ACIP Anthrax Vaccine Work Group

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ACIP Anthrax Vaccine Work Group

Advisory Committee for Immunization Practices
February 27, 2019
AV7909 Outline

- Policy Issue
- Background
- Public health importance
- Benefits and harms
  - Non-clinical Findings
  - Immunogenicity
  - Clinical Safety
- Work Group Discussions
- Proposed AV7909 vaccine recommendations
Policy Issue

- Use of AV7909 for post-exposure prophylaxis (PEP) in persons with suspected or known exposure to aerosolized *Bacillus anthracis* spores when anthrax vaccine adsorbed (AVA) availability is limited

- AVA is approved for PEP in persons with suspected or known exposure to aerosolized *Bacillus anthracis* spores

- AV7909 is the next-generation anthrax vaccine
  - Only available for emergency use authorization
Types of Anthrax

- **Cutaneous**
  - Incubation: 1-14 days
  - Transmission: spores introduced through skin lesions
  - Case fatality rate:
    - Without treatment: ~24%
    - With antimicrobial treatment: <2%

- **Ingestion**
  - Incubation: 1-14 days
  - Transmission: ingestion of raw/undercooked contaminated meat
  - Case fatality rate with treatment: 40%
Types of Anthrax

- **Inhalation**
  - Incubation range in humans: 1-43 days
  - Transmission: inhalation of aerosolized spores
  - Case fatality rate with treatment
    - 1900-2000: 92%
    - 2001 and after: 47%

- **Injection**
  - Transmission: injection of contaminated material
  - Incubation: 2-10 days
  - Case fatality rate with treatment: 37%
Anthrax Epidemiology: Naturally Occurring Disease

- Primarily a disease of herbivores that ingest spores
- Human contact with infected animals/animal products
  - Woolsorter’s disease (inhalation anthrax)
- Butchering and eating of contaminated carcasses
  - Both cutaneous and gastrointestinal cases
- Incidental inhalation of spores
- from work or hobby
  - Drummer cases
Bacillus anthracis spores: The most likely bioweapon

- Relatively easy and cheap to produce
- Can be stored for a long time
- Can be aerially dispersed a variety of ways
- Odorless, colorless, tasteless
- May survive in the environment > 40 yrs
- Inhalation anthrax has a high mortality rate

Can cause widespread illness and death among unprotected persons

- Sverdlosk incident, 1979
- US mail incident, 2001
Hypothetical Wide Area Outdoor Release
U.S. Licensed Anthrax Vaccine for Postexposure Prophylaxis (PEP)

Anthrax Vaccine Adsorbed (AVA; BioThrax®)

- Manufacturer: Emergent BioSolutions
- Sterile, cell-free filtrate made from avirulent, non-encapsulated B. anthracis
- Primary immunogen is protective antigen (PA)
- Adjuvant 1.2 mg/mL aluminum (Al(OH)₃, 0.85% NaCl)
- Vaccine for PEP
  - Three dose primary series administered subcutaneously (SC) at 0, 2, 4 weeks
  - 60 days of antimicrobials.
ACIP 2010 AVA Recommendations for PEP

- General Adult Population
  - ACIP recommends 3 SC doses of AVA (administered at 0, 2, and 4 weeks postexposure) combined with 60 days of appropriate antimicrobial as prophylaxis for previously unvaccinated persons aged ≥18 years who have been exposed to aerosolized *B. anthracis* spores under an EUA.

- Pregnant and Breastfeeding Women
  - Pregnant and breastfeeding women at risk for inhalation anthrax should receive AVA and 60 days of antimicrobial therapy under an EUA.

- Children
  - The use of AVA in children is not contraindicated in a post-event setting that poses a high risk for exposure to aerosolized *B. anthracis* spores. Under an IND protocol, 3 doses of vaccine should be administered in conjunction with 60 days of appropriate antimicrobial therapy to children aged 0-17 years.
ACIP Recommendations Changes to AVA for PEP since 2010

- **Licensed Indication**
  - Licensed for persons 18-65 years exposed to *B. anthracis*

- **ACIP Recommendations**
  - Intramuscular route as an alternative during a public health emergency
  - Antimicrobial duration 42 days or 2 weeks after last dose in healthy adults
  - Dose sparing with 2 full doses or 3 half doses can be used to expand coverage if need exceeds supply
AV7909 - Description of Product

- AV7909 (NuThrax®); Anthrax Vaccine Adsorbed with CPG 7909 Adjuvant
  - Emergent BioSolutions Inc.
- Dosage / Administration
  - Route: Intramuscular
  - Volume: 0.5 mL per dose
  - Dose: 0.5 mL AVA + 0.25 mg CPG 7909
  - Schedule: Two doses, two weeks apart
- Anticipated to be added to the Strategic National Stockpile starting in July 2019 for post-exposure prophylaxis for *Bacillus anthracis* exposure in combination with antimicrobial therapy
- Target BLA submission Q4/2021 using the animal rule
PUBLIC HEALTH IMPORTANCE
Public Health Importance

- Currently stockpiled quantity of anthrax vaccine (FDA-approved AVA) may be insufficient for vaccine coverage in a large-scale event.
- Use of AV7909 under an EUA and IND would be crucial to increasing supply of anthrax vaccine.
- AV7909 may provide the following advantages:
  - 2 IM doses administered 2 weeks apart may accelerate the development of a protective level of immunity by 1 or 2 weeks over the licensed AVA 3-dose PEP regimen.
  - The IM route for AV7909 may have fewer injection site reaction compared to licensed AVA regimen with SC route.
Benefits and Risks

NON-CLINICAL CORRELATE OF PROTECTION DATA
Primary Serological Assays

- Anti-PA IgG ELISA
  - Measures total IgG against PA in μg/mL
  - Uses species-specific reference standard and conjugate
  - Reference standards were calibrated independently

- Toxin Neutralization Activity assay (TNA)
  - Measures ability of antibodies to neutralize Lethal Toxin (LTx)
  - Not specific to antibody type or PA (anti-LF antibodies also neutralize)
  - Measures toxin activity, species neutral measurement
Primary Serological Assays (Con’t)

- **TNA units**
  - Effective Dose 50 (ED50) is the reciprocal of the serum dilution which neutralized 50% of in vitro LTx cytotoxicity
  - Scale is from ~50 up to >10,000
  - Neutralization Factor 50 (NF50) is the ED50 of the sample divided by the ED50 of the reference standard on the run
    - This normalizes some run-to-run variation
    - Also makes the NF50 specific to the reference standard
    - All data presented here use the same reference standard (AVR801)
    - Scale is from ~0.1 up to >10
Guinea Pig Model

- GP immunized with dilutions of AV7909 on days 0 and 14
- Challenged at Day 28 or Day 70
- TNA titers measured on day of challenge

AV7909 Study 3580 (GP) Day 28 Challenge

AV7909 Study 3580 (GP) Day 70 Challenge

n=107

n=106

0.062

0.081
Non-Human Primate Model

- NHP immunized with dilutions of AV7909 on days 0 and 14
- Challenged at Day 28 or Day 70
- TNA titers measured on day of challenge

Graphs showing the relationship between TNA titers and survival probability for days 28 and 70. For Day 28, the TNA titers range from 0.01 to 100, with a threshold of 0.15 for survival. For Day 70, the range is similar, with a threshold of 0.26. Both graphs show data points with n=64 for each challenge day.
Benefits and Risks

CLINICAL STUDIES - IMMUNOGENICITY
## Summary of AV7909 Clinical Studies Completed to Date

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Trial Objectives</th>
<th>Trial Design and Type of Control</th>
<th>Test Product(s)/ Formulation, Dosage Regimen, and Route</th>
<th>No. Subjects Entered/ Treated/ Completed</th>
<th>Gender (%)</th>
<th>Mean Age (Range); Race (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1a</td>
<td>Safety and kinetics of immune response</td>
<td>Randomized (1:1:1), double-blind, controlled, parallel arms</td>
<td>3 IM injections 2 wks apart: AVA, CPG 7909, AVA + CPG 7909</td>
<td>22/22/22, 23/23/23, 24/24/23</td>
<td>52% M/ 48% F; 28.0 (20-44) years; 77% white, 2% black, 10% Asian, 11% unk/other</td>
<td></td>
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<tr>
<td>Phase 1b</td>
<td>Safety, reactogenicity and immunogenicity of 4 lots/formulations</td>
<td>Randomized (6:6:6:6:6:6:5), double-blind, placebo-controlled, dose-ranging, parallel arms</td>
<td>2 IM injections 2 weeks apart: AVA, AV7909 #1, AV7909 #2, AV7909 #3, AV7909 #4, Saline</td>
<td>18/18/15, 18/18/18, 17/17/16, 19/19/18, 18/18/18, 15/15/15</td>
<td>49% M/ 51% F; 32.0 (18-50) years; 83% white, 14% black, 1% Asian, 2% other</td>
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</tr>
<tr>
<td>Phase 2</td>
<td>Safety, reactogenicity and immunogenicity at Day 63 (10) and earlier times</td>
<td>Randomized (4:3:2:4: 2), double-blind, active-controlled parallel arms</td>
<td>3 IM injections at 0/2/4 wks: AV7909/ AV7909 /saline AV7909/ saline/ AV7909 AV7909 x3 ½ dose AV7909 x 3 AVAx 3</td>
<td>44/44/32, 34/34/31, 23/23/22, 44/44/42, 23/23/21</td>
<td>51%M/ 49% F; 32.5 (18-50) years; 92% white, 7% black, 1% Asian, 1% Hawaiian/Pacific Islander</td>
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Phase 1: Geometric Mean TNA Concentration Over Time
Phase 1b: Geometric Mean TNA NF50 After IM Administration of AV7909
Phase 2 Study Design

- Randomized, parallel group, AVA-controlled, double-blind PEP study
- IM route (AV7909 and AVA) with two- and three-dose AV7909 schedules at two dose levels (full dose and ½ dose by volume)

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>N</th>
<th>Day 0</th>
<th>Day 14</th>
<th>Day 28</th>
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<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>AV7909</td>
<td>AV7909</td>
<td>Placebo</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>AV7909</td>
<td>Placebo</td>
<td>AV7909</td>
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<tr>
<td>3</td>
<td>23</td>
<td>AV7909</td>
<td>AV7909</td>
<td>AV7909</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>½ Dose AV7909</td>
<td>½ Dose AV7909</td>
<td>½ Dose AV7909</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>BioThrax</td>
<td>BioThrax</td>
<td>BioThrax</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>168</strong></td>
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- Immunogenicity on Days 0, 21, 28, 35, 42, 49, 63, 84
Phase 2 study: Geometric Mean TNA NF50 Over Time

Semi-Logarithmic Scale

0, 14 Day AV7909 Peak Response at Day 28

AVA Peak Response at Day 45

Arms:
1 – AV7909 Full dose 0-2 wk
2 – AV7909 Full dose 0-4 wk
3 – AV7909 Full dose 0-2-4 wk
4 – AV7909 Half dose 0-2-4 wk
5 – AVA full dose 0-2-4 wk

GMT and 95% CI for TNA (NF50)

Day
0 10 20 30 40 50 60 70 80 90

Treatment:
ARM 1
ARM 2
ARM 3
Benefits and Risks

CLINICAL STUDIES - SAFETY
Safety Findings

- 241 subjects in three clinical trials
- Systemic reactogenicity
  - Fatigue
  - Muscle ache
  - Headache
- Local reactions
  - Pain, tenderness
  - Arm motion limitation
- AEs associated activation of local proinflammatory innate immune responses
- Most reactions are mild to moderate in intensity
- Reviewed clinical trials
  - Rash
  - Positive antinuclear antibody (ANA)
  - Generalized pruritus; urticaria
  - Fever
- No deaths or serious adverse events
## Timeline to Licensure

<table>
<thead>
<tr>
<th>Year</th>
<th>Regulatory</th>
<th>Non-clinical</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>2018</td>
<td>EUA</td>
<td>Animal Safety Studies</td>
<td>Phase 2 Older Adults Study</td>
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<tr>
<td>2019</td>
<td></td>
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<tr>
<td>2020</td>
<td></td>
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<td>Phase 2 Abx interference Study</td>
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<td>2021</td>
<td></td>
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<tr>
<td>2022</td>
<td>BLA</td>
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<td>Phase 3 Study</td>
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WORK GROUP DISCUSSIONS
AV7909 Work Group Discussions

- AV7909 generates a similar magnitude but faster immune response than AVA given by the IM route

- There are limited safety data available at this time

- Given the high mortality associated with inhalation anthrax, the benefits of AV7909 outweigh the risk of potential unknown AEs

- AV7909 is an option for PEP if AVA supplies are exhausted or unavailable
PROPOSED AV7909 VACCINE WORDING FOR POLICY UPDATE
AVA is preferred for PEP for potential exposure to aerosolized *B. anthracis* spores as it is licensed for this indication. Additional safety data will be reviewed by ACIP as they become available, and recommendations on preferential use will be updated as needed.

However, based on very limited safety and immunogenicity phase 2 data, AV7909 appears safe and elicits a robust immune response in healthy adults.

AV7909 could be an option for PEP if AVA is not available. As with AVA, antimicrobials should be taken for up to 60 days in conjunction with the vaccine.

CDC guidance for AV7909 will include statements on dosing schedules and special populations.
Questions?