The immune Response to Vaccines and Adverse Events

Neal A. Halsey
1. Are there noteworthy differences in the immune response to the various types of vaccines (live attenuated, protein, split virus, toxoid, conjugate)?

Yes, many

General rules, many exceptions
2. What are the noteworthy differences in the immune response to vaccine compared to the immune response to the natural infection?

• Are there generalities or is it vaccine specific?

• If vaccine-specific, for which vaccines is the immune response most notably DIFFERENT than the response to natural infection?
Differences Between Immune Responses to Vaccines and Natural Infection

- Live attenuated vaccines:
  - Qualitatively: similar to wild-type infection.
  - Quantitatively: Antibody response often lower.
  - Both CMI(CD8) and humoral responses.
  - Immune responses are generated to multiple antigens, often measure only one.
“Natural” bacterial infections involve exposure to large numbers of antigens

Figure 1 The structure of *Bordetella pertussis* and its components (Koenig and Finger 2001)

www.uea.ac.uk
<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Vaccine type</th>
<th>Serum IgG</th>
<th>Mucosal IgG</th>
<th>Mucosal IgA</th>
<th>T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria toxoid</td>
<td>toxoid</td>
<td>+</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>killed</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B (HbsAg)</td>
<td>protein</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib PS</td>
<td>PS</td>
<td>++</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib glycoconjugates</td>
<td>PS-protein</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>killed, subunit</td>
<td>++</td>
<td></td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>Influenza intranasal</td>
<td>live attenuated</td>
<td>++</td>
<td></td>
<td>+</td>
<td>a(CD8+)</td>
</tr>
<tr>
<td>Measles</td>
<td>live attenuated</td>
<td>++</td>
<td></td>
<td></td>
<td>+ (CD8+)</td>
</tr>
<tr>
<td>Meningococcal PS</td>
<td>PS</td>
<td>++</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal conjugates</td>
<td>PS-protein</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>live attenuated</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillomavirus</td>
<td>VLPs</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertussis, whole cell</td>
<td>killed</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertussis, acellular</td>
<td>protein</td>
<td>++</td>
<td></td>
<td></td>
<td>+?(CD4+)</td>
</tr>
<tr>
<td>Pneumococcal PS</td>
<td>PS</td>
<td>++</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugates</td>
<td>PS-protein</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Testing for Immunity
Antibody Tests

- Neutralizing (measles, RSV)
- Antibody to surface antigen or toxin:
  - Hemagglutinin (measles, influenza)
  - Anticapsular (*H. influenzae, S. pneumoniae, N. meningitis*)
  - Specific protein (Lp1 for HPV)
  - Anti-toxin (tetanus, diphtheria, pertussis)
### Factors Influencing the Immune Response to Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of antigen</td>
<td>Age</td>
</tr>
<tr>
<td>Dose</td>
<td>Gender</td>
</tr>
<tr>
<td>Number of doses</td>
<td>Smoking</td>
</tr>
<tr>
<td>Interval between doses</td>
<td>Genetics</td>
</tr>
<tr>
<td>Route of administration</td>
<td>BMI</td>
</tr>
<tr>
<td>Adjuvants</td>
<td>Prior exposure</td>
</tr>
<tr>
<td></td>
<td>Passive antibody</td>
</tr>
<tr>
<td></td>
<td>Immune deficiency</td>
</tr>
<tr>
<td></td>
<td>– Primary, Secondary</td>
</tr>
<tr>
<td></td>
<td>– Drugs (chloroquine)</td>
</tr>
</tbody>
</table>
Log Normal Distribution of Maternal HAI Measles Antibody Titers, Haiti 1982
Antibody from “Natural” measles

Unpublished data from:
Halsey N Engl J Med; 313:544-9, 1985
## Edmonston B Measles Vaccine

<table>
<thead>
<tr>
<th>Year</th>
<th>Tissue Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1954</td>
<td>24 passages human kidney tissue</td>
</tr>
<tr>
<td></td>
<td>28 passages primary human amnion tissue</td>
</tr>
<tr>
<td></td>
<td>6 passages chick embryos</td>
</tr>
<tr>
<td></td>
<td>Vaccine 1963</td>
</tr>
</tbody>
</table>

**Authors:**
- John Enders
- Sam Katz

**Institute for Vaccine Safety**

**Johns Hopkins Bloomberg School of Public Health**
Fever and Rash Following Measles Vaccination With and Without GG

<table>
<thead>
<tr>
<th>Category</th>
<th>Percent Fever &gt; 103°F</th>
<th>Percent Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Measles (33)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Edmonston &quot;B&quot; No GG (175)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Edmonston &quot;B&quot; + GG 0.01-0.02 ml/LB (854)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Further Attenuated No GG (569)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Further Attenuated GG 0.2 ml (452)</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Krugman Pediatrics 31:919;1963
Measles HI GMT Antibody Response and Persistence Following Disease and Vaccines

Further attenuated ~ 4-fold less than "natural"

Krugman S: J Pediatr 1977;90:1
Measles Antibody Response Following Further Attenuated Vaccine

Krugman ~1976
Frequency Distribution of Postimmunisation Antibody Titres And GMT For MMR And Measles Vaccine

Live Viral Vaccines

- Quantitatively: Usually lower responses
- High levels of protection with one dose
- Second dose primarily for coverage of the initial nonresponders
  - Waning immunity does occur
Mumps Vaccine Efficacy/Effectiveness

- Jeryl Lynn strain 72.8% to 91%
- Urabe strain 54.4% to 93%
- Rubini strain 0% to 33%

Waning Immunity – even after 2 doses

Dayan and Rubini (FDA) Clin Infect Dis. 2008 Oct 29
Children 19-35 months of Age with Varicella by Year and Vaccination Status: Los Angeles County

Increased Rate of vaccine Failure by Time Since Vaccination

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5 yr</td>
<td>2.60</td>
<td>1.20–5.80</td>
<td>0.01</td>
</tr>
<tr>
<td>&lt;5 yr</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2 yr</td>
<td>0.42</td>
<td>0.15–1.15</td>
<td>0.13</td>
</tr>
<tr>
<td>3–5 yr</td>
<td>0.56</td>
<td>0.25–1.24</td>
<td>0.56</td>
</tr>
<tr>
<td>≥6 yr</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calendar year</td>
<td>0.96</td>
<td>0.81–1.31</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Rotavirus Reassortant to Generate Oral Live Virus Vaccine

9 Bovine WC3 genes.
2 Human VP7 gene.

Attenuated Infection, but no disease, immunity to human rotavirus.
Exceptions: Salmonella Ty 21a Replication Deficient Mutant Live attenuated vaccine

- No UDP gal 4-epimerase
- 80% reduction 2 other enzymes
- No Vi capsular polysaccharide antigen
- Protection via intestinal anti- O and H
- 3-4 doses of 2-6 x 10^9 bacteria

Qualitatively and quantitatively different from wild type infections
Killed or Subunit Vaccines

- No replication
- No or minimal CD8 stimulation
- Vaccines often have limited antigens:
  - S. typhi: Vi polysaccharide only
  - Toxoids (diphtheria, tetanus)
  - Surface proteins (HPV LP1)
  - Acellular pertussis (PT, FHA, Pertactin)
Killed vaccines: General Rules

• Multiple doses to induce immunity

• Primarily induce antibody (IgG)

• Waning immunity, booster doses needed
Antibody Response to Tetanus Toxoid

Interval between doses

- 4 wks
- 6-12 mos
- 1-5 yrs
- 1-10 yrs

Tetanus antitoxin levels in IU/ml

WHO: Galazka 1993
Exceptions: Hepatitis A Vaccines
High Rates of Protective Responses after one Dose

Anti-HAV GMT after vaccination with a 1,440 EL.U. hepatitis A vaccine. Vaccination schedule: 0-6 and 0-12 months.
Comparative Levels of Antibody to Hepatitis A Vaccine

HPV Vaccines: Virus-like Particles Grown in Yeast

HPV L1 protein

Self Assemble

Brewer’s yeast (S. cerevisiae)

Schematic of HPV Virus Like Particle

Stimulates immune responses that protect against the viruses
Bivalent HPV Vaccine
HPV 16 Antibody in Women >25 Years

- Efficacy study 15 to 25y
- 15–25y
- 26–35y
- 36–45y
- 46–55y

HPV-16 GMC EU/ml (log)

Month

Natural Infection

3. What are the qualitative and quantitative differences in immune response to vaccines for specific age groups (e.g. preemies, neonates, infants, children, adolescents, adults, elders)?
Decreased Responses to Some Vaccines in Infants

1. Immature responses to multiple antigens
2. Shorter duration of protection
3. Decreased affinity maturation
4. Passive maternal antibodies
Antibody Response to Plain Polysaccharide Hib Vaccine in Finnish Children by Age
Plain Polysaccharides: T independent Responses

Extrafollicular B cell responses to polysaccharide antigens

Siegrist Vaccine Immunology in Plotkin Vaccines 5th Ed 2008
Kinetics of serum antibody responses after vaccination with one, two, or three doses of *Haemophilus influenzae* type b capsular polysaccharide (Hib) vaccine in different age groups. First dose was given at time 0, and children who were then younger than 18 months received a second dose 3 months later. A further dose was given 3½ years after the first one. Serum antibody levels were followed for 7 years in children immunized according to this schedule (solid triangle), and levels are compared with those in unimmunized children (solid circle) and those in children who received their first vaccine dose at indicated age (solid square).

source: Peltola 1984
Proportion of Children Who Developed Measles Hemagglutinin-inhibiting Antibody after Vaccination

Francis Black 1980
Routine Age for First Dose of Vaccines

- **Birth**
  - BCG, OPV, Hepatitis B
- **6 weeks**
  - DTaP, Hib, IPV, Rotavirus, Pneumococcal conjugate
- **9 -12 months:**
  - Measles, yellow fever
- **12 months**
  - Hepatitis A
- **24 months (plain polysaccharide)**
  - Meningococcal, pneumococcal, Typhoid Vi
OPV administered p.o.
Serum antibody does not block replication in GI tract
### Qualitative and Quantitative Differences in Infants

| Limitations of Vaccine Responses at the Extremes of Life (Mechanisms Presumed) |
|----------------------------------|--------------------------------------------------------------------------------|
| **In early life**                |                                                                                  |
| Limited magnitude of Ab responses to PS | Immaturity of marginal zone, low CD21 expression on B cells, limited availability of complement |
| Limited magnitude of Ab responses to proteins | Limited GC responses (? delayed FDC development). Inhibitory influence of maternal antibodies |
| Short persistence of Ab responses to proteins | Limited establishment of BM plasma cell pool (? survival niches ?) |
| Shorter duration of immune memory (?) | Limited GC responses (? magnitude of initial memory B cell pool) |
| Limited IFN-γ responses | Suboptimal APC/T cell interaction (IL-12, IFN-α) |
| Limited CD8+ T cell responses ? | Insufficient evidence |
| Influence of maternal antibodies | Inhibition of B cell but not T cell responses |
Outcome of Hepatitis B Virus Infection by Age at Infection

- **Chronic Infection (%):**
  - Symptomatic Infection

- **Symptomatic Infection (%):**
  - Chronic Infection

- Age at Infection:
  - Birth
  - 1-6 mos
  - 7-12 mos
  - 1-4 yrs
  - Older Children and Adults
Decreased Response to Multiple Vaccines After age ~50

- Hepatitis B
- Influenza
- Pneumococcal polysaccharide
Impact of Age at Enrollment on Month 7 Anti-HPV 6 GMTs (PPI Population – Gardasil™)

Serum cLIA GMT with 95% CI, mMU/mL

Age at Enrollment (Years)

Immunogenicity Bridge

Efficacy Program
### Decreased Responses With Age

**“Aged” (50, 60, 70, 80?)**

<table>
<thead>
<tr>
<th>In aged individuals</th>
<th>Low reservoir of IgM+ memory B cells. Weaker differentiation into PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited magnitude of Ab responses to PS</td>
<td>Limited GC responses: suboptimal CD4+ helper responses, suboptimal B cell activation, ? limited FDC network development. Changes in B/T cell repertoire</td>
</tr>
<tr>
<td>Limited quality (affinity, isotype) of antibodies</td>
<td>Limited GC responses</td>
</tr>
<tr>
<td>Changes in B/T cell repertoire</td>
<td></td>
</tr>
<tr>
<td>Short persistence of Ab responses to proteins</td>
<td>Limited PC survival ?</td>
</tr>
<tr>
<td>Limited induction of CD4+/CD8+ responses</td>
<td>Decline in naïve T cell reservoir (accumulation of effector memory and CD8+ T cell clones)</td>
</tr>
<tr>
<td>Limited persistence of CD4+ responses</td>
<td>Limited induction of new effector memory T cells (IL-2, IL-7)</td>
</tr>
</tbody>
</table>
4. Are there special populations (other than by age or the severe immunodeficiencies) who respond qualitatively differently to vaccines and/or natural infections?
Females
Joint Symptoms Associated With HPV-77 Rubella Vaccine in Females by Age

Weibel JAMA 202:805;1972
Swartz Am J Epidem 94:246;1971
Increased Rates of Complications from “Natural” Infections

- Pregnancy:
  - Hepatitis A and B
  - Influenza
  - Smallpox

- Milder forms of immune disorders
  - HIV infected
  - Complement deficiency (meningoccal)
  - Asplenic (meningoccal)
Increased Severity of Measles Disease in Selected Populations

- Developing Countries:
  - Hawaii 1848: 10%-30% mortality
  - Fiji 1875: 40% mortality
  - Vitamin A deficiency
  - Crowding (inoculum)
  - HIV?

Schulman PIDJ. 2009;28(8):728-733
Measles Case-Fatality Rates By Country 1980s

WHO global estimate (2000) ~ 3%

Adapted from Aaby, et al 1987 and CDC 1990
Measles Case Fatality Rates
Publications: 1985-2007

C. Sudfeld and Halsey
Vitamin A Deficiency

Keratitis and Corneal Scarring Following Measles

AI Sommer/WHO
Increased Case Fatality Rates for Secondary Measles in Household Contacts 1-4 Years of Age


Mortality Following High Titer Vaccines by Country and 1990 Infant Mortality Rates

<table>
<thead>
<tr>
<th>Increased Female Mortality</th>
<th>IMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea Bissau</td>
<td>122</td>
</tr>
<tr>
<td>Senegal</td>
<td>78</td>
</tr>
<tr>
<td>Haiti</td>
<td>110</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No Increased Mortality</th>
<th>IMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>29</td>
</tr>
<tr>
<td>Peru</td>
<td>56</td>
</tr>
<tr>
<td>Philippines</td>
<td>52</td>
</tr>
<tr>
<td>U.S.</td>
<td>8</td>
</tr>
</tbody>
</table>

Halsey PIDJ; 12(6):462-5, 1993
Standard Titer Measles Vaccines in Developing Countries

No increased rates of complications in malnourished and/or vitamin A deficient children
Persons With Eczema at Increased risk of Complications from Smallpox Vaccine: Eczema Vaccinatum

Adverse Reactions: Eczema Vaccinatum

Courtesy Mike Lane

Vincent A. Fulginiti
Populations with Different Responses to Vaccines

1. HIV infected: decreased and shorter duration of protection
2. Other mild immune deficiency (DiGeorge): under investigation by CISA
3. Thymus irradiation or removal: Yellow fever vaccine associated viscerotrophic syndrome
4. Cigarette smokers: decreased responses
Populations with Different Responses to Vaccines

5. Underlying metabolic or mitochondrial disorders
   • CISA studies in progress

6. Finland: Better responses to Hib PRP-D and rotavirus

7. Hypersensitivity to a vaccine component
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
IgE mediated Immediate Hypersensitivity

- Plasma cell (produces IgE antibody)
- Mast cell (releases mediators)
- IgE cross linking by antibody
- Mast cell
- Histamine and other mediators
- Symptoms
Delayed Hypersensitivity: Erythema Multiforme after Smallpox Vaccine

Vincent A. Fulginiti, M.D.
5. What is known about genetic susceptibility to differences in immune response, particularly qualitative differences?

- **Qualitative:**
  - Little

- **Quantitative:**
  - Rapidly evolving field of study
Hohler T et al. Lancet 2002; 360: 991

Schematic of Primary Antibody Response
Antibody Response in 598 HCW After a Standard Course of Intramuscular Immunization with Hep B Vaccine

HLA B8, SC01, DR3 associated with poor response

Factors Influencing the immune Response to Hepatitis A Vaccine

<table>
<thead>
<tr>
<th>Predictive variable</th>
<th>Estimated β coefficient (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>0.65 (0.30 to 0.99)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.57 (-0.94 to -0.22)</td>
<td>0.0047</td>
</tr>
<tr>
<td>DRB1*11</td>
<td>-0.40 (-0.77 to -0.03)</td>
<td>0.0449</td>
</tr>
</tbody>
</table>

Table 3: Factors contributing to anti-HAV (log) immune response

Hohler T et al. Lancet 2002; 360: 991
### HLA Associations with Non-response and High Response to Measles Vaccine

#### Table 1. HLA class I, class II and HLA-DM allelic associations with measles vaccine seronegativity.

<table>
<thead>
<tr>
<th>Locus</th>
<th>Risk of seronegativity per allele</th>
<th>OR$^*$</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I HLA [60]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B7</td>
<td>0.27</td>
<td>0.13, 0.57</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>B8</td>
<td>2.48</td>
<td>1.42, 4.32</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>B13</td>
<td>7.78</td>
<td>1.53, 39.56</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>B44</td>
<td>1.82</td>
<td>1.05, 3.14</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>B51</td>
<td>0.21</td>
<td>0.05, 0.90</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td><strong>Class II HLA [61,62]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRB1*03</td>
<td>2.22</td>
<td>1.28, 3.87</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>DQA1*0102</td>
<td>0.60</td>
<td>0.35, 1.01</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>DQA1*0201</td>
<td>1.97</td>
<td>0.99, 3.92</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>DQA1*0501</td>
<td>1.64</td>
<td>1.06, 2.55</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>DQB1*0201</td>
<td>1.90</td>
<td>1.21, 2.97</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>DPA1*0201</td>
<td>1.71</td>
<td>1.02, 2.85</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>
Differences in Immune Response or Efficacy in Different Populations

• Hib PRP-D:
  – Finland 90% efficacy
  – Alaska natives 35% efficacy

• Rotavirus vaccines:
  – Higher efficacy per dose in Finland than U.S.
  – Lower protection with RRV in developing countries
TABLE III. Combinations of HLA-A Alleles Phenotypically Encompassing at Least 50% and 80% of Each Population Within the Groups Specified

<table>
<thead>
<tr>
<th>Populations</th>
<th>Cumulative phenotypic frequency(^a)</th>
<th>HLA-A alleles</th>
<th>Cumulative phenotypic frequency in each of 5 populations considered(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>All</td>
<td>&gt;50%</td>
<td>A2, A11, A24, A30</td>
<td>.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>.91</td>
</tr>
<tr>
<td>Cauc</td>
<td>&gt;50%</td>
<td>A1, A2</td>
<td>.58</td>
</tr>
<tr>
<td>Black</td>
<td>&gt;50%</td>
<td>A2, A28, A30</td>
<td>.64</td>
</tr>
<tr>
<td>Asian</td>
<td>&gt;50%</td>
<td>A2, A24</td>
<td>.84</td>
</tr>
<tr>
<td>All</td>
<td>&gt;80%</td>
<td>A1, A2, A11, A23, A24, A28, A30</td>
<td>.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>.92</td>
</tr>
<tr>
<td>Cauc</td>
<td>&gt;80%</td>
<td>A1, A2, A3, A11, A24</td>
<td>.87</td>
</tr>
<tr>
<td>Black</td>
<td>&gt;80%</td>
<td>A1, A2, A3, A23, A28, A30, A33</td>
<td>.84</td>
</tr>
<tr>
<td>Asian</td>
<td>&gt;80%</td>
<td>A2, A11, A24</td>
<td>.91</td>
</tr>
</tbody>
</table>
6. What is the current thinking about how specifics of immune response could predict adverse effect occurrence?

- **Immediate hypersensitivity:**
  - IgE to a component

- **Delayed type hypersensitivity:**
  - Under investigation
  - Specific markers difficult to measure
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.
Neurologic Adverse events Under Investigation Following Vaccines

- GBS and other vaccines
- Acute Disseminated Encephalomyelitis
- Transverse myelitis
- ALS
- Brachial neuritis

No specific laboratory markers to identify antigen responsible for triggering response
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 car-
Animal Model for Atypical Measles
Rhesus Macaques

- Antibody and immunity waned
- Antibody of low avidity
- No cytotoxic T-cell response
- Immune complexes and eosinophils in lungs of animals with atypical measles

Polack et al. Nat Med. 1999 :629-34
### Enhanced RSV Disease 9-10 Months Following Formalin Inactivated RSV Vaccine

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

Kapikian AZ. Amer. J. Epid., 1969, 89:405-21
Kim HW et al 1969
7. Are corticosteroid levels tested on any children after vaccines?

- **BCG**: increased

*Bull Exp Biol Med. 2008 Dec;146(6):705-7*
Salivary Cortisol Following Infant “Inoculations” at Well Child Visits

Figure 1. Cortisol level (in µg/dl) over time.

Maternal and Infant Salivary Cortisol Levels Pre and 27 min. Post DTP/Hib Immunization


Fig. 2. Mean proportional level of cortisol in the two sub-groups of groups of infants and mothers: pre- and post-inoculation.
Physiologic Changes after Typhoid Vi Vaccine in Adults

- Systolic BP
- Diastolic BP
- Heart Rate

Vaccine/Stress
Vaccine/rest
Placebo/stress
Placebo/rest

Cortisol increased
Data not shown

IL6 Increase After Typhoid Vi Vaccine +/- Psychological Stress

8. What parameters are examined in clinical trials of vaccines?

- Phase I: safety and immunogenicity
- Phase II: safety and immunogenicity
- Phase III: safety, immunogenicity, efficacy
- Phase IV: safety and/or effectiveness
Immunogenicity

- Parameters usually based on animal and/or human correlate of protection against wild-type disease
- Specific assays vary by organism
- Usually antibody:
  - Neutralizing, HI, EIA(IgG), other
- Rarely CMI studies against specific antigen
Safety

• Varies by phase:
  – Immediate, Diary cards, Daily visits, active calls
  – Special questions: e.g. stool patterns and liver enzymes post rotavirus vaccines
• Phase I and II: All signs and symptoms
• Phase III all illnesses, focus on serious
• Phase IV: usually just serious
• Special studies
9. Could there be a difference in reactions if inoculation was spread over a longer period? Please summarize current information regarding any studies that have made this comparison for a particular vaccine, if you are aware of them. MMR MMRV, TOPV, MOPV, HIB DTAP
Erythema following Combined or Separate Administration of DTaP and Hib

No difference in systemic or serious AEs
Effect of 2 smaller areas > 1 injection?

Pichichero et al PIDJ 1997;16:863
Anti-PRP concentrations 1 month after a primary vaccination series with four types of Hib conjugate vaccine or mixed PRP-T and DTPa

US: DTPa (DTaP) combined with Hib
Not approved

Europe: Approved

Adverse Events Following MMR Similar to Monovalent Vaccines

- Fever 10-20%
  Similar to measles vaccine

- Rash 5-10%
  Similar to measles vaccine

- Arthralgia
  Similar to rubella vaccine
Measles Antibody Response and Fever Following MMR given Separately vs. Combined with Varicella

<table>
<thead>
<tr>
<th></th>
<th>MMR + V</th>
<th>MMRV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles GMT</td>
<td>2138.3</td>
<td>2985.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Fever &gt; 38.9°C (days 0-42)</td>
<td>33%</td>
<td>39%</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Varicella Virus Titers in Available Vaccines

- Varicella (Varivax) 3,800-4,800 pfu
- MMRV (Proquad) ~44,400 pfu
- Zoster (Zostavax) ~19,000* pfu
Outpatient Fever Visits Among 12-23 Month Olds after First Dose Vaccine: VSD Automated Data 2000-2008*

Fever 0-42 days after Vaccine, 12-23 Months of Age, 2000-11/2008

--- Temporal Scan Table ---

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Days</th>
<th>RR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRV (N=83,107)</td>
<td>7-10</td>
<td>6.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>MMR + V (N=376,354)</td>
<td>7-10</td>
<td>4.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>MMR (N=145,302)</td>
<td>7-10</td>
<td>4.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Varicella (N=107,744)</td>
<td>9-14</td>
<td>1.2</td>
<td>0.06</td>
</tr>
</tbody>
</table>

--- Graph Details ---

- MMRV
- MMR + V
- MMR
- VAR

--- Footnote ---
*N. Klein, ACIP presentation, June 25, 2009; excludes KPSC site
### Prelicensure Studies:
**Vaccine-related Fever and Systemic Rash during Days 0–42 in Children Aged 12–23 Months Administered Dose 1 MMRV or MMR and Varicella Vaccine**

<table>
<thead>
<tr>
<th>Dose 1</th>
<th>MMRV N=4,497</th>
<th>MMR+V N=2,038</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days 0–42</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever ≥ 102°F or abnormal</td>
<td>21.5%*</td>
<td>14.9%</td>
</tr>
<tr>
<td>Measles-like rash</td>
<td>3.0%*</td>
<td>2.1%</td>
</tr>
<tr>
<td>Varicella-like rash</td>
<td>2.1%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

* Rate significantly higher in MMRV group

- Among subjects who had fever after vaccination, the proportion who had fever during the 5–12 days was 45% for MMRV and 36% for MMR + V
- Among subjects who had measles-like rash after vaccination, the proportion who had this rash during the 5–12 days was 82% for MMRV and 81% for MMR + V

Source: Package insert 2-2008 and unpublished data from Merck on 10-20-08

K. Broder ACIP 6/25/09
Logistic Regression Analyses:
Risk of seizure 7-10 days Post-Vaccination using Chart Verified Febrile Seizures

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio*</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRV versus MMR + V</td>
<td>2.3</td>
<td>1.6, 3.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for age and influenza season.

Attributable risk ~ 1/2000

N for MMRV = 43,353, MMR + V = 314,599.

Nicola Klein ACIP Feb 27, 2008
## Summary Results from VSD and Merck-sponsored Studies for Confirmed Febrile Seizures after Dose 1 MMRV vs. MMR and Varicella Vaccines*

<table>
<thead>
<tr>
<th>Post-vaccination Interval</th>
<th>VSD All aged 12–23 months</th>
<th>Merck-sponsored 99% aged 12–23 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weeks 1-2</strong></td>
<td>7–10 days†</td>
<td>7–10 days</td>
</tr>
<tr>
<td>RR: 2.0 (95% CI: 1.4, 2.9)</td>
<td>RR: 1.7 (95% CI: 0.8, 3.7)</td>
<td></td>
</tr>
<tr>
<td>AR: 4.3 per 10,000 (95% CI: 2.6, 5.6)</td>
<td>AR: 2.2 per 10,000 (95% CI: -1.1, 5.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Weeks 1-2</strong></td>
<td>5–12 days†</td>
<td>5–12 days†</td>
</tr>
<tr>
<td>RR: 1.9 (95% CI: 1.3, 2.6)</td>
<td>RR: 2.2 (95% CI: 1.0, 4.7)</td>
<td></td>
</tr>
<tr>
<td>AR: 4.1 per 10,000 (95% CI: 2.1, 5.4)</td>
<td>AR: 3.8 per 10,000 (95% CI: 0.3, 7.4)</td>
<td></td>
</tr>
</tbody>
</table>

* Sources: 2008-09 ACIP presentations; Jacobsen, Vaccine 2009, in press
†Significant p<0.05
Italics indicated analysis not pre-specified
RR = relative risk; AR = attributable risk; CI = confidence interval

K. Broder ACIP 6/25/09
Cumulative Seroresponses to Trivalent Oral Poliovirus Vaccine

Proportion of children protected against type 1 paralytic poliovirus by dose from mOPV vs tOPV Uttar Pradesh, India

Grassly *Lancet.* 2007 Apr 21;369(9570):1356
Risk of VAPP After mOPV

- No or incomplete data
- Theoretically possible on a per dose basis, esp. for type 3
- Higher response rate, no interference
Summary

- Complex questions
- Large variability in diseases, populations, and vaccines
- Some general rules, many exceptions