ACIP Anthrax Vaccine Work Group

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Advisory Committee for Immunization Practices
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Division of High-Consequence Pathogens and Pathology

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

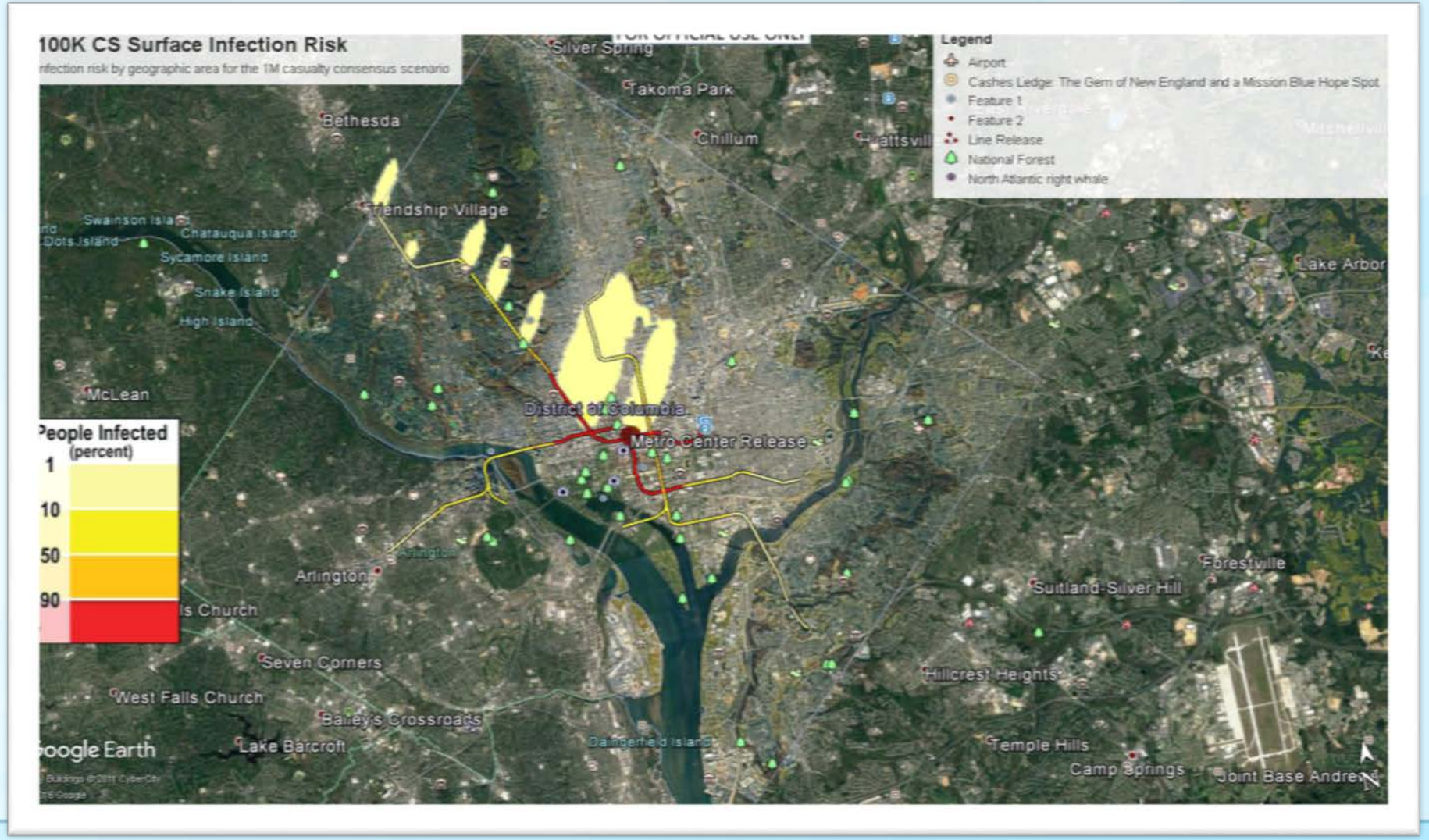
Anthrax PrEP Vaccine History

- **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

Reductions to Booster Schedule?

- 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)

Author, year	Study design (# enrolled)	Interventions
Quinn, 2012	RCT (137)	• Vaccinated IM with full strength AVA or dilutions of 1:5, 1:10, 1:20, or 1:40 at 0, 1, and 6 months • Challenged with 200-400 LD_{50} *Bacillus anthracis* spores at 12, 30, or 52 months • Outcome: Survival
Chen, 2014	RCT (137)	• Vaccinated IM with full strength AVA or dilutions of 1:5, 1:10, 1:20, or 1:40 at 0, 1, and 6 months • Challenged with 200-400 LD_{50} *Bacillus anthracis* spores at 12, 30, or 52 months • Outcome: Comprehensive analysis of 21 humoral and cell-mediated NHP immune-response variables

3-IM AVA Provides Long Term Protection in NHP

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

- 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

Quinn CP, et al. A Three-Dose Intramuscular Injection Schedule of Anthrax Vaccine Adsorbed Generates Sustained Humoral and Cellular Immune Responses to Protective Antigen and Provides Long-Term Protection against Inhalation Anthrax in Rhesus Macaques. Clin Vaccine Immunol. 2012 Nov; 19(11): 1730–1745.

Human Immunogenicity Studies

Author, year	Study design (# enrolled)	Interventions
Wright, 2014	RCT (781)	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

Pittman, 2014	OBS (600)	AVA given:
		• 6 month dose SC on schedule
		• 6 month dose SC delayed
		  • 18-36 months
		  • 37-60 months
		  • > 60 months

Pittman, 2013	OBS (373)	AVA given SC: • 1, 2, or 3 doses • Fourth dose received 18-24 months later

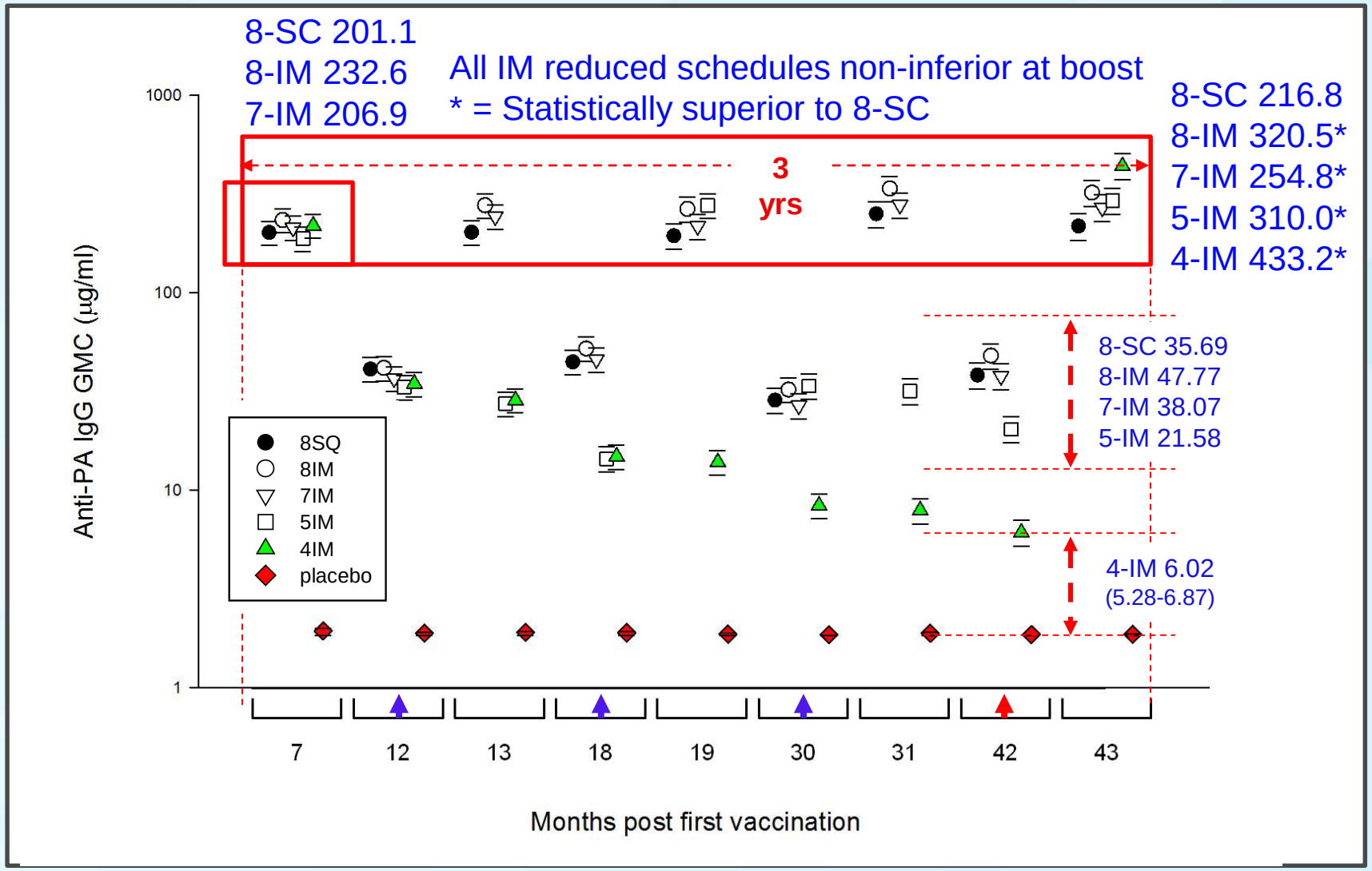
Vaccine Schedule for the Wright Study

Study Group (N)	Month 0	Month 0.5	Month 1	Month 6	Month 12	Month 18	Month 30	Month 42
8-SC (260)	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA
8-IM (262)	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA
7-IM (256)	AVA	S	AVA	AVA	AVA	AVA	AVA	AVA
5-IM (258)	AVA	S	AVA	AVA	S	AVA	S	AVA
4-IM (268)	AVA	S	AVA	AVA	S	S	S	AVA
Placebo (260)	S	S	S	S	S	S	S	S

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

Wright JG, et al. Vaccine 2014: 32;1019-28.

Long Term Immune Response to Vaccination in Humans



Robust Immune Response following Delayed Booster Dose

Geometric mean anti-PA IgG antibody concentration and *B. anthracis* lethal toxin neutralization activity by cohorts stratified by days post vaccination

Antibody	Time point	On-schedule			Delayed			p-value
		N	GM	95% CI	*N*	GM	95% CI	
Anti-PA IgG concentration	Day 28	220	283.3	(251.6, 319.0)	229	545.3	(486.3, 611.5)	<0.0001
	Day 180	138	53.8	(46.3, 62.6)	113	155.8	(126.5, 191.8)	<0.0001
TNA ED_{50} titer (reciprocal)	Day 28	220	1061.5	(926.0, 1216.8)	228	2284.1	(2027.7, 2573.0)	<0.0001
	Day 180	137	208.5	(171.8, 253.1)	112	748.6	(603.5, 928.6)	<0.0001

Pittman PR, et al. Anthrax vaccine adsorbed: Further evidence supporting continuing the vaccination series rather than restarting the series when doses are delayed. Vaccine 32 (2014) 5131–5139.

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 that the licensed booster interval
- While in the high-risk area, the licensed booster schedule for high risk exposure applies

Proposed Wording for Priming Persons Not Currently at High Risk of Exposure to Anthrax

- 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			
PrEP Doses	Interval Since Last Dose	AVA PEP	Duration of Antimicrobial PEP
0		Dose 1 (day 0) Dose 2 (day 14) Dose 3 (day 28)	42 days after first dose of AVA or 14 days after last dose, whichever is later
1		Dose 2 (day 0) Dose 3 (day 14)	28 days after first dose of AVA or 14 days after the last dose, whichever is later
2		Dose 3 (day 0)	14 days
≥ 3	> 6 months	Booster dose	14 days
≥ 3	≤ 6 months	No booster	No antimicrobials needed

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?