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ACIP Anthrax Vaccine Work Group

Advisory Committee for Immunization Practices
February 27, 2019
Anthrax Vaccine Adsorbed (AVA) Preexposure Prophylaxis (PrEP) Booster Dose Interval Outline

- Policy question
- Background
- Public health importance
- Benefits and harms
- Work group discussions
- Proposed AVA PrEP booster dose interval recommendations
- Vote to recommend policy change
Policy Question

- Can persons who are not at current high risk of exposure to *Bacillus anthracis* maintain adequate immunity by being boosted with AVA every 3 years after immunological priming, with the caveat that if they were required to enter a high-risk area, they would receive a booster with or without antimicrobials, depending on the timing of their last booster dose?
  - Population: Persons aged ≥18 years with potential future, but not current, exposure to aerosolized *B. anthracis* spores
  - Intervention: Six-month priming schedule at 0, 1, 6 months followed by boosters every three years
  - Comparison: Current Recommendations; six-month priming schedule at 0, 1, 6 months followed by boosters at 12 and 18 months, then annually
  - Outcomes: Protection
BACKGROUND
Anthrax Vaccine for Preexposure prophylaxis (PrEP)

- Anthrax Vaccine Adsorbed (AVA; BioThrax®)
  - Sterile, cell-free filtrate made from cultures of avirulent, non-encapsulated *B. anthracis*
  - Primary immunogen is Protective Antigen (PA)
  - Adjuvant 1.2 mg/mL aluminum (Al(OH)₃)
  - Preservatives: 25 µg/mL benzethonium chloride and 100 µg/mL formaldehyde
  - Manufacturer: Emergent BioSolutions
  - Licensed for persons at high risk for exposure to anthrax
  - Administered intramuscular (IM)
    - Primary series – 0, 1, 6 months
    - Booster series – 12 and 18 months, then annually
Anthrax PrEP Vaccine History

- **1970**
  - “Lansing” formulation recommended for PrEP for those at high risk of exposure
  - Licensed for 0, 2, and 4 weeks and 6, 12, and 18 months by subcutaneous (SC) route

- **2008**
  - Change in priming schedule to drop dose at two weeks
  - Change in route of administration from SC to IM

- **2012**
  - Change from a 5-dose primary series to a 3-dose primary series at 0, 1, and 6 months, with boosters at 12 and 18 months and annually thereafter
  - This enables lab work or deployment in 6 months rather than 18 months previously
ACIP 2010 AVA Recommendations for Preexposure Prophylaxis (PrEP)

- Emergency and Other Responders
  - Emergency and other responders are not recommended to receive routine pre-event anthrax vaccination because of the lack of a calculable risk assessment. However, responder units engaged in response activities that might lead to exposure to aerosolized *B. anthracis* spores may offer their workers voluntary pre-event vaccination.

- Delayed Doses
  - Available data on AVA dosages suggest that increasing the interval between doses does not decrease the ultimate serologic response achieved or adversely affect the safety profile. Therefore, as with other vaccines, interruption of the vaccination schedule does not require restarting the entire series or the addition of extra doses.
Hypothetical Wide Area Outdoor Release
PUBLIC HEALTH IMPORTANCE
Rationale for Current Review of AVA PrEP Booster Dose Interval Recommendations

- Consideration for a change to indications for preexposure prophylaxis in groups not at current high risk
  - Military personnel
  - Emergency and other responders

- New data suggest the booster interval can be extended

- If approved, incorporate new indication into updated MMWR Recommendations and Reports
BENEFITS AND RISKS
Question:
- How would declining antibody levels impact predicted probability of survival in humans, particularly when antibody levels fall below those of the current booster series?

Approach:
- Identify the immune correlates of protection (COP) in nonhuman primates (NHP)
- Demonstrate comparable immunological profiles in humans
- Apply immunological correlates to trough levels in humans
- Estimate minimum survival probability for reduced schedules
## Nonhuman Primate Studies (NHP)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design (# enrolled)</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinn, 2012</td>
<td>RCT (137)</td>
<td>• Vaccinated IM with full strength AVA or dilutions of 1:5, 1:10, 1:20, or 1:40 at 0, 1, and 6 months&lt;br&gt;• Challenged with 200-400 LD$_{50}$ <em>Bacillus anthracis</em> spores at 12, 30, or 52 months&lt;br&gt;• Outcome: Survival</td>
</tr>
<tr>
<td>Chen, 2014</td>
<td>RCT (137)</td>
<td>• Vaccinated IM with full strength AVA or dilutions of 1:5, 1:10, 1:20, or 1:40 at 0, 1, and 6 months&lt;br&gt;• Challenged with 200-400 LD$_{50}$ <em>Bacillus anthracis</em> spores at 12, 30, or 52 months&lt;br&gt;• Outcome: Comprehensive analysis of 21 humoral and cell-mediated NHP immune-response variables</td>
</tr>
</tbody>
</table>
### 3-IM AVA Provides Long Term Protection in NHP

<table>
<thead>
<tr>
<th>Time of Challenge (month)</th>
<th>Number Survived/ Number Challenged (Survival Rate)</th>
<th>Fisher’s Exact Test Comparison of Challenge Times over Dilutions (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HuAVA (Undiluted) 1:5 1:10 1:20 1:40 Combined over Dilutions 30 Months 52 Months</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>8/10 (80.0%) 11/20 (55.0%) 13/20 (65.0%) 32/50 (64.0%)</td>
<td>0.013 0.217</td>
</tr>
<tr>
<td>30</td>
<td>10/10 (100.0%) 8/8 (100.0%) 6/9 (66.7%) 7/8 (87.5%) 31/35 (88.6%)</td>
<td>0.491</td>
</tr>
<tr>
<td>52</td>
<td>8/10 (80.0%) 9/9 (100.0%) 6/10 (60.0%) 23/29 (79.9%)</td>
<td></td>
</tr>
</tbody>
</table>

- Fishers exact comparisons indicated that survival after challenge at 12 and 52 months were not significantly different
- Subsequent COP analyses combined all survival data over all time points

## Human Immunogenicity Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design (# enrolled)</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright, 2014</td>
<td>RCT (781)</td>
<td>AVA priming series given IM at 0, 1, and 6 months AVA booster doses given IM at: • 12, 18, 30, and 42 months • 18 and 42 months • 42 months</td>
</tr>
<tr>
<td>Pittman, 2014</td>
<td>OBS (600)</td>
<td>AVA given: • 6 month dose SC on schedule • 6 month dose SC delayed • 18-36 months • 37-60 months • &gt; 60 months</td>
</tr>
<tr>
<td>Pittman, 2013</td>
<td>OBS (373)</td>
<td>AVA given SC: • 1, 2, or 3 doses • Fourth dose received 18-24 months later</td>
</tr>
</tbody>
</table>
# Vaccine Schedule for the Wright Study

<table>
<thead>
<tr>
<th>Study Group (N)</th>
<th>Month 0</th>
<th>Month 0.5</th>
<th>Month 1</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 18</th>
<th>Month 30</th>
<th>Month 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-SC (260)</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
</tr>
<tr>
<td>8-IM (262)</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
</tr>
<tr>
<td>7-IM (256)</td>
<td>AVA</td>
<td>S</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
<td>AVA</td>
</tr>
<tr>
<td>5-IM (258)</td>
<td>AVA</td>
<td>S</td>
<td>AVA</td>
<td>AVA</td>
<td>S</td>
<td>AVA</td>
<td>S</td>
<td>AVA</td>
</tr>
<tr>
<td>4-IM (268)</td>
<td>AVA</td>
<td>S</td>
<td>AVA</td>
<td>AVA</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>AVA</td>
</tr>
<tr>
<td>Placebo (260)</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

AVA – Anthrax Vaccine Absorbed  
S – Saline  
IM – Intramuscular route  
SC – Subcutaneous route

Long Term Immune Response to Vaccination in Humans

8-SC 201.1
8-IM 232.6  All IM reduced schedules non-inferior at boost
7-IM 206.9  * = Statistically superior to 8-SC
5-IM 310.0*
4-IM 433.2*

3 yrs

Placebo

8-SC 216.8
8-IM 320.5*
7-IM 254.8*
5-IM 310.0*
4-IM 433.2*

8-SC 35.69
8-IM 47.77
7-IM 38.07
5-IM 21.58
4-IM 6.02
(5.28-6.87)
Geometric mean anti-PA IgG antibody concentration and *B. anthracis* lethal toxin neutralization activity by cohorts stratified by days post vaccination

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Time point</th>
<th>On-schedule</th>
<th>Delayed</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>GM 95% CI</td>
<td>N</td>
</tr>
<tr>
<td>Anti-PA IgG concentration</td>
<td>Day 28</td>
<td>220</td>
<td>283.3 (251.6, 319.0)</td>
<td>229</td>
</tr>
<tr>
<td></td>
<td>Day 180</td>
<td>138</td>
<td>53.8 (46.3, 62.6)</td>
<td>113</td>
</tr>
<tr>
<td>TNA ED$_{50}$ titer (reciprocal)</td>
<td>Day 28</td>
<td>220</td>
<td>1061.5 (926.0, 1216.8)</td>
<td>228</td>
</tr>
<tr>
<td></td>
<td>Day 180</td>
<td>137</td>
<td>208.5 (171.8, 253.1)</td>
<td>112</td>
</tr>
</tbody>
</table>

Delayed Booster Dose Survival Prediction Summary

- All schedules establish robust immunological priming and sustained immunological memory to at least month 42
  - The most reduced 4-IM schedule produces survival estimates of 75.6% - 86.8%
  - The 5-IM schedule produces survival estimates of 84.0% - 93.3%

- Delayed booster schedules produced higher response to boost
  - 4-IM was statistically significantly superior to 7-IM at month 43 (anti-PA IgG of 433.2 μg/mL vs. 254.8 μg/mL)
  - Assuming similar decline curves, this implies higher protection for the 4-IM schedule at least until the next boost in higher boost schedules
  - Pittman data show similar higher response to delayed boost, and slower decay
Delayed Booster Dose Survival Prediction Summary

- Delayed booster schedules lessen burden of vaccination
  - Increasing the booster interval to greater than 1 year will reduce adverse events
  - Disease prevalence is extremely low

- Operational use for response or deployment
  - When troops or emergency responders are being deployed to high risk zones, a boost prior to deployment could be given to those >1 year post-boost
  - Kinetics studies showed anamnestic response within 3 days of boost, peaking at ~9 days post boost
WORK GROUP DISCUSSIONS
AVA PrEP Booster Interval  Work Group Discussions

- No change to current indications for persons at high risk of exposure to anthrax

- Data support that, after the initial 6-month priming series, a booster interval of up to 3 years is adequate to maintain memory response in persons not currently at high risk of exposure to anthrax
  - More data are needed to make a recommendation on booster intervals >3 years
AVA PrEP Booster Interval Work Group Discussions

- Population under consideration: Persons who are in the process of receiving the 6 month priming series and who are required to enter a high-risk area prior to completing the priming series.
- Data suggest that persons who have initiated but not completed the preexposure priming series can transition to the postexposure schedule prior to entering an area of high risk.
- While in the high-risk area, the licensed booster schedule for high risk exposure risk applies.
PROPOSED AVA PREEXPOSURE PROPHYLAXIS VACCINE RECOMMENDATIONS
Proposed Recommendations for PrEP in Persons Not Currently at High Risk of Exposure to Anthrax

- AVA is licensed for prevention of anthrax in persons at high risk of exposure to *B. anthracis*. There are no proposed changes to this indication.

- For persons who are NOT currently at high risk of exposure, but who may need to deploy to a high risk area quickly, we are proposing a booster interval that is longer than the licensed booster interval.

- While in the high-risk area, the licensed booster schedule for high risk exposure applies.
We are proposing:

- For persons who lack current, but may have future, high risk of exposure to *B. anthracis*, AVA may be given as an intramuscular (IM) three-dose priming series (0, 1, and 6 months), followed by an IM booster every 3 years.

- After receiving the three-dose priming series, persons who have not received a booster dose in the last 6 months who need to enter an area where *B. anthracis* is suspected or known to be in use would be given an IM booster dose and either:
  - Wait 2 weeks to enter the high risk area
  - OR
  - If required to enter immediately, take antimicrobial postexposure prophylaxis for 2 weeks.
Table: Transition from PrEP to PEP schedule for persons who have not completed priming series who need to immediately enter an area with high risk of anthrax exposure

<table>
<thead>
<tr>
<th>PrEP Doses</th>
<th>Interval Since Last Dose</th>
<th>AVA PEP</th>
<th>Duration of Antimicrobial PEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Dose 1 (day 0)</td>
<td>42 days after first dose of AVA or 14 days after last dose, whichever is later</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 (day 14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 3 (day 28)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Dose 2 (day 0)</td>
<td>28 days after first dose of AVA or 14 days after the last dose, whichever is later</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 3 (day 14)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Dose 3 (day 0)</td>
<td>14 days</td>
</tr>
<tr>
<td>≥ 3</td>
<td>&gt; 6 months</td>
<td>Booster dose</td>
<td>14 days</td>
</tr>
<tr>
<td>≥ 3</td>
<td>≤ 6 months</td>
<td>No booster</td>
<td>No antimicrobials needed</td>
</tr>
</tbody>
</table>
VOTE: Anthrax Vaccine Use for PrEP in Persons Not at Current High Risk of Exposure to Anthrax

- A booster dose of AVA may be given every 3 years to persons not currently at high-risk of exposure to *B. anthracis* who have been previously primed with AVA and wish to maintain protection.
Questions?