Adverse Events Associated With Vaccination

How Vaccines Cause Adverse Events
Neal A. Halsey

Will not address:
Alleged adverse events
Causality assessment
Multiple past mistakes
Pathogenesis of Adverse Events Caused by Vaccines

1. Injection process
2. Contamination
3. Replication of live agent
4. Direct effect of vaccine component
5. Host immune response to component
6. Unknown
Injections alone can trigger serious adverse events
Syncope per 1000 Vaccines Visits Following Td, Tdap, Menactra, and Varicella

Syncope per 1,000 Vaccines

Calendar Year Groups

96-98 99-01 2002-04 2005-June 06 concurrent: 8/06 to wkst 6/29/08

9 to 10
11 to 12
13 to 14
15 to 17
18 to 21
22 to 26

J. Gee VSD report ACIP Oct 2008
Injection Related: Fainting

- Falls can lead to serious head injuries
- Neurologic sequelae, rare deaths
- Auto accidents
Incorrect Injection Site

Ulnar nerve damage following anthrax Vaccine*

Incorrect administration of TT - wrong site
Appropriate IM Injection Sites

**IM site for infants**

Insert needle at a 90° angle into the anterolateral thigh muscle.

**IM site for children (after the 1st birthday) and adults**

Insert needle at a 90° angle into the thickest portion of deltoid muscle—above the level of the axilla and below the acromion.

Adapted by the Immunization Action Coalition, courtesy of the Minnesota Department of Health.
Respiratory Arrest Following Measles Vaccine

- Latin America, Asia, Africa
- Succinyl choline and pancuronium bromide mistaken as vaccine diluent
- Diluent and drug vials identical size, color, and print type. Stored in same refrigerator
10 Dose Measles Vaccine Vial plus Diluent
Bacterial Contamination of Measles Vaccine Vials: India 1985-1994

- Multi-dose vials
- 39 clusters of fever, rash, shock: day of vaccination
- 81 deaths
- Bacterial contamination after reconstitution
  - Staph aureus and other

Prevention: discard vials after 2 (WHO 6) hours. Sterile syringe and needle for reconstituting. Smaller (5 dose) vials now used in most of India

### Group A Streptococcal Infections From 15-dose DTP Vials: U.S.

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indiana</td>
<td>1981</td>
<td>7</td>
</tr>
<tr>
<td>Georgia</td>
<td>1982</td>
<td>12</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>1982</td>
<td>7</td>
</tr>
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Source: Bernier et al  
Contamination of Multi-dose vials Associated with Severe Disease

- Measles
- DTP
- Yellow fever
- BCG
Injection Related Serious Adverse Events

1. Fainting-head injury
2. Injury to tissue: e.g. Nerve, joint
3. Inappropriate diluents
4. Contamination of multi-dose vials
5. Bleeding
6. Transmission of blood-borne pathogens
   • Inappropriate reuse of needles and syringes
7. Provocation polio: incubating WT polio
   • Increased risk of paralysis in injected limb
Vaccine Factors Associated With Adverse Events

1. Type: live vs. killed vs subcomponent
2. Strain
3. Attenuation
4. Dose
5. Adjuvants
6. Preservatives
7. Stabilizers
8. Purity:
   • contamination
   • extra products in vaccine
Bacterial Structure

http://www.bact.wisc.edu/Bact330
Adverse Events Following Whole Cell and Acellular Pertussis Vaccines Days 0-3 (DTwP vs DTaP)

- Fever >38.4
- Swelling >20mm
- Pain
- Fussiness

Percent With Reaction

Decker Pediatrics 96:557;1995
Limb Swelling After 4th Dose of DTaP

Pathogenesis unknown

Edmonston B Measles Vaccine

1954

24 passages human kidney tissue

28 passages primary human amnion tissue

6 passages chick embryos

Chick embryo cells

Vaccine 1963
Fever and Rash Following Measles Vaccination With and Without Immune Globulin (GG)

- **Natural Measles (33)**
- **Edmonston "B" No GG (175)**
- **Edmonston "B" + GG 0.01-0.02 ml/LB (854)**
- **Further Attenuated No GG (569)**
- **Further Attenuated GG 0.2 ml (452)**

Krugman 1965
Percent of Children with Fever Following Edmonston B Measles Vaccine (1963)

Adapted from Martin CM. Am J of Dis of Children 1963;106:270.
Percent of Children with Fever by Week after First or Second Dose of MMR

LeBaron, C. W. et al. Pediatrics 2006;118:1428
# Transient Arthritis/Arthralgia Associated With Rubella Vaccines in Women by Strain

<table>
<thead>
<tr>
<th>Vaccine Strain</th>
<th>Joint Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-77 Dog kidney</td>
<td>35-63%</td>
</tr>
<tr>
<td>HPV 77 duck embryo</td>
<td>27-33%</td>
</tr>
<tr>
<td>Cendehill</td>
<td>8-10%</td>
</tr>
<tr>
<td>RA 27/3</td>
<td>13-15%</td>
</tr>
</tbody>
</table>

Polk Am J Epidemiol 115:19;1982
Host Factors
Joint Symptoms Associated With HPV-77 Rubella Vaccine in Females by Age

Weibel JAMA 202:805;1972
Swartz Am J Epidem 94:246;1971
### Arthritis Associated With RA 27/3

#### Rubella Vaccines by Gender

<table>
<thead>
<tr>
<th>Age(yrs)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>5%</td>
<td>20-25%</td>
</tr>
</tbody>
</table>

**Arthralgia**: females > males:
- Anthrax
- Lyme disease
- Yellow fever vaccines
Pathogenesis of Joint Symptoms Following Rubella Vaccines

- HPV-77 vaccine virus in joint fluid
  - RA 27/3?
- Arthralgia pathogenesis?
  - Cytokine mediated?
  - Also with inactivated vaccines
Host Related Factors Associated With Adverse Events

- Age
- Gender
- Prior doses of vaccine
- Prior infection with agent
- Skin color
- Preexisting hypersensitivity
- Immune deficiency
- Genetics
Immediate Hypersensitivity Reactions

- Hives, angioedema, anaphylaxis
- IgE mediated
- Allergens in vaccines:
  - Media (e.g. egg in influenza or YF)
  - Gelatin
  - Antibiotics (neomycin, polymixin)
  - Yeast (hepatitis B, HPV)
  - Preservatives (thimerosal)

www.allergycapital.com

www.vaccinesafety.edu/components-Allergens
Delayed Hypersensitivity: Erythema Multiforme after Smallpox Vaccine

Vincent A. Fulginiti, M.D.
10 days after varicella vaccine

Do vaccines cause serum sickness?
Course of the Platelet Count after Measles Immunization in 5 Infants


Clinical thrombocytopenia (ITP) ~1/30,000

Repeated Depression of Platelet Count After 3 Separate Vaccinations in the Same Infant

Guillain-Barre syndrome relative risks for population over 17 years by week of onset after A/New Jersey influenza vaccination, US 10/3/76 - 1/29/77*

- excluding AR, CT, DE, WA. Data for CA, FL, GA, MO, NC, NJ, NY
- and TX included for 10/3-12/18/76 only.
Action potentials propagated along the nerve fibre.

GBS: Demyelinating: Axonal: antibodies terminate action potential propagation.
Attributable Risk of GBS following influenza vaccine

- **1976-1977**: $1/100,000$
- **1978-1991**: 0
- **1992-1994**: $\sim 1/1,000,000^*$
- **1995-2008**: ?
- **2009-10 (H1N1)**: ?

*“Swine influenza”*  

Chen NEJM 1998
Enhancement of the Target Disease
Inactivated Respiratory Syncytial Virus Vaccine: 1960’s

- Formalin inactivated
- Administered to infants
- Minimal reactions
- Induced neutralizing antibody

Kapikian AZ. Amer. J. Epid., 1969, 89:405-21
Kim HW et al 1969
Enhanced RSV Disease 9-10 Months Following Inactivated RSV Vaccine

<table>
<thead>
<tr>
<th></th>
<th>RSV Vaccine</th>
<th>No Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>9/13 (69%)</td>
<td>4/47(9%)</td>
</tr>
<tr>
<td></td>
<td><em>p</em> &lt; .001</td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>80%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td><em>p</em> &lt; .001</td>
<td></td>
</tr>
</tbody>
</table>

Kapikian AZ. Amer. J. Epid., 1969, 89:405-21
Kim HW et al 1969
Formalin Inactivated (Killed) Measles Vaccine

- Licensed 1963
- Administered in 3 doses
- Induced HI antibody responses (protective)
- Protected against measles for up to 2 yrs
Atypical Measles in Child Who Received Killed Measles Vaccine 12 Years Earlier
Increased Rates of Pneumonia in Atypical Measles

Figure 2. Chest roentgenogram of an 18-year-old boy (Patient 1) with atypical measles showing right lower lobe infiltrate and cardiac silhouette.
Animal Model for Atypical Measles
Rhesus Macaques

- Immune complexes and eosinophils in lungs of animals with atypical measles
- Waning protection from neutralizing antibody following formalin inactivated vaccine
- No cytotoxic T-cell response

Polack et al. Nat Med. 1999 :629-34
Differences in Rates of Hospitalization between Live and Inactivated Vaccine by Age and History of Wheezing Illness before Vaccination

Rotavirus Vaccines

- Rhesus “Rotashield” (RRV)
- Bovine “Rotateq” (RV5)
- Human “Rotarix” (RV1)
Intussusception after Rhesus Rotavirus Vaccine

Pathogenesis
Unknown

No increased risk with RV5 or RV1?

Administered at younger age.

Live Vaccines: Unrecognized immune Deficiencies

- Innate immune system
- B cell deficiency
- HIV infection
- Severe Combined Immune Deficiency
Delayed Onset of Severe Adverse Events Following Live Attenuated Measles Vaccines

- Pneumonia in children with leukemia or patient with AIDS: 3-9 mo.

- Inclusion body encephalitis: 5 wk - 6 mo.
Yellow Fever Vaccine-Associated Viscerotropic Disease

- Onset 2-5 days post-vaccination
- Fever, myalgia, arthralgia
- Elevated liver enzymes & bilirubin
- Thrombocytopenia, lymphocytopenia
- Rhabdomyolysis
- Hypotension
- Renal failure
- Respiratory failure
- CFR >50%

Vaccine virus isolated from liver and lung tissue.
Pathology consistent with YF.

Michelle Russell, MPH
Age Related Complications
Yellow Fever Vaccine Associated Encephalitis

- >9 months ~1/million
- < 4 months 0.4-5/1000
  - 1000 fold increase

Monath in Plotkin and Orenstein  Vaccines 2004
Yellow Fever Vaccine Transmitted via Breast Feeding: Brazil

- Mother: YF vaccine 15 days post partum
- Infant: At 23 days developed seizures, lethargy, poor feeding
  - CSF: 128 wbc
  - 17DD YF vaccine virus by PCR in CSF
  - YF specific IgM antibody in sera and CSF
- Infant recovered completely

In U.S. ACIP updating recommendations
Breastfeeding likely to be a relative contraindication
WHO no comment yet
Oral Polio Vaccine
OPV-Associated Paralytic Poliomyelitis
VAPP

• One case per 750,000 first doses
• Recipients and close contacts
• 250-500 cases per year globally
• Host or selection of more virulent virus?
• >1000 fold Increased risk in patients with B cell immunodeficiency
Provocation Poliomyelitis
Association Between Numbers of Injections in Preceding 30 Days and VAPP: Romania

Polio Incidence in USA, 1964-2004 and Vaccine Associated Paralytic Poliomyelitis (VAPP)

Reported Cases

Year

Last wild poliovirus case

IPV/OPV or OPV

IPV

Polio Eradication

iVDPV: Prolonged Excretion of Type 1 Poliovirus Vaccine 7 years After OPV: 1981 U.S.

Years of Age

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

IPV x 3  OPV   OPV  OPV  CVID  Paralysis

Long-Term Poliovirus Excretors (iVDPVs: 1° immunodeficiency-associated VDPVs)

39 iVDPVs (> 6 mos excretion)

2 known to excrete >5 years.

Type 2 > Type 1 > Type 3

From:
- Industrialized countries (23)
- Middle income countries (15)
- Low income countries (1)

Immunodeficiencies linked to prolonged poliovirus excretion

- cvid
- agamma
- ab deficient
- scid
- hypogamma
- ICF
- MHC-II def
- XLA
- unknown

Unknown immunodeficiencies linked to prolonged poliovirus excretion
Total 11 outbreaks
2009 Ongoing:
Nigeria
DR Congo
Ethiopia

>300 cases

SOURCE: WHO POLIO LABNET
Smallpox Vaccine

WHO
Lesions during the first week of disseminated disease (day 5)

Extensive scarring of the resolving lesions after 9 weeks of passive immunotherapy.

Eczema Vaccinatum in Contact of Vaccinee

Vincent A. Fulginiti

Courtesy Mike Lane
BCG Vaccination Often at Birth

BCG Interdental Vaccination

www.satvi.uct.ac.za
Lymphadenitis after BCG

Differences in rates by vaccine strain and technique

Bolger Arch Dis Child 2006
### Age-Specific Estimated Risks for Complications After Administration of BCG Vaccine

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence per 1 Million Vaccinations</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Age &lt;1 yr</td>
</tr>
<tr>
<td>Local subcutaneous abscess, regional lymphadenopathy</td>
<td>387</td>
</tr>
<tr>
<td>Musculoskeletal lesions</td>
<td>0.39− 0.89</td>
</tr>
<tr>
<td>Multiple lymphadenitis, nonfatal disseminated lesions</td>
<td>0.31− 0.39</td>
</tr>
<tr>
<td>Fatal disseminated lesions</td>
<td>0.19− 1.56</td>
</tr>
</tbody>
</table>

Risk of Disseminated BCG

- **HIV uninfected Infants:** ~ 1/million
  - IFN-gamma-receptor deficiency
  - Other undefined innate immunity defects?

- **HIV infected:** 110-417/100,000
  - >1000 fold increased risk
  - Often delayed several months

Hesseling *Vaccine*. 2007 Jan 2;25(1):14-8
7 Cases of Persistent Rotavirus Vaccine and SCID

- Present at 3-6 months of age
- Persistent diarrhea and growth failure
- Treat with Bone Marrow Transplant

Catherine Yen ACIP Feb 2010
Patel abstracts, J Allergy Clin Immunol (2009)
U.S. Considering Newborn Screening for SCID

- Advisory Committee for Heritable Disorders in Newborns and Children recommended
- Under consideration
- Adenosine deaminase deficiency
Theoretical Risks

• More challenging
March 22, 2010 US FDA Calls for Temporary Suspension of RotaRix

- Porcine circovirus 1 DNA in vaccine
- Not known to cause disease
European Medicines Agency statement on new information on Rotarix oral vaccine

The European Medicines Agency is aware of new information reported by the manufacturer of Rotarix, GlaxoSmithKline Biologicals, relating to the unexpected presence of DNA of a non-disease causing viral strain in batches of the oral vaccine. Through its own tests, the company has confirmed the finding of DNA originating from porcine circovirus type 1. This virus is commonly found in certain meat and other food products, and is not known to cause disease in either animals or humans.
Conclusions

1. All vaccines can cause adverse events
2. Multiple pathogenic mechanisms, some not yet defined
3. New vaccines will result in new questions and adverse events
4. Good post-marketing surveillance essential for monitoring vaccine safety