Anthrax Vaccine Adsorbed (AVA): Safety

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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/
# 2019 Recommended Immunizations for Children from Birth Through 6 Years Old

<table>
<thead>
<tr>
<th>Age</th>
<th>Birth</th>
<th>1 month</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>19–23 months</th>
<th>2–3 years</th>
<th>4–6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines</td>
<td>HepB</td>
<td>HepB</td>
<td>RG</td>
<td>DTaP</td>
<td>Hib</td>
<td>PCV13</td>
<td>IPV</td>
<td>IPV</td>
<td>Fluenza (Yearly)*</td>
<td>MMR</td>
<td>Varicella</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

**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.

![Baby icon]

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

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**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.

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

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

American Academy of Pediatrics
Dedicated to the health of all children

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See back page for more information on vaccine-preventable diseases and the vaccines that prevent them.
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>19–21 years</th>
<th>22–26 years</th>
<th>27–49 years</th>
<th>50–64 years</th>
<th>≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza inactivated (IIV) or</td>
<td></td>
<td></td>
<td>1 dose annually</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza recombinant (RIV)</td>
<td></td>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza live attenuated (LAIV)</td>
<td></td>
<td></td>
<td>1 dose annually</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Tdap or Td)</td>
<td></td>
<td></td>
<td>1 dose Tdap, then Td booster every 10 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella (MMR)</td>
<td></td>
<td></td>
<td>1 or 2 doses depending on indication (if born in 1957 or later)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella (VAR)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Zoster recombinant (RZV) (preferred)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 doses</td>
</tr>
<tr>
<td>Zoster live (ZVL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or 1 dose</td>
</tr>
<tr>
<td>Human papillomavirus (HPV) Female</td>
<td></td>
<td></td>
<td>2 or 3 doses depending on age at initial vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (HPV) Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 or 3 doses depending on age at initial vaccination</td>
</tr>
<tr>
<td>Pneumococcal conjugate (PCV13)</td>
<td></td>
<td></td>
<td></td>
<td>1 dose</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal polysaccharide (PPSV23)</td>
<td></td>
<td></td>
<td></td>
<td>1 dose</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A (HepA)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B (HepB)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Meningococcal A, C, W, Y (MenACWY)</td>
<td></td>
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</tr>
<tr>
<td>Meningococcal B (MenB)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b (Hib)</td>
<td></td>
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</tr>
</tbody>
</table>

- Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
- Recommended vaccination for adults with an additional risk factor or another indication
- No recommendation

| 12 |
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)

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. 

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. Contácte a su proveedor de salud.
2. Reporte una reacción adversa utilizando el formulario de VAERS en línea o la nueva versión PDF descargable. 

What is VAERS?
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
### VAERS Strengths and Limitations

<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>National data; accepts reports from anyone</td>
<td>Reporting bias</td>
</tr>
<tr>
<td>Rapid signal detection</td>
<td>Inconsistent data quality and completeness</td>
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<td>Can detect rare AEs</td>
<td>Lack of unvaccinated comparison group</td>
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<tr>
<td>Collects information about vaccine, characteristics of vaccinee, AE*</td>
<td>Cannot assess if vaccine caused an AE</td>
</tr>
<tr>
<td>Data available to public</td>
<td>Pregnancy inconsistently reported</td>
</tr>
</tbody>
</table>

*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

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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%)

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.

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%)
STUDIES USING NON-VAERS DATA SOURCES
### Serious Adverse Events in Studies with AVA, 2008-2016

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>~AVA Doses (recipients x schedule)</th>
<th>Serious Adverse Events</th>
<th>Possibly Related to AVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang</td>
<td>2008</td>
<td>770</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Rynkiewicz</td>
<td>2011</td>
<td>50</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Hopkins</td>
<td>2013</td>
<td>40</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ionin</td>
<td>2013</td>
<td>800</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bernstein</td>
<td>2014</td>
<td>820</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
## Serious Adverse Events in Studies with AVA, 2008-2016 (2 of 2 slides)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>~ AVA Doses (recipients x schedule)</th>
<th>Serious Adverse Events</th>
<th>Possibly Related to AVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hopkins</td>
<td>2014</td>
<td>600</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>Wright*</td>
<td>2014</td>
<td>8320</td>
<td>231</td>
<td>6 (no deaths)</td>
</tr>
<tr>
<td>King</td>
<td>2015</td>
<td>950</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hopkins</td>
<td>2016</td>
<td>70</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

* 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.

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

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

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.

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 Sl. 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.

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

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
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
After adjustment, AVA receipt during first trimester vs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Time period</th>
<th>Odds Ratio</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any other time</td>
<td>1.1</td>
<td>(0.93 – 1.29)</td>
</tr>
<tr>
<td></td>
<td>Prepregnancy</td>
<td>1.05</td>
<td>(0.88 – 1.24)</td>
</tr>
<tr>
<td></td>
<td>Postpregnancy</td>
<td>1.17</td>
<td>(0.97 – 1.43)</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>1.03</td>
<td>(0.86 – 1.23)</td>
</tr>
</tbody>
</table>

Conclusions: No strong associations between AVA vaccination during pregnancy and birth defects risk were observed.
## Summary of Studies Since 2010 ACIP Guidelines

### Risk of Morbidity in AVA Recipients

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

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