**Grading of Recommendations Assessment, Development, and Evaluation (GRADE): Use of Serogroup B Meningococcal (MenB) Vaccines in Persons at Increased Risk for Serogroup B Meningococcal Disease**

## Introduction

In October 2014, the Food and Drug Administration (FDA) licensed the first serogroup B meningococcal (MenB) vaccine (MenB-FHbp [Trumenba®, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc., Philadelphia, Pennsylvania]) as a 3-dose series. The FDA licensed a second MenB vaccine (MenB-4C [Bexsero®, Novartis Vaccines, Siena, Italy]) in January 2015 as a 2-dose series. Both vaccines were approved for use in persons aged 10 through 25 years. 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 persons aged ≥10 years at increased risk for serogroup B meningococcal disease or at increased risk for serogroup B disease because of an outbreak?"

## Methods for GRADE

The benefits outcomes considered for each vaccine included short-term immunogenicity (1 month after vaccination) and persistence of immunogenicity (11–24 months after vaccination, if data available). The harms outcome considered for each vaccine included occurrence of serious adverse events (SAEs) after vaccination.

Safety and immunogenicity data from seven clinical trials (6 RCTs and one immunogenicity extension study) of MenB-4C (2-7) (Novartis, unpublished data) and nine clinical trials (6 RCTs and 3 open label studies) of MenB-FHbp (8-13) (Pfizer unpublished data) were considered in the assessment.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 (11–24 months after vaccination, if data available) were based on demonstration of immune response, as measured by serum bactericidal activity using human complement (hSBA) against a small number of serogroup B strains. In studies supporting US 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) (see package inserts; available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM431447.pdf and http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM421139.pdf). The LLOQ was defined as the lowest amount of the antibody in a sample that can be reliably quantified.

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**Results:**

**Table 1a: Use of MenB-4C (Bexsero®) in Persons at Increased Risk: Evidence Table**

| Outcome | 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** (-2) | Not Serious | Unable to assess | Yes## (+1) | 3 | 3 |
| | 2 Obs | 3 | Not serious | Not serious | Serious# (-2) | Not Serious | Unable to assess | None | 4 | |
| **Persistence of immunogenicity (11-24 months)** | 2 RCTs | 1 | Serious#* (-1) | Not serious | Serious** (-2) | Not Serious | Unable to assess | None | 4 | 4 |
| **Harms** | | | | | | | | | | |
| **Serious Adverse Events** | 3 RCTs | 1 | Not serious | Not serious | Serious> (-1) | Serious*** (-1) | Unable to assess | None | 3 | 3 |

**Footnotes:**

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

**** Focused on healthy adolescents and young adults, not persons at increased risk of serogroup B meningococcal disease; studies assessed correlate of protection and not directly efficacy – downgraded by 2**

**## Strong strength of association. RR ranges between 2.46 and 4.25 – upgraded by 1**

**# One study focused on laboratory workers only, other groups at increased risk (e.g., persons with compliment deficiencies or asplenia) not considered; studies assessed correlate of protection and not directly efficacy – downgraded by 2**

**#* 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**

**> Focused on healthy adolescents and young adults, not persons at increased risk of serogroup B meningococcal disease – downgraded by 1**

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

**Table 1b: Use of MenB-4C (Bexsero®) During Outbreaks: 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** | 3 RCTs | 1 | Not Serious | Serious** (-1) | Serious# (-1) | Not Serious | Unable to assess | Yes## (+1) | 2 | 2 |
| | 2 Obs | 3 | Not Serious | Not serious | Serious# (-1) | Not Serious | Unable to assess | None | 4 | |
| **Harms** | | | | | | | | | | |
| **Serious Adverse Events** | 3 RCTs | 1 | Not serious | Not serious | Not serious | Serious*** (-1) | Unable to assess | None | 2 | 2 |

**Footnotes**
**** High heterogeneity, I-squared > 97% across all strains – downgraded by 1**
**# Studies assessed correlate of protection and not directly efficacy – downgraded by 1**
**## Strong strength of association. RR ranges between 2.46 and 4.25 – upgraded by 1**
***** The CI around the effect estimate includes both effect and non-effect –downgraded by 1**

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

| Key Factors | Comments |
|---|---|
| **Balance between benefits and harms** | Vaccine is immunogenic in the short-term, and immunogenicity persists (1-2 years) for healthy adolescents and adults, and is safe. Low disease burden lowers overall benefits. |
| **Evidence type for benefits and harms** | |
| **Use of MenB-4C in persons at increased risk** | Benefits: Evidence Type: 3<br>Harms: Evidence Type: 3<br>**Overall: Evidence Type: 3** |
| **Use of MenB-4C during outbreaks** | Benefits: Evidence Type: 2<br>Harms: Evidence Type: 2<br>**Overall: Evidence Type: 2** |

## Table 2a: Use of MenB-FHbp (Trumenba®) in Persons at Increased Risk: 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** (-2) | Not serious | Unable to assess | Yes*** (+1) | 3 | 3 |
| | 3 Obs | 3 | Serious> (-1) | Minor | Serious** (-2) | Not serious | Unable to assess | None | 4 | |
| **Harms** | | | | | | | | | | |
| **Serious Adverse Events** | 5 RCTs | 1 | Not serious | Not serious | Serious# (-1) | Serious## (-1) | Unable to assess | None | 3 | 3 |

**Footnotes:**
*** Significant heterogeneity; I-square ranges between 40-91% – Downgraded 1**
**** Studies focused on healthy adolescents and young adults, not persons at increased risk of serogroup B meningococcal disease; studies assessed correlate of protection and not directly efficacy – downgraded by 2**
***** Very strong strength of association: relative risk ranges between 4 between 9 – upgraded by 1**
**> In one study, no statistical consideration taken into account when determining sample size; sample size was small in a second study – downgraded by 1**
**# With the exception of one study, all other studies did not focus on persons at increased risk of serogroup B meningococcal disease – downgraded by 1**
**## The CI around the effect estimate includes both effect and non-effect – downgraded by 1**

## Table 2b: Use of MenB-FHbp (Trumenba®) During Outbreaks: 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 |
| | 3 Obs | 3 | Serious> (-1) | Minor* | Serious** (-1) | Not serious | Unable to assess | None | 4 | |
| **Harms** | | | | | | | | | | |
| **Serious Adverse Events** | 5 RCTs | 1 | Not Serious | Not serious | Not serious | Serious## (-1) | Unable to assess | None | 2 | 2 |

**Footnotes:**
*** Significant heterogeneity; I-square ranges between 40-91 % – downgraded by 1**
**** Studies assessed correlate of protection and not directly efficacy –-downgraded by 1**
***** Very strong strength of association: relative risk ranges between 4 between 9 – upgraded by 1**
**> In one study, no statistical consideration taken into account when determining sample size; sample size was small in a second study – downgraded by 1**
**##The CI around the effect estimate includes both effect and non-effect –downgraded by 1**

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

| Key Factors | Comments |
|---|---|
| **Balance between benefits and harms** | Vaccine is immunogenic in the short-term for healthy adolescent and adults, and is safe. Low disease burden lowers overall benefits. |
| **Evidence type for benefits and harms** | |
| **Use of MenB-FHbp in persons at increased risk** | Benefits: Evidence Type: 3<br>Harms: Evidence Type: 3<br>**Overall: Evidence Type: 3** |
| **Use of MenB-FHbp during outbreaks** | Benefits: Evidence Type: 2<br>Harms: Evidence Type: 2<br>**Overall: Evidence Type: 2** |

**Summary:** The evidence type for both vaccines was determined to be type 2 (moderate level of evidence) for use in outbreak settings, and type 3 (low level of evidence) for use in persons at increased risk of serogroup B meningococcal disease; the recommendation was designated Category A (recommended for all persons in an age- or risk-factor-based group). The GRADE methodology is not entirely objective and there are areas in the methodology that are subject to interpretation by the evaluator. A head to head comparison of the two vaccines was not done because the vaccines target different antigens. Certain groups of individuals are known to be at increased risk for meningococcal disease and are currently recommended to be routinely vaccinated with a quadrivalent meningococcal conjugate vaccine (MenACWY) which protects against serogroups A, C, W, and Y. Many of these groups are also at increased risk for serogroup B meningococcal disease. On February 26, 2015, the Advisory Committee on Immunization Practices (ACIP) recommended use of MenB vaccines among certain groups of persons aged ≥10 years who are at increased risk for serogroup B meningococcal disease; these persons include those with persistent complement component deficiencies; persons with anatomic or functional asplenia; microbiologists routinely exposed to isolates of Neisseria meningitidis; and persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak. Available immunogenicity and safety data support the use of MenB vaccines in groups at increased risk for serogroup B meningococcal disease. Both MenB vaccines are approved for use in individuals aged 10 through 25 years; however, due no theoretical differences in safety for those aged >25 years as compared to those aged 10 through 25 years, the ACIP supported routine use of MenB vaccines in persons aged ≥10 years at increased risk for meningococcal disease, including in persons at increased risk because of a serogroup B meningococcal disease outbreak. These recommendations do not apply to children younger than 10 years of age.

**References**

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