Availability, safety and effectiveness of serogroup B/protein meningococcal vaccines

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Meningococcal serogroup B vaccines

• MenB capsule poorly immunogenic

• Main approach in past was outer membrane vesicle vaccines
  • Efficacy shown in older trials in South America and Norway
  • Poor protection in younger children
• Recent use in New Zealand epidemic
  • Short term effectiveness of 73% (95% CI 52 to 85)
  • No evidence of major impact on carriage
Correlates of protection

• The surrogate of protection for serogroup B meningococci is the serum bactericidal antibody assay utilising human complement (hSBA).

• Efficacy correlates with:
  - % of subjects with hSBA titres ≥ 4 and/or
  - % of subjects with ≥4 fold rises pre- to post-vaccination.
  - derived from efficacy and immunogenicity of OMV vaccine studies.
  - against the homologous strain with the same PorA.

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The solution

• Subcapsular, surface exposed, conserved, induces bactericidal activity.

• Two approaches:
  
  Fractionation, protein purification, and proteomics steps - Pfizer.

  Reverse vaccinology – Novartis

• Final candidates have some shared component

• If prevents acquisition of carriage, vaccination strategies including adolescents/young adults have the potential to provide indirect (herd immunity) benefits
Investigational vaccine is based upon LP2086, a surface-exposed lipoprotein of *N. meningitidis*.

LP2086 was identified as a factor H binding protein (fHBP), important for survival of the organism *in vivo*.

The gene is present in all meningococcal serogroup B disease isolates examined.

fHBP *in vitro* surface expression has been shown in > 98% of MenB isolates.

fHBP also a component of Novartis vaccine.
Factor H (fH) binding protein (fHBP)

Variant or family groups:

- Novartis
- Variant 1
- Variants 2 & 3
- Pfizer
- Family B
- Family A

Intra-family cross-reactivity good.
Inter-family cross reactivity poor.
The vaccine is composed of two recombinant LP2086 proteins, one from each subfamily.

Early clinical studies demonstrated excellent safety profile and broad immunological response to clinical isolates representing the two subfamilies.

Results have been extended in three phase I/II trials in young adults and adolescents, and support continued development:

- Acceptable safety profile
- Robust SBA response rates against a diverse panel of MenB invasive disease isolates
- Variation with fHBP present in strain
Immunogenicity of the Pfizer investigational MenB vaccine in adolescents (11 – 18 yrs) in 0, 2, 6 month schedule

Novartis has submitted its meningococcal vaccine Bexsero to European regulators for marketing approval.

If approved Bexsero would be the first broad-coverage vaccine for MenB.

Novartis 4CMenB (Bexsero®) contains 4 main antigens:

- fHBP 1.1
- NadA
- NHBA
- PorA (presented as part of an OMV)
Novartis 4CMenB (Bexsero®) clinical program

• Phase 3 studies in infant, toddlers and adolescents complete.
  — Over 5000 infants/toddlers and 2000 adolescents/adults vaccinated.

• Acceptable safety and tolerability profile in all age groups.
  — Short-lived fever in infants without medical consequences.
  — No excess fever in adolescents/adults.

• Co-administered infant vaccines elicit expected immune responses when given with 4CMenB.

• Additional studies are ongoing (i.e., 2, 3, 4 month primary vaccination, long-term persistence, carriage study in adolescents).
Novartis 4CMenB Phase III study in infants
% of subjects with hSBA ≥ 1:5 one month after dose 3 (2, 4, 6 month schedule)

N = 1149 to 1152

UK infant trial: proportion of subjects with hSBA titres ≥ 4 before & after Novartis 4CMenB vaccine

Summary of systemic reactogenicity after receipt of Novartis 4CMenB vaccine

Estimating vaccine coverage with the Novartis 4CMenB vaccine – MATS - Meningococcal Antigen Typing System

- Unique system predicting coverage based on circulating strains.
- Validated by SBA for panel of epidemiologically diverse MenB strains using pooled sera from toddlers vaccinated at 2, 4, 6 and 12 months.
- Potentially covers 77% (95% CI 66 to 91) of more than 800 genetically diverse disease causing MenB strains from Europe.

Conclusions

• Meningococcal outer membrane vesicle vaccines are useful in clonal outbreaks.

• Pfizer approach – targeting adolescents/young adults for direct & indirect effects.

• Novartis approach – infants through to adults, direct and indirect effects.

• Need to demonstrate whether there is an effect on acquisition of carriage:
  - Novartis carriage study ongoing.