Recommendations for Anthrax Vaccination of Pregnant and Breastfeeding Women

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Outline of Session

- I. Statement outline
- 2. Use of AVA
- 3. Pre-event recommendations
- 4. Vote
- 5. Delayed dosing
- 6. Vote
- 7. Post-exposure prophylaxis (PEP)
- 8. Vote
- 9. PEP for repeated occupational exposures
- 10. Vote
- 11. Pregnancy data
- 12. Vote

Anthrax Vaccine Adsorbed

- Not a live vaccine
  - No biologically plausible mechanism for reproductive effect*
- FDA Pregnancy Category D
  - Based on preliminary analysis of the Ryan, et al study
  - "There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks."

* Wiesen A and Littell C, JAMA 2002

Current AVA Use in Pregnancy

- "No studies have been published…Pregnant women should be vaccinated against anthrax only if the potential benefits of vaccination outweigh the potential risks to the fetus"*
- Pre-event use
  - DoD defers vaccination if pregnancy reported
- Post-exposure
  - If potential benefits outweigh potential fetal risks

*CDC. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices.MMWR Morb Mortal Wkly Rep. 2000 Dec 15;49(RR15):1-20.

Current AVA Use While Breastfeeding*

- **No data suggest increased risk for side effects or temporally related adverse events associated with receipt of anthrax vaccine by breast-feeding women or breast-fed children. Administration of non-live vaccines (e.g., anthrax vaccine) during breast-feeding is not medically contraindicated.**

*CDC. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices.MMWR Morb Mortal Wkly Rep. 2000 Dec 15;49(RR15):1-20.

ACIP Pregnancy Principles Document

- New document
- Ensure recommendation development is consistent and rigorous
- Ensure recommendations are clear and uniform

- Addresses how and where in the statement to address pregnancy and breastfeeding
- Provides 7 core topics for WGs to review

http://www.cdc.gov/vaccines/recs/acip/downloads/preg-principles05-01-08.pdf

New ACIP Pregnancy Guidelines
Core Topics

- Reviewed
  - Disease burden
  - Vaccination during pregnancy
    - Rationale, safety, immunogenicity, efficacy, timing
  - Vaccination during breastfeeding
    - Rationale, safety, immunogenicity, efficacy, timing
  - Alternatives to vaccination
- Not reviewed
  - Cost effectiveness
  - Logistics
  - Future research

Precaution/Contraindication

- **Specifically address whether vaccination is a precaution or a contraindication**

- **<u>Precaution</u> - condition in a recipient that might increase the risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce immunity. *Under usual circumstances, vaccination should be deferred. However, vaccination might be indicated because benefits outweigh risks***

- **<u>Contraindication</u> -condition in a recipient that increases the risk for a serious adverse reaction. *A vaccine will not be administered when a contraindication is present***

Issues Considered
AVA Administration During Pregnancy/Breastfeeding

	+/-
Burden of Disease	-/+
Immunogenicity and Efficacy	
Safety Trimester-specific issues	
Post-exposure alternatives	

+ Favorable
- Not favorable

Immunogencity and Efficacy

- AVA produces robust immune response in non-pregnant adults
  - No AVA-specific immunogenicity or efficacy studies of pregnant or breastfeeding women
- WG reviewed studies of other vaccines[1,2] for effect of pregnancy on immune response
  - Studies gave no indication that pregnancy decreases efficacy/immune response

1 Baker, et al. Immunization of pregnant women with group B streptococcal type III capsular polysaccharide-tetanus toxoid conjugate vaccine. Vaccine. 2003 Jul 28;21(24):3468-72.
2 Quiambaio, et al. Immunogenicity and reactogenicity of 23-valent pneumococcal polysaccharide vaccine among pregnant Filipino women and placental transfer of antibodies. Vaccine. 2007 May 30;25(22):4470-7.

Issues Considered
AVA Administration During Pregnancy/Breastfeeding

	+/-
Burden of Disease	-/+
Immunogenicity and Efficacy	+
Safety Trimester-specific issues	
Post-exposure alternatives	

+ Favorable
- Not favorable

Female Fertility Study*

- Cohort study of 385 military women vaccinated pre-pregnancy
  - Primary outcome = pregnancy
- Did not support hypothesis that AVA results in decreased pregnancy rates or adverse fetal outcome
- No evidence of miscarriage, infertility, other reproductive problems
  - Low power to detect low incidence adverse birth outcomes

*"Relationship between Prepregnancy Anthrax Vaccination and Pregnancy and Birth Outcomes Among US Army Women." JAMA. 2002.287:12(1556-1560).

Birth Defects Among Infants Born to Women Who Received Anthrax Vaccine in Pregnancy*

- 37,140 infants born to vaccinated women
- Utilized ICD-9 codes for birth defect diagnoses
- Primary referent group = Infants born to women vaccinated during first trimester compared with all other vaccinated women
- Alternative referent groups utilized

*Ryan, MAK, et al. Birth Defects among Infants Born to Women Who Received Anthrax Vaccine in Pregnancy. Amer J Epi; July 2008

Comparison of Primary and Alternative Models: Adjusted Odds of Birth Defects Among Infants of Military Women, by Maternal Anthrax Vaccination Status, 1998-2004.*

Exposure Groups with Associated Odds Ratios and 95% Confidence Intervals	Referent Group for Maternal Vaccination					
	Vaccinated outside of 1st trimester (primary model)		Vaccinated post-pregnancy		Never vaccinated	
	1st trimester vaccinated	1.18 (0.997, 1.41)	1st trimester vaccinated	1.20 (1.005, 1.43)	1st trimester vaccinated	1.20 (1.02, 1.42)
			Pre-pregnancy vaccinated	1.09 (0.98, 1.22)	Pre-pregnancy vaccinated	1.08 (0.99, 1.17)
			Late-pregnancy vaccinated	0.86 (0.58, 1.27)	Late-pregnancy vaccinated	0.86 (0.59, 1.26)
					Post-pregnancy vaccinated	1.02 (0.95, 1.10)
					Ever-vaccinated	1.05 (0.98, 1.12)

*Ryan, MAK, et al. Birth Defects among Infants Born to Women Who Received Anthrax Vaccine in Pregnancy. Amer J Epi; July 2008

Specific Birth Defects

- Further explored 10 specific birth defects with ≥5 cases per group
- Atrial septal defect (ASD) represented a statistically significant increase from the referent group
  - OR=1.38, 95% CI=1.04-1.82
  - Not statistically significant upon exclusion of isolated ASD cases in preterm infants
  - Not statistically significant if adjustment for multiple comparisons applied.

*Ryan, MAK, et al. Birth Defects among Infants Born to Women Who Received Anthrax Vaccine in Pregnancy. Amer J Epi; July 2008

ACIP WG Assessment of Ryan, et al Paper

- Associations between AVA and birth defects neither strong nor consistent
- Evidence not conclusive to associate vaccination with birth defects
  - Demographic differences between never vaccinated and vaccinated women
  - ASD association not found when pre-term infants removed
- Being vaccinated during first trimester may be indicative of late maternal recognition of pregnancy
  - May be marker for other risk factors for birth defects

*Ryan, MAK, et al. Birth Defects among Infants Born to Women Who Received Anthrax Vaccine in Pregnancy. Amer J Epi; July 2008

Safety of Other Inactivated Vaccines During Pregnancy

- Maternal vaccination has not been established to cause birth defects
- Other inactivated vaccines are recommended for use in at risk women during pregnancy
  - Tetanus, hepatitis B, poliovirus, influenza
- WG reviewed additional studies evaluating vaccine safety during pregnancy [1,2]
- Animal evidence that stimulation of maternal immune system associated with decreased birth defect risk[3,4]

1 Baker, et al.. Vaccine. 2003 Jul 28;21(24):3468-72.
2 Quiambaio, et al. Vaccine. 2007 May 30;25(22):4470-7.
3 Holladay, et al. Teratology. 2000;62:413–19.
4 Yitzhakie, et al. J Repro Immunology. 1999;45:49–66.

AVA Safety During Breastfeeding

- No AVA specific data
- No biologic plausibility to suggest increased risk for adverse events
- ACIP previously recognized that administration of other inactivated vaccines during breast-feeding is not medically contraindicated*

* Centers for Disease Control and Prevention. General recommendations on immunization recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2006; Vol. 55 (No. RR-15)

Issues Considered
AVA Administration During Pregnancy/Breastfeeding

	+/-
Burden of Disease	-/+
Immunogenicity and Efficacy	+
Safety	+
Trimester-specific issues	+
Post-exposure alternatives	

+ Favorable
- Not favorable

Alternatives to Vaccination

- Pre-event
  - Defer vaccination
- Post-exposure
    - ≥60 days antimicrobials

Benefits of PEP Combination Therapy

- Vaccination maximizes protection with:
  - Spore germination and outgrowth
  - Imperfect adherence to antimicrobials
- Antimicrobial agents provide protection for the duration of their utilization
- Unvaccinated persons need both to provide protection following exposure

Issues Considered
AVA Administration During Pregnancy/Breastfeeding

	+/-
Burden of Disease	-/+
Immunogenicity and Efficacy	+
Safety	+
Trimester-specific issues	+
Post-exposure alternatives	-

+ Favorable
- Not favorable

Summary of WG deliberations

- The burden and severity of disease in the event of exposure may be high
- No biologic plausibility for decreased immunogenicity of vaccine
- No biologic plausibility for increased risk of birth defects
  - Available safety data are reassuring
- Post-exposure alternatives to vaccination are not acceptable

Work Group Draft Recommendations for Use of AVA in Pregnant and Breastfeeding Women

Draft Recommendation for Pre-Event Use of AVA in Pregnant Women

In a pre-event setting, where the risk of exposure to aerosolized *B. anthracis* spores is presumably low, vaccination should be deferred until after pregnancy.

Draft Recommendation for Pre-Event Use of AVA in Breastfeeding Women

Breast feeding is neither a precaution nor a contraindication to vaccination. In a pre-event setting vaccination need not be deferred if the mother's occupation puts her at risk for encountering *B. anthracis*.

Draft Recommendation for Post-exposure Use of AVA
Pregnant Women

In a post-event setting with a high risk of exposure to aerosolized *B. anthracis* spores, pregnancy is neither a precaution nor a contraindication. Pregnant women at risk for inhalation anthrax should receive AVA and 60 days antimicrobials as described in Antimicrobial Considerations for Pregnant or Breastfeeding Women.

(Pregnant and lactating women exposed to *B. anthracis* should be counseled as to the risk- benefit profile of post-exposure prophylaxis use of the vaccine as well as the recommended antimicrobial therapy).

Draft Recommendation for Post-exposure Use of AVA
Breastfeeding Women

In a post event setting with a high risk of exposure to aerosolized *B. anthracis* spores, breast-feeding remains neither a precaution nor a contraindication. Breast-feeding women at risk for anthrax inhalation anthrax should receive AVA and 60 days antimicrobials as described in Antimicrobial Considerations for Pregnant or Breastfeeding Women.

(Pregnant and lactating women exposed to *B. anthracis* should be counseled as to the risk- benefit profile of post-exposure prophylaxis use of the vaccine as well as the recommended antimicrobial therapy.)

Discussion/Vote