Vaccine Safety Processes: Pre-Post Licensure Trials & Monitoring

Dean A. Blumberg, MD, FAAP

- Disclosure
  - clinical research grants: Novartis
  - speakers bureau: sanofi pasteur, Merck

- Discussion
  - vaccines not approved by FDA
  - “off label” use of FDA approved vaccines
Vaccine Safety Processes: Pre-Post Licensure Trials & Monitoring

- Vaccine development
- Vaccine licensure
- Safety monitoring
- Concerns
- Hesitancy
- AB2109
- Addressing hesitancy
Vaccine Development

- Identify causative organism
- Understand biology and pathogenesis of disease agent
- Purify the organism
- Develop vaccine
- Test vaccine
- Manufacture product
- Deliver vaccine to target population
Vaccine Regulation--Premarketing Phase: Investigational New Drug (I)

- **Preclinical**
  - laboratory characterization
  - animal testing

- **Phase I**
  - initial testing in humans
    - adult volunteers
  - small number of subjects
  - primary concern: safety
Vaccine Regulation--Premarketing Phase: Investigational New Drug (II)

- **Phase II**
  - larger studies
  - target population
  - safety
  - immunogenicity

- **Phase III**
  - larger studies
  - more thorough assessment of safety
  - efficacy
Vaccine Regulation: License Application

- FDA review
  - vaccine study data
    » safety and efficacy
  - manufacture
    » plant evaluation
    » production protocols
    » quality testing
Vaccine Regulation: Postmarketing Phase

- Studies for additional indications
- Continued surveillance of vaccine lots
- Continued inspection of production facilities
- Adverse reaction reports
### Vaccine-Preventable Diseases: Baseline 20th Century & Current Morbidity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Baseline</th>
<th>2013</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164</td>
<td>0</td>
<td>100.00</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885</td>
<td>0</td>
<td>100.00</td>
</tr>
<tr>
<td>Measles</td>
<td>503,282</td>
<td>187</td>
<td>99.96</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209</td>
<td>584</td>
<td>99.62</td>
</tr>
<tr>
<td>Pertussis</td>
<td>147,271</td>
<td>28,639</td>
<td>80.55</td>
</tr>
<tr>
<td>Polio (par.)</td>
<td>16,316</td>
<td>1</td>
<td>99.99</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>9</td>
<td>99.98</td>
</tr>
<tr>
<td>CRS</td>
<td>823</td>
<td>1</td>
<td>99.88</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1,314</td>
<td>26</td>
<td>98.02</td>
</tr>
<tr>
<td>Hib</td>
<td>20,000</td>
<td>26</td>
<td>99.87</td>
</tr>
</tbody>
</table>

MMWR 1999;48:245, 2014;63(32)
Post-Licensure Vaccine Safety Monitoring

- CDC/FDA
  - Vaccine Adverse Events Reporting System (VAERS)
  - Vaccine Safety Datalink (VSD)

- Manufacturer
  - Post marketing studies
Vaccine Adverse Events Reporting System (VAERS)

- National post-licensure safety surveillance system jointly operated by CDC and FDA
- Spontaneous reporting system in existence since 1990
  - reports submitted by clinicians, manufacturers, patients/parents and others
- Subject to well-described limitations of passive surveillance
VAERS

- **Advantages**
  - covers US population
  - permits monitoring for known adverse events
  - detects signals for previously unrecognized / rare adverse events
  - generates hypothesis

- **Limitations**
  - risk of underreporting or overreporting
  - incomplete data
  - lack of availability of denominator data
VAERS HPV Data: Venous Thromboembolism

- Total reports: 65; US reports: 41
  - Pending evaluation: 6; Unable to follow-up or “no case”: 17
  - Confirmed cases: 18
    » Hormonal contraception current use (n=14)
      • 12 cases – Oral Contraceptive Pills
      • 2 cases on Nuvaring (increase risk of clots)
      • Some have additional risk factors
    » No hormonal contraception use (n=4)
      • 1 case of pregnancy
      • 1 case obesity, smoking, truck driver
      • 1 case long bus ride preceded to the VTE onset
      • 1 case had no reported risk factors
Vaccine Safety Datalink (VSD)
# Rapid Cycle Analysis, VSD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure window (days)</th>
<th>Medical Setting</th>
<th>Signal?</th>
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<tbody>
<tr>
<td>Guillain Barré Syndrome (GBS)</td>
<td>1 to 42</td>
<td>All</td>
<td>NO</td>
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<tr>
<td>Seizures</td>
<td>0 to 42</td>
<td>Inpatient, ED</td>
<td>NO</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>All</td>
<td>NO</td>
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<tr>
<td>Appendicitis</td>
<td>0 to 42</td>
<td>Inpatient, ED</td>
<td>NO</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 to 42</td>
<td>Inpatient, ED</td>
<td>NO</td>
</tr>
<tr>
<td>Venous Thromboembolism (VTE)</td>
<td>1 to 42</td>
<td>All</td>
<td>NO</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0 to 2</td>
<td>All</td>
<td>NO</td>
</tr>
<tr>
<td>Other Allergic rxns</td>
<td>0 to 2*</td>
<td>All</td>
<td>NO</td>
</tr>
</tbody>
</table>
Clinical Immunization Safety Assessment (CISA) Project

CISA's Clinical Immunization Safety Assessment (CISA) Project was established in 2001 to address the unmet vaccine safety clinical research needs of the United States.

CISA is a national network of vaccine safety experts from the CDC's immunization safety office (ISO), seven medical research centers, and other partners, which provides a comprehensive vaccine safety public health service to the nation.

To request a CISA Clinical Consultation:
If you are a US healthcare provider with a vaccine safety question about a specific patient residing in the US, you can contact CISA at CISAeval@cdc.gov to request a case evaluation. This service is provided free of charge. View here for more information.

Current CISA Project Sites

- Boston Medical Center
- Cincinnati Children’s Hospital Medical Center
- Columbia University
- Duke University
- Johns Hopkins University
- Kaiser Permanente Northern California
- Vanderbilt University
Vaccine Adverse Event Myths

- No credible scientific evidence that vaccines cause:
  - autism
  - multiple sclerosis
  - diabetes
  - asthma
  - inflammatory bowel disease
  - SIDS
  - overwhelm immune system
Parental Vaccine Safety Concerns

Freed et al, Pediatr 2010;125:654
Overwhelm Immune System?

- Infant immune system
  - naïve
  - can respond to thousands of antigens simultaneously
- Challenges other than vaccines
  - natural environmental exposures
    - strep throat: >50 antigens
    - otitis media: >2,000 antigens
## Number of Immunogens in Vaccines

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine</th>
<th>Immunogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>Smallpox</td>
<td>~200</td>
</tr>
<tr>
<td></td>
<td>Diphtheria</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tetanus</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pert-WC</td>
<td>~3000</td>
</tr>
<tr>
<td></td>
<td>Polio</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>~200</td>
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<table>
<thead>
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<tr>
<td>1960</td>
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<tr>
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<td>Diphtheria</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tetanus</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pert-WC</td>
<td>~3000</td>
</tr>
<tr>
<td></td>
<td>Polio</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>~3217</td>
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</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine</th>
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<tbody>
<tr>
<td>1980</td>
<td>Diphtheria</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tetanus</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pert-WC</td>
<td>~3000</td>
</tr>
<tr>
<td></td>
<td>Polio</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Measles</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Mumps</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>~3041</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Year</th>
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<th>Immunogens</th>
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<tbody>
<tr>
<td>2014</td>
<td>Diphtheria</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tetanus</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pert-AC</td>
<td>2-5</td>
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<tr>
<td></td>
<td>Polio</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Measles</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Mumps</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>2</td>
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<tr>
<td></td>
<td>Varicella</td>
<td>69</td>
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<td></td>
<td>PCV</td>
<td>14</td>
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<td></td>
<td>Hepatitis B</td>
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<tr>
<td></td>
<td>Hepatitis A</td>
<td>1</td>
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<tr>
<td></td>
<td>MCV</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>RV</td>
<td>2-7</td>
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<tr>
<td></td>
<td>HPV</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Influenza*</td>
<td>6-114</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>142-258</td>
</tr>
</tbody>
</table>

*Influenza yearly, new strains every year

Offit et al, Pediatrics 2002;109:124
Thimerosal Concerns: Neurotoxin?

- Thimerosal
  - preservative
  - ethylmercury
- Toxicity data
  - methylmercury
- 7 well done studies
  - methods
    » both retrospective & prospective
    » ecological & cohort
    » several 100,000 children
  - results: no association
## Thimerosal Content: US Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Thimerosal Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td>Tripedia®</td>
<td>Sanofi Pasteur</td>
<td>≤0.00012%</td>
</tr>
<tr>
<td></td>
<td>Infanrix®</td>
<td>GlaxoSmithKline</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Daptacel®</td>
<td>Sanofi Pasteur</td>
<td>0</td>
</tr>
<tr>
<td>DTaP-HepB-IPV</td>
<td>Pediariix®</td>
<td>GlaxoSmithKline</td>
<td>0</td>
</tr>
<tr>
<td>Tdap</td>
<td>Adacel®</td>
<td>Sanofi Pasteur</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Boostrix®</td>
<td>GlaxoSmithKline</td>
<td>0</td>
</tr>
<tr>
<td>Haemophilus influenzae type b conjugate (Hib)</td>
<td>ActHIB®</td>
<td>Sanofi Pasteur</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PedvaxHIB®</td>
<td>Merck &amp; Co, Inc</td>
<td>0</td>
</tr>
<tr>
<td>Hib/Hepatitis B combo</td>
<td>Comvax®</td>
<td>Merck &amp; Co, Inc</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Engerix B®</td>
<td>GlaxoSmithKline</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Recombivax HB®</td>
<td>Merck &amp; Co, Inc</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis A/Hepatitis B</td>
<td>Twinrix®</td>
<td>GlaxoSmithKline</td>
<td>&lt;0.0002%</td>
</tr>
<tr>
<td>Influenza*</td>
<td>Various</td>
<td>Various</td>
<td>Varies</td>
</tr>
</tbody>
</table>
Aluminum Concerns

- Aluminum in vaccines
  - adjuvant
  - maximum amount 0.85 mg/dose

- Aluminum exposure
  - deodorant
  - food
    » adults average 7-9 mg/day
    • 200 mg in antacids
  - breast milk
    » 0.04 mg/L
  - formula
    » 0.225 mg/L
Aluminum Exposure: 1st 6 Months of Life

Source

Robison et al NIC 2008
MMR & Autism

- **1998**: Wakefield Lancet publication
  - case series
    » 12 children
- **Biological plausibility**: no
- **10 well done studies**
  - methods
    » both retrospective & prospective
    » ecological & case control
    » millions of children
  - results: no association
Permanent Medical Exemptions & Personal Beliefs Exemptions, Kindergarten Students, California

Year of Assessment

Percent of Students

0.0% 0.5% 1.0% 1.5% 2.0% 2.5% 3.0% 3.5%

PME  PBE

Lee et al. NVIC 2010

Permanent Medical Exemptions & Personal Beliefs Exemptions, Kindergarten Students, California

Year of Assessment

Percent of Students

0.0% 0.5% 1.0% 1.5% 2.0% 2.5% 3.0% 3.5%

PME  PBE

Lee et al. NVIC 2010
Kindergarten PBEs by County

2000

2010

PBE
PERCENT
0.0 - 0.9
1.0 - 2.4
2.5 - 4.9
5.0 - 15.0
AB2109: Implementation

- Effective January 1, 2014
- Parents wanting to exempt their children from one or more required immunizations – must use form
- Students affected – newly admitted to CA school (K-12th) – advancing to 7th grade – newly admitted to child care
- Form must be signed no sooner than 6 months before admission to school/child care/advancing to 7th grade
AB2109: Health Care Providers

- Provide information
  - benefits and risks of required immunizations
  - health risks of specific vaccine-preventable diseases to child and community
- Sign form along with parent
  - only parent signs for religious exemption
- Who can sign form
  - MD, DO, NP, PA, naturopathic doctor, credentialed school nurse
Vaccine Hesitant Parents

✦ Concerns
  – vaccines highly purified
    » immune system not overwhelmed
    » no thimerosal in virtually all routine pediatric vaccines
    » aluminum vaccine content trivial vs. environment
  – no MMR association with autism

✦ Vaccine schedule
  – protect children when they are most vulnerable
  – delayed vaccines = delayed protection
Listen carefully to concerns
  - encourage questions
Discuss known risks and benefits
  - risks to unimmunized child
Concerns about specific vaccines
  - discuss
  - administer other vaccines
Multiple injection concerns
  - modify schedule
Revisit discussion in future visits
Document
Vaccine Safety Discussion Strategies

- Empathize: acknowledge that there are many conflicting messages in the media
- Assess level of scientific evidence desired
- Maximize benefits to their child
  - not a public health discussion
  - vaccines provide protection
  - risk of disease for omitted vaccines
- Provide appropriate resources
  - e.g., CDC, AAP, NNII, CHOP
Continued Vaccine Refusal

- **Challenges**
  - time commitment for discussions
    - frustration

- **Agree to disagree**
  - acknowledge differences
    - “it sounds like you and I have different philosophies”
  - offer referral to a different practice/clinic
    - “you might be more comfortable with this group”
Vaccine Safety Processes: Pre-Post Licensure Trials & Monitoring--Summary

- Many vaccine-preventable disease successes
- Safety concerns
  - hesitancy
- New PBE process
- Addressing hesitancy