SARS-CoV-2 Vaccines in Pregnant Women

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Operation Warp Speed

Moncef Slaoui, a former pharmaceutical executive and now the chief scientist of the White House's initiative to develop a coronavirus vaccine, in the Rose Garden last week. Samuel Corum for The New York Times

Dr. Moncef Slaoui, chief advisor of Operation Warp Speed

CNN politics Donald Trump Supreme Court Congress Facts First 2020 Election

Trump administration's 'Operation Warp Speed' identifies 14 vaccines to focus on

- Operation Warp Speed is the Trump administration's national program to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics.

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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

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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

Review

Pregnant women & vaccines against emerging epidemic threats: Ethics guidance for preparedness. research, and response

Carleigh B. Krubiner [a,1,*], Ruth R. Faden [a,b], Ruth A. Karron [b], Margaret O. Little [c], Anne D. Lyerly [d], Jon S. Abramson [e]. Richard H. Beigi [f]. Alejandro R. Cravioto [g], Anna P. Durbin [b], Bruce G. Gellin [h], Swati B. Gupta [i], David C. Kaslow [j], Sonali Kochhar [k], Florencia Luna [l], Carla Saenz [m], Jeanne S. Sheffield [n]. Paulina O. Tindana [o,2], The PREVENT Working Group

https://doi.org/10.1016/j.vaccine.2019.01.011

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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

Outcome	Pregnant women (n=8,207) No. (%)	Nonpregnant women (n=83,205) No. (%)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Hospitalization	2,587 (31.5)	4,840 (5.8%)	5.4 (5.2-5.7)	5.4 (5.1-5.6)
ICU admission	120 (1.5)	757 (0.9)	1.6 (1.3- 1.9)	1.5 (1.2-1.8)
Mechanical ventilation	42 (0.5)	225 (0.3)	1.9 (1.4 – 2.6)	1.7 (1.2 – 2.4)

Source: https://www.cdc.gov/mmwr/volumes/69/wr/mm6925a1.htm?s_cid=mm6925a1_w#T2_down

Report from Sweden

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

Population	Relative risk	95% Confidence limits	
SARS-CoV-2	5.39	2.89	10.08
Sensitivity analysis[1], SARS-CoV-2	3.48	1.86	6.52
Sensitivity analysis[2], SAIRS-CoV-2	4.00	1.75	9.14
Sensitivity analysis[3], SAIRS-CoV-2	2.59	1.13	5.91
2015-2016 seasonal influenza epidemic	2.17	0.94	4.99

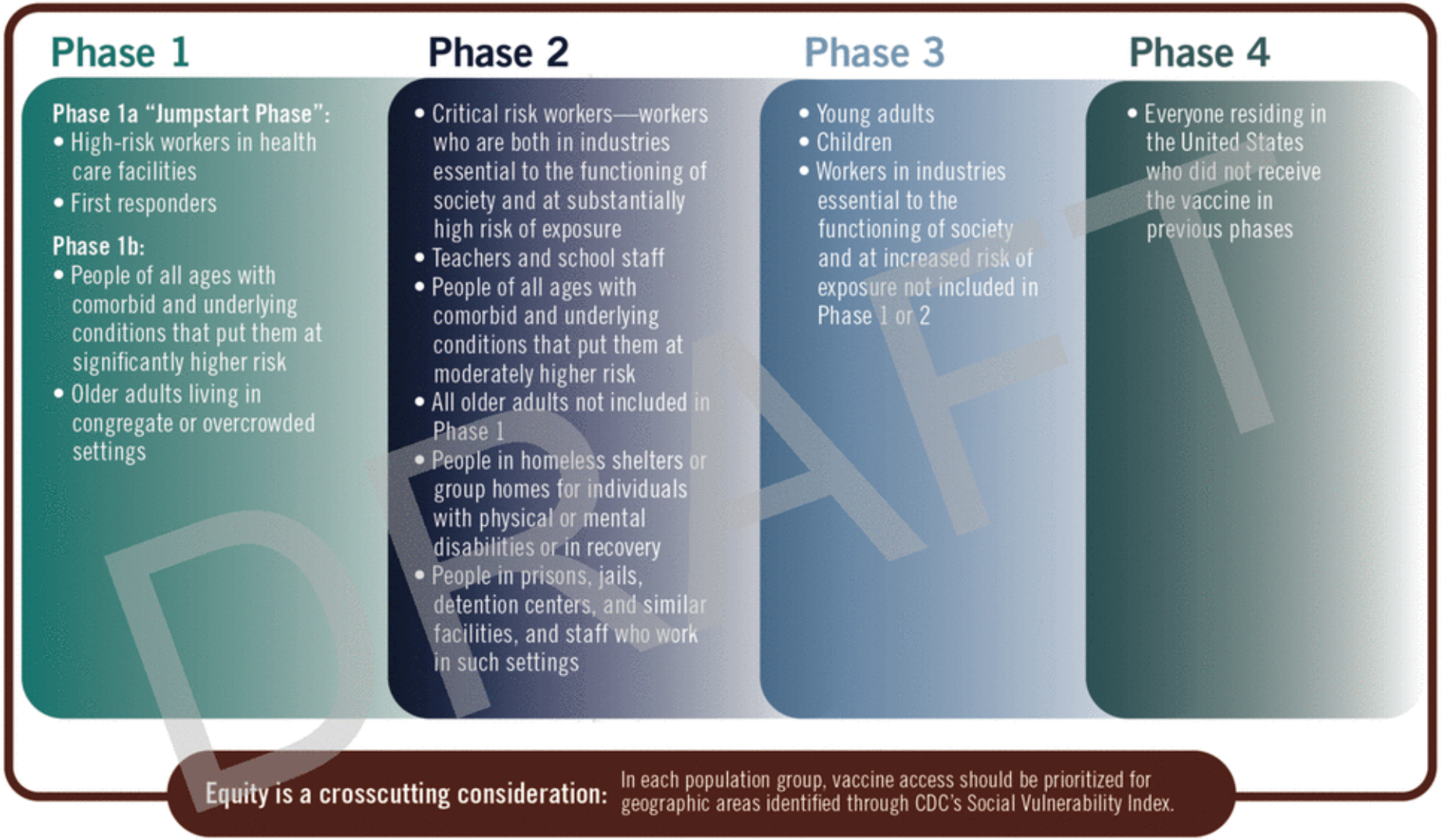
1 50% more pregnant women.

2 Only cases requiring invasive mechanical ventilation.

3 Sensitivity analyses 1 and 2 combined.

Source: https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/aogs.13901

Tiering of target groups in vaccine implementation



* 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

Development and licensure of vaccine to prevent COVID-19 | Pregnancy

- 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

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

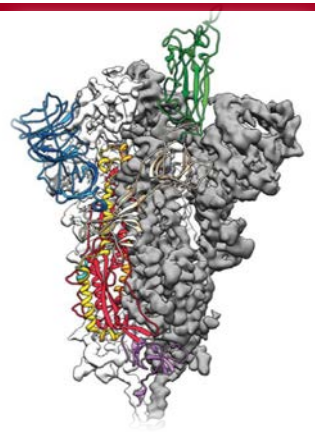
Proposed Timelines: COVID-19 Prevention Network Phase 3 Efficacy Trial Program

2020		
Summer	Fall	Winter
Moderna mRNA AstraZeneca AZD1222	Janssen Ad26 Novavax Recombinant Nanoparticle	Sanofi Baculovirus Prefusion Protein

Others: Pfizer/BioNTech mRNA vaccine; Merck VSV and measles vector.

Platform vaccine technologies

Protein vaccines



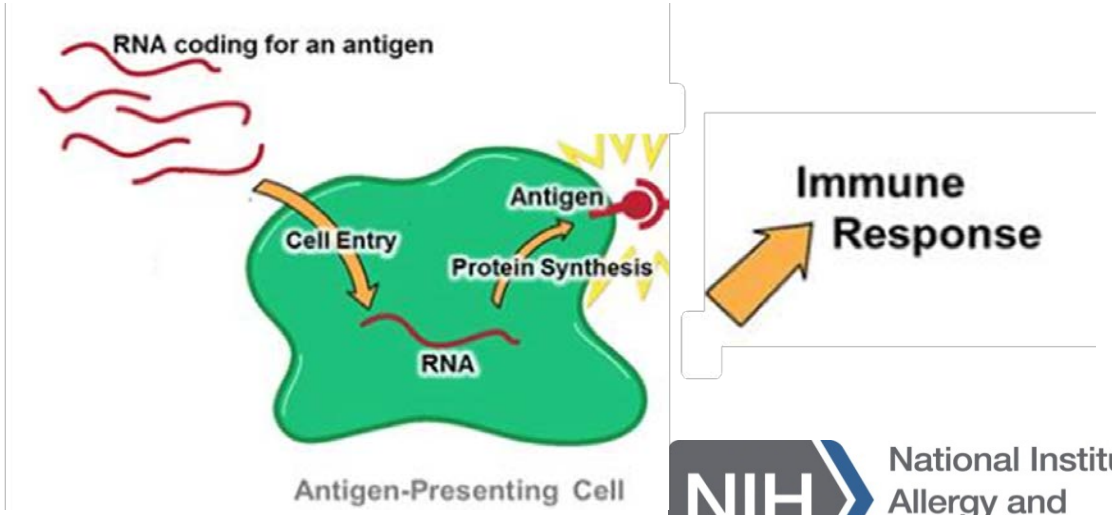
- Novavax
- GSK/Sanofi

Viral vector vaccines

- Oxford/AstraZeneca
- Janssen

RNA technology

- Moderna
- BioNTech/Pfizer



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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