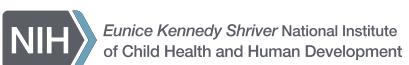


Updates on COVID-19 in Children and People of Reproductive Age

Diana W. Bianchi, M.D.

June 9, 2022





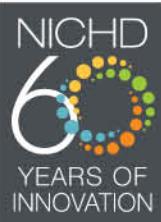
Overview of Presentation

- COVID-19 Effects on Female and Male Reproductive Systems
- COVID-19 and Vaccination in Pregnancy and Lactation
- Multi-system Inflammatory Syndrome in Children (MIS-C)
 - Progress in PreVAIL kids initiative
- Future Challenges



COVID-19 Effects on Female and Male Reproductive Systems

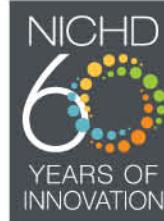
COVID-19 Vaccinations and Menstruation



- Anecdotal reports of changes to menstrual cycles amplified by major media outlets
 - Reported changes to cycle timing (longer or shorter cycles, skipped periods, breakthrough bleeding between cycles), flow (heavier or lighter than normal), and comorbidities such as increased pain during cycles
- Data on menstrual changes were not collected during vaccine safety trials
- NICHD surveyed potentially applicable parent studies, wrote and published a NOSI (NOT-HD-21-035)
- Awarded \$1.67M to five institutions in August 2021



COVID-19 Vaccination and Menstruation Awards



- Prospective pre-conception study of >15,000 **geographically and racially/ethnically diverse women**. Extensive **control of confounders** like stress and information bias.
(Boston University, PI: Lauren A. Wise, ScD)
- **Focuses on adolescents** who are being followed in a gynecologic pain study; will **collect saliva for hormone and immune markers**.
(Harvard Medical School, PI: Laura Allen Payne, PhD)
- Supplements existing cohort using **menstrual diary tracking** with additional recruitment; **examining menstrual effluent**
(Johns Hopkins University, PI: Mostafa Borahay, PhD)
- Uses existing cohorts (>65,000 female participants) with menstrual tracking for years; one **oversamples for people with endometriosis** and regularly collects blood samples.
(Michigan State University, PI: Stacey Ann Missmer, ScD)
- Uses preexisting US-based datasets from **FDA-approved fertility awareness applications** (pandemic data from >2 million US women
(Oregon Health and Science University, PI: Alison B. Edelman, MD)



COVID-19 Vaccination and Menstruation – Early Results



- Analyzed de-identified data from nearly 4,000 women via a fertility tracking app
- One dose of a COVID-19 vaccine during a single menstrual cycle increased cycle length by nearly one day compared to unvaccinated women
 - Two vaccine doses in same menstrual cycle increased cycle length by ~ 2 days
 - Increased cycle length not associated with change in the number of days of menses
 - **Changes were temporary**; cycle length returned to normal in subsequent cycles
 - International Federation of Gynecology and Obstetrics classifies a variation in cycle length as normal if the change is less than eight days
- Additional research may determine if COVID-19 vaccination influences associated menstrual symptoms (e.g., pain, mood changes) and characteristics of bleeding (e.g., heaviness of flow)

Edelman, A. et al. *Obstetrics & Gynecology*.
[DOI:10.1097/AOG.0000000000004695](https://doi.org/10.1097/AOG.0000000000004695) (2022)

COVID-19 Effects on the Male Reproductive System



- NICHD has a research portfolio in male reproductive health
- COVID-19 can temporarily reduce male fertility
 - 18% lower chance of conception if male partner has **SARS-CoV-2 infection** within 60 days before menstrual cycle
 - Testing positive for SARS-CoV-2 did not appear to affect overall conception rates
- COVID-19 causes higher rates of erectile dysfunction
 - Coronavirus can infect tissue within the male genital tract, where it may linger long after the initial infection
 - Not enough evidence yet for a causal link

A Prospective Cohort Study of COVID-19 Vaccination, SARS-CoV-2 Infection, and Fertility

Amelia K. Wesselink*, Elizabeth E. Hatch, Kenneth J. Rothman, Tanran R. Wang, Mary D. Willis, Jennifer Yland, Holly M. Crowe, Ruth J. Geller, Sydney K. Willis, Rebecca B. Perkins, Annette K. Regan, Jessica Levinson, Ellen M. Mikkelsen, and Lauren A. Wise

<http://doi.org/10.1093/aje/kwac011>

The New York Times

Can Covid Lead to Impotence?

Some studies find higher rates of erectile dysfunction among men recovering from the illness. But other factors related to the pandemic, like heightened anxiety, may also be to blame.



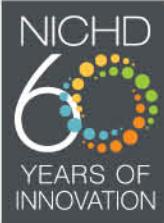
A patient with long Covid is examined in a hospital in Israel. Some research indicates that the coronavirus may linger in cells in the male genital tract. Amir Cohen/Reuters





COVID-19 and Vaccination in Pregnant and Lactating People

Maternal, Placental and Fetal Immune Response to the COVID-19 Vaccines



- Increased SARS-CoV-2 antibody levels in pregnant people post-vaccination vs. natural infection (Gray KJ et al. *AJOG*, 2021)
- Maternal immune responses were superior if vaccinated during the third or first trimester (Atyeo et al., *Medrxiv*, 2021)
 - Maternal cord transfer was highest in 1st trimester vaccination
 - Potential maternal and fetal benefits with earlier vaccination in pregnancy
- Vaccine-induced antibodies are present in breast milk samples (Gray KJ et al. *AJOG*, 2021)
- Best protection for an infant is to vaccinate the mother during the third trimester and have the mother breast feed



Vaccinating Pregnant People Protects Infants Against COVID-19



- CDC case-control study examined data including 379 COVID-positive infants at 20 pediatric hospitals in 17 states from July 1, 2021–January 17, 2022
- Effectiveness of maternal mRNA vaccination during pregnancy against COVID-19 hospitalization in infants aged <6 months was 61%
- First epidemiologic evidence for the protective benefits of maternal immunization during pregnancy against COVID-19 in infants

Morbidity and Mortality Weekly Report

Effectiveness of Maternal Vaccination with mRNA COVID-19 Vaccine During Pregnancy Against COVID-19–Associated Hospitalization in Infants Aged <6 Months — 17 States, July 2021–January 2022

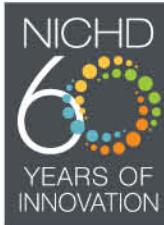
Natasha B. Halasa, MD^{1,*}; Samantha M. Olson, MPH^{2,*}; Mary A. Staat, MD³; Margaret M. Newhams, MPH⁴; Ashley M. Price, MPH²; Julie A. Boom, MD⁵; Leila C. Sahni, PhD⁵; Melissa A. Cameron, MD⁶; Pia S. Pannaraj, MD⁷; Katherine E. Bline, MD⁸; Samina S. Bhumbra, MD⁹; Tamara T. Bradford, MD¹⁰; Kathleen Chiotos, MD¹¹; Bria M. Coates, MD¹²; Melissa L. Cullimore, MD¹³; Natalie Z. Cvijanovich, MD¹⁴; Heidi R. Flori, MD¹⁵; Shira J. Gertz, MD¹⁶; Sabrina M. Heidemann, MD¹⁷; Charlotte V. Hobbs, MD¹⁸; Janet R. Hume, MD¹⁹; Katherine Irby, MD²⁰; Satoshi Kamidani, MD²¹; Michele Kong, MD²²; Emily R. Levy, MD²³; Elizabeth H. Mack, MD²⁴; Aline B. Maddux, MD²⁵; Kelly N. Michelson, MD¹²; Ryan A. Nofziger, MD²⁶; Jennifer E. Schuster, MD²⁷; Stephanie P. Schwartz, MD²⁸; Laura Smallcomb, MD²⁹; Keiko M. Tarquinio, MD³⁰; Tracie C. Walker, MD²⁸; Matt S. Zinter, MD³¹; Suzanne M. Gilboa, PhD²; Kara N. Polen, MPH²; Angela P. Campbell, MD²; Adrienne G. Randolph, MD^{4,32,†}; Manish M. Patel, MD^{2,†}; Overcoming COVID-19 Investigators

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Multi-system Inflammatory Syndrome in Children (MIS-C)

Predicting Viral-Associated Inflammatory disease severity in children with Laboratory diagnostics and artificial Intelligence (PreVAIL kIds)



*Note: MIS-C is a form of post acute sequelae of COVID-19 also known as Long COVID

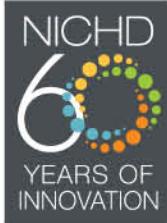
Goals: Develop translational tools to **understand the spectrum of pediatric SARS-CoV-2 illness, rapidly diagnose and characterize MIS-C associated with SARS-CoV-2, and predict the longitudinal risk of disease severity after exposure to and/or infection by SARS-CoV-2**

Includes:

- Genetics, Omics, and other Biomarkers
 - Viral Dynamics and Immune Profiling Studies
 - Digital Health Platforms Leveraged for Children
 - Artificial Intelligence
- Funded through RADx®-Radical initiative**

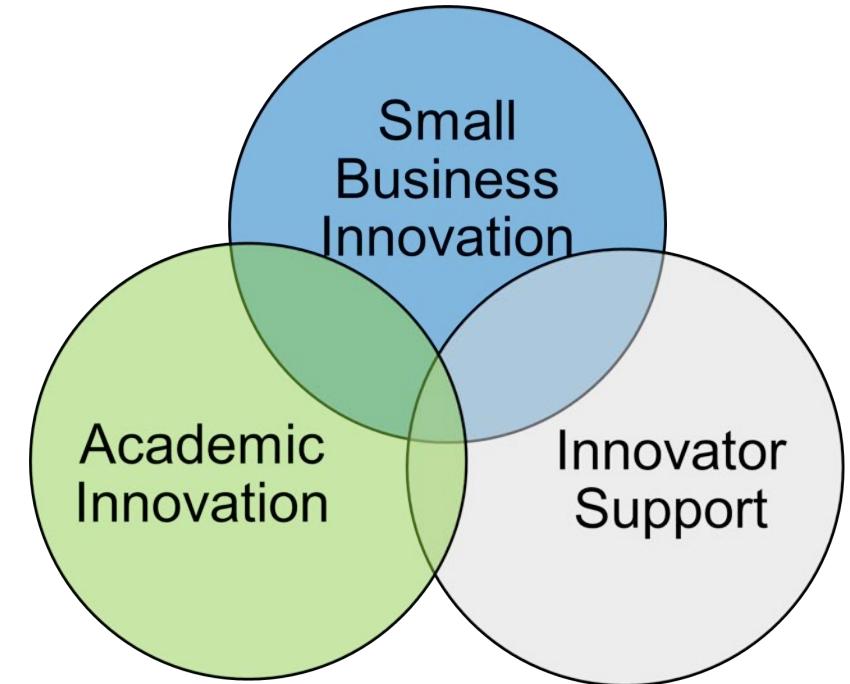


More than Funding: Small Business Education and Entrepreneurial Development (NIH SEED)



NIH Office of the Director / NIH Office of Extramural Research

- Supports the NIH innovator community (funding and resources) to validate and advance discoveries to products that improve patient care and health
- Allows investigators to:
 - Develop relationships with strategic partners and build opportunities for NIH innovators to further their product development efforts.
 - Meet early with the FDA and apply for EUAs
 - Move quickly to translation



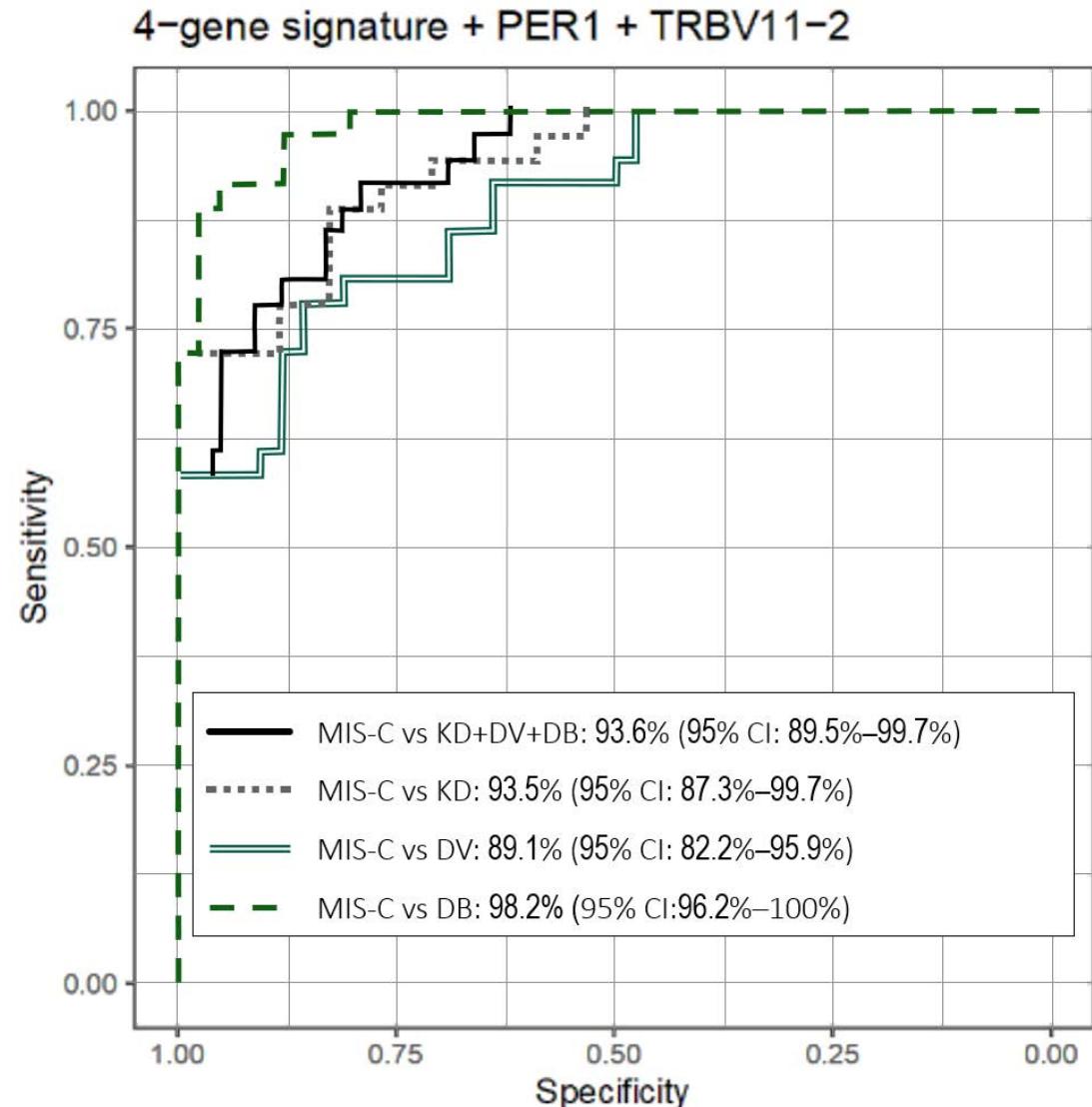
seed.nih.gov

Diagnosing and predicting risk in children with SARS-CoV-2 related illness

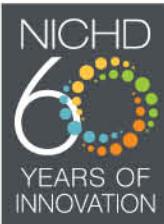
Jane Burns, MD - UCSD

Project Aim: To use RNA, protein, antibody, or clinical parameters to predict progression to severe COVID and MIS-C

- Enrolled ~3200 participants in a US cohort with a collaboration in the UK
- Pre-EUA package for the diagnostic algorithm, KIDMATCH, is currently being reviewed by FDA. Diagnostic algorithm demonstrated to distinguish MIS-C, Kawasaki, and other febrile illnesses with >95% accuracy
- Team plans to expand the prediction algorithm work by validating by qPCR a previously identified diagnostic signature for MIS-C
- Analyzing proteins that can identify MIS-C by lateral flow using technologies like Somamers and ELISA



AI Signature Shows Shared Immune Response Between Kawasaki Disease and MIS-C



- Study based on publicly available KD datasets, newly recruited cohorts of KD and MIS-C, data on children with COVID-19, and data on a set of febrile control children
- Used AI to assess the host immune response
- Similar profiles of host immune response in COVID-19, MIS-C and KD: upregulation of IL15/IL15RA pathways
- A genetic signature for KD that previously distinguished KD from other febrile diseases was similar in MIS-C
- KD and MIS-C share molecular markers; thus they may share proximal pathways of immunopathogenesis, but immune features may diverge later in disease process
 - Degree of host response in MIS-C higher than in KD
 - Pro-inflammatory pathways MIP1a, TNFa and IL1 significantly induced in MIS-C compared to KD
- Authors therefore recommend anakinra + infliximab to treat MIS-C

Ghosh, P. et al. *Nat Commun* **13**, 2687 (2022). <https://doi.org/10.1038/s41467-022-30357-w>

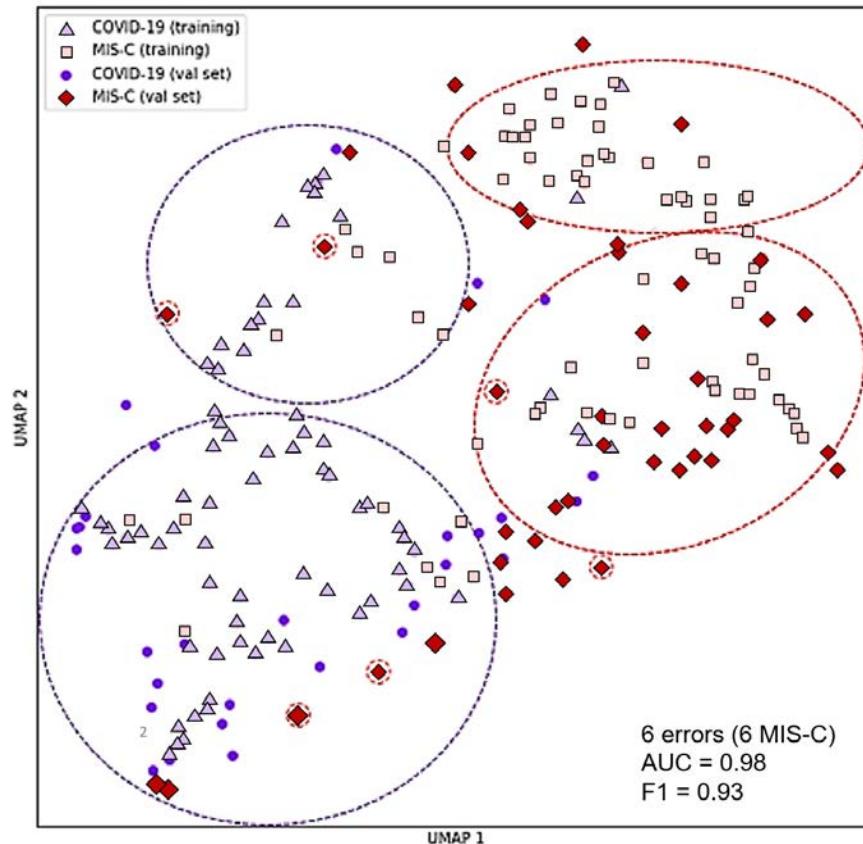


Artificial Intelligence COVID-19 Risk AssEssment for kids

Ananth Anapragada, PhD, - Baylor College of Medicine

Project Aims: To characterize a full range of markers across the pediatric COVID patient population to train machine learning algorithms/ensembles to identify progressive disease cases at initial presentation

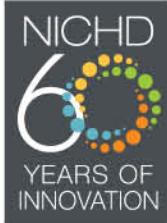
- Enrolled about 400 participants prospectively and about 50,000 participants retrospectively in or near Texas
- Preparing a Pre-EUA package based on an inflammatory cytokine/chemokine panel (*image at right*)
- Plans to expand this prediction algorithm to standard lab records, EMR free text, and chest radiographic images
- Highlighted impact of socio-economic disparities and race association with disease severity. Non-Hispanic Black children and children in high deprivation index areas are significantly more likely to require intubation and/or vasoactive support (adjusted for gender and BMI)



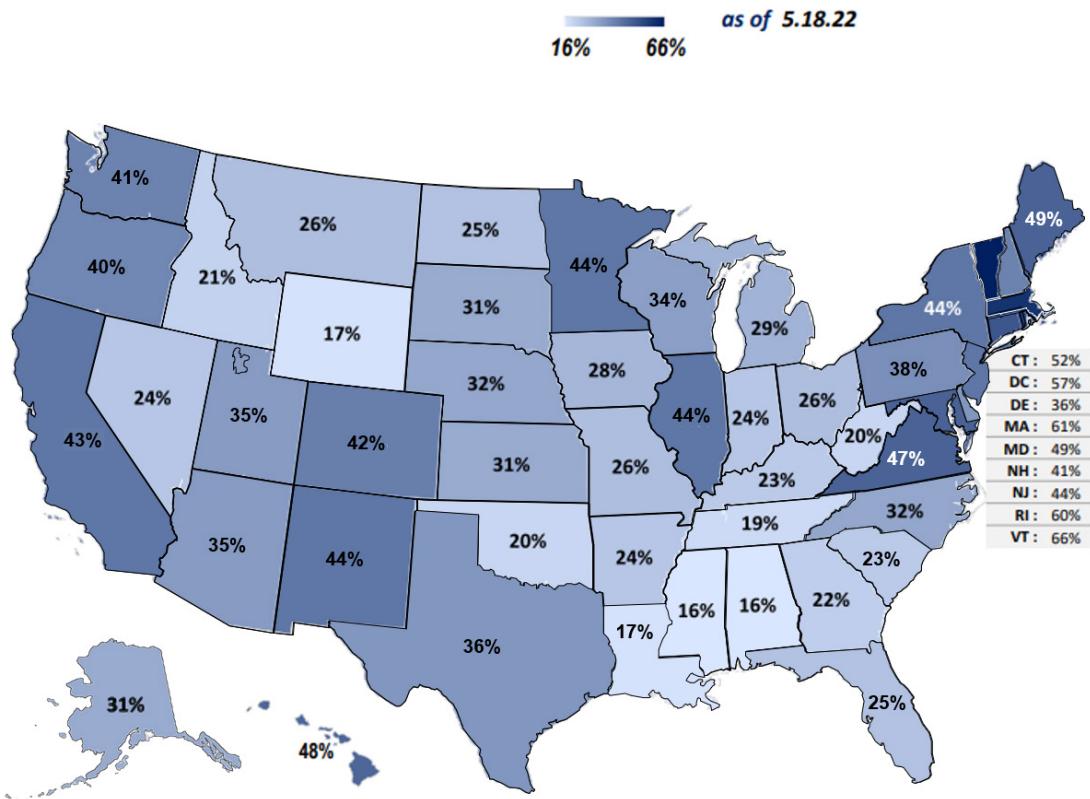


Future Challenges

WEEKLY VACCINATION TRENDS REPORT (AAP)



as of 5.18.22
16% 66%



Percent of Children Ages 5-11 Who Received At Least One Dose of COVID-19 Vaccine by State

- **9.9 M** children ages **5-11** (35%) have received **at least one dose** of COVID-19 vaccine
- **8.1 M** children ages **5-11** (28%) are **fully vaccinated**
- **17.2 M** children and adolescents ages **12-17**(68%) have received **at least one dose** of COVID-19 vaccine
- **14.7 M** children and adolescents ages **12-17** (58%) are **fully vaccinated**
- **25K** children and adolescents ages **12-17** received their first dose this week

Potential Impact of Maternal SARS-CoV-2 Infection on Fetal Neurodevelopment

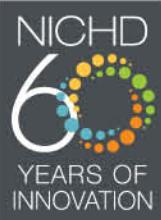


- Past pandemics have provided a window into potential neurodevelopmental consequences in subsequent generations
- Maternal and placental immune activation can affect the developing brain
- Some reports show potential connection between prenatal SARS-CoV-2 exposure and neurodevelopmental disorders in offspring; too early for definitive diagnosis for many conditions
- Future variants with enhanced immune escape or transmissibility could impact risk for transplacental infection (currently rare)
- Future research needs
 - Cellular models of fetal brain development to better understand potential short- and long-term impacts of maternal SARS-CoV-2 infection on offspring
 - To understand not only direct/immediate effects, but also persistent effects on cells
 - More data on all trimesters for holistic risk assessment

L.L. Shook, et al., *Trends in Molecular Medicine* (2022), <https://doi.org/10.1016/j.molmed.2022.02.004>



Future Pandemic Preparedness: *Include Pregnant and Lactating People in Research*



- Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)
 - Representation across all sectors
 - Issued **recommendations** in 2018 and an **implementation plan** in 2020
 - <https://www.nichd.nih.gov/About/Advisory/PRGLAC>
- Change the culture to protect pregnant people *through* research instead of *from* research
- **Need to plan for the inclusion of pregnant and lactating people for evaluation of treatments and vaccines in future pandemics**

Viewpoint

February 10, 2021

Involving Pregnant Individuals in Clinical Research on COVID-19 Vaccines

Diana W. Bianchi, MD¹; Lisa Kaeser, JD¹; Alison N. Cernich, PhD¹

» Author Affiliations | Article Information

JAMA. 2021;325(11):1041-1042. doi:10.1001/jama.2021.1865





Thank You!

Questions?