Considerations for Use of Serogroup B Meningococcal (MenB) Vaccines in Adolescents

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National Center for Immunization and Respiratory Diseases
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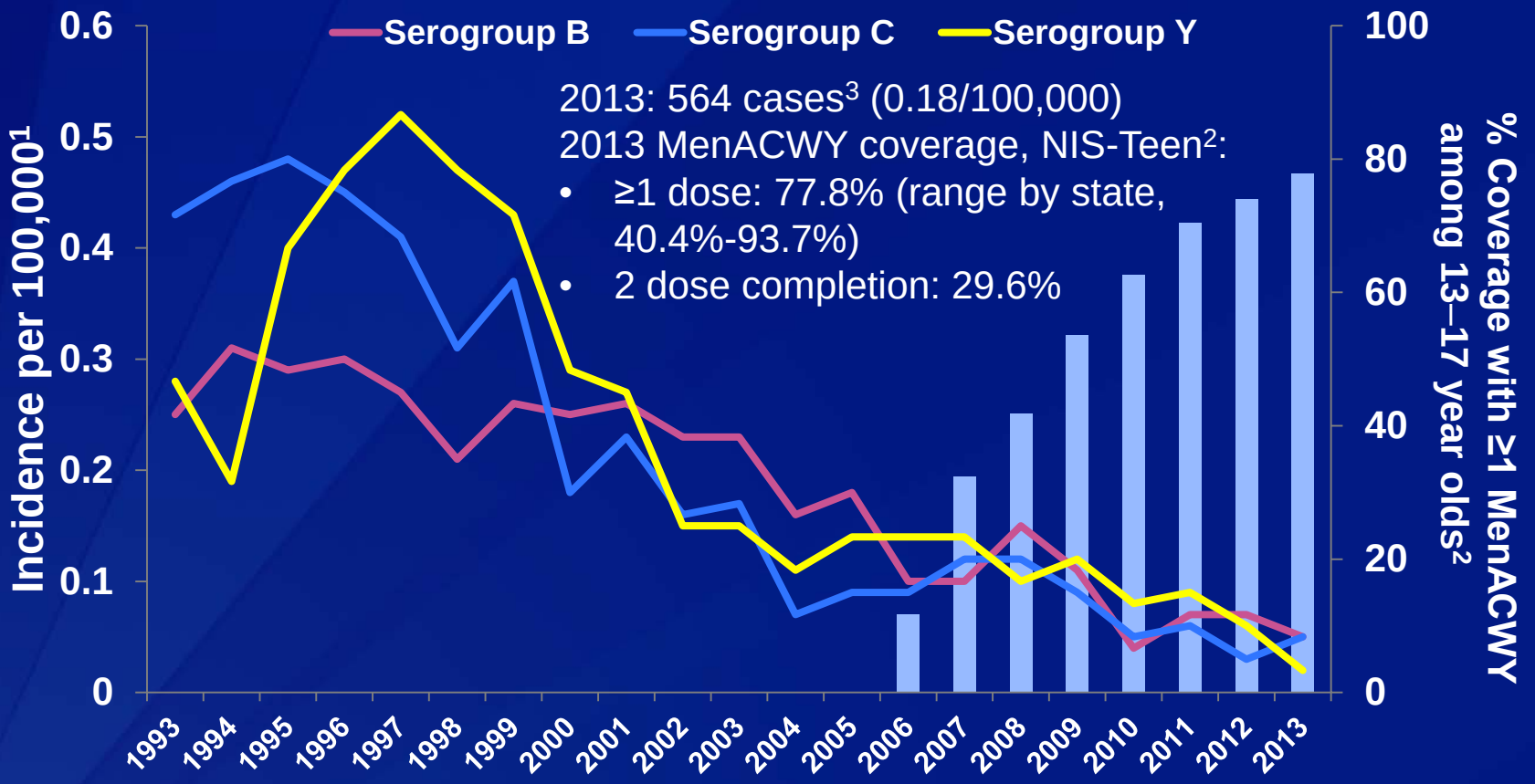
Presentation Overview

- **Summary of data reviewed:**
  - Epidemiology and burden of meningococcal disease in adolescents and young adults
  - MenB immunogenicity
  - MenB safety
  - Additional data
- **Policy options and Work Group considerations**
- **Proposed policy option language**

Meningococcal Incidence in All Ages by Serogroup and Adolescent MenACWY Vaccine Coverage, 1993–2013



[1]Source: Active Bacterial Core surveillance (ABCs) cases from 1993-2013 estimated to the U.S. population with 18% correction for nonculture confirmed cases. In 2010, estimated case counts from ABCs were lower than cases reported to the National Notifiable Diseases Surveillance System (NNDSS) and might not be representative.

[2]National Immunization Survey-Teen; 2006-2013.

[3]NNDSS 2013 final case count

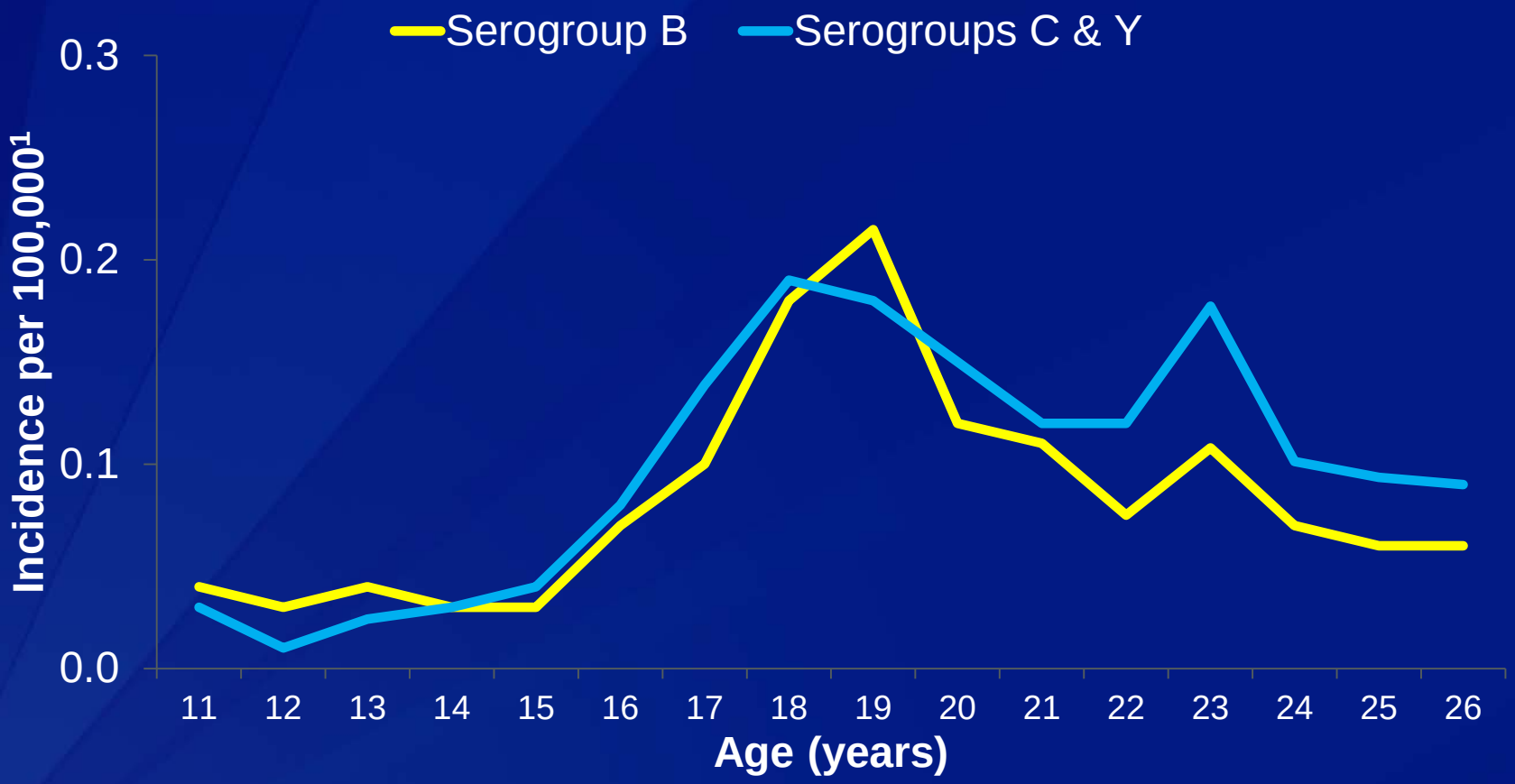
Decreasing Incidence of Serogroup C, W, Y Meningococcal Disease in 11–19 Year Olds

Year	Incidence per 100,000 (95% confidence intervals)[1]		
	<1 year	11–19 years	≥20 years
2004-2005	0.77 (0.33, 1.55)	0.27 (0.17, 0.39)	0.17 (0.14, 0.21)
2006-2007	1.20 (0.61, 2.11)	0.31 (0.21, 0.45)	0.23 (0.19, 0.28)
2008-2009	0.93 (0.48, 1.69)	0.15 (0.08, 0.26)	0.23 (0.19, 0.27)
2010-2011	1.37 (0.74, 2.33)	0.05 (0.02, 0.12)	0.14 (0.11, 0.18)
2012-2013	0.74 (0.39, 1.32)	0.05 (0.02, 0.10)	0.12 (0.10, 0.15)

- 80% decrease in serogroup C, W, Y meningococcal disease among 11–19 year olds

[1]Source: Active Bacterial Core surveillance (ABCs) cases from 2004-2013 estimated to the U.S. population with 18% correction for nonculture confirmed cases. In 2010, estimated case counts from ABCs were lower than cases reported to the National Notifiable Diseases Surveillance System (NNDSS) and might not be representative.

Meningococcal Incidence in Adolescents and Young Adults by Serogroup, 2009–2013



[1]Source: National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments
Unknown serogroup (19%) and other serogroups (8%) excluded

Estimated Average Annual Cases, Deaths, and Sequelae by Age Group and Serogroup, 2009–2013

	Age Group	Cases[1]	Deaths[2]	Sequelae[3]
Serogroup B	<5 years	74–94	7-14	7-19
	11-24 years	54–67	5-10	5-13
	All ages	203–260	20-39	20-52
Serogroups C & Y	<5 years	34–43	3-6	3-9
	11-24 years	62–77	6-12	6-15
	All ages	307–393	31-59	31-79

- The majority (~80%) of serogroup B cases that occur in 11–24 year olds occur in older adolescents and young adults aged 16–24 years

[1]Range in estimated cases: Low=NNDSS data supplemented with additional serogroup data from ABCs and state health departments, High= NNDSS data supplemented with additional serogroup data from ABCs and state health departments + proportion serogroup B or serogroup C & Y applied to cases with unknown serogroup.

[2]10-15% case fatality ratio

[3]10-20% cases with long term sequelae

Average Annual Cases, Deaths, and Incidence from Serogroup B, 2009–2013

	Cases[1]	Deaths[1]	Incidence per 100,000[3]
All 18–23 year olds	36	5	0.14
Estimated cases:			
College students[2]	14	2	0.09
Non-college students[2]	22	3	0.21

[1]National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments

[2]40% of serogroup B cases in 18–23 year olds from ABCs were in college students (excluding unknown or missing), 2005–2013

[3]Assume 61% of persons age 18–23 years enrolled in college

Recent University Based Serogroup B Clusters/Outbreaks†

University	Outbreak Period	Number of cases
University 1	Feb – Mar 2009	4
University 2	Nov 2011	2
University 3	Jan 2008 – Nov 2010	13
University 4	Mar 2013 – Mar 2014	9
University 5	Nov 2013	4*
University 6	Jan – Feb 2015	2
University 7	Jan – May 2015	7

†Where CDC consulted
*1 additional associated case identified after retrospective case review

Recent Experience With Serogroup B Meningococcal Disease in College Students

- **Enhanced surveillance for cases of meningococcal disease among college students began in 2013***
  - Serogroup B cases reported among 18–23 year olds:

Year	Total Cases	Cases in College Students	Deaths in College Students	Incidence in College Students
2013	22	14 (64%)	2	0.14/100,000
2014	12	8 (67%)	2	0.08/100,000

- **Three deaths in college students reported to CDC in 2014****

*Enhanced surveillance area includes 10 ABCs sites and 18 state and large city health departments, covers ~61% of US population

**One death not included in enhanced surveillance area

Work Group Interpretation: Burden of Disease

- **Incidence of disease has declined for <u>all</u> meningococcal serogroups, including serogroup B**
  - Currently at a stable low in disease incidence
- **Approximately 55–65 cases of serogroup B meningococcal disease occur in adolescents and young adults each year**
  - The majority of those cases occur in older adolescents and young adults aged 16–24 years
- **Approximately 40-70% of serogroup B cases in 18–23 year olds occur in college students**
  - Incidence in college and non-college students is similar

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Two MenB Vaccines For Persons Aged 10–25 Years in the United States

- **MenB-FHbp (Trumenba®, Pfizer)**
  - Components: fHbp subfamily A/v2,3; subfamily B/v1
  - 3 dose series, administered at 0, 2, 6 months
  - Licensed in the U.S. on October 29, 2014
- **MenB-4C (Bexsero®, Novartis/GSK)**
  - Components: fHbp subfamily B/v1, NhbA, NadA, Por A1.4
  - 2 dose series, administered at 0 and ≥1 month
  - Licensed in the U.S. on January 23, 2015
  - Licensed in >37 countries for persons ≥2 months of age

Licensure 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
- **Data for MenB-FHbp and MenB-4C are not directly comparable**

*Serum bactericidal activity using human complement (hSBA)

MenB-FHbp Immunogenicity Summary

- **Demonstrated immune response in general adolescent population**
  - 84% of adolescents had a composite hSBA response to four strains after 3 doses
  - 50% had a composite hSBA response after 2 doses
- **Data on concomitant administration is reassuring**
  - No immunological interference observed for serogroup B or vaccine antigens (HPV types 6, 11, 16, MenACWY, tetanus, diphtheria, pertussis, and IPV antigens)
  - HPV type 18 non-inferiority criteria* were not met for the GMT ratio at one month after the third 4vHPV vaccination
    - 99% of subjects achieved seroconversion for all 4 HPV antigens

*Lower bound of the 95% confidence-interval of the geometric mean titer (GMT) ratio >0.67 (lower bound was 0.62)
Package Insert: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM421139.pdf

MenB-4C Immunogenicity Summary

- **Demonstrated immune response in general adolescent population**
  - 63-94% of adolescents had a composite hSBA response to three strains after 2 doses
    - 63% (95% CI 57%, 68%) 1 month after vaccination with 2 doses among Canadian/Australian adolescents aged 11–17 years
    - 88% (95% CI 82%, 93%) 1 month after vaccination with 2 doses among UK university students aged 18–24 years
    - 90% -94% 1 month after vaccination with 2 doses among Chilean adolescents aged 11–17 years
- **Immunogenicity data from the Canadian/Australian (aged 11–17 years) and UK (aged 18–24 years) subjects included in the package insert**

Package Insert: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM431447.pdf

MenB-4C Immunogenicity Summary

- **Persistence in immunogenicity**
  - 66% (95% 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
- **No concomitant administration data available for MenB-4C**

*hSBA≥1:4 used as correlate of protection

Princeton Post-Vaccination Seroprevalence Survey

- **Outbreak of serogroup B meningococcal disease from March 2013–March 2014 (9 cases, 1 death)**
  - ST-409, uncommonly seen in US
- **Mass vaccination campaign using MenB-4C held**
  - December 2013 (dose 1) and February 2014 (dose 2)
  - Among undergraduates, 98% received dose 1 and 93% dose 2
- **A cross-sectional seroprevalence survey launched in April 2014, 607 participants enrolled**

Reference: Basta et al. Immunological Response following the Introduction of a Novel Meningococcal B Vaccine during an Outbreak at a University in 2013-2014. In preparation.

Work Group Interpretation: Immunogenicity

- **Immunogenicity suggests short term efficacy**
- **Evidence of waning antibody levels within 6 months post dose 3 for MenB-FHbp**
  - Appears to stabilize 6-48 months post dose 3
- **Modest waning in antibody observed through 24 months post dose 2 for MenB-4C**
  - Data from Chilean adolescents with higher baseline bactericidal antibodies compared to U.S. adolescents
- **Proportion of vaccinees who develop bactericidal antibodies may vary with each outbreak or circulating strain**

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MenB Safety in Clinical Trials

- **Post-vaccination local and systemic complaints are common**
  - Frequently reported solicited adverse events were: pain at the injection site, fever, headache, fatigue, myalgia, arthralgia
  - Reactions were typically self limited
- **MenB vaccines are more reactogenic than other routine vaccines for adolescents***
  - Based on the proportion of subjects who report the most severe category of local and systemic adverse events
- **Rates of serious adverse events were similar between vaccine recipients and controls**

*see package inserts for MenB-FHbp and MenB-4C

Other Sources of Safety Data for MenB Vaccines

- **Limited experience with MenB vaccines outside of clinical trials**
- **MenB-4C**
  - United States: approximately 17,000 persons vaccinated under an expanded access IND program for outbreak response at two universities
  - Canada: over 40,000 persons vaccinated in a regional public health program in Quebec (persons 2 months–20 years)
  - No concerning patterns among the adverse events observed
- **MenB-FHbp**
  - Safety data collected during recent outbreak response; data not yet available

Additional Vaccine Safety Considerations

- **Theoretical concern raised from animal models showing auto-antibodies in some animals following MenB vaccination[1-3]**
  - FDA reviewed the clinical data and did not observe differences in rates of auto-immune disorders between vaccine recipients and controls; data does not suggest a higher incidence of autoimmune conditions following vaccination than what is observed in the general population
  - Theoretically, onset of auto-immune symptoms could be delayed well beyond vaccination
- **Postlicensure safety surveillance will be conducted to detect any potential safety signals**
  - After sufficient doses have been administered, potential safety signals can be studied in the Vaccine Safety Datalink (VSD)
  - VAERS for passive surveillance

[1]Costa I, et al. mBio. September/October 2014; 5(5): e10625-14. [2]Granoff D. 2014. Microbe. 9(8):321-327. [3]Granoff D. JID. 2015

Adverse Reactions That May Occur Following Any Type of Vaccine

- **Adverse reactions that may occur following any vaccine administered by injection:**
  - Shoulder injury related to vaccine administration (very rare)
  - Syncope (~1 per 1,000 doses)
- **Anaphylaxis may occur following any type of vaccine:**
  - Incidence: 0.21 to 1.53 per 1 million doses
  - MenB-FHbp and MenB-4C have each had one case of anaphylaxis related to vaccination reported to date

For additional information refer to the ACIP General Recommendations on Immunization

Work Group Interpretation: Safety

- **Post-vaccination local and systemic complaints are common, but reactions are self-limited**
  - Most common AE was pain at injection site
- **Potentially serious AEs may occur following any vaccine**
  - Should be considered in light of the current low disease burden
- **To date no concerning patterns of SAEs reported for MenB vaccines**
  - Theoretical concerns about autoimmune disease from animal studies showing auto-antibodies

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Cost-Effectiveness Analysis

- **Analysis completed by Ismael Ortega-Sanchez, CDC**
- **Full presentation included in background materials**
- **Monte Carlo simulation analysis**
  - Hypothetical 4 million birth cohort, 2.8 million college cohort
  - Time frame: 15 year
  - Analytic Horizon: Age-specific Life Expectancy
  - Discount rate: 3% (0%-5%)

Source: Ismael Ortega-Sanchez

Key Assumptions

- **Age and serogroup B specific average incidence rates and case-fatality ratios from 1994-2013**
- **Initial vaccine effectiveness of 85-95%**
- **Waning protection based on available antibody persistence data for MenB-FHbp and MenB-4C**
  - Waning of protection over 10 years
- **Cost of vaccination per series (2 or 3 doses)**
  - $402 (cost of vaccine + adm + AE + wastage)

Source: Ismael Ortega-Sanchez

Potential Cases and Deaths Prevented per 4M Cohort

	Cases Prevented	Deaths Prevented	NNV* to prevent case	NNV to prevent death	Cost ($) per QALY
Series at 11 years	15	2	203,000	1,512,000	$8.700.000
Series at 16 years	28	5	107,000	788,000	$4,100,000
Series at 18 years	29	5	102,000	638,000	$3,700,000
College students	9	1	368,000	2,297,000	$9,400,000

*Number needed to vaccinate
Source: Ismael Ortega-Sanchez

Impact of MenB Vaccines on Carriage

- **United Kingdom**
  - At study entry, 31-34% carried any *N. meningitidis**
  - No significant difference in carriage was detected between the study groups at 1 month after vaccination with MenB-4C
    - Modest decrease in carriage observed during the 12 months after vaccination
- **United States**
  - Carriage surveys initiated at two schools experiencing serogroup B outbreaks
    - Survey in conjunction with MenB-FHbp mass vaccination
      - Dose 1 (baseline carriage), Dose 2 (post-dose 1 carriage)
      - Additional round planned for Fall 2015
  - Preliminary results show no change in carriage* in the student population from baseline to post-dose 1

*Includes nongroupable, and all serogroups of *N. meningitidis*

Breadth of Coverage

- **Genetic and antigen expression data predict the MenB vaccines should cover a wide range of circulating strains in the United States – but not all**
- **Available immunogenicity data is directed against a few select strains**
- **The proportion of the population that will develop antibodies active against each circulating strain is currently unclear (e.g. Princeton strain)**
  - Currently available data does not allow us to predict the proportion who will be protected against each outbreak or sporadic disease causing strain

Challenges when Considering Routine Use of MenB Vaccines in Adolescents

- **Proportion of serogroup B cases that could be prevented with MenB vaccines is unknown**
  - Breadth of strain coverage estimated; actual breadth of strain coverage unclear
  - Available antibody persistence data suggests limited duration of protection
- **Effectiveness data are not available**
  - Licensure is based on bactericidal activity
  - Universal programs not implemented in any country to date
- **Impact on carriage unknown**
- **Potential impact of vaccine pressure on circulating strains unknown**

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Policy Options for Broader Use of MenB Vaccines

- **Administration of a MenB series at:**
  - 11–12 years, booster (anticipated) @ 16 years
  - 16 years
  - 18 years
  - College students only
- **Recommendation type:**
  - Category A (recommendations are made for all persons in an age- or risk-factor-based group)
  - Category B (recommendations are made for individual clinical decision making)
  - No recommendation

Considerations for "All Adolescents" Rather Than "College Students Only"

- **Approximately 30-60% of serogroup B cases in 18–23 year olds occur in persons not attending college**
- **Would be challenging to get students vaccinated with 2-3 doses before arriving on college campuses**
- **Vaccinating college students would prevent the fewest cases and deaths of options considered**
- **The Work Group acknowledges the impact that cases and outbreaks have on college campuses**
  - Cost for vaccination campaigns
  - Public concern

Considerations for Timing of Administration of the MenB Series

- **Need to administer series in late adolescence in order for protection to last into the highest risk period**
  - Concern is that protection may not be long lasting
- **Young adults may still be under the care of a pediatrician at 16 years of age, but less likely at 18 years**
  - Receive booster at age 16 years for MenACWY
- **Majority of work group members prefer administration between 16–18 years**
  - For college-bound population, more likely to receive 2–3 doses before entering college and highest age-related risk period

Considerations for Category B Rather Than Category A Recommendation

- **Current low burden of disease**
  - Number needed to vaccinate to prevent a case/death is high
  - Number of cases prevented may be comparable to the number of serious adverse reactions to vaccine
- **Additional data to consider routine recommendations is needed**
  - Understanding the true proportion of serogroup B cases that could be prevented with MenB vaccines
    - Vaccine effectiveness and duration of protection
    - Impact on carriage and herd immunity

History of Category B Recommendation for Men ACWY Polysaccharide Vaccine in College Students

- **In 2000, ACIP and AAP recommended :**
  - College students and their parents be informed by health-care providers of the risks of meningococcal disease and of the potential benefits of vaccination with MPSV4
  - College and university health services facilitate implementation of educational programs about meningococcal disease and the availability of vaccination services
  - MPSV4 be made available to those persons requesting vaccination
- **Legislation passed in several states requiring colleges to provide information on risks of meningococcal disease to students or mandated vaccination for certain students**

Programmatic Considerations

- **MenB multi-dose schedules make implementation challenging**
- **No platform for 2–3 dose vaccine series in late adolescence**
- **Current MenACWY vaccine program in adolescents at 11–12 years, with a booster dose at 16 years**
  - Communications challenge of differing recommendations for MenACWY and MenB vaccines
- **MenACWY is not recommended for other groups with similar or higher risk (e.g., infants, HIV+, etc.)**

Working Group Summary

- **Meningococcal disease is a rare, but serious illness and each case is life-threatening**
- **Key data on MenB vaccines are not yet available**
- **Desire for access to MenB vaccines**
- **Additional work still needed to reinforce the second dose of MenACWY in the current adolescent program**
- **Risk for disease is low**
  - In the absence of vaccination there may be cases that are preventable
  - Even with a fully implemented vaccination program the MenB vaccines will not prevent all cases

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Proposed Policy Option Language

- **A serogroup B meningococcal (MenB) vaccine series may be administered to adolescents and young adults 16 through 23 years of age 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. (Category B)**

Guidance for Use

- MenB should be administered as either a 2-dose series of MenB-4C or a 3-dose series of MenB-FHbp
- The same vaccine product should be used for all doses
- Based on available data and expert opinion, MenB-4C and MenB-FHbp may be administered concomitantly with other vaccines indicated for this age, but at a different anatomic site, if feasible
- No product preference to be stated

Thank You

For more information please contact Centers for Disease Control and Prevention
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