SARS-CoV-2 Vaccines in Pregnant Women

Emily Erbelding, M.D., M.P.H.
Director
Division of Microbiology and Infectious Diseases (DMID)
NIAID, NIH, HHS
Operation Warp Speed

- Operation Warp Speed is the Trump administration's national program to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics.
Special populations: Who is “special”?

- Special regulatory or ethical considerations
  - Pregnancy: Developmental and reproductive toxicity testing usually required in preclinical package for FDA approval
  - Age < 18 years: Parental consent usually required
- Elderly: high risk of poor outcomes with COVID-19, so included in adult efficacy trials
- HIV+: no valid reason for exclusion from adult efficacy trials
Vaccine research in pregnancy

- Traditional and sequential approach:
  - Conduct efficacy trials in non-pregnant adults
  - Conduct intensive follow-up of pregnancy outcomes when it occurs
  - If vaccine shows efficacy, conduct bridging studies enrolling pregnant volunteers
Pros/cons to this approach

**Pros**
- Pregnant women and offspring they carry are protected from risk
- Timing allows for correlates of protection to be identified

**Cons**
- Will delay vaccine implementation to women of childbearing age for over a year
- A large proportion of first responders and essential workers may remain unvaccinated

- This “traditional” approach was deemed unsuitable for vaccines for some emerging infectious diseases (Ebola, Zika, others).
Paradigm Shift: Presumptive Inclusion of Pregnant Women

- Normalizes the position that pregnant women are to be included in vaccine deployment and vaccine R&D
- Pregnant women of legal standing to consent have the ability to give voluntary and informed consent and should be given the opportunity to enroll in trials
  - They aren’t a “vulnerable” population
- Burden of proof falls on those who want to argue for exclusion
- Vaccine studies that include women of childbearing age should have plans to systematically collected data on immunogenicity and pregnancy-specific factors
COVID-19 and Pregnancy

- Increased risk of infection
  - Women of childbearing age represent substantial proportions of health care workers and first responders
- Increased risk of severe outcomes
  - Maternal: Data emerging
  - Fetal: Undetermined at present
  - Infant: Undetermined at present
- Altered immune response?
  - Antibody quality
- Interference with infant vaccines
  - n/a at present
## Pregnancy and risk of severe disease

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pregnant women (n=8,207) No. (%)</th>
<th>Nonpregnant women (n=83,205) No. (%)</th>
<th>Crude risk ratio (95% CI)</th>
<th>Adjusted risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>2,587 (31.5)</td>
<td>4,840 (5.8%)</td>
<td>5.4 (5.2-5.7)</td>
<td>5.4 (5.1-5.6)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>120 (1.5)</td>
<td>757 (0.9)</td>
<td>1.6 (1.3-1.9)</td>
<td>1.5 (1.2-1.8)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>42 (0.5)</td>
<td>225 (0.3)</td>
<td>1.9 (1.4 – 2.6)</td>
<td>1.7 (1.2 – 2.4)</td>
</tr>
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Source: [https://www.cdc.gov/mmwr/volumes/69/wr/mm6925a1.htm?s_cid=mm6925a1_w#T2_down](https://www.cdc.gov/mmwr/volumes/69/wr/mm6925a1.htm?s_cid=mm6925a1_w#T2_down)
TABLE 1. Relative risk of requiring intensive care for pregnant women with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or influenza, respectively

<table>
<thead>
<tr>
<th>Population</th>
<th>Relative risk</th>
<th>95% Confidence limits</th>
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<tbody>
<tr>
<td>SARS-CoV-2</td>
<td>5.39</td>
<td>2.89</td>
</tr>
<tr>
<td>Sensitivity analysis¹, SARS-CoV-2</td>
<td>3.48</td>
<td>1.86</td>
</tr>
<tr>
<td>Sensitivity analysis², SAIRS-CoV-2</td>
<td>4.00</td>
<td>1.75</td>
</tr>
<tr>
<td>Sensitivity analysis³, SAIRS-CoV-2</td>
<td>2.59</td>
<td>1.13</td>
</tr>
<tr>
<td>2015-2016 seasonal influenza epidemic</td>
<td>2.17</td>
<td>0.94</td>
</tr>
</tbody>
</table>

1 50% more pregnant women.
2 Only cases requiring invasive mechanical ventilation.
3 Sensitivity analyses 1 and 2 combined.

Tiering of target groups in vaccine implementation

**Phase 1**
- **Phase 1a “Jumpstart Phase”**:
  - High-risk workers in health care facilities
  - First responders
- **Phase 1b**:
  - People of all ages with comorbid and underlying conditions that put them at significantly higher risk
  - Older adults living in congregate or overcrowded settings

**Phase 2**
- Critical risk workers—workers who are both in industries essential to the functioning of society and at substantially high risk of exposure
- Teachers and school staff
- People of all ages with comorbid and underlying conditions that put them at moderately higher risk
- All older adults not included in Phase 1
- People in homeless shelters or group homes for individuals with physical or mental disabilities or in recovery
- People in prisons, jails, detention centers, and similar facilities, and staff who work in such settings

**Phase 3**
- Young adults
- Children
- Workers in industries essential to the functioning of society and at increased risk of exposure not included in Phase 1 or 2

**Phase 4**
- Everyone residing in the United States who did not receive the vaccine in previous phases

Equity is a crosscutting consideration: In each population group, vaccine access should be prioritized for geographic areas identified through CDC’s Social Vulnerability Index.

* From the Discussion Draft of the Preliminary Framework for Equitable Allocation of COVID-19 Vaccine, Committee on Equitable Allocation of Vaccine for the Novel Coronavirus, National Academies of Sciences, Engineering, and Medicine
FDA encourages developers to consider early in their development programs that might support inclusion of pregnant women and women of childbearing potential not avoiding pregnancy.

Prior to enrolling pregnant women and women of childbearing potential who are not actively avoiding pregnancy in clinical trials, sponsor should conduct developmental and reproductive toxicity (DART) studies.

Alternatively, sponsors may submit data from DART studies with a similar product using comparable platform technology.

All pregnancies in participants for whom date of conception is prior to vaccination or within 30 days after vaccination should be followed for pregnancy outcomes.

Pregnancy exposure registry that actively collects information on vaccination during pregnancy and associated pregnancy and infant outcomes.
## Proposed Timelines: COVID-19 Prevention Network Phase 3 Efficacy Trial Program

<table>
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<tr>
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<th>2020</th>
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<tbody>
<tr>
<td></td>
<td>Summer</td>
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<tr>
<td>Moderna mRNA</td>
<td>AstraZeneca AZD1222</td>
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<tr>
<td>Novavax Recombinant Nanoparticle</td>
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Others: Pfizer/BioNTech mRNA vaccine; Merck VSV and measles vector.
Platform vaccine technologies

Protein vaccines
- Novavax
- GSK/Sanofi

Viral vector vaccines
- Oxford/AstraZeneca
- Janssen

RNA technology
- Moderna
- BioNTech/Pfizer
VTEU draft protocol for pregnancy: general features

- Originally developed for H7N9 influenza vaccine (never implemented)
- Assess safety and immunogenicity of vaccine in 2nd and 3rd trimester of pregnancy
- N=130-150 women
- Maternal follow up 12 months; infant 3 months
- Participant study duration: 13 months
- Time to complete: 15 months
Other “special” populations: pediatrics

- Age < 18 years not first responders
- Low risk of severe COVID-19 with infection*
- Is vaccine to prevent COVID-19 in children? Or to prevent transmission?
- Traditional approach: After efficacy and safety is proven in adult populations, conduct bridging studies for correlates of protection in age cohorts de-escalating by age (17-9 yrs, 9-3 yrs, 36-6 mos)

*Though emerging data continue to challenge this generalization
Thank you