NICHD COVID-19 Activities

Current as of 12 January 2021

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
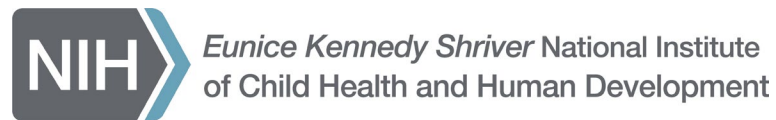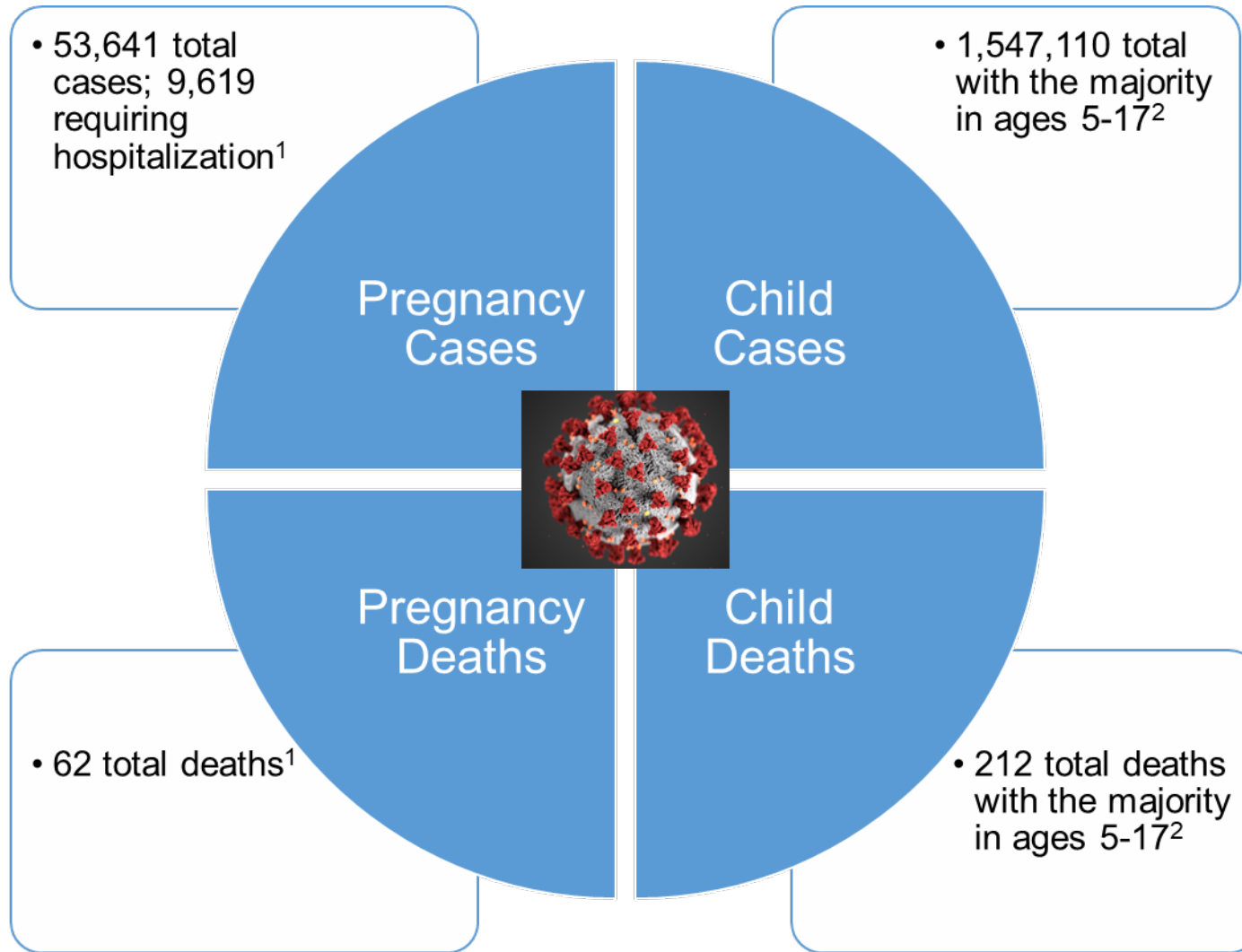
Summary of Ongoing NICHD Activities

- **Gestational research assessments for covid-19 (GRAVID)**

  - Analysis of medical records of up to 24,500 women within NICHD's [Maternal-Fetal Medicine Units Networks](#) to examine maternal and neonatal outcomes for pregnant women with and without SARS-CoV-2 infection

- **Global Research Network: COVID19 Infection Prevalence During Pregnancy and Impact on Pregnancy Outcomes**

  - Enrollment of 2,000 pregnant women at [8 active international sites](#) to compare the maternal, fetal, and neonatal outcomes of women infected with SARS-CoV-2 to those of non-infected women

- **SARS-CoV-2 and Breast Milk:** [Studies of breast milk](#) as a potential source of viral transmission as well as protective antibodies

- Studies on **Multisystem Inflammatory Syndrome – Children (MIS-C)** and other complications of SARS-CoV-2 related illness coordinated with NHLBI and NIAID; NICHD focuses on [therapeutics](#)

- **Intramural research:** Studies of specific tissues (e.g., placenta) to understand the mechanisms of infection

Context: COVID-19 in Pregnancy and Pediatrics

- 53,641 total cases; 9,619 requiring hospitalization[1]

- 1,547,110 total with the majority in ages 5-17[2]

Pregnancy Cases

Child Cases

Pregnancy Deaths

Child Deaths

- 62 total deaths[1]

- 212 total deaths with the majority in ages 5-17[2]

- Primary concern is the rate of increase in pediatric COVID-19 cases; in recent data from AAP, there was a **15% increase** in cases over a two-week period (12/24-1/7/21)[3]

- Children account for 12.5% of all cases of COVID-19 in states reporting cases by age[3]

[1]https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/special-populations/pregnancy-data-on-covid-19.html
[2]https://covid.cdc.gov/covid-data-tracker/#demographics
[3]https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/

Gestational research assessments for covid-19 (GRAVID)

- Analysis of medical records of up to 24,500 women who have given birth at a clinical center within NICHD's Maternal-Fetal Medicine Units Networks to examine maternal and neonatal outcomes for pregnant women with and without SARS-CoV-2 infection

- Objectives

  - Evaluate whether pregnant or immediately postpartum women experience higher maternal morbidity and mortality during the COVID-19 pandemic than before the pandemic

  - Evaluate whether women with SARS-CoV-2 infection, both in- and out-patient, have higher maternal morbidity and mortality rates than pregnant women without SARS-CoV-2 infection

  - Describe maternal and neonatal outcome data for all pregnant and immediately postpartum women with a confirmed SARS-CoV-2 infection and contribute these data to an NICHD COVID-19 pregnancy registry

- Endpoint - Maternal morbidity and mortality composite defined as at least one of the following during pregnancy and through 6 weeks postpartum: mortality; morbidity related to hypertensive disorders of pregnancy; morbidity related to postpartum hemorrhage; or morbidity related to infection

12 Centers; 39 individual hospital sites

COVID-19 Infection Prevalence During Pregnancy and Impact on Pregnancy Outcomes

RESEARCH PARTNERS

1. **Democratic Republic of Congo:** Antoinette Tshefu, Kinshasa School of Public Health; Carl Bose, University of North Carolina at Chapel Hill

2. **Kenya:** Fabian Esamai, Moi University; Ed Liechty, Indiana University

3. **Zambia:** Elwyn Chomba, University Teaching Hospital; Wally Carlo, University of Alabama Birmingham

4. **Guatemala:** Ana Garces, Institute of Nutrition of Central America And Panama (INCAP); Nancy Krebs, University of Colorado Denver

5. **Bangladesh:** Rashidul Haque, icddr,b; Bill Petri, University of Virginia

6. **India, Belagavi:** Shiva Goudar, KLE University; Richard Derman, Thomas Jefferson University

7. **India, Nagpur:** Archana Patel, Lata Medical Research Foundation (LMRF); Pat Hibberd, Boston University

8. **Pakistan:** Sarah Saleem, The Aga Khan University; Robert Goldenberg, Columbia University

9. **RTI International:** Elizabeth McClure, Tracy Nolen

- Study active in 8 low- and middle-income countries

- Goals:

  - Determine the **prevalence of COVID-19 infection** during pregnancy using antibody testing at delivery

  - Determine the impact of COVID-19 exposure during pregnancy on **maternal, fetal, and neonatal outcomes**

  - Assess **knowledge, attitudes, and practices** of pregnant women related to COVID-19 infection during pregnancy

SARS-CoV-2 and Breast Milk

- Investigator initiated work in an existing collaborative network supported by NICHD, NIAID and NIMH

- Replication-competent (active) virus is not transmitted to uninfected infant via breast milk

- With proper hygiene, it is safe to breast feed

- Human milk contains antibodies directed against SARS-CoV-2

- Might suggest the potential to use milk-derived antibodies for therapeutic use

Multisystem Inflammatory Syndrome in Children (MIS-C)

- Collaborative effort with NHLBI and NIAID to coordinate and integrate data from three studies:

| NIAID: Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM)	NICHD: Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care (POPS)	NHLBI: Long-Term Outcomes after the Multisystem Inflammatory Syndrome in Children (MUSIC)
• Determine the proportion with SARS-CoV-2 related death, rehospitalization or ongoing major complications at 12 months after presentation • Determine immunologic mechanisms, immune signatures and predictive biomarkers associated with disease phenotypes	• Study the influence of genetic factors, metabolic, protein profiles on therapeutic exposure and response • Evaluate PK/PD of understudied drugs in hospitalized children with SARS-CoV-2 related illness • Establish drug safety profile and adverse events with specific cardiac or neurologic impact	• Characterize the occurrence and time course of coronary artery involvement and ventricular dysfunction • Characterize the occurrence and time course of non-cardiac organ dysfunction, inflammation and major medical events

- Enrolling across 75 sites; new site selection ongoing in areas with growing case numbers

- Common data elements and protocol coordination ensures integration of these data

- Data will be publicly available across three data platforms: BioData Catalyst, Kids First Data Resource Center, and ImmPort

NICHD Intramural Activities: COVID-19

- The Perinatology Research Branch highlighted the possible mechanism for why so few fetuses are infected during pregnancy with maternal COVID-19 infections

- In their examination of single cell RNA sequencing of (mainly) women infected with COVID-19 in their 3rd trimester they found the placenta:

  - Lacks the mRNA required to manufacture the ACE2 receptor, the main cell surface receptor used by the SARS-CoV-2 virus to cause infection

  - Lacks the mRNA to make the TMPRSS2 enzyme that SARS-CoV-2 uses to enter a cell

- The receptor and enzyme are present in only miniscule amounts in the placenta, suggesting a possible explanation for why SARS-CoV-2 has only rarely been found in fetuses or newborns of women infected with the virus.

https://www.the-scientist.com/features/human-fetuses-can-contract-sars-cov-2-but-its-rare-68293
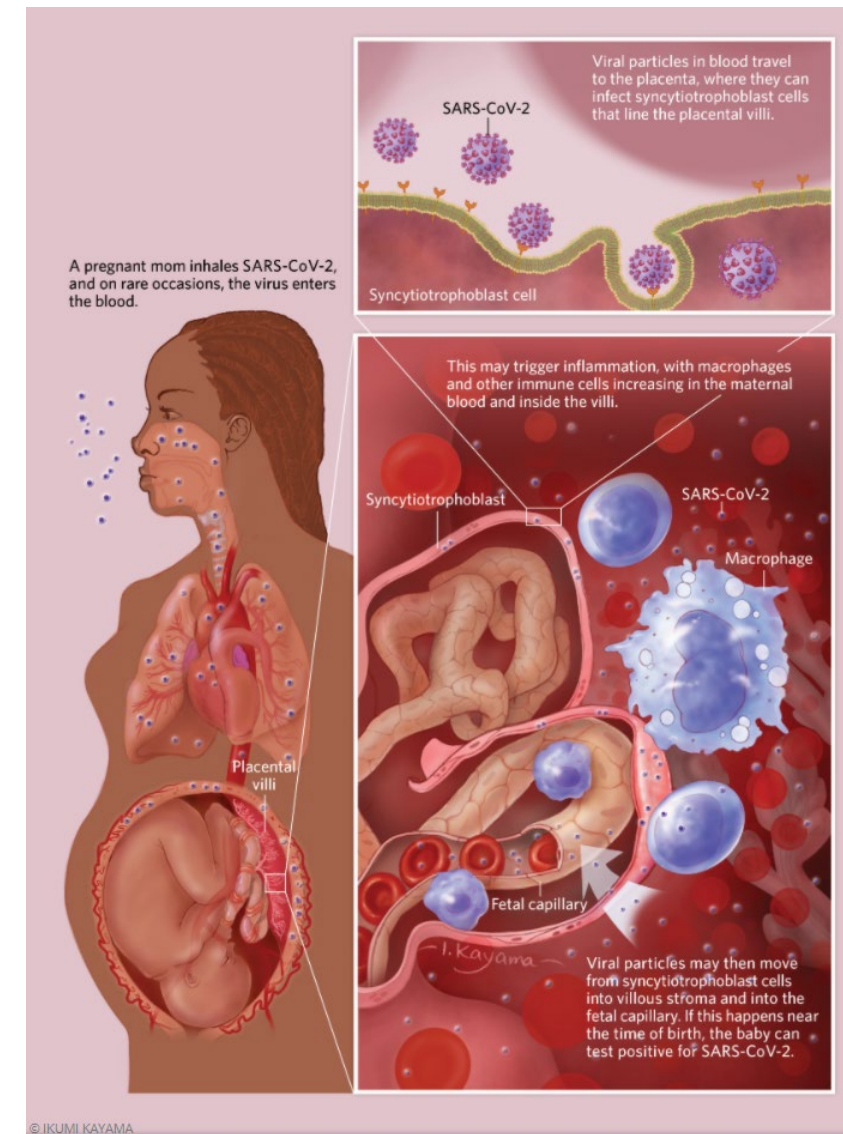
NICHD Intramural Activities: COVID-19

Viral-like particle production

Production of viral-like particles that express SARS-CoV-2 spike protein and other envelope proteins suitable for vaccine production (Zimmerberg)

Viral cell targets in the lung

Studies underway using human lung tissue to identify viral cell targets and preclinical studies of antiviral therapeutics; others using bronchial tissues to study inhibitors of the virus using electron microscopy (Margolis)

Point of Care multimodal biosensor

Development and testing of a biosensor used during pathogenesis and recovery using modalities such as NIRS, pulse oximetry and skin temperature (Gandjbakhche)

Testing the innate immune response and determining virus propagation

Development of an assay to test human antiviral protein kinases and how they interact with SARS-CoV-2 and examining the impact of ribosomal frameshifting on SARS-CoV-2 (Dever)

Preclinical therapeutic target identification and testing

Studies ongoing to study targets of the essential proteins in the enveloped virus, inhibitors of specific kinases, and inhibitors of specific host cell proteins for therapeutics (Banerjee, Bezrukov, DePamphilis)

Molecular Biology of SARS-CoV-2

Studies of the physicochemical properties of the spike protein, its interaction with the host receptors, membrane activity, properties of the envelope protein, and requirements for blocking the virus at the molecular level (Maraia)

NICHD Workshops: COVID-19

- COVID-19 in Pregnancy: Clinical, Research and Therapeutics Updates (9/15/2020)

  - Approach to obstetric therapeutics development in COVID-19

  - Pregnancy registries for COVID-19

- Child Health Services Research in Light of COVID-19: A Listening Session (Collaborative workshop with HRSA and AHRQ; 10/29/2020)
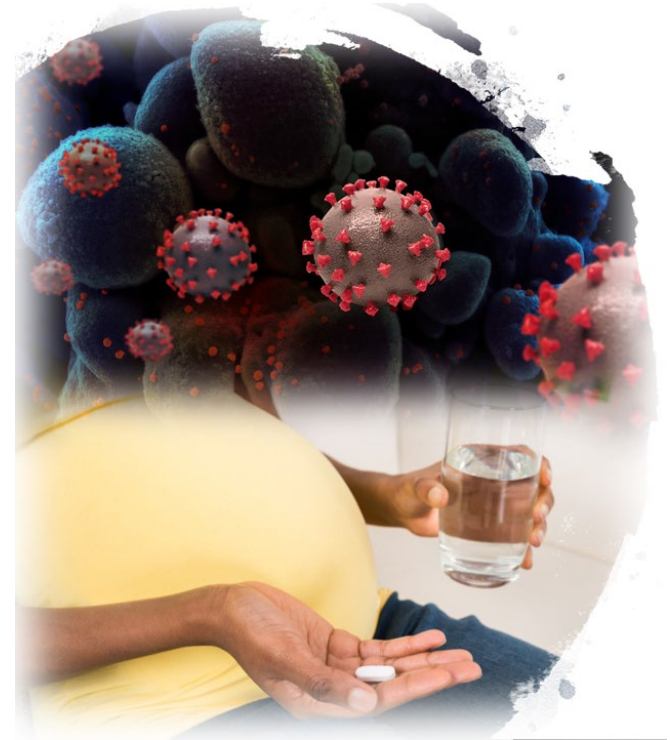
Participation in Trans NIH Activities

Predicting Viral-Associated Inflammatory Disease Severity in children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds)

RADx℠ Radical (RADx-rad)

RADx-rad will support new, non-traditional approaches, including rapid detection devices and home-based testing technologies, that address current gaps in COVID-19 testing. The program will also support new or non-traditional applications of existing approaches to make them more usable, accessible, or accurate. These may lead to new ways to identify the current SARS-CoV-2 virus as well as potential future viruses.

Budget: $200 Million

Develop novel, nontraditional approaches, testing strategies, and technologies to *understand the spectrum of pediatric SARS-CoV-2 illness, rapidly diagnose and characterize MIS-C associated with SARS-CoV-2,* and *predict the longitudinal risk of disease severity* after exposure to and/or infection by SARS-CoV-2 to tailor management and optimize health outcomes (R61/R33 Clinical Trial Optional)

Application Title	PI Last Name	Institution
AICORE-kids: Artificial Intelligence COVID-19 RiskAssEssment for kids	ANNAPRAGADA	BAYLOR COLLEGE OFMEDICINE
Diagnosing and predicting risk in children with SARS-CoV-2-related illness	BURNS	UNIVERSITY OF CALIFORNIA, SAN DIEGO
Discovery and clinical validation of host biomarkers of disease severity and multi-system inflammatory syndrome in children (MIS-C) with COVID	CHIU	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
COVID-19 Network of Networks Expanding Clinical and Translational approaches toPredict Severe Illness in Children(CONNECT to Predict	KLEINMAN	ROBERT WOOD JOHNSONMEDICALSCHOOL
A data science approach to identify and manage Multisystem InflammatorySyndrome in Children (MIS-C) associated with SARS-CoV-2	MANLHIOT	JOHNS HOPKINS UNIVERSITY
Diagnosis of MIS-C in febrile children	ODOM JOHN	CHILDREN'S HOSPITAL OFPHILADELPHIA
Identifying biomarker signatures of prognostic value for Multisystem InflammatorySyndrome in Children (MIS-C)	SALAZAR	CONNECTICUT CHILDREN'SMEDICALCENTER
Severity Predictors Integrating salivary Transcriptomics and proteomics with Multi neural network Intelligence in SARS-CoV2 infection in children	SETHURAMAN	CENTRAL MICHIGANUNIVERSITY

8 awards in Phase 1; 2-3 expected to transition to Phase 2

https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-20-023.html

Supplements to NICHD Awards

- WUIDDRC Supplement - Supporting the Health and Well-being of Children with Intellectual and Developmental Disability during COVID-19 Pandemic (Washington University at St. Louis, PI: Constantino)

  - This study will determine the best implementation strategies to maximize the use of an FDA-approved diagnostic test for vulnerable children with intellectual and developmental disabilities (IDD) in a school setting at Washington University.

  - Goal: Provide 50,000 saliva-based tests for SARS-CoV-2 students, teachers, and staff in 6 special education schools in St. Louis and assess national perspectives among parents with IDD and school staff regarding the impact

- Safety, Testing/Transmission, and Outcomes in Pregnancy with COVID-19 (STOP-COVID-19 study; Washington University at St. Louis; PI: Mysorekar)

  - This study will include antibody testing to determine how asymptomatic COVID-19 infection in pregnancy increases risk of adverse pregnancy outcomes.

https://www.nih.gov/research-training/medical-research-initiatives/radx/funding#radx-up

# Pregnancy Data Harmonization & Common Data Elements: Trans NIH Project Clinical Data Coordination (#5)

Goal: Increase the overall impact of NIH-supported COVID-19 research in pregnancy studies by planning for data harmonization and future analyses with combined datasets

We convened trans-NIH and extramural researchers…

KEY ACCOMPLISHMENTS

- Created three working groups with membership across eight NIH-funded studies: **Psychosocial**, **Biomedical, and Biospecimens** (in progress)

- **Prioritized top ~45 data elements** (from an initial set of 400+) to address key psychosocial and biomedical research questions

- Selected **recommended measures** for collecting information on each prioritized data element from existing surveys, CRFs, and validated measures

IMPACT
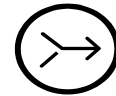
Incorporate data elements into planned and ongoing studies where possible

Serve as guidelines for future FOAs related to Pregnancy and COVID-19 (and potentially any study that includes women of reproductive age)

Inform Project 5 CDE efforts and aid in data harmonization across studies

…to create best-practice recommendations for researching the impact of COVID-19 on pregnant and lactating women

Data Element Recommendations: Trans NIH Project #5

Biomedical Data Elements

- Baseline Maternal Characteristics

- Maternal COVID-19 Treatment

- Maternal Outcomes

- Obstetric/Pregnancy Outcomes

- Neonatal Characteristics

- Neonatal COVID-19 Testing

- Neonatal Outcomes

Psychosocial Data Elements

- Socioeconomic Status, Housing, and Financial Strain

- Medical Care

- Impact on Parenting

- Stressful Life Events

- Maternal Mental Health

- Health Related Behaviors

Person-focused CDEs for COVID-19 Clinical Data Coordination and Data Warehouse include reproductive elements and pregnancy due to the efforts of this group

Trans NIH Project : Pregnant and Lactating Women and Children

- Administrative supplements targeting the impact of COVID-19 on pregnant women and children; co-led with NIDA

- Three NICHD projects received supplements to pursue the following goals:

  - Molecular and Vascular MRI of Placenta Accreta (PI: Annapragada; Texas Children's Hospital): This project will generate important data on viral attachment, entry, and transport within the placenta

  - Penn State University's Translational Center for Child Maltreatment Studies (PI: Schreier/Noll; Penn State University): Investigators will augment the biopsychosocial data already being collected to examine vulnerability and resilience towards COVID-19 infections among youth (aged 8-13y) and also examine a broad range of physiological (endocrine, immune and metabolic) and demographic characteristics of youth associated with infections of COVID-19.

  - Maternal Inflammation during Pregnancy and Neurodevelopmental Disorders (PI: Croen; Kaiser Foundation Research Institute; co-funding by NIEHS): Establish a new pregnancy cohort to investigate the impact of the COVID-19 pandemic on child neurodevelopment