

# Meningococcal Disease and Meningococcal Vaccine

October, 2015

# *Neisseria meningitidis*

- ❑ Aerobic gram-negative bacteria
- ❑ At least 13 serogroups based polysaccharide capsule
- ❑ Most invasive disease caused by serogroups A, B, C, Y, and W
- ❑ Relative importance of serogroups depends on geographic location and other factors (e.g., age)

# Meningococcal Disease Pathogenesis

- ❑ Organism colonizes nasopharynx
- ❑ In some persons organism enters the bloodstream and causes infection at distant site
- ❑ Antecedent URI may be a contributing factor

# Neisseria meningitidis Clinical Features

- ❑ Incubation period 3-4 days (range 2-10 days)
- ❑ Abrupt onset of fever, meningeal symptoms, hypotension, and rash
- ❑ Fatality rate 10%-15%, up to 40% in meningococemia

# Meningococcal Meningitis

- ❑ Most common presentation of invasive disease
- ❑ Results from hematogenous dissemination
- ❑ Clinical findings
  - fever
  - headache
  - stiff neck

# Meningococemia

- ❑ Meningococemia
- ❑ Bloodstream infection
- ❑ May occur with or without meningitis
- ❑ Clinical findings
  - fever
  - petechial or purpuric rash
  - hypotension
  - shock
  - acute adrenal hemorrhage
  - Multi-organ failure

# Meningococcal Disease



# Meningococcal Disease



*N Engl J Med.* 2001;344:1372

# *Neisseria meningitidis*

## Risk Factors for Invasive Disease

### ❑ Host Factors:

- Persistent complement component deficiency
  - 10,000 fold increased risk, can experience recurrent disease
- Functional or anatomic asplenia
- Selected genetic factors (altered genes: mannose-binding lectin and tumor necrosis factor)

### ❑ Chronic underlying illness

### ❑ Environmental factors

- antecedent viral infection
- household crowding
- active and passive smoking

### ❑ Occupational (microbiologists)

# *Neisseria meningitidis*

## Risk Factors for Invasive Disease (3)

### □ College Students:

- Studies in 1990s – overall incidence similar to or lower than their counterparts in general population\*
- Case control study of 50 cases and other studies in the 1990s#
  - First-year college students living in residence halls at higher risk

\* JAMA 1999;281:1906-10

#Abstracts of the 39<sup>th</sup> Meeting of the IDSA. Philadelphia, PA: IDSA; 1999:276

Epidemiol Infect 1999;122:351–7

Clin Infect Dis 1999;29:215–6.

# Meningococcal Disease Laboratory Diagnosis

- ❑ Bacterial culture
  
- ❑ Gram stain
  
- ❑ Non-culture methods
  - PCR
  - Antigen detection in CSF
  - Serology

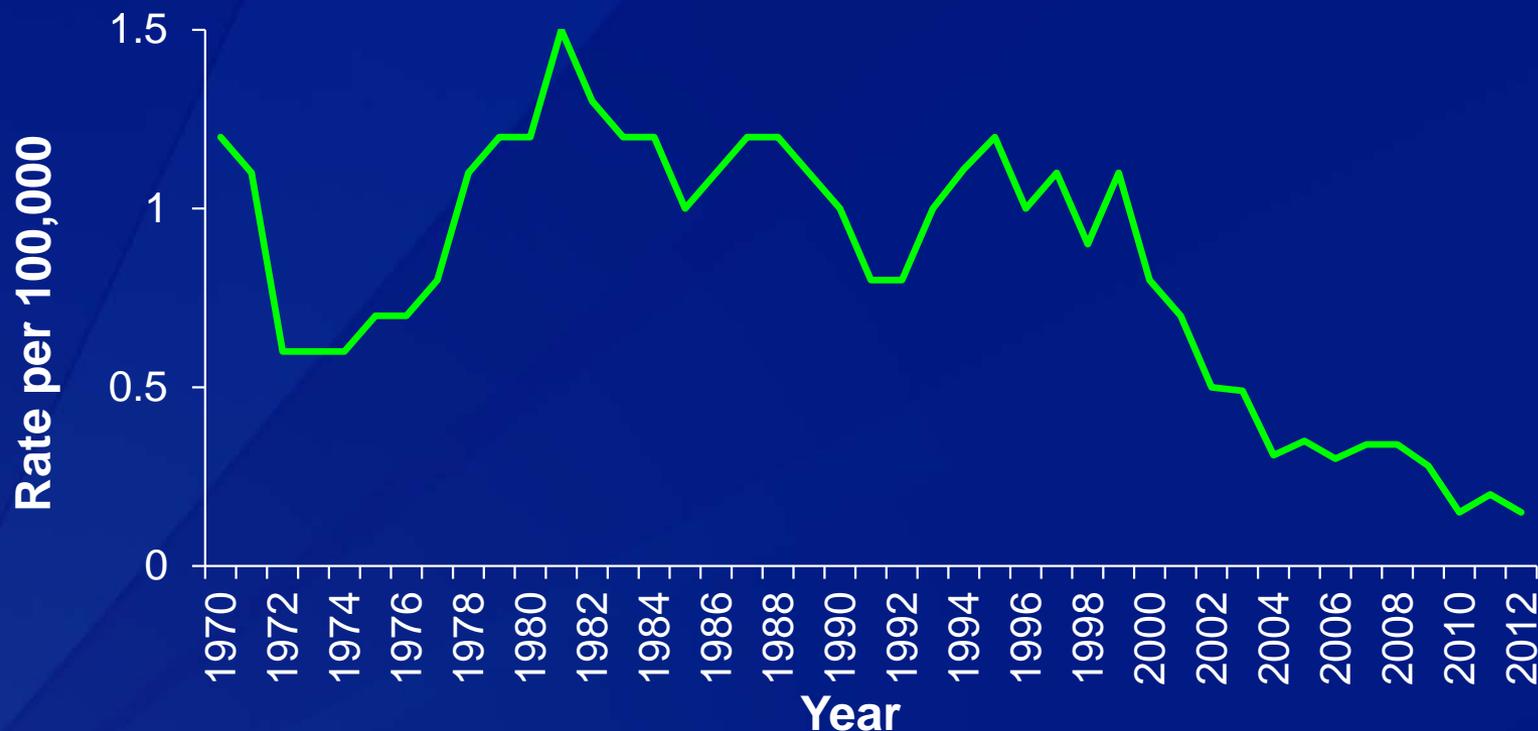
# *Neisseria meningitidis* Medical Management

- ❑ Empiric antibiotic treatment after appropriate cultures are obtained
- ❑ Treatment with penicillin alone recommended after confirmation of *N. meningitidis*

# Meningococcal Disease Epidemiology

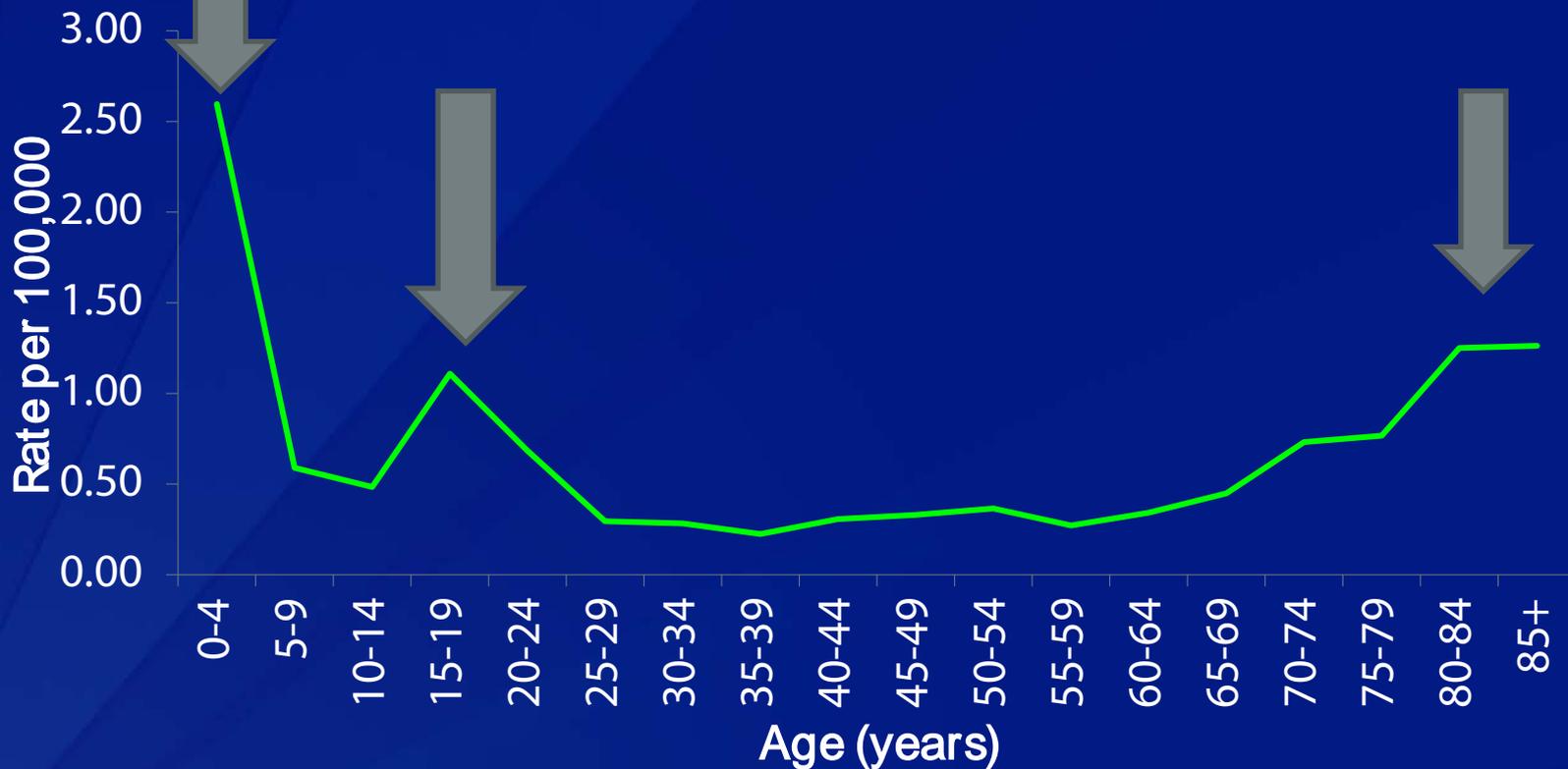
- **Reservoir** Human
- **Transmission** Respiratory droplets
- **Temporal pattern** Peaks in late winter-early spring
- **Communicability** Generally limited

# Meningococcal Disease Incidence, United States, 1970-2012



1970-1996 NNDSS data, 1997-2012 ABCs data estimated to U.S. population

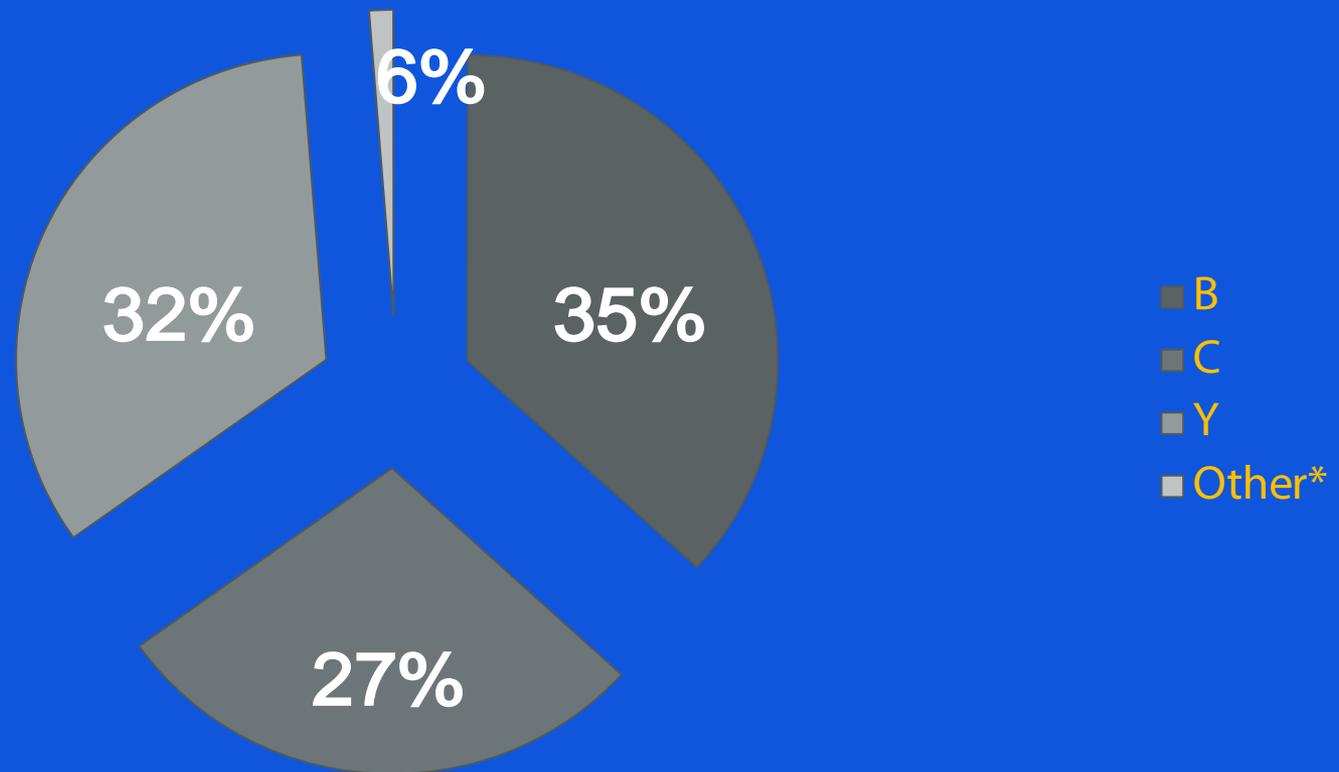
# Three Age Peaks in Meningococcal Disease Incidence



ABCs cases from 1993-2012 and projected to the U.S. population with 18% correction for under reporting

# Meningococcal Disease Serotypes in the U.S., 2005-2011

Meningococcal Serotypes in the U.S.



\*Includes serogroup W135, nongroupable, and other serogroups.

MMWR, March 22, 2013; Recommendations and Reports / Vol. 62 / No. 2

# Meningococcal Outbreaks in the United States

- ❑ Outbreaks account for 2%-3% of reported cases
- ❑ Most recent outbreaks caused by serogroup C and B

MMWR March 22, 2013 Recommendations and Reports / Vol. 62 / No. 2, at <http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf>, and <http://www.cdc.gov/meningococcal/outbreaks/index.html>

# Meningococcal Polysaccharide Vaccine (MPSV4)

- ❑ Menomune (sanofi pasteur)
- ❑ Quadrivalent polysaccharide vaccine (A, C, Y, W-135)
- ❑ Administered by subcutaneous injection
- ❑ 10-dose vial contains thimerosal as a preservative
- ❑ Single-dose vial available

# Polysaccharide Vaccines

- ❑ Age-related immune response
- ❑ Not consistently immunogenic in children younger than 2 years
- ❑ Little or no booster response
- ❑ Antibody with less functional activity
- ❑ Response improved by conjugation to a protein antigen

# MPSV4 Recommendations

- ❑ Approved for persons 2 years of age and older
- ❑ Not recommended for routine vaccination of civilians
- ❑ Should be used only for persons at increased risk of *N. meningitidis* infection who are 56 years of age or older, expected to need meningococcal vaccine once

# Meningococcal Conjugate Vaccines

- ❑ Meningococcal polysaccharide conjugated to protein carrier
- ❑ Elicit both T- and B-cell immunity (T-cell dependent immunity)
- ❑ 3 brands currently licensed in the United States
  - Menactra (Sanofi Pasteur)
  - Menveo (Novartis)
  - MenHibrix (GlaxoSmithKline)

# Menactra MenACWY Vaccine

- ❑ Quadrivalent polysaccharide vaccine (A, C, Y, W-135) conjugated to diphtheria toxoid
- ❑ Licensed by FDA in January 2005
- ❑ Approved for persons **9 months\*** through 55 years of age
  - 2 – dose series in 9- through 23-month olds
  - Single dose for persons 2 through 55 years (except HIV patients)
- ❑ FDA approval based on serologic non-inferiority compared to meningococcal polysaccharide vaccine

\*As of April 22, 2011

# Menveo MenACWY Vaccine

- ❑ Licensed by FDA in February 2010
- ❑ Approved for persons 2 months through 55 years of age (as of 8/1/2013)
- ❑ Lyophilized serogroup A vaccine reconstituted with liquid containing serogroups C, Y, and W135
- ❑ May be used for any person 2 months through 55 years of age for whom MCV4 is indicated, including revaccination
- ❑ Single dose (except HIV patients)

# (Hib-MenCY-TT) MenHibrix

- ❑ FDA licensed June 2012
- ❑ Combination vaccine for infants/ children 6 weeks through 18 months to prevent invasive disease from *N. meningitidis* C and Y and Hib.
- ❑ Lyophilized powder reconstituted with saline diluent
- ❑ Single dose administered as a 4-dose series at 2, 4, 6, and 12 - 15 months
  - 1<sup>st</sup> dose may be given at 6 weeks
  - 4<sup>th</sup> dose may be given as late as 18 months

# Interchangeability of Conjugate Vaccine Brands

- ❑ Limited data suggest that different conjugate vaccine products can be used interchangeably.
- ❑ Data are available regarding vaccination of Menveo after prior vaccination of either Menveo or Menactra
- ❑ Whenever feasible, the same brand of vaccine should be used for all doses of the vaccination series
- ❑ If vaccination providers do not know or have available the type of vaccine product previously administered, any product should be used to continue or complete the series

# Meningococcal Serogroup B Vaccines

- ❑ Two vaccines recently licensed for persons 10-25 yrs in the U.S.
  - Trumenba®(Pfizer), 3-dose series (0,2,6 months)
    - Components fHbp subfamily A/v2,3, subfamily B/v1
    - Licensed October 29, 2014
  - Bexsero®(Novartis), 2-dose series (0,1-6 months)
    - Components fHbp subfamily B/v1, NnbA, NadA, Por A1.4
    - Licensed January 23, 2015
    - Licensed in >30 countries for persons  $\geq 2$  months of age

# **Routine Adolescent Vaccine Recommendations**

**Figure 1. Recommended immunization schedule for persons aged 0 through 18 years – United States, 2015.**

**(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 2]).**

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16–18 yrs
Hepatitis B <sup>1</sup> (HepB)	1 <sup>st</sup> dose	← 2 <sup>nd</sup> dose →			← 3 <sup>rd</sup> dose →											
Rotavirus <sup>2</sup> (RV) RV1 (2-dose series); RV5 (3-dose series)			1 <sup>st</sup> dose	2 <sup>nd</sup> dose	See footnote 2											
Diphtheria, tetanus, & acellular pertussis <sup>3</sup> (DTaP: <7 yrs)			1 <sup>st</sup> dose	2 <sup>nd</sup> dose	3 <sup>rd</sup> dose				← 4 <sup>th</sup> dose →			5 <sup>th</sup> dose				
Tetanus, diphtheria, & acellular pertussis <sup>4</sup> (Tdap: ≥7 yrs)														(Tdap)		
Haemophilus influenzae type b <sup>5</sup> (Hib)			1 <sup>st</sup> dose	2 <sup>nd</sup> dose	See footnote 5				← 3 <sup>rd</sup> or 4 <sup>th</sup> dose → See footnote 5							
Pneumococcal conjugate <sup>6</sup> (PCV13)			1 <sup>st</sup> dose	2 <sup>nd</sup> dose	3 <sup>rd</sup> dose				← 4 <sup>th</sup> dose →							
Pneumococcal polysaccharide <sup>6</sup> (PPSV23)																
Inactivated poliovirus <sup>7</sup> (IPV: <18 yrs)			1 <sup>st</sup> dose	2 <sup>nd</sup> dose	← 3 <sup>rd</sup> dose →						4 <sup>th</sup> dose					
Influenza <sup>8</sup> (IV; LAIV) 2 doses for some: See footnote 8					Annual vaccination (IV only) 1 or 2 doses						Annual vaccination (LAIV or IV) 1 or 2 doses		Annual vaccination (LAIV or IV) 1 dose only			
Measles, mumps, rubella <sup>9</sup> (MMR)					See footnote 9				← 1 <sup>st</sup> dose →			2 <sup>nd</sup> dose				
Varicella <sup>10</sup> (VAR)									← 1 <sup>st</sup> dose →			2 <sup>nd</sup> dose				
Hepatitis A <sup>11</sup> (HepA)								← 2-dose series, See footnote 11 →								
Human papillomavirus <sup>12</sup> (HPV2: females only; HPV4: males and females)																(3-dose series)
Meningococcal <sup>13</sup> (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥ 9 mos; MenACWY-CRM ≥ 2 mos)					See footnote 13									1 <sup>st</sup> dose		Booster

Range of recommended ages for all children
  Range of recommended ages for catch-up immunization
  Range of recommended ages for certain high-risk groups
  Range of recommended ages during which catch-up is encouraged and for certain high-risk groups
  Not routinely recommended

This schedule includes recommendations in effect as of January 1, 2015. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at <http://www.cdc.gov/vaccines/hcp/acip-recs/index.html>. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (<http://www.vaers.hhs.gov>) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (<http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm>) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (<http://www.cdc.gov/vaccines/acip>), the American Academy of Pediatrics (<http://www.aap.org>), the American Academy of Family Physicians (<http://www.aafp.org>), and the American College of Obstetricians and Gynecologists (<http://www.acog.org>).

**NOTE: The above recommendations must be read along with the footnotes of this schedule.**

# MenACWY Recommendations\*

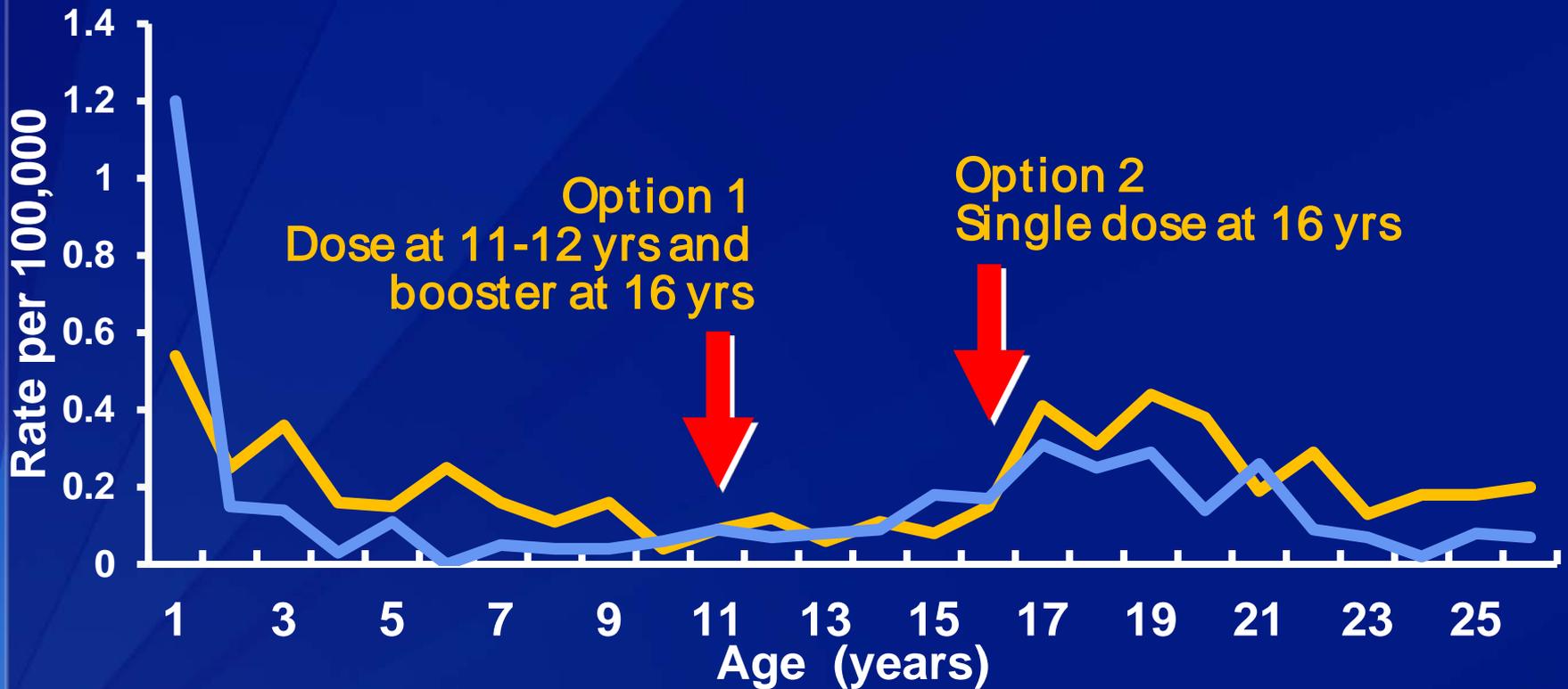
- ❑ New recommendations since 2010
  - Administer MenACWY at age 11 or 12 years with a **booster dose** at 16 years of age
  - Administer 1 dose at age 13 through 15 years if not previously vaccinated
  - For persons vaccinated at age 13 through 15 years, administer a one-time booster dose is recommended, preferably at or after 16 through 18 years of age
  - The minimum interval between doses is 8 weeks

\*Off-label recommendation. *MMWR*2013;62(RR-2):10-11

# Meningococcal Conjugate (MenACWY) Revaccination

- ❑ In its 2005 recommendations for MenACWY, ACIP made no recommendation about revaccination pending the availability of additional data
- ❑ Serologic data are now available from the manufacturer that show significant decline in antibody 3-5 years after vaccination, although few breakthrough cases have been reported

# Rates of Meningococcal Disease (C and Y) by Age, 1999-2008



Active Bacterial Core surveillance (ABCs), 1998-2008

# MenACWY Adolescent Vaccination Recommendations

- ❑ A booster dose is **not recommended** for healthy persons if the first dose is administered at or after 16 years of age
- ❑ A booster dose is **not recommended** for healthy persons after 21 years of age who are not at increased risk of exposure
  - A booster dose is not recommended for healthy persons 22 years of age and older even if the first dose was administered at 11-15 years of age

# **Vaccine Recommendations for Persons at Increased Risk for Meningococcal Disease**

# High-risk Groups: Functional or Anatomic Asplenia\*

- ❑ Younger than 19 months infant series at 2, 4, 6, and 12-15 months with HibMenCY-TT or MenACWY-CRM
- ❑ 19-23 months who have not received a complete series
  - 2-dose primary series of MenACWY-CRM at least 3 months apart\*\*
- ❑ 24 months and older who have not received a complete series
  - 2-dose primary series of either MenACWY at least 3 months apart\*\*

\*Including sickle-cell disease

\*\*Doses valid if 8 weeks apart

# High-risk Groups: Persistent Complement Component Deficiency

- ❑ Children 2-18 months
- ❑ infant series at 2, 4, 6, and 12-15 months with HibMenCY-TT or MenACWY-CRM OR 2-dose primary series of MenACWY-D starting at 9 months at least 3 months apart \*
- ❑ 19-23 months without complete series of HibMenCY-TT or MenACWY
  - 2-dose primary series of MenACWY at least 3 months apart\*

\*Doses valid if 8 weeks apart

# High-risk Groups: Persistent Complement Component Deficiency (continued)

- ❑ 24 months and older who have not received a complete series of HibMenCY-TT or MenACWY
  - 2-dose primary series of either MenACWY at least 3 months apart\*

\*Doses valid if 8 weeks apart

# Meningococcal Vaccination of Children 2-18 Months at Increased Risk

- ❑ With persistent complement deficiencies
- ❑ With functional or anatomic asplenia
- ❑ At risk during a community outbreak attributable to a vaccine serogroup
- ❑ Are traveling to or residing in regions where meningitis is epidemic or hyperendemic (use Menveo only)
- ❑ Administer 4 doses of Hib-MenCY-TT (MenHibrix), at 2, 4, 6, and 12–15 months or MenACWY-CRM (Menveo)
- ❑ Booster doses to be administered if continue to be at high risk (see later slide)

# Meningococcal Vaccine Recommendations for Persons 2 through 55 years at High Risk

## □ Persons who:

- Have persistent complement deficiencies
- Have functional or anatomic asplenia
- Have HIV, if another indication for vaccination exists

## □ Administer 2 doses of MenACWY, 8–12 weeks apart

# MenACWY Recommendations and HIV

- ❑ HIV infection alone is **not** an indication for MenACWY vaccination
- ❑ Persons with HIV infection show evidence of suboptimal response to vaccination
- ❑ Some persons with HIV infection should receive MenACWY (adolescents, some international travelers, microbiologists, etc.)
- ❑ Persons with HIV infection who are vaccinated with MenACWY should receive 2 doses at least 8 weeks apart

# Meningococcal Vaccine Recommendations for Persons 2 through 55 years at High Risk

## □ Persons who:

- Are first-year college students aged  $\leq 21$  years living in residential housing
- Travel to, or are residents of, countries where meningococcal disease is hyperendemic or epidemic
- Are microbiologists routinely exposed to isolates of *Neisseria meningitidis*
- Military recruits

## □ Administer: 1 dose of MenACWY

# Meningococcal Vaccine Use in Outbreaks

- ❑ Both MenACWY, and MPSV4 recommended for use in control of outbreaks caused by A, C, W, and Y
- ❑ HibMenCY-TT may be used for age-appropriate persons in outbreaks specifically caused by C and Y
- ❑ **Outbreak definition:**
  - at least 3 confirmed or probable primary cases of the same serogroup
  - period of 3 months or less
  - primary attack rate of more than 10 cases per 100,000 population

# The “Meningitis Belt”

Map 2-6. Areas with frequent epidemics of meningococcal meningitis



# Meningococcal Vaccine Booster Doses

- Children who receive primary immunization and remain at increased risk should receive booster doses
  - if primary immunization complete by 7 years of age first booster should be 3 years after primary immunization and every 5 years thereafter if at continued risk
  
- If primary immunization complete on or after 7 years of age
  - first booster should be 5 years after primary immunization and every 5 years thereafter if at continued risk

# MenACWY Revaccination Recommendations

- ❑ Other high-risk persons recommended for boosters:
  - Microbiologists with prolonged exposure to *Neisseria meningitidis*
  - Frequent travelers to or persons living in areas with high rates of meningococcal disease (see next slide)
- ❑ Revaccinate **every 5 years** as long as the person remains at increased risk
  - MenACWY for persons 2 through 55 years of age
  - MenACWY for persons 56 years and older also (off-label recommendation) if repeated vaccination anticipated

\*Off-label recommendation. *MMWR*2013;62(RR-2):10-11

# International Travelers and Revaccination\*

- International travelers should receive a booster dose of MenACWY if the last dose was administered 5 or more years previously
  - Vaccination in the 3 years before the date of travel is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj

\*CDC Travelers Health website at <http://www.cdc.gov/travel>

# What Do You Think?

## Text a CODE to 22333



A 6-month-old child with asplenia comes into your office today. If you had all of the following vaccines in stock, which one would you give?

- A. IZS17A - MCV4 (Menactra)
- B. IZS17B - MCV4 (Menveo)
- C. IZS17C - Hib-MenCY (MenHibrix)
- D. IZS17D - MPSV4 (Menommune)
- E. IZS17E - None, meningococcal vaccine is

Note: Message and Data Rates May Apply

[Show Poll Results](#)

not indicated

# What Do You Think?

## Text a CODE to 22333



- ❑ A 6-month-old child with asplenia comes into your office today. He is accompanying his family on a vacation to South Sudan (in the meningococcal belt). If you had all of the following vaccines in stock, which one would you give?
- ❑ A. IZS17A – MCV4-D (Menactra)
- ❑ B. IZS17B – MCV4-CRM (Menveo)
- ❑ C. IZS17C – Hib-MenCY (MenHibrix)
- ❑ D. IZS17D – MPSV4 (Menomune)

# Meningococcal Serogroup B (MenB) Vaccine Recommendations

- MMWR/ June 12, 2015 / Vol. 64 / No. 22:
  - Either vaccine should be administered to persons  $\geq 10$  years of age at increased risk of meningococcal disease, including persons
    - With persistent complement component deficiencies<sup>1</sup>
    - With anatomic or functional asplenia<sup>2</sup>
    - Who are microbiologists routinely exposed to isolates of *Neisseria meningitidis*
    - Identified to be at increased risk because of a serogroup B meningococcal disease outbreak

<sup>1</sup>including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab (Soliris®)

<sup>2</sup>including sickle cell disease

# ACIP MenB Vaccine June, 2015 Vote

- 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
  - Permissive recommendation (Category B)

Pending CDC Director's approval and publication of ACIP recommendations

# ACIP MenB Recommendations

- ❑ 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

# Meningococcal Vaccines

## Adverse Reactions

	MPSV	MenACWY
Local reactions for 1-2 days	4%-48%	11%-59%
Low-grade fever	3%	5%-17%
Systemic reactions (headache, malaise, fatigue)	3%-60%	4%-54%

# Meningococcal Conjugate Vaccine and Guillain-Barré Syndrome (GBS)

- ❑ Early reports to VAERS suggested an increased risk of GBS after receipt of Menactra MenACWY
- ❑ Subsequent studies have not demonstrated an increased risk
- ❑ On June 23, 2010, ACIP voted to remove a history of GBS as a precaution to MenACWY
- ❑ GBS still listed as precaution in package inserts

# Meningococcal Vaccine Contraindications and Precautions

- ❑ Severe allergic reaction to vaccine component or following prior dose
- ❑ Moderate or severe acute illness

# Meningococcal Disease Chemoprophylaxis

- ❑ Please see the Pink Book, and
  
- ❑ APPENDIX B: *Recommendations and Reports*, March 22, 2013 / 62(RR02);25-27
  - At  
<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a3.htm>

# MenACWY Administration Errors

- ❑ Providers inadvertently administer MenACWY by the subcutaneous (subQ) route
- ❑ There are few data on the efficacy or safety of MenACWY given by the subQ route
- ❑ Sanofi pasteur recommends REPEATING the dose given subQ
- ❑ CDC does not recommend revaccination



# Menveo Vaccine Administration Errors

- ❑ Liquid C-Y-W135 component administered without using it to reconstitute the lyophilized A component
- ❑ Revaccination may not be needed
  - Serogroup A disease is rare in the U.S., so revaccination **not** needed if the person does not plan to travel outside the U.S.
  - Revaccinate (no minimum interval) if international travel anticipated, especially to Africa

# Resources

## □ Information for these slides obtained from:

- <http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf>
- Prevention and Control of Meningococcal Disease, Recommendations of the ACIP
- *MMWR*/ March 22, 2013 / Vol. 62 / No. 2 and
- *MMWR*/ June 20, 2014 / Vol. 63 / No. 24
- *MMWR*/ June 12, 2015 / Vol. 64 / No. 22
- Pink Book:  
<http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/mening.pdf>



# Meningococcal Resources

- ❑ ACIP's Meningococcal Recommendations web page  
[www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html](http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html)
- ❑ CDC's Meningococcal Infection web page  
[www.cdc.gov/meningococcal/index.html](http://www.cdc.gov/meningococcal/index.html)
- ❑ CDC's Meningococcal Vaccination web page  
[www.cdc.gov/vaccines/vpd-vac/mening/default.htm](http://www.cdc.gov/vaccines/vpd-vac/mening/default.htm)
- ❑ Immunization Action Coalition Meningococcal web page  
[www.immunize.org/meningococcal/](http://www.immunize.org/meningococcal/)
- ❑ Children's Hospital of Philadelphia Vaccine Education Center Meningococcal web page  
[www.chop.edu/service/vaccine-education-center/a-look-at-each-vaccine/meningococcus-vaccine.html](http://www.chop.edu/service/vaccine-education-center/a-look-at-each-vaccine/meningococcus-vaccine.html)