Anthrax Vaccine Adsorbed (AVA): Safety

Kate Hendricks, MD, MPH&TM
Medical Officer
Bacterial Special Pathogens Branch,
Centers for Disease Control and Prevention

October 3, 2019

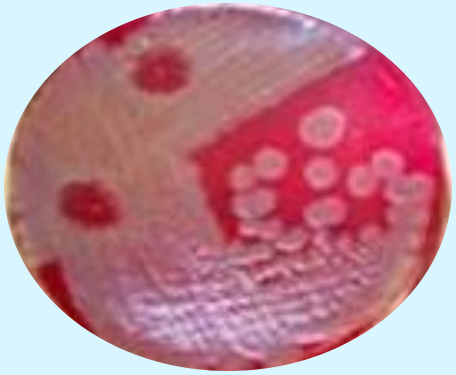
AVA Safety Data

- **Background**
  - Anthrax types and mortality rates
  - Anthrax Vaccine Adsorbed (AVA)
- **VAERS surveillance studies**
- **Studies using other data sources**

BACKGROUND

The Agent

- ***Bacillus anthracis*** **is the causative agent of anthrax**
  - Gram positive spore-forming bacterium
- **Spores are the infective form**
  - Can be mass produced and released as an aerosol as a bioweapon
- **Vegetative form produces two major toxins**



Epidemiology: Naturally Occurring Disease

- **Primarily disease of herbivores that ingest spores**
- **Butchering and eating of contaminated carcasses**
  - Both cutaneous and gastrointestinal cases
- **Human contact with infected animals/animal products**
  - Woolsorter's disease

Cutaneous Anthrax

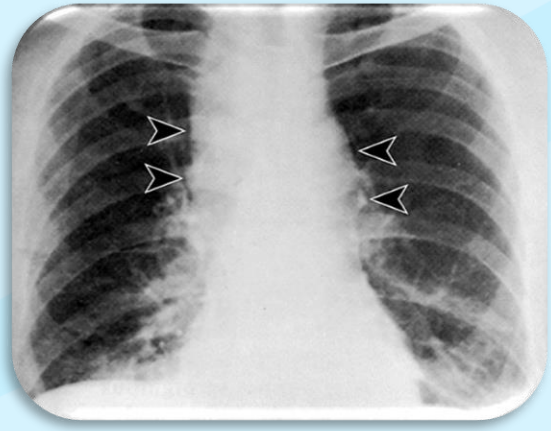
- **Most common form**
- **Transmission:** spores introduced through skin (often, but not always through pre-existing abrasions)
- **Germination:** 1-3 hours after inoculation
- **Incubation:** 1-17 days
- **Case fatality rate:**
  - Without treatment: ~24%
  - With antimicrobial treatment: <2%

Ingestion Anthrax

- **2nd most common form of naturally occurring anthrax**
- **Transmission:** ingestion – unclear whether it is spores or vegetative cells in poorly cooked meat
- **Two forms:** oropharyngeal and abdominal
- **Incubation:** 1- 14 days
- **Case fatality rate with treatment:** ~40%; but may be higher in children

Inhalation Anthrax

- **Transmission:** inhalation of aerosolized spores from animals/hair/hides or BW- or BT-related events
- **Incubation:**
  - Range in humans: 1-43 days
  - Sverdlovsk: 2-43 days (mode 9,10)
  - 2001: 5-13 days (mode 7)
- **Case fatality rate with treatment**
  - 1900-2000: 92%
  - 2001 and after: 47%



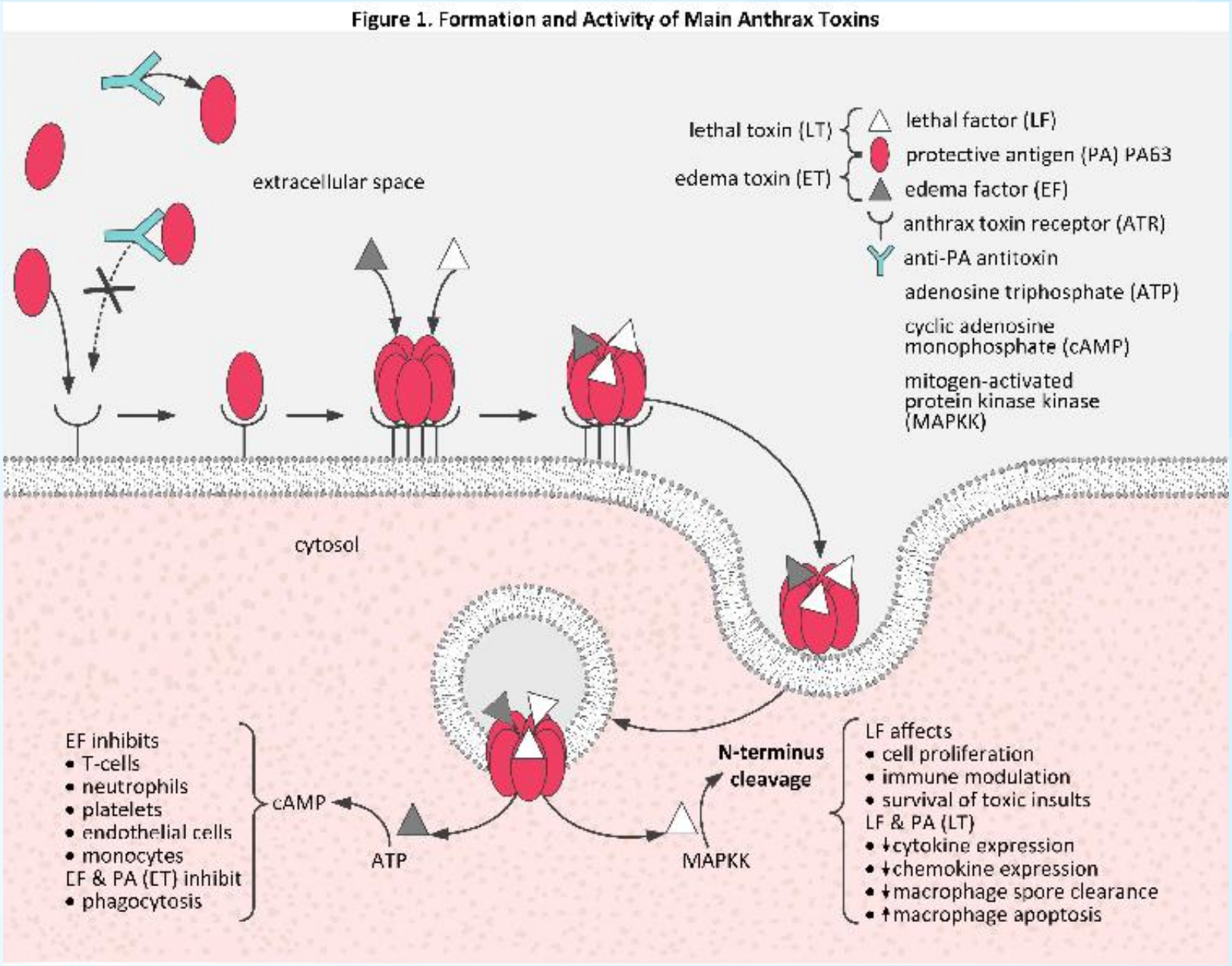
Anthrax Vaccine Facts

- **Anthrax Vaccine Adsorbed (BioThrax®)**
  - Sterile, cell-free filtrate made from microaerophilic cultures of avirulent, non-encapsulated *B. anthracis**
  - Manufactured by Emergent BioSolutions

- **Final product***
  - 1.2 mg/mL aluminum (added as aluminum hydroxide in 0.85% sodium chloride)
  - Contains as preservatives: 25 µg/mL benzethonium chloride and 100 µg/mL formaldehyde

* http://www.biothrax.com/

Figure 1. Formation and Activity of Main Anthrax Toxins



2019 Recommended Immunizations for Children from Birth Through 6 Years Old

Vaccine	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
HepB	HepB	HepB			HepB						
RV			RV	RV	RV						
DTaP			DTaP	DTaP	DTaP		DTaP				DTaP
Hib			Hib	Hib	Hib	Hib					
PCV13			PCV13	PCV13	PCV13	PCV13					
IPV			IPV	IPV	IPV						IPV
Influenza (Yearly)*											
MMR						MMR					MMR
Varicella						Varicella					Varicella
HepA§						HepA§					

Is your family growing? To protect your new baby against whooping cough, get a Tdap vaccine. The recommended time is the 27th through 36th week of pregnancy. Talk to your doctor for more details.

Shaded boxes indicate the vaccine can be given during shown age range.

NOTE:
If your child misses a shot, you don't need to start over. Just go back to your child's doctor for the next shot. Talk with your child's doctor if you have questions about vaccines.

FOOTNOTES:

* Two doses given at least four weeks apart are recommended for children age 6 months through 8 years of age who are getting an influenza (flu) vaccine for the first time and for some other children in this age group.

§ Two doses of HepA vaccine are needed for lasting protection. The first dose of HepA vaccine should be given between 12 months and 23 months of age. The second dose should be given 6 months after the last dose. HepA vaccination may be given to any child 12 months and older to protect against hepatitis A. Children and adolescents who did not receive the HepA vaccine and are at high risk should be vaccinated against hepatitis A.

If your child has any medical conditions that put him at risk for infection or is traveling outside the United States, talk to your child's doctor about additional vaccines that he or she may need.

See back page for more information on vaccine-preventable diseases and the vaccines that prevent them.

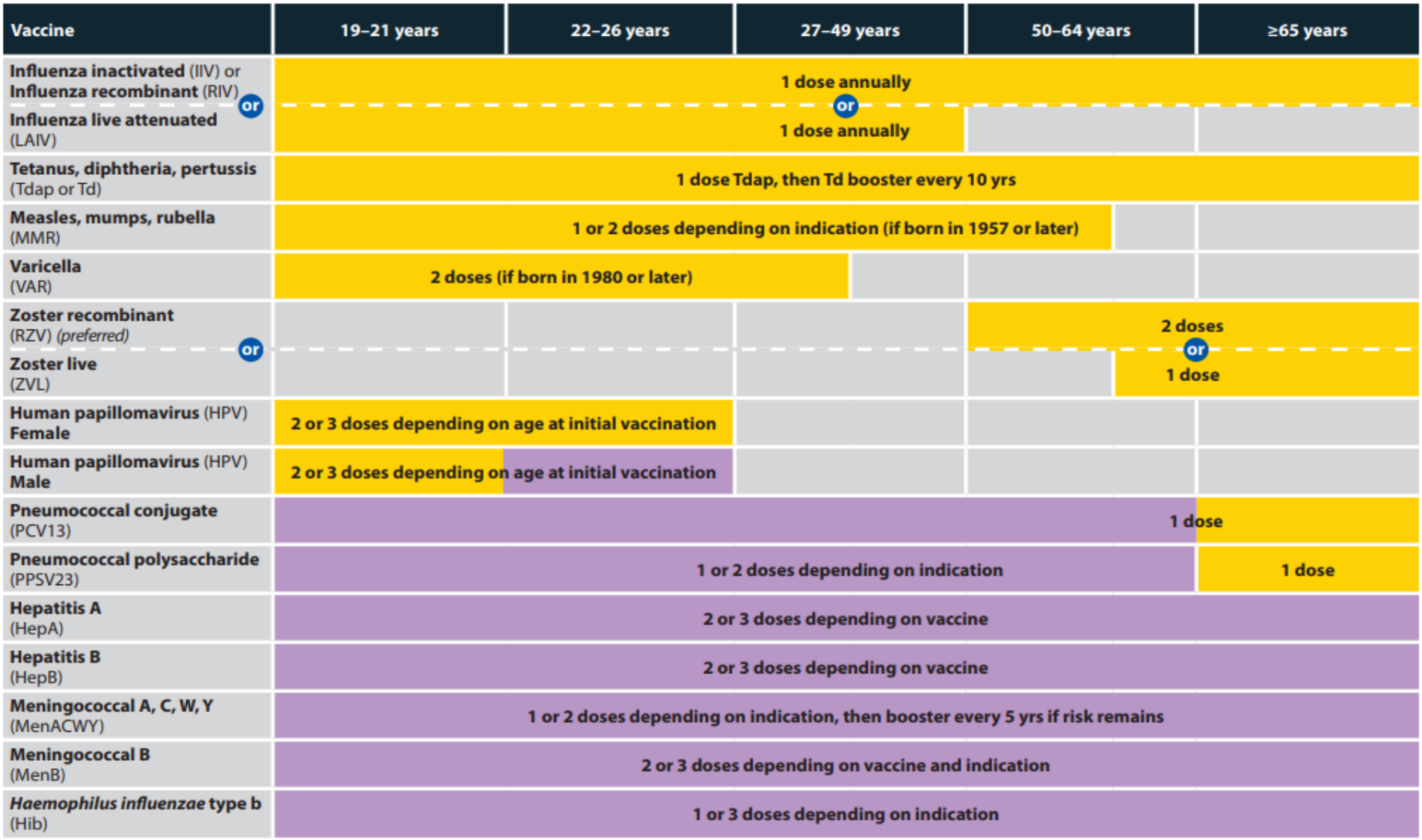
For more information, call toll-free
1-800-CDC-INFO (1-800-232-4636)
or visit
www.cdc.gov/vaccines/parents

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

AAFP
AMERICAN ACADEMY OF FAMILY PHYSICIANS

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Table 1 Recommended Adult Immunization Schedule by Age Group United States, 2019



MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports | July 23, 2010 / Vol. 59 / No. RR-6

Use of Anthrax Vaccine in the United States

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009

2010 ACIP Guidelines: Adverse Event Surveillance

- **Local Reactions**
  - 6,985 persons received 16,435 doses of AVA
  - Mild local reactions (<30 mm induration) occurred after 20%
  - Moderate local reactions (30-120 mm induration) occurred after 3%
  - Severe local reactions (>120 mm induration) occurred after 1%
- **Systemic Reactions**
  - occurred in <0.06% (4/~7000 vaccine recipients)

Nat. Comm. Dis Center. FDA No. DBS-IND. 1970.

vaers.hhs.gov/ — Vaccine Adverse Event Rep...

VAERS

Vaccine Adverse Event Reporting System
www.vaers.hhs.gov

Have you had a reaction following a vaccination?

1. Contact your healthcare provider.
2. Report an Adverse Event using the VAERS online form or the new downloadable PDF. ***New!***

Important: If you are experiencing a medical emergency, seek immediate assistance from a healthcare provider or call 9-1-1. CDC and FDA do not provide individual medical treatment, advice, or diagnosis. If you need individual medical or health care advice, consult a qualified healthcare provider.

¿Ha tenido una reacción después de recibir una vacuna?

1. Contacte a su proveedor de salud.
2. Reporte una reacción adversa utilizando el formulario de VAERS en línea o la nueva versión PDF descargable. ***Nuevo!***

What is VAERS?

16 a

Report an Adverse Event - Patient Information

Instructions | en Español

Note: Fields marked with an * are essential and should be completed.

Item 1

Patient first name:

Patient last name:

Street address:

City:

State: Select State

County:

Zip code:

Phone:

Email:

Item 2

* Date of birth (☑ mm/dd/yyyy or ☐ mm/yyyy)

mm/dd/yyyy

Item 3

* Sex:

○ Male ○ Female ○ Unknown

Item 4

VAERS Strengths and Limitations

Strengths

- National data; accepts reports from anyone
- Rapid signal detection
- Can detect rare AEs
- Collects information about vaccine, characteristics of vaccinee, AE*
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Cannot assess if vaccine caused an AE
- Pregnancy inconsistently reported

Some reports have no adverse event

2010 ACIP Guidelines: Adverse Event Surveillance

- **January 1, 1998-December 31, 2008**
  - Nearly 12.4 million doses of AVA distributed; <1% were distributed to nonmilitary sources
- **VAERS: 6,015 reports following AVA receipt**
  - 600 considered serious (i.e., death, hospitalization, or permanent disability)[1]
  - 74% in persons <40 years of age
  - 26% in women and 72% in men
  - 75% received AVA alone

1. 21 CFR. Sect 600.80. 2009

2010 ACIP Guidelines: Adverse Event Surveillance

- **800 MedDRA terms were reported in conjunction with AVA for 1998- 2008**
- **10 most common adverse events**
  - Arthralgia (17.2%)
  - Headache (16.3%)
  - Pruritus (14.6%)
  - Pain (13.7%)
  - Injection site erythema (12.5%)
  - Fever (10.9%)
  - Erythema (10.4%)
  - Injection site pain (10.2%)
  - Rash (10.1%)
  - Myalgia (9.7%)

Wasserman GM. *J Occup Environ Med*. 2003.

Adverse Events Reported to VAERS Following AVA, 1990-2007

- **Review of deaths and other serious reports following AVA receipt**
- **VAERS reports from January 1, 1990 through January 16, 2007**
  - 4753 filed
    - 4273 (90%) nonserious
    - 455 (9.6%) serious
    - 25 (0.5%) deaths

Niu, MT. *Vaccine*. 2009.

Adverse Events Reported to VAERs Following AVA, 1990-2007 (cont.)

- **Most commonly reported conditions**
  - Myalgia (39%)
  - Arthralgia (35%)
  - Pain (29%)
  - Headache (28%)
  - Depression (26%)
  - Asthenia (25%)
  - Rash, anxiety, and insomnia (24%)
  - Back pain (20%).
- **Conclusions:**
  - No serious adverse event definitely linked to AVA vaccination.
  - No causal relationship suggested for SAEs or death.

Niu, MT. *Vaccine.* 2009.

Adverse Events Reported to VAERS Following AVA, 2009-2017

- **VAERS:** From January 1, 2009 through June 30, 2017
- **2439 nonduplicate reports following AVA receipt**
  - 329 (13.5%) considered serious (i.e., death, hospitalization, or permanent disability)
  - 80% in persons < 40 years of age
  - 25% in women and 75% in men
  - 46% received AVA alone

Unpublished

Adverse Events Reported to VAERS Following AVA, 2009-2017 (cont.)

- **1770 MedDRA terms were reported in conjunction with AVA for 2009-2017**
- **10 most common adverse events**
  - Headache (14.7%)
  - Injection-site erythema (13.6%)
  - Pain (12.6%)
  - Fever (11.6%)
  - Fatigue (11.5%)
  - Arthralgia (11.2%)
  - Erythema (11.2%)
  - Pain at the injection site (9.9%)
  - Injection site swelling (9.8%)
  - Rash (9.4%)

Unpublished

STUDIES USING NON-VAERS DATA SOURCES

Serious Adverse Events in Studies with AVA, 2008-2016 (1 of 2 slides)

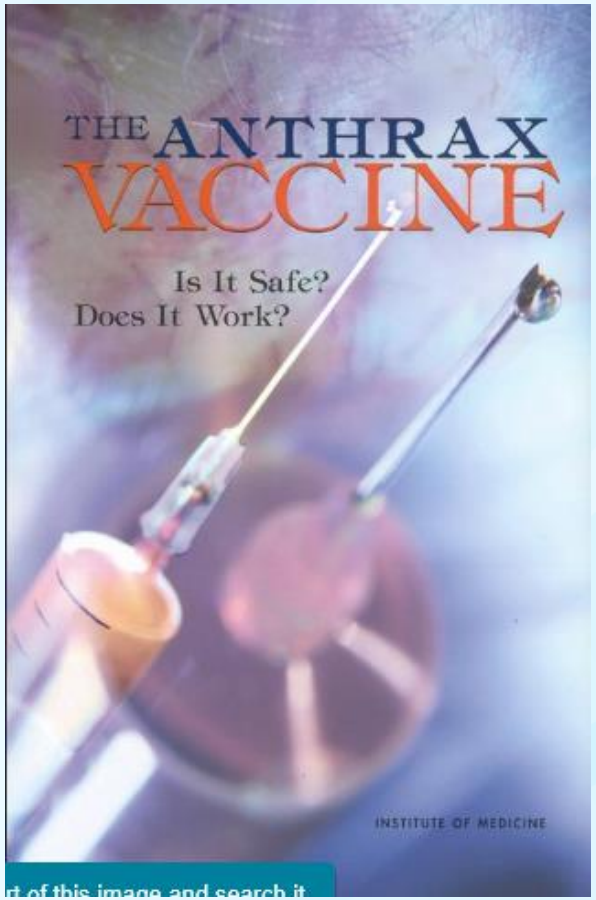
Author	Year	~AVA Doses (recipients x schedule)	Serious Adverse Events	Possibly Related to AVA
Zhang	2008	770	None	None
Rynkiewicz	2011	50	1	None
Hopkins	2013	40	None	None
Ionin	2013	800	None	None
Bernstein	2014	820	None	None

Serious Adverse Events in Studies with AVA, 2008-2016 (2 of 2 slides)

Author	Year	~ AVA Doses (recipients x schedule)	Serious Adverse Events	Possibly Related to AVA
Hopkins	2014	600	2	None
Wright*	2014	8320	231	6 (no deaths)
King	2015	950	None	None
Hopkins	2016	70	None	None

* AVA human clinical trial

2010 ACIP Guidelines: Adverse Event Surveillance



- No evidence that AVA recipients had a higher risk than the general population for life-threatening or permanently disabling adverse events immediately after receiving AVA
- The rates and types of immediate or short-term reactions comparable to those for other vaccines routinely administered to adults

Joellenbeck I. *Nat Acad Press*. 2002.

2010 ACIP Guidelines: Route of Administration & Adverse Events

- **AVRP Clinical Trial**
  - Injection site adverse events lower in the group receiving 4-intramuscular (IM) injections compared to the group receiving 4-subcutaneous (SC) injections

Marano N. *JAMA*. 2008

2010 ACIP Guidelines: Route of Administration & Adverse Events

- **Local reactions**
  - All local reactions (i.e., tenderness, erythema, warmth, induration, and subcutaneous nodules) were significantly more common after SC injections than after IM injections
- **Systemic adverse events**
  - Uncommon
  - Similar for intramuscular (IM) and subcutaneous (SC) routes of administration

Pittman PR. *Vaccine.* 2002.

2010 ACIP Guidelines: Long-Term Health Effects Following AVA Receipt

- **Department of Defense Studies (6 studies, 2002 – 2007):**[1,2,3,4,5,6]
  - No increase in cancer or infertility
- **Vaccine Analytic Unit**[7,8]
  - DMSS database
  - No increase in optic neuritis
  - No increased risk of hospitalization in military

1. Sulsky SI (disability). *J. Ocup Environ Med.* 2004.
2. Smith B. (health measures) *Am J. Prev Med.* 2007.
3. Rehme PA. (hospitalizations) *Vaccine.* 2002.
4. Downing J. (safety assessment by physican exam) *Mil Med.* 2002.
5. Pittman PR. (long-term health effects multiple vaccines). *Vaccine.* 2004.
6. Catherino WH. (semen, embryo). *Fertil Steril.* 2005.
7. Payne DC. (optic neuritis). *Arch Neurol.* 2006.
8. Payne DC (hospitalizations). *Ann. Epidemiol.* 2007.

Squalene Antibodies in Gulf War Veterans with Multisymptom Illness

- **Cohort study of Seabees who served from Sept. 1990 until time of survey in 1994**
  - 970 nondeployed
  - 527 Gulf War veterans
- **Squalene antibodies**
  - Were not associated with chronic multisystem illness
  - Were similar in deployed and nondeployed veterans
- **Conclusion:**
  - No association found between squalene antibody status and chronic multi-symptom illness.

Phillips CJ. *Vaccine*. 2009.

Disability Risk among Army Personnel Following AVA Receipt, 1998-2005

- **Cohort study**
  - Soldiers who received an anthrax vaccination December 15, 1997 through February 15, 2005
  - 1,001,546 soldiers with at least 1 dose of AVA
- **Data source:** Total Army Injury and Health Outcomes Database (TAIHOD)
- **Disabilities assessed:**
  - Musculoskeletal
  - Neurological
  - Respiratory
  - Mental
  - Digestive
  - Cardiac
  - Endocrine
  - Other

Sulsky SI. *Vaccine.* 2011.

Disability Risk among Army Personnel Following AVA Receipt, 1998-2005 (cont.)

- **Unadjusted rates**
  - Vaccinated 60/100,000
  - Unvaccinated 177/100,000
- **Conclusion:** No consistent patterns or statistically significant differences in risk of disability evaluation, disability determination, or reason for disability were associated with anthrax vaccination.

Sulsky SI. *Vaccine*. 2011.

Disability among US Army Veterans Following AVA Receipt

- **Case-control study**
  - Active duty personnel separated from the US Army
  - From December 1, 1997 through December 31, 2005
- **Data source:** TAIHOD and Veterans Benefit Administration (VBA) Compensation and Pension and Benefits database
- **Cases:**
  - ≥10% disabled according to Army (N=5,846)
  - or Veterans Benefits Administration (N=148,934)
- **Controls**
  - Separated without disability and not on VBA disability

Sulsky SI. *Vaccine.* 2012.

Disability among US Army Veterans Following AVA Receipt (cont.)

- **Results:**
  - After adjustment for covariates, Veterans who had been vaccinated against anthrax had lower odds of later receiving VBA benefits compared to those who had not been vaccinated
  - There was no association between prior vaccination against anthrax and odds of disability separation from the Army, overall
- **Conclusion:** Vaccination against anthrax is not associated with long-term disability

Sulsky SI. *Vaccine.* 2012.

Health-Related Quality of Life Following AVA Receipt

- **Cross-sectional study design – AVRP subjects**
  - 1562 participants from 5 study sites, 18-61 years of age
- **Health-related quality of life measured with the SF-36 health survey at 0, 12, 18, and 42 months after vaccination**
- **Outcomes:**
  - Mean physical and mental scores tended to decrease after baseline
  - No difference between the groups, including saline
- **Conclusion:** No association between receipt of AVA and altered quality of life over a 42-month period

Stewart B. *Vaccine.* 2012.

Type 1 Diabetes & AVA Receipt

- **Retrospective population-based cohort**
- **Data source:** Defense Medical Surveillance System
- **Active military, 17-35 year of age**
  - 2.3 million individuals followed for 7.6 million person years
  - Incident diabetes based on ICD-9 codes
  - 2002 – 2008
  - AVA exposure and type 1 diabetes
  - RR (1.0, 95% CI 0.85-1.1)
- **Conclusion:** No increased risk for AVA and type 1 diabetes

Duderstadt, SK. *Vaccine.* 2012

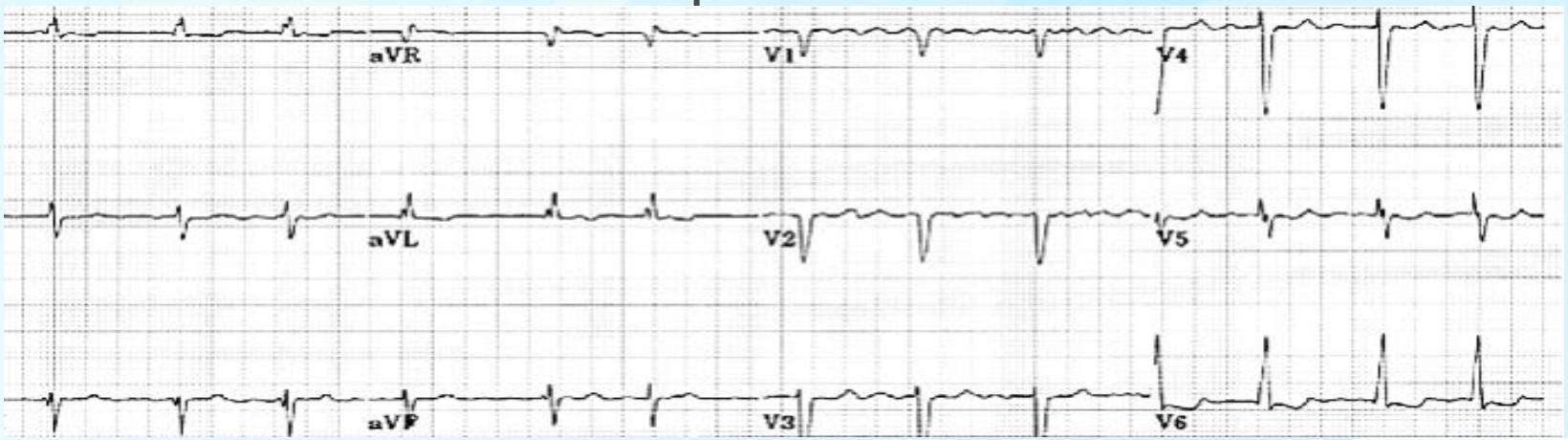
Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) & AVA Receipt

- **Matched case-control**
- **Data source:** Defense Medical Surveillance System
  - Inpatient and outpatient ICD-9 codes for RA and SLE
- **RA and receipt of AVA**
  - 1095 days – OR 1.0, 95% CI 0.5-2.2
  - 90 days OR 3.9, 95% CI 1.18-14.3
- **SLE and ever receipt of AVA –** OR 0.9, 95% CI 0.3-3.3
- **Conclusions:**
  - AVA associated with recent onset but not long term RA
  - No association with the number of doses
  - No association with SLE

Bardenheier, BH. *Military medicine.* 2016

Lone Atrial Fibrillation & AVA Receipt

- **Retrospective population based cohort**
- **2,957,091 individuals followed for 11,329,746 person-years**
- **2,435 with lone atrial fibrillation**
- **Conclusion:** No detectable association between atrial fibrillation and AVA receipt



McNeil, M. *Human Vaccines & Immunotherapeutics*. 2019

Pregnancy and Infant Health Outcomes among Women Who Received AVA

- **Retrospective cohort of women exposed to AVA**
- **Data source:** National Smallpox Vaccine in Pregnancy Registry
  - 155 smallpox vaccine (unexposed)
  - 308 AVA & smallpox vaccine (exposed)

Conlin, AM. *Vaccine*. 2015

Pregnancy and Infant Health Outcomes among Women Who Received AVA (cont.)

- **Results:** Compared to military exposed to neither vaccine, both the unexposed and exposed groups had
  - Similar fetal outcomes: ectopics, elective and spontaneous abortions, and stillbirths
  - Similar infant health outcomes: preterm births, low birth weight, mean birth weight, male sex, and major birth defects.

Conlin, AM. *Vaccine*. 2015

Birth Defects among Infants Born to Military Women Who Received AVA in Pregnancy

- **Retrospective cohort of infants born to military women from 2003 – 2010**
- **Data source:** DoD Birth and Infant Health Registry
- **ICD-9 coded birth defects**
  - 126,839 liveborn infants

Conlin AMS. *Vaccine*. 2017

Birth Defects among Infants Born to Military Women Who Received AVA in Pregnancy (cont.)

- **Covariates in multivariable model**
  - Birth year,
  - Infant sex,
  - Plurality
  - Maternal
  - Age at delivery
  - Race/ethnicity
  - Marital status
  - Occupation
  - Military service branch
  - Rank
  - Reserve status
  - Deployment during pregnancy & amount of time deployed
  - Other potentially risky vaccinations in first trimester

Conlin AMS. *Vaccine*. 2017

Birth Defects among Infants Born to Military Women Who Received AVA in Pregnancy (cont.)

- **After adjustment, AVA receipt during first trimester vs**

Comparison Time period	Odds Ratio	Confidence Interval
Any other time	1.1	(0.93 – 1.29)
Prepregnancy	1.05	(0.88 – 1.24)
Postpregnancy	1.17	(0.97 – 1.43)
Never	1.03	(0.86 – 1.23)

- **Conclusions:** No strong associations between AVA vaccination during pregnancy and birth defects risk were observed.

Conlin AMS. *Vaccine*. 2017

Summary of Studies Since 2010 ACIP Guidelines

Risk of Morbidity in AVA Recipients

Author	Published	Outcome	Conclusion
Phillips	2009	squalene	No association between squalene Ab and chronic multi-symptom illness
Sulsky	2011	disability	No difference in risk of disability
Sulsky	2012	disability	vaccination against anthrax is not associated with long term disability
Stewart	2012	quality of life	No effect
Duderstadt	2012	type I diabetes	No increased risk of type 1 diabetes
Bardenheier	2016	rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)	• short-term (3 month), but not long-term (3 year) increased risk for RA • no association with number of doses • no association with SLE
McNeil	2019	Lone atrial fibrillation	No detectable risk
Conlin	2015	birth defects	Rates of birth defects and preterm births were similar among exposed and unexposed
Conlin	2017	birth defects	No strong associations between inadvertent AVA vaccination during pregnancy and birth defects risk

Conclusion

- **Summary:** No significant safety concerns since December 2008 based on VAERS or the published literature

Questions?

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