Considerations for Serogroup B Meningococcal (MenB) Vaccine Booster Doses in Persons at Increased Risk for Serogroup B Meningococcal Disease

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Timeline of ACIP Recommendations for Groups at Increased Risk of Meningococcal Disease

MPSV4 polysaccharide vaccine recommended for groups at increased risk

~1980

2005

MenACWY conjugate vaccine recommended for persons 11–55 years at increased risk

- Original age indication for licensure
- Recommended for children 2–10 years and infants as licensed indication expanded
- MPSV4 was available for other age groups

2010

Booster doses of MenACWY conjugate vaccine added for certain groups who remain at increased risk

MenACWY Conjugate Vaccine Booster Recommendations

- Rationale for MenACWY booster recommendations:
  - Small targeted groups
  - Demonstrated increased risk for meningococcal disease
  - Evidence of waning functional antibody 3–5 years after a single dose of MenACWY
  - Evidence of booster response to revaccination
  - Low-risk for serious adverse events
  - Accepted standard of care for high-risk groups

- Booster doses of MenACWY recommended every 5 years* throughout life for certain persons who remain at increased risk for meningococcal disease

*If most recent dose received before age 7 years, a booster dose should be administered 3 years later.

Two Serogroup B Meningococcal (MenB) Vaccines Licensed for Persons Aged 10–25 Years in 2014 and 2015

- MenB-FHbp (Trumenba®, Pfizer)
  - Two components (fHbp subfamily A/v2,3; subfamily B/v1)
  - 3-dose series, administered at 0, 1–2, and 6 months
    - Persons at increased risk for serogroup B meningococcal disease
  - 2-dose series, administered at 0 and 6 months
    - Healthy adolescents who are not at increased risk for meningococcal disease
- MenB-4C (Bexsero®, GlaxoSmithKline)
  - Four components (fHbp subfamily B/v1; NhbA; NadA; Por A1.4)
  - 2 dose series, administered at 0 and ≥1 month
  - Licensed in >35 countries for persons ≥2 months of age

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2015

MenB vaccine recommended for persons ≥10 years at increased risk

Current ACIP MenB Vaccine Recommendations

- Certain persons aged ≥10 years who are at increased risk for meningococcal disease should receive MenB vaccine (Category A); February 2015:
    - Persons with persistent complement component deficiencies[1]
    - Persons with anatomic or functional asplenia[2]
    - Microbiologists routinely exposed to isolates of *Neisseria meningitidis*
    - Persons identified as at increased risk because of a serogroup B meningococcal disease outbreak
- Adolescents and young adults aged 16–23 years may receive MenB vaccine to provide short-term protection against most strains of serogroup B meningococcal disease (Category B); June 2015
- No ACIP guidance for booster doses to date

[1]Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab (Soliris®)

[2]Including sickle cell disease

Statement of Problem

- Certain persons at increased risk for meningococcal disease likely remain at increased risk throughout their lifetime
- Data suggest waning of antibodies after vaccination with MenB vaccines
- Limited data on:
  - Immunogenicity of MenB primary series among immunocompromised subjects
  - Duration of protection of MenB vaccines among persons at increased risk
  - Efficacy of MenB booster doses among persons at increased risk
- Unlikely more data will become available for persons at increased risk
- Need to optimize protection for persons at increased risk for meningococcal disease

Outline

- Review of groups at increased risk for serogroup B meningococcal disease
- Immunogenicity of MenB-4C (Bexsero®) among immunocompromised subjects
- Antibody persistence and response to booster dose following primary series of MenB-FHbp (Trumenba®) or MenB-4C (Bexsero®) among healthy subjects
- Proposed policy option

Persons at Increased Risk for Serogroup B Meningococcal Disease

Persons with Persistent Deficiencies in the Complement Pathway

- Persistent (i.e., genetic) deficiencies in the complement pathway (e.g., C3, properdin, Factor D, Factor H, or C5-C9)
  - Up to 10,000-fold increased risk and can experience recurrent disease
  - Prevalence of ~0.03% in general population (all complement component deficiencies)[1]
- Complement component deficiencies are often recognized as a result of a meningococcal infection
  - Frequency of complement component deficiency among individuals with meningococcal disease in the U.S. estimated between 7%–25%[2]

[1]Densen R. Clin Exp Immunol. Oct 1991; 86(Suppl 1): 57-62.

[2]Figueroa JE. Clinical Microbiology Reviews. July 1991; 4(3):359-95.

Eculizumab (Soliris®)

- Monoclonal antibody indicated for treatment of atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH)
  - Binds to C5 and inhibits the terminal portion of the complement cascade
- 16 cases of meningococcal infection (1 death) out of 5207 person-years of eculizumab exposure during 2007–2014[1]
  - 2000 times the occurrence of meningococcal disease among U.S. population
  - 1 serogroup B, 2 serogroup C, 2 serogroup Y, 11 unknown serogroup[1]
  - All vaccinated with MenACWY[1]
- Recent MenB vaccine failure identified among patient taking eculizumab in UK[2]
- The number of patients taking eculizumab is unknown
  - aHUS and PNH are rare conditions (~300 persons with aHUS[3] and ~10,000[4] with PNH in U.S.)

[1]http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM423031.pdf

[2]Abstract O54: http://neisseria.org/ipnc/2016/IPNC2016AbstractBook.pdf; [3]http://atypicalhus.ning.com/page/what-is-ahus;
[4]http://imgjp1.pnhsource.jp/Downloads/pdf/UnderstandingPNHBrochure.pdf

Persons with Functional or Anatomic Asplenia

- Asplenic persons are at increased risk for invasive infection caused by many encapsulated bacteria, including *Neisseria meningitidis*
- Includes sickle cell disease which affects ~100,000 persons of all ages[1]
- Higher case-fatality ratio (40%–70%)[2]
  - Compared to 10–20% case-fatality ratio among U.S. population[3]
- Demonstrated significantly lower response to 1 dose of MenC vaccine[4]

[1]www.cdc.gov/ncbddd/sicklecell/data.html [2]MMWR. January 28,2011; 60(3): 72-76.

[3]Cohn AC. Clin Infect Dis 2010;50:184-91

[4]Balmer P. Infection and Immunity, Jan 2004, 332-337

Microbiologists

- Attack rate of 13/100,000 among U.S. microbiologists who work with *Neisseria meningitidis*[1]
  - Compared to rate of 0.1–0.2/100,000 among U.S. population
  - High case fatality ratio, possibly due to exposure to high concentrations of organisms and highly virulent strains
  - Majority of cases occurred in clinical microbiologists who were not using respiratory protection at the time of exposure

[1]Sejvar JJ. Journal of Clinical Microbiology. Sept 2005;43(9):4811-14.

Outbreaks of Meningococcal Disease

- Meningococcal outbreaks are rare, historically causing ~2–3% of US cases[1]
- Five serogroup B meningococcal disease clusters/outbreaks on college campuses during 2008–2014
  - 200–1400 fold increased risk in students during outbreak period
- Six additional serogroup B meningococcal disease clusters/outbreaks on college campuses during 2015–2016

[1] National Notifiable Diseases Surveillance System

Active Bacterial Core surveillance (ABCs)

- Active laboratory- and population-based surveillance in 10 states
  - Covers 43 million persons, ~13% of U.S. population
- Collects information in the medical record for meningococcal disease cases with:
  - Anatomic/functional asplenia and sickle cell disease (since 1995)
  - Complement component deficiencies (since 2005)
    - Limitation: information on diagnosis of complement component deficiencies may not be available until after hospitalization for meningococcal disease and therefore may not be captured in ABCs

How Many People Fall into Each Risk Group?

Group	Estimated Persons in Risk Group	Reported Cases
Complement component deficiencies	Prevalence of 0.03%[2] ~70,000 persons (adults)	6 cases since 2005 in ABCs[1] (none serogroup B)
Anatomic or Functional Asplenia (including sickle cell)	Sickle cell ~100,000 (all ages)[3]	13 cases since 1995 in ABCs[1] (3 serogroup B)
Microbiologists	~100,000 clinical; 400 research	22 cases worldwide 1985-2014 (at least 10 serogroup B)[4]
Total	**~270,000 persons**	

[1]Active Bacterial Core surveillance (ABCs)

[2]Densen P. Clin Exp Immunol. Oct 1991; 86(Suppl 1): 57-62.

[3]www.cdc.gov/ncbddd/sicklecell/data.html

[4]Sejvar JJ. J Clin Microbiol 2005; 43:4811-4; MMWR 2002;51:141-4; Borrow R. J of Infection 2014; 68:305-312.

How Many People Fall into Each Risk Group?

Group	Estimated Persons in Risk Group[1]	Reported Cases[1]
Outbreak at-risk populations (2008–2016)	~180,000 students identified as at risk during 11 serogroup B university outbreaks	50 cases (3 deaths) (2008–2016)
Total	**~20,000 students per year or ~16,000 students per outbreak**	

[1]Outbreaks where CDC was consulted

Summary: Persons at Increased Risk for Serogroup B Meningococcal Disease

- Persons at increased risk for serogroup B meningococcal disease represent
  - Small targeted groups
  - Demonstrated increased risk for meningococcal disease

- For persons with complement component deficiencies, anatomic/functional asplenia, and most microbiologists increased risk is ongoing

- For persons at increased risk because of serogroup B meningococcal disease outbreak the risk period may be more limited

Immunogenicity of MenB-4C (Bexsero®) among Immunocompromised Subjects

MenB-4C (Bexsero®): Safety, Tolerability, and Immunogenicity of Two Doses When Administered to Immunocompromised Subjects Aged 2–17 Years at Increased Risk of Meningococcal Disease

Data courtesy of Glaxo Smith Kline

MenB-4C (Bexsero®): Immunogenicity (hSBA ≥1:5 Using Exogenous Complement*) of Two Doses When Administered to Immunocompromised Subjects Aged 2–17 Years at Increased Risk of Meningococcal Disease

*Complement derived from healthy adult sera added during the hSBA assay

Data courtesy of Glaxo Smith Kline

MenB-4C (Bexsero®): Immunogenicity (hSBA ≥1:4 with Endogenous Complement*) of Two Doses When Administered to Immunocompromised Subjects Aged 2–17 Years at Increased Risk of Meningococcal Disease

*Source of complement for the hSBA assay is the test serum itself

Data courtesy of Glaxo Smith Kline

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*Source of complement for the hSBA assay is the test serum itself

Data courtesy of Glaxo Smith Kline

Summary: Immunogenicity of MenB-4C (Bexsero®) among Immunocompromised Subjects

- Increase in hSBA response observed in subjects aged 2–17 years with complement component deficiency and asplenia and in subjects receiving eculizumab after two doses of MenB-4C (Bexsero®)
  - Comparable responses were observed in healthy subjects and subjects with asplenia
  - Lower responses were reported in subjects with complement component deficiencies, especially if endogenous complement was used in the hSBA assay
  - Subjects receiving eculizumab showed an increase in hSBA titers, but had the lowest response

Antibody Persistence and Response to Booster Dose among Healthy Subjects

Available Antibody Persistence and Booster Response Data for MenB-FHbp (Trumenba®) and MenB-4C (Bexsero®)

Population	MenB-FHbp (Trumenba®)		MenB-4C (Bexsero®)	
	Antibody persistence	Booster response	Antibody persistence	Booster response
Adolescents (11–17 or 11–18 years old)	up to 48 months	at 48 months	up to 11–24 months	-
Children (4–7 and 8–12 years old)	-	-	up to 24–36 months	at 24–36 months

MenB-FHbp (Trumenba®): Antibody Persistence (hSBA ≥1:4) up to 48 Months in European Adolescents Aged 11–18 Years following Completion of 2-Dose (0, 6 m) and 3-Dose (0, 2, 6 m) Primary Series

Data courtesy of Pfizer Vaccines

MenB-FHbp (Trumenba®): Antibody Persistence (hSBA ≥1:4) up to 48 Months in European Adolescents Aged 11–18 Years following Completion of 2-Dose (0, 6 m) and 3-Dose (0, 2, 6 m) Primary Series and hSBA Responses to a Booster Dose at 48 Months Post Primary Series

Data courtesy of Pfizer Vaccines

MenB-4C (Bexsero®): Antibody Persistence (hSBA ≥1:4 or ≥1:5) up to 11–24 Months following Completion of 2-Dose Primary Series in Adolescents

Time interval	Percentage of subjects with protective titers* 1 month after series completion				Percentage of subjects with protective titers after time interval			
	fHbp	NadA	PorA	NHBA	fHbp	NadA	PorA	NHBA
11 months[1] (U.K.)	100	100	100	NA	95	97	85	NA
18–24 months[2] (Chile)	100	100	99	NA	82	94	77	NA

[1]https://clinicaltrials.gov/ct2/show/results/NCT01214850?sect=Xy0156#outcome28 accessed 12/1/2016
[2]Santolaya ME. Hum Vaccin Immunother. 2013;9:2304-2310.

MenB-4C (Bexsero®): Antibody Persistence (hSBA ≥1:4) at 24–36 Months Post Primary Series and hSBA Responses to a Booster Dose at 24–36 Months Post Primary Series in Children Aged 4–7 and 8–12 Years*

Data courtesy of Glaxo Smith Kline; study countries Spain and Hungary

Anticipated Studies

- 4 year antibody persistence and booster response among adolescents from Canada and Australia after completion of primary series of MenB-4C (Bexsero®)
  - Anticipate by Q2 2017

Safety Summary

- MenB vaccines are more reactogenic than other vaccines given during adolescence
  - Most common adverse event reported is pain at injection site
- The safety and tolerability profiles are similar for the primary series and one additional booster dose

Summary: MenB Vaccine Antibody Persistence and Booster Response Among Healthy Subjects

- Evidence of waning antibody for both MenB vaccines
  - As early as 12 months after completion of the primary series
  - Different waning rates observed to each antigen/strain
- Data from two MenB vaccines not directly comparable
- Evidence of booster response to revaccination
- Low-risk for serious adverse events

Work Group Interpretation

Work Group Interpretation

- Persons at increased risk for serogroup B meningococcal disease represent small targeted groups with a demonstrated increased risk for meningococcal disease
- MenB vaccines are immunogenic in persons at increased risk for meningococcal disease
- Waning of antibody observed as early as 12 months post-vaccination
- Booster response observed in previously vaccinated subjects following one additional MenB dose

Working Group Rationale

- Rationale for MenB booster doses:
  - Small targeted groups
  - Demonstrated increased risk for meningococcal disease
  - Evidence of waning antibody as early as 12 months after MenB vaccination
  - Evidence of booster response to revaccination
  - Low-risk for serious adverse events
  - Accepted standard of care for high-risk groups

Timing of Booster Doses

- The Work Group discussed the appropriate timing/interval for MenB booster doses extensively
  - Persons who remain at increased risk for serogroup B meningococcal disease (i.e., persons with complement component deficiencies, asplenia, and microbiologists)
  - In outbreak settings
- Desire to harmonize timing of booster recommendations with MenACWY for persons who remain at increased risk
  - To improve compliance with booster doses of both vaccines
  - Ensure some level of protection is maintained over time in these higher-risk individuals
  - Recognition that there is evidence of waning antibody as early as 12 months after MenB vaccination
- In outbreak settings, where the period of increased risk is more limited, a booster dose at a shorter interval (i.e., ≥6-12 months) may help to ensure antibody is maximized during the outbreak period

Consensus of Work Group

- The Meningococcal Work Group supports routine MenB booster doses for persons at increased risk of serogroup B meningococcal disease
- Harmonize timing of booster doses with MenACWY boosters for groups at prolonged increased risk for meningococcal disease
- In outbreak settings, booster doses should be administered if it has been ≥6 months since their last MenB dose

Policy Option

- Booster doses of MenB vaccine should be administered every 5 years throughout life to persons aged ≥10 years in each of the following groups:
  - Persons with persistent complement component deficiencies including persons taking eculizumab
  - Persons with anatomic or functional asplenia
  - Microbiologists routinely exposed to isolates of *Neisseria meningitidis* (as long as exposure continues)
- Booster doses of MenB vaccine should be administered to persons identified as at increased risk because of a serogroup B meningococcal disease outbreak if it has been ≥6 months since their last MenB dose
  - When multi-year or prolonged outbreaks occur, CDC should be consulted and recommendations for additional booster doses will be considered on a case-by-case basis

Next Steps: June 2017 ACIP Meeting

- GRADE evaluation of data supporting MenB booster doses
- An ACIP vote on routine MenB booster doses in persons aged ≥10 at increased risk for serogroup B meningococcal disease will be proposed at the June 2017 ACIP meeting

Discussion

- Are there additional data that ACIP would like to review?
- Does ACIP agree with the proposed policy option language and timing for booster doses in persons with complement component deficiencies, asplenia, and microbiologists?
- Does ACIP agree with the proposed policy option language and timing for booster doses in outbreak settings?
  - For persons previously vaccinated who later are in an outbreak?
  - For persons within a prolonged outbreak scenario?

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov