ACIP Anthrax Vaccine Work Group

William Bower, MD, FIDSA

February 21, 2018

National Center for Emerging and Zoonotic Disease
Division of High-Consequence Pathogens and Pathology

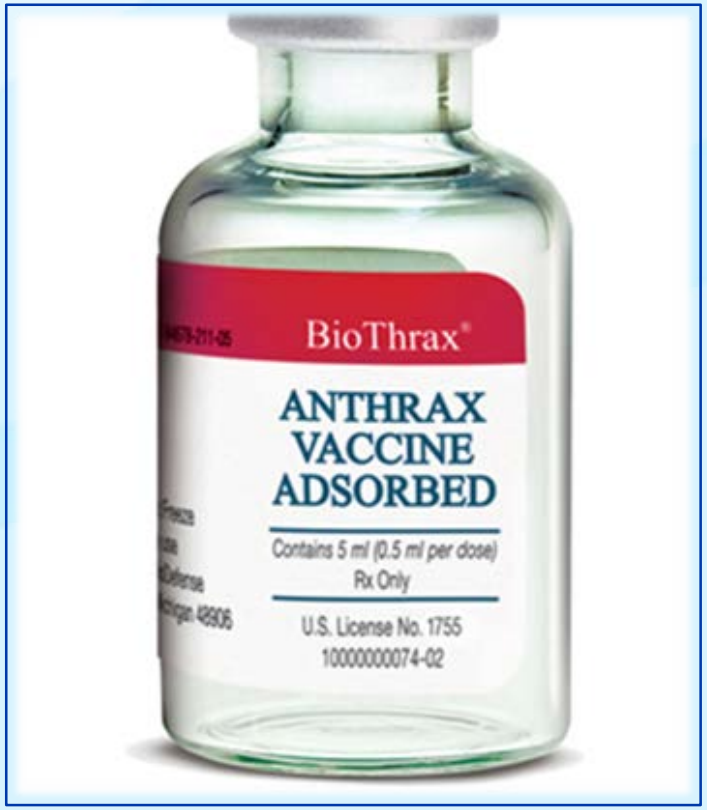
Outline

- Update on route of administration for AVA
- Dose-sparing strategies when demand for AVA exceeds supply
- Duration of antimicrobial component of PEP when used in combination with anthrax vaccine

AVA Licensed Indications

- 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



UPDATE ON ROUTE OF ADMINISTRATION FOR AVA

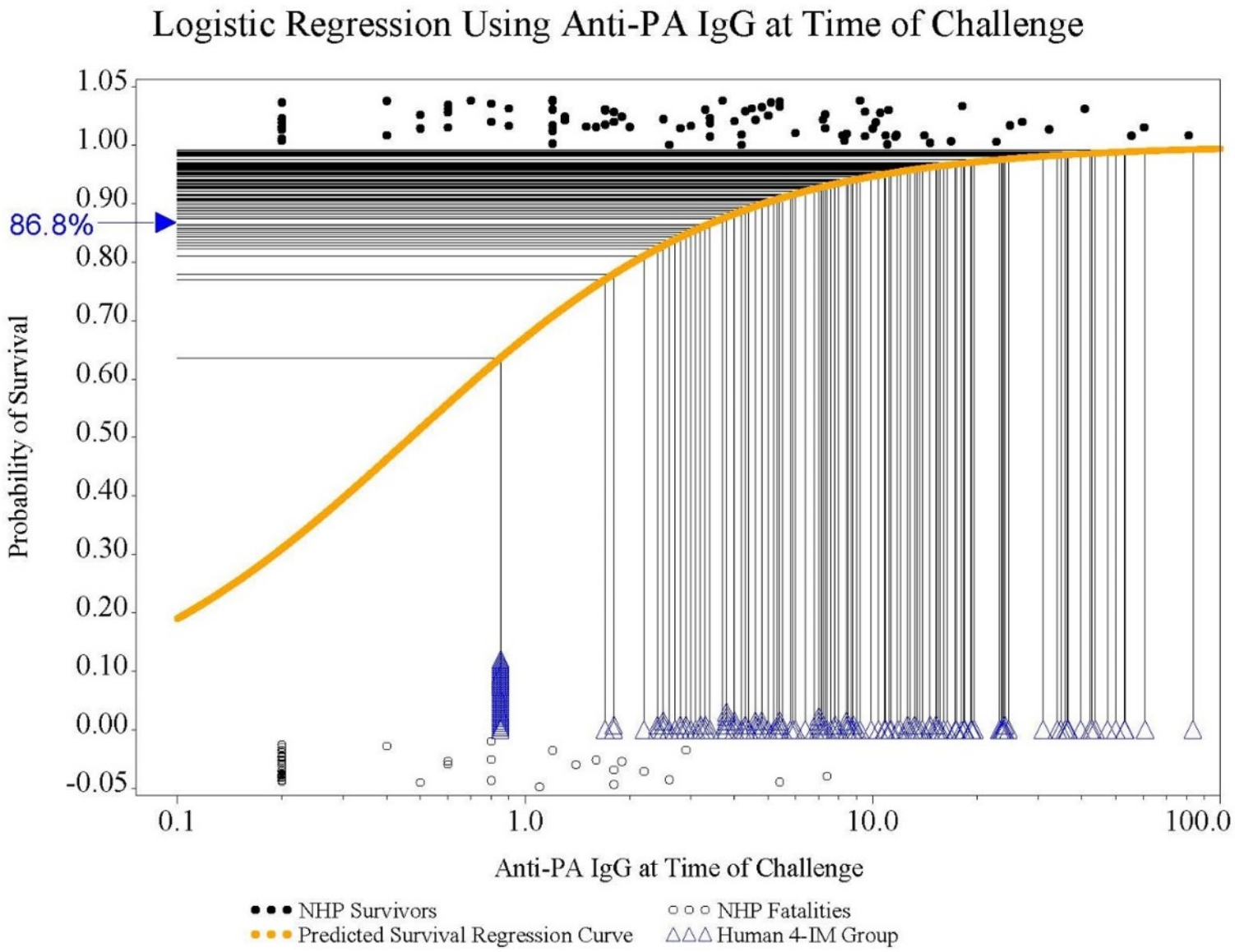
Considerations for Route of Administration

- Adherence to antimicrobial PEP
  - ~50% after being on antimicrobials for 30 days
- Adherence to vaccine PEP
  - Intramuscular (IM) administration results in a lower proportion of injection site adverse events compared to subcutaneous (SC) administration

Operational Concerns

- Supplies for administering vaccine
  - CDC SNS does not stockpile sufficient numbers of 5/8” needles to administer stockpiled vaccine via subcutaneous (SC) route
  - 1” needles for intramuscular (IM) vaccinations are more available and come closer to meeting needs
- Vaccination errors
  - Two formulations of anthrax vaccines with 2 different routes of administration (SC – AVA; IM – NuThrax)
  - Potentially 2 different routes of administration for different target populations (SC – adults; IM – children)
- In a large anthrax event, efficiency of administering vaccine to a large number of people is a major concern

Predicting Survival Using COP – AVRP Data



Survival Probability Model: 'Last' Anti-PA IgG Predicted Survival of 4-IM at 42 months is 86.8%

NIAID PEP Study Objectives

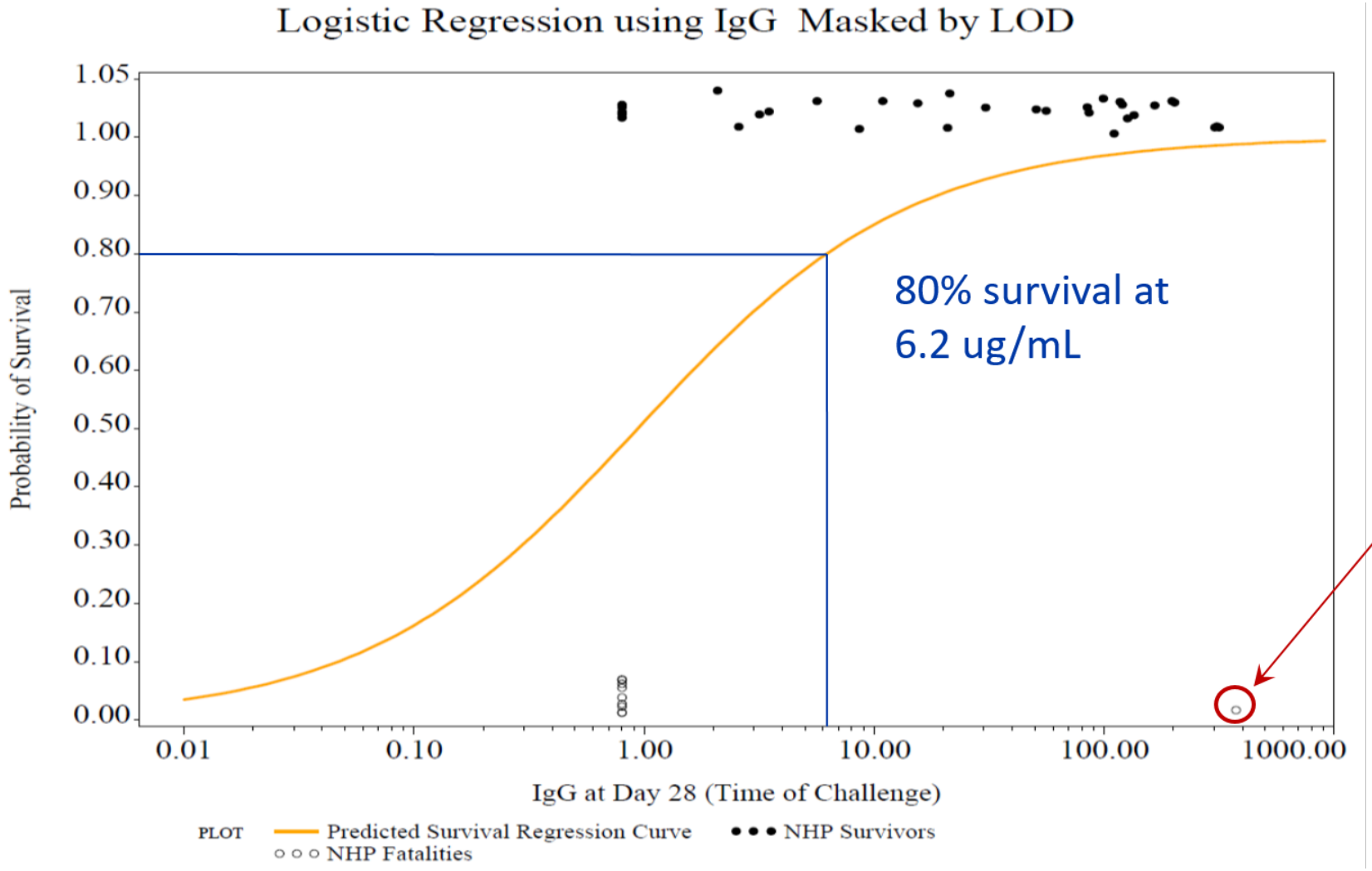
- Measure immunological profiles and protection at Day 28 from vaccination at Days 0 and 14 in Cynomolgous non-human primate (cNHP)
- Use cNHP immunological responses and survival data as correlates of protection (COP) for cross-species survival prediction
- Predict survival probability in humans receiving reduced schedules
- Inform decisions on appropriate AVA schedules and duration of antimicrobial use

Study Design

- cNHP Non-Clinical Study – Sivko et al.
  - 0, 14 Day vaccination schedule
  - Dose ranging from 1/3 - 1/243 human dose
  - 42 AVA vaccinated animals, 6 saline vaccinated controls
  - High-dose infectious challenge on Day 28

- Human Clinical Study – Stark et al.
  - 4 Study groups
    - Arm A: Days 0, 14 Full Dose
    - Arm B: Days 0, 28 Full Dose
    - Arm C: Days 0, 14, 28 Full Dose (current PEP schedule)
    - Arm D: Days 0, 14, 28 Half Dose

Day 28 Antibody Levels Predicted Protection at Day 28 Challenge



High Titer NHP that died had anthrax meningitis. Meninges are immune-privileged site, no antibodies present

Predicting Human Survival for IM vs SC Route at Days 28 and 56

Day	Intramuscular (IM)	Subcutaneous (SC)
28	N = 241 88.6%	N = 242 92.4%
56	N = 234 95.6%	N = 235 96.1%

WG Considerations for Route of Administration

- Operational considerations for mass vaccination following wide-area release of *B. anthracis* spores
  - Lack of sufficient 5/8” needles to administer AVA subcutaneously
  - Potential errors due to having two vaccines for PEP with different routes of administration
  - IM administration might be more efficient in a mass vaccination campaign
- Adverse events were significantly higher in several parameters via SC route of administration
  - Adherence to vaccine might be higher if given by IM route, but no data to support
- Data suggest adherence to antimicrobial component of PEP may drop by 25-50% at four weeks
- <u>Antibody titers are significantly higher at 4 weeks for SC versus IM administration</u>

Question to NACCHO and ASTHO

- National Association of County and City Health Officials (NACCHO) Medical Countermeasures (MCM) Workgroup Call
- Association of State and Territorial Health Officers All 62 MCM Coordinators Call
- CDC requested input on efficiency of response and potential for medical errors to anthrax vaccination implementation during an event that may involve:
  - Potentially 2 different routes of administration for different target populations (SC – adults; IM – children)
  - Two formulations of anthrax vaccines with 2 different routes of administration (SC – AVA; IM – NuThrax)

Summary: Discussions with State Partners

- Adherence
  - Use the route that has the least complications
  - Potentially have to separate parents from children
- Medical errors
  - “New York State feels strongly that multiple routes are asking for medication errors”
  - Increased number of vaccination errors due to administration mistakes must be anticipated; VAERs reports must be submitted for each error
- Supplies
  - Matching needle size to vaccine supply at a large number of points of distribution (POD) sites will present logistical challenges
- Training
  - Local public health preparedness programs have more persons trained to give IM
  - Just-in-time (JIT) training is different for SC than IM. IM administration is easier for clinicians to learn. Response slowed if JIT training is for two ROA. “More time would be taken to administer by SC since they are not as familiar with it”
  - To minimize errors, may need to assign individuals to give either IM or SC; however, this would require more staff

Proposed Guidance for SC and IM Routes of Administration

- The SC route of administration is preferred over the IM route of administration forPEP due to the higher antibody titers achieved at 4 weeks in healthy adults.
- There are little to no data on immunogenicity or reactogenicity for pediatric or other special populations. In the absence of data, the working group considers it reasonable to anticipate similar risk-benefit of post exposure vaccination in pediatric or special populations as in general adult population. Therefore, SC is preferred over the IM route of administration for AVA PEP in all populations. However, in a large-scale emergency event, these populations should receive AVA by the route that results in the most efficient vaccination campaign.

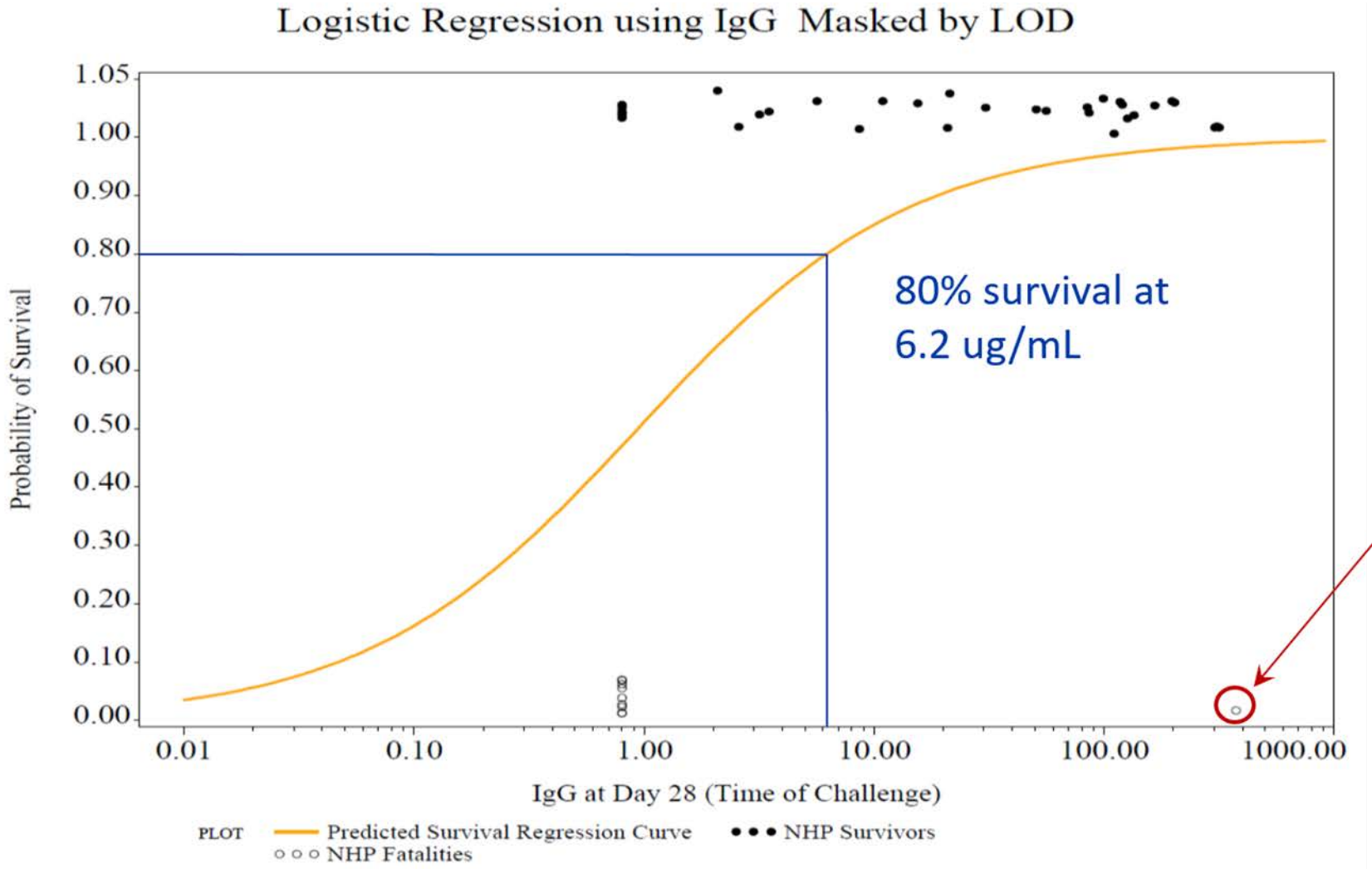
Proposed Guidance for SC and IM Routes of Administration (cont.)

- 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.

DISCUSSION

DOSE-SPARING STRATEGIES WHEN DEMAND FOR VACCINE EXCESS SUPPLY

Day 28 Antibody Levels Predicted Protection at Day 28 Challenge



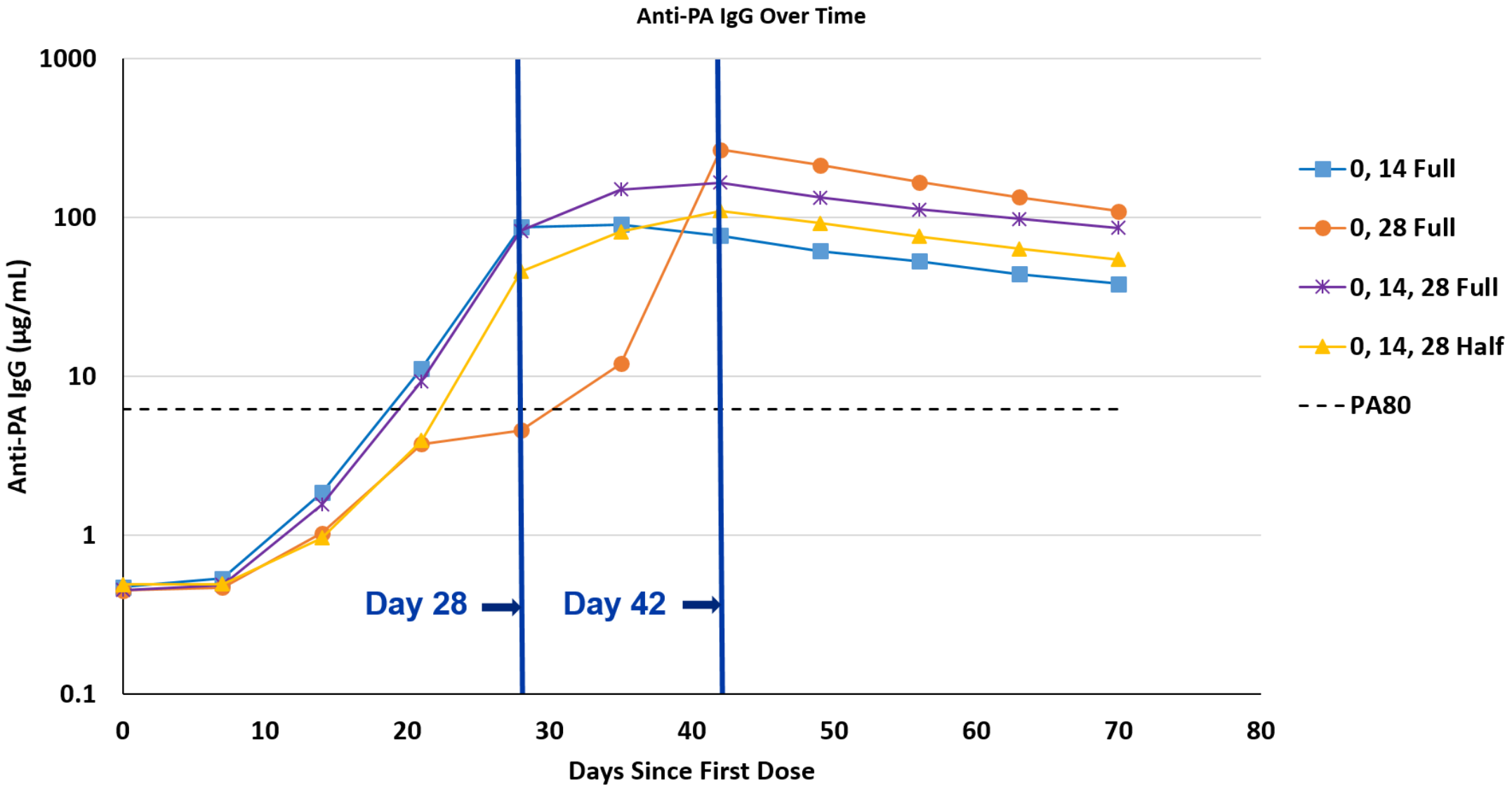
High Titer NHP that died had anthrax meningitis. Meninges are immune-privileged site, no antibodies present

Study Design

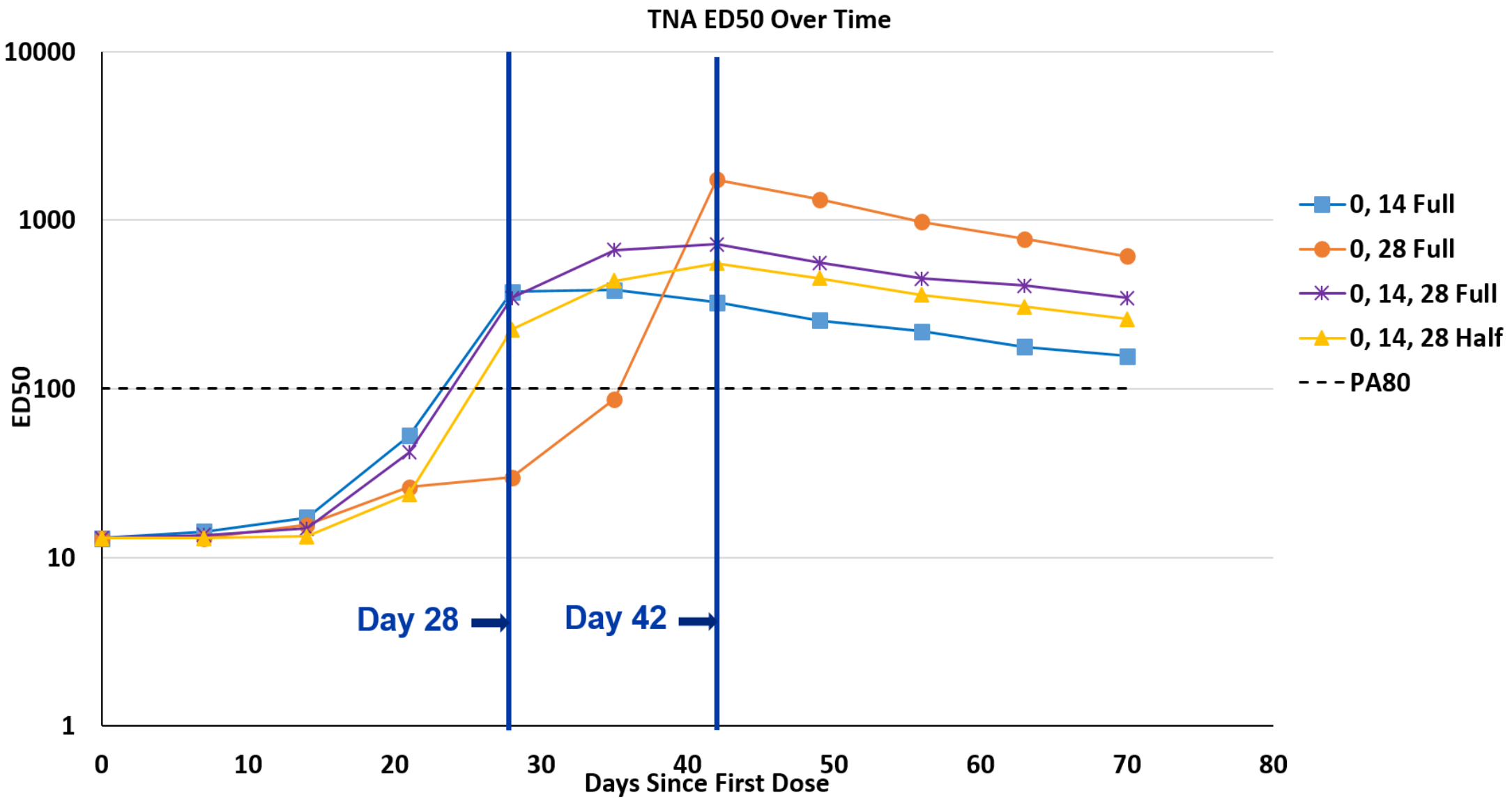
- cNHP Non-Clinical Study – Sivko et al.
  - 0, 14 Day vaccination schedule
  - Dose ranging from 1/3 - 1/243 human dose
  - 42 AVA vaccinated animals, 6 saline vaccinated controls
  - High-dose infectious challenge on Day 28

- Human Clinical Study – Stark et al.
  - 4 Study groups
    - Arm A – 0, 14 Day Full Dose
    - Arm B – 0, 28 Day Full Dose
    - Arm C – 0, 14, 28 Day Full Dose (current PEP schedule)
    - Arm D – 0, 14, 28 Day Half Dose

Human Immunogenicity (Anti-PA IgG)



Human Immunogenicity (TNA ED_{50})



Synopsis of Immunogenicity

- Groups that received a dose at day14 have higher antibody levels at day 28 than the group that did not
- Two full doses 28 days apart produce the highest antibody responses from day 42 onward
- Full dose produces higher antibody levels than half dose with the same schedule
- Peak response is 2 weeks after the last dose for all schedules
- Peak response is highly protective

Human Survival Predictions
2 Weeks After Last Dose

Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	95.7%	98.1%	97.4%	96.1%
TNA NF_{50}	89.1%	96.7%	94.0%	91.9%

Work Group Discussion on Dose-sparing Schedules

- All dose-sparing schedules provided high levels of protection by two week after the last dose.
- If number of potentially exposed individuals exceeds vaccine supply, it may be beneficial to protect larger numbers of individuals with slightly lower protective levels
- In a large scale event, a mass vaccination campaign will be difficult
- It is unlikely people will show up at exactly 2 week intervals for boosters

Work Group Proposed Recommendations on Dose-sparing Schedules

- Alternate vaccine schedules can provide effective immune protection and extend vaccine supplies when demand for vaccine exceeds supplies.

- Either of the following dose-sparing strategies provide high levels of protection by two weeks after the last dose:
  - Two full doses (0.5 mL) at 0 and 2-4 weeks
  - Three half doses (0.25 mL) at 0, 2, and 4 weeks

- 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.

Work Group Proposed Recommendations on Dose-sparing Schedules (cont.)

- Following an exposure to aerosolized *B. anthracis*, PEP has two components taken concurrently: an oral antimicrobial component (AbxPEP) and a vaccine component (VxPEP).
- When taken as prescribed, AbxPEP prevents anthrax.
- VxPEP generates a protective immune response that can also prevent anthrax; however this immune response takes time to develop. AbxPEP is critical during this time and must be continued until at least two weeks after the last dose of VxPEP to allow the protective immune response to fully develop.

DISCUSSION

DURATION OF ANTIMICROBIAL COMPONENT OF PEP WHEN USED IN COMBINATION WITH ANTHRAX VACCINE

Peak Immune Response

- 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

Protection Estimates Over Time

Table 1. Day 28

Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	95.8	72.6	95.8	91.1
TNA ED_{50}	89.5	59.9	89.5	83.4

Table 2. Day 42

Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	95.5	98.1	97.4	96.1
TNA ED_{50}	88.9	96.4	93.7	91.9

Table 3. Day 63

Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	93.3	97.0	96.4	94.2
TNA ED_{50}	84.1	93.9	91.0	88.1

Work Group Discussion on Antimicrobial Duration

- High levels of protection are achieved two weeks after last dose in all schedules.
- 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

Work Group Proposed Recommendations on Antimicrobial Duration

- For immunocompetent individuals, AbxPEP should be given concurrent with VxPEP and AbxPEP should continue for at least 42 days or two weeks after their last dose of the vaccine series, whichever comes last. Individuals that do not start or complete the vaccine series should receive AbxPEP for 60 days. AbxPEP should not exceed 60 days.
- Persons with an immunocompromising condition that might interfere with their ability to develop an adequate immune response should complete 60 days of AbxPEP concurrent with vaccine. Immunocompromising conditions include [will define].
- Once VxPEP doses and AbxPEP have completed, any illness within 2 weeks should prompt evaluation for anthrax. If anthrax is suspected, treatment should include at least two classes of antimicrobials with activity against *B. anthracis* and anthrax antitoxin. The classes of antimicrobial that are chosen should differ from the class/es of antimicrobial/s used for prophylaxis of that individual.

DISCUSSION