Possible Immunological Basis for the Reduction in Antibody Response to Hib with Combination Vaccines

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Antibody (Ab) to HibPS Induced by DTPa/Hib Combination Vaccines

- ↓ total, IgG Ab and ↓ % >1μg/ml with 1° immunization series (2° or 3° imm)
- ↓ total, IgG Ab to booster- either HibPS or DTPa/HibPS
- IgG/Ig and IgG1/IgG2 Ab same
- ↓ Ab to carrier protein (TT, DT)
Decreased Immunogenicity of DTPa/Hib Combination Vaccines

- ↓ HibPS Ab = ↓ HibPS plasma cells

- ↓ HibPSAb to 2° and 3° imm and to HibPS or DTPa/Hib booster = 
  ↓ # +/- Fx. of HibPS memory B cells
B Cell Activation in Secondary Lymphoid Tissues
Germinal Center B Cell Differentiation
to Memory B Cells and Plasma Cells

Plasma Cell

Centrocytes

Centroblasts

Light Zone

Dark Zone

FDC

Memory B Cell

Isotype Switching

Affinity Maturation Selection

Apoptosis

Hypermutation Proliferation
$T_\text{H}$ cell interactions with Ag-presenting PS-specific B-cells

Carrier protein-specific $T_\text{H}$ cell

Conjugate Vax
PS-Protein Carrier

PS-specific B-cell
Decreased Immunogenicity of Hib Combination Vaccines: Issues

- Alum
- Carrier protein
- Pa vs. Pw
- AbSC vs. B cell memory
- Hib Ab specific
Decreased Immunogenicity of Hib Combination Vaccines: Alum

- Decreased desorption of PRP off aluminum hydroxide - time dependent
- Hydrolysis of PRP on aluminum hydroxide

(Vaccine 17:1169, 1999)

→ Decreased Hib Ag capture and epitope presentation
Decreased Immunogenicity of Hib Combination Vaccines: Carrier Protein

- High Dose Carrier Protein
  - T cell anergy, immune deviation, suppression
- Carrier-Induced Epitopic Suppression
Decreased Hib and TT Ab with Increased TT Protein

Carrier-Induced Epitopic Suppression (CIES): Pathogenesis

- Increased carrier-specific B cells
- Memory B cells generated but fail to differentiate to AbSC - reversible
- Antigen presenting cells (APC) altered
- Suppressor cells
Antigen Uptake and Presentation of Combination Vaccines
Antigen Uptake and Presentation of Carrier Protein with Combination Vaccines
TT and Hib PS B Lymphocytes Competition for Ag Capture/Presentation of TT and T Cell Help
Decreased Immunogenicity of Hib Combination Vaccines: Pa vs. Pw

- Differences in adsorption to alum
- Loss of “adjuvant effect”
- Soluble vs. particulate
- ↑ PT and FHA
- Alteration of CIES-like effects
- Immune deviation effects
Antigen Uptake and Presentation of Combination Vaccines
Decreased Immunogenicity of Hib Combination Vaccines: AbSC vs. Memory B cells

- Activation requirements different
- Hib-OMP- AbSC vs. Memory
- Early Hib conjugate experience
- CIES- Memory B cells fail to generate AbSC, reversible
Decreased Immunogenicity of Hib Combination Vaccines: Hib Ab

- Low B cell number
- B cell immaturity
Decreased Immunogenicity of Hib Combination Vaccines: Conclusions

- Alum- decreased Hib epitopes
- Carrier protein- T cell anergy, CIES
- Pa vs. Pw- alum effects, CIES,
- AbSC vs. B cell memory- differences
- Hib Ab specific- B cell #, immaturity