Conjugate vaccines : A great technology that needs to be improved

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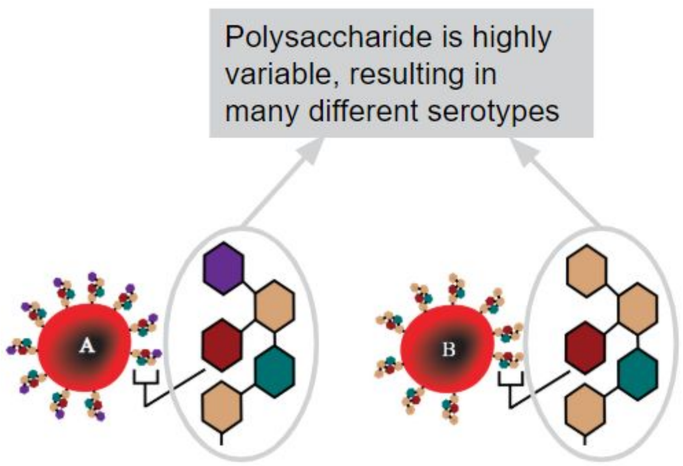
Introduction

The immune system of infants and the elderly are incapable of responding to encapsulated bacteria. Many encapsulated pathogens such as Haemophilus influenzae or Campylobacter jejuni are major causes of serious childhood diseases. Conjugate vaccines are designed to induce anti-polysaccharide immune responses and protect infants during the susceptible period of 2 months to 2 years old.

The polysaccharide capsule



Environmental adaptation results in polysaccharide variation, which is generated by rearrangements in the DNA.

Different serotypes will lead to distinct anti-polysaccharide responses by white blood cells.

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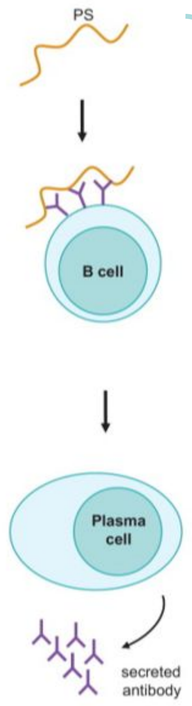
Immunoglobulin specificity

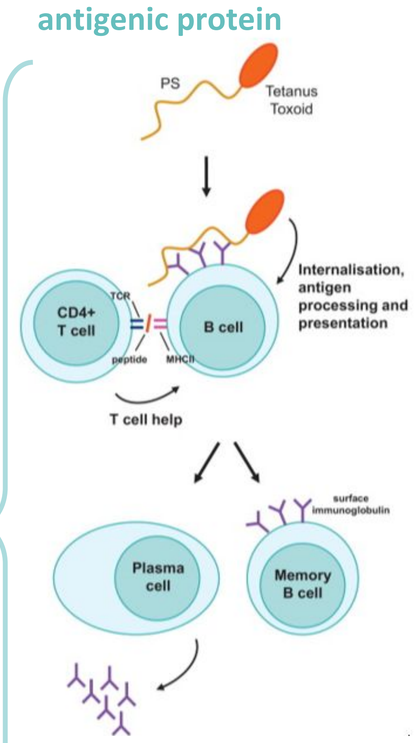
Changing a T cell independent response to a T cell dependent response

Subunit vaccine: polysaccharide (PS)



T cell independent response
- **Weak** immune response
- Antibody has **low** affinity for antigen
- No memory cells generated

Conjugate vaccine: PS + antigenic protein



T cell dependent response
- **Strong** immune response
- Antibody has **high** affinity for antigen
- Memory cells generated

Haemophilus influenzae

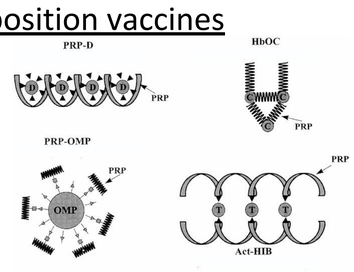
87% decrease of the number of cases of HiB in the US

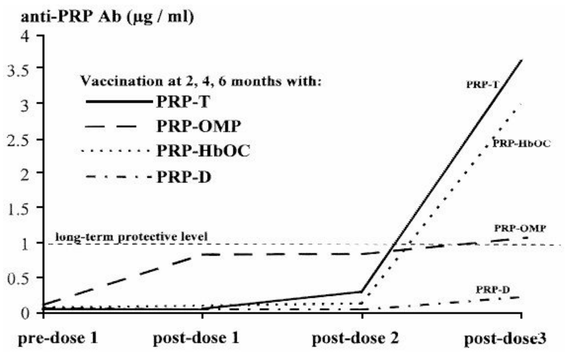
- one of the leading causes of invasive bacterial infection in young children worldwide
- first conjugate vaccines extensively used
- gram negative bacteria, exclusively human

Disease:
- severe pneumonia and meningitis
- transmission: respiratory droplets and direct contact the respiratory secretions

Composition of the capsule and virulence:
- 6 distinct capsular serotypes: a,b,c,d,e,f
  - type b is most virulent
- special cap: cap b (DNA duplication)

Composition vaccines





Vaccine	Polysaccharide Size	Carrier Protein	Linkage
PRP-D	Medium	Diptheria Toxoid	6-carbon
HbOC	Small	Diptheria Toxoid Mutant	None
PRP-OMP	Medium	N meningitidis outer membrane protein	Thioether
PRP-T	Large	Tetanus toxoid	6-carbon

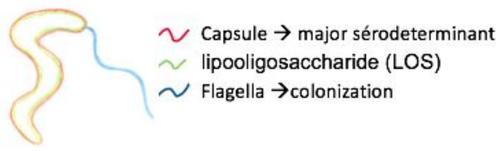
Campylobacter jejuni

hyperendemic : 40% children affected in developing regions of the world

- One of the four worldwide causes of diarrhea
- Most common bacterial cause of enterogastritis in humans
- Encapsulated, Gram negative, zoonotic

Disease:
predominant symptom complex :acute diarrhea, fever, and abdominal pain

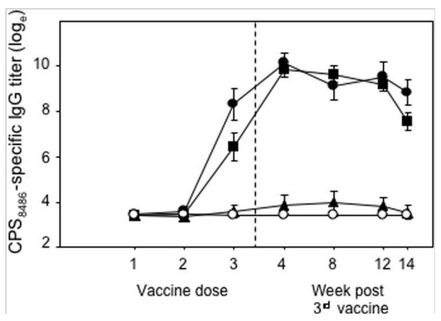
Post infectious serious sequelae
- mimicry of the outer lipooligosaccharide (LOS) regions of some strains with human gangliosides => Guillain-Barré syndrome (autoimmune disease)
- Reactive arthritis
- Irritable bowel syndrome (IBS)



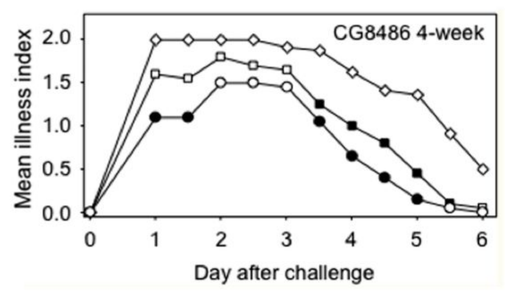
Composition of the capsule and virulence:
- Capsule = major serodeterminant
- 47 different serotypes (HS1, HS2, and HS4 most common 50% of the strains, HS 23/36 most common in developing countries)

Composition vaccines
- no licensed vaccines -> 2 prototypes
- against strains without mimicry

CPS (HS 23/36 strain) and (HS 4) ← → Diphtheria toxin subunit



=> Long–term protection



=>Immunogenicity

Future: A better understanding of pathogenesis and virulence factors is first needed to provide adequate vaccine coverage.

Limitations

- Design of conjugate vaccines remains expensive and the accessibility for the developing region of the world which are the most affected stay difficult.
- Problem of multivalence : conjugate vaccines remains too specific to a unique strain and design multivalent vaccines is still difficult for bacteria that have as many serotypes as Campylobacter jejuni .
- The problem of multivalence leads to the emergence of other virulent strains which tend to replace the previously dominating strain .
- Administration of multiple conjugate vaccinations containing the same protein carrier may increase the chance of immune interference. This could be ameliorated by using novel carriers.
- Evolution of the capsule: polysaccharide variation results from environmental adaptation. This variation is generated by DNA rearrangements.

Conclusion

Conjugate vaccines have saved many lives, they have already had a major impact on vaccination of infants against H. influenzae type b for example. The impact of conjugate vaccines will continue to grow as we apply this technology to other important diseases like Campylobacter jejuni. However, there are still some problems like the valence or the cost we must solve to improve the efficiency and the accessibility of conjugate vaccines.