Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Evidence for Use of MenB Vaccines in Adolescents and Young Adults (including College Students)

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June 24, 2014

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Outline

- **GRADE process for MenB vaccines**
  - Study question
  - Quality of meningococcal disease burden data
  - Breadth of MenB strain coverage
  - Evidence of outcomes

STUDY QUESTION

Study Question

- **Should MenB vaccines be administered routinely to all adolescents and young adults (including college students)?**

MenB Vaccines

- **MenB-4C (Bexsero®)**
  - Multicomponent vaccine
    - Factor H binding protein (FHbp), neisserial adhesion A (NadA), *Neisseria* heparin binding antigen (NhbA), and PorA1.4
  - Manufactured by Novartis/GSK
  - 2-dose series
- **MenB-FHbp (Trumenba®)**
  - Bivalent recombinant lipoprotein vaccine
    - FHbp
  - Manufactured by Pfizer
  - 3-dose series

Overview of Critical Outcomes

Assessment	Outcome
Modified assessment	Burden of disease
	- Cases and Incidence
	- Mortality of disease
	- Long-term sequelae
	Breadth of MenB strain coverage
Quality of evidence assessed using standard GRADE approach	Short-term immunogenicity against MenB
	Persistence in immunogenicity against MenB
	MenB immunogenicity with concomitant vaccines
	Safety with concomitant vaccination
	Serious adverse events

QUALITY OF MENINGOCOCCAL DISEASE BURDEN DATA

What is the Quality of Our Data on Meningococcal Disease Burden?

- **Unable to use GRADE format to evaluate data**
  - Surveillance
  - No intervention tested
- **Important to objectively assess these data**
  - Accuracy
  - Applicability
  - Representativeness

Active Bacterial Core surveillance (ABCs)

- **Population-based active surveillance in 10 sites**
  - Observed cases used to estimate incidence in the United States
- **Limited to culture-confirmed cases**
  - 18% correction added to ABC's estimates to account for PCR-confirmed cases
- **Provides data on historical trends, risk factors, vaccination, molecular data, etc.**
- **Low case counts in ABCs in recent years has led to an integrated approach for meningococcal disease surveillance data**

National Notifiable Diseases Surveillance System (NNDSS)

- **Passive reporting by all U.S. states/territories**
  - Includes culture and PCR-confirmed cases
- **Historically, limited serogroup and case outcome information**
  - Additional serogroup and outcome information collected from ABCs and state health departments since 2005
- **Accuracy of meningococcal disease reporting assessed through a capture-recapture analysis, Maine, 2001-2006**
  - Demonstrated high sensitivity when compared to hospital discharge records

Quality of Meningococcal Disease Burden Data

- **Accuracy**
  - Improved when using an integrated approach to surveillance
- **Applicability**
  - Captures meningococcal disease incidence in adolescents and young adults
- **Representativeness**
  - ABCs limited to 10 sites and may not representative of national meningococcal disease incidence
  - NNDSS reported by all states and representative of national meningococcal disease incidence

Quality of Meningococcal Disease Mortality and Long-Term Sequelae Data

- **Sources for case outcome data**
  - Mortality data collected from ABCs and NNDSS
  - Long-term sequelae captured in published manuscripts
- **Accuracy**
  - Estimates of CFR range from 2-10%
  - Estimates of long-term sequelae range from <5-50%*
- **Applicability/representativeness**
  - Captures meningococcal deaths among adolescents
  - Long-term sequelae from all-cause bacterial meningitis
    - Studies often have small numbers, hospital-based
    - Limited analysis by age group/serogroup

*Bedford et al., BMJ 2001, 323: 533-7;Chandran et al., PIDJ 2011, 30:3-6.; Erickson and De Wals. CID 1998, 26:1159-64; Kaplan et al., Pediatrics 2006, 118(4):e979-84

Evaluation of Meningococcal Disease Burden Data: Overall High Quality Data

Criteria	Incidence	Mortality	Morbidity
Representativeness	Minor	Minor	Minor
Accuracy	Minor	Minor	Minor
Applicability	Minor	Minor	Minor

BREADTH OF MENB STRAIN COVERAGE

Breadth of Coverage

- Vaccine targets for MenB vaccines antigenically diverse within circulating serogroup B strains in the U.S.
- No data demonstrating bactericidal activity against all circulating invasive MenB strains in the U.S.

Assessment of Breadth of Coverage for MenB-FHbp

- **FHbp sequence analysis and flow cytometry for surface expression performed on a representative collection of 1,263 serogroup B isolates (432 U.S. isolates)**
  - FHbp expressed in ~95% of invasive serogroup B strains
- **Variability between subfamilies and surface expression of FHbp**
- **Moderate or high level expression of FHbp predictive of bactericidal activity**

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

Assessment of Breadth of Coverage for MenB-4C

- **Meningococcal 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 antigens
- **MATS was performed on 3,269 isolates (442 U.S. isolates)**
  - MenB-4C estimated strain coverage 91% (95% CI: 72%-96%) in U.S.*

* Donnelly et al., PNAS (2010) vol. 107, no. 45. Based on representative strain panel of invasive MenB isolates from 2000-2008 selected by US CDC (adjusted with respect to strains from Oregon).

Assessment Summary

- True breadth of coverage for endemic MenB disease estimated for both MenB vaccines
  - Level of antigenic expression used as a marker to predict bactericidal activity
- Different methods used to assess breadth of coverage
- Secondary studies to evaluate immunogenicity against additional strains pending

EVIDENCE OF OUTCOMES

Outcomes for Consideration

Outcomes	Description
Short-term immunogenicity against MenB	Licensure immunogenic endpoints achieved 1 month after last dose of vaccine
Persistence in immunogenicity against MenB	Licensure immunogenic endpoints achieved 11-24 months (MenB-4C) or 48months (MenB-FHbp) after last dose of vaccine
MenB immunogenicity with concomitant vaccines	Non-inferiority in MenB immune response following concomitant vaccination
Serious adverse events	Defined as any medical occurrence that results in death, is life-threatening, requires hospitalization, results in disability/incapacity, is an important medical event
Safety with concomitant vaccination	SAEs related to concomitant administration

- Data sources: published and unpublished data, Investigator's Brochure
- Inclusion criteria: U.S. and non-U.S. populations, final formulation and manufacturers' proposed dosing of the vaccine

Immunogenicity Endpoints

- **Vaccine efficacy is estimated from serum bactericidal antibodies against a small number of serogroup B strains**
- **Immunogenicity assessed by:**
  - Proportion of subjects who achieved a ≥4-fold increase in hSBA* titer for each strain tested
  - Proportion of subjects who achieved a titer ≥LLOQ (lower limit of quantitation) of the assay for all strains (composite response)
    - LLOQ was defined as the lowest amount of antibody in a sample that can be reliably quantified

*Serum bactericidal activity using human complement (hSBA)

GRADE Criteria

- Risk of bias (methodological limitations)
- Inconsistency
- Indirectness
- Imprecision
- Other considerations (publication bias, strength of association, dose gradient)

Algorithm for Determining Final Evidence Type

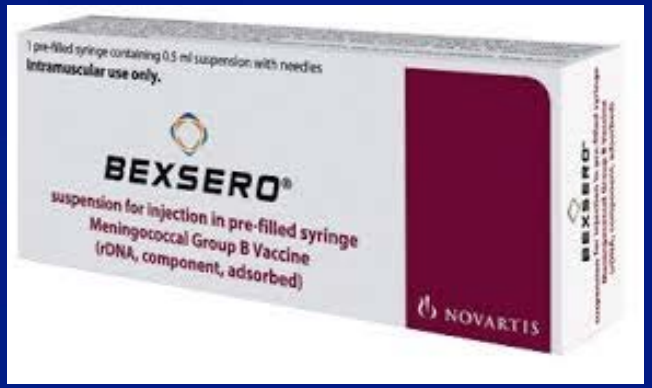
Study design	Initial evidence Type	Criteria for moving down*	Criteria for moving up*^	Final evidence type
RCTs	1	**Risk of bias** -1 Serious -2 Very serious **Inconsistency** -1 Serious -2 Very serious **Indirectness** -1 Serious -2 Very serious **Imprecision** -1 Serious -2 Very serious **Publication bias** -1 Likely -2 Very likely	**Strength of association** + 1 Large + 2 Very large **Dose response** + 1 Evidence of a gradient **Direction of all plausible residual confounding** + 1 Would reduce a demonstrated effect, or + 1 Would suggest a spurious effect when results show no effect	1
				2
Observational studies	3			3
				4

* 1= move up or down 1 level, 2= move up or down 2 levels

^Observational studies that were moved down cannot be moved up.

MenB-4C (Bexsero®):

BEXSERO®
Meningococcal Group B Vaccine
(rDNA, component, adsorbed)



MenB-4C: Evidence of Outcomes

	Outcome	Evidence Type (# of studies) for MenB-4C
Benefits	Short-term immunogenicity (1 month post vaccination)	RCT(3) Non-controlled open label study (1)
	Persistence in immunogenicity (11-24 months post vaccination)	RCT(2)
	MenB immunogenicity with concomitant vaccination	None
Harms	Serious adverse events	RCT(3)
	Safety with concomitant vaccination	None

- 5 studies in total: 1 non-controlled study and 4 RCTs
- 4 papers published
- 3 post-vaccination campaign data

MenB-4C: Evidence of Benefits

- **Short-term immunogenicity**
  - 63-94% of adolescents demonstrated a composite hSBA response to three strains after 2 doses
    - 63% (CI - 57%, 68%) 1 month after vaccination with 2 doses among Canadian and Australian adolescents
    - 88% (CI - 82%, 93%) 1 month after vaccination with 2 doses among UK university students
    - 90%-94% 1 month after vaccination with 2 doses among Chilean adolescents
- **Persistence in immunogenicity**
  - 66% (CI- 58%, 72%)* 11 months after vaccination with 2 doses among UK university students
  - 77%-94%**, 18-24 months after vaccination with 2 doses among Chilean adolescents

*Composite response to 3 strains used as correlate of protection, **hSBA≥1:4 used as correlate of protection

MenB-4C: Evidence of Harms
Severe Adverse Events

- **3,140 participants received at least one dose of the MenB-4C**
  - 67 SAEs were reported
    - 5 SAEs* determined to be related to vaccine
    - 2 deaths** reported - unrelated to vaccine

* Tremor, dyspnea, acute thyroiditis and 2 cases of juvenile arthritis
**Deaths were due to complicated craneo-cerebral trauma secondary to a car accident and acute hepatic failure secondary to paracetamol intoxication

MenB-4C: Evidence of Harms
Post Vaccination Campaign SAEs Data

- **59,091 participants received at least one dose of MenB-4C**
  - 60 SAEs were reported
    - 3 SAEs* determined to be related to the vaccine
    - 1 death** reported - unrelated to vaccine

* Rhabdomyolysis, anaphylaxis and fever
**Cause of death was drowning

Evidence Table: Routine Administration of MenB-4C to Healthy Adolescents and Young Adults (Including College Students)

Outcomes	Design (# studies)	Initial Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Others	Final Evidence	Overall Evidence Type
				Benefits						
Short-term immunogenicity	3 RCTs	1	Not Serious	**Serious** (-1)**	**Serious*** (-1)**	Not Serious	Unable to assess	**Yes## (+1)**	2	2
	1 Obs	3	Not serious	Not serious	**Serious*** (-1)**	Not Serious	Unable to assess	None	4	
Persistence of immunogenicity (11-24 months)	2 RCTs	1	**Serious* (-1)**	Not serious	**Serious*** (-1)**	Not Serious	Unable to assess	None	3	3
MenB Immunogenicity with concomitant vaccination	No available studies									
				Harms						
Serious Adverse Events	3 RCTs	1	Not serious	Not serious	Not Serious	**Serious# (-1)**	Unable to assess	None	2	2

Footnotes:

* No formal statistical hypothesis testing or sample size calculation planned in the protocol for one study. Potential selection bias for participants in the other study – downgraded by 1

** High heterogeneity, I-squared > 90% across all strains – downgraded by 1

*** Studies assessed correlate of protection and not directly efficacy – downgraded by 1

The CI around the effect estimate includes both effect and non-effect – downgraded by 1

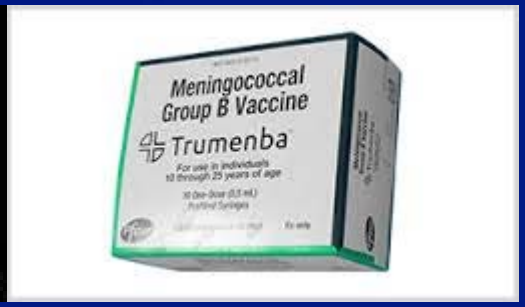
Strong strength of association. RR ranges between 4.44 and 5.19 – upgraded by 1

MenB-4C: Considerations for Vaccine Use

Key Factors	Comments
Balance between benefits and harms	Among healthy adolescents and young adults (including college students), the vaccine is immunogenic in the short-term and persists 1-2 years after vaccination. Low disease burden lowers overall benefits.
	Evidence type for benefits and harms
MenB-4C vaccine use among healthy adolescents and young adults (including college students)	**Benefits:** Short-term immunogenicity: **Evidence Type 2** Persistence in immunogenicity (11-24 months): **Evidence Type 3** MenB immunogenicity with concomitant vaccination: **Not assessed** **Harms:** Serious Adverse Events: **Evidence Type 2** SAEs following concomitant vaccination: **Not assessed**

MenB-FHbp (Trumenba®)

Trumenba®
Meningococcal Group B Vaccine



MenB-FHbp: Evidence of Outcomes

	Outcome	Evidence Type (# of studies) for MenB-FHbp
Benefits	Short-term immunogenicity (1 month post vaccination)	RCT(2) Non-controlled open label study (1)
	Persistence in immunogenicity (48 months post vaccination)	Non-controlled open label study (1)
	MenB immunogenicity with concomitant vaccination	RCT(2)
Harms	Serious adverse events	RCT(5)
	Safety with concomitant vaccination	RCT(2)

- 7 studies in total: 2 non-controlled studies and 5 RCTs
- 3 papers published

MenB-FHbp: Evidence of Benefits

- **Short-term immunogenicity**
  - 83.9% (CI- 81.1%, 86.4%) 1 month after vaccination with a 3-dose series among U.S. adolescents
  - 81.0% (CI- 78.0%, 83.7%) 1 month after a 3-dose series was co-administered with 4vHPV vaccine among U.S. adolescents
    - No immunological interference observed for serogroup B or vaccine antigens (MenACWY, Tdap, DTaP/IPV, HPV types 6, 11, 16)
      - HPV type 18 non-inferiority criteria* were not met, however 99% of subjects achieved seroconversion for all 4 HPV antigens
- **Persistence in immunogenicity**
  - At 48 months, >50% of vaccinees continue to demonstrate hSBA titers >LLOQ against three reference strains, among adolescents in Australia, Spain and Poland

*Lower bound of the 95% confidence-interval of the geometric mean titer (GMT) ratio >0.67 (lower bound was 0.62)

MenB-FHbp: Evidence of Harms

- **11,338 participants received at least one dose of MenB-FHbp**
  - 190 SAEs were reported in the vaccine group
    - 7 SAEs* determined to be related to vaccine
    - 1 death** reported - unrelated to vaccine

* Pyrexia, vomiting, vertigo, chills, headache, anaphylaxis and neutropenia
**Death due to road accident

Evidence Table: Routine Administration of MenB-FHbp to Healthy Adolescents and Young Adults (Including College Students)

Outcome	Design (#studies)	Initial Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Others	Final Evidence Type	Overall Evidence Type
				Benefits						
Short-term Immunogenicity	2 RCTs	1	Not serious	Not serious	**Serious ** (-1)**	Not serious	Unable to assess	**Yes## (+1)**	2	2
	1 Obs	3	Not serious	Not applicable	**Serious ** (-1)**	Not serious	Unable to assess	None	3	
Persistence in Immunogenicity 48 months post vaccination	1 Obs	3	**Serious* (-1)**	Not applicable	**Serious ** (-1)**	**Minor *****	Unable to assess	None	4	4
MenB immunogenicity with concomitant vaccination (Non-inferiority) +	2 RCTs	1	Not serious	Not serious	**Serious ** (-1)**	Not serious	Unable to assess	None	2	2
				Harms						
Serious Adverse Events (SAEs)	5 RCTs	1	Not serious	Not serious	Not serious	**Serious # (-1)**	Unable to assess	None	2	2
Safety with Concomitant vaccination (SAEs)	2 RCTs	1	Not serious	Not serious	Not serious	**Serious # (-1)**	Unable to assess	None	2	2

Footnotes:

+ Concomitant administration with TdaP/IPV or HPV4

* Very small sample size

** Studies assessed correlate of protection and not directly efficacy – downgraded by 1

*** The CI around the effect estimate includes both effect and non-effect in two strains not common in the U.S.

The CI around the effect estimate includes both effect and non-effect – downgraded by 1

Very strong strength of association: relative risk ranges between 4.64 between 12.26 – upgraded by 1

MenB-FHbp: Summary Considerations for Vaccine Use

Key Factors	Comments
Balance between benefits and harms	Among healthy adolescents and young adults (including college students), the vaccine is immunogenic in the short-term and persists up to 4 years after vaccination. MenB-FHbp is safe for concomitant vaccination with 4vHPV, MenACWY, Tdap and DTaP/IPV. Low disease burden lowers overall benefits.
	Evidence type for benefits and harms
MenB-FHbp vaccine use among healthy adolescent and young adults (including college students)	**Benefits:** Short term immunogenicity: **Evidence Type 2** Persistence in Immunogenicity(48 months): **Evidence Type 4** MenB immunogenicity with concomitant vaccination: **Evidence Type 2** **Harms:** Serious Adverse Events: **Evidence Type 2** SAEs following concomitant vaccination: **Evidence Type 2**

Considerations for Vaccine Use: MenB-4C and MenB-FHbp

MenB-4C/MenB-FHbp Vaccine use among healthy adolescents and young adults (including college students)	
MenB-4C (Bexsero®)	**MenB-FHbp (Trumenba®)**
Benefits: Short-term immunogenicity: **Evidence Type 2** Persistence in Immunogenicity (11-23 months): **Evidence Type 3** MenB immunogenicity with concomitant vaccination: **Not assessed**	**Benefits:** Short-term immunogenicity: **Evidence Type 2** Persistence in Immunogenicity (48 months): **Evidence Type 4** MenB immunogenicity with concomitant vaccination: **Evidence Type 2**
Harms: Serious Adverse Events: **Evidence Type 2** SAEs following concomitant vaccination: **Not assessed**	**Harms:** Serious Adverse Events: **Evidence Type 2** SAEs following concomitant vaccination: **Evidence Type 2**

Acknowledgements

- Jessica MacNeil
- Stacey Martin
- Elizabeth Briere
- Manisha Patel
- Fabien Diomande
- Doug Campos-Outcalt
- ACIP Meningococcal Vaccines Work Group
- Pfizer Vaccines
- Novartis (GSK) Vaccines

Thank you!

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