Overview of Serogroup B Meningococcal Vaccines and Considerations for Use

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October 30, 2014

National Center for Immunization & Respiratory Diseases
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Presentation Overview

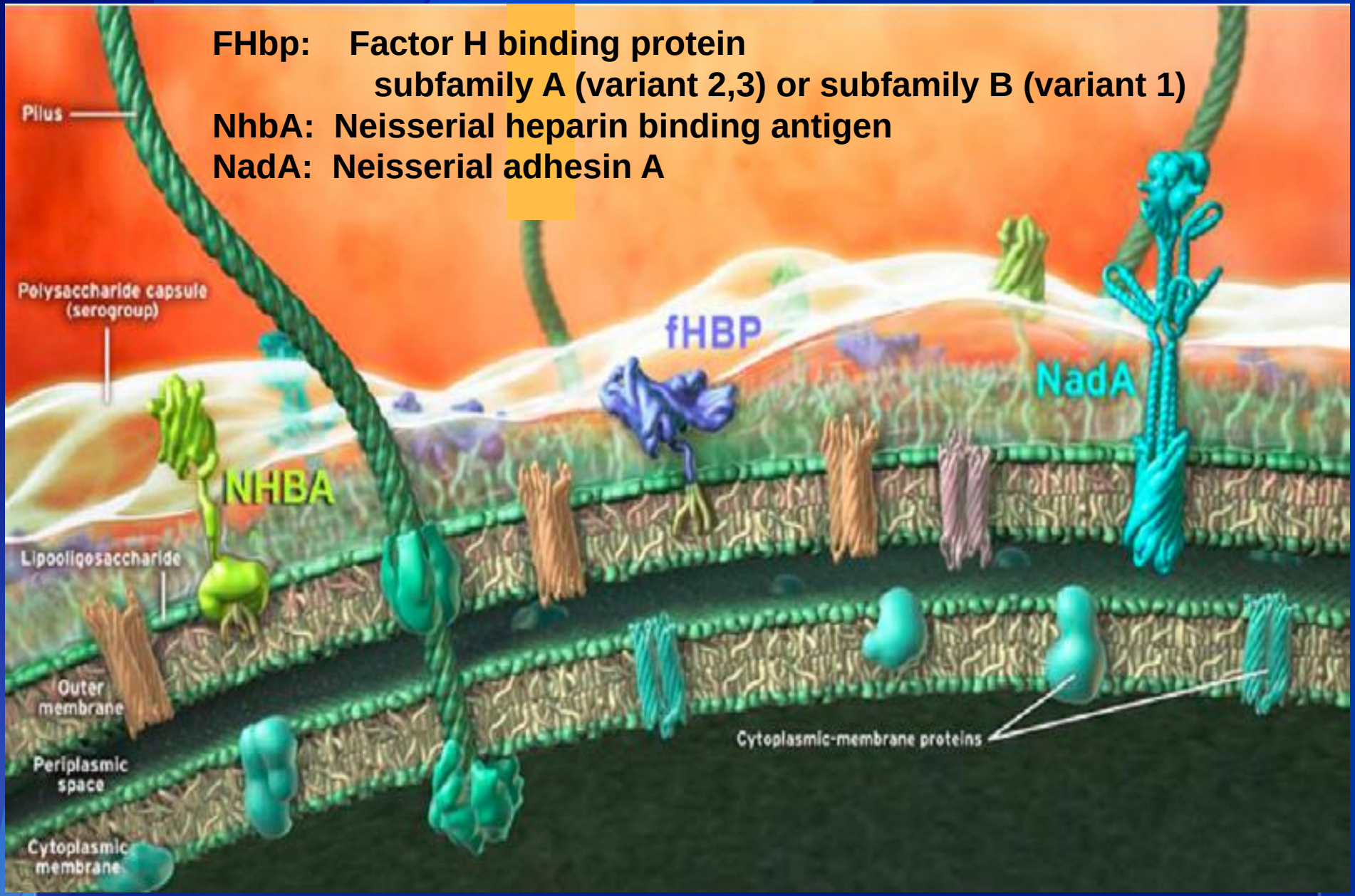
- Summary of serogroup B meningococcal (MenB) vaccines
- Meningococcal Vaccines Work Group considerations for use of MenB vaccines

SUMMARY OF SEROGROUP B (MENB) VACCINES

Development of MenB Vaccines Challenging

- **Polysaccharide capsule vaccine target for MenACWY, but poorly immunogenic for MenB**
- **Outer membrane vesicle (OMV) vaccines used to control MenB outbreaks**
  - Limited cross-protection with heterologous strains
  - Limited duration of protection
  - Limited efficacy in younger children
- **Ideal vaccine targets**
  - Essential gene
  - Immunogenic
  - Low diversity
  - Surface exposed

FHbp: Factor H binding protein
subfamily A (variant 2,3) or subfamily B (variant 1)
NhbA: Neisserial heparin binding antigen
NadA: Neisserial adhesin A



Vaccine 30S:B87,2012

Two MenB Vaccines for Persons 10-25 years of age

- **rLP2086, Trumenba ® (Pfizer) 3-dose series (0, 2, 6 months)**
  - FHbp subfamily A/v2,3; subfamily B/v1
  - Licensed in the U.S. on October 29, 2014
- **4CMenB, Bexsero® (Novartis) 2-dose series (0, 1-6 months)**
  - FHbp B/v1, NhbA, NadA, Por A1.4
  - Licensed in Europe, Australia and Canada in 2013 for ≥2 months of age
  - Expanded access investigational new drug protocol to control two recent university outbreaks
  - Granted Priority Review designation with announcement regarding licensure expected by early 2015

Correlates of Protection

- **Pre-licensure trials using clinical outcomes not feasible**
- **Human serum bactericidal activity (hSBA) shown to correlate with protection**
  - Bactericidal antibodies protective against invasive serogroup C disease in military recruits
  - Bactericidal antibodies in persons immunized with OMV vaccines during MenB outbreaks
- **hSBA established as serologic marker to infer protection with MenB vaccines during the 2011 VRBPAC meeting**

Challenges in Assessing Immunogenicity of MenB Vaccines for the US

- Evaluation of clinical efficacy in higher incidence countries not appropriate because molecular epidemiology different that U.S.
- Measurement for hSBA is assay-specific
- Bactericidal activity against multiple strains needed to evaluate antigen-specific responses
- Number of strains limited by hSBA methodology
  - Require large volumes of sera
  - Identification of complement source for each assay

Assessment of Immunogenicity: Selection of Strains

- **4CMenB, Bexsero® (Novartis)**
  - strains selected to evaluate immunogenicity to each antigen individually
- **rLP2086, Trumenba® (Pfizer)**
  - strains systematically selected to assess immunogenicity from a representative collection of circulating strains in the US

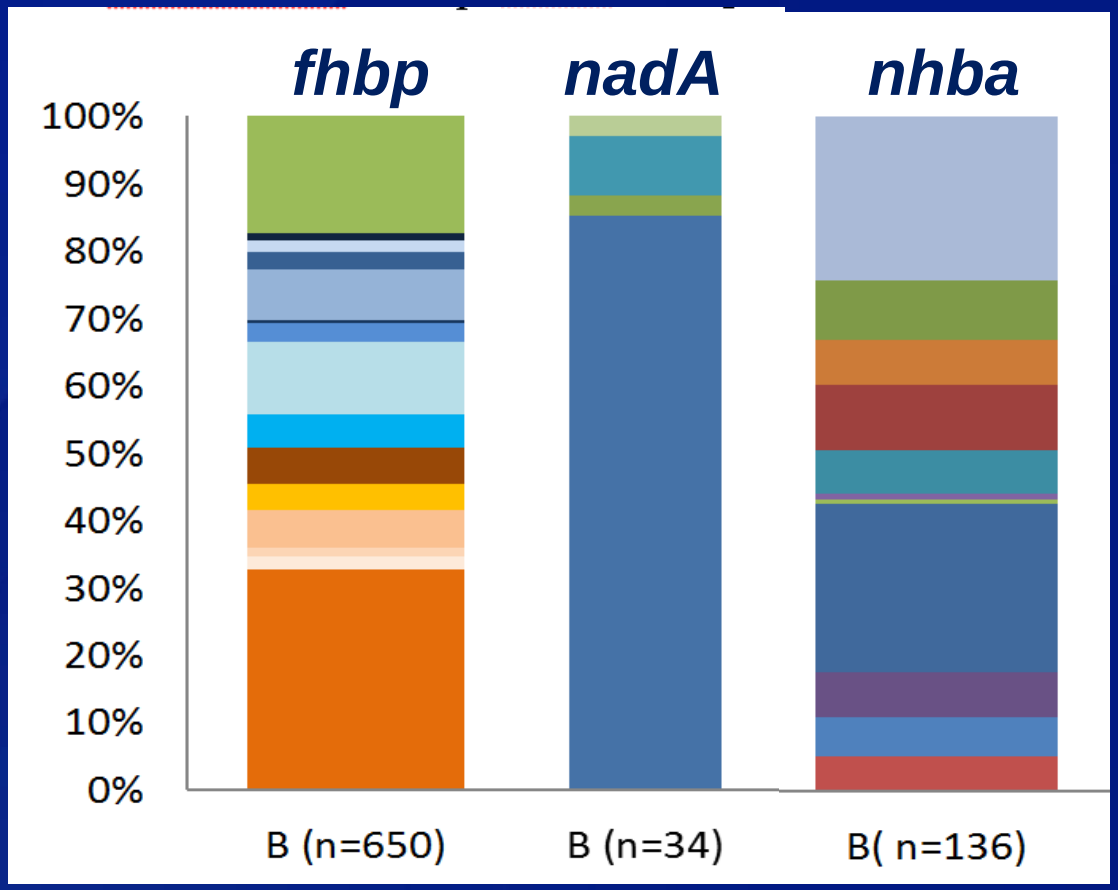
Assessment of Immunogenicity: Primary Endpoints

- **4CMenB, Bexsero® (Novartis)**
  - proportion of subjects with hSBA titers ≥1:4 or ≥1:5
  - 73-100% of adolescents demonstrated protective titers following two doses
  - Immunity wanes by 5-25% at two years
- **rLP2086, Trumenba® (Pfizer)**
  - proportion of subjects with hSBA titers four-fold increase from baseline (minimum titer ≥1:16); composite endpoint (hSBA ≥ 1:8 or 1:16)
  - 75-100% demonstrate protective titers following 3 doses
  - No long-term immunogenicity data available

Breadth of Coverage

- **Polysaccharide capsule highly conserved among strains within each serogroup**
- **Vaccine targets for MenB vaccines antigenically diverse within circulating MenB strains in the US**
- **Multifactorial approach to estimate coverage**
  - Presence or absence of gene
  - Genetic sequences
  - Level of expression of antigen
  - Bactericidal activity

Diversity of *fHbp*, *nadA* and *nhbA* Subvariants Among MenB Isolates Active Bacterial Core surveillance 2000-2008



Wang et al., Vaccine 29 (2011) 4739-4744

Proportion of Isolates with Gene for MenB Vaccine Antigens

- **All MenB isolates contain *fHbp***
  - 59% B/v1 (4CMenB, rLP2086)
  - 41% A/2-3 (rLP2086)
- ***nadA* present in 39% of MenB isolates**
  - NadA increase coverage of 4CMenB from 59% to 63%
- ***nhbA* found on all MenB isolates**
- **PorA P1.4 found in <5% of isolates**

Wang et al., Vaccine 29 (2011) 4739-4744

Assessment of Breadth of Coverage for rLP2086, Trumenba® (Pfizer)

- ***fHbp*** **sequence analysis and flow cytometry for surface expression performed on a representative collection of 1,263 MenB isolates (432 US isolates)**
- **Variability between subfamilies and surface expression of FHbp**
- **In a subset of isolates, moderate or high level expression of FHbp predictive of bactericidal activity**
  - Lower correlation in strains with low level expression of fHbp

Jiang et al., Vaccine 28 (2010) 6086-6093

Assessment of Breadth of Coverage for 4CMenB, Bexsero® (Novartis)

- **Meningoccocal Antigen Typing System (MATS)**
  - Sandwich ELISA measures cross-reactivity with vaccine antigens and level of expression of each antigen
- **MATS bridged to hSBA in a subset of diverse strains**
  - >80% predictive of bactericical activity with one antigen, >90% with two or more antigen
- **MATS was performed on 3,269 isolates (442 US isolates)**
  - 4CMenB estimated strain coverage 91% (95% CI: 72%-96%) in U.S.

Donnelly et al., PNAS (2010) vol. 107, no. 45

Summary

- Two MenB vaccines available in the US
- Serologic marker used as correlate to infer protection against MenB disease
- Breadth of coverage against diverse strains critical for vaccine effectiveness
- Potential differences in immunogenicity and breadth of coverage between MenB vaccines due to different vaccine targets

CONSIDERATIONS FOR USE OF MENB VACCINES

Overview

- **Rates of meningococcal disease at historic lows**
  - All serogroups
- **Vaccination with MenACWY at 11-12 years of age and a booster at 16 years of age**
  - Increasing vaccination coverage contributing to decreasing rates in adolescents
- **Serogroup B accounts for ~40% of meningococcal**
  - 50 cases annually among adolescents in recent years

Challenges when Considering Use of MenB Vaccines

- Breadth of coverage estimated; actual breadth of coverage unknown
- Duration of protection unknown
- Impact on carriage unknown
- Impact of vaccine pressure on circulating strains unknown
- Multi-dose schedules make implementation challenging
- Burden of MenB disease is low and not all cases will be prevented with vaccination

Options for Use of MenB vaccines

- **Recommendation for high risk groups only**
  - Medical conditions high risk for meningococcal disease
    - Persistent complement component deficiencies
    - Anatomic or functional asplenia
  - Microbiologists
  - Outbreak response
- **Routine recommendation for expanded groups**
  - Adolescent recommendation
  - College recommendation

Additional Data Needed to Inform Policy Decisions

- **Duration of protection**
- **Immunogenicity against additional strains to evaluate breadth of coverage**
- **Safety and immunogenicity**
  - Concomitant vaccination
  - High risk groups
  - Other age groups
- **Additional safety data**

Considerations for Use in High Risk Persons

- Limited to persons ≥ 10 years of age
- Persons with high risk medical conditions and microbiologists account for <300,000 people in the U.S.
- Based on CDC interim guidelines, vaccination recommended for 5 MenB outbreaks reported on college campuses (~60,000 people)
- Align high risk and outbreak recommendations for both MenB and MenACWY vaccines

Future ACIP Meetings

- **February 2015**
  - GRADE for high risk groups
  - Use of MenB vaccines in persons ≥10 years of age with high-risk medical conditions, microbiologists, and outbreaks
  - Planned vote on high risk groups
- **June/October 2015**
  - Review of evidence for expanded target groups
    - GRADE
    - Economic and impact analysis
  - Updated outbreak guidelines for all serogroups

Conclusions

- Considerations regarding use of MenB vaccines in the U.S. is complex
- Additional data following licensure will help inform policy decisions
- ACIP Meningococcal Vaccines Work Group will continue discussions on use of MenB vaccines in expanded groups

Discussion

- **Feedback on two-tiered approach**
  - High risk recommendation in February 2015
  - Continued discussions regarding use of MenB vaccines in broader target groups
- **Additional data ACIP would like to have presented at future meetings**

Thank you

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