ACIP Anthrax Vaccine Work Group

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ACIP Anthrax Vaccine Work Group

Advisory Committee for Immunization Practices
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National Center for Emerging and Zoonotic Disease
Division of High-Consequence Pathogens and Pathology

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

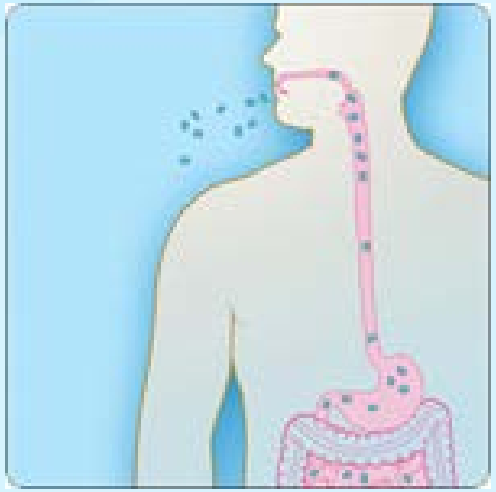
- AVA is approved for PEP in persons with suspected or known exposure to aerosolized *Bacillus anthracis* spores

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

BACKGROUND

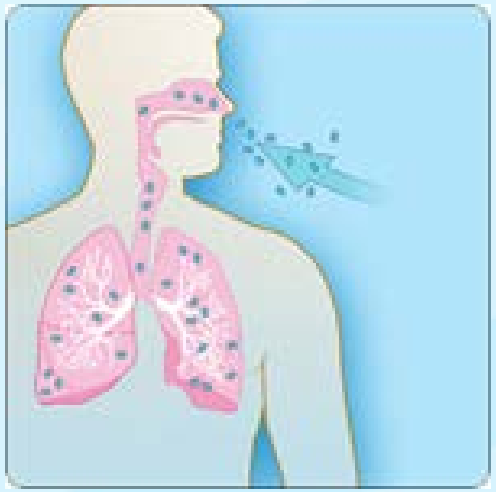
Types of Anthrax

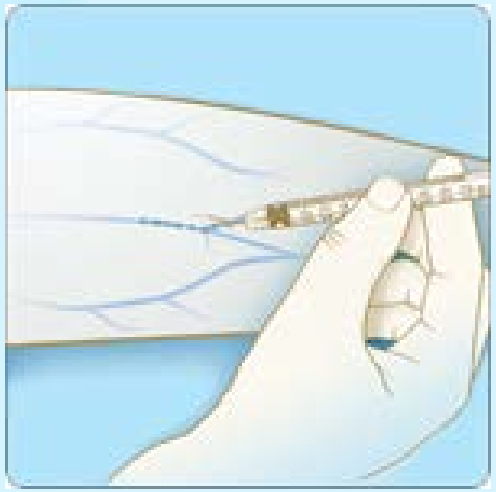
- Cutaneous
  - Incubation: 1- 14 days
  - Transmission: spores introduced through skin lesions
  - Case fatality rate:
    - Without treatment: ~24%
    - With antimicrobial treatment: <2%
- Ingestion
  - Incubation: 1- 14 days
  - Transmission: ingestion of raw/undercooked contaminated meat
  - Case 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%





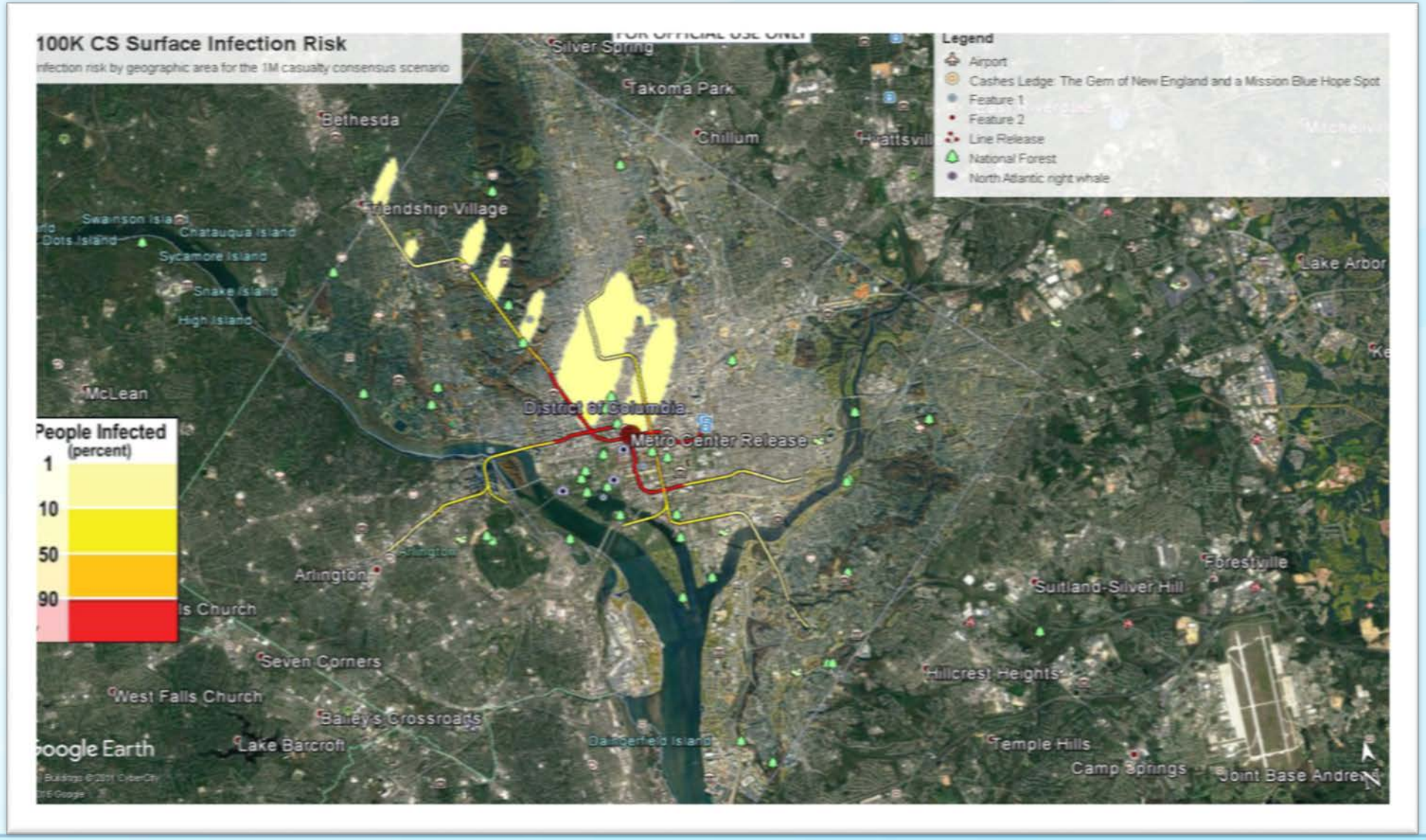
Anthrax Epidemiology: Naturally Occurring Disease

- 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

Epidemiology: Bioterrorism

- 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

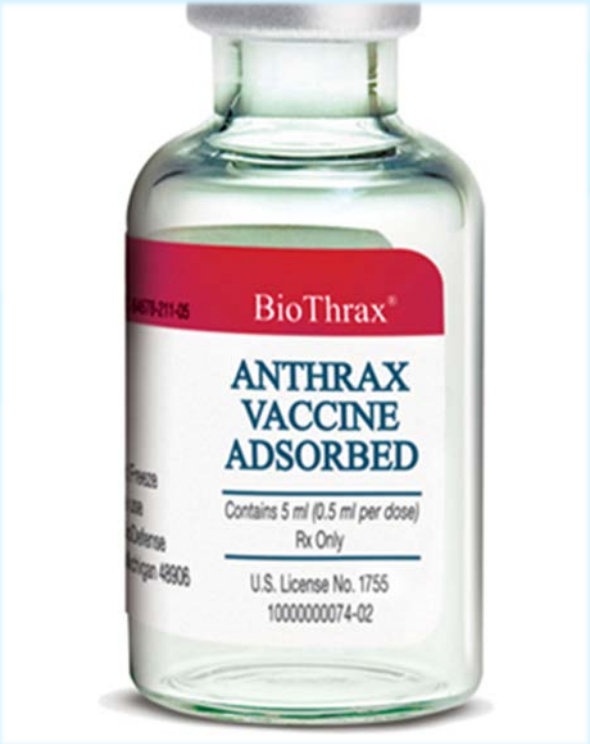
Hypothetical Wide Area Outdoor Release



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

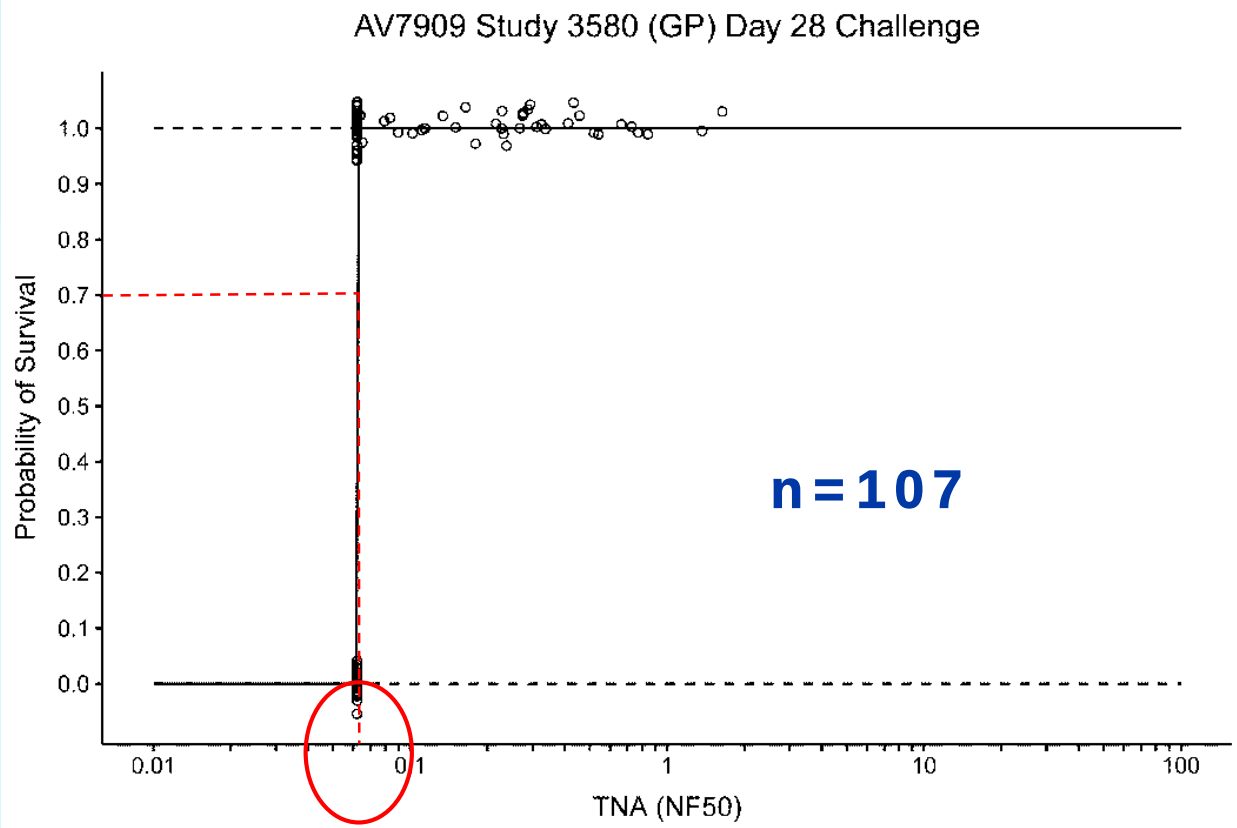
- Toxin Neutralization Activity assay (TNA)
  - Measures ability of antibodies to neutralize Lethal Toxin (LTx)
  - Not specific to antibody type or PA (anti-LF antibodies also neutralize)
  - Measures toxin activity, species neutral measurement

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



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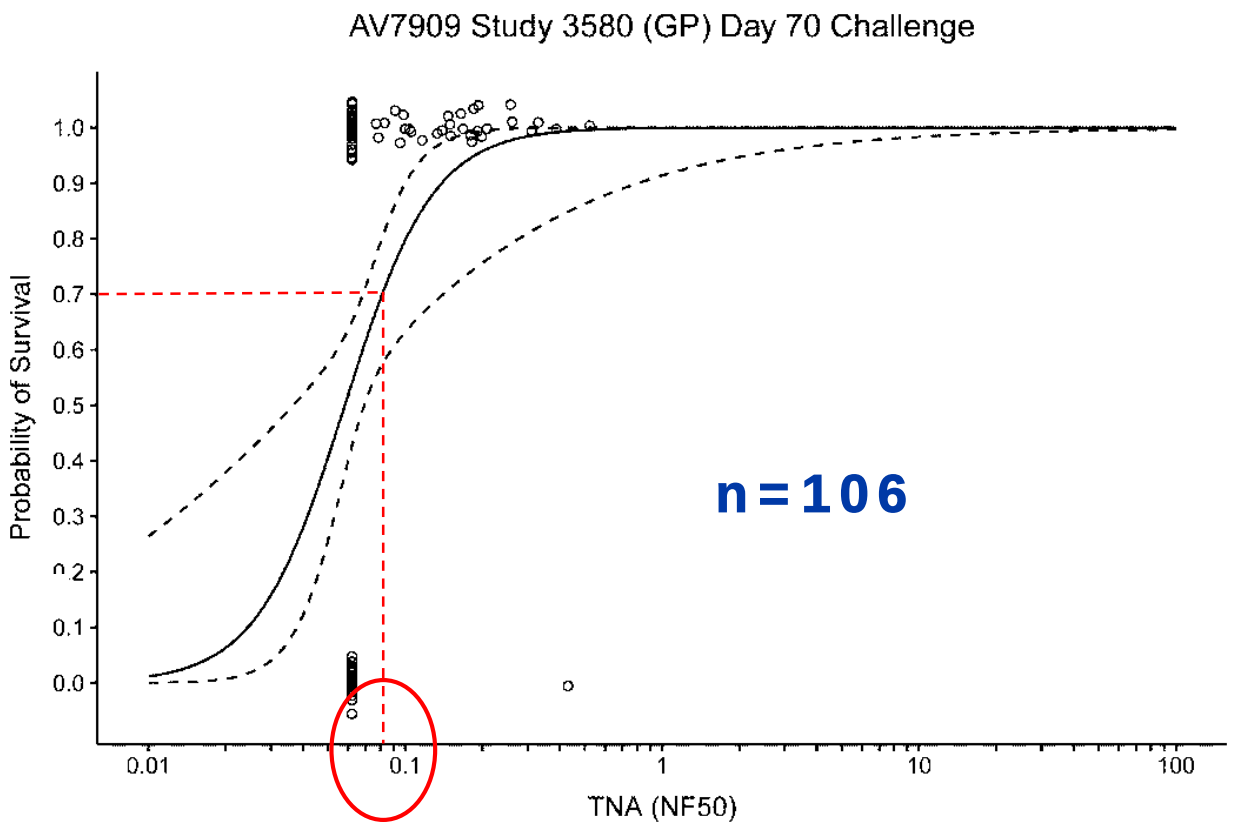

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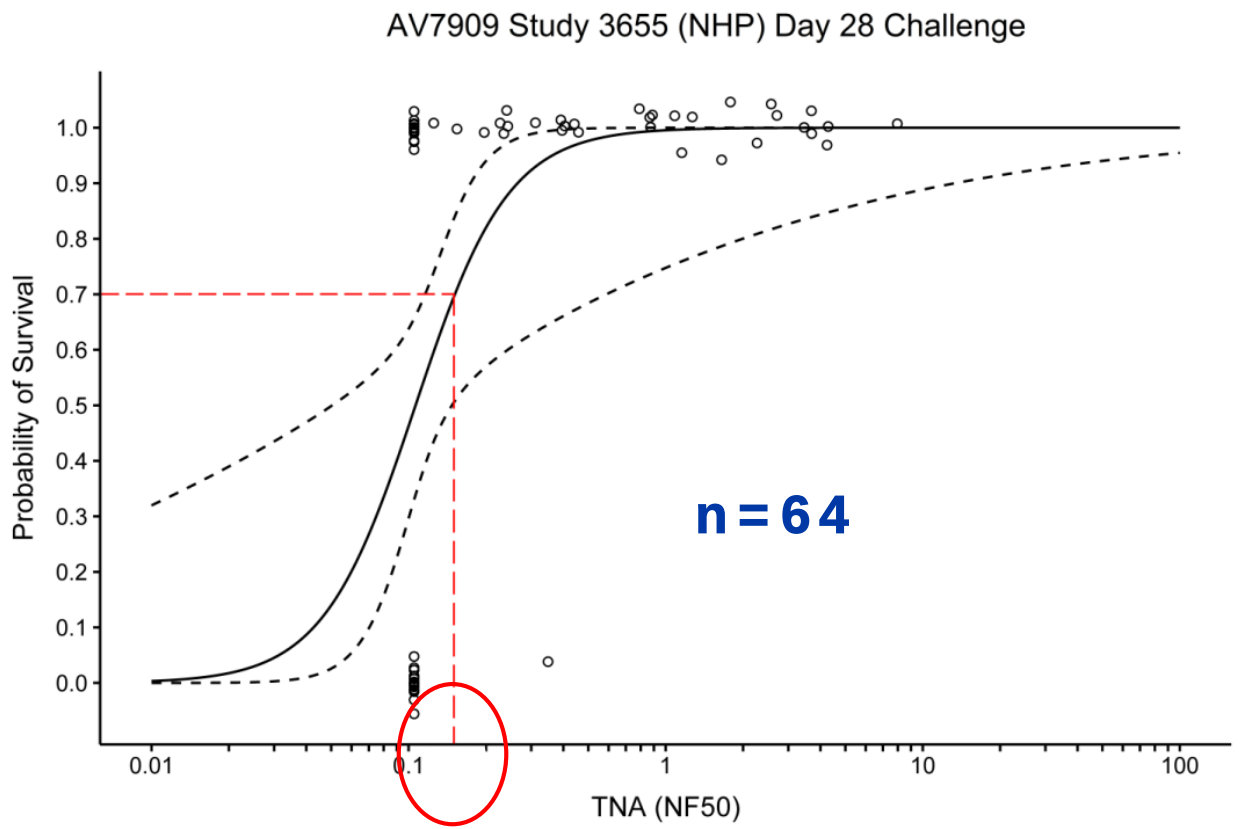
Non-Human Primate Model

- 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



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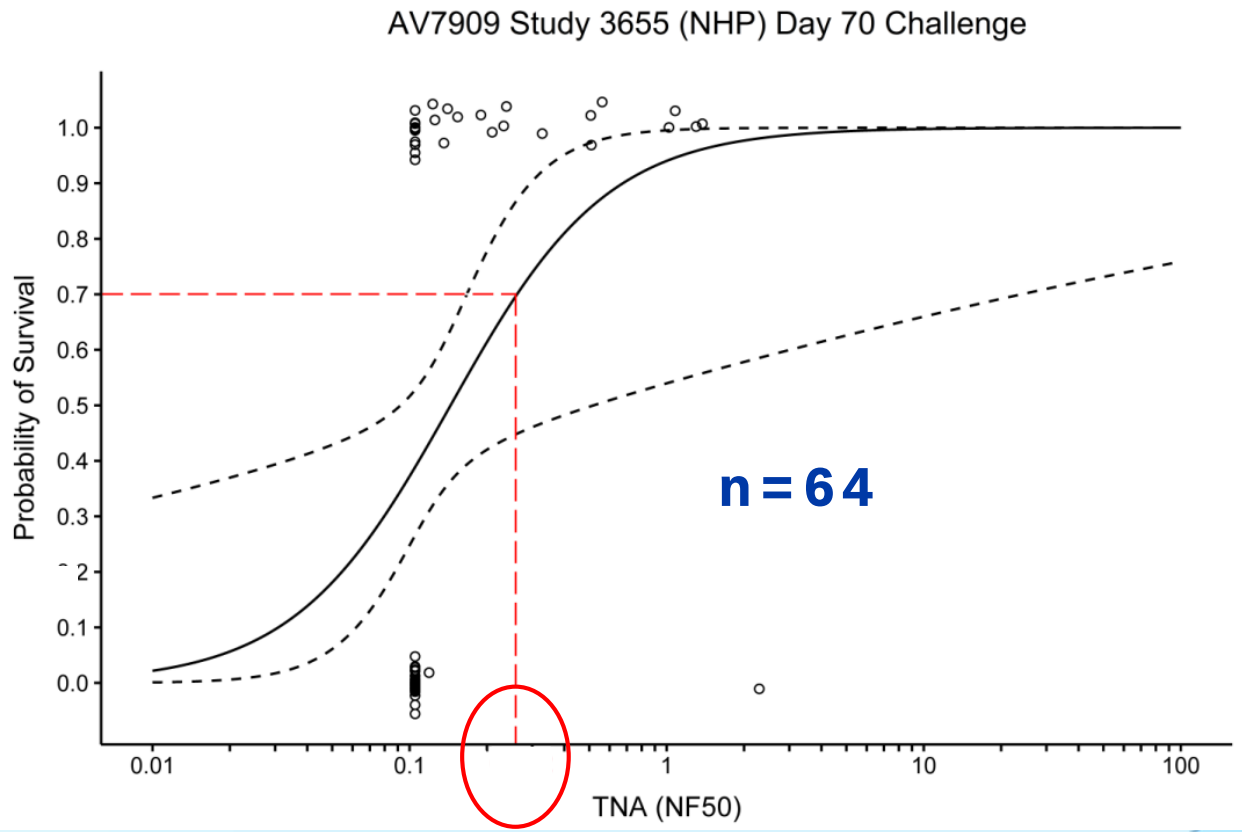

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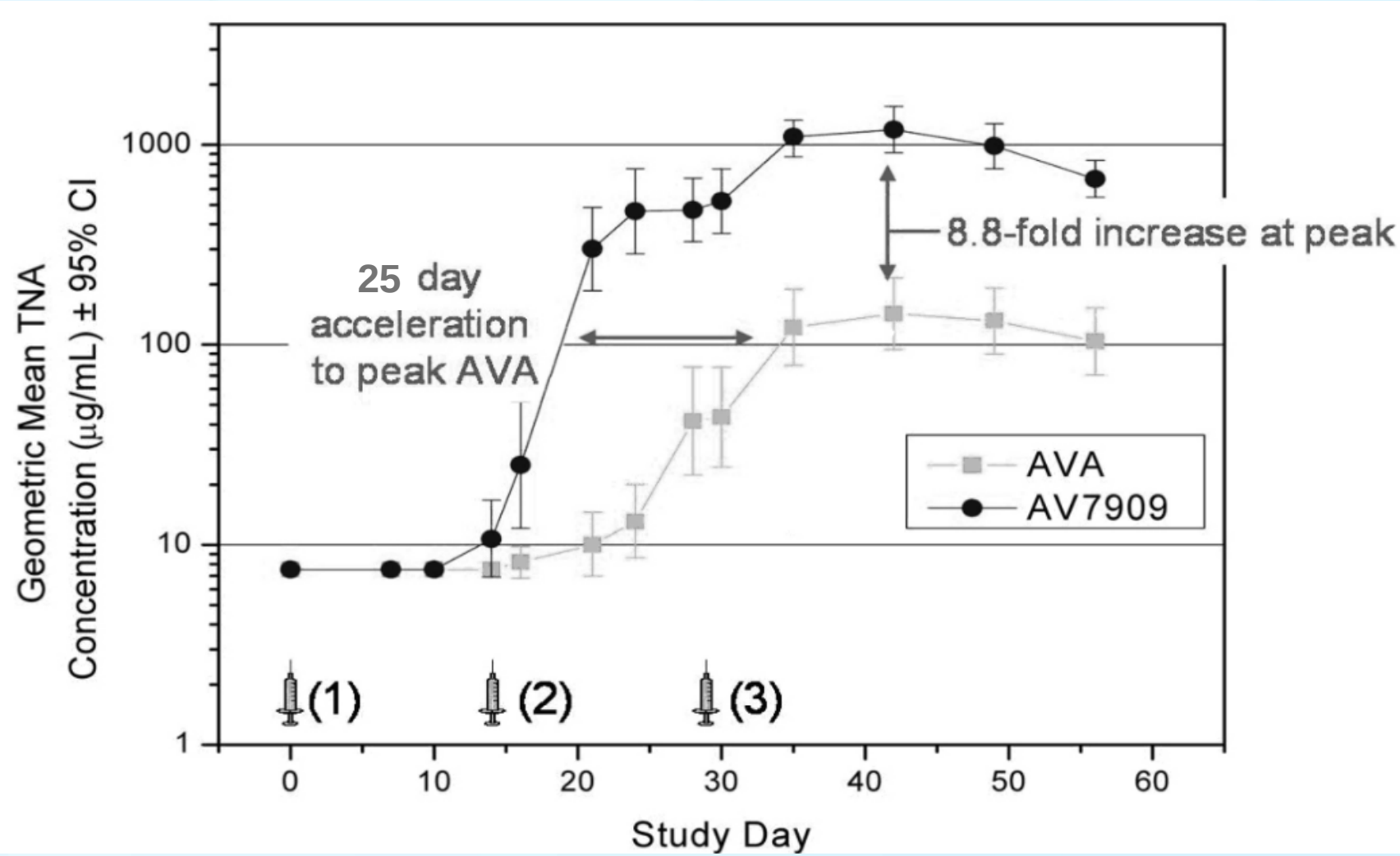
Benefits and Risks

CLINICAL STUDIES - IMMUNOGENICITY

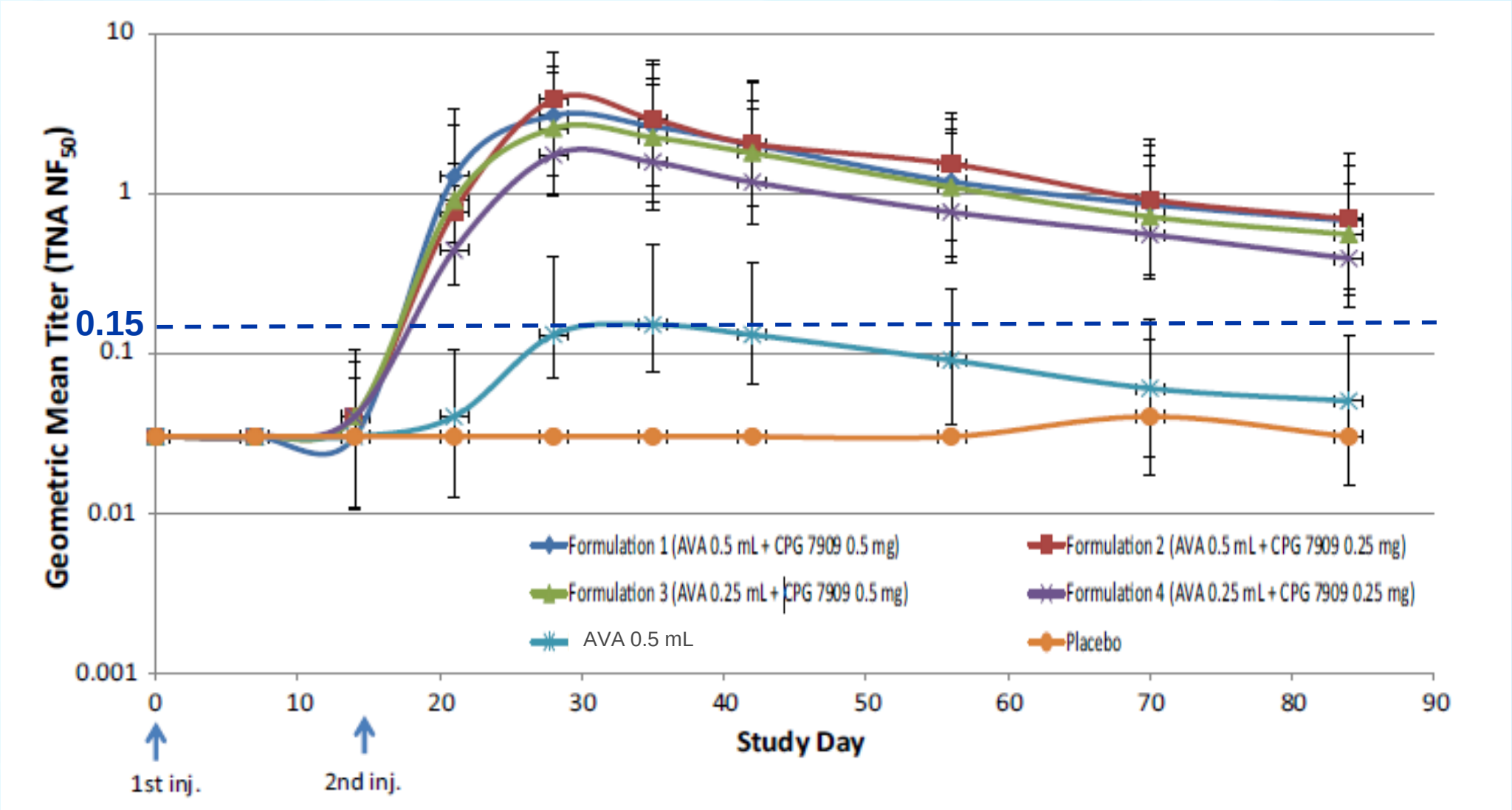
Summary of AV7909 Clinical Studies Completed to Date

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

Phase 1: Geometric Mean TNA Concentration Over Time



Phase 1b: Geometric Mean TNA NF50 After IM Administration of AV7909



Phase 2 Study

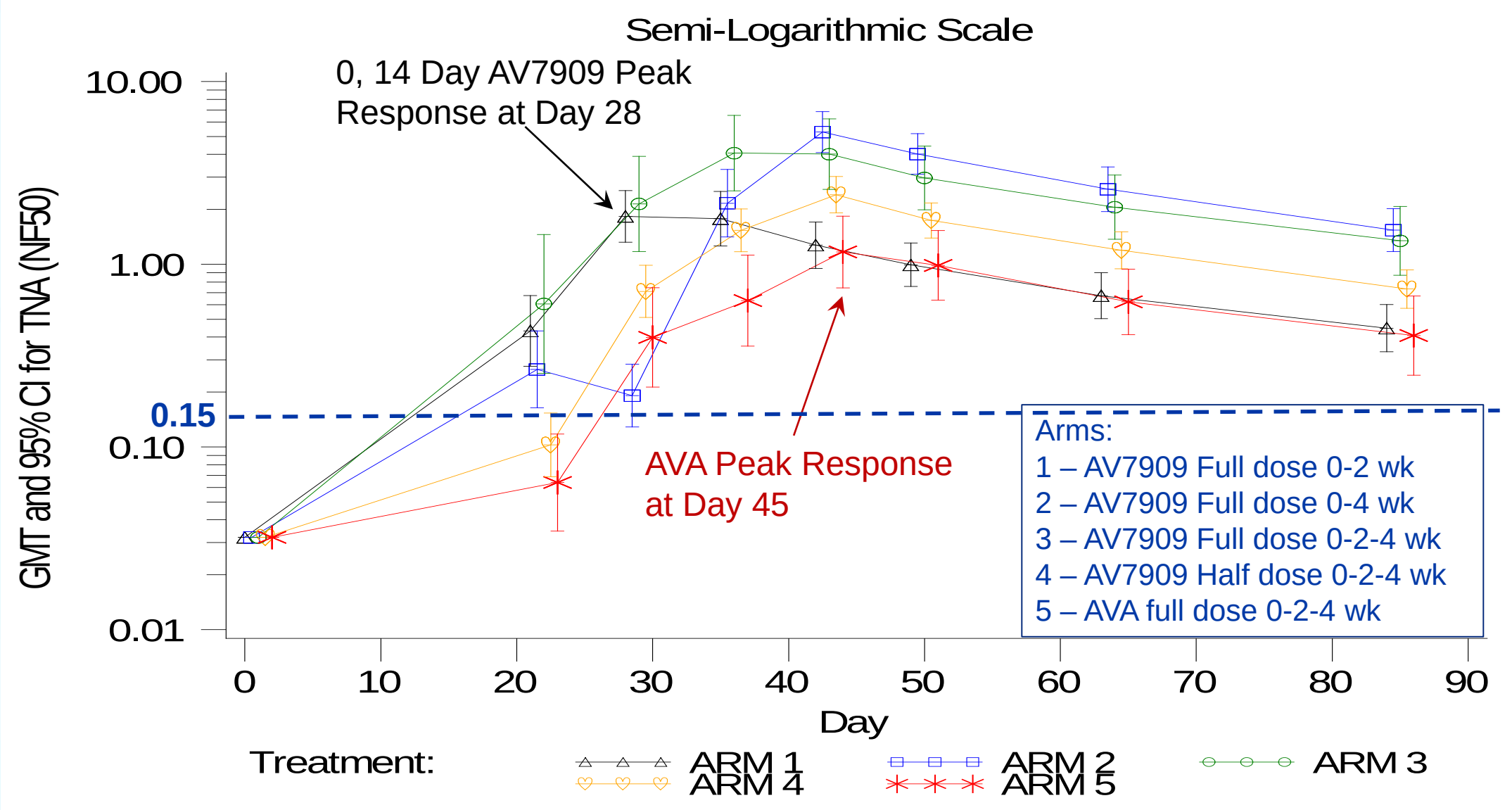
Phase 2 Study Design

- 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)

Study Arm	N	Day 0	Day 14	Day 28
1	44	AV7909	AV7909	Placebo
2	34	AV7909	Placebo	AV7909
3	23	AV7909	AV7909	AV7909
4	44	½ Dose AV7909	½ Dose AV7909	½ Dose AV7909
5	23	BioThrax	BioThrax	BioThrax
Total	168			

- Immunogenicity on Days 0, 21, 28, 35, 42, 49, 63, 84

Phase 2 study: Geometric Mean TNA NF50 Over Time



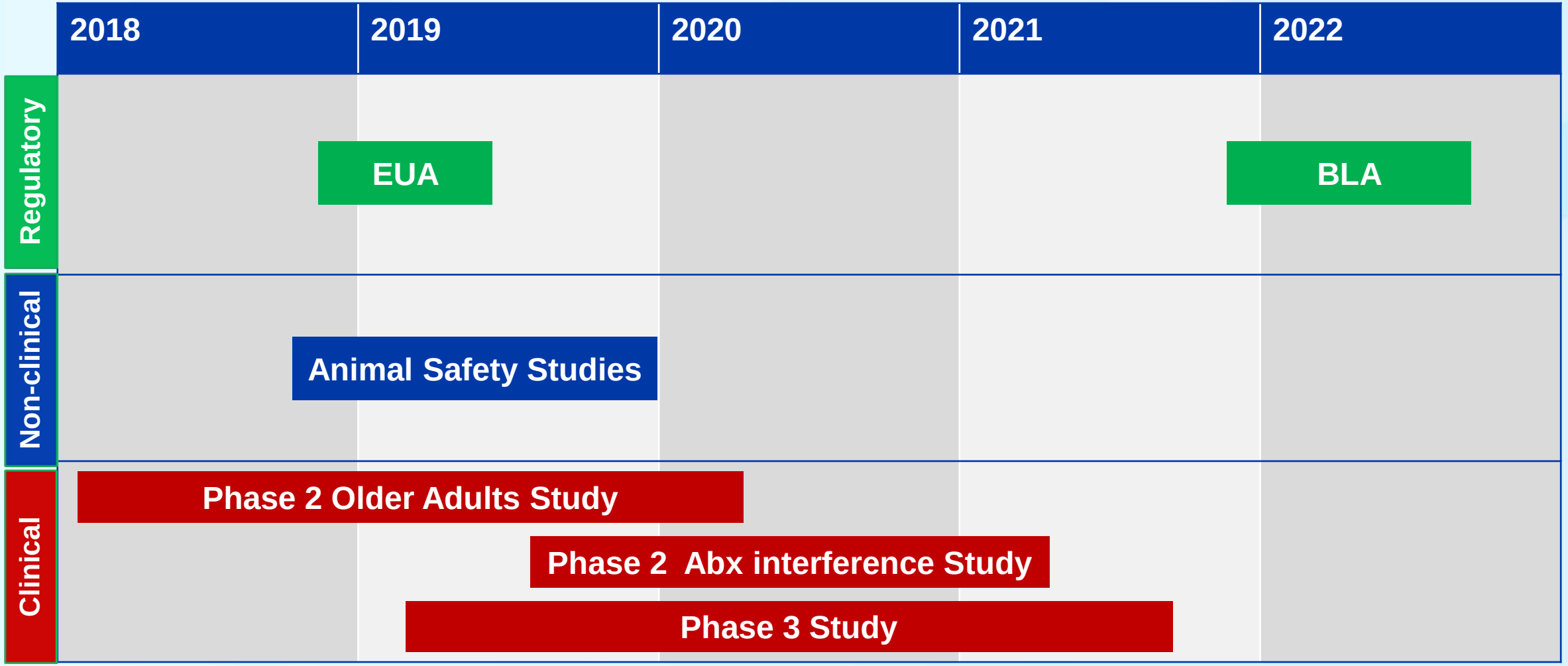
Benefits and Risks

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



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

Proposed AV7909 Language for MMWR 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?