Carbohydrate Based Vaccines

READ (on the WEB SITE):


Why Carbohydrate Vaccines?

Historical Factors (by the 1940s):

1. Polysaccharides (PS), on killed cells or purified, produced protective immune responses.
2. Infants and young children did not produce antibodies (either from the PS, the killed cells, or from actual disease).
3. Specific PS molecules characteristic of the particular strain (or type) produced the protective response.
4. Vaccination with PS reduced the need to vaccinate with the organism itself.
5. When the PS was coupled to a protein, it produced a much higher titer (in rabbits).
Why the Late Development of Carbohydrate Vaccines?

1. The introduction of antibiotics.
2. By 1970s it was recognized that antibiotics would not be the ultimate solution.
3. Numerous failures due to the rise of resistant forms of the disease organisms.
4. Advances in understanding of the immune system.
5. Structural determination of numerous carbohydrate structures leads way to development of defined glycoconjugates.
Haemophilus influenzae type b (Hib)

**Diseases:** meningitis, epiglottitis, septicemia, facial cellulitis, pneumonia, arthritis, and others.

**Prevaccine era:**
1. 30 to 60 cases per 100,000 in children under 5 years of age in Europe and 50 to 100 cases/100,000 in the U.S.
2. Native Americans and Australian aborigines had up to 300 cases per 100,000.
3. Case study of 100,000 children: >18 months were protected; 12 to 18 months some protection; 3 to 12 months had no protection.
1. *H. influenzae* strains are mostly non-encapsulated and are, therefore, “non-typeable” (NTHi).
2. A number do have CPS and there are six different CPS types.
3. One CPS type, type “b”, is the most common and most virulent.
Hib Carbohydrate Vaccine

The lack of protection in children under 12 months (i.e. no Hib antibodies) together with the role of T and B cells in immune memory, suggested the need for the development of Hib CPS-protein conjugate vaccines.

Hi type b (Hib) capsular polysaccharide, polyribitol/ribose phosphate (PRP).
Hib Carbohydrate-Conjugate Vaccine

![Diagram of Hib carbohydrate-conjugate vaccine](image)

- **HbOC (Hib Titer)**
  - Lederle-Praxis

- **PRP-D or T (Act Hib)**
  - Pasteur-Mérieux

- **PRP-OMP (PedVax Hib)**
  - Merck, Sharpe & Dohme
Hib Vaccine Results
Streptococcus pneumoniae

Diseases: otitis media, bronchopneumonia, meningitis.

In the U.S. each year: 3000 cases of meningitis, 50,000 bacteremia, 500,000 pneumonia, 7,000,000 otitis media; 40,000 deaths. World wide deaths per year: more than 4,000,000, most under age of 5.
**S. pneumoniae Capsular Polysaccharides**

1. 90 different CPS serogroups (different CPS structures).

2. 7 CPS types cover 85% of all infections.

3. 23 CPS types cover up to 90% of all infections.

4. CPS vaccines offer >90% protection, if over 2 years of age.

5. CPS-protein conjugate vaccines are under development.
**S. pneumoniae Capsular Polysaccharide-Conjugate Vaccine**

Multivalent vaccines needed to cover majority of infections.

A 23 valent conjugate vaccine resulted in an 89.1% efficacy against invasive disease in children under 5 years of age.

“In infants and vulnerable children throughout the world, PNCRM7 vaccine has the potential to reduce the mortality and morbidity rates associated with *S. pneumoniae* infections. In disabling infections but its impact in developing countries will be more pronounced with the potential to greatly reduce mortality.”

**Neisseria meningitidis**

Infections are more rare than other infections we have discussed but it causes meningitis with a high mortality rate.

33% of infections occur from 0 to 4 years old, 33% from 5 to 9 years of age, and 33% at age 20 and above.

There are 12 serogroups based on their differing CPS structures; A, B, C, 29E, H, I, K, L, W135, X, Y, and Z. Almost all infections are caused by types A, B, C, W135, and Y. A=sub-saharan Africa; B=Europe and Latin America; C=North America; W135=Saudi Arabia (Hajj outbreak)

There are current CPS-based vaccines against A, C, W135, and Y. They are not conjugate vaccines (except for C) and, therefore, do not work in young children.
Type A

-6-ManNAc-α-1-OPO₃-

Type B

-8-NeuNAc-α-2-

Type C

-9-NeuNAc-α-2-

Type Y

-6-Glc-α-1-4-NeuNAc-α-2-

Type W135

-6-Gal-α-1-4-NeuNAc-α-2-
Neisseria meningitidis Capsular Polysaccharide-Conjugate Vaccine

Meningitec®: Wyeth
Menjugate®: Chiron
NeisVac-C®: Baxter

Type C conjugate Vaccines.

Protein-CPS conjugate vaccines are currently under preparation for W135, A, and Y. The goal will be to make a tetravalent vaccine.
What about *Neisseria meningitidis* Type B?

Not suitable for a vaccine as it mimics host structures and may be (a.) non-immunogenic, or (b.) induce and autoimmune reaction.

Type B LOS: There are seven different immunotypes (structures), L1-L7.

\[
\beta-\text{Gal-1} \rightarrow 4-\beta-\text{GlcNAc-1} \rightarrow 4-\beta-\text{Glc-1} \rightarrow 4-\alpha-\text{Hep-1} \rightarrow 5-\text{Kdo}_2 \rightarrow \text{PEA-6} \\
\alpha-\text{Glc-1} \rightarrow 3-\alpha-\text{Hep-1} \\
\text{rfaK} \alpha-\text{GlcNAc-1}
\]
Neisseria meningitidis Type B LOS as a Vaccine Candidate

β-Gal-1→4-β-GlcNAc-1→4-β-Glc-1→4-α-Hep-1→5-Kdo₂

PEA-6

PEA or α-Glc-1→3-α-Hep-1

α-GlcNAc-1

Neisseria meningitidis Type B LOS as a Vaccine Candidate

[Diagram showing chemical structures and reactions involving hydrazine, Alkaline phosphatase, borate, pH 9.0, and Reduction]
*Neisseria meningitidis* Type B LOS as a Vaccine Candidate

\[
\beta-\text{Gal-1} \rightarrow 4-\beta-\text{GlcNAc-1} \rightarrow 4-\beta-\text{Glc-1} \rightarrow 4-\alpha-\text{Hep-1} \rightarrow 3-\beta-\text{Gal-1} \rightarrow 4-\alpha-\text{Hep-1} \rightarrow 3-\beta-\text{Gal-1} \rightarrow 4-\alpha-\text{Hep-1} \rightarrow 3-\beta-\text{Gal-1} \rightarrow 4-\alpha-\text{Hep-1} \rightarrow 3-
\]

**Produce Ab**

**Bactericidal**

**antiseria**

\[
\begin{align*}
\beta-\text{Gal-1} & \rightarrow 4-\beta-\text{GlcNAc-1} \\
lgtB & lgtA lgtF \\
\end{align*}
\]

**Produce Ab**

**Bactericidal**

**antiseria**

\[
\begin{align*}
\alpha-\text{GlcNAc-1} & \\
rfaK & \\
\end{align*}
\]
Neisseria meningitidis Type B LOS as a Vaccine Candidate

\[ \beta\text{-Gal-1} \rightarrow 4\beta\text{-GlcNAc-1} \rightarrow 4\beta\text{-GlcNAc-1} \rightarrow 4\alpha\text{-Hep-1} \]

\[ lgtB \hspace{1cm} lgtA \]

PEA-6

PEA or \( \alpha\text{-Glc-1} \rightarrow 3\alpha\text{-Hep-1} \)

\[ lpt3 \hspace{1cm} lgtG \]

\( rfaK \)

\[ R \]
Neisseria meningitidis Type B LOS as a Vaccine Candidate

α-Hep-1
3
PEA-6
PEA or α-Glc-1→3-α-Hep-1
PEA or α-Glc-1→2-α-Hep-1
α-GlcNAc-1
rfak

R

NH-Protein