Update on Meningococcal Disease and the Southern California Outbreak among Men Who Have Sex with Men

By

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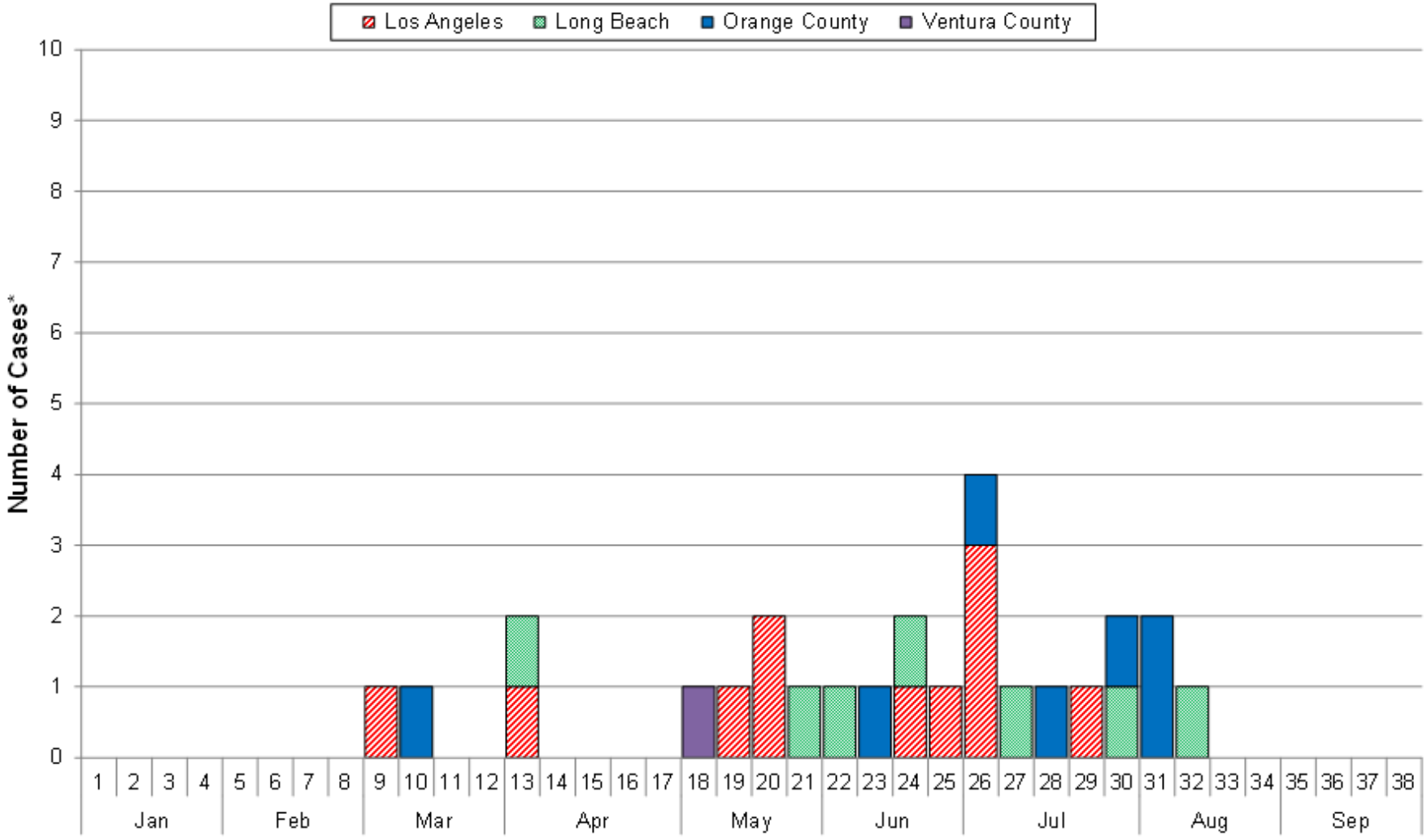
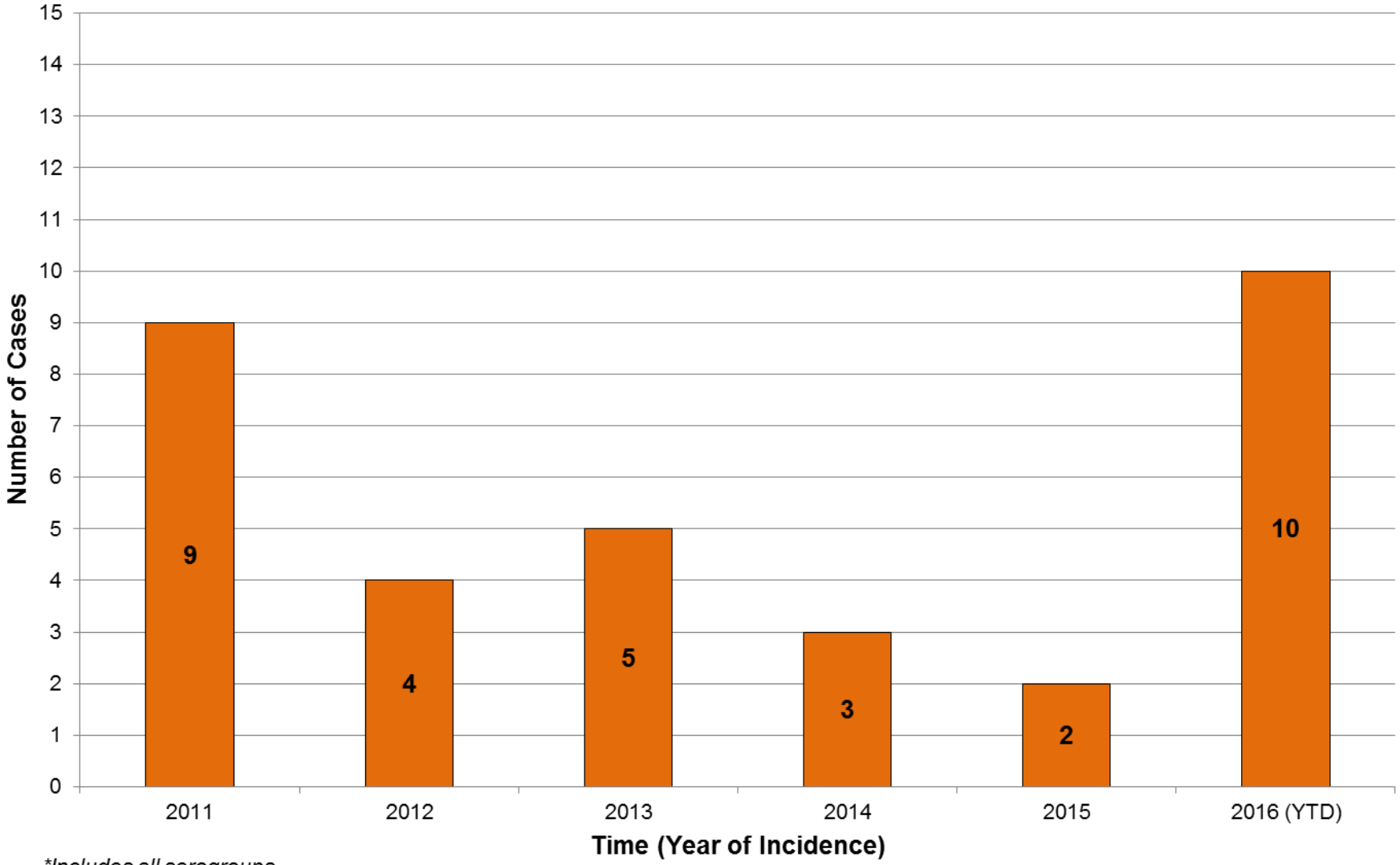
Epidemic Curve: Cluster of Invasive Meningococcal Disease, Serogroup C, by Jurisdiction. Southern California, 2016.



*Cases include those who are confirmed or possibly linked to the cluster.

Invasive Meningococcal Disease* (IMD) Cases in Orange County Residents by Year, 2011 - 2016 YTD.



*Includes all serogroups.

Data Source: Orange County Health Care Agency, Epidemiology & Assessment, Unpublished Data.

Last updated: 8/26/16

Serogroup C Patient Characteristics

- 24/26 Male 92%
- 20/26 MSM 77%
- Age range 19-61 years
- 11/26 Hispanic 42%
- 2 HIV+ 8%
- 1 homeless 4%
- 7 with drug use 27%
- 6 smokers 23%
- Multiple report visiting bars, night clubs frequently
- 0 vaccinated within last 5 years

Organism Summary

- Genotyping completed on 16 of 26 isolates
  - 4 of 7 OC cases completed
- All cases serogroup C
- All genetically identical
  - Multilocus sequence typing Clonal Complex: CC11

Prophylaxis Options

- Ceftriaxone
- Rifampin
- Ciprofloxacin
- Azithromycin is less well studied
  - All have 85-95% efficacy
- Vaccination for those exposed

Case #	Relation to Case	Number Prophylaxed
1		36
	Household	*3*
	Partner/Close Contact	*0*
	Sports Team	*~33*
2		6
	Household	*1*
	Partner/Close Contact	*0*
	Unknown Relation	*5*
3		3
	Household	*1*
	Partner	*1*
	Family	*1*
4		9
	Household	*3*
	Partner/Close Contact	*0*
	Family	*6*
5		0
	Household	--
	Partner/Close Contact	--
6		10
	Household	*8*
	Partner/Close Contact	*2*
7		41
	Family	*7*
	Medical Staff	*33*
	Partner/Close Contact	*1*

Meningococcal Disease in MSM Population

- Outbreaks and clusters of serogroup C meningococcal disease have been identified among MSM since 2001
- Toronto- 2001
- Chicago- 2003 and 2015
- NYC- 2010-13, 2014
- Los Angeles- 2014
- Belgium, Germany, France reported clusters from 2012-14
- MSM who are HIV+ have been more likely to be cases
- Overall rate in MSM population in US estimated at 4:100,000

California Meningococcal Disease Among MSM 2013-15

- 77 cases in males age 18-64
- 15 (19%) were identified as MSM; 7 of these were HIV+
- 10 serogroup C
- 1 serogroup Y
- 4 serogroup B
- 3 additional cases HIV+ but not identified as MSM

Los Angeles Meningococcal Epidemiology

January 1 through April 10, 2014:

- Total of eight IMD cases
- Four cases were reported among MSM
- Three were HIV-positive
- Three deaths
- Three reported residence or socializing ar ound the West Hollywood and North Holly wood areas
- Three were 27- 28 years of age

Meningococcal Outbreak Assessments in MSM Populations is Challenging

- Outbreaks are defined by CDC as 10 cases/100,000
- In our “event”
  - What is the denominator?
  - Which subpopulations are at risk?
  - When is an outbreak over?
- Community perception can clash with public health perception

Los Angeles Meningococcal Recommendations, 2014

- Recommend conjugate meningococcal vaccination to the following groups of MSM:
- All HIV-positive MSM
- All MSM, regardless of HIV status, who regularly have close or intimate contact with multiple partners or who seek partners through the use of digital applications (“apps”
- Particularly those who share cigarettes/marijuana or use illegal drugs

Meningococcal Conjugate Vaccines

- Cover serogroups A, C, Y, and W135
- Available conjugate vaccines:
  - HibMenCY-TT for 6 weeks-18 months
  - MenACWY-CRM for ages 2 months-55 years
  - MenACWY-D for ages 9 months-55 years
- Serogroup B not covered

Meningococcal Conjugate Vaccination Recommendations

- All 11 to 12 year olds should be vaccinated with a single dose of quadrivalent meningococcal conjugate vaccine
- Booster dose is recommended at age 16 years
- HIV-infected patients ages 2 months and older should receive a two-dose series 8 weeks apart

April, 2014 Orange County Recommendations

Based on the current situation, and after consultation with the California Department of Public Health, Orange County Public Health is recommending meningococcal vaccination be offered to:

- **All HIV-positive MSM who socialize regularly in Los Angeles County**
- **All MSM, regardless of HIV status, who regularly have close or intimate contact with multiple partners or who seek partners through the use of digital applications ("apps"), particularly those who share cigarettes/marijuana or use illegal drugs.**

MSM Epidemiology in LA and OC, 2014-15

Table 1. Characteristics of IMD Cases: Los Angeles County, 2015										
		Demographics			Serogroups					
	Number Confirmed[1]	Gender M/F	Median Age (Range)	MSM	B	C	Y	W-135	Not Typed	Deaths
This Year	12	7/5	48 (16-84)	1	6	2	0	2	2	0
Last Year Total	11	7/4	34 (22-61)	6	4	4	3	0	0	3

- One MSM case in Orange County in 2014
- No MSM cases in OC in 2015
- Recommendation for vaccination of HIV+ MSM and high risk groups remained

The Chicago and New York Experiences

Conversations with public health staff from those communities found:

- Mainstream media still matters
  - New York Times article about the outbreak was most effective advertiser in that city
- It can be challenging to reach the right population
  - Chicago initially reached affluent, white, MSM population before reaching African American MSM community at risk
- People misunderstand the recommendations
  - No one thinks that they are the ones at risk
- Need a champion at the site
- Outreach takes months to operationalize

August, 2016 OC, LA, LB Vaccination Recommendation:

- All MSM in these counties are recommended to receive one dose of conjugated meningococcal vaccination
- HIV+ patients are recommended to receive two doses separated by 8-12 weeks

How can I get the vaccine?

You can talk to your doctor about getting vaccinated or you can get vaccinated at **1725 W. 17th Street in Santa Ana, CA 92706**:

- If you just need the vaccine, go to the **Immunization Clinic**:
  Monday - Friday: 7:30 a.m. to 4:30 p.m. (closed 11:45 a.m. - 12:45 p.m.)
- If you need the vaccine and STD and/or HIV testing, go to **Testing, Treatment and Care Clinic**:
  Monday, Wednesday, Thursday, Friday, 8 a.m. to 4 p.m.
  Tuesday: 10 a.m. to 4 p.m.
- Additionally, you may get vaccinated on the following dates/times at the identified locations:

Date	Time	Location	
8/16/2016	4:30 p.m. - 7 p.m.	**The LGBT Center OC**	1605 N. Spurgeon St., Santa Ana, CA 92701
8/18/2016	10 p.m. - 12 a.m.	**Velvet Lounge**	416 W 4th Street, Santa Ana, CA 92701
8/20/2016	9 p.m. - 11 p.m.	**Frat House**	8112 Garden Grove Blvd., Garden Grove, CA 92844
8/23/2016	4:30 p.m. - 7 p.m.	**The LGBT Center OC**	1605 N. Spurgeon St., Santa Ana, CA 92701
8/26/2016	9 p.m. - 11 p.m.	**Frat House**	8112 Garden Grove Blvd., Garden Grove, CA 92844
8/28/2016	10 p.m. - 12 a.m.	**Velvet Lounge**	416 W 4th Street, Santa Ana, CA 92701
8/30/2016	4:30 p.m. - 7 p.m.	**The LGBT Center OC**	1605 N. Spurgeon St., Santa Ana, CA 92701

Call (800) 564-8448 for more information.

Meningococcal Doses Given by OCHCA Since Outbreak Identified

- 269 doses in 9 outreach events
- 315 doses given in STD/HIV clinic
- 67 doses given in OCHCA immunization clinic
- OCHCA will continue to look for community partners going forward

Logistical Issues

- Healthy population
- Not interested in accessing healthcare
- Highest risk are least likely to be vaccinated
- Vaccination recommendations need to be interpretable

Vaccination Outreach Event Challenges

- Labor intensive
- Sites chosen because that's where population at risk is likely to be
  - But people don't always want to get vaccinated when they go to a bar
- People need to come knowing that they will have the chance to get vaccinated
- No real MSM communities in OC

Meningococcal Urethritis

- Urethral carriage of *Neisseria meningitidis* occurs, though unusual
- Rates increased in the 1970s
- Rates in MSM populations somewhat higher than in general male population-
  - 0.7% in MSM vs 0.4-0.7% in general population
- 2-4% rectal carriage rate in MSM
- Southern California counties will study urethral carriage rate given current outbreak

Summary

- Rates of IMD in MSM are elevated
- Clusters of cases occur
- Outbreaks can include sporadic cases spread over many months
- Immunization outreach in high risk population MSM can be problematic
- Any effective outreach program will take time to establish
- Long term efforts will be needed to consistently immunize MSM populations

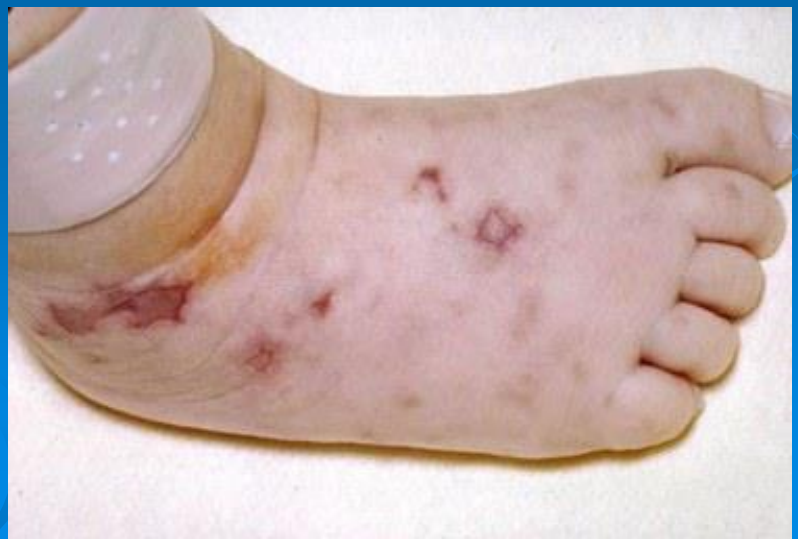
Meningococcal Infection

- Range of disease from occult bacteremia to fulminant sepsis
- Meningitis and pneumonia most common focal disease
- Overall mortality rate is approximately 10%
- 11-19% of survivors have permanent disabilities
  - Hearing loss
  - Neurologic injury

Rash is Classic Sign

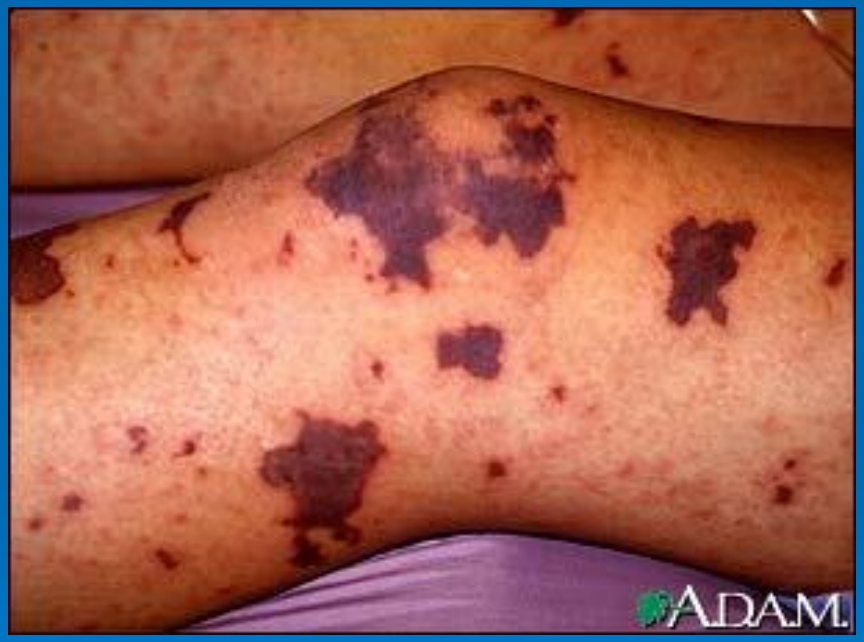
100 children in Los Angeles:

- 71% had rash
- 49% had petechiae or purpura
- 10% had maculopapular rash
- 16% had purpura fulminans



Am J Public Health. 1993 December; 83(12): 1790–1791.

Vasculature Affects of Meningococcemia



- Increased vascular leak
- Vascular dysfunction
- Clotting irregularities
- Cardiac dysfunction

Complications

- Recovery may be complicated by:
  - ARDS
  - Anuria
  - Multiple-organ failure
  - Skin and limb necrosis

Chronic Benign Meningococcemia

- Probably less than 1%
- Present with one or more episodes of:
- Spiking fever
- Arthralgia or arthritis
- Recurrent rash
- Mainly adults

Meningococcal Testing

- Gram stain and culture of blood, CSF, or other normally sterile site is usual method of diagnosis
- Gram negative diplococci on gram stain is justification for calling public health to begin contact investigation
- CDPH can perform PCR testing on blood and CSF, especially in pre-treated patients

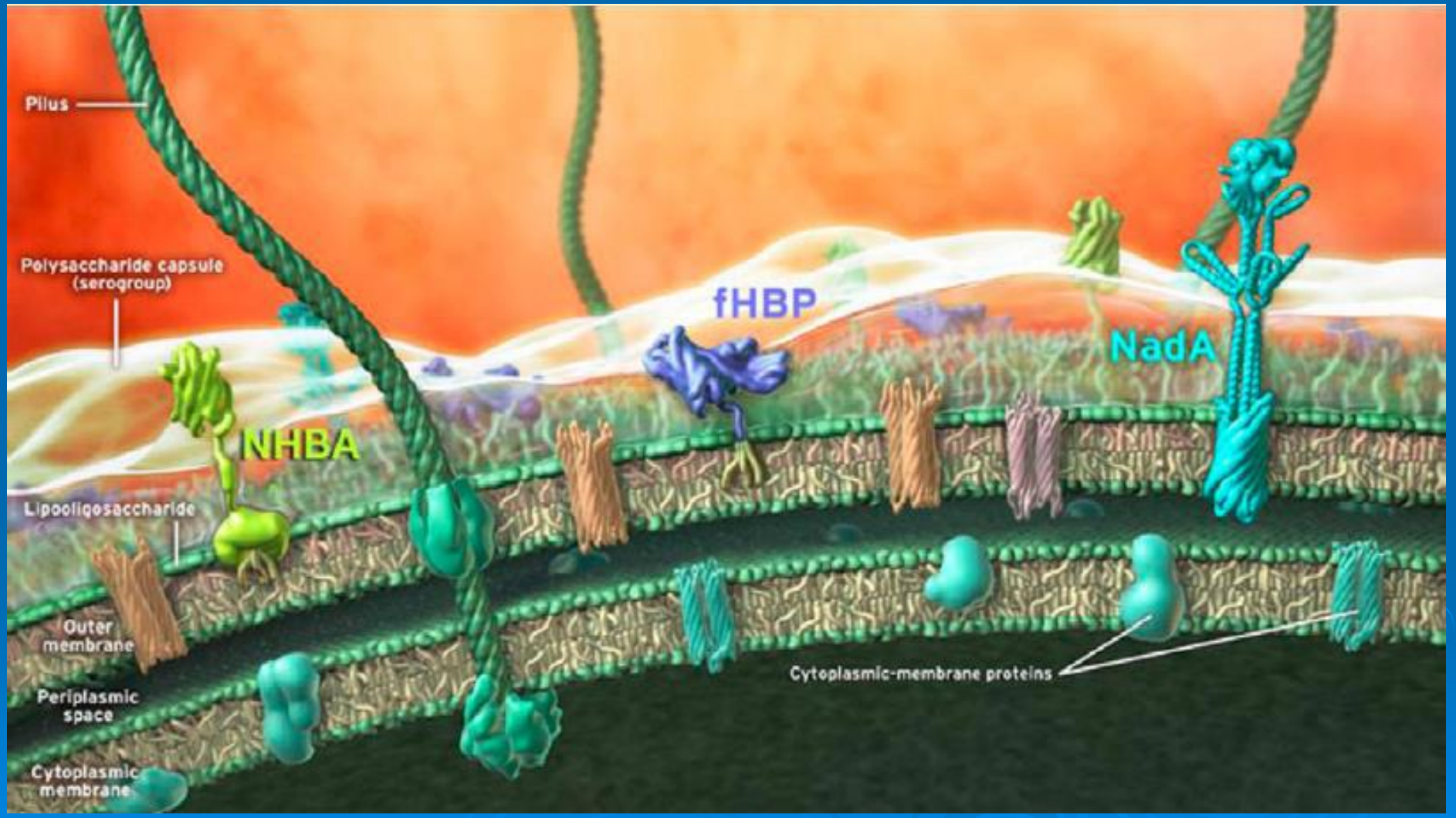
Adjunctive Therapies

- Activated Protein C
  - Largest trial was suspended due to lack of evidence of efficacy and serious bleeding events
- Steroid treatment for meningitis
  - Best studied for other bacterial meningitis causes
  - Trend toward benefit in meningococcal meningitis
  - If used, dexamethasone 0.15mg/kg daily for four days

Van de Beek, Lancet ID 2004;4:139

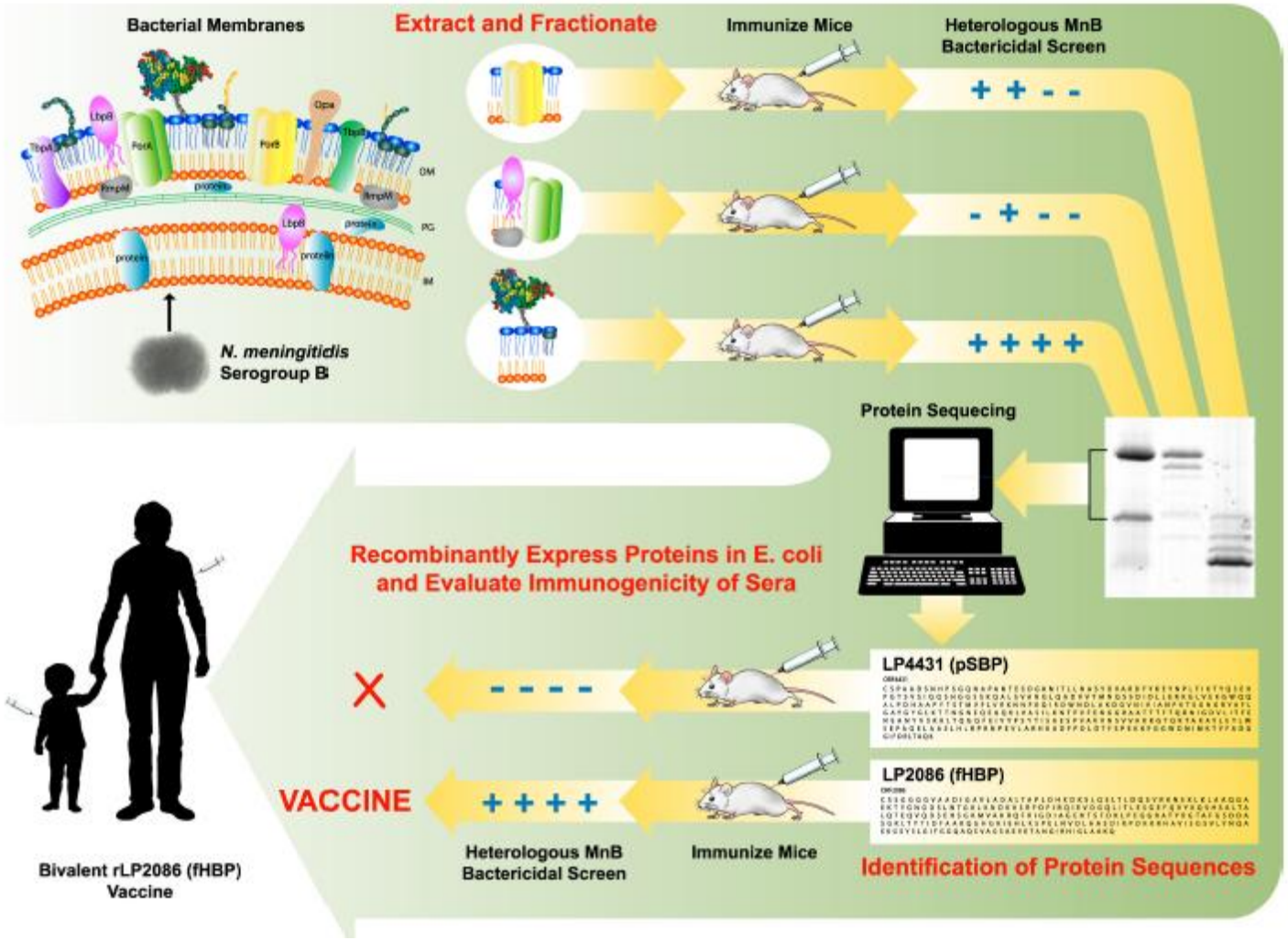
Meningococcal Polysaccharide Vaccine Recommended for:

- MPSV4 is the only licensed meningococcal vaccine for ≥56 years
- For meningococcal vaccine-naïve persons aged ≥56 years who anticipate requiring a single dose of meningococcal vaccine, MPSV4 is preferred
- For adults who have received conjugated meningococcal vaccine previously, give conjugated vaccine
- For persons aged ≥56 years for whom multiple doses are anticipated, give conjugate vaccine


Pilus
Polysaccharide capsule (serogroup)
fHBP
NadA
NHBA
Lipooligosaccharide
Outer membrane
Periplasmic space
Cytoplasmic membrane
Cytoplasmic-membrane proteins

Outer Membrane Vesicle Vaccines

- OMV vaccines have been utilized internationally since 1970s
- Public health interventions conducted in Cuba, Norway, New Zealand, Brazil
- Cuba, 1987-89
  - 106,000 10-14 yos vaccinated
  - Effectiveness of 83%
- Sao Paolo, 1989-90
  - 2.4 million children vaccinated
  - Effectiveness of 74%
- Primarily utilized to combat outbreaks associated with specific strains



Mcneil LK, et al. MMBR June 2013 234-252

Factor H Binding Protein Vaccine (fHbp)

- fHBP has been found to be one of the most immunnologically active OMV antigens
- Elicits a broad and effective bactericidal response against meningococcal serogroup B strains
- Different meningococcal B strains have different fHBPs
- fHBPs are categorized as either subfamilies or variants

fHBP Vaccine: Trumenba

- Trumenba is a sterile suspension composed of two recombinant lipidated factor H binding protein (fHBP)
- Proteins are individually produced in E. coli
- The recombinant proteins are:
  - Extracted from the production strains and purified through a series of column chromatography steps
  - Polysorbate 80 (PS80) is added to the drug substances

Trumenba Package Insert

fHBP Vaccine: Trumenba

- FDA licensed in October, 2014
- 3-dose series: 0, 2, 6 months
- Licensed for age 10-25 years
- Composed of two factor H binding proteins:
  - fHbp subfamily A/v2,3
  - fHbpsubfamily B/v1

fHBP Vaccine Immunogenicity

- 788 children 11-17 years of age
- Received 3 doses of fHBP vaccine
- 81.0% (95% CI 78, 83.7) had serum bactericidal activity against fHBP from 4 diverse meningococcal B strains

Trumenba Package Insert

MenB-4C Vaccine: Bexsero

- FDA licensed in January, 2015
- 2-dose series: 0, 1-6 months
- Approved for use in persons aged 10–25 years
- Licensed in >30 countries for persons ≥2 months of age

Bexcero Components

- Outer membrane vesicle (porin A)
- Factor H Binding Protein (fHbp) subfamily B/v1
  - Binds factor H, which down-regulates complement activation
- Neisseria heparin binding antigen (NHBA)
  - Helps bacteria resist human serum bactericidal activity
- Neisseria adhesin (NadA)
  - Involved in colonization and invasion

MenB-4C Immunogenicity

- 88% (95% CI 82, 93) of 974 UK university students aged 18-24 yo had a composite serum bactericidal activity (SBA) response to three serogroup B strains after 2 doses
- 63% of 342 Canadian/Australian 11-17 yos had composite SBA develop after 2 doses

Bexsero package insert

Estimate of MenB-4C Efficacy in United States

- Meningococcal Antigen Typing System (MATS) bridged to serum bactericidal activity in a subset of diverse strains
- >80% predictive of bactericidal activity with one antigen, >90% with two or more antigens matched
- MATS was performed on 3,269 isolates (442 US isolates)
- 4CMenB estimated strain coverage of 91% (95% CI: 72%-96%) in U.S.

PNAS Nov 9 2010 19490-5

Maintenance of Immunity

- Persistence of immunogenicity
  - 66% (95% CI 58%, 72%) of UK university students maintained serologic evidence of immunity 11 months after vaccination with 2 doses
- No concomitant administration data available for MenB-4C
- Evidence of waning antibody levels within 6 months post dose 3 for MenB-fHBP

Adapted from June, 2015 ACIP

MenB Vaccination and Meningococcal 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

Adapted from June, 2015 ACIP

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

ACIP Recommendations February, 2015

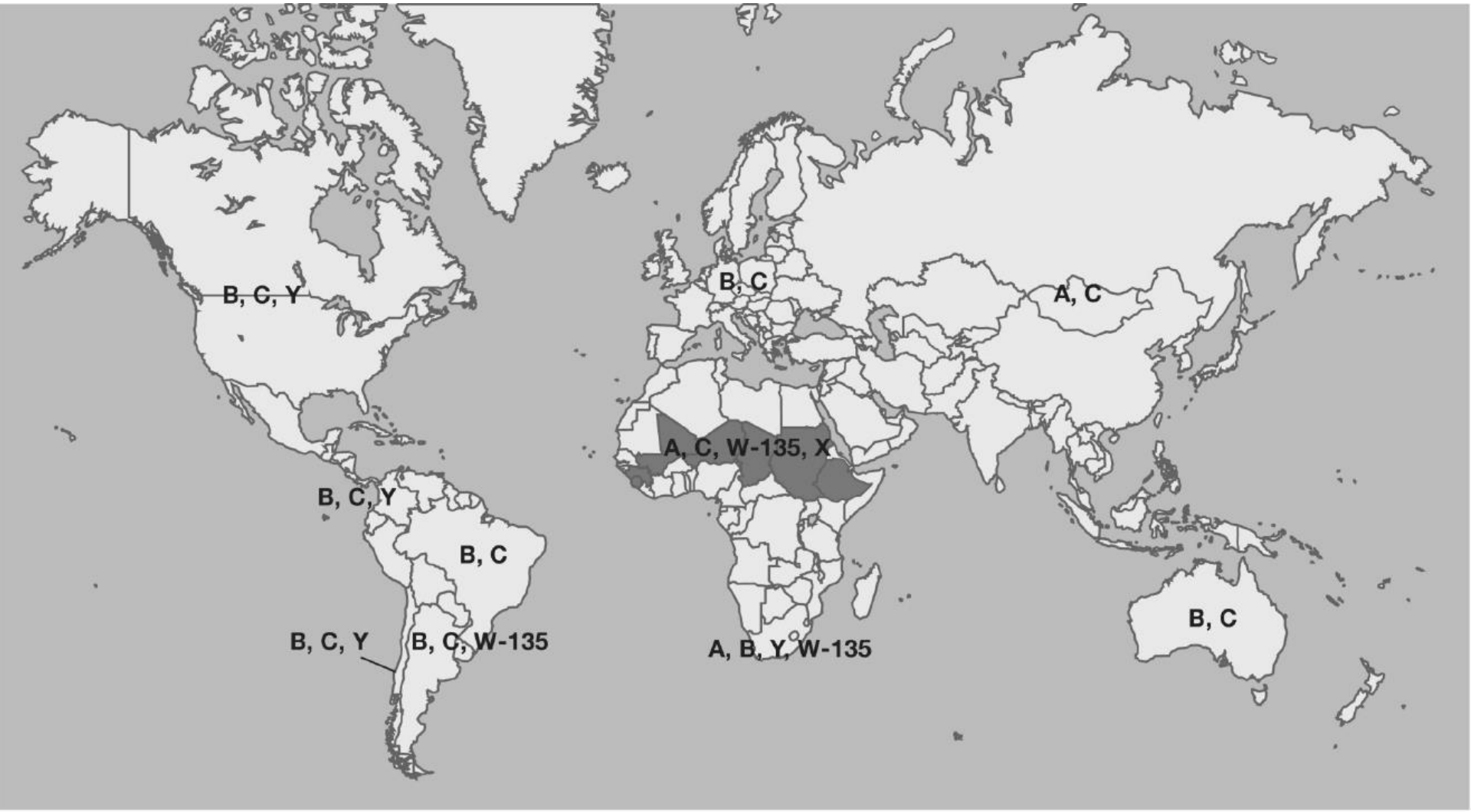
- A serogroup B meningococcal vaccine series should be administered to persons aged ≥10 years at increased risk for meningococcal disease. This includes:
  - Persons with persistent complement component deficiencies:
    - Deficiencies in C3, C5-9, properdin,factor D, factor H, or taking eculizumab
  - Persons with anatomic or functional asplenia including sickle cell disease
  - Microbiologists routinely exposed to isolates of *Neisseria meningitidis*
  - Persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak

Issues to Consider in Recommending MenB Vaccine

- Low rate of disease
- Severity of Disease
- Difficulty of implementing schedule in adolescent age group
- Importance of equal access to all
- Uncertainty of length of immunity provided

Meningococcal Immunity

- Development of neutralizing antibody is key to immunity
- Most people have some immunity to pathogenic organisms
- Those without immunity are at high risk of developing invasive meningococcal disease when exposed to a pathogenic organism for the first time
- Complement response also key to immune reaction to meningococcal infection



CID, 3/2010

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.

ACIP meeting, June, 2015

ACIP Recommendation June, 2015

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 recommendation
- No product preference indicated

Threshold for vaccination for serogroup B outbreaks

For outbreaks involving:

- 2 cases in population <5,000 persons
- 3 cases in population ≥5,000 persons

Recent MSM Recommendations

- Minnesota DOPH recommended meningococcal vaccination to all MSM after one case noted in association with Chicago Gay Pride Festival
- Multiple travel advisories made
- ACIP is revisiting MSM issue in February, 2016