, gestational age > 37 weeks and birth weight ≥ 2.5 kg
7	0 days to < 56 days of age, gestational age ≤ 37 weeks and birth weight ≥ 1.5 kg
8	< 12 years and weight ≥ 40 kg

→ open cohorts

Convalescent Plasma in Children

Oren Gordon, MD; Senior Fellow, Pediatric Infectious Diseases

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Safety and Pharmacokinetics of High-Titer Anti-SARS-CoV-2 Human Convalescent Plasma in High-Risk Children (NCT04377672)

- Human convalescent plasma has been used for infection prevention and treatment, including in children, for over a century (e.g., pneumococcus, measles, influenza, SARS)
- While little information was available at the initiation of the study (May 2020), data had accumulated since:
  - Administration of convalescent plasma has been demonstrated to be safe in adults
  - One randomized, double-blind, placebo-controlled trial demonstrated significant benefit in preventing severe respiratory disease with administration of high-titer (>1:1000) convalescent plasma within 72 hours of symptom onset
- On-going studies to test efficacy in adults: early outpatient treatment (NCT04373460; PI: David Sullivan) and prevention following high-risk exposure (NCT04323800; PI: Shmuel Shoham)

Rationale for Pediatric studies

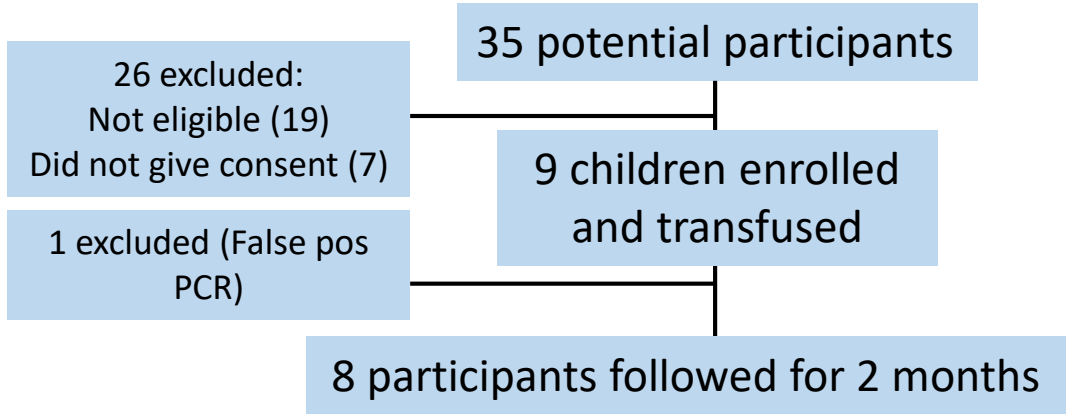
Primary endpoint: Safety (Incidence of SAE)
Secondary objectives: Antibody PK and endogenous immune response

- Convalescent plasma may be different in children:
  - Safety (ADE, allergic reaction, TACO, TRALI)
  - Pharmacokinetics (size and developmental stage may affect antibody distributing and elimination)
  - Potential alteration in endogenous immunological response due to convalescent plasma
- Due to mild disease in children, a more than minimal risk intervention required some potentia
- Therefore, high risk children were chosen as the target population

Casadevall & Pirofski, *J Clin Invest,* 2020; Chen *et al., Lancet Infect Dis,* 2020; Klein *et al., J. Clin. Invest.,* 2020; Joyner *et al., Mayo Clinic Proceedings.,* 2020; Libster *et al., N Engl J Med.,* 2021; Joyner *et al., N Engl J Med.,* 2021

Safety and Pharmacokinetics of High-Titer Anti-SARS-CoV-2 Human Convalescent Plasma in High-Risk Children (NCT04377672)

- First prospective Pediatric study for COVID-19 convalescent plasma; Funded by the State of Maryland and Michael Bloomberg
- FDA IND (20185; April 2020) → study protocol shared on-line
- Formed a Pediatric COVID-19 convalescent plasma working group and multi-center registry

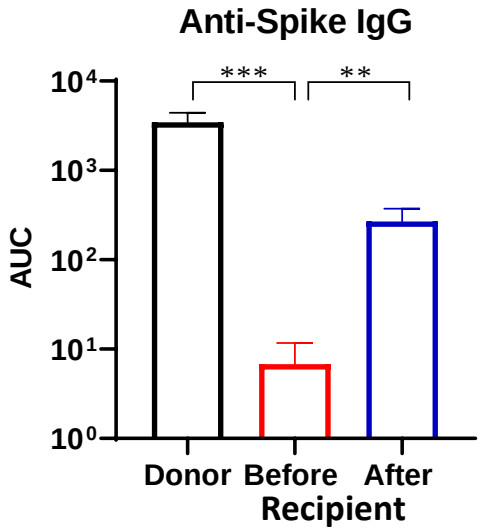


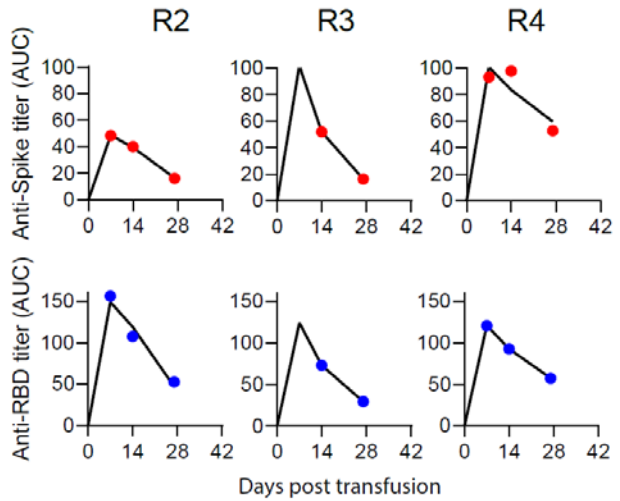
Safety outcomes

- No SAE reported in any participant
- Information from registry available for additional 33 children (17 males, 16 females, median age 14 years; range 0-19 years)
- No transfusion reactions reported there as well

PK analysis and modeling

- Transfer of multiple specific anti-SARS-CoV-2 antibodies
- Half-lives of anti-S and anti-RBD were 7-23 days, regardless of weight or age and within the expected range for IgG
- Since a "protective titer" in recipients is not well defined, the duration of potential protection remains unknown





Gordon *et al., Unpublished data.*, 2021

Studies at All Children's
The COVAC-TP Trial

PI:Anthony Sochet

Coordinating Site Investigators:

John Morrison, MD, PhD

Neil Goldenberg, MD, PhD

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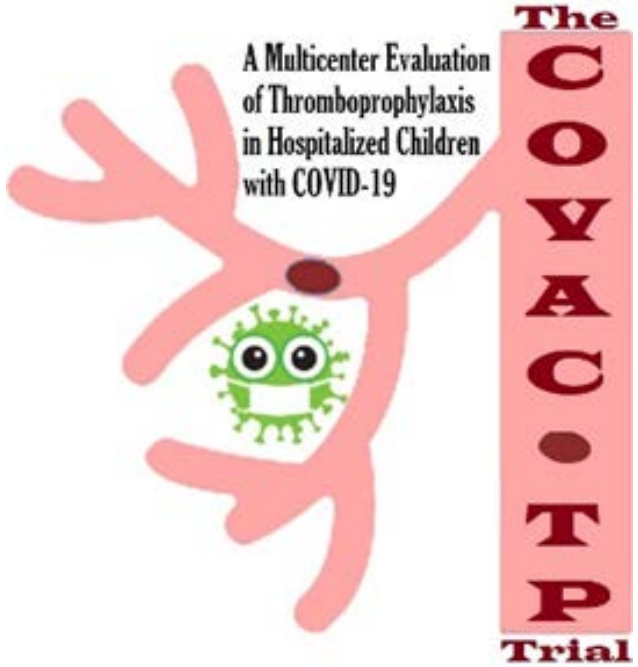
COVID-19 Anticoagulation in Children –Thromboprophylaxis (COVAC-TP): National (U.S.) Phase 2 Clinical Trial

- *Supported via a COVID Rapid Response Grant from the Johns Hopkins All Children's Foundation Institutional Research Awards Program*



Assistant Prof, JHU SOM ACCM, (based on JHAC campus): Since 2016
Fellowship: Children's National (D.C.)
Masters in Clinical Research: GWU

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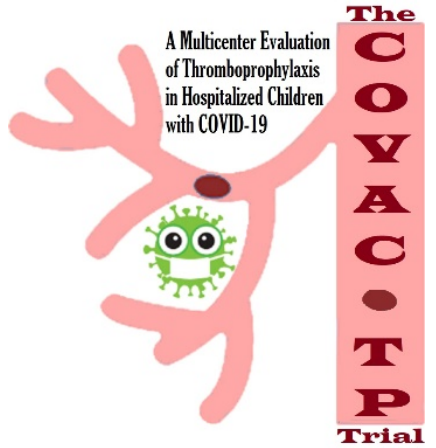
March 2020 – First recognition of clotting complications in patients hospitalized for COVID-19

- Within 3 weeks:
  - —Protocol developed & submitted via a multidisciplinary team based in JHAC ICTR
  - —Grants developed & submitted
    - > U01 Supplement (Goldenberg)
    - > JHAC Foundation IRAP (Sochet)
  - —FDA IND waiver filed & granted
  - —Consortium LOS/LOI obtained from 15 centers (leveraged existing U01 trial network)



March 2020 – Trial Design

- Agent: Lovenox
- Dosing: 0.5mg/kg sc q12h
- Primary endpoint: Safety (ISTH-defined bleeding: major + clinically-relevant non-major)
- Secondary endpoint: Dose requirements (mg/kg) by age group (to achieve plasma anti-Xa activity levels in target range)
- Exploratory endpoint: Efficacy (ISTH-defined venous thromboembolism [VTE] or VTE-related death)

The COVAC-TP Trial
A Multicenter Evaluation of Thromboprophylaxis in Hospitalized Children with COVID-19

April 2020 – Trial opened

- Enrollment began at JHACH
- Activated 9 of 15 sites
- JHAC ICTR served as:
  - —Clinical Coordinating Center
  - —Data Coordinating Center
  - —Central Biorepository (CAP-accredited pediatric biorepository)

Children's Hospital Los Angeles
Children's of Alabama
Lurie Children's Hospital
Children's Medical Center of Dallas
Johns Hopkins Hospital & Children's Center
Johns Hopkins All Children's Hospital
Children's Hospital of New Orleans
Children's Hospital of Atlanta
Rady Children's Hospital
Boston Children's Hospital
Akron Children's Hospital
Children's Hospital of Michigan
Children's Hospital Pittsburgh
Rush University Medical Center
Cohen Children's Medical Center
UC Davis Children's Hospital

Update: March 2021

- Enrollment is ~80% complete
- Steering Ctte, Clinical Endpoint Adjudication Committee, and Data and Safety Monitoring Committee have met regularly
- Timely data collection in REDCap with Study Quality Monitoring Reports produced monthly by the DCC in JHAC ICTR
- Serial plasma biospecimens collected on all patients to date, locally stored at -80C, and batch-shipped to central biorepository at JHACH

The Impact of COVID-19 on Families of Young Children in the PREDICT Cohort

Raquel G. Hernandez MD MPH

Sara Johnson PhD

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PREDICT

P Prospective
R Research on
E Early
D Determinants of
I Illness and
C Children's Health
T Trajectories

Specific Aims

- **Aim 1:** Describe the prevalence of COVID-19 symptoms, testing, and treatment among families with young children
  - Characterize variation by socioeconomic status, maternal pre-pandemic health status, and health insurance status

- **Aim 2:** Evaluate the impact of COVID-19 on economic conditions, family routines, family functioning, psychosocial stress, and food access among families with young children.
  - Using primary care medical records, characterize child health status and healthcare utilization before and during the pandemic.

COVID Impact: Early Results

- n=194 mothers (203 children)
- 11% of mothers had a positive COVID test, 45% had been tested
- 6% of children had a positive COVID test and 17% had been tested
- **63% of mothers reported COVID impact in 8 of 9 domains**
  - racial/ethnic minority participants had greater impact than whites, $p<0.03$
- Financial stress scores ↑ 48% pre-pandemic to pandemic, $p<0.0001$
- Anxiety symptom scores ↑ 17% pre-pandemic to pandemic, $p<0.0001$

- Factors **associated** with increased COVID impact:
  - Not living with the father in pregnancy, financial stress in pregnancy
- Factors **not associated** with COVID impact:
  - Essential employee status, education level, anxiety symptoms in pregnancy

Acknowledgements

- JHAC Foundation Institutional Research Grant
- JHU Alliance for a Healthier World
- Collaborators: Drs. Heather Volk, Rachel Thornton, Nakiya Showell, Sharon Ghazarian
- Co-PIs: S. Johnson & N. Goldenberg who pioneered building of the study and funding the work
- Study coordinators: S. Flanagan, L. Dallas for their ongoing efforts

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SARS-Co-V-2 Vaccines and Children

Kawsar Talaat, MD, Assistant Professor, Johns Hopkins Bloomberg School of Public Health

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SARS-CoV2 Epidemiology And Response in Children

- Study of SARS-CoV-2 infection, transmission, and immunity in households with 1 or more children under age 5
- CDC-funded, complements 4 other U.S. household studies that focus on older children and adults
- Weekly nasal swabs for 8 months; weekly and monthly questionnaires
  - SARS-CoV-2 PCR (Marshfield RI)
  - SARS-CoV-2+ to be tested for genetic variants
  - Swabs from ill children <5 to be tested by multiplex PCR for other pathogens in Ruth's lab
- Monthly oral swabs; + weekly for 8 weeks in SARS-CoV-2+
  - Tested for SARS-CoV-2 IgG to spike and internal proteins in Chris Heaney's lab
- Sera collected at enrollment and at 4 and 8 months post enrollment
  - SARS-CoV-2 IgG to spike and internal proteins; microneut for IgG+ specimens
- **175 households, 682 individuals, 255 children < 5 years** enrolled Nov 2020-Feb 2021
  - At enrollment: ~50% of children under 5 attend daycare outside the home; 25% of adults work outside the home; 75% of households have one or more household members attending work/school/childcare outside the home
  - Study compliance to date is high :
    - 98% of weekly nasal swabs and 92% of oral swabs collected and received on time; 99% of weekly and 97% of monthly surveys completed
- To date, 9 households and 23 individuals SARS-CoV-2 PCR+
  - Only 1 of 9 households had all household members infected
- More to come!

SEARCH

Ruth Karron, PI

Johns Hopkins Institute for Clinical & Translational Research

Evaluation of the Pfizer/BioNTech mRNA Vaccine in Children 5-11 years of age

P.I. Kawsar Talaat

- Phase 1: Starting late March/Early April
  - —Open Label, Dose Finding up to 48 children across 4 sites
  - —Safety, Tolerability, and Immunogenicity
  - —Start with 10 mcg/dose going up or down based on tolerability, immunogenicity
- Expanding to Phase 2/3 in June
  - —Placebo controlled, multi-site. Randomized 2:1
  - —Dose from Phase 1
  - —Safety, immunogenicity
  - —Unblinded at 6 months- placebo recipients invited to receive vaccine
- Anticipated Protocol amendment to expand groups to age 2-5 years and 6mo-2 years

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Emergency Pediatrics During the COVID-19 Pandemic

Kemi Badaki-Makun, MD, Assistant Professor, Pediatric Emergency Medicine

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Home Activities & Injury
2,011 respondents, weighted to adult US pop

Daily Activities

- 23% began WFH
- 33% ^ home improvement projects
- 15% ^ alcohol
- 48% ^ home cleaning & maintenance
- 31% ^ exercise; 20% ^ active recreation
- 13% v supervising of kids' sports or play

Injuries in HH

- 26% of HH had someone injured:
  - 32% falls
  - 20% cut
  - 9% burns
- 11% of HH had medication ingestion
- 6% of HH had household project ingestion

Medical Care

- 34% in person medical care
- 12% virtual or phone visit

DID NOT SEEK CARE

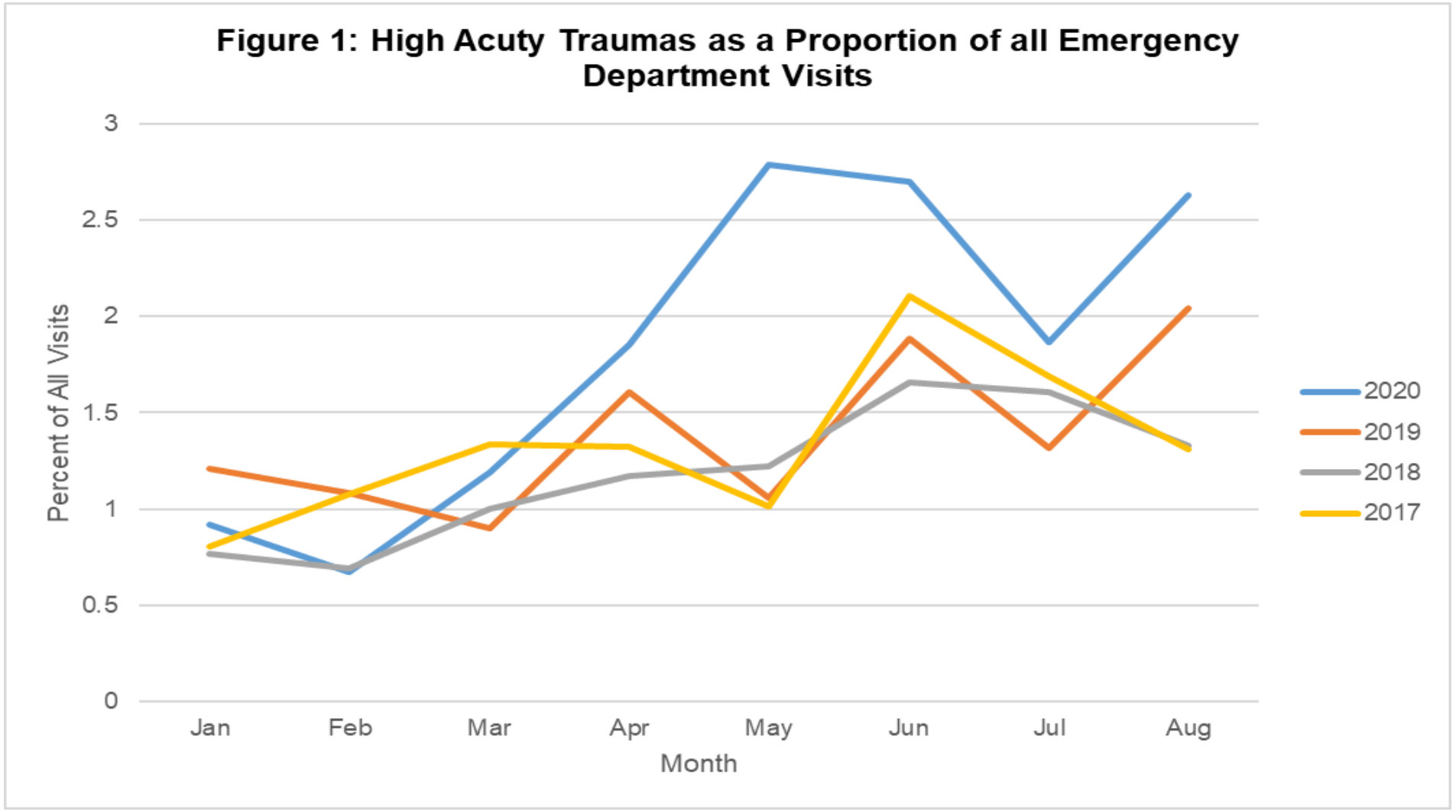
- 42% not serious enough
- 7% COVID concerns

- 25% thought very or somewhat likely they would get infected
- 83% thought it would be very or somewhat serious

68% ^ time spent at home from COVID

Gielen AC, Bachman G, Badaki-Makun O et al. National survey of home injuries during the time of COVID-19: who is at risk? Inj Epidemiol. 2020 Nov;

High Acuity Traumas
2020 vs. 2017-19



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High Acuity Traumas
2020 vs. 2017-19

Trauma Type	2017-2019 Mean	95% Confidence Interval	2020 Count	Percent Change (%)	p value
Assaults	6.7	5.2–8.2	10	+ 49.3	<0.001
Motor Vehicle Accidents	77.3	76.3–78.3	63	- 18.5	<0.001
Falls	68.7	66.7–70.7	51	- 25.8	<0.001
Drowning	8.7	7.8–9.5	6	- 31.0	<0.001
Child Abuse	8.7	7.4–9.9	16	+ 83.9	<0.001
Animal Attack	5.7	4.1–7.2	5	- 12.3	=0.38

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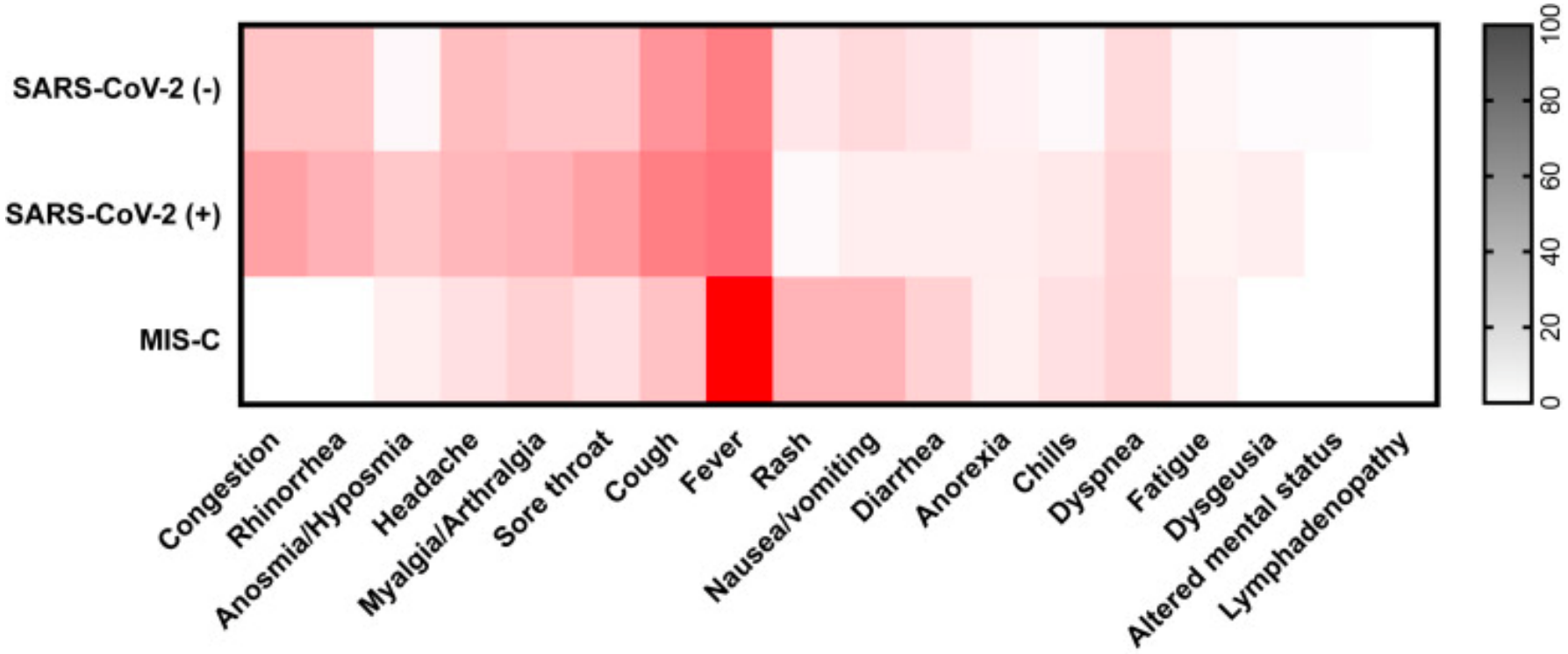
Identifying MIS-C
Role of the Monocyte Distribution Width (MDW)



Yonker LM et al. Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Clinical Presentation, Infectivity, and Immune Responses. J Pediatr. 2020 Dec

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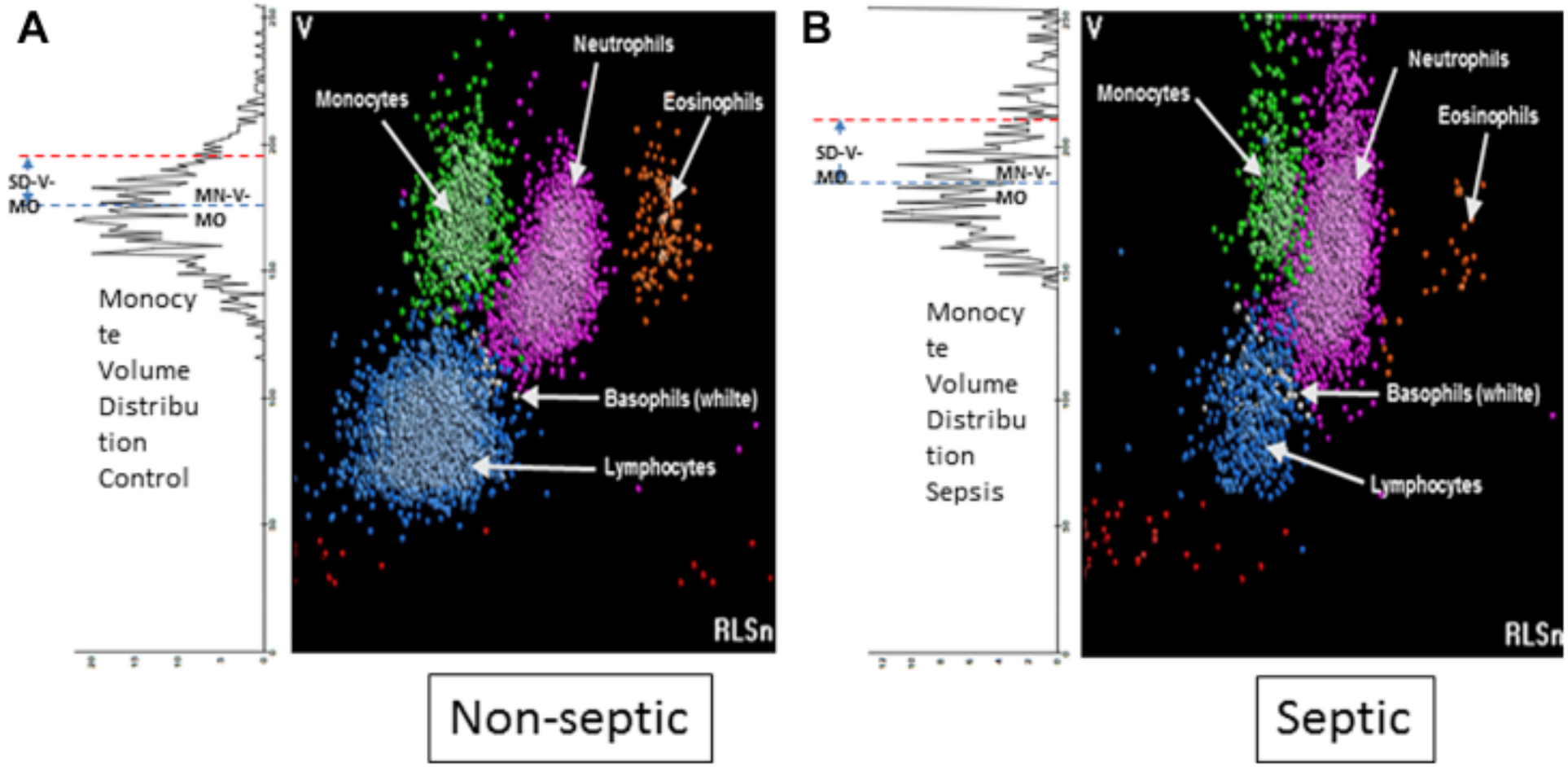
Role of the Monocyte Distribution Width (MDW)



Crouser ED et al.. Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker. Chest. 2017 Sep;152(3):518-526.

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Cardiac Complications of SARS-CoV-2

Cedric Manlhiot, Assistant Professor, Pediatric Cardiology

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COVID-19 Research Center Town Hall

March 10, 2021

A data science approach to identify and manage Multisystem Inflammatory Syndrome in Children (MIS-C) associated with SARS-CoV-2 infection and Kawasaki disease in pediatric patients

C. Manlhiot (NPI), B.W. McCrindle, N. Dahdah, T. Giglia, S. Kutty

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PreVAIL kIds
NIH
NICHD

Study rationale and objectives

- **MIS-C and KD have overlapping features, significance of overlap still unknown**
- **COVID/MIS-C is new, few predictive algorithms to use as part of CDSS**
- **But, KD has been extensively studied and predictive algorithms have been developed**
- Can we retrain algorithms designed for KD in patients with COVID/MIS-C?
- Will use 3 classes of algorithms previously designed for KD for use in COVID/MIS-C:
  - 1) Diagnosis and clinical identification
  - 2) Optimization and personalization of therapy
  - 3) Prediction of refractory diseases/severe complications
- CDSS designed to be useful for any patient along the KD to MIS-C clinical spectrum

PreVAIL kids
NIH NICHD

Phased approach to algorithm development

Phase 1: Data exploration and algorithms development

- Collect data for training dataset (N=450, 1:1:1 MIS-C:COVID:KD)
- Clinical profiling of patient cohorts
- Re-train previously developed algorithms in new populations

Phase 2: Algorithms expansion and performance evaluation

- Collect data for validation dataset (N=450, 1:1:1 MIS-C:COVID:KD)
- Add inflammatory/cardiac biomarkers to the algorithms
  - Focusing on biomarkers that are usually available in standard clinical labs
- Estimate performance metrics of algorithms in internal validation

Phase 3: Algorithms validation, implementation and clinical utility

- Collect data for external validation dataset (N=450, 1:1:1 MIS-C:COVID:KD)
- Add local and global epidemiology data to the diagnostic algorithm
- Determine performance metrics of algorithms in external validation
- Algorithm packaging, deployment and certification in standalone CDSS
- Shadow testing to validate implementation strategy
- Assessment of clinical utility and human factor evaluation

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Performance sites and key people

23 clinical enrollment sites (17 USA, 6 international)

Benjamin T. Barnes, Johns Hopkins University, Baltimore MD
Jean Ballweg, Children's Hospital & Medical Center, Omaha NE
Nagib Dahdah, CHU Sainte-Justine, Montreal QC (Co-PI)
Prasad Deepa, Banner Children's at Desert, Mesa AZ
Audrey Dionne, Boston Children's Hospital, Boston MA
Matthew Elias, Children's Hospital Philadelphia, Philadelphia PA
Ashraf Harahsheh, Children's National Hospital, Washington DC
Supriya Jain, Maria Fareri Children's Hospital, Ney York NY
Manaswitha Khare, Rady Children's Hospital/UCSD, San Diego CA
Dan Mauriello, John's Hopkins All Children's, St. Petersburg FL
Brian W. McCrindle, Hospital for Sick Children, Toronto ON (Co-PI)
Misra Nilanjana, Cohen Children's Medical Center, New York NY
Todd T. Nowlen, Phoenix Children's Hospital, Phoenix AZ
Michael Portman, Seattle Children's Hospital, Seattle WA
Geetha Raghuveer, Children's Mercy Hospital, Kansas City, MO
Kristen Sexson Tejtel, Texas Children's Hospital, Houston TX
Jackie Szmuszkovicz, Children's Hospital Los Angeles, Los Angeles CA
Deepika Thacker, Nemours A.I. Dupont Hospital, Newark DE
Dongngan Truong, Primary Children's Hospital, Salt Lake City, UT
Sundaram Balasubramanian, Kanchi Kamakoti Childs, Chennai, India
Elisa F. Cooke, Hospital Universitario 12 de Octubre, Madrid, Spain
Fanny Bajolle, Hôpital Necker Enfants Malades, Paris, France
Mona El-Ganzoury, Ain Shams University, Cairo, Egypt

IKD Registry

@Toronto SickKids

Program manager
Sunita O'Shea BSc

Clinical specialists
Martha Rolland
Patricia Walter

Data management
Tanveer Collins
Bailey Bernknopf

Data analysis
Kyle Runeckles
Brigitte Mueller

Clinical lead
Therese Giglia, CHOP (PI)

Cardiovascular Analytic Intelligence Initiative (CV-Ai²)

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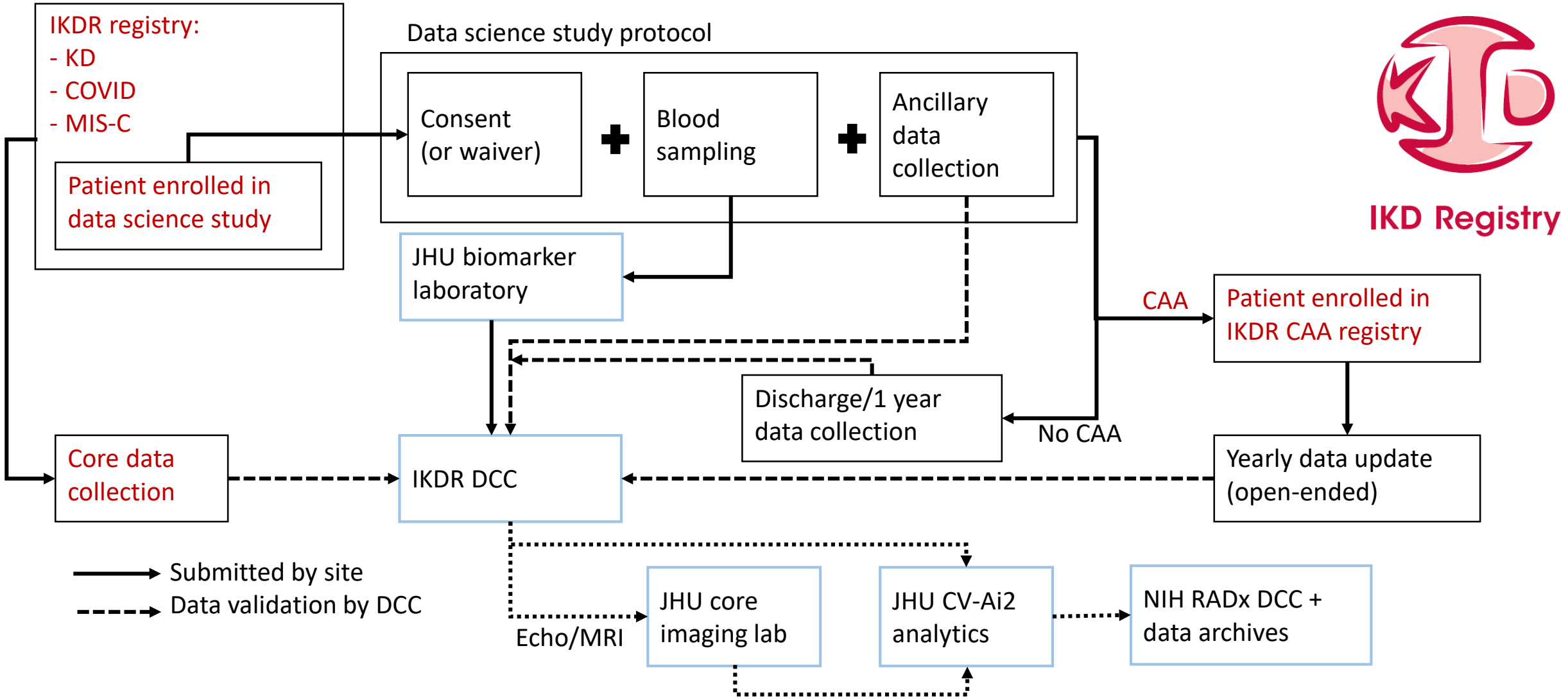
Lead analytics
Cedric Manlhiot (NPI)

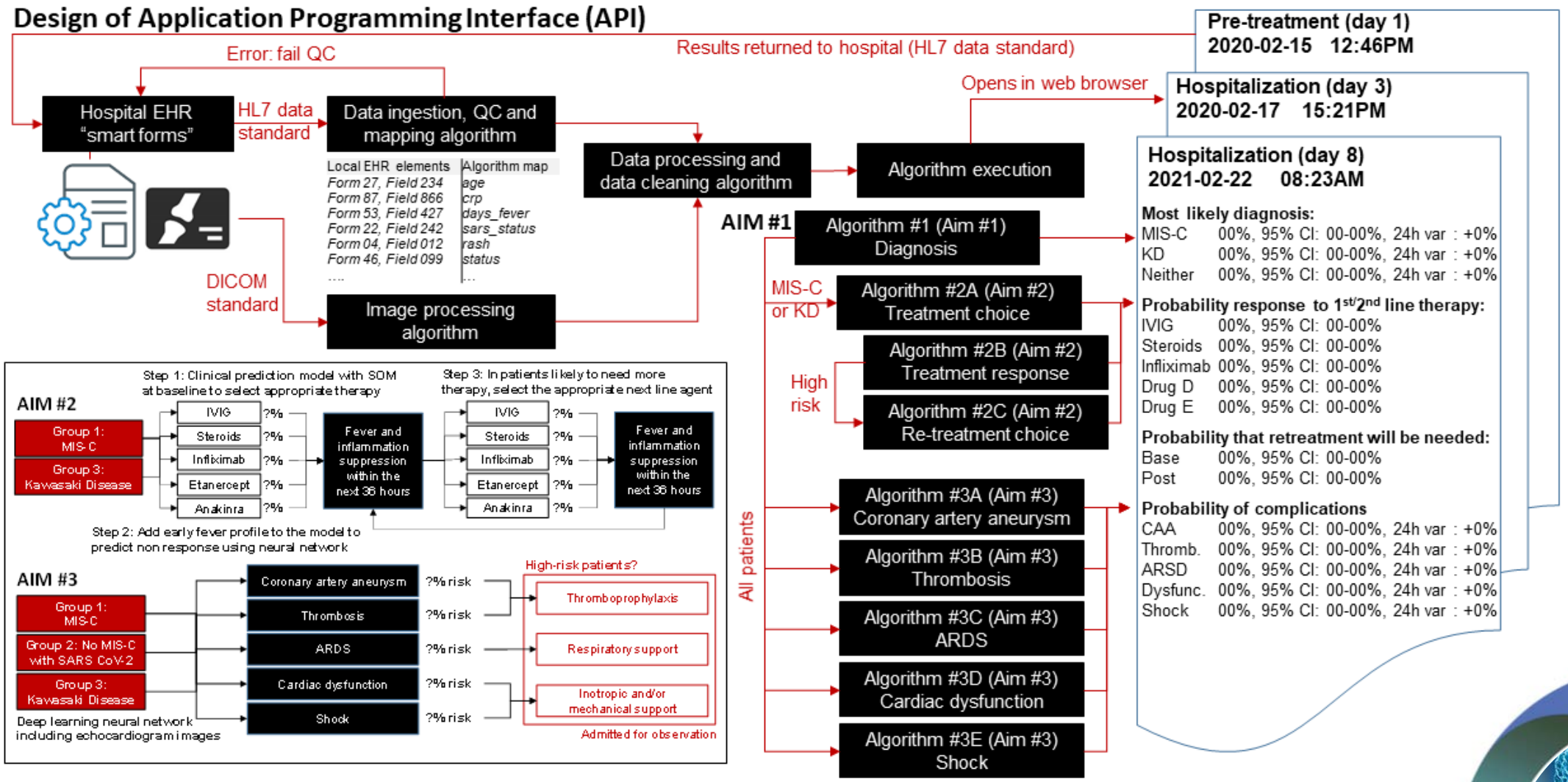
Lead imaging
Shelby Kutty, JHU (PI)
Lasya Gaur, JHU

Lead biomarker
Allen Everett, JHU

Research manager
Love Ko

Observational study embedded in the IKD Registry





Anticipated results

- Algorithms meet minimal standards for performance and utility
- Functional prototype of the CDSS shown above at the end of phase 2
- Clinically-approved, deployment ready platform of the CDSS at the end of phase 3

COVID-19 in Pregnancy, an Overview plus Remdesivir in Pregnancy, A Clinical Trial

Ahizechukwu Eke, MD, PhD, Assistant Professor, Maternal-Fetal Medicine, Department of Obstetrics and Gynecology

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Clinical Course of COVID-19 in Pregnancy

- Overall spectrum of COVID-19 symptoms similar in pregnant and nonpregnant women.
- Early data from systematic review of studies to April 29, 2020, suggested pregnant women had similar COVID-19 course as nonpregnant adults[1]

Clinical Outcome, % (95% CI)	Total (N = 538*)
Severe disease	15.3 (11.1-20.8)
Critical disease	1.4 (0.5-4.1)
ICU admission	3.0 (1.6-5.9)

- However, several recent studies demonstrated **increased rate of hospitalizations, ICU care, and mechanical ventilation**, but not death, in pregnant women vs age-matched nonpregnant controls[2-4]

*China, n = 420; US, n = 76; Europe, n = 42.

1. Huntley. Obstet Gynecol. 2020;136:303. 2. Ellington. MMWR. 2020;69:769.
3. Badr. Am J Obstet Gynecol. 2020;[Epub]. 4. Blitz. Am J Obstet Gynecol. 2020;223:290.

FDA Approval for Remdesivir: Use in Special Populations

Population	Recommendation
Pregnancy	**No adequate and well-controlled studies. No pharmacokinetic studies**
Nursing mothers	No information regarding remdesivir in human milk, effects on breastfed infants, or effects on milk production; in animal studies, remdesivir and metabolites are detected in the nursing pups of mothers given remdesivir, suggesting the presence of remdesivir in milk
Pediatric	Safety and efficacy for treating COVID-19 have not been assessed in pediatric patients younger than 12 yrs or weighing less than 40 kg; FDA EUA in effect for pediatric patients younger than 12 yrs or weighing less than 40 kg
Geriatric	Clinical experience has not identified differences in responses between elderly and younger patients; no dosage adjustment required; should be monitored closely for hepatic, renal, and cardiac function
Renal impairment	Remdesivir PK not evaluated in patients with renal impairment; not recommended patients with eGFR < 30 mL/min
Hepatic impairment	Remdesivir PK not evaluated in patients with hepatic impairment; perform hepatic testing prior to starting and while receiving remdesivir

Remdesivir PK Study in women – IMPAACT 2032

- **Purpose:** To describe the pharmacokinetic (PK) properties and safety of remdesivir (GS-5734TM) (RDV) administered to pregnant and non-pregnant women with COVID-19.

- **Design:** Phase IV, prospective, open label, non-randomized opportunistic PK study

16 participating centers in 9 US States and PR

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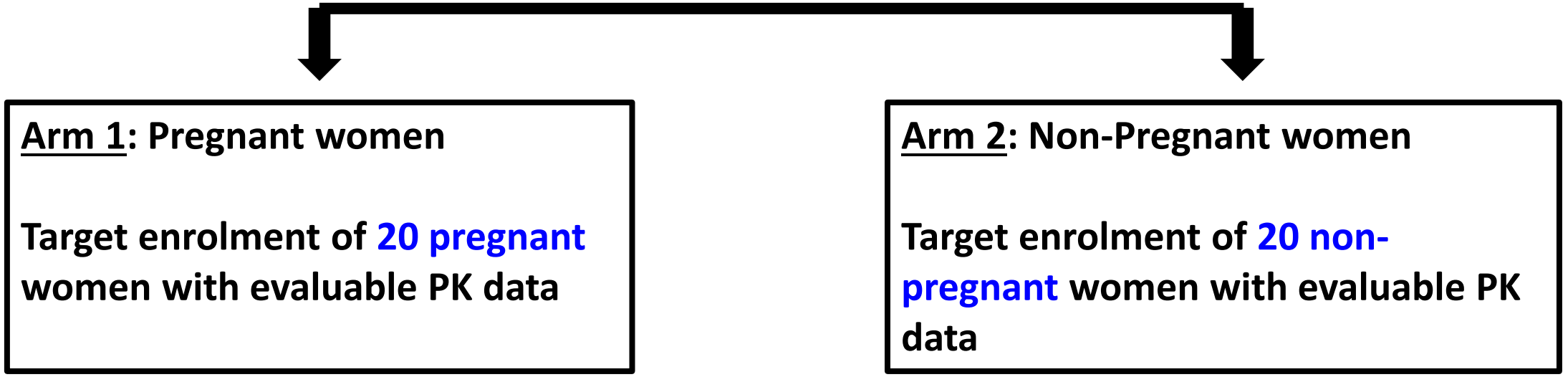
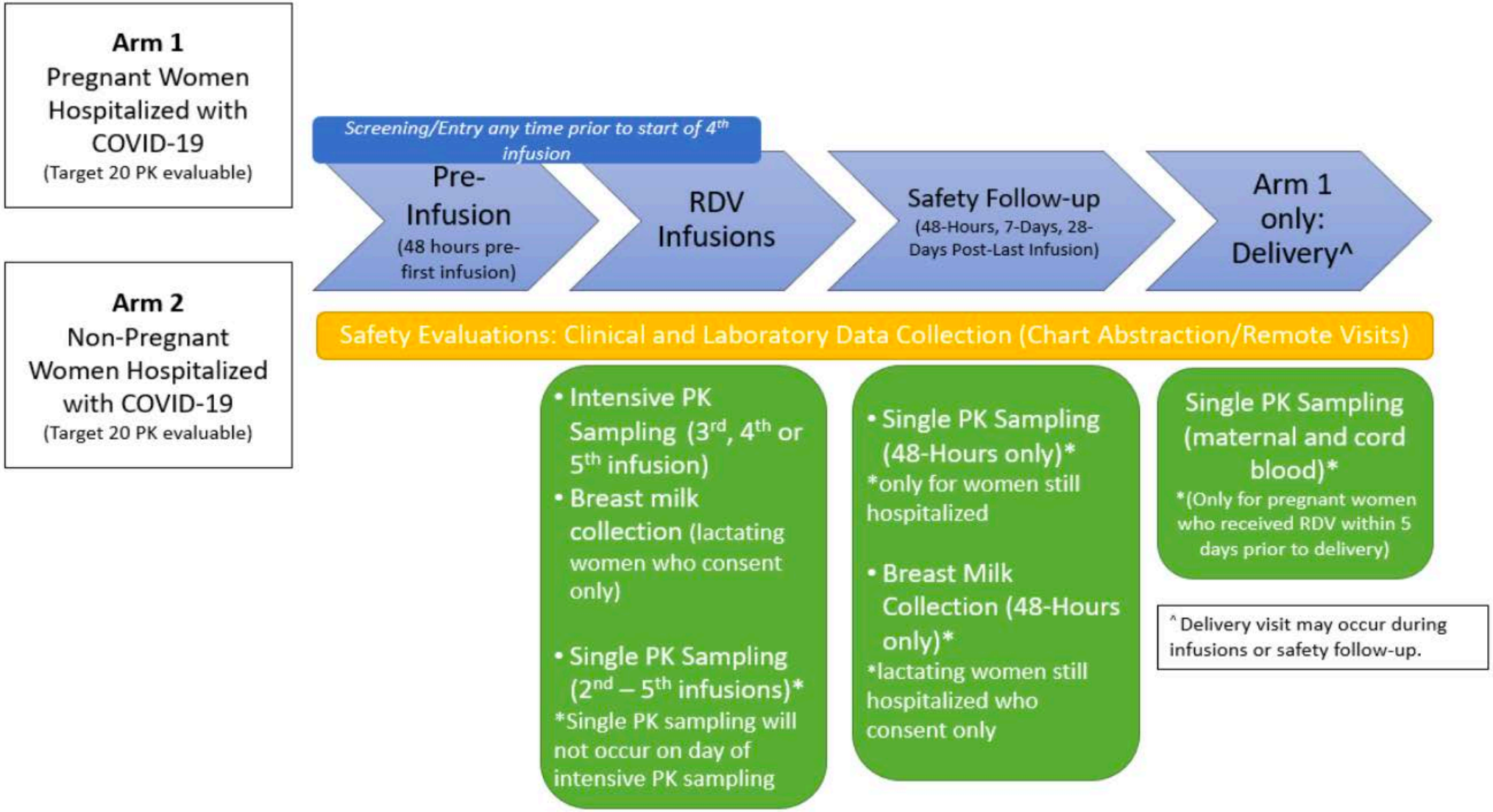
Remdesivir PK Study in women – IMPAACT 2032

Study Population and sample size: There are 2 arms: Pregnant and non-pregnant women of childbearing potential hospitalized and receiving RDV for treatment of COVID-19.



Overview of Study Design



Remdesivir PK Study in women

- **Drug under study:** Participants will be administered RDV intravenously once daily for up to 10 days per clinical care.

- **Study Duration:**
  - Approximately 15 months total
  - Accrual is expected to be completed within approximately 6 months from first enrollment
  - Enrolled women in Arm 1 will be followed for 4 weeks after the last RDV infusion or through delivery, whichever comes later. Enrolled women in
  - Arm 2 will be followed for 4 weeks after the last RDV infusion.
- **Status:** Open to accrual at JHH
- **Contact: aeke2@jhu.edu**

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Convalescent Plasma in Pregnancy

Jeanne Sheffield, Professor of Obstetrics and Gynecology,
Division Director, Maternal-Fetal Medicine

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Clinical Infectious Diseases
MAJOR ARTICLE

Compassionate Use of Remdesivir in Pregnant Women With Severe Coronavirus Disease 2019

- 3/21/2019-6/13/2019 86 hospitalized pregnant women with PCR confirmed disease and oxygen saturations <94%.
- Well tolerated, low AEs
- No safety signals

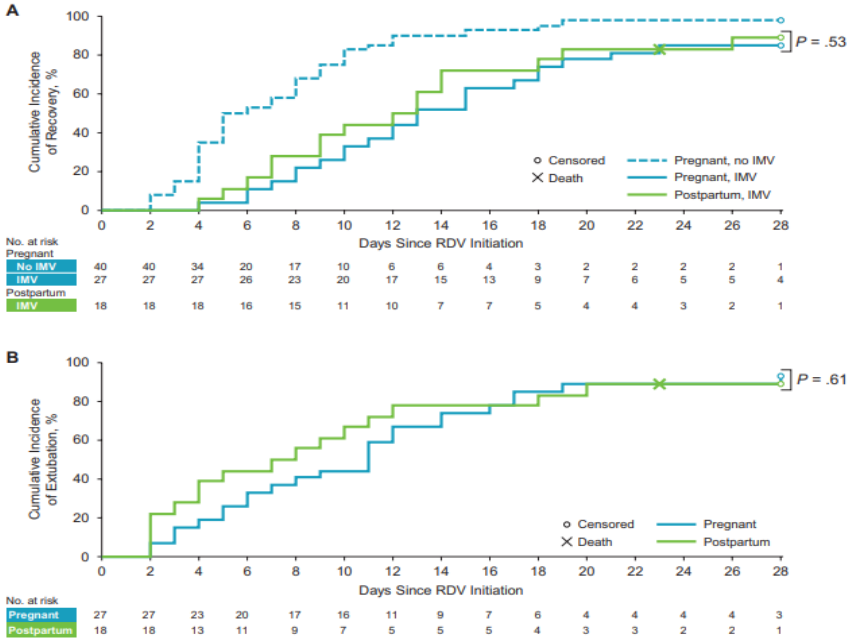

Figure 2. Time to recovery and extubation in pregnant women who received remdesivir. *A*, Time to recovery by baseline oxygen support status (invasive vs not invasive). *B*, Time to extubation: baseline invasive oxygen support. Abbreviations: IMV, invasive mechanical ventilation; RDV, remdesivir.

A Pregnant

Posttreatment O_2 Support Status — No. (%)*	BL O_2 Support Status: 5 (ECMO/IMV) n = 27†	4 (NIPPV/high-flow O_2) n = 12	3 (low-flow O_2) n = 25	2 (room air) n = 3
6 (death)	0	0	0	0
5 (ECMO/IMV)	2 (7)	0	0	0
4 (NIPPV/high-flow O_2)	1 (4)	1 (8)	0	0
3 (low-flow O_2)	1 (4)	0	0	0
2 (room air)	1 (4)	0	1 (4)	0
1 (discharge)	22 (81)	11 (92)	24 (96)	3 (100)
Any improvement (≥1 point)	**93%** (25/27)	**92%** (11/12)	**100%** (25/25)	**100%** (3/3)

B Postpartum

Posttreatment O_2 Support Status — No. (%)*	BL O_2 Support Status: 5 (ECMO/IMV) n = 18†	4 (NIPPV/high-flow O_2) n = 1	3 (low-flow O_2) n = 0	2 (room air) n = 0
6 (death)	1 (6)	0	0	0
5 (ECMO/IMV)	1 (6)	0	0	0
4 (NIPPV/high-flow O_2)	0	0	0	0
3 (low-flow O_2)	0	0	0	0
2 (room air)	1 (6)	0	0	0
1 (discharge)	15 (83)	1 (100)	0	0
Any improvement (≥1 point)	**89%** (16/18)	**100%** (1/1)	**0**	**0**

Worsened
No change
1-point improvement
≥2-point improvement

Figure 1. Clinical outcomes in pregnant (*A*) and postpartum (*B*) women treated with remdesivir at day 28. Mechanical ventilation includes invasive ventilation by endotracheal tube or tracheostomy. Blue shading indicates improvement from baseline oxygen support. *%s calculated from BL O2 support groups; †IMV includes invasive ventilation by endotracheal tube or tracheostomy. Abbreviations: BL, baseline; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; NIPPV, noninvasive positive pressure ventilation; O_2, oxygen.

Human Coronavirus Immune Plasma (HCIP) and Use in Pregnant Patients with Sars-CoV-2 infection David Sullivan PI

- Convalescent plasma is not contraindicated in pregnancy
- Randomized double-blind Phase 2 trial
  - —Efficacy and safety of HCIP compared to control plasma
  - —Endpoints: hospitalization, death, duration or symptoms and viral shedding, antibody titers
- Positive RNA or antigen test and symptoms
- Outpatient only

HCIP Study

- This is not a pregnancy study. However, due to the known risk of severe disease and death in pregnant women and the lack of contraindication of plasma therapy in pregnancy, pregnant women are being enrolled using the same inclusion and exclusion criteria.

COVID-19 in Pregnancy: Implications of dysregulated maternal immunity

Irina Burd, MD, PhD

Professor and Director

Integrated Research Center for Fetal Medicine

Maternal Fetal Medicine, Gynecology and Obstetrics

Johns Hopkins University

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Dysregulated maternal immunity

Pregnancy alters IL-1β expression and anti-viral antibody responses during SARS-CoV-2 infection

- Morgan L. SHERER, PhD, Jun LEI, PhD, Patrick CREISHER, PharmD, Minyoung JANG, BA, Ramya REDDY, BS, Dr. Kristin VOEGTLINE, PhD, Ms. Sarah OLSON, MPH, Kirsten LITTLEFIELD, BS, Dr. Han-Sol PARK, PhD, Ms. Rebecca L. URSIN, MS, Abhinaya GANESAN, ScM, Theresa BOYER, BA, Nada ELSAYED, BS, Diane M. BROWN, RN, MSN, Samantha N. WALCH, Annukka A. R. ANTAR, MD, PhD, Yukari C. MANABE, MD, Kimberly JONES-BEATTY,CNM,
- William CHRISTOPHER GOLDEN, MD, Andrew J. SATIN, MD,
- Jeanne S. SHEFFIELD, MD, Andrew PEKOSZ, PhD,
- **Sabra L. KLEIN, PhD, and Irina BURD, MD, PhD**

Main findings:

- Pregnant women who delivered <14 days after positive SARS-CoV-2 test expressed more *IL1β* mRNA in their blood compared to pregnant women who were uninfected or delivered >14 days after a confirmed test.
- Pregnant women with confirmed infection had lower anti-spike-receptor binding domain IgG titers and were less likely to have detectable neutralizing antibodies compared to non-pregnant women.
- Protein concentrations of placental FcRn, a receptor essential for maternal transfer of antibodies to the fetus were not affected by SARS-CoV-2 infection during pregnancy.

In revision with *Amer J Ob Gyn*

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Pediatric Follow Up of the Cohort

Co-PIs

- Irina Burd, MD, PhD
- W. Christopher Golden, MD
- Robert Yolken, MD

Cohort

- 100 enrolled patients
  - —Maternal blood
  - —Cord blood
  - —Placenta
  - —Neonatal Blood
  - —Stool
  - —Breast milk
  - —Neurologic follow up with Kennedy Krieger

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Pregnancy Outcomes In SARS-CoV-2 Epidemic (POISE): Maryland State Study

- Collaboration with University of Maryland
- Capture all of COVID-19 pregnancy outcome data in Maryland
- BEAD core
- Findings will be presented at the **Society for Reproductive Investigations** Annual Meeting in July 2021

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Thank you

COVID-19 Clinical Research Center

https://ictr.johnshopkins.edu/covid-research-center/town-halls/

COVID19ResearchCtr@jhmi.edu

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