

Immunogenicity Data for Anthrax Vaccine Licensure Changes

Jarad Schiffer, MS

Chief, Microbial Pathogenesis and Immune Response Laboratory
Division of Bacterial Diseases, Meningitis and Vaccine Preventable Disease Branch

Advisory Committee for Immunization Practices
October 26, 2017



Licensed Indications for AVA

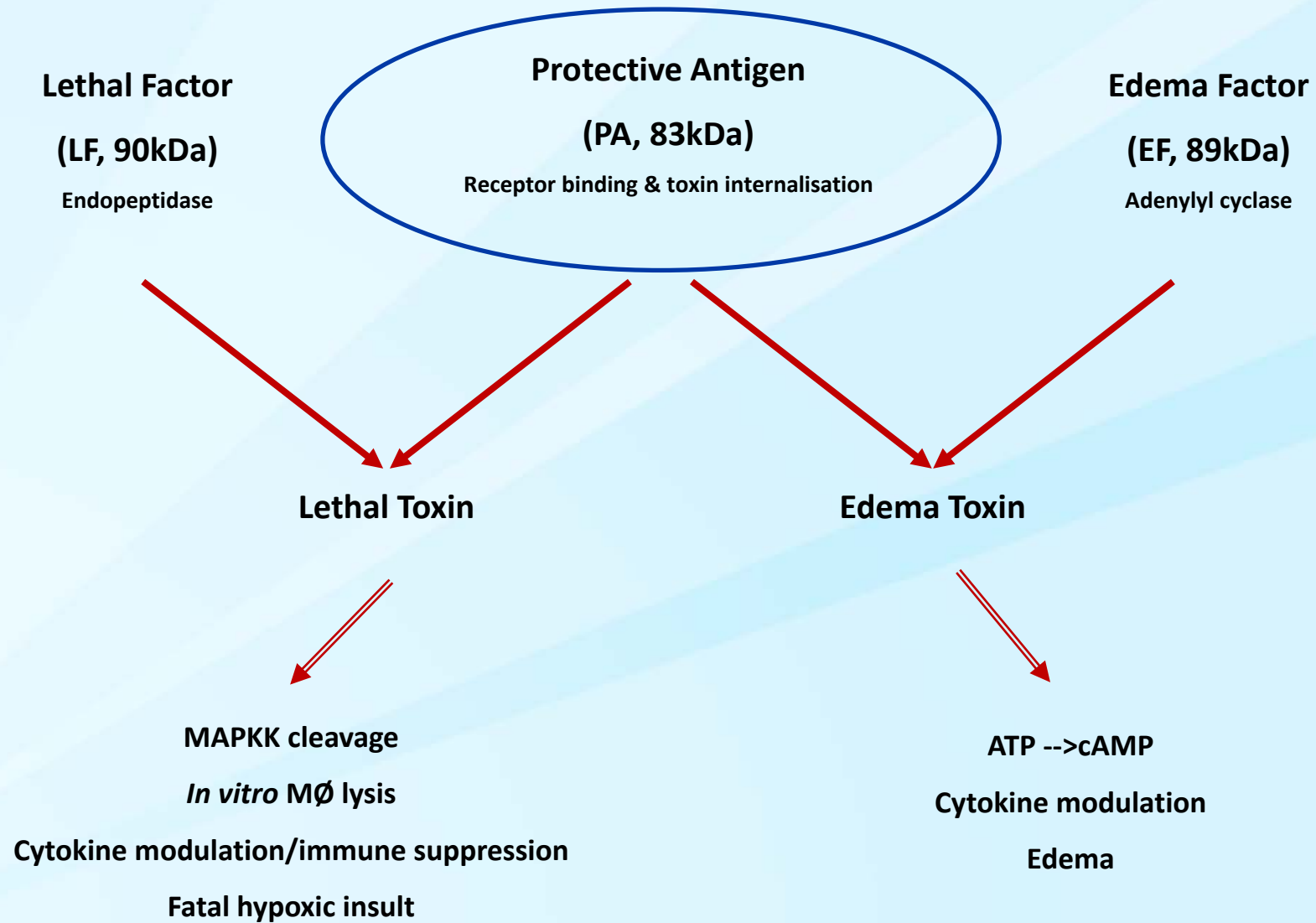
❑ Pre-Exposure Prophylaxis (PrEP)

- Intramuscular (IM) route
- Simplified regimen – 2012
 - Reduction in priming series to 3 IM doses (0, 1, 6 months)
 - Protection in 6 months
- Priming series shortened by 12 months

❑ New Indication for Post-Exposure Prophylaxis (PEP) - 2015

- Subcutaneous (SC) route
- 3-dose series at 0, 2 and 4 weeks
- Co-administration of antibiotics for 60 days

Anthrax is a Toxin Mediated Disease



Vaccine Mechanism of Protection

- ❑ AVA vaccination produces antibodies against PA
- ❑ Anti-PA antibodies that bind to free PA or the toxin complexes can block any of the intoxication steps
- ❑ This protects host immune system cells from intoxication, allowing normal immune response to clear the bacteria
- ❑ The immune response includes many other components (cellular responses, rapid increase in antibody levels in response to antigen detection, etc.), but antibody level at time of challenge is an accurate correlate of protection

Primary Serological Assays

□ Anti-PA IgG ELISA

- Measures total IgG against PA in $\mu\text{g}/\text{mL}$
- 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

Vaccine and Related Blood Products Advisory Committee (VRBPAC) Meeting Nov 2010

- Pathways to Licensure for Protective Antigen-Based Anthrax Vaccines for a Post-Exposure Indication Using the Animal Rule**

- Final recommendations:**
 - Antibody levels are an appropriate marker to use to bridge between animal efficacy and human immunogenicity
 - Bridging using the “Kohberger method” is an appropriate model for predicting human survival using animal challenge models
 - Using a PrEP animal model design is appropriate for use for the PEP licensure

Inter-Species Bridging Meta Analysis

- ❑ **Fay et al.* identified 5 aspects that should be matched as closely as possible when bridging between species:**
 - Genus and Species
 - Different non-human primate (NHP) species behave more similarly than NHP vs rabbit
 - Vaccine formulation
 - Vaccine schedule
 - Time of immune response measurement
 - Time of challenge

- ❑ **Fay et al. focused on the TNA assay because it is considered to be species-neutral.**

*Fay et al., 2012 Sci Transl Med. 4(151): p. 151ra126

Studies Supporting AVA Changes

❑ CDC Anthrax Vaccine Research Program (AVRP)

- Phase IV Human clinical trial
 - Compared IM and SC route in original PrEP schedule
 - Evaluated reduced booster schedules in IM route out to 42 months
- Matched NHP non-clinical challenge trial
 - NHP given 3-dose priming schedule
 - Anthrax lethal challenge to measure duration of protection at 12, 30 and 52 months

❑ Emergent Biosolutions Pivotal PEP trial

- Phase III Human Clinical Trial
 - SC route only – decision based on data from AVRP
 - PEP schedule – 0, 2 and 4 weeks
 - Immunogenicity measured to day 70
- Matched rabbit and NHP non-clinical challenge trials
 - 0, 28 day immunizations
 - Anthrax lethal challenge at day 70

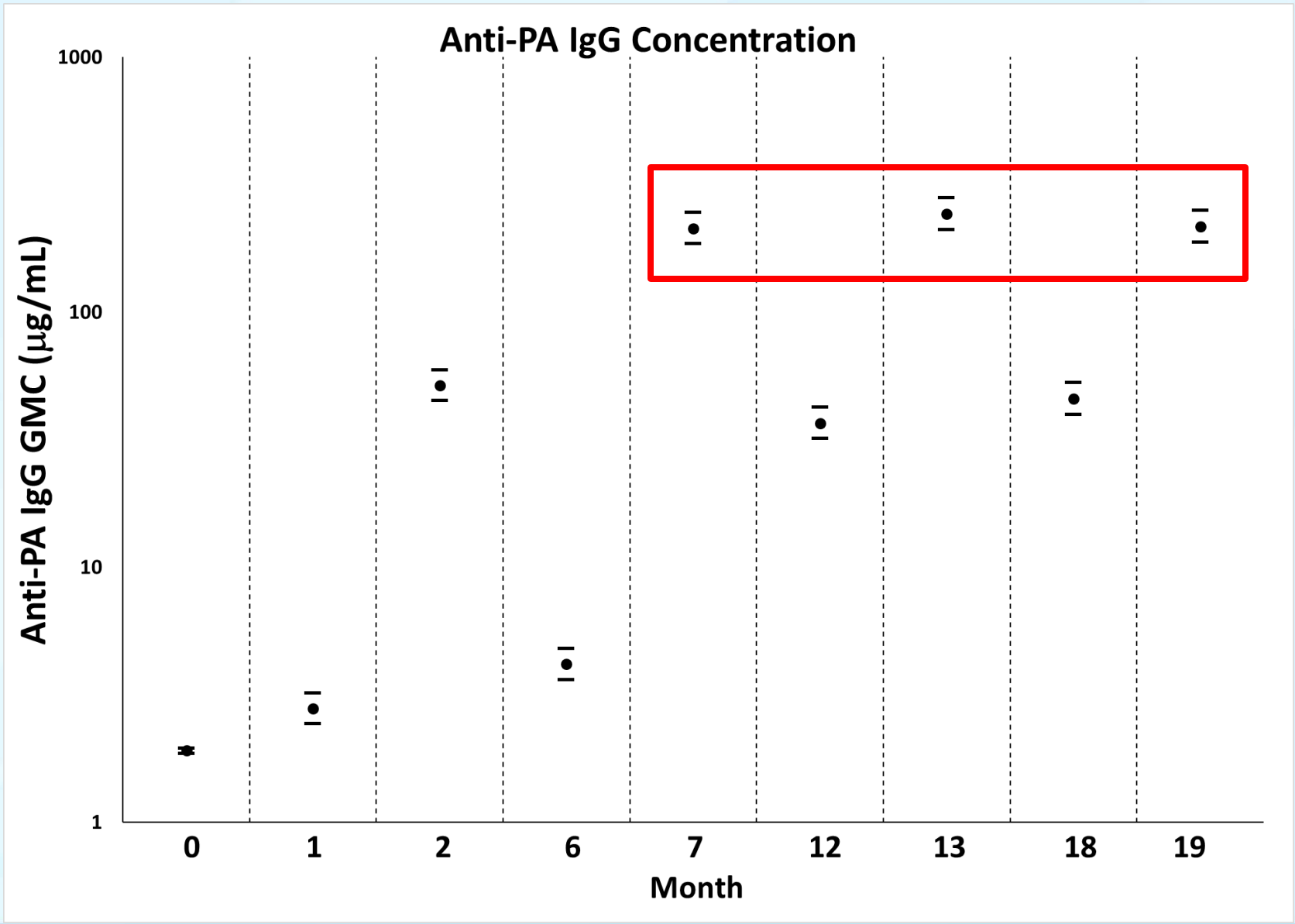
PrEP Priming Series Change

Immunogenicity Data Supporting PrEP Change

□ Subset of AVRP immunogenicity data

- Human clinical trial data using the licensed route (IM) and schedule (0, 1, 6, 12 and 18 months)
- Magnitude of anamnestic response to the month 6 dose is comparable to the response at months 12 and 18
- This indicates that priming is complete after the 6 month dose

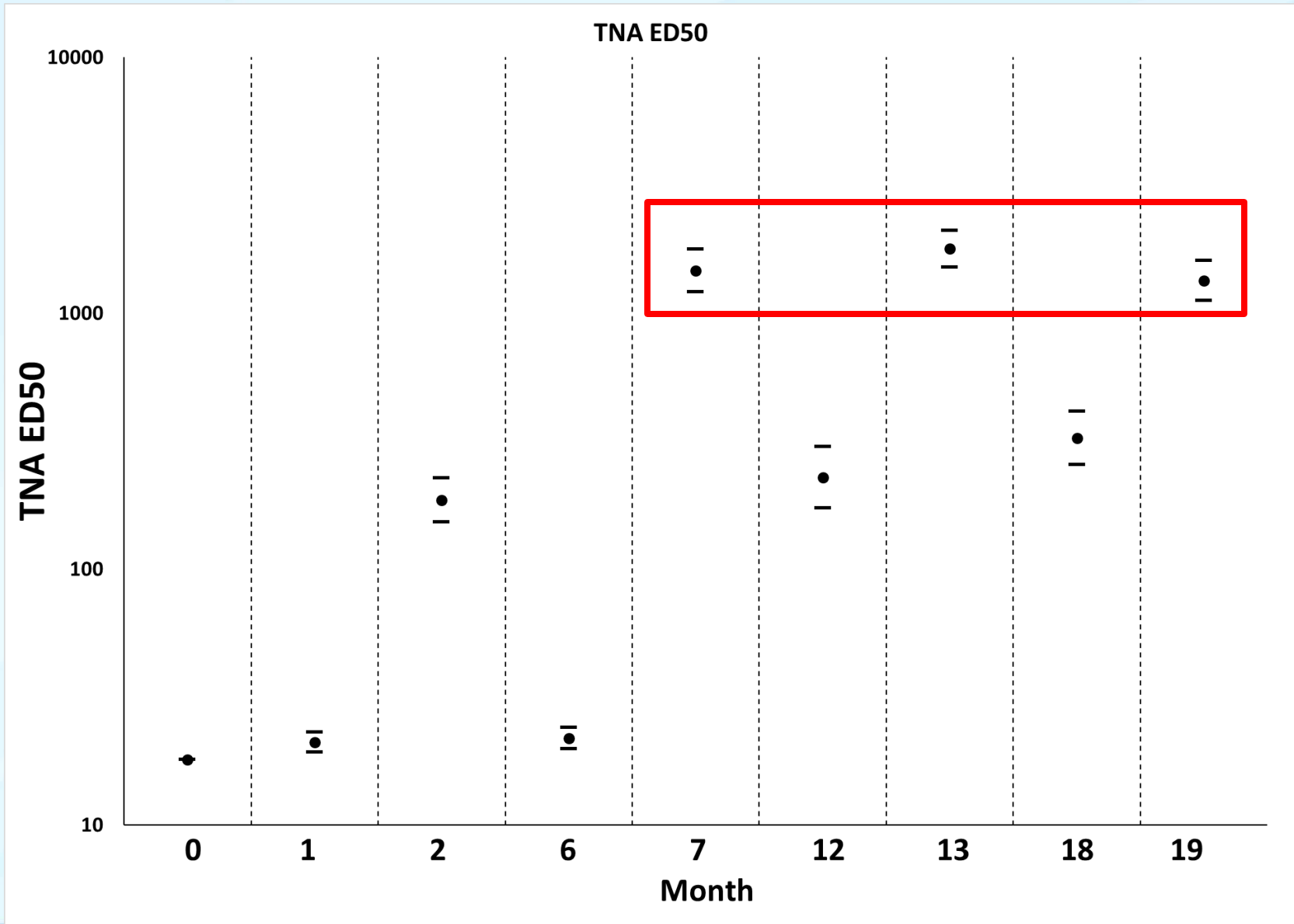
Immunological Priming is complete after Month 6 (1 of 2)



Response to the month 6 dose is equivalent to month 12 and 18 responses

*Wright *et al.*, 2014 *Vaccine*. 32(8): p. 1019-1028

Immunological Priming is complete after Month 6 (2 of 2)



Response to the month 6 dose is equivalent to month 12 and 18 responses

Immunological Priming is complete after Month 6

Month		Anti-PA IgG GMC ($\mu\text{g/mL}$)	TNA ED50 GMT
6	N	223	108
	GMC/GMT	4.17	21.83
	95% CI	(3.62 – 4.79)	(19.81 – 24.06)
7	N	214	102
	GMC/GMT	213.18	1465.27
	95% CI	(185.13 – 245.47)	(1208.4 – 1776.74)
12	N	211	99
	GMC/GMT	36.75	228.07
	95% CI	(31.90 – 42.33)	(173.38 – 300.02)
13	N	203	91
	GMC/GMT	243.11	1784.79
	95% CI	(210.79 – 280.39)	(1510.67 – 2108.64)
18	N	194	79
	GMC/GMT	45.93	325.27
	95% CI	(39.77 – 53.04)	(255.09 – 414.76)
19	N	192	100
	GMC/GMT	216.78	1343.22
	95% CI	(187.64 – 250.44)	(1120.81 – 1609.76)

Anti-PA IgG concentration and TNA ED50 at Month 7 are not significantly different than at Month 19, indicating that priming is complete after dose at Month 6

AVA PrEP Indication Change- 2012

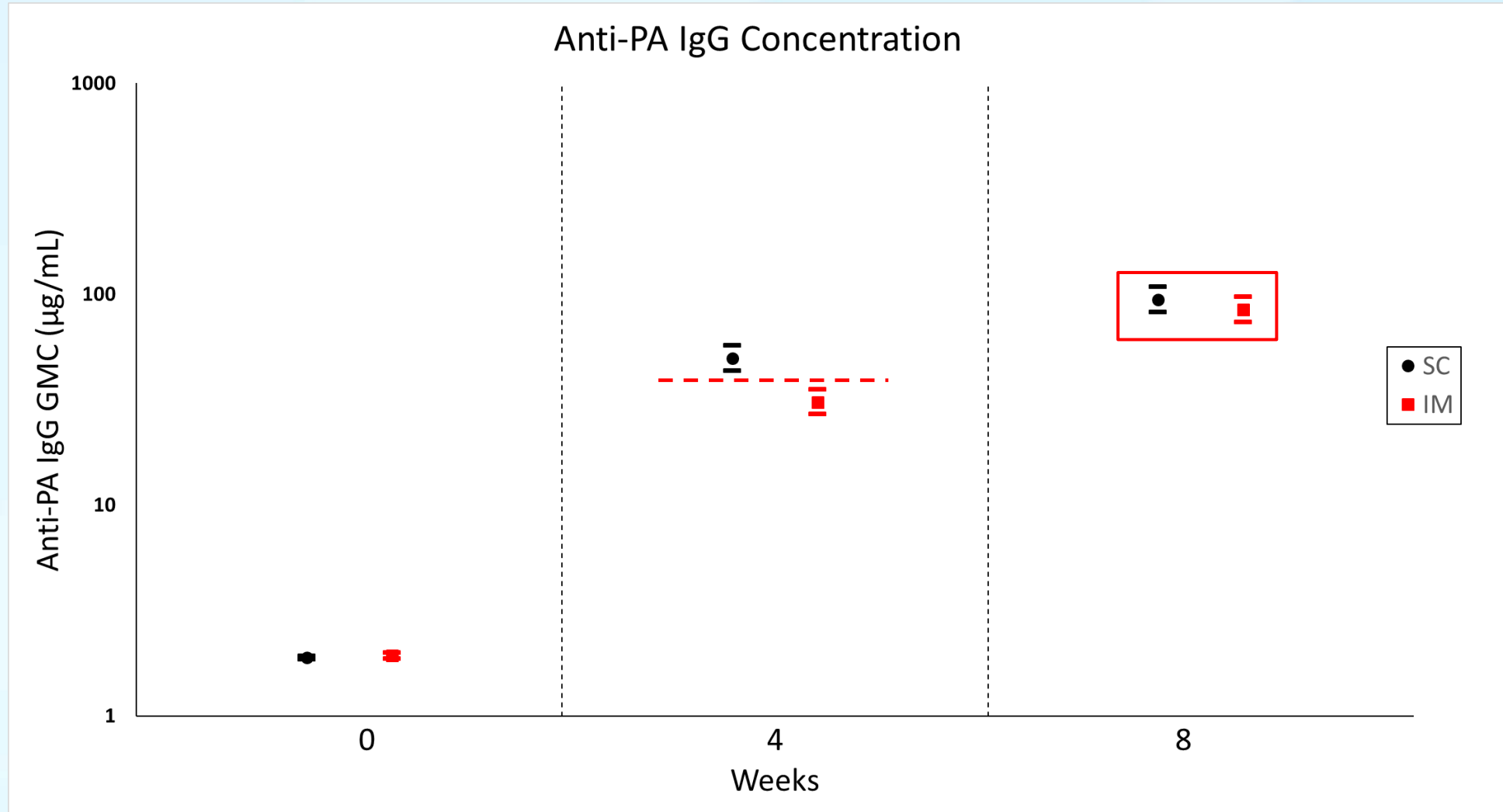
- ❑ **FDA licensed AVA priming schedule was simplified from 5 IM doses over 18 months to 3 IM doses over 6 months**
 - Vaccine recipients are considered protected after the 6 month dose
 - Priming completed 12 months sooner than previous licensure
 - Major impact on time to deployment or approval to work for emergency responders and laboratory workers
- ❑ **Dosing schedule for primary series will be updated in revised recommendations**

PEP Licensure

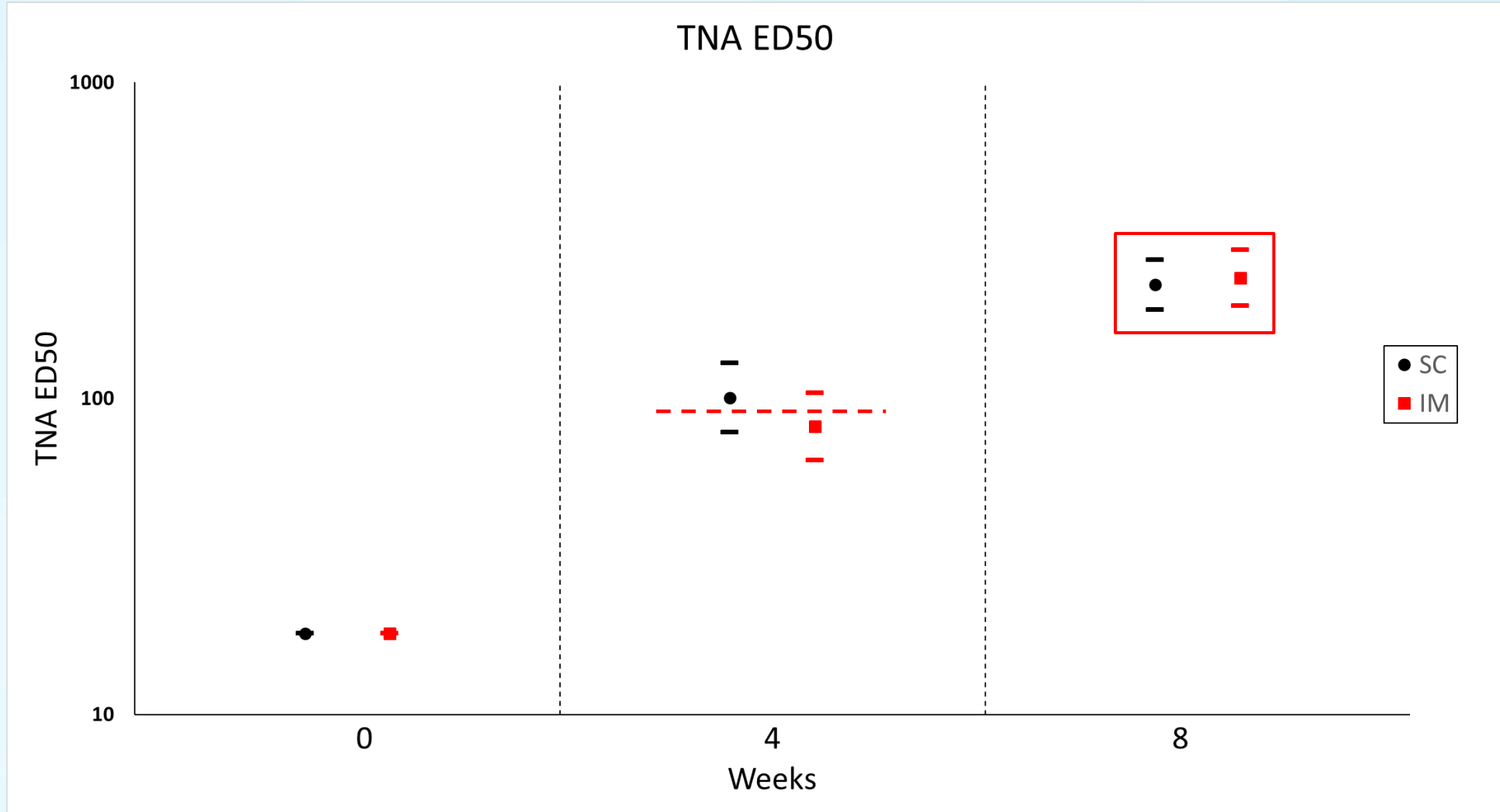
Background: PEP Using Subcutaneous Route

- ❑ PEP studies designed using subcutaneous route for the human clinical trial**
- ❑ Decision based on CDC AVRVP data**
- ❑ SC administration elicits statistically significantly higher anti-PA IgG at week 4**
- ❑ While IM has ~50% reduction in frequency, severity and duration of injection site AEs compared to SC route, rapid onset of response was prioritized over reduction in AEs for PEP indication**

SC Route has Statistically Significantly Higher Response at Week 4 by Anti-PA IgG Concentration



SC Route has Higher Response at Week 4 by TNA ED50, but is not statistically significant



SC Route has Statistically Significantly Higher Response at Week 4

Week		Subcutaneous	Intramuscular	Subcutaneous	Intramuscular
		Anti-PA IgG GMC ($\mu\text{g}/\text{mL}$) (95% CI)	Anti-PA IgG GMC ($\mu\text{g}/\text{mL}$) (95% CI)	TNA ED50 (95% CI)	TNA ED50 (95% CI)
0	N	259	262	111	112
	GMC/GMT	1.89	1.93	18	18
	95% CI	(1.85 – 1.92)	(1.87 – 1.99)	(–)	(–)
4	N	242	241	105	108
	GMC/GMT	49.79	30.81*	100.41	81.38
	95% CI	(43.38 – 57.14)	(26.90 – 35.29)	(77.91 – 129.41)	(63.74 – 103.88)
8	N	235	234	112	103
	GMC/GMT	94.43	84.58	229.07	240.84
	95% CI	(82.20 – 108.47)	(73.78 – 96.97)	(190.86 – 274.93)	(196.52 – 295.16)

* Statistically significantly different

PrEP Animal Model used for PEP Licensure

- ❑ **PEP licensure is intended for use post-exposure with concomitant antibiotic treatment**

- ❑ **It is difficult to develop an animal model for post-exposure prophylaxis**
 - Even a very low vaccination dose with concomitant antibiotics resulted in close to 100% survival¹
 - Unable to generate correlates of protection

- ❑ **Antibiotics do not interfere with vaccine immunogenicity**
 - Vaccination provides significant improvement in protection vs antibiotics alone²

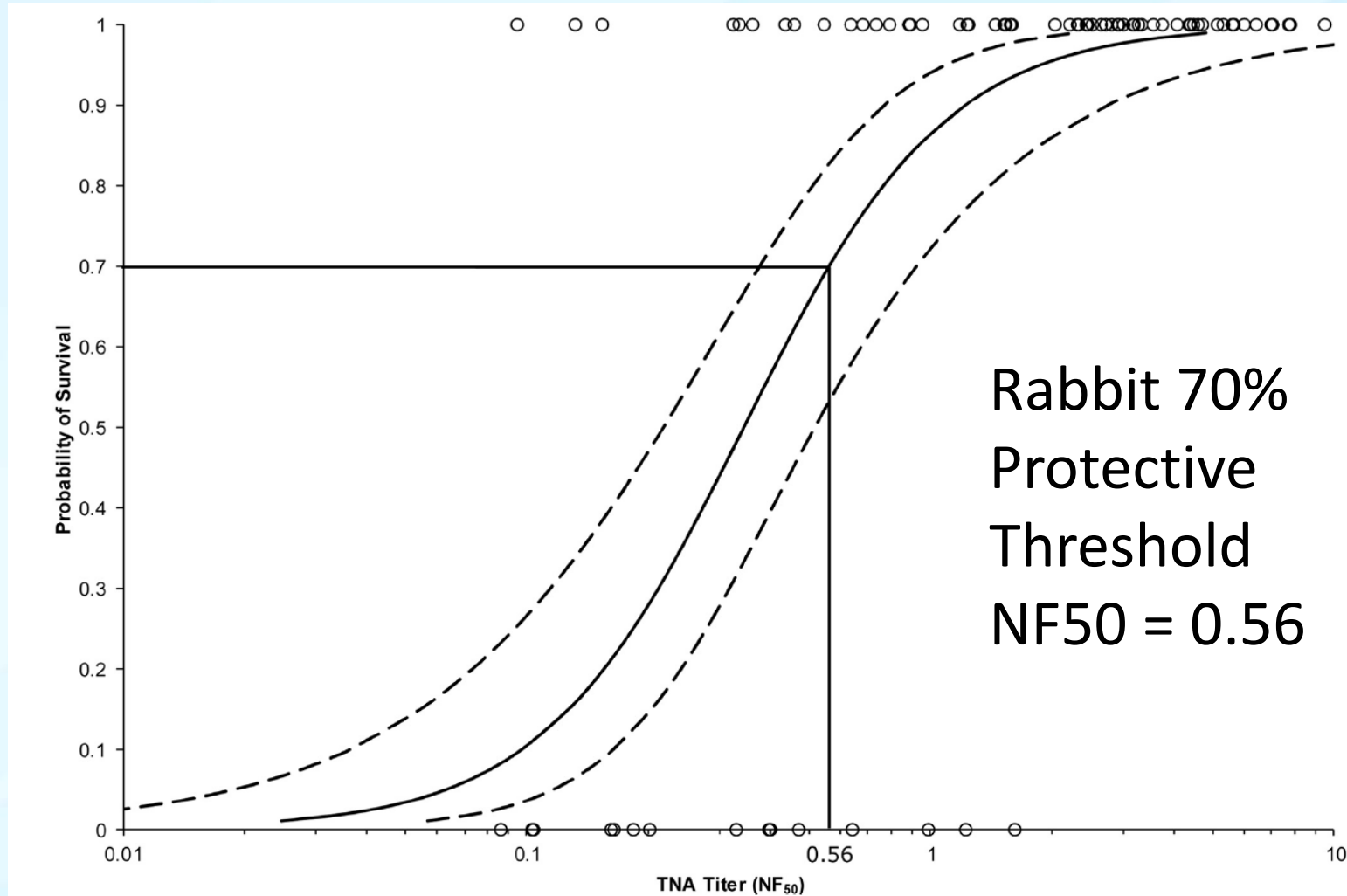
¹Leffel *et al.*, 2012 Clin. Vaccine Immunol. 19(8): p. 1158-1164

²Vietri *et al.*, 2006 PNAS. 103(20):p. 7813-7916

PrEP Animal Model for PEP Licensure (Con't)

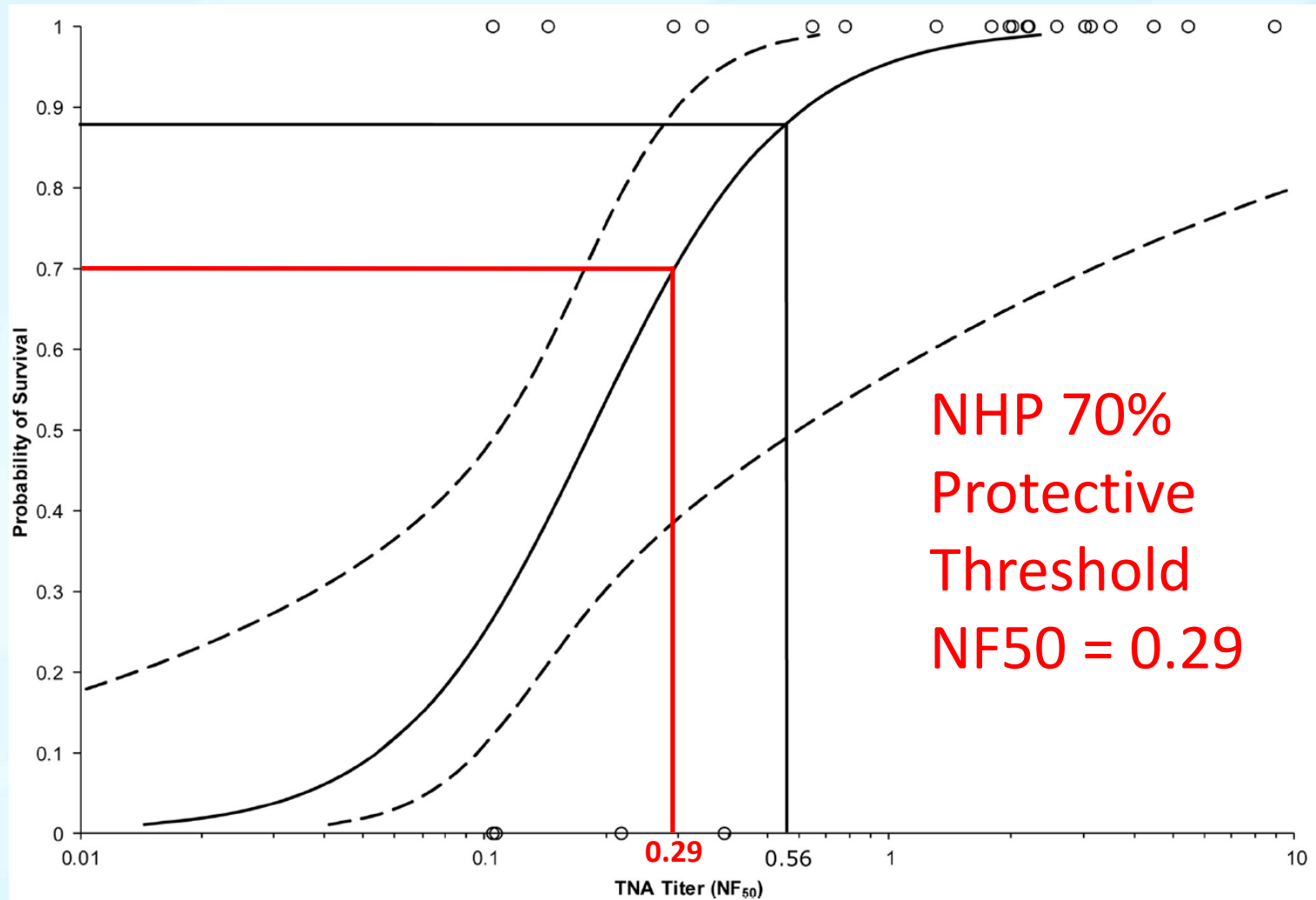
- ❑ Rabbits or non-human primates (NHP) vaccinated with graded vaccine doses at 0 and 4 weeks
- ❑ High dose aerosolized *Bacillus anthracis* spores challenge at Day 70
 - Tests protection at time when antibiotic treatment stops
 - Very conservative model - the 200 LD50 challenge dose should be far larger than residual spores in the lung at 70 days post exposure
- ❑ TNA NF50 used as reportable value for antibody response
- ❑ Logistic Regression used to generate correlation between antibody response and survival
- ❑ Antibody level required to provide 70% protection used as a protective threshold

Rabbit Model Correlate of Protection



*Ionin *et al.*, 2013 Clin. Vaccine Immunol. 20(7): p. 1016-1026

NHP Model Correlate of Protection



*Ionin *et al.*, 2013 Clin. Vaccine Immunol. 20(7): p. 1016-1026

Human PEP Clinical Trial

- ❑ Participants vaccinated SC at 0, 2, and 4 weeks
- ❑ Immune response (TNA NF50) measured out to Day 63
- ❑ Percent of human subjects who achieved $\geq 70\%$ protective level at Day 63 used to evaluate vaccine efficacy
 - Two thresholds of 0.29 and 0.56
- ❑ This is a simplified bridging model, not the “Kohberger Method”

*Hopkins *et al.*, 2014 Vaccine 32: p. 2217-2224

PEP Schedule Elicits Protective Human Immune Response

Table 4: Proportion of Subjects Achieving TNA NF₅₀ Threshold^a in the Pivotal Clinical Study (PP Population^b)

Animal Model	Time Point Human/Animal	n	Human GMT TNA NF ₅₀ (SD)	Animal TNA NF ₅₀ Threshold ^c	Number of Subjects Meeting Threshold	Proportion of Subjects Meeting Threshold (%) ^d		
						Point Est. (%)	95% CI (%)	
							Lower Bound	Upper Bound
Rabbit ^e	Day 63/Day 69	184	0.86 (2.09)	0.56	131	71.2	64.1	77.6
Non-human Primate ^f	Day 63/Day 70	184	0.86 (2.09)	0.29	172	93.5	88.9	96.6

CI = confidence interval; NF₅₀ = 50% neutralization factor; PP = per protocol; SD = standard deviation; TNA = toxin neutralizing antibody.

Note: Sample size (N) and denominators used for percentages are based on the number of subjects meeting the PP criteria at specified day(s).

^a TNA NF₅₀ threshold is defined as the TNA NF₅₀ value associated with 70% survival in the animal challenge studies.

^b Human data are from the pivotal clinical study (NCT01491607).

^c A logistic regression model with log₁₀-transformed TNA NF₅₀ values as the predictor and survival as the response is used to derive the TNA NF₅₀ threshold associated with 70% probability of survival in rabbits and non-human primates, respectively.

^d 95% CI is calculated with the exact (Clopper-Pearson) method.

^e The proportion of subjects achieving a TNA NF₅₀ response at Day 63 that met or exceeded the TNA NF₅₀ threshold in the rabbit model at Day 69 comprised the primary immunogenicity endpoint.

^f Comparison of the human TNA NF₅₀ response at Day 63 with the NHP TNA NF₅₀ threshold at Day 70 was defined as an immunogenicity endpoint and was supportive of the bridging of human immunogenicity data to rabbit survival.

Summary

- ❑ **There have been 2 changes to Biothrax licensure since 2010**

- ❑ **PrEP priming series simplified from 5 doses over 18 months to 3 doses over 6 months**
 - Magnitude of human anamnestic response to month 6 dose measured at month 7 is equivalent to response to month 18 dose measured at month 19

- ❑ **PEP Licensure**
 - 0, 2, 4 week SC schedule with concomitant antibiotics for 60 days
 - SC route chosen based on superior response at week 4
 - Licensure based on percentage of human response exceeding 70% protective levels established in rabbit and NHP models

Questions?

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.