ACIP Anthrax Vaccine Work Group

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June 20, 2018

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REVIEW “ANIMAL RULE” AND CORRELATES OF PROTECTION MODEL

Predicting Human Survival Based on "Animal Rule" Data

- Data from animal challenge studies was used to generate a correlate of protection model to predict survival based on the measured immune response to vaccination
- The model was applied to human clinical trial data to predict the level of protection in the human cohorts
- The predicted survival levels generated are indirect measures, therefore the data was downgraded to reflect the lack of direct measurement of protection in humans

Data Used to Determine AVA Effectiveness Based on "Animal Rule" Data

- Animal survival data (Sivko, 2016)
  - Supporting data (Quinn, 2012; Ionin, 2013)

- Immune response in humans
  - Subset of a pre-exposure (0, 14 and 28 days, then 6, 12, and 18 months) regimen study used to compare IM vs SC route of administration (Wright, 2014)
  - Dose sparing schedules (Bernstein, 2014)
    - 2 full doses at 0 and 14 days
    - 2 full doses at 0 and 28 days
    - 3 half doses at 0, 14, and 28 days

QUESTIONS FOR ACIP COMMITTEE

Summary of Policy Questions for ACIP Consideration

Optimizing use of vaccine during a large mass vaccination event

1) May the intramuscular (IM) route of administration (ROA) be used if the subcutaneous (SC) ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?
2) Should there be an inadequate supply of anthrax vaccine available for PEP, may either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?

Use of antimicrobials in conjunction with vaccine

3) In immunocompetent individuals who are being vaccinated with anthrax vaccine, do antimicrobials provide adequate protection when given for:
   a) At least 42 days after the first vaccine dose, or
   b) 2 weeks after the last vaccine dose, whichever comes later

GRADE

Nonhuman Primate Studies

Author, year	Study design (# enrolled)	Interventions
Sivko, 2016	RCT (48)	• Vaccinated with serial dilutions of AVA on Days 0 and 14 • Challenged with 205 LD_{50} *Bacillus anthracis* spores on Day 28 • Survival
Ionin, 2013	RCT (48)	• Vaccinated with serial dilutions of AVA on Days 0 and 28 • Challenged with 200 LD_{50} *Bacillus anthracis* spores on Day 70 • Survival
Quinn, 2012	RCT (114)	• Vaccinated with serial dilutions of AVA on Days 0 and 14 • Challenged with 200-400 LD_{50} *Bacillus anthracis* spores at 12, 30, or 52 months • Survival

Human Immunogenicity / AE Studies

Author, year	Study design (# enrolled)	Interventions/Outcomes
Immunogenicity and AE Studies		
Wright, 2014 (direct comparison IM vs SC ROA)	RCT (781)	AVA given: • Subcutaneous (SC) at days 0, 14, and 28 • Intramuscular (IM) at days 0, 14, and 28 Anti-PA IgG concentration at days 0, 28, and 56
Bernstein, 2014 (Dose-sparing schedules)	RCT (328)	AVA given: • Full dose at days 0, 14 • Full dose at days 0, 28 • Half-dose at days 0, 14, and 28 • Full dose at days 0, 14, and 28 Anti-PA IgG concentration at days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70

Human Immunogenicity / AE Studies cont'd

Author, year	Study design (# enrolled)	Interventions/Outcomes
Immunogenicity and AE Studies		
Hopkins, 2014	Obs (200)	• AVA full dose at days 0, 14, and 28 • Anti-PA IgG concentration at days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70
Rynkiewicz, 2011	RCT (69)	• AVA full dose at days 0, 14, and 28 • Anti-PA IgG concentration at days 0, 7, 14, 21, 28, 35, 42, 49, and 56
King, 2015	Obs (321)	• AVA full dose at days 0, 14, and 28 • Anti-PA IgG concentration at days 28 and 56
Zhang, 2008	Obs (128)	• Six AVA full doses on pre-exposure schedule • Anti-PA IgG concentration immediately prior to AVA dose
Immunogenicity Studies only		
Ionin, 2013	Obs (150)	• AVA full dose at days 0, 14, and 28 • Anti-PA IgG concentration at days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70
Minang, 2014	RCT (200)	• AVA full dose at days 0, 14, and 28 • Anti-PA IgG concentration at days 0,14, 28, 42, and 70

Policy Question for ACIP to Consider

Optimizing use of vaccine during a large mass vaccination event

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Policy Question 1: May the intramuscular (IM) route of administration (ROA) be used if the subcutaneous (SC) ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?

Populations	Healthy Adults (18-65 y/o)
Interventions	3 doses of AVA administered IM at 0, 2, and 4 weeks
Comparison	3 doses of AVA administered SC at 0, 2, and 4 weeks (current licensed schedule)
Outcomes	Immunogenicity Adverse Events

IM ROA as an alternative to SC ROA

Outcome	Design (# studies	Initial Evidence	Bias Risk	Inconsistent	Indirect	Imprecise	Pub Bias	Others	Final Evidence	Overall Evidence Type
Benefits										
Immune response	RCT (4)	1	No	None	Yes (-1)	None	None	None	2	2
	OBS (4)	3	No	None	Yes (-1)	None	None	SOA +1 DR +1	2	
Harm										
Adverse Events	RCT (3)	1	No	None	None	None	None	None	1	1
	OBS (3)	3	No	None	Yes (-1)	None	None	DR +1	3	

SOA – Strength of Association
DR – Dose Response

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Policy Question 2: Should there be an inadequate supply of anthrax vaccine available for PEP, can either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?

Populations	Healthy Adults (18-65 y/o)
Interventions	• 2 full doses of AVA administered SC at 0 and 2 weeks • 2 full doses of AVA administered SC at 0 and 4 weeks • 3 half doses of AVA administered SC at 0, 2, and 4 weeks
Comparison	3 doses of AVA administered SC at 0, 2, and 4 weeks (current licensed schedule)
Outcomes	Immunogenicity

Dose-sparing Strategies

2 Full Doses at 0 and 2 weeks
2 Full Doses at 0 and 4 weeks
3 Half Doses at 0, 2, and 4 weeks

Outcome	Design (# studies	Initial Evidence	Bias Risk	Inconsistent	Indirect	Imprecise	Pub Bias	Others	Final Evidence	Overall Evidence
Immune response	Human Data									2
	RTC (1)	1	No	None	Yes (-1)	None	None	None	2	
	Non-human Primate Data									
	RCT (3)	1	No	None	Yes (-2)	None	None	None	3	

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Policy Question 3: Can the antimicrobial component of PEP be decreased to less than 60 days?

Populations	Healthy Adults
Intervention	• 2 full doses of AVA administered SC at 0 and 2 weeks • 2 full doses of AVA administered SC at 0 and 4 weeks • 3 half doses of AVA administered SC at 0, 2, and 4 weeks • 3 doses of AVA administered SC at 0, 2, and 4 weeks (current licensed schedule)
Comparison	Placebo or no vaccination
Outcomes	Immunogenicity

Antimicrobial Duration for PEP

2 Full Doses at 0 and 2 weeks
2 Full Doses at 0 and 4 weeks
3 Half Doses at 0, 2, and 4 weeks

Outcome	Design (# studies	Initial Evidence	Bias Risk	Inconsistent	Indirect	Imprecise	Pub Bias	Others	Final Evidence	Overall Evidence
Immune response	Human Data									2
	RTC (1)	1	No	None	Yes (-1)	None	None	None	2	
	Non-human Primate Data									
	RCT (3)	1	No	None	Yes (-2)	None	None	None	3	

Antimicrobial Duration for PEP

3 Full Doses at 0, 2 and 4 weeks

Outcome	Design (# studies	Initial Evidence	Bias Risk	Inconsistent	Indirect	Imprecision	Publication Bias	Others	Final Evidence	Overall Evidence Type
Immune response	Human Data									2
	RCT (4)	1	No	None	Yes (-1)	None	None	None	2	
	OBS (4)	3	No	None	Yes (-1)	None	None	None	2	
	Non-human Primate Data									
	RCT (3)	1	No	None	Yes (-2)	None	None	None	3	

SOA – Strength of Association
DR – Dose Response

GRADE Summary

Policy Change	Overall GRADE	
IM ROA as an alternative to SC ROA	Benefit	2
	Harm	1
Dose-sparing strategies	Benefit	2
	Harm	N/A
Antimicrobial duration for PEP	Benefit	2
	Harm	N/A