Ethics, Research and Pregnancy

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CDC recommends **urgent action** to increase Coronavirus Disease 2019 (COVID-19) vaccination among people who are pregnant, recently pregnant (including those who are lactating), who are trying to become pregnant now, or who might become pregnant in the future. CDC **strongly recommends COVID-19 vaccination either before or during pregnancy** because the benefits of vaccination outweigh known or potential risks.
COVID-19 vaccination among pregnant people aged 18-49 years overall, by race/ethnicity, and date reported to CDC - Vaccine Safety Datalink,* United States

Figure 1: Percent of Pregnant People Aged 18-49 Years Fully Vaccinated with COVID-19 vaccine Prior to and during Pregnancy, by Timing of Vaccination and Date Reported to CDC – Vaccine Safety Datalink*, United States December 14, 2020 – September 18, 2021

- **Overall:** 31%
  - Asian: 46%
  - NH White: 35%
  - Latina: 27%
  - Black: 16%

Mississippi health officials plea for vaccination after 'significant' number of COVID-19 fatalities in pregnant women

The eight women who recently died were unvaccinated, health officials said.

By Meredith Deliso
September 10, 2021, 4:57 PM • 5 min read

- **Cases:** 125,250
- **Deaths:** 161
- **97%** of hospitalized are unvaccinated
Vaccines authorized - December 2019

**F.D.A. Clears Pfizer Vaccine, and Millions of Doses Will Be Shipped Right Away**

An initial shipment of about 2.9 million doses of the vaccine will be sent around the United States over the next week.

**F.D.A. Authorizes Moderna Vaccine, Adding Millions of Doses to U.S. Supply**

The Food and Drug Administration authorized a second coronavirus vaccine for emergency use, clearing the way for millions more Americans to be immunized next week.
Priority Groups for Vaccination (ACIP)

• Phase 1a: **Health care workers** and long-term care facility residents
• Phase 1b: Persons aged ≥75 years and **frontline essential workers**
• Phase 1c: Persons aged 65-75 years, persons aged **16-64 years with high risk medical conditions (including pregnancy)**, and other essential workers

➤ **Pregnant people represented across priority groups**
ACOG Practice Advisory, December 2020

• Vaccines available under EUA have not been tested in pregnant women, no pregnancy-specific data.

• COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups.

• Pregnancy testing should not be a requirement prior to receiving any EUA-approved COVID-19 vaccine.
WHO recommends vaccination in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks.
COVID-19 and pregnancy

- Increased risk for severe illness
- Increased risk associated with comorbidities
- Increased risk for ICU admission
- Increased risk for mechanical ventilation
- Increased risk for preterm birth
- Increased risk for death
- Black and Hispanic individuals bear disproportionate burden of infection, morbidity and death
Assessing vaccine risk and pregnancy

Authorized mRNA vaccines:

- theoretical
- animal
- human
- human pregnancy
MEDICAL DISPATCH

THE CORONAVIRUS VACCINE PRESENTS A DILEMMA FOR PREGNANT WOMEN

Vaccine trials have excluded the pregnant population, even though women of reproductive age make up a majority of frontline workers.

By Anna Louie Sussman
February 1, 2021
The journey toward ethical inclusion
The first wave: Women as research subjects

- Early 1990s women noted to be underrepresented in research
  - Excluded from studies
  - Health concerns not investigated
- Alleged justifications
  - Women’s physiologies complicate
  - Protection of women and fetuses
  - Recruitment difficulties
- 1993 NIH Revitalization Act
  - New requirements for inclusion of women and minorities in research
  - Justify exclusion on basis other than cost
- Women now majority of research participants (gaps remain)
  - Pregnant people – left behind
The Second Wave:  
Pregnant people as research subjects

- As a matter of justice, all people deserve to safe and effective treatment throughout the lifespan – *including during pregnancy* – and deserve an evidence base adequate to that fact.

- Ethics requires protecting pregnant people not *from* research, but *through* research.
Pregnancy specific data: lacking

Pregnancy-specific data in drugs approved since 2010:

- 90% - Animal data
- 10% - Human data

Byrne et al, JAMA 2020

- Limited or no data at time of approval
- Post approval delays in pregnancy-specific data - extensive
Pregnancy-specific evidence: a critical need

- **Dosing**
  - Toxicity
  - Exposure to disease

- **Fetal safety**
  - Unacceptable or unanticipated risk, reticence

- **Maternal outcomes**
  - Unacceptable or unanticipated risk, reticence
Dosing

• Pregnancy changes drug metabolism, dosing
  • Pharmacokinetics (PK)
• Dearth of PK data for treatment, prevention, co-l
• Average delay for approved ARVs = 6 years

• Harms: underdosing (exposure to disease); overdosing (toxicity)
• Example: cobicistat
Cobicistat - PK

Momper et al, AIDS, 2018
Fetal Safety

• Safety of drugs for fetus is prominent concern
• Most drugs come to market with animal data only
• Post approval data delayed, limited

• Harms:
  • Potential for inappropriate risk
  • Barriers to access
• Examples: malaria, TB treatments
Maternal outcomes

- Drugs may carry risks specific to pregnancy (preeclampsia, hemorrhage, liver toxicity), especially where drugs are used in combination
- Tendency to focus on/prioritize fetal/neonatal outcomes
- Harms: increased risk of maternal morbidity/death
- Example: ARTs and liver toxicities
Risk shifting

Research

Clinical

Risk
Causes of evidence gaps

• Drug approval and development pathway
  • Lack of requirements, incentives

• Pregnant women and research
  • Myths and misconceptions
  • History of “protectionism”
  • Lack of training
  • Legal and logistical challenges
  • Justificatory asymmetry

• Pregnant women and risk
  • Vessels and vectors
  • Risk distortions
[A] **cultural shift** is necessary to emphasize the importance and public health significance of building a knowledge base to inform medical decision-making for pregnant and lactating women. *Research on therapies for these populations must be facilitated and greatly augmented.*

**PRGLAC, 2018 Report to HHS**
FDA: Draft Guidance

“Filling the knowledge gaps regarding safe and effective use of drugs is a critical public health need, but one that raises complex issues”
Ending the evidence gap for pregnant women around HIV & co-infections:

A CALL TO ACTION

The PHAGES Working Group
Pregnancy and HIV/AIDS: Seeking Equitable Study
Issued July 2020
The PHASES Project

Engagement
Consultations
Empirical Research

Conceptual-Analytic Research

Guidance Development
The PHASES Project

Engagement
Consultations
Empirical Research

140 Interviews with stakeholders
- 70 in United States
- 70 in Botswana, Malawi, and South Africa

140 Interviews with pregnant/recently pregnant women
- 70 in Malawi
- 70 in US
  - 35 HIV +
  - 35 HIV −

Legal & Ethical Analysis
The PHASES Project

Engagement
Consultations
Empirical Research

Conceptual-Analytic
Research

Guidance Development
Ethical Foundations

protection  access  respect

PHASES Working Group, 2020
Equitable protection from drug-related risks

- Mission of research – gather evidence to decrease risks in clinical settings
- Pregnant women and offspring need and deserve such protection
- Exclusion from research doesn’t eliminate risks – it exports them to the clinical setting, where they expand
Equitable **access** to medications and vaccines

- Pregnant people deserve timely access to medications and vaccines
- Lack of data leads to reticence to prescribe or take medicines; cautions against use in public health guidance
- Leaves pregnant people and offspring exposed to risks of disease
Equitable respect for pregnant women’s health

- Tendency for fetal or child outcomes to overshadow attention to maternal outcomes.
- Decisions about research (and treatment) should reflect due consideration for the woman’s health.
- Failure to do so treats her as a “vessel or vector” rather than a person in her own right.
Three Conceptual Shifts

- **Vulnerable population** → **Complex population**
- **Protection from research** → **Protection through research**
- **Presumptive exclusion** → **Fair inclusion**
PHASES Guidance

→ 12 specific, concrete, and immediately actionable recommendations

→ Consistent with current regulatory frameworks

→ Directed to multiple stakeholders across the arc of drug development and post-approval research.
Recommendations
Building Capacity

1. Affirm the need for research with pregnant women
2. Formalize a global network for advocacy and resources
3. Enhance training
“Pregnant people have historically been left out of research agendas and clinical trials due to the added complexities of ensuring their safety and that of their children.”

“We urge you to account for the unique risks and concerns of populations that have historically been excluded from pandemic research agendas.”

MATERNAL HEALTH PANDEMIC RESPONSE ACT
Supporting Inclusion

4. Design for inclusion

5. Review for and facilitate inclusion

6. Ensure equitable attention to pregnant women’s own health
Burden of justification

- Shifting burden – require justifying *exclusion*
Achieving Priority Research

7. Integrate pharmacokinetic (PK) studies
8. Enhance post-approval safety assessments
9. Address legacy evidence gaps
Ensuring Respect

10. Ensure fair access to life-saving experimental drugs
11. Respect and support women’s decisional authority
12. Contextualize risk findings
“It is critical to not just view a pregnant mother, or any woman of childbearing potential, as a vessel for a baby, but as an individual in her own right, who deserves access to the very best, evidence-based treatment available and the right to be adequately informed to make a choice that she feels is best for her.”

Communique of the Kigali Dolutegravir Stakeholder Meeting of African Women Living with HIV, 2018
PFIZER AND BIONTECH COMMENCE GLOBAL CLINICAL TRIAL TO EVALUATE COVID-19 VACCINE IN PREGNANT WOMEN

Thursday, February 18, 2021 - 01:30pm EST

New York, USA and Mainz, Germany, February 18, 2021 — Pfizer Inc. (NYSE: PFE) and BioNTech SE (Nasdaq: BNTX) announced today that the first participants have been dosed in a global Phase 2/3 study to further evaluate the safety, tolerability, and immunogenicity of the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) in preventing COVID-19 in healthy pregnant women 18 years of age and older.
Thank you!

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