Vaccinology 101 for Fellows

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Disclosures

I have no disclosures.

I may be mentioning off label uses of vaccines.
Objectives/Outcomes

Understand the immunologic basis for immunization and mechanisms to elicit

Review route of vaccine administration

Discuss the role of adjuvants

Define correlates and surrogates
Basis for immunization

Passive immunization: preformed antibody provided, temporary protection

Active immunization: antigen(s) presented to evoke immunologic response, temporary or long lasting depending on the agent
Immunizing Antigens

Live attenuated viruses or bacteria: serial passage, reassortants

Killed microbes

Inactivated components: purified proteins or polysaccharides, chemical modifications (conjugates), recombinant technology
Antibody Response

T cell independent: B cells acting alone, polysaccharides, do not induce memory

T cell dependent: T and B cells together, induces memory for boosted responses

Antibodies: neutralize, opsonize, activate complement, promote phagocytosis
Routes and Sites

Mucosal: oral or intranasal

Intramuscular: a must for some adjuvants, avoid injecting into fat, use thigh or deltoid

Subcutaneous: thigh or deltoid preferred

Intradermal: volar forearm preferred
Preservatives, Additives, Adjuvants and Residuals

- Thimerosal, phenol, 2-phenoxyethanol
- Sugars, amino acids, proteins (gelatin, albumen, cow derived stuff)
- Aluminum salts enhance immune response
- Antibiotics, formaldehyde, cellular products (egg, yeast)
Adjuvants
Enhance immune response, or not
Aluminum salts were the first used
Novel adjuvants being studied
New adjuvants: ASO4 = adjuvant system 04 contains a derivative of monophosphoryl lipid A (MPL) absorbed onto aluminum salt
Correlates of Protection

Absolute, relative, cocorrelate, surrogate

Seroologic: antibody - most often used

Cell mediated immunity: rarely measured

Surrogates: usually antibody, predictors

Efficacy studies are the gold standard
Vaccine Preventable Diseases

Hepatitis B

This woman is not pregnant. She has a liver tumor as a result of hepatitis B infection.
Hepatitis B vaccines

Purified hepatitis B surface antigen

Recombinant uses: *Saccharomyces cerevisiae*

Intramuscular, avoid fat

Formaldehyde treated, adjuvant (aluminum)

Correlate: ELISA anti-HBs 10mIU/ml
**Rotavirus**

- Child gastroenteritis – ER visits, hospitalization, clinic visits, lost work time

- Live, oral vaccines:
  - Rotateq (Merck): pentavalent, human-bovine reassortant
  - Rotarix (GSK): monovalent, attenuated

- Both vaccines:
  - Effective
  - Well-tolerated
  - No increase in intussusception
Rotavirus Reassortant Vaccines

RotaShield: tetravalent rhesus reassortant (G types 1, 2, 3, 4) – withdrawn

RotaTeq: pentavalent bovine reassortant (G types 1, 2, 3, 4 and P1A)

Oral route, no adjuvants

No clear correlate, surrogate: serum IgA
Attenuated Rotavirus Vaccine

Rotarix: Serial passage of human strain (RIX4414); propagated on Vero cells
Oral
No adjuvant
No clear correlate, surrogate: serum IgA
**Diphtheria**

Pharyngeal diphtheria with membranes covering the tonsils and uvula

Bull neck appearance of diphtheric cervical lymphadenopathy
Diphtheria Vaccine

Toxoid: formaldehyde treatment of *Corynebacterium diphtheriae* toxin

Combined with tetanus toxoid +/- pertussis

Intramuscular

Aluminum salt adjuvant

Correlate: toxin neutralization 0.01-0.1 IU/mL
Tetanus

The baby has neonatal tetanus and is completely rigid.

The child has painful muscle spasms from tetanus; it is nearly impossible for her to move or control the muscles in her body.
Tetanus Vaccine

Formaldehyde treatment of *Clostridium tetani* toxin
Combined with tetanus toxoid +/- pertussis
Intramuscular
Aluminum salt adjuvant
Correlate: toxin neutralization 0/1 OI/mL
Pertussis

A Medical Media Production
Dalhousie University 1991

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Click here for video
Pertussis Vaccines

Whole cell: suspension of inactivated bacteria

Acellular: purified components: pertussis toxoid + filamentous hemagglutinin +/- pertactin, +/- fimbriae types 2 and 3

Combined with tetanus, diphtheria toxoids

Intramuscular

Correlate of protection unknown
Oral Polio Vaccine

Live attenuated; types 1, 2 and 3 propagated in monkey kidney cells (VERO)

Oral

No adjuvants

Correlate: serum neutralization 1:4 to 1:8 dilution
Inactivated Polio Vaccine

Formaldehyde inactivated viruses propagated in monkey kidney or human diploid cells

- Intramuscular
- No adjuvants

Correlate: serum neutralization 1:4 to 1:8 dilution
Haemophilus influenzae type b

Haemophilus influenzae type b sepsis with gangrene of hand.

Child with buccal cellulitis.
Hib Polysaccharide Vaccine

Purified polysaccharide capsule: polyribosylribitol phosphate (PRP)
Intramuscular
No adjuvant

Correlate: ELISA 1 mcg/mL
Hib Conjugate Vaccines

PRP covalently linked to a carrier protein:
tetanus toxoid, diphtheria toxoid, CRM$_{197}$
(mutant diphtheria toxin), OMP (outer membrane protein complex of *N. meningitidis*)

Intramuscular

Adjuvant in OMP product

Correlate: ELISA 0.15 mcg/mL
**Pneumococcal Disease**

- Leading cause of bacterial meningitis, bacteremia, acute otitis media in children
- Antibiotic resistant bacteria - Use the vaccine!

**Images:**
- Periorbital cellulitis
- Sepsis
Pneumococcal Polysaccharide

23 purified capsular polysaccharides: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F

Intramuscular or subcutaneous

No adjuvant

Correlate: ELISA 0.20-0.35 mcg/mL
Pneumococcal Conjugate

Saccharides of capsular antigens of 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to diphtheria CRM$_{197}$ protein

Intramuscular

Aluminum phosphate adjuvant

Correlate: ELISA 0.20-0.35 mcg/mL
Influenza
Inactivated influenza Vaccines

Viruses propagated in embryonated chicken eggs; inactivated and then split – processes vary by vaccine (see package inserts)

Intramuscular

No adjuvants

Correlate: hemagglutination inhibition 1:40
Live Cold Adapted Vaccine

Reassorted strains: cold adapted, temperature sensitive, attenuated

Master donor virus (6): H and N from wild

Nasal spray

No adjuvant

Correlate: hemagglutination inhibition 1:40
Measles

Rash and conjunctivitis in a child with measles

Measles pharyngitis in an adult showing striking inflammation
Measles Vaccine

Attenuated measles virus derived from Enders' attenuated Edmonston strain; propagated in chick embryo cell culture

Subcutaneous

No adjuvant

Correlate: microneutralization 120 mIU/mL
Mumps parotitis and submandibular lymphadenopathy
Mumps Vaccine

Jeryl Lynn (B level) strain of mumps Virus; propagated in chick embryo cell culture
Subcutaneous
No adjuvant
Correlate: not determined; neutralizing antibodies are detected
Rubeola infection early in pregnancy can lead to fetal death, premature delivery, congenital defects, spontaneous abortion, stillbirth, blindness, deafness, heart defects, or mental retardation.
Rubella Vaccines

RA 27/3 attenuated strain; propagated in WI-38 human diploid lung fibroblasts

Subcutaneous

No adjuvant

Correlate: immunoprecipitation 10-15 mIU/mL
Bullous lesions, negative cultures

Hemorrhagic varicella with cellulitis

VARICELLA
Varicella Vaccine

Oka/Merck attenuated strain; propagated in a variety of cell lines (human embryonic lung, embryonic guinea pig, human diploid cells)

Subcutaneous

No adjuvant

Correlate: neutralization 1:64
Hepatitis A

- **Vaccine (2 doses, 6 mos. apart):**
  - Children starting at age 1 year
  - High risk adults:
    - Household or sexual contacts of infected persons
    - Living in or travel to endemic area
    - Men who have sex with men
    - Injecting and non-injecting drug users

- **Prevention:** vaccine and handwashing

2003 outbreak in Pennsylvania—more than 660 cases.
Hepatitis A Vaccines

Inactivated vaccines; propagated in human diploid cells

Intramuscular

Aluminum salt adjuvant (hydroxide or hydroxyphosphosphate sulfate)

Correlate: ELISA 10 mIU/mL
Meningococcal Disease

- One dose MCV4:
  - 11-12 year olds
  - Next 2-3 years, teens entering high school
  - Students entering college

http://nfid.org

Check web for resources: “STOP Meningitis” campaign
Meningococcal Polysaccharide

Polysaccharide antigens from *N meningitidis*,
Group A, C, Y and W-135
Subcutaneous
No adjuvant
Surrogate: serum bacteriocidal antibodies
Meningococcal Conjugate

Polysaccharide antigens from \( N\) meningitidis, Group A, C, Y and W-135 individually conjugated to diphtheria toxoid protein

Intramuscular

No adjuvant

Surrogate: serum bacteriocidal antibodies
Human Papilloma Virus (HPV)

- Affects anogenital area of women and men (cervical cancer and warts)
- 2nd leading type of cancer among women
- Most HPV infections do not cause symptoms
- Strains 16, 18: 2/3 of cervical cancer
- Strains 6, 11: > 90% of anogenital warts

HPV vaccine combined with screening - cervical cancer prevention
HPV Vaccine: Gardasil

Recombinant uses *S. cerevisiae*: capsid (L1) proteins-Types 6, 11, 16, 18 produced and self-assembled into virus-like particles (VLP)

Intramuscular

Aluminum hydroxyxiphosphate sulfate sulfate adjuvant

Correlate: not established
HPV Vaccine: Cervarix

Recombinant uses Baculovirus in *Trichoplusia ni* insect cells: capsid (L1) protein produced and self assemble (VLP)

Intramuscular

ASO4 adjuvant: MLP on aluminum hydroxide

Correlate: not established
Smiling is a contagious condition!