Grading of Recommendations Assessment, Development, and Evaluation (GRADE): Use of Serogroup B Meningococcal (MenB) Vaccines in Adolescents and Young Adults (Including College Students)

Introduction

Two serogroup B meningococcal (MenB) vaccines have recently been licensed for use in the U.S. (MenB-FHbp [Trumenba, Wyeth Pharmaceuticals, Inc.] and MenB-4C [Bexsero, Novartis Vaccines]). Both vaccines were approved for use in persons aged 10 through 25 years. MenB-FHbp was licensed as a three-dose series and MenB-4C was licensed as two-dose series. Evidence of benefits and harms were reviewed in accordance with GRADE methods (1). The primary policy question was "Should MenB vaccines be administered routinely to all adolescents and young adults (including college students)?"

Methods for GRADE

The benefits outcomes considered for each vaccine included short-term immunogenicity (1 month after vaccination), persistence of immunogenicity (11–48 months after vaccination, if data available), and MenB immunogenicity with concomitant vaccines. The harms outcome considered for each vaccine included occurrence of serious adverse events (SAEs) after vaccination and safety of concomitant administration with other vaccines.

Immunogenicity and safety data from five clinical trials (3 randomized controlled trials (RCT), 1 randomized uncontrolled trial, and 1 immunogenicity extension study) of MenB-4C (2-6) and seven clinical trials (5 RCTs and 2 open label studies) of MenB-FHbp (7-10) (Pfizer, unpublished data) were considered in the assessment. The evidence type for each outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, imprecision and other considerations (strength of association, dose response gradient and opposing plausible residual confounding or bias).

Estimates of short-term immunogenicity and persistence of immunogenicity (11–48 months after vaccination, if data available) were based on demonstration of immune response, as measured by human serum bactericidal activity (hSBA) against a small number of serogroup B strains. In studies supporting U.S. licensure, immunogenicity was assessed by the proportion of subjects who achieved a ≥4-fold increase in hSBA titer for each of the strains tested, and the proportion of subjects who achieved a titer greater than or equal to the lower limit of quantitation (LLOQ) of the assay for all strains (composite response). The LLOQ was defined as the lowest amount of the antibody in a sample that can be reliably quantified.

Results:

Table 1a: Use of MenB-4C (Bexsero®) in adolescents and young adults (including college students): Evidence Table

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
Safety with Concomitant vaccination (SAEs)	No available studies									

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

Table 1b: Considerations for Vaccine Use: MenB-4C (Bexsero®)

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**

Table 2a: Use of MenB-FHbp (Trumenba®) in adolescents and young adults (including college students): Evidence Table

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	Serious** (-1)	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	4	
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 4vHPV
*** Very small sample size**
****Significant heterogeneity; I-square ranges between 43-81% — Downgraded 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 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

Table 2b: Considerations for Vaccine Use: MenB-FHbp (Trumenba®)

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 Tdap/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**

Summary:

After reviewing the available data, including the result of the GRADE analysis, the Advisory Committee on Immunization Practices (ACIP) recommended that adolescents and young adults aged 16 through 23 years may be vaccinated with a MenB vaccine to provide short term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16 through 18 years of age (recommendation Category B). Category B recommendations are made for individual clinical decision making. The full recommendations for the use of MenB vaccines in adolescents and young adults (including college students) are available on the ACIP website [ADD LINK TO RECOMMENDATION].

References

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