Summary of 2010 ACIP Recommendations for Anthrax Vaccine Adsorbed (AVA)

- **Pre-Exposure Prophylaxis (PrEP)**
  - Intramuscular (IM) route
  - 5-dose priming series at 0, 1, 6, 12, and 18 months
  - Then annual booster

- **Post-Exposure Prophylaxis (PEP) under IND/EUA**
  - Subcutaneous (SC) route
  - 3-dose series at 0, 2, and 4 weeks postexposure
  - Co-administration of antibiotics for 60 days
Changes to the Licensed Indications since 2010

- **Pre-Exposure Prophylaxis (PrEP)**
  - Intramuscular (IM) route
  - 3-dose priming series at 0, 1, and 6 months
  - Booster doses at 12 and 18 months, then annually

- **Post-Exposure Prophylaxis (PEP)**
  - Subcutaneous (SC) route
  - 3-dose series at 0, 2, and 4 weeks
  - Co-administration of antibiotics for 60 days
Use of AVA in Special Populations

- AVA is licensed for persons 18 through 65 years of age
- There are little to no data on the use of AVA in special populations.
- Benefit of vaccine outweighs the potential harm of unknown AEs
- Use under an IND or EUA
- Policy changes are for all ages
## Recent AVA Safety Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design (# Participants)</th>
<th>Measure(s)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phillips CJ. Vaccine. 2009</td>
<td>Cohort study (1497)</td>
<td>Develop Squalene Antibodies</td>
<td>No association between squalene antibody status and chronic multi-symptom illness</td>
</tr>
<tr>
<td>Sulsky SI. Vaccine. 2011</td>
<td>Cohort study (1,001,546)</td>
<td>Disability Risk</td>
<td>AVA not associated with differences in risk of disability</td>
</tr>
<tr>
<td>Sulsky SI. Vaccine. 2011</td>
<td>Case-control study (154,780)</td>
<td>Disability</td>
<td>No association between receipt of AVA and long-term disability</td>
</tr>
<tr>
<td>Stewart B. Vaccine. 2012.</td>
<td>Randomized controlled trial (1562)</td>
<td>Health-Related Quality of Life</td>
<td>No association between receipt of AVA and quality of life over a 42-month period</td>
</tr>
<tr>
<td>Duderstadt, SK. Vaccine. 2012</td>
<td>Retrospective population-based cohort (2.3 million)</td>
<td>Type 1 Diabetes</td>
<td>No increased risk for AVA and type 1 diabetes</td>
</tr>
<tr>
<td>Conlin AM. Vaccine. 2015</td>
<td>Retrospective cohort (126,839)</td>
<td>Birth Defects</td>
<td>No associations between AVA vaccination during pregnancy and birth defect risk</td>
</tr>
<tr>
<td>Bardenheier BH. Military Medicine. 2016</td>
<td>Matched case-control (463)</td>
<td>Rheumatoid Arthritis (RA) Systemic Lupus Erythematousus (SLE)</td>
<td>AVA associated with recent onset but not long term RA No association with SLE</td>
</tr>
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</table>
AVA Safety

- No new safety concerns since December 2008 based on updated VAERS review and a review of the published literature.
- Data support safety of AVA for use as pre-exposure and post-exposure prophylaxis given high mortality associated with anthrax.
- More data are needed to evaluate safety in pediatric populations.
Understanding AVA Effectiveness: Predicting Human Survival Based on “Animal Rule” Data

- Animal survival data (Sivko, 2016)
  - Supporting data (Ionin, 2013 and Quinn, 2012)

- Immune response in humans
  - Subset of a pre-exposure (0, 14 and 28 days, then 6, 12, and 18 months) regimen study used to compare IM vs SC route of administration (Wright, 2014)
  - Dose sparing schedules (Bernstein, 2014)
    - 2 full doses at 0 and 14 days
    - 2 full doses at 0 and 28 days
    - 3 half doses at 0, 14, and 28 days
Predicting Survival Using COP

Correlate of Protection Model: Anti-PA IgG
Predicted Survival of 0, 14, 28 ½ dose group at day 42 is 96.1%
Summary of Policy Questions for ACIP Consideration

Optimizing use of vaccine during a large mass vaccination event
1) May the intramuscular (IM) route of administration (ROA) be used if the subcutaneous (SC) ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?
2) Should there be an inadequate supply of anthrax vaccine available for PEP, may either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?

Use of antimicrobials in conjunction with vaccine
3) In immunocompetent individuals who are being vaccinated with anthrax vaccine, do antimicrobials provide adequate protection when given for:
   a) At least 42 days after the first vaccine dose, or
   b) 2 weeks after the last vaccine dose, whichever comes later
Policy Questions for ACIP to Consider

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### IM versus SC Route of Administration Considerations - Immunogenicity

**Predicting survival for IM vs SC at Days 28 and 56**

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<th>SC</th>
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<tr>
<td><strong>Day 28</strong></td>
<td>n = 241&lt;br&gt;Anti-PA IgG = 30.6 μg/mL*&lt;br&gt;Predicted Survival = 88.6%</td>
<td>n=242&lt;br&gt;Anti-PA IgG = 52.6 μg/mL*&lt;br&gt;Predicted Survival = 92.4%</td>
</tr>
<tr>
<td><strong>Day 56</strong></td>
<td>n = 234&lt;br&gt;Anti-PA IgG = 87.5 μg/mL&lt;br&gt;Predicted Survival = 95.6%</td>
<td>n = 235&lt;br&gt;Anti-PA IgG = 100.6 μg/mL&lt;br&gt;Predicted Survival = 96.1%</td>
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*Statistically significant difference*
IM versus SC Route of Administration Considerations – Adverse Events

- SC route of administration produced significantly more frequent localized adverse events in most all parameters evaluated.

- There was a higher occurrence of generalized muscle ache amongst IM recipients compared to SC
Adherence to antimicrobial PEP wanes over time

- Higher titers at 30 days would protect more individuals that are not adherent to antimicrobial PEP

Adherence to vaccine PEP

- IM administration results in a lower proportion of localized adverse events compared to SC administration

In a large anthrax event, efficiency of administering vaccine to a large number of people is a major concern
ACIP Work Group Conclusions

- The SC route of administration is preferred over the IM route of administration for PEP due to the higher antibody concentrations achieved at 4 weeks
- Supported IM use when operationally challenging
- During a large-scale emergency response, AVA for PEP may be administered using an IM route if the SC route of administration poses significant materiel, personnel, or clinical challenges that may delay or preclude vaccination
- Individuals that experienced significant adverse events from AVA administered by the SC route of administration may elect to receive the subsequent vaccine dose(s) by the IM route in consultation with a provider
Policy Questions for ACIP to Consider

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Human Immunogenicity with Dose Sparing Schedules

Anti-PA IgG Over Time

Days Since First Dose

Anti-PA IgG (μg/mL)

0, 14 Full
0, 28 Full
0, 14, 28 Full
0, 14, 28 Half
PA80
### Predicted Survival at Days 28, 42, and 63

#### Day 28

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<tr>
<th>Assay</th>
<th>0, 14 Full</th>
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<th>0, 14, 28 Full</th>
<th>0, 14, 28 Half</th>
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<tbody>
<tr>
<td>Anti-PA IgG (N)</td>
<td>95.8% (79)</td>
<td>72.6% (81)</td>
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#### Day 42

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<tr>
<td>Anti-PA IgG (N)</td>
<td>95.5% (69)</td>
<td>98.1% (78)</td>
<td>97.4% (79)</td>
<td>96.1% (74)</td>
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#### Day 63

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<th>Assay</th>
<th>0, 14 Full</th>
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<td>Anti-PA IgG (N)</td>
<td>93.3% (69)</td>
<td>97.0% (77)</td>
<td>96.4% (63)</td>
<td>94.2% (72)</td>
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Work Group Conclusions

- All dose-sparing schedules provided high levels of protection by two week after the last dose.
- The two-full-dose strategy will expand the vaccine supply by 50% and the three-half-dose strategy will expand it by 100%. The choice of dose-sparing schedule depends on anticipated vaccine shortage.
- If number of potentially exposed individuals exceeds vaccine supply, it would be beneficial to protect larger numbers of individuals with slightly lower protective levels.
Policy Questions for ACIP to Consider

Optimizing use of vaccine during a large mass vaccination event
1) May the intramuscular (IM) route of administration (ROA) be used if the subcutaneous (SC) ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?
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Decrease Duration of Antimicrobial PEP

Anti-PA IgG Over Time

- 0, 14 Full
- 0, 28 Full
- 0, 14, 28 Full
- 0, 14, 28 Half
- PA80

Day 28 → Day 42
## Decrease Duration of Antimicrobial PEP

### Predicted Survival at Days 28, 42, and 63

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- Peak Protection
Decrease Duration of Antimicrobial PEP

- For most of the dose-sparing schedules as well as the licensed schedule, day 42 is two weeks after the last dose. For the day 0 and 14 dose sparing schedule, day 28 is two weeks after the last dose.

- Peak response for all dosing schedules is 2 weeks after the last dose.

- Peak response is highly protective.

- Allowing antimicrobial use to stop once peak immune response is reached would shorten antimicrobial requirement and potentially reduce adverse events related to continued antimicrobial use.

- Emphasis on adherence until immune response is sufficient may improve adherence for the shorter duration.
Decrease Duration of Antimicrobial PEP

- For immunocompetent individuals, AbxPEP should be given concurrent with VxPEP and AbxPEP should continue for at least 42 days after their first dose or two weeks after their last dose of the vaccine series, whichever comes last.

- Individuals with immunocompromising medical conditions, or on immunosuppressive medication, or in groups in whom immunologic responses to AVA are unknown, should take 60 days of AbxPEP concurrent with vaccine.
Policy Consideration Summary for ACIP Committee

- May the IM ROA be used if the SC ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?

- Should there be an inadequate supply of anthrax vaccine available for PEP, may either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?

- In immunocompetent individuals may AbxPEP be discontinued at 42 days after the first vaccine dose or 2 weeks after the last vaccine dose, whichever comes later?
  - If yes, can this be extended to healthy 2 to 17 year olds?
VOTE: Anthrax Vaccine Use for PEP in a Mass Vaccination Campaign

- The IM ROA may be used if the SC ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination.
- Should there be an inadequate supply of anthrax vaccine available for PEP, either 2 full doses or 3 half doses of AVA may be used to expand vaccine coverage.
- In immunocompetent individuals, antimicrobials given in conjunction with vaccine may be discontinued at 42 days after the first vaccine dose or 2 weeks after the last vaccine dose, whichever comes later.